Review: Clinical Trial Methodology

CLINICAL INVESTIGATION

Novel clinical trials in neuro-oncology

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Clinical research within neuro-oncology is complicated by several factors, including complex tumor biology and a variable impact on patients, as a consequence both of disease location and degree of malignancy. Clinical studies are complicated by these factors as well as issues of determining optimal clinical end points. This review highlights relevant aspects of neuro-oncologic diseases, including treatment, gliomagenesis and prognostic and predictive markers of gliomas. These factors are discussed in the context of clinical trial design and the challenges of using novel designs that strive to maximize efficiency and minimize patient exposure to ineffective treatments.

Keywords: adaptive randomized • astrocytoma • Bayesian • biomarker • glioblastoma • glioma • oligodendroglioma

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Although there has been great progress over the last few decades, the cure for most cancers remains elusive. This is particularly true for patients with primary CNS tumors such as gliomas where only the non-infiltrative neoplasms (e.g., pilocytic astrocytoma) have a meaningful cure rate. Traditional cancer treatments have included surgical resection, radiation and typically cytotoxic chemotherapy, and this approach remains the standard of care for primary brain tumors. However, as our understanding of the molecular mechanisms responsible for neoplastic transformation has evolved, the focus of therapeutic investigations has transitioned from identifying either cytotoxic agents or combinations of these agents, to leveraging the advances in molecular profiling in order to identify cancer specific targets, thereby improving efficacy while limiting toxicity.

Therapeutic advances for primary CNS malignancies have been hindered by a number of obstacles not encountered with cancers outside of the CNS. First, although advances in surgery such as microsurgical techniques, advances in imaging technology and combined surgical and imaging suites have led to more extensive resections with a reduction in post-operative morbidity, the invasive nature of primary brain tumors and the common occurrence of tumors within the eloquent brain limit the curative potential of surgery in this setting. Second, difficulty in delivering agents across the blood–brain barrier has limited the effectiveness of therapies that have shown promise in systemic cancers and has severely curtailed the possible treatment armamentarium. The effectiveness of agents that cross the blood–brain barrier is limited by the low average mitotic rates of even the more aggressive brain tumors relative to numerous systemic cancers. Finally, clinical research evaluating new treatments for primary brain tumors has been challenging, as the overall incidence of the disease is relatively low, determination of treatment efficacy is complicated by often complicated and potentially misleading imaging changes (e.g., reatment related pseudoprogression or necrosis) and ongoing controversy regarding the optimal measure of efficacy.

Overall survival, although definitive, may be compromised by differences in salvage therapy. Conversely, measures of progression-free survival, although not subject to impact by subsequent (salvage) treatment, are compromised by the limitations

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of current imaging such as MRI and CT scanning. For example, pseudoprogression mimics tumor growth, but is now known to be a generally self-limited process that may actually be associated with an improved prognosis [1]. In recognition of this difficulty, it is being recommended that the Macdonald criteria [2], which is commonly used for radiographic response assessment and takes only a 2D measure of contrast enhancement into account, be replaced by a more flexible measure that takes in to account both 3D contrast enhancing and nonenhancing disease, as well as where in the course of treatment a patient is (e.g., the Response Assessment in Neuro-Oncology [RANO]; [3]), in an effort to improve interpretation of imaging despite the inherent ambiguity. Conversely, some treatments may improve imaging without truly impacting tumor growth. This is particularly germane for anti-angiogenic treatments where the therapy improves the integrity of the blood–brain and blood–tumor barrier, resulting in less contrast diffusion and an improved image, or pseudo-response. Similar challenges exist for the determination of objective response (partial or complete response). In an effort to make progression-related end points a more viable and reliable option in future neuro-oncology trials, much work is being done to validate advanced imaging techniques, such as dynamic-contrast enhanced imaging, diffusion and perfusion imaging, spectroscopy and PET imaging, as well as to develop imaging markers of treatment response and progression that can measure apoptosis, proliferation and other dynamic aspects of treatment [4]. Ultimately, overall survival needs to be incorporated into trial end points in some fashion, as improvements in progression-free survival that do not affect the outcome overall may not justify the potential added toxicity of treatment.

However, despite the challenges associated with clinical research for primary brain tumors, there has been a great expansion in the number of trials for this disease. Much of this is the consequence of an increasing number of identified molecular targets that have further underscored the need for more efficient and expedient means of determining potential efficacy and safety of each agent, as well as its potential use in combination regimens. This review aims to outline some of the challenges, as well as the novel approaches to help address these challenges, in the context of an exponential increase in the number of potential treatments. We will highlight important discoveries in gliomagenesis and prognostic markers, and discuss how their inclusion in trial design can lead to more efficient clinical trials that screen new agents or combinations using molecular markers to both enhance patient stratification and enrich the patient population. The overall goal is to maximize efficiency while limiting patient exposure to inferior therapeutic regimens.

Clinical trial accrual has also been a challenge. The incidence of glioblastoma multiforme (GBM), the most common primary malignant brain tumor, is 3–4/100,000 [5,101], corresponding to approximately 13,000 new cases per year in the USA. This relative paucity of patients limits accrual and leads to prolonged enrollment periods, particularly of large-scale randomized trials. For the lower grade tumors, not only are they even less common, but the time to progression after diagnosis and initial treatment is generally measured in years, leading to even longer trial duration. Large collaborative efforts have helped address the issues of large-scale randomized clinical trials. Examples include Radiation Therapy Oncology Group (RTOG) 0825 [102], aimed at assessing bevacizumab (BEV) use in first-line treatment of GBM; RTOG 0834/European Organization for Research and Treatment of Cancer (EORTC) 26053/National Cancer Institute of Canada (NCIC) (Phase III Trial on Concurrent and Adjuvant Temozolomide Chemotherapy in Non-1p/19q Deleted Anaplastic Glioma [CATNON]; [103]), comparing radiation alone, chemoradiation alone, radiation plus adjuvant temozolomide (TMZ), and chemoradiation plus adjuvant TMZ in 1p19q intact anaplastic gliomas; and RTOG/North Central Cancer Treatment Group (NCCTG) 0577 (Phase III Intergroup Study of Radiotherapy Versus Temozolomide Alone Versus Radiotherapy With Concomitant and Adjuvant Temozolomide for Patients With 1p/ 19q Codeleted Anaplastic Glioma (CODEL); [104]), comparing radiation alone, TMZ alone or chemoradiation with TMZ followed by adjuvant TMZ in 1p19q co-deleted gliomas. A brief review of these and other recent and ongoing multicenter Phase III trials in anaplastic glioma can be found in a recent paper by Giglio and Villano [6].

A search of the Clinical Trials website [105] using the search terms: glioma, Phase II, Phase III, interventional and adult and senior age groups (not including trials where accrual was ended at 21 years of age), returned 14 Phase III **(Figure 1)** and 103 Phase II **(Figure 2)** trials that are currently active. The Phase III trials are all randomized and contain 2–4 arms. Of the 103 Phase II trials, 28 of them are integrated Phase I/II trials. The majority (70 of 103) are single arm trials. Of the 33 multi-arm trials, 21 are randomized and one utilizes sequential accrual. This makes the case that within neuro-oncology more trials need to be undertaken that employ more time and cost-efficient design, such as those further discussed below.

Molecular pathogenesis & targeted therapy

Much of the increased interest and excitement for examining new therapies for malignant brain tumors stems from the enormous advances that have been made in

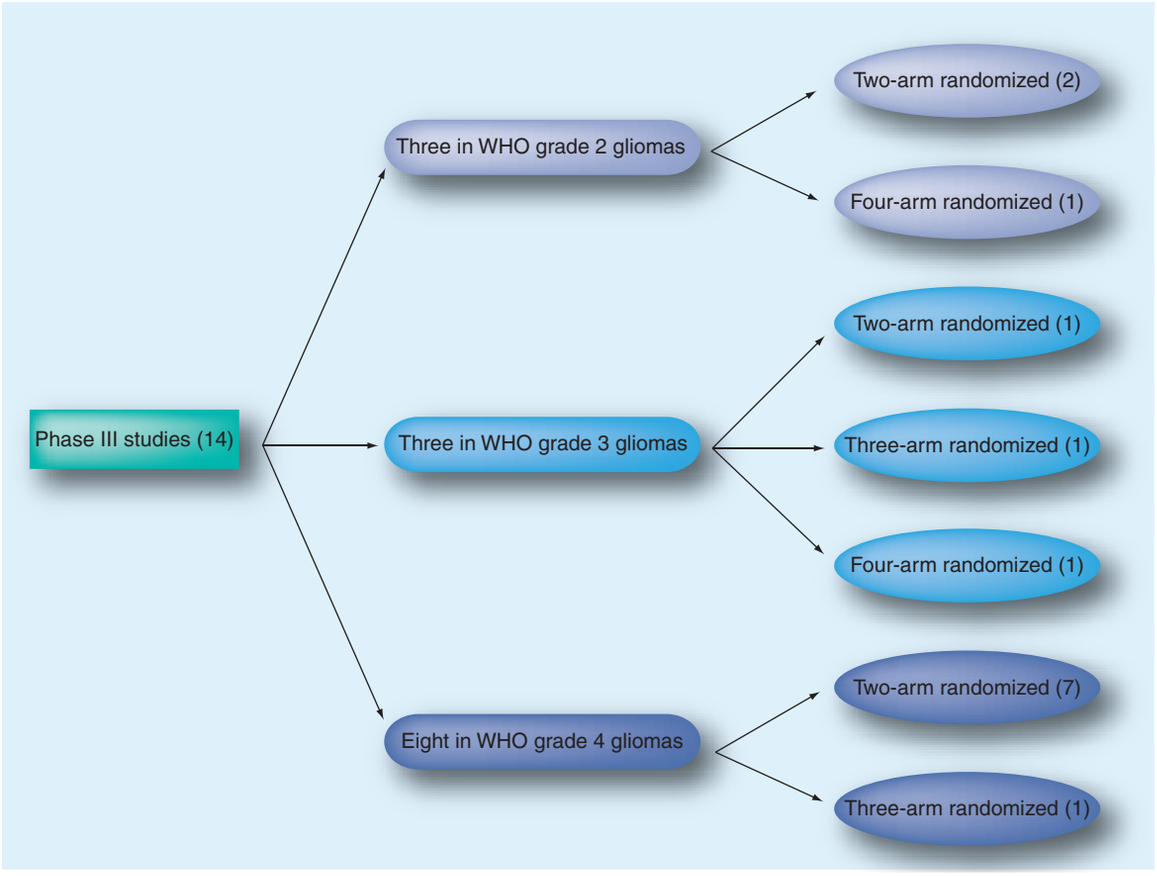

Figure 1. Design utilization of current Phase III trials in glioma.

understanding the molecular pathogenesis of gliomas and other primary brain tumors. In other cancers, these molecular discoveries have led to seminal advances in treatment. The success of imatinib mesylate in treating patients with Philadelphia chromosome-positive chronic myelogenous leukemia by targeting the constitutively active tyrosine kinase responsible for disease, marked the beginning of this paradigm shift toward targeted therapy [7]. Not only was imatinib a much more effective treatment for this disease, but given the specificity of the drug, there were very limited systemic side effects, and therefore it was better tolerated than the interferon/cytarabine combination that had previously been standard of care.

The success of imatinib started a trend of trying to identify a 'magic bullet,' or a highly effective, well-tolerated single-agent treatment, for other malignancies. After the results of EORTC 22981/26981 NCIC CE.3, led by Stupp and colleagues [8], established concurrent chemoradiation followed by adjuvant chemotherapy with TMZ as the standard of care for GBM, several clinical trials tested targeted agents for patients who failed the front-line chemoradiation regimen. Table 1 lists some of the single targeted agents tested in the series of clinical trials. PDGF receptor (PDGFR)-α is commonly overexpressed in both low- and high-grade astrocytomas, with expression of PDGF-A and -B ligand increased in malignant gliomas [9], and is believed to play a role in transformation to higher grades. EGF receptor (EGFR) overexpression, via gene amplification or mutation, is a common finding in primary GBM [10], with the EGFR vIII mutation that is responsible for constitutive activity of the Ras signaling pathway found in 20–30% of patients [11]. The presence of an EGFR alteration portends a poor overall treatment response and prognosis in patients [12].

The limited success of single agents in the treatment of malignant glioma underscores the considerable heterogeneity within tumors, as well as issues of drug delivery that limit efficacy of many of the agents tested. PDGFR and EGFR mutations, as noted above, are only two of the numerous known mutations. As the number of known molecular markers present in glioma continues to expand, so do the number of potential treatment targets (Table 2). A comprehensive review of the basic science of glioma is outside of our purview, and updated

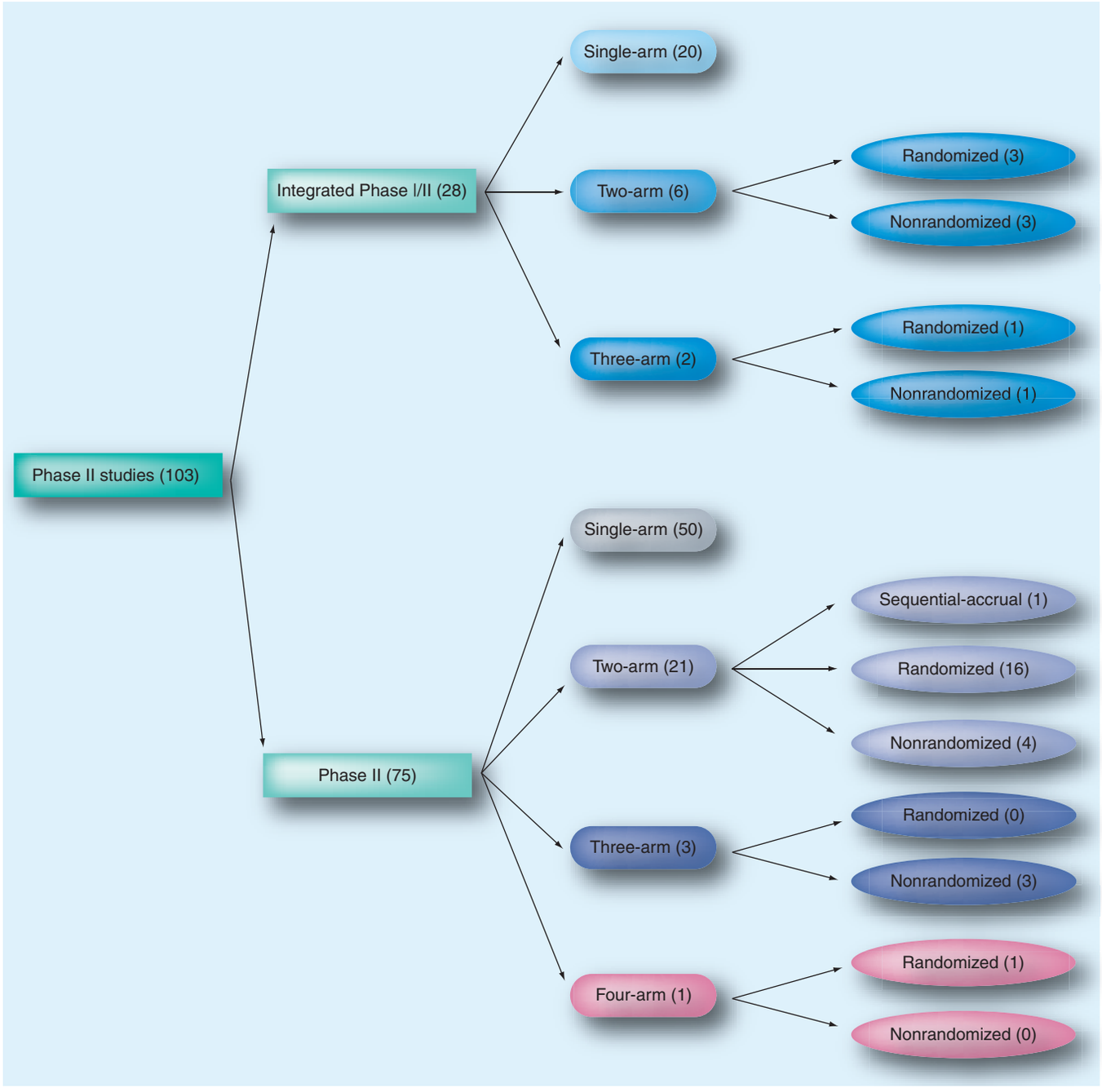

Figure 2. Design utilization of current Phase II studies in glioma.

articles from different areas within the subject are frequently published [13–16]. Here, we provide a framework of the molecular pathogenesis of glioma in an effort to provide perspective on the scope of the complexity of the disease and treatments. Mutations and alterations within cell-cycle regulatory pathways are common in gliomas. In primary GBM, amplification and overexpression of *MDM2* and *MDM4*, two negative regulators of p53, is common and confers resistance to p53 tumor suppressor function [17,18]. Loss of $p14^{ARF}$ expression occurs in up to 76% of GBM [15]. Mutations in p53 are also common in oligodendroglial tumors [19]. Within the retinoblastoma (RB) pathway, inactivating mutations of *RB1* and *p16* or activating mutations of *CDK4* or *cyclin D* are common [15]. Acquisition of a *RB* gene mutation is a common step in the transformation of a diffuse (WHO II) oligodendroglioma to a more aggressive anaplastic (WHO III) oligodendroglioma [19].

Table 1. Single-agent targeted therapeutic trials in malignant glioma[†].

Target	Author, year	Agent	Number of patients (eligible histology)	6-month PFS (%)	Comments	Ref.
PDGFRα					Commonly overexpressed in glioma	
	Wen *et al.*, 2006	Imatinib	55 (MG)	3 (GBM), 10 (AG)	Small-molecule TKI of PDGFRα and PDGFRβ, as well as Bcr-Abl, c-Fms and c-kit	[52]
EGFR					Commonly amplified, overexpressed or constitutively activated in primary GBM	
	van den Bent *et al.*, 2009	Erlotinib	110 (GBM)	11.4	Small-molecule EFGR TKI. Randomized Phase II trial vs TMZ or BCNU, with control arm exhibiting 6 months PFS 24%	[53]
	Franceschi *et al.*, 2007	Gefitinib	28 (MG)	14.3	Reversible small-molecule EGFR TKI	[54]
	Rich *et al.*, 2004	Gefitinib	57 (GBM)	13	Reversible small-molecule EGFR TKI	[55]
Farnesyl transferase					Involved in activation of Ras pathway, downstream of EGFR and VEGFR	
	Cloughesy *et al.*, 2006	Tipifarnib	89 (MG)	11.9 (GBM) 9.1 (AG)	Inhibits Ras activation, which is a downstream component of VEGF, EGF and PDGF pathways, which are commonly mutated in gliomas	[56]
Protein kinase C					Functions downstream in EGFR and VEGFR activated pathways	
	Kreisl *et al.*, 2010	Enzastaurin	118 (MG)	7 (GBM), 16 (AG)	Protein kinase C inhibitor with mechanism of action downstream in both EGF and VEGF pathways	[57]
	Wick *et al.*, 2010	Enzastaurin	266 (GBM)	11	Randomized Phase III in recurrent GBM vs lomustine (6 months PFS 19%)	[58]
mTOR					Loss of PTEN results in activation PI3K/Akt pathway and increased activation of mTOR	
	Chang *et al.*, 2005	Temsirolimus (CCI-779)	43 (GBM)	<3	Functions as an inhibitor of mTOR	[59]
Integrins					Transmembrane receptors that modulate tumor invasion, migration, proliferation, survival and angiogenesis	
	Reardon *et al.*, 2008	Cilengitide (4–500 mg or 40–2000 mg)	81 (GBM)	4–500 mg: 10, 40–2000 mg: 15	Competitive inhibitor of αvβ3 and αvβ5 integrin receptors	[60]
Histone deacetylase					Prevents expression of genes associated with cell-cycle arrest, apoptosis and tumor cell differentiation among others	
	Galanis *et al.*, 2009	Vorinostat	66 (GBM)	15.2	Small-molecule inhibitor of most human class I and class II histone deacetylases	[61]

[†]Examples of ineffective single-agent targeted therapeutic trials that were conducted in patients with malignant gliomas. It was found that 6 month PFS was significantly worse than when controls were utilized. The failure of single-agent targeted therapies is not unexpected given the significant genomic heterogeneity evidenced within gliomas.

AG: Anaplastic glioma; BCNU: *Bis*-chloroethylnitrosourea; EGFR: EGF receptor; GBM: Glioblastoma multiforme; MG: Malignant glioma (WHO grade 3 & 4); PDGFR: PDGF receptor; PFS: Progression-free survival; TKI: Tyrosine kinase inhibitor; TMZ: Temozolomide; VEGFR: VEGF recptor.

Table 2. Categories of molecular targets.

Categories of molecular targets	Action/target
EGF/EGFR	Activation of EGFR results in cell proliferation, invasion, migration, survival and differentiation. Amplification or overexpression occurs in glioblastoma
Farnesyl transferase	Involved in activation of the Ras/MAPK signal transduction pathway
Histone deacetylase	Prevents expression of genes associated with cell-cycle arrest, apoptosis and tumor-cell differentiation among others
Integrins	Transmembrane receptors that modulate tumor invasion, migration, proliferation, survival and angiogenesis
IGF-1R	Involved in activation of PI3K/Akt and Ras/MAPK signaling pathways
mTOR	Loss of PTEN results in activation PI3K/Akt pathway and increased activation of mTOR
PDGF/PDGFR	Activation of signal transduction pathways including Ras/MAPK pathway. Overexpression occurs in glioblastoma
PKC (PKCα, PKCβ, PKCδ)	Involved in signaling pathways for cell migration, angiogenesis and invasion
Proteasome	Ubiquitin-proteasome pathway involved in the degradation of intracellular regulatory proteins
RAF kinase	Involved in activation of the Ras/MAPK signal transduction pathway
TGF-β/TGF-β receptor	Elevated in gliomas, involved in angiogenesis, cell invasion and proliferation
VEGF/VEGFR	Involved in angiogenesis

EGFR: EGF receptor; IGF-1R: IGF-1 receptor; PDGFR: PDGF receptor; VEGFR: VEGF receptor.

Signaling pathways commonly exhibit alterations that result in uncontrolled growth, proliferation, angiogenesis and invasion. This can be as a result of overexpression, amplification or mutation of the cell membrane receptor tyrosine kinases that activate these pathways, as in the aforementioned cases of EGFR and PDGFR, or as a result of alterations within the pathways themselves. Pathways commonly affected in glioma include Ras-Raf-MAPK-ERK and PI3K–PTEN–Akt–mTOR [13]. Mutations that are common to both primary GBM and progression of anaplastic astrocytoma to secondary GBM include loss of heterozygosity (LOH) of 10q (the location of the *PTEN* gene), as well as mutation or loss of PTEN [20] itself, and mutation or amplification of phosphoinositide 3-kinase with associated increases in phosphorylated Akt levels [21]. In oligodendroglial tumors, combined LOH of 1p and 19q is a common early alteration [19], as is LOH of 4q [22]. Recently, *IDH1* and *IDH2* mutations were identified as common early alterations in the development of both diffuse astrocytic and oligodendroglial tumors [23]. The mutation results in a loss of function that ultimately renders a cell less resistant to apoptosis, as well as a gain of function leading to the accumulation of 2-hydroxyglutarate, which is believed to function as an oncometabolite by increasing oxidative stress. These mutations are not common in either primary GBM or in pilocytic astrocytoma [24]. Overexpression of VEGF is a common characteristic of both primary and secondary GBM, as well as anaplastic oligodendroglioma [13,16]. The resulting increased vascularity can be targeted therapeutically using agents that bind VEGF itself (e.g., BEV and aflibercept), bind to the VEGF receptor (e.g., ramucirumab and CT-322) or that interfere with signaling pathways that play a role in vascular proliferation (e.g., cediranib, pazopanib, sunitinib and XL184) [25].

In addition to targeting aberrant signaling pathways and angiogenesis, there has be a great deal of attention paid recently to glioma stem cells and mechanisms of invasion/migration, as these characteristics are believed to play a significant role in refractoriness/recurrence of disease after initial treatment. CD 133$^+$ glioma cells, the first cells to show evidence of 'stemness' in brain tumor models [26], have been shown to be more radioresistant than CD 133$^-$ cells [27]. Investigational therapeutic strategies aimed at stem cells include promoting differentiation and targeting developmental signaling pathways such as Notch, Sonic Hedgehog, Wingless, Homeobox and PTEN [28]. Glioma cell migration and invasion is also an area of active research. Tissue microenvironment, especially in the setting of hypoxia, is postulated to play a role in migration and invasion. Much research is being conducted on hypoxia inducible factor 1 and other factors [29]. The possibility of matrix metalloproteins and integrins as a target for therapeutics against migration and invasion has also been explored, as have TGFs [30].

Prognostic/predictive factors

In an effort to minimize patient exposure to ineffective treatment, while at the same time maximizing the likelihood that a targeted treatment will prove effective, biologic markers are being sought that will

predict either response or resistance to a drug. For example, only patients with breast cancer overexpressing HER2/neu receptor benefit from treatment with trastuzumab, a monoclonal antibody targeted against this receptor [31]. Without HER2/neu overexpression as an entry criterion, the definitive randomized clinical trial would have required over 5000 patients and more likely, a smaller trial would not have clearly defined the efficacy of this agent. Similarly, the presence of the Philadelphia chromosome predicts for response to imatinib, and specific mutations in the EGFR receptor in lung cancers are predictive of response to erlotinib and gefitinib. Unfortunately, despite the identification of numerous markers in gliomas, thus far none have proved to be predictive.

Despite the absence of established predictive factors, prognostic factors are critically important for clinical trial design. Prognostic factors must be balanced between arms for optimal comparisons. Recent studies suggest that the methylation status of the promoter region of the DNA-repair gene *MGMT* is prognostic for patients with GBM, and although it may also be associated with responsiveness to TMZ, it has not been clearly determined if *MGMT* methylation status is truly predictive [32,33]. In addition, the discovery of molecular alterations in anaplastic oligodendroglioma, namely allelic loss of the 1p 19q chromosome arms, is associated with a high rate of response to both radiation and chemotherapy, and the marked improvement in prognosis has altered the approach to treatment in community practice and clinical trial design. Early chemotherapy versus salvage at recurrence has not been shown to impact survival [34,35]. Since 1p 19q LOH does not identify a specific treatment, it remains an important prognostic, but not predictive factor. Protocol stratification of patients with anaplastic oligodendroglioma is now dictated by the results of molecular analysis and in fact, the prognosis of patients with oligodendroglioma is so different based on the 1p19q LOH determination, that these tumors are now considered independently. Likewise, the relatively recent discovery of mutations in the *IDH1* gene appear to occur frequently as an early mutation in a subgroup of low-grade gliomas, prior to differentiation to astrocytic or oligodendroglial lineage, and are associated with improved prognosis but are not predictive of response to specific treatment. *IDH1* mutations that have been identified in a select group of gliomas correlated with longer overall survival, but are unrelated to specific chemotherapy [36,37].

In addition to the identification of single molecular factors, there has been increasing interest in determining molecular profiles that are prognostic or predictive for specific diseases. For example, an expression panel of 38 genes isolated from 110 GBM specimens from four separate large cancer institutions was found to be highly correlated with prognosis [38]. From this panel, a nine-gene assay was developed that could yield important prognostic information with the added benefit of using formalin-fixed paraffin embedded tumor tissue. Similarly, a CpG-island methylation profile for glioma (G-CIMP) has been identified that is associated with improved outcomes across all grades of glioma [39]. Other modalities of characterizing tumors such as protein-expression profiling [40] and micro RNA profiling [41,42] are also underway. Incorporation of these molecular profiles into clinical trial designs will enhance the veracity of stratification for randomized studies, as well as provide opportunities to develop predictive factors for treatment response and failure.

Novel trial designs

Evaluation of new agents and treatment regimens has been slowed by conventional Phase I/II approaches that are time consuming and inefficient, particularly for combination regimens. Studies to date demonstrate that treatment with a single signal-transduction modulator has only modest efficacy. Given the complex molecular pathways, combination strategies may be superior, which in the context of the growing number of therapeutics designed to target the abnormal signaling pathways, makes testing of the possible combination regimens quite daunting. Simple doublet combinations of selected agents from the more than 12 pathway targets yield >4000 possible combination regimens. It is for this reason that when designing clinical trials we need to utilize designs that improve efficiency by rapidly eliminating arms containing ineffective regimens, test combinations simultaneously and shorten the path to definitive testing in Phase III trials.

Sequential accrual

Combined Phase I/II sequential accrual trials are designed to avoid the down time associated with closure of a cohort at the completion of accrual to a specific dose level. This design is based on the 3 + 3 Phase I design, but is modified to test several agents or therapeutic combinations in a single trial. As the first agent/combination finishes accruing and is on hold while awaiting toxicity data, the next arm testing a separate agent/combination can begin accruing. This pattern continues as each arm continues its evaluation until reaching the goal dose or the maximum tolerated dose within each arm. Once all dose levels have been set, the Phase II portion of the study ensues, and is most efficient for trials with a two-stage design. Patients are again sequentially enrolled so that evaluation of the stage I efficacy of arm 1 should be possible soon after the initial accrual to stage I of

arm 3 is complete. If arm 1 shows efficacy, accrual is completed. The same analysis occurs for arms 2 and 3 in sequential order.

Employing this strategy within neuro-oncology trials has several benefits. The sequential nature of this design ensures that arms will be open when eligible patients are available for enrollment, which is important due to the low incidence rates of these diseases. In addition, this design allows the investigator to arrange for testing of multiple drugs/drug combinations with a single protocol, making it both more time and cost efficient, while maximizing the information obtained from conducting the trial.

■ 'Pick the winner' design

This schema can be employed as a retrospective analysis of a series of single-arm Phase II trials with similar eligibility criteria and primary end points. The results of the trials are compared and the most promising agent(s) or combination(s) are taken forward for further testing. This approach can be problematic because of the confounding effects of each independent trial, such as referral bias, differences in supportive or ancillary care, and identifying trials with similar eligibility criteria and primary end points. When these factors are taken into account, however, this design can aid in interpreting the numerous single-arm Phase II studies that have been performed within the field of neuro-oncology over the preceding decade. This design does not allow for a definitive comparison of treatments; however, it does provide some degree of assurance, as more promising regimens are taken forward for further testing.

Another possible iteration of the design consists of prospectively testing multiple promising regimens, schedules or single drugs, and performing a randomized trial with several arms. This design eliminates the confounding factors noted with the retrospective version. It is also more time and cost efficient, as it tests multiple combinations within a single protocol. This serves as a screening design to take the superior regimen(s) forward for more definitive clinical testing. This type of design is not powered to obtain statistical validation of the superior treatment, but, as with the retrospective design, it does provide some assurance that the chosen regimen is likely not inferior. From a logistic standpoint, this is commonly done with therapies that have already obtained an indication for treating another condition, as combining unproven therapies from competing pharmaceutical companies in the same trial often proves challenging.

■ Factorial

The factorial-trial design allows for evaluation of multiple treatment combinations simultaneously, while requiring fewer patients per combination than an equivalent series of Phase II trials. Ideally, all treatment arms are interrelated, but the individual components should not have direct interactions. This design may be most useful at looking at combined treatment iterations. For example, the factorial design was successfully utilized in a recently published clinical trial that combined a dose-dense regimen of TMZ with three well-tolerated agents (celecoxib, thalidomide and isotretinoin) leading to eight distinct treatment arms (Figure 3) [43]. This strategy, with 20 patients enrolled in each arm, can look at the impact of including each of the agents (e.g., 80 patients received a celecoxib containing regimen and 80 patients did not) with reasonable statistical power (the impact of each individual agent powered at 95% to detect a 50% reduction in hazard rate). In addition, the impact of combined therapies can be tested, in particular if there is benefit of a triplet combination (TMZ plus two agents, 60 patients) versus a doublet combination (60 patients) that can be evaluated (powered at 90% to see a reduction of hazard rate of 50%).

There are limitations to the factorial design, including unpredictable impact of unforeseen treatment interactions among agents in combination affecting efficacy, resulting in increased complexity of the statistical analysis, particularly if the observed interaction negatively affects the efficacy of a treatment or if the magnitude of the interaction between agents is large [44]. Statistical interactions whereby a model designed with the expectation that the effect of a combination will be additive, but in fact the interaction is multiplicative, or *vice versa*, can also negatively affect the ability to interpret a factorial study [45].

■ Randomized discontinuation

Randomized discontinuation trials were first proposed by Amery in 1975 [46]. This design assesses the clinical activity of a drug while minimizing the use of placebo. In this design, all patients receive the study drug for an initial period, followed by blinded randomization of patients with stable disease to either continue the study drug or switch to placebo, while patients with response continue on treatment and patients with progression stop treatment (Figure 4). From a patient perspective the fact that all of the arms of this trial contain the study drug may present more of an acceptable 'risk' and therefore may aid in patient accrual. Patients randomized to placebo who progress are unblinded and allowed to crossover to the treatment group. This type of design increases statistical power with a smaller number of patients and again represents a more efficient means of obtaining meaningful data than the standard single arm Phase II design. Ratain *et al.* performed a Phase II placebo-controlled randomized discontinuation trial of

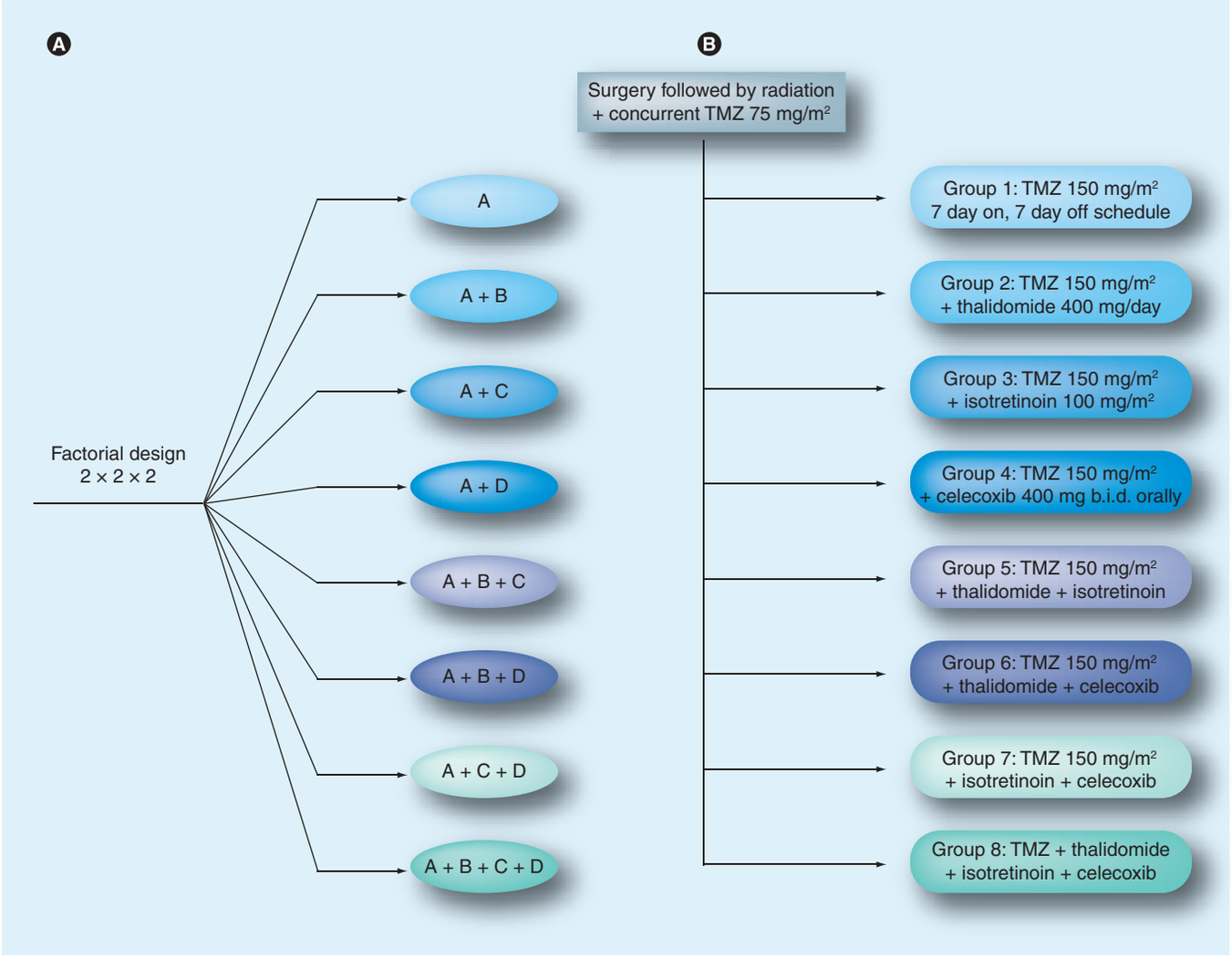

Figure 3. Factorial trial design. (A) Design for an eight arm 2 × 2 × 2 factorial trial featuring drug A as the 'backbone' used alone or in doublet, triplet or quadruplet combinations of drugs B, C and D. **(B)** Design of trial 2004–0662, a combined MD Anderson Cancer Center/CCOP factorial trial utilizing a dose-intensified regimen of temozolomide as a 'backbone,' alone or in doublet, triplet or quadruplet combinations of thalidomide, isotretinoin and celecoxib.
b.i.d.: Twice daily; TMZ: Temozolomide.

sorafenib in patients with metastatic renal cell carcinoma; 202 patients were treated with sorafenib for 12 weeks, at which point the 65 patients that had stable disease were randomly assigned to sorafenib or placebo for 12 additional weeks. At 24 weeks, 50% of the sorafenib-treated patients were progression free versus 18% of the placebo-treated patients (p = 0.0077) [47].

While this design is likely to be most effective in testing monotherapy for logistic reasons the potential exists to use this schema for combination regimens, as well. One could envision testing a targeted therapy in combination with a cytotoxic backbone, such as TMZ, and then randomizing patients with stable disease to either continued combination treatment or TMZ and placebo, or even discontinuing TMZ and randomizing to single agent study drug or placebo once they have reached a specified timepoint (e.g., median progression free survival, 12 cycles of treatment). This design could help to more definitively answer the question of whether or not many of these newer therapies have activity against glioma.

■ Adaptive randomization design

The Bayesian-based adaptive randomization design is a multiple-arm study. Allocation of patients is based on Bayesian probability of treatment efficacy. Accrual to the arms can be equal from the start or can take into consideration available data to weight accrual positively

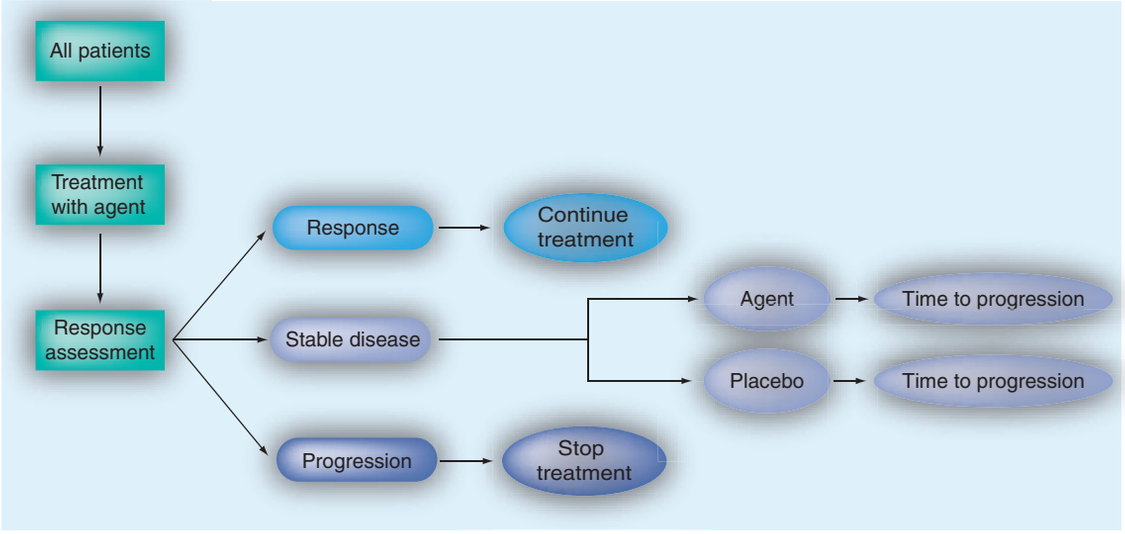

Figure 4. Randomized discontinuation trial design. At enrollment, all patients receive study treatment. Patients with a response continue treatment; patients with progression are discontinued from treatment; patients with stable disease are randomized in a blinded fashion to either continued study treatment or placebo. There is the option of crossover for patients who progress on placebo.

or negatively to various arms. In trials with equal weighting of arms at the outset, accrual of ten–20 patients to each arm is followed by an interim analysis to integrate acquired information and adjust the formula for patient allocation to various arms. Treatment arms with success are more likely to accrue patients. Treatment arms with poor results have decreased probability of accruing and ultimately can be dropped depending on design, alternative arms can be added depending on design and accrual continues until clear evidence of superior treatment(s) emerges (Figure 5). The benefit of this design is that arms with less chance of success accrue fewer patients over time and arms with greater chance of success accrue more patients. Not only is this more time and cost effective, as more resources are directed towards more promising treatments, it is also preferable to patients as it becomes more likely over time that they will receive an efficacious treatment. This stands to improve accrual to the trial when discussing this aspect of the trial design with patients. The clinicaltrials.gov search referenced previously in this review revealed two trials that currently employ this design, though neither is yet recruiting patients [105]. NCT01266031 is a Phase I/II adaptive randomized trial of single agent BEV versus BEV plus vorinostat in recurrent GBM. NCT01110876 is a Phase I/II adaptive randomized trial of the combination of vorinostat and erlotinib ± carboplatin for recurrent GBM.

In the neuro-oncology field, much like the rest of oncology, targeted therapies are widely studied, and biomarker assessment in an effort to find a predictor of treatment efficacy has become a critical component. Adaptive randomized trial design can allow for integration of new information obtained about biomarkers and their potential predictive capability, which at the beginning of the trial was not available. While examples of this within neuro-oncology have yet to take place, trials in other cancers such as Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis 2 (I-SPY2) in breast cancer and Biomarker Integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE) in lung cancer, which are further discussed below, are now showing the potential that designs such as this have in guiding treatment based on the predictive power of biomarkers, allowing for further biomarker discovery, elucidating differences in disease subtypes and furthering the idea of personalized cancer therapy.

■ Seamless integrated Phase II/III trials

There have been a large number of noncomparative single-arm Phase II trials conducted in many areas of oncology. Within the field of neuro-oncology, this had occurred most frequently in the setting of recurrent malignant glioma. Integrated Phase II/III trial designs can be utilized to facilitate the rapid definitive evaluation of a promising regimen. This design is typically employed in the setting of testing agents or combinations of agents that have promising preliminary data, but where more evidence is needed prior to committing to the undertaking of a Phase III trial [48]. The initial stage

of the trial employs a randomized, multi-arm Phase II study. A control standard of care arm can be included as a reference arm to ensure no significant deviation from historical controls (frequently with randomization weighted towards the experimental arms in a defined ratio; i.e., 2:1). The trial is not powered for direct comparison of experimental arms or against the reference arm, although it can be powered to ascertain non-inferiority. Newer designs are integrating an adaptable approach to allocate patients to arms that are showing more benefit, while eliminating underperforming arms for efficiency of accrual and limiting patient exposure to drugs with inferior efficacy [49]. When the Phase II portion is completed, the most promising arm(s) is (are) carried forward to a Phase III trial. This design is more time efficient in that the Phase III portion of the trial is written upfront and therefore the approval process for the Phase II and III portions is simultaneous. It is also more resource and patient efficient, since the patients enrolled in the Phase II arms count towards the accrual for the Phase III study. Progression-free survival end points are often utilized in the Phase II portion and are typically replaced with overall survival end points for the Phase III portion, often permitting patients accrued to the Phase II component to be included in the accrual and evaluation of the Phase III study, as noted above. In the event that none of the arms of the Phase II study ultimately demonstrate efficacy to warrant continuation on to a Phase III study, the trial can be closed.

Continuing evolution of study designs

The concepts underlying many of these study designs have been present for decades. As technology advances, so too does our ability to accurately model these proposed designs. In addition, ever-advancing molecular evaluation techniques raise the possibility of establishing response predictors leading to enrichment or selection strategies. As such, adaptive designs based on biomarkers are being developed, permitting optimal assessment of treatment efficacy while advancing the concept of personalized treatment. There are an increasing number of cancer clinical trials using some of these novel clinical trial designs. Recently, an adaptive Phase II multicenter trial in non-small-cell lung cancer, BATTLE, was designed to assign treatment based on the presence of predictive biomarkers. The markers were chosen ahead of time, and included EGFR and KRAS mutations, increased copy number of EGFR and cyclin D1, and increased VEGFR expression. The four treatment arms were erlotinib, sorafenib, and vandetanib or erlotinib plus bexarotene. Primary end points were disease control at 8 weeks. Patients were initially randomly accrued to the treatment arms with equal probability. After a predetermined accrual, analysis was conducted to determine biomarker prediction of response or resistance to treatment arms, and probability of accrual to these arms was then adjusted. Preliminary results indicated that patients with KRAS mutations responded better to sorafenib, EGFR mutations responded better to erlotinib, increased copy number of cyclin D1 and EGFR responded better to the erlotinib and bexarotene combination, and elevated expression of VEFGR2 responded better to vandetinib. A follow-up trial, BATTLE-2, is being planned with fewer predetermined stratifying biomarkers, with the intention of conducting extensive molecular analysis and allowing for discovery of predictive markers as the trial accrues [50].

A similar biomarker-driven trial is being conducted in the neoadjuvant setting for locally advanced (>3 cm) breast cancer. I-SPY2 is an adaptive Phase II study with a primary end point of complete tumor response. However, the trial is enhanced by the secondary end points that are designed to validate biomarkers in the evaluation of new drugs with the goal of adaptive randomization based on these signatures. The trial has seven arms, with two standard of care arms and five arms combining standard treatment with an investigational drug. Pretreatment tumor molecular profiling and tumor biopsies during treatment are important features of the trial. Each combination will be tested on a minimum of 20 patients and a maximum of 120 patients, with underperforming arms eliminated and arms with a high Bayesian probability of Phase III success 'graduated' to further investigation in a Phase III trial [51].

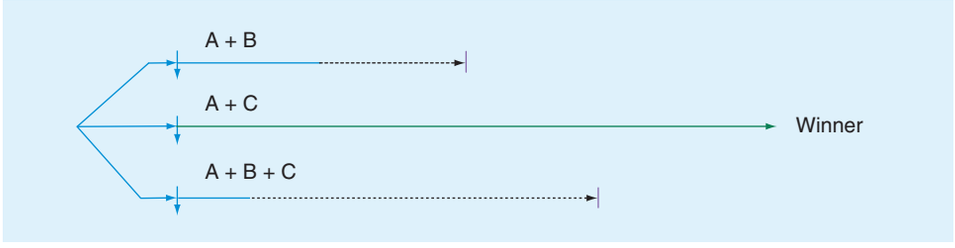

Figure 5. Adaptive randomized trial design. Randomization to multiarm studies in this design is weighted based on the regimen's probability of efficacy. This allows for utilization of data as it is accrued and minimizes the probability that patients will be enrolled to an arm with an ineffective treatment regimen, while maximizing the probability that they will be treated with a regimen that is demonstrating efficacy. The vertical arrows represent a predetermined interim accrual point (e.g., ten patients/arm) at which time available data is analyzed and randomization probability to the arms is adjusted.

Future perspective

Tremendous strides are being made in our understanding of the molecular biology of malignancy as the biotechnology industry continues to expand and refine the techniques by which we study these diseases. Genetic and other tumor-specific information is being gathered at a very rapid rate, leading to the uncovering of many possible therapeutic targets. This has led to an increasing need to rapidly test new agents and combinations, recognizing limits in patient and economic resources. The new clinical trial designs, particularly when integrated with tumor molecular profiling and other predictors of response, will help accelerate improvement in therapy.

Standard treatment regimens for malignant brain tumors will likely evolve to personalized treatment combinations consisting of a cytotoxic agent such as TMZ in combination with several targeted agents that are selected specifically for patients and their cancer. This change in approach, accompanied by continued improvement in patient outcomes, will usher in the dawn of true personalized cancer therapy.

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Executive summary

- Despite improved techniques, surgery for malignant brain tumors is not curative.
- The blood–brain barrier, disease heterogeneity and suboptimal vascular supply limit the effectiveness of many agents that are efficacious in the treatment of systemic cancers.
- Clinical research in neuro-oncology is complicated by low incidence rates leading to prolonged enrollment, long time to progression in lower grade tumors leading to prolonged trial duration, and ambiguous outcome measures resulting in difficulty standardizing trial evaluation.

Gliomagenesis

- Malignant gliomas are commonly distinguished by their cell of origin (astrocyte or oligodendrocyte) and by whether or not they originated as a high-grade tumor (primary glioblastoma) or evolved from a lower grade tumor (diffuse astrocytoma, anaplastic astrocytoma or secondary glioblastoma). These distinctions are commonly associated with well-described genetic mutations.
- *IDH1* and *IDH2* mutations were recently identified as common early alterations in diffuse astrocytic and oligodendroglial tumors.

Prognostic/predictive factors

- While numerous isolated molecular factors as well several molecular profiles of malignant brain tumors exist and are associated with prognosis, as of yet predictive markers of treatment response for brain tumors do not exist.
- As further prognostic factors are identified, their use in patient stratification for clinical trials needs to be taken into account.

Novel trial designs

- Utilization of designs that minimize trial down time, account for incorporation of accumulating information, minimize patient exposure to placebo or ineffective therapies, maximize data acquisition, allow for efficiency in the approval process and integrate biomarker discovery and utilization, are needed to efficiently evaluate the increasing number of therapies available.
- Trial objectives need to be carefully considered when weighing the advantages and disadvantages of implementation of novel trial designs.

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