STN 125085/169
Bevacizumab (Avastin®) for Previously Treated Glioblastoma Multiforme

ODAC Meeting
March 31, 2009

Clinical Review - Lee Pai-Scherf, M.D.
Statistical Review - Yuan Li Shen, Dr. P.H.
DBOP/OODP/CDER/FDA

Proposed Indication for Accelerated Approval

Avastin®, as a single agent,

is indicated for the treatment of patients with previously treated glioblastoma

Overview

- Regulatory Background
- AVF3708g
  - Efficacy
  - Safety
- NCI 06-C-0064E
- Summary of Findings and Conclusion
- Questions to ODAC

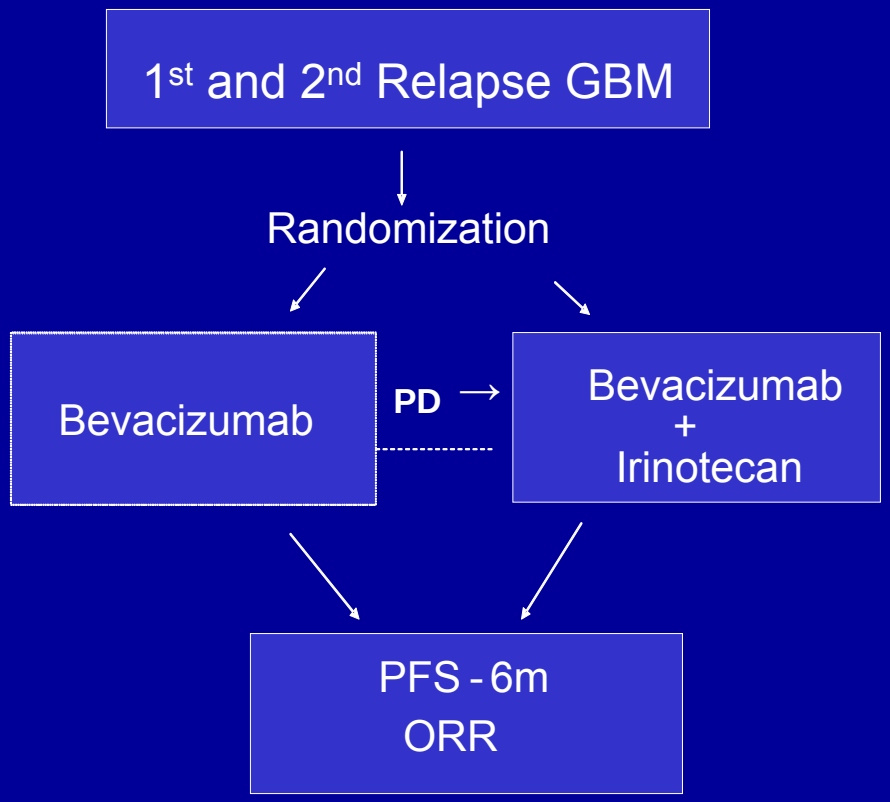
Regulatory Background

Avastin® Approved Indications

- Metastatic colorectal cancer
  - 1st and 2nd line with 5FU based chemo (OS)
- Metastatic non-squamous non-SC lung cancer
  - 1st line in combination with carbo/paclitaxel (OS)
- Metastatic breast cancer (Accelerated Approval)
  - 1st line in combination with paclitaxel (PFS)

Regulatory Background

AVF3708g **Randomized, Non Comparative**



FDA's comments (letter of 07/ 06)

The proposed trial, as designed is not adequate to support regulatory approval:

- There is no internal comparison for the primary efficacy endpoint of PFS-6m
- The effect of bevacizumab is not isolated in the bevacizumab plus irinotecan combination arm

Regulatory Background (cont.)

January 2008 - meeting to discuss results of AVF3708g and proposal for a randomized controlled study.

- Proposal for sBLA for accelerate approval
- Higher 6-month PFS and ORR compared with historical controls

FDA comments

- Time to event endpoints must be evaluated in randomized, controlled clinical studies. Historically-controlled trials do not provide direct evidence of treatment effect

FDA's comment to Genentech (cont.)

- Questions regarding potential surrogate endpoints in GBM are still unanswered, as discussed at the January 2006 Workshop on Brain Tumor Clinical Trial Endpoints

- FDA would consider the results of AVF3708g to support AA of bevacizumab monotherapy, based on evidence of a clinically meaningful and durable objective tumor response; determined by an independent radiologic review

FDA's comment to Genentech (cont.)

- Genentech should obtain and submit data from the single-arm, single center study, conducted by Dr. Howard Fine to support the application
- A confirmatory trial designed to demonstrated clinical benefit is required. The study should be ongoing and performed with "due diligence" at the time of regulatory action

- September 2008 – pre – sBLA meeting

Regulatory Background (cont.)

Nov 2008 - Confirmatory trial (Special Protocol Assessment) to demonstrated clinical benefit

- AVF4396g/BO21990: Phase III, randomized, placebo-controlled study of bevacizumab in combination with radiotherapy and temozolomide for 1st line GBM
- Study to be conducted by Roche, world-wide
- N = 920
- Co-primary endpoints: OS and PFS
- Overall survival is the regulatory endpoint

sBLA STN 125085/169

AVF3708g

NCI 06-C-0064E

AVF3708g

AVF3708g

1st and 2nd Relapsed GBM

1:1 Randomization

Arm 1

- Bevacizumab 10 mg/kg every 2 weeks up to 104 weeks

PD = >

Arm 2

- Bevacizumab
- Irinotecan 125mg/m^2 (340 mg/m^2 if EIAEDs) every other week

Follow up until PD, Survival q 3 months

AVF3708g – Major Eligibility Criteria

- Histologically confirmed GBM in 1st or 2nd relapse
- Prior standard RT and temozolomide
- Radiographic evidence of PD following prior therapy
- Bi-dimen. measurable disease (≥ 1 cm on MRI)
- If on steroids, stable or ↓ dose for ≥ 5 d prior to baseline MRI

AVF3708g – Major Eligibility Criteria (Cont.)

- KPS ≥ 70
- Adequate organ function
- No co-morbid conditions that preclude use of bevacizumab
- Recovery from effects of prior therapy:

  > 4 weeks after surgery

  > **8 weeks from last RT** * (4 weeks if new lesion outside the RT field)

Regulatory Efficacy Endpoints

- Primary endpoint

  IRF determined objective response rate (ORR) – Bevacizumab monotherapy arm

- Secondary endpoints:

  Duration of response

Endpoint Assessment

- Objective Response
  - Independent radiographic review (IRF)
  - MRI at baseline and every 6 weeks until disease progression
  - Modified WHO response criteria taking into consideration corticosteroid use

- Safety assessment
  - MedDRA
  - NCI CTC v 3.0

AVF3708g

- Conducted by Genentech at 10 US sites
- June 06 – September 07
- N = 167

  Arm A - Bevacizumab arm: 85

  Arm B – Bevacizumab + Irinotecan: 82

AVF3708g - Investigators

Center	Investigator	No. of subjects
UCLA	T. Cloughesy	30
UCSF	M. Prados	23
Dana-Farber CC	P. Y.C. Wen	20
Duke University	H. Friedman	21
Henry Ford H Sy	T. Mikkelsen	17
U of Virginia	D. Schiff	16
MSKCC	L. Abrey	15
MDACC	W-K A. Yung	10
Northwestern, IL	N. Paleologos	9
U of Chicago	M.K. Nicholas	6
		Total = 167

AVF3708g
Patient disposition

Reason off study	Bevacizumab N=85 (%)	Bev + Irinotecan N=82 (%)
Not treated	1 (1)	3 (4)
PD	9 (12)	43 (52)
PD – post PD phase	44 (52)	N/A
SAE	3 (4)	12 (15)
Patient withdrawal	2 (2)	2 (2)
Still receiving Bev	22(26)	19 (23)
Irinotecan	0	18 (22)
Death	3 (4)	1 (1)
Other	1 (1)	1 (1)

AVF3708g
Demographic and Baseline Characteristics

Characteristics		Bevacizumab N=85 (%)	Bev + Irinotecan N=82 (%)
Gender	male	58 (68)	57 (70)
	female	27 (32)	25 (30)
Age median (range)		54 (23 – 78)	57.0 (23 – 79)
Race	White	77 (91)	73 (88)
	Black	3 (4)	2 (2)
KPS	70 - 80	47 (55)	51 (62)
	90 – 100	38 (45)	31 (38)
Steroids at Baseline		43 (51)	43 (52)

AVF3708g

Prior Therapy fro GBM

Treatment		Bevacizumab % (N=85)	Bev + Irinotecan N=82 (%)
Surgery		100	100
Radiation Therapy		100	100
Temozolomide		100	100
Surgery	Partial Resection	49	54
	Complete resection	42	38
	Biopsy Only	8	9
Systemic therapy	1st relapse	81	81
	2nd relapse	19	19

Diagnosis of Glioblastoma

	Bevacizumab N=85 (%)	Bev + Irinotecan N=82 (%)
Initial diagnosis		
GBM	**78 (92)**	76 (93)
Anaplastic astrocytoma	**2 (2)**	5 (6)
Other	**5 (6)**	1 (1)
Independent central path		
GBM	**83 (98)**	82 (100)
Anaplastic astrocytoma	**1 (1)**	0
Missing baseline slides	**1 (1)**	0

AVF3708g
Quality of the Study Conduct

- Protocol violations/deviation:
  - Did not meet eligibility criteria: 2
  - Bevacizumab dose differed > 5% from specified: 7

- Tumor assessment:
  - One patient had missing tumor assessment by investigator at wk 18 and 3 at week 36.
  - All MRI except 1 scan for 1 patient in the bevacizumab arm were available for reviewed by the IRF

Efficacy

AVF3708g

Summary of Statistical Issues

- Single arm study
- Historical control
- Objective response and 6-month PFS have not been shown to be reasonably likely to predict the OS

Regulatory Efficacy Endpoints

- Primary endpoint

  IRF determined objective response rate (ORR) – Bevacizumab monotherapy arm

- Secondary endpoints:

  Duration of response

Definition of Objective Response Independent Review

Objective response is defined as a complete response (CR) or partial response (PR) determined on two consecutive assessments ≥ 4 weeks apart, using modified WHO Response Evaluation Criteria

Incorporates corticosteroid use

CR - corticosteroids dose < 20 mg hydrocortisone/day

PR - corticosteroid dose at the time of the MRI should be ≤ the maximum dose used in the 1st six weeks from treatment initiation

Objective Response Rate and Duration of Response (Genentech per IRF)

	Bevacizumab N=85	Bev + Irinotecan N=82
Objective Response n (%) CR PR 97.5% CI	24 (28.2%) 1 23 [18.5%, 40.3%]	31 (37.8%) 2 29 [26.5%, 50.8%]
Median Duration of Response (95% CI) # progression	5.6 m [3.0, 5.8] 19	4.3 m [4.2, -] 16

Objective Response/Duration of Response – Bevacizumab Arm

	Bevacizumab N = 85 (%)		
	Investigator	**Genentech IRF**	**FDA**
Objective Response CR/PR 97.5% CI	35 **(41.2)** 2/33 [29.7, 53.9]	24 (**28.2**) 1/23 [18.5, 40.3]	**22 (25.9)** **0/22** [15.9, 37.8]
Median Duration of Response (95% CI) # progression	**8.1 m** (5.6, -) 17	**5.6 m** (3.0, 5.8) 19	**4.2 m** (3.0, 5.7) 19

Response Rate by Baseline Characteristics (FDA)

Characteristics		n/N	%	95% CI
Age	< 65	19/74	(25.7)	[16.2%, 36.9%]
	≥ 65	3/11	(27.3)	[7.9%, 61.0%]
Sex	Female	11/27	(40.7)	[22.4%, 59.8%]
	Male	11/58	(19.0)	[10.5%, 30.4%]
Race	White	19/77	(24.7)	[15.6%, 35.3%]
	Other	3/8	(37.5)	[11.1%, 71.1%]
KPS	70, 80	10/47	(21.3)	[10.7%, 34.6%]
	90, 100	12/38	(31.6)	[17.5%, 48.6%]
Relapse	First	20/69	(29.0)	[19.1%, 40.8%]
	Second	2/16	(12.5)	[2.3%, 35.4%]

6-month PFS – Bevacizumab Arm FDA

	Bevacizumab N = 85 (%)		
	Investigator	**Genentech IRF**	**FDA**
Pts with PFS event up to 6 m PD Death	47 (55) 41 (48) 6 (7)	44 (52) 38 (45) 6 (7)	50 (59) 42 (49) 8 (9)
Event free at 6 m (97.5% C.I.)	44 % (31, 55)	43% (30, 56)	36 % (24, 48)

Post-Radiation Effects on Brain Parenchyma

- **RT induced toxicity may mimic recurrent tumor, which shown as an increase in area of gadolinium update on MRI.**
- **Subacute radiation injury can occur 2 to 12 weeks after radiation (pseudoprogression)**
- **Late radiation injury or "necrosis" can occur months to years after treatment. Necrosis leads to increase capillary leakage and destruction of surrounding CNS parenchyma.**
- **MRI changes should not be mistaken for disease progression**

Interval between last RT and baseline MRI

Time between last RT and baseline MRI	Bevacizumab N = 82 [a]	Bev + Irinotecan N= 76 [b]
< 3 months	8 (10%)	11 (14%)
3 – 6 months	32 (39%)	24 (32%)
> 6 months	42 (51%)	41 (54%)

a: two missing baseline scan dates

b: three missing baseline scan dates

Interval between last RT and baseline MRI Responders and Non-Responders

	Bevacizumab arm N = 85		
Time between last RT and baseline MRI	All treated N=82[a]	**Responders N= 22 (%)**	Non-Responders N=60 (%)
< 3 months	8	**4 (50)**	4 (50)
3 – 6 months	32	**11 (34)**	21 (66)
> 6 months	42	**7 (17)**	35 (83)

a: two missing baseline scan date

Exploratory analysis

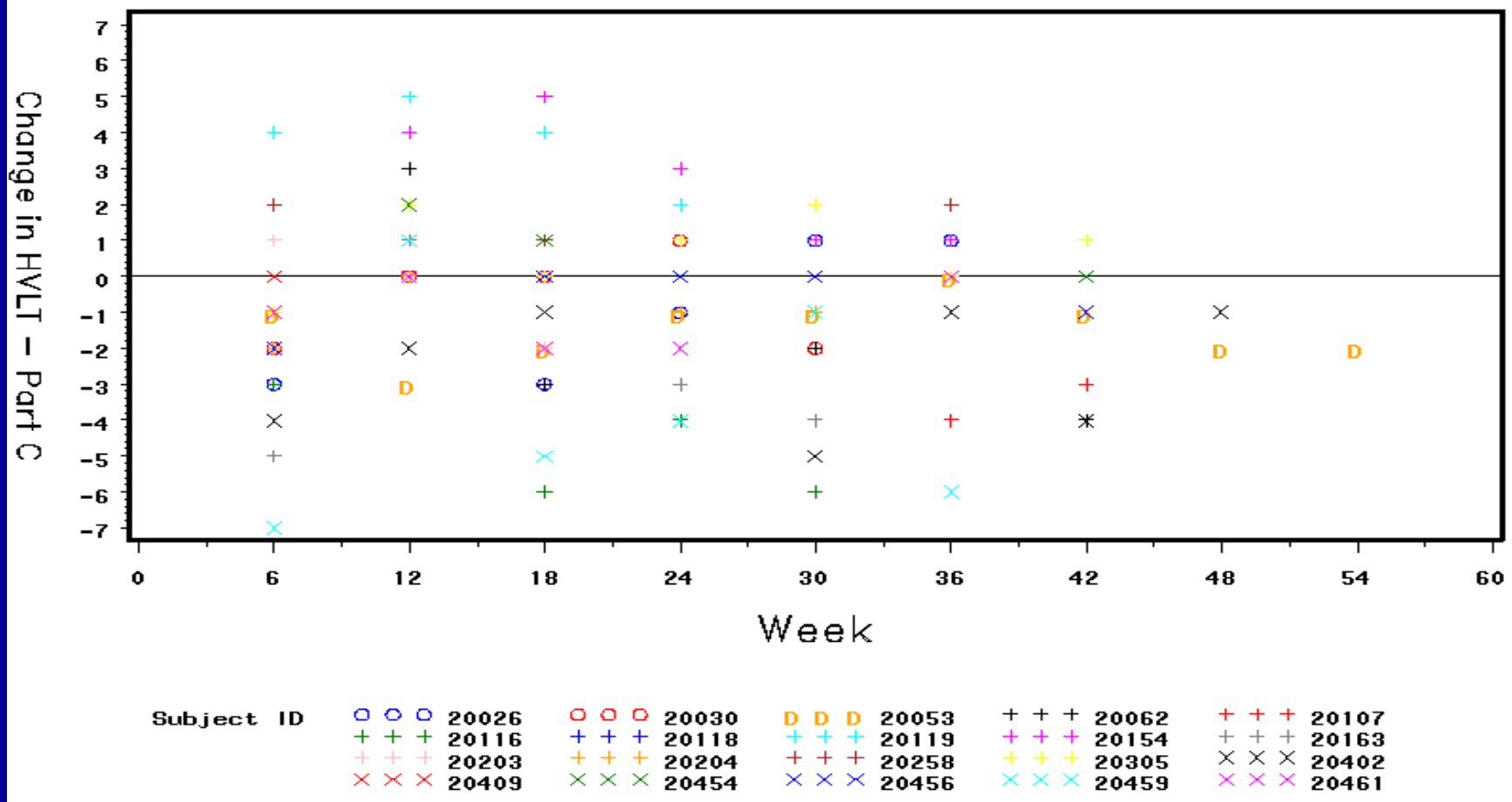
- Neurocognitive function
  - Memory (Hopkins Verbal Learning Test)
  - Visual-motor scanning speed (Trail making Test A)
  - Executive function (Controlled Oral Word Association and Trail Making Test B)

Neurocognitive Function Analysis

Issues:

- No comparator arm included
- Validity and reliability of the instrument

Example of Exploratory Analysis: Memory score change from baseline (delayed recognition, HVLT-Part C) in **Responders**



Safety

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Overall incidence of AEs

	Bevacizumab % (N=84)	Bev + Irinotecan % (N=79)
Any AE	99	100
SAE	26	43
Grade 3-4 AE	46	66
D/C bev due to AE	5	18
Adverse event/other	4	3

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Most Common AEs with > 20 % Incidence

Adverse Event MedDRA Preferred term (all grades)	Bevacizumab % (N=84)	Bev + Irinotecan % (N=79)
Overall	99	100
Fatigue	45	76
Headache	38	33
Hypertension	30	22
Epistaxis	19	23
Diarrhea	21	75
Nausea vomiting	19	68
Constipation	14	41
Abdominal pain	4	29

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Serious Adverse Events ≥ 2 % Incidence

Serious AE	Bevacizumab N=84	Bev + Irinotecan N=79
Any	22 (26.2)	34 (43.0)
Confusion	5 (6.0)	9 (11.4)
Deep venous thrombosis	1 (1.2)	2 (2.5)
Cerebral hemorrhage	1 (1.2)	2 (2.5)
Diarrhea	0	2 (2.5)
Pneumonia	0	3 (3.8)
Hyperglycemia	2 (2.4)	0

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Bevacizumab Induced Adverse Events

AE	Safety Population N = 163 (%)	
	Any AE	Grade 3-5
Bleeding/Hemorrhage	65 (40)	3 (1)
Epistaxis	42 (26)	-
CNS hemorrhage	**8 (5)**	**2 (1)**
Hypertension	52 (32)	8 (5)
Venous Thromboembolic Event	**13 (8)**	**12 (7)**
Arterial Thromboembolic Event	10 (6)	5 (3)
Wound-healing complications	**9 (6)**	**4 (3)**
Proteinuria	6 (4)	1 (1)
Gastrointestinal perforation	3 (2)	3 (2)
RPLS	1 (1)	0 (0.0)
Infection/neutropenic infection N = 84 (bevacizumab alone)	46 (55)	8 (10)

AVF3708g
Deaths due to AE /other cause

Bevacizumab N = 3

- Neutropenia/sepsis
- Pulmonary emboli
- Complications due to tumor debulking surgery

Bevacizumab + Irinotecan N= 3

- Retroperitoneal hemorrhage
- Convulsion
- Clinical deterioration

Supportive study: NCI 06-C-0064E

A Phase II trial of Bevacizumab for Patients with Recurrent High-Grade Gliomas

NCI 06-C-0064E

- Open-label, single institution
- Population: histologically confirmed intracranial malignant glioma, progressed after radiotherapy
- Two patient cohorts:
  - Recurrent high grade glioma (GBM and gliosarcoma)
  - Recurrent Anaplastic Astrocytoma
- Bevacizumab 10 mg/kg every 2 weeks
- Study endpoints: ORR, PFS, safety
- MRI at baseline and every 4 weeks

NCI 06-C-0064E
Patient characteristics

- Jan 2006 – Sept 2007

- N = 56 with GBM
- All patients progressed after surgery, RT and TMZ
- 98% white
- 54% male
- 75% ages 41-64
- 68% had KPS 90-100

NCI-06-C-0064
Objective Tumor Response

	Bevacizumab N = 55 (%)	
	Genentech IRF	**FDA**
Objective response Partial Remission n (%) (95% CI)	**11 (19.6)** 10.9,31.3	**11 (19.6)** 10.9,31.3
Median Duration of Response	**3.9 months** (2.3, 17.4)	**3.9 months** (2.3, 17.4)

NCI-06-0064
Incidence of Bevacizumab induced AE
Grade 3-4 AE per Investigator

Grade 3-4 AE	Bevacizumab N=55 (%)
Thrombosis/thrombus/embolism	7 (13)
Hypertension	2 (4)
Arterial Thromboembolic event	1 (2)
Gastrointestinal perforation	1 (2)
Wound healing	1 (2)

NCI-06-0064
Deaths

- 45/56 patients (80.4%) died as of June 3, 2008
- Cause of death:
  - Disease progression (77%)
  - Pulmonary emboli and CVA (2 %)
  - Venous Thromboembolic Event/Sudden Death (2%)

Safety Summary

1. Incidence of bevacizumab induced AEs does not appeared to be significantly increased in patient with GBM based on these two single arm studies. There were two deaths (1.2%) possibly related to bevacizumab treatment.

2. Bevacizumab induced AEs of special concern are CNS hemorrhage, wound-healing and VTE:
   - events are inherent to patients with GBM and associated prior surgery/radiation therapy
   - attribution of these AEs to either bevacizumab or primary disease or both can not be determined with certainty.

Efficacy Summary
Objective Response Rate and Duration of Response

	AVF3708g N=85	NCI 06-C-0064E N=55
Objective Response n (%)	**22 (25.9 %)**	**11 (19.6 %)**
95% CI [a]	**17.0%, 36.5%**	**10.9%, 31.3%**
Duration of Response	**4.2 months**	**3.9 months**
95% CI	**(3.0, 5.7)**	**(2.4, 17.4)**

Conclusion

1. Due to the diffuse and infiltrative nature of GBM histology, anatomical measurement of enhancing tumors on MRI is problematic.

   Difficulty is even greater for relapsed gliomas after prior surgery and radiation therapy, the target population for this application.

Conclusion (cont.)

2. Questionable relevance of standard MRI response criteria in the setting of VEGF inhibition
   - Bevacizumab neutralizes VEGF-induced vascular permeability → improvement in edema → improvement in the MRI
   - Bevacizumab reduce radiation necrosis by ↓ capillary leakage, ↓ edema → ↓ corticosteroid requirement

Conclusion (cont.)

- It is unclear whether the MRI improvement accompanied by ↓ steroid requirement observed in this application is the result of an anti-tumor effect of bevacizumab or represents radiographic improvement due to reduction in tumor associated edema and radiation induced necrosis, or both.

Questions to ODAC

Questions to ODAC

1. Please discuss the validity of objective response as determined by standard MRI, in the setting of VEGF inhibition to support accelerated approval of GBM.

2. Is the response seen in this application of sufficient magnitude (i.e., clinically meaningful) to serve as a surrogate reasonably likely to predict clinical benefit for the purpose of accelerated approval in refractory GBM ? (voting)