

# **Avastin<sup>®</sup> (bevacizumab)**

**United States Food and Drug Administration  
Oncologic Drugs Advisory Committee  
March 31, 2009**

# Introduction

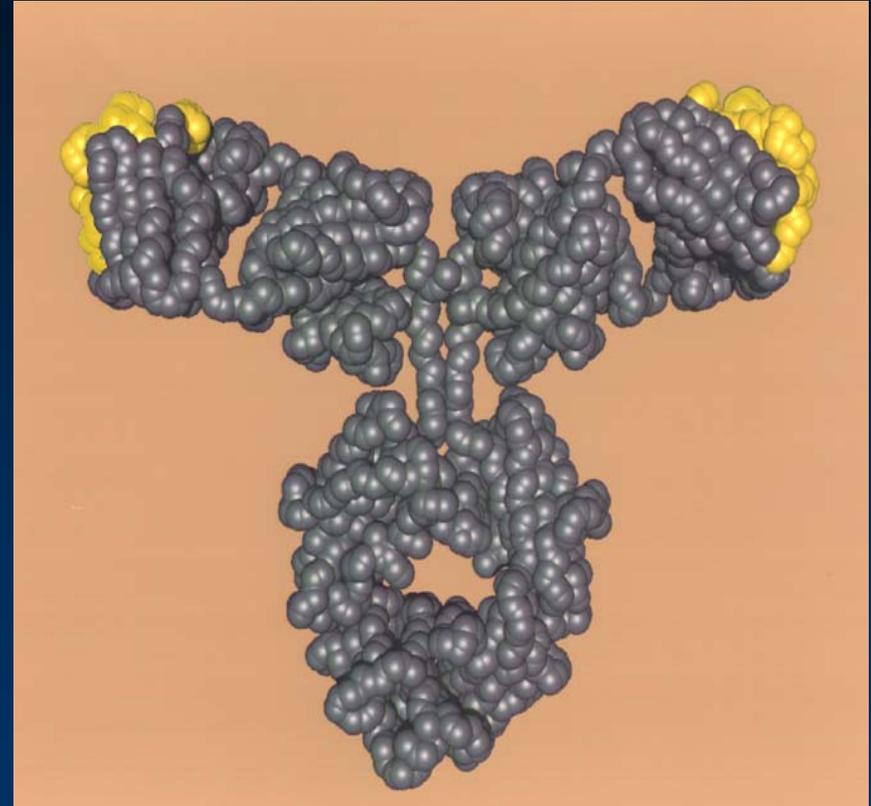
**David Schenkein, MD**  
**Genentech, Inc.**

# Proposed Indication Statement

**Avastin<sup>®</sup>, as a single agent,  
is indicated for the treatment of patients  
with previously treated glioblastoma**

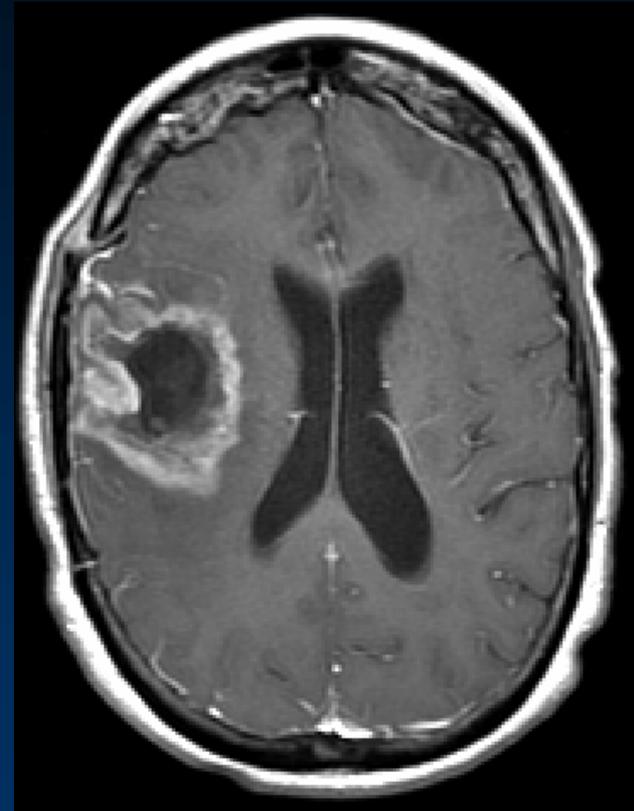
# Avastin Targets the Angiogenesis Factor VEGF-A

- VEGF-A cloned 1989
- Avastin is a humanized monoclonal antibody specific for VEGF ligand
  - Approved in 4 indications
  - > 370,000 patients treated worldwide with Avastin



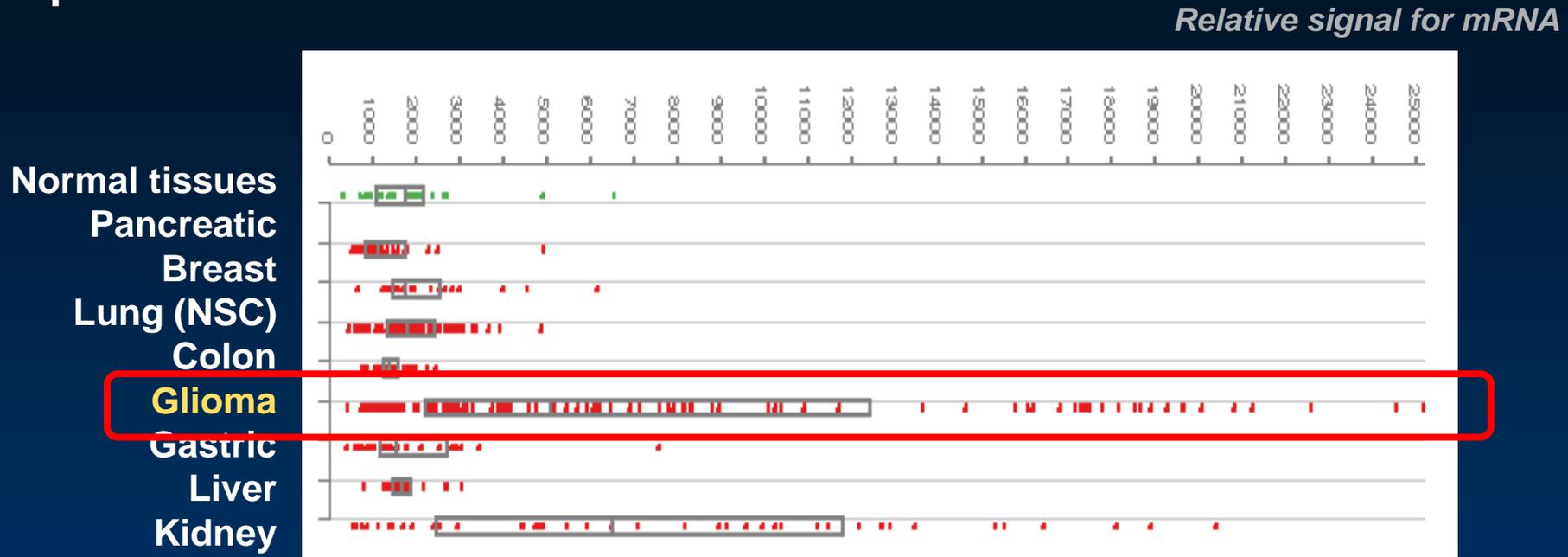
# Relapsed Glioblastoma

- **Universally fatal**
- **Incidence: 10,000 patients**
- **Treatment-associated toxicities common**
- **Many patients will receive no additional therapies other than best supportive care**

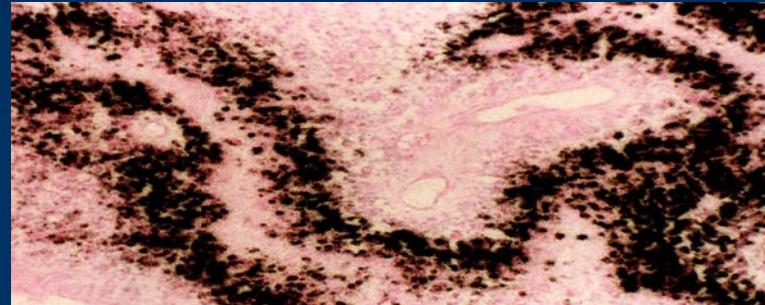


# VEGF and Malignant Gliomas

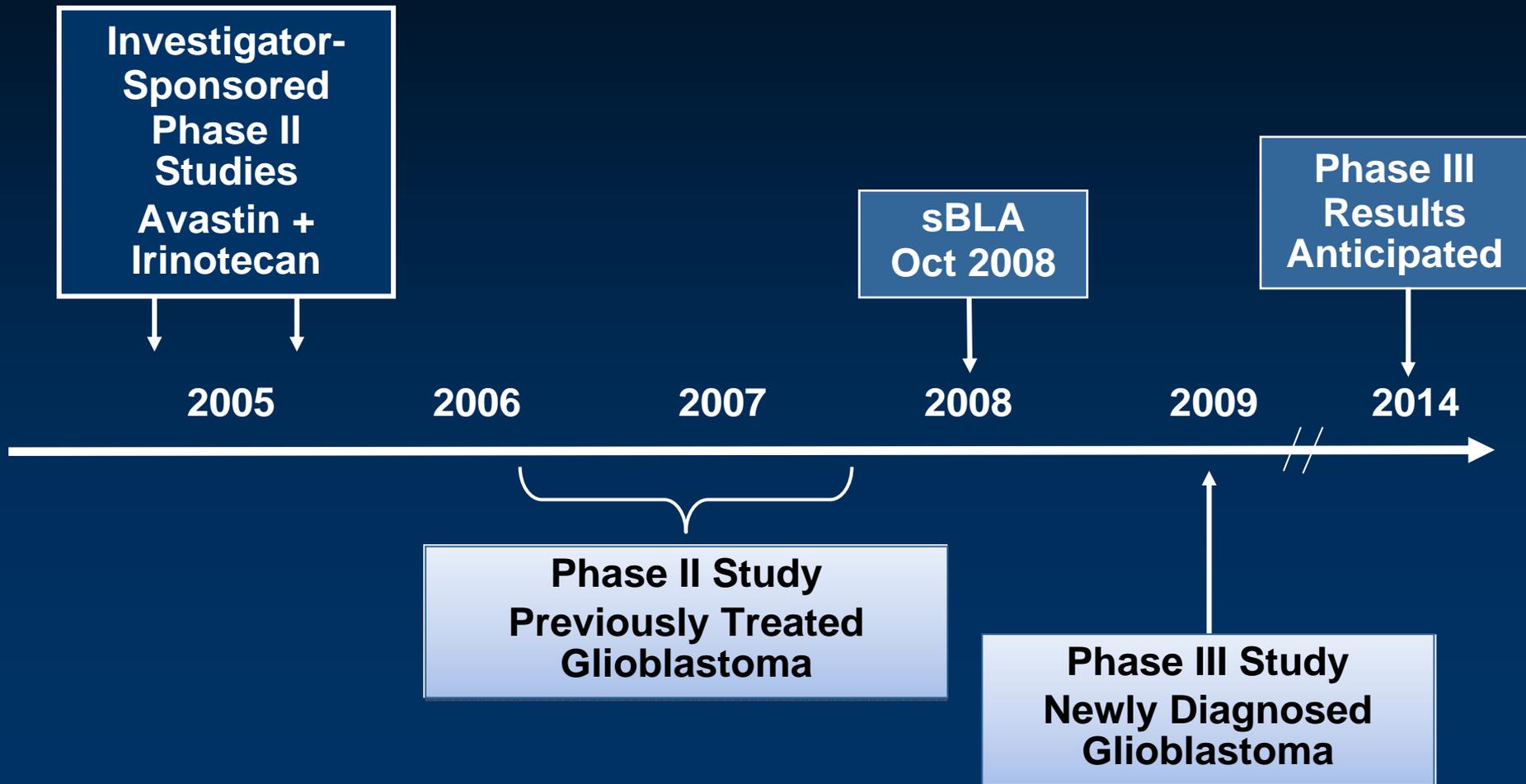
- Glioblastomas are highly vascularized tumors and express extremely high levels of vascular endothelial growth factor (VEGF) and predict poor survival



Intense expression of VEGF mRNA (black) is seen in GBM tumor cells surrounding necroses;  
Phillips et al, *Int J Onc.* 1993



# Genentech Development Plan for Avastin in Glioblastoma



# Accelerated Approval

Effect on a surrogate endpoint reasonably likely to predict clinical benefit

1. Changes on MRI as evidence of clinical activity
2. Response rate substantially higher than historical controls

# Executive Summary

- **Avastin therapy led to a high rate of durable responses**
  - **Conservative response criteria and methodology (IRF)**
  - **Supportive secondary endpoints**
  - **Landmark response analysis linking response to survival**
  - **Second supporting trial (NCI)**
- **Response rate and 6-month progression-free survival (PFS6) significantly higher than historical controls**

# Today's Agenda

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**A. Gregory Sorensen, MD**  
**MGH**

**MR Imaging in Glioblastoma**

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**Julie Hambleton, MD**  
**Genentech**

**Study AVF3708g and NCI-Fine  
(Avastin)<sup>1</sup>**

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**Michael Prados, MD**  
**UCSF**

**Recurrent Glioblastoma  
Avastin Study in Context**

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**David Schenkein, MD**  
**Genentech**

**Conclusions**

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<sup>1</sup> NCI 06-C-0064E.

# Experts Available for Questions

- **Tim Cloughesy, MD**  
Director, Neuro-Oncology  
Program, UCLA  
Los Angeles, CA
- **Jeffrey Wefel, PhD**  
Assistant Professor of  
Neuropsychology  
UT MD Anderson Cancer Center  
Houston, TX

# Imaging in Glioblastoma

**A. Gregory Sorensen, MD**

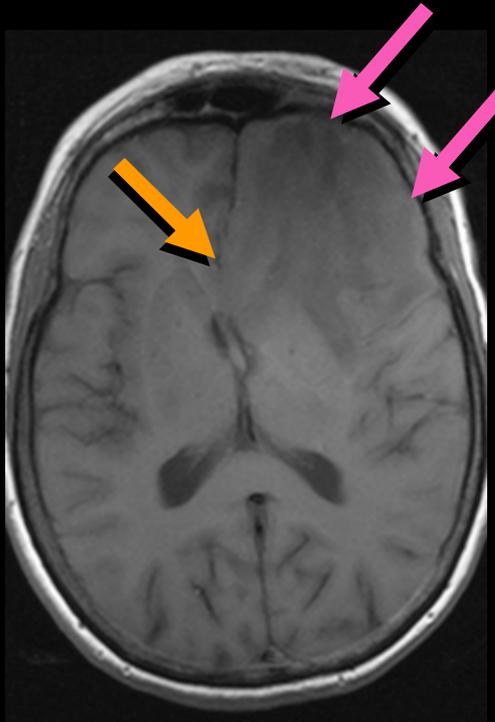
**MGH-HST Center for Biomarkers in Imaging  
A. A. Martinos Center  
Massachusetts General Hospital**

**Harvard Medical School &  
Massachusetts Institute of Technology  
Division of Health Sciences and Technology**

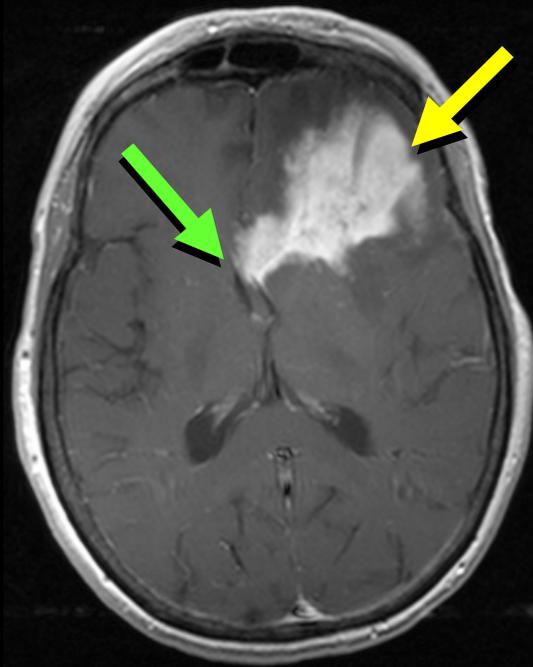
# Outline

- **Part 1: Imaging Assessment of GBM**
  - MRI methods
  - Assessing biological effects
  - Centralized review for treatment response in clinical trials
- **Part 2: Imaging After anti-VEGF Therapies**
  - Rapid change in blood-brain barrier
  - Assessment of treatment effect

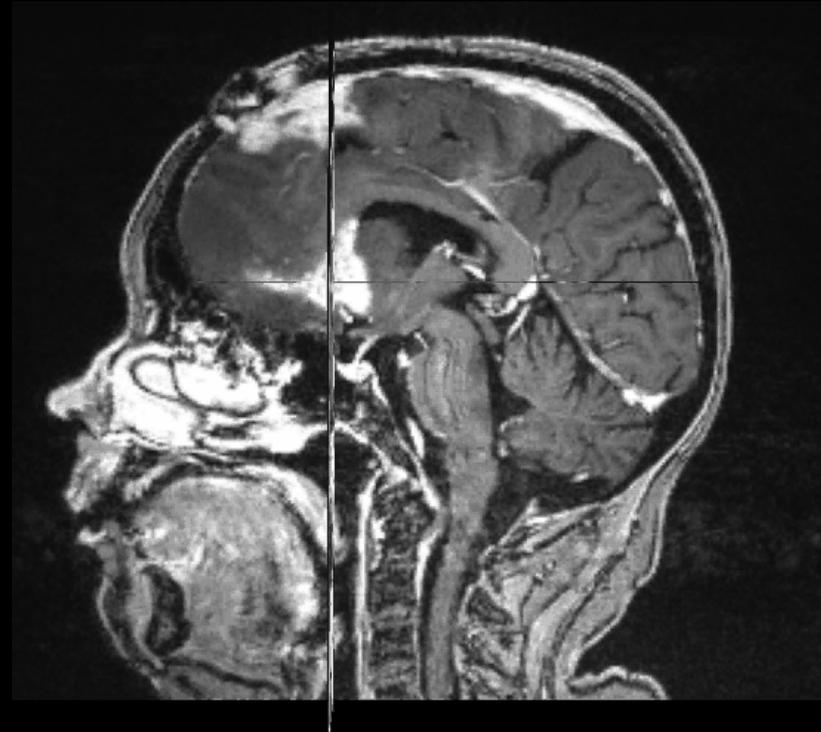
# T1-weighted Imaging: Tumor Bulk With and Without Gadolinium



T1 Pre-Gd

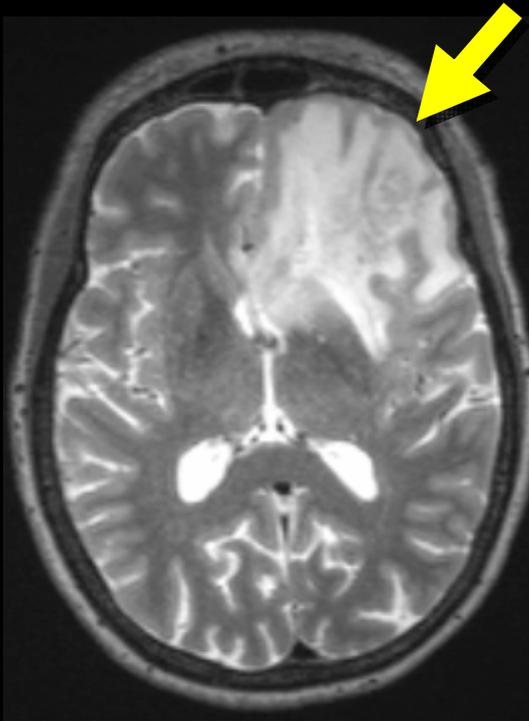


T1 Post-Gd

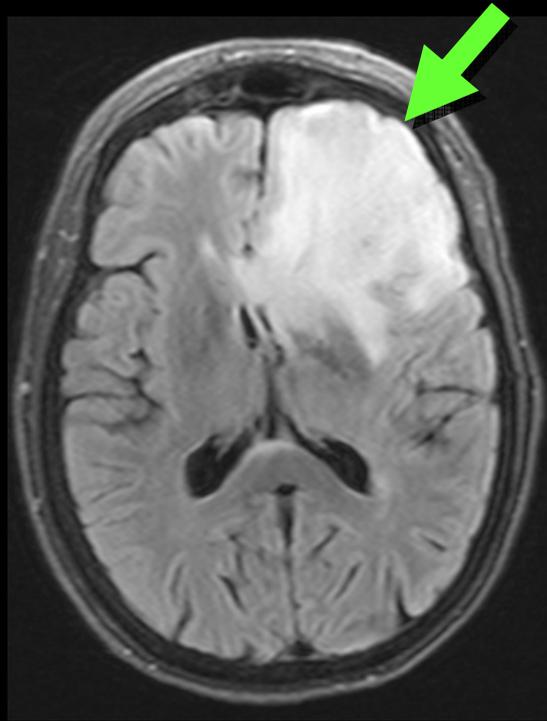


Post-Gd 3D volume

# T2-weighted Imaging: Edema and Tumor Infiltration



T2

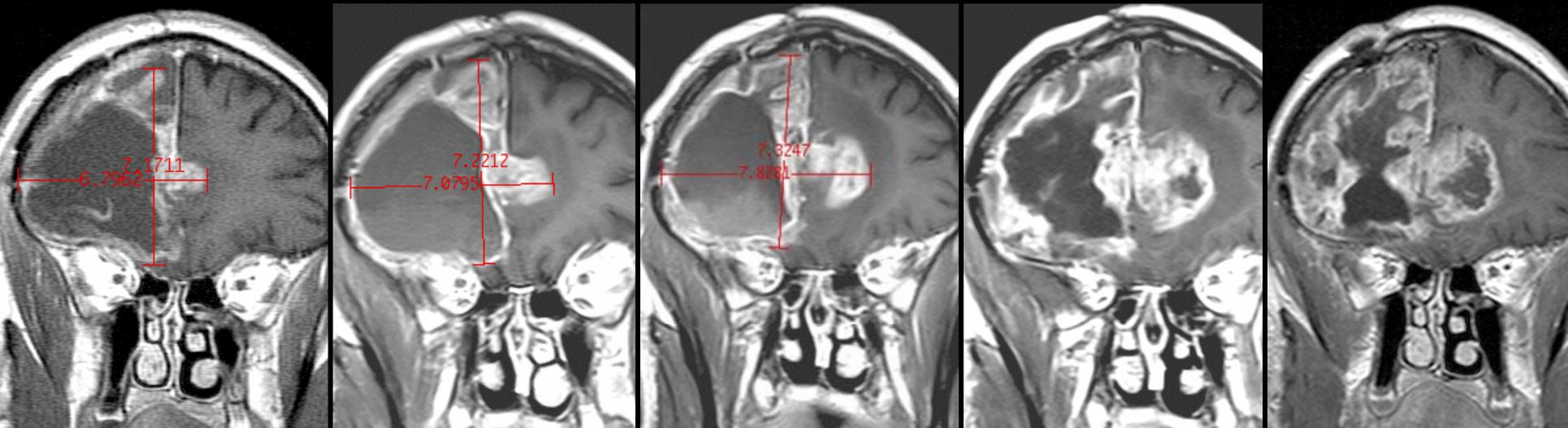


FLAIR



T2 3D volume

# Typical Course of Glioblastoma: Relentless Growth



Sep

Oct

Dec

Jan

Mar

# Macdonald Response Criteria

WHO response criteria adapted for brain tumors (+ steroids/clinical)

<b>Criteria</b>	<b>Macdonald (1990)</b>
<b>Changes in corticosteroid doses</b>	<b>CR: Off steroids</b> <b>PR: Stable or reduced steroids</b>
<b>Partial response (PR)</b>	<b>50% reduction in enhancing lesions compared to baseline</b>
<b>Complete response (CR)</b>	<b>Disappearance of all index and non-index lesions and off steroids</b>
<b>Confirmation of response</b>	<b>Confirm at next tumor assessment, <math>\geq 1</math> month apart</b>
<b>Neurological symptoms</b>	<b>Included in criteria for CR, PR, PD</b> <i>Definition not specified</i>
<b>Progressive disease (PD)</b>	<b><math>\geq 25\%</math> growth of contrast-enhancing lesions from nadir or any new lesion</b>
<b>Non-enhancing lesions PD (T2/FLAIR)</b>	<i>Not included historically</i>

# Part 2:

## Effects of Anti-VEGF Treatments

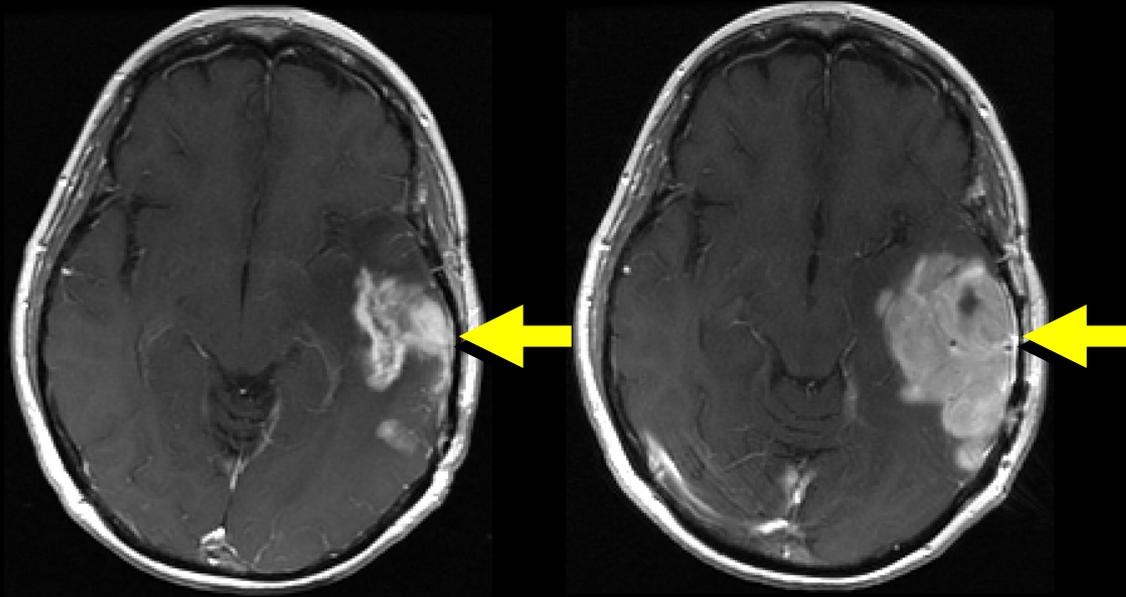
- Changes in gadolinium enhancement have been reported as soon as one day after treatment begins
  - Day 1 change seems unlikely to be all anti-tumor effect
- VEGF (vascular endothelial growth factor) is also known as VPF (vascular permeability factor)
- How do we modify our response criteria?
  - Durability of response (**no change needed**)
  - Not intensity of enhancement but size (**no change needed**)
  - Look at non-enhancing tumor (T2 or FLAIR) images
  - Secondary features such as mass effect change

# Examples From Genentech's Phase II Study

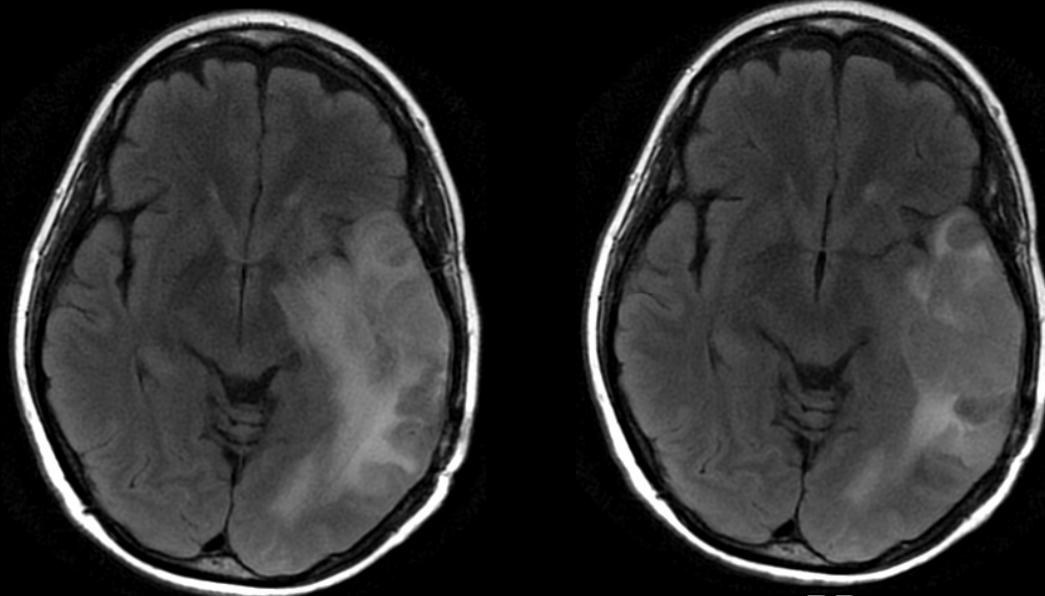
- **Non-response**
- **Response**
- **T2/FLAIR-based progression**

# Example: Non-Response

Axial T1w  
post-contrast



Axial  
FLAIR



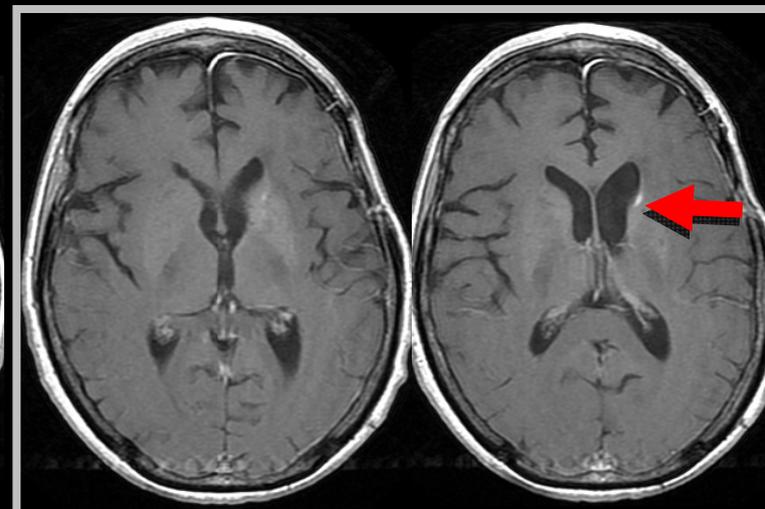
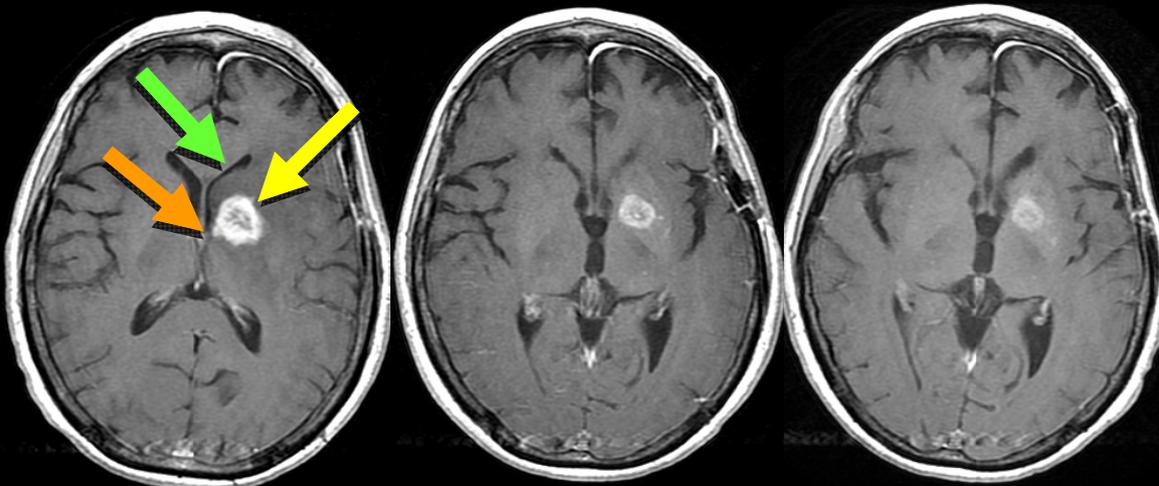
Baseline  
Nov 06

PD  
6 weeks  
Jan 07

AVF3708g  
20309

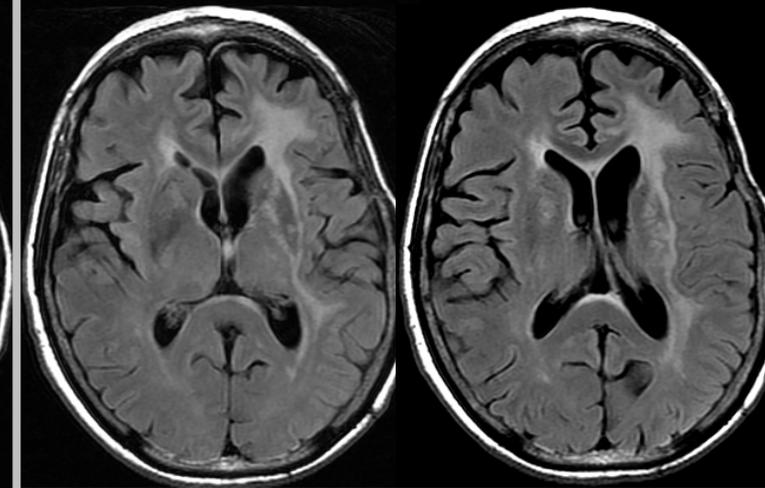
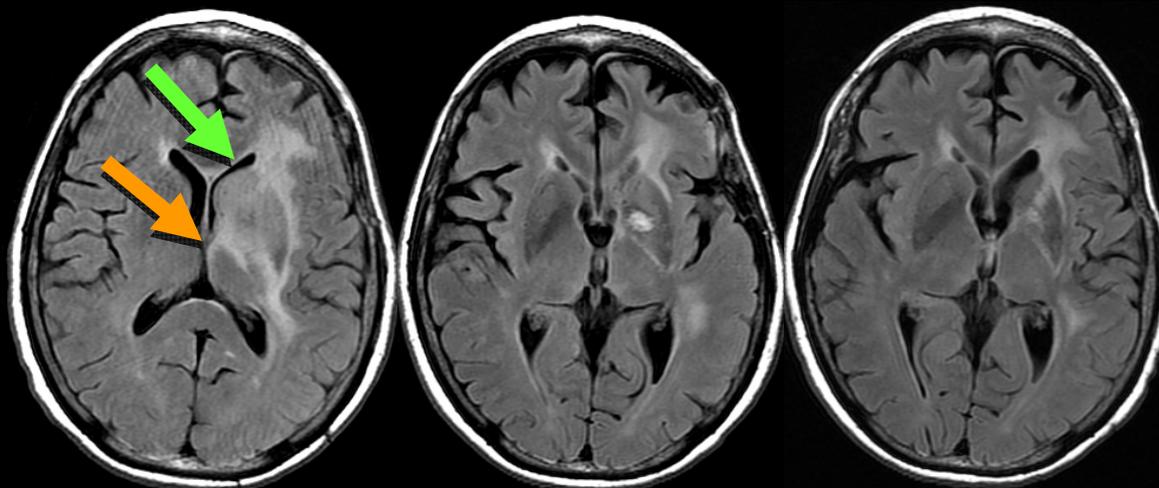
# Example: Response

Axial T1w post-contrast



New enhancement

Axial FLAIR



Baseline

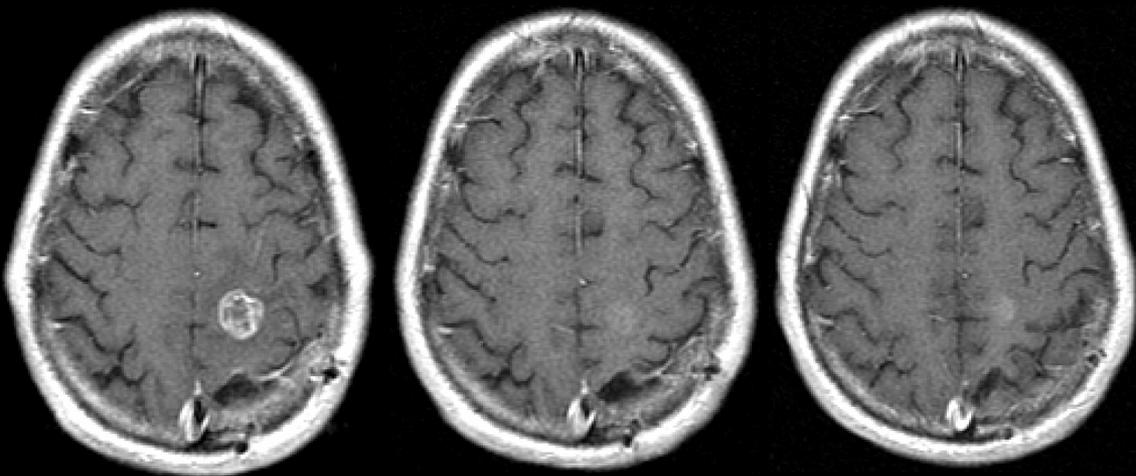
1st PR  
12 weeks  
Jan 07

Confirmed PR  
18 weeks  
Mar 07

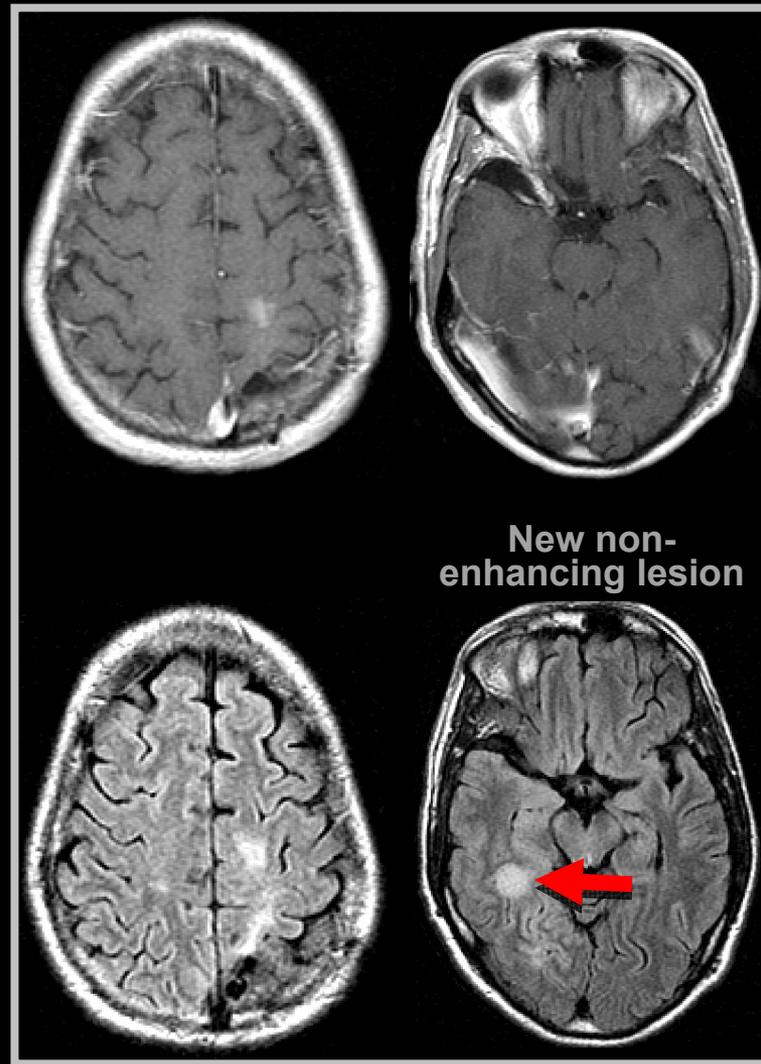
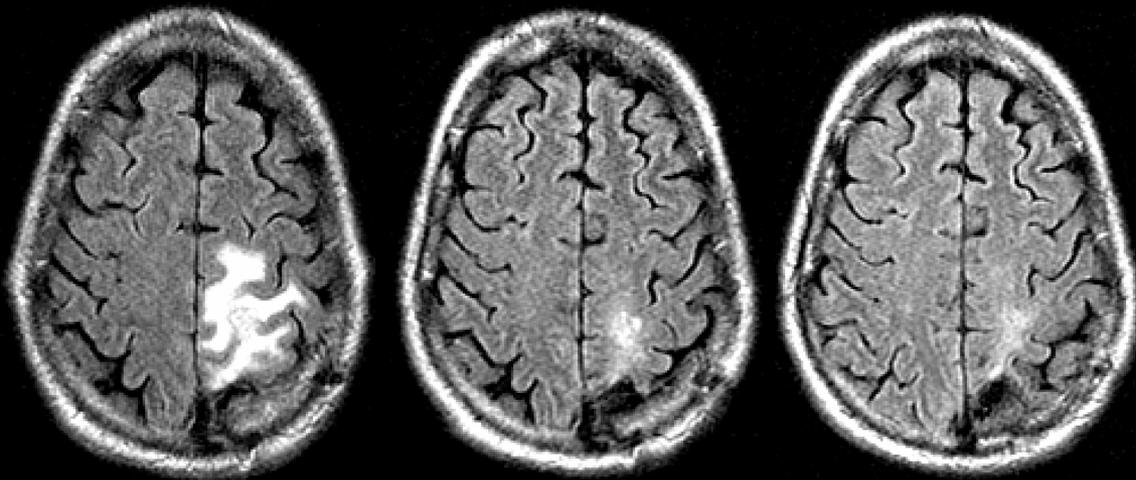
PD  
36 weeks  
Jul 07

# Example: PD by T2-weighted FLAIR MRI

Axial T1w post-contrast



Axial FLAIR



New non-enhancing lesion

Baseline  
Nov 06

1st PR  
6 weeks  
Dec 06

Confirmed PR  
12 weeks  
Jan 07

PD  
36 weeks  
Jun 07

AVF3708g  
20456

# Summary

- **Current clinical practice for MRI is T1-weighted imaging post-gadolinium and T2-weighted imaging**
- **Neither shows true tumor cells, but effects of tumor**
- **While bevacizumab rapidly decreases enhancement, this should be expected if it is having a biological effect**
- **Features such as:**
  - **Durable shrinkage of lesion**
  - **Decreased mass effect****suggest sustained real benefit above and beyond an impact on the vasculature alone**

# Study AVF3708g and NCI-Fine (Avastin<sup>®</sup>)

Julie Hambleton, MD

Genentech, Inc.

# Phase II Study (AVF3708g) Design



- **Primary endpoints:**

- Objective Response Rate, and
- 6-month PFS (PFS6) by independent radiologic review

- Clinical and tumor assessments by MRI were performed every 6 weeks

# Pre-sBLA Meeting—FDA/GNE Agreements

- **AVF3708g could serve as basis of sBLA**
- **Efficacy based on**
  - **Independently confirmed Objective Response Rate in Avastin single-agent arm**
  - **Independently confirmed Objective Response Rate in a second 56-patient trial conducted at the NCI**
- **Safety based on**
  - **Both the single-agent Avastin arm and the Avastin + Irinotecan arm**

# Response and Progression Criteria

- WHO adapted for brain tumors, using Macdonald criteria
  - Bi-dimensional measurements of contrast-enhancing lesions (index)
  - **Complete response:** disappearance of all lesions and no steroids above physiologic dose
  - **Partial response:**  $\geq 50\%$  shrinkage and stable or decreased steroids
  - **Progression:** new lesion, unequivocal progression of non-index lesions,  $\geq 25\%$  growth of index lesions, or clear clinical deterioration in the absence of radiologic progression
- Conservative aspects
  - Non-enhancing disease assessed as non-index lesions
  - All responses confirmed  $\geq 4$  weeks
  - Assessments performed by independent radiologic review

# Independent Radiologic Review

- **Objective and blinded assessment of radiographic endpoints by trained neuro-radiologists at a third-party facility**
  - Charter reviewed and approved by FDA
- **Standard two-reader assessment, with a third reader adjudicating discrepancies in determination of**
  - Best overall response (CR, PR, SD, PD)
  - Progression status
  - Date of progression
- **Independent oncologist reviewed assigned response status and corticosteroid dosing records to confirm responders met Macdonald criteria**

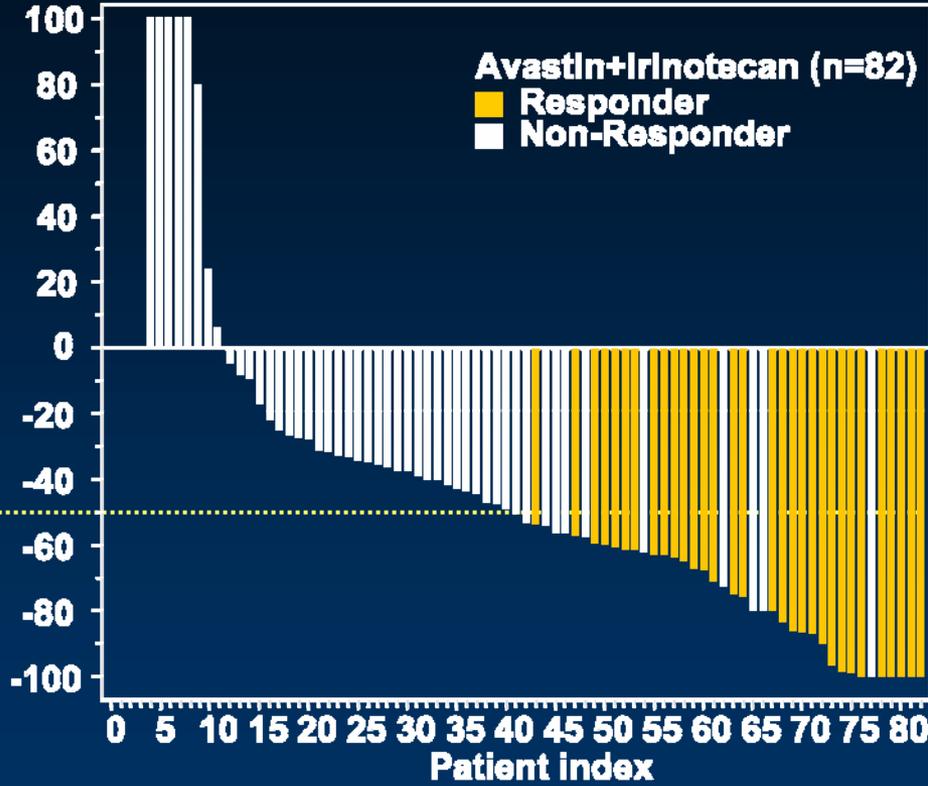
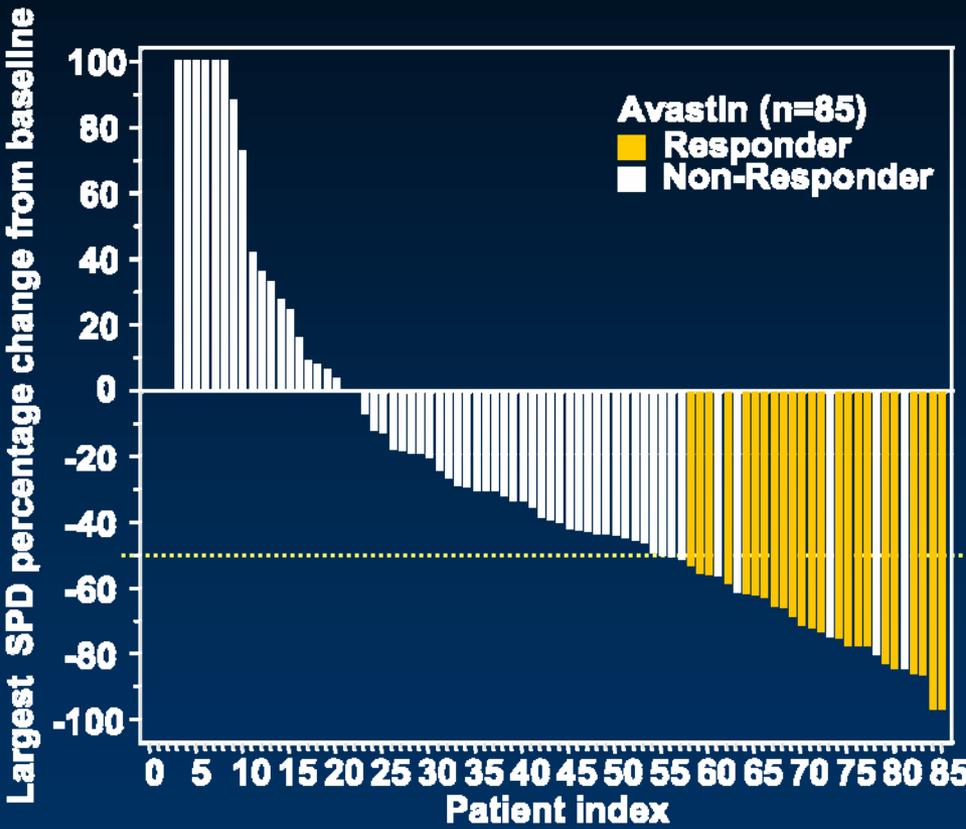
# Baseline Characteristics

	<b>Avastin (n=85)</b>	Avastin + Irinotecan (n=82)
<b>Median age, years (range)</b>	<b>54 (23-78)</b>	57 (23-79)
<b>Patients ≥ 65 years, %</b>	13	22
<b>Relapse: First, %</b>	<b>81</b>	80
<b>Second, %</b>	19	20
<b>KPS: 90-100, %</b>	45	38
<b>70-80, %</b>	55	62
<b>Corticosteroid use, %</b>	<b>51</b>	52

# Objective Response by Independent Review

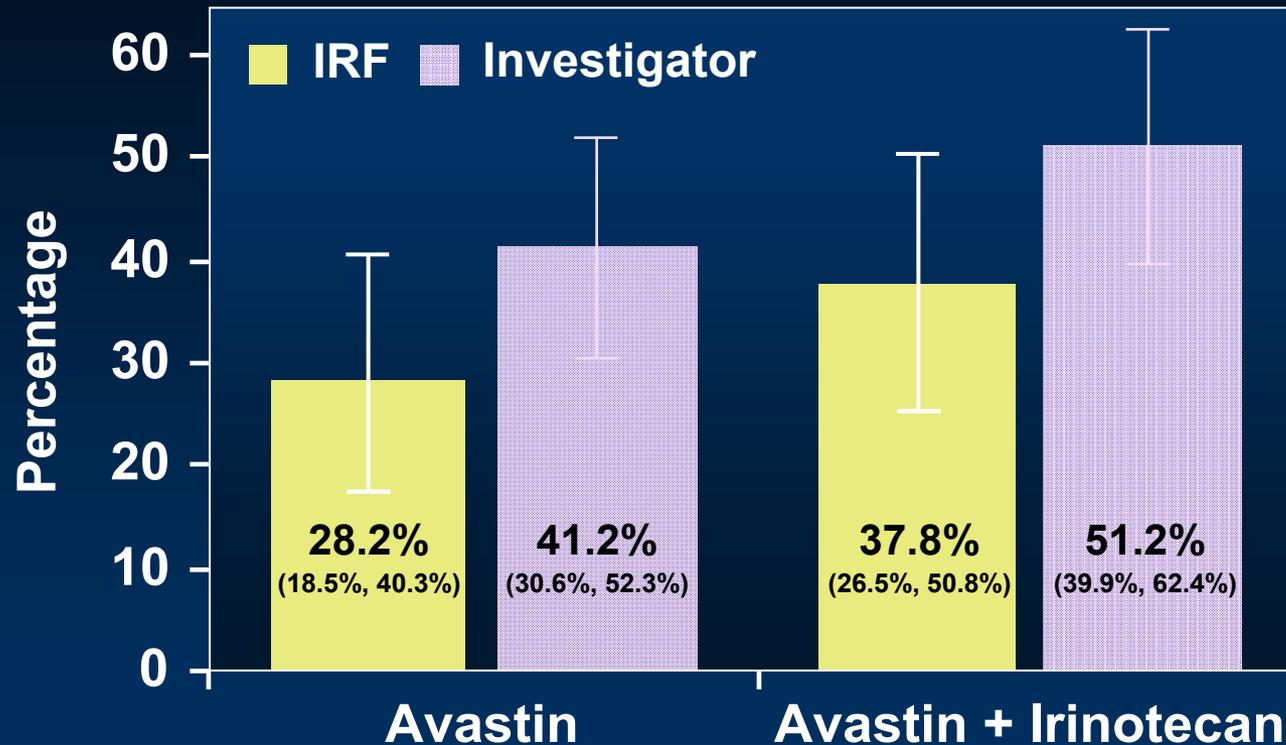
	<b>Avastin (n=85)</b>	Avastin + Irinotecan (n=82)
<b>Objective Response Rate</b>	<b>24 (28.2%)</b>	31 (37.8%)
<b>Complete Response</b>	1 (1.2%)	2 (2.4%)
<b>Partial Response</b>	<b>23 (27.1%)</b>	29 (35.4%)
<b>Stable Disease</b>	<b>40 (47.1%)</b>	38 (46.3%)
<b>Disease control rate (ORR + SD)</b>	<b>75.3%</b>	84.1%

# Tumor Shrinkage in Patients Receiving Avastin



SPD = Sum of the products of the diameters.

# Objective Response Rate



97.5% CI displayed for IRF results and 95% CI displayed for investigator results

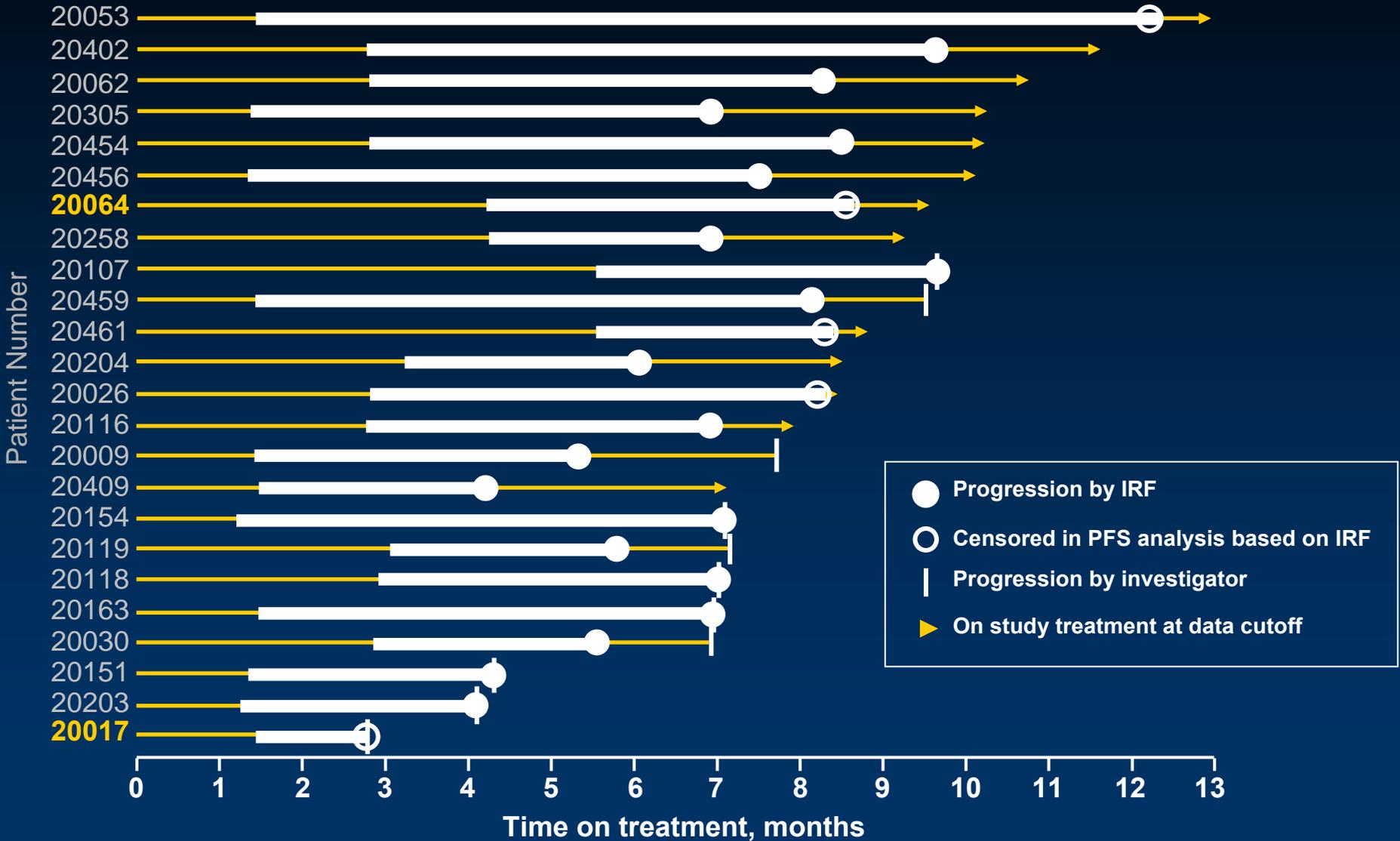
- IRF and FDA agreed on objective responses in 22 of 24 patients in the Avastin arm

# Duration of Response

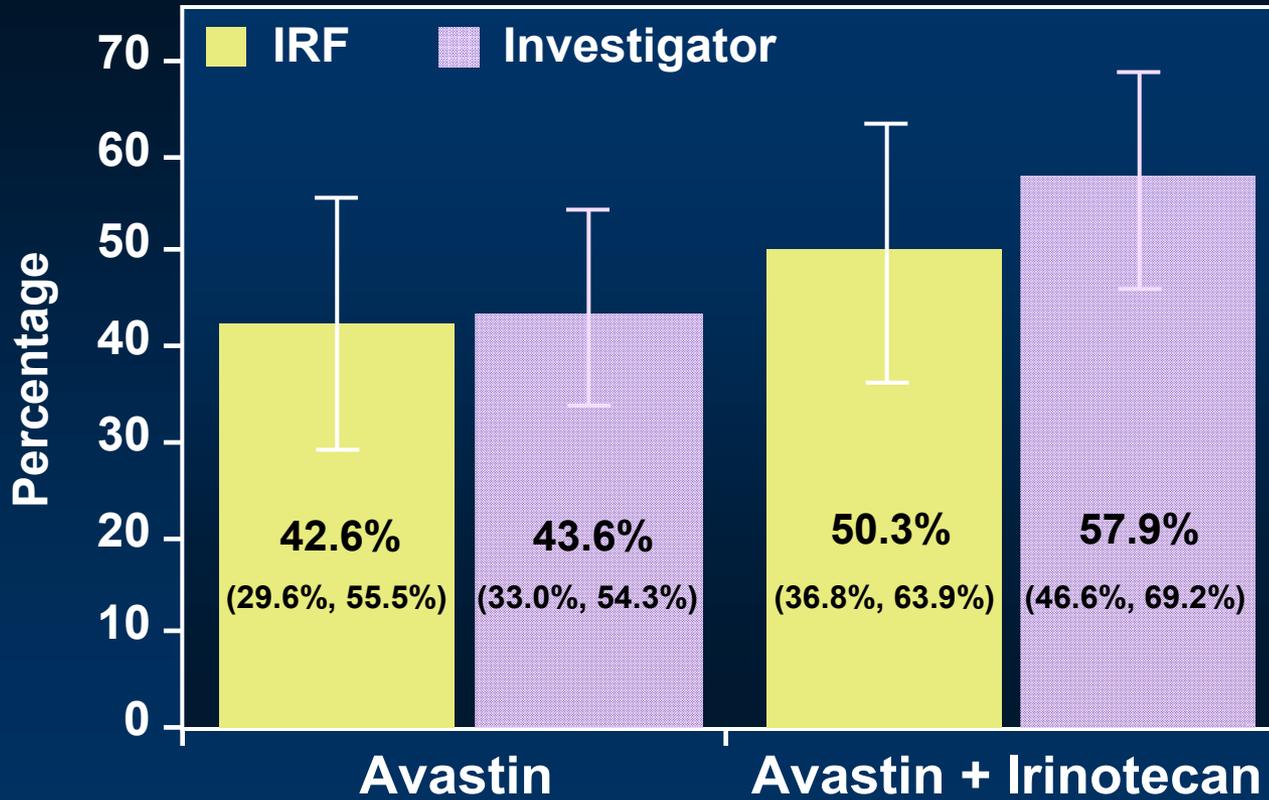
	<b>Avastin (n=85)</b>	Avastin + Irinotecan (n=82)
<b>IRF: median duration of response, months</b>	<b>5.6</b>	4.3
<b>Range</b>	<b>1.4<sup>+</sup> to 11.1<sup>+</sup></b>	1.4 <sup>+</sup> to 9.7 <sup>+</sup>
<b>Investigator: median duration of response, months</b>	<b>8.1</b>	8.3
<b>Range</b>	<b>1.4<sup>+</sup> to 11.1<sup>+</sup></b>	1.4 <sup>+</sup> to 11.1 <sup>+</sup>

- FDA-determined duration of response was 4.2 months in the Avastin arm

# Duration of Response—Avastin Patients



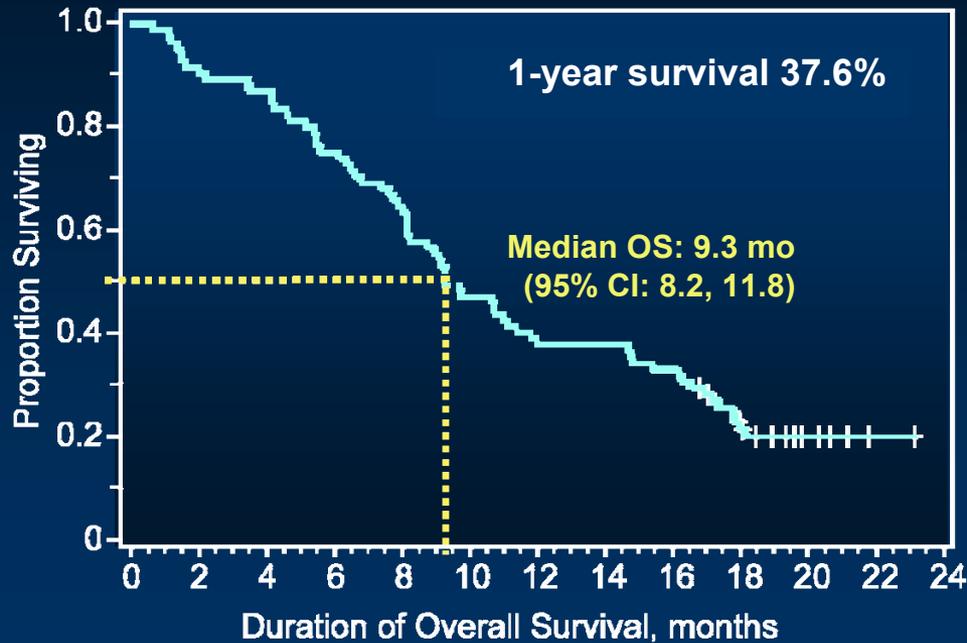
# Progression-Free Survival at 6 Months



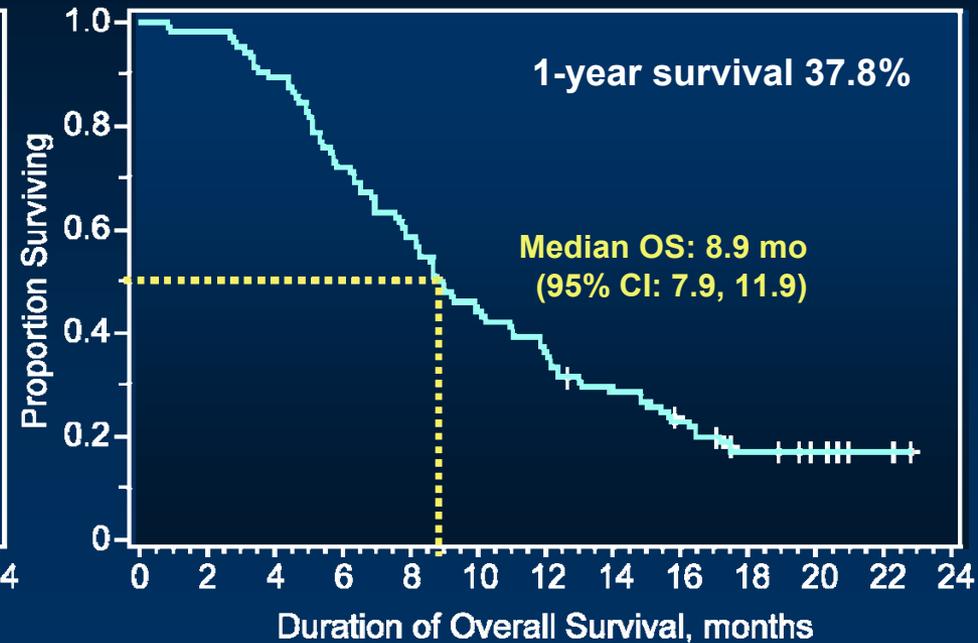
97.5% CI displayed for IRF results and 95% CI displayed for investigator results

# Median Overall Survival = 9.3 Months and 1-Year Survival Rate = 38%

## Avastin



## Avastin + Irinotecan



# Relationship Between Objective Response and Overall Survival

- **Exploratory analysis of overall survival in responders and non-responders for the 2 treatment arms pooled**
- **Well-known biases (survivorship and selection bias) addressed by standard analysis approaches**
  - **Landmark analyses at 9, 18, 26 weeks adjusted for baseline prognostic characteristics**

# Exploratory Analysis Shows Association of Response and Residual Survival—AVF3708g

Landmark analysis	9 weeks		18 weeks		26 weeks	
	Responders	Non-Responders	Responders	Non-Responders	Responders	Non-Responders
n	30	127	46	101	51	72
Hazard ratio	0.52		0.48		0.43	
P value (Cox model)	0.0091		0.0010		0.0002	

Results support the hypothesis that response status based on IRF was a predictor of survival in this study

# Neurocognitive Testing

- **Three domains of neurocognitive function were measured as exploratory endpoints:**
  - **Memory**
  - **Visuomotor scanning speed (complex visual scanning with a motor component)**
  - **Executive function (mental flexibility)**
- **These domains were assessed every 6 weeks by trained test administrators**

# Neurocognitive Function by RCI for Key Patient Subsets—Avastin Arm

	Stable or Improved on All Tests, n (%)	Declined on at Least 1 Test, n (%)
<b>Responders at time of IRF response (n=24)</b>	<b>18 (75.0%)</b>	<b>6 (25.0%)</b>
<b>PFS &gt; 6 months at Week 24 (n=27)*</b>	<b>19 (70.4%)</b>	<b>8 (29.6%)</b>
<b>Patients at time of investigator PD (n=49)**</b>	<b>15 (30.6%)</b>	<b>34 (69.4%)</b>

\*2 patients had missing neurocognitive data and were dropped from the analysis.

\*\*8 patients had missing neurocognitive data and were dropped from the analysis.

# NCI-Fine (Avastin) Single-Arm Study Design

- **Patients with previously treated glioblastoma**
  - No maximum of prior therapies
  - KPS 60 eligible
- **Single-agent Avastin**
- **Primary objective: PFS6 by investigator**
- **Secondary objective: ORR**
- **One treatment cycle = 4-week period of therapy**
- **Disease assessment by MRI every 4 weeks**

# Independent Radiology Review of NCI Study Supportive of Avastin Results

	<b>IRF (n=56)</b>	<b>INV* (n=48)</b>
<b>ORR, n (%) (95% CI)</b>	<b>11 (19.6) (10.9, 31.3)</b>	<b>17 (35) (22.2, 50.0)</b>
<b>CR, n</b>	<b>0</b>	<b>1</b>
<b>PR, n</b>	<b>11</b>	<b>16</b>
<b>Median duration of response, months (95% CI)</b>	<b>3.9 (2.4, 17.4)</b>	<b>Not reported</b>

**3 responses confirmed 1, 2, 5 days short of 4-week criterion not included**

# Safety in AVF3708g

# Primary Cause of Death in Most Patients Who Received Avastin Was Disease Progression

	<b>Avastin (n=84)</b>	<b>Avastin + Irinotecan (n=79)</b>
<b>Patients who died</b>	<b>38</b>	<b>41</b>
<b>Primary cause of death</b>		
<b>Disease progression</b>	<b>35</b>	<b>39</b>
<b>Neutropenic infection</b>	<b>1</b>	<b>0</b>
<b>Pulmonary embolism</b>	<b>1</b>	<b>0</b>
<b>Complication due to surgery</b>	<b>1</b>	<b>0</b>
<b>Seizure</b>	<b>0</b>	<b>1</b>
<b>Clinical deterioration</b>	<b>0</b>	<b>1</b>

1 patient developed retroperitoneal hemorrhage more than 30 days post-treatment and expired in the setting of progressive disease.

# Adverse Events Leading to Discontinuation

	<b>Avastin (n=84)</b>	<b>Avastin + Irinotecan (n=79)</b>
<b>Avastin discontinuations due to adverse event, n (%)</b>	<b>4 (4.8%)</b>	<b>14 (17.7%)</b>
	<ul style="list-style-type: none"> <li>1 CNS hemorrhage</li> <li>1 Myocardial infarction</li> <li>1 Neutropenic infection</li> <li>1 Adenocarcinoma</li> </ul>	<ul style="list-style-type: none"> <li>3 CNS hemorrhage</li> <li>2 Fatigue</li> <li>1 Reversible posterior leukoencephalopathy (RPLS)</li> <li>1 Stroke</li> <li>1 Pulmonary embolism</li> <li>1 Gastrointestinal perforation</li> <li>1 Wound healing complication</li> <li>1 General physical deterioration</li> <li>1 Status epilepticus</li> <li>1 Convulsion</li> <li>1 Skin disorder</li> </ul>

# Overview of Adverse Events

	Planned Treatment Period, n (%)		Optional Post-Progression Period, n (%)
	Avastin (n=84)	Avastin + Irinotecan (n=79)	Avastin + Irinotecan (n=44)
Adverse events (AEs) of any grade	83 (98.8%)	79 (100%)	43 (97.7%)
Grade $\geq$ 3 AEs	39 (46.4%)	52 (65.8%)	23 (52.3%)
Serious AEs	22 (26.2%)	34 (43.0%)	13 (29.5%)

# Avastin-Associated Adverse Events Grade $\geq 3$ Are Consistent With Product Label

Selected Adverse Events	AVF3708g (n=163) n (%)		Avastin Product Label
	Any Adverse Event	Grade 3-4	
Hypertension	52 (31.9%)	8 (4.9%)	8-18%
Arterial thromboembolic events	10 (6.1%)	5 (3.1%)	2.6%*
Gastrointestinal perforation	3 (1.8%)	3 (1.8%)	0-3.7% (any grade)
Proteinuria	6 (3.7%)	1 (0.6%)	$\leq 3.0\%$
Congestive heart failure	0 (0.0%)	0 (0.0%)	2.2%
Reversible posterior leukoencephalopathy syndrome (RPLS)	1 (0.6%)	0 (0.0%)	$< 0.1\%$ (any grade)

\*sBLA on 5 pooled studies including colorectal, breast, and lung cancer.

# Events of Special Interest in Previously Treated Glioblastoma

Event (all grades)	Avastin		Non-Avastin
	AVF3708g (n=163) n (%)	Avastin Product Label	Malignant Glioma Historical Data
Craniotomy wound-healing complications	4 (2.5%)	Not Reported	0.5-2.1% <sup>1</sup>
CNS hemorrhages	8 (4.9%)	1.2%	1.6-7.8% <sup>2</sup>
Venous thromboembolic events	13 (8.0%)	5-15.1%	4.2-31.1% <sup>3</sup>
Seizures	39 (23.9%)	Not Reported	19.3-47.3% <sup>4</sup>

• Wound-healing complications include incision site infection, healing abnormalities, and CSF leak

1.Chang 2003; Atennello 2008; 2.Chang 2003; Kondziolka 1987; Lieu 1999; Wakai 1982.

3. NDA 21029. Chang 2003; Simanek 2007; Salmaggi 2005; Semrad 2007; Streiff 2005; Brandes 1997; Everaert 2004.

4. NDA 21029; Pace 1998, Hildebrand 2005, Hwang 2004, Moots 1995, Salmaggi 2005.

# Efficacy and Safety Conclusions

- **Efficacy**
  - Objective response rate of 28.2% based on independent review with median duration of 5.6 months
  - Supported by independent review of NCI study
  - Supported by 6-month PFS of 42.6%, 1-year survival of 37.6%, stable neurocognitive function in responding patients, and consistent efficacy in the combination arm
- **Safety**
  - Single-agent Avastin was generally well tolerated
  - Safety profile consistent with other tumor types
  - No new safety signals in previously treated glioblastoma

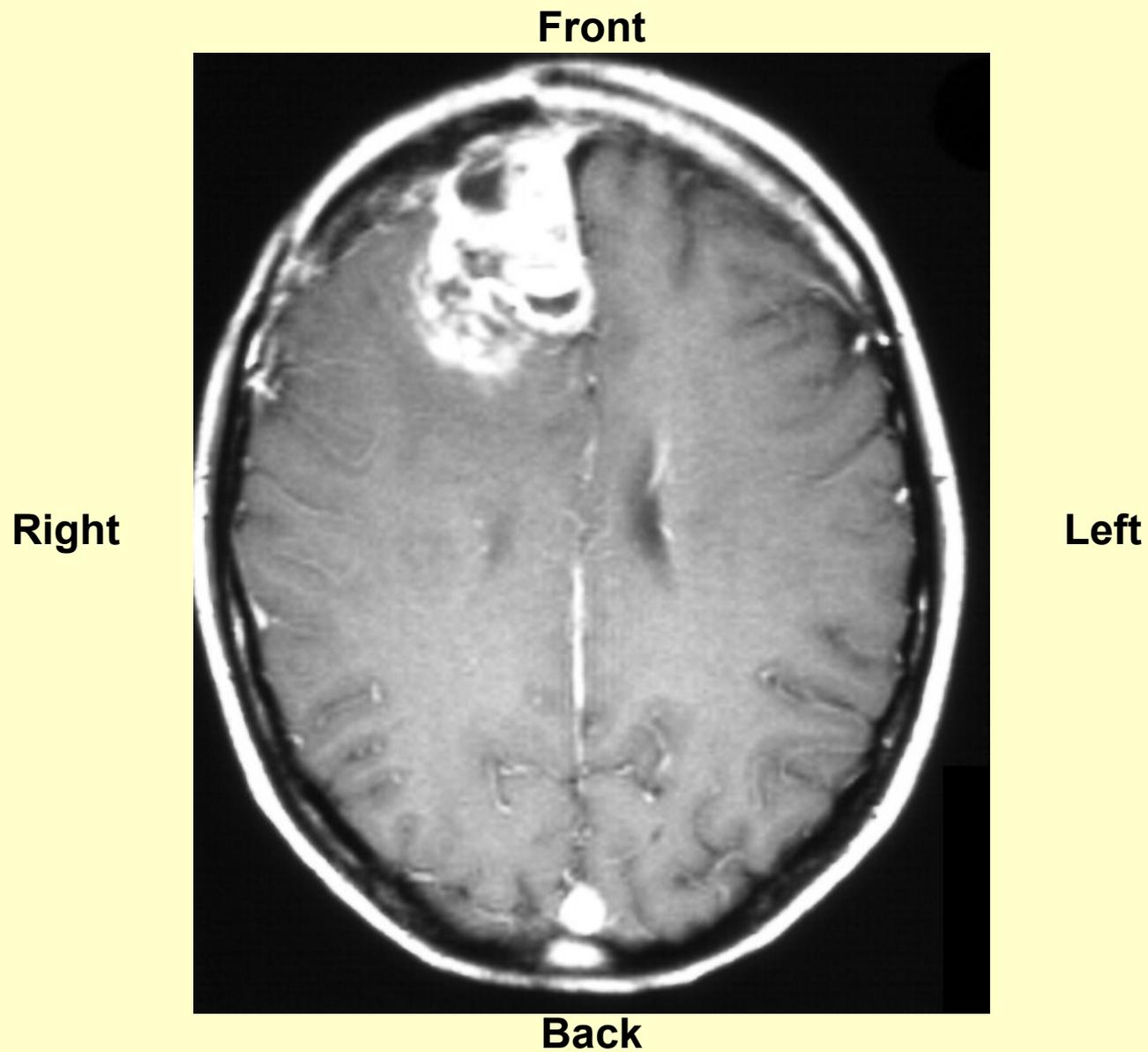
# Recurrent Glioblastoma

**Michael Prados, MD**

**Charles B. Wilson Professor of Neurosurgery  
Director of Division of Translational Research  
University of California San Francisco**

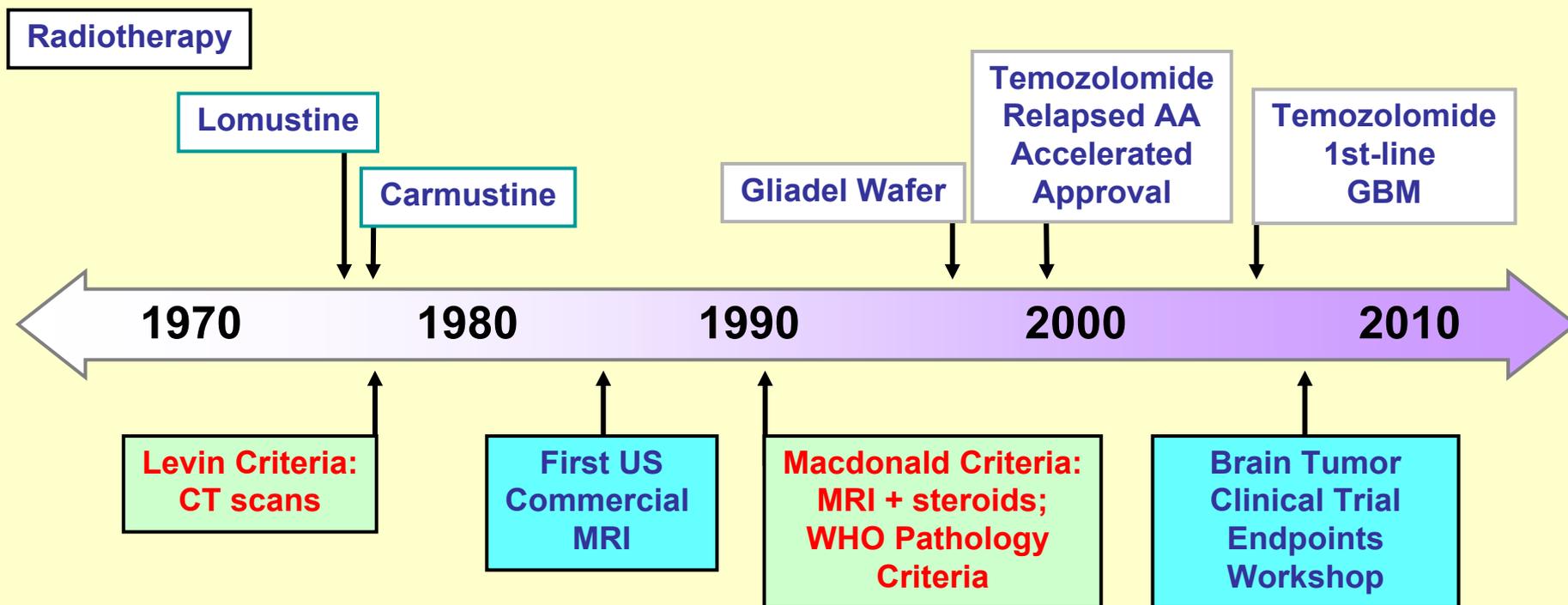
**Project Leader: North American Brain Tumor  
Consortium (NABTC)**

# Recurrent Glioblastoma



# Milestones in Neuro-Oncology

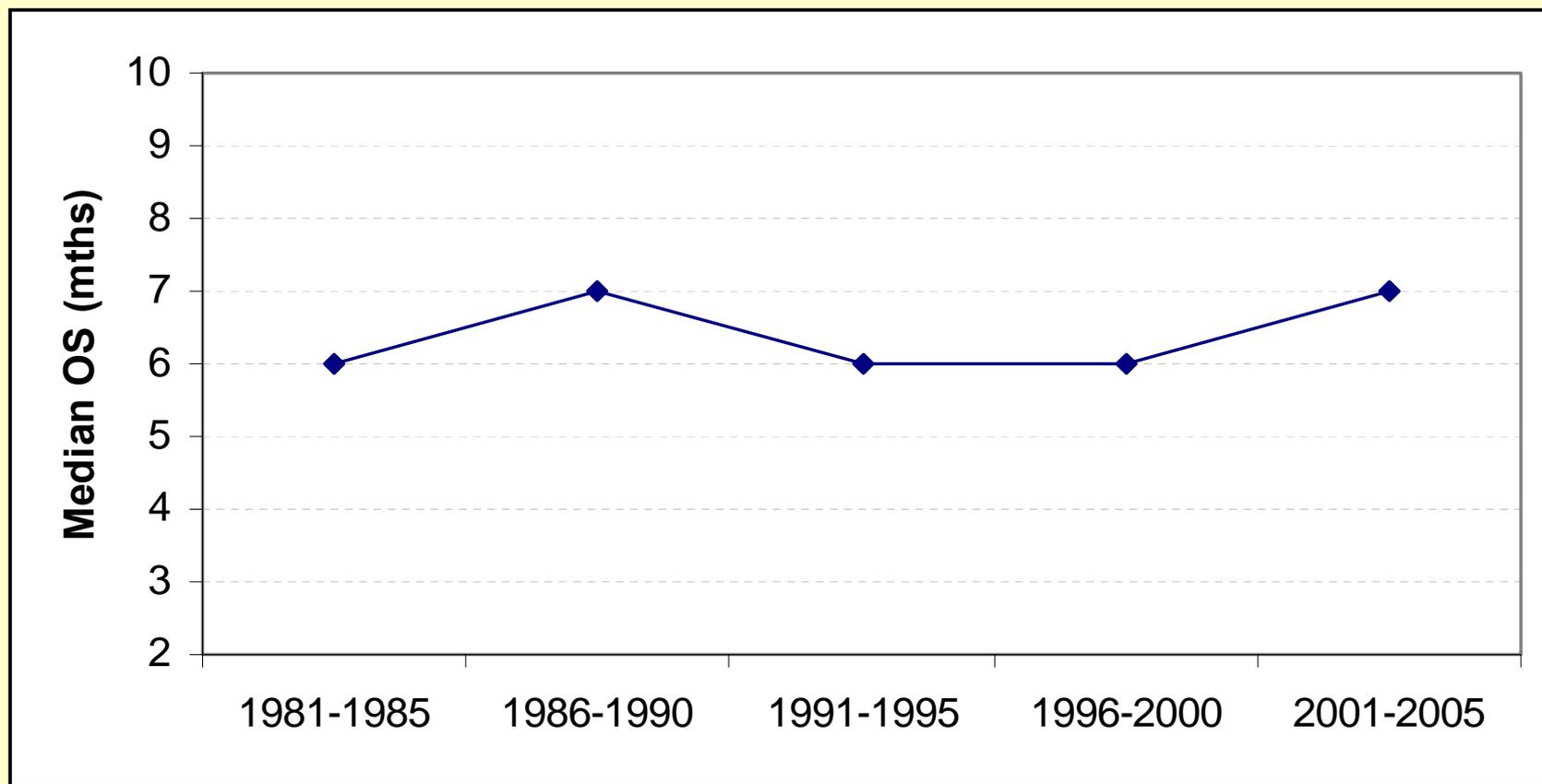
## Approvals



## Technology Advances

AA = Anaplastic Astrocytoma.

# Overall Survival in All Patients With Newly Diagnosed Glioblastoma 1973-2005



**Data Source: SEER Program ([www.seer.cancer.gov](http://www.seer.cancer.gov)) 1973-2005, released in April 2008, based on the November 2007 submission.**

# What Do We Look for When Assessing New Drugs for the Treatment of Glioblastoma?

- **2006 FDA/AACR/ASCO Workshop**
  - Central pathology review
  - Rigorous response assessments
  - Endpoints to consider
    - Durable objective response rate
    - Improved progression-free survival at 6 months (PFS6)
  - Improved overall survival
  - Symptomatic improvement or delay onset of clinical morbidity
  - Predictable and manageable treatment-related toxicity

# Response Rate and PFS6 in Pooled Analyses of Trials for Relapsed Glioblastoma

GBM-006

Publication	Sample Size	Response Rate	6-month PFS	Overall Survival	12-month Survival
8 MD Anderson trials 1986-1995 (Wong 1999)	225	6%	15%	5.7 mo	21%
16 NCCTG trials 1980-2004 (Ballman 2007)	345	n/a	9%	5.1 mo	14%
12 NABTC trials 1998-2002 (Lamborn 2008)	437	7%	16%	6.9 mo	25%
Lomustine control arm from Phase III study of enzastaurin (Fine et al 2008)	92	4.3%	19%	7.1 mo	24%

**AVF3708g****85****28.2%****42.6%****9.3 mo****37.6%**

## Study Characteristics of AVF3708g and NABTC Trials

	<b>NABTC Trials (n=142)</b>	<b>AVF3708g Avastin (n=85)</b>
<b>Enrollment period</b>	<b>1998-2002</b>	<b>2006-07</b>
<b>Tumor assessments</b>	<b>MRI q8wk</b>	<b>MRI q6wk</b>
<b>Independent review?</b>	<b>Central review of responders</b>	<b>Yes</b>
<b>Prior radiation</b>	<b>Yes (≥ 4 weeks)</b>	<b>Yes (≥ 8 weeks)</b>
<b>Prior temozolomide</b>	<b>Yes</b>	<b>Yes</b>
<b>Median age, years</b>	<b>51</b>	<b>54</b>
<b>Male</b>	<b>61%</b>	<b>68%</b>
<b>Karnofsky PS</b>		
<b>90-100</b>	<b>45%</b>	<b>45%</b>
<b>70-80</b>	<b>55%</b>	<b>55%</b>
<b>Line of therapy</b>		
<b>First relapse</b>	<b>42%</b>	<b>81%</b>
<b>Second relapse</b>	<b>58%</b>	<b>19%</b>

## Results of Current Study Compared With NABTC Database in Similar Population

Subset of patients who received temozolomide prior to enrollment into NABTC clinical trials

Outcome parameter	NABTC patient subset (n=142)	Avastin (AVF 3708g) (n=85)
PFS > 6 months	7%	42.6%
Median PFS	1.6 months	4.2 months
Median OS	5.9 months	9.3 months
1-yr survival rate (95% CI)	19%	37.6%
Objective Response Rate	6.5%	28.2%

# Final Thoughts

- **The data being presented to this Committee are compelling, particularly within the context of our recent experience in neuro-oncology clinical trials**
- **We have not seen a drug reduce tumor burden so much and so frequently, in such a durable fashion, in the years that I have been in practice**
- **The progression-free and overall survival are impressive and very encouraging, and safety is very acceptable**
- **The academic community is moving forward with new ideas and strategies for this agent, and patients are looking to us to continue building on these results**
- **Based on these data and my own experience, it is clear to me that this agent does help patients with recurrent glioblastoma and, hopefully, will be made available to more patients going forward**

# Conclusions

David Schenkein, MD  
Genentech, Inc.

## **Avastin for Relapsed GBM**

- **Genentech is seeking accelerated approval for Avastin in patients with previously treated glioblastoma on the basis of our Phase II study**
- **This approval will provide labeling guidance to physicians and will help ensure the availability of Avastin to a severely under-served patient population**

# Commitment to Randomized Phase III Trial to Establish Clinical Benefit

- **Commitment to conduct further studies to confirm the clinical benefit of Avastin for patients with this disease**
- **Global Phase III trial in newly diagnosed patients with glioblastoma**
  - **Will compare standard of care (temozolomide and radiation) to standard of care with Avastin**
  - **Have obtained agreement with the FDA on trial design and major endpoints through the Special Protocol Assessment Process**
  - **Will not read out primary endpoints of overall survival and PFS until 2014**

# Accelerated Approval

Effect on a surrogate endpoint reasonably likely to predict clinical benefit

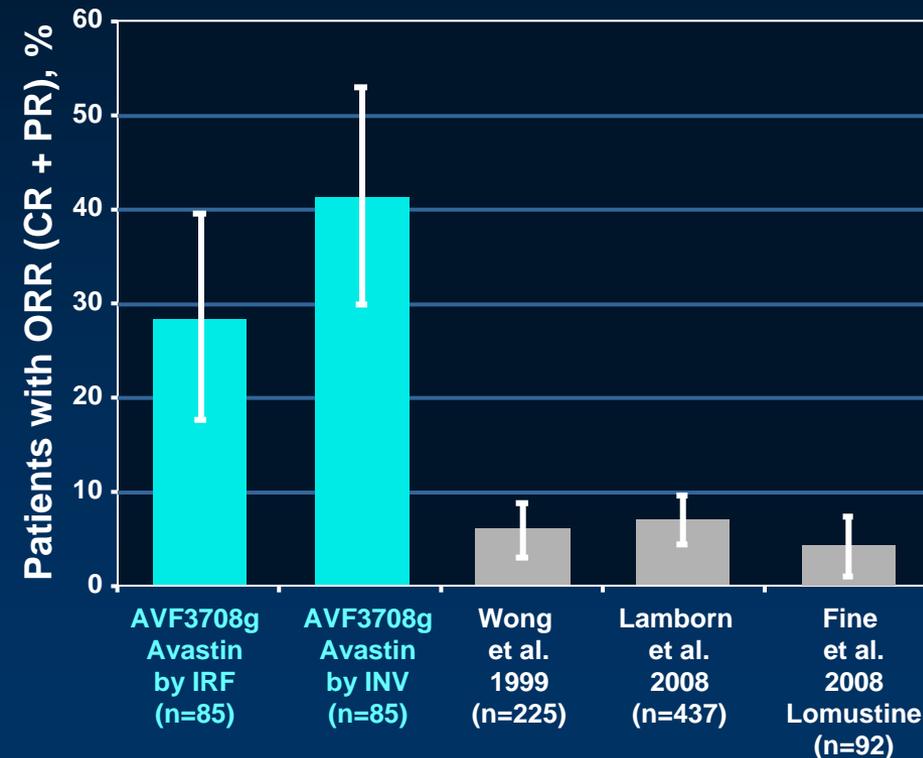
1. Changes on MRI as evidence of clinical activity
2. Response rate substantially higher than historical controls

# Executive Summary

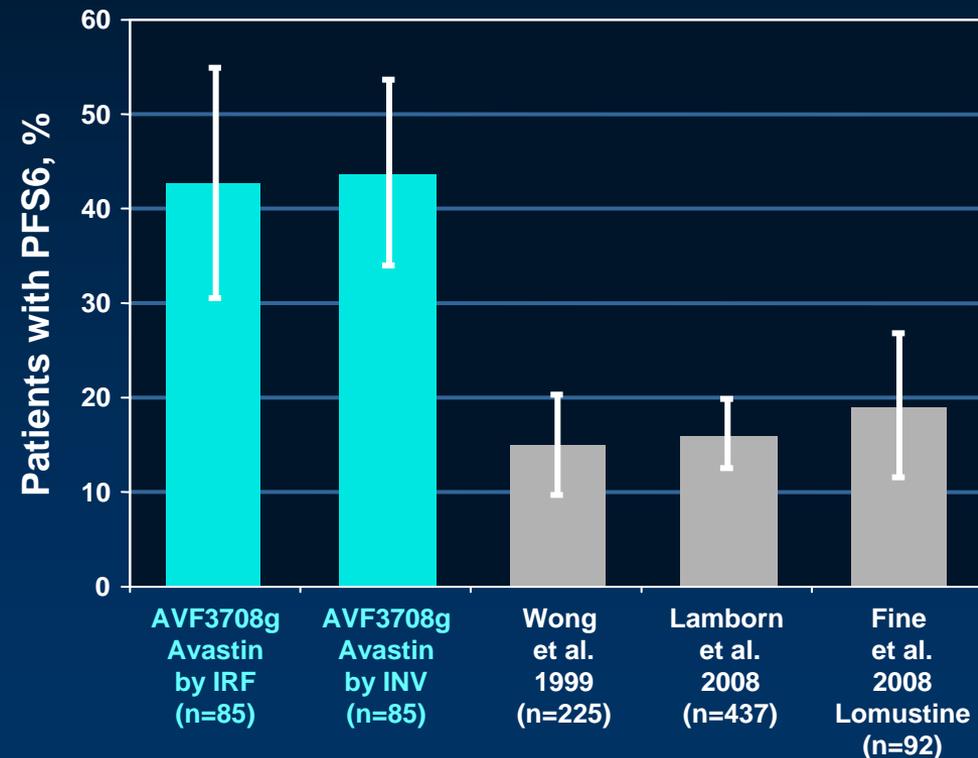
- **Avastin therapy led to a high rate of durable responses**
  - **Conservative response criteria and methodology (IRF)**
- **Supportive secondary endpoints**
- **Landmark response analysis linking response to survival**
- **Second supporting trial (NCI)**

# Response Rate and PFS6 Significantly Higher Than Historical Controls

Response rate:  
Avastin arm vs historical controls



Six-month progression-free survival:  
Avastin arm vs historical controls



# Proposed Indication Statement

**Avastin<sup>®</sup>, as a single agent,  
is indicated for the treatment of patients  
with previously treated glioblastoma**

# Study Characteristics of AVF3708g and Lomustine Control Arm From Fine 2008

	<b>AVF3708g Avastin (n=85)</b>	<b>Fine 2008 Lomustine (n=92)</b>
<b>Enrollment period</b>	<b>2006-07</b>	<b>2006-08</b>
<b>Tumor assessments</b>	<b>MRI q6wk</b>	<b>MRI q6wk</b>
<b>Independent review</b>	<b>Yes</b>	<b>Yes</b>
<b>Prior radiation</b>	<b>Yes</b>	<b>Yes</b>
<b>Prior chemotherapy</b>	<b>Yes</b>	<b>Yes</b>
<b>Median age</b>	<b>54</b>	<b>55</b>
<b>Percent male</b>	<b>68</b>	<b>61</b>
<b>Karnofsky PS</b>		
<b>90-100</b>	<b>45%</b>	<b>50%</b>
<b>70-80</b>	<b>55%</b>	<b>50%</b>
<b>Line of therapy</b>		
<b>First relapse</b>	<b>81%</b>	<b>77%</b>
<b>Second relapse</b>	<b>19%</b>	<b>23%</b>

# Subgroup Analysis Based on Time From Last Radiotherapy to Baseline MRI

Time (weeks)	# of Pts included	ORR (97.5% CI)
< 8	84	28.6% (19%, 40%)
< 12	79	25.3% (15%, 38%)

- Median time from last radiotherapy to baseline MRI scan was 26 weeks
  - 6 patients had time < 12 and 2 had pathologic confirmation of relapse

# Subset Analyses of Objective Response

	<b>Avastin (n=85)</b>	<b>Avastin + Irinotecan (n=82)</b>
<b>Randomized patients</b> Patients with objective response	85 24 (28.2%)	82 31 (37.8%)
<b>Efficacy-evaluable patients*</b> Patients with objective response	84 24 (28.6%)	79 31 (39.2%)
<b>Patients with measurable disease at baseline by IRF</b> Patients with objective response	83 23 (27.7%)	79 31 (39.2%)
<b>Patients with central pathology-confirmed GBM</b> Patients with objective response	83 24 (28.9%)	82 31 (37.8%)

\*Efficacy-evaluable patients are randomized patients who received at least 1 dose of study treatment and either had at least 1 post-baseline tumor assessment or failed to return for any tumor assessments because of death or clinical determination of progression.

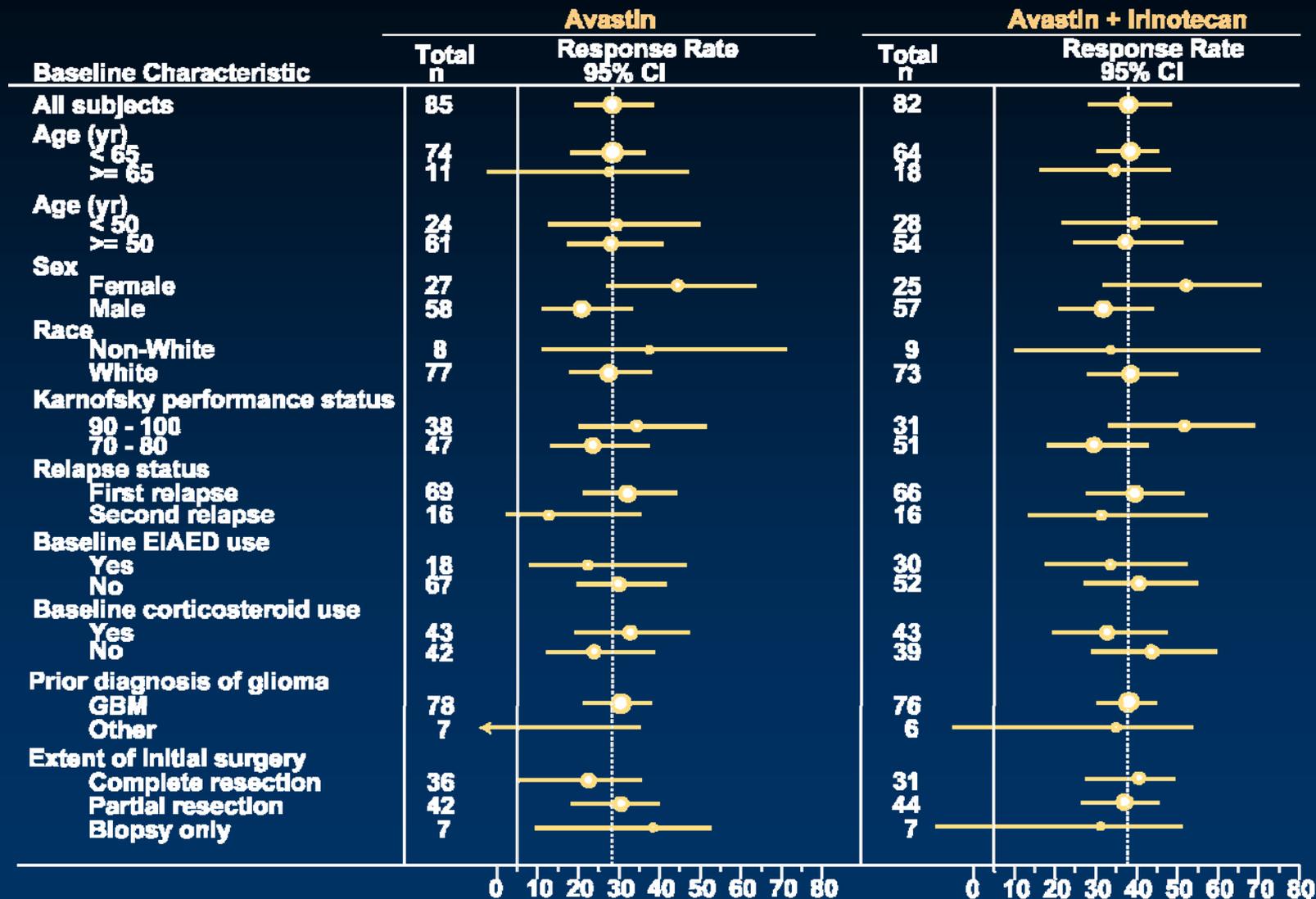
IRF = Independent Review Facility.

# Relationship Between ORR and Residual Survival—AVF3708g

		9 weeks		18 weeks		26 weeks	
		Responders	Non-Responders	Responders	Non-Responders	Responders	Non-Responders
Landmark analyses	N	30	127	46	101	51	72
	HR* (95% CI)	0.52 (0.32, 0.85)		0.48 (0.31, 0.74)		0.43 (0.27, 0.67)	
	P value (Cox model)	0.0091		0.0010		0.0002	

\*Analyses are adjusted for age (< 65, ≥ 65), baseline KPS (70-80, 90-100), relapse status (Y/N), and treatment (Avastin, Avastin + Irinotecan).

# Study AVF3708g: Objective Response Rate, Based on Independent Review, by Baseline Characteristics



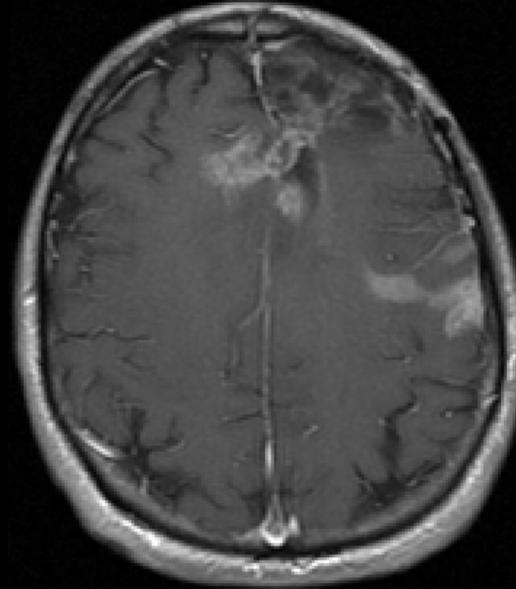
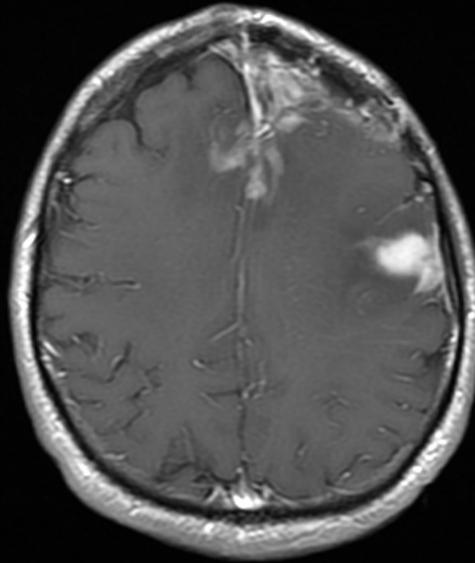
The 95% CI for objective response rate was computed using the Blyth-Still-Casella method.

(Expanded Forest plot to be provided in final document).

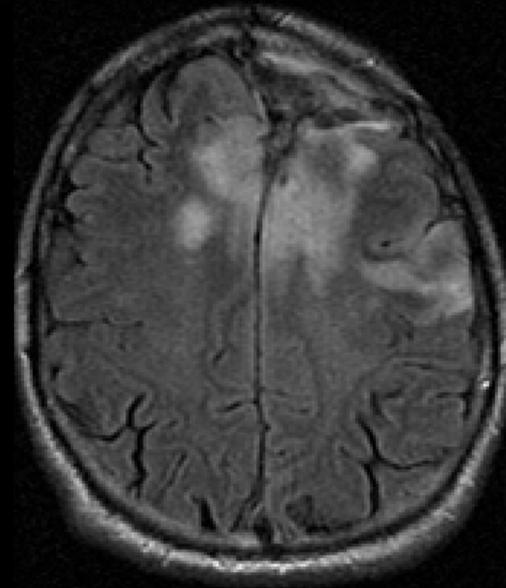
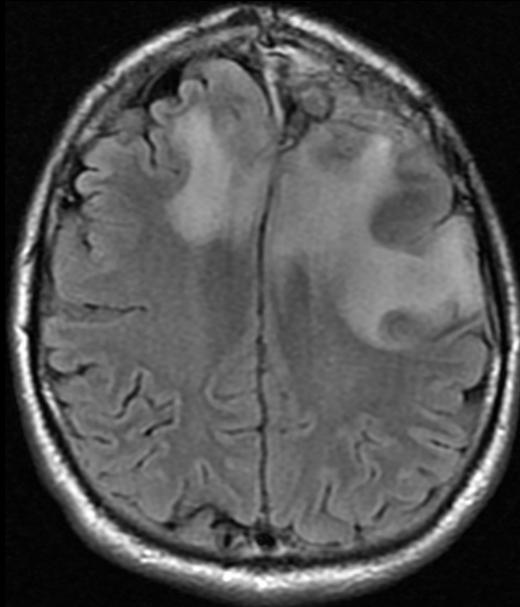
CI = Confidence interval; EIAED = Enzyme-inducing anti-epileptic drug.

# AVF3708g Example: Non-Responder <sup>NR\_002</sup>

**Axial T1w  
post-contrast**



**Axial  
FLAIR**



**Baseline  
03 Oct 06**

**PD  
6 wks  
17 Nov 06**

**20157**

# Ruben et al, 2006: Incidence of Radiation Necrosis in High-Grade Gliomas

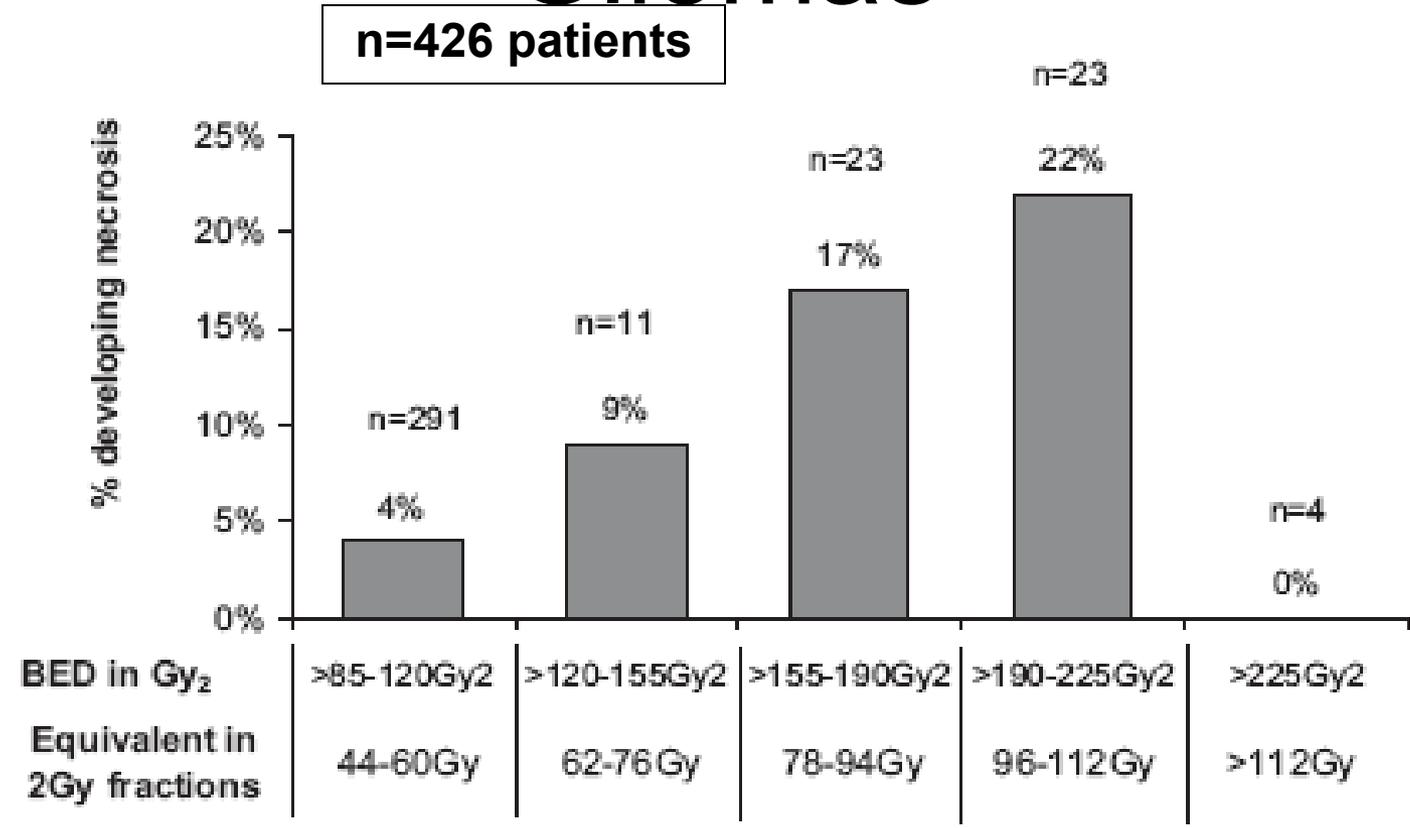
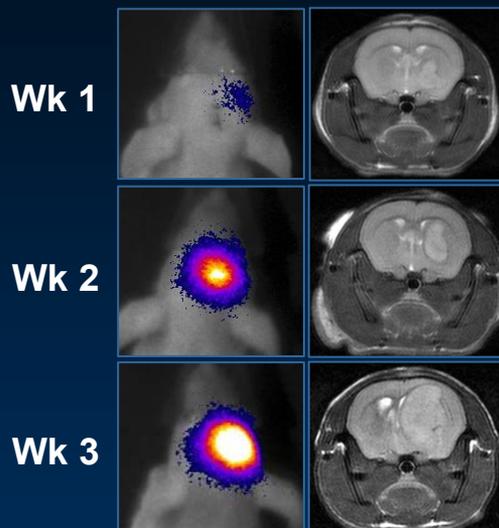


Fig. 2. Incidence of radiation necrosis across a range of radiation doses. BED = biologically equivalent dose.

# Changes in MRI in Response to Anti-VEGF Therapy Are Mirrored by Bioluminescence Monitoring of Tumor Burden

BLI and MRI validation for glioma imaging

BLI MRI



Monitoring tumor response to anti-VEGF treatment using MRI, BLI and survival

Day 0 Day 1 Day 12

