special article

Individualized Screening Trial of Innovative Glioblastoma Therapy (INSIGhT): A Bayesian Adaptive Platform Trial to Develop Precision Medicines for Patients With Glioblastoma

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abstract

PURPOSE Adequately prioritizing the numerous therapies and biomarkers available in late-stage testing for patients with glioblastoma (GBM) requires an efficient clinical testing platform. We developed and implemented INSIGhT (Individualized Screening Trial of Innovative Glioblastoma Therapy) as a novel adaptive platform trial (APT) to develop precision medicine approaches in GBM.

METHODS INSIGhT compares experimental arms with a common control of standard concurrent temozolomide and radiation therapy followed by adjuvant temozolomide. The primary end point is overall survival. Patients with newly diagnosed unmethylated GBM who are *IDH* R132H mutation negative and with genomic data available for biomarker grouping are eligible. At the initiation of INSIGhT, three experimental arms (neratinib, abemaciclib, and CC-115), each with a proposed genomic biomarker, are tested simultaneously. Initial randomization is equal across arms. As the trial progresses, randomization probabilities adapt on the basis of accumulating results using Bayesian estimation of the biomarker-specific probability of treatment impact on progression-free survival. Treatment arms may drop because of low probability of treatment impact on overall survival, and new arms may be added. Detailed information on the statistical model and randomization algorithm is provided to stimulate discussion on trial design choices more generally and provide an example for other investigators developing APTs.

CONCLUSION INSIGhT (NCT02977780) is an ongoing novel biomarker-based, Bayesian APT for patients with newly diagnosed unmethylated GBM. Our goal is to dramatically shorten trial execution timelines while increasing scientific power of results and biomarker discovery using adaptive randomization. We anticipate that trial execution efficiency will also be improved by using the APT format, which allows for the collaborative addition of new experimental arms while retaining the overall trial structure.

INTRODUCTION

Clinical development of new therapies and biomarkers is costly and inefficient and frequently results in failure.[1] Such problems are particularly acute for glioblastoma (GBM), where there has been little change in the standard of care over decades, and late-stage failure is common.[2,3] Phase II trials based on end points different than follow-up phase III studies and single-arm designs compared to historical controls may over- or underestimate treatment effects, which may lead to poor therapeutic development.[4]

With the advent of the precision medicine era, trial design has been additionally complicated by the need for clinical development of biomarkers. Developing precision medicines requires not only demonstrating therapeutic efficacy but also understanding the relative benefits of experimental therapies in biomarker-defined patient populations. This makes comparisons with historical controls more difficult and adds complexity to trial design choices. Clinical trials in the era of precision medicine must consider how to develop biomarker data during the trials, make efficient use of multiplexed biomarker screening, and develop assignment algorithms for patients positive for more than one biomarker. Clinical trials often also have logistic and bureaucratic challenges that delay development of new therapies and reduce trial opportunities for patients with deadly diseases. The upfront fixed cost for developing a trial infrastructure is most commonly only amortized over the relatively short life of a single clinical trial.

ASSOCIATED CONTENT

Appendix

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Master protocols and adaptive platform trials (APTs) have been proposed as attractive solutions to efficiently address multiple therapeutic and biomarker hypotheses.[5-7] We developed INSIGhT (Individualized Screening Trial of Innovative Glioblastoma Therapy), a multisite investigator-initiated phase II screening APT, as a solution to precision medicine development challenges for patients with GBM. INSIGhT was specifically designed to enable efficient use of randomly assigned controls, generate information to support genomic biomarker development, and leverage the fixed cost of trial development across more experimental therapies.

METHODS

Eligibility

Patients are eligible for INSIGhT if they have newly diagnosed GBM with unmethylated *O*^{6}*-methylguanine–DNA methyltransferase* (*MGMT*) gene promoters and negative IDH1 R132H mutation–specific immunohistochemistry. The marginal benefit of temozolomide (TMZ) in patients with unmethylated MGMT promoters[8] offers the opportunity to test experimental therapies without combinations with TMZ.[9,10] This potentially accelerates the overall time for drug development (by not needing prior separate phase I studies with TMZ) and eliminates the potential for subtherapeutic dose of the experimental agent as a result of overlapping toxicity with TMZ.[2,3] INSIGhT therefore can support experimental arms with TMZ combinations or with the experimental agent alone. INSIGhT was approved by the Dana-Farber/Harvard Cancer Center Institutional Review Board and by local institutional review boards before site activation.

Treatment Arms and Biomarkers

The overall schema for INSIGhT is shown in Figure 1. The control arm is standard chemoradiotherapy per the European Organisation for Research and Treatment of Cancer NCIC.CE3 study.[11] For experimental arms, therapies may be added to this standard backbone if there are sufficient safety data in combination with TMZ. Experimental therapies may also replace TMZ in the concurrent radiation therapy (RT) portion (if there is a compelling radiosensitizing hypothesis), the adjuvant portion, or both. A pure radiosensitizing agent or experimental RT regimen could theoretically replace standard RT/TMZ while keeping the adjuvant TMZ intact.

Eligibility for INSIGhT requires sufficient genotyping data to define the predetermined biomarker categories for arms currently in the trial. Additional details regarding the initial experimental arms and biomarkers are included in the Data Supplement.

Statistical Considerations

End points and modeling. The primary end point of INSIGhT is overall survival (OS). Progression-free (PFS) survival analysis is used to influence randomization, as described in Results. Power computations, simulations evaluating operating characteristics, and secondary analyses use the proportional hazards (PH) model for both PFS and OS.

There are several arguments to support the use of different outcomes for adaptive randomization (PFS) and final efficacy evaluation (OS). PFS data involve less risk of delayed reporting and capture signals at earlier time points. The relationship between accrual rate and event timing is crucial for response-adaptive trials, because effective variation of randomization probabilities requires rapid generation of treatment effect estimates on the basis of an adequate number of individual outcomes. In addition, treatment effects may have a stronger signal on PFS, a relationship illustrated previously.[12] Finally, potential issues with pseudoprogression and pseudoresponse[13,14] are mitigated by preserving OS as the foundation for stopping rules and final efficacy analyses. That is, promising early results of an experimental treatment accelerate the accrual rate of the corresponding arm without reducing the final sample size of the other experimental arms.

Group-specific adaptive randomization probabilities. Biomarker status (positive or negative) is accounted for both at the individual randomization level and in final analyses. A biomarker group is defined by the subpopulation with identical status for all of the three markers. Patients are randomly assigned using an adaptive algorithm that updates randomization probabilities for the various arms in each biomarker group monthly.[15] The algorithm uses available information generated by INSIGhT (the individual biomarker groups combined with individual PFS) to determine the randomization probabilities that will be used to allocate patients for the subsequent month. The algorithm translates this preliminary evidence on the basis of PFS data into unbalanced randomization probabilities that may vary across biomarker groups. We previously presented simulation results with adaptive randomization probabilities driven by PFS and OS probability models.[16]

PFS model. We use a Bayesian PH model with treatment-biomarker interactions.[17] This accounts for possible effect variations across subgroups. The hazard function for each patient assigned to an experimental arm is modeled, rescaling the baseline by a factor that depends on treatment (main effect), biomarker-specific coefficients, and biomarker-treatment interaction terms. We previously described the use of PH models for the computation of randomization probabilities.[17] We indicate the individual profile with $X = (X_1, X_2, X_3)$. All three biomarkers are binary. The hazard function $\lambda_{X,a}(t)$ for the time-to-event outcome of a patient with biomarker profile X, randomly assigned to experimental arm a, is proportional to the baseline $\lambda(t)$. More specifically,

$$\lambda_{X,a}(t) = \lambda_X(t)\exp(\beta_a + X_1\beta_{a,1} + X_2\beta_{a,2} + X_3\beta_{a,3})$$

with

$$\lambda_X(t) = \lambda(t)\exp(\beta_X X).$$

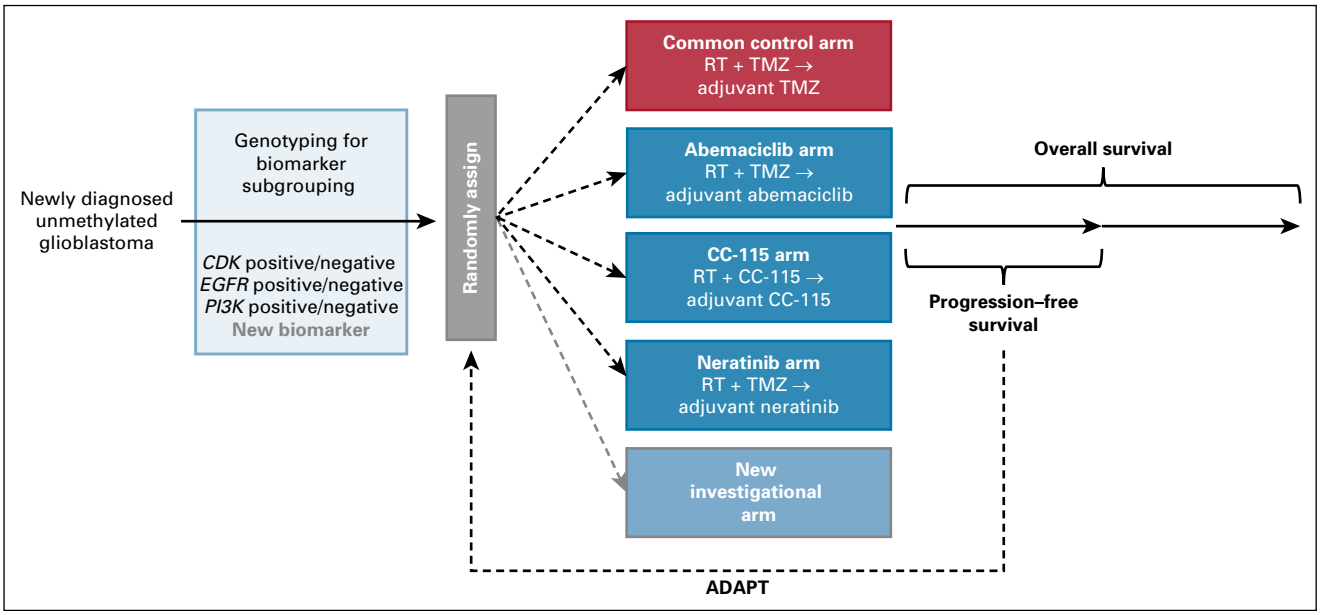

FIG 1. Overall schema for INSIGhT. RT, radiation therapy; TMZ, temozolomide.

The coefficients β_X capture possible differences in the time-to-event distributions across profiles under the control treatment. The described model is used with Bayesian analyses to adapt the randomization probabilities and predict future outcomes.

Sample size. INSIGhT will randomly assign a maximum of 70 patients to each experimental arm. The sample size for the initial set of arms is 70 patients per arm across four arms, for a total of 280 patients, but there are early stopping rules for futility in each arm, and other arms may be added as the trial is ongoing. If new arms are added, the overall sample size can increase to more than 280 patients. Such an increase will depend on the number of experimental arms added and the time at which they will start enrollment. The later new arms start enrolling, the larger the corresponding sample size expansion will be. Indeed, when a new experimental arm is added, the design increases the control-specific sample size to guarantee enrollment of 70 patients in the control after the addition of a novel arm. We previously described the adjustment of the control sample size with the addition of novel arms and potential futility early stopping of experimental arms in platforms.[18]

Operating characteristics of outcome adaptive randomization are related to the accrual rate relative to the event rate, because information from events is used to alter probability of random assignment for newer patients. We estimated an accrual rate of seven patients per month based on prior experience. Sensitivity analyses on the trial operating characteristics considered a range of hypothetic accrual rates, from five to 14 patients per month. Biomarker frequencies were assumed on the basis of data from prior genomic profiling.[19] Monthly updates of the randomization probabilities are combined with a sequential decision rule that drops experimental arms when there is insufficient preliminary evidence to warrant additional investigation of the treatment based on the primary end point (OS). We describe a linear boundary that provides thresholds for predictive probabilities to define the decision rule.

Prior Normal distributions were used for the regression parameters β. They are a priori independent, and the variance ${\sigma_a}^2$ of the main effect β_a is set to have the 80th and 20th percentiles that correspond to (log[2]; duplication of the hazard) and (log[1/2]). The variance ${\sigma_{X,a}}^2$, which regulates the a priori magnitude of interaction terms, is lower; we set ${\sigma_{X,a}}^2 = 0.25{\sigma_a}^2$. Approximate posterior analyses are performed by using the partial likelihood method, because it is standard in both frequentist and Bayesian analyses. Posterior computations during the trial provide, for every combination of biomarker profile X and treatment a, the probability that patients with profile X will benefit from the experimental treatment a:

$$\Pr(\lambda_X > \lambda_{X,a} \mid data)$$

By PH assumptions, either $\lambda_X(t) > \lambda_{X,a}(t)$ at all $t > 0$ with $\lambda_X(t) > 0$ or the opposite holds.

Randomization probabilities. Bayesian adaptive randomization is defined with the probability for a patient (conditionally on random assignment to an experimental treatment) with biomarker profile X of being randomly assigned to experimental arm a proportional to $\Pr(\lambda_{X,a} > \lambda_X \mid data)^h$, with $h \geq 0$, a function that increases linearly with the number of enrollments. More specifically, when applied to the initial three experimental arms, h increases with the number of patients assigned to any of these arms or the control,

whereas for a hypothetic arm added later during the study, it increases with the number of patients randomly assigned to the novel arm and the concomitant random assignments to the control arm. Adaptive randomization intervenes only after the initial burn-in period.

As we discussed previously,[17,20] to preserve the power of detecting treatment effects, it is important to guarantee sufficient enrollment in the control arm. Randomization probabilities for the control are obtained by matching (under the hypothesis that all the active arms will complete accrual and will not be stopped for futility) the expected number of patients randomly assigned to the control and the planned sample size specific to the control. For example, if after 10 enrollments two patients have been assigned to the control, then the 11th patient is assigned to the control with a probability of (70 – 2)/(280 – 10). The same approach is used if one experimental arm is dropped for futility or a novel arm is added, with the consequence of an expansion of the control sample size.[18]

Burn-in randomization. All experimental arms are assigned with fixed randomization probability until enrollment reaches 20% of the planned arm-specific sample size. This holds both for arms active from the onset of the trial as well as arms added during the course of the trial. During this time period, the randomization probability matches $(1/K)$, the inverse of the number of active arms. If arms are added after the onset of the platform study, this determines an expansion of the control arm.

Noncompeting arm-specific final sample sizes. Because the overall trial sample size is not fixed, the presence of arms with positive treatment effects does not reduce the final sample size of the remaining arms. That is, there is little dependence between the final arm-specific sample sizes, considerably less compared with alternative response-adaptive randomization (RAR) approaches. This is an important difference with respect to other adaptive designs, which include a component of competition and negative correlation with the final number of patients enrolled by different experimental arms. Instead, INSIGhT specifies a maximum number of patients per arm. By preserving arm-specific sample size, power is maintained even in the presence of other effective arms. The accrual can be stopped earlier for an experimental arm (before this maximum is reached) only when the likelihood of a positive final result becomes insufficient and triggers the early stopping on the basis of futility. As a consequence, the adaptive algorithm has a substantial impact on the duration of the arm-specific accrual period, which tends to be shortened for the arms with positive treatment effects, with little effect on other operating characteristics. It can also affect the arm-specific biomarker distributions. Variability of the arm-specific sample size results only from early stopping rules. Bayesian randomization can only modify the enrollment rate and accelerate accrual to the most promising arms, particularly for the patients who are more likely to benefit from these treatments. Symmetrically, a decrease in the enrollment rate for the worst performing experimental arms guarantees more time and a larger proportion of OS events available before all or a majority (eg, 60%) of the total 70 patients have been enrolled and therefore allows more time for better futility stopping.

Early stopping for futility. The Bayesian model is updated monthly; this allows prediction of future outcomes and future randomizations. We also predict future biomarker profiles X using a standard Dirichlet conjugate model. Monthly, Bayesian sampling is used to generate final trial data from the predictive distribution, including the enrollment of future patients, and PFS and OS outcomes, both for patients previously enrolled and for those who have not yet been enrolled. Using Bayesian terminology, we sample multiple times from the predictive distribution every month. These data sets, including the actual data generated up to a time point by the trial and a complementary component of probabilistically imputed data, describe expectation and uncertainty on how we predict the data to look at completion of the study (including censored data points) on the basis of the available information. These computations assume that the open arms will reach the final sample size of 70 patients and allow us to derive a single predictive probability of interest for each experimental arm, at each interim analysis, of a well-defined event. The event is the rejection of the primary null hypothesis (absence of a treatment effect on OS in the overall population) at completion of the study. Prediction (the probability that the arm-specific result will be significant) is used monthly to decide either to continue or to discontinue the study of the experimental arm. A key step of the process is the simulation of the baseline λ and the PH model parameters β from the posterior at each interim analysis. Conditionally on these parameters, the final data set is imputed by generating the current missing data accordingly into the PH model. Next, P values to evaluate the primary null hypotheses are computed using this partially imputed data set. These steps are iterated so that the relative frequency of generated arm-specific P values below the significance threshold α approximates the targeted prediction probability.

The arm is stopped if the prediction probability of a positive result becomes small. A linear boundary that increases with the number of enrollments from 0 at the onset of the study up to 0.1 is used to define monthly the cutoff for discontinuing or proceeding with the study of the experimental treatment. Interim futility analyses start after the burn-in phase of the experimental arm.

RESULTS

The early stopping rule that we described reduces the average number of patients allocated to an experimental arm without effects (hazard ratio [HR], 1) to 49.0, and the

average size is 69.8 (69.0) with an HR of 0.6 (0.65). Sensitivity analyses were used to describe variations of the average sample size for arms without treatment effects. By varying accrual rate and treatment effects of the remaining arms, we obtained averages between 47 and 50 patients. In scenarios with an experimental arm having a negative effect (ie, HR $>$ 1), early stopping tended to occur frequently and earlier during enrollment. For example, with an HR of 3/2 (4/3), futility early stopping in simulations occurred for $>$ 90% of the simulated studies, with an average enrollment for the arm with negative effects equal to 33 (43) patients. Appendix Table A1 shows the probability of early stopping on the basis of futility for various simulation scenarios considering HRs between 0.7 and 1.15.

In power calculations, we estimated that if any of the experimental arms had a PFS HR of 0.6 (0.65) for the overall population, then the power of rejecting the corresponding null hypothesis (overall population PFS HR $\geq$ 1) at completion of the study would be 0.9 (0.79). Power remained stable when we considered variations of accrual rates and outcome distributions for the remaining arms with values from 0.85 to 0.92. In the comparison of these simulations with a balanced design, keeping the described early stopping mechanism for futility, enrollment in arms with positive treatment effects was completed faster, with an average time reduction between 16% and 27% across simulation scenarios.

A similar power analysis like that for PFS was repeated for OS. For example, with an OS HR of 0.6 (0.65) for the overall population, the power of rejecting the null hypothesis at completion of the study was 0.89 (0.78; Table 1). Using simulations, we also estimated arm-specific type I error probabilities (empiric estimates) between 4% and 5% across scenarios with various accrual rates. The power of rejecting the same primary null hypothesis decreased to 0.37 when only a smaller stratum of patients (eg, CDK-positive patients) benefited from the treatment. Although the power to reject the null was of course considerably reduced, the power to detect a significant biomarker/treatment interaction (null hypothesis: no treatment effect in the CDK-positive group) in the secondary analyses was higher (0.66; Table 2). The noncompeting maximum number of patients (ie, 70) per arm maintained the power of detecting a positive treatment effect for each experimental arm stable with respect to the presence of treatment effects on the remaining arms.

Sensitivity to PFS and OS correlation seemed limited. We considered both different magnitudes of PFS and OS HRs contrasting an experimental treatment and a control (Appendix Table A2) and various PFS-OS correlation degrees at the individual level. We used the concordance C-statistic to measure PFS-OS dependency (Appendix Table A3). Multiple primary hypotheses, one for each arm, were tested without correction for multiplicity.[21] Each test was based on the Cox model contrasting data from the control and the corresponding experimental arm, with biomarkers used as covariates, and a treatment effect coefficient. Additional sensitivity analyses, including the probability of reporting a positive treatment effect for the biomarker-positive group under selected scenarios (Appendix Table A4), the power for arms added later during the course of the platform trial (Appendix Table A5), and the power assuming different possible accrual rates (Appendix Table A6), are included in the Appendix. In contrast to alternative response-adaptive designs, the low correlation of accrual rate with final arm-specific sample size (which, as described in Methods, can be fewer than 70 patients only as a result of early stopping for futility) induces little variations of power estimates across

TABLE 1. Power of Rejecting Null Hypotheses of No Treatment Effect at Completion of Study

HR	Power	
	Single Arm With Positive Treatment Effects	Additional Arm With Positive Treatment Effect
0.55	0.94	0.94
0.6	0.89	0.88
0.65	0.78	0.78
0.7	0.64	0.64
0.75	0.51	0.52
0.8	0.35	0.37

NOTE. *P* values computed using standard Cox proportional hazards analyses. Analyses include the three biomarkers used as covariates. Results computed with 10,000 simulations per scenario. In the middle column, only a single arm has positive treatment effects. In the right column, one additional arm has a positive treatment effect (hazard ratio [HR], 0.6). HRs are constant across biomarker subgroups. Hypothesis testing: one-sided $\alpha = 0.05$.

TABLE 2. Probability of Reporting Positive Biomarker-Treatment Interaction

HR	Power	
	Single Arm With Positive Treatment Effects	Additional Arms With Positive Treatment Effect
0.55	0.78	0.77
0.6	0.66	0.66
0.65	0.54	0.53
0.7	0.42	0.41
0.75	0.35	0.34
0.8	0.24	0.24

NOTE. Results computed with 10,000 simulations per scenario. In the middle column, only a single arm has positive treatment effects restricted to a single biomarker-positive subpopulation (prevalence, 0.5) and hazard ratios (HRs) of 1 for the rest of the patients. In the right column, there is an additional arm with positive treatment effects (HR, 0.6) across all subgroups. We used standard Cox proportional hazards analyses with biomarker-treatment interaction terms. Hypothesis testing: one-sided $\alpha = 0.05$.

scenarios with positive treatment effects and various accrual rates. Accrual rate therefore correlates with time required to complete the arm evaluation, but it does not correlate with power.

DISCUSSION

Clinical trials under master protocols have been proposed as a methodologic innovation to more efficiently answer therapeutic development questions.[6,7,22] Such innovations are particularly important in the era of precision medicine, where biomarker testing adds complexity by increasing the number of testable hypotheses. Platform trials under master protocols are intended to "study multiple targeted therapies in the context of a single disease in a perpetual manner, with therapies allowed to enter or leave the platform on the basis of a decision algorithm."[7(p63)] Potential efficiencies include the conservation of control arms, multiplexed biomarker screening data, and reduced downtime because the trial infrastructure is maintained as treatment arms enter or leave the trial. Platforms also enable innovative statistical approaches to increase efficiency.[23-27] INSIGhT is the first biomarker-based APT designed to apply these general solutions to specific problems in therapeutic development for GBM.[28]

Late-stage clinical trial failures are a major issue for therapeutic development in general[1] and in GBM specifically.[2,3] Failure in phase III may be linked to erroneous go/no-go decisions on the basis of phase II results that have different end points than the desired pivotal trial, overestimate treatment effects on the basis of comparisons with historical controls, or both. Discordant end points may be a significant issue in GBM. Prior data have shown that effects on imaging-based end points such as response rate and PFS may not translate to effects on OS.[4,13,29-31] Furthermore, comparison of end points like PFS and OS with historical controls may overestimate treatment effects through selection bias, temporal drift, and failure to account for control variability.[4] For these reasons, we chose to use OS as the primary end point of the trial. In unmethylated GBM, survival postprogression is generally short, and there are no proven effective therapies at recurrence that increase the chance of detecting a true therapeutic impact on OS.[12] We included a randomly assigned control arm to avoid the pitfalls associated with comparison with historical controls for OS in GBM.[4] The platform design affords considerable efficiency by using a single control arm for comparison against multiple therapies and offers patients a higher probability of being randomly assigned to an experimental arm. Furthermore, we use Bayesian RAR[17] based on accumulating PFS results to increase the probability of random assignment to arms that showed more promise.[28,32] We had previously shown that RAR using an OS end point was possible for recurrent GBM[17] and additionally supported this approach in our simulations during the development of INSIGhT. However, to increase efficiency, we opted to use PFS, because earlier end point assessment can more rapidly influence randomization.[16] If we were to find a discordance between therapeutic impact on PFS and OS, randomization probability would be altered, but decision making on the primary end point would remain unchanged.

Another advantage of platform trials is the efficient use of multiplexed genomic biomarker data for treatment assignments. GBM is characterized by redundant and overlapping alterations in several molecular pathways rather than mutually exclusive driver mutations.[33] As such, patients can be positive for multiple genomic biomarkers. Some platform trials like NCI-MATCH (National Cancer Institute Molecular Analysis for Therapy Choice),[34] Lung MAP (Lung Cancer Master Protocol),[35] BATTLE (Biomarker-Integrated Approaches of Targeted Therapy for Lung Cancer Elimination),[36] and N^2M^2 (National Center for Tumor Diseases Neuro Master Match)[37] generally deal with this situation through an assignment algorithm on the basis of accrual and/or relative evidence of biomarker-specific therapeutic efficacy. I-SPY 2 (Investigation of Serial Studies to Predict Your Therapeutic Response With Imaging and Molecular Analysis 2), in contrast, uses biomarker subgroup–specific randomization probabilities to allow data generated during the trial to drive the biomarker specificity of arm assignments.[38] INSIGhT does the latter, starting with equal randomization among the experimental arms and allowing the RAR procedure to prioritize randomization in a biomarker-specific way. For example, if only patients with *EGFR* amplification in the neratinib arm were living longer than those in the control, the randomization algorithm would increase the probability of *EGFR*-amplified patients assigned to neratinib (regardless of their other biomarkers) while potentially reducing assignment to neratinib for *EGFR* wild-type patients. In fact, this situation occurred in I-SPY 2, where the adaptive randomization algorithm stopped assigning patients with human epidermal growth factor receptor 2 (HER2) –negative/hormone receptor–positive cancer and those with HER2-negative/hormone receptor–negative cancer to neratinib during the course of the trial, even as it reached the prespecified efficacy threshold in the HER2-positive/hormone receptor–negative signature.[39] This strategy may be optimal when there are limited pretrial data or a weak hypothesis suggesting a biomarker-specific effect. However, future experimental arms may have a strong biomarker-specific rationale supported by preclinical or clinical data. In these situations, more biomarker specificity may be desired from the start of the trial, and we have suggested ways to integrate this into a platform design.[40]

More generally, adding future biomarkers specific to additional experimental arms increases design complexity and requires appropriate definitions of the randomization probabilities. This capacity is possible in INSIGhT, although current simulations do not account for future biomarkers. GBM AGILE is another platform trial in development for GBM; it considers these potentially future predictive markers (denoted enrichment biomarkers) in the design.[41]

Additional comparisons between INSIGhT, GBM AGILE (Adaptive, Global, Innovative Learning Environment), and N^2M^2 have previously been discussed.[42]

Biomarker-based clinical trials must consider not only the potential effect differences between biomarker-positive and biomarker-negative groups (predictive effect) but also that preselected biomarker categories have an independent association with the primary outcome (prognostic effect). INSIGhT accounts for this possibility through randomization within biomarker subgroups. However, there may be biomarker categories with low frequency such that randomization is unattractive. In these cases, it would be helpful to know the natural history of these biomarker subpopulations. Knowing that a biomarker had no prognostic significance might allow a trial to assign all biomarker-positive patients to the targeted experimental therapy and compare with unselected controls. Even though INSIGhT used randomization, we queried clinically annotated genomic data[33,43] to investigate the possibility that the biomarkers we used had prognostic significance or a variable relationship between PFS and OS and found no such associations.[19]

Although the perpetual clinical trial framework that is provided by the APT framework can provide significant efficiencies, it can create additional challenges as well. Maintaining ongoing operations requires both financial models that support ongoing concerns and active pipeline development to maintain a regular flow of experimental arms. More complex Bayesian designs require engaged clinical and statistical investigators and new ways of determining operating characteristics through simulation.[44] Reporting of trial results is complicated because of the separation between the master protocol and the arm-specific data. Arms that leave the trial because of success or failure need to be reported while the overall trial is still ongoing, which does not lend itself to traditional trial reporting best practices like CONSORT. Two recent publications from I-SPY 2 are examples.[39,45] Conversely, reporting on the overall master protocol does not have a natural time point, although most groups publish a general description of the overall trial structure without results.[35,36,38,41]

In conclusion, INSIGhT is an ongoing novel biomarker-based Bayesian APT for patients with newly diagnosed unmethylated GBM. Our goal is to dramatically shorten trial execution timelines while increasing scientific power of results and biomarker discovery using adaptive randomization. We anticipate that trial execution efficiency will also be improved by using the APT format, which allows for the collaborative addition of new experimental arms while retaining the overall trial structure.

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Research Funding: Novartis, TRACON Pharma, Novocure, Spectrum Pharmaceuticals, Eli Lilly/ImClone, Boehringer Ingelheim, AstraZeneca

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Research Funding: Newlink Genetics, Plexxikon, Kadmon, Orbus Therapeutics, Merck, DNAtrix, AbbVie, BeiGene

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Leadership: ZIOPHARM Oncology (I)
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Consulting or Advisory Role: Celldex, Deciphera, Vascular Biogenics, Foundation Medicine, Genentech/Roche, Omniox, Oxigene, AbbVie, Novogen, Kadmon, Merck, Five Prime Therapeutics, Insys Therapeutics, AstraZeneca, Boston Biomedical, GW Pharmaceuticals, CarThera
Research Funding: Deciphera, Novartis, Eli Lilly, Sanofi, EMD Serono, Mundipharma
Patents, Royalties, Other Intellectual Property: Sanofi, research support; AstraZeneca, research support; EMD Serono, research support; Eli Lilly, research support; Novartis, research support; Deciphera Pharmaceuticals, research support

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Patents, Royalties, Other Intellectual Property: UpToDate

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Consulting or Advisory Role: BioClinica, AbbVie, Sapience Therapeutics, AstraZeneca, Novocure, Kadmon, Cortice, Celgene, Agios
Research Funding: AbbVie (Inst), Novartis (Inst), Karyopharm Therapeutics (Inst), Genentech/Roche (Inst), Novocure (Inst), Aeterna Zentaris (Inst), Pfizer (Inst), Bayer HealthCare Pharmaceuticals/Onyx Pharmaceuticals (Inst), Agenus (Inst), GlaxoSmithKline (Inst), Stemline Therapeutics (Inst), Northwest Biotherapeutics (Inst), Plexxikon (Inst), Tocagen (Inst), Regeneron (Inst), VBL Therapeutics (Inst), e-Therapeutics (Inst), Bristol-Myers Squibb (Inst), ImmunoCellular Therapeutics (Inst), Merck (Inst), Amgen (Inst), Celldex (Inst), Millennium Pharmaceuticals (Inst), MedImmune (Inst), Boehringer Ingelheim (Inst), Kadmon (Inst), RTOG Foundation (Inst), Boston Biomedical (Inst), BeiGene (Inst), Diffusion Pharmaceuticals (Inst), Agios (Inst), Celgene (Inst), Vascular Biogenics (Inst), Angiochem (Inst), Northwest Biotherapeutics (Inst), Orbus (Inst), VBI Vaccines (Inst)
Travel, Accommodations, Expenses: Karyopharm Therapeutics, Tocagen, Radiological Society of North America, AbbVie, Agios, Novocure, NRG Oncology Foundation, Celgene, Kadmon, Bristol-Myers Squibb
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Patents, Royalties, Other Intellectual Property: Molecular diagnostics assay patent

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APPENDIX

EXPERIMENTAL AGENTS

CC-115

CC-115 is a potent and selective oral dual inhibitor of mammalian target of rapamycin (mTOR) kinase (both mTORC1 and mTORC2) and DNA-dependent protein kinase (Mortensen DM, et al: J Med Chem 58: 5599-5608, 2015). The phosphatidylinositol 3-kinase (PI3K)/Akt/mTOR signaling axis plays a central role in cell growth, survival, motility, and metabolism in a variety of cancers (Fruman DA, et al: Nat Rev Drug Discov 13:140-156, 2014; Engelman JA: Nat Rev Cancer 9: 550-562, 2009), including glioblastoma (GBM; Brennan CW, et al: Cell 155:462-477, 2013). DNA-dependent protein kinase is a serine/threonine kinase involved in the repair of DNA double-strand breaks (Collis SJ, et al: Oncogene 24:949-961, 2005), which are considered to be the most lethal DNA lesions and the main driver of cellular death after treatment with ionizing radiation therapy (RT). Therefore, beyond its hypothesized growth-inhibitory effect as monotherapy, CC-115 has the potential to be a radiation-sensitizing agent in the treatment of GBM (Zhao Y, et al: Cancer Res 66:5354-5362, 2006). One phase Ia/Ib multicenter open-label clinical study established 10 mg twice per day as the recommended dose for cohort expansion and phase II with near-maximal inhibition of phosphorylated Akt and partial inhibition of phosphorylated 4EBP (Munster PN, et al: J Clin Oncol 34, 2016 [suppl; abstr 2505]). CC-115 also showed reasonable penetration into GBM tissue in a surgical expansion cohort (Munster PN, et al). Given the therapeutic hypothesis of radiosensitivity supported by preclinical data, CC-115 will replace temozolomide (TMZ) in both the concurrent and adjuvant phases of treatment. Because this dose has never been combined with RT, the treatment arm will start with a safety lead-in with the combination before expansion to the full phase II setting.

Abemaciclib

Retinoblastoma (Rb) protein is a key tumor suppressor that inhibits progression through the G1 checkpoint (Sherr CJ: Science 274:1672-1677, 1996). Cyclin D and CDK4/6 phosphorylate and inactivate Rb, thereby allowing the cell cycle to progress. Abemaciclib is a highly specific ATP-competitive CDK4/6 inhibitor that induces reversible G1 phase cell-cycle arrest in Rb-proficient tumor models and is approved for hormone receptor–positive, human epidermal growth factor receptor 2 (HER2) –negative advanced or metastatic breast cancer. Orally dosed abemaciclib achieved brain exposures in excess of the concentrations required for CDK4/6 inhibition in an orthotopic rat GBM model and significantly increased survival alone or in combination with TMZ (Raub TJ, et al: Drug Metab Dispos 43:1360-1371, 2015). Ten patients from a phase I dose-escalation and tumor-specific cohort expansion study had cerebrospinal fluid concentrations available and showed abemaciclib concentrations in a range (2.2 to 14.7 nmol/L) that exceeded the dissociation constant (Ki, 0.6 nmol/L) for the CDK4/cyclin D1 complex (Patnaik A, et al: Cancer Discov 6:740-753, 2016). Of the 17 patients with GBM, three patients with GBM achieved stable disease, two of whom continued to receive ongoing treatment without progression for 19 and 23 cycles, respectively (Patnaik A, et al). Abemaciclib will be administered in place of TMZ after standard concurrent RT/TMZ.

Neratinib

Epidermal growth factor receptor (EGFR) is a receptor tyrosine kinase that regulates cell growth and differentiation, and EGFR aberrations are important in oncogenesis (Hynes NE, et al: Nat Rev Cancer 5:341-354, 2005) and common in GBM (Brennan CW, et al). Neratinib, an orally available potent irreversible small-molecule pan–ERBB family tyrosine kinase inhibitor that targets the intracellular tyrosine kinase domains in EGFR, is approved for HER2-positive breast cancer (Martin M, et al: Lancet Oncol 18:1688-1700, 2017; Cancer Discov 7:OF1, 2017)[39] and has shown activity in controlling and delaying CNS progression of breast cancer metastases (Awada A, et al: JAMA Oncol 2:1557-1564, 2016). In preclinical GBM studies, neratinib was shown to selectively cause cell death in cell lines harboring genetic activation of *EGFR* and was more effective than other EGFR inhibitors in lines harboring the extracellular domain mutations seen in GBM (Vivanco I, et al: Cancer Discov 2:458-471, 2012). Neratinib has also been shown to exhibit potential for potent inhibition of amplified *EGFRvII* and *EGFRvIII* in GBM patient-derived cell-line models (Francis JM, et al: Cancer Discov 4:956-971, 2014). Neratinib is significantly more potent than lapatinib in limiting the growth of primary GBM cell lines, and this increased potency is an attractive feature, given that negative clinical trials for lapatinib have been attributed to inadequate tumor concentrations of the drug (Vivanco I, et al). Neratinib will be administered in place of TMZ after standard concurrent RT/TMZ.

BIOMARKERS

Prospective patients may have biomarker data already available from academic or commercial sources, or they may take advantage of a companion consortium (ABC2 ALLELE Consortium) that generates free portable genotyping data using whole-exome sequencing and copy array testing performed in a Clinical Laboratory Improvement Amendments–certified clinical laboratory for patient use in clinical trials. The biomarkers determined are as follows: *EGFR* positive defined as patients with *EGFR* amplification or mutation; *PI3K* positive defined as patients with *PIK3CA* mutation/amplification, *PIK3R1* mutation, *AKT3* amplification, *PIK3C2B* > one copy gain, or *PTEN* dual allele inactivation through either homozygous deletion or deletion plus an inactivating mutation; and *CDK* positive defined as patients with *RB1* wild type and *CDK4* amplification, *CDK6* amplification, or *CDKN2A* or *CDKN2B* > one copy loss, or *CDKN2A* or *CDKN2B* one copy loss plus an inactivating mutation.

For amplifications listed, the genotyping report must state clear gene amplification and not gain, which is typically greater than a log2 ratio of +2.0. Copy number losses would be values of < –0.3, and more than single copy deletions are inferred relative to baseline for the chromosome on which they are located (eg, single copy chromosome 9 loss with additional loss of *CDKN2A/B* below this level in focal region). The general criteria to be included for mutations would be single-nucleotide variants that are present at > 3% allelic fractions and have > five prior events reported in COSMIC or are well-established hotspots known to be activating or inactivating mutations through experimental data or novel mutations that are predicted to be clearly inactivating, such as nonsense and frameshift mutations. All genotyping data are centrally reviewed by a neuropathologist for ultimate determination of biomarker categories.

TABLE A1. Estimated Probability of Arm-Specific Early Stopping for Futility

HR	Early Stopping Probability
0.7	0.02
1.0	0.53
1.05	0.57
1.15	0.72

NOTE. Estimated probability based on simulation scenario with no treatment effects in any other experimental arm.

Abbreviation: HR, hazard ratio.

TABLE A2. Sensitivity Analysis With Respect to PFS Treatment Effects

	Power			
	PFS HR (× OS HR)			
	1.2		0.9	
OS HR	Scenario A	Scenario B	Scenario A	Scenario B
0.55	0.93	0.95	0.95	0.94
0.6	0.88	0.89	0.89	0.89
0.65	0.78	0.79	0.79	0.79
0.7	0.65	0.64	0.65	0.64
0.75	0.51	0.50	0.51	0.50
0.8	0.35	0.36	0.37	0.35

NOTE. Power of rejecting null hypotheses of no overall survival (OS) treatment effects at completion of study. Analyses include the three biomarkers used as covariates. Results computed with 10,000 simulations per scenario. In scenario A, only a single arm has positive treatment effects. In scenario B, one additional arm has positive treatment effects (OS hazard ratio [HR], 0.6). HRs are constant across biomarker subgroups. We modified the simulation scenarios of Table 1 by changing the progression-free survival (PFS) HRs. Also, in this case, type I error is controlled at $\alpha = 0.1$.

TABLE A3. Power Based on OS-PFS Correlation

	Power			
	PFS-OS Concordance Index			
	1		0.7	
OS HR	Scenario A	Scenario B	Scenario A	Scenario B
0.55	0.93	0.95	0.94	0.94
0.6	0.88	0.89	0.88	0.89
0.65	0.78	0.79	0.79	0.78
0.7	0.65	0.64	0.64	0.63
0.75	0.51	0.50	0.50	0.51
0.8	0.35	0.36	0.36	0.36

NOTE. Power of rejecting null hypotheses of no overall survival (OS) treatment effects at completion of study. Analyses include the three biomarkers used as covariates. Results have been computed with 10,000 simulations per scenario. In scenario A, only a single arm has positive treatment effects. In scenario B, one additional arm has positive treatment effects (hazard ratio [HR], 0.6). HRs are constant across biomarker subgroups. We modified the simulation scenarios of Table 1 by modifying the progression-free survival (PFS) –OS concordance index.

TABLE A4. Power Based on Biomarker Frequency

	Power	
	Biomarker Prevalence	
HR	0.65	0.4
0.55	0.85	0.66
0.6	0.74	0.56
0.65	0.62	0.44
0.7	0.49	0.35
0.75	0.35	0.27
0.8	0.26	0.20

NOTE. Probability of reporting a positive treatment effect in the biomarker-positive group. We used scenarios where the positive treatment effect is limited to the biomarker-positive subpopulation. Results computed with 10,000 simulations per scenario. In this example, only a single arm has positive treatment effects restricted to a single biomarker-positive subpopulation of varying prevalence.

Abbreviation: HR, hazard ratio.

TABLE A5. Power of Rejecting Null Hypotheses of No OS Treatment Effect

	Power	
HR	Scenario A	Scenario B
0.55	0.94	0.94
0.6	0.88	0.88
0.65	0.77	0.78
0.7	0.64	0.64
0.75	0.48	0.48
0.8	0.34	0.34

NOTE. Power for an experimental arm added after onset of the platform study. Reported power probabilities refer to a single arm added after enrollment of 140 patients. In scenario A, only the single arm added after onset of the study has positive treatment effects. In scenario B, one additional arm available from onset of the platform study has positive effects (hazard ratio [HR], 0.6).

Abbreviation: OS, overall survival.

TABLE A6. Power Sensitivity Analysis Based on Accrual Rate

	Power	
	Accrual (patients per month)	
HR	5	14
0.55	0.93	0.94
0.6	0.90	0.89
0.65	0.77	0.78
0.7	0.64	0.62
0.75	0.52	0.51
0.8	0.36	0.36

Abbreviation: HR, hazard ratio.