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Brain Malignancy Steering Committee clinical trials planning workshop: Report from the Targeted Therapies Working Group

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Glioblastoma is the most common primary brain malignancy and is associated with poor prognosis despite aggressive local and systemic therapy, which is related to a paucity of viable treatment options in both the newly diagnosed and recurrent settings. Even so, the rapidly increasing number of targeted therapies being evaluated in oncology clinical trials offers hope for the future. Given the broad range of possibilities for future trials, the Brain Malignancy Steering Committee convened a clinical trials planning meeting that was held at the Udvar-Hazy Center in Chantilly, Virginia, on September 19 and 20, 2013. This manuscript reports the deliberations leading up to the event from the Targeted Therapies Working Group and the results of the meeting.

Keywords: adaptive randomization, biomarkers, clinical trials, glioblastoma.

Glioblastoma is associated with poor prognosis and there are limited viable treatment options in both the newly diagnosed and recurrent settings.[1,2] The current clinical trial environment for targeted therapies is shaped by many possibilities: numerous targets, various drugs for any given target, molecularly defined subgroups, and combinations of drugs. These possibilities combine to form a myriad of therapeutic hypotheses, and the mechanisms for prioritizing these hypotheses are largely qualitative or based on preclinical models that have ambiguous predictive capabilities. In addition to the difficulties with preclinical models, "positive" early phase clinical trial results infrequently progress to successful registration trials, largely due to questionable endpoints or lack of effective control arms. For these reasons, future clinical screening trials of targeted therapies should incorporate multiple therapeutic hypotheses simultaneously, incorporate robust control arms, and maximize the efficiency of control arms through the use of multiple experimental arms. Given the wealth of molecular data available for glioblastoma (GBM), molecularly defined subgroups should be considered for specific therapies in some capacity. The topics that drove the deliberations of the Targeted Therapies Working Group—biomarkers, endpoints, and trial design—will be discussed below, followed by a summary of recommendations that culminated in a clinical trial proposal for screening targeted molecular therapies in glioblastoma patients.

Discussion Topics

Biomarkers

From a diagnostic and treatment perspective, glioblastoma is no longer considered one homogeneous disease. Advances in genetic, epigenetic, gene expression, metabolomic, and other profiling technologies have rapidly been applied to GBM to classify the disease into several different, molecularly defined subtypes.[3–9] Such groupings may have direct relevance to diagnostics, prognosis, and the application of targeted therapy. Currently, *MGMT* promoter methylation and *IDH1* mutation

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status are routinely used as prognostic[10–12] or predictive[13,14] biomarkers in GBM with some success. Therapeutics directed at precise molecular targets logically lead to hypothetical interactions with alterations in tumor signaling pathways based on the available models or "wiring diagrams." The hope for these interactions is 2-fold: first, that there is an advantageous therapeutic index generated by the interaction, and second, that prospective identification of biomarker-based subgroups can lead to more efficient trials by separating signal from noise. Despite the promise and success in other cancers, the strength of evidence supporting an interaction of targeted therapies with specific molecular abnormalities in GBM to date has been limited, variable, and inconsistent, potentially due to a lack of trials attempting to identify biomarkers of the most relevant subgroups for study.

With respect to clinical trial design and efficiency, conducting a biomarker-enriched study has several benefits, the degree of which depend both on the frequency of marker-positive subgroups and the relative effect size in the biomarker-positive versus biomarker-negative groups. For example, if a biomarker subgroup comprises 75% of the population and the negative subgroup still has 50% of the treatment effect of the marker-positive subgroup, then only small efficiency gains are seen (sample size ratio of 1.3x).[15] However, if the biomarker-positive subgroup comprises only 25% of the population and the biomarker group has no treatment effect, then 16 times fewer patients are required for similar trial-operating characteristics.[15]

Prognostic Versus Predictive Biomarkers

Identifying and leveraging molecular subgroups requires developing assays that can be used as predictive biomarkers while acknowledging the potential for such biomarkers to also have prognostic capacity. A prognostic-only biomarker is one that stratifies patients into groups with clinically distinct outcomes, independent of an interaction with a specific treatment. Predictive biomarkers define subgroups that are more likely to respond to a specific therapy and are thus valuable for both clinical trials and clinical practice. Randomized studies with control arms are necessary for determining whether a specific biomarker is prognostic or predictive. This relationship is illustrated in Fig. 1. In order to know the nature of the biomarker/therapeutic interaction, all boxes of the 2×2 table must be known. The numbers in this simplified example could represent median survival for patients with newly diagnosed GBM. The case in the top row would be a single-arm trial in a selected biomarker population. Adding a control arm, but keeping only biomarker-selected groups, provides the information in the left column of the boxes. However, this is not enough to determine whether the marker is predictive, prognostic, or neither in most cases, as can be seen from the examples in the bottom row. This relationship can only be distinguished reliably when all boxes are filled in both biomarker groups and there is a control arm.

Selection of Biomarker-defined Groups

The selection of relevant biomarker-defined subgroups was another important topic of discussion. There are now many accessible, standardized, and relatively inexpensive multiplexed biomarker assays that can be used to define molecular subsets including transcriptional,[4,7] genomic,[6] and epigenomic.[3] It was quickly decided that the molecular analysis in clinical trials should be conducted using multiplexed assays that can assess multiple molecular eligibility criteria while generating additional data that can be mined for exploratory studies after the study

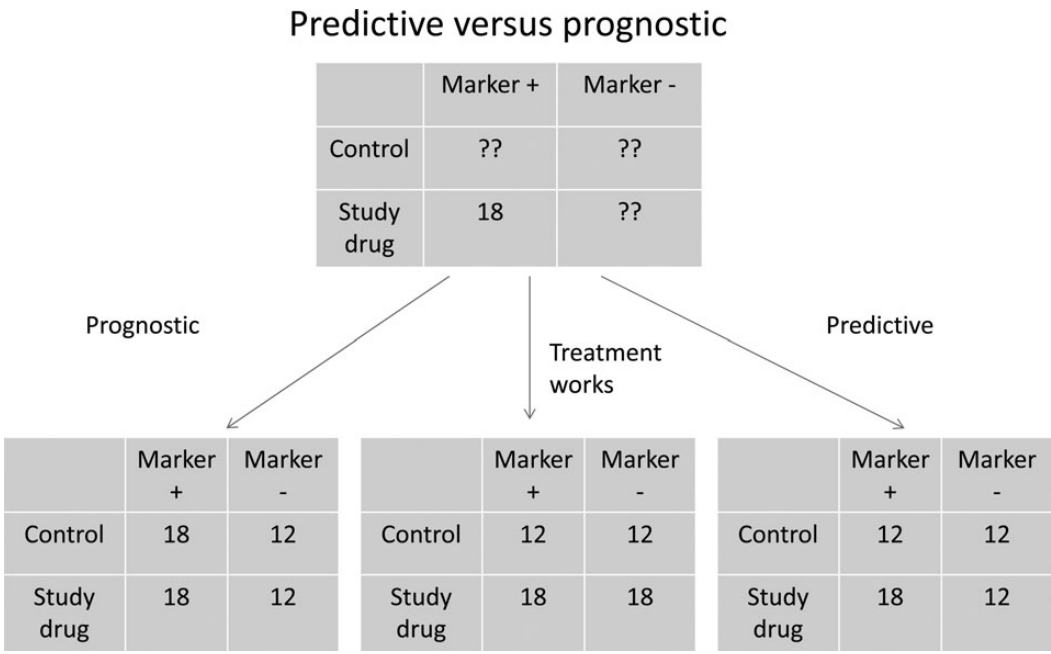

Fig. 1. Potential interactions between biomarker-defined subgroups and experimental therapies. Numbers in the boxes are unitless and are used solely to illustrate hypothetical relative treatment effects but may represent data such as median survival in this simplified model.

has been completed. Major design considerations for a chosen platform are: (i) a Clinical Laboratory Improvement Amendment (CLIA) certified environment; (ii) a relatively rapid turnaround time (ideally <3 weeks) for results reporting so that patients can be classified prior to treatment randomization; and (iii) technically feasible and reproducible to maximize eventual utility to the community. Additionally, as a biomarker-based screening trial would ideally develop data to ultimately be used for registration purposes, regulatory requirements must be considered.

Several biomarker studies in GBM are based on RNA expression profiling.[4,7] Multiple studies and technologies have been applied to GBM to generate expression profiles leading to subclasses that were most commonly identified by unsupervised clustering. The most recently referenced subclasses by RNA have been described in The Cancer Genome Atlas (TCGA) program, in which 4 GBM subgroups were proposed. Recapitulation of the most relevant subclasses has been effectively performed by reverse transcriptase (RT)-PCR in real time for use in clinical trial enrollment by prognostic group in the recently completed Radiation Therapy Oncology Group (RTOG) 0825 study, although the robustness of the prognostic capability is unclear.[16] Newer technologies, such as the NanoString platform, have been adapted to recognize TCGA categories of GBM. This assay offers potential value because it requires only small amounts of formalin-fixed paraffin-embedded (FFPE) tissue and has been successfully applied to CNS cancers[17] (J.T.H. unpublished observations, 2014).

Genomic analyses and tools are generally less complex and more reliable as biomarkers than RNA-based assays. Testing for DNA can range from targeted single mutation genotyping (eg, IDH 1R132H) to whole genome sequencing. Cost, complexity, and turnaround time are major factors to consider when designing a trial. The more broad-based the assay, however, the more opportunity there will be to conduct exploratory analyses of subgroup benefits and to develop predictive biomarker hypotheses in case the initial hypotheses are not supported by the data. Routine genomic analysis is increasingly used in clinical practice and is becoming progressively broader as sequencing costs decrease. The first generation of targeted multiplexed somatic-mutation genotyping technologies were applied to GBM early on and included both SNaPshot (Massachusetts General Hospital[18]) and Sequenom based platforms (Dana-Farber/Brigham and Women's Cancer Center OncoMap assay,[19] MDACC, and MSKCC[20]). Genotyping has recently evolved to next-generation sequencing technologies that sequence entire genes known to be related to cancer. Several versions are in use (some examples being DF/BWCC [OncoPanel][21] and Foundation Medicine[22]) and have had rapid success with high throughput (thousands of samples per year). This approach still identifies genes of interest a priori but generates data on the entire gene and thereby allows more robust mutational calls, especially in tumor-suppressor genes that have more mutational variability and lack mutation hot spots. Importantly, these tests can be performed in 2–3 weeks.

Copy number data is perhaps the most important category of aberration in GBM, and dedicated, reliable whole-genome copy number assays are now available for FFPE tissue at several centers. The OncoCopy assay developed at DF/BWCC has been applied to nearly 500 FFPE GBM samples and has replaced the multiple fluorescence in situ hybridization tests that were often performed for this disease.[23] Such data can then be integrated with sequencing results to deliver a level of pathway assessment that was not previously possible in clinical trials and is more likely to allow identification of meaningful associations of targeted agents with their pathways. While copy number data can be obtained from several sequencing-based technologies, methods for reliable calling of aberrations from such data are still in development and are not yet ready for full clinical implementation. The exceptions are high-level gene amplifications (EGFR) or large gains/losses of chromosomal arms (1p/19q) that are technically less difficult to predict and may therefore be read from sequencing data. Overall, however, more robust copy number analysis is needed to examine single copy and more complex rearrangements resulting in copy changes.

The FDA recommends that "if a companion diagnostic is required for therapeutic selection, an FDA-approved or -cleared test will be required at the same time that the drug is approved" and "when prospective strategies to apply genetic information to the use of a drug are planned, early consultation with the appropriate centers (ie, CDER, CBER, and/or Center for Devices and Radiological Health (CDRH)) is highly recommended."[24] Therefore, while earlier phase exploratory biomarker analyses will generally not develop sufficient data to support drug approval in various subsets, forethought must be used when designing earlier phase trials so that data supporting biomarker hypotheses can be used for further development of a possible companion diagnostic. Analytical validation is therefore paramount, and the FDA may require approval under an Investigational Device Exemption by the CDRH if the results of a genomic test will be used to assign patients to specific treatment arms.

The logistics of incorporating biomarker information into clinical trials that include targeted agents are not trivial. Biomarker information must be reliably generated and captured from patient tissue samples, often from a multitude of centers, in a timely fashion to allow determination of eligibility, stratification, or assignment to a treatment arm. Biomarker classes, particularly with respect to genomic aberrations, also may not be mutually exclusive; therefore, either a hierarchy or a process for determining subgroup assignment must be generated in advance. Finally, in the case of adaptively randomized trials, biomarker information must be incorporated into the informatics system that feeds the randomization procedure in a robust and efficient manner to minimize data processing time and thereby maximize the value of the data when brought to bear on the next participant's treatment assignment.

Endpoints

Relevant clinical trial endpoints for clinical trials in GBM have been a topic of much discussion. Because the ultimate goal for conducting a phase II screening trial is to develop evidence supporting a larger phase III trial for FDA approval of targeted therapies in GBM, FDA guidance on clinical trial endpoints in cancer is a critical foundational point. The FDA states that: "Survival is considered the most reliable cancer endpoint, and when studies can be conducted to adequately assess survival, it is usually the preferred endpoint."[25] Overall survival (OS) is precise

and easy to measure, but it should most often be assessed in randomized controlled trials because comparison with historical data is often misleading for small-to-moderate efficacy signals. For many types of cancer, effects on OS may be difficult to measure based on long follow-up periods, more limited events, and heterogeneous application of hypothetically beneficial subsequent therapies. These factors are somewhat mitigated for GBM: the median survival after progression in the EORTC 26981/NCIC CE.3 study was 6.2 months in each arm,[11,26] there is a lack of documented beneficial therapies beyond temozolomide (TMZ) and radiation, and there is almost universal use of bevacizumab in the adjuvant setting despite lack of a survival benefit in patients treated with anti-angiogenic therapy at recurrence.

Endpoints based on a measurement of tumor response (overall response rate [ORR], progression-free survival [PFS]) have some benefits but also have several limitations. ORR is more directly attributable to treatment effect than other endpoints—the natural history of GBM is not spontaneous regression—and is thus the most appropriate endpoint for single-arm studies. ORR has the additional advantage of being a relatively early endpoint compared with others. Although the linkage to treatment effect may be more direct, other factors that confound the assessment of contrast enhancement (eg, vascular permeability) make radiography-based measurement problematic. Pseudoprogression in response to standard therapy[27,28] and pseudoresponse from treatment with anti-VEGF agents are well described,[27,29] and there is variable linkage of tumor response to a meaningful clinical benefit. In the FDA guidance document, brain tumors are specifically referenced as one setting in which endpoints based on tumor measurement are difficult due to lack of well-demarcated margins.[25] Conversely, agents may have a clinical meaningful benefit but not have dramatic tumor responses based on cytostatic effects or otherwise.

Progression-free survival (PFS), another endpoint incorporating radiographic tumor measurements, mitigates some of the issues inherent in identifying a clinical benefit unrelated to tumor response. However, stability may be related to natural history; therefore, control arms are critical. PFS has an advantage over OS in terms of time to event, potential lack of confounding by subsequent therapies, and potentially bigger effect sizes, but the clinical benefit is indirect; therefore, establishing PFS as an appropriate endpoint either relies on association with a direct clinical benefit (such as quality of life or OS), or as a substitute if the translation of treatment effect is confounded by long survival post progression and/or crossover effects.[30] The relationship between PFS, either at a discreet time point or as a continuous variable, and OS is not easily predictable.

There have been several studies examining the relationship between PFS and OS endpoints. Ballman et al examined the correlation of PFS-6 and OS-12 in prior clinical trials conducted through the North Central Cancer Treatment Group (NCCTG) and found only moderate concordance between these endpoints.[31] Much of the discordance, however, can be attributed to the difficulties with associating 2 endpoints consisting of one-time assessments (at 6 and 12 months, respectively). In the simulation portion of the study, the investigators found that clinical trial decisions made on the basis of the PFS endpoint and those made on OS were in agreement ~90% of the time. Furthermore, when progression was considered a time-dependent variable, the hazard ratio (HR) for death was 16.2 for those who had progressed by 6 months versus those who did not progress in newly diagnosed patients, showing a strong overall correlation between these endpoints.[31] Polley et al similarly found that progression status at 2, 4, and 6 months was a strong predictor of OS in upfront GBM studies at University of California, San Francisco.[32] While these studies show that progression is associated with greater hazard for death, they did not specifically analyze whether the impact of a therapy on PFS can predict the effect in OS. The fact that the Stupp study[11] showed a consistent median OS following progression in both treatment arms suggests that the effect of TMZ on OS can be predicted by the length of time to the progression time point. This suggestion was reinforced by a recent meta-analysis showing a strong correlation between PFS HR and OS HR for non-bevacizumab containing studies.[33] Conversely, Ye et al analyzed data from 3 separate NABTT phase II trials and showed that the magnitude of treatment effects on PFS were not correlated with treatment effects on OS.[34] It should be noted, however, that all 3 studies showed a benefit in both PFS and OS compared with historical controls. Therefore, it could be argued that all 3, analyzed on a PFS basis, would have made similar trial decisions to reject the null hypothesis as compared with OS, only that true surrogacy and the magnitude of benefit may not have been predicted. Furthermore, as the referenced trials utilized historical controls, the examined associations may have represented correlations of selection bias rather than treatment effects. The point stands, however, that different therapies may have different relationships between PFS and OS. This is most evident in the recently reported AVAGlio and RTOG 0825 studies,[16,35] which demonstrated benefits in PFS but not OS that were possibly related to the impact of antiangiogenic therapy on the determination of progression rather than an actual antitumor effect. A screening study for targeted therapies would need to heed this experience and not assume equal relationships (or surrogacy) between assessment of PFS and OS among the treatment arms. Furthermore, the potential for crossover effect limiting the translation of a true PFS signal to OS must also be considered. Broglio and Berry showed that a true drug effect on PFS can become significantly diluted as the survival postprogression period becomes longer and more heterogeneous (possibly due to crossover). While the significance of this issue for GBM trials is debatable,[36] intratrial modeling of the PFS/OS relationship is certainly possible.

Trial Structure

There is substantial variability in the structure of biomarker-based clinical trial designs in practice, but this variability can be reduced by common characteristics to fewer distinct categories.[37] In the taxonomy proposed by Tajik et al, biomarker-based studies can be classified into 4 basic groups and their combinations (single-arm studies, enrichment strategies, randomize-all, and biomarker-strategies). Single-arm studies enroll all patients to experimental therapy regardless of biomarker status. Enrichment strategies incorporate a control arm but enroll only patients from a specific biomarker subcategory. Randomize-all studies randomize patients in all biomarker subcategories, which may include conventional

biomarker stratification, or adaptive designs incorporating an initial training period. Finally, biomarker strategy trials utilize entirely different management algorithms that are dependent on the biomarker profile at study entry. As discussed above, each of these designs yields different information with respect to a potential biomarker/therapeutic interaction.

The proposed clinical trial endpoint provides some guidance for overall trial design. ORR is more amenable to single-arm studies because response out of the range of expected variation can be more easily attributed to the treatment and not the overall natural history of the disease. When endpoints with multiple explanatory variables are used, such as PFS or overall OS, a robust control arm is necessary unless the effect size is extremely large and out of the range of possible normal variation and selection.

If the goal of the trial is to determine the treatment effect, the biomarker effect, and the interaction between the two, only designs that include some randomize-all characteristics can provide enough relevant data (Fig. 1). Trials limiting experimental therapies to biomarker-only subgroups will either not be able to determine the treatment/biomarker interaction (in enrichment studies) or determine any of the 3 desired parameters (in single arm studies, save for those with response endpoints). Furthermore, enrichment designs would not be able to determine the prognostic versus predictive capacity of the biomarkers in question. The FDA's guidance on enrichment strategies states: "We encourage inclusion of some predictive marker-negative patients in most trials intended to provide primary effectiveness support, unless it has been well established in earlier studies that the marker-negative patients do not respond, or there is a strong mechanistic rationale that makes it clear that they will not respond."

Trials enriching to biomarker-positive only subsets would not only have the limitations described above, but would also result in approval of the drug only for use in biomarker-positive patients, thereby potentially excluding patients that might benefit as the effect in biomarker-negative subgroup would be unknown.

Randomize-all biomarker studies offer the best possible information regarding possible biomarker and biomarker/treatment parameters, therefore a trial with this characteristic was desired. Furthermore, this design is the most effective for generating a dataset using exploratory analyses. It is unlikely that the best predictive genomic biomarker signature, should one exist, would be the one hypothesized prior to the study. A dataset with an initial cohort of patients randomized to various targeted therapies and a control arm with robust genomic data would be a unique dataset from generating hypotheses for future trials or for refining predictive signatures. A limitation of the conventional randomize-all design is the larger overall sample size. For this reason, the desired trial would incorporate some randomize-all elements but would be adjusted accordingly once better information is available to improve the efficiency of the study. Potential adaptive strategies include multiple stopping points or Bayesian adaptive randomization.[38–41] For patients with recurrent GBM, an adaptive strategy for a multiarm study in the absence of biomarkers led to increased efficiencies in most cases from a modeling study incorporating clinically relevant estimates of survival time and accrual rates.[41] A Bayesian-adaptive randomized approach with molecular signatures is currently employed in the breast cancer I-SPY 2 screening trial,[42] the lessons of which can be applied to the setting of GBM.[43]

Several other statistical designs could have also been considered, but a more nuanced discussion of the comparative advantages and disadvantages of each was beyond the scope of the meeting. The Response Assessment in Neuro-Oncology (RANO) group published an extensive review of such designs for neuro-oncology trials.[44] Potentially applicable designs for a phase II screening trial include a balanced randomized screening design with relaxed standards of type I and type II errors, randomized discontinuation, "pick the winner," factorial designs, and others. Each of these designs may have different benefits and trade-offs that are contingent upon the specific choices made for operating characteristics and complexity. Combining those specific choices with the various trial structures led to an innumerable set of potential comparators. Briefly, we chose a Bayesian framework to be the focal point of discussion because of its added flexibility in dealing with multiple hypotheses including biomarkers[45] and the modeling work that had been done in GBM showing potential gains in efficiency. A discussion about the relative benefits versus additional complexity that Bayesian designs might add to GBM trials, as well as the possible non-Bayesian alternatives, is referenced here.

Eligible Study Populations

The eligible study population was also a topic of extensive discussion, and the group considered trials in both the recurrent and upfront settings. For the upfront study, logistics regarding the collection and analysis of tumor specimens were more straightforward than in the recurrent setting, given the universal surgical intervention prior to enrollment and the longer time to treatment initiation. Potential problems in the newly diagnosed setting related to the longer time to event and issues regarding potential combinations with both temozolomide and radiation. These combinations might necessitate extensive phase I data and were difficult to rectify because of the complexities of incorporating multiple targeted therapy arms into a single study. One potential solution was to conduct the newly diagnosed study in an *MGMT* promoter-unmethylated population. Based on the EORTC 26981/NCIC CE.3 and RTOG 0525 data in unmethylated patients[11,26,46] it was felt that TMZ in addition to radiation therapy (RT) was not essential for this patient population, so a safety run-in with experimental agent alone in combination with RT would be feasible. This would also be attractive because the experimental therapy drug levels would not need to be adjusted to mitigate potential TMZ toxicity. Furthermore, FDA guidance states that "For any given desired power in an event-based study, the appropriate sample size will depend on effect size and the event rate in the placebo group." For this reason, the unmethylated population offered a potential prognostic enrichment strategy; patients with unmethylated tumors have more events and earlier times to events, which would better inform the randomization procedure. Similar trial principles could be applied in the recurrent setting, but there would be additional complicating factors (availability of tissue) to consider. Given the largely unknown temporal heterogeneity but expected increase in the

mutational landscape in previously treated GBM,[47] repeat biopsy or resection would be highly desired to confirm the presence of various biomarkers. The need for additional tissue limits the patient population eligible for the study; thus, prioritizing pretreatment biopsies in recurrent glioblastoma is critical for making progress in glioblastoma outcomes. Furthermore, even in patients who have tissue available for analysis, the turnaround time from surgical procedure to treatment initiation is generally less than in the newly diagnosed setting, necessitating even more efficient biomarker analysis and communication.

A Biomarker-enriched Adaptive Trial for Patients with Glioblastoma

Overview

The Targeted Therapies Working Group proposed a multiarm, adaptively randomized, controlled, screening trial for both biomarkers and targeted therapies, with the goal of providing robust biomarker/targeted therapy hypotheses to bring forward for phase III confirmatory trials. Randomization would initially be balanced, coinciding with a safety run-in period, but would then adapt to preferentially randomize patients from prespecified biomarker signatures to treatment arms that showed evidence of efficacy. Efficacy would be determined by a learning model based on OS. Initial randomization would be impacted by OS, but if the model found factors associated with risk of death (progression, KPS, etc.), then the randomization would incorporate this information.

Eligibility

Patients with newly diagnosed GBM, unmethylated *MGMT* promoter, adequate performance status, and sufficient tumor resection for molecular analyses will be eligible for the study. Inclusion of only *MGMT* promoter unmethylated patients will serve multiple purposes. First, prognostic enrichment will limit the interpatient variability of outcome (making true signals easier to see) and have earlier time-to-event data, thereby increasing the efficiency of the adaptive procedure. Second, because outcomes for unmethylated patients are poor following treatment with RT/TMZ and the predictive capacity of *MGMT* promoter methylation in the monotherapy setting,[48] the group felt that use of TMZ as part of the standard backbone was not necessary, thus allowing experimental therapeutics to be combined with RT alone and used as monotherapy following RT. This would enable inclusion of drugs in the study (without prior phase I data) in combination with TMZ and would eliminate the potential confounder of TMZ toxicity potentiation when attempting to give therapeutic levels of targeted therapy.

Trial Structure

Newly diagnosed patients will be randomized to multiple treatment arms using an adaptive procedure that takes into account biomarker signatures and outcomes relative to treatment arms (Fig. 2). The initial phase of the trial will be designed to equally randomize patients to all treatment arms. This will be done for several reasons. First, the model should not be overly sensitive to early results, which might lower the randomization probability inappropriately to trivial levels before adequate data have been developed. Second, an early equal randomization phase will allow for a coincident safety run-in period in which toxicity is being measured and analyzed for those drugs that have not been combined with radiation in other phase I studies. Finally, the early equal randomization will allow for robust comparator groups to evaluate the

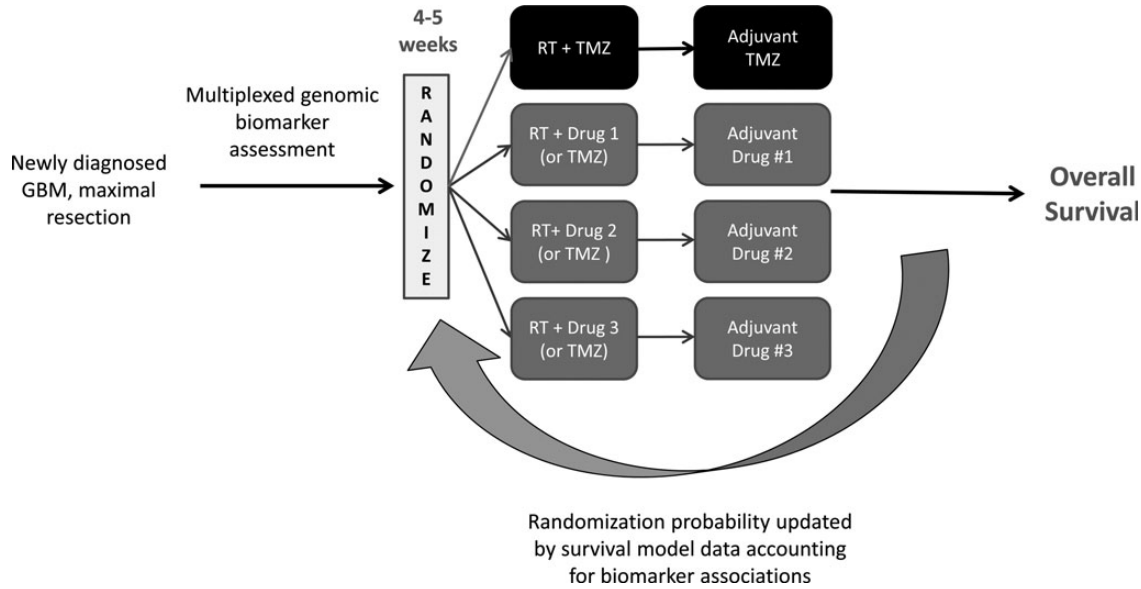

Fig. 2. Proposed clinical trial schema. Randomization would initially be balanced, but would ultimately be adapted based on accumulating survival data relating to different biomarker/therapeutic groups. Overall survival would form the foundation of the endpoint, but other factors such as progression and clinical status that were found to be associated with survival during the course of the study would be leveraged to provide earlier, additional information.

biomarker effect and treatment effect and provide a rich dataset for future exploratory analyses.

Following the initial equal randomization phase, the model will preferentially enroll patients from biomarker signature subgroups to those arms that are showing evidence of efficacy. This will initially be based on OS, but could eventually use other data (such as PFS) that are found to correlate with OS as the trial matures. When treatment arm/biomarker combinations have reached prespecified levels of probability of success or failure in phase III studies, these combinations will either graduate or drop from the study. In the case of dropping arms, the randomization procedure may lower the probability of assignment to that therapy in several tumor signature subgroups before formally withdrawing the arm from the study. Ideally, newer therapeutic arms would take their place in a seamless manner.

Drugs

Molecular targets prioritized by the group were EGFR amplification and/or mutation, PI3 kinase activation, cell cycle targets, and the p53 axis. Potential drugs directed at the EGFR group may include pulse lapatinib, neratinib, or dacomitinib. PI3 kinase inhibitors might include drugs such as GDC0084, XL765, buparlisib (BKM120), or MLN0128. The cell cycle group drug could include palbociclib (PD-0332991), LY2835219, or LEE011. Concerns were raised regarding the ability to employ compounds from different pharmaceutical companies in the same study, but these concerns were somewhat mitigated by the experience of I-SPY 2. Alternatively, several companies have early phase drugs in each of these categories, making a single company-based trial feasible. Furthermore, conducting the trial with Cancer Therapy Evaluation Program pipeline drugs only was raised as another option. The list of potential therapeutics is likely to change as more novel agents enter clinical evaluation.

The trial structure would ideally be flexible enough to add new therapeutic/biomarker hypotheses as others either successfully graduate to larger phase III trials or drop out due to low probability of further success. Hypotheses would be added based on a prioritization procedure that will be developed in parallel with the study. Potential criteria for metrics of prioritization would be developed including therapeutic/biomarker rationale (subjective), preclinical pharmacodynamic proof of concept (subjective/objective), preclinical in vitro and in vivo efficacy (objective), blood-brain barrier penetration, phase I toxicity data, etc. Each of these categories would have specific metrics and benchmarks to allow quantification and prioritization. Categories for prioritization would also be weighted based on the correlation to clinical success (objective) and subjective value. For example, blood-brain barrier penetration would be heavily weighted but also considered in the context of other factors such as preclinical efficacy and the target localization (LDE225 targeting the tumor microenvironment; VEGFR inhibitors targeting the vasculature). Alternatively, if a specific preclinical model/metric were found to be correlated with clinical outcomes, that model would be weighted very heavily in the model.

Biomarker Evaluation

Biomarker evaluation in this study will be conducted in a hypothesis-driven exploratory (FDA definition: "not intended to provide the definitive evidence of safety and effectiveness needed to support drug approval ") manner. The trial would have a safety run-in for each arm that will correspond to the initial equal randomization phase prior to engagement of the adaptive procedure. Tumor tissue will be centrally reviewed and initially assayed for known prognostic factors (*MGMT* promoter methylation and IDH1 R132H mutation status) using methylation-specific PCR and immunohistochemistry, respectively. Patients will be eligible if they have unmethylated *MGMT* promoters and are IDH1 R132H-mutation negative. If the clinical prognostic utility of other biomarkers becomes apparent during trial development, this data will be considered for eligibility or stratification purposes as well. Following registration, tumor tissue will be analyzed using onco-exome or whole exome sequencing to generate mutational data. FFPE-based array CGH methods will be used to determine whole genome copy number.

Initial biomarker classifiers will be based on 4 specific pathway markers: EGFR amplification/mutation(45%), PI3K activation (PTEN loss through homozygous deletion or mutation plus deletion, PIK3CA mutation, PIK3R1 mutation; 49%), p53 status (MDM 2/4 amplification or p53 wild-type; 65%), and CDK (CDK4/6 amplification or CDKN2A nullisomy; 68%). Four binary classification markers generate 2^4 possible biomarker signatures (+/+/+/+, +/+/+/-, etc.), not all of which are highly populated (Table 1) or that have hypothesized value. A relevant hypothesized signature would be compound specific. Initially, the proposed signature to consider would be each of the entire cohort, the 4 categories independently, PI3K activation/EGFR

Table 1. Possible distributions of proposed biomarker subgroups based on The Cancer Genome Atlas data[6]

EGFR[a]	PI3K[b]	MDM2[c]	CDK4/6[d]	*n*
−	−	−	−	**24 (26%)**
+	−	−	−	**18 (20%)**
−	+	−	−	**17 (19%)**
+	+	−	−	**11 (12%)**
+	−	+	+	**4 (4%)**
−	−	−	+	**4 (4%)**
+	+	+	−	**3 (3%)**
+	+	−	+	**3 (3%)**
−	+	+	+	**2 (2%)**
+	+	+	+	**1 (1%)**
+	−	−	+	**1 (1%)**
−	+	+	−	**1 (1%)**
−	−	+	+	**1 (1%)**
−	−	+	−	**1 (1%)**
+	−	+	−	**0 (0%)**
−	+	−	+	**0 (0%)**
41 (18)	**38 (17)**	**13 (1)**	**16 (4)**	**91**

[a]EGFR: EGFR amplification/mutation.
[b]PI3K: PI3K activation (PTEN loss through homozygous deletion or mutation plus deletion, PIK3CA mutation, PIK3R1 mutation).
[c]MDM: MDM 2/4 amplification or p53 wild-type.
[d]CDK: CDK4/6 amplification or CDKN2A nullisomy.

nonamplified, and EGFR amplification/PI3K nonactivated for 7 total signatures.

Endpoints

The primary endpoint of the study will be the predictive probability of success in a phase III study based on OS. Overall survival was chosen as the foundation, given the clinical relevance, unambiguous assessment, and short enough time to event relative to predicted accrual rate to still produce relevant information for randomization based on modeling. During the course of the study, other parameters such as progression and performance status will be analyzed for association with survival; the model would incorporate this information to allow for even more efficient randomization should there be a linkage. This type of modeling is currently being used in I-SPY 2 to correlate MRI response with the endpoint of interest, pathologic complete response. Should there be no association between progression and OS, randomization will only be informed by death. While this would lead to a less efficient trial than one with randomization informed by an earlier event such as progression, designing such a trial would result in erroneous randomization that would be a far worse consequence than loss of efficiency if there were truly no correlation between progression and survival.

Conclusions

The era of targeted therapies and genomic medicine provides much hope for progress in the treatment of glioblastoma. In order to fully leverage the potential of molecular data as biomarkers and to efficiently evaluate novel therapeutics, flexible clinical trial designs that test multiple hypotheses are needed. In this context, the Targeted Therapies Working Group proposed a biomarker-enriched, adaptively randomized trial for patients with glioblastoma in an effort to realize the promise of the current era.

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