Incidence:
Primary Brain Tumors

• An estimated 51,210 new cases of primary nonmalignant and malignant brain tumors projected for 2007\(^1\)
• 20,500 new cases of primary malignant brain and CNS tumors are expected to be diagnosed in the United States in 2007 (11,170 in males; 9,330 in females)\(^1\)
• Above represents 1.42% of all primary malignant cancers\(^1\)
• An estimated 12,740 deaths will be attributed to primary malignant brain and CNS tumors in the United States in 2007\(^1\); this represents 2.4% of all cancer deaths\(^2\)
• Brain tumors often have devastating neurologic complications and negative impact on quality of life

2000-2004 data from the Central Brain Tumor Registry of the United States. [www.cbtrus.org/factsheet.htm](http://www.cbtrus.org/factsheet.htm), obtained 2/11/09
Etiology of Primary Brain Tumors

- Causes unknown
- Ionizing radiation is the only definitive risk factor
  - Scalp irradiation to treat tinea capitus results in increased incidence of meningiomas, gliomas, and nerve sheath tumors (Sadetzki et al, 2000; Ron et al, 1988)
- Studies report an association between allergic conditions, antihistamine use and the occurrence of gliomas (Wigertz et al, 2007; Scheurer, et al, 2008)
- Relation to aspartame unsubstantiated (Lim et al, 2006)
- Cell phone radiation exposure a controversial “hot issue” yielding both negative and positive studies (Hardell, 2006; Inskip, 2001; Hardell et al, 2006)
  - Recent meta-analysis reported no overall risk among cell phone users (Kan et al, 2008)
WHO Classification of CNS Tumors: Main Categories*

- Astrocytic tumors
  - ~40% of all tumors
  - ~80% of all malignant tumors
- Choroid plexus tumors
- Cranial & peripheral nerve tumors
- Embryonal tumors
- Ependymal tumors
- Germ-cell tumors
- Hemopoietic system tumors
- Meningeal tumors
- Metastatic tumors of the CNS
- Neuroepithelial tumors of uncertain origin
- Neuronal & mixed neuronal-glial tumors
- Oligodendrogial tumors & mixed gliomas
- Pineal parenchymal tumors
- Sellar region tumors

*Alphabetically arranged

Staging & Classification of Gliomas

- Two general types of gliomas: oligodendrogliomas and astrocytomas*

- TNM classification not relevant
  - Primary gliomas rarely spread outside of the central nervous system

- Grading determined by histologic characteristics

- Issues:
  - Interobserver variability
  - Different Outcome with similar histologic diagnosis

<table>
<thead>
<tr>
<th>WHO Classification</th>
<th>Histologic Subtype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>Pilocytic astrocytoma</td>
</tr>
<tr>
<td>Grade II</td>
<td>Astrocytoma Oligodendroglioma</td>
</tr>
<tr>
<td></td>
<td>Mixed oligoastro</td>
</tr>
<tr>
<td>Grade III</td>
<td>Anaplastic astro</td>
</tr>
<tr>
<td></td>
<td>Anaplastic oligo</td>
</tr>
<tr>
<td></td>
<td>Anaplastic mixed</td>
</tr>
<tr>
<td>Grade IV</td>
<td>Glioblastoma</td>
</tr>
</tbody>
</table>

Scheithauer, Fuller, & VandenBerg, 2008
Pathways in the Development of Malignant Gliomas

Cell-of-Origin: Differentiated Glial or Stem or Progenitor Cells

- **Olig2 expression (100%)**
- **PS3 mutated (>65%)**
- **PDGFA/PDGFR-α overexpressed (~60%)**

**Low-Grade Astrocytoma (5–10 yr)**
( WHO Grade II)
- **LOH 19q (~50%)**
- **RB mutated (~25%)**
- **CDK4 amplified (15%)**
- **MDM2 overexpressed (~10%)**
- **P16INK4A/P14ARF loss (~4%)**
- **LOH 11p (~30%)**

**Anaplastic Astrocytoma (2–3 yr)**
( WHO Grade III)
- **LOH 10q (~70%)**
- **DCC loss (~50%)**
- **PDGFR-α amplified (~10%)**
- **PTEN mutated (~10%)**
- **PI3K mutated/amplified (~10%)**
- **VEGF overexpressed**

**Secondary Glioblastoma (12–15 mo)**
( WHO Grade IV)

**Primary Glioblastoma (12–15 mo)**
( WHO Grade IV)

- **Olig2 expression (100%)**
- **EGFR amplified (~40%)**
- **EGFR overexpressed (~60%)**
- **EGFR mutated (~20–30%)**
- **MDM2 amplified (~10%)**
- **MDM2 overexpressed (~50%)**
- **LOH 10q (~70%)**
- **P16INK4A/P14ARF loss (~30%)**
- **PTEN mutated (~40%)**
- **PI3K mutated/amplified (~20%)**
- **RB mutated**
- **VEGF overexpressed**

**Low-Grade Oligodendroglioma (5–10 yr)**
( WHO Grade II)
- **Olig2 expression (100%)**
- **LOH 1p, 4q, 19q**
- **EGFR overexpressed**
- **PDGFA/PDGFR overexpressed**

**Anaplastic Oligodendroglioma (3–5 yr)**
( WHO Grade III)
- **P16INK4A/P14ARF loss**
- **RB mutated (~65%)**
- **p53 mutated**
- **PTEN loss**
- **LOH 9p, 10q**
- **CDK4/EGFR/MYC amplified**
- **VEGF overexpressed**
Astrocytoma

Key Features

- **Histology:**
  - Increased astrocytic cellularity

- **Median Survival:**
  - 5 - 7 years

- **Notes:**
  - Often present with seizures
  - May "dedifferentiate"

Rousseau, Mokhtari, & Duyckaerts, 2008
Anaplastic Astrocytoma:
Key Features

- Histology:
  - Increased astrocytic cellularity
  - Cellular atypia and mitosis, no necrosis

- Median Survival:
  - 2 - 3 years

- Notes:
  - Tissue sampling a major issue
  - Progression to glioblastoma in some

Rousseau, Mokhtari, & Duyckaerts, 2008
Glioblastoma: Key Features

• Histology
  – Necrosis (pseudopallisading), mitosis, and neovascularization
  – 2000 WHO guidelines: hypercellular, mitosis, pleomorphism, and neovascularization or necrosis
  – New WHO guidelines devised in 2007 (no change from 2000*)
  – Systemic staging not necessary

• Median Survival
  – 9 - 12 months

*Rousseau, Mokhtari, & Duyckaerts, 2008

*The World Health Organization did recommend dropping the word “multiforme” from glioblastoma multiforme; these are now referred to simply as “glioblastoma” tumors
Patient Presentation

• Patients typically present with a new onset neurologic symptom
  – General Neurologic Signs
    • Headache, Nausea, Vomiting
    • Papilledema
    • Mental Status Changes
    • Seizures
  – Focal Neurologic Signs
    • Location Dependent

• Leads to neuroimaging
  – Magnetic Resonance Imaging with contrast is the test of choice

Source: ABTA www.abta.org

Armstrong, 2003
Imaging
Surgical Management of Malignant Glioma
Management of Patients with Gliomas

After presenting with a neurologic event, imaging is performed.

Tissue sampling is undertaken.

Standard of care for most patients will include radiation therapy +/- chemotherapy.

Gilbert & Armstrong, 2007
Surgical Approach

• Tissue sample always necessary for primary tumors to make a proper diagnosis
  – Exceptions: some brainstem tumors

• Surgical approach dependent upon
  – Size and location of lesion
    • Associated with frontal cortex
    • Associated with edema or herniation
  – Whether focal or multi-focal
  – Whether margins delineated or diffuse

• Review of 81 cases of biopsy followed by resection:
  – 38% of diagnoses changed with results of tumor resection, most commonly an increase in tumor grade
  – Altered prognosis in 49% of patients
  – Altered treatment in 33%

Bohan & Glass-Macenka, 2007

Limitations of Chemotherapy in Treating Brain Tumors

• Poor drug penetration into tumor (e.g., blood-brain barrier, hypoxia, intracranial pressure, etc.)
• Systemic toxicity
  – Grade 3/4 myelosuppression
• Drug-drug interactions
  – Corticosteroids (phenytoin concentration)
  – Anticonvulsants (paclitaxel and CPT-11 clearance)
• Intrinsic resistance of brain tumors
  – AGAT overexpression, for example

Gilbert & Armstrong, 2007
History of Conventional Chemotherapy for Malignant Gliomas

- Nitrosoureas (e.g., BCNU, CCNU)
- Other alkylating agents (e.g., procarbazine, temozolomide)

- Response rate in GBM
  - 20% - 35% in newly diagnosed
  - 5% - 15% in recurrent cases

- Effect on survival modest

- Salvage agents used include platinoids, CPT-11, and others

Gilbert & Armstrong, 2007
Temozolomide

- Alkylating agent; converted to active MTIC at physiologic pH
- Crosses the blood-brain-barrier
- Nearly 100% oral bioavailability
- Linear pharmacokinetics
- Oral agent, well tolerated in clinical trials
- Metabolism unaffected by concurrent anticonvulsants or corticosteroids

Stupp, et al, 2005
Supportive Care and Management

• Symptom Mgt & Fatigue
• Seizure management
• Thromboembolic disease
• Cognitive Dysfunction

Wen, Schiff, Kesari, et al, 2006
Impact of the Tumor on the Patient

- Patients with CNS tumors often suffer devastating effects as a consequence of the tumor or treatment

  - One study from UCSF indicated 82% had symptoms which prevented return to work after diagnosis (Fobair et al, 1990)

  - Qualitative studies indicate patients spend significant portion of their lives feeling ill and unable to perform usual activities (Salander et al, 2000; Strang & Strang, 2001)
Background on Symptoms & Brain Tumors

- Primary Brain tumors tend not to spread outside of the CNS. As a consequence are associated with concomittant neurologic symptoms, such as poor cognition, and hemibody weakness.

- Cause symptoms by four mechanisms:
  - Invasion of brain parenchyma
  - Brain compression
  - Cerebrospinal fluid obstruction (hydrocephalus)
  - Brain herniation

- Broad grouping of neurologic symptoms into:
  - Those associated with focal brain disease
  - Those associated with increased intracranial pressure

Reprinted with permission from the ABTA
Fatigue

• Common and often most severe symptom reported by patients

• Multifactorial, including Radiation therapy, AEDs, chemotherapy, anemia, depression, weight gain, endocrine dysfunction, and myopathy from chronic steroid use

• Use of stimulants such as Methylphenidate or Modafinil may improve symptoms

• Current studies evaluating biologic correlates of fatigue

Wen et al, 2006
Corticosteroids

- Use the lowest dose possible
- Dexamethasone most widely used steroid (less mineralcorticoid activity)
- Caution: Significant side effects; may need to check for adrenal function before stopping steroid after chronic use

Dermatologic
- Acneform rash, skin/hair thinning and breakdown, poor wound healing, night sweats

Gastrointestinal
- Bleeding, constipation

Bone
- Osteoporosis, aseptic necrosis, fractures

Behavioral
- Depression, agitation, insomnia, psychosis

Miscellaneous
- Hypothyroidism, weight gain, appetite stimulation, potassium wasting

Wen et al, 2006
Anticonvulsant management

• Patients with tumors in the cerebral hemispheres are at risk

• Use of prophylactic anticonvulsants is controversial
  – Metaanalysis suggests prophylaxis is ineffective, but study is faulty

• Some anticonvulsants (DPH, CBZ, PHB) alter some chemotherapy metabolism
  – Studies of paclitaxel in brain tumor patients in the 1990s uncovered that anticonvulsants markedly alter chemotherapy clearance
  – Similar findings for other agents: 9-aminocamptothecin, methotrexate, new signal transduction agents (gefitinib, imatinib) and CPT-11
  – CPT-11*
  – Stratify patients
    • non-EIACD = max tolerated dose (MTD) = 125 mg/m²
    • EIACD MTD = 410 mg/m²
  – More than 3-fold increase in dose

Gilbert MR, et al. 2003
Seizure Management

- Appropriate management
  - Maintain safety and prevent injury
  - Appropriate triage – when is 911 the answer?

- General Guidelines
  - If this is the *first seizure* the person has experienced
  - If *two focal seizures* occur without a *rest* period between occurrences
  - If a seizure lasts *longer than 5-10 minutes*
Social Impact of Seizure Occurrence

• Recreational Activities

• Driving
  – www.efa.org

• Employment

Armstrong, Kanusky, & Gilbert, 2003
Management of Deep Vein Thrombosis & Pulmonary Emboli

- Incidence of DVT and/or pulmonary emboli estimated at 30%-40%
- Often classic symptoms (e.g. pain, overt dyspnea) are diminished by corticosteroids
- Lower extremity Dopplers useful to diagnose DVT
- Chest CT angio best test for pulmonary emboli

Gerber DE, et al. 2006
Cognitive Dysfunction, Depression & Anxiety

• Common in glioma patients, with significant impact on QOL

• Multifactorial

• Use of stimulants, antidepressants, and anxiolytics warranted

Wen, Schiff, Kesari, et al, 2006
The Pivotal Trial of Temozolomide: Phase 3 EORTC/NCIC Trial Comparing Radiotherapy Alone to Radiotherapy Plus Concomitant and Adjuvant Temozolomide for Glioblastoma
Pivotal Trial of Temozolomide: Study Design

- This was a Phase 3 EORTC/NCIC randomized, multicenter study.
- Patients were randomly assigned to receive either radiotherapy (RT) 5 days a week for 6 weeks or radiotherapy plus concomitant temozolomide (TMZ) followed by maintenance TMZ for 6 cycles.

- Primary end point
  - Overall survival

- Secondary end points
  - Progression-free survival
  - Safety
  - Quality of life

EORTC = European Organisation for Research and Treatment of Cancer; NCIC = National Cancer Institute of Canada.

Pivotal Trial of Temozolomide: Treatment Regimens

Concomitant RT/TMZ

- Temozolomide 75 mg/m² PO qd for 6 weeks, then 150–200 mg/m² PO qd Days 1–5 every 28 days for 6 cycles
- Focal RT daily—30 x 200 cGy Total dose, 60 Gy

Adjuvant TMZ

RT Alone

- Pneumocystis carinii pneumonia (PCP) prophylaxis was required for patients receiving temozolomide during the concomitant phase.

R = regimen; RT = radiotherapy; TMZ = temozolomide; cGy = centigray; Gy = gray.

## Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Concomitant Phase Radiotherapy + Temozolomide (n=288)</th>
<th>Maintenance Phase Temozolomide (n=224)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td>Alopecia</td>
<td>199 (69)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>156 (54)</td>
<td>19 (7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>105 (36)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>57 (20)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>56 (19)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Headache</td>
<td>56 (19)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Constipation</td>
<td>53 (18)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Convulsions</td>
<td>17 (6)</td>
<td>10 (3)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>11 (4)</td>
<td>8 (3)</td>
</tr>
</tbody>
</table>
**Dosing in Concomitant and Maintenance Phases**

**Course of therapy:** Concomitant phase followed by maintenance phase

TEMODAR® (temozolomide) 75 mg/m² for 42 consecutive days with radiation followed by a 4-week break, then for 6 cycles of maintenance monotherapy

<table>
<thead>
<tr>
<th><strong>Concomitant Phase</strong></th>
<th><strong>Maintenance Phase</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>TEMODAR + Radiotherapy</td>
<td>TEMODAR Alone (6 Cycles)</td>
</tr>
<tr>
<td><strong>TEMODAR</strong></td>
<td><strong>4-week break</strong></td>
</tr>
<tr>
<td>TEMODAR (75 mg/m²/d) for 42 consecutive days with concomitant radiotherapy 5 days per week. TEMODAR is given consecutively, even on days with no RT.</td>
<td>Cycle 1</td>
</tr>
<tr>
<td><strong>Radiation</strong></td>
<td>Cycles 2–6</td>
</tr>
<tr>
<td>Focal Radiotherapy (30 x 2 Gy, 00:00)</td>
<td>150 mg/m²/d</td>
</tr>
<tr>
<td>TEMODAR (75 mg/m²/d) 42 Consecutive Days</td>
<td>Dosage Cycle 1 (maintenance)</td>
</tr>
<tr>
<td><strong>Concomitant Phase</strong></td>
<td>TEMODAR 150 mg/m² once daily for 5 days followed by 23 days without treatment</td>
</tr>
<tr>
<td><strong>Administer PCP Prophylaxis</strong></td>
<td>200 mg/m²/d</td>
</tr>
<tr>
<td></td>
<td>Dosage Cycles 2–6 (maintenance)</td>
</tr>
<tr>
<td></td>
<td>Dose is escalated to 200 mg/m²</td>
</tr>
<tr>
<td></td>
<td>— If hematologic criteria are met and nonhematologic toxicity is within predefined limits</td>
</tr>
<tr>
<td></td>
<td>— Providing the same criteria are met on Day 1 of each cycle (3–6), the dose of TEMODAR for that cycle remains at 200 mg/m² per day</td>
</tr>
<tr>
<td></td>
<td>— If dose was not escalated at Cycle 2, escalation should not be done in subsequent cycles</td>
</tr>
</tbody>
</table>

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Oral Chemotherapy May Not Be Appropriate for All Patients

- Difficulty swallowing
- GI obstruction
- Intractable nausea and vomiting
- Comorbidities affecting systemic absorption

TEMODAR® (temozolomide) for Injection: An Option for Patients for Whom Capsules May Not Be Appropriate

- Difficulty swallowing
  - Oropharyngeal dysfunction
  - Increased intracranial pressure
  - Brainstem involvement
- Comorbidities affecting systemic absorption
- Gastrointestinal obstruction
- Intractable nausea and vomiting

Indication

- TEMODAR® (temozolomide) is indicated for the treatment of adult patients with newly diagnosed glioblastoma multiforme concomitantly with radiotherapy and then as maintenance treatment.
Selected Important Safety Information for TEMODAR® (temozolomide)

- TEMODAR is contraindicated in patients who have a history of hypersensitivity (such as urticaria, allergic reaction including anaphylaxis, toxic epidermal necrolysis, and Stevens-Johnson syndrome) to any of its components, or to DTIC.

- Patients treated with TEMODAR may experience myelosuppression including prolonged pancytopenia, which may result in aplastic anemia, which in some cases has resulted in a fatal outcome. In some cases, exposure to concomitant medications associated with aplastic anemia including carbamazepine, phenytoin, and sulfamethoxazole/trimethoprim complicates assessment. Geriatric patients and women have been shown in clinical trials to have a higher risk of developing myelosuppression. Cases of myelodysplastic syndrome and secondary malignancies, including myeloid leukemia, have also been observed.
Selected Important Safety Information for TEMODAR® (temozolomide) (continued)

- Prophylaxis against *Pneumocystis carinii* pneumonia is required for all patients receiving concomitant TEMODAR and radiotherapy for the 42-day regimen. There may be a higher occurrence of PCP when temozolomide is administered during a longer dosing regimen. However, all patients receiving temozolomide, particularly patients receiving steroids, should be observed closely for the development of PCP regardless of the regimen.

- TEMODAR can cause fetal harm when administered to a pregnant woman. In nursing women, a decision should be made whether to discontinue nursing or to discontinue TEMODAR, taking into account the importance of the drug to the mother. The safety and effectiveness of TEMODAR in children have not been established.
Selected Important Safety Information for TEMODAR® (temozolomide) (continued)

- As bioequivalence between TEMODAR Capsules and TEMODAR for Injection has been established only when TEMODAR for Injection was given over 90 minutes, infusion over a shorter or longer period of time may result in suboptimal dosing. Additionally, the possibility of an increase in infusion-related adverse reactions cannot be ruled out.

- TEMODAR Capsules should not be opened or chewed. If capsules are accidentally opened or damaged, rigorous precautions should be taken with the capsule contents to avoid inhalation or contact with the skin or mucous membranes.

- Caution should be exercised when administered to those with severe hepatic or renal impairment.

- The adverse event profile was similar in patients <65 years of age and those ≥65 years.
Bevacizumab in Glioblastoma (GBM)

Genentech BioOncology
Medical Science Liaison Field Team
Background: NCCN Guidelines for Newly Diagnosed Glioblastoma

- **Treated with carmustine (BCNU) wafer**
  - Good performance status (KPS≥70)
  - Poor performance status (KPS<70)
- **No carmustine (BCNU) wafer**
  - Good performance status (KPS≥70)
  - Poor performance status (KPS<70)

**Adjuvant Treatment**
- Fractionated external beam RT ± concurrent and adjuvant TMZ
  - Fractionated external beam RT (standard or hypofractionated) OR chemotherapy OR best supportive care
  - Fractionated external beam RT + concurrent and adjuvant TMZ
- Fractionated external beam RT ± concurrent and adjuvant TMZ

**Follow-up**
- MRI 2-6 wks after RT, then every 2-4 months for 2-3 years, then less frequently

**Adjuvant Treatment**
- Concurrent (with RT) TMZ 75 mg/m² daily
- Post RT TMZ 150-200 mg/m² 5/28 schedule

KPS=Karnofsky performance status; RT=radiotherapy; TMZ=temozolomide
Background: NCCN Guidelines for Recurrent Anaplastic Gliomas and Glioblastoma

Recurrence

Diffuse or multiple

Recurrence/Salvage therapy
- BEV
- BEV + chemo (irinotecan, BCNU, TMZ)
- TMZ
- Nitrosourea
- Combination PCV
- Cyclophosphamide
- Platinum-based regimens

Treatment

Best supportive care if poor performance status
OR
Systemic chemotherapy
OR
Surgery for symptomatic, large lesion

Recurrent disease for anaplastic gliomas and glioblastoma

Local

Resectable

Resection + carmustine (BCNU) wafer

Unresectable

Resection without carmustine (BCNU) wafer

Best supportive care if poor performance status
OR
Systemic chemotherapy
OR
Consider reirradiation

Resectable

Best supportive care

BCNU=carmustine; BEV=bevacizumab; PCV=procarbazine, lomustine, and vincristine; TMZ=temozolomide

Background: [Relapsed] Glioblastoma Treatment Overview

Poor outcomes for refractory glioblastoma based on historical data¹

- RR ~6%
- PFS6 ~15%

Encouraging data with bevacizumab + CPT-11 from 2 small, single-institution reports

- Stark-Vance: RR 43%²
- Vredenburgh: RR 63%, PFS6 38%³

Bevacizumab was approved for use in recurrent glioblastoma in 2009,⁴ based upon 2 phase II trials: BRAIN and NCI⁵-⁷*/**

Bevacizumab is indicated for the treatment of glioblastoma as a single agent for adult patients with progressive disease following prior therapy⁵

CPT-11=irinotecan; PFS6=6-month PFS; RR=response rate


*Genentech/Roche Sponsored Study
**Independently Sponsored Study that is supported by Genentech/Roche with study drug and, in some instances, funds

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BRAIN* (AVF3708g) Phase II Bevacizumab Alone or in Combination With Irinotecan for Glioblastoma: Study Design

Noncomparative trial

Primary endpoints:
- Objective response rate
- 6-month PFS (PFS6) by independent radiologic review

Clinical, neurocognitive, and tumor assessments by MRI were performed every 6 weeks

Bevacizumab 10 mg/kg q2w (n=85) (104-week maximum)

Optional Post-PD Phase
Bevacizumab + Irinotecan (n=44)

First PD

Stratification by
- Karnofsky score (70%-80% vs 90%-100%)
- First vs second relapse

- 167 patients with GBM in first or second relapse
- Prior radiotherapy and temozolomide

*Genentech/Roche Sponsored Study

BRAIN* (AVF3708g) Phase II Bevacizumab Alone or in Combination With Irinotecan for Glioblastoma: Inclusion Criteria

- Age ≥18 years
- Histologically confirmed GBM in first or second relapse
- Prior chemotherapy: first-relapse subjects
  - All first-relapse subjects must have received temozolomide
- Prior chemotherapy: second-relapse subjects
  - All second-relapse subjects must have received temozolomide either for first-line treatment or after first relapse
- Prior standard radiation for GBM completed at least 8 weeks prior to receiving bevacizumab
- Karnofsky performance status ≥70
- Radiographic demonstration of disease progression
- Bidimensionally measurable disease on MRI performed within 14 days prior to first treatment (Day 0)
- Patients taking steroids were required to be on a stable or decreasing dose for ≥5 days prior to baseline MRI
- Patients on anticoagulation were allowed

GBM=glioblastoma


*Genentech/Roche Sponsored Study
Disease and treatment history

- Prior treatment with CPT-11, bevacizumab, or other VEGF- or VEGFR-targeted agent
- Prior treatment with prolifeprospan 20 with carmustine wafer
- Prior intracerebral investigational agents
- Evidence of recent hemorrhage on baseline MRI of the brain

Laboratory criteria

- Abnormal hematologic and organ function

VEGF=vascular endothelial growth factor; VEGFR=VEGF receptor

*Genentech/Roche Sponsored Study
**BRAIN** (AVF3708g) Phase II Bevacizumab Alone or in Combination With Irinotecan for Glioblastoma: **Efficacy Outcomes**

<table>
<thead>
<tr>
<th>IRF-Determined Outcome</th>
<th><strong>BEV</strong> (n=85)</th>
<th><strong>BEV + CPT-11</strong> (n=82)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response, a n (%)</td>
<td>24 (28.2)</td>
<td>31 (37.8)</td>
</tr>
<tr>
<td>Complete response, a n (%)</td>
<td>1 (1.2)</td>
<td>2 (2.4)</td>
</tr>
<tr>
<td>Partial response, a n (%)</td>
<td>23 (27.1)</td>
<td>29 (35.4)</td>
</tr>
<tr>
<td>6-month PFS, a %</td>
<td>42.6</td>
<td>50.3</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>4.2 (2.9-5.8)</td>
<td>5.6 (4.4-6.2)</td>
</tr>
<tr>
<td>Median survival, months (95% CI)b</td>
<td>9.3 (8.2-11.8)</td>
<td>8.9 (7.9-11.9)</td>
</tr>
</tbody>
</table>

*a* Based on September 2007 cutoff; *b* Based on July 2008 cutoff  
BEV=bevacizumab; CI=confidence interval; CPT-11=irinotecan; IRF=independent review facility; PFS=progression-free survival
**BRAIN** (AVF3708g) Phase II Bevacizumab Alone or in Combination With Irinotecan for Glioblastoma: **Progression-Free Survival (PFS)**


Bevacizumab (BEV) and irinotecan (CPT-11) were evaluated in a Phase II trial for glioblastoma. The graph shows the progression-free survival (PFS) over time for two treatment groups: BEV alone and BEV + CPT-11.

- **BEV (n=85)** median PFS 4.2 months (95% CI, 2.9-5.8)
- **BEV + CPT-11 (n=82)** median 5.6 months (95% CI, 4.4-6.2)

No. at risk:
- BEV (n=85): 85, 61, 39, 26, 14, 4, 1, 0
- BEV + CPT-11 (n=82): 82, 65, 47, 24, 15, 7, 1, 0

**BEV**=bevacizumab; **CPT-11**=irinotecan

*Genentech/Roche Sponsored Study*
**BRAIN** (AVF3708g) Phase II Bevacizumab Alone or in Combination With Irinotecan for Glioblastoma: **Overall Survival (OS)**

Median Months to Survival (95% CI)
- **BEV=9.33 (8.18-11.83)**
- **BEV + CPT-11=8.90 (7.85-11.89)**

<table>
<thead>
<tr>
<th>Months</th>
<th>No. at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>85 78 74 64 55 40 32 32 28 20 16 15 14 10 9 8 3 1 0</td>
</tr>
<tr>
<td>8</td>
<td>82 80 73 59 48 37 31 24 19 37 15 14 13 13 11 10 6 0 0</td>
</tr>
</tbody>
</table>

BEV=bevacizumab; CPT-11=irinotecan

*Genentech/Roche Sponsored Study*
**BRAIN** (AVF3708g) Phase II Bevacizumab Alone or in Combination With Irinotecan for Glioblastoma: **Survival Rates**

<table>
<thead>
<tr>
<th>Survival From Randomization to Death, %</th>
<th>BEV (n=85)</th>
<th>BEV + CPT-11 (n=82)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 months</td>
<td>38</td>
<td>38</td>
</tr>
<tr>
<td>18 months</td>
<td>24</td>
<td>18</td>
</tr>
<tr>
<td>24 months</td>
<td>16</td>
<td>17</td>
</tr>
<tr>
<td>30 months</td>
<td>11</td>
<td>16</td>
</tr>
</tbody>
</table>

*Genentech/Roche Sponsored Study

As of 07/2009

BEV = bevacizumab; CPT-11 = irinotecan

**BRAIN** (AVF3708g) Phase II Bevacizumab Alone or in Combination With Irinotecan for Glioblastoma: **Objective Response as a Predictor of Survival**

Exploratory landmark analysis of patients from BRAIN to evaluate the association between OR and survival

<table>
<thead>
<tr>
<th></th>
<th>Study Week</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>9</td>
</tr>
<tr>
<td><strong>Responders (n=30)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Non-responders (n=127)</strong></td>
<td>58 (43-63)</td>
</tr>
<tr>
<td><strong>Responders (n=46)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Non-responders (n=101)</strong></td>
<td>21 (18-29)</td>
</tr>
<tr>
<td><strong>Responders (n=51)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Non-responders (n=72)</strong></td>
<td>17 (12-22)</td>
</tr>
</tbody>
</table>

**Median weeks residual survival**

- **Unadjusted Kaplan-Meier estimates:**
  - 9: 58 (43-63)
  - 18: 30 (27-36)
  - 26: 49 (35-60)

**HR (95% CI)**

- 9: 0.52 (0.32-0.85)
- 18: 0.48 (0.31-0.74)
- 26: 0.43 (0.27-0.67)

**P value**

- 9: 0.0091
- 18: 0.0010
- 26: 0.0002

---

*a* Unadjusted Kaplan-Meier estimates; *b* From Cox model adjusted for baseline characteristics (Age, KPS, relapse status, treatment)

---


*Genentech/Roche Sponsored Study*
Two grade ≥3 wound-dehiscence events were related to craniotomy sites

There were 2 (2.4%) adverse event–associated deaths in the BEV group and 1 (1.3%) adverse event–associated death in the BEV + CPT-11 group

BEV=bevacizumab; CPT-11=irinotecan; RPLS=Reversible posterior leukoencephalopathy syndrome


*Genentech/Roche Sponsored Study
Two grade ≥3 wound dehiscence events were related to craniotomy sites²

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BEV=bevacizumab; CPT-11=irinotecan; RPLS=reversible posterior leukoencephalopathy syndrome


*Genentech/Roche Sponsored Study
Bevacizumab is an active agent in recurrent GBM\(^1\)

- Alone and in combination with CPT-11
- PFS6, RR, and OS in patients treated with BEV alone or BEV with CPT-11 provide evidence of significant activity in this poor prognosis population
- Responding patients had stable or decreasing corticosteroid use

Bevacizumab is well tolerated\(^1\)

- Low rates of CNS bleeding and wound healing complications

Patients who had an OR while being treated with BEV or BEV+CPT-11 in BRAIN did not have a significantly increased incidence of diffuse disease at the time of progression compared with nonresponders\(^2\)

Patients treated with BEV or BEV+CPT-11 who had local-to-local or local-to-diffuse progression patterns had similar efficacy\(^2\)

The majority of patients in BRAIN did not have a shift in pattern of recurrence following BEV-based therapy\(^2\)

---


*Genentech/Roche Sponsored Study*
(Radiographic) Patterns of Relapse in GBM: Results and Conclusions

<table>
<thead>
<tr>
<th>Pattern/Time</th>
<th>Presentation (n=80)</th>
<th>First Recurrence (Post RT + TMZ, Onset BEV Only) (n=80)</th>
<th>Second Recurrence (Progression on BEV Only) (n=80)</th>
<th>Third Recurrence (Progression on BEV + Alternative) (n=57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local</td>
<td>70 (87.5%)</td>
<td>64 (80%)</td>
<td>57 (71.3%)</td>
<td>41 (71.9%)</td>
</tr>
<tr>
<td>Local to other</td>
<td>–</td>
<td>6 (8.5%)</td>
<td>8 (12.5%)</td>
<td>1 (1.75%)</td>
</tr>
<tr>
<td>Distant</td>
<td>5 (6.25%)</td>
<td>6 (7.5%)</td>
<td>7 (8.75%)</td>
<td>4 (7.0%)</td>
</tr>
<tr>
<td>Multifocal</td>
<td>3 (3.75%)</td>
<td>5 (6.25%)</td>
<td>7 (8.75%)</td>
<td>4 (7.0%)</td>
</tr>
<tr>
<td>Diffuse</td>
<td>2 (2.5%)</td>
<td>5 (6.25%)</td>
<td>9 (11.25%)</td>
<td>8 (14.0%)</td>
</tr>
</tbody>
</table>

BEV=bevacizumab; GBM=glioblastoma; RT=radiotherapy; TMZ=temozolomide
NCI 06-C-0064E* Phase II Trial of Single-Agent BEV Followed by BEV + CPT-11 at Tumor Progression in rGBM: **Study Design**

Main objective: to evaluate single-agent activity of bevacizumab in patients with recurrent glioblastoma

Supportive trial for approval of bevacizumab in glioblastoma

- **Primary endpoint:** PFS6 by investigator
- **Secondary endpoint:** ORR

1 treatment cycle=4-week period of therapy
Disease assessment by MRI every 4 weeks

BEV=bevacizumab; CPT-11=irinotecan; ORR=objective response rate; PFS6=6-month PFS; rGBM=recurrent glioblastoma; TMZ=temozolomide


*Independently Sponsored Study that is supported by Genentech/Roche with study drug and, in some instances, funds
**NCI 06-C-0064E**  Phase II Trial of Single-Agent BEV Followed by BEV + CPT-11 at Tumor Progression in rGBM: **Efficacy Summary**

<table>
<thead>
<tr>
<th></th>
<th>Bevacizumab (n=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, weeks (95% CI)</td>
<td>16 weeks (12-26)</td>
</tr>
<tr>
<td>PFS6, % (95% CI)</td>
<td>29% (18%-48%)</td>
</tr>
<tr>
<td>6-month survival rate, % (95% CI)</td>
<td>57% (44%-75%)</td>
</tr>
<tr>
<td>Median OS, weeks (95% CI)</td>
<td>31 weeks (21-54)</td>
</tr>
<tr>
<td>ORR (Macdonald), n (%)</td>
<td>17 (35)</td>
</tr>
<tr>
<td>CR, n</td>
<td>1</td>
</tr>
<tr>
<td>PR, n</td>
<td>16</td>
</tr>
<tr>
<td>ORR (Levin), n (%)</td>
<td>34 (71) (all PRs)</td>
</tr>
</tbody>
</table>

CR=complete response; NCI=National Cancer Institute; ORR=objective response rate; PFS6=6-month PFS; PR=partial response

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**NCI 06-C-0064E**\* Phase II Trial of Single-Agent BEV Followed by BEV + CPT-11 at Tumor Progression in rGBM: **Progression-Free Survival (PFS)**

---


NCI=National Cancer Institute

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**NCI 06-C-0064E** Phase II Trial of Single-Agent BEV Followed by BEV + CPT-11 at Tumor Progression in rGBM: **Overall Survival (OS)**

![Graph showing overall survival (OS) with median OS of 31 weeks.](image)

- Median (Median OS is 31 weeks)
- 95% CI

**OS (proportion)**

**Time Since Start of Therapy (weeks)**

NCI=National Cancer Institute


*Independently Sponsored Study that is supported by Genentech/Roche with study drug and, in some instances, funds*
24 patients (50%) experienced decreased cerebral edema while on study

15 (58%) of 26 patients receiving corticosteroids at start of study treatment achieved an average corticosteroid dose reduction of 59%

25 patients (52%) had improved neurologic symptoms, including a number who did not meet the PFS6 landmark

Baseline KPS and the number of prior chemotherapy regimens had no effect on PFS. Age did have a major effect: \( P < 0.001 \)

- Patients with median age \( \geq 53 \): PFS=30 weeks
- Patients with median age <53: PFS=11 weeks

KPS=Karnofsky performance status; NCI=National Cancer Institute; PFS6=6-month PFS

Single-agent bevacizumab has biologic activity in patients with rGBM

- There were significant reductions in gadolinium enhancement, T2 abnormalities, and diminished uptake of FDG on PET scans
- The observed PFS6=29% compares favorably with historical controls of ineffective regimens
- A significant number of patients derived clinical benefit from bevacizumab treatment, including decreased cerebral edema, improved neurologic symptoms, and decreased requirement for corticosteroids

Single-agent bevacizumab is well tolerated

- Thromboembolic events and controllable hypertension were the most common drug-related adverse events
- No patients had intracranial hemorrhage

FDG=[18F]fluorodeoxyglucose; NCI=National Cancer Institute; PFS6=6-month PFS; rGBM=recurrent glioblastoma

Trials of Bevacizumab in Frontline Glioblastoma
AVF3778s* Phase II Addition of BEV to Standard Radiation and TMZ followed by BEV/TMZ/Irinotecan in Newly Diagnosed GBM (n=75): **Study Design**

EIAED=enzyme-inducing antiepileptic drug; GBM=glioblastoma; BEV=bevacizumab; TMZ=temozolomide


*Independently Sponsored Study that is supported by Genentech/Roche with study drug and, in some instances, funds
# AVF3778s* and AVF3770s* Phase II Trials in Patients With Newly Diagnosed GBM: Summary of Trial Differences

| Weeks post surgery | **Vredenburgh**¹  
|                   | (n=75)  | **Lai**²  
|                   | (n=70)  |
|--------------------|---------|---------|
|                    | 2-6     | 3-6     |

| Treatment schedule | Bevacizumab administered every 2 weeks  
|--------------------|-----------------------------------------|
|                    | Concurrently with TMZ and RT for the first 6 weeks  
|                    | Followed by a 2-week break  
|                    | Followed by 6-12 cycles of TMZ days 1-5, Bevacizumab and irinotecan days 1 and 15  
|                    | Bevacizumab administered every 2 weeks  
|                    | Concurrently with TMZ and RT for the first 6 weeks  
|                    | Followed by a 2-week break  
|                    | Administered with adjuvant TMZ from week 8 up to 24 months  

**GBM=glioblastoma; RT=radiotherapy; TMZ=temozolomide**


*Independently Sponsored Study that is supported by Genentech/Roche with study drug and, in some instances, funds.
Bevacizumab in Newly Diagnosed GBM: **Efficacy**

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Vredenburgh$^1$ (n=75)</th>
<th>Lai$^2$ (n=70)</th>
<th>Lai External Controls$^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>UCLA/KP RT/TMZ (n=110)</td>
</tr>
<tr>
<td>Median PFS</td>
<td>14.2 months</td>
<td>13.6 months</td>
<td>7.6 months</td>
</tr>
<tr>
<td>6-month PFS</td>
<td>NR</td>
<td>88%</td>
<td>58%</td>
</tr>
<tr>
<td>12-month PFS</td>
<td>62.7%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>24-month PFS</td>
<td>13.3%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Median OS$^a$</td>
<td>21.2 months</td>
<td>19.6 months</td>
<td>21.1 months</td>
</tr>
<tr>
<td>18-month OS</td>
<td>NR</td>
<td>54%</td>
<td>61%</td>
</tr>
<tr>
<td>24-month OS</td>
<td>44.9%</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

$^a$Vredenburgh et al measured OS from time of registration, and Lai et al measured OS from time of initial diagnosis.

EORTC=European Organization for Research and Treatment of Cancer; GBM=glioblastoma; NCIC=National Cancer Institute of Canada; NR=not reached; RT=radiotherapy; TMZ=temozolomide

Phase III Trials of Bevacizumab in Frontline Glioblastoma
AVAglio* Phase III BEV + TMZ and Radiotherapy in Newly Diagnosed GBM: Study Design

Debulking surgery or biopsy
Randomization with stratification 4-7 weeks post surgery
Based on RPA class and country

(n=460)

RT 2 Gy 5 days/week for 6 weeks
TMZ 75 mg/m²/qd
Placebo 10 mg/kg q2w

(n=460)

4-Week Treatment Break

RT 2 Gy 5 days/week for 6 weeks
TMZ 75 mg/m²/qd
Bevacizumab 10 mg/kg q2w

TMZ 150-200 mg/m²,qd
days 1-5 q28d
Placebo 10 mg/kg q2w

Bevacizumab 15 mg/kg q3w monotherapy until disease progression

Placebo 15 mg/kg q3w monotherapy until disease progression

Monotherapy phase until PD

Concurrent phase

Maintenance phase for 6 cycles

GBM=glioblastoma; PD=progressive disease; RPA=recursive partitioning analysis; RT=radiotherapy; TMZ=temozolomide

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RTOG 0825* Phase III Concurrent Chemoradiation and Adjuvant TMZ Plus BEV vs Conventional Concurrent Chemoradiation and Adjuvant TMZ in Newly Diagnosed GBM: Study Design

GBM=glioblastoma; RT=radiotherapy; RTOG=Radiation Therapy Oncology Group; TMZ=temozolomide; BEV=bevacizumab

http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0825 as of 12/11.

*Independently Sponsored Study that is supported by Genentech/Roche with study drug and, in some instances, funds.
RTOG 0825* Phase III Concurrent Chemoradiation and Adjuvant TMZ Plus BEV vs Conventional Concurrent Chemoradiation and Adjuvant TMZ in Newly Diagnosed GBM: **Study Objectives**

Composite primary endpoints
- OS
- PFS

Secondary endpoint
- Treatment-related toxicity

Exploratory endpoints
- Quality of life as measured by MDASI-BT tool and EORTC QLQ-C30/BN20
- Neurocognitive function measured by HVLT-R, Trail Making Test Part A, Trail Making Test Part B, and COWAT

COWAT=Controlled Oral Word Association Test; EORTC=European Organization for Research and Treatment of Cancer; HVLT-R=Hopkins Verbal Learning Test, Revised; MDASI-BT=MD Anderson Symptom Inventory-Brain Tumor Module; RTOG=Radiation Therapy Oncology Group

http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0825 as of 12/11.

*Independently Sponsored Study that is supported by Genentech/Roche with study drug and, in some instances, funds
Patients with progressive disease either during or after protocol treatment might receive unblinded bevacizumab

- As a single agent
- In combination with irinotecan
- In combination with temozolomide
- No other investigational agents are permitted

The arm to which the patient was randomized will be revealed. An MRI scan must be performed within 2 weeks prior to starting salvage treatment.

Toxicity and efficacy will be monitored for all patients receiving unblinded bevacizumab.

The patient must not have received any other anticancer therapy since the protocol-based therapy and must not have acute intracranial bleeding.

The patient must have a Karnofsky performance status ≥60 and adequate bone marrow and renal function.

RTOG=Radiation Therapy Oncology Group
http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0825 as of 12/11.
### Key Similarities Between AVAglio* and RTOG 0825**: Overview

<table>
<thead>
<tr>
<th></th>
<th>AVAglio</th>
<th>RTOG 0825</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trial design</strong></td>
<td>• Double blind, placebo controlled • 2 arms</td>
<td>• Double blind, placebo controlled • 2 arms</td>
</tr>
<tr>
<td><strong>Patient eligibility</strong></td>
<td>• Newly diagnosed GBM</td>
<td>• Newly diagnosed GBM</td>
</tr>
<tr>
<td><strong>Measures of HRQoL</strong></td>
<td>• EORTC QLQ-C30, BN20</td>
<td>• EORTC QLQ-C30, BN20</td>
</tr>
<tr>
<td><strong>Measures of NCF</strong></td>
<td>• Mini mental status exam (all patients) • Hopkins Verbal Learning Test-Revised (HVLT-R) • Trail-Making Test A&amp;B (TMT A&amp;B) • Controlled Oral Word Association (COWA)</td>
<td>• Mini mental status exam (all patients) • Hopkins Verbal Learning Test, Revised (HVLT-R) • Trail-Making Test A&amp;B (TMT A&amp;B) • Controlled Oral Word Association (COWA)</td>
</tr>
</tbody>
</table>

EORTC=European Organization for Research and Treatment of Cancer; GBM=glioblastoma; HRQoL=health-related quality of life; NCF=neurocognitive function; RTOG=Radiation Therapy Oncology Group


*Genentech/Roche Sponsored Study

**Independently Sponsored Study that is supported by Genentech/Roche with study drug and, in some instances, funds
**Key Differences Between AVAglio* and RTOG 0825**: Overview

<table>
<thead>
<tr>
<th></th>
<th>AVAglio</th>
<th>RTOG 0825</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient eligibility</strong></td>
<td>Biopsy-only patients allowed</td>
<td>Stereotactic biopsy is not allowed</td>
</tr>
<tr>
<td><strong>Stratification factors</strong></td>
<td>RPA class region</td>
<td>MGMT status Molecular profile</td>
</tr>
<tr>
<td><strong>Start of bevacizumab therapy</strong></td>
<td>Bevacizumab started concomitantly with RT/TMZ</td>
<td>3 weeks RT/TMZ only; bevacizumab added to last 3 weeks of RT/TMZ</td>
</tr>
<tr>
<td><strong>Bevacizumab treatment post-RT</strong></td>
<td>Patients take a 4-week treatment break following completion of RT</td>
<td>Bevacizumab treatment continues uninterrupted</td>
</tr>
<tr>
<td><strong>Length of maintenance therapy</strong></td>
<td>6 cycles of TMZ; bevacizumab to progression</td>
<td>Maximum of 12 cycles of TMZ ± bevacizumab</td>
</tr>
<tr>
<td><strong>Treatment options at progression</strong></td>
<td>Treatment only unblinded if necessary for deciding on further treatment</td>
<td>All patients unblinded</td>
</tr>
</tbody>
</table>

RPA=recursive partitioning analysis; RT=radiotherapy; RTOG=Radiation Therapy Oncology Group; TMZ=temozolomide


*Genentech/Roche Sponsored Study
**Independently Sponsored Study that is supported by Genentech/Roche with study drug and, in some instances, funds...
Bevacizumab for the treatment of GBM

February 2009
NCI study results published
May 2009
Accelerated FDA approval
October 2009
BRAIN study results published
2009 Initiation of AVAglio and RTOG 0825 studies
January 2011
Phase II frontline trial results published
June 2011
Phase II frontline trial results published

AVAglio and RTOG 0825 expected to report (estimated late 2012 - early 2014)

Bevacizumab GBM Development** Timeline (All Lines): Overview


*Genentech/Roche Sponsored Study
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