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# Reissuance of RFA-CA-08-504 Adult Brain Tumor Consortium

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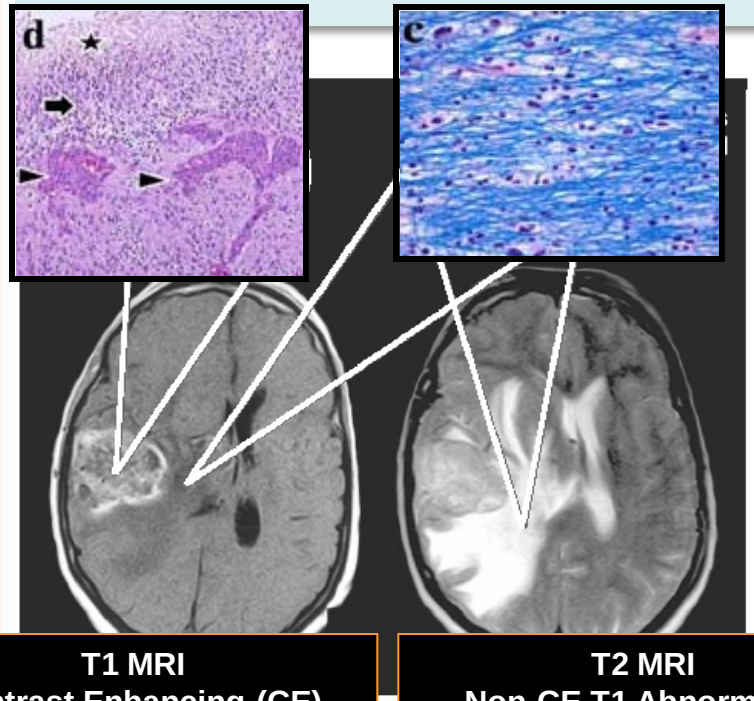
# ABTC Focus—Glioblastoma Multiforme

**Incidence**

- Malignant Brain Tumors: 22,000 annually; 13,000 deaths
- Glioblastoma Multiforme (GBM): 60 – 70%

**Current Treatment**

- Newly diagnosed: Maximal Resection + RT and Concurrent TMZ + Adjuvant TMZ—Median OS ~ 14 months
- Recurrent: Bevacizumab—Median OS ~ 9 months




**T1 MRI**
**Contrast Enhancing (CE)**
**Tumor + Non-CE Abnormality**

**T2 MRI**
**Non-CE T1 Abnormality**
**—T2 Hyperintense Infiltration**

- Constraints on efficacy of GBM treatments:
  - Infiltrating malignant cells—unable to resect normal brain to get negative margins
  - Radiation tolerance of the normal brain
  - Drug entry across the BBB

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# Evolving Understanding of GBM Biology

## The Cancer Genome Atlas (TCGA)

- Typical GBM harbors >60 genetic alterations
- Three cellular pathways are affected:
  - Cell proliferation signaling: RTK/PI3K/PTEN
  - Tumor suppressor: p53
  - Tumor suppressor: Rb1
- Gene expression profiling identifies 4 molecular classes:
  - Proneural
  - Neural
  - Classical
  - Mesenchymal

- Opportunity to identify new drug targets
- ~8% of GBM patients participate in clinical trials

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# Improving GBM Treatment

***Translate*** accumulating knowledge of ***tumor biology*** into patient focused ***clinical applications***

Need for readily available neuro-oncology expertise for early clinical studies of drugs and other agents likely to be active in GBM—operationally well organized structure, with capacity to adapt new technology rapidly, and incorporate emerging disease biology into early drug development studies

- Obtain *tumor tissue*—before and after (or with and without) drug administration
- Evaluate *drug exposure in tumor* and the *drug effects on the relevant cellular targets*

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# ABTC: Operational Since 2009

1999-2008
NABTC (North American Brain Tumor Consortium) and
NABTT (New Approaches to Brain Tumor Therapy)

2009
NABTC and NABTT combined to form
the Adult Brain Tumor Consortium (ABTC)

| | | |
|---|---|---|
| Co-chair: | Skip Grossman, MD | JHU |
| Co-chair : | Mike Prados, MD | UCSF |
| | | |
| Central Operations Office | | JHU |
| Biostatistics Center | | JHU |
| Pharmacology Center | | MGH |
| Imaging Center | | UCSF |

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# ABTC: Strategy Since Inception 2009

## Focus on Early Drug Development

➢Rapidly conduct phase I and II studies with emphasis on PK and PD—*incorporate pre- and post- treatment assays: imaging and tissue based biomarkers*

➢Conduit for new ideas between SPOREs, P01, and Cooperative Groups (NCTN)

•New Agents Committee
•Imaging Committee

•Advisory Committee (Members from Brain SPOREs, US Groups, EORTC)

•Investigational Drugs SC
•Brain Malignancies SC
•Planning Committee for the coming CTPM

**ABTC Member Institutions:**

**Cleveland Clinic**
**Emory University**
**Harvard University**
**Henry Ford Hospital**
**Johns Hopkins University**
**Memorial Sloan Kettering CC**
**Moffitt Cancer Center**
**University of Alabama**
**University of California at LA**
**University of California at SF**
**University of Pennsylvania**
**University of Pittsburgh**
**University of Wisconsin**
**Wake Forest University**

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# ABTC Studies: Accruing or Recently Completed

| Study | Phase New/Rec | Agent | Comments |
|---|---|---|---|
| 0901 | II Recurrent | Olaratumab + Ramucirumab | Anti-PDGFRα + Anti-VEGFR2 Monoclonal Antibodies |
| 0902 | I and II New | Vorinostat | HDACI<br>Phase II with NCCTG |
| 0903 | II Recurrent | Cediranib + Cilengitide | VEGFR2 TKI + Inhibition of endothelial cell migration, survival, tumor cell invasion |
| 0904 | II Recurrent | GDC-0449 | Hedgehog signaling pathway inhibitor |
| 0906 | II Recurrent | RO4929097 | γ-secretase inhibitor—inhibits Notch signaling in tumor cells<br>+/- Surgery |
| 1002 | I and II Recurrent | RO4929097 | +/- Bevacizumab |
| 1101 | I Recurrent | Mibefradil | Inhibits Ca entry through Cav3 Ca channel leading to cell cycle arrest<br>+ Temozolomide |

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# ABTC Studies: In Review or Development

| Study | Phase New/Rec | Agent | Comments |
|---|---|---|---|
| LOI | II Recurrent | Cabozantinib | C-Met and VEGFR2 Inhibitor |
| LOI | II Recurrent | Ipilimumab | Anti-CTLA-4 Mo Ab |
| LOI | I and II New | MK-1775 | Wee1 Kinase Inhibitor Phase II with Alliance |
| LOI | II Recurrent | MK-8776 | CHK1 Inhibitor |
| LOI Solicit | 0,I,II Recurrent | MLN0128 | TORC1/2 Inh:Cancer cell-tumor microenvironment interaction Phase 0/1 followed by RP2 of bev vs. bev + MLN0128 |

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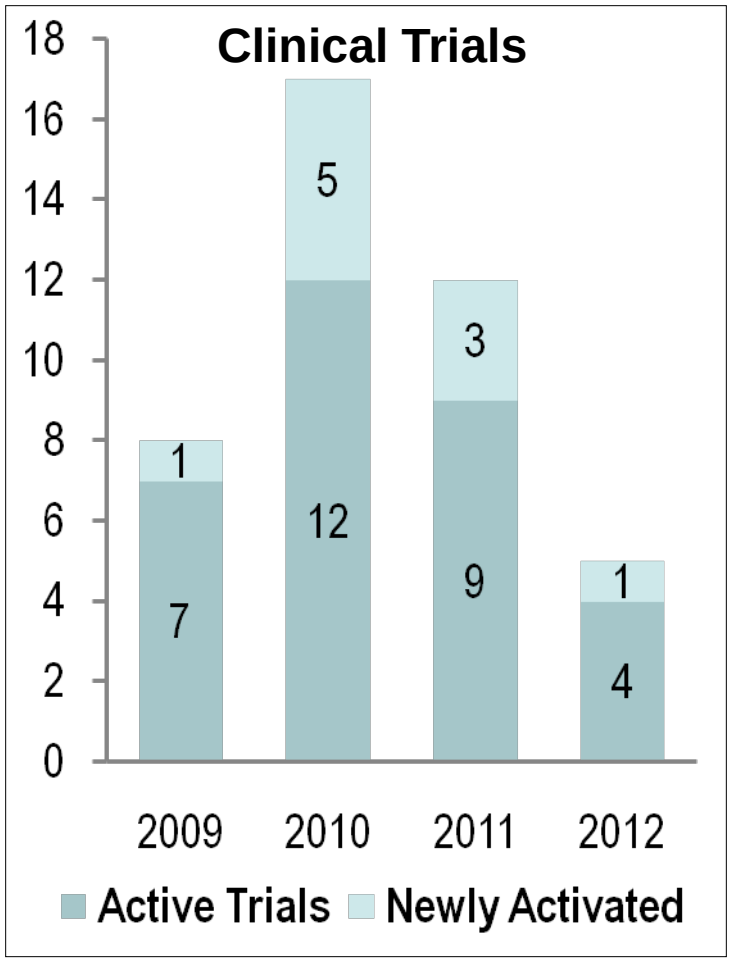
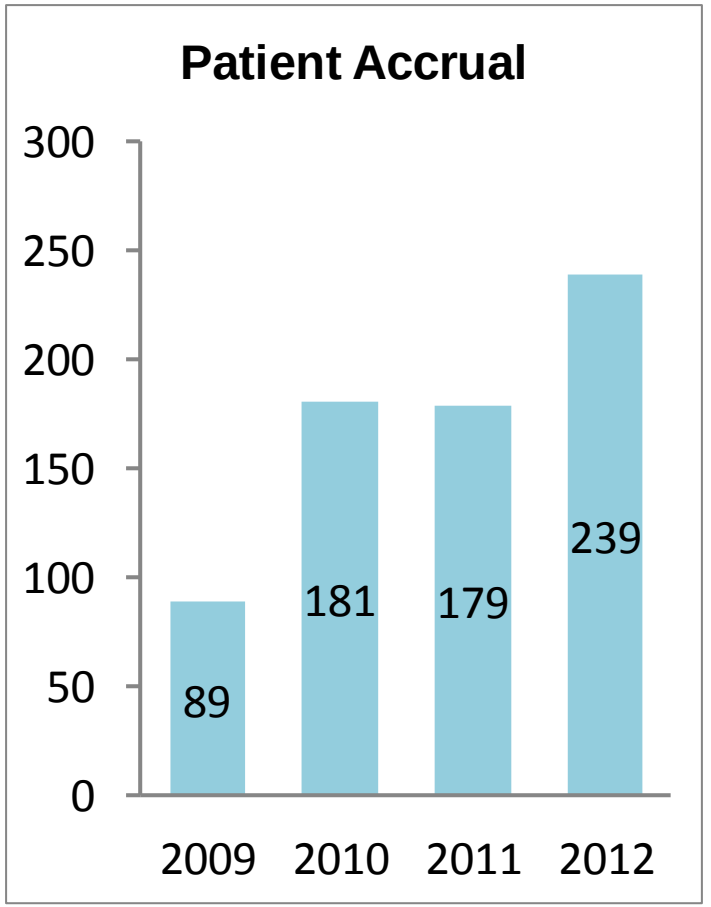
# ABTC: Clinical Trials and Accrual




- Current funding can support enrollment of ~150 patients/year
- Two phase I and three phase II studies
- Two additional studies in 2010 due to ARRA funds

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# ABTC: Leverage of CTEP-supported Clinical Trials Infrastructure

Adult Brain Tumor Consortium

- is integrated within the CTSU for regulatory and patient enrollment
- utilizes Medidata Rave®
- will have its trials reviewed in the CIRB
- follows OEWG timelines

➢ Thus ABTC is able to do more trials, accrue more patients with less funding

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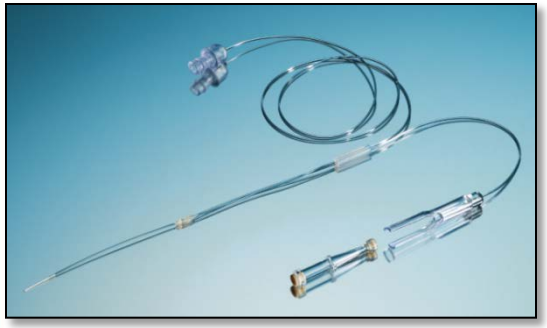
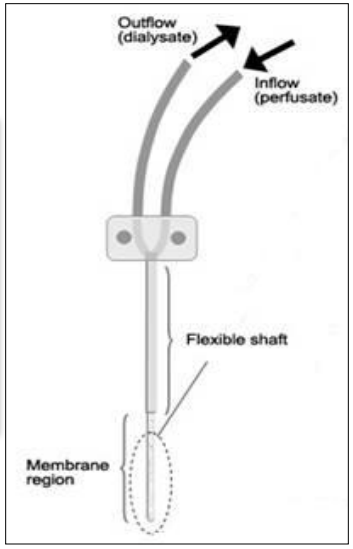
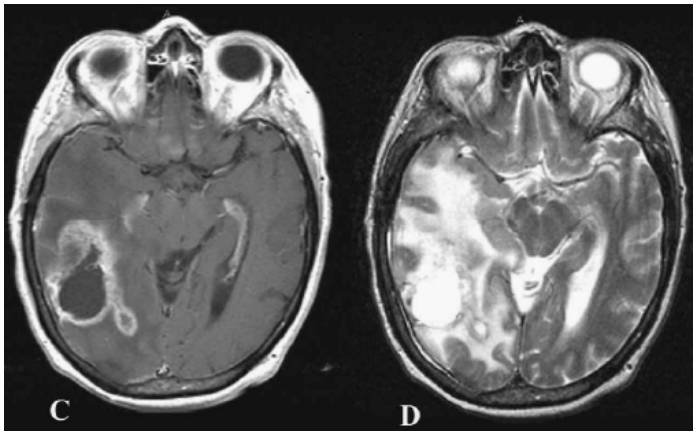
# Microdialysis Studies: Drug Entry Across the BBB

Early determination during drug development: Whether the drug crosses BBB and concentrates adequately in malignant tissue?






**ABTC investigators are able to conduct MD studies**

- **MD catheter in 3 locations: CE tumor, NCE region (T2), and normal brain**
- **Confirm catheter locations, administer drug IV, collect tissue MD samples**
- **Assess drug entry: CE, NCE, and normal brain compared to plasma levels**

- Experience with MTX is published
- Concentration higher in enhancing tumor
- *Proof-of-principal study in gliomas; HDMTX active in PCNSL*

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# ABTC 0904: Phase II Study of GDC-0449 (hedgehog signaling inhibitor) in Recurrent GBM

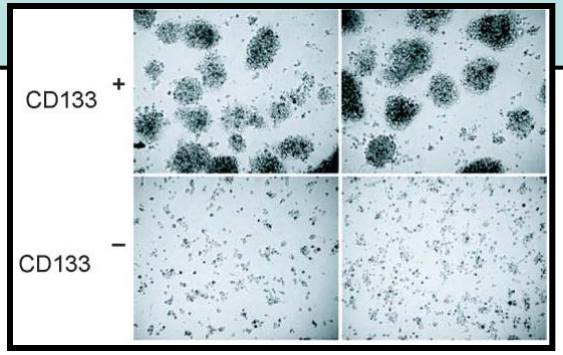
**Recurrent GBM**
**Surgery eligible patients**

| Arm 1 | Arm 2 |
|---|---|
| 7days of GDC-0449 Pre-op | No drug pre-op (Control) |

**Surgery**
**Tissue for correlative studies**

## Biomarkers Studies for Drug Effect

- Culture of glioma-derived CD133 + cells by neurosphere assay
- CD133: Neural stem cell surface marker expressed by brain tumor stem cells
- CD133+ cells form neurospheres on cell culture




## Clinical Trial Logistics

- Training neurosurgeons in tissue collection
- Coordinating collection and transport of 46 fresh tumor specimens from 8 centers to the central lab at CCCC
  - Tumor mass: 4.5g
  - Time from OR to Lab at CCCC: 20 hrs
  - Viability: 70%

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# Feb 2012: ABTC External Evaluation

## Summary

- Well organized and developed infrastructure
- Highly qualified group for early translational studies
- Fruitful collaborations with SPORES and groups

## Recommendations

- Focus on studies with tumor tissue acquisition and incorporation of imaging & tissue biomarkers to fully use early drug development capabilities
- Further operational improvements:
  - Eliminate low accruing sites
  - Add new members / sites

## Impact Score = 2.1

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# ABTC—Unique Strengths

A core of investigators with expertise in conducting early drug development studies in GBM

- Neuro -surgery, -oncology, -pathology, -imaging expertise
- Central operations to coordinate multiple sites for timely accrual into technically demanding clinical trials
- Manage specialized logistics
  - Training neurosurgeons in viable tumor tissue collection
  - Transport of fresh tumor tissue to a central lab for correlative studies (tumor cell culture)

➢Resources required for early development of GBM treatments are not available under the standard CTEP phase I-II-III drug development programs

➢ABTC functions are distinct from Brain SPOREs: ABTC has the ability to plan and conduct multicenter, early drug development clinical trials

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# ABTC Funding

| Current Award | |
|---|---|
| $ 2.0 M / year | |
| **Current Expenditures** (After administrative reductions) | |
| Administration (Central office, imaging chair, biostatistics and pathology support) | $ 530,500 |
| PK core | $ 121,000 |
| Capitation | $ 1,100,000 |
| **Requested** | |
| $2.0 M / year for 5 years | |

**ABTC has unique abilities in early drug development: Clinical trials with emphasis on PK and PD; rapidly incorporate tumor biology studies—translational studies required to improve GBM therapy**