**Introduction**

Glioblastoma, previously known as glioblastoma multiforme, is the most aggressive among infiltrative gliomas, a group of primary tumors arising from the central nervous system (CNS). Patients with this cancer type face significant morbidity and mortality, with over 13,000 deaths per year in the United States. Recent advances in our biological understanding of gliomas have led to important and substantive changes in their classification, in the identification of prognostic and predictive molecular markers, as well as in the therapeutic management of newly diagnosed glioma.

**Classification**

The term ‘glioblastoma multiforme’ was introduced in the 1926 classification system devised by Cushing and Bailey,[1] ‘Multiforme,’ which refers to a heterogeneous, histological appearance and proliferation of multiple cell types, was abandoned from the revised nomenclature in the 2007 World Health Organization Classification of Tumors of the Central Nervous System, and is now simply called ‘glioblastoma’. [2] Glioblastoma is histologically defined by neoplastic cells with astrocytic characteristics and the presence of either endothelial proliferation—often in a glomeruloid morphology—and/or necrosis, which may resemble a pseudopalisading pattern (a false fence of neoplastic cells surrounding an area of necrotic tissue).

Due to its aggressive and highly proliferative course, glioblastoma is considered a grade IV astrocytoma. Molecular characterization has allowed for further refinement of the condition’s classification and is now an integral part of the diagnosis of malignant glioma.[3] Patients are classified into one of two distinct categories based on the presence or absence of mutations in the isocitrate dehydrogenase (IDH) 1 (IDH1) or IDH2 genes.

---

**Primary glioblastoma/glioblastoma IDH wild-type (IDH-wt)**

The majority of glioblastomas are IDH-wt and correspond to the longstanding clinical description of primary glioblastomas, which arise rapidly from non-neoplastic brain and progress quickly. In addition, a subgroup of lower-grade glioma may carry molecular features and signatures similar to glioblastoma, with a similarly aggressive natural course[4] for which an intensive treatment strategy is advocated. These facts stress that a microscopic histological diagnosis alone is insufficient to make informed and rational clinical decisions; therefore, it is essential that molecular alterations be integrated when...
Glioblastoma remains a macabre tumor with only incremental improvement over the last 4 to 5 decades. Fortunately, we practice in a time of remarkable growth in our neuroscience and cancer biology knowledge base. This leads one to hope that innovation in the management of glioblastoma is close at hand.

In the near future, operative methods will continue to trend toward decreased invasiveness, through techniques such as guided laser thermal ablation. Surgical precision will improve through fluorescence-guided resection of tumors. Drug delivery, too, will be optimized with the use of transport vesicles steered by engineered proteins and nanoparticles, used as vehicles to deliver therapeutic agents across the blood-brain barrier. Consequently, many drugs previously thought unsuitable for glioblastoma due to systemic toxicity or blockage by the blood-brain barrier may prove useful.

Moreover, it is expected that big data, next-generation sequencing, and genetic identification algorithms will guide operative intervention, clinical trials, and medication selection. Such methods will also account for the marked heterogeneity in glioblastoma and lead to an era of molecular polytherapy, guided by analysis from numerous tumor samples from the same patient. Such tailored ‘molecular cocktails’ will improve efficacy by targeting upstream initiators, alterations enabling cell growth, and predicted downstream compensation/resistance mechanisms.

Recent advances in sequencing of tumor DNA from circulating tumor markers will make such clinical trials easier to preform and less reliant on operative procedures such as invasive tumor biopsies. Hope, too, remains that combination immunotherapy will play a role in glioblastoma management, whether by tailoring immune cells to target glioblastoma or by reinvigorating appropriate microglial function.

Insights on stem cell biology will also help to advance our management of glioblastoma. While radiation and traditional chemotherapy may serve a waning role in the future, their efficacy will be improved by simultaneous use of agents targeting tumor stem cell quiescence. Realistically, though, salvage therapy will still be required, and one can envision the use of self-replicating viruses to fight tumor stem cells, finally partially fulfilling the promise inherent in our present knowledge base.

To completely fulfill our promise to our patients, we’ll have to accept that glioblastoma is a disease of information and mixed-up signals among the genome, epigenome, microbiome, proteome, transcriptome, metabolome, etc. As such, we’ll need a better bibliome of all the expanding information that separates the inessential from the pertinent.

FINANCIAL DISCLOSURE: Dr. Butowski has no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.

Glioblastoma—What’s Next?

Nicholas Butowski, MD

Secondary glioblastoma/ glioblastoma, IDH mutated

Up to 10% of patients with glioblastoma harbor a mutation in the IDH1 or IDH2 genes, an early event in gliomagenesis. Since these glioblastomas often arise from a prior, lower-grade glioma, they are considered secondary glioblastoma.

In the past, both primary and secondary glioblastoma were considered to be the same clinical entity. However, recent studies clearly indicate that IDH-mutated glioblastoma has a more protracted natural course. As such, secondary glioblastomas are to be classified as a distinct biological and molecular entity for which different treatment strategies will ultimately be proposed. Former series of long-term survivors are commonly enriched for patients with IDH-mutated tumors.[3]

Epidemiology

Primary CNS tumors represent only 2% of adult cancer diagnoses; however, due to their location and often rapid clinical course, they are associated with high morbidity and mortality. About 50% of primary malignant CNS tumors are glioblastoma, with an incidence rate of 3.20 per 100,000 population. Incidence is higher in whites than in blacks (3.46 vs 1.79 per 100,000 population, respectively), with a 1.93:1 ratio (P < .05), a difference for which no biological explanation exists. Compared with whites, the incidence of glioblastoma is somewhat lower in Asians. The condition occurs more frequently in men than in women, with a 1.58:1 ratio (P < .05).[6] Over the last 3 decades, the incidence of glioblastoma in the United States has been relatively stable[7]; however, an aging population and better diagnostic tools may lead to a higher incidence of disease, as has been suggested in other countries[8]. Further study is needed to confirm changes in incidence, and, if
mutations in the TERT gene appeared hypermutated phenotype. When present, found within these tumors, can exhibit a being regionally exclusive. Distinct areas, with approximately half of the mutations al profile and clonality of tumor cells, intratumoral differences in the mutation-IDH-wt glioblastomas, there are spatial drawbacks.[16-19]

each with their favorable attributes and models have been conducted in this area, precancerous cells, including neural stem cells, development of glioma. However, con-
temporary thought favors primitive plu-
ripotent cells, including neural stem cells, glial precursor cells, and oligodendrocyte precursor cells.[15] Numerous preclinical models have been conducted in this area, each with their favorable attributes and drawbacks.[16-19]

Research demonstrates that, amongst IDH-wt glioblastomas, there are spatial intratumoral differences in the mutation-
profile and clonality of tumor cells, with approximately half of the mutations being regionally exclusive. Distinct areas, found within these tumors, can exhibit a hypermutated phenotype. When present, mutations in the TERT gene appeared across all clones.[20] Recent studies utilizing xenografts in murine models have shown that these tumors consist of a slow-cycling population of stem-like cells which give rise to a rapidly dividing progenitor cell population, a proportion of whose daughter cells develop into terminal differentiated cells, supporting a hierarchical model of gliomagenesis. [21] A minority of the clonal population proves resistant to chemotherapy.[21] In turn, this cell population will require different treatments. When evaluated longitudinally, recurrent glioblastoma can accumulate additional mutations[22], and can appear similar to the primary tu-
ror or may resemble a distinct subclonal population.[23,24] It is thought that this genomic heterogeneity is driven, at least in part, by the uneven cellular inheritance patterns of extra-chromosomal DNA. [25] As we garner a clearer understanding of the pathophysiology of gliomagenesis, new areas for potential therapeutic intervention will open up.

In addition to the difficulties associ-
ated with treating heterogeneous tumors, which evolve over the course of the disease and harbor treatment-resistant subpopulations of cells, the blood-brain barrier is another impediment to the effective treatment of these tumors. The blood-brain barrier is a dynamic, func-
tional system which both precludes and modulates the traversing of systemically administered therapeutics into the CNS, including CNS tumors.[26] Numerous means have been utilized to overcome this obstacle. Thus far, the most successful have included systemically-administered drugs with adequate CNS penetration (eg, temozolomide) and locally delivered, alternating electrical fields (tumor-treat-
ing fields, TTFIELDS). Direct intracranial application of both chemotherapy (eg, biodegradable carbamoyl-impregnated wafers) and radiation (eg, brachyther-
apy) has also been explored.

Intratumoral injection of oncolytic viruses and chimeric antigen receptor (CAR) T-cell therapies is a modern example of a similar strategy that is under-
going active investigation.[27,28] Disruption of the blood-brain barrier to facilitate transmission of a systemically-
administered therapy has been under investigation for many decades. Initial studies utilized intra-arterially-adminis-
tered agents.[29] A recent strategy being studied includes ultrasound to open up the barrier.[30] Another, which has had varying degrees of success, is avoiding the need to overcome the blood-brain barrier. The utilization of therapeutics whose direct activity occurs on the luminal side of the blood-brain barrier (eg, bevac-
izumab)[31]—or which act on the lumi-
nal side, with a goal of affecting function on the tumoral side of the barrier (eg, immune checkpoint inhibitors)—is an-
other way to attempt to circumvent this obstacle. It is reasonable to surmise that more than one approach may prove to be successful.

Therapeutic Management
The therapeutic management of newly-di-
agnosed glioblastoma typically involves a four-pronged approach. First, surgical resection is completed to the maximal safe extent, thereby reducing the tumor load and establishing a histopathological and molecular diagnosis. Following surgery, adjuvant radiotherapy is given with concomitant and maintenance che-
motherapy, as is treatment of alternating electrical fields.
Surgery

Surgery plays an important diagnostic and therapeutic role in the management of glioblastoma: it offers tissue for histological and molecular diagnosis, immediate relief of the tumor-related mass effect and its associated symptoms, and potential cytoreduction. However, due to the invariably infiltrative nature of the disease, even macroscopically complete resection is not curative. Numerous retrospective studies have evaluated the value of the extent of resection in glioblastoma. While early work suggested a dichotomous picture with a need for a substantial extent of resection of the contrast-enhancing tumor,[32] subsequent studies demonstrated the graded benefit of the extent of resection.[33,34] A more recent meta-analysis also supports a more extensive resection with improved 1- and 2-year survival rates as well as prolonged progression-free survival.[35] In low-grade glioma, the extent of resection is influenced by the area of increased signal on T2/fluid-attenuated inversion recovery (FLAIR) imaging.[36-39] Similarly, glioblastoma tumors are not limited to the area of enhancement but rather involve the area of increased T2/FLAIR signal. The extent of resection of this non-enhancing glioblastoma may also be of clinical impact, as demonstrated in a recent retrospective study.[40]

Although the association between extent of resection and survival has been reported and consistently confirmed in numerous studies, it is subject to several potential confounders, biases, and occult prognostic factors. While cytoreduction—the act of removing the bulk of tumor cells—may intuitively delay disease recurrence, the non-linear growth of tumor cells seen in glioblastoma could quickly recover the tumor burden that was removed during surgery, negating the survival benefit of small increments of cytoreduction. The durability of the effect of cytoreduction, and whether it leads to a survival benefit, is likely related to the rate of tumor cell proliferation. On the other hand, patients with neurological deficits have lower functional status, which ultimately impacts their overall survival. Thus, it is possible that relief of mass effect leading to improved functional status from resection might prolong survival in symptomatic patients, irrespective of cytoreduction. Finally, the tumor location may also reflect the underlying biology and dictate the natural history of the disease. Determination of the influence of these previously described variables on overall survival is complicated, as resectable tumors may have an overall better prognosis, regardless of the actual extent of resection.

Resectable tumors often present in “silent areas of the brain” that tolerate injury for a long period of time prior to becoming symptomatic. In addition, resectable tumors, such as fronto-polar tumors, are more likely to harbor IDH1 mutations, which are associated with a better prognosis. In contrast, unresectable tumors, such as midline/diencephalic or brainstem tumors, often bear H3K27 mutations, which indicate an overall more aggressive biology and a worse prognosis.[41] Further dissection of the relationship between the extent of resection and survival requires controlling for tumor resectability per se. Yet, this complicated variable is difficult to capture by established scales, and is influenced by anatomical considerations as well as neurosurgeon-related factors.[42]

Maximizing extent of resection. A number of technological advances have been developed to safely maximize the extent of resection, although their availability and usage may vary greatly. These techniques have become more widespread over time because, in addition to maximizing the extent of resection, they also optimize the safety of intra-axial brain tumor surgery. The major technological tools that surgeons use for improving the safety and accuracy of resection can be divided into three groups, as follows.

Intraoperative navigation technology. This technology involves the use of volumetric imaging (eg, MRI or CT scan), which is used as a reference to locate a lesion/anatomical structure within the surgical field. Navigation involves an optical or electromagnetic system that uses a physical reference to register the location and position of a patient’s head in space, and allows real-time visualization of instruments within the images, which are loaded to a computer. These technologies help minimize the extent of the open craniotomy exposure; optimize

<table>
<thead>
<tr>
<th>Author</th>
<th>Minimum Age</th>
<th>Fractional Dose</th>
<th>Total Dose</th>
<th>Duration</th>
<th>Concurrent Chemotherapy</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baumann et al (1994)[83]</td>
<td>65 y (or KPS ≤ 50)</td>
<td>3.0 Gy</td>
<td>30.0 Gy</td>
<td>10 d</td>
<td>No</td>
<td>6 mos</td>
</tr>
<tr>
<td>Roa et al (2004)[115]</td>
<td>60 y</td>
<td>2.67 Gy</td>
<td>40.0 Gy</td>
<td>15 d</td>
<td>No</td>
<td>5.6 mos</td>
</tr>
<tr>
<td>Malmstrom et al (2012)[81]</td>
<td>60 y</td>
<td>3.4 Gy</td>
<td>34.0 Gy</td>
<td>10 d</td>
<td>No</td>
<td>7.5 mos</td>
</tr>
<tr>
<td>Roa et al (2015)[84]</td>
<td>65 y (or KPS 50–70)</td>
<td>5.0 Gy</td>
<td>25.0 Gy</td>
<td>5 d</td>
<td>No</td>
<td>7.9 mos</td>
</tr>
<tr>
<td>Perry et al (2017)[82]</td>
<td>65 y</td>
<td>2.67 Gy</td>
<td>40.0 Gy</td>
<td>15 d</td>
<td>Yes</td>
<td>9.3 mos</td>
</tr>
</tbody>
</table>

KPS = Karnofsky Performance Status.
a trajectory to access lesions that avoids critical neural structures, such as white matter pathways; and provides an anatomical reference during the operation. However, they are limited by the fact that the referenced images are not updated as resection progresses, and brain shift in space in relation to the skull makes this information less reliable as the case advances. To address this, several groups have introduced intraoperative MRI, which provides a real-time update of the field for navigation.[43,44] The true utility and cost-effectiveness ratio of intraoperative MRI remains a highly debated topic, as cost and added time during the procedure are not insignificant. The use of intraoperative ultrasound is a dynamic, easy to use, and affordable alternative for real-time imaging during surgery.

Electrophysiological monitoring and functional brain mapping. Wilder Penfield and George Ojemann pioneered the use of electrodes to functionally map sensory and motor cortical regions and related subcortical circuits as the spinohalamic and corticospinal tracts to avoid postoperative deficits. [45-48] Over the last few decades, work by George Ojemann, Hugues Duffau, Mitchell Berger, and others has incorporated the routine use of awake brain mapping techniques, which have greatly improved the surveillance of motor circuits, language/comprehension, coordination, vision, and some higher cognitive functions by enabling them to be mapped and preserved.[49-53]

Fluorescent markers to maximize tumor visualization. Fluorescent dyes—which are either metabolized by tumor cells, or accumulate in areas of blood-brain barrier breakdown—have been incorporated to maximize tumor tissue visualization in the operating room. This is helpful, as gross tumor tissue often has a similar texture or color as the surrounding edematous brain and is not always easy to distinguish under bright light. The use of 5-aminolevulinic acid under blue light allows the neurosurgeon to view residual tumor in real-time during surgery. A phase III trial demonstrated an improved rate of complete resection for contrast-enhancing tumor with 5-aminolevulinic acid compared with conventional microsurgery with white light (65% vs 36%; \( P < .0001 \)) and 6-month progression-free survival (41% vs 21%; \( P = .0003 \)). However, this did not translate into an improvement in overall survival.[54] Fluorescein has also been used to visualize enhancing tumor, as this dye leaks through areas with defective blood-brain barrier.[55,56] Here, no special light source is needed.

Radiation therapy

Radiotherapy has been shown to improve survival in glioblastoma and plays a key role in treatment. Modern conformal radiotherapy—which utilizes three-dimensional, computerized planning and multi-beam modulation—locally treats MRI-evident disease plus margin to a cumulative absorbed dose of 60 Gy. Given in daily doses of 1.8 to 2.0 Gy fractions, total treatment lasts approximately 6 weeks and is usually initiated 3 to 4 weeks after surgery. While some reports have suggested that delayed radiotherapy has a detrimental effect, other investigators have reported better outcomes; this question has yet to be definitively answered.[57,58] Up to 6 to 7 weeks of postoperative recovery is considered acceptable as part of the established standard of care.

Earlier studies have examined doses of more than 60 Gy, some of which incorporated stereotactic radiosurgery. However, they failed to demonstrate improved outcomes with doses of up to 76 Gy.[59] An ongoing randomized phase II study, NRG BN001 (ClinicalTrials.gov identifier: NCT02179086), is evaluating dose escalation to 75 Gy compared with standard 60 Gy radiotherapy.[60] This study includes distinct cohorts utilizing photons or protons, and the primary endpoint is survival.

For elderly patients or those with substantially altered performance status and poor prognosis, an abbreviated course of “hypofractionated” radiotherapy allows for a shortened overall treatment time. Long-term toxicity is of less concern in this population due to a commonly short survival. Hypofractionated radiation, which has been widely investigated, has been utilized to improve tolerability of radiotherapy (Table 1). Tumor volume often guides the selection of a radiation regimen because the risk of toxicity is theoretically greater with high vs low daily doses. Omitting radiotherapy (even less than the standard 60 Gy) leads to significantly worse survival compared with best supportive care alone.[61] Recent prospective data have demonstrated that abbreviated courses can also be safely and effectively combined with concurrent chemotherapy, as covered in the section below regarding treatment strategies for elderly patients.

A direct prospective comparison between full-course radiotherapy with concurrent and adjuvant chemotherapy vs abbreviated course radiotherapy with concurrent and adjuvant chemotherapy has not been conducted. In addition to an abbreviated course of radiotherapy, the shorter course also employs a shorter course of concomitant chemotherapy. This lack of direct comparison leaves an important question not fully answered. In many clinical practices, the full course of radiotherapy and chemotherapy will be utilized in elderly patients with good performance status.

Research suggests that prolonged administration and dose intensification of adjuvant temozolomide do not improve disease control.
<table>
<thead>
<tr>
<th>Trial Designation</th>
<th>Author</th>
<th>Year</th>
<th>Phase</th>
<th>n</th>
<th>Age</th>
<th>Study Design</th>
<th>Median OS</th>
<th>Median PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/A Walker[116]</td>
<td></td>
<td>1978</td>
<td>III</td>
<td>222</td>
<td>NR</td>
<td>HGG patients</td>
<td>34.5 wks</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BCNU/RT + BCNU vs BCNU vs RT vs Supportive care</td>
<td>vs 18.5 wks vs 35 wks vs 14 wks</td>
<td></td>
</tr>
<tr>
<td>N/A Westphal[117]</td>
<td></td>
<td>2003</td>
<td>III</td>
<td>240</td>
<td>18-65 y</td>
<td>HGG patients</td>
<td>13.9 mo vs 11.6 mo in HGG patients</td>
<td>5.9 mo vs 5.9 mo in HGG patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BCNU-wafers + RT vs Placebo-wafers + RT</td>
<td>13.5 mo vs 11.4 mo in GBM subgroup</td>
<td></td>
</tr>
<tr>
<td>EORTC 26981/22981; NCIC CE3 Stupp[63-64]</td>
<td></td>
<td>2005</td>
<td>III</td>
<td>573</td>
<td>18-71 y</td>
<td>RT/TMZ + TMZ vs RT</td>
<td>14.6 mo vs 12.1 mo</td>
<td>6.9 mo vs 5.1 mo</td>
</tr>
<tr>
<td>N/A Keime-Guibert[61]</td>
<td></td>
<td>2007</td>
<td>N/A</td>
<td>85</td>
<td>≥ 70 y</td>
<td>RT/supportive care vs Supportive care</td>
<td>29.1 wks vs 16.9 wks</td>
<td>14.9 wks vs 5.4 wks</td>
</tr>
<tr>
<td>RTOG 0525 Gilbert[72]</td>
<td></td>
<td>2013</td>
<td>III</td>
<td>833</td>
<td>≥ 18 y</td>
<td>RT/TMZ + TMZ vs RT/TMZ + TMZ</td>
<td>16.6 mo vs 14.9 mo</td>
<td>5.5 mo vs 6.7 mo</td>
</tr>
<tr>
<td>RTOG 0525 Gilbert[72]</td>
<td></td>
<td>2014</td>
<td>III</td>
<td>637</td>
<td>≥ 18 y</td>
<td>RT/TMZ/bev + TMZ/bev vs RT/TMZ + TMZ</td>
<td>15.7 mo vs 16.1 mo</td>
<td>10.7 mo vs 7.3 mo</td>
</tr>
<tr>
<td>AAVglio Chinot[74]</td>
<td></td>
<td>2014</td>
<td>III</td>
<td>921</td>
<td>≥ 18 y</td>
<td>RT/TMZ/bev + TMZ/bev vs RT/TMZ + TMZ</td>
<td>16.8 mo vs 16.7 mo</td>
<td>10.6 mo vs 6.2 mo</td>
</tr>
<tr>
<td>CENTRIC EORTC 26071-22072 Stupp[118]</td>
<td></td>
<td>2014</td>
<td>III</td>
<td>545</td>
<td>≥ 18 y</td>
<td>MGMT methylated</td>
<td>26.3 mo vs 26.3 mo</td>
<td>10.6 mo vs 7.9 mo</td>
</tr>
<tr>
<td>GLARIUS Herrlinger[107]</td>
<td></td>
<td>2016</td>
<td>II</td>
<td>182</td>
<td>NR</td>
<td>RT/bev + bev/CPT11 vs RT/TMZ + TMZ</td>
<td>16.6 mo vs 17.5 mo</td>
<td>9.7 mo vs 5.99 mo</td>
</tr>
<tr>
<td>ACT IV Weller[110]</td>
<td></td>
<td>2017</td>
<td>III</td>
<td>745</td>
<td>≥ 18 y</td>
<td>Enrolled after completion of RT/TMZ</td>
<td>21.1 mo vs 20.0 mo</td>
<td>8.0 mo vs 7.4 mo</td>
</tr>
<tr>
<td>EF–14 Stupp[87,88,93]</td>
<td></td>
<td>2017</td>
<td>III</td>
<td>695</td>
<td>≥ 18 y</td>
<td>Enrolled after completion of RT/TMZ</td>
<td>20.9 mo vs 16.0 mo</td>
<td>6.7 mo vs 4.0 mo</td>
</tr>
<tr>
<td>CCTG CE.6, EORTC 26062-22061, TROG 00.02 Perry[82]</td>
<td></td>
<td>2017</td>
<td>III</td>
<td>562</td>
<td>≥ 65 y</td>
<td>Short-course RT/TMZ + TMZ vs Short-course RT</td>
<td>9.3 mo vs 7.6 mo</td>
<td>5.3 mo vs 3.9 mo</td>
</tr>
<tr>
<td>CeTeG/NOA-09 Herrlinger[119]</td>
<td></td>
<td>2019</td>
<td>III</td>
<td>141</td>
<td>18-70 y</td>
<td>MGMT methylated</td>
<td>31.4 mo vs 48.1 mo</td>
<td>16.7 mo vs 16.7 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RT/TMZ + TMZ vs RT/CCNU/TMZ + CCNU/TMZ</td>
<td>vs 16.7 mo vs 16.7 mo</td>
<td></td>
</tr>
</tbody>
</table>

bev = bevacizumab; BCNU-wafers = carmustine wafers; CCNU = lomustine; CCTG = Canadian Cancer Trials Group; CPT11 = irinotecan; EORTC = European Organisation for Research and Treatment of Cancer; GBM = glioblastoma; HGG = high-grade glioma, including glioblastoma; N/A = not available; NCIC = National Cancer Information Center; NR = not reported; OS = overall survival; PFS = progression-free survival; RT = radiotherapy; RTOG = Radiation Therapy Oncology Group; TMZ = temozolomide; TROG = Trans Tasman Radiation Oncology Group; TTFields = tumor-treating fields.
Systemic therapy

We recently reviewed in detail the pivotal, late-phase trials that led to the current standard of care for patients with newly diagnosed glioblastoma.[62] These trials are summarized in Table 2. Temozolomide is a DNA-alkylating chemotherapy agent that is designed to readily cross the blood-brain barrier to achieve therapeutic concentrations in the brain. In 2005, a large, international, randomized, phase III trial (European Organisation for Research and Treatment of Cancer [EORTC] 26098/National Cancer Institute of Canada [NCIC] CE3) demonstrated prolonged survival when daily temozolomide chemotherapy (75 mg/m2 daily x 40–49 days) is added concomitantly to radiotherapy followed by 6 cycles of maintenance temozolomide (150–200 mg/m2 x 5/28 days). Based on this landmark trial, temozolomide/radiotherapy followed by maintenance temozolomide has become the worldwide standard of care for patients with a newly diagnosed glioblastoma.[63,64] Temozolomide adds a methyl group to the DNA residues at the O6, N3, and N7 positions that, if unrepaired, leads to DNA toxicity, impaired bone marrow reserve for subsequent second-line chemotherapy, and increased risk of secondary malignancies is concerns with prolonged treatment. In some trials, treatment was allowed per local practice to be extended to up to 12 cycles. A pooled meta-analysis of individual patient outcomes data stemming from four randomized trials compared the duration of maintenance temozolomide chemotherapy (6 cycles vs 7+ cycles) among individuals who were non-progressive after 6 cycles.[71] While there was a slight improvement in progression-free survival, no difference in survival was seen for those who received 6 cycles vs more than 6 cycles of chemotherapy. This suggests that prolonged administration and dose intensification do not improve disease control. At this time, the value of temozolomide during radiotherapy, independent of adjuvant temozolomide in the treatment of glioblastoma, is unknown.

Alternative temozolomide dosing schedules. Alternative dosing schedules have been investigated in the newly-diagnosed and recurrent disease settings. However, none of these regimens have been shown to be superior to the standard temozolomide dosing schedule. The randomized RTOG0525 study found no benefit with intensified maintenance chemotherapy. Patients were randomized at the end of chemoradiotherapy to either standard maintenance therapy (150–200 mg/m2/day x 5/28 days) or an intensified daily regimen (75 mg/m2/day x 21/28 days), effectively doubling the cumulative dose of chemotherapy. No difference in outcomes was noted, and a higher incidence of grade 3/4 toxicities was observed in the investigational arm.[72]

Hopes and disappointments with bevacizumab. The addition of the anti-angiogenic agent bevacizumab to radiotherapy and temozolomide has been explored in two phase III trials focusing on newly diagnosed glioblastoma[73,74] and one phase III trial focusing on recurrent glioblastoma[75]. The observed and expected improvement in progression-free survival based on imaging did not translate into any improvement in overall survival when bevacizumab was added. Unplanned post-hoc analyses found an association of improved overall survival in a molecularly-defined subset of patients.[76] The addition of bevacizumab to hypofractionated radiotherapy demonstrated no improvement in overall survival compared with hypofractionated radiotherapy alone in elderly (≥65 years) patients with newly diagnosed glioblastoma.[77] Based on the results of these trials, bevacizumab should not be administered as part of primary treatment of glioblastoma. Of note, some phy-
Physicians utilize bevacizumab as a corticosteroid-sparing agent to decrease cerebral edema, so that treatment with standard radiotherapy and chemotherapy is feasible without high doses or prolonged use of corticosteroids.

De-escalation of treatment in the elderly. De-escalation of therapeutic interventions has been extensively explored in the elderly and in frail populations with glioblastoma. This interest is driven by the overall brief survival of elderly glioblastoma patients, and thus the desire to shorten the duration of medical intervention. This topic has recently been reviewed in detail.\[78,79\] Several studies have prospectively evaluated abbreviated courses of radiotherapy in these patients (as covered earlier in the “Radiation Therapy” section).

Two large randomized trials have evaluated the exclusive administration of temozolomide chemotherapy in the elderly. Consistently, both trials demonstrated that withholding radiotherapy and instead treating patients with temozolomide alone may be an option for elderly patients with tumors harboring a methylated MGMT gene promoter, while this strategy is detrimental in the absence of MGMT methylation.\[80,81\] Monotherapy with temozolomide offers the advantage of an oral treatment regimen without the need for daily radiotherapy. The utilization of a short-course, hypofractionated radiotherapy regimen (of 40 Gy in 15 treatments) with concomitant temozolomide, followed by adjuvant temozolomide, was shown to improve outcomes in the elderly, which is consistent with the observed benefit reported 10 years earlier by the EORTC/}

### Table 3: Ongoing Late-Phase Clinical Trials for Newly Diagnosed Glioblastoma

<table>
<thead>
<tr>
<th>Trial Designation</th>
<th>NCT Number</th>
<th>Phase</th>
<th>Planned n</th>
<th>Novel Treatment</th>
<th>Treatment Regimen</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTOG 3508A (Intellance1)</td>
<td>NCT02573324 [111]</td>
<td>IIb/III</td>
<td>640</td>
<td>ABT-414, an EGFR-targeting antibody-drug conjugate</td>
<td>EGFR amplified or EGFRvIII mutated RT/TMZ + TMZ vs RT/TMZ/ABT-414 + TMZ/ABT-414</td>
<td>Completed accrual</td>
</tr>
<tr>
<td>A071102</td>
<td>NCT02152982 [120]</td>
<td>II/III</td>
<td>440</td>
<td>Veliparib, a PARP inhibitor</td>
<td>MGMT promoter methylated Post-RT/TMZ enrollment TMZ +/- TTP vs TMZ/veliparib +/- TTP</td>
<td>Completed accrual</td>
</tr>
<tr>
<td>N/A</td>
<td>NCT00045968 [121,122]</td>
<td>III</td>
<td>348</td>
<td>DCVax®-L, an autologous dendritic cell vaccine</td>
<td>Post-RT/TMZ enrollment TMZ/placebo vs TMZ/DCVax®-L</td>
<td>Completed accrualb</td>
</tr>
<tr>
<td>CheckMate-548</td>
<td>NCT02667587 [112]</td>
<td>III</td>
<td>693</td>
<td>Nivolumab, a PD-1 antibody</td>
<td>MGMT promoter methylated RT/TMZ + TMZ vs RT/TMZ/nivolumab + TMZ/nivolumab</td>
<td>Completed accrual</td>
</tr>
<tr>
<td>CheckMate-498</td>
<td>NCT02617589 [111]</td>
<td>III</td>
<td>550</td>
<td>Nivolumab, a PD-1 antibody</td>
<td>MGMT promoter unmethylated RT/TMZ + TMZ vs RT/nivolumab + nivolumab</td>
<td>Completed accrual</td>
</tr>
<tr>
<td>N/A</td>
<td>NCT03345095 [123]</td>
<td>III</td>
<td>750</td>
<td>Marizomib, a proteasome inhibitor</td>
<td>RT/TMZ + TMZ vs RT/TMZ/marizomib + TMZ/marizomib</td>
<td>Open to accrual</td>
</tr>
</tbody>
</table>

### Notes

- Decision to use TTFields is made prior to enrollment but is then continued throughout study treatment.
- Preliminary results
- DCVax®-L = lysate-pulsed dendritic cell vaccine; NCT = National Clinical Trial; PD-1 = programmed death ligand 1; RT = radiotherapy; RTOG = Radiation Therapy Oncology Group; TMZ = temozolomide; TTFields = tumor-treating fields.
The clinical circumstances, including chronicologic age, performance status, concurrent medical problems, MGMT promoter methylation status, and logistical concerns should all be weighed during therapeutic decision-making for elderly patients with glioblastoma. In healthy, MGMT-methylated elderly patients with good performance status, a more aggressive approach, including full-course radiotherapy and temozolomide, can be considered.

Poor performance status. Both de-escalation and escalation of care for patients with poor performance status have been considered. Many of these evaluations have been performed specifically in the elderly population, thus potentially limiting their generalizability to younger patients. De-escalation approaches attempt to limit the toxicity of treatment in a patient population that may not tolerate and is less likely to benefit from therapy. These approaches also attempt to shorten treatment duration as well as the amount of travel to the treatment facility, particularly for patients with limited mobility. The previously discussed abbreviated radiotherapy courses for elderly patients are also often used in the frail population with a poorer performance status; some prospective studies on abbreviated radiotherapy included patients on the basis of performance status alone.[83,84] The use of temozolomide chemotherapy alone has been studied in patients with poor performance status (Karnofsky Performance Score [KPS] of ≤ 70); it was shown to be associated with an improvement in performance status or an improvement to the level of self-care (KPS ≥ 70) in one-third and one-fourth of patients, respectively.[85] Increasing the number of concomitant therapies has been performed with the goals of extending survival and improving functionality. One treatment intensification approach adds bevacizumab to the standard of care, relying on the corticosteroid-sparing effects described earlier. This approach has demonstrated only a transient improvement in performance status, and the data thus far do not justify its routine employment, as median overall survival remained short at 5.6 months (95% CI, 4.4–6.4).[86]

**TTFields**

The addition of TTFields to maintenance temozolomide chemotherapy for newly-diagnosed glioblastoma patients has recently been incorporated as a new standard of care.[87-89] TTFields are applied via multiple electrodes that are directly fixed to the scalp. These low-intensity, alternating electrical fields of 200 Hz interfere with polar organelles (eg, tubulins), which are required for normal cell division. Mitotic disruption ultimately leads to cell cycle arrest, aneuploidy, and apoptosis.[90,91] Additional mechanisms potentially contributing to therapy-associated effects include a disruption of organelles and an induction or modulation of the anti-glioma immune response.[92]

The effect of TTFields was evaluated in two large prospective, non-blinded randomized trials. In recurrent disease, TTFields failed to show superiority over best physicians’ choice (chemo)therapy in patients with recurrent glioblastoma.[93] In a pivotal large, randomized, phase III trial, 695 patients with newly diagnosed glioblastoma were randomized to receive adjuvant temozolomide and TTFields or standard maintenance therapy of temozolomide alone after the end of initial treatment with temozolomide/radiotherapy. Patients who received adjuvant temozolomide and TTFields fared much better than those treated with temozolomide alone. Survival was prolonged with a hazard ratio of 0.63 (95% CI, 0.52–0.76; P < .001), and durable survival was achieved in some patients.[88] This improvement was observed without a measurable negative impact on health-related quality of life (HRQL).

In the real-world setting, the rate of compliance among patients utilizing TTFields is high.[95] The primary toxicity noted in the trials was mild-to-moderate cutaneous toxicity, which typically resolves with minimal intervention.[96]

**Impact of Other Medications**

It has been hypothesized that certain medications commonly used to treat other conditions may potentially benefit patients with glioblastoma. These range from those prescribed for tumor-related conditions—such as epilepsy[97,98] and cerebral edema—to those which are independent of the neoplastic disease, including hypertension, hyperlipidemia, and venous thromboembolism.[99,100] Thus far, none have been proven to be beneficial. When thoroughly evaluated, none of the associations observed in several studies could be validated in larger cohorts, underscoring the importance of prospective (rather than retrospective) trials with strong biological hypotheses.

**Corticosteroids**

Corticosteroids are frequently used to decrease cerebral edema. Their off-target effects also lead to the suppression of immune system activity. Recent preclinical and clinical work suggests that these unfavorable effects contribute to shortened survival.[101] This is of particular importance as we evaluate the role of immunotherapeutic approaches for the treatment of glioma.[102] Despite the lack of a clear benefit in survival, bevacizumab has been shown to decrease the utilization of corticosteroids in patients with glioblastoma in numerous trials.[73,74,103-105]
In routine clinical practice, functional improvement is often seen in association with radiographic improvement; however, it has not been proven to correlate with improved overall survival.

Future Directions
Efforts are continuously being undertaken to improve outcomes for patients with newly diagnosed glioblastoma. The diminishing return of second- and subsequent-line oncologic therapies supports the testing of promising new therapeutic approaches in the newly diagnosed population. This is underscored by the strong survival benefit seen among patients treated with TTFields in the newly diagnosed setting compared with those with progressive disease. A number of novel regimens are being studied in the newly diagnosed setting (Table 3). While many contemporary trials for newly diagnosed glioblastoma build upon the standard of care, as previously described, trials for patients with unmethylated MGMT promoter may omit temozolomide without losing treatment efficacy.[106-108]

EGFR remains an attractive therapeutic target, as it is frequently upregulated in glioblastoma, and its expression is associated with a worse prognosis; it is constitutionally activated in 30% of glioblastomas with a VIII variant. However, randomized trials targeting EGFR have repeatedly failed.[109,110] The addition of a novel peptide vaccine, rindopepimut, to the standard of care has been studied in a phase III trial. While the preclinical and early-phase studies held substantial promise, the phase III trial failed to demonstrate improved survival.[110] Phase III trial evaluation of the antibody drug conjugate depanautuzumab maftodotin (ABT-414) in combination with standard of care treatment for patients with EGFR-amplified, newly diagnosed glioblastoma is eagerly awaited.[111] Finally, the results of two separate trials evaluating the anti-PD1 monoclonal antibody nivolumab in newly diagnosed glioblastoma patients with unmethylated (CheckMate-498)[112] and methylated (CheckMate-548)[113] MGMT promoter are anticipated. Biomarkers that may help predict benefit from immunotherapies[114] will require prospective evaluation, but may provide insight into the role of immunotherapeutic approaches in glioblastoma.

Conclusion
The therapeutic management of newly diagnosed glioblastoma is well-defined and includes surgery, radiation, temozolomide, and TTFields. Nuances to management in the elderly or frail exist; in these populations, treatment de-escalation is often considered on a patient-specific basis. The addition of other systemic therapies—such as antiangiogenic agents or other routinely administered medications, such as anti-epileptic or blood pressure agents—has not been shown to improve survival in newly diagnosed glioblastoma. Concerns exist, substantiated by both preclinical and clinical data, that corticosteroid utilization may negatively impact outcomes of immunotherapeutic approaches for the treatment of these patients. This will need to be carefully considered in the design, administration, and interpretation of clinical trials for this disease. As outcomes in glioblastoma remain poor, continued investigation into promising therapeutics is necessary.

FINANCIAL DISCLOSURE: Dr. Lukas, Dr. Wainwright, Dr. Sonabend, and Dr. Stupp receive funding support from P50CA221747 SPORE for Translational Approaches to Brain Tumors. Dr. Wainwright receives funding support from the NIH/National Institute of Neurological Disorders and Stroke R01NS097851 grant. Dr. Lukas is a consultant for AbbVie, and has served as a consultant for NewLink Genetics and ReNeuron; he has also served on an advisory board for Monteris Medical; served as a medical editor for EBSCO and MedLink Neurology; and has presented CME board review courses for the American Physician Institute. Dr. Sonabend is a consultant for AbbVie. Dr. Stupp receives travel support from NovoCure; he also served on one-time advisory boards for Boehringer Ingelheim, Celgene, and Northwest Biotherapeutics.

For references visit cancernetwork.com/newly-dxed-glioblastoma