NCI Clinical Trials and Translational Research Advisory Committee (CTAC)

Glioblastoma Working Group Final Report

Drs. Walter J. Curran and Chi V. Dang

CTAC: July 17, 2019

NIH > NATIONAL CANCER INSTITUTE

Today's Topics

- Glioblastoma (GBM) Working Group - Overview and Functions

- GBM Background & Treatment Challenges

- GBM Working Group Process

- Recommendations

- Next Steps

Translational Research Strategy Subcommittee (TRSS)

- **2017**: NCAB BSA SPORE Evaluation Working Group recommended forming a subcommittee on identify the most important translational research opportunities to benefit patients

- Membership comprised of current and former CTAC, BSA, and NCAB members

- Co-Chairs: Chi Dang, M.D., Ph.D.

  Nancy Davidson, M.D.

Working Group on Glioblastoma

The NCI CTAC ad hoc Translational Research Strategy Subcommittee (TRSS) convened an ad hoc Working Group on Glioblastoma to survey the scientific horizons broadly to:

1. Help identify the most provocative and impactful glioblastoma translational research questions to advance treatment

2. Identify the most important opportunities for application of new technologies to glioblastoma translational research

3. Identify glioblastoma translational research knowledge gaps

NCI Clinical Trials and Translational Research Advisory Committee

CTAC
Chair: Patrick Loehrer, M.D

Translational Research Strategy Subcommittee
Chair(s): Chi Dang, M.D., Ph.D.
Nancy Davidson, M.D.

Ad Hoc Working Group on Radiation Oncology
Chair(s): Adam Dicker, M.D., Ph.D.
Sylvia Formenti, M.D.

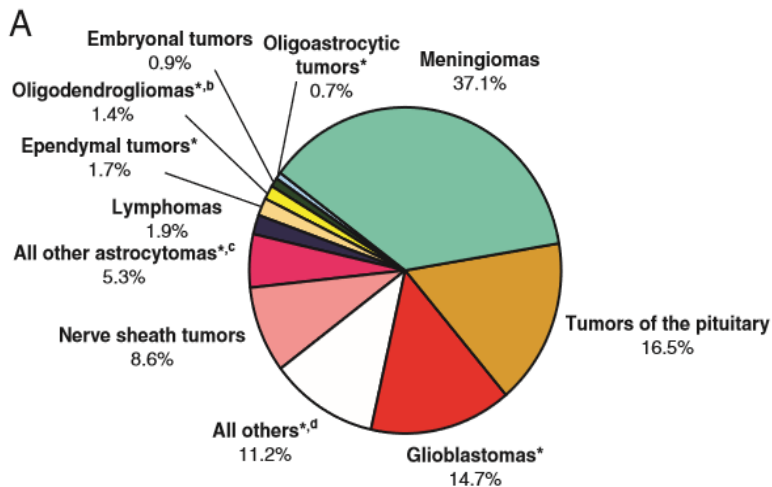**Ad Hoc Working Group on Glioblastoma**
Chair(s): Chi Dang, M.D., Ph.D.
Walter Curran, M.D.

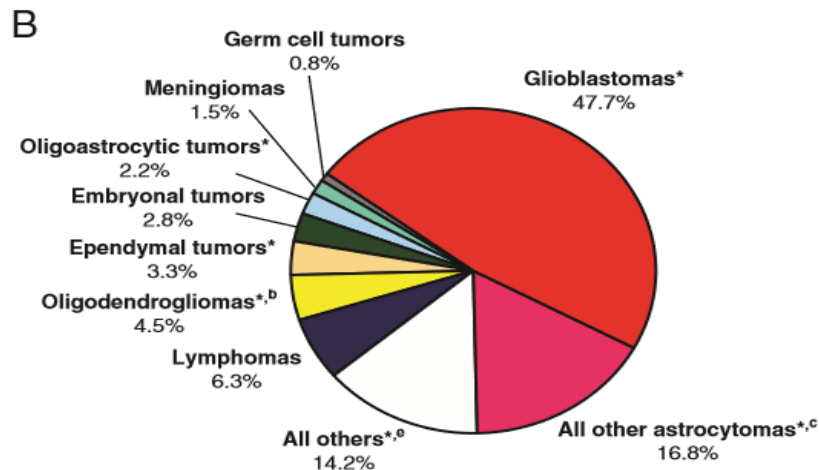# GBM Background & Treatment Challenges

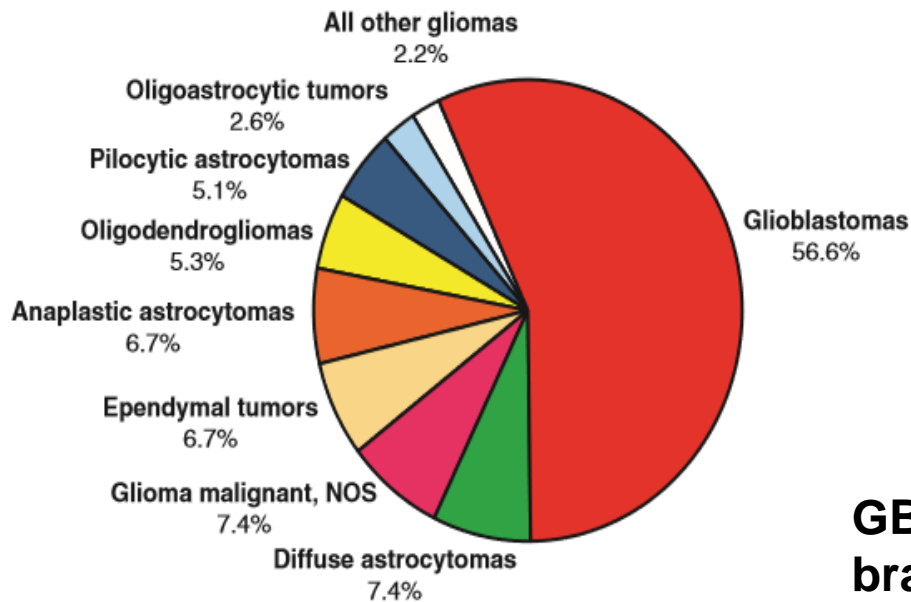# Distribution of Primary Brain and Other CNS Tumors by Histology Groupings and Histology and Behavior

A

Embryonal tumors 0.9%
Oligoastrocytic tumors* 0.7%
Meningiomas 37.1%
Oligodendrogliomas*,b 1.4%
Ependymal tumors* 1.7%
Lymphomas 1.9%
All other astrocytomas*,c 5.3%
Nerve sheath tumors 8.6%
Tumors of the pituitary 16.5%
All others*,d 11.2%
Glioblastomas* 14.7%

Overall

B

Germ cell tumors 0.8%
Meningiomas 1.5%
Glioblastomas* 47.7%
Oligoastrocytic tumors* 2.2%
Embryonal tumors 2.8%
Ependymal tumors* 3.3%
Oligodendrogliomas*,b 4.5%
Lymphomas 6.3%
All others*,e 14.2%
All other astrocytomas*,c 16.8%

Malignant

Ostrom et al., Neuro Oncol. 2018

Distribution of Gliomas by Histology Subtypes

All other gliomas
2.2%

Oligoastrocytic tumors
2.6%

Pilocytic astrocytomas
5.1%

Oligodendrogliomas
5.3%

Anaplastic astrocytomas
6.7%

Ependymal tumors
6.7%

Glioma malignant, NOS
7.4%

Diffuse astrocytomas
7.4%

Glioblastomas
56.6%

Ostrom et al., Neuro Oncol. 2018

GBM is the most common malignant brain tumor, approximately 13,000 new cases diagnosed annually in the U.S.

GBM Treatment Outcomes

- Limited progress has been made in the development of curative therapies in the past half century despite enormous private and public research investment.

- Median survival is approximately 15 months despite aggressive combination chemoradiation therapy following surgical resection.

- 5-year survival rate around 3 percent.

Unique Tumor & Brain Biology

Malignant cells infiltrate locally beyond contrast enhancing tumor.

T1 MRI Image (left): Contrast Enhancing (CE) tumor with a central necrotic area surrounded by a Non-CE abnormality.

T2 MRI Image (right): Non-Contrast Enhancing (NCE) abnormality seen on T1 shows up as a large hyper-intense abnormality.

Contrast Enhancing Component: *In the CE component, blood brain barrier (BBB) is disrupted and neurological function is absent or severely compromised. This is the visible tumor that is resected maximally at surgery and subsequently irradiated.*

Non-Contrast Enhancing Component: *Malignant infiltration extends into the NCE zone. Here the BBB is intact, neurological function is preserved, and ability to resect maximally or obtain a biopsy is often restricted, i.e., neurologically silent vs eloquent brain zones need critical consideration at surgery.*

Tumor cells

Tumor cells and normal neurons
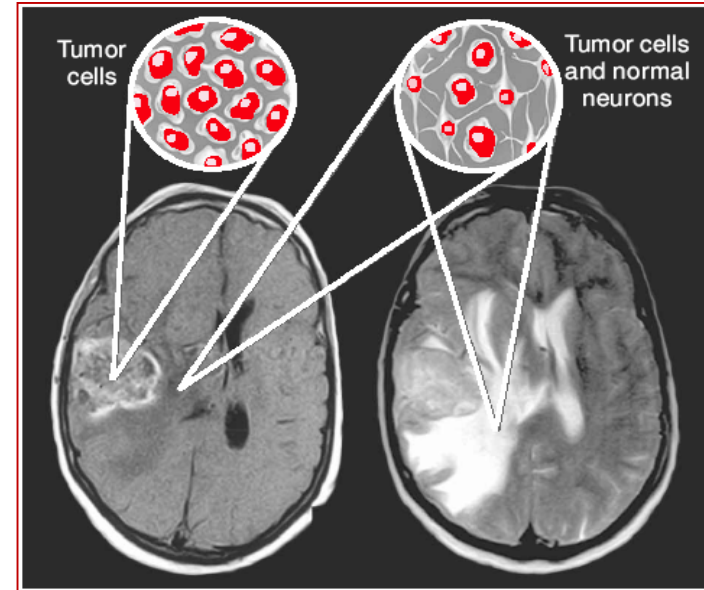
Hentschel and Lang, *The Cancer Journal*, **2003**

Unique Features that Limit Treatment Efficacy

Treatment Limitations

- Surgery: Limit ability to resect to negative surgical margin without compromising neurological and physiological function.

- Radiation Therapy: Normal brain radiation tolerance.

- Drugs: Limited entry across BBB.

- Targeted Agents: Intra- and Inter-tumor genomic heterogeneity.

- Immunotherapy: Microenvironment less amenable to immunotherapy, cold tumor.

Biological Limitations

- Locally infiltrative malignancy without a well defined border.

- Focus has been the CE component, for a treatment to be effective, both CE and NCE components must be treated.

- Presumed that significant treatment failure results from inadequate treatment of the NCE zone.

- Need for accurate assessment of treatment efficacy in the NCE zone.

GBM Therapeutics: Key Considerations

Development of effective GBM therapies will require:

- A better understanding of GBM biology.

- Animal models that recapitulate human disease.

- Rigorous evaluation of drugs at both preclinical and early clinical trial stages.

- A better understanding of therapeutic vulnerabilities and mechanisms of treatment resistance.

- A well-integrated effort from preclinical to clinical.

GBM Working Group

GBM Working Group

- **Goal**: To identify critical research gaps and opportunities to improve the outcomes of patients   with GBM

- **Focus**: Adult GBM Therapeutics

- **Deliverables**: Recommendations for research capabilities and needs that are critical for improving GBM therapeutics

Working Group met on January 14, 2019 following several teleconferences to identify scientific gaps and opportunities to advance treatment for GBM and build on recommendations from several recent meetings: 1) National Brain Tumor Society; 2) US Brain Cancer Mission Roundtable Planning Summit; and 3) NCI CTEP and SPORE meetings.

2019 GBM Working Group Members

Co-Chairs: Walter Curran Jr., MD, FACR and Chi Dang, MD, PhD

Members:

Francis Ali-Osman, DSC

David Arons, JD

Tracy Batchelor, MD, MPH

Melissa Bondy, PhD

Jerry Boxerman, MD, PhD

Timothy Cloughesy, MD

Nancy Davidson, MD

Ira Dunkel, MD

Stuart Grossman, MD

Amy Heimberger, MD

John Sampson, MD, PhD, MBA

Jan Sarkaria, MD

Patrick Wen, MD

Nicole Willmarth, MD

W. K. Alfred Yung, MD

Nicole Willmarth, PhD

***Ex Officio* Members:**

James Doroshow, MD

Kenneth Aldape, MD

Jane Fountain, Ph.D

Mark Gilbert, MD

Bhupinder Mann, MBBS

Margaret Mooney, MD

Jeffery Hildesheim, Ph.D

Katherine Warren, MD

Executive Secretary:

Abdul Tawab Amiri, Ph.D

Process Leading to GBM Working Group Report

- GBM WG in-person meeting (January 14)

- Draft report and recommendations developed by GBM WG

- Summary of draft report presented to TRSS by Drs. Curran and Dang (May 8) and accepted with modifications (July 11)

- Present to CTAC (July 17)

Recommendations

Overarching Recommendations (1)

- Develop a <u>national infrastructure</u> for preclinical testing and qualification of novel therapeutics for patients with GBM that seamlessly integrates with an early phase clinical trials program and leverages existing NCI resources.

- These studies should be driven by molecular pharmacodynamics and guided by current understanding of GBM biology, therapeutic vulnerabilities, and mechanisms of resistance.

Overarching Recommendations (2)

Broad capabilities of the national infrastructure should include:

1. Ability to conduct preclinical qualification studies of new agents targeting GBM.

2. Conduct early phase clinical trials driven by molecular pharmacodynamics and imaging.

3. Development of novel immunotherapy strategies.

4. Approaches to improve radiation sensitivity and overcome radiation resistance.

5. A focus on enhancing the quality of life of patients and family members.

Overarching Recommendations (3)

- Leverage industry support and public-private partnerships in the development of GBM therapeutics.

- Expand the NCI's Cancer Therapeutics Evaluation Program's (CTEP) portfolio of drugs available for preclinical and clinical testing.

- Bridge National Institute of Neurological Disease and Stroke (NINDS) basic neuroscience research with NCI's GBM research.

Capability 1: Preclinical qualification of new agents
Specific Recommendations

Models

- Require replication of preclinical results from cell lines in more representative models such as PDXs GEMMs.
- Support development and use of orthotopic models of brain tumors closely reflecting the biology of tumors.
- Continue incentives for harmonizing and sharing models across research groups.

Drugs

- Expand the CTEP portfolio for pre-clinical testing and access to pharmaceutical grade agents.

Target Validation

- Further development of PK/PD models and biomarkers.
- Assurance of fidelity in translating from preclinical to clinical.

Capability 2: Clinical Trials
Specific Recommendations

- Conduct early phase, proof-of-mechanism clinical studies to demonstrate that drug reaches its molecular target at the required concentration.

- Obtain biopsies of contrast-enhancing and non-contrast-enhancing tumor components, pre- and post- treatment, using standardized protocols.

- Further develop molecular and functional imaging capabilities.

- Foster use of novel clinical trial designs.

- Develop consensus on the threshold of evaluation required to move an agent into clinical trials, i.e., go/no go decisions.

Capability 3: Immunotherapy
Specific Recommendations

- Support mechanistic studies of antigen presentation and processing, immunosuppression and confirmatory animal studies.

- Develop predictive and prognostic biomarkers of response and resistance to immunotherapy.

- Develop imaging methods that can reliably assess immunotherapy response.

- Determine patients' baseline immune status uniformly.

- Better understand the impact of steroids on immune response to checkpoint inhibitors.

Capability 4: Radiation Therapy
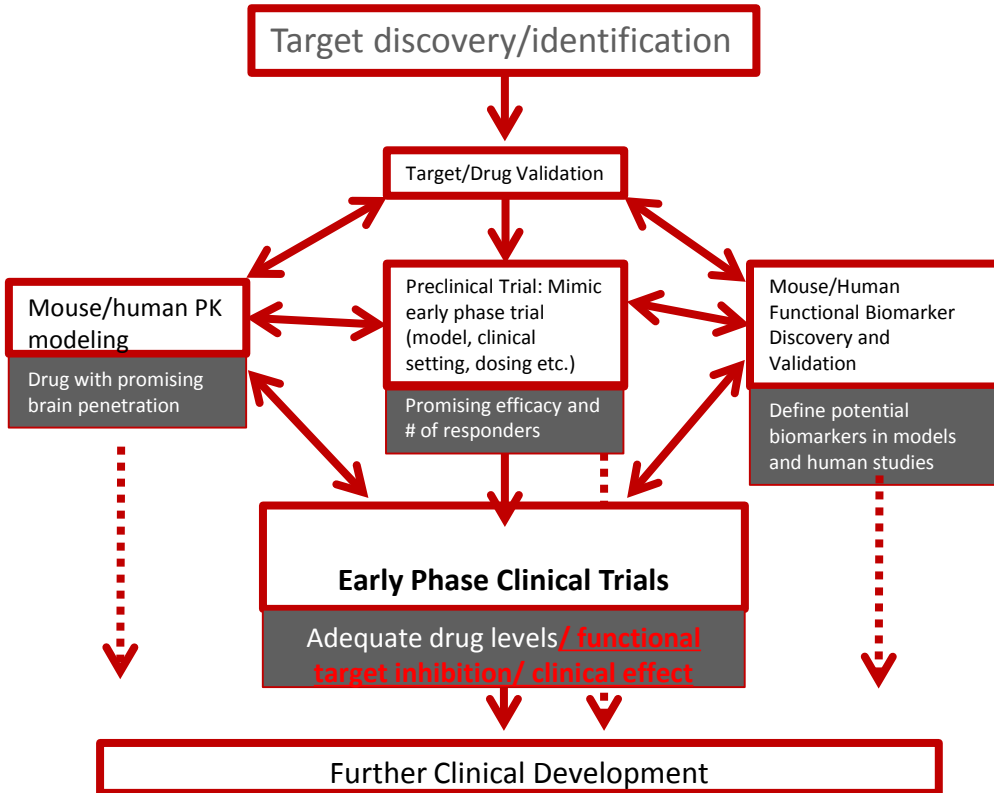## *Specific Recommendations*

- Support research to identify future directions and approaches for RT.

- Assure that a preclinical program integrated with early phase clinical trials networks has the capability to rapidly evaluate and qualify promising RT agents and evaluate neurotoxicity.

- Utilize novel trial designs to conduct early studies rapidly and efficiently.

- Explore and select RT modalities by comparative studies of photon therapy and non-photon therapy.

- Harmonize RT techniques across different radiation platforms to reduce variability.

Capability 5: Quality of Life
Specific Recommendations

- Support QOL research to better understand needs of families and caregivers.

- Develop clinical outcomes assessment tools that include cognitive decline.

- Encourage the incorporation of clinical trials education, evaluation and referral into the standard of care of GBM patients from the first line of treatment forward.

- Evaluate existing longitudinal studies and epidemiological research to update priorities and identify new opportunities.

- Identify strategies for applying novel data science techniques to patient data and improving risk models.

Summary

- Recommendations
  - Address the most important challenges that must be overcome to ensure rapid progress in the development of novel therapeutic strategies for GBM.
  - Lay the groundwork for accelerating progress toward improving the outcome for patients with GBM.

Questions?

www.cancer.gov   www.cancer.gov/espanol