Brain Malignancies Steering Committee (BMSC)

Clinical Trials Planning Meeting (CTPM)

Improving the Treatment of Glioblastoma

Udvar-Hazy Center - Chantilly, Virginia, September 19-20,

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Introduction

The National Cancer Institute (NCI) Brain Malignancy Steering Committee (BMSC) convened a Clinical Trials Planning Meeting, co-sponsored by Accelerating Brain Cancer Cure (ABC^2), to develop strategies for improving the treatment of glioblastoma. The meeting was held at the Udvar-Hazy Center in Chantilly, Virginia on September 19th and 20th, 2013. Meeting attendees included BMSC members, clinicians, clinical trials experts, biostatisticians, translational scientists, health-related quality of life scientists, patient advocates, and NCI staff.

Background

Glioblastoma is the most common primary brain malignancy and is associated with poor prognosis despite aggressive local and systemic therapy associated with a paucity of viable treatment options in both the newly diagnosed and recurrent settings. Even so, the rapidly advancing immunotherapy strategies as well as the increasing number of targeted therapies being evaluated in oncology clinical trials offer hope for the future. Given the broad range of possibilities for future trials, the Brain Malignancy Steering Committee and ABC^2 organized this meeting in order to translate advances in both immunotherapy and targeted therapies into concepts for clinical trials in glioblastoma.

The objectives and goals of the meeting were to:

1. Bring together leading academicians, clinicians, industry and government representatives to identify challenges and potential solutions in the clinical development of novel immunotherapy and targeted therapies for glioblastoma
2. Frame the clinical and translational questions that are of highest priority
3. Develop two clinical trial designs focusing on immunotherapy and signal transduction modulation
4. Publish summary report from the meeting

The meeting approached these core issues in five sessions over a day and a half. The first session covered an overview of genomics of GBM, novel adaptive trials and therapeutic opportunities.
The second session focused on immunotherapy by addressing T cell immunomodulatory approaches, challenges in response assessment including imaging and pseudoprogression, as well as monitoring of immune related toxicities.
The third session addressed regulatory topics as well as industry aspects of trials in glioblastoma.
The final two sessions focused on personalized medicine and on designing two clinical trials based on immunotherapy and on signal transduction modulation, respectively.

Consensus and recommendations

The group thought that future clinical screening trials of targeted therapies should be able to consider multiple therapeutic hypotheses simultaneously, incorporate robust control arms, and maximize the efficiency of control arms through the use of multiple experimental arms. There was also a consensus that, given the wealth of molecular data available for GBM, molecularly defined subgroups be considered in some fashion.

Extensive discussion on biomarkers, endpoints, and trial design lead to recommendations for considering a biomarker-enriched adaptive trial for screening targeted molecular therapies for patients with GBM.

Proposed

Targeted therapy trial

The Targeted Therapies Working Group proposed a multi-arm, adaptively randomized, controlled, screening trial for both biomarkers and targeted therapies, with the goal of providing robust biomarker/targeted therapy hypotheses to bring forward to phase III confirmatory trials. Patients with newly diagnosed GBM with an unmethylated MGMT promoter, an adequate performance status, and sufficient tumor size….. Randomization would include a safety run-in period for each arm, but then adapt to preferentially randomize patients from pre-specified biomarker signatures to treatment arms that showed evidence of efficacy.

Following the initial equal randomization phase, the model will preferentially enroll patients from biomarker signature subgroups preferentially to those arms that are showing evidence of efficacy. This will initially be based on overall survival, but could eventually use other data that is found to be correlated with survival as the trial matures such as PFS. When treatment arm/biomarker combination have reached pre-specified levels of probability of success or failure in phase III studies, these combinations will either graduate or drop from the study.

Molecular targets prioritized by the group were: EGFR amplification and/or mutation, PI3 kinase activation, cell cycle, and the p53 axis.

Biomarker evaluation in this study will be conducted in a hypothesis-driven exploratory manner.

Tumor tissue will be centrally reviewed and initially assayed for known prognostic factors MGMT promoter methylation and IDH1 R132H mutation. Patients will be eligible if they have unmethylated MGMT promoters and are IDH1 R132H negative. The primary endpoint of the study will be the predictive probability of success in a phase III study based on overall survival. During the course of the study, other parameters such as progression and performance status will be analyzed for association with survival and should there be a linkage, the model would incorporate this information to allow for even more efficient randomization.

This Executive Summary presents the consensus arising from the CTPM. These recommendations are not meant to address all clinical contexts, but rather represent priorities for publicly funded clinical research.