Neuro-Oncology 15(8):972–978, 2013.
doi:10.1093/neuonc/not088

Biomarker-based adaptive trials for patients with glioblastoma—lessons from I-SPY 2

Brian M. Alexander, Patrick Y. Wen, Lorenzo Trippa, David A. Reardon, Wai-Kwan Alfred Yung, Giovanni Parmigiani, and Donald A. Berry

Department of Radiation Oncology (B.M.A.) and the Center for Neuro-Oncology (B.M.A., P.Y.W., D.A.R.), Dana-Farber/Brigham and Women's Cancer Center, Harvard Medical School, Boston, Massachusetts; Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Department of Biostatistics, Harvard School of Public Health, Boston, Massachusetts (L.T., G.P.); Department of Neuro-Oncology (W.K.A.Y.) and Department of Biostatistics (D.A.B.), The University of Texas MD Anderson Cancer Center, Houston, Texas

The traditional clinical trials infrastructure may not be ideally suited to evaluate the numerous therapeutic hypotheses that result from the increasing number of available targeted agents combined with the various methodologies to molecularly subclassify patients with glioblastoma. Additionally, results from smaller screening studies are rarely translated to successful larger confirmatory studies, potentially related to a lack of efficient control arms or the use of unvalidated surrogate endpoints. Streamlining clinical trials and providing a flexible infrastructure for biomarker development is clearly needed for patients with glioblastoma. The experience developing and implementing the I-SPY studies in breast cancer may serve as a guide to developing such trials in neuro-oncology.

Keywords: adaptive, Bayesian, biomarker, clinical trials, glioblastoma.

Clinical trials for patients with glioblastoma are at a crossroad. The Cancer Genome Atlas[1] and others[2] have generated detailed molecular data that, in turn, have increased excitement to identify new therapeutic targets and personalize therapy. The growing number of compounds available for targeting specific pathways combined with increasingly sophisticated strategies to molecularly subclassify high-grade gliomas has created a multitude of testable therapeutic hypotheses. Furthermore, ambiguity regarding the relevance of clinical trial endpoints and inaccuracy of preclinical models for predicting trial success in humans place additional roadblocks to development of novel therapeutics for patients with glioblastoma. The current clinical trials infrastructure is poorly suited to prioritize the myriad testable hypotheses that each of these problems suggests. Additionally, $<10\%$ of patients with gliomas in the US are enrolled in clinical trials. For a disease that has no cure, this is an unacceptable number, both for individual patients and for the overall research enterprise. Patients outside of clinical trials are consigned to a standard of care associated with poor results and represent a lost opportunity to improve clinical outcome.

In parallel, with improved understanding of biology, the current early-phase clinical trials infrastructure has been criticized for not effectively screening therapies for larger confirmatory studies. The lack of effective control arms has overestimated the extent of success in early-phase trials.[3,4] The need for more effective drug screening trials in addition to the increasing number of testable hypotheses has led many to search for alternative clinical trial designs. In 2006, the FDA's Critical Path Initiative stated that the 2 most important areas for improving medical product development were biomarker development and streamlining of clinical trials.[5,6] Multi-arm Bayesian-based adaptive clinical trials offer the possibility of both. There have been arguments against such trials, as well as barriers to their real-world implementation.[7] The focus of this review is to describe challenges to designing and implementing novel clinical trial designs for malignant glioma patients. We highlight the trial experience of the Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging And moLecular analysis 2 (I-SPY TRIAL 2)[3,8] as a potential roadmap to overcome some of these challenges.

Received March 11, 2013; accepted April 28, 2013.

Corresponding Author: Brian M. Alexander, MD, MPH, Dana-Farber/Brigham and Women's Cancer Center, Department of Radiation Oncology, 75 Francis Street, ASB1-L2 Boston, MA 02115 (bmalexander@lroc.harvard.edu).

Adaptive Trials

To hasten progress in treating cancer patients, clinical trials must address multiple questions related to subject

stratification, subject allocation to experimental arms, stopping rules, and others. Adaptive designs are well suited for addressing multiple questions in a single trial framework.[3,7] The FDA defines an adaptive trial as one that incorporates prospectively planned opportunities for modification of one or more specified aspects of the study design and integrates hypotheses based on analysis of accumulating data while the study is ongoing.[9] Adaptive designs have the potential to make oncology drug development more efficient and address many questions (including biomarker and surrogate endpoints) at once, thereby potentially reducing trial subjects' exposure to ineffective treatments and allowing for more flexible, less costly incorporation of other promising therapies.[3,10] A simple example of an adaptive trial is represented by an interim analysis with a stopping rule based on frequentist criteria, while a more complex adaptive trial may include a multi-arm adaptively randomized design based on Bayesian predictive probabilities that incorporates biomarker data and attempts to match patients with therapies.[8,11] The I-SPY 2 study in breast cancer and the Biomarker Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE) study for non–small-cell lung cancer are 2 examples of the latter.[8,11,12]

Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging And moLecular Analysis 2 (I-SPY TRIAL 2)

Background

I-SPY 2 was formed as a collaborative effort between the National Cancer Institute, academic investigators, the FDA, and industry, with the goal of improving the efficiency of identifying novel efficacious treatment regimens for molecularly defined subsets of patients with breast cancer.[8] The sponsor of the trial is the Foundation for the National Institutes of Health. The overall trial design includes a multi-institutional, multi-arm, adaptively randomized framework with therapeutic arms introduced as older arms graduate or are dropped due to their high or low, respectively, Bayesian predictive probability of being more efficacious than standard therapy. The study tests novel therapeutic arms against a standard therapy control arm. As more mature treatment/signature combinations drop for futility or graduate to a subsequent confirmatory phase, newer arms are designated to take their place, thereby generating increased efficiency in terms of streamlining. As of November 1, 2012, the trial had enrolled 290 patients and addressed the efficacy of experimental agents from 5 different pharmaceutical companies.

Implementation of Adaptive Trials in Neuro-oncology

The numerous therapeutic hypotheses currently being generated in neuro-oncology are in critical need of a streamlined and efficient clinical trial framework. Before such a framework can be constructed, however, a number of considerations must be addressed, from the scientific to the logistic. Scientifically, care must be taken to specifically define trial goals so that the correct approach is applied. Overall trial framework considerations include patient selection, allocation, endpoints, stopping rules, and decision rules regarding biomarkers. Logistically speaking, organizing a successful collaborative team, creating a system for providing real-time biomarker and endpoint data, developing a robust bioinformatics infrastructure, and gaining buy-in from regulators and industry must also be accomplished. The following sections will consider each of these issues with perspective from the experience of the I-SPY 2 trial.

Framework

Poor translation of phase II results into confirmatory phase III trials is an important problem for oncology,[3,4] and this is especially so in neuro-oncology.[13] Potential sources for lack of translation in neuro-oncology include changing survival trends in patients with glioblastoma[13,14] and increasing complexity defining clinical endpoints such as progression.[13,15] As such, single-arm studies using historical controls for comparison are inadequate, and increasing emphasis is being placed on randomization in phase II studies.[16] Multi-arm studies are attractive in this regard as the efficient use of a single control arm is attained. Multi-arm, adaptive studies may be designed using either frequentist or Bayesian techniques, and while the overall differences between these 2 approaches are beyond the scope of this article (although well reviewed recently[17–19]), the relative benefit of Bayesian approaches may be more apparent as the number of questions (including treatment arms) increases.[7] Furthermore, a Bayesian paradigm is in most cases easier to implement for planning a flexible adaptive trial, enabling treatment arms to be added and dropped without recreating the entire enterprise. These approaches enable flexibility while maintaining a high degree of scientific rigor; standard measures of type I error and power can be estimated prospectively through simulation.

I-SPY 2 was designed as a multi-arm Bayesian adaptive randomized trial with the primary decision criterion being the Bayesian predictive probability of being successful in a subsequent confirmatory phase III study, for each drug/biomarker signature pair.[8] Drugs that were found during the trial to have a "sufficiently low" probability of success were dropped from the study, allowing new treatment arms to take their place, thereby creating a dynamic and flexible framework.

An adaptive clinical trials infrastructure in neuro-oncology could adopt this design framework as well. Subject patients with newly diagnosed glioblastoma could be randomized to standard of care with radiotherapy and temozolomide (RT/TMZ), as defined by the study by the European Organisation for Research and Treatment of Cancer/National Cancer Institute of Canada (EORTC/NCIC),[20] or to one of several

treatment arms (eg, RT/TMZ/X_1, RT/TMZ/X_2, . . . RT/TMZ/X_n). For patients with recurrent glioblastoma multiforme (GBM), the situation may be more complex because there is no generally adopted standard of care that has demonstrated an overall survival (OS) advantage. Possibilities might include bevacizumab as the de facto standard-of-care arm, with either the addition (bev/X_1, bev/X_2, . . . bev/X_n) or the substitution (bev, X_1, X_2, . . . X_n) of experimental therapeutics or otherwise the consideration of CCNU or another cytotoxic regimen as standard for comparison with the experimental arms. Alternatively, a trial including only experimental arms could be initiated with an adaptive randomization wherein the best performing arm automatically becomes the standard, perhaps with biomarker-defined subsets. Potentially, as most patients with glioblastoma demonstrate recurrence at some point, a flexible multi-arm structure might incorporate both newly diagnosed and recurrent patients, enrolling subjects at initial diagnosis and following them until death with a re-randomization at first recurrence. The inferential issues with respect to OS in such a study would be complicated, with comparisons based on strategies incorporating an inherent correlation structure.

Biomarkers

One recurring issue for trial design in neuro-oncology (and oncology in general) is how to most effectively incorporate putative biomarkers.[21] There are 2 broad approaches to biomarker classification for clinical trials: (i) identifying biologically relevant molecular subtypes that would hypothetically respond differently to a specific treatment and (ii) matching targeted therapeutics with expression of specific molecular targets. For the first case, molecular characteristics such as O^6-DNA methylguanine-methyltransferase (*MGMT*) promoter methylation,[22] gene-expression subclass,[23–25] and isocitrate dehydrogenase 1 or 2 mutations[26–28] have demonstrated prognostic value suggesting biologically relevant subclasses of the overall histologic classification. How these molecular subclasses interact with various therapies is mostly unknown, however.[21] There is evidence that *MGMT* promoter methylation has predictive value for TMZ response for multiple clinical endpoints,[22,29] and both *MGMT* promoter methylation and a 9-gene expression signature were used as stratification variables for the recently completed Radiation Therapy Oncology Group (RTOG) 0825 study.[30] For the second case, there is much interest in personalizing clinical trial assignment by molecular profiling. The idea is to find specific molecular abnormalities that are present in a given tumor and then identify the best possible trials or arms for patients with that tumor type using targeted therapies. For example, patients whose tumors express mutant epidermal growth factor receptor (EGFR) variant (v)III may potentially be treated with an EGFR inhibitor. Assigning patients a priori to a given therapy based on molecular characteristics presupposes the validity of the hypothesized predictive biomarker, however. Caution should be exercised with this approach, especially given the long history of therapeutic trials in GBM with extremely limited success in identifying predictive biomarkers.[31] Furthermore, even with a positive biomarker association, biomarker-therapeutic linkage cannot be shown without an agnostic approach, at least initially, or without further study in a population with both biomarker + and biomarker - subjects.

Biomarker hypotheses are not all equal; there may be more direct logical connections supporting a claim or varying levels of supporting preclinical data. Some therapeutic hypotheses are strictly limited to certain patient subsets. Maybe the best example of such a therapeutic hypothesis is the rindopepimut tumor vaccine that targets the EGFR vIII mutation.[32] In this approach, an EGFR vIII–specific 14-amino acid peptide is used to generate an EGFR vIII–specific antitumor immune response, leveraging the oncospecific truncated extracellular domain in the mutant form to provide a therapeutic advantage. As this therapeutic is designed to prime the immune system against EGFR vIII, it would follow that tumors without that target would not be expected to respond. In this case, perhaps the a priori assumption is appropriate (although the accuracy of a potential biomarker assay might still be in question). Even so, there may be patients without the hypothesized target who could respond to therapy, as has been seen with trastuzumab.[33] Most biomarker-therapeutic hypothetical linkages, however, are based on more complex reasoning founded on currently incomplete knowledge of pathway interactions, complicated assumptions, and conjecture. Hypotheses have varying amounts of prior clinical or preclinical validity and should therefore be considered differently for trial design.

I-SPY 2 designated 3 tiers of potential biomarkers: standard, qualifying, and exploratory. Standard biomarkers were those that had been accepted and approved by the FDA, including the statuses of estrogen receptor, progesterone receptor, and Human Epidermal Growth Factor Receptor 2 (HER2) by either immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH) and MammaPrint.[8] Because these biomarkers had already demonstrated predictive value in prior studies, they were deemed appropriate for patient eligibility determination and randomization. Qualifying biomarkers, including HER2 gene expression and phosphorylated HER2, were those that had not yet been approved by the FDA but were building clinical data toward that goal. These biomarkers were included either under Investigational Device Exemptions or through Clinical Laboratory Improvement Amendment certified laboratories. Lastly, exploratory biomarkers were those that had some preliminary data but were in the earliest phases of clinical validation.[8] The qualifying biomarkers in the I-SPY 2 study highlight the notion that although a predictive molecular correlation (HER2) has been identified, the specific technical assays to assess biomarker status must be validated independently, owing to either technical differences or varying biological implications of the assay. I-SPY 2 utilized mainly the first approach to biomarker incorporation. While the 2 overall cohorts were defined by HER2 status assessed by either FISH or IHC, this was

done to assign patients to an initial standard therapy backbone with or without an already known therapeutic, trastuzumab. Based on the validated biomarkers (hormone receptor, HER2, MammaPrint), 10 biomarker signatures of interest were defined. As the trial unfolds, drugs that show a higher number of complete responses within a given biomarker signature will be assigned with increased probabilities to that signature class. Drugs are dropped from the trial only if the Bayesian predictive probability of future success drops below a set level for all signatures. Successful drug/signature combinations are graduated for further testing in phase III studies.[3]

For adaptive trials in neuro-oncology, an approach similar to I-SPY 2 might be taken. As stated previously, the recent RTOG 0825 trial stratified patients based on a 9-gene expression score and *MGMT* promoter methylation status. Perhaps these markers could be used to define biologically relevant subclasses that may or may not have varied responses to different therapeutics. This might be more problematic for the recurrent setting, where GBM-specific subtyping is not as well defined. For targeted therapeutics, biomarker hypotheses could be layered onto that framework and tested during the course of the trial in an exploratory manner. It is also possible in an adaptive design to define drug signatures dynamically based on accumulating results in the trial and to confirm such signatures as well.

Endpoints

For an adaptively randomized trial, appropriate endpoints must be selected to enable an informative randomization procedure. If these endpoints are auxiliary, then relationships between such endpoints and more clinically relevant primary endpoints must be established either prior to initiation or during the course of the trial.[34] During the I-SPY TRIAL 2, for example, a relationship was made between MRI and the rate of pathologic complete response (pCR; which had been previously linked to recurrence-free survival [RFS][35]). In an adaptive trial, it is critical to model patients longitudinally to assess correlations among various endpoints. An important consideration is that the endpoint must be measurable and actionable in a timeframe short enough relative to the accrual rate to allow for meaningful adaptive randomization. For example, if a trial accrues all of the subjects prior to the reporting of the first event, randomization will not be altered. Alternatively, if each patient is accrued only following a longer-term event, any efficiency gain will be lost even though there is ideal information for randomization. For GBM trials, the issue of choosing an appropriate primary endpoint is also problematic. The most important and relevant endpoint is OS. Although the median OS achieved in clinical trials for glioblastoma patients is not as long as for breast cancer, the length of time may still be too long relative to accrual for many multi-institutional trials. For example, the commonly cited median survival for patients with newly diagnosed glioblastoma is the 14.6 months from the landmark EORTC/NCIC trial.[20] Other studies have shown that for patients enrolled in phase II studies, this number is probably even higher in practice,[14,36] meaning that unless trial accrual is slow, waiting until an OS endpoint may be problematic. For patients with recurrent GBM, the use of OS as an endpoint may be more feasible given the shorter survival in this clinical setting.

Endpoints based on progression (progression-free survival [PFS], PFS at 6 months [PFS6]) may be an option but may have several pitfalls, some similar to those reported by the I-SPY group. Difficulties with measuring progression stem from reliance on MRI, which may show false negatives and positives. Pseudoprogression in response to chemoradiotherapy and pseudoresponses following anti-angiogenic therapy have been well described[15] and have the potential to falsely inform the randomization procedure if longer-term primary endpoints are the most clinically relevant. Furthermore, problems with accurate assessment of progression are not random in that false imaging readouts are both therapy and tumor specific. For example, patients with tumors that have *MGMT* promoter methylation have a higher likelihood of showing pseudoprogression[37] but have a better prognosis with respect to OS.[22] This is similar to the association with pCR and RFS based on biological subclass in I-SPY 1, where no patients with low-risk tumors based on a 70-gene profile had pCR, yet none recurred during the course of the study.[38] Furthermore, taking biological subclass into account allowed for stronger correlations between pCR and RFS in the high-risk subset.[35] Therefore, in order to use progression as an appropriate endpoint for randomization in GBM, linkage to OS based on tumor subtype should be demonstrated either before or longitudinally during the course of the study.

For the recurrent GBM setting, OS might be the best option for informing randomization, though incorporation of other longitudinal data would still be critical. The North American Brain Tumor Consortium examined data from several phase II protocols and found that PFS6 had a strong correlation with OS.[39] This linkage may be treatment specific, however, with the relationship in the setting of anti-angiogenic agents being less clear. If PFS was validated as an earlier endpoint through correlation with OS for a given agent, then PFS could be used as well. We recently performed a modeling study using clinical trial data from modern-era phase II studies as well as an accrual rate comparable to what has been demonstrated historically and found efficiency gains and informative randomization.[30] In the newly diagnosed setting, longer OS could be more problematic for quickly accruing trials. PFS has been shown to correlate with OS for newly diagnosed patients receiving standard chemoradiation[40,41] and could potentially be used as a randomization parameter. As OS is the more clinically relevant endpoint, the association between PFS and OS could be modeled and assessed during the course of the trial within biomarker and therapeutic subgroups. MRI perfusion,[42] diffusion mapping,[43] and various positron emission tomography tracers[44] have demonstrated associations with OS in other studies and could also be incorporated in an exploratory manner.

Drug Selection

The selection of therapeutics to be tested is a complex process that must incorporate both scientific rationale and pragmatic considerations, including the availability of different compounds during the appropriate time of their developmental lives. For neuro-oncology, additional complexity is introduced because compounds must be able to penetrate the blood–brain barrier to achieve clinically significant concentrations.

I-SPY 2 employed a number of criteria for selection of potential agents to be included in the study. Drugs required prior testing when combined with paclitaxel in a phase I study. Drugs were experimental but required some evidence of potential efficacy, and there was an explicit attempt to include only 1 representative drug from a particular class.[8] The selection process was described as multitiered, with an independent group of experts making selections based on phase I and preclinical data. Because neoadjuvant breast cancer patients may have long-term survival, toxicity was also a concern. The trial's accrual rate influenced whether additional arms could be included; the explicit goal was to finish accrual to an arm within 18 months, and too many arms would limit the accrual rate to individual treatment arms.

Logistical Considerations

Industry and Regulatory Buy-in

The FDA has been supportive of adaptive clinical trials,[3] first issuing a call to streamline clinical trials in the Critical Path Initiative,[5,6] followed by publication of a draft guidance for industry regarding the use of adaptive trial designs.[9] Industry has also been forward looking in this regard. In 2005, the Pharmaceutical Research and Manufacturers of America created a working group to study issues around adaptive designs and subsequently issued a white paper describing their findings.[45] Nonetheless, obstacles regarding trial implementation are not trivial. For example, one issue offered by many as perhaps the most significant impediment to multi-arm adaptive trials is that pharmaceutical companies, and even divisions within the same company, may not be willing to include their compounds in such trials. From the regulatory standpoint, a clear roadmap from a potentially adaptively randomized study to confirmatory trial to approval is essential and may help in getting buy-in from industry. Fortunately, I-SPY 2 is evidence that such obstacles can be overcome.

I-SPY 2 is sponsored by the Foundation for the National Institutes of Health and executed by the Cancer Steering Committee of the Biomarkers Consortium.[46] Drugs that have been evaluated and being evaluated currently are from Abbott, Pfizer/Puma, Amgen, Genentech, and Merck, with others in the queue.[30] Two hundred ninety patients were randomized as of November 2012.

Bioinformatics Infrastructure

I-SPY 2 leveraged the bioinformatics infrastructure that was developed in I-SPY 1. A data warehouse and portal hosted by the National Cancer Institute Center for Bioinformatics formed the hub for data collation from various sources, including clinical data, pathology, radiology, gene expression, and proteomics, among others. Standard operating procedures for frozen and paraffin-embedded tissue were developed. Importantly, this infrastructure is available to other groups interested in setting up an adaptive clinical trial.

Data Sharing and Oversight

I-SPY 2 developed a data sharing agreement that set up publication, steering committees, and authorship guidelines with broad investigator access to data for analysis purposes. Data for drugs that graduate and their concurrent controls are made available to the drug's developer when the last patient on the drug has had surgery and been assessed for the trial's primary endpoint, pCR. Six months later, the data are made available to the public. Many of these considerations for neuro-oncology may already be in place through various cooperative groups or institutional collaborations and could be leveraged or developed further depending on the sponsors of such a trial.

Potential Options for Bayesian Adaptive Phase II Screening Trials

Recurrent Disease

Trials for patients with recurrent GBM might be built on modeling work already performed.[30] A potential starting point could consist of an ongoing multi-arm adaptively randomized trial with a control arm of bevacizumab alone and experimental arms using bevacizumab combined with investigational agents from different classes. Arms not using bevacizumab could be considered as well. Alternatively, because such a trial would serve as a phase II screening, it may consist entirely of experimental arms, which would be dropped and replaced once the predictive probability of success in a phase III confirmatory trial was low. The phase III comparison could then be to bevacizumab alone as the putative standard. Considerations are the size of the desired effect and the tolerance for false negatives based on small sample size, as well as the likelihood of false positives. Different groups may come to different conclusions; for example, one group may prioritize rapid assessment of drugs for "home runs" while sacrificing the potential to find those with incremental gains, while another group may design the trial for a sufficiently low false negative rate with larger numbers to find smaller effect sizes. It is important to recognize that large effects would require smaller phase III trials, but if biomarker-driven, the potential

patient population might be small. In fact, adaptive designs may be more beneficial compared with standard trials in cases where larger efficacy signals are sought,[47] which may be particularly important when targeted therapy/biomarker associations are possible. Biomarker incorporation would be limited to exploratory biomarkers at first, as the subtyping of tumors and the prognostic value of various molecular markers are less well defined in the recurrent setting. Assays that identify potential molecular abnormalities that hypothetically predict sensitivity to a given agent would be explored in this setting. The relationship of PFS, based on current MRI and clinical definitions, to OS would be assessed during the trial, as would imaging biomarkers of progression.

Newly Diagnosed GBM

For newly diagnosed GBM, radiation and TMZ could be combined with various novel agents in the multi-arm trial. Initial biomarker classes could be determined by *MGMT* promoter methylation status and gene-expression subclass. Additional biomarkers, including those hypothetically for which specific targeted therapies are available, would be included as exploratory. At least initially, PFS6 would be used to determine randomization probability, while the utility of this endpoint as a surrogate would be updated with trial results. Alternatively, an adaptive trial in the newly diagnosed setting might randomize following standard chemoradiotherapy, thereby allowing more time for biomarker analysis and stratification, and would also remove the requirement for phase I studies in combination with radiotherapy. Again, decisions would need to be made regarding the increment of benefit to be evaluated, as discussed previously for the recurrent setting.

Possible Steps Toward Implementation

One potential way forward is for cooperative groups or consortia in neuro-oncology to interact with experts in adaptive trial design to develop and simulate specifics of a potential trial. This approach is currently being used by the Adaptive Designs Accelerating Promising Trials Into Treatment (ADAPT-IT) project.[10] In this project, a multidisciplinary group of researchers is applying adaptive principles within the Neurological Emergencies Treatment Trials (NETT) cooperative group while studying the design and implementation process. Researchers within NETT discuss goals of various trials with the ADAPT-IT researchers, followed by ADAPT-IT proposals for alternative design approaches. Proposed trials are then simulated and refined followed by a multistage review process involving both the National Institutes of Health and FDA prior to trial initiation.[10,48]

Summary/Conclusions

The combination of a dramatically growing number of novel "pipeline" therapeutics with increasingly sophisticated glioma molecular characterization has led to an extraordinary number of therapeutic hypotheses to be tested. Early-phase clinical trials must become more efficient but also must provide more reliable information for go/no-go decisions for phase III testing. The I-SPY 2 trial experience offers many potential lessons for moving forward with novel biomarker-driven adaptive trials in glioma. Such trials will require close collaboration between statisticians and clinicians due to the number of glioma-specific issues that must be addressed. In this regard, the I-SPY and ongoing ADAPT-IT experiences offer good paradigms of process and logistics in addition to scientific considerations.

References

1. Cancer Genome Atlas Research Network Comprehensive genomic characterization defines human glioblastoma genes and core pathways. *Nature*. 2008;455(7216):1061–1068.
2. Parsons DW, Jones S, Zhang X, et al. An integrated genomic analysis of human glioblastoma multiforme. *Science*. 2008;321(5897):1807–1812.
3. Berry DA. Adaptive clinical trials in oncology. *Nat Rev Clin Oncol*. 2011;9(4):199–207–.
4. Zia MI, Siu LL, Pond GR, Chen EX. Comparison of outcomes of phase II studies and subsequent randomized control studies using identical chemotherapeutic regimens. *J Clin Oncol*. 2005;23(28):6982–6991.
5. FDA. Critical Path Initiative. http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/ucm076689.htm. Accessed October 7, 2012.
6. FDA. Critical path opportunities report. 2006; http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPathOpportunitiesReports/UCM077254.pdf. Accessed May 8, 2013.
7. Berry DA. Adaptive clinical trials: the promise and the caution. *J Clin Oncol*. 2011;29(6):606–609.
8. Barker AD, Sigman CC, Kelloff GJ, Hylton NM, Berry DA, Esserman LJ. I-SPY 2: an adaptive breast cancer trial design in the setting of neoadjuvant chemotherapy. *Clin Pharmacol Ther*. 2009;86(1):97–100.
9. FDA. Guidance for industry: adaptive design clinical trials for drugs and biologics. 2010; http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm201790.pdf. Accessed May 8, 2013.
10. Meurer WJ, Lewis RJ, Tagle D, et al. An overview of the Adaptive Designs Accelerating Promising Trials Into Treatments (ADAPT-IT) project. *Ann Emerg Med*. 2012;60(4):451–457.
11. Kim ES, Herbst RS, Wistuba II, et al. The BATTLE trial: personalizing therapy for lung cancer. *Cancer Disc*. 2011;1(1):44–53.
12. Berry DA, Herbst RS, Rubin EH. Reports from the 2010 Clinical and Translational Cancer Research Think Tank meeting: design strategies for personalized therapy trials. *Clin Cancer Res*. 2012;18(3):638–644.
13. Galanis E, Wu W, Cloughesy T, et al. Phase 2 trial design in neuro-oncology revisited: a report from the RANO group. *Lancet Oncol*. 2012;13(5):e196–e204.

14. Grossman SA, Ye X, Piantadosi S, et al. Survival of patients with newly diagnosed glioblastoma treated with radiation and temozolomide in research studies in the United States. *Clin Cancer Res*. 2010;16(8): 2443–2449.
15. Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: Response Assessment in Neuro-Oncology working group. *J Clin Oncol*. 2010;28(11):1963–1972.
16. Seymour L, Ivy SP, Sargent D, et al. The design of phase II clinical trials testing cancer therapeutics: consensus recommendations from the clinical trial design task force of the National Cancer Institute investigational drug steering committee. *Clin Cancer Res*. 2010;16(6):1764–1769.
17. Berry DA. Bayesian statistics and the efficiency and ethics of clinical trials. *Stat Sci*. 2004;19(1):175–187.
18. Berry DA, Eick SG. Adaptive assignment versus balanced randomization in clinical trials: a decision analysis. *Stat Med*. 1995;14(3):231–246.
19. Berry DA. A case for Bayesianism in clinical trials. *Stat Med*. 1993;12(15–16):1377–1393; discussion 1395–1404.
20. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005;352(10):987–996.
21. Galanis E, Wu W, Sarkaria J, et al. Incorporation of biomarker assessment in novel clinical trial designs: personalizing brain tumor treatments. *Curr Oncol Rep*. 2011;13(1):42–49.
22. Hegi ME, Diserens A-C, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Engl J Med*. 2005;352(10): 997–1003.
23. Phillips HS, Kharbanda S, Chen R, et al. Molecular subclasses of high-grade glioma predict prognosis, delineate a pattern of disease progression, and resemble stages in neurogenesis. *Cancer Cell*. 2006;9(3): 157–173.
24. Verhaak RG, Hoadley KA, Purdom E, et al. Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NF1. *Cancer Cell*. 2010; 17(1):98–110.
25. Colman H, Zhang L, Sulman EP, et al. A multigene predictor of outcome in glioblastoma. *Neuro Oncol*. 2010;12(1):49–57.
26. Alexander BM, Mehta MP. Role of isocitrate dehydrogenase in glioma. *Expert Rev Neurother*. 2011;11(10):1399–1409.
27. Hartmann C, Hentschel B, Wick W, et al. Patients with IDH1 wild type anaplastic astrocytomas exhibit worse prognosis than IDH1-mutated glioblastomas, and IDH1 mutation status accounts for the unfavorable prognostic effect of higher age: implications for classification of gliomas. *Acta Neuropathol*. 2010;120(6):707–718.
28. Yan H, Parsons DW, Jin G, et al. IDH1 and IDH2 mutations in gliomas. *N Engl J Med*. 2009;360(8):765–773.
29. Wick W, Platten M, Meisner C, et al. Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: the NOA-08 randomised, phase 3 trial. *Lancet Oncol*. 2012;13(7): 707–715.
30. Trippa L, Lee EQ, Wen PY, et al. Bayesian adaptive randomized trial design for patients with recurrent glioblastoma. *J Clin Oncol*. 2012;30(26): 3258–3263.
31. FDA. Table of pharmacogenomic biomarkers in drug labels. http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm (accessed September 13, 2012).
32. Heimberger AB, Sampson JH. The PEPvIII-KLH (CDX-110) vaccine in glioblastoma multiforme patients. *Exp Opin Biol Ther*. 2009;9(8): 1087–1098.
33. Fornier M, Risio M, Van Poznak C, Seidman A. HER2 testing and correlation with efficacy of trastuzumab therapy. *Oncology (Williston Park)*. 2002;16(10):1340–1348, 1351–1352; discussion 1352, 1355–1358.
34. Berry DA. Bayesian clinical trials. *Nat Rev Drug Disc*. 2006;5(1): 27–36.
35. Esserman LJ, Berry DA, Demichele A, et al. Pathologic complete response predicts recurrence-free survival more effectively by cancer subset: results from the I-SPY 1 TRIAL—CALGB 150007/150012, ACRIN 6657. *J Clin Oncol*. 2012;30(26):3242–3249.
36. Shahar T, Nossek E, Steinberg DM, et al. The impact of enrollment in clinical trials on survival of patients with glioblastoma. *J Clin Neurosci*. 2012;19(11):1530–1534.
37. Brandes AA, Franceschi E, Tosoni A, et al. MGMT promoter methylation status can predict the incidence and outcome of pseudoprogression after concomitant radiochemotherapy in newly diagnosed glioblastoma patients. *J Clin Oncol*. 2008;26(13):2192–2197.
38. Esserman LJ, Berry DA, Cheang MC, et al. Chemotherapy response and recurrence-free survival in neoadjuvant breast cancer depends on biomarker profiles: results from the I-SPY 1 TRIAL (CALGB 150007/150012; ACRIN 6657). *Breast Cancer Res Treat*. 2012;132(3): 1049–1062.
39. Lamborn KR, Yung WK, Chang SM, et al. Progression-free survival: an important end point in evaluating therapy for recurrent high-grade gliomas. *Neuro Oncol*. 2008;10(2):162–170.
40. Polley MY, Lamborn KR, Chang SM, Butowski N, Clarke JL, Prados M. Six-month progression-free survival as an alternative primary efficacy endpoint to overall survival in newly diagnosed glioblastoma patients receiving temozolomide. *Neuro Oncol*. 2010;12(3):274–282.
41. Ballman KV, Buckner JC, Brown PD, et al. The relationship between six-month progression-free survival and 12-month overall survival end points for phase II trials in patients with glioblastoma multiforme. *Neuro Oncol*. 2007;9(1):29–38.
42. Hu LS, Eschbacher JM, Heiserman JE, et al. Reevaluating the imaging definition of tumor progression: perfusion MRI quantifies recurrent glioblastoma tumor fraction, pseudoprogression, and radiation necrosis to predict survival. *Neuro Oncol*. 2012;14(7):919–930.
43. Hamstra DA, Chenevert TL, Moffat BA, et al. Evaluation of the functional diffusion map as an early biomarker of time-to-progression and overall survival in high-grade glioma. *Proc Natl Acad Sci U S A*. 2005;102(46):16759–16764.
44. Chen W, Delaloye S, Silverman DH, et al. Predicting treatment response of malignant gliomas to bevacizumab and irinotecan by imaging proliferation with [18F] fluorothymidine positron emission tomography: a pilot study. *J Clin Oncol*. 2007;25(30):4714–4721.
45. Gallo P, Chuang-Stein C, Dragalin V, Gaydos B, Krams M, Pinheiro J. Adaptive designs in clinical drug development—an executive summary of the PhRMA Working Group. *J Biopharm Stat*. 2006;16(3):275–283.
46. Foundation for the National Institutes of Health. The Biomarkers Consortium—cancer steering committee. http://www.biomarkersconsortium.org/steering_cancer.php (accessed May 8, 2013).
47. Lee JJ, Chen N, Yin G. Worth adapting? Revisiting the usefulness of outcome-adaptive randomization. *Clin Cancer Res*. 2012;18(17): 4498–4507.
48. Couzin-Frankel J. FDA's $25 million pitch for improving drug regulation. *Science Insider*. 2010; http://news.sciencemag.org/scienceinsider/2010/10/fdas-25-million-pitch-for-improving.html?0. Accessed May 8, 2013.