

Running Title: ADAPTIVE GLOBAL INNOVATIVE LEARNING ENVIRONMENT FOR GBM

Title: Adaptive Global Innovative Learning Environment for Glioblastoma: GBM

AGILE

Authors: Brian M. Alexander¹, Sujuan Ba², Mitchel S. Berger³, Donald A. Berry^{4,5},
Webster K. Cavenee⁶, Susan M. Chang³, Timothy F. Cloughesy⁷, Tao Jiang⁸, Mustafa
Khasraw⁹, Wenbin Li¹⁰, Robert Mittman^{11, 12}, George H. Poste^{12, 13}, Patrick Y. Wen¹, W.
K. Alfred Yung¹⁴, and Anna D. Barker^{11, 12, 15} on behalf of the GBM AGILE Network

Author Affiliations: ¹Center for Neuro-Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; ²National Foundation for Cancer Research, Bethesda, MD; ³Department for Neurological Surgery, University of California-San Francisco; Department of Biostatistics, ⁴The University of Texas MD Anderson Cancer Center, Houston, TX; ⁵Berry Consultants, Austin, TX; ⁶Ludwig Institute for Cancer Research, University of California-San Diego; ⁷Neuro-Oncology Program, University of California-Los Angeles; ⁸Department of Clinical Oncology, Capital Medical University, Beijing, China; ⁹NHMRC Clinical Trials Centre, The University of Sydney Medical School, Australia; ¹⁰Glioma Department, Beijing Shijitan Hospital, Capital Medical University, Beijing, China; ¹¹School of Biological and Health Systems Engineering, School of Computing, Informatics, and Decision Systems Engineering, Ira A. Fulton Schools of Engineering, Arizona State University; ¹²National Biomarker Development Alliance, Arizona State University, Tempe, AZ; ¹³Complex Adaptive Systems Initiative, Arizona State University, Tempe, AZ; ¹⁴Department of Neuro-Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; ¹⁵School of Life Sciences, Arizona State University, Tempe, AZ

Running Title: ADAPTIVE GLOBAL INNOVATIVE LEARNING ENVIRONMENT FOR GBM

Corresponding Author Information: Brian M. Alexander MD, MPH, Center for
Neuro-Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Postal Address: 450 Brookline Avenue, Boston, MA 02215

Email Address: brian_alexander@dfci.harvard.edu

Phone Number: (617) 732 7560

Running title: Adaptive Global Innovative Learning Environment for GBM

Keywords: *Glioblastoma, Platform Trials, Adaptive Clinical Trials, Biomarkers,
Seamless Clinical Trials*

Financial Support: Supported through the National Biomarker Development Alliance,
the Cure Brain Cancer Foundation, the National Foundation for Cancer Research, the
National Brain Tumor Society, a Burroughs Wellcome Innovations in Regulatory Science
Award, and anonymous patient advocate donors.

Conflict of Interest Disclosure Statement: No Conflicts of Interest to Disclose.

Word Count: 2,904

Number of Tables and Figures: 3

Running Title: ADAPTIVE GLOBAL INNOVATIVE LEARNING ENVIRONMENT FOR GBM

Abstract:

Glioblastoma (GBM) is a deadly disease with few effective therapies. While much has been learned about the molecular characteristics of the disease, this knowledge has not been translated into clinical improvements for patients. At the same time, many new therapies are being developed. Many of these therapies have potential biomarkers to identify responders. The result is an enormous amount of testable clinical questions that must be answered efficiently. The GBM Adaptive Global Innovative Learning Environment (GBM AGILE) is a novel, multi-arm, platform trial designed to address these challenges. It is the result of the collective work of over 130 oncologists, statisticians, pathologists, neurosurgeons, imagers, and translational and basic scientists from around the world. GBM AGILE is comprised of two stages. The first stage is a Bayesian adaptively randomized screening stage to identify effective therapies based on impact on overall survival compared with a common control. This stage also finds the population in which the therapy shows the most promise based on clinical indication and biomarker status. Highly effective therapies transition in an inferentially seamless manner in the identified population to a second confirmatory stage. The second stage uses fixed randomization to confirm the findings from the first stage in order to support registration. Therapeutic arms with biomarkers may be added to the trial over time while others complete testing. The design of GBM AGILE enables rapid clinical testing of new therapies and biomarkers to speed highly effective therapies to clinical practice.

Introduction

Traditional phase II and III trials include two arms in preset patient populations with preset sample sizes and address a single question. A small number of phase II trials have departed from this traditional design and seek to address multiple hypotheses within a single trial. Some include many experimental arms, adding and dropping arms over time (1). Others strive to match treatment arms with patient subtypes (including those defined by biomarkers), adaptively randomizing patients based on accumulating results of the trial (2), and adapting the sample size to the results (3-5).

In this article we describe an inferentially seamless (6) phase II/III platform trial for glioblastoma (GBM). GBM AGILE (GBM Adaptive Global Innovative Learning Environment) is a two-stage, multi-arm, platform trial. Arms enter the trial, are compared with a common control arm for impact on survival, and leave the trial when their evaluation is complete. The initial stage uses adaptive randomization among the experimental arms within clinical and biomarker patient subtypes. This screening stage evaluates many therapies (including combinations) and identifies indications for each promising arm. Highly effective therapies move to a second stage designed to confirm that signal and indication in a small cohort of patients using fixed randomization versus control to enable registration. The GBM AGILE trial design offers the opportunity to accelerate delivery of improved therapies to trial participants, while the broadly defined eligibility criteria will leverage information learned from more patients. The seamless inferential design means that highly effective treatment arms proceed rapidly through the trial, enabling faster registration, regulatory review, and adoption for routine clinical care. Promising arms that do not meet criteria for the confirmatory stage exit the trial with a

Running Title: ADAPTIVE GLOBAL INNOVATIVE LEARNING ENVIRONMENT FOR GBM

wealth of data to refine biomarker hypotheses and enable go/no go decisions outside of the trial.

GBM AGILE is also a novel clinical research network designed to speed the process of developing therapies for patients with rare diseases. It focuses the therapeutic development process around a specific disease, leverages the expertise of the research community, and optimizes the clinical testing for that population. The planning processes that shaped the trial and its international scope comprises the efforts of over 130 oncologists, statisticians, pathologists, neurosurgeons, imagers, and translational and basic scientists.

Background and Rationale

GBM is a deadly disease with few effective therapies. There were an estimated 22,810 cases of primary malignant brain tumors in United States in 2014, of which GBM is the most common type (7). According to the International Agency for Research on Cancer, there are more than 250,000 tumors of the central nervous system worldwide each year, and approximately 190,000 deaths (8). Patients with newly diagnosed GBM are treated with maximal safe surgical resection followed by radiation and temozolomide (TMZ). Median survival time for patients with tumors harboring methylation of the DNA repair gene *O6-methylguanine DNA methyltransferase (MGMT)* is 23 months with a 5-year survival of 14% (9). Patients with tumors that have unmethylated *MGMT* promoters fare worse with a median survival time of 13 months and a 5-year survival of 8% (10). Once GBM recurs, there are currently no options with meaningful efficacy.

Running Title: ADAPTIVE GLOBAL INNOVATIVE LEARNING ENVIRONMENT FOR GBM

Despite numerous phase II and III clinical trials performed over several decades, only minimal advances have been made and little has been learned. This contrasts with the substantial molecular information available for GBM due to large-scale genome sequencing projects such as The Cancer Genome Atlas (TCGA) (11) and others (12). In parallel, many new therapies have been developed for clinical testing. These scientific advances lead to optimism that molecularly based precision medicine may improve outcomes for GBM patients but they also highlight the limitations of current clinical trial designs that do not test multiple therapies and biomarker combinations simultaneously.

One potential solution for testing multiple hypotheses within the same clinical trial is a multi-arm, Bayesian adaptively randomized platform trial (13-15). These trials may incorporate common control arms for meaningful endpoints, a fluid infrastructure for adding or dropping experimental arms, and an ability to use data as it is available during the trial to alter decision-making in a pre-specified manner. The most notable example is I-SPY 2 in breast cancer (3,16,17). Using such a design to evaluate new therapies for GBM requires some changes but the overall concepts and goals may still be applied (18). Outcome adaptive randomization for GBM would be more efficient than balanced randomization, even when longer time to event endpoint such as overall survival (OS) is used (19), and such designs have been advocated by expert panels (20).

The GBM AGILE Trial

GBM AGILE is the first global, disease-specific, platform trial for GBM designed to specifically capitalize on the growing knowledge base from the molecular sciences, incorporate novel clinical trial innovations, and leverage the emerging global capabilities

Running Title: ADAPTIVE GLOBAL INNOVATIVE LEARNING ENVIRONMENT FOR GBM

to undertake more innovative and complex trial protocols. The trial will be initiated in the US and Australia, followed by China and potentially others to accelerate recruitment of large numbers of patients. As a consequence of both the scope and innovative crowd sourced design, GBM AGILE will create a learning environment to identify effective therapies and biomarkers for GBM. By including patients with both newly diagnosed and recurrent tumors and accounting for their presentation in a statistical model, the trial design will facilitate integration of knowledge that might have otherwise been disparate. Importantly, while GBM AGILE is designed to identify effective therapies and develop biomarkers for GBM, the overall process and philosophy could also be adapted for other rare cancers and diseases.

Trial Design

GBM AGILE has several important statistical innovations and is designed as a registration trial to accelerate availability of effective therapies and biomarkers for routine standard of care (SOC). As shown in Figures 1 and 2, it is a Bayesian, adaptively randomized, multi-arm, platform trial. The primary endpoint is overall survival. GBM AGILE identifies and validates candidate biomarkers under a single platform master protocol. Experimental therapies can enter the trial at any time, accrual rate permitting. A therapy that is sufficiently promising in an adaptively randomized screening stage will move to a confirmatory stage with fixed randomization. Simulations ensure control of type I error to support registration.

Running Title: ADAPTIVE GLOBAL INNOVATIVE LEARNING ENVIRONMENT FOR GBM

Inclusion/exclusion criteria

Patients with a histopathologic diagnosis of GBM based on World Health Organization (WHO) criteria (21) will be eligible for GBM AGILE provided they are *IDH R132H* mutation negative by local immunohistochemistry (IHC). *IDH*-mutant GBM has a sufficiently different genomic landscape and phenotypic behavior that the WHO has created separate classifications for *IDH*-mutant and *IDH*-wildtype GBM in the 2016 update. In particular, patients with either newly diagnosed or recurrent tumors will be included, regardless of *MGMT* promoter methylation status. Other standard clinical trial eligibility characteristics also apply.

Biomarker assessment

GBM AGILE is also an efficient platform to explore the utility of various biomarkers. The trial will evaluate several kinds of biomarkers (22) as described below and summarized in Figure 2. In contrast with the experience with other cancers, GBM has very limited well-defined *a priori* molecular biomarker subgroups with clinical utility (18). As stated above, *IDH1* immunohistochemistry will be used for diagnostic and eligibility purposes while *MGMT* promoter methylation status will be used as a *stratification* variable to help assign patient *subtype* (Figures 2 and 3). Clinical presentation as either newly diagnosed or recurrent disease will serve as the other stratification variable in addition to *MGMT* promoter methylation status. Stratification variables define three *subtypes* of GBM: newly diagnosed methylated (NDM), newly diagnosed unmethylated (NDU), and recurrent disease (RD).

Running Title: ADAPTIVE GLOBAL INNOVATIVE LEARNING ENVIRONMENT FOR GBM

Some experimental arms will enter the trial with an associated *enrichment biomarker* identified through central testing that is specific to the arm. Enrichment markers are hypothesized predictive markers for the experimental agent. For that reason, enrichment markers are “context dependent” and only considered with respect to the associated experimental arm; other arms are evaluated irrespective of that arm’s biomarker. For example, an *EGFR* inhibitor might enter the trial with a proposed enrichment biomarker of *EGFR* mutation or amplification identified through next-generation sequencing. Testing for these alterations as enrichment markers would continue as long as the *EGFR* inhibitor was being evaluated on the trial and be considered only for that arm. Enrichment markers that define indications for effective therapies become *stratification* markers when that new therapy becomes part of a new standard of care. Each experimental arm can have at most one *a priori* defined enrichment marker. There may be other biomarkers that are better at finding responders that are unknown at the time of entry onto the trial, however. The wealth of biomarker data generated as part of GBM AGILE will therefore be a valuable resource for retrospective exploratory analyses to identify such biomarkers.

The addition of enrichment markers to the stratification markers doubles the possible subtypes relative to the relevant experimental agent – NDM, NDU, and RD each have biomarker positive and biomarker negative subtypes (Figure 3). *Subtypes* are characteristics specific to the tumor or patient; each patient belongs to one and only one subtype relative to a given experimental arm. This should be contrasted with biomarker *signatures*, described below, which are therapy-specific characteristics.

Running Title: ADAPTIVE GLOBAL INNOVATIVE LEARNING ENVIRONMENT FOR GBM

For patients with RD, contemporary tissue for biomarker assessment will not initially be required. There will be a subset of patients with RD that do have re-resection prior to enrollment, however. For such patients, the most contemporary tissue will be used for biomarker analysis. Furthermore, biomarker subgroups in such patients will be compared to tissue from the original diagnosis to analyze the stability of biomarker subgroups over time. If there is evidence of relevant biomarker subgroup change due to selection, requirements for contemporary tissue analysis will be revisited.

Bayesian adaptive randomization.

The three subtypes defined by stratification markers have different standard of care control arms and different ways that experimental arms are comprised. Control arms for the different subtypes are radiation therapy (RT) and TMZ for NDM and NDU, and lomustine (CCNU) for RD. These controls may be updated through amendment if standard of care changes over time. Experimental arms for NDM use RT and TMZ as a backbone and add the experimental agent or combination while those for NDU may omit TMZ due to limited efficacy in this population. For RD, the experimental agent or combination can be combined with CCNU or considered alone.

Control therapy is assigned to 20% of the patients within all patient subtypes throughout the trial. Experimental arms are compared against control therapy, and randomization probabilities are assigned accordingly within subtypes. Experimental therapies are assigned in proportion to their (Bayesian) probabilities of prolonging survival longer than control. Initially, randomization probabilities are equal. These probabilities are updated monthly based on the outcomes available in the trial at the time.

Running Title: ADAPTIVE GLOBAL INNOVATIVE LEARNING ENVIRONMENT FOR GBM

While overall survival (OS) was chosen as the primary endpoint for GBM AGILE, adaptive randomization is not reliant on OS in general. Other endpoints, such as progression-free survival or response rate, could also have been used to inform adaptive randomization. With faster time to event, such endpoints may lead to more efficiency gains. But there also exists the potential that a treatment might positively impact these endpoints without impacting survival. Because of this potential, GBM AGILE will initially use OS to inform adaptive randomization but leaves open the possibility of using earlier data through the longitudinal model (described below).

During each experimental arm's screening stage, its performance in comparison with control will be prospectively evaluated in predefined *signatures*. Signatures are groupings of the stratification and enrichment biomarker defined subtypes that are potential indications for the experimental therapy. Example signatures include "all newly diagnosed patients" or "patients with *EGFR* positive recurrent disease." There are ten possible signatures for an arm with an enrichment biomarker and five possible signatures for arms without an enrichment marker. In contrast to subtypes, each patient or tumor belongs to multiple possible signatures, but effective therapies will graduate with only one signature. The signature is the biomarker-defined group for which there is the best chance of success.

An experimental arm that is performing sufficiently well during its initial stage will "graduate." Graduation signals a seamless move into the arm's confirmatory stage within its graduating signature. During an arm's confirmation stage, it will be randomly assigned to a fixed proportion (40%) of the patients within its graduating signature, up to a maximum of 50 patients. The final and primary analysis of all experimental arms,

Running Title: ADAPTIVE GLOBAL INNOVATIVE LEARNING ENVIRONMENT FOR GBM

whether or not they have a confirmatory stage, will be a comparison of the primary end point (OS) against control. The primary analyses will be the arm's (Bayesian) probabilities of superiority over control for each of the arm's signatures. All controls accrued to the trial up until the time the last patient was accrued to the experimental arm in question will be used in this comparison via a time-adjusted, covariate-adjusted, and arm-adjusted analysis that utilizes the results of all patients assigned to all arms in the trial.

The number of experimental arms will vary as arms are added or removed due to graduation or futility. An arm can be added to the trial at any time after it is approved by the relevant committees on GBM AGILE, provided the patient accrual rate is sufficient. Arms that do not graduate may still be worth further study. In those cases, data from GBM AGILE will be invaluable in making further go/no-go decisions, effectively powering follow up trials, and determining the value of biomarkers for eligibility decisions.

Response biomarkers

Biomarkers to assess response and monitor patients will also be collected. These may be in the form of *pharmacodynamic (PD) or response biomarkers* (22) that may factor into trial conduct if there is a potential association with OS through the longitudinal model (described below). PD/response biomarkers that show associations with treatment effects on OS may also generate data to support development along the surrogate endpoint hierarchy (i.e., *reasonably likely to be validated*) (22). This is an example of how GBM AGILE's platform structure with continuous learning may be used

Running Title: ADAPTIVE GLOBAL INNOVATIVE LEARNING ENVIRONMENT FOR GBM

to develop other biomarkers and improve the overall development process in addition to those associated with specific therapies.

While there are no restrictions on the types of assessments that may be used as response biomarkers, imaging will play a major role. The Jumpstarting Brain Tumor Drug Development Coalition Imaging Standardization Steering Committee has undertaken an extensive effort to standardize MRI protocols for multicenter studies to maximize the potential of MR imaging techniques as both pre and post-treatment biomarkers (23).

Longitudinal model

The primary endpoint for GBM AGILE is OS. However, patients in the trial for the same length of time may have different future life expectancies. We are building a longitudinal model that will take each patient's current circumstances into account in predicting time of death. This model will be developed in coordination with regulators and will be incorporated via protocol amendment after the trial starts enrollment. Factors in the model include measurements over time using MRI, the patient's performance status, and importantly, the treatment arm. For example, immune-based therapy may have little effect on measurable tumor burden but still prolong survival. For such an arm the model will learn that MRI measurements offer little help in predicting the patient's time of death. The various parameters in the model will have probability distributions that will be updated via Bayes' rule as OS information becomes available in the trial and potentially be utilized by the randomization algorithm for additional efficiency (24).

Running Title: ADAPTIVE GLOBAL INNOVATIVE LEARNING ENVIRONMENT FOR GBM

Treatment Selection and Target/Biomarker Identification

GBM AGILE will plan to add therapies and associated biomarkers during the course of the trial. Identification of robust data supporting these treatments and biomarkers is paramount. Potential experimental arms and associated enrichment markers can be identified by investigators within GBM AGILE or proposed by outside investigators. These therapies and biomarkers are then prioritized and reviewed by the various GBM AGILE committees prior to inclusion. The treatment and biomarker selection processes will accord high priority to timely communication and transparency. Decisions for inclusion of potential therapies in the trial will be made on the quality of the science and the readiness for phase II testing.

Summary

GBM AGILE is a major departure from standard clinical trials. Several innovations are common to other platform trials: adding and dropping arms, adaptive randomization within biomarker-defined subgroups, and the ability to address multiple hypotheses in a single trial protocol. GBM AGILE takes these innovations a step further by including a seamless transition to a second confirmatory stage to enable registration. This could potentially cut years from the drug development process and substantially reduce cost. Even arms that do not progress to a confirmatory stage may generate valuable data to refine biomarker hypotheses and inform better decision making for trials outside of GBM AGILE. Including both newly diagnosed and recurrent patients and having an ongoing platform structure also enables more patients to participate. This results in more opportunities to learn from those who develop this deadly tumor and to

Running Title: ADAPTIVE GLOBAL INNOVATIVE LEARNING ENVIRONMENT FOR GBM

offer better treatment options. These factors and an environment that fosters collaboration and innovation make GBM AGILE a model for the future development of new therapies for rare diseases.

Acknowledgment

The GBM AGILE Network includes the following members: P. David Adelson, Brian M. Alexander, Joe Alper, Michelle M. Arnold, David F. Arons, David N. Ashley, Sujuan Ba, Anna D. Barker, Mitchel S. Berger, Donald A. Berry, Jerrold L. Boxerman, Daniel J. Brat, Cameron W. Brennan, Michael Buckland, Kenneth Buetow, Meredith Buxton, Lewis C. Cantley, Webster K. Cavenee, Susan M. Chang, Ling Chen, Lynda Chin, E. Antonio Chiocca, Timothy F. Cloughesy, Darrel P. Cohen, Howard Colman, Carolyn Compton, Jason Connor, Laurence James-Neil Cooper, Vladimir Coric, Joseph F. Costello, John F. de Groot, Jayesh Desai, Giulio Draetta, Benjamin M. Ellingson, Laura Jean Esserman, Howard A. Fine, Evanthia Galanis, Hui Gan, Val Gebski, Elizabeth R. Gerstner, Robert Gillies, Jonathan G. Goldin, Charles Goldthwaite, Federico Goodsaid, Todd Graves, Steven Gutman, Wendy Hague, James R. Heath, Amy B. Heimberger, Jonathan Hirsch, Kyle Holen, Jason T. Huse, Nola Hylton, Tao Jiang, Mustafa Khasraw, Alec Kimmelman, Robert Latek, Sean Leong, Wenbin Li, Ping Li, Linda Liao, Michael Lim, David N. Louis, Pedro Lowenstein, Wenbin Ma, Mark Maclean, Carlo Maley, Zhiqi Mao, Qing Mao, Ingo K. Mellinghoff, Tom Mikkelsen, Paul S. Mischel, Robert Mittman, Sarah J. Nelson, Hideho Okada, Melissa C. Paoloni, Luis Parada, Tom Parke, David R. Parkinson, Kristyn Pineda, Whitney B. Pope, George H. Poste, Michael D. Prados, Xiaoguang Qiu, John Quackenbush, David A. Reardon, Gregory J. Riggins, Mark

Running Title: ADAPTIVE GLOBAL INNOVATIVE LEARNING ENVIRONMENT FOR GBM

Rosenthal, John H. Sampson, Jann N. Sarkaria, Trevor Saxman, R. John Simes, David Spetzler, Catherine Stace, Michelle Stewart, Robert Strausberg, Daniel C. Sullivan, Erik P. Sulman, Kristin Swanson, Donald E. Thornton, Carrie Treadwell, Laura van 't Veer, Scott R. Vandenberg, Roeland Verhaak, Inder Verma, Max Wallace, Renzhi Wang, Xiang Timothy Wang, Xinghe Wang, Yi Michael Wang, Yu Wang, Anthony Weeks, Michael Weller, Patrick Y. Wen, Forest White, Wolfgang Wick, Otmar Wiestler, Nicole Willmarth, Elizabeth M. Wilson, Benjamin Winograd, Ji Xiong, Hai Yan, Yu Yao, Mao Ying, Xinguang Yu, W. K. Alfred Yung, Wei Zhang, Xin Vincent Zhang, Zhenyu Zhao, and Fan Zhao

References

1. Berry SM, Connor JT, Lewis RJ. The platform trial: an efficient strategy for evaluating multiple treatments. *JAMA*. 2015;313(16):1619-1620.
2. Meurer WJ, Lewis RJ, Berry DA. Adaptive clinical trials: a partial remedy for the therapeutic misconception? *JAMA*. 2012;307(22):2377-2378.
3. 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.
4. Berry SM, Petzold EA, Dull P, Thielman NM, Cunningham CK, Corey GR, *et al*. A response adaptive randomization platform trial for efficient evaluation of Ebola virus treatments: a model for pandemic response. *Clin Trials*. 2016;13(1):22-30.
5. Ritchie K, Ropacki M, Albala B, Harrison J, Kaye J, Kramer J, *et al*. Recommended cognitive outcomes in preclinical Alzheimer's disease: consensus statement from the European Prevention of Alzheimer's Dementia project. *Alzheimers Dement*. 2016;13(2):186-195.
6. Berry DA. Adaptive clinical trials in oncology. *Nat Rev Clin Oncol*. 2011;9(4):199-207.
7. Ostrom QT, Gittleman H, Farah P, Ondracek A, Chen Y, Wolinsky Y, *et al*. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2006-2010. *Neuro Oncol*. 2013;15(Suppl 2):ii1-ii56.

Running Title: ADAPTIVE GLOBAL INNOVATIVE LEARNING ENVIRONMENT FOR GBM

8. Cancer International Agency for Research on Cancer. Global Cancer Observatory. 2016; <http://gco.iarc.fr/>. Accessed September 4, 2016.
9. Stupp R, Mayer M, Kann R, Weder W, Zouhair A, Betticher DC, *et al.* Neoadjuvant chemotherapy and radiotherapy followed by surgery in selected patients with stage IIIB non-small-cell lung cancer: a multicentre phase II trial. *Lancet Oncol.* 2009;10(8):785-793.
10. Hegi ME, Diserens AC, Gorlia T, Hamou MF, de Tribolet N, Weller M, *et al.* MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Engl J Med.* 2005;352(10):997-1003.
11. TCGA. Comprehensive genomic characterization defines human glioblastoma genes and core pathways. *Nature.* 2008;455(7216):1061-1068.
12. Parsons DW, Jones S, Zhang X, Lin JCH, Leary RJ, Angenendt P, *et al.* An integrated genomic analysis of human glioblastoma multiforme. *Science.* 2008;321(5897):1807-1812.
13. Berry DA. Bayesian clinical trials. *Nat Rev Drug Discov.* 2006;5(1):27-36.
14. Berry DA. The Brave New World of clinical cancer research: adaptive biomarker-driven trials integrating clinical practice with clinical research. *Mol Oncol.* 2015;9(5):951-959.
15. Berry DA. Emerging innovations in clinical trial design. *Clin Pharmacol Ther.* 2016;99(1):82-91.
16. Park JW, Liu MC, Yee D, Yau C, van 't Veer LJ, Symmans WF, *et al.* Adaptive randomization of neratinib in early breast cancer. *N Engl J Med.* 2016;375(1):11-22.

Running Title: ADAPTIVE GLOBAL INNOVATIVE LEARNING ENVIRONMENT FOR GBM

17. Rugo HS, Olopade OI, DeMichele A, Yau C, van 't Veer LJ, Buxton MB, *et al.*
Adaptive randomization of veliparib–carboplatin treatment in breast cancer. *N Engl J Med.* 2016;375(1):23-34.
18. Alexander BM, Wen PY, Trippa L, Reardon DA, Yung WKA, Parmigiani G, *et al.*
Biomarker-based adaptive trials for patients with glioblastoma – lessons from I-SPY 2. *Neuro Oncol.* 2013;15(8):972-978.
19. Trippa L, Lee EQ, Wen PY, Batchelor TT, Cloughesy T, Parmigiani G, *et al.*
Bayesian adaptive randomized trial design for patients with recurrent glioblastoma. *J Clin Oncol.* 2012;30(26):3258-3263.
20. Alexander BM, Galanis E, Yung WKA, Ballman KV, Boyett JM, Cloughesy TF, *et al.* Brain Malignancy Steering Committee clinical trials planning workshop: report from the Targeted Therapies Working Group. *Neuro Oncol.* 2015;17(2):180-188.
21. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, *et al.* The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. *Acta Neuropathol.* 2016;131(6):803-820.
22. Group F-NBW. BEST (Biomarkers, EndpointS, and other Tools) Resource. 2016; <http://www.ncbi.nlm.nih.gov/books/NBK326791/?report=classic>. Accessed February 9th, 2016.
23. Ellingson BM, Bendszus M, Boxerman J, Barboriak D, Erickson BJ, Smits M, *et al.* Consensus recommendations for a standardized Brain Tumor Imaging Protocol in clinical trials. *Neuro Oncol.* 2015;17(9):1188-1198.

Running Title: ADAPTIVE GLOBAL INNOVATIVE LEARNING ENVIRONMENT FOR GBM

24. Trippa L, Wen PY, Parmigiani G, Berry DA, Alexander BM. Combining progression-free survival and overall survival as a novel composite endpoint for glioblastoma trials. *Neuro Oncol.* 2015;17(8):1106-1113.

Figure legends

Figure 1: Lifecycle of GBM AGILE – As new patients are added to GBM AGILE, their biomarker subtype is assessed and they are randomized to an experimental arm or control based on the randomization algorithm that is powered by data accruing during the trial.

Each experimental arm may participate in two stages during the trial: an initial adaptively randomized screening stage and a second confirmatory stage for those experimental arms that graduate. Patient outcome data is updated during the trial, which is used to update the longitudinal model that estimates the probability of the primary endpoint (survival).

Following update of the longitudinal model, the probability of each stage 1 experimental arm being better than control in each signature is calculated, after which predetermined decision rules will be applied that will allow the arm to: 1. stop for futility, 2. complete maximum accrual, 3. graduate and stop accrual (predetermined), 4. graduate and proceed to stage 2 (predetermined), 5. continue in stage 1. Following graduation, the decision to stop accrual or proceed to stage 2 will depend on the estimated time for stage 2

completion. If an arm graduates with a sufficiently small biomarker-defined signature such that that the accrual rate would not enable completion of stage 2 within two years, the arm would not proceed. As stage 1 continues, the probability of experimental arms being better than control are calculated for each subtype, a patient-specific characteristic and the locus of randomization, and randomization probabilities will be updated.

Experimental arms that continue to stage 2 will proceed with a fixed randomization for a fixed sample size to confirm the signal found in stage 1.

Running Title: ADAPTIVE GLOBAL INNOVATIVE LEARNING ENVIRONMENT FOR GBM

Figure 2: Overall structure and role of biomarkers in GBM AGILE – Diagnostic markers (GBM histopathology and *IDH1 R132H* immunohistochemistry) will be used to assess trial eligibility. Stratification markers (*MGMT* promoter methylation status and clinical context of newly diagnosed versus recurrent) will be combined with enrichment markers to determine patient subtypes. A patient can only belong to one subtype. Enrichment markers are biomarkers hypothesized to be predictive of response to a specific experimental arm and will only be considered as long as the corresponding experimental arm is in the study and only for that arm. The longitudinal model combines assessments made following randomization (tumor growth, performance status) to explore for associations with survival. Additional biomarkers may be evaluated in an exploratory manner to assess for predictive, prognostic, or response utility and be formally incorporated in the prospective trial in future updates should a discovery be made.

Figure 3: Segmentation of patient space into *subtypes* based on stratification and enrichment biomarkers – When there is no enrichment biomarker present, there are three subgroups: newly diagnosed methylated (NDM), newly diagnosed unmethylated (NDU), and recurrent disease (RD). If an enrichment marker is present for a specific arm, this space is further divided into six subgroups as shown. Subgroups for an arm with an enrichment marker pertain only to that arm. Subgroups are patient/tumor characteristics and are mutually exclusive and exhaustive.

Figure 1:

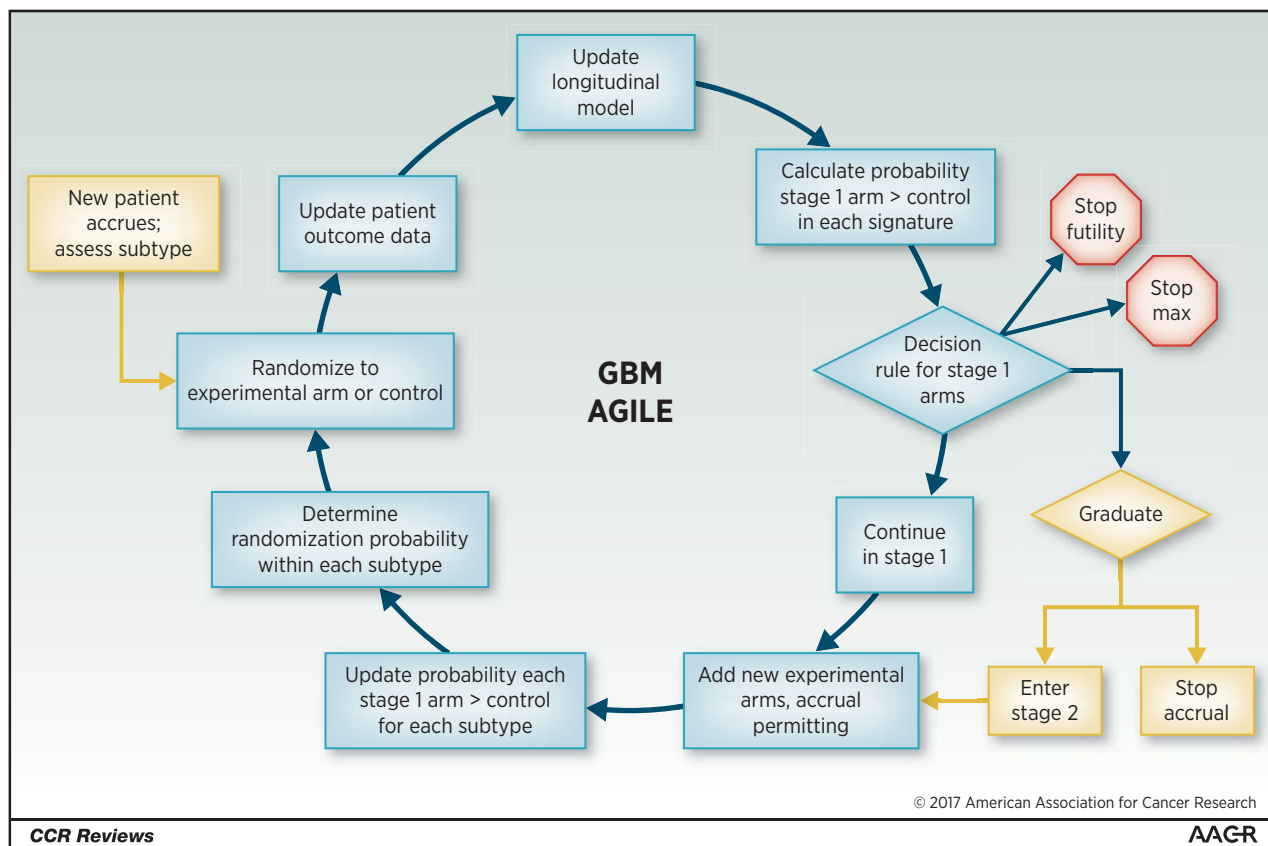


Figure 2:

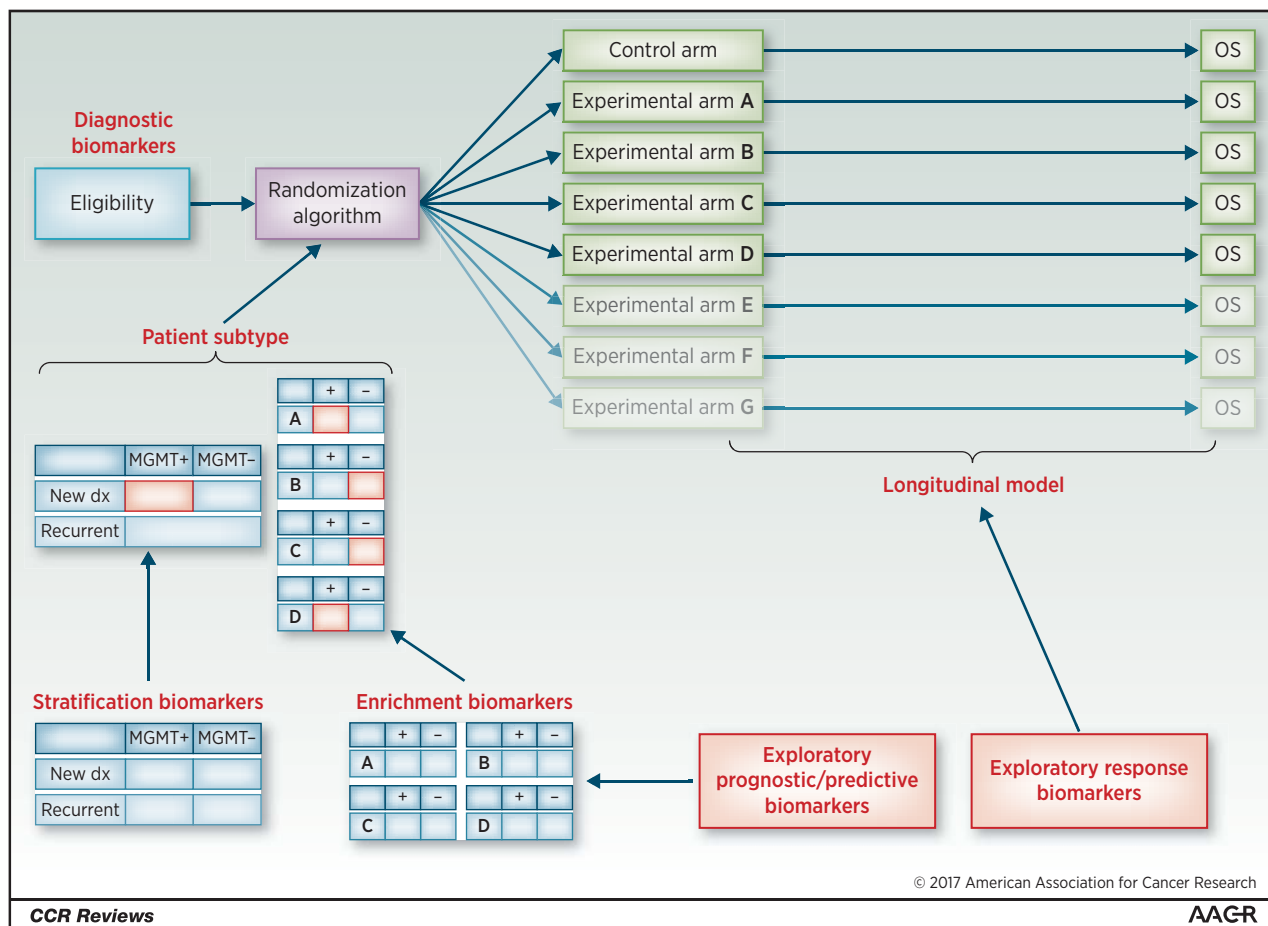
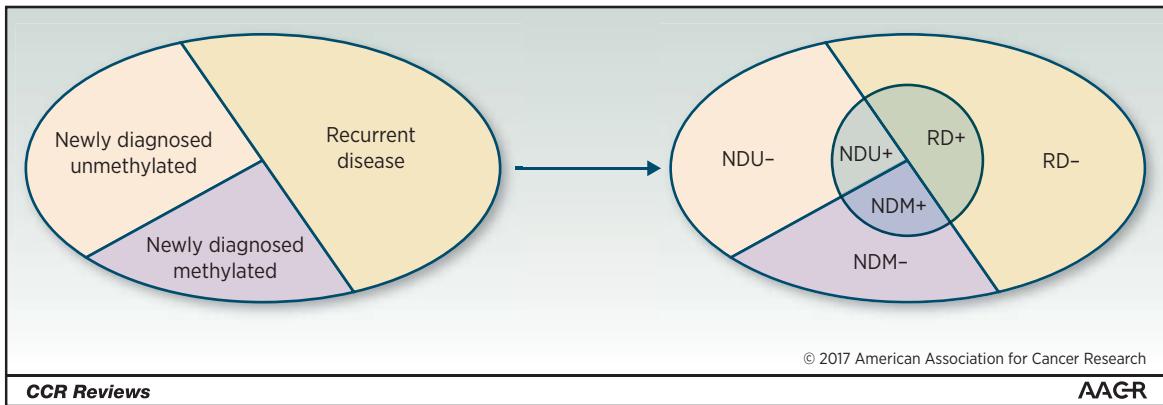


Figure 3:



Clinical Cancer Research

Adaptive Global Innovative Learning Environment for Glioblastoma: GBM AGILE

Brian M Alexander, Sujuan Ba, Mitchel S. Berger, et al.

Clin Cancer Res Published OnlineFirst August 16, 2017.

Updated version Access the most recent version of this article at:
doi:[10.1158/1078-0432.CCR-17-0764](https://doi.org/10.1158/1078-0432.CCR-17-0764)

Author Manuscript Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

E-mail alerts [Sign up to receive free email-alerts](#) related to this article or journal.

Reprints and Subscriptions To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.