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REVIEW ARTICLE

Adult Glioblastoma

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A B S T R A C T

Glioblastoma (GBM) is a rare tumor and one of the most challenging malignancies to treat in all of oncology. Although advances have been made in the treatment of GBM, encouraging outcomes typically are not observed; patients diagnosed with these tumors generally have a dismal prognosis and poor quality of life as the disease progresses. This review summarizes the clinical presentation of GBM, diagnostic methods, evidentiary basis for the current standards of care, and investigational approaches to treat or manage GBM. Because the track record for developing effective therapies for GBM has been dismal, we also review the challenges to successful therapeutic and biomarker development.

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INTRODUCTION

Adult glioblastoma (GBM) is one of the most deadly and recalcitrant of all malignant solid tumors. In the United States alone, an estimated 12,120 patients were diagnosed with GBM in 2016, with a 5-year survival rate of 5%.[1] Despite considerable effort, little progress has been made toward prolonged survival in GBM, with much of the perceived improvement coming from the recognition of two prognostic biomarkers: mutations in isocitrate dehydrogenase (*IDH*) and O6-methylguanine-methyltransferase (*MGMT*) promoter methylation.

Malignant gliomas, including GBM, are rare. The peak age-adjusted incidence of GBM is estimated to be 3.2 per 100,000 population in the United States.[1] The incidence increases dramatically after the age of 54 years and reaches a peak incidence of 15.24 per 100,000 population at age 75 to 84 years.[1] Given the higher incidence rate in the elderly and the increased longevity of people in developed countries, the last several decades have seen the median age of GBM increase to 64 years.

For a majority of patients with GBM, there is no known cause of the disease. A small minority of patients ($< 5\%$) have a critical germline alteration, predisposing them to many tumor types including GBM,[2,3] and fewer than 20% of patients with GBM have a strong family history of cancer. The only well-established causative exposure is from ionizing radiation[4]; however, only a small minority of the cranial tumors caused by radiation exposure are GBMs.[5] Other exposures (eg, cell phones),[6-8] viral triggers (cytomegalovirus),[9] and germline predispositions[10] continue to be explored, but they have not been clearly established as causative factors. No early detection of GBM is available. Currently, standard magnetic resonance imaging provides the most sensitive tool for the initial detection of GBM; however, once a GBM definable lesion is identified with imaging, the tumor is at an advanced state.

DIAGNOSIS

Clinical Presentations of GBM

The clinical presentations of GBM are typically related to the functional aspect of the involved area of the brain. Tumors in certain areas cause obvious symptoms such as persistent weakness, numbness, loss of vision, or alteration of language. With these symptoms, the size of the tumor on imaging tends to be smaller. Tumors in other areas of the brain may result in more subtle symptoms such as executive dysfunction, mood disorders, fatigue, and mild memory disorders. Such tumors are frequently centered in the frontal lobe, temporal lobe, or corpus callosum and tend to be larger upon discovery. Seizures occur in only a minority of patients newly diagnosed with GBM (approximately 25%) and are typically easy to control with anticonvulsants throughout the course of the disease[11]; however, there is no clear role for anticonvulsants in patients without seizures. Headaches as an initial symptom are not

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uncommon and usually are associated with significant mass effect, either directly from the tumor or through obstruction of the ventricular system.

Imaging Features of Initial GBM

The typical imaging features of GBM include an infiltrative, heterogeneous, ring-enhancing lesion with central necrosis and surrounding peritumoral edema. Involvement of the deep white matter and the corpus callosum is common. Although the enhancement is not commonly multifocal, there can be smaller satellite areas of enhancement and regional necrosis. Rarely, a small nonenhancing or partially enhancing lesion is initially seen, yet rapid change to a ring-enhancing, necrotic lesion with peritumoral edema in just weeks is typical (Fig 1). *IDH*-mutant GBM (approximately 5% of newly diagnosed cases[12,13]) has different initial imaging characteristics, showing a predominance of bulky nonenhancing tumor, cortical infiltration, large size, minimal edema and necrosis, and a predilection for the frontal and temporal lobes.[14] *IDH*-mutant GBM has corresponding features that are best associated with what was previously called secondary GBM.[15] Differentiating GBM from other nonglial tumors and infection can be done with the use of standard and more advanced magnetic resonance imaging.[16] Other imaging modalities rarely help with the diagnosis.

Pathologic Diagnosis

The diagnosis of GBM is commonly made with formalin-fixed, paraffin-embedded tissue from resected or biopsied tumor. The microscopy and immunostains typically show an infiltrating glial fibrillary acidic protein immunopositive tumor with marked pleomorphism, brisk mitotic activity, microvascular proliferation, and necrosis. The necrosis may be palisading or geographic. Typically, the cellular morphology is predominantly astrocytic, but in some cases, a subset of tumor cells may have oligodendroglial or primitive neuroectodermal tumor features. The designation of GBM based upon *IDH* status is typically determined using immunohistochemistry and/or sequencing.[17] In the setting of diverse cellular morphologies, molecular analysis can help clarify the diagnosis.

STANDARDS OF CARE FOR GBM

The evidentiary basis for standard therapy for GBM is heterogeneous, with varying levels of evidence applied for different treatment modalities. Specific populations may also have multiple sources of data that can be applied. The standards for different clinical presentations and the evidence supporting the approaches are discussed in this section.

Patients Younger Than Age 70 Years With Newly Diagnosed GBM

The current standard of care for this population is maximal safe surgical resection, followed by radiation therapy (RT) and concomitant temozolomide (TMZ) and then adjuvant TMZ. There are no randomized trials comparing more surgery with less surgery, and retrospective data are inextricably linked to selection bias, making the true value of the extent of resection difficult to isolate. However, the retrospective data consistently show an association of greater extent of resection with better outcomes after controlling for other factors.[18-21] Additionally, a randomized trial of 5-aminolevulinic acid, which helps achieve more comprehensive resection, showed an association with progression-free survival (PFS).[22] These data and others have led to a recommendation of resection of the maximal amount of tumor that is safely possible, because postoperative morbidity can also contribute to a poor outcome.

The BTSG (Brain Tumor Study Group) 6901 randomized trial showed that the addition of whole-brain RT more than doubled survival over supportive care alone after surgery and substantially improved survival compared with 1,3-*bis*(2-chloroethyl)-l-nitrosourea (BCNU). These results established RT as the backbone of adjuvant therapy after surgery.[23] RT volumes have since been reduced based on the observation of predominantly local recurrence patterns[24] and randomized data from the BTCG (Brain

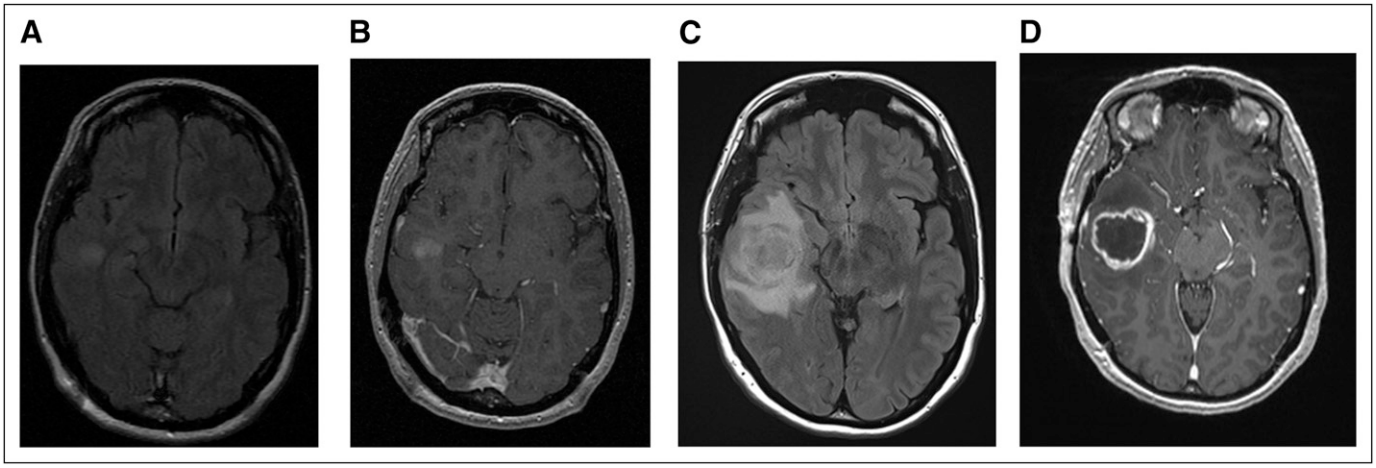

Fig 1. Magnetic resonance (MR) images of a patient with new-onset seizure. (A, B) Small lesion in the right temporal lobe with faint enhancement and no edema. (C, D) Repeat MR images 20 days later with rapid evolution to a large ring-enhancing mass with a necrotic center and significant perilesional edema. Pathology showed glioblastoma.

Tumor Cooperative Group) 8001 trial showing similar outcomes for patients receiving part of the total RT dose as a local cone down.[25] Even so, no standard for radiation target volumes currently exists. Radiation dose for this population has been consistent at 60 Gy in 30 fractions. A pooled analysis of serial BTSG trials showed a dose-response relationship for survival between 45 and 62 Gy,[26] and the Medical Research Council (BR2) randomized trial showed a survival benefit for 60 Gy compared with 45 Gy.[27] Conversely, a Radiation Therapy Oncology Group (RTOG)/Eastern Cooperative Oncology Group randomized trial showed that 70 Gy did not improve survival compared with 60 Gy,[28] and hyperfractionated schedules with higher total doses similarly have not improved survival in randomized trials.[29,30] Additionally, the RTOG showed stereotactic radiosurgery offered no benefit in addition to standard RT and BCNU in a randomized clinical trial (RTOG 93-05).[31]

The randomized clinical trial (RCT) EORTC (European Organisation for Research and Treatment of Cancer) 26981-22981/NCIC CTG (National Cancer Institute of Canada Clinical Trials Group) CE.3 established TMZ as part of the standard of care for GBM. The trial compared TMZ administered concurrently and after RT with RT alone and showed an improvement in overall survival (OS), with a hazard ratio (HR) of 0.64, leading to a 2.5-month improvement in median survival and absolute increases in 2- and 5-year survival of approximately 16% and 8%, respectively.[32] Patients with tumors harboring methylation of the *MGMT* promoter, thereby turning off the expression of a gene involved in repair of damage from TMZ, received greater relative and absolute benefit from combination therapy in a post hoc analysis. *MGMT* promoter methylation was also a favorable prognostic factor. Patients with *MGMT* promoter methylation had an HR of 0.51, an 8-month improvement in median survival, and absolute increases in 2- and 5-year survival of approximately 25% and 9%, respectively, with the addition of TMZ.[33] Patients with unmethylated *MGMT* promoters derived less benefit, with an HR of 0.69, a 1-month improvement in median survival, and absolute increases in 2- and 5-year survival of approximately 13% and 8%, respectively.[32,33] The marginal benefit of combination therapy for the unmethylated population has brought into question the use of combination therapy as an absolute standard,[34] particularly in the clinical trial setting.[35]

Other randomized trials have shown positive benefit from experimental therapies, with much less application of these therapies in clinical practice. One RCT evaluated the use of BCNU wafers, a biodegradable polymer that is implanted at surgery for controlled release of BCNU, followed by standard RT. The median survival for patients with GBM was 13.5 months with BCNU wafers compared with 11.4 months for RT alone after maximal safe resection, with an HR of 0.76 ($P = .10$).[36] *MGMT* methylation status was not measured. Given the limited clinical benefit, occurrence of concerning adverse events of the CNS, and imaging changes that are often difficult to interpret, these results did not substantially change clinical practice. More recently, an RCT using tumor-treating fields (TTFs) as maintenance therapy for patients with newly diagnosed GBM was reported.[37] TTFs deliver low-intensity, intermediate-frequency (200 Hz), alternating electric fields through transducer arrays applied to the shaved scalp for at least 18 hours a day, which is thought to disrupt cell division. Patients in the TTF arm were allowed to continue beyond progression. The median OS (from registration) was 24.5 months with TTFs compared with 19.8 months without TTFs (HR, 0.65; $P < .001$), and the 2-year survival rate (from random assignment) was 42.5% versus 30%, respectively. Although the mechanism of action proposed is as an antimitotic, it is not straightforward, and there is no understanding of the mechanism of escape. The clinical development of this modality might be viewed similarly to the early development of RT; there is ample room for additional exploration and optimization, including array density and coverage, intensity and frequency, impact of duration of use each day, and use beyond progression. These data represent a modest incremental effect on survival and establish TTFs as a novel cancer treatment modality; however, the marginal benefit, lack of a placebo control arm in the trial, strong prior beliefs of the neuro-oncology community, issues related to compliance, and patient concerns about the arduous and intrusive nature of the apparatus may be limiting more widespread acceptance and adoption.[37,38]

Elderly Patients With Newly Diagnosed GBM

It is difficult to define elderly, especially with the increase in longevity and improving functional abilities of the aging population in developed countries. Older age has consistently been one of the most significant negative prognostic factors for GBM[39] and has been hypothesized to potentially be predictive of response to therapy.[40] There are also concerns about the impact of therapy on quality of life and the potential irreversible impact of therapy on the aged brain. Frequently, older age and decreased or lower standards of performance status are used together as eligibility criteria for trials investigating the utility of any or minimal treatment in these populations. However, other trials isolate only by age and include mostly well-functioning patients when evaluating de-escalated treatments. The Association of French-Speaking Neuro-Oncologists showed that RT (50.4 Gy) was superior to comfort care alone for patients older than age 70 years with good performance, with an HR of 0.47 ($P = .002$) and increase in median survival from 16.9 to 29.1 weeks.[41] Although the eligibility criteria included Karnofsky performance score greater than 60, most patients had a score of 70 or 80. Shorter, de-escalated RT courses may have similar or better outcomes than standard fractionation based on small randomized studies and subset analyses.[42-44] Similar to standard RT in the nonelderly population, the addition of TMZ to short-course RT improves survival. Perry et al[45] showed that TMZ administered concurrently during a 3-week course of RT and as adjuvant therapy improved survival compared with the 3-week RT course alone (HR, 0.67; 1.7-month improvement in median OS).[45] Additionally, similar to the EORTC 26981-22981/NCIC CTG CE.3 RCT, there was greater benefit for patients with *MGMT* promoter methylation (HR, 0.53; 5.8-month improvement in median OS) compared with those with unmethylated tumors (HR, 0.75; 2.1-month improvement in median OS).[46] The standard 6-week course of RT has never been compared directly with shorter courses when both are administered concurrently with TMZ, however. For older patients who cannot receive combined therapy with RT and TMZ, TMZ alone is also a reasonable option for patients with methylated *MGMT* promoters. Patients with *MGMT* promoter methylation do better with TMZ compared with RT, whereas those with unmethylated tumors do worse based on data from the German Neuro-oncology Working Group –8 and Nordic RCTs.[44,47] For elderly populations

with poor performance status, Roa et al[42] showed that a 1-week course of RT did not lead to detectable differences in OS compared with a 3-week course in a small randomized trial. In elderly populations with poor performance status, efforts should be made to reduce the overall treatment and hospitalization burden. In a SEER-Medicare analysis of elderly patients with GBM, it was shown that up to 22% of the remaining lifespan after diagnosis is spent as an inpatient.[48]

Recurrent/Progressive GBM

Currently, the National Comprehensive Cancer Network guidelines consider several therapeutic approaches reasonable for use in recurrent GBM.[49] However, the data supporting these approaches are not based on superiority in any RCT, other than BCNU wafers.[50] Upon closer inspection, it is not clear that BCNU wafers showed statistical significance as a therapy for GBM, although the effect of BCNU wafers compared with placebo showed a numerically different median OS of 31 versus 23 weeks, with an HR of 0.83 (P = .19). Only through post hoc analysis, when attempting to balance prognostic factors, did HRs improve and provide statistical significance. The combination of the lack of superiority with prospective analysis, limited patient population eligible for such an approach, and difficulty in interpreting scans post-treatment has lessened enthusiasm for the BCNU wafer. RCT results with bevacizumab as first-line therapy for GBM[51,52] in recurrence[53] have been consistent: decrease in the intensity and volume of contrast enhancement, decrease in peritumoral edema, decrease in corticosteroid use, statistically significant prolongation in PFS, and no improvement in OS. This disconnect between early determinates of effect (objective response rates and PFS) and survival has been attributed to many factors, including crossover; however, there are other concerns about the inability of contrast enhancement on T1 sequences, the measure used to determine objective response rate and PFS, to accurately represent tumor burden during treatment with bevacizumab. Controversy exists regarding the potential negative impact of bevacizumab on health-related quality of life and neurocognitive function in the first-line setting,[51,52,54,55] but no controversy exists regarding stability of these same measures in the recurrent setting during bevacizumab treatment.[56] The best setting in which to use bevacizumab may not be well defined within traditional lines of therapy; rather, it may be based on the clinical circumstance. Practitioners commonly use bevacizumab if there is significant mass effect, vasogenic peritumoral edema, and/or decline in clinical function that cannot be easily remedied by surgical intervention or short-course corticosteroids. Recent preclinical and clinical data provide further rationale for limiting corticosteroid use.[57] This use of bevacizumab most commonly occurs with recurrent GBM, although most patients receive bevacizumab at some point during their treatment for GBM.

INVESTIGATIONAL APPROACHES

Targets and Challenges

The molecular mechanisms underlying the origins of GBM are unknown, although glial precursors are speculated to be the cells of origin. Sampling GBM at various stages (formation/maintenance, treatment, and progression) has provided rich data on genetics, gene expression, and promoter methylation; these data have been explored in detail by others.[58] Despite efforts toward the molecular characterization of GBM, only a few molecular features, *MGMT* promoter methylation and *IDH1/2* mutation, are considered clinically relevant, and none have been prospectively targeted to improve OS with success. GBMs with *IDH1/2* mutations have a less aggressive course and distinct genetic, epigenetic, pathologic, and clinical features. For these reasons, they are increasingly considered separately in clinical trials. Although the extensive molecular characterization tends to highlight cell autonomous targets, other targets worth considering are a manifestation of the interplay of the progressing tumor with local and systemic processes. These include tumor infiltration and migration, hypoxia, angiogenesis, vasculogenesis, gliosis, microglia activation, myeloid-derived cell trafficking, tumor-cell clonal evolution, and immune suppressive effects, among others. Strategies and targets that are currently being pursued for GBM based on GBM- or brain-specific data or through activity in other cancers are available in other reviews.

Development of Novel Therapies for GBM

Other than the few positive trials previously described, the decades of research dedicated to finding new therapies for GBM have largely resulted in failure, including several in late-stage disease[51-53,56,59-71] (Table 1). Many potential barriers to successful therapeutic development in GBM have been suggested, but the causes of failure are largely unknown. General issues include questionable utility of preclinical models and early-phase clinical trial designs that overestimate the probability of success and lead to late-stage failures. Other potential barriers are related to the unique characteristics of GBM and its host organ, the brain.

Drug delivery is often suggested as a major impediment to therapeutic development. Patients with GBM have abnormal blood vessels and areas of necrosis that could lead to heterogeneous drug distribution. Nonenhancing tumor is associated with an intact blood-brain barrier, which either physically restricts entry of drugs or actively pumps drugs out. A recent study of lapatinib demonstrated significant interpatient variability of drug in tumor, with median concentrations below what would be expected in preclinical experiments that led to full inhibition and cell kill.[72] Such data are essential in determining sources of drug failure, but these studies are not frequently performed. The limitations of directly accessing the brain and tumor for pharmacokinetics, pharmacodynamics (PDs), and pathologic response to drugs have also created a greater reliance on imaging to determine activity in the early phase. Imaging-based assessment of response has had a weak correlation with more meaningful end points such as OS.[73] Additionally, although effects on PFS, based mostly on imaging, may correlate with effects on OS for standard chemotherapy,[73] PFS and OS effects for antiangiogenic agents do not correlate,[51,52] and there is concern about possible pseudoprogression with immunotherapeutic agents.[74] This limitation is critical in early-stage trials, in which efficacy signals must be found to justify larger randomized trials (Fig 2). Imaging will also be critical in a future state where OS effects may not be as easily measured because of longer survival postprogression with more effective therapeutics.[75] Finally, the brain has been thought to be an immune-privileged environment, possibly leading to

Table 1. Phase III Studies in GBM With Unmet OS End Point and Limitations of Early-Phase Results

Drug	Study Name	Rationale for Phase III Study	Limitation of Phase II Results
Cilengitide	CENTRIC	Three phase II single-arm, first-line studies showed improvement in OS compared with historical control[59] and impact on landmark PFS in methylated *MGMT* population compared with historical control[60]	In single-arm studies, historical controls for PFS and OS frequently overestimated effect because of selection bias and drift[61]; PFS end point in first-line setting not an established meaningful end point[60]
Bevacizumab	AVAglio,[51] RTOG 0825[52]	Phase II single-arm, first-line studies showed prolonged PFS and survival compared with historical controls[62,63]	Contrast imaging end points (ORR and PFS) in the setting of VEGF inhibition may not correlate with survival; first-line and recurrent phase III studies showed similar improvement in ORR and PFS but not OS[51,53]
	EORTC 26101[53]	Phase II study without control population showed promising response rate, 6-month PFS, and OS compared with historical controls[56]	
Cediranib	Phase III randomized trial compared efficacy of cediranib as monotherapy and in combination with lomustine, *v* lomustine alone in recurrent GBM	Phase II single-arm study showed response rate of 27% and improved PFS[65]	Contrast imaging end points (ORR and PFS) in the setting of VEGF inhibition may not correlate with survival; first-line and recurrent phase III studies showed similar improvement in ORR and PFS but not OS[64]
Enzastaurin	Phase III study compared enzastaurin with lomustine in recurrent intracranial GBM[66]	Phase I/II single-arm study showed 25% response rate[67]	ORR an unreliable end point with respect to impact on OS; ORR also not confirmed, and other measures of treatment effect not encouraging (PFS, 1.3 months; PFS, 7%; OS, 4.6%)[67]
Rindopepimut	ACT IV: international, double-blind, phase III trial of rindopepimut in newly diagnosed, EGFRvIII-expressing GBM[68]	Single-center[69,70] and multicenter[71] single-arm studies showed prolonged PFS and OS compared with contemporary controls	In single-arm studies, historical controls for PFS and OS frequently overestimated effect because of selection bias and drift

Abbreviations: AVAglio, Avastin in Glioblastoma; CENTRIC, Cilengitide in Combination With Temozolomide and Radiotherapy in Newly Diagnosed Glioblastoma Phase III Randomized Clinical Trial; EGFRvIII, epidermal growth factor receptor variant III; EORTC, European Organisation for Research and Treatment of Cancer; GBM, glioblastoma; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RTOG, Radiation Therapy Oncology Group; VEGF, vascular endothelial growth factor.

reduced efficacy of immunotherapies, but this idea has largely been abandoned with more modern research.[76]

The Cancer Genome Atlas shows that GBM is characterized more by recurrent pathway alterations that take several different forms rather than by specific targetable drivers.[77] This characteristic of GBM makes treatment with targeted agents more difficult because redundant signaling pathways may limit efficacy.[78] GBM also does not have a high somatic mutational load compared with other cancers,[79] suggesting fewer possible neoantigens and less intrinsic immunogenicity. However, mutational load for recurrent tumors, particularly those treated with TMZ, may harbor a hypermethylator phenotype.[80,81] This phenotype may identify an attractive target population, and it is potentially a predictive biomarker for immunotherapies.

The therapeutic development culture for GBM may also be limiting. Rarely are therapies developed for GBM specifically, resulting in investigational therapies that do not address GBM-specific biology and that may be engineered not to cross the blood-brain barrier. Additionally, limited data may be available from preclinical GBM models to inform clinical trial decision making. Furthermore, a history of failure makes marginal success seem significant, which could slow progress. An example is the use of TMZ for patients with unmethylated *MGMT* promoters. TMZ likely has a real but marginal benefit in this population; however, requiring TMZ in the backbone standard therapy can lead to a delay in phase II testing because phase I data for combinations with TMZ (a drug not used in many other indications) are unavailable. More concerning is that overlapping toxicity with TMZ either stops development or results in recommended doses that are too low for efficacy. Increasingly, the neuro-oncology field has been more comfortable omitting TMZ,[34] particularly in experimental arms in trials for patients with unmethylated *MGMT* promoters,[35] mitigating the overlapping toxicity concern. However, the omission of TMZ for patients with unmethylated tumors highlights the need for more standardized MGMT testing.

Potential Solutions for Better Therapeutic Development for GBM

Improvements in the development process can lead to more efficiency in therapeutic and biomarker development and create an environment where more is learned from failures. This approach would lead to more therapies and biomarkers entering testing, better evaluation of the probability of success at each point along the development continuum, and a more attractive environment in which pharmaceutical and biotechnology companies may focus their efforts.

The preclinical phase of GBM therapeutic development should develop strong hypotheses based on GBM-specific basic science. Effectively moving these hypotheses into clinical testing requires preclinical models with knowable ability to predict the chances of clinical success. Improving the specific models and creating a system to formally evaluate the model effectiveness for

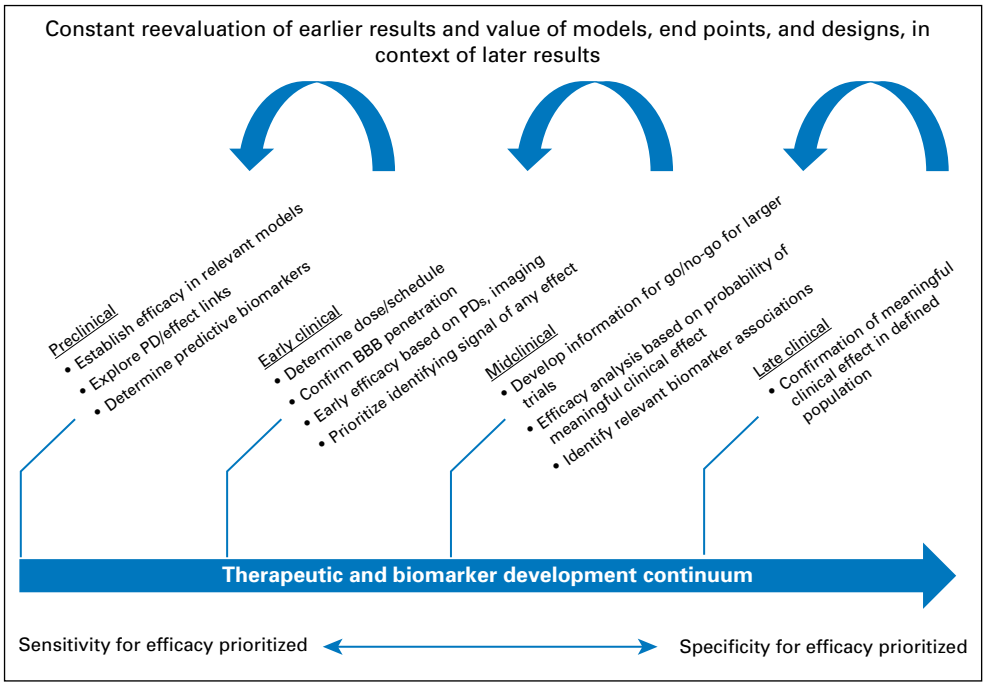

Fig 2. Proposed priorities along the therapeutic and biomarker development continuum. In the earlier stages of development, emphasis is placed on identifying therapeutics with effects on tumors, necessary but not sufficient measures of efficacy such as pharmacodynamics (PDs), and exploring for biomarker associations for each of these. As development proceeds later, more emphasis is placed on confirming an effect on a clinically meaningful end point. With limited effective therapies and relatively short postprogression survival, this clinically meaningful end point should be overall survival. As more effective therapies are added, signal may need to be found in more proximate end points such as progression-free survival. In each part of the continuum, formal evaluations for the predictive value of preclinical models, end points, and trial designs with regard to ultimate success should be performed to improve the system. If the true sensitivity and specificity of these actors in the continuum were known, sensitivity would be prioritized in the early parts and shift toward specificity during late stages.

predictive success would form a solid foundation. Particularly for a deadly disease like GBM with limited available treatments, an initial preclinical screen might prioritize sensitivity over specificity and refine such predictions based on therapeutic effect magnitudes. Ideally, in vitro and in vivo preclinical effects on cell or animal survival would be causally linked to specific PD effects that could be measurable in early-phase clinical trials. The preclinical phase would also be the time to develop evidence to support predictive biomarker hypotheses.

For early-phase clinical trials, the goals are to establish a safe dose, show that the dose reaches the enhancing and nonenhancing tumors in relevant concentrations, and demonstrate an efficacy signal. Given the problems with using historical control data for end points such as PFS and OS, these trials would focus on end points that are more directly attributable to the drug, such as a PD end point or imaging-based response. Developing such end points will also be critical for evaluating therapies targeting small subpopulations of patients with GBM based on specific molecular aberrations. Random assignment in such small populations may not be feasible within the biomarker-defined group, and inclusion of GBM in non–tumor-specific basket trials generally relies on such end points.[82] Having robust preclinical models will enable interpretation of the results if a PD effect is necessary for cell or animal survival; it would be expected that this relationship would also hold in humans. Therapies that are unable to reach the target or affect the desired PD end point may need dose or schedule adjustments, or a decision may need to be made to discontinue development.

Currently, late-stage and pivotal trials should be based on improving OS. This may not always be the case once there are more effective therapies and longer survival postprogression, because OS signals would be harder to isolate. Reliably determining that a therapy improves OS requires random assignment or a signal that is remarkably large and outweighs all prognostic factors. The decision to move from early signs of efficacy based on PDs or imaging response to late-stage randomized trials is critical. Many times this link is made with smaller single-arm trials using either PFS or OS as an end point. The potential for overestimating efficacy by using end points that do not correlate with OS or through selection bias and population drift by comparison with historical controls is high. Random assignment in this middle phase has often been criticized as being inefficient and unattractive to patients.

Platform trials under master protocols for GBM with conserved control arms to compare OS would mitigate some of these concerns.[35,83,84] Such trials could also provide significant efficiency.[85,86] These platforms could also efficiently use multiplexed biomarker analysis for predictive biomarker development across therapies.[86] A system to evaluate the relationship of earlier end points to OS could validate such response biomarkers and further improve efficiency.[87] Finally, ongoing platforms could create a longitudinal focus of therapeutic development around GBM, which may lead to more critical evaluation of the data for each new testable therapy or biomarker. Ideal platform trials would enable investigators to ask and answer many therapeutic and biomarker questions simultaneously,[88] use a common control arm for OS, limit downtime between studies, reorganize development around GBM, develop mechanisms for efficient prioritization based on evidence and generation of meta-evidence, limit silos between investigators, and reduce qualitative decision making.

In conclusion, GBM remains an aggressive disease, with limited survival and poor treatment options. Although there have been many randomized trials conducted that guide standard therapy for various presentations of the disease, few successful therapies or biomarkers have been developed. Improving the future outcomes of patients with GBM may require a rethinking of the research and clinical trials enterprise. New incentives for scientific discovery and investment in the disease, better information to make development decisions, and a system to more efficiently evaluate promising candidate therapies and biomarkers are needed.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: All authors
Administrative support: All authors
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Final approval of manuscript: All authors
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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Adult Glioblastoma

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