A Focus on
Newly Diagnosed Glioblastoma

Newsletter based on the prIME Oncology Glioblastoma Podcast Series

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Target Audience
This educational activity is specifically designed for medical oncologists, neurologists, neurosurgeons, radiation oncologists, and other healthcare professionals interested in the treatment of patients with glioblastoma.

Learning Objectives
After successful completion of this educational activity, participants should be able to:

- Discuss the pathologic and the molecular features of glioblastoma
- Incorporate current guidelines and best practices for the accurate diagnosis of glioblastoma
- Discuss potential prognostic and predictive biomarkers in glioblastoma and the role they may play in treatment selection
- Evaluate the limitations of current standard therapy for newly diagnosed glioblastoma and the clinical challenges that these pose

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Faculty

James Perry, MD
Sunnybrook Health Sciences Centre
Toronto, Ontario, Canada

Wolfgang Wick, MD
Heidelberg University Medical Center &
German Cancer Research Center
Heidelberg, Germany

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Introduction

Glioblastoma is a devastating malignancy of the central nervous system. It is the most prevalent and aggressive form of brain tumor in adults, comprising 45.2% of all primary brain malignancies and affecting approximately 3 out of every 100,000 people.[1] This tumor type typically arises quickly with few early symptoms and rapidly invades the surrounding normal brain tissue.[2,3] Despite improvements in our understanding of the biology of glioblastoma and progress in the diagnosis and treatment of this malignancy, less than 5% of patients survive 5 years beyond diagnosis.[4-7] The heterogeneity of glioblastoma indicates that a "one-size-fits-all" approach is not optimal and suggests the need for continued investigation into personalized treatment strategies. Comprehensive, multidisciplinary care and utilization of the most effective therapeutic strategies are imperative to providing the best possible patient care.[8] The aim of this newsletter is to shed light on the treatment of this deadly malignancy and provide perspectives on the difficult issues faced by clinicians treating patients with newly diagnosed glioblastoma.

Pathologic and Molecular Features of Glioblastoma

From a molecular standpoint, glioblastoma is perhaps one of the most fascinating of all human malignancies. This highly invasive tumor type is characterized by diffusely infiltrative growth into the surrounding brain structures and areas of vascular proliferation and necrosis.[9-10] The exact origin of glioblastoma cells remains unclear. The currently leading hypothesis suggests the cells of origin may be attributed to transformation of neural stem cells or progenitor cells. The significant heterogeneity observed within this tumor type has lead to speculation that distinct glioblastoma subgroups may arise from unique cellular origins.[2] The heterogeneity of glioblastoma is evidenced by distinct cellular and molecular differences between tumors and within a single tumor (intratumoral heterogeneity).[11]

Interaction between glioma tumor cells and their microenvironment is complex, including communication with the surrounding vasculature cells, microglia, astrocytes, peripheral immune cells, and extracellular matrix.[12] These interactions play a pivotal role in the pathogenesis of glioblastoma. One of the most important outcomes of this interplay is pathologic angiogenesis, which represents a hallmark of glioblastoma. Tumor angiogenesis is controlled by a multitude of interacting signaling pathways, including vascular endothelial growth factor (VEGF)/ VEGF receptor (VEGFR), angiopoietin-2 (Ang2)/Tie2, ephrin(Eph)/Eph receptors, and integrin signaling.[13] The multiple pathways driving pathologic angiogenesis provide the tumor ample opportunity to escape the body's normal regulation of vascularization and develop mechanisms for resistance to antiangiogenic therapies. Tumor vasculature is often disorganized and leaky, which can hamper delivery of systemic therapies and prevent effector immune cells from accessing poorly perfused areas of the tumor. Vascular dysfunction also results in hypoxia, driving proangiogenic signaling and resistance to apoptosis.

The blood-brain barrier presents an additional unique challenge in the management of patients with brain malignancies.[14] This highly-selective permeability barrier regulates trafficking of microbial, cellular, and

metabolic elements between the blood stream and the brain, protecting the brain from infection. The blood-brain barrier can be disrupted in patients with glioblastoma, particularly around the main tumor focus or nucleus. While this should presumably increase the number of therapeutic agents that can penetrate into glioblastoma tumors, the blood-brain barrier is heterogeneous throughout the tumor and is often functional in the surrounding large, infiltrative tumor rim. This prevents permeability of many anticancer therapies, protecting tumor cells from agents that directly interfere with tumor growth or progression.

In addition to interactions with the microenvironment, improvements in the genomic, epigenetic, and proteomic characterization of glioblastoma has identified molecular anomalies such as promoter methylation of *MGMT* (O^6-methylguanine DNA-methyltransferase), isocitrate dehydrogenase (*IDH*) 1/2 mutations, and chromosome 1p/19q co-deletion.[2] Molecular features like these could represent an Achilles heel for glioblastoma, creating novel therapeutic targets and biomarkers. For example, gene silencing of *MGMT* via promoter methylation occurs in approximately 35% of glioblastomas and reduces the ability of tumor cells to repair DNA damage induced by chemotherapy, making it a predictive biomarker for benefit from alkylating agents.[2,8]

Unfortunately, the distinct alterations in signaling pathways observed in glioblastoma may only be functional for a short period of time. Studies suggest multiple glioma cell populations can coexist within a single tumor, each possessing unique mutations and other genetic abnormalities.[14-18] One glioblastoma cell clone may take over for a time, then regress while another clone takes the lead. This type of tumor evolution leads to rapid resistance to therapy and would require continuous alteration of treatment strategies over the course of disease, making it extremely difficult to accurately target therapy.

Numerous areas of uncertainty remain and further investigation is needed to move the field of glioblastoma forward. Studies are needed to improve our understanding of the role of the blood-brain barrier and why glioblastoma tumors are protected from systemic therapies despite disruption of this protective barrier. Better understanding of the molecular make-up of glioblastoma and communication with the microenvironment as it relates to underlying tumor heterogeneity is also vital to improving treatment options and patient care.

Clinical Presentation of Glioblastoma and Strategies for Making an Accurate Diagnosis

Recognition and diagnosis of glioblastoma is challenging, although improved understanding of the pathophysiology of this disease and advances in tumor imaging continue to make strides in this area. There is no stereotypic presentation of glioblastoma and symptoms vary depending on the location of the tumor and the severity of intracranial pressure.[19] Patients may experience generalized seizures or focal seizures such as abnormal arm movements. Motor weakness, numbness, and language dysfunction can occur, as well as personality changes, headache, confusion, and memory loss. Despite the heterogeneity in clinical presentation, all glioblastomas are characterized by relentless progression that necessitates rapid evaluation and diagnosis.

Neurologic imaging plays an important role in the initial evaluation of patients suspected to have a brain tumor and greatly influences the planning of subsequent treatments such as surgery and radiation therapy.[19,20] Computed tomography (CT) scans can identify disruptions in the blood-brain barrier and are sometimes used as the first imaging modality for patients with acute symptoms or in patients not able to undergo a magnetic resonance imaging (MRI). However, MRI demonstrates higher sensitivity and better resolution of the soft-

tissue, making it the gold standard for neurologic cancer imaging. MRI scans can help define the location of the tumor as it relates to adjacent brain structures, identify necrosis and bleeding, and determine whether the tumor is compressing or infiltrating surrounding healthy tissue.[20] A thorough MRI evaluation of a patient with suspected glioblastoma would include contrast-enhanced T1-weighted and T2-weighted sequences, as well as a fluid attenuated inversion recovery (Flair) sequence. While the nucleus of a glioblastoma is typically identified as a large heterogeneous mass in the white matter with areas of necrosis and hemorrhage by CT or MRI scan, the diffuse infiltrative tumor rim is often not sufficiently visible with these imaging techniques.[19,20]

Advanced physiology-based imaging techniques are also useful for assessment of glioblastomas, including contrast-enhanced perfusion MRI and positron emission tomography (PET) scans for glucose metabolism and amino acid transport.[19] Perfusion MRI can provide quantitative assessment of cerebral blood volume, which correlates with tumor angiogenesis and tumor grade.[21-23] Dynamic contrast-enhanced perfusion MRI can also provide information regarding vascular and endothelial permeability and the integrity of the blood-brain barrier. Furthermore, there is potential to use this imaging modality to monitor response to antiangiogenic therapies, as this technique can detect changes in tumor vascularization.

Despite cutting edge imaging modalities, no imaging technique alone is sufficient to determine the presence and extent of glioblastoma and surgery is ultimately required to make a definitive diagnosis. While either surgical resection or stereotactic biopsy can be utilized to evaluate grade and histology, current treatment guidelines recommend performing the most complete surgical resection possible without compromising neurological function.[8] Stereotactic biopsy is useful for tumors that are not amenable to resection based on location and is minimally invasive with low risk for sequelae. However, small biopsies may not provide adequate tissue for comprehensive molecular analysis and the tissue sampled may not be representative of the entire tumor given the considerable heterogeneity observed in glioblastomas. In contrast, maximal tumor resection improves tumor control, which impacts long-term outcome in patients with glioblastoma, and provides more tissue for subsequent diagnostic and molecular analysis. The invasiveness of resection can put patients at higher risk for sequelae compared to biopsy. Therefore, surgical decisions should be based on careful assessment of the tumor location, extent of infiltration, and risk for surgery-related complications.

Once diagnosis of glioblastoma has been confirmed, testing for biomarkers such as *MGMT* promoter methylation and *IDH* mutations assists in determining prognosis and making treatment decisions.[8] Obtaining adequate tumor tissue during biopsy or resection is important, as it allows the opportunity to test a broader spectrum of biomarkers that are currently exploratory or may emerge in the future.[24,25] This type of molecular analysis can also determine eligibility for clinical trials based on the presence of a particular genetic abnormality, which is becoming an increasingly common component of clinical trial design. Lastly, there is potential to develop vaccines from glioblastoma tumor antigens, which is only possible if adequate tissue is available.[26]

The degree to which clinical presentation of glioblastoma varies suggests patients must be carefully evaluated to determine the precise cause of these neurologic symptoms. Magnetic resonance imaging and additional imaging techniques should be utilized to identify the lesions and the extent of disease. Subsequent surgical resection or biopsy confirms the diagnosis and disease stage, as well as provides tissue for evaluation of current and future prognostic and predictive biomarkers.

Promising Prognostic and Predictive Biomarkers in Glioblastoma

Development of biomarkers for any tumor type represents the Holy Grail in patient care, creating the opportunity to personalize therapy based on the specific characteristics of a patient's tumor. This is particularly important in glioblastoma given the heterogeneity of this disease and propensity for tumor progression and resistance.[9] While molecular signatures, genetic and epigenetic analysis, and functional imaging has identified clinically relevant glioblastoma subtypes, much work remains to be done to translate these advances to clinical practice.[2,19] Several biomarkers are currently in development and are demonstrating potential as prognostic and predictive tools for clinical decision-making.[27]

The most established glioblastoma biomarker is promoter methylation of *MGMT*, primarily based on data from the phase III trial conducted by the European Organisation for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCIC) that investigated radiotherapy with or without temozolomide in patients with newly diagnosed glioblastoma.[6] As mentioned previously, epigenetic silencing of *MGMT* in glioblastoma cells reduces the ability to repair DNA damage associated with alkylating chemotherapy like temozolomide.[10] In a retrospective subgroup analysis of 206 patients from the EORTC-NCIC trial, *MGMT* promoter methylation was a significant favorable prognostic factor for overall survival (OS) irrespective of treatment received (hazard ratio [HR] 0.45; $P<.001$). Importantly, this biomarker was also significantly predictive for responsiveness to temozolomide, with most of the benefit of chemoradiotherapy restricted to patients with a methylated *MGMT* promoter. The addition of temozolomide to radiotherapy significantly improved median OS in the methylated MGMT promoter subgroup (21.7 months vs 15.3 months, HR 0.51; $P = .007$), but not in the unmethylated subgroup (12.7 months vs 11.8 months, HR 0.69; $P = .06$). Since these data come from a retrospective subgroup analysis and some patients with unmethylated *MGMT* promoter status for yet to be determined reasons were long-term survivors on temozolomide,[6,10] this biomarker is not routinely used in clinical practice to select patients for temozolomide therapy outside the elderly population or clinical trials.[28,29]

In elderly patients with glioblastoma, *MGMT* promoter status has become a standard tool for treatment selection in the clinic based on two randomized European clinical trials comparing temozolomide alone to radiotherapy alone in elderly patients with newly diagnosed glioblastoma.[30,31] In the phase III Neuro-oncology Working Group (NOA)-08 trial, the event-free survival (EFS) benefit from temozolomide appeared to be restricted to patients with methylated *MGMT* promoter (8.4 months vs 3.3 months for unmethylated *MGMT* status), while methylation status had no effect on EFS for those receiving radiotherapy (4.6 months for both groups).[30] The phase III Nordic trial showed similar results, with significantly longer median OS with temozolomide treatment in patients who had *MGMT* promoter methylation compared to those who did not (9.7 months vs 6.8 months, HR 0.56; $P = .02$).[31] Methylation status did not influence OS in patients receiving radiotherapy. Thus *MGMT* promoter methylation can predict which elderly patients may respond more to temozolomide than radiotherapy and guide treatment decisions.[29-31]

As genomic analysis becomes more sophisticated, the potential to identify biomarkers and unique genetic signatures that delineate disease subtypes and predict for benefit from specific therapies expands. Genome-wide mutational analysis identified inactivating mutations of *IDH1* or *IDH2* in some glioblastomas, which specify patients who have secondary glioblastoma arising from a prior lower grade tumor and confer a more favorable prognosis.[32] Imaging biomarkers are also emerging, such as relative cerebral blood volume, which can be obtained with MRI perfusion studies.[33] High relative cerebral blood volume correlates with poorer OS

in patients with glioblastoma and adds to the information obtained from currently used molecular subtype classification schemes using genomic expression signatures.

There is currently a significant unmet need for predictive biomarkers for antiangiogenic therapies across all tumor types, including bevacizumab for the treatment of patients with glioblastoma. A recent retrospective analysis of one-third of the patients enrolled in the phase III AVAglio trial, which evaluated the efficacy and safety of temozolomide/radiation therapy plus bevacizumab in patients with newly diagnosed glioblastoma, classified patients into known glioblastoma molecular subtypes based on gene expression analysis.[34] The data suggest that the proneural molecular signature, as defined by Phillips et al,[35] is associated with a progression-free survival (PFS) and OS benefit from bevacizumab therapy.[34] In contrast, patients with a proliferative subtype do not benefit at all from bevacizumab, whereas the mesenchymal subtype resembles the general intent-to-treat population from the AVAglio study with a PFS, but not OS, benefit from the addition of bevacizumab.[34]

A promising molecular diagnostic has recently emerged, PRoB-GBM, that predicts for response to bevacizumab based on real-time polymerase chain reaction (RT-PCR)–based analysis of tumor tissue.[36] Genes correlating with an existing mesenchymal expression signature were expanded to develop a unique model that separates patients into favorable and unfavorable groups.[36,37] In a retrospective analysis of patients from the phase III Radiation Therapy Oncology Group (RTOG)-0825 trial investigating front-line chemoradiotherapy with or without bevacizumab, 71% of patients had bevacizumab-favorable signatures.[36]

PRoB-GBM was significantly predictive for median OS in patients receiving upfront bevacizumab in the training and validation sets (OS in the training set: 20.3 months for favorable vs 10.4 months for unfavorable; $P<.0001$; OS in the validation set: $P = .014$).[36] This was not the case for patients receiving standard chemoradiotherapy, suggesting this is indeed a predictive marker, not simply a prognostic marker. PRoB-GBM was independent of standard prognostic markers such as *MGMT* status (HR 0.28; $P<.0001$). Interestingly, PRoB-GBM was not predictive for OS in patients receiving salvage bevacizumab. When examined according to treatment arm, the addition of bevacizumab was superior to standard therapy alone with regards to PFS in the favorable group, while it appeared to negatively impact OS in those assigned to the unfavorable group. Further evaluation in prospective studies is needed to validate this novel molecular predictor.

Development of biomarkers for glioblastoma has proven to be challenging, but is an important goal as the treatment landscape continues to move toward more individualized care. While *MGMT* methylation is the only established biomarker currently, it is not routinely used to direct temozolomide therapy decisions. There is an urgent need for predictive biomarkers for targeted agents and for specific patient subgroups that may benefit from emerging treatment strategies.

Benefits and Limitations of Standard Therapies for Newly Diagnosed Glioblastoma

Treatment of glioblastoma is complicated by numerous factors, including the hindrance of the blood-brain barrier, presence of multiple molecular abnormalities (aberrant activation of signaling pathways, gene mutations, etc), scarcity of clinically-relevant disease biomarkers, and the rapid development of resistant disease.[2,14] Standard treatment consists of surgery, radiation therapy, and systemic therapy.[8] Surgery is important both for tumor control and to obtain tissue for diagnosis and subsequent molecular analysis.

Maximal safe resection is recommended, as the extent of resection correlates with patient survival.[8] Standard radiation therapy consists of single-fraction therapy (60 Gy delivered over 30 fractions) initiated within 2 weeks to 4 weeks of surgery.

Since 2005, temozolomide has been considered the standard of care for systemic therapy in patients with newly diagnosed glioblastoma.[5] In the pivotal phase III EORTC/NCIC trial, the addition of temozolomide to radiotherapy significantly improved median PFS and OS compared to radiotherapy alone (median OS: 14.6 months vs 12.1 months, HR 0.63; $P<.001$).[5] Temozolomide is administered daily concurrent with adjuvant radiotherapy and then as maintenance therapy 5 days every 28-day cycle for the next 6 months.[8] Attempts to improve upon this schedule, including dose intensification of maintenance temozolomide, have not prolonged survival to date.[8,38]

Elderly patients constitute approximately 50% of the glioblastoma population and are managed differently than younger adults based on reduced tolerability of therapy and increased comorbidities.[39] In this patient population, randomized clinical trial data have demonstrated superiority for radiotherapy over supportive care alone and established the efficacy of a short hypofractionated radiation course in patients >70 years of age.[31,40,41] Temozolomide monotherapy has also emerged as a reasonable treatment option for select elderly patients with glioblastoma based on results from the previously mentioned phase III NOA-08 and Nordic trials directly comparing radiotherapy alone to temozolomide.[30,31] NOA-08 demonstrated non-inferiority for temozolomide compared to standard radiotherapy with regards to median OS (8.6 months vs 9.6 months, HR 1.09) and EFS (3.3 months vs 4.7 months, HR 1.15).[30] Similarly, in the Nordic study, median OS was similar for temozolomide and hypofractionated radiotherapy (8.4 months vs 7.4 months, HR 0.82; $P=.12$).[31] Temozolomide was particularly efficacious in patients with *MGMT* promoter methylation, suggesting that chemotherapy alone would be the optimal front-line choice in this subset and radiotherapy could be reserved for disease progression.[30,31]

Several challenges and limitations remain regarding the treatment of newly diagnosed glioblastoma. Accurate response evaluation is important to detect potential drug resistance and provide the opportunity to change treatment approaches early in the disease course.[8] However, approximately 20% to 30% of patients who receive upfront chemoradiotherapy with temozolomide experience pseudoprogression, a phenomenon characterized by contrast enhancement detected on MRI immediately following completion of radiotherapy not associated with actual tumor progression.[42,43] These lesions typically remain stable or regress on their own. Thus, it is imperative that pseudoprogression be distinguished from true progression to prevent premature discontinuation of effective adjuvant chemotherapy.[43] Current Response Assessment in Neuro-Oncology Working Group (RANO) criteria recommend that within 12 weeks of completion of radiochemotherapy, true progression requires the majority of new tumor enhancement to be outside the radiation field or pathologic confirmation of progressive disease. However, this cut-off of three months is based on uncontrolled data series and is biologically arbitrary. Data challenging both the threshold of three months and the reported high frequency, which may in fact only be approximately 10%, have been published.[44]

In spite of the efficacy of current front-line treatment strategies, prognosis remains very poor and median OS is in the 12 months to 15 months range.[45,46] Disease progression occurs early and development of resistance to standard chemotherapy is unfortunately common. This creates an urgent need for newer therapeutic approaches, particularly for those who do not respond to standard front-line therapies. This includes patients with an unmethylated *MGMT* promoter, since temozolomide-based chemoradiotherapy

is less effective in this patient subgroup.[29] Lastly, steroids such as dexamethasone are commonly used in patients with newly diagnosed glioblastoma to alleviate edema and intracranial pressure. However, prolonged exposure can lead to adverse events such as hyperglycemia, myopathy, osteoporosis, infection, and gastrointestinal and cardiovascular complications,[47] as well as specific resistance to alkylating chemotherapy.[48] Thus, the use of steroids should be limited and rapid tapering and discontinuation is recommended to minimize these serious toxicities.[8]

Beyond temozolomide, therapeutic options for newly diagnosed disease are largely experimental. Novel agents are under investigation, but there remains a distinct lack of agents with a confirmed OS benefit. This presents the greatest challenge in the treatment of newly diagnosed disease and drives continued efforts to expand the treatment landscape.

Novel Treatment Strategies for Newly Diagnosed Glioblastoma: Significant Investigational Findings From the Past Year

While the past decade has witnessed significant advances in the management of newly diagnosed glioblastoma, limitations associated with current standards of care are motivating continued investigation of novel treatment approaches. Strategies to optimize surgery with image-guided or fluorescence-guided resection allows neurosurgeons to more precisely excise glioblastomas with minimal impact on surrounding normal tissues.[19,49] For example, the use of tumor fluorescence with 5-aminolevulinic acid (5-ALA) has been shown to improve detection of residual glioma intraoperatively and increase complete resection rates and PFS.[49]

The vast majority of glioblastoma recurrences occur locally, within the high-dose radiation field.[50] As a result, techniques to deliver more precise radiotherapy to the tumor are desirable to reduce damage to surrounding normal brain tissue. Strategies to provide tumor-targeted radiotherapy are currently under investigation utilizing techniques such as stereotactic procedures, proton beam radiotherapy, and carbon ion radiotherapy.[19,50] Ongoing studies and future investigations will continue to explore the potential for personalized radiotherapy, seeking to understand on the molecular level which specific radiotherapy strategy should be used for an individual patient.

The short survival benefit seen with current standard chemoradiotherapy in patients with newly diagnosed glioblastoma and the proclivity for resistance to radiation therapy and chemotherapy has resulted in exploration of targeted agents and immunotherapy as a strategy to improve patient outcomes.[51,52] Based on the pivotal role for angiogenesis in glioblastoma pathophysiology, the VEGF-targeted monoclonal antibody bevacizumab was investigated in patients with recurrent and newly diagnosed disease.[51,53-59] In the relapsed setting, bevacizumab showed clinical benefit, including improved PFS, and is currently approved in several countries for patients with relapsed glioblastoma.

In newly diagnosed disease, phase II studies suggested the addition of bevacizumab to standard front-line therapy may improve clinical outcomes.[56,57] This subsequently lead to two large, randomized, placebo-controlled phase III trials evaluating radiochemotherapy with or without bevacizumab.[58,59] The designs of the AVAglio trial and the RTOG-0825 trial were strikingly similar, with bevacizumab administered concurrently with adjuvant temozolomide and as maintenance therapy in patients with newly diagnosed glioblastoma. The coprimary endpoints of both trials were PFS and OS. Both studies showed a PFS benefit

of 3 to 4 months, although this did not reach the prespecified threshold for significance in the RTOG-0825 trial. Median PFS in the AVAglio trial was 10.6 months with bevacizumab versus 6.2 months for placebo (HR 0.64; *P*<.0001),[58] while the RTOG-0825 study showed a median PFS of 10.7 months versus 7.3 months (HR 0.79; *P* = .007).[59] Bevacizumab did not prolong median OS in either trial. Bevacizumab was associated with a tolerable safety profile, although both studies demonstrated increased incidence of serious adverse events with bevacizumab compared to placebo.

Interestingly, the results from these two studies differ with regards to patient quality of life (QoL).[58,59] Health-related QoL (HRQoL) is an important consideration for patients with glioblastoma given the incurable nature of the disease, relatively short survival, and substantial impact on neurologic and overall physical function.[60] In addition to prolonging survival, glioblastoma therapies aim to reduce morbidity while maintaining neurologic function and the ability to perform daily activities for as long as possible. Patient questionnaires are often used to assess QoL, including the EORTC quality of life questionnaire core-30 (QLQ-C30) and the brain cancer module (BN20).[58,59] Unfortunately, few QoL assessment tools are specifically validated for patients with brain cancer and frequent data collection is required.[60] Achievement of consistent, accurate HRQoL assessment becomes increasingly challenging as patients' overall health and neurocognitive ability diminishes, reflected by a high percentage of missing data in the currently available literature.

In the AVAglio trial, patients receiving bevacizumab showed significant improvements in HRQoL and longer maintenance of functional independence (performance status ≥70) compared to placebo.[58] Bevacizumab also reversed or delayed the requirement for glucocorticoid therapy. Furthermore, the prespecified secondary endpoint of deterioration-free survival, which was defined as deterioration in HRQoL or disease progression or death, was significantly longer among patients receiving bevacizumab (HR 0.64; *P*<.001). In contrast, results from the RTOG-0825 trial showed deterioration of neurocognitive function and a negative impact on symptom burden with bevacizumab.[59] The precise reasons for these differences are unclear, but could be related to subtle differences in the assessment and analysis of patient-reported outcomes in these two studies.[58,59] Regardless, further evaluation of these data will be required to definitively determine the impact of bevacizumab on neurocognitive function and patient QoL, which will greatly influence its future role in the treatment of patients with newly diagnosed glioblastoma.

In addition to targeted agents, modulation of the immune system has emerged as a promising strategy to safely and specifically target glioblastoma cells, potentially eliminating distinct tumor cell populations resistant to standard therapy.[26] Glioblastoma is characterized by an immunosuppressive microenvironment and impaired immune function due to the disease itself and the effect of systemic therapies. Immunotherapy can bolster immune response and elicit strong antitumor activity. Immunotherapy strategies have demonstrated efficacy and good tolerability in a variety of tumor types and several are currently under investigation in glioblastoma. For instance, passive immunotherapy strategies such as immune checkpoint blockade via inhibitors of programmed death-1 (PD1) and cytotoxic lymphocyte antigen-4 (CTLA-4) or adoptive therapy with activated T-cells are currently in early-phase clinical trials.[26,52]

Active immunotherapy strategies, including dendritic cell vaccines and peptide vaccines, have demonstrated exciting efficacy against glioblastoma.[52] Rindopepimut (CDX-110) is a peptide vaccine targeting the epidermal growth factor receptor variant III (*EGFRvIII*) mutation, which occurs in approximately one-third of all patients with glioblastoma.[61-63] Rindopepimut significantly improved median PFS and OS compared to historical controls in a small phase II study and is the focus of the ongoing phase III ACT IV trial evaluating

the addition of rindopepimut to standard frontline chemoradiotherapy with temozolomide in patients with newly diagnosed, EGFRvIII-positive glioblastoma.[61,64] The autologous dendritic cell vaccine ICT-107 targets 6 distinct tumor-associated antigens and demonstrated significant improvement in median PFS compared to controls (11.2 months vs 9.0 months, HR 0.57; $P = .011$) in a phase II study of patients with newly diagnosed glioblastoma.[65] The glioma tumor marker *IDH* also represents a target for immunotherapy and early studies are examining an IDH-targeted peptide vaccine approach.[66] Also attractive is the active personalized approach with next-generation sequencing, peptidome analysis, and *in vitro* immunogenicity testing of multiple tumor-specific (mutated) peptides like in the GAPVAC consortium.[67]

Ultimately, there is much work to be done to improve the treatment of newly diagnosed glioblastoma, including refinement of current standards of care and elucidation of novel therapeutic options for those who may not benefit from standard therapy such as patients with unmethylated *MGMT* promoters.[9] Patient selection is an important issue that needs further investigation, including who should be considered for upfront bevacizumab. Up to half of all patients never receive salvage therapy due to age, performance status, and other complications, indicating the focus should be making first-line therapy as safe and effective as possible. Future clinical trial design also needs to reflect the importance of QoL as an endpoint for patients with glioblastoma, including the use of qualified PFS and OS where diminished QoL or neurocognitive function is considered a survival event.[60] This will appropriately reflect the difficult reality for most patients with glioblastoma, which is that a PFS benefit is only meaningful when neurocognitive function and QoL are maintained and they are able to continue their daily lives. At the end of the day, this is the desire for all patients and clinicians battling glioblastoma.

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