National Cancer Institute
Clinical Trials and Translational Research
Advisory Committee (CTAC)

Glioblastoma (GBM) Working Group

Working Group Report
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NATIONAL CANCER INSTITUTE
CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE (CTAC)

TRANSLATIONAL RESEARCH STRATEGY SUBCOMMITTEE
GLIOBLASTOMA WORKING GROUP (GBM WG)

GBM WORKING GROUP REPORT, JULY 2019

INTRODUCTION

Glioblastoma multiforme (GBM) is the most common type of primary malignant brain tumor in the United States with approximately 13,000 individuals diagnosed annually (1). Limited progress has been made in the development of curative therapies for GBM in the past half century despite enormous private and public research investment. Median survival is only about 15 months despite aggressive combination chemoradiation therapy following surgical resection (2) (3) (4). GBM remains an essentially incurable disease with a 5-year survival rate of approximately 3 percent. Thus, there is an urgent need to develop more effective therapies for this devastating disease.

The NCI convened the Glioblastoma Working Group (GBM WG) of the Clinical Trials and Translational Research Advisory Committee (CTAC) to identify critical research gaps and opportunities to improve the outcomes of patients with GBM. The focus of this group was on adult GBM therapeutics. The GBM WG was co-chaired by Drs. Chi Dang (Ludwig Institute for Cancer Research) and Walter Curran (Winship Cancer Institute of Emory University) and comprised of members with expertise across the neuro-oncology field.

The Working Group met on January 14, 2019 following several teleconferences to identify scientific gaps and opportunities to advance treatment for GBM. The development of effective GBM therapies will require a well-integrated research effort from preclinical to clinical trials. The group identified five broad areas of research capabilities and needs that are important for therapeutics: 1) Preclinical Qualification of New Agents; 2) Clinical Trials Driven by Molecular Pharmacodynamics and Imaging; 3) Immunotherapy; 4) Improving Radiation Sensitivity and Overcoming Radiation Resistance; and 5) Improving the Quality of Life of Patients. Discussion leaders and working group members were identified for each topic area and webinars were held to discuss research needs in advance of the in-person meeting. This report summarizes the WG's deliberations and recommendations for improving the outcomes of patients with GBM.

BACKGROUND AND KEY CONSIDERATIONS

The NCI has been investing in GBM research for decades, but there has been minimal progress in finding a cure or significantly extending survival. Unique to GBM are pathophysiology constraints that impede the development of effective treatments. GBM is a locally infiltrative malignancy without a well-defined border. Malignant infiltration consists of a contrast-enhancing (CE) part on MRI imaging that has a disrupted blood brain barrier (BBB) and has a high density of cancer cells. GBM also contains a non-contrast-enhancing (NCE) component with an intact BBB in which cancer cells intermix with normal brain tissue (5) (6) (7) (8). In many cases the CE portion of the GBM can be surgically resected while the NCE portion does not lend itself to resection. For treatment to be effective, both the CE and NCE components must be treated. Thus, chemotherapy and/or radiotherapy is required in addition to surgery. For chemotherapy to be effective, drugs and other treatment agents must cross the BBB and reach infiltrating GBM cells in both the CE and NCE components in adequate tumoricidal concentrations. Additionally, genetic diversity (intratumoral heterogeneity) is a hallmark of GBM. Differing malignant sub-clones co-exist within the same tumor and are another likely reason behind treatment failure. GBM is highly immunosuppressive and is poorly infiltrated with T-cells that are the therapeutic targets of current therapies (6) (9) (10) (11) (12).

Thus, the development of effective GBM therapies will require a well-integrated effort from preclinical to clinical trials guided by an understanding of GBM biology, therapeutic vulnerabilities, and mechanisms of treatment resistance. While data from integrated drug development efforts can facilitate selection of the most likely drug or drug combinations for testing in phase 2 and 3 clinical trials, leveraging industry support and developing public-private partnerships in this area is essential for making effective progress.

The goals of an integrated NCI effort in GBM therapeutics should be focused on preclinical vetting of candidate agents that might come from industry or academia. This includes animal models, with preclinical imaging, blood-brain barrier pharmacokinetic (PK) determinations, and pharmacodynamic (PD) studies on all agents prior to clinical testing. Pilot studies (phase 1 and early phase 2) should be performed by an integrated clinical arm of this GBM program so that findings can move readily between the preclinical and clinical investigations. The clinical studies should be limited in size, but intense in their translational requirements, utilizing appropriate advanced functional and molecular neuroimaging techniques, and including requirements for baseline and additional biopsies for PK and PD measures. Once an agent is qualified by this new preclinical to early phase clinical trials infrastructure, it is envisioned that larger phase 2 and 3 studies would be mounted using existing NCI trials networks to test the effects of the agent on standard clinical outcome measures. (See Figure 1)

The group identified five broad areas of infrastructure capabilities and research needs deemed essential for such an integrated preclinical to clinical trials effort and made specific recommendations as described in the following sections. There is overlap among these research capabilities and an overall summary of capabilities for an integrated preclinical to clinical NCI effort in GBM therapeutics is provided at the end of the report.

RESEARCH CAPABILITY 1: PRECLINICAL QUALIFICATION OF NEW AGENTS TARGETING GBM

The failure rate of promising agents for GBM in the definitive phase 2 and 3 clinical trials is high. In retrospect, preclinical efforts are often inadequate, and effective new drugs need to be developed from a foundation of well-qualified GBM preclinical models. The testing of drugs found effective in other solid tumors has not been successful for GBM patients. The WG discussed several key aspects of preclinical studies that need close consideration to help decrease late phase clinical failures of seemingly promising agent.

Better Model Systems to Qualify Compounds: When preclinical studies are used to credential an agent for clinical development, leading to clinical trials in which hundreds of patients will be exposed to the risks associated with the new drug, fidelity of the preclinical models is a key consideration. Translational relevance of the preclinical studies is necessary. Using the GBM preclinical model that accurately captures tumor biology in humans is essential. Commonly used tumor cell sources are established glioma cell lines, organoids, patient-derived xenografts (PDXs), and genetically engineered mouse models (GEMMs). Pragmatic considerations when choosing a specific cell source for use in preclinical experiments includes total expense, laboratory experience and expertise, and the availability of specific models.

Established glioma cell lines originally derived from human or murine tumors are convenient to use. Commonly used cell lines (U87, U251, A172, T98G) were originally derived from patient tumors but subsequently have been maintained through extended serial passage in serum-containing media (13). Growth conditions have caused significant molecular drifts and cell lines are poor representatives of primary GBM. Glioma models from cell lines have distinct interactions with the brain microenvironment and have a more disrupted blood-brain barrier than in human GBM. Thus, the WG recommends that preclinical results obtained in glioma cell lines be replicated in more representative GBM models prior to human clinical testing.

Selection of drugs for human clinical trials will be optimized with use of preclinical models that closely reflect human GBM biology. Therefore, development and use of patient-derived xenografts (PDXs) and genetically engineered mouse models (GEMMs) are essential (14) (15). PDX and GEMM models each have specific advantages and liabilities and the existing data do not support the use of one over the other for advancing cancer drug discovery. Patient tumor derived models provide the genetic diversity representative of human glioma and are an excellent system for preclinical studies; glioma driver genomic alterations are preserved, which mimics the human tumor genomics. PDXs and GEMMs both contain brain tumor initiating cells (BTIC), also known as tumor stem cells. Greater research efforts should be invested in developing and using orthotopic models of brain tumors which closely reflect the biology of patients' tumors, including the BBB characteristics and their treatment history. An important shortcoming of current PDX models is the failure to accurately model the complex microenvironment of GBM, which poses particular challenges for testing immune therapeutics especially those that rely on the adaptive arm of the immune system for therapeutic effect. In this case, syngeneic murine xenograft

models can be considered for the initial steps of screening and establishing dose and schedule but a second validating model such as a GEMM or humanized mouse model should be considered. Given their advantages and limitations, PDX and GEMM models can be viewed as complementary platforms for cross-validating the most compelling therapeutic strategies. Focused investments to improve existing preclinical models of GBM hold the promise for accelerating translation. Additionally, leveraging data from canine models, when available, was also considered to be of value.

Efforts need to be made to harmonize and catalogue existing GEMMs. Most major neuro-oncology centers in the United States have collections of PDXs. To reduce barriers to access, the Jackson Laboratories, NCI PDXnet, Mayo Clinic and other groups have widely distributed their models across the neuro-oncology community. Continued support of these programs will ensure use of the most relevant models in neuro-oncology research and drug development.

Improved Selection of Agents for Clinical Development: The first step in selecting a drug for clinical testing is to ensure it has well-validated molecular target(s). This requires an understanding of tumor biology and cell signaling and evaluating the effect of chemical or molecular inhibitors on the related targets. Target discovery is moving towards high-throughput genetics discovery screens. Along with resistance mechanism studies, these screens can be used to develop combination regimens designed to block compensatory signaling that leads to resistance. Further investment in target validation for glioma therapy was felt by the WG to be a highly relevant capacity to support.

Drug formulation is an important consideration. Although compounds can be purchased from chemical companies, specific drug formulations can significantly change the pharmacokinetic behavior of a compound and alter results of preclinical studies. Also, for many validated drug targets such as Epidermal Growth Factor Receptor (EGFR), Mouse Double Minute 2 Homolog (MDM2), and Fibroblast Growth Factor Receptor (FGFR), multiple drugs are available across the pharmaceutical sector. Knowing all available drugs within a target class is a challenge. Identifying drugs that have not yet entered clinical development is especially challenging. Providing a mechanism for working with industry for a comprehensive knowledge of available agents and access to pharmaceutical grade compounds would accelerate brain tumor research.

The blood brain barrier (BBB) is another critical consideration in GBM drug development (6) (8). Surgical biopsy and imaging studies have shown that essentially all GBMs have tumor cells infiltrating the normal brain tissue even in the regions with an intact BBB (non-contrast-enhancing tissue around contrast-enhancing tumor). The BBB may significantly limit the efficacy of otherwise highly effective agents, such as antibodies, nanoparticles, or viruses. Additionally, evaluation of drug exposure in brain and GBM is complex, as non-specific binding of lipophilic drugs within brain or tumor tissue can obfuscate the actual concentration of free drug able to engage the molecular target. Research to understand the limitations of drug delivery into brain tumors and methods to enhance drug delivery of promising biomolecules is needed.

Develop Pharmacokinetic and Pharmacodynamic (PK/PD) Models and Biomarkers: Adequate drug delivery to the relevant target is a basic requirement for drug effect and due to the BBB, a key consideration in GBM. The pharmacokinetics in rodent models may significantly differ from human. Ability to mimic key pharmacokinetic parameters in rodent vs. human may improve translational fidelity. Intratumoral heterogeneity of drug delivery due to limited tissue perfusion and distribution across BBB may limit efficacy in both animal models and human tumors. Acute and chronic adaptive responses to pharmacologic manipulations can also hamper response to therapies. In this context, application of systems biology analyses applied in drug-treated models and patient tumors can provide insight into limitations of a therapy and help develop strategies to enhance therapeutic efficacy.

Translation from Preclinical to Clinical with Assurance of Fidelity—Ensuring Reliability of Preclinical Evidence: Attention to detail is required to design and conduct preclinical studies that will inform in human clinical trials. There was universal agreement in the WG that assessment of preclinical data with regards to models, quality and signal should be performed by experts in the field. Key considerations include the use of appropriate *in vivo* models to validate conclusions of *in vitro* studies. Similarly, while preliminary flank tumor studies are valuable to check the presence of a drug effect, evaluation of treatment efficacy in orthotopic tumor models will be eventually required. Finally, the number of models analyzed, the fraction of responding animals in individual models, and the fraction of responsive models are key considerations in interpreting efficacy. While extensive preclinical data may not be required to support early human trials (e.g. phase 1) as a drug moves into phase 2 and 3 trials, either early promising clinical efficacy signals or more extensive preclinical testing in a panel of PDX or GEMM models can provide key insights for go/no go decisions for clinical development. This is especially important for a new agent being combined with standard of care when clinical response in non-randomized clinical trial cannot be attributed to one or the other treatment. Moreover, adequate testing across genetically diverse GBM models may identify likely predictive biomarkers before launching of a clinical trial. This strategy was used in development of the Alliance A071102 clinical trial (Temozolomide With or Without Veliparib in Treating Patients With Newly Diagnosed Glioblastoma Multiforme) which led to restricting the patient population to O^6-Methylguanine-DNA methyltransferase (MGMT) methylated GBM only, the subset most likely to respond to the study treatment (16).

Specific Recommendations:

- Develop and utilize better model systems for preclinical testing and qualification of novel compounds.
- Require preclinical results in glioma cell lines to be replicated in more representative GBM models such as PDXs and genetically engineered mouse models (GEMMs).
- Support research to develop and use orthotopic models of brain tumors which closely reflect the biology of patients' tumors including the BBB characteristics and their treatment history.
- Continue incentives for harmonizing, cataloguing and sharing models across research groups.
- Improve selection of agents for clinical development through investment in target validation and fostering research related to delivery of novel therapeutics to brain tumors.

- Expand the NCI's Cancer Therapeutics Evaluation Program's (CTEP) portfolio of drugs available for preclinical testing.
- Develop PK and PD models and biomarkers.
- Ensure reliability of preclinical evidence by translating from preclinical to clinical with assurance of fidelity.

RESEARCH CAPABILITY 2: CLINICAL TRIALS DRIVEN BY MOLECULAR PHARMACODYNAMICS AND IMAGING

Clinical trials driven by molecular pharmacodynamics and imaging are essential to the development of effective new therapies. Early phase proof-of-mechanism clinical studies that focus on demonstrating that the therapy reaches its molecular target in the GBM and in the microenvironment are required. These trials rely on accurate molecular pharmacodynamic markers (genomic, transcriptomic, proteomic, metabolic, imaging, and immunologic) of treatment effect. A better understanding of brain tumor biology and enhanced alignment between preclinical drug development and subsequent in human testing are needed. The development of functional markers of treatment effect, using samples from various sources (tumor, blood, CSF) along with metabolic studies, advanced imaging, immune-monitoring and implanted probes could be instrumental in accelerating development of GBM therapies.

A variety of imaging opportunities hold promise including PK evaluation by PET and MRI using radiolabeled drug, metabolic assessment by PET and MRI, tumor microenvironment studies using emerging radiomic techniques and vascular imaging, and response assessment using MRI T1 subtraction. Challenges include standardization of protocols and imaging sequences as well as availability of PET and access to radioactive probes.

Sampling methods to show that drug can cross the blood-brain-barrier (BBB) and reach the target in the appropriate concentration are needed. Repeat biopsies (pre- and post-treatment) are desirable, but surgical suitability of a patient and sample size limitations are important pragmatic issues. Advanced imaging techniques have the potential to provide complementary non-invasive approaches for pharmacodynamic monitoring. Longitudinal monitoring and identification of time and durability of treatment effect, and mechanisms of resistance, are also key considerations for treatment advances in this disease.

GBM tumors are known to contain a mixture of neoplastic cells that differ in terms of genomic composition, state of differentiation and cellular plasticity. This intratumoral heterogeneity likely impacts initial responses to chemical, immunological, and radiation therapies; and likely promotes disease recurrence. The intratumoral heterogeneity in GBM should be carefully evaluated in patient samples and studied in relevant model systems such that more effective treatment strategies for patients can be developed.

Strengthening the GBM clinical program requires addressing both resource and infrastructure constraints and harmonization across different NCI funding mechanisms. Identification of bottlenecks in

existing programs, centralization and coordination of research efforts, and better alignment of processes can inform the development of a program with parallel process and collaboration among various entities to improve efficiency. In addition, the GBM drug development pipeline needs to be expanded to bring more drugs to NCI clinical trials networks. A system for quick responses to actionable findings and streamlining of trials (e.g. by comparing multiple GBM therapies using a single control arm may improve the speed of clinical development). Developing a network with multiple components, including an early phase PK/PD program to evaluate tissue by biomarkers and histology is desirable.

Specific Recommendations:

- Conduct early phase, proof-of-mechanism clinical studies to demonstrate that drug reaches the tumor and its molecular target at the required concentration.
- Obtain clinical biopsies of contrast-enhancing and non-contrast-enhancing tumor components, pre- and post- treatment, using standardized protocols for assessment of genetic evolution and resistance.
- Further develop molecular and functional imaging capabilities including the use and development in preclinical model systems.
- Assure capability for comprehensive molecular characterization (genomic, transcriptomic, proteomic, radiomics, and immunologic) of tumors.
- Foster use of novel clinical trial designs that facilitate movement of agents through the pipeline from preclinical to early phase studies that feed into late phase trials.
- Develop consensus on the evidence threshold required to move an agent into clinical trials, i.e., go/no go decisions.

RESEARCH CAPABILITY 3: IMMUNOTHERAPY

Given the success of immunotherapy in other solid tumors, an investment in understanding its potential as a therapeutic approach for GBM is recommended. The WG discussed several research areas to better understand the potential use of immunotherapy in GBM.

GBM Microenvironment: Natural and iatrogenic immunosuppression is found in nearly 50 percent of GBM patients and persistently low CD4 counts after treatment are associated with poor outcomes. Thus, understanding immunosuppression in the context of the normal brain-GBM microenvironment is critical. A better understanding of antigen presentation and processing, variations in immune surveillance, and genetic and anatomic heterogeneity of immune response is needed to improve efficacy of treatment (6) (10).

Clinical Trials: Early phase studies including window of opportunity and phase zero clinical trials to ascertain if immune functional responses are occurring in the GBM and the microenvironment need to be performed prior to conducting large scale immunotherapy trials. Therapeutic agents need to be rationally selected based on presence of the target and applicability to the GBM patient population. Understanding the impact of steroids on immune response to checkpoint inhibitors should be

addressed. Additionally, uniform determination of patients' baseline immune status through harmonizing variables such as interval and timing of specimen collection for systemic biomarkers will be useful for understanding immunotherapy responses in GBM.

Biomarkers: Development of predictive and prognostic biomarkers of response and resistance to immunotherapy will help optimize treatment efficacy. The ability to predict a therapeutic response and assess immunological clearance of the tumor will likely require interrogation of multiple variables using complex assays (nano-string, poly-ligand profiling, dialysis) rather than single parameter biomarkers. Co-development of companion diagnostics immune therapeutics to enrich for the likely responder population may be the key to advancing GBM immunotherapy.

Immunosuppression: GBM induced and iatrogenic immunosuppression is an important factor to consider in the development of GBM treatments. Studies of mechanisms of immunosuppression including T-cell count and phenotype, mechanisms of T-cell sequestration in the bone marrow of GBM patients (17), and the role of suppressive immune cell populations including macrophages and myeloid suppressor cells, are urgently needed. Similarly, developing and defining appropriate animal models that recapitulate human immunosuppression and recovery are needed to better understand mechanisms of both endogenous and treatment-induced immunosuppression and recovery.

Novel Immunotherapy Approaches: Neoantigen vaccines, checkpoint inhibitors, innate immune cell modulators, chimeric antigen receptors, adoptive immunotherapy, and viral therapy are novel immunotherapy approaches under investigation. Viral therapy is heterogeneous and only a few institutions are conducting clinical trials. Clear evidence that viral therapies can produce an anti-tumor immune response is presently lacking. Defining uniform criteria for efficacy and generating confirmatory data of viral therapies are a critical need. Rational combinations of standard of care agents and efficacious immunomodulators will likely have a therapeutic impact and require further study (18) (19) (20).

Imaging Capabilities for Assessment of Immunotherapy Response: Imaging technologies are currently used in brain tumor immunotherapy with variable results. Immunotherapy Response Assessment in Neuro-Oncology (iRANO) criteria for imaging that include pseudo-response assessment have been developed but are still evolving and need further validation (21). MRI is used for assessing overall response and newer techniques such textural MRI are promising but need appropriately designed studies to determine predictive capability. Radiomics and machine learning to gain additional information from automated approaches to MRI are research opportunities that may prove useful. Use of minibodies (antibody fragments) is promising, but progress has been slow in exploring radio-labeled minibodies to track T-cell migration to tumor.

Specific Recommendations:

- Support for mechanistic studies of antigen presentation and processing, immunosuppression and confirmatory animal studies in the context of brain-GBM microenvironment.

- Conduct early phase clinical trials that ascertain immune functional responses in the GBM and the microenvironment prior to conducting large scale immunotherapy trials and develop predictive and prognostic biomarkers of response and resistance to immunotherapy.
- Immunotherapy agents should be prioritized for study based on applicability and relevance to GBM.
- Better understand the impact of steroids on immune response to checkpoint inhibitors.
- Determine patients' baseline immune status uniformly.
- Bridge National Institute of Neurological Disease and Stroke (NINDS) basic neuroscience research with NCI's GBM research.
- Develop imaging methods that can reliably assess immunotherapy response.

RESEARCH CAPABILITY 4: IMPROVING RADIATION SENSITIVITY AND OVERCOMING RADIATION RESISTANCE

Use of radiation therapy (RT) in newly diagnosed GBM is well-established. RT prolongs the overall survival beyond the maximal surgical resection. Immunological effects of RT as a mechanism of efficacy have become apparent recently and are an area of interest. Radiation biology, especially the immunological effects of radiation, needs to be better understood at the basic level to aid in the understanding of the effects of radiation on GBM and normal brain, as well as the mechanisms of resistance and immunobiology. The discussion of the research needs and opportunities for improving radiation sensitivity and overcoming resistance was divided into three broad categories relevant to radiation therapy: scientific, preclinical, and clinical.

Scientific: There is a need for research to identify future direction and approaches for RT for GBM including new agents for radiosensitivity and novel RT fraction schedules. Discovery studies are needed to assess how to deliver radiation into the brain, the impact of radiation on brain and tumor tissue, and the vulnerability of the brain to radiation damage. Targeting the DNA repair pathway, which has many potential targets to enhance radiosensitivity, may be an effective approach to identifying novel agents to enhance radiosensitivity. Mathematical modeling and other methods to reduce immunosuppression and lymphopenia (e.g. flash radiotherapy delivering the RT dose more rapidly to reduce exposure of cells in circulation to radiation) may aid in the identification of novel RT fraction schedules. Other areas of research identified include the need to improve our understanding of the effect of RT on the BBB, mechanisms of neurotoxicity, and the role of advanced imaging in defining the RT target.

Preclinical: There is a need for an efficient preclinical program that is closely integrated with early phase clinical trials networks to rapidly evaluate and qualify promising RT agents. A systematic preclinical approach to the evaluation of RT agents (e.g. DNA repair agents) is critical to the identification of candidates to advance to the clinic. The program should have the capability to evaluate combinations of RT and immunotherapy. Additionally, preclinical studies to evaluate neurotoxicity of RT and strategies to mitigate these are needed.

Clinical: An efficient early-phase clinical trials program that translates promising preclinical findings into proof-of-mechanism clinical trials that determine the recommended phase 2 dose is needed. Novel clinical trial design strategies would help conduct early studies more rapidly and efficiently. For example, phase 1 studies of novel agents with RT using current 3+3 phase 1 designs are particularly time-consuming given the 8 to 10-week dose limiting toxicity evaluation period (22). Consideration of adaptive designs for randomized phase 2 studies with multiple arms sharing one control arm (similar to Individualized Screening Trial of Innovative Glioblastoma Therapy (23) (24) or GBM Adaptive Global Innovative Learning Environment (GBM AGILE)) may improve efficiency and accelerate development of novel therapies (25). Clinical questions include optimal RT schedules, RT combination with targeted agents and immunotherapies, and comparisons of photon and non-photon therapies. Harmonization of RT techniques across different radiation platforms would help reduce variability in clinical trials.

Specific Recommendations:

- Support research to Identify future directions and approaches for RT for GBM. Recommendations for research include:
    - Identify new agents for enhancing GBM radiation sensitivity (e.g. targeting DNA repair pathway).
    - Ascertain new fractionation schedules (using mathematical modeling and other methods) to reduce immunosuppression and lymphopenia, e.g., flash radiotherapy delivering the RT dose more rapidly to reduce exposure of cells in circulation to radiation.
    - Better understand RT effects on GBM immune microenvironment and immune system as well as abscopal and synergistic effects to develop more effective combinations of radiation and immunotherapy.
    - Investigate RT effects on the BBB with focus on the impact of barrier disruption on drug entry.
    - Develop and utilize advanced imaging methods for defining RT targets.
    - Reduce radiation neurotoxicity by studying different mitigation strategies (e.g. fractionation, to improve the neurocognitive function and quality of life after RT).

- Assure that a preclinical program integrated with early phase clinical trials networks has the capability to rapidly evaluate and qualify promising RT approaches and evaluate neurotoxicity.
- Utilize novel clinical trial design strategies to conduct early studies more rapidly and efficiently.
- Explore and select radiation modalities by comparative studies of photon therapy and non-photon therapy.
- Harmonize RT techniques across different radiation platforms to reduce variability.
- Facilitate the efficient transition from early phase programs to phase 2 and 3 clinical trials networks.

RESEARCH CAPABILITY 5: IMPROVING THE QUALITY OF LIFE OF PATIENTS

The working group discussed several research areas to improve the outcome and quality of life for GBM patients and their caregivers.

Family and Caregiver Quality of Life: Patients with GBM face a traumatic, physically and emotionally debilitating disease that remains incurable. There is a paucity of research on the impact of the disease and its treatment sequelae on family members and caregivers. There is an opportunity to improve the quality of life of patients, families, and caregivers by investing in research to better understand their support needs.

Patient Reported Outcomes Assessment: To assess care as well as efficacy in clinical trials, it is important to collect standardized data on patient reported outcomes, including cognitive decline. Collecting data using standardized methods is critical for its usefulness. Innovation is needed in the methods of collection, such as digital tools and wearable devices, for domains relevant to GBM and important to patients, researchers, and sponsors.

Improving Patient Access to Trials: Enrollment in cancer clinical trials is suboptimal with less than 5 percent of patients with cancer participating in clinical trials. Current guidelines for treatment of newly diagnosed patients with GBM recommend the consideration of clinical trials as an adjuvant therapy treatment option (NCCN Guidelines V) (26). Thus, access to clinical trials is critical for improving the outcome of GBM patients. Strategies to improve trial enrollment and improve acceptability of innovative therapeutic approaches in the newly diagnosed setting are needed. Clinical trials education, evaluation and referral as appropriate, should be incorporated into the standard of care of GBM patients from the first line of treatment forward.

Improving Tissue Sampling and Access to Biospecimens: Improving tissue sampling, collection, and access to biospecimens is critical for the translational research that is essential to advance GBM therapy. Research to improve neuro-surgical techniques and patient acceptance of tissue sampling will help. Patients seeking treatment for GBM may be seen at multiple hospitals often resulting in difficulty accessing their biospecimens.

Improving Collection and Use of Patient Data: Data collected about patients and their specimens is fragmented across many community and research institutions. New opportunities in data collection and analysis such as application of artificial intelligence and machine learning to mine data should be explored. Requests for patients and families to give their data abound without clear direction. Better organization and coordination to reduce duplication and maximize knowledge gained is needed.

Developing Better Risk Models: Opportunities exist to improve knowledge of the risk factors for susceptibility to GBM and determinants of prognosis, survival, cognitive impairment, and quality of life through epidemiological studies building on existing studies and incorporating genetics, imaging (radiomics, metabolic imaging, and connectomics/brain network connectivity, etc.) and other information that can be garnered through artificial intelligence and machine learning. A workshop with

key stakeholders in brain tumor and cancer patient data collection should be convened to identify strategies for applying novel data science techniques to patient data and improving risk models.

Specific Recommendations:

- Support quality of life research to better understand needs of families and caregivers of patients with GBM.
- Develop clinical outcomes assessment tools that include cognitive function status.
- Identify strategies to improve trial enrollment and improve acceptability of innovative therapeutic approaches in the newly diagnosed setting.
- Encourage the incorporation of clinical trials education, evaluation and referral as appropriate into the standard of care of GBM patients from the first line of treatment forward.
- Support research to advance neuro-surgical techniques, technologies, and trials designs to better enable tissue sampling.
- Identify strategies for applying novel data science techniques to patient data and improving risk models.
- Evaluate existing longitudinal studies and epidemiological research to update priorities and identify new opportunities.

OVERARCHING RECOMMENDATIONS

- Develop a national infrastructure 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. Support for longitudinal collection of biospecimens, including tumor tissue, blood, and CSF for multi-omic analyses is recommended. Studies should be driven by molecular pharmacodynamics and guided by current understanding of GBM biology, therapeutic vulnerabilities, and mechanisms of resistance.

  Broad capabilities of this infrastructure should include:

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

- 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.

SPECIFIC RECOMMENDATIONS FOR INFRASTRUCTURE CAPABILITIES AND RESEARCH NEEDS

1. Preclinical

- Develop and utilize better model systems for preclinical testing and qualification of novel compounds.
- Require preclinical results in glioma cell lines to be replicated in more representative GBM models such as patient-derived xenografts (PDXs) and genetically engineered mouse models (GEMMs).
- Support research to develop and use orthotopic models of brain tumors which closely reflect the biology of patients' tumors including the blood brain barrier (BBB) characteristics and their treatment history.
- Continue incentives for harmonizing, cataloguing and sharing models across research groups.
- Improve selection of agents for clinical development through investment in target validation and fostering research related to delivery of novel therapeutics to brain tumors.

- Expand the NCI's Cancer Therapeutics Evaluation Program's (CTEP) portfolio of drugs available for preclinical testing.
- Develop pharmacokinetic and pharmacodynamic (PK/PD) models and biomarkers.
- Ensure reliability of preclinical evidence by translating from preclinical to clinical with assurance of fidelity.

2. Clinical Trials

- Conduct early phase, proof-of-mechanism clinical studies to demonstrate that drug reaches the tumor and its molecular target at the required concentration.
- Obtain clinical biopsies of contrast-enhancing and non-contrast-enhancing tumor components, pre- and post- treatment, using standardized protocols for assessment of genetic evolution and resistance.
- Further develop molecular and functional imaging capabilities including the use and development in preclinical model systems.
- Assure capability for comprehensive molecular characterization (genomic, transcriptomic, proteomic, radiomics, and immunologic) of tumors.
- Foster use of novel clinical trial designs that facilitate movement of agents through the pipeline from preclinical to early phase studies that feed into late phase trials.
- Develop consensus on the evidence threshold required to move an agent into clinical trials (i.e. go/no go decisions).

3. Immunotherapy

- Support for mechanistic studies of antigen presentation and processing, immunosuppression and confirmatory animal studies in the context of brain-GBM microenvironment.
- Conduct early phase clinical trials that ascertain immune functional responses in the GBM and the microenvironment prior to conducting large scale immunotherapy trials and develop predictive and prognostic biomarkers of response and resistance to immunotherapy.
- Immunotherapy agents should be prioritized for study based on applicability and relevance to GBM.
- Better understand the impact of steroids on immune response to checkpoint inhibitors.
- Determine patients' baseline immune status uniformly.
- Bridge National Institute of Neurological Disease and Stroke (NINDS) basic neuroscience research with NCI's GBM research.
- Develop imaging methods that can reliably assess immunotherapy response.

4. Radiation Therapy

- Support research to Identify future directions and approaches for RT for GBM. Recommendations for research include:

    - Identify new agents for enhancing GBM radiation sensitivity (e.g. targeting DNA repair pathway).

- Ascertain new fractionation schedules (using mathematical modeling and other methods) to reduce immunosuppression and lymphopenia, e.g., flash radiotherapy delivering the RT dose more rapidly to reduce exposure of cells in circulation to radiation.
- Better understand RT effects on GBM immune microenvironment and immune system as well as abscopal and synergistic effects to develop more effective combinations of radiation and immunotherapy.
- Investigate RT effects on the BBB with focus on the impact of barrier disruption on drug entry.
- Develop and utilize advanced imaging methods for defining RT targets.
- Reduce radiation neurotoxicity by studying different mitigation strategies (e.g. fractionation) to improve the neurocognitive function and quality of life after RT.

- Assure that a preclinical program integrated with early phase clinical trials networks has the capability to rapidly evaluate and qualify promising RT approaches and evaluate neurotoxicity.
- Utilize novel clinical trial design strategies to conduct early studies more rapidly and efficiently.
- Explore and select radiation modalities by comparative studies of photon therapy and non-photon therapy.
- Harmonize RT techniques across different radiation platforms to reduce variability.
- Facilitate the efficient transition from early phase programs to NCI phase 2 and 3 clinical trials networks.

5. Quality of Life

- Support quality of life research to better understand needs of families and caregivers of patients with GBM.
- Develop clinical outcomes assessment tools that include cognitive function.
- Identify strategies to improve trial enrollment and improve acceptability of innovative therapeutic approaches in the newly diagnosed setting.
- Encourage the incorporation of clinical trials education, evaluation and referral as appropriate into the standard of care of GBM patients from the first line of treatment forward.
- Support research to advance neuro-surgical techniques, technologies, and trials designs to better enable tissue sampling.
- Identify strategies for applying novel data science techniques to patient data and improving risk models.
- Evaluate existing longitudinal studies and epidemiological research to update priorities and identify new opportunities.

CONCLUSION

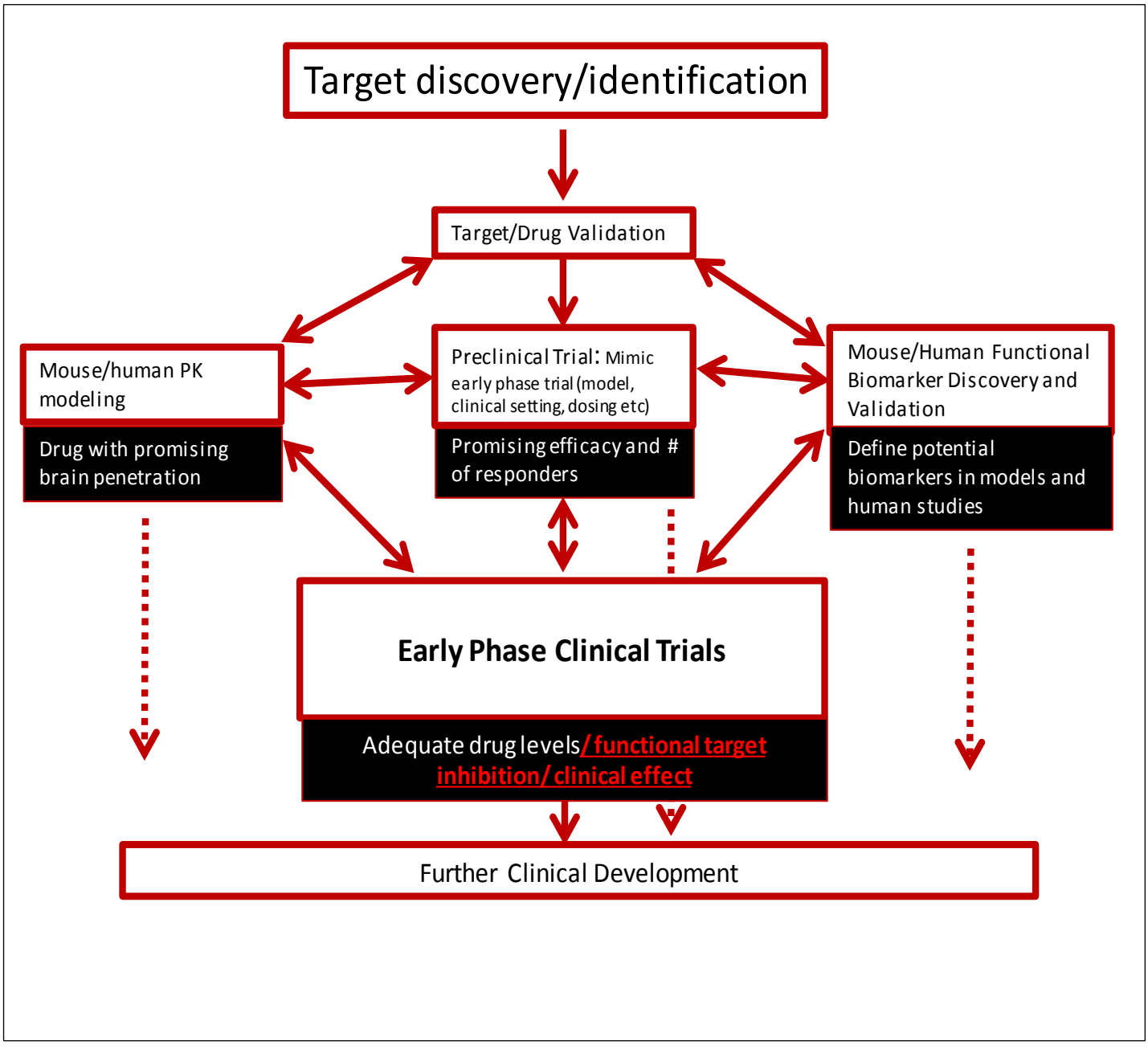
NCI's current research infrastructure lacks multiple drug development capabilities required for development of effective treatment for GBM. Based on the past 20 years of experience it seems clear that unless agents are rigorously evaluated mechanistically at both preclinical and early clinical trial stages, it is unlikely that the poor track record for development of active GBM agents will be reversed. An adequate and efficient program, capable of preclinical and clinical evaluation of CNS-penetrating drugs is required to qualify new agents for GBM clinical trials. The program should have the capability to test agents in small, early phase clinical trials that are focused on PK, PD, and molecular characterization of the tumor and microenvironment, with intensive imaging and tissue correlates as well as tissue sampling. There is also a need for resource intensive surgical and imaging pharmacodynamic studies in human. Leveraging existing NCI resources (e.g., the Cancer Immune Monitoring and Analysis Centers, etc.) to support implementation of these recommendations is encouraged. The consensus of the WG is that additional resources are needed to bridge the gap in translating biological understanding of GBM vulnerabilities into the development of effective treatments.

Leveraging industry support and the development of public-private partnerships would assist in the development of GBM specific agents. Industry has not invested specifically in developing agents tailored to the issues involved in achieving effective drug concentrations in the CNS with a focus on GBM. The reasons for this are multiple, including the relative rarity of GBM and the long history of negative clinical trials using novel agents in this disease. A NCI-funded, national infrastructure for preclinical testing and qualification of novel therapeutics that seamlessly integrates with early phase clinical trials driven by molecular pharmacodynamics could help to de-risk the effort and leverage industry support. It may also carry the potential for development as a public-private partnership, with the goal of bringing much more highly qualified compounds into the clinic for patients with GBM. The output of this effort is also likely to significantly enhance NCI's late stage clinical research programs in GBM, such as those supported by the NCTN, as well as the disease-based discovery investigations funded by several brain tumor Specialized Programs of Research Excellence (SPORE) grants.

This report outlines a series of recommendations that could be instrumental in addressing the most important challenges that must be overcome to ensure rapid forward progress in the development of novel therapeutic strategies for GBM. Although not exhaustive, this series of recommendations can lay the ground for accelerating progress toward improving the outcome for patients with GBM.

FIGURE 1

Figure 1: Framework for seamless integration of pre-clinical testing and early clinical trial testing to provide robust set of information to base decisions regarding further clinical development.



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APPENDICES – SUPPLEMENTAL RESOURCES

Appendix 1: GBM Working Group Roster

Appendix 2: GBM Working Group January 14, 2019 Meeting Agenda

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute
Clinical Trials and Translational Research Advisory Committee

Ad hoc Working Group on Glioblastoma

CO-CHAIR
Walter J. Curran, Jr., M.D., F.A.C.R.
Executive Director
Winship Cancer Institute of Emory University
Atlanta, Georgia

CO-CHAIR
Chi V. Dang, M.D., Ph.D.
Scientific Director
Ludwig Institute for Cancer Research, New York
Professor, The Wistar Institute
Philadelphia, Pennsylvania

MEMBERS

Francis Ali-Osman, D.Sc.
Margaret Harris and David Silverman
Distinguished Professor of Neuro-Oncology Research
Professor of Surgery
Professor of Pathology
Department of Surgery and Pathology
Duke University Medical Center
Durham, North Carolina

David F. Arons, J.D.
Chief Executive Officer
National Brain Tumor Society
Watertown, Massachusetts

Tracy T. Batchelor, M.D., M.P.H.
Giovanni Armenise - Harvard Professor of Neurology
Harvard Medical School
Executive Director
Stephen E. and Catherine Pappas Center for Neuro-Oncology
Massachusetts General Hospital
Boston, Massachusetts

Melissa L. Bondy, Ph.D.
Professor and Associate Director Department of Medicine
Dan L. Duncan Comprehensive Cancer Center Baylor College of Medicine
Houston, Texas

Jerrold Boxerman, M.D.
Associate Professor of Diagnostic Imaging
The Warren Alpert Medical School
Medical Director
Brain Science Program MRI Research Facility Brown University
Providence, Rhode Island

Timothy F. Cloughesy, M.D.
Director
Neuro-Oncology
Program Professor of Neurology
University of California, Los Angeles Los Angeles, California

Nancy E. Davidson, M.D.
Senior Vice President, Director and Full Member
Clinical Research Division
Fred Hutchinson Cancer Research Center
President & Executive Director
Seattle Cancer Care Alliance
Head, Division of Medical Oncology
Department of Medicine
University of Washington
Seattle, Washington

Ira J. Dunkel, M.D. Professor of Pediatrics Department of Pediatrics Weill Cornell Medical College
Memorial Sloan Kettering Cancer Center
New York, New York

Stuart A. Grossman, M.D.
Co-Director
Brain Cancer Research Program
Professor of Oncology
Johns Hopkins Sidney Kimmel Comprehensive Cancer Center
John Hopkins University
Baltimore, Maryland

Amy B. Heimberger, M.D.
Professor
Department of Neurosurgery
The University of Texas MD Anderson Cancer Center
Houston, Texas

John H. Sampson, M.D., Ph.D., M.B.A.
Robert H., M.D. and Gloria Wilkins Professor of Neurosurgery
Chair
Department of Neurosurgery
Duke Cancer Center Durham,
North Carolina

Jann N. Sarkaria, M.D.
Professor
Department of Radiation Oncology
Mayo Clinic
Rochester, Minnesota

Patrick Y. Wen, M.D. Professor of Neurology
Harvard Medical School Director
Center for Neuro-Oncology
Dana-Farber Cancer Institute
Boston, Massachusetts

Nicole Willmarth, Ph.D.
Chief Science Officer
American Brain Tumor Association
Chicago, Illinois

W.K. Alfred Yung, M.D.
Professor
Department of Neuro-Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Ex Officio Members

Jeffrey S. Abrams, M.D.
Acting Director for Clinical Research
Associate Director
Cancer Therapy Evaluation Program
Division of Cancer Treatment and Diagnosis
National Cancer Institute
National Institutes of Health
Bethesda, Maryland

Kenneth D. Aldape, M.D.
Chief
Laboratory of Pathology
Center for Cancer Research
National Cancer Institute
National Institutes of Health
Bethesda, Maryland

James H. Doroshow, M.D.
Deputy Director
Clinical and Translational Research
Director
Division of Cancer Treatment and Diagnosis
National Cancer Institute
National Institutes of Health
Bethesda, Maryland

Jane W. Fountain, Ph.D.
Program Director, Neural Environment
Division of Neuroscience
National Institute of Neurological Disorders and Stroke
National Institutes of Health
Rockville, Maryland

Mark Gilbert, M.D.
Chief
Neuro-Oncology Branch
Center for Cancer Research
National Cancer Institute
National Institutes of Health
Bethesda, Maryland

Jeffrey Hildesheim, Ph.D.
Chief
Tumor Biology and Microenvironment
Branch Division of Cancer Biology
National Cancer Institute
National Institutes of Health
Bethesda, Maryland

Bhupinder S. Mann, M.D.
Head
Genitourinary and Brain Cancer Therapeutics
Cancer Therapy Evaluation Program
National Cancer Institute
National Institutes of Health
Bethesda, Maryland

Katherine E. Warren, M.D.
Senior Investigator
Pediatric Oncology Branch
Center for Cancer Research
National Cancer Institute
National Institutes of Health
Bethesda, Maryland

Executive Secretary

Abdul Tawab Amiri, Ph.D.
Program Director
Coordinating Center for Clinical Trials
National Cancer Institute
National Institutes of Health
Bethesda, Maryland

Clinical Trials and Translational Research Advisory Committee
Ad hoc Working Group on Glioblastoma

AGENDA
Face-To-Face Meeting
Monday, January 14, 2019
NIH Main Campus, Natcher E1/E2
8:30 AM – 4:30 PM ET

8:30 – 8:40	Welcome and Introductions	Drs. Curran and Dang
8:40 – 9:00	Review of Meeting Goal	Dr. Doroshow
SUBGROUP SESSIONS		
9:00 – 10:00	Subgroup 1: Preclinical Qualification of New Agents Targeting GBM	Drs. Sarkaria and Ali-Osman Subgroup Participants
10:00 – 10:15	Break	
10:15 – 11:45	Subgroup 2: GBM Clinical Trials Driven by Molecular Pharmacodynamics and Imaging	Drs. Cloughesy, Batchelor and Boxerman Subgroup Participants
11:45 – 12:45	Subgroup 3: Immunotherapy for GBM	Drs. Heimberger and Sampson Subgroup Participants
12:45 – 1:30	Lunch Break	
1:30 – 2:30	Subgroup 4: Improving Radiation Sensitivity and Overcoming Radiation Resistance for Patients with GBM	Drs. Curran and Wen Subgroup Participants
2:30 – 3:30	Subgroup 5: Improving the Quality of Life of Patients with GBM?	Dr. Bondy and Mr. Arons Subgroup Participants
3:30 – 4:30	Final Recommendations and Conclusion	Drs. Curran and Dang
4:30	Adjourn	