Surgical Neurology International

SNI: Neuro-Oncology, a supplement to Surgical Neurology International

OPEN ACCESS

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Editor: Daniel Silbergeld, University of Washington Medical Center, Seattle, Washington, USA

The future of high-grade glioma: Where we are and where are we going

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Received: 16 May 14 Accepted: 15 October 14 Published: 13 February 15

This article may be cited as:
Rhun EL, Taillibert S, Chamberlain MC. The future of high-grade glioma: Where we are and where are we going. Surg Neurol Int 2015;6:S9-44.
Available FREE in open access from: http://www.surgicalneurologyint.com/text.asp?2015/6/2/9/151331

Abstract

High-grade glioma (HGG) are optimally treated with maximum safe surgery, followed by radiotherapy (RT) and/or systemic chemotherapy (CT). Recently, the treatment of newly diagnosed anaplastic glioma (AG) has changed, particularly in patients with 1p19q codeleted tumors. Results of trials currenlty ongoing are likely to determine the best standard of care for patients with noncodeleted AG tumors. Trials in AG illustrate the importance of molecular characterization, which are germane to both prognosis and treatment. In contrast, efforts to improve the current standard of care of newly diagnosed glioblastoma (GB) with, for example, the addition of bevacizumab (BEV), have been largely disappointing and furthermore molecular characterization has not changed therapy except in elderly patients. Novel approaches, such as vaccine-based immunotherapy, for newly diagnosed GB are currently being pursued in multiple clinical trials. Recurrent disease, an event inevitable in nearly all patients with HGG, continues to be a challenge. Both recurrent GB and AG are managed in similar manner and when feasible re-resection is often suggested notwithstanding limited data to suggest benefit from repeat surgery. Occassional patients may be candidates for re-irradiation but again there is a paucity of data to commend this therapy and only a minority of selected patients are eligible for this approach. Consequently systemic therapy continues to be the most often utilized treatment in recurrent HGG. Choice of therapy, however, varies and revolves around re-challenge with temozolomide (TMZ), use of a nitrosourea (most often lomustine; CCNU) or BEV, the most frequently used angiogenic inhibitor. Nevertheless, no clear standard recommendation regarding the prefered agent or combination of agents is avaliable. Prognosis after progression of a HGG remains poor, with an unmet need to improve therapy.

Key Words: Anaplastic glioma, anti-angiogenic agents, bevacizumab, chemotherapy, glioblastoma, high grade glioma, immunotherapy, nitrosourea, temozolomide, targeted therapy

Access this article online

Website: www.surgicalneurologyint.com

DOI: 10.4103/2152-7806.151331

Quick Response Code:

INTRODUCTION

High-grade glioma (HGG) are the most frequent malignant primary brain tumor, which account for 80% of all gliomas in the United States, and are encountered with an annual incidence of 5.26 per 100,000 population, or 17,000 new cases diagnosed per year.[82] Despite recent advances in treatment, the prognosis of HGG remains poor with comparatively short overall survival (OS) and importantly profound impact on quality of life (QoL). The main objective in the treatment of HGG is twofold: Prolong survival and maintain or improve the QoL that includes elementary neurological function as well as cognitive function. The World Health Organization (WHO) classification of gliomas is used to define the type and grade of tumor, but the prognosis and response to treatment may vary among tumors even in the same subtype of tumor. Molecular characterization and Biomarkers are becoming increasingly important in the management of HGG especially with respect to anaplastic glioma (AG) that have refined prognosis and increasingly are predictive with respect to treatment. Molecular characterization has also defined new driver mutations that represent potential druggable targets. Surgery remains a fundamental treatment both to confirm diagnosis and relieve symptom as as they relate to an intracranial mass. In addition, extent of surgery also appears to have prognostic relevance. The role of combination of radiotherapy (RT) and chemotherapy (CT) is now well established in both codeleted AG (RT preceded or followed by PCV [procarbazine, lomustine, vincristine] CT and in glioblastoma [GB] concomitant temozolomide [TMZ] and TMZ CT followed by adjuvant post-RT TMZ CT) has become the current standard of care (SOC). Nevertheless many questions remain such as the choice of best treatment of recurrent HGG, best management of noncodeleted AG, the role of bevacizumab (BEV) in HGG and whether new approaches such as vaccine-based immunotherapy have a role in the management in HGG.

ANAPLASTIC GLIOMA

Histological and molecular data

According to the WHO classification, which is based on morphological criteria, three histological subtypes of AG are described: Anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO), and anaplastic oligoastrocytoma also called mixed anaplastic glioma (AOA).[179] AGs with an oligodendroglial component account for 30–50% of all AG and can be divided into anaplastic AO and AOA.[82] The histological classification of AG is limited due to interobserver subjectivity often resulting in inaccurate pathological classification.[101,112,182] Anaplastic mixed glioma (AOA), with both astrocytic and oligodendroglial features, are particularly subject to high interobserver variation.[161]

Different molecular subtypes are present within each histologic subtype of AG.[87] AA most often is characterized by nondeletion of 1p/19q, mutation of tumor protein p53 (TP53) and alpha thalassemia mental retardation X-linked gene (ATRX) and have the poorest prognosis amongst AG. By contrast pure AO typically presents with 1p/19q codeletion and isocitrate dehydrogenase 1 (IDH1) mutation and have the best prognosis amongst AG.[292] The radio- and chemosensitivity of AO appears linked to the presence of the 1p/19q deletion.[25,51,318]

Molecular markers are becoming increasingly important in the management of AG, and may at times asssit in the determination of diagnosis. Additionally molecular markers have prognostic value and help to resolve the discrepancy between WHO classification and clinical outcomes. Lastly, they may be predictive with response to treatment. The molecular markers that currently are most informative with respect to either treatment or prognosis include 1p19q codeletion status (determined by fluorescence *in situ* hybridization [FISH]), IDH1/2 mutation (determined by immunohistochemistry [IHC]), O-6 methylguanine-DNA-methyltransferase (MGMT) promoter methylation (determined by polymerase chain reaction [PCR]), and ATRX mutation (determined by IHC).[77,182,326] The frequence and the impact on OS of these markers in Radiation Treatment Oncology Group (RTOG) 9402 trial of anaplastic oligodendroglial tumors are described in Table 1.

In the NOA-4 trial of AG (radiation therapy [RT] vs. CT), 1p/19q codeletion was detected in 40.9% of AG (14.9% of patients with AA, 77.4% of patients with AO, and 58.7% of patients with AOA).[318] In the recent RTOG 9402 and European Organization for the Research and Treatment of Cancer (EORTC) 26951 trials of AO and AOA tumors, 1p/19q codeletion was detected in 48% and 25% of the patients, respectively.[25,51] 1p/19q codeletion was more frequent in AO (76%) than AOA (24%) in the RTOG 9402 study.[51] The 1p/19q codeletion has been identified as both a strong prognostic and predicitive factor in AG treated with RT, CT (TMZ or PCV), or both.[22,25,26,30,45,51,52,58,102,112,134,136,271,290,318] In the RTOG 9402 and EORTC 26951 trials, 1p/19q codeletion was a predictive factor for improved survival in AO or AOA patients treated with PCV and RT compared with RT alone and strongly support the prognostic and predictive roles of the 1p/19q codeletion.[25,51] However, 1p/19q codeletion is a marker not a mechanism of sensitivy to treatment.[51]

The *IDH1* gene, a cytosolic enzyme, functions as a tumor suppressor that when mutationally inactivated contributes to tumorigenesis in part through induction of the hypoxia inducible factor-1 pathway.[339] IDH2

Table 1: Frequence and the impact on overall survival of the different molecular markers in RTOG 9402 (Cairncross 2014)

Anaplastic oligodendroglial tumors AO/AOA	Frequency (%)	Median overall survival (years)	
		Radiotherapy	Radiotherapy+PCV
Molecular signatures			
IDH1 mutation	74	5.7	9.4
IDH wild type	26	1.3	1.8
1p/19q codeletion+IDH1 mutation (90% codeleted tumors with IDH1 mutation; 78% AO)	42	6.8	14.7
Non deleted+IDH1 mutation (64% AOA; 72% ATRX mutated)	32	3.3	5.5
+ ATRX mutation		2.7	11.0
+ ATRX wild type		3.5	4.4
Nondeleted+IDH1 wild type	21	1.0	1.3
1p/19q codeletion+IDH1 wild type	5		

AO: Anaplastic glioma, AOA: Anaplastic oligodendroglioma, IDH: Isocitrate dehydrogenase, ATRX: Alpha thalassemia mental retardation X-linked gene, PCV: Procarbazine, lomustine, vincristine

gene codes for a mitochondrial enzyme with a similar function.[335] More importantly IDH mutations contribute to gliomagenesis by the production of an oncometabolite, d-2-hydroxyglutarate, which inhibits deoxy-oxygeases that in turn modify chromation configuration.[75,291] In the NOA-4 trial, *IDH1* codon 132 mutations were detected in 65.6% of the patients (71% of AO, 73% of AOA, and 57% of AA) and IDH2 mutations were detected in only 3.1% of the patients.[318] In the EORTC 26951 trial, IDH1 mutations were observed in 46% of the patients with a confirmed AO at central review and in 86% of patients with 1p/19q codeletion. IDH2 mutations were rare (1/159; <1%).[27] In the EORTC study, IDH1 mutations were more frequent in younger patients, patients with a prior low-grade glioma, patients without necrosis, patients with frontal involvement, patients without epidermal growth factor receptor (EGFR) amplification, trisomy 7 or loss of chromosome 10.[27] Mutation of IDH1 has been reported as a positive prognostic factor in multiple studies.[25,27,47,51,99,138,318] In the NOA-4 trial, IDH mutations were associated with response to RT or CT. In the multivariate analysis, IDH1 mutation was the strongest prognostic factor as compared with 1p/19q codeletion, O-6 methylguanine-deoxyribonucleic acid (DNA)-methyltransferase (MGMT) promoter methylation, or histology.[318] In two other studies, a significant co-association was observed between IDH1 and MGMT promoter methylation status. An IDH1 mutation was observed in 58–62% in methylated tumors, as opposed to only 10–26% in unmethylated tumors.[27,259] In the EORTC 26951 study, IDH1 mutations were also associated with 1p/19q codeletion.[27] In this study, the presence of IDH1 mutation showed a strong prognostic value but was not a predictive marker for the response to treatment to PCV.[27] There is preclinical data to suggest that IDH1 may represent a druggable target.[36,75,225,249,304]

Expression of the DNA repair protein MGMT results in resistance of gliomas to alkylating and methylating agents.[28,104] Methylation of MGMT promoter methylation can be detected in 55–80% of AO.[45,47,194] In the NOA-4 study, methylation of MGMT promoter was detected in 60.9% of the patients with AG and was more common in AO (71%) and AOA (70.7%) than in AA (50%).[318] In the EORTC 26951 study of AO and AOA, MGMT promoter methylation was observed in 80%.[25] A high level of methylation has been observed in AO up to 88% particularly in 1p/19q codeleted tumors.[44,194] In the NOA-4 trial, MGMT promoter methylation was associated with 1p/19q loss in AO and AOA but not in AA.[318] In the EORTC 26951 study, the MGMT promoter methylation was also strongly associated with the 1p/19q codeletion.[28] It is generally agreed that MGMT promoter methylation in AG is prognostic but not predictive.[88,214] In the EORTC 26951 trial, the prognostic significance of MGMT promoter methylation was equally strong in the both arms of treatment for progression-free survival (PFS) and OS. Though MGMT does not play a mechanistic role in the repair of RT-induced DNA damage, *MGMT* promoter methylation was correlated with a statistically and clinically significant increased PFS, including the control arm treated with RT only.[28] In this study, MGMT promoter methylation had prognostic significance only without any predictive value for response to adjuvant PCV CT.[28] Nevertheless, when IDH1 mutation status was added, the independant prognostic significance of MGMT was lost.[27] In NOA-4 trial, the prognostic significance of MGMT promoter methylation status was equivalent to 1p/19q codeletion, and the improvement in PFS in methylated patients was similar in patients treated with RT and CT. In this study, the efficacy of RT was improved in methylated tumors. These results suggest MGMT promoter methylation not only is a prognostic marker for good outcome but also may be a predictive factor for response to RT.[318] In conclusion, MGMT methylation is of prognostic significance in AG, but there are insufficient data to support a predictive value.[28] In a retrospective study, Wick explored the prognostic and the predictive value for PFS of MGMT promoter methylation in grade III/IV gliomas with or without IDH mutation.[319] In IDH1 mutated tumors, MGMT promoter methylation was associated with improved PFS with CT, combination CT + RT, or RT only groups, and thus showed prognostic value. In tumors without IDH1 mutation, MGMT promoter methylation was associated with increased PFS in patients treated with CT, but not in those who received

RT alone as first-line treatment. This suggested CT was predictive in IDH1 wild-type MGMT promoter methylated HGG [Figure 1].[319]

ATRX loss has been reported to be rare in oligodendroglial tumors[141,177] and mutually exclusive with 1p/19q co-deletion.[139] ATRX loss has been detected in 40–73% of AA and 25–77% of mixed AOA, but was infrequent (7%) in AO.[139,326] ATRX in conjunction with 1p/19q status may be diagnostically useful to classify mixed gliomas as either astrocytic or oligodendroglial glioma, and may as well be of prognostic value. In the prospective cohort of Wiestler, patients with astrocytic tumors harboring ATRX loss, that is, mutated have a significantly better prognosis than IDH mutant patients with astrocytic tumors who express ATRX, that is, wild type.[326] In the study of Wiestler exploring the distribution of ATRX status, the authors suggested grouping AA and mixed AOA without 1p/19q codeletion but with ATRX loss as "molecular anaplastic astroctymas" and AOA with 1p/19q codeletion and AO as "molecular oligodendroglioma."[326]

Recent studies have evaluated the genetic landscape of AG by exome sequencing and identified frequent markers as IDH1 mutation, ATRX loss, TP53 in addition to mutations in the Notch pathway genes.[148] Subgroups of AG can also be identified according to their molecular status using an unsupervised analysis of gene expression profiling.[97,274,293] Intrinsic glioma subtypes (IGS) have been reported to correlate better with outcome as compared with histology.[98,111,171,214,223] Intrinsic glioma subtyping was performed for patients included in the EORTC 26951 study. All previously identified six IGS were observed confirming that different molecular subtypes co-exist within well-defined histologic subtypes of AG. After central pathology review, each histologic subtype still contained various IGS. In multivariate analysis, the IGS was a significant prognostic factor that was independent of clinical (age, sex, performance status [PS], tumor location and type of surgery), molecular (IDH1 mutation, MGMT promoter methylation, 1p/19q codeletion), and histologic (local diagnosis or central review diagnosis) parameters both for OS and PFS.[87] One subtype, IGS-9, characterized by high percentage of 1p/19q codeletion and *IDH1* mutations, significantly benefited from PCV CT. Nevertheless, the prognostic value of IGS was lower than the prognostic values of other markers. Molecular markers such as IDH1 mutation or 1p/19q codeletion may be show a greater predictive value than IGS or histology.[112]

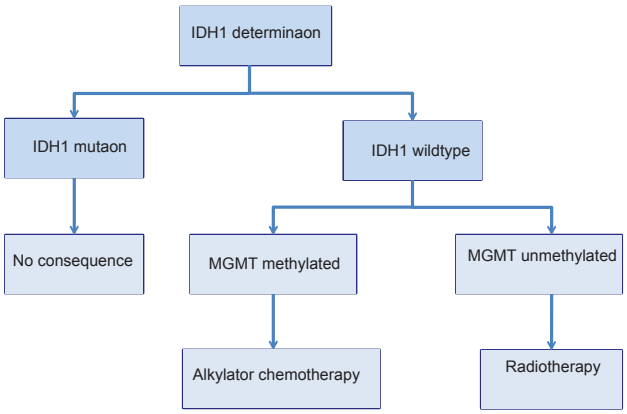

Figure 1: Biomarker interactive model based upon NOA-04. IDH: Isocitrate dehydrogenase MGMT: 0-6 methylguanine DNA methyltransferase

The best characterized epigenetic event in cancer is DNA methylation at gene promoter regions. Cancers are frequently characterized by specific methylation patterns. Abberant methylation is usually associated with silencing and loss of function of the concerned genes.[6,88] The prognostic role of DNA methylation at CpG sites (CpG island methylator phenotype; CIMP+) has been shown in glioma.[15,28,164] A link between CIMP status and genetic status (IDH mutation, 1p/19q codeletion, TP53 mutation) have also been demonstrated.[29,71,85,164,291] Three CIMP groups have been described in oligodendroglial glioma: 1p/19q codeleted CIMP+ tumors that are associated with the best prognosis, CIMP+ tumors usually nondeleted for 1p19q are associated with an intermediate prognosis and CIMP– tumors have by comparison a poor prognosis.[200] Using molecualr subtypes defined by gene expression of Verhaak, AG were preferentially assigned to the proneural, IDH-1 mutant, G-CIMP+ category.[115]

In conclusion, molecular classification represents a major advance in prognostication of AG.[112] Histological data, commonly used to enroll AG patients in clinical trials, needs to be complimented by molecular data to insure better categorization of patients in trials. AG may now be classified into: Double positive (1p19q codeleted/IDH1 mutated or ATRX mutated), single positiv (1p19q nondeleted/IDH1 mutated, 1p19q codeleted/IDH1 nonmutated, ATRX mutated/IDH1 nonmutated, ATRX nonmutated/IDH1 mutated), and double negative (1p19q nondeleted/IDH1 nonmutated, ATRX nonmutated/IDH1 nonmutated).

Upfront treatment of anaplastic glioma

Since the early 1990s, initial therapy for newly diagnosed AO was PCV with or without RT.[170] The German randomized phase III trial NOA-4 compared the efficacy and safety of RT alone (A) versus CT with either PCV (B1) or TMZ (B2) as initial therapy in 274 patients with newly diagnosed AG including 130 patients with AO and AOA after initial surgery (resection or biopsy).[318] The design and the treatment assigned initially and at progression are detailed in Figure 2. Brief interruption for toxicity were observed in 3% in arm A, and cycles were delayed because of hematotoxicity in 18% of cycles in arm B1 and 6% of cycles in arm B2. The median number of completed cycles was

four for PCV (range, 1–5 cycles) and eight for TMZ (range, 0–12 cycles). Median time to tumor failure (TTF) was 42.7 months in arm A versus 43.8 months in arm B (P = 0.28). Median PFS was 30.6 months in arm A and 31.9 months in arm B (P = 0.87). Median OS was 72.1 months in arm A and 82.6 months in arm B. No difference was observed between patients treated with PCV or TMZ, in median TTF, PFS, and OS. Multivariate analysis showed that extent of resection (P = 0.0006), age less than 50 years (P = 0.0004), histology (P = 0.0237), IDH1 mutation (P = 0.0128), and MGMT promoter methylation status (P = 0.0172) were associated with TTF. AO and AOA share a similar and better prognosis compared with AA. In this study, initial RT or CT achieved comparable results in terms of PFS or OS. No difference in PFS between patients treated with PCV versus TMZ was observed, however, TMZ was much better tolerated.

The long-term results of the two randomized phase III studies (RTOG 9402 and EORTC 26951) changed the managment of newly diagnosed anaplastic oligodendroglial tumors. The aim of both studies was to determine the role of the addition of neoadjuvant or adjuvant CT with PCV to RT in the initial treatment as compared with RT only. In the RTOG 9402 trial, patients with newly diagnosed AO or AOA were randomly assigned to 4 cycles of neoadjuvant intensive PCV plus RT versus RT only.[134] The design is detailed in Figure 3. The median number of neoadjuvant PCV cycles was 4 and only 46% of the patients received the 4 full cycles of PCV. PCV was stopped for toxicity in 20%, tumor progression in 17%. Ninety-five patients (64%) had a grade III or higher toxicity. RT was stopped in 10% of the PCV/RT arm and 5% of the RT arm. The most frequent and serious toxicities were myelosuppression, cognitive or mood change, neuropathy, vomiting,

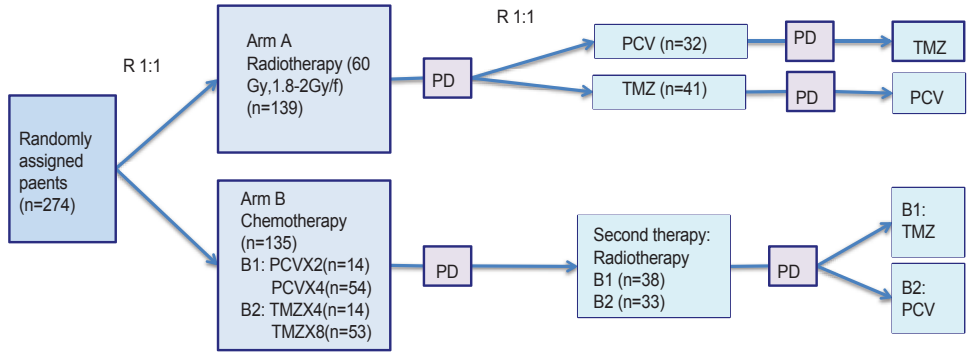

Figure 2: NO 04-design. n Number of patients, R: Randomization; PD: Progression disease; TMZ: Temozolomide; PCV: Lomustine, vincristine, procarbazine. PCV: Lomustine 110 mg/m² on day1, vincristine 2 mg on days 8 and 29, and procarbazine 60 mg/m² on days 8 through 21 TMZ: 200 mg/m² on days 1 through 5, every 28 days

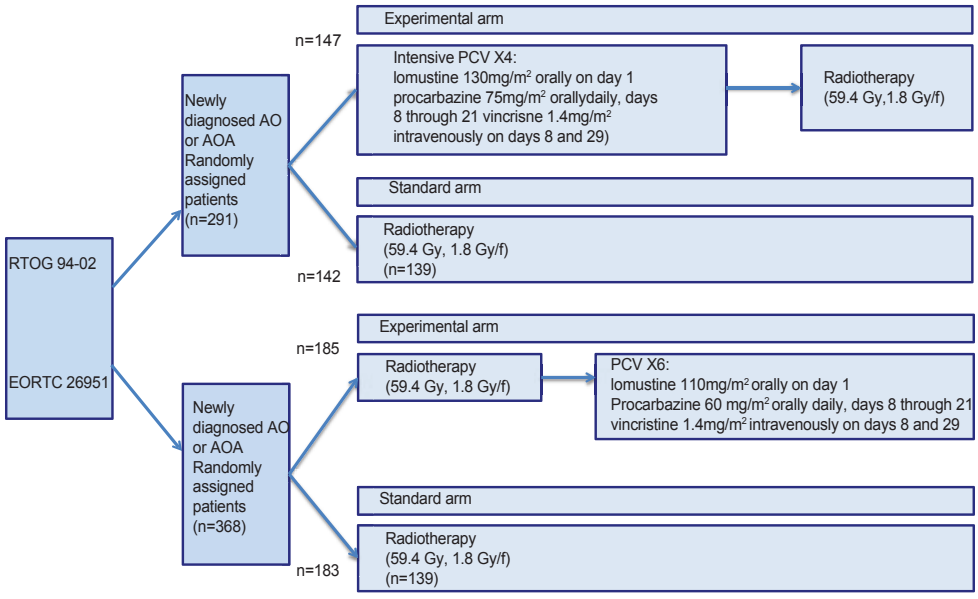

Figure 3: RTOG 94-02 and EORTC 26951 trial design. AO: Anaplastic oligodendroglioma; AOA: Anaplastic oligoastrocytoma; n: Number of patients; PCV: Lomustine, vincristine, procarbazine

hepatic dysfunction, and allergic rash.[134] At progression, surgery rates were similar between the treatment arms (43% after PCV/RT vs. 56% after RT alone). Salvage CT rates differed between groups: 41% after PCV/RT arm versus 79% after RT alone ($P < 0.001$).[51] Early results from RTOG 9402, published in 2006 when 55% of the patients had died after a median follow-up of 38 months, showed that PFS was prolonged in the PCV/RT arm compared with the RT alone arm, and that patients with codeleted tumors lived longer. No difference was observed in terms of OS.[134] In the subsequent publication in 2013, after a median follow-up of 186 months, 72% of the patients had died, there was no difference for the entire cohort in median survival by treatment (4.6 years for PCV plus RT vs. 4.7 years for RT; $P = 0.1$). In patients with 1p/19q codeletion, OS was significanlty prolonged in the PCV/RT arm versus RT only arm (14.7 years vs. 7.3 years, $P = 0.03$). The results are shown in Table 2.[51]

In the EORTC 26951 trial, patients with newly diagnosed AO or AOA were randomly assigned to either RT or RT followed by 6 cycles of adjuvant PCV [Figure 3]. PCV CT was started within 4 weeks after the completion of RT. The median number of PCV cycles was three; only 30% of the patients completed the intended six cycles. Most patients discontinued PCV prematurely for hematologic toxicity (33%) or tumor progression (24%).[26] The QoL analysis showed that patients in the RT/PCV arm had more frequent nausea/vomiting, loss of appetite, and drowsiness during and shortly after PCV CT.[289] At progression, surgery rates were 25% in the RT/PCV arm and 18% in the RT arm. Salvage CT was administrated in 52.5% (PCV, $n = 18\%$ or TMZ, $n = 76\%$) in the RT/PCV arm and in 74.5% (PCV, $n = 75\%$ or TMZ, $n = 54\%$) in the RT arm.[25,26] Initial results of EORTC 26951 were published in 2006, when 217 (59%) of the patients had died.[26] In the first publication, after a median follow-up of 62.6 months in the RT/PCV arm and 59 months in the RT arm, 55.7% patients of the RT/PCV and 62.3% of the patients in the RT arm had died. An increase was observed in PFS in adjuvant treated patients without any significant difference in OS. In the publication of 2013, after a median follow-up of 140 months, 81% of the patients had been diagnosed with progression and 76.4% had died. Median PFS (24.3 vs. 13.2 months, $P = 0.003$) and OS (42.3 vs. 30.6 months, $P = 0.018$) were both significantly longer in the RT/PCV arm [Table 2]. The correlation between survival and the 1p/19q codeletion,

Table 2: Survival based on the 1p/19q codeletion status in the RTOG 9402 and EORTC 26951 trials

	PFS	HR 95% CI *P* value	OS	HR 95% CI *P* value
RTOG 9402				
Whole population ($n=291$)				
RT alone arm ($n=143$)	NS	HR: 0.68	4.7 years	HR: 0.79
PCV/RT arm ($n=148$)	NS	95% CI: 0.53-0.88 $P=0.003$	4.6 years	95% CI: 0.60-1.04 $P=0.1$
1p/19q codeleted patients ($n=126$)				
RT alone arm ($n=67$)	2.9 years	HR: 0.47 95% CI: 0.30-0.72	7.3 years	HR: 0.59 95% CI 0.37-0.95
PCV/RT arm ($n=59$)	8.4 years	$P<0.001$	14.7 years	$P=0.03$
Non 1p/19q codeleted patients ($n=137$) (50% of the entire cohort)				
RT alone arm ($n=61$)	1.0 years	HR: 0.81	2.7 years	HR: 0.85;
PCV/RT arm ($n=76$)	1.2 years	95%CI: 0.56-1.16 $P=0.24$	2.6 years	95% CI: 0.58-1.23 $P=0.39$
EORTC 26951				
Whole population ($n=368$)				
RT alone arm ($n=183$)	13.2 months	HR: 0.66;	30.6 months	HR: 0.75;
RT/PCV arm ($n=185$)	24.3 months	95% CI: 0.52-0.83; $P=0.003$	42.3 months	95% CI: 0.60-0.95; $P=0.018$
1p/19q codeleted patients ($n=80$) (25% of the entire cohort)				
RT alone arm ($n=37$)	49.9 months	HR: 0.42;	111.8 months	HR: 0.56;
RT/PCV arm ($n=43$)	156.8 months	95% CI: 0.24-0.74 $P=0.002$	Not reached	95% CI: 0.31-1.03; $P=0.069$
Non 1p/19q codeleted patients ($n=236$)				
RT alone arm ($n=122$)	8.7 months	HR: 0.73;	21.1 months	HR: 0.83;
RT/PCV arm ($n=114$)	14.8 months	95% CI: 0.56-0.97 $P=0.026$	25 months	95% CI: 0.62-1.10 $P=0.195$

PFS: Progression-free survival, OS: Overall survival, HR: Hazard ratio, *n*: Number of patients, RT: Radiotherapy, PCV: Procarbazine, lomustine, vincristine, HR: Hazard ratio, NS: Not stated

the mutational status of IDH, and the methylation status of the MGMT was retrospectively determined. In patients with a 1p/19q codeletion, OS was increased with a trend toward more benefit from adjuvant PCV (OS not reached in the RT/PCV group vs. 112 months in the RT group) [Table 2]. A total of 81 of 178 patients tested were IDH1 mutated and a total of 136 of 183 patients tested were MGMT methylated. In a multivariate prognostic model with these three factors, IDH1 and 1p/19q were independently significant but not MGMT. In this study, the addition of six cycles of PCV after RT increased both PFS and OS in anaplastic oligodendroglial tumors irrespective of 1p19q deletion status. Tumors with 1p/19q-codeletion and IDH1 mutations were the only group to derive significant benefit from adjuvant PCV.[25]

In both the RTOG and EORTC trials, the addition of PCV to RT significantly improved the survival, especially in the population of 1p/19q codeleted anaplastic oligodendroglial tumors and currently represents the SOC. The results of both studies suggest that neither the timing of PCV administration (immediatly before or after RT) nor the dose-intensity of the PCV schedule matter.[25] The phase III intergroup CODEL (N0577 EORTC 26081) study initially was designed to compare in newly diagnosed 1p/19q codeleted AG the efficacy of RT alone versus TMZ alone versus RT with concomitant and adjuvant TMZ. Enrollment had started across North America and in Europe. This trial was temporarily suspended in December 2011 and was revised as a result of the findings from the EORTC 26951 and RTOG 9402. The new design of CODEL compares RT + PCV to RT + TMZ (concurrent and adjuvant) with a small exploratory arm assessing TMZ only. The primary endpoint is PFS and enrollment commenced in 2013. This trial is of practical importance as currently it is unclear if RT + PCV is equivalent or superior to RT + TMZ and consequently its results may be practice changing. In the codeleted population, the prolonged OS in the recent updated RTOG and EORTC phase III trials (14.7 years in the the RTOG study and median OS not reached after a median follow-up of 11 years in the EORTC trial) led to a new French multicenter randomized phase III trial, POLCA. This trial is designed to determine whether treating newly diagnosed 1p19q codeleted AG with PCV alone (and delay of RT until recurence) versus RT + PCV can spare potential RT-related cognitive deterioration and achive similar results with respect to PFS and OS.

An important question regarding QoL is the respective roles of TMZ and PCV as they impact QoL in the initial treatment of AG. PCV CT has been reported as being more effective than TMZ in a large retrospective study,[168] but in several small single institution studies TMZ alone or in association with RT result in excellent response rates and an apparent survival benefit but with less toxicity than seen with PCV.[84,102,191,288,318] In many centers, TMZ is used as first-line CT in 1p/19q codeleted AOs notwithstanding lack of evidence that this approach is comparable to RT + PCV.[1,83] Furthermore, TMZ has been reported as the most frequently used CT in AO and often substitutes for PCV among patients receiving CT alone or with RT (87% vs. 2% in 2005–2007).[1,219] The main cohort or phase II studies evaluating TMZ in newly diagnosed AG are described in Table 3. An important question is to determine whether the safety and the eficacy of RT-TMZ and RT-PCV regimen are equivalent as will be determined by the CODEL trial. The results of concurrent RT and TMZ have been reported in four series of patients: Two with pre-RT-TMZ followed by concurrent RT-TMZ,[191,299] two with concurrent RT-TMZ followed by TMZ alone (up to 12 cyles).[149,192] Two other cohorts have also reported the role of RT and CT in AG.[168,267] The results are reported in Table 4.

Until now, limited data regarding best upfront treatment is avaliable in uni- or nondeleted AG. In the cohort of AO or AOA, Lassman reported a longer median time to progression (TTP) following CT + RT (concurrent CT-RT, RT followed by CT or CT followed by RT) (3.1 years) than CT alone (TMZ or PCV) (0.9 years, $P = 0.0124$) or RT (1.1 years, $P < 0.0001$). OS was also better in the CT + RT group of patients (5.0 years) than CT (2.2 years, $P = 0.02$) or RT (1.9 years, $P < 0.0001$).[168] In the NOA4 trial, no difference was observed in time to second disease progression, the primary study endpoint, according to treatment allocation (CT alone vs. RT alone followed by crossover at time of first disease progression).[318] Both the EORTC and RTOG trials suggest that there was no benefit with addition of PCV to RT in noncodeleted AG.[25,51] The only exception may be in IDH1 and ATRX mutated tumors. Consequently in uni- or nondeleted AG, no SOC is curently defined and there are no prospective data suggesting RT + TMZ should be recommended for these patients.

The CATNON trial (concurrent and adjuvant TMZ CT in non-1p/19q codeleted AG; EORTC 26053-22054) is an ongoing phase III multicenter trial (Europe, Australia, and North America), which will inform as to the contribution of TMZ and RT in patients with nondeleted AG tumors. This study is comparing the efficacy of OS of RT only to RT + TMZ (concomitant and adjuvant) to RT followed by adjuvant TMZ to RT with concomitant TMZ in patients with non-1p/19q deleted newly diagnosed AG. The design of CATNON is detailed in Figure 4.

In conclusion, in the population of newly diagnosed AG and in patients with 1p/19q codeletion, the SOC is currently RT + PCV.[25,51] The role of TMZ remains to be determined. In the 1p/19q noncodeleted population of AG, there does not appear to be benefit with addition of PCV to RT and there is insufficient data to recommend concomitant RT and TMZ. In this

Table 3: Phase II studies of newly diagnosed anaplastic oligodendroglioma and oligoastrocytoma treated with Temozolomide

Authors	Patients and tumor's characteristics	Chemotherapy regimen	Response of the whole cohort and according to the molecular status
Taliansky-Aronov 2006	20 patients with AO Median age: 47 years (26-65) Median KPS: 70% Resection: 9 Biopsy: 11 Newly diagnosed AO: 20 pts Secondary AO: 10 pts 1p deletion: 58% (7/12) 19q deletion: 83% (10/12) 1p/19q codeletion: Not detailed	TMZ 200 mg/m^2/day 5 days/28 up to 24 cycles Median #of cycles: 14 (3-24)	Whole cohort Clinical improvment: 12 pts (60%), stabilization: 5 pts, progression: 9 pts Objective response rate: 15 pts (75%) Median TTP: 24 months (3-34) According to the molecular data 24 months PFS: 1p LOH group=100%; 1p intact=20%; P=0.057 TTP not reached for the 1p del, 8 months for pts with no del 1p
Mikkelsen 2009 Description of the cases with CT	36 patients with 1p/19q codeletion Median age: 46.5 years (22-68) Median KPS 90 (60-100) Gross total resection: 8 (22.2%) Subtotal resection: 22 (61.1%) Biopsy: 6 (16.7%) AO: 5 pts (13.9%) AOA: 30 pts (83.3%) Anaplastic mixed: 1 pt (2.8%)	TMZ alone 150-200 mg/m^2/day for 5 days every 28 days Median # of completed cycles: 12 (2-24)	Whole cohort TTP: 28.7 months CR: 3 (8.6%), PR: 18 pts (51.4%), stabilization: 2 pts (20%), progression: 2 pts (20%) 6 mo PFS: 94.3% (95% CI 79.0-98.6) 12 mo PFS: 76.7% (95% CI 58.7-87.6) OS 12 mo: 97.2% (95% CI 81.9-99.6) OS 24: 90.1% (95% CI 72.2-96.7)
Gan 2010	40 patients (2203-2006) Median age: 43 years (18-71) ECOG PS: 0=14 (35%); 1=23 (58%); 2=3 (7%) Total macroscopic resection: 9 pts (22%) Subtotal resection: 27 pts (68%) Biopsy only: 4 pts (10%) 1p/19q codel: 47% (18/38) methylation MGMTP: 48% (10/21) AO (n=11) (1p/19q codel: 71%; MGMTP methyl 100%) AOA (n=29) (1p/19q codel: 31%; MGMTP methyl 23%)	TMZ 200mg/m2, d1-d5, every 4 weeks X6	Whole cohort Complete response: 15 (38%), Partial response: 6 (15%), Stable disease: 9 (23%) 6-mo PFS: 77% (95% CI 64.5-79.3%) Median PFS: 21 mo (95% CI 3-39 mo) Median OS: 43 mo (95% CI, 20-66 mo) According to the molecular status RR 1p/19q codeletion: RR was significantly increased (72% vs. 37%, P=0.049) MGMTP methylation: RR was significantly increased (70% vs. 27%, P=0.086) PFS and OS The presence of either 1p/19q codeletion or MGMT methylation did not improved PFS or OS
Ducray 2011	41 patients (2000-2005) Median age: 74 years (70-90) Median KPS: 60 (30-100) Complete resection: 2 pts (11%) Partial resection: 9 pts (14%) Biopsy: 33 pts (75%) MGMTP methylation: 50% (/38) 1p/19q codeletion: 7% (1/14)	TMZ alone 150 mg/m2/day for 5 days every 28 days Median # of completed cycles: 5 (1-13)	Whole cohort PR: 13 pts (32%), SD: 17 pts (41%), PD: 11 pts (27%) Median PFS: 6.9 months Median OS: 12.4 months According to the molecular status MGMTP associated with both longer PFS (8.7 vs. 5.7 months, P=0.01) and longer OS (16.1 vs. 12.4 months, P=0.05) Rate of responders to chemotherapy similar in MGMTP-methylated (38%) and in MGMTP-unmethylated patients (31%) Duration of response significantly longer in responders with methylated MGMTP than in responders with unmethylated MGMTP (16.1 vs. 9.6 months, P=0.0004)

Pts: Patients, KPS: Karnofsky Performance status, ECOG PS: Eastern Cooperative Oncology Group Performance Status, nb: Number, AO: Anaplastic oligodendroglioma, AOA: Anaplastic oligoastrocytoma, del: Deletion, TMZ: Temozolomide, PFS: Progression-free survival, OS: Overall survival, TTP: Time to progression, mo: Months, RR: Response rate, CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease, MGMTP: O-6-methylguanine-DNA methyltransferase promoter, methyl: Methylation, codel: Codeletion, #: Number

Table 4: Main cohorts and phase II studies of newly diagnosed anaplastic glioma treated with radiotheray and chemotherapy

Authors	Patient and tumor's characteristics	Regimen	Response of the whole cohort and according to the molecular status
Vogelbaum 2009	39 patients (2002-2004) Median age: 45 (18-71) Zubrod PS=0: 27 AO: 13 pts Mixed glioma oligo-dominant: 13 pts Mixed glioma, oligo=astro: 10 pts Mixed glioma, astro-dominant: 1 pt Mixed glioma, not specified: 2 pts 1p/19q codeletion: 60.7% (23/36) MGMT methylation: 80% (16/20)	Preradiation TMZ (150 mg/m^2/day, 7 on/off) ×6 cycles followed by RT (59.4 Gy) + concomitant TMZ (75 mg/m^2/day) 32 pts completed RT-TMZ	Whole cohort Pre-RT response rate: 32% (CR: 6%; PR: 26%) Pre-RT progression rate: 10% Only and 13 pts had progressed and 8 pts have died at the time of the analysis According to the molecular data All pts with 1p/19q codeletion free of PD at 6 mo All pts with MGMTpromoter methylation free of PD at 6 mo
Mikkelsen 2009 Description of the cases with CT+RT only	12 patients without 1p/19q codeletion Median age: 32 (18-81) Median KPS: 90 (60-100) Gross total resection: 3 pts (25%) Subtotal resection: 8 pts (66.7%) Biopsy: 1 pt (8.3%) AO: 3 pts (25%) AOA: 9 pts (75%)	Pre-radiation TMZ (150-200 mg/m^2/day) ×2-4 cycles followed by chemo-radiation (RT 60 Gy) + concomitant TMZ (75 mg/m^2/day)	Whole cohort PFS: 13.5 months PFS 6 months: 75% (95% CI 40.8-91.2) PFS 12 months: 58.3% (95% CI 27.0-80.1) Median PFS: 13.5 months (95% CI 10.6-39.9) OS 12 months: 83.3% (95% CI 48.2-95.6) OS 24 months: 83.3% (95% CI 48.2-95.6)
Kim 2011	33 patients (2003-2008) Median age=41 years (17-60) KPS ≥70: 88% >75% tumor resection: 58% AA: 21 pts (64%) AO: 12 pts (36%) 1p/19q codeletion: 53% (8/15) MGMT promoter methylation: 55% (11/20)	RT (59.4 Gy) + concomitant TMZ (75 mg/m^2, 7 days/week) followed by adjuvant TMZ (150-200 mg/m^2 5 days/28) cycles Median # of completed cycles of adjuvant TMZ: 6.2 (2-12)	Whole cohort Response rate: 61% Mean PFS: 48.7 mo (95% CI 36-61.4) Mean OS: 66.4 mo (95% CI 0.02-0.73) According to the molecular data Not done because of the small number of patients
Minniti 2013 Minniti 2014	84 patients (2004-2011) Median age: 44 years (22-67) Complete/subtotal resection: 47 pts (56%) Incomplete resection: 29 pts (33%) Biopsies: 8 pts (11%) Median KPS: 90 (60-100) AO: 59 pts (70%) AOA: 25 pts (30%) Initial grade 2: 24 pts (28.5%) 1p/19q codel: 57% (48/84) IDH1 mutation: 63% (52/82) MGMT promoter methylation: 74% (57/77)	RT (59.4 Gy) + concomitant TMZ (75 mg/m^2 7 days/week) followed by adjuvant TMZ (150-200 mg/m^2 5 days every 28 days) (up to 12 cycles)	Whole cohort Response rate: 49% (CR: 14%, PR 25%, stabilization 40%) Median OS 55.6 mo (95% CI 37-76) 5 year survival: 48% (95% CI 35-65) Median PFS: 45.2 mo (95% CI 25.5-66.5) 5 year PFS rate: 41% (95% CI 31-53%) According to the molecular data Median OS 1p/19q codel: Not reached versus 1p/19q noncodel: 34 mo (P=0.0001) IDH1 mutated: Not reached versus IDH1 nonmutated: 31 mo (P=0.0001) MGMT promoter methylation: 78 mo versus MGMTP unmethylated promoter: 30 mo (P=0.0001) Median PFS 1p/19q codel: Not reached versus 1p/19q noncodel: 16 mo (P=0.0001) IDH1 mutated: 76 mo versus IDH1 nonmutated: 23 mo (P=0.0001) MGMTP methylated: 65 mo versus MGMTP unmethylated: 16 mo (P=0.0001)

Table Contd...

Table 4: Continue...

Authors	Patient and tumor's characteristics	Regimen	Response of the whole cohort and according to the molecular status
Lassman 2011* Description of the cases with CT+RT only	528 patients (1981-2007) Median age: 43 years (20-83) KPS ≥70: 453 (86%) Resection: 466 (88%) AO: 262 pts (50%) AOA: 266 pts (50%) Prior LGG: 64=12% 1p19q codeletion: 40% (133/334)	CT+RT (*n*=528) CT followed by RT (*n*=132) RT+concurrent CT (*n*=112) RT followed by CT (*n*=281) Doses not detailed	Whole cohort Median OS: 7.3 years (95% CI: 5.9-8.4) Median TTP: 4.1 years (95% CI: 3.5-5.4) According to the molecular data 1p/19q codeletion: Median OS: 8.4 (7.1-16.1) - Median TTP: 7.2 (5.2-8.1) 1p/19q noncodeletion: Median OS: 5 (3.8-6.7) - Median TTP 3.1 (2.5-4.3)
Shonka 2013 Description of the cases with concomitant RT-CT only	52 patients AA (2003-2009) Median age: 42 years (18-69) Median KPS: 90 (60-100) Biopsy: 17 (36.2%) Resection: 30 (63.8%) Unknow: 5	RT (60 Gy) + Concurrent CT drug: BCNU: 3 (5.8%) TMZ: 49 (94.2%)	Whole cohort Median PFS: 1.5 years 3 years estimated PFS: 0.37 (0.24, 0.50) Median OS: 4.8 years 3 years estimated OS: 0.68 (0.53, 0.79)

AO: Anaplastic glioma, AOA: Anaplastic oligoastrocytoma, AA: Anaplastic astrocytoma, LGG: Low-grade glioma, codel: Codeletion, IDH: Isocitrate dehydrogenase, MGMTP: O-6-methylguanine-DNA methyltransferase, pts: Patients, PS: Performance status, KPS: Karnofsky performance status, CR: Complete response; RR: Response rate, PD: progressive disease, PFS: Progression-free survival, OS: Overall survival, TTP: Time to progression, RT: Radiotherapy, CT: Chemotherapy, TMZ: Temozolomide, #: Number

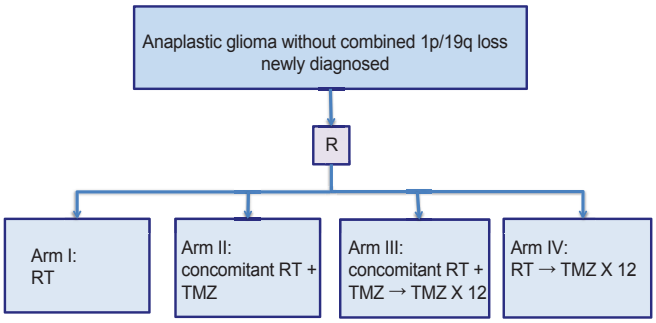

Figure 4: CATNON trial design. R: Randomization; RT: Radiotherapy, TMZ: Temozolomide

population, the standard initial treatment remains RT or CT alone.[25,51,318]

Treatment of recurrent anaplastic glioma

The treatment of recurrent AG requires a consideration of patient age and PS, the magnetic resonance imaging (MRI) characteristic of the glioma at progression (local, diffuse, eloquent location or not), response to initial treatment, and time between initial treatment and first progression. When feasible re-resection is often suggested notwithstanding limited data to suggest benefit from repeat surgery. Occasional patients may be candidates for re-irradiation but again there is a paucity of data to commend this therapy and only a minority of selected patients are eligible for this approach. Consequently systemic therapy continues to be the most often utilized treatment in recurrent HGG.

No SOC regarding choice of CT is universally agreed upon for the treatment of recurrent AG. In NOA-4, patients initially treated with TMZ or PCV received RT at first progression. In patients initially treated with RT, at first progression patients were treated with either TMZ or PCV.[317] In the EORTC 26951 and RTOG 9402, different CT regimens (TMZ or PCV depending upon initial treatment) were used at progression. In general, a similar CT philosophy (rechallenge with TMZ, lomustine or PCV, or BEV) is used for recurrent AG as is used for recurrent GB as is discussed below.[25,51]

In the EORTC 26972, a phase II prospective nonrandomized trial, the role of TMZ in recurrent AO and AOA after prior PCV CT and RT was investigated. Twenty-eight evaluable patients, enrolled following first recurrence after prior adjuvant RT + PCV or adjuvant RT followed by PCV administered at first recurrence, received TMZ for 12 cycles. In patients with proven anaplastic oligodendroglial pathology, the response rate was 25% (7/28; 95% CI 11–45%). Median time to progression for responding patients was 8.0 months. Of the 24 patients evaluable for response to prior PCV CT, 12 (50%) had initially responded to PCV (5 complete response and 7 partial responses). No difference was observed in response rate to TMZ regardless of prior PCV response.[24]

The role of BEV in the treatment of recurrent AG remains to be determined. The available data for patients with AG treated with BEV are derived primarily from retrospective studies that demonstrate response rates from 15% to 79%, median PFS from 5.0 to 13.4 months, and median OS from 6.8 to 12.6 months[63,64,80,105,128,160,195,211,226,236,262,266,287,341] [Table 5]. Interpretation of these data is difficult because the studies often combined WHO grade III and IV tumors and described a variety of combinations of BEV with other cytotoxic drugs such as irinotecan (IRI), carboplatin, and TMZ. In a phase II trial, Kreisl assessed the activity of BEV as single agent in 31 patients with

recurrent AG. Patients received a median of two prior CT regimens before treatment with BEV (range 0–7). At study entry, 58% of patients were on steroids. Thirteen (43%) patients achieved a partial response. Median PFS was 2.93 months (95% CI: 2.01–4.93), 6-month PFS was 20.9%, and median OS was 12 months. Of the 31 patients in this study, 6 had an OS greater than 24 months. The most common grade ≥3 treatment-related toxicities were hypertension, hypophosphatemia, and thromboembolism.[160] In historical controls, patients with recurrent AG have a median survival of 9–11.8 months and a median PFS 2–6 months.[167,332] Ongoing trials will help to determine the role of BEV in recurrent AG. The EORTC 26091 randomized trial, TAVAREC (NCT01164189), will determine whether TMZ is more effective when given with or without BEV at first recurrence in tumors that demonstrate contrast enhancement by MRI, in patients with either initial grade II or III noncodeleted glioma. In this study, TMZ will be administered orally on day 1–5, 150–200 mg/m^2, and will be repeated every 4 weeks up to 12 cycles. BEV will be administrated at a dose of 10 mg/kg bodyweight on day 1 and day 14 of a 4-week cycle and administered up to 12 cycles. The aim is to establish the activity of TMZ alone or when combined with BEV in patients with recurrent grade II or grade III glioma without 1p/19q co-deletion. The primary objective is OS at 1 year. Secondary objectives include safety, QoL, and cognition.

GLIOBLASTOMA

Histological data and molecular data

GB is considered by the WHO classification as a single histological entity including described variants such as gliosarcoma, GB with oligodendroglial features, and small cell GB. Nonetheless considerable variability in the response to treatment and in prognosis is observed.[187,306] Molecular markers and gene expression profile now compliment the WHO classification and assist with respect to prognostication. Two molecular markers are of particular interest: The MGMT promoter methylation status and the presence or absence of the IDH 1 mutation.

MGMT is a single enzyme DNA repair protein that removes alkylation or methylation adducts from the O6 position of guanine, a cytotoxic lesion induced by alkylating agents. Methylation of the MGMT gene promoter results in epigenetic translational silencing of the methyltransferase, resulting in increased tumor senstivity to alkylator-induced genotoxic injury. MGMT promoter is methylated in 32–45% in newly diagnosed GB.[69,107,109,121] Additionally, MGMT status appears to be retained in recurrent GB.[92,110,307] Various methods for MGMT testing have been evaluated.[31,78,227,228,232] Methylation-specific PCR is recognized as the method of choice for the evaluation of the MGMT status.[130,307,308] The prognostic role of the MGMT promoter methylation status in GB is now well established.[129,130,281] The predictive role of MGMT promoter methylation and response to TMZ has also been established in several studies.[109,121,246,308] Nevertheless and despite its prognostic and predictive value, the clinical utility of MGMT remains poor primarily because of the lack of therapeutic options for patients with unmethylated GB. The only exception regarding the clinical utility of MGMT determination is in the management of elderly patients with GB. Indeed, two randomized trials in newly diagnosed elderly GB patients demonstrated that a methylated MGMT promoter is predictive for benefit

Table 5: Bevacizumab in recurrent anaplastic glioma

Author	Trial design	nb pts	Regimen	Median PFS (months)	6 months PFS	Median OS (months)
Desjardin 2008	Prospective	AG: $n=33$	BEV+IRI	7.5	55%	16.2
Norden 2008	Retrospective	AG: $n=21$	BEV+various CT	6 for the entire cohort with GBM	32%	9.1 for the entire cohort with GB
Chamberlain JNO 2009	Retrospective	AA: $n=31$	BEV	7	60%	9
Chamberlain Johnston Cancer 2009	Retrospective	AO: $n=22$	BEV	8	68%	8
Taillibert 2009	Retrospective	AO/AOA: $n=25$	BEV+IRI	4.6	42%	ND
Reardon 2009	Prospective	AG: $n=32$	BEV+VP16	6	41%	15.7
Zuniga, 2009	Retrospective	AG: $n=13$	BEV+IRI	13.4	78.6%	ND
Poulsen 2009	Retrospective	AG: $n=47$	BEV+IRI	5.5	32%	8
Sathmonsumetee 2010	Prospective	AG: $n=32$	BEV+erlotinib	5.4	44%	10.1
Hofer 2011	Retrospective	AG: $n=49$	BEV+various CT	ND	ND	9.1
Kreisl 2011	Prospective	AG: $n=31$	BEV	2.9	20.9%	12
Moller 2012	Prospective	AG: $n=33$	BEV+IRI	3.7	30%	6.9
Gil 2012	Retrospective	AG: $n=36$	BEV+IRI	4.6	43%	11.2
Seystahi 2013	Retrospective	AG: $n=13$	BEV or BEV+IRI	3.3/8.1	25/60%	7.4/18.5

Nb pts: Number of patients, PFS: Progression-free survival, OS: Overall survival, GB: Glioblastoma, AG: Anaplastic glioma, AA: Anaplastic astrocytoma, AO: Anaplastic oligodendroglioma, AOA: Anaplastic oligoastrocytoma, BEV: Bevacizumab, IRI: Irinotecan, CT: Chemotherapies

from TMZ alone compared with RT alone.[181,321] In elderly patients considered for treatment with RT or TMZ alone, MGMT testing should be determined to assist in treatment decision making.[307]

Although primary and secondary GBs are histomorphologically identical, these tumors develop though different genetic pathways. The status of the IDH 1/2 (mutation or wild type) distinguish between primary (IDH wild type) and secondary GB (IDH mutated). Point mutations at codon 132 of IDH1 and codon 172 of the IDH2 gene occur in more than 80% of low-grade gliomas and secondary GB, which represent a minority of all GB (<8%).[115,130,209,259,335] IDH1/2 mutations result in the production of d-2-hydroxyglutarate, a oncometabolite, instead of α-ketoglutarate.[75,291] Furthermore the IDH status does not appear to change during the progression from lower grade glioma to secondary GB.[130] Mutated IDH can easily be detected by IHC or PCR/sequencing, and magnetic resonance spectroscopy may also detect d-2-hydroxyglutarate associated with IDH1/2 mutant tumors.[55,70,130,307] IDH1 mutations, or less frequently IDH2 mutations, have been shown to be a prognostic marker in HGG.[130,209,259,335,340] Mutations in the telomerase reverse transcriptase (TERT) promoter occur in 74.2% of all GB. Patients with TERT promoter mutations are predominately primary GB and are associated with a poor OS (11.5 months). Patients with IDH1/2 mutations and therefore secondary GB are associated with an intermediate survival (57 month OS). Patients with GB manifesting both TERT promoter and IDH1/2 mutations predominately exhibit GB with oligodendroglial features and exhibit the longest survival (median OS of 125 months).[147] However, no predictive role of IDH1 status has been determined and consequently treatment of a secondary GB is similar to that of a primary GB.[130,307] IDH1/2 wild-type GB by contrast undergo further genomic changes at recurrence.[246] Importantly, IDH mutations are expressed only in tumor cells and appear to be a druggable target. There is currently a single drug that targets mutated IDH1 (AG-210) and new trials with this agent are just commencing.[36,75,225,249,304]

Other markers are of interest in GB include the ATRX mutation, which is observed in 57% of the secondary GB.[139] The tumor-specific epidermal growth factor receptor variant III (EGFRvIII), present in 20% of primary GB, is another potential druggable target. Expression of EGFRvIII results in constitutive activation of the receptor's tyrosine kinase activity and is the antigen target of the peptide vaccine rindopepimut.[14,124,130,331] BRAF mutations, another druggable target, have been found especially in the epitheloid variant of primary GB (a rare and uniform morphologic subtype of GB).[130,154,206] The genetic alterations in primary and secondary GB are outlined in Table 6.

Verhaak *et al*. using The Cancer Genome Atlas (TCGA) data, defined a novel gene-expression-based molecular classification of GB that includes *classical*, *mesenchymal*, *proneural*, and *neural* subtypes. Aberrations and gene expression of EGFR, Neurofibromin 1 gene (NF1), and platelet-derived growth factor receptor A (PDGFR-A)/IDH1 each define the *classical*, *mesenchymal*, and *proneural* subtypes, respectively. The *classical* subtype is characterized by EGFR amplification and the absence of p53 mutations and PDGFR-A amplification. The *mesenchymal* subtype is characterized by deletions or mutation of NF1. The *proneural* subtype is characterized by IDH1 and p53 mutations and PDGFRA amplification. The *neural* subtype was typified by the expression of neuronal markers. The molecular subtypes have been shown to be associated with differing survival and varying response to therapy with the best outcome seen in the *proneural* subtype.[50,174,294] In a recent cohort of 941 HGG, 32.73% were *proneural*, 15.09% *neural*, 19.77% *classical*, and 32.41% *mesenchymal*.[174] Proteomic analysis have also revealed three subtypes of expression and activation of proteins in glioma-relevant signaling pathways associated with EGFR activation, PDGFR activation and loss of the RAS regulator NF1 [Table 7].[49]

Upfront treatment of glioblastoma

Standard of care

The current SOC for patients with newly diagnosed GB is maximum safe surgical resection followed by concurrent TMZ (75 mg/m^2/day for 6 weeks) and RT (60 Gy in 30 fractions) and then 6 maintenance cycles of post-RT adjuvant TMZ (150–200 mg/m^2/day for consecutive 5 days therapy every 28 days, standard 5/28 TMZ [sdTMZ]) according to the results of the pivotal trial by the EORTC/National Cancer Institute

Table 6: Genetic alterations in primary and secondary glioblastoma

	Primary glioblastoma (%)		Secondary glioblastoma (%)	
	Clinical criteria	Genetic criteria: IDH1 wild type	Clinical criteria	Genetic criteria: IDH1 mutated
IDH1 mutations	4-7	0	73-88	100
TP53 mutations	17-35	19-27	60-88	76-81
ATRX mutations	4-7		57-80	
EGFR amplification	36-45	35-39	0-8	0-6.5
CDKN2A deletion	31-52	30-45	19-20	7-22
PTEN mutations	23-25	24-26	4-12	0-8
19q loss	6	4	54	32
1p/19q loss	2-8		0-13	
10p loss	47		8	
10q loss	70	67	63	73

IDH: Isocitrate dehydrogenase, EGFR: Epidermal growth factor receptor, ATRX: Alpha-thalassemia/mental retardation syndrome X-linked, PTEN: Phosphatase and tensin homolog, CDKN2A: Cyclin-dependent kinase inhibitor 2A

of Canada (NCIC) Clinical Trials Group, in which both PFS and OS were improved with combination therapy (RT + TMZ) relative to RT only.[281] Furthermore this trial in a retrospective analysis seggregated outcome of GB by MGMT methylation and showed improved outcome in the subset with methylated MGMT promoter regardless of treatment (RT or RT + TMZ) and as well, markedly improved outcome in this cohort with combination therapy.[121] This improvement in methylated tumors with receipt of RT + TMZ was recapitulated in the RTOG 0525 study.[109] Notwithstanding these findings all new GB continue to be treated with combination therapy (RT + TMZ) despite the limited if any benefit of this therapy (RT + TMZ) in the larger cohort of GB patients with unmethylayed MGMT tumors.

Elderly glioblatoma

The elderly, defined as individuals aged >65 years, comprise at least 20% of newly diagnosed GB patients.[60] In a retrospective cohort of 293 patients older than 65 years, multivariate analysis revealed a benefit for the RT+ concomitant and adjuvant CT (TMZ) treatment.[23]

Importantly this group of patients were not evaluated in the above-mentioned EORTC/NCIC trial as inclusion criteria mandated age to be <71 years, consequently the value of RT + TMZ has never been prospectively evaluated.[133] Two randomized studies in elderly patients first demonstrated that involved-field fractionated RT (50 Gy in 28 fractions) is superior to supportive care only (median survival: 7 vs. 4 months) and that conventional fractioned RT (total dose 60 Gy in 30 fractions) is comparable to hypofractionated RT (40 Gy in 15 fractions).[144,248] The German NOA-08 study demonstrated that upfront dose dense TMZ (TMZ 100 mg/m^2/day for 7 consecutive days every 14 days, dose dense temozolomide [ddTMZ]) was noninferior to conventional fractioned RT (60 Gy in 30 fractions) alone in elderly patients with HGG (defined as age >65 years, Karnofsky performance status [KPS] ≥60), with median survival of 8.6 vs. 9.6 months.[321] As, the RTOG 0525 and Medical Reseach Council studies demonstrated no survival benefit to post-RT ddTMZ[38,109] and noted the increased toxicity of ddTMZ regimens compared with sdTMZ,[60,305] there is now general agreement that sdTMZ is the preferrable and equivalent TMZ drug schedule. The randomized Nordic trial compared sdTMZ to standard dose RT (60 Gy in 30 fractions) to hypofractionated RT (30 Gy in 10 fractions) in elderly GB patients (defined as age >60 years and PS ≥50) and demonstrated that TMZ and hypofractionated RT were superior to standard dose RT (median survival 8.3 vs. 7.5 vs. 6 months) and should be considered as standard treatment options in these patients.[181] Based on these prospective studies, it would appear that treatment with either sdTMZ or hypofractionated RT is equivalent for elderly GB patients. Both studies suggested that TMZ is particularly beneficial in the MGMT-methylated tumour subset, and consequently MGMT promoter methylation status in elderly patients is recommended as it determines treatment allocation (hypofractionated RT only for unmethylated tumors; TMZ only for methylated tumors). The currently open and randomized NCIC/EORTC (NCT00482677) phase III study of TMZ and short-course (hypofractioned) RT versus short-course RT alone in the treatment of newly diagnosed GB in elderly patients (>65 years of age, PS 0–2) is exploring the role of combination treatment in this population.

Two French studies evaluated treatment options in elderly GB patients with a poor PS. In the first single arm multi-institutional phase 2 study, patients with GB, age >70 years, 90% biopsy only and KPS <70, sdTMZ only treatment resulted in a median OS of 6 months.[220] In another study, no benefit of adding BEV to sdTMZ upfront was found.[244] The role of BEV and TMZ in elderly patients (≥70) with a newly diagnosed GB and a ≥60 PS score is currently ongoing in a USA phase II study (NCT01149850). Another randomized study (NCT01443676) is exploring the efficacy of BEV combined with RT compared with RT alone in the treatment of newly diagnosed GB in the elderly (age ≥ 65 years) with a > 60 PS status. The different treatment options in elderly GB patients and treatment results are outlined in Table 8. Importantly in this population, treatment should be adapted according to the general status of the patients with consideration of PS and co-existing medical comorbidities.

Dose of temozolomide

Dose dense schedules of TMZ (ddTMZ; alternating 7-days-on, 7-days-off [7/14] and 21-days on 7 off [21/28]) have been designed to deplete tumor MGMT levels and thereby improve activity of TMZ particularly in the MGMT unmethylated GB cohort. Nonrandomized studies in progressive or recurrent disease first reported treatment efficacy that compared favorably with the established sdTMZ schedule without an increase in

Table 7: Molecular classification of glioblastoma

GB	Genetic/epigenetic profile				
	DNA methylation (G-CIMP)	Gene expression	Characteristic gene mutations	Proportion all GB (%)	Median overall survival (months)
1	+	Proneural	IDH1	6-10	36-48
2	-	Mesenchymal	NF-1	30	12
3	-	Others	EGFR	60	15

GB: Glioblastoma, IDH: Isocitrate dehydrogenase, NF-1: Neurofibromin 1, EGFR: Epidermal growth factor receptor; CIMP: CpG island methylator phenotype

Table 8: Elderly glioblastoma trials

Author	Age (years)	KPS	Number of pts	Treatment								Median suvival
				RT60	RT50	RT40	RT34	RT40+TMZ	TMZ	RT40+BEV	Supportive care alone	
Roa 2004												
	≥ 60	≥ 50	100	X (*n*=51)		X (*n*=49)						5.1/5.6
Keime Guibert 2007												
	≥ 70	≥ 70	85		X (*n*=38)						X (*n*=42)	29.1 w/16.9 w
Wick 2013												
	>65	≥ 60	373	X (*n*=178)					X (n=195)			9.6/8.6
Malmström 2013												
	60-69		100	X (*n*=59)			X (*n*=58)		X (*n*=51)			7.5/7/7.9
	70+		191	X (*n*=41)			X (*n*=40)		X (n=42)			5.2/7.1/9
Gallego Perez-Larraya 2011												
	70+	<70	70						X			6 (25 w)
Reyes-Botero 2013												
	≥ 70	<70	66						+ BEV			24 w
NCIC - NCT00482677												
	≥ 65	≥ 70	562			X		X				Ongoing
NCT01443676												
	>65	≥ 60				X				X		Ongoing
NCT01149850												
	≥ 70	≥ 60							+ BEV			Ongoing

KPS: Karnofsky Performance Status; n: Number of patients; RT: Radiotherapy; BEV: Bevacizumab; TMZ: Temozolomide; w: Weeks; Yrs: Years, pts: Patients, RT: Radiotherapy, TMZ: Temozolomide, BEV: Bevacizumab, NCIC: National Cancer Institute, Canada

treatment-related toxicity.[38,314] sdTMZ (n = 112) was then compared in a randomized study to ddTMZ (n = 111) or PCV (n = 224) in first recurrence after RT only in CT-naive HGG.[38] Toxicities were similar between the three groups. Survival was not different between PCV and TMZ. Three-month PFS were similar while comparing sdTMZ and ddTMZ (P = 0.745), but sdTMZ improved overal PFS (P = 0.023) and global QoL (C30 EORTC QoL questionnaire) (P = 0.005).

The RTOG 0525 phase III trial prospectively compared the sdTMZ schedule and the ddTMZ schedules in the post-RT adjuvant setting. A total of 833 patients were initially treated with RT (60 Gy administered in 2 Gy fractions) and concomitant TMZ. After completion of concomitant chemoradiotherapy, patients were randomly assigned to sdTMZ (n = 411) or ddTMZ (75–100 mg/m2 days 1 through 21 of a 28-day cycle) (n = 422) for 6–12 cycles. The median OS (16.6 vs. 14.9 months, P = 0.63) and the median PFS (5.5 vs. 6.7 months, P = 0.06) were not significantly different between the two arms of treatment. As mentioned above, patients with a MGMT promoter methylated tumor had improved OS (21.2 vs 14 months, P < 0.001) and PFS (8.7 vs. 5.7 months, P < 0.001), but without any significant difference between the two post-RT TMZ treatment arms. Treatment was interrupted for toxicity or intercurrent illness in 49 patients (12%) on the sdTMZ and 94 patients (22%) on the ddTMZ arm. There was increased grade ≥3 toxicity in ddTMZ arm (34% vs. 53%, P < 0.001).[109] Moreover, a greater deterioration was observed in the dose-dense arm from baseline to cycle 4 in the Global Health and Motor Function subscales (EORTC QLQ-C30/BN20) as well as in overall symptom burden, overall symptom interference, and activity-related symptom interference subscales (MDASI-BT).[10] These results were practice changing as now the sdTMZ regimen is recommended in essentially all glioma treatment scenarios.[305]

Length of post-RT TMZ treatment

The defined length of the TMZ adjuvant phase is 6 months based on the results of the EORTC/NCICC trial wherein only 47% of patients were able to complete the prescribed 6-month post-RT TMZ treatment.[281] However and despite no data to support longer post-RT TMZ treatment, 12-month adjuvant treatment is often employed particularly in the USA. Currently no trial

has yet to compare differing durations of post-RT TMZ in a randomized fashion and only several retrospective cohorts have assessed the role of additional cycles of TMZ with respect to survival. Reportedly good tolerance without significant toxicity following prolonged adminsitration of TMZ (12 months) was reported in a cohort of 46 patients. Similar findings were seen in a small cohort of three patients treated with 90 months of post-RT TMZ.[146,180] Severe hematological toxicity due to TMZ when seen occurs early as with most cytotoxic systemic chemotherapies.[265,296] In series of small case reports, prolonged administration of adjuvant TMZ was reported in newly diagnosed GB.[76,120,250,265] The median PFS ranged from 7 to 28.4 months.[76,120,250,265] In another retrospective study, a total of 114 patients with newly diagnosed GB were treated with chemoradiotherapy followed by adjuvant TMZ until progression or toxicity. A median of 6 cycles (range, 1–57) of adjuvant TMZ was administered. PFS and OS directly correlated with the amount of TMZ cycles (each $P < 0.0001$).[265] In another retrospective cohort evaluating 52 patients with newly diagnosed GB, TMZ for more than 6 cycles was an independent prognostic factor for both PFS and OS.[250] In a French retrospective study, the PFS in patients receving 6 cycles of TMZ ($n = 38$) and in patients receiving at least 9 cycles ($n = 20$) were 82.9% versus 100% at 12 months, 52.5% versus 73.3% at 18 months, 25.7% versus 65.9% at 24 months, and 11.0% versus 43.5% at 36 months, respectively. Prolonged treatment improved PFS ($P = 0.03$) and OS ($P = 0.01$) in multivariate analysis without a significant increase in toxicity.[76] Nevertheless, numerous bias are inherent in these nonrandomized cohorts as, for example, only patients with a response or a stable disease at the end of the sixth cycle of TMZ were selected for prolonged TMZ treatment, whereas in the initial trial of Stupp, 53% of patients did not complete the planned 6 cycle of post-RT TMZ (with 22% of them never starting on adjuvant TMZ).[281] In addition data on other prognostic factors (age, extent of resection, PS) are often not avaliable.

Gliadel (carmustine) implantable wafers

Biodegradable carmustine (BCNU) wafers, implanted into the tumor bed after near or complete tumor resection, has been approved by the US Food and Drug Administration (FDA) for first-line treatment of GB and AG. Nevertheless, the use of carmustine wafers remains controversial due to the questionable survival benefit and potential adverse events.[46] The role of the carmustine wafers was explored in a single phase III trial in patients with newly diagnosed GB. A total of 240 patients were randomly assigned to either BCNU or placebo wafers at the time of primary surgical resection. All patients were treated with RT only after surgery. The median OS were 13.9 vs. 11.6 months ($P = 0.03$) in the BCNU wafer and the placebo group, respectively. A 29% absolute reduction in the risk of death was seen in the treatment group. In multivariate analysis, the carmustine wafer treatment effect remained positive with a risk of reduction of 28% ($P = 0.03$). Time to decline in KPS and neurocognitive measures (determined by mini-mental status examination) were statistically prolonged in the BCNU wafer treated group ($P \leq 0.05$). Cerebrospinal fluid leak and intracranial hypertension were more frequent in the BCNU wafers groupe (5% vs. 0.8% and 9.1% vs. 1.7%, respectively).[312] However, this study had several methodological problems and the frequency of adverse events such as brain edema, infection, and seizures, precluded wide adoption of this treatment.[217] Furthermore, when central pathology review was performed and patients were excluded if non-GB histology was determined, the OS benefit between the two arms disappeared suggesting little benefit to BCNU wafer implanation. In addition, the study was designed before the adoption of the now standard RT and TMZ treatment for newly diagnosed GB. A randomized study comparing the RT + TMZ with or without carmustine wafers has never been performed although numerous retrospective and prospective single arm studies have evaluated the combination carmustine wafers, TMZ and RT.[4,13,33,35,59,116,153,169,184,185,190,210,218,257,258,311] Several reviews have also been published.[46,81,117,221,255,256]

In a review of the literature by Bregy, 19 studies with 795 patients were evaluated in whom carmustine wafters were used in conjunction with RT + TMZ. Survival appeared modestly improved and varied from 8.7 to 22.8 months, with a mean of 16.2 months. An adverse event ratio was calculated by computing the number of adverse events in the study per patient receiving carmustine wafers. In this review, the rate of complications was 42.7% suggesting that Gliadel wafers should be used with caution.[46] A decision to combine Gliadel with RT + TMZ should be determined on a case by case basis recognizing there is no defined sub-group of patients that benefit from such an approach. It is highly unlikely a randomized trial will be conducted to determine the utility of this approach.

Bevacizumab in newly diagnosed GB

BEV, a monoclonal antibody that targets vascular endothelial growth factor (VEGF) when used for recurrent GB, has resulted in the best response and 6-month PFS (PFS-6) rates when compared with previously used therapies as discussed below.[107,305] Consequently it was rationale to assess BEV in the upfront setting of newly diagnosed GB.

Two single institution phase II trials evaluated the role of BEV in newly diagnosed GB. In the study by Lai (concomitant RT, TMZ, and BEV followed by adjuvant TMZ and BEV) the median PFS was 13.6 months and the median OS was 19.6 months. In the study by Vredenburgh (concomitant RT, TMZ,

and BEV followed by adjuvant TMZ, BEV, and IRI), the median PFS was 14.2 months and the median OS was 21.2 months.[165,302] In both studies, comparison with contemporary institutional historical controls demonstrated an improvement in PFS but not in OS.

Three prospective randomized trials of upfront BEV have been completed and replicate the findings of the above-mentioned single arm phase II trials [Table 9]. The upfront GLARIUS study was designed based on the results of the study by Friedman in recurrent GB that showed promising efficacy of the combination of BEV plus IRI (BEV/IRI) with a PFS-6 of 50%.[100] The randomized (2:1) phase II GLARIUS study compared the combination of BEV/IRI versus TMZ as first-line therapy in MGMT nonmethylated GB.[127] Patients were randomly assigned to BEV 10 mg/kg q2w and concomitant RT (60 Gy, in 2 Gy fractions) followed by BEV 10 mg/kg q2w and concomitant IRI 125–340 mg/m^2 q2w (BEV/IRI) until progression (n = 119 patients) or standard treatment with TMZ 75 mg/m^2/day and concomitant RT (60 Gy, in 2 Gy fractions) followed by sdTMZ for 6 cycles (n = 66). The PFS-6 was significantly higher in BEV/IRI arm (79.8% vs. 41.3%, $P < 0.0001$). Median PFS were 9.74 versus 5.99 months, respectively, in the BEV/IRI group and the TMZ group, $P < 0.0001$. The mean daily steroid dose was lower in BEV/IRI arm than in TMZ arm. The preliminary data on OS showed a median of OS 16.6 months in 49.1% of patients in the BEV/IRI arm and 14.8 months in 49.1% of patients in the TMZ arm, $P = 0.031$. A higher rate of severe vascular events was observed in the BEV/IRI group and a higher rate of severe hematotoxicity was observed in the TMZ arm. In this study, BEV/IRI was superior to sdTMZ in newly diagnosed patients with MGMT nonmethylated GB.[127]

The RTOG 0825 study was a randomized phase III double-blind placebo-controlled trial evaluating BEV with or without SOC in patients with newly diagnosed GB. The co-primary objectives were OS and PFS. The secondary objectives included a comparison of toxicity, symptom burden, health-related (QoL) and neurocognitive function. The study design is detailed in Figure 5. A total of 637 patients were randomly assigned to receive either placebo (317 patients) or BEV (320 patients). At progression, salvage treatment was administrated in 56.1% of the patients in the BEV arm and in 71.9% in the placebo arm. Among these patients, BEV was continued in 25.5% in the BEV group and was administered in 48.3% of the control group. A trend for longer PFS was observed in the BEV group (10.7 vs. 7.3 months, $P = 0.07$). The median OS were similar in both groups (median, 15.7 and 16.1 months, $P = 0.21$). MGMT promoter methylation status was prognostic regardless of the treatment assignment. The nine-gene assay, designed in the RTOG 0525 trial and believed to profile the *mesenchymal* molecular subtype of GB, was not prognostic in either treatment arm. The significant prognostic value of the RTOG Recursive Partitioning Analysis (RPA) class was confirmed in this study both with respect to OS and PFS. The most common serious adverse events observed with BEV arm were hypertension, thromboembolic events, wound dehiscence, serious hemorrhage, intestinal perforation, and neutropenia. Importantly in this study, an increased symptom burden (MD Anderson Symptom Inventory–Brain Tumor Module [MDASI-BT]), a worse QoL, (EORTC QLQ-C30/BN20), and a decline in neurocognitive function (Hopkins Verbal Learning Test-Revised [HVLT-R], Trail Making Test [TMT], and Controlled Oral Word Association [COWA]) were significantly more frequent over time in the BEV treated group. These analyses were restricted to patients who were deemed to be progression-free at the time of the assessment. The study concluded that OS was not improved by upfront use of BEV and PFS though prolonged in the BEV group did not reach the prespecified improvement target. Thus, the use of BEV as first-line or as salvage therapy were equivalent in OS, and no clear benefit of initial treatment with BEV was demonstrated.[107]

Table 9: Bevacizumab in newly diagnosed glioblastoma

	Regimen	Number of patients (*n*)	PFS-6	Median PFS (mo)	Median OS (mo)
Vredenburgh 2011 Phase II	Concomitant RT TMZ BEV followed by adjuvant TMZ BEV irinotecan	75	NS (PFS12: 62.7%)	14.2	21.2
Lai 2011 Phase II	Concomitant RT TMZ BEV followed by adjuvant TMZ and BEV	70	PFS6: 88%	13.6	19.6
Herrlinger 2013 Phase II (GLARIUS)	Concomitant RT TMZ BEV followed by adjuvant BEV and irinotecan	182	PFS6: 79.8%	9.74	16.6
	Concomitant RT TMZ followed by adjuvant TMZ	56	PFS6: 41.3%	6	14.8
Gilbert 2014 Phase III (RTOG 0825)	Concomitant RT TMZ BEV followed by adjuvant TMZ and BEV	320	NS	10.7	15.7
	Concomitant RT TMZ followed by adjuvant TMZ	317	NS	7.3	16.1
Chinot 2014 Phase III (AVAglio)	Concomitant RT TMZ BEV followed by adjuvant TMZ and BEV	458	NS	10.6	16.8
	Concomitant RT TMZ followed by adjuvant TMZ	463	NS	6.2	16.7

RT: Radiotherapy, TMZ: Temozolomide, BEV: Bevacizumab, PFS: Progression-free survival, PFS6: Progression-free survival at 6 months, OS: Overall survival, ND: Not Stated, *n*: Number of patients, mo: Months

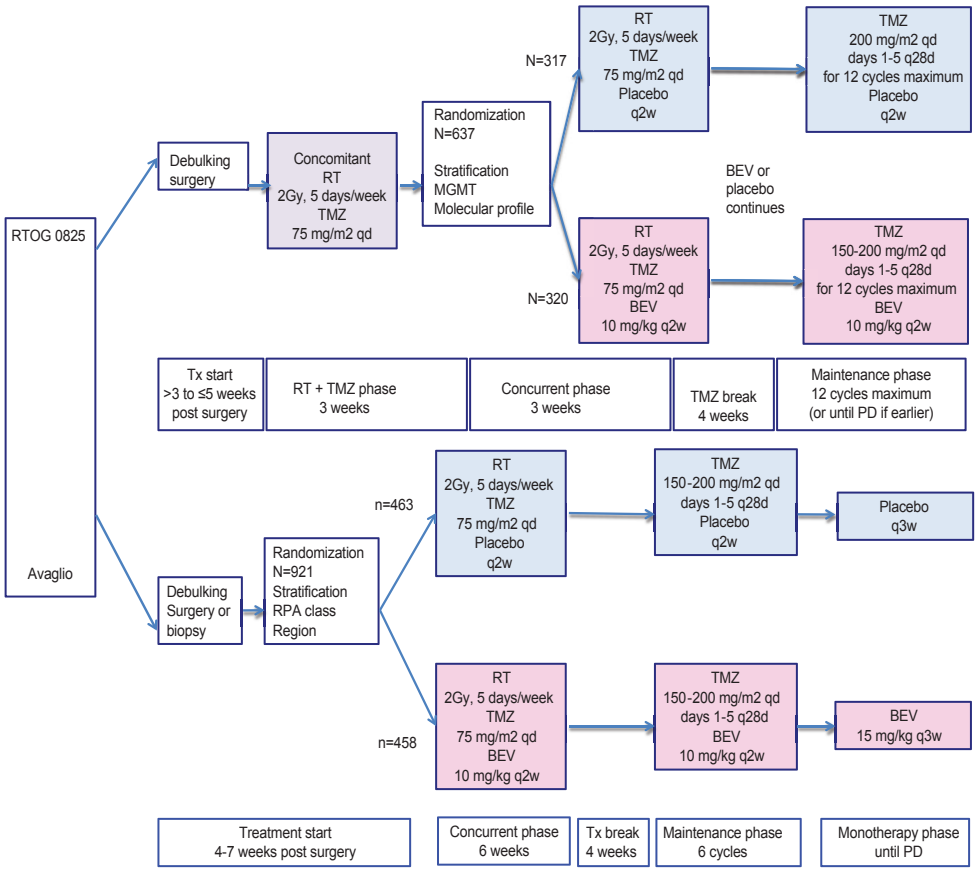

Figure 5: RTOG 0825 and AVAglio trial design. Tx: Treatment; RPA: Recursive Partitioning Analysis; RT: Radiotherapy; TMZ: Temozolomide; BEV: Bevacizumab; N: Number of patients; qd: Every day; q2w: Every 2 weeks; qd28: Every 28 days; q3w: Every 3 weeks; Tx: Treatment; PD: Progression disease

The AVAglio study, another double-blind randomized phase III trial of BEV plus TMZ and RT in newly diagnosed GB, is outlined in Figure 5. In this study, the two co-primary objectives were investigator assessed PFS and OS. The secondary objectives included PFS assessed by an independant review facility, the 1- and 2-year OS rates, QoL measures, and safety. A total of 458 patients were assigned to the BEV group, and 463 patients to the SOC group.[69] The pattterns of radiographic disease progression were similar between treatment arms.[316] At progression, salvage treatment was administrated in 62% of the patients in the BEV arm and in 69.3% in the placebo arm. Among these patients, BEV was continued in 23.6% in the BEV group and was started in 31.1% in the control group. The median PFS was significantly longer in the BEV group than in the placebo group (10.6 vs. 6.2 months, $P < 0.001$); however, the median OS did not differ between groups (16.8 and 16.7 months, respectively, $P = 0.10$). The respective OS rates with BEV and placebo were 72.4% and 66.3% at 1 year ($P = 0.049$) and 33.9% and 30.1% at 2 years ($P = 0.24$). The benefit in PFS with BEV according to the independent review was consistent with the benefit accorded by the investigator assessment. PFS and OS were not different between the two arms based on the MGMT promoter methylation status nor did other prognostic factors such as the extent of surgery, performance, age, and the RPA classification affect the results. The most common serious adverse events observed with BEV arm were hypertension, arterial thromboembolic events, proteinuria, and noncerebral hemorrhage. Grade 3-5 adverse events were observed in 51.3% of cases in the TMZ only arm and in 66.8% in the BEV arm, and grade 3 or higher adverse events were more often associated with BEV (32.5% vs. 15.8%).

Health-related QoL was explored by deterioration-free survival (DFS), including progressive disease as an event and time to deterioration (TTD) not including progressive disease as an event. In both cases, the global health status (QLQ-C30 and BN20) was better preserved in the BEV arm ($P < 0.0001$ and $P = 0.0041$ for DFS and TTD, respectively). The functional status (PS) was also better preserved in the BEV arm ($P < 0.0001$ and $P = 0.0153$ for DFS and TTD, respectively). The median time to corticosteroid initiation in patients off corticosteroids at baseline was shorter in the group without BEV (3.7 vs. 12.3 months, $P = 0.0018$). The rate of corticosteroid discontinuation in patients on steroids at baseline was 45% in the placebo group and 61% in the

BEV arm. The neurocognitive function (as assessed by mini-mental status) did not differ between arms. AVAglio concluded the addition of BEV significantly improved PFS, with better preservation of QoL but the final OS analysis did not reach statistical significance.[69]

The two trials, RTOG 0825 and AVAglio, were similar in design, patient characteristics, and the primary end points of PFS and OS.[94] Nevertheless, some methodological differences were oberved: In the RTOG 0825 study, patients who had undergone a biopsy were excluded, whereas biopsy patients could be randomized in the AVAglio trial; stratification factors differed between the two studies (MGMT status and molecular profile in the RTOG study vs. RPA class and geographic region in the AVAglio study); RT had to start within 3–5 weeks in RTOG study versus 4–7 weeks in AVAglio, BEV was initiated 3 weeks postinitial RT + TMZ in RTOG 0825 versus at initiation of RT + TMZ in AVAglio; BEV was not interrupted after RT in RTOG 0825, whereas a 4-week treatment break following completion of RT was used in AVAglio; the duration of post-RT therapy differed (a maximum of 12 cycles of TMZ + BEV was adminsitrated in RTOG 0825 vs. 6 cycles of TMZ + BEV followed by BEV only until disease progression in AVAglio). The radiological criteria also differed between the two studies: The adapted Macdonald response criteria, which anticipated some of the key features of the Response Assessment in Neurooncology (RANO) criteria were used in AVAglio versus standard Macdonald response criteria in RTOG 0825.[69,107]

In both trials, the PFS was prolonged by 3–4 months in the BEV arms, but no difference was observed in OS.[94,309] The gain in PFS was statistically significant in AVAglio but not in RTOG 0825. In both studies, nearly one-third of the patients in TMZ only arms reveived BEV at progression.[94] No particular subgroup, as defined by age, extent of resection, MGMT promoter methylation status, or the nine-gene assay used in the RTOG study derived benefit from BEV. Safety and tolerability data were comparable between the two trials.[309] The major difference between the two trials were the contradictory results on cognitive function and QoL. Whereas the RTOG 0825 trial showed a worsening of QoL and a decline in cognitive function before progression in the BEV arm, the AVAglio trial showed decreased steroid use, improvement in or prolonged maintenance of QoL and PS until progression in the BEV arm.[69,107,309] Despite methodological differences between the two studies, no clear reason was found to explain the divergence in QoL and cognition.[94] In a prospective trial of single agent BEV in recurrent GB, stabilization only was observed in health-related QoL and cognition in patients with a radiographic response to BEV not dissimilar to the conclusions of the RTOG 0825 study.[100] The use of updated imaging criteria in AVAglio limited the possibility of unrecognized progression that may be associated with a decline in QoL or neurocognitive function.[69] However, AVAglio was limited in assessing neurocognitive function based on the simple instruement used, that is, the mini-mental status examination. The deterioration observed in the RTOG 0825 study may suggest either unrecognized tumor progression or BEV-related neurotoxicity. The possible effect on health-related QoL and cognition of BEV or the combination BEV + RT remain unclear. Because use of BEV at GB disease progression seems not to be associated with diminished efficacy,[224] the data on QoL and cognition[94] as well as the lack of biomarkers predictive of response constitutes a major concern in the decision to use BEV as initial therapy in GB.

The prognosis of unresectable GB is particularly poor, with a median survival of 6–10 months.[137,208,231,278,281] The role of the upfront combination of BEV + TMZ was explored in a French association des neurooncologues d'expression française (ANOCEF) phase II trial for unresectable or multifocal GB.[178] A total of 41 patients were included and received up to 4 cycles TMZ at 200 mg/m^2 on days 1–5, and BEV at 10 mg/kg on days 1 and 15 of a 28-day cycle. Partial responses were observed in 24.4%, stable disease in 68.3%, and progressive disease in 2.4%. The median OS was 11.7 months, and the 6-month OS and 12-month OS were 70.7% and 48%, respectively. Treatment-related toxicities included seven grade 4 toxicities and one grade 5 toxicity. The response rate after neoadjuvant treatment was also evaluated in another randomized phase II trial comparing BEV/IRI versus BEV + TMZ, before, while and after standard RT in newly diagnosed GB. Response rate were 23% and 32%, respectively, in the BEV/IRI group and in the BEV + TMZ group. The median PFS were 7.3 and 7.7 months, respectively, in the these groups, the median OS were 15.1 and 11.8 months, respectively.[131] A randomized phase II trial (NCT01022918) failed to demonstrate an improvement in 6-month PFS while comparing BEV/IRI as neo-adjuvant and adjuvant treatment combined with TMZ-based chemoradiation in 120 patients with unresectable GB.[67] Whether neoadjuvant therapy is a promising strategy requires further validation.

Other systemic agents in newly diagnosed GB

Cilengitide, a selective αvβ3-αvβ5-integrin inhibitor, had shown promising results in phase II trials,[201,238,279] with benefit more pronounced in GB with methylated MGMT promoter. In the multicenter randomized open-label controlled phase III study CENTRIC, Cilengitide was combined with standard treatment for newly diagnosed GB only in patients with a methylated MGMT gene promoter. Patients were randomly assigned to Cilengitide 2000 mg iv twice

weekly + TMZ (75 mg/m^2/day)/RT (30 × 2 Gy) followed up by TMZ (150–200 mg/m^2 5 days/28 × 6 cycles) (n = 272) or TMZ (75 mg/m^2/day)/RT (30 × 2 Gy) followed by TMZ (150–200 mg/m^2 5 days/28 × 6 cycles) (n = 273). Median OS was 26.3 months in the Cilengitide arm and 26.3 months in the control group, P = 0.8623. Median PFS, assessed by the investigator, was 13.5 months in the Cilengitide arm and 10.7 in the control arm, P = 0.4570. Median PFS, assessed by an independent reviewer, was 10.6 months in the Cilengitide arm and 7.9 in the control arm, P = 0.918. Observed toxicity was consistent with previous reports of Cilengitide in recurrent GB. In conclusion, Cilengitide in the CENTRIC study did not improve PFS or OS and there was no subgroup of patients identified that sustained a clinical benefit from antiintegrin treatment. OS of this population with methylated MGMT promoter was comparable to prevoius reports.[280]

The CORE study was an open-label controlled randomized phase II study evaluating Cilengitide in combination with standard treatment for patients with newly diagnosed GB with unmethylated MGMT promoter. Patients were randomized 1:1 to a control-group (75 mg/m^2/day)/RT (30 × 2 Gy) followed up by TMZ (150–200 mg/m^2 5 days/28 × 6 cycles), Cilengitide-group (same standard regimen plus Cilengitide 2000 mg iv, 2×/week) or intensive Cilengitide group (same standard regimen plus Cilengitide 5×/week during TMZ/RT [weeks 1–6] and 2×/week in week -1 and >6 weeks).

A total of 265 patients were randomized (89 in the control group, 88 in the Cilengitide, and 88 in the intensive Cilengitide group). Median OS was 13.4 months in the control group, 16.3 months in the Cilengitide group (P = 0.033 vs. control), and 14.5 months in the intensive group (P = 0.38 vs. control). Median PFS per independent reviewer assessment was 4.1 months with control, 5.6 months with Cilengitide (P = 0.23 vs. control), and 5.9 months with intensive cliengitide (iP = 0.16 vs. control). Safety results were in line with the known Cilengitide safety profile. Cilengitide combination treatment showed a nonsignificant trend only in increasing OS in GB patients with unmethylated MGMT promoter, a finding that replicated the failure of Cilengitide to improve OS seen in the CENTRIC trial.[202]

CENTRIC and CORE trials determined that there is no survival advantage for adding anti-αvβ3-αvβ5-integrin therapy (Cilengitide) to SOC for patients with newly diagnosed GB. Nevertheless, other integrin inhibitors (β1, β8…) may represent another promising strategy.[56,243,251]

Enzastaurin, a potent inhibitor of protein kinase C-beta, an angiogenenic inhibitor and with direct cytotoxic activity against glioma cells, was evaluated before and concomitant with RT, followed by enzastaurin maintenance therapy in patients with newly diagnosed GB without MGMT promoter methylation in a multicenter open-label uncontrolled phase II (EORTC 26981/22981 NCIC CE.3). The PFS-6 was 53.6%. The median OS was 15.0 months for all patients, 3.9 months for patients with biopsy, 15.4 months for patients with partial resection, and 18.9 months for patients with complete resection. The safety profile in this study was as seen in previous trials and therapy was well tolerated. In this trial, PFS-6 of >55% was the prespecified endpoint and consequently failed to achieve its primary planned outcome.[323]

The results of a phase II open label trial (NCT01019434) evaluating RT and temsirolimus, a mTOR inhibitor, in patients with newly diagnosed GB without methylation of the MGMT gene promoter should soon be avaliable. In arm 1, standard treatment with TMZ (75 mg/m^2/day)/RT (30 × 2 Gy) followed up by TMZ (150–200 mg/m^2 5 days/28 days) administered up to 12 cycles is given. In arm 2, temsirolimus was given once one week before RT and then once every week (25 mg iv) concomitanty with RT. After completion of chemoradiotherapy, patients receive maintenance temsirolimus once weekly in the absence of disease progression and unacceptable toxicity. The primary outcome is OS at 1 year and the secondary outcomes were safety, PFS at 6 and 12 months, OS at 2 years, and correlative biomarkers.

Immunotherapy

A variety of vaccination strategies based on either whole GB tumor lysate or tumor-specific antigens (TSAs) have shown consistent safety as well as preliminary and encouraging immunogenicity and efficacy.[241] The most promising immune-based therapies will be reviewed here.

The most common EGFR mutation in GB is EGFRvIII, which results from an in-frame deletion of 267 amino acids in the extracellular domain.[162] EGFRvIII, a GB TSA is being targeted for vaccination-based therapy in GB. EGFRvIII is present in 20–25% of GB patients[14,124,330] but is absent on normal tissues.[21,166,196,328] Based on a single study, the presence of EGFRvIII was rarely associated with the occurrence of point mutations that would hinder the effect of specific antibodies against EGFRvIII.[17] EGFRvIII expression is only seen in primary GB,[152,125,215] and is found in nearly 50% of tumors with EGFR ampification.[306] A male predominance has also been reported.[124,125] The expression of EGFRvIII does not significantly affect survival of patients.[124,125,175,306] A variety of immunotherapies targeting EGFRvIII in GB are currently under investigation including monoclonal antibodies, dendritic cell (DC) vaccination

therapy, genetically modified T-cells, and peptide vaccines [Table 10]. Peptide vaccines are the most studied and well understood immunotherapies in GB.

Rindopepimut (PEPvIII-KLH; CDX-110; Celldex Therapeutics, Phillipsburg, NJ), is a peptide vaccine that elicits humoral and cellular immune responses.[126,197] Rindopepimut phase I and II clinical trials (VICTORI, ACTIVATE, ACT II, ACT III [NCT00458601]) have demonstrated significantly higher PFS and OS compared with historic controls in vaccinated patients with EGFRvIII-expressing GB tumors.[123] Side effects were minimal and mainly consisted of hypersensitivity reactions. An international randomized double-blind phase III trial (ACT IV) for newly diagnosed GB (NCT01480479) is currently investigating the efficacy and safety of the addition of rindopepimut to standard RT + TMZ. The primary outcome is OS. The secondary outcome measures are PFS, safety and tolerability (measured by neurological examination, adverse events, Eastern Cooperative Oncology Group performance status [ECOG PS], EORTC QoL questionnaires). Patients qualifying for study in addition to expressing EGFRvIII on the primary tumor need also demonstrate no evidence of progressive disease following chemoradiotherapy. All patients will receive TMZ (150–200 mg/m^2 for 5 days during each 28 day-cycles of TMZ for a minimum of 6 cycles or a maximum of 12 cycles) dependent upon drug tolerance or until tumor progression. Half of the patients will be randomly assigned to receive rindopepimut and half of the patients will be assigned to receive a control (keyhole limpet hemocyanin [KLH]) vaccine.

Another approach utilizes a DC vaccine, DCVax-L. The vaccine is manufacturated using the patient's autologous DCs loaded with a tumor cell lysate prepared from surgically resected primary tumor tissue. The DCs are collected by leukapheresis. Different methods to activate DC have been explored.[132] This approach offers a potential immunotherapy for every patient as no specific tumor antigen is required; however, does requires collection of tumor tissue at time of surgery, a delay of several weeks for vaccine generation, and often limited production of vaccine.[241] In preliminary studies, adverse events were mild and limited to localized reactions, low-grade fever and headache. Early preclinical studies and small clinical studies in patients as well as case reports have shown an antitumor effect suggesting DCVax-L induces an immune response.[7-9,12,90,122,172,173,216,229,253,268,297,298,313,329,333,334,336,337] A randomized double-blind phase III trial is ongoing to test the efficacy of DCVax-L (NCT00045968). The primary endpoint is PFS. Secondary endpoints include OS, safety, and induction of immune responses. Eligible patients must have newly diagnosed GB that requires resective surgery (required for production of the tumor lysate), and able to receive concomitant TMZ-based chemoradiotherapy. In addition, eligible patients need demonstrate absence of measurable disease progression after completion of primary chemoradiotherapy. Immunization starts following RT and is given at weeks 0, 2, and 4 and at months 2, 4, 8, 12, 18, 24, and 30. Cross over to DCvax-L is permitted at progression in patients otherwise randomized to the SOC arm only. A preliminary report suggests vaccination with a DC-based vaccine targeting glioma stem cells inducing an immune response in seven GB patients, another potential strategy for treating GB (NCT00846456).[193]

In conclusion, avaliable data regarding vaccine therapy for GB – whether utilizing whole cell lysates or synthetic antigens, suggest a therapy with excellent tolerance, that is, minimal toxicity and preliminary evidence of tumor immunogenicity and antitumor efficacy. Nevertheless, several issues need to be considered. First, immunotherapies have to date demonstraterd very little activity in other solid tumor cancers including metastatic melanoma. Second, a selection bias is observed in all studies to date as patients are required to have minimal residual disease following first surgery as well as after completing chemoradiotherapy, a subgroup of patients in which there is no well-defined survival data when treated with SOC. Third, all studies to date have enrolled a small number of patients with highly favorable prognostic features and been performed as single institution trials. Currently there are no identified biomarkers that predict for response or serve as surrogates for response to immunotherapy. Currently response to immunotherapies

Table 10: Upfront glioblastoma vaccine trials

Vaccine	Sponsor	Study design	Primary endpoint	Accrual randomization	Number vaccinations	Crossover at recurrence
DC Tumor lysate	NW Biotherapeutics	Randomized phase 2	Overall survival	240 2:1	10	Yes
Peptide EGFRvIII	Celldex (Act IV)	Randomized phase 2	Overall survival	450 1:1	6-12	No
DC 6 TAA	Immunocellular Therapeutics (ICT 107)	Randomized phase 2	Overall survival	200 1:1	8	No
DC HSP PC95	Antigenics	Single arm phase 2	Overall survival	55	17	ND

DC: Dendritic cells, EGFRvIII: Epidermal growth factor receptor variant III , HSP: Heat-shock protein, ND: Not detailed

utilizes the same assessment criteria as with systemic CT. There is a theoretical possibility that immune response specific criteria may be required as witnessed with ipilimumab therapy for metastatic melanoma.[330]

Heat-shock proteins (HSPs), which function as intracellular chaperones, can be used to deliver a variety of tumor antigens to antigen presenting cells for immune stimulation.[276] HSP90 alpha has a role in tumor survival and progression and is highly expressed in GB while absent in normal tissue and cell lines and may be a target for cancer therapy taking into acount its potential role in tumor progression and in the antiapoptotic pathway.[186] The safety and efficacy of an autologous HSP complex-96 (HSPPC-96) vaccine for patients with recurrent GB has been evaluated in a phase II study in adult patients with resected recurrent GB. The HSPPC-96 vaccine was safe and concluded further study of efficacy for the treatment of recurrent GB was warranted.[32]

Immune check point inhibitors such an anti-VLTA4 and antiprogrammed cell death 1 (anti-PD1) monoclonal antibodies are just begining clinical trials in GB. These targeted agents represent a novel immune therapy that has shown success in metastatic melanoma as well as nonsmall cell lung cancer. A trial using nivolumab (anti-PD1 antibody) with or without ipilimumab (anticytotoxic T lymphocyte antigen-4 [CTLA4] antibody) in recurrent GB has recently commenced (NCT02017717).

NOVOCURE trial

Alternating electric fields (AEF) have been shown to inhibit by an antimicrotubule mechanism of action, cancer cell growth *in vitro and in vivo* when applied at low intensity and intermediate frequency[150] Therapeutic applications were based on the hypothesis that nonhomogeneous electric fields generate unidirectional forces that disrupt the normal polymerization–depolymerization process of tubulin during mitosis.[150] The Novo TTF-100A (Novo Tumor Treatment Fields) device generates AEF with a frequency of 100-300 kHz and an intensity of 1–2 V/cm and is battery operated. An ongoing multicenter phase III designated EF-14 is assessing the NovoTTF-100A device in more than 700 patients with a newly diagnosed GB. All patients will undergo standard RT with concomitant TMZ and will then be randomized (2:1) one month after the completion of RT between adjuvant adjuvant TMZ plus NovoTTF-100A (>18 hours per day) versus adjuvant TMZ alone. This trial is based on a controversial phase III in recurrent GB that purportedly showed benefit with the device.[282] In the first interim analysis of the phase III, a total of 315 patients were randomized (210 in the NovoTTF + adjuvant TMZ). The median PFS were statistically different (7.1 vs. 4.0 months from randomization and 10.9 vs. 7.9 months from diagnosis, $P = 0.0014$). The median overall survival significantly differed as well (19.6 vs. 16.6 months from randomization and 22.6 vs. 19.6 months from diagnosis, $P = 0.034$) in ITT analysis. Grades 1/2 procedural complications were observed in 49% of the patients in the NovoTTF arm (43% of device site reaction) vs. 5% in the standard arm. Grades 1/2 skin tissue disorders were observed in 24% of the patients in the NovoTTF arm vs. 15% in the standard arm, grades 1/2 psychiatric disorders were noted in 33% of the patients in the NovoTTF arm vs. 15% in the standard arm.[283] Preclinical studies show a synergy between AEF and CT using the human glioma cell line U-118. In addition, results of a small pilot study of 10 newly diagnosed GB patients treated with the same combination given in the experimental arm of EF-14 demonstrated a median OS and PFS of 39 and 36.2 months, respectively.[151] These studies serve as the catalyst for the current randomized EF-14 trial.

Viral-based therapy

Viral therapies can be divided into two categories. Replication-deficient viral vectors are used as delivery vehicles for therapeutic genes with antitumor activities. Alternatively, replication-competent oncolytic viruses specifically infect and replicate in cancer cells and thereby, kill their tumor cell hosts sparing normal tissue, spread throughout the tumor, and thus have the potential to amplify themselves *in situ* and spread throughout the tumor. Additionally, tumor cell kill is also mediated by antitumor immune activation and disruption of tumor blood supply.[143,207,252]

The role of the cytomegalovirus (CMV) in GB remains controversial. CMV DNA and proteins are expressed in several types of human cancers[74,241,286] but not in normal surrounding tissues.[275] Sodeberg examined more than 250 cases of GB, of whom only 1 was CMV negative suggesting a high prevalence of CMV expression in GB.[272] Other work also demonstrated that glioma stem cells also express CMV antigens.[241] The prognostic value of CMV expression in GB was evaluated in a cohort of 75 patients. The median OS was 33 months in those with low-grade CMV infection and 13 months in those with high-grade CMV infection ($P = 0.04$), the median rates of 2-year survival were 63.6% and 17.2%, respectively ($P = 0.003$), suggesting that CMV level of infection may have a prognostic value.[233] Nevertheless, CMV persists after a usually unrecognized infection lifelong in the body[270] and represents a frequent opportunistic infection in severely immunocompromised patients. Moreover, the evaluation of the CMV (ribonucleic acid [RNA]) RNA/DNA levels in GB samples remains controversial, and for some authors CMV is unlikely to be implicated in the development of human malignant gliomas.[254] A positive IHC of the CMV immediate early antigen in the tumor tissue does not constitute an infection *per se*.[320] The VIGAS randomized, double-blind,

placebo-controlled trial was conducted to evaluate the safety and the efficacy of valgancyclovir (Valcyte®), an anti-CMV therapy, as an add-on therapy for GB. A total of 42 newly diagnosed GB patients were randomized to receive valganciclovir or placebo in addition to standard therapy for 6 months. Eligible patients were newly diagnosed GB with a surgical resection of at least 90% and CMV infection demonstrated histologically and immunonohistochemically. Patients could take valgancyclovir for compassionate use after the study phase. Trends but no significant differences were observed in tumor volumes in valgancyclovir and placebo-treated patients at 3 (3.58 vs. 7.44 cm^3, respectively, $P = 0.2881$) and 6 (3.31 vs. 13.75 cm^3, $P = 0.2120$) months. Median PFS were 5.6 months in the valgancyclovir group and 5.5 months in the placebo group ($P = 0.30$). Median OS was similar in both groups (17.9 vs. 17.4 months, $P = 0.430$) suggesting no added benefit with the addition of valgancyclovir. The authors subsequently collated a subgroup of patients that benefited from valgancyclovir comprised of patients from both arms of the VIGAS trial as well as patients from a compassionate use study. In this highly selected and heterogenous group of patients, the authors described a significant prolongation of OS (24 vs. 13.1 months, $P < 0.0001$) and OS at 4 years (27.3% vs. 5.9%, $P = 0.0466$) in patients receiving >6 months of Valganciclovir.[277,320,324,325]

Treatment of recurrent glioblastoma

The treatment of GB at recurrence depends on several factors, including age of the patient, PS of the patient, extent and location of disease at recurrence, response to initial treatment, time between initial treatment and first recurrence, and prior treatment.[305] As in recurrent AG, only a minority of selected patients are eligible for re-resection or re-irradiation and systemic therapy continues to be the most often utilized treatment.

Chemotherapy

A variety of alkylator-based CT regimens (Carmustine [BCNU], Lomustine [CCNU], Fotemustine, TMZ in TMZ-naive patients, TMZ in TMZ-pretreated patients) have been evaluated at recurrence of GB and constitute the current SOC.[305] Six-months PFS varies from 17.5% to 52%, median PFS varies from 1.6 to 6.7 months, and OS varies from 7.1 to 9.6 months.[3,16,18,19,37,39,40,42,43,45,66,89,91,95,103,118,142,145,155,156,203,212,222,242,261,263,264,284,285,314-316,322,338] The results of the several studies utilizing alkylator-based CT at recurrence are described in Table 11.

In an attempt to improve on TMZ only therapy, a variety of agents both cytotoxic and targeted have been combined with TMZ including BEV, nitrosoureas, alpha-interferon, IRI, cisplatin in more than 12 phase I or II studies. None of these combinations have proved superior to TMZ alone.[34,41,73,79,101,114,239,240,245,260,269,295,305]

Bevacizumab

In 2005, Stark Vance presented the first results of BEV in recurrent HGG using the combination of BEV/IRI in 21 patients. Patients received 6-week cycles with BEV (5 mg/kg, every other week) and IRI (125 mg/m^2 every 4 weeks), followed by a 2-week rest. Toxicities included neutropenia, diarrhea, epistaxis, emesis, and asthenia. One patient died of an intracranial hemorrhage and one patient died of complications of gastrointestinal perforation. One complete response, 8 partial responses, and 11 stable diseases were observed, suggesting a possible role for BEV in recurrent HGG.[2] In 2007, a phase II study of 23 patients at first GB recurrence were treated with BEV (10 mg/kg/q2w) + IRI and another 12 patients received BEV (15 mg/kg/q3w) + IRI. The median PFS was 24 weeks, PFS-6 was 46% and the median OS was 42 weeks. Toxicities, mainly fatigue and thrombo-embolic events required an interruption of treatment in 11 patients.[300] In another phase II study, BEV alone (10 mg/kg/q2w) was evaluated in 48 patients with recurrent GB at second disease recurrence.[159] Patients were to receive BEV + IRI (125 or 340 mg/m2/q2w based on antiepileptic use) at recurrence on BEV only. The median PFS was 31 weeks, PFS-6 was 29% and median OS was 16 weeks. The objective response rate was 35%. In the randomized phase II BRAIN study of GB at first recurrrence, a total 85 patients received BEV alone (10 mg/kg/q2w) and 82 patients BEV (10 mg/kg/q2w) + IRI (125–340 mg/m^2/q2w). At progression, patients in the BEV alone arm received BEV + IRI. The 6 month-PFS was 42.6% and 50.3% ($P < 0.0001$), median PFS was 4.2 and 5.6 months in the BEV alone and in the BEV + IRI arm, respectively. The median OS were 9.2 and 8.7 months.[100] Interruption of treatment due to toxicity was observed in 4.8% and 21.5% in the BEV alone and in the combined arms, respectively. The results of this study confirmed the activity of BEV in these patients, and BEV was approved by the FDA in May 2009 for recurrent (1st or 2nd) GB.

A variety of retrospective and prospective studies have evaluated combining BEV with various agents including IRI, etoposide, TMZ, carboplatin, cetuximab, erlotinib, and to date none have proved more effective than BEV only [Table 12].[2,5,57,62,65,79,93,96,100,105,106,119,140,159,195,198,204,205,211,235-237,262,273,284,295,300,301,305] These various studies demonstrate a median PFS-6 rate that varied from 25% to 42.6%, median OS from 6.5 to 9.2 months, and radiological response rates from 29% to 42% in the BEV alone groups. In the BEV-combined arms, the PFS-6 rates varied from 19% to 50%, median OS from 6 to 10.2 months, and radiological response rates from 20% to 57%.[273] In a sequential two-part randomized phase II trial (CABARET), 122 patients at first progression of GB were initially treated with BEV (10 mg/kg/q2w) alone or BEV (10 mg/kg/q2w) + carboplatin (AUC 5 q4w) (part 1). At progression, patients were randomized to continue or stop BEV (part 2). The

Table 11: Chemotherapy regimens: Recurrent glioblastoma

Author	Trial design	Agent	Nb of pts	PFS-6	PFS	OS
Carmustine						
Brandes 2004	Prospective	Carmustine	40	17.5%	ND	7.53
Reithmeier 2010	Retrospective	Carmustine	35	13%	2.6	5.1
Lomustine						
Wick 2010	Prospective	Lomustine	92	19%	1.6	7.1
Batchelor 2010 Batchelor 2013	Prospective	Lomustine	65	24.5%	2.9	9.8
Taal 2013 (BELOB)	Prospective	Lomustine	46	13%	ND	12
Fotemustine						
Scoccianti 2008	Prospective	Fotemustine	27	48.15%	5.7	9.1
Brandes 2009	Prospective	Fotemustine	43	20.9%	1.7	6
Fabrini 2009	Prospective	Fotemustine	50	52%	6.1	8.1
Addéo 2011	Prospective	Fotemustine	40	61%	6.7	11.1
De Felice 2013	Prospective	Fotemustine	15	33.3%	5.0	7.5
Santoni 2013	Prospective	Fotemustine (pts>65y)	65	35.4%	4.2	7.1
PCV						
Yung 2000	Prospective	PCV	113	8%	1.9	ND
Klapelle 2001	Retrospective	PCV or iPCV	63	29%	ND	7.7
Schmidt 2006	Retrospective	PCV	86	38.4%	4.0	7.8
Temozolomide						
Brandes 2001	Prospective	TMZ (TMZ-naive pts)	22	31.8%	3.0	7.6
Khan 2002	Prospective	TMZ (TMZ-naive pts)	28	19%	2.3	7.7
Brandes 2002	Prospective	TMZ (TMZ-naive pts)	42	24%	ND	7.0
Wick 2004	Prospective	TMZ (TMZ-naive pts)	21	48%	4.9	ND
Chan 2005	Prospective	TMZ (TMZ-naive pts)	13	21%	ND	ND
Brandes 2006	Prospective	TMZ (TMZ-naive pts)	33	30.3%	3.8	9.3
Nagane 2007	Prospective	TMZ (TMZ-naive pts)	19	22.2%	2.2	9.9
Balmaceda 2010	Prospective	TMZ (TMZ-naive pts)	68	35%	4.0	9
Brada 2011	Prospective	TMZ (TMZ-naive pts)	126	18%	2.1	5.4
Yung 2000	Prospective	TMZ (TMZ pretreated pts)	112	21%	2.9	ND
Franceschi 2005	Retrospective	TMZ (TMZ pretreated pts)	9	ND	7.0	12+
Wick 2007	Prospective	TMZ (9 TMZ pretreated pts)	64	43.8%	5.5	ND
Kong 2006	Prospective	TMZ (TMZ pretreated pts)	12	58.3%	6.0	11
Wick 2009	Retrospective	TMZ (TMZ pretreated pts)	14	27.7%	5.1	5.8
Kong 2010	Prospective	TMZ (TMZ pretreated pts)	38	32.5%	4.0	9.6
Perry 2010	Prospective	TMZ (TMZ pretreated pts)	91	23.9%	ND	9.3

Table Contd...

Table 11: Continued

Hammond 2011	Prospective	TMZ (TMZ pretreated pts)	47	23%	2.3	13
Taal 2012	Retrospective	TMZ (TMZ pretreated pts)	24	29%	ND	9
Norden 2013	Prospective	TMZ (TMZ pretreated pts)	58	11%	1.83	11.7
Han 2014	Prospective	TMZ (TMZ pretreated pts)	40	10%	2.0	5.4

Nb of pts: number of patients, PFS6: Progression-free survival at 6 months, PFS: Progression-free survival, OS: Overall survival, PCV: Procarbazine, lomustine, vincristine, iPCV: Intensive procarbazine, lomustine, vincristine TMZ: Temozolomide, ND: Not detailed, y: Year

Table 12: Bevacizumab containing chemotherapy regimens: Recurrent glioblastoma

Authors	Trial design	Agents	Number of patients	PFS-6	Median PFS (months)	Median OS (months)
Bevacizumab alone						
Kreisl 2009	Prospective	Bevacizumab	48	29%	3.7	7.2
Friedman 2009	Prospective	Bevacizumab	85	42.6%	4.2	9.2
Raizer 2010	Prospective	Bevacizumab	61	25%	2.7	6.5
Nghiemphu 2010	Retrospective	Bevacizumab	44	41%	4.25	9.01
Chamberlain 2010	Retrospective	Bevacizumab	50	42%	10	8.5
Nagane 2012	Retrospective	Bevacizumab	29	33.9%	3.3	10.5
Kaloshi 2013	Retrospective	Bevacizumab	14	32%	3.6	6.4
Fields 2013	Prospective	Bevacizumab	?/122	24%	ND	6.4
Taal 2013	Prospective	Bevacizumab	50	18%	ND	12
Cecchi 2013	Retrospective	Bevacizumab	9	45%	5.1	6.8
Bevacizumab+Irinotecan						
Stark Vance 2005	ND	Bev+iri	11	ND	ND	ND
Vredenbrugh CCR 2007	Prospective	Bev+iri	23	30%	4.7	9.3
Vredenburgh JCO 2007	Prospective	Bev+iri	12	46%	5.6	9.8
Norden 2008	Retrospective	Bev+iri	33	42%	ND	ND
Ali 2008	Retrospective	Bev+iri	13	ND	6	6.75
Friedman 2009	Prospective	Bev+iri	82	50.3%	5.6	8.7
Gilbert 2009	Prospective	Bev+iri	57	37%	ND	ND
Moller 2012	Prospective	Bev+iri	32	28%	5.2	7.9
Gil 2012	Retrospective	Bev+iri	94	42%	5.1	8.8
Cecchi 2013	Retrospective	Bev+iri	10	69%	15.4	11.1
Bevacizumab+Temozolomide						
Verhoeff 2010	Prospective	Bev+TMZ	15	6.7%	2.4	3.7
Desjardins 2012	Prospective	Bev+TMZ	32	18.8%	3.7	8.7
Bevacizumab+Lomustine						
Taal 2013	Prospective	Bev+Lomustine	44	42%	ND	8
Bevacizumab+Fotemustine						
Soffietti 2014	Prospective	Bev+Fotemustine	44 pts	42.6%	5.2	9.1
Bevacizumab+Carboplatine						
Mrugala 2012	Retrospective	Bev+Carboplatine	14	40%	4.75	10
Fields 2013	Prospective	Bev+Carboplatine	ND/122	26%	ND	6.9
Bevacizumab+Miscellanous						
Reardon 2009	Prospective	Bev+Etoposide	27	44.4%	4.2	10.8
Francesconi 2010	Retrospective	Bev+Carboplatine+Etoposide	6	22%	4.4	7.0
Hasselbach 2010	Prospective	Bev+iri+Cetuximab	43	33%	3.7	7.0
Sathornsumetee 2010	Prospective	Bev+Erlotinib	25	29.2%	4.2	10.3
Reardon 2012	Prospective	Bev+iri+carboplatine	40	46.5%	ND	8.3

PFS 6: Progression-free survival at 6 months, PFS: Progression-free survival, OS: Overall survival, Bev: Bevacizumab, Iri: Irinotecan, TMZ: Temozolomide, ND: Not detailed

PFS-6 was 26% in the BEV + carboplatin arm versus 24% in the BEV alone arm ($P = 0.82$). The response rates (15% vs. 13%, $P = 0.82$), median OS (6.9 vs. 6.4 months, $P = 0.68$) were similar in both groups.[93] Part 2 of the study has not been reported as yet.

The BELOB phase II study (Landelijke Werkgroep Neuro-Oncologie [LWNO] trial 0901) compared BEV alone versus BEV plus Lomustine versus Lomustine alone in patients with a first recurrence of GB. The initial design of BELOB consisted in a 2-arm study, evaluating BEV versus BEV plus Lomustine in recurrent GB. The primary endpoint was 6-PFS. After the negative ruling of EMA in Europe on the use of BEV at first recurrence for GB, the trial was amended to include three arms. The new protocol was thus a three-arm randomized open label controlled phase II study with a primary endpoint of OS at 9 months. The treatment arms were Lomustine alone (110 mg/m^2 every 6 weeks for 6 cycles), Lomustine (90 mg/m^2 every 6 weeks for 6 cycles) + BEV (10 mg/kg every 2 weeks until progression), and BEV alone (10 mg/kg every 2 weeks until progression). Initially Lomustine was administered at 110 mg/m^2, but due to hematological toxicity, the dose of Lomustine was reduced. A total of 148 eligible patients were enrolled: 50 patients were assigned to BEV alone, 46 patients to Lomustine alone, and 52 patients to the combined group. Treatment was interrupted for toxicity for two patients in BEV alone arm and five patients in the combination arm. The most frequent adverse events were hypertension and fatigue. The 9 months OS was 43% (range, 29–57%), 38% (range 25–51%), and 63% (range, 49–75%) in the Lomustine arm, in the BEV arm, and in the combination arm, respectively. The median OS was 8 months in either the Lomustine only or BEV alone arms, and 12 months in the BEV + Lomustine arm. The PFS at 6 months was 13% (range, 5–24%), 18% (7–27%) and 42% (range, 29–55%) in the Lomustine arm, the BEV arm and in the combination arm, respectively.[284] The study concluded that combination therapy was most effective and suggested for the first time likely chemosynergy with BEV and a cytotoxic agent (Lomustine) in the treatment of recurrent GB. Additionally, the study proposed that the results were sufficiently robust to pursue a phase III study.

EORTC 26101 (NCT01290939) was recently modified as a three-arm phase III adressing results of BELOB. This trial will determine whether the combination of BEV and Lomustine in patients with first reccurence of GB is superior to BEV or Lomustine only. The primary endpoint is the OS, and the secondary outcomes are median PFS, PFS at 6 and 12 months, OS at 9, 12, and 24 months, response rate and duration of response and progression parttern, safety, clinical DFS, steroid use, QoL and development of cognitive deterioration, and identification of biomarkers that hopefully will translate into advances in screening, diagnosis, treatment, and monitoring patients with recurrent GB. In arm 1, patients will recieve Lomustine (90–110 mg/m^2 every 6 weeks) plus BEV (10 mg/kg every 2 weeks). In arm 2, patients will receive Lomustine as single agent (110 mg/m^2 every 6 weeks). At progression, treatment is at the discretion of the investigator.

BEV when used for recurrent GB is usually administrated intravenously at 10 mg/kg every 2 weeks. Other schedules of BEV have been evaluated in small cohorts of patients with recurrent GB.[140,235] A total of 61 patients with recurrent GB received 15 mg/kg/q3W of BEV in the study by Raizer. The PFS-6 was 25%, the median time to progression was 10.8 weeks, and the median OS was 25.6 weeks. A partial response was observed in 24% and stable disease in 50.8%. In the study of 14 patients by Kaloshi, using a dose of 5 mg/kg/q2w, median PFS was 3.6 months and median OS 6.4 months. Five partial responses and seven stable disease patterns of radiographic response were observed. Robust data on the best BEV dose and schedule are still lacking.

The median OS after progression on BEV is usually poor (average 3–4.6 months) nothwithstanding attempted further treatment.[86,135,230,235,273,327] Continuation of BEV after progression on BEV is still debated and various conclusions have been offered in retrospective studies.[62,237] The randomized TAMIGA phase IIIb trial is evaluating the efficacy and safety of continous BEV (in conjunction with RT + TMZ) treatment following progression of disease (vs. no further BEV and treatment at physician discretion) in patients with GB after first-line treatment with RT, TMZ and BEV. This trial will allow a comparison of BEV continuation versus discontinuance in patients treated with BEV and in whom there is evidence of disease progression.

Nonbevacizumab angiogenic inhibitors

Other antiangiogenic agents have been evaluated in recurrent GB. Median PFS-6 was 25.8% with cediranib (vascular endothelial growth factor receptor 2 [VEGFR2] inhibitor, 31 patients), 7.7% with aflibercept ($n = 42$ patients; VEGF ligand decoy) and 15% with cilengitide ($n = 40$ patients; antiintegrin inhibitor).[18-20,108,113,238] Cabozatinib (XL184), is a small molecule kinase mesenchymal-epithelial transition (MET), VEGFR2, and rearranged during transfection (RET) inhibitor, was evaluated in a phase II trial at 125 and 175 mg. PFS-6 was 21%.[310] None of these agents has achieved an effectiveness that improves upon BEV.

A phase III open label study compared the efficacy and safety of enzastaurin versus Lomustine in patients with recurrent GB. A total of 266 patients were randomly assigned (2:1) to receive 6-week cycles of enzastaurin 1125–500 mg/d ($n = 174$) or Lomustine

(100–130 mg/m^2, day 1) (n = 92). Median PFS (1.5 vs. 1.6 months, P = 0.08), OS (6.6 vs. 7.1 months, P = 0.25), and 6-month PFS rate (11.1% vs. 19%, P = 0.13) did not differ significantly between enzastaurin and Lomustine, respectively. Stable disease occurred in 38.5% and 35.9% of patients and objective response occurred in 2.9% and 4.3% of patients, respectively. Time to deterioration of physical and functional well-being and symptoms did not differ between arms (P = 0.54). Four patients discontinued enzastaurin because of drug-related serious adverse events (AEs). Grade 3 to 4 hematologic toxicities were significantly higher with Lomustine than with enzastaurin ($P \leq 0.001$). In this study, enzastaurin was not superior to Lomustine in patients with recurrent GB.[322]

REGAL was a randomized phase III placebo controlled partially blinded trial to determine the efficacy of cediranib, an oral pan-VEGF receptor tyrosine kinase (RTK) inhibitor, either as monotherapy or in combination with Lomustine versus Lomustine only in patients with recurrent GB.[19] A total of 325 patients with a first recurrent GB previously treated with RT + TMZ were randomly assigned 2:2:1 to receive (i) cediranib (30 mg) monotherapy; (ii) cediranib (20 mg) plus Lomustine (110 mg/m^2); (iii) Lomustine (110 mg/m^2) plus a placebo. The median PFS were not different between groups: 92 days in the cediranib arm (P = 0.9, vs. Lomustine), 125 days in the cedirabine + Lomustine arm (P = 0.16, vs. Lomustine), 82 days in the placebo + Lomustine arm.

This study did not meet its primary end point of PFS prolongation with cediranib either as monotherapy or in combination with Lomustine versus Lomustine in patients with recurrent GB, but did confirm the benefit of Lomustine similar to the conclusions of the enzastaurin trial mentioned above.

Molecular targeted therapy

The anaplastic lymphoma kinase (ALK) and the hepatocyte growth factor receptor (HGFR or, more commonly MET) are both members of the RTK family and included within the insulin-like receptor superfamily. This signaling pathway has a role in modulating mitosis, migration, and survival in cancer cells.[188,303] Expression of MET has been shown to be associated with a worse clinical outcome in GB.[11,157,158,176] GB expressing MET mutations or amplifications occur in only ~ 5% of all patients.[53,303] Crizotinib, is an orally available ATP-competitive selective inhibitor of ALK and MET tyrosine kinases.[72,183] Several additional ALK inhibitors are currently being tested in clinical trials.[188] In a case report, a patient received crizotinib 250 mg twice daily at the first progression of a GB with MGMT promoter methylation and MET gene amplification. A rapid and 6 months-prolonged clinical and radiological improvment was observed. The only adverse effects attributed to crizotinib were asymptomatic elevated alanine amino transferase (ALT) (grade 2) and hypophosphatemia (grade 2).[68]

BRAF mutations, another uncommon mutation in GB, may represent another druggable target using specific BRAF inhibitors such as vemurafenib or dabrafenib. BRAF V600E mutations have been identified in a less than 5% of adult GB and when seen are mostly observed in epithelioid-GB, a tumor subtype seen in pediatric and young adults.[54,154,206]

Vaccine-based immunotherapy

ReACT (NCT01498328) a phase II trial with granulocyte-macrophage colony-stimulating facto (GM-CSF) and KLH in combination with the EGFRvIII peptide vaccine rindopepimut, is evaluating vaccine-based therapy in patients with recurrent EGFRvIII-positive GB. Group 1 are patients who have never been treated with BEV and will be randomly assigned to receive either rindopepimut/GM-CSF + KLH vaccine and BEV or BEV only in conjunction with a non-EGFRvIII peptide containing vaccine. Treatment assignment for Group 1 will be blinded. Group 2 patients are refractory to BEV (recurrence or progression of GB while on BEV or within 2 months of discontinuing BEV). These patients will receive rindopepimut/GM-CSF vaccine in conjunction with BEV. The primary objective is PFS in Groups 1 and 2 and objective response rate in the Group 2. The secondary outcome measures are safety and tolerability, antitumor activity and EGFRvIII-specific immune response.

Gliadel trial

A total of 222 patients with recurrent GB who underwent reoperation were randomized in a phase III study comparing resection + carmustine wafers (Gliadel) (n = 110) versus resection + placebo wafers (n = 112). The median OS were 31 versus 23 weeks (P = 0.006) in the carmustine wafer and placebo arm, respectively.[48] No clinically important adverse reactions related to the carmustine polymer, either in the brain or systemically were observed. In another cohort, 22 patients received carmustine wafers at first progression of GB. The median PFS and OS rates after recurrence were 3.6 and 9.9 months, respectively, and the 6-month PFS rate after recurrence was 27.2%. On multivariate analysis, only MGMT promoter hypermethylation at recurrence, as determined by using MethyLight technology (P = 0.019) and methylation-specific PCR (MSP) analysis (P = 0.046), was associated with better OS.[189] The rate of complications remains unclear in this population, but data in newly diagnosed GB suggest that gliadel wafers should be used with caution.[46]

Convection-enhanced delivery

Convection-enhanced delivery (CED) was designed to improve the delivery of drugs that would normally not

cross the blood–brain barrier. Agents are delivered through one to several catheters placed stereotactically within the tumor or in brain surrounding tumor. Different classes of drugs are amenable to this technology including standard chemotherapeutics or novel experimental targeted drugs. Nevertheless, trials have failed to demonstrate a success when utilizing CED as means of drug delivery.[61,199] Two randomized trials have been completed and in both instances there was no evidence of benefit in the CED groups: One using modified pseudomonas toxin (PRECISE study) and the other a diphtheria toxin (TransMID trial).[163,234]

Alternating electric fields or tumor treating fields

Two clinical trials have assessed the effect of AEF using the NovoTTF-100A device (Novocure Ltd, Haifa, Israël) in the recurrent setting. In the first trial, a small pilot study of 10 patients, the device was used continuously for a minimum of 18 h/day and used until disease progression. Median OS was 62.2 weeks, 6-month PFS rate was 50%, TTP was 6.1 months. These results compared favorably with historical controls that showed a median OS of 29.3 weeks, a 6-month PFS rate of 15.3%, and a TTP of 9.5 weeks. Tolerance profile was excellent with dermatitis beneath the electrodes being the most frequent side effect.[150,151] Based on these results, a pivotal study designated EF 11 was initiated. This phase III randomized multicenter clinical trial was designed to compare the safety and effectiveness of NovoTTF 100A to the investigator determined best standard of care (BSC) CT for recurrent GB. The trial was designed to demonstrate the superiority of NovoTTF 100A compared with BSC. Twenty eight US and European centers enrolled a total of 237 patients (120 TTF patients, 117 BSC patients). In the analysis, the intent to treat (ITT) population comprised of six groups, all determined *post hoc*: Group 1 = TTF patients who never started therapy (n = 4); Group 2 = TTF patients who received less than 4 weeks of therapy (n = 23); Group 3 = TTF patients treated per protocol (PP) (n = 93); Group 4 = BSC patients who never started therapy (n = 26); Group 5 = BSC patients with protocol violations (n = 12); Group 6 = BSC patients treated PP (n = 79). Patients were analysed with regard to efficacy using four different approaches: ITT (all 6 groups), PP (Groups 3 and 6), modified ITT 1 (mITT 1 – Groups 3, 4, 5, and 6), and modified ITT 2 (mITT 2 – Groups 3, 5, and 6). For safety, all patients in Groups 2, 3, 5, and 6 (i.e. all patients who had received one or more treatments) were included. The primary endpoint of the study was OS. There was no significant difference in OS between the TTF and BSC groups (6.0 vs. 6.6 months, P = 0.27), except for the PP and mITT 1 populations, which showed that OS was significantly higher following TTF. No difference was observed regarding the 1-year survival rate between the two treatment arms in ITT population (20% in both). Although the 1-year survival rate appeared higher in the TTF group in the PP population, no statistical analysis were provided to determine whether this difference was significant. Median PFS and 6 month-PFS (21.4% vs. 15.1%, P = 0.13) was similar between the two groups in the ITT population; however, in the three remaining populations, PFS was significantly higher following TTF. There were no significant differences in TTP when comparing TTF and BSC in the ITT and mITT 2 populations; however, TTF treatment resulted in significantly longer in the PP and mITT 1 populations. Response rates were also similar in both arms in ITT (14% vs. 9.6%, P = 0.19). QoL analyses favoured TTF for role, cognitive and emotional functioning. Increased pain and fatigue were reported with CT but not with TTF. Symptom scale analysis revealed increased CT-related toxicities in the no-Novocure arm. Notwithstanding the fact that the trial was never designed as a noninferiority trial and therefore was unable based on power analysis to determine equivalence with BSC, the NovoTTF 100A device was approved by the FDA in April 2011 for the treatment of adult patients with recurrent GB after receiving upfront SOC.[282]

CONCLUSION

Molecular markers and gene expression profiles increasingly assist in determining prognosis and response to treatment in HGG, and particularly in AG, in which, treatment is dependent upon the 1p/19q status. In the GB population, the molecular markers and classification does not currently influence treatment except in elderly patients. Potentially and recently identified mutations markers may be druggable (cMET, ALK, BRAF, EGFRvIII, IDH…) and reprent new treatment strategies. HGG when feasible are first treated with maximum safe surgery, followed by RT and/or systemic CT. The standard treatment of newly diagnosed 1p19q codeleted AG has changed after publication of the long-term results of the RTOG 9402 and EORTC 26951 trials, and now includes RT + PCV, with PCV administered either immediately before or after RT. The role of TMZ in lieu of PCV, which is less toxic than PCV, remains to be determined and is the primary hypothesis in the currently on going trial CODEL. In the 1p/19q noncodeleted AG population, there is insufficient data to recommend concomitant RT + TMZ and in this population, the standard initial treatment remains RT or CT alone based on the NOA-04 trial. Results of CATNON are awaited, which will hopefully inform as to the role of TMZ in the first-line treatment of nondeleted AG.

The addition of BEV to the SOC of newly diagnosed GB has shown no impact on OS and consequently cannot be commended for use in GB except at recurrence. Similarly there is no evidence that Cilengitide adds addional

benefit to the initial treatment of GB. The role of vaccine-based immunotherapy in the upfront treatment of GB will be determined upon completion of two large Phase 3 trials, ACT 4 and DCvax. New targeted agents, such as inhibitors of BRAF, cMET, or ALK, are currently exploratory and may be applicable to a small select subpopulation. Vaccines directed at HSP and IDH1 may be another promising approach.

There continues to be SOC identified in recurrent HGG. Several factors should be taken into account such as age and PS of the patient, extent and location of disease at recurrence, response to initial treatment, time between initial treatment and first recurrence, and prior treatment. Both recurrent GB and AG are managed in a similar manner. Re-resection or re-irradiation may be options in a minority of select patients. Systemic treatment remains the most often utilized option for recurrent HGG. Re-challenge with TMZ or alternative use of a nitrosourea (most often Lomustine) are one of standard options. BEV alone has also shown an improvment of PFS-6 in the GB population. The role of combination therapy with BEV and Lomustine recently was suggested to be more effective (BELOB trial) and is currently being examined in an EORTC phase III trial in recurrent GB. The use of immune check point inhibitors such as anti-PD1 monoclonal antibodies is just commencing and is a potential new stratgey for recurrent HGG. Nevertheless, there is no clear standard recommendation regarding the prefered agent or combination of agents for recurrent HGG. Prognosis after progression remains poor, with an unmet need to improve therapy.

REFERENCES

1. Abrey LE, Louis DN, Paleologos N, Lassman AB, Raizer JJ, Mason W, *et al.* Survey of treatment recommendations for anaplastic oligodendroglioma. Neuro Oncol 2007;9:314-8.
2. Abstracts from the World Federation of Neuro-Oncology Second Quadrennial Meeting and the Sixth Meeting of the European Association for Neuro-Oncology. Neuro Oncol 2005;7:279-402.
3. Addeo R, Caraglia M, De Santi MS, Montella L, Abbruzzese A, Parlato C, *et al.* A new schedule of fotemustine in temozolomide-pretreated patients with relapsing glioblastoma. J Neurooncol 2011;102:417-24.
4. Affronti ML, Heery CR, Herndon JE 2nd, Rich JN, Reardon DA, Desjardins A, *et al.* Overall survival of newly diagnosed glioblastoma patients receiving carmustine wafers followed by radiation and concurrent temozolomide plus rotational multiagent chemotherapy. Cancer 2009;115:3501-11.
5. Ali SA, McHayleh WM, Ahmad A, Sehgal R, Braffet M, Rahman M, *et al.* Bevacizumab and irinotecan therapy in glioblastoma multiforme: A series of 13 cases. J Neurosurg 2008;109:268-72.
6. Alonso ME, Bello MJ, Gonzalez-Gomez P, Arjona D, Lomas J, de Campos JM, *et al.* Aberrant promoter methylation of multiple genes in oligodendrogliomas and ependymomas. Cancer Genet Cytogenet 2003;144:134-42.
7. Aoki H, Mizuno M, Natsume A, Tsugawa T, Tsujimura K, Takahashi T, *et al.* Dendritic cells pulsed with tumor extract-cationic liposome complex increase the induction of cytotoxic T lymphocytes in mouse brain tumor. Cancer Immunol Immunother 2001;50:463-8.
8. Ardon H, Van Gool S, Lopes IS, Maes W, Sciot R, Wilms G, *et al.* Integration of autologous dendritic cell-based immunotherapy in the primary treatment for patients with newly diagnosed glioblastoma multiforme: A pilot study. J Neurooncol 2010;99:261-72.
9. Ardon H, Van Gool SW, Verschuere T, Maes W, Fieuws S, Sciot R, *et al.* Integration of autologous dendritic cell-based immunotherapy in the standard of care treatment for patients with newly diagnosed glioblastoma: Results of the HGG-2006 phase I/II trial. Cancer Immunol Immunother 2012;61:2033-44.
10. Armstrong TS, Wefel JS, Wang M, Gilbert MR, Won M, Bottomley A, *et al.* Net clinical benefit analysis of radiation therapy oncology group 0525: A phase III trial comparing conventional adjuvant temozolomide with dose-intensive temozolomide in patients with newly diagnosed glioblastoma. J Clin Oncol 2013;31:4076-84.
11. Arrieta O, Garcia E, Guevara P, Garcia-Navarrete R, Ondarza R, Rembao D, *et al.* Hepatocyte growth factor is associated with poor prognosis of malignant gliomas and is a predictor for recurrence of meningioma. Cancer 2002;94:3210-8.
12. Ashley DM, Faiola B, Nair S, Hale LP, Bigner DD, Gilboa E. Bone marrow-generated dendritic cells pulsed with tumor extracts or tumor RNA induce antitumor immunity against central nervous system tumors. J Exp Med 1997;186:1177-82.
13. Attenello FJ, Mukherjee D, Datoo G, McGirt MJ, Bohan E, Weingart JD, *et al.* Use of Gliadel (BCNU) wafer in the surgical treatment of malignant glioma: A 10-year institutional experience. Ann Surg Oncol 2008;15:2887-93.
14. Babu R, Hatef J, McLendon RE, Cummings TJ, Sampson JH, Friedman AH, *et al.* Clinicopathological characteristics and treatment of rhabdoid glioblastoma. J Neurosurg 2013;119:412-9.
15. Bady P, Sciuscio D, Diserens A-C, Bloch J, van den Bent MJ, Marosi C, *et al.* MGMT methylation analysis of glioblastoma on the Infinium methylation BeadChip identifies two distinct CpG regions associated with gene silencing and outcome, yielding a prediction model for comparisons across datasets, tumor grades, and CIMP-status. Acta Neuropathol (Berl.) 2012;124:547-60.
16. Balmaceda C, Peereboom D, Pannullo S, Cheung YKK, Fisher PG, Alavi J, *et al.* Multi-institutional phase II study of temozolomide administered twice daily in the treatment of recurrent high-grade gliomas. Cancer 2008;112:1139-46.
17. Banaszczyk M, Stoczynska-Fidelus E, Winiecka-Klimek M, Bienkowski M, Och W, Rieske P, *et al.* EGFRvIII--a stable target for anti-EGFRvIII therapy. Anticancer Res 2013;33:5343-8.
18. Batchelor TT, Duda DG, di Tomaso E, Ancukiewicz M, Plotkin SR, Gerstner E, *et al.* Phase II study of cediranib, an oral pan-vascular endothelial growth factor receptor tyrosine kinase inhibitor, in patients with recurrent glioblastoma. J Clin Oncol 2010;28:2817-23.
19. Batchelor TT, Mulholland P, Neyns B, Nabors LB, Campone M, Wick A, *et al.* Phase III randomized trial comparing the efficacy of cediranib as monotherapy, and in combination with lomustine, versus lomustine alone in patients with recurrent glioblastoma. J Clin Oncol 2013;31:3212-8.
20. Batchelor TT, Sorensen AG, di Tomaso E, Zhang WT, Duda DG, Cohen KS, *et al.* AZD2171, a pan-VEGF receptor tyrosine kinase inhibitor, normalizes tumor vasculature and alleviates edema in glioblastoma patients. Cancer Cell 2007;11:83-95.
21. Batra SK, Castelino-Prabhu S, Wikstrand CJ, Zhu X, Humphrey PA, Friedman HS, *et al.* Epidermal growth factor ligand-independent, unregulated, cell-transforming potential of a naturally occurring human mutant EGFRvIII gene. Cell Growth Differ 1995;6:1251-9.
22. Bauman GS, Ino Y, Ueki K, Zlatescu MC, Fisher BJ, Macdonald DR, *et al.* Allelic loss of chromosome 1p and radiotherapy plus chemotherapy in patients with oligodendrogliomas. Int J Radiat Oncol Biol Phys 2000;48:825-30.
23. Behm T, Horowski A, Schneider S, Bock HC, Mielke D, Rohde V, *et al.* Concomitant and adjuvant temozolomide of newly diagnosed glioblastoma in elderly patients. Clin Neurol Neurosurg 2013;115:2142-6.
24. Van den Bent MJ, Chinot O, Boogerd W, Bravo Marques J, Taphoorn MJ, Kros JM, *et al.* Second-line chemotherapy with temozolomide in recurrent oligodendroglioma after PCV (procarbazine, lomustine and vincristine) chemotherapy: EORTC Brain Tumor Group phase II study 26972. Ann Oncol 2003;14:599-602.
25. Van den Bent MJ, Brandes AA, Taphoorn MJ, Kros JM, Kouwenhoven MC, Delattre JY, *et al.* Adjuvant procarbazine, lomustine, and vincristine chemotherapy in newly diagnosed anaplastic oligodendroglioma: Long-term follow-up of EORTC brain tumor group study 26951. J Clin Oncol 2013;31:344-50.

26. Van den Bent MJ, Carpentier AF, Brandes AA, Sanson M, Taphoorn MJ, Bernsen HJ, *et al*. Adjuvant procarbazine, lomustine, and vincristine improves progression-free survival but not overall survival in newly diagnosed anaplastic oligodendrogliomas and oligoastrocytomas: A randomized European Organisation for Research and Treatment of Cancer phase III trial. J Clin Oncol 2006;24:2715-22.
27. Van den Bent MJ, Dubbink HJ, Marie Y, Brandes AA, Taphoorn MJ, Wesseling P, *et al*. IDH1 and IDH2 mutations are prognostic but not predictive for outcome in anaplastic oligodendroglial tumors: A report of the European Organization for Research and Treatment of Cancer Brain Tumor Group. Clin Cancer Res 2010;16:1597-604.
28. Van den Bent MJ, Dubbink HJ, Sanson M, van der Lee-Haarloo CR, Hegi M, Jeuken JW, *et al*. MGMT promoter methylation is prognostic but not predictive for outcome to adjuvant PCV chemotherapy in anaplastic oligodendroglial tumors: A report from EORTC Brain Tumor Group Study 26951. J Clin Oncol 2009;27:5881-6.
29. Van den Bent MJ, Gravendeel LA, Gorlia T, Kros JM, Lapre L, Wesseling P, *et al*. A hypermethylated phenotype is a better predictor of survival than MGMT methylation in anaplastic oligodendroglial brain tumors: A report from EORTC study 26951. Clin Cancer Res 2011;17:7148-55.
30. Van den Bent MJ, Looijenga LH, Langenberg K, Dinjens W, Graveland W, Uytdewilligen L, *et al*. Chromosomal anomalies in oligodendroglial tumors are correlated with clinical features. Cancer 2003;97:1276-84.
31. Berghoff AS, Preusser M. Clinical neuropathology practice guide 06-2012: MGMT testing in elderly glioblastoma patients--yes, but how? Clin Neuropathol 2012;31:405-8.
32. Bloch O, Parsa AT. Heat Shock Protein Peptide Complex-96 (HSPPC-96) Vaccination for Recurrent Glioblastoma: A Phase II, Single Arm Trial. Neuro Oncol 2014;16:758-9.
33. Bock HC, Puchner MJA, Lohmann F, Schütze M, Koll S, Ketter R, *et al*. First-line treatment of malignant glioma with carmustine implants followed by concomitant radiochemotherapy: A multicenter experience. Neurosurg Rev 2010;33:441-9.
34. Boiardi A, Silvani A, Eoli M, Lamperti E, Salmaggi A, Gaviani P, *et al*. Treatment of recurrent glioblastoma: Can local delivery of mitoxantrone improve survival? J Neurooncol 2008;88:105-13.
35. De Bonis P, Anile C, Pompucci A, Fiorentino A, Balducci M, Chiesa S, *et al*. Safety and efficacy of Gliadel wafers for newly diagnosed and recurrent glioblastoma. Acta Neurochir (Wien) 2012;154:1371-8.
36. Borodovsky A, Salmasi V, Turcan S, Fabius AWM, Baia GS, Eberhart CG, *et al*. 5-azacytidine reduces methylation, promotes differentiation and induces tumor regression in a patient-derived IDH1 mutant glioma xenograft. Oncotarget 2013;4:1737-47.
37. Brada M, Hoang-Xuan K, Rampling R, Dietrich PY, Dirix LY, Macdonald D, *et al*. Multicenter phase II trial of temozolomide in patients with glioblastoma multiforme at first relapse. Ann Oncol 2001;12:259-66.
38. Brada M, Stenning S, Gabe R, Thompson LC, Levy D, Rampling R, *et al*. Temozolomide versus procarbazine, lomustine, and vincristine in recurrent high-grade glioma. J Clin Oncol 2010;28:4601-8.
39. Brandes AA, Ermani M, Basso U, Amistà P, Berti F, Scienza R, *et al*. Temozolomide as a second-line systemic regimen in recurrent high-grade glioma: A phase II study. Ann Oncol 2001;12:255-7.
40. Brandes AA, Tosoni A, Cavallo G, Bertorelle R, Gioia V, Franceschi E, *et al*. Temozolomide 3 weeks on and 1 week off as first-line therapy for recurrent glioblastoma: Phase II study from gruppo italiano cooperativo di neuro-oncologia (GICNO). Br J Cancer 2006;95:1155-60.
41. Brandes AA, Basso U, Reni M, Vastola F, Tosoni A, Cavallo G, *et al*. First-line chemotherapy with cisplatin plus fractionated temozolomide in recurrent glioblastoma multiforme: A phase II study of the Gruppo Italiano Cooperativo di Neuro-Oncologia. J Clin Oncol 2004;22:1598-604.
42. Brandes AA, Ermani M, Basso U, Paris MK, Lumachi F, Berti F, *et al*. Temozolomide in patients with glioblastoma at second relapse after first line nitrosourea-procarbazine failure: A phase II study. Oncology 2002;63:38-41.
43. Brandes AA, Tosoni A, Franceschi E, Blatt V, Santoro A, Faedi M, *et al*. Fotemustine as second-line treatment for recurrent or progressive glioblastoma after concomitant and/or adjuvant temozolomide: A phase II trial of Gruppo Italiano Cooperativo di Neuro-Oncologia (GICNO). Cancer Chemother Pharmacol 2009;64:769-75.
44. Brandes AA, Tosoni A, Cavallo G, Reni M, Franceschi E, Bonaldi L, *et al*. Correlations between O6-methylguanine DNA methyltransferase promoter methylation status, 1p and 19q deletions, and response to temozolomide in anaplastic and recurrent oligodendroglioma: A prospective GICNO study. J Clin Oncol 2006;24:4746-53.
45. Brandes AA, Tosoni A, Vastola F, Pasetto LM, Coria B, Danieli D, *et al*. Efficacy and feasibility of standard procarbazine, lomustine, and vincristine chemotherapy in anaplastic oligodendroglioma and oligoastrocytoma recurrent after radiotherapy. A Phase II study. Cancer 2004;101:2079-85.
46. Bregy A, Shah AH, Diaz MV, Pierce HE, Ames PL, Diaz D, *et al*. The role of Gliadel wafers in the treatment of high-grade gliomas. Expert Rev Anticancer Ther 2013;13:1453-61.
47. Brell M, Tortosa A, Verger E, Gil JM, Viñolas N, Villá S, *et al*. Prognostic significance of O6-methylguanine-DNA methyltransferase determined by promoter hypermethylation and immunohistochemical expression in anaplastic gliomas. Clin Cancer Res 2005;11:5167-74.
48. Brem H, Piantadosi S, Burger PC, Walker M, Selker R, Vick NA, *et al*. Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas. The Polymer-brain Tumor Treatment Group. Lancet 1995;345:1008-12.
49. Brennan C, Momota H, Hambardzumyan D, Ozawa T, Tandon A, Pedraza A, *et al*. Glioblastoma subclasses can be defined by activity among signal transduction pathways and associated genomic alterations. PloS One 2009;4: e7752.
50. Brennan CW, Verhaak RG, McKenna A, Campos B, Noushmehr H, Salama SR, *et al*. The somatic genomic landscape of glioblastoma. Cell 2013;155:462-77.
51. Cairncross G, Wang M, Shaw E, Jenkins R, Brachman D, Buckner J, *et al*. Phase III trial of chemoradiotherapy for anaplastic oligodendroglioma: Long-term results of RTOG 9402. J Clin Oncol 2013;31:337-43.
52. Cairncross JG, Ueki K, Zlatescu MC, Lisle DK, Finkelstein DM, Hammond RR, *et al*. Specific genetic predictors of chemotherapeutic response and survival in patients with anaplastic oligodendrogliomas. J Natl Cancer Inst 1998;90:1473-9.
53. Cancer Genome Atlas Research Network. Comprehensive genomic characterization defines human glioblastoma genes and core pathways. Nature 2008;455:1061-8.
54. Capper D, Berghoff AS, von Deimling A, Preusser M. Clinical neuropathology practice news 2-2012: BRAF V600E testing. Clin Neuropathol 2012;31:64-6.
55. Capper D, Weissert S, Balss J, Habel A, Meyer J, Jäger D, *et al*. Characterization of R132H mutation-specific IDH1 antibody binding in brain tumors. Brain Pathol 2010;20:245-54.
56. Carbonell WS, DeLay M, Jahangiri A, Park CC, Aghi MK. β1 integrin targeting potentiates antiangiogenic therapy and inhibits the growth of bevacizumab-resistant glioblastoma. Cancer Res 2013;73:3145-54.
57. Cecchi M, Vaiani M, Ceroti M, Banfi R. A retrospective observational analysis to evaluate the off-label use of bevacizumab alone or with irinotecan in recurrent glioblastoma. Int J Clin Pharm 2013;35:483-7.
58. Chahlavi A, Kanner A, Peereboom D, Staugaitis SM, Elson P, Barnett G. Impact of chromosome 1p status in response of oligodendroglioma to temozolomide: Preliminary results. J Neurooncol 2003;61:267-73.
59. Chaichana KL, Zaidi H, Pendleton C, McGirt MJ, Grossman R, Weingart JD, *et al*. The efficacy of carmustine wafers for older patients with glioblastoma multiforme: Prolonging survival. Neurol Res 2011;33:759-64.
60. Chamberlain MC. Treatment of newly diagnosed malignant glioma in the elderly people: New trials that impact therapy. Int J Clin Pract 2013;67:1225-7.
61. Chamberlain MC. Convection-enhanced delivery of a transforming growth factor-beta2 inhibitor trabedersen for recurrent high-grade gliomas: Efficacy real or imagined?, in reference to Bogdahn *et al*. (Neuro-Oncology 2011;13:132-142). Neuro Oncol 2011;13:558-9.
62. Chamberlain MC. Role for cytotoxic chemotherapy in patients with recurrent glioblastoma progressing on bevacizumab: A retrospective case series. Expert Rev Neurother 2012;12:929-36.
63. Chamberlain MC, Johnston S. Bevacizumab for recurrent alkylator-refractory anaplastic oligodendroglioma. Cancer 2009;115:1734-43.
64. Chamberlain MC, Johnston S. Salvage chemotherapy with bevacizumab for recurrent alkylator-refractory anaplastic astrocytoma. J Neurooncol 2009;91:359-67.
65. Chamberlain MC, Johnston SK. Salvage therapy with single agent bevacizumab for recurrent glioblastoma. J Neurooncol 2010;96:259-69.
66. Chan DT, Poon WS, Chan YL, Ng HK. Temozolomide in the treatment of recurrent malignant glioma in Chinese patients. Hong Kong Med J 2005;11:452-6.

67. Chauffert B, Feuvret L, Bonnetain F, Taillandier L, Frappaz D, Taillia H, *et al*. Randomized phase II trial of irinotecan and bevacizumab as neo-adjuvant and adjuvant to temozolomide-based chemoradiation compared to temozolomide-chemoradiation for unresectable glioblastoma: Final results of the TEMAVIR study from ANOCEF. Ann Oncol 2014;25:1442-7.
68. Chi AS, Batchelor TT, Kwak EL, Clark JW, Wang DL, Wilner KD, *et al*. Rapid radiographic and clinical improvement after treatment of a MET-amplified recurrent glioblastoma with a mesenchymal-epithelial transition inhibitor. J Clin Oncol 2012;30:e30-3.
69. Chinot OL, Wick W, Mason W, Henriksson R, Saran F, Nishikawa R, *et al*. Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. N Engl J Med 2014;370:709-22.
70. Choi C, Ganji SK, DeBerardinis RJ, Hatanpaa KJ, Rakheja D, Kovacs Z, *et al*. 2-hydroxyglutarate detection by magnetic resonance spectroscopy in IDH-mutated patients with gliomas. Nat Med 2012;18:624-9.
71. Chou AP, Chowdhury R, Li S, Chen W, Kim AJ, Piccioni DE, *et al*. Identification of retinol binding protein 1 promoter hypermethylation in isocitrate dehydrogenase 1 and 2 mutant gliomas. J Natl Cancer Inst 2012;104:1458-69.
72. Christensen JG, Zou HY, Arango ME, Li Q, Lee JH, McDonnell SR, *et al*. Cytoreductive antitumor activity of PF-2341066, a novel inhibitor of anaplastic lymphoma kinase and c-Met, in experimental models of anaplastic large-cell lymphoma. Mol Cancer Ther 2007;6:3314-22.
73. Chua SL, Rosenthal MA, Wong SS, Ashley DM, Woods AM, Dowling A, *et al*. Phase 2 study of temozolomide and Caelyx in patients with recurrent glioblastoma multiforme. Neuro Oncol 2004;6:38-43.
74. Cobbs CS, Harkins L, Samanta M, Gillespie GY, Bharara S, King PH, *et al*. Human cytomegalovirus infection and expression in human malignant glioma. Cancer Res 2002;62:3347-50.
75. Dang L, White DW, Gross S, Bennett BD, Bittinger MA, Driggers EM, *et al*. Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. Nature 2009;462:739-44.
76. Darlix A, Baumann C, Lorgis V, Ghiringhelli F, Blonski M, Chauffert B, *et al*. Prolonged administration of adjuvant temozolomide improves survival in adult patients with glioblastoma. Anticancer Res 2013;33:3467-74.
77. DeAngelis LM. Anaplastic glioma: How to prognosticate outcome and choose a treatment strategy. [corrected]. J Clin Oncol 2009;27:5861-2.
78. Von Deimling A, Korshunov A, Hartmann C. The next generation of glioma biomarkers: MGMT methylation, BRAF fusions and IDH1 mutations. Brain Pathol 2011;21:74-87.
79. Desjardins A, Reardon DA, Coan A, Marcello J, Herndon JE 2nd, Bailey L, *et al*. Bevacizumab and daily temozolomide for recurrent glioblastoma. Cancer 2012;118:1302-12.
80. Desjardins A, Reardon DA, Herndon JE, Marcello J, Quinn JA, Rich JN, *et al*. Bevacizumab Plus Irinotecan in Recurrent WHO Grade 3 Malignant Gliomas. Clin Cancer Res 2008;14:7068-73.
81. Dixit S, Hingorani M, Achawal S, Scott I. The sequential use of carmustine wafers (Gliadel®) and post-operative radiotherapy with concomitant temozolomide followed by adjuvant temozolomide: A clinical review. Br J Neurosurg 2011;25:459-69.
82. Dolecek TA, Propp JM, Stroup NE, Kruchko C. CBTRUS statistical report: Primary brain and central nervous system tumors diagnosed in the United States in 2005-2009. Neuro Oncol 2012;14 Suppl 5:v1-49.
83. Douw L, Klein M, Fagel SS, van den Heuvel J, Taphoorn MJ, Aaronson NK, *et al*. Cognitive and radiological effects of radiotherapy in patients with low-grade glioma: Long-term follow-up. Lancet Neurol 2009;8:810-8.
84. Ducray F, del Rio MS, Carpentier C, Psimaras D, Idbaih A, Dehais C, *et al*. Up-front temozolomide in elderly patients with anaplastic oligodendroglioma and oligoastrocytoma. J Neurooncol 2011;101:457-62.
85. Duncan CG, Barwick BG, Jin G, Rago C, Kapoor-Vazirani P, Powell DR, *et al*. A heterozygous IDH1R132H/WT mutation induces genome-wide alterations in DNA methylation. Genome Res 2012;22:2339-55.
86. Lu-Emerson C, Norden AD, Drappatz J, Quant EC, Beroukhim R, Ciampa AS, *et al*. Retrospective study of dasatinib for recurrent glioblastoma after bevacizumab failure. J Neurooncol 2011;104:287-91.
87. Erdem-Eraslan L, Gravendeel LA, de Rooi J, Eilers PH, Idbaih A, Spliet WGM, *et al*. Intrinsic molecular subtypes of glioma are prognostic and predict benefit from adjuvant procarbazine, lomustine, and vincristine chemotherapy in combination with other prognostic factors in anaplastic oligodendroglial brain tumors: A report from EORTC study 26951. J Clin Oncol 2013;31:328-36.
88. Esteller M. Epigenetics in cancer. N Engl J Med 2008;358:1148-59.
89. Fabrini MG, Silvano G, Lolli I, Perrone F, Marsella A, Scotti V, *et al*. A multi-institutional phase II study on second-line Fotemustine chemotherapy in recurrent glioblastoma. J Neurooncol 2009;92:79-86.
90. Fadul CE, Fisher JL, Hampton TH, Lallana EC, Li Z, Gui J, *et al*. Immune response in patients with newly diagnosed glioblastoma multiforme treated with intranodal autologous tumor lysate-dendritic cell vaccination after radiation chemotherapy. J Immunother 2011;34:382-9.
91. De Felice F, Bulzonetti N, Musio D, D'Elia A, Salvati M, Tombolini V. Low-dose fotemustine as second-line chemotherapy for recurrent glioblastoma multiforme. Anticancer Res 2013;33:4013-6.
92. Felsberg J, Thon N, Eigenbrod S, Hentschel B, Sabel MC, Westphal M, *et al*. Promoter methylation and expression of MGMT and the DNA mismatch repair genes MLH1, MSH2, MSH6 and PMS2 in paired primary and recurrent glioblastomas. Int J Cancer 2011;129:659-70.
93. Field KM, Simes J, Wheeler H, Hovey EJ, Nowak AK, Cher L, *et al*. A randomized phase II study of carboplatin and bevacizumab in recurrent glioblastoma multiforme (CABARET). J Clin Oncol 2013;31. Available from: http://meetinglibrary.asco.org/content/115649-132. [Last accessed on 2014 May 03].
94. Fine HA. Bevacizumab in glioblastoma--still much to learn. N Engl J Med 2014;370:764-5.
95. Franceschi E, Omuro AM, Lassman AB, Demopoulos A, Nolan C, Abrey LE. Salvage temozolomide for prior temozolomide responders. Cancer 2005;104:2473-6.
96. Francesconi AB, Dupre S, Matos M, Martin D, Hughes BG, Wyld DK, *et al*. Carboplatin and etoposide combined with bevacizumab for the treatment of recurrent glioblastoma multiforme. J Clin Neurosci 2010;17:970-4.
97. French PJ, Peeters J, Horsman S, Duijm E, Siccama I, van den Bent MJ, *et al*. Identification of differentially regulated splice variants and novel exons in glial brain tumors using exon expression arrays. Cancer Res 2007;67:5635-42.
98. French PJ, Swagemakers SM, Nagel JH, Kouwenhoven MC, Brouwer E, van der Spek P, *et al*. Gene expression profiles associated with treatment response in oligodendrogliomas. Cancer Res 2005;65:11335-44.
99. Frenel JS, Leux C, Loussouarn D, Le Loupp AG, Leclair F, Aumont M, *et al*. Combining two biomarkers, IDH1/2 mutations and 1p/19q codeletion, to stratify anaplastic oligodendroglioma in three groups: A single-center experience. J Neurooncol 2013;114:85-91.
100. Friedman HS, Prados MD, Wen PY, Mikkelsen T, Schiff D, Abrey LE, *et al*. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. J Clin Oncol 2009;27:4733-40.
101. Fuller CE, Schmidt RE, Roth KA, Burger PC, Scheithauer BW, Banerjee R, *et al*. Clinical utility of fluorescence *in situ* hybridization (FISH) in morphologically ambiguous gliomas with hybrid oligodendroglial/astrocytic features. J Neuropathol Exp Neurol 2003;62:1118-28.
102. Gan HK, Rosenthal MA, Dowling A, Kalnins R, Algar E, Wong N, *et al*. A phase II trial of primary temozolomide in patients with grade III oligodendroglial brain tumors. Neuro Oncol 2010;12:500-7.
103. Gaviani P, Salmaggi A, Silvani A. Combined chemotherapy with temozolomide and fotemustine in recurrent glioblastoma patients. J Neurooncol 2011;104:617-8.
104. Gerson SL. MGMT: Its role in cancer aetiology and cancer therapeutics. Nat Rev Cancer 2004;4:296-307.
105. Gil MJ, de Las Peñas R, Reynés G, Balañá C, Peréz-Segura P, García-Velasco A, *et al*. Bevacizumab plus irinotecan in recurrent malignant glioma shows high overall survival in a multicenter retrospective pooled series of the Spanish Neuro-Oncology Research Group (GEINO). Anticancer Drugs 2012;23:659-65.
106. Gilbert MR, Wang M, Aldape K, Lassman A, Sorensen AG, Mikkelson T, *et al*. RTOG 0625: A phase II study of bevacizumab with irinotecan in recurrent glioblastoma (GBM). J Clin Oncol 2009;27:15.
107. Gilbert MR, Dignam JJ, Armstrong TS, Wefel JS, Blumenthal DT, Vogelbaum MA, *et al*. A randomized trial of bevacizumab for newly diagnosed glioblastoma. N Engl J Med 2014;370:699-708.
108. Gilbert MR, Kuhn J, Lamborn KR, Lieberman F, Wen PY, Mehta M, *et al*. Cilengitide in patients with recurrent glioblastoma: The results of NABTC 03-02, a phase II trial with measures of treatment delivery. J Neurooncol 2012;106:147-53.

109. Gilbert MR, Wang M, Aldape KD, Stupp R, Hegi ME, Jaeckle KA, *et al*. Dose-dense temozolomide for newly diagnosed glioblastoma: A randomized phase III clinical trial. J Clin Oncol 2013;31:4085-91.
110. Grasbon-Frodl EM, Kreth FW, Ruiter M, Schnell O, Bise K, Felsberg J, *et al*. Intratumoral homogeneity of MGMT promoter hypermethylation as demonstrated in serial stereotactic specimens from anaplastic astrocytomas and glioblastomas. Int J Cancer 2007;121:2458-64.
111. Gravendeel LA, Kouwenhoven MC, Gevaert O, de Rooi JJ, Stubbs AP, Duijm JE, *et al*. Intrinsic gene expression profiles of gliomas are a better predictor of survival than histology. Cancer Res 2009;69:9065-72.
112. De Groot JF. Prediction of response to chemotherapy in anaplastic glioma: How many markers does it take? J Clin Oncol 2013;31:297-8.
113. De Groot JF, Lamborn KR, Chang SM, Gilbert MR, Cloughesy TF, Aldape K, *et al*. Phase II study of aflibercept in recurrent malignant glioma: A North American Brain Tumor Consortium study. J Clin Oncol 2011;29:2689-95.
114. Groves MD, Puduvalli VK, Gilbert MR, Levin VA, Conrad CA, Liu VH, *et al*. Two phase II trials of temozolomide with interferon-alpha2b (pegylated and non-pegylated) in patients with recurrent glioblastoma multiforme. Br J Cancer 2009;101:615-20.
115. Guan X, Vengoechea J, Zheng S, Sloan AE, Chen Y, Brat DJ, *et al*. Molecular subtypes of glioblastoma are relevant to lower grade glioma. PloS One 2014;9:e91216.
116. Gutenberg A, Bock HC, Brück W, Doerner L, Mehdorn HM, Roggendorf W, *et al*. MGMT promoter methylation status and prognosis of patients with primary or recurrent glioblastoma treated with carmustine wafers. Br J Neurosurg 2013;27:772-8.
117. Gutenberg A, Lumenta CB, Braunsdorf WE, Sabel M, Mehdorn HM, Westphal M, *et al*. The combination of carmustine wafers and temozolomide for the treatment of malignant gliomas. A comprehensive review of the rationale and clinical experience. J Neurooncol 2013;113:163-74.
118. Han SJ, Rolston JD, Molinaro AM, Clarke JL, Prados MD, Chang SM, *et al*. Phase II trial of 7 days on/7 days off temozolmide for recurrent high-grade glioma. Neuro Oncol 2014;16:1255-62.
119. Hasselbalch B, Lassen U, Hansen S, Holmberg M, Sørensen M, Kosteljanetz M, *et al*. Cetuximab, bevacizumab, and irinotecan for patients with primary glioblastoma and progression after radiation therapy and temozolomide: A phase II trial. Neuro Oncol 2010;12:508-16.
120. Hau P, Koch D, Hundsberger T, Marg E, Bauer B, Rudolph R, *et al*. Safety and feasibility of long-term temozolomide treatment in patients with high-grade glioma. Neurology 2007;68:688-90.
121. Hegi ME, Diserens AC, Gorlia T, Hamou MF, de Tribolet N, Weller M, *et al*. MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med 2005;352:997-1003.
122. Heimberger AB, Crotty LE, Archer GE, McLendon RE, Friedman A, Dranoff G, *et al*. Bone marrow-derived dendritic cells pulsed with tumor homogenate induce immunity against syngeneic intracerebral glioma. J Neuroimmunol 2000;103:16-25.
123. Heimberger AB, Archer GE, Mitchell DA, Bigner DD, Schmittling RJ, Herndon JE, *et al*. Epidermal growth factor receptor variant III (EGFRvIII) vaccine (CDX-110) in GBM. J Clin Oncol 2009;27:15s. Available from: http://meetinglibrary.asco.org/content/34913-65. [Last accessed on 2014 May 03].
124. Heimberger AB, Hlatky R, Suki D, Yang D, Weinberg J, Gilbert M, *et al*. Prognostic effect of epidermal growth factor receptor and EGFRvIII in glioblastoma multiforme patients. Clin Cancer Res 2005;11:1462-6.
125. Heimberger AB, Suki D, Yang D, Shi W, Aldape K. The natural history of EGFR and EGFRvIII in glioblastoma patients. J Transl Med 2005;3:38.
126. Heimberger AB, Sun W, Hussain SF, Dey M, Crutcher L, Aldape K, *et al*. Immunological responses in a patient with glioblastoma multiforme treated with sequential courses of temozolomide and immunotherapy: Case study. Neuro Oncol 2008;10:98-103.
127. Herrlinger U, Schaefer N, Steinbach JP, Weyerbrock A, Hau P, Goldbrunner R, *et al*. Bevacizumab, irinotecan, and radiotherapy versus standard temozolomide and radiotherapy in newly diagnosed, MGMT-nonmethylated glioblastoma patients: First results from the randomized multicenter GLARIUS trial. J Clin Oncol 2013;31. Available from: http://meetinglibrary.asco.org/content/114388-132. [Last accessed on 2014 May 03].
128. Hofer S, Elandt K, Greil R, Hottinger AF, Huber U, Lemke D, *et al*. Clinical outcome with bevacizumab in patients with recurrent high-grade glioma treated outside clinical trials. Acta Oncol 2011;50:630-5.
129. Hofer S, Lassman AB. Molecular markers in gliomas: Impact for the clinician. Target Oncol 2010;5:201-10.
130. Hofer S, Rushing E, Preusser M, Marosi C. Molecular biology of high-grade gliomas: What should the clinician know? Chin J Cancer 2014;33:4-7.
131. Hofland KF, Hansen S, Sorensen M, Engelholm S, Schultz HP, Muhic A, *et al*. Neoadjuvant bevacizumab and irinotecan versus bevacizumab and temozolomide followed by concomitant chemoradiotherapy in newly diagnosed glioblastoma multiforme: A randomized phase II study. Acta Oncol 2014;53:939-44.
132. Hofman FM, Stathopoulos A, Kruse CA, Chen TC, Schijns VE. Immunotherapy of malignant gliomas using autologous and allogeneic tissue cells. Anticancer Agents Med Chem 2010;10:462-70.
133. Holdhoff M, Rosner GL, Alcorn S, Grossman SA. "Elderly" patients with newly diagnosed glioblastoma deserve optimal care. J Neurooncol 2013;113:343-4.
134. Intergroup Radiation Therapy Oncology Group Trial 9402; Cairncross G, Berkey B, Shaw E, Jenkins R, Scheithauer B, *et al*. Phase III trial of chemotherapy plus radiotherapy compared with radiotherapy alone for pure and mixed anaplastic oligodendroglioma: Intergroup Radiation Therapy Oncology Group Trial 9402. J Clin Oncol 2006;24:2707-14.
135. Iwamoto FM, Abrey LE, Beal K, Gutin PH, Rosenblum MK, Reuter VE, *et al*. Patterns of relapse and prognosis after bevacizumab failure in recurrent glioblastoma. Neurology 2009;73:1200-6.
136. Jenkins RB, Blair H, Ballman KV, Giannini C, Arusell RM, Law M, *et al*. A t (1;19)(q10;p10) mediates the combined deletions of 1p and 19q and predicts a better prognosis of patients with oligodendroglioma. Cancer Res 2006;66:9852-61.
137. Jeremic B, Grujicic D, Antunovic V, Djuric L, Stojanovic M, Shibamoto Y. Influence of extent of surgery and tumor location on treatment outcome of patients with glioblastoma multiforme treated with combined modality approach. J Neurooncol 1994;21:177-85.
138. Jiang H, Ren X, Cui X, Wang J, Jia W, Zhou Z, *et al*. 1p/19q codeletion and IDH1/2 mutation identified a subtype of anaplastic oligoastrocytomas with prognosis as favorable as anaplastic oligodendrogliomas. Neuro Oncol 2013;15:775-82.
139. Jiao Y, Killela PJ, Reitman ZJ, Rasheed AB, Heaphy CM, de Wilde RF, *et al*. Frequent ATRX, CIC, FUBP1 and IDH1 mutations refine the classification of malignant gliomas. Oncotarget 2012;3:709-22.
140. Kaloshi G, Brace G, Rroji A, Bushati T, Roci E, Hoxha M, *et al*. Bevacizumab alone at 5 mg/kg in an every-3-week schedule for patients with recurrent glioblastomas: A single center experience. Tumori 2013;99:601-3.
141. Kannan K, Inagaki A, Silber J, Gorovets D, Zhang J, Kastenhuber ER, *et al*. Whole-exome sequencing identifies ATRX mutation as a key molecular determinant in lower-grade glioma. Oncotarget 2012;3:1194-203.
142. Kappelle AC, Postma TJ, Taphoorn MJ, Groeneveld GJ, van den Bent MJ, van Groeningen CJ, *et al*. PCV chemotherapy for recurrent glioblastoma multiforme. Neurology 2001;56:118-20.
143. Kaufmann JK, Chiocca EA. Glioma virus therapies between bench and bedside. Neuro Oncol 2014;16:334-51.
144. Keime-Guibert F, Chinot O, Taillandier L, Cartalat-Carel S, Frenay M, Kantor G, *et al*. Radiotherapy for glioblastoma in the elderly. N Engl J Med 2007;356:1527-35.
145. Khan RB, Raizer JJ, Malkin MG, Bazylewicz KA, Abrey LE. A phase II study of extended low-dose temozolomide in recurrent malignant gliomas. Neuro Oncol 2002;4:39-43.
146. Khasraw M, Bell D, Wheeler H. Long-term use of temozolomide: Could you use temozolomide safely for life in gliomas? J Clin Neurosci 2009;16:854-5.
147. Killela PJ, Pirozzi CJ, Healy P, Reitman ZJ, Lipp E, Rasheed BA, *et al*. Mutations in IDH1, IDH2, and in the TERT promoter define clinically distinct subgroups of adult malignant gliomas. Oncotarget 2014;5:1515-25.
148. Killela PJ, Pirozzi CJ, Reitman ZJ, Jones S, Rasheed BA, Lipp E, *et al*. The genetic landscape of anaplastic astrocytoma. Oncotarget 2014;5:1452-7.
149. Kim YH, Park CK, Cho WH, Kim IA, Moon S, Choe G, *et al*. Temozolomide during and after radiation therapy for WHO grade III gliomas: Preliminary report of a prospective multicenter study. J Neurooncol 2011;103:503-12.
150. Kirson ED, Dbalý V, Tovarys F, Vymazal J, Soustiel JF, Itzhaki A, *et al*. Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors. Proc Natl Acad Sci U S A 2007;104:10152-7.
151. Kirson ED, Schneiderman RS, Dbalý V, Tovarys F, Vymazal J, Itzhaki A, *et al*. Chemotherapeutic treatment efficacy and sensitivity are increased by adjuvant alternating electric fields (TTFields). BMC Med Phys 2009;9:1.

152. Kleihues P, Ohgaki H. Primary and secondary glioblastomas: From concept to clinical diagnosis. Neuro Oncol 1999;1:44-51.
153. Kleinberg LR, Weingart J, Burger P, Carson K, Grossman SA, Li K, *et al.* Clinical course and pathologic findings after Gliadel and radiotherapy for newly diagnosed malignant glioma: Implications for patient management. Cancer Invest 2004;22:1-9.
154. Kleinschmidt-DeMasters BK, Aisner DL, Birks DK, Foreman NK. Epithelioid GBMs show a high percentage of BRAF V600E mutation. Am J Surg Pathol 2013;37:685-98.
155. Kong DS, Lee JI, Kim JH, Kim ST, Kim WS, Suh YL, *et al.* Phase II trial of low-dose continuous (metronomic) treatment of temozolomide for recurrent glioblastoma. Neuro Oncol 2010;12:289-96.
156. Kong DS, Lee JI, Kim WS, Son MJ, Lim DH, Kim ST, *et al.* A pilot study of metronomic temozolomide treatment in patients with recurrent temozolomide-refractory glioblastoma. Oncol Rep 2006;16:1117-21.
157. Kong DS, Song SY, Kim DH, Joo KM, Yoo JS, Koh JS, *et al.* Prognostic significance of c-Met expression in glioblastomas. Cancer 2009;115:140-8.
158. Koochekpour S, Jeffers M, Rulong S, Taylor G, Klineberg E, Hudson EA, *et al.* Met and hepatocyte growth factor/scatter factor expression in human gliomas. Cancer Res 1997;57:5391-8.
159. Kreisl TN, Kim L, Moore K, Duic P, Royce C, Stroud I, *et al.* Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumor progression in recurrent glioblastoma. J Clin Oncol 2009;27:740-5.
160. Kreisl TN, Zhang W, Odia Y, Shih JH, Butman JA, Hammoud D, *et al.* A phase II trial of single-agent bevacizumab in patients with recurrent anaplastic glioma. Neuro Oncol 2011;13:1143-50.
161. Kros JM, Gorlia T, Kouwenhoven MC, Zheng PP, Collins VP, Figarella-Branger D, *et al*. Panel review of anaplastic oligodendroglioma from European Organization For Research and Treatment of Cancer Trial 26951: Assessment of consensus in diagnosis, influence of 1p/19q loss, and correlations with outcome. J Neuropathol Exp Neurol 2007;66:545-51.
162. Kuan CT, Wikstrand CJ, Bigner DD. EGF mutant receptor vIII as a molecular target in cancer therapy. Endocr Relat Cancer 2001;8:83-96.
163. Kunwar S, Chang S, Westphal M, Vogelbaum M, Sampson J, Barnett G, *et al.* Phase III randomized trial of CED of IL13-PE38QQR vs Gliadel wafers for recurrent glioblastoma. Neuro Oncol 2010;12:871-81.
164. Laffaire J, Everhard S, Idbaih A, Crinière E, Marie Y, de Reyniès A, *et al.* Methylation profiling identifies 2 groups of gliomas according to their tumorigenesis. Neuro Oncol 2011;13:84-98.
165. Lai A, Tran A, Nghiemphu PL, Pope WB, Solis OE, Selch M, *et al.* Phase II study of bevacizumab plus temozolomide during and after radiation therapy for patients with newly diagnosed glioblastoma multiforme. J Clin Oncol 2011;29:142-8.
166. Lal A, Glazer CA, Martinson HM, Friedman HS, Archer GE, Sampson JH, *et al.* Mutant epidermal growth factor receptor up-regulates molecular effectors of tumor invasion. Cancer Res 2002;62:3335-9.
167. Lamborn KR, Yung WK, Chang SM, Wen PY, Cloughesy TF, DeAngelis LM, *et al.* Progression-free survival: An important end point in evaluating therapy for recurrent high-grade gliomas. Neuro Oncol 2008;10:162-70.
168. Lassman AB, Iwamoto FM, Cloughesy TF, Aldape KD, Rivera AL, Eichler AF, *et al.* International retrospective study of over 1000 adults with anaplastic oligodendroglial tumors. Neuro Oncol 2011;13:649-59.
169. Lechapt-Zalcman E, Levallet G, Dugué AE, Vital A, Diebold MD, Menei P, *et al.* O (6) -methylguanine-DNA methyltransferase (MGMT) promoter methylation and low MGMT-encoded protein expression as prognostic markers in glioblastoma patients treated with biodegradable carmustine wafer implants after initial surgery followed by radiotherapy with concomitant and adjuvant temozolomide. Cancer 2012;118:4545-54.
170. Levin VA, Silver P, Hannigan J, Wara WM, Gutin PH, Davis RL, *et al.* Superiority of post-radiotherapy adjuvant chemotherapy with CCNU, procarbazine, and vincristine (PCV) over BCNU for anaplastic gliomas: NCOG 6G61 final report. Int J Radiat Oncol Biol Phys 1990;18:321-4.
171. Li A, Walling J, Ahn S, Kotliarov Y, Su Q, Quezado M, *et al.* Unsupervised analysis of transcriptomic profiles reveals six glioma subtypes. Cancer Res 2009;69:2091-9.
172. Liau LM, Black KL, Martin NA, Sykes SN, Bronstein JM, Jouben-Steele L, *et al.* Treatment of a patient by vaccination with autologous dendritic cells pulsed with allogeneic major histocompatibility complex class I-matched tumor peptides. Case Report. Neurosurg Focus 2000;9:e8.
173. Liau LM, Prins RM, Kiertscher SM, Odesa SK, Kremen TJ, Giovannone AJ, *et al.* Dendritic cell vaccination in glioblastoma patients induces systemic and intracranial T-cell responses modulated by the local central nervous system tumor microenvironment. Clin Cancer Res 2005;11:5515-25.
174. Lin N, Yan W, Gao K, Wang Y, Zhang J, You Y. Prevalence and clinicopathologic characteristics of the molecular subtypes in malignant glioma: A multi-institutional analysis of 941 cases. PloS One 2014;9:e94871.
175. Liu L, Bäcklund LM, Nilsson BR, Grandér D, Ichimura K, Goike HM, *et al.* Clinical significance of EGFR amplification and the aberrant EGFRvIII transcript in conventionally treated astrocytic gliomas. J Mol Med (Berl) 2005;83:917-26.
176. Liu W, Fu Y, Xu S, Ding F, Zhao G, Zhang K, *et al.* c-Met expression is associated with time to recurrence in patients with glioblastoma multiforme. J Clin Neurosci 2011;18:119-21.
177. Liu XY, Gerges N, Korshunov A, Sabha N, Khuong-Quang DA, Fontebasso AM, *et al.* Frequent ATRX mutations and loss of expression in adult diffuse astrocytic tumors carrying IDH1/IDH2 and TP53 mutations. Acta Neuropathol (Berl) 2012;124:615-25.
178. Lou E, Peters KB, Sumrall AL, Desjardins A, Reardon DA, Lipp ES, *et al.* Phase II trial of upfront bevacizumab and temozolomide for unresectable or multifocal glioblastoma. Cancer Med 2013;2:185-95.
179. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, *et al.* The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol (Berl) 2007;114:97-109.
180. Malkoun N, Chargari C, Forest F, Fotso MJ, Cartier L, Auberdiac P, *et al.* Prolonged temozolomide for treatment of glioblastoma: Preliminary clinical results and prognostic value of p53 overexpression. J Neurooncol 2012;106:127-33.
181. Malmström A, Grønberg BH, Marosi C, Stupp R, Frappaz D, Schultz H, *et al.* Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: The Nordic randomised, phase 3 trial. Lancet Oncol 2012;13:916-26.
182. Matthews S, Succar P, Jelinek H, McParland B, Buckland M, McLachlan CS. Diagnosis of oligodendroglioma: Molecular and classical histological assessment in the twenty-first century. Asia Pac J Clin Oncol 2012;8:213-6.
183. McDermott U, Iafrate AJ, Gray NS, Shioda T, Classon M, Maheswaran S, *et al.* Genomic alterations of anaplastic lymphoma kinase may sensitize tumors to anaplastic lymphoma kinase inhibitors. Cancer Res 2008;68:3389-95.
184. McGirt MJ, Than KD, Weingart JD, Chaichana KL, Attenello FJ, Olivi A, *et al.* Gliadel (BCNU) wafer plus concomitant temozolomide therapy after primary resection of glioblastoma multiforme. J Neurosurg 2009;110:583-8.
185. McPherson CM, Gerena-Lewis M, Breneman JC, Warnick RE. Results of phase I study of a multi-modality treatment for newly diagnosed glioblastoma multiforme using local implantation of concurrent BCNU wafers and permanent I-125 seeds followed by fractionated radiation and temozolomide chemotherapy. J Neurooncol 2012;108:521-5.
186. Mehta A, Shervington L, Munje C, Shervington A. A novel therapeutic strategy for the treatment of glioma, combining chemical and molecular targeting of hsp90a. Cancers 2011;3:4228-44.
187. Le Mercier M, Hastir D, Moles Lopez X, De Nève N, Maris C, Trepant AL, *et al.* A simplified approach for the molecular classification of glioblastomas. PloS One 2012;7:e45475.
188. Mesaros EF, Ott GR, Dorsey BD. Anaplastic lymphoma kinase inhibitors as anticancer therapeutics: A patent review. Expert Opin Ther Pat 2014;24:417-42.
189. Metellus P, Coulibaly B, Nanni I, Fina F, Eudes N, Giorgi R, *et al.* Prognostic impact of O6-methylguanine-DNA methyltransferase silencing in patients with recurrent glioblastoma multiforme who undergo surgery and carmustine wafer implantation: A prospective patient cohort. Cancer 2009;115:4783-94.
190. Miglierini P, Bouchekoua M, Rousseau B, Hieu PD, Malhaire JP, Pradier O. Impact of the per-operatory application of GLIADEL wafers (BCNU, carmustine) in combination with temozolomide and radiotherapy in patients with glioblastoma multiforme: Efficacy and toxicity. Clin Neurol Neurosurg 2012;114:1222-5.
191. Mikkelsen T, Doyle T, Anderson J, Margolis J, Paleologos N, Gutierrez J, *et al.* Temozolomide single-agent chemotherapy for newly diagnosed anaplastic oligodendroglioma. J Neurooncol 2009;92:57-63.
192. Minniti G, Arcella A, Scaringi C, Lanzetta G, Di Stefano D, Scarpino S, *et al.* Chemoradiation for anaplastic oligodendrogliomas: Clinical outcomes and prognostic value of molecular markers. J Neurooncol 2014;116:275-82.
193. Vik-Mo EO, Nyakas M, Mikkelsen BV, Moe MC, Due-Tønnesen P, Suso EM, *et al.* Therapeutic vaccination against autologous cancer stem cells with

mRNA-transfected dendritic cells in patients with glioblastoma. Cancer Immunol Immunother 2013;62:1499-509.
194. Möllemann M, Wolter M, Felsberg J, Collins VP, Reifenberger G. Frequent promoter hypermethylation and low expression of the MGMT gene in oligodendroglial tumors. Int J Cancer 2005;113:379-85.
195. Møller S, Grunnet K, Hansen S, Schultz H, Holmberg M, Sorensen M, *et al*. A phase II trial with bevacizumab and irinotecan for patients with primary brain tumors and progression after standard therapy. Acta Oncol 2012;51:797-804.
196. Moscatello DK, Holgado-Madruga M, Godwin AK, Ramirez G, Gunn G, Zoltick PW, *et al*. Frequent expression of a mutant epidermal growth factor receptor in multiple human tumors. Cancer Res 1995;55:5536-9.
197. Moscatello DK, Ramirez G, Wong AJ. A naturally occurring mutant human epidermal growth factor receptor as a target for peptide vaccine immunotherapy of tumors. Cancer Res 1997;57:1419-24.
198. Mrugala MM, Crew LK, Fink JR, Spence AM. Carboplatin and bevacizumab for recurrent malignant glioma. Oncol Lett 2012;4:1082-6.
199. Mueller S, Polley MY, Lee B, Kunwar S, Pedain C, Wembacher-Schröder E, *et al*. Effect of imaging and catheter characteristics on clinical outcome for patients in the PRECISE study. J Neurooncol 2011;101:267-77.
200. Mur P, Mollejo M, Ruano Y, de Lope ÁR, Fiaño C, García JF, *et al*. Codeletion of 1p and 19q determines distinct gene methylation and expression profiles in IDH-mutated oligodendroglial tumors. Acta Neuropathol (Berl) 2013;126:277-89.
201. Nabors LB, Mikkelsen T, Hegi ME, Ye X, Batchelor T, Lesser G, *et al*. A safety run-in and randomized phase 2 study of cilengitide combined with chemoradiation for newly diagnosed glioblastoma (NABTT 0306). Cancer 2012;118:5601-7.
202. Nabors LB, Fink KL, Mikkelsen T, Grujicic D, Tamawski R, Nam DH, *et al*. Cilengitide in combination with standard treatment for patients with newly diagnosed glioblastoma with unmethylated O6-methylguanine-DNA methyltransferase (MGMT) gene promoter: Key results of the open label, controlled, randomized Phase II CORE study. Neuro Oncol 2013; 15 (suppl 3):75-84
203. Nagane M, Kobayashi K, Ohnishi A, Shimizu S, Shiokawa Y. Prognostic significance of O6-methylguanine-DNA methyltransferase protein expression in patients with recurrent glioblastoma treated with temozolomide. Jpn J Clin Oncol 2007;37:897-906.
204. Nagane M, Nishikawa R, Narita Y, Kobayashi H, Takano S, Shinoura N, *et al*. Phase II study of single-agent bevacizumab in Japanese patients with recurrent malignant glioma. Jpn J Clin Oncol 2012;42:887-95.
205. Nghiemphu PL, Liu W, Lee Y, Than T, Graham C, Lai A, *et al*. Bevacizumab and chemotherapy for recurrent glioblastoma: A single-institution experience. Neurology 2009;72:1217-22.
206. Nicolaides TP, Li H, Solomon DA, Hariono S, Hashizume R, Barkovich K, *et al*. Targeted therapy for BRAFV600E malignant astrocytoma. Clin Cancer Res 2011;17:7595-604.
207. Ning J, Wakimoto H, Rabkin SD. Immunovirotherapy for glioblastoma. Cell Cycle 2014;13:175-6.
208. Nitta T, Sato K. Prognostic implications of the extent of surgical resection in patients with intracranial malignant gliomas. Cancer 1995;75:2727-31.
209. Nobusawa S, Watanabe T, Kleihues P, Ohgaki H. IDH1 mutations as molecular signature and predictive factor of secondary glioblastomas. Clin Cancer Res 2009;15:6002-7.
210. Noël G, Schott R, Froelich S, Gaub MP, Boyer P, Fischer-Lokou D, *et al*. Retrospective comparison of chemoradiotherapy followed by adjuvant chemotherapy, with or without prior gliadel implantation (carmustine) after initial surgery in patients with newly diagnosed high-grade gliomas. Int J Radiat Oncol Biol Phys 2012;82:749-55.
211. Norden AD, Young GS, Setayesh K, Muzikansky A, Klufas R, Ross GL, *et al*. Bevacizumab for recurrent malignant gliomas: Efficacy, toxicity, and patterns of recurrence. Neurology 2008;70:779-87.
212. Norden AD, Lesser GJ, Drappatz J, Ligon KL, Hammond SN, Lee EQ, *et al*. Phase 2 study of dose-intense temozolomide in recurrent glioblastoma. Neuro Oncol 2013;15:930-5.
213. Nutt CL, Costello JF, Bambrick LL, Yarosh DB, Swinnen LJ, Chambers AF, *et al*. O6-methylguanine-DNA methyltransferase in tumors and cells of the oligodendrocyte lineage. Can J Neurol Sci 1995;22:111-5.
214. Nutt CL, Mani DR, Betensky RA, Tamayo P, Cairncross JG, Ladd C, *et al*. Gene expression-based classification of malignant gliomas correlates better with survival than histological classification. Cancer Res 2003;63:1602-7.
215. Ohgaki H, Kleihues P. Genetic pathways to primary and secondary glioblastoma. Am J Pathol 2007;170:1445-53.
216. Okada N, Masunaga Y, Okada Y, Mizuguchi H, Iiyama S, Mori N, *et al*. Dendritic cells transduced with gp100 gene by RGD fiber-mutant adenovirus vectors are highly efficacious in generating anti-B16BL6 melanoma immunity in mice. Gene Ther 2003;10:1891-902.
217. Omuro A, DeAngelis LM. Glioblastoma and other malignant gliomas: A clinical review. JAMA 2013;310:1842-50.
218. Pan E, Mitchell SB, Tsai JS. A retrospective study of the safety of BCNU wafers with concurrent temozolomide and radiotherapy and adjuvant temozolomide for newly diagnosed glioblastoma patients. J Neurooncol 2008;88:353-7.
219. Panageas KS, Iwamoto FM, Cloughesy TF, Aldape KD, Rivera AL, Eichler AF, *et al*. Initial treatment patterns over time for anaplastic oligodendroglial tumors. Neuro Oncol 2012;14:761-7.
220. Pérez-Larraya JG, Ducray F, Chinot O, Catry-Thomas I, Taillandier L, Guillamo JS, *et al*. Temozolomide in elderly patients with newly diagnosed glioblastoma and poor performance status: An ANOCEF Phase II trial. J Clin Oncol 2011;29:3050-5.
221. Perry J, Chambers A, Spithoff K, Laperriere N. Gliadel wafers in the treatment of malignant glioma: A systematic review. Curr Oncol 2007;14:189-94.
222. Perry JR, Bélanger K, Mason WP, Fulton D, Kavan P, Easaw J, *et al*. Phase II trial of continuous dose-intense temozolomide in recurrent malignant glioma: RESCUE study. J Clin Oncol 2010;28:2051-7.
223. Phillips HS, Kharbanda S, Chen R, Forrest WF, Soriano RH, Wu TD, *et al*. Molecular subclasses of high-grade glioma predict prognosis, delineate a pattern of disease progression, and resemble stages in neurogenesis. Cancer Cell 2006;9:157-73.
224. Piccioni DE, Selfridge J, Mody RR, Chowdhury R, Li S, Lalezari S, *et al*. Deferred use of bevacizumab for recurrent glioblastoma is not associated with diminished efficacy. Neuro Oncol 2014;16:815-22.
225. Platten M, Schumacher T, Bunse L, Sahm F, Pusch S, Quandt J, *et al*. A vaccine targeting mutant IDH1 induces antitumor immunity. Neurology 2014;512:324-7.
226. Poulsen HS, Grunnet K, Sorensen M, Olsen P, Hasselbalch B, Nelausen K, *et al*. Bevacizumab plus irinotecan in the treatment patients with progressive recurrent malignant brain tumours. Acta Oncol 2009;48:52-8.
227. Preusser M, Elezi L, Hainfellner JA. Reliability and reproducibility of PCR-based testing of O6-methylguanine-DNA methyltransferase gene (MGMT) promoter methylation status in formalin-fixed and paraffin-embedded neurosurgical biopsy specimens. Clin Neuropathol 2008;27:388-90.
228. Preusser M. MGMT analysis at DNA, RNA and protein levels in glioblastoma tissue. Histol Histopathol 2009;24:511-18.
229. Prins RM, Soto H, Konkankit V, Odesa SK, Eskin A, Yong WH, *et al*. Gene expression profile correlates with T-cell infiltration and relative survival in glioblastoma patients vaccinated with dendritic cell immunotherapy. Clin Cancer Res 2011;17:1603-15.
230. Quant EC, Norden AD, Drappatz J, Muzikansky A, Doherty L, Lafrankie D, *et al*. Role of a second chemotherapy in recurrent malignant glioma patients who progress on bevacizumab. Neuro Oncol 2009;11:550-5.
231. Quigley MR, Flores N, Maroon JC, Sargent B, Lang S, Elrifai A. Value of surgical intervention in the treatment of glioma. Stereotact Funct Neurosurg 1995;65:171-5.
232. Quillien V, Lavenu A, Karayan-Tapon L, Carpentier C, Labussière M, Lesimple T, *et al*. Comparative assessment of 5 methods (methylation-specific polymerase chain reaction, MethyLight, pyrosequencing, methylation-sensitive high-resolution melting, and immunohistochemistry) to analyze O6-methylguanine-DNA-methyltranferase in a series of 100 glioblastoma patients. Cancer 2012;118:4201-11.
233. Rahbar A, Orrego A, Peredo I, Dzabic M, Wolmer-Solberg N, Strååt K, *et al*. Human cytomegalovirus infection levels in glioblastoma multiforme are of prognostic value for survival. J Clin Virol 2013;57:36-42.
234. Rainov NG, Söling A. Clinical studies with targeted toxins in malignant glioma. Rev Recent Clin Trials 2006;1:119-31.
235. Raizer JJ, Grimm S, Chamberlain MC, Nicholas MK, Chandler JP, Muro K, *et al*. A phase 2 trial of single-agent bevacizumab given in an every-3-week schedule for patients with recurrent high-grade gliomas. Cancer 2010;116:5297-305.
236. Reardon DA, Desjardins A, Vredenburgh JJ, Gururangan S, Sampson JH,

Sathornsumetee S, *et al*. Metronomic chemotherapy with daily, oral etoposide plus bevacizumab for recurrent malignant glioma: A phase II study. Br J Cancer 2009;101:1986-94.
237. Reardon DA, Desjardins A, Peters KB, Gururangan S, Sampson JH, McLendon RE, *et al*. Phase II study of carboplatin, irinotecan, and bevacizumab for bevacizumab naïve, recurrent glioblastoma. J Neurooncol 2012;107:155-64.
238. Reardon DA, Fink KL, Mikkelsen T, Cloughesy TF, O'Neill A, Plotkin S, *et al*. Randomized phase II study of cilengitide, an integrin-targeting arginine-glycine-aspartic acid peptide, in recurrent glioblastoma multiforme. J Clin Oncol 2008;26:5610-7.
239. Reardon DA, Quinn JA, Rich JN, Desjardins A, Vredenburgh J, Gururangan S, *et al*. Phase I trial of irinotecan plus temozolomide in adults with recurrent malignant glioma. Cancer 2005;104:1478-86.
240. Reardon DA, Vredenburgh JJ, Desjardins A, Peters K, Gururangan S, Sampson JH, *et al*. Effect of CYP3A-inducing anti-epileptics on sorafenib exposure: Results of a phase II study of sorafenib plus daily temozolomide in adults with recurrent glioblastoma. J Neurooncol 2011;101:57-66.
241. Reardon DA, Wucherpfennig KW, Freeman G, Wu CJ, Chiocca EA, Wen PY, *et al*. An update on vaccine therapy and other immunotherapeutic approaches for glioblastoma. Expert Rev Vaccines 2013;12:597-615.
242. Reithmeier T, Graf E, Piroth T, Trippel M, Pinsker MO, Nikkhah G. BCNU for recurrent glioblastoma multiforme: Efficacy, toxicity and prognostic factors. BMC Cancer 2010;10:30.
243. Reyes SB, Narayanan AS, Lee HS, Tchaicha JH, Aldape KD, Lang FF, *et al*. αvβ8 integrin interacts with RhoGD11 to regulate Rac1 and Cdc42 activation and drive glioblastoma cell invasion. Mol Biol Cell 2013;24:474-82.
244. Reyes-Botero G, Honnorat J, Chinot OL, Taillandier L, Catry-Thomas I, Barriere J, *et al*. Temozolomide plus bevacizumab in elderly patients with newly diagnosed glioblastoma and poor performance status: An Anocef phase II trial. J Clin Oncol 2013;31. Available from: http://meetinglibrary.asco.org/content/112330-132. [Last accessed on 2014 May 03].
245. Reynés G, Balañá C, Gallego O, Iglesias L, Pérez P, García JL. A phase I study of irinotecan in combination with metronomic temozolomide in patients with recurrent glioblastoma. Anticancer Drugs 2014;25:717-22.
246. Riehmer V, Gietzelt J, Beyer U, Hentschel B, Westphal M, Schackert G, *et al*. Genomic profiling reveals distinctive molecular relapse patterns in IDH1/2 wild-type glioblastoma. Genes Chromosomes Cancer 2014;53:589-605.
247. Rivera AL, Pelloski CE, Gilbert MR, Colman H, De La Cruz C, Sulman EP, *et al*. MGMT promoter methylation is predictive of response to radiotherapy and prognostic in the absence of adjuvant alkylating chemotherapy for glioblastoma. Neuro Oncol 2010;12:116-21.
248. Roa W, Brasher PMA, Bauman G, Anthes M, Bruera E, Chan A, *et al*. Abbreviated course of radiation therapy in older patients with glioblastoma multiforme: A prospective randomized clinical trial. J Clin Oncol 2004;22:1583-8.
249. Rohle D, Popovici-Muller J, Palaskas N, Turcan S, Grommes C, Campos C, *et al*. An inhibitor of mutant IDH1 delays growth and promotes differentiation of glioma cells. Science 2013;340:626-30.
250. Roldán Urgoiti GB, Singh AD, Easaw JC. Extended adjuvant temozolomide for treatment of newly diagnosed glioblastoma multiforme. J Neurooncol 2012;108:173-7.
251. Roth P, Silginer M, Goodman SL, Hasenbach K, Thies S, Maurer G, *et al*. Integrin control of the transforming growth factor-β pathway in glioblastoma. Brain J Neurol 2013;136:564-76.
252. Russell SJ, Peng KW, Bell JC. Oncolytic virotherapy. Nat Biotechnol 2012;30:658-70.
253. Rutkowski S, De Vleeschouwer S, Kaempgen E, Wolff JEA, Kühl J, Demaerel P, *et al*. Surgery and adjuvant dendritic cell-based tumour vaccination for patients with relapsed malignant glioma, a feasibility study. Br J Cancer 2004;91:1656-62.
254. Sabatier J, Uro-Coste E, Pommepuy I, Labrousse F, Allart S, Trémoulet M, *et al*. Detection of human cytomegalovirus genome and gene products in central nervous system tumours. Br J Cancer 2005;92:747-50.
255. Sabel M, Giese A. Safety profile of carmustine wafers in malignant glioma: A review of controlled trials and a decade of clinical experience. Curr Med Res Opin 2008;24:3239-57.
256. Salmaggi A, Duri S, Silvani A, Gaviani P, Milanesi I, Casali C, *et al*. Loco-regional treatments in first-diagnosis glioblastoma: Literature review on association between Stupp protocol and Gliadel. Neurol Sci 2011;32 Suppl 2:S241-5.
257. Salmaggi A, Milanesi I, Silvani A, Gaviani P, Marchetti M, Fariselli L, *et al*. Prospective study of carmustine wafers in combination with 6-month metronomic temozolomide and radiation therapy in newly diagnosed glioblastoma: Preliminary results. J Neurosurg 2013;118:821-9.
258. Salvati M, D'elia A, Frati A, Brogna C, Santoro A, Delfini R. Safety and feasibility of the adjunct of local chemotherapy with biodegradable carmustine (BCNU) wafers to the standard multimodal approach to high grade gliomas at first diagnosis. J Neurosurg Sci 2011;55:1-6.
259. Sanson M, Marie Y, Paris S, Idbaih A, Laffaire J, Ducray F, *et al*. Isocitrate dehydrogenase 1 codon 132 mutation is an important prognostic biomarker in gliomas. J Clin Oncol 2009;27:4150-4.
260. Santoni M, Paccapelo A, Burattini L, Onofri A, Cascinu S. Twice-daily dosing of temozolomide in combination with fotemustine for the treatment of patients with refractory glioblastoma. Anticancer Res 2012;32:1099-101.
261. Santoni M, Scoccianti S, Lolli I, Fabrini MG, Silvano G, Detti B, *et al*. Efficacy and safety of second-line fotemustine in elderly patients with recurrent glioblastoma. J Neurooncol 2013;113:397-401.
262. Sathornsumetee S, Desjardins A, Vredenburgh JJ, McLendon RE, Marcello J, Herndon JE, *et al*. Phase II trial of bevacizumab and erlotinib in patients with recurrent malignant glioma. Neuro Oncol 2010;12:1300-10.
263. Schmidt F, Fischer J, Herrlinger U, Dietz K, Dichgans J, Weller M. PCV chemotherapy for recurrent glioblastoma. Neurology 2006;66:587-9.
264. Scoccianti S, Detti B, Sardaro A, Iannalfi A, Meattini I, Leonulli BG, *et al*. Second-line chemotherapy with fotemustine in temozolomide-pretreated patients with relapsing glioblastoma: A single institution experience. Anticancer Drugs 2008;19:613-20.
265. Seiz M, Krafft U, Freyschlag CF, Weiss C, Schmieder K, Lohr F, *et al*. Long-term adjuvant administration of temozolomide in patients with glioblastoma multiforme: Experience of a single institution. J Cancer Res Clin Oncol 2010;136:1691-5.
266. Seystahl K, Wiestler B, Hundsberger T, Happold C, Wick W, Weller M, *et al*. Bevacizumab alone or in combination with irinotecan in recurrent WHO grade II and grade III gliomas. Eur Neurol 2013;69:95-101.
267. Shonka NA, Theeler B, Cahill D, Yung A, Smith L, Lei X, *et al*. Outcomes for patients with anaplastic astrocytoma treated with chemoradiation, radiation therapy alone or radiation therapy followed by chemotherapy: A retrospective review within the era of temozolomide. J Neurooncol 2013;113:305-11.
268. Siesjö P, Visse E, Sjögren HO. Cure of established, intracerebral rat gliomas induced by therapeutic immunizations with tumor cells and purified APC or adjuvant IFN-gamma treatment. J Immunother Emphas Tumor Immunol 1996;19:334-45.
269. Silvani A, Eoli M, Salmaggi A, Lamperti E, Maccagnano E, Broggi G, *et al*. Phase II trial of cisplatin plus temozolomide, in recurrent and progressive malignant glioma patients. J Neurooncol 2004;66:203-8.
270. Sinclair J. Human cytomegalovirus: Latency and reactivation in the myeloid lineage. J Clin Virol 2008;41:180-5.
271. Smith JS, Perry A, Borell TJ, Lee HK, O'Fallon J, Hosek SM, *et al*. Alterations of chromosome arms 1p and 19q as predictors of survival in oligodendrogliomas, astrocytomas, and mixed oligoastrocytomas. J Clin Oncol 2000;18:636-45.
272. Söderberg-Nauclér C, Rahbar A, Stragliotto G. Survival in patients with glioblastoma receiving valganciclovir. N Engl J Med 2013;369:985-6.
273. Soffietti R, Trevisan E, Bertero L, Cassoni P, Morra I, Fabrini MG, *et al*. Bevacizumab and fotemustine for recurrent glioblastoma: A phase II study of AINO (Italian Association of Neuro-Oncology). J Neurooncol 2014;116:533-41.
274. Sørlie T, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen H, *et al*. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci U S A 2001;98:10869-74.
275. Soroceanu L, Matlaf L, Bezrookove V, Harkins L, Martinez R, Greene M, *et al*. Human cytomegalovirus US28 found in glioblastoma promotes an invasive and angiogenic phenotype. Cancer Res 2011;71:6643-53.
276. Srivastava PK, Callahan MK, Mauri MM. Treating human cancers with heat shock protein-peptide complexes: The road ahead. Expert Opin Biol Ther 2009;9:179-86.
277. Stragliotto G, Rahbar A, Solberg NW, Lilja A, Taher C, Orrego A, *et al*. Effects of valganciclovir as an add-on therapy in patients with cytomegalovirus-positive glioblastoma: A randomized, double-blind, hypothesis-generating study. Int J Cancer 2013;133:1204-13.
278. Stupp R, Hegi ME, Mason WP, van den Bent MJ, Taphoorn MJB, Janzer RC, *et al*.

Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncol 2009;10:459-66.
279. Stupp R, Hegi ME, Neyns B, Goldbrunner R, Schlegel U, Clement PMJ, *et al*. Phase I/IIa study of cilengitide and temozolomide with concomitant radiotherapy followed by cilengitide and temozolomide maintenance therapy in patients with newly diagnosed glioblastoma. J Clin Oncol 2010;28:2712-8.
280. Stupp R, Hegi ME, Gorlia T, Erridge S, Grujicic D, Steinbach JP, *et al*. Cilengitide combined with standard treatment for patients with newly diagnosed glioblastoma and methylated O6-methylguanine-DNA methyltransferase (MGMT) gene promoter: Key results of the multicenter, randomized, open-label, controlled, phase III CENTRIC study. J Clin Oncol 2013;31. Available from: http://meetinglibrary.asco.org/content/112780-132. [Last accessed on 2014 May 03].
281. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJB, *et al*. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352:987-96.
282. Stupp R, Wong ET, Kanner AA, Steinberg D, Engelhard H, Heidecke V, *et al*. NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: A randomised phase III trial of a novel treatment modality. Eur J Cancer 2012;48:2192-202.
283. Stupp R, Wong ET, Scott CB, Taillibert S, Kanner A, Kesari S, Ram Zvi. Interim analysis of the EF-14 trial: A prospective multicenter trial of NovoTTF-100A together with temozolomide compared to temozolomide alone in newly diagnosed glioblastoma; late breaking abstract. Society for neurooncology; 2014 Nov 13-16; Miami, USA.
284. Taal W, Oosterkamp HM, Walenkamp AME, Beerepoot LV, Hanse M, Buter J, *et al*. A randomized phase II study of bevacizumab versus bevacizumab plus lomustine versus lomustine single agent in recurrent glioblastoma: The Dutch BELOB study. J Clin Oncol 2013;31. Available from: http://meetinglibrary.asco.org/content/109069-132. [Last accessed on 2014 May 03].
285. Taal W, Segers-van Rijn JM, Kros JM, van Heuvel I, van der Rijt CC, Bromberg JE, *et al*. Dose dense 1 week on/1 week off temozolomide in recurrent glioma: A retrospective study. J Neurooncol 2012;108:195-200.
286. Taher C, de Boniface J, Mohammad AA, Religa P, Hartman J, Yaiw KC, *et al*. High prevalence of human cytomegalovirus proteins and nucleic acids in primary breast cancer and metastatic sentinel lymph nodes. PloS One 2013;8:e56795.
287. Taillibert S, Vincent LA, Granger B, Marie Y, Carpentier C, Guillevin R, *et al*. Bevacizumab and irinotecan for recurrent oligodendroglial tumors. Neurology 2009;72:1601-6.
288. Taliansky-Aronov A, Bokstein F, Lavon I, Siegal T. Temozolomide treatment for newly diagnosed anaplastic oligodendrogliomas: A clinical efficacy trial. J Neurooncol 2006;79:153-7.
289. Taphoorn MJ, van den Bent MJ, Mauer ME, Coens C, Delattre JY, Brandes AA, *et al*. Health-related quality of life in patients treated for anaplastic oligodendroglioma with adjuvant chemotherapy: Results of a European Organisation for Research and Treatment of Cancer randomized clinical trial. J Clin Oncol 2007;25:5723-30.
290. Thiessen B, Maguire JA, McNeil K, Huntsman D, Martin MA, Horsman D. Loss of heterozygosity for loci on chromosome arms 1p and 10q in oligodendroglial tumors: Relationship to outcome and chemosensitivity. J Neurooncol 2003;64:271-8.
291. Turcan S, Rohle D, Goenka A, Walsh LA, Fang F, Yilmaz E, *et al*. IDH1 mutation is sufficient to establish the glioma hypermethylator phenotype. Nature 2012;483:479-83.
292. Ueki K, Nishikawa R, Nakazato Y, Hirose T, Hirato J, Funada N, *et al*. Correlation of histology and molecular genetic analysis of 1p, 19q, 10q, TP53, EGFR, CDK4, and CDKN2A in 91 astrocytic and oligodendroglial tumors. Clin Cancer Res 2002;8:196-201.
293. Valk PJ, Verhaak RG, Beijen MA, Erpelinck CA, Barjesteh van Waalwijk van Doorn-Khosrovani S, Boer JM, *et al*. Prognostically useful gene-expression profiles in acute myeloid leukemia. N Engl J Med 2004;350:1617-28.
294. Verhaak RG, Hoadley KA, Purdom E, Wang V, Qi Y, Wilkerson MD, *et al*. Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NF1. Cancer Cell 2010;17:98-110.
295. Verhoeff JJ, Lavini C, van Linde ME, Stalpers LJ, Majoie CB, Reijneveld JC, *et al*. Bevacizumab and dose-intense temozolomide in recurrent high-grade glioma. Ann Oncol 2010;21:1723-7.
296. Villano JL, Letarte N, Yu JM, Abdur S, Bressler LR. Hematologic adverse events associated with temozolomide. Cancer Chemother Pharmacol 2012;69:107-13.
297. De Vleeschouwer S, Van Calenbergh F, Demaerel P, Flamen P, Rutkowski S, Kaempgen E, *et al*. Transient local response and persistent tumor control in a child with recurrent malignant glioma: Treatment with combination therapy including dendritic cell therapy. Case report. J Neurosurg 2004;100:492-7.
298. De Vleeschouwer S, Fieuws S, Rutkowski S, Van Calenbergh F, Van Loon J, Goffin J, *et al*. Postoperative adjuvant dendritic cell-based immunotherapy in patients with relapsed glioblastoma multiforme. Clin Cancer Res 2008;14:3098-104.
299. Vogelbaum MA, Berkey B, Peereboom D, Macdonald D, Giannini C, Suh JH, *et al*. Phase II trial of preirradiation and concurrent temozolomide in patients with newly diagnosed anaplastic oligodendrogliomas and mixed anaplastic oligoastrocytomas: RTOG BR0131. Neuro Oncol 2009;11:167-75.
300. Vredenburgh JJ, Desjardins A, Herndon JE 2nd, Dowell JM, Reardon DA, Quinn JA, *et al*. Phase II trial of bevacizumab and irinotecan in recurrent malignant glioma. Clin Cancer Res 2007;13:1253-9.
301. Vredenburgh JJ, Desjardins A, Herndon JE 2nd, Marcello J, Reardon DA, Quinn JA, *et al*. Bevacizumab plus irinotecan in recurrent glioblastoma multiforme. J Clin Oncol 2007;25:4722-9.
302. Vredenburgh JJ, Desjardins A, Reardon DA, Peters KB, Herndon JE 2nd, Marcello J, *et al*. The addition of bevacizumab to standard radiation therapy and temozolomide followed by bevacizumab, temozolomide, and irinotecan for newly diagnosed glioblastoma. Clin Cancer Res 2011;17:4119-24.
303. Wallace GC 4th, Dixon-Mah YN, Vandergrift WA 3rd, Ray SK, Haar CP, Mittendorf AM, *et al*. Targeting oncogenic ALK and MET: A promising therapeutic strategy for glioblastoma. Metab Brain Dis 2013;28:355-66.
304. Wang F, Travins J, DeLaBarre B, Penard-Lacronique V, Schalm S, Hansen E, *et al*. Targeted inhibition of mutant IDH2 in leukemia cells induces cellular differentiation. Science 2013;340:622-6.
305. Weller M, Cloughesy T, Perry JR, Wick W. Standards of care for treatment of recurrent glioblastoma--are we there yet? Neuro Oncol 2013;15:4-27.
306. Weller M, Kaulich K, Hentschel B, Felsberg J, Gramatzki D, Pietsch T, *et al*. Assessment and prognostic significance of the epidermal growth factor receptor vIII mutation in glioblastoma patients treated with concurrent and adjuvant temozolomide radiochemotherapy. Int J Cancer 2014;134:2437-47.
307. Weller M, Stupp R, Hegi ME, van den Bent M, Tonn JC, Sanson M, *et al*. Personalized care in neuro-oncology coming of age: why we need MGMT and 1p/19q testing for malignant glioma patients in clinical practice. Neuro Oncol 2012;14 Suppl 4:iv100-8.
308. Weller M, Stupp R, Reifenberger G, Brandes AA, van den Bent MJ, Wick W, *et al*. MGMT promoter methylation in malignant gliomas: Ready for personalized medicine? Nat Rev Neurol 2010;6:39-51.
309. Weller M, Wick W. Neuro-oncology in 2013: Improving outcome in newly diagnosed malignant glioma. Nat Rev Neurol 2014;10:68-70.
310. Wen PY, Prados M, Schiff D, Reardon DA, Cloughesy T, Mikkelsen T, *et al*. Phase II study of XL184 (BMS 907351), an inhibitor of MET, VEGFR2, and RET, in patients (pts) with progressive glioblastoma (GB). J Clin Oncol 2010;28:15s. Available from: http://meetinglibrary.asco.org/content/44555-74. [Last accessed on 2014 May 03].
311. Westphal M, Ram Z, Riddle V, Hilt D, Bortey E, Executive Committee of the Gliadel Study Group. Gliadel wafer in initial surgery for malignant glioma: Long-term follow-up of a multicenter controlled trial. Acta Neurochir (Wien) 2006;148:269-75.
312. Westphal M, Hilt DC, Bortey E, Delavault P, Olivares R, Warnke PC, *et al*. A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma. Neuro Oncol 2003;5:79-88.
313. Wheeler CJ, Black KL, Liu G, Mazer M, Zhang X, Pepkowitz S, *et al*. Vaccination elicits correlated immune and clinical responses in glioblastoma multiforme patients. Cancer Res 2008;68:5955-64.
314. Wick A, Felsberg J, Steinbach JP, Herrlinger U, Platten M, Blaschke B, *et al*. Efficacy and tolerability of temozolomide in an alternating weekly regimen in patients with recurrent glioma. J Clin Oncol 2007;25:3357-61.
315. Wick A, Pascher C, Wick W, Jauch T, Weller M, Bogdahn U, *et al*. Rechallenge with temozolomide in patients with recurrent gliomas. J Neurol 2009;256:734-41.

316. Wick W, Steinbach JP, Küker WM, Dichgans J, Bamberg M, Weller M. One week on/one week off: A novel active regimen of temozolomide for recurrent glioblastoma. Neurology 2004;62:2113-5.
317. Wick W, Cloughesy TF, Nishikawa R, Mason W, Saran F, Henriksson R, *et al*. Tumor response based on adapted Macdonald criteria and assessment of pseudoprogression (PsPD) in the phase III AVAglio trial of bevacizumab (Bv) plus temozolomide (T) plus radiotherapy (RT) in newly diagnosed glioblastoma (GBM). J Clin Oncol 2013;31. Available from: http://meetinglibrary.asco.org/content/113028-132. [Last accessed on 2014 May 03].
318. Wick W, Hartmann C, Engel C, Stoffels M, Felsberg J, Stockhammer F, *et al*. NOA-04 randomized phase III trial of sequential radiochemotherapy of anaplastic glioma with procarbazine, lomustine, and vincristine or temozolomide. J Clin Oncol 2009;27:5874-80.
319. Wick W, Meisner C, Hentschel B, Platten M, Schilling A, Wiestler B, *et al*. Prognostic or predictive value of MGMT promoter methylation in gliomas depends on IDH1 mutation. Neurology 2013;81:1515-22.
320. Wick W, Platten M. CMV infection and glioma, a highly controversial concept struggling in the clinical arena. Neuro Oncol 2014;16:332-3.
321. Wick W, Platten M, Meisner C, Felsberg J, Tabatabai G, Simon M, *et al*. Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: The NOA-08 randomised, phase 3 trial. Lancet Oncol 2012;13:707-15.
322. Wick W, Puduvalli VK, Chamberlain MC, van den Bent MJ, Carpentier AF, Cher LM, *et al*. Phase III study of enzastaurin compared with lomustine in the treatment of recurrent intracranial glioblastoma. J Clin Oncol 2010;28:1168-74.
323. Wick W, Steinbach JP, Platten M, Hartmann C, Wenz F, von Deimling A, *et al*. Enzastaurin before and concomitant with radiation therapy, followed by enzastaurin maintenance therapy, in patients with newly diagnosed glioblastoma without MGMT promoter hypermethylation. Neuro Oncol 2013;15:1405-12.
324. Wick W, Wick A, Platten M. Challenging cytomegalovirus data in glioblastoma. Neuro Oncol 2014;16:165.
325. Wick W, Wick A, Platten M. Good maths is needed to understand CMV data in glioblastoma. Int J Cancer 2014;134:2991-2.
326. Wiestler B, Capper D, Holland-Letz T, Korshunov A, von Deimling A, Pfister SM, *et al*. ATRX loss refines the classification of anaplastic gliomas and identifies a subgroup of IDH mutant astrocytic tumors with better prognosis. Acta Neuropathol (Berl) 2013;126:443-51.
327. Wiestler B, Radbruch A, Osswald M, Combs SE, Jungk C, Winkler F, *et al*. Towards optimizing the sequence of bevacizumab and nitrosoureas in recurrent malignant glioma. J Neurooncol 2014;117:85-92.
328. Wikstrand CJ, Hale LP, Batra SK, Hill ML, Humphrey PA, Kurpad SN, *et al*. Monoclonal antibodies against EGFRvIII are tumor specific and react with breast and lung carcinomas and malignant gliomas. Cancer Res 1995;55:3140-8.
329. Witham TF, Erff ML, Okada H, Chambers WH, Pollack IF. 7-Hydroxystaurosporine-induced apoptosis in 9L glioma cells provides an effective antigen source for dendritic cells and yields a potent vaccine strategy in an intracranial glioma model. Neurosurgery 2002;50:1327-34.
330. Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbé C, *et al*. Guidelines for the evaluation of immune therapy activity in solid tumors: Immune-related response criteria. Clin Cancer Res 2009;15:7412-20.
331. Wong AJ, Ruppert JM, Bigner SH, Grzeschik CH, Humphrey PA, Bigner DS, *et al*. Structural alterations of the epidermal growth factor receptor gene in human gliomas. Proc Natl Acad Sci U S A 1992;89:2965-9.
332. Wong ET, Hess KR, Gleason MJ, Jaeckle KA, Kyritsis AP, Prados MD, *et al*. Outcomes and prognostic factors in recurrent glioma patients enrolled onto phase II clinical trials. J Clin Oncol 1999;17:2572-8.
333. Yamanaka R, Abe T, Yajima N, Tsuchiya N, Homma J, Kobayashi T, *et al*. Vaccination of recurrent glioma patients with tumour lysate-pulsed dendritic cells elicits immune responses: Results of a clinical phase I/II trial. Br J Cancer 2003;89:1172-9.
334. Yamanaka R, Homma J, Yajima N, Tsuchiya N, Sano M, Kobayashi T, *et al*. Clinical evaluation of dendritic cell vaccination for patients with recurrent glioma: Results of a clinical phase I/II trial. Clin. Cancer Res 2005;11:4160-7.
335. Yan H, Parsons DW, Jin G, McLendon R, Rasheed BA, Yuan W, *et al*. IDH1 and IDH2 mutations in gliomas. N Engl J Med 2009;360:765-73.
336. Yu JS, Wheeler CJ, Zeltzer PM, Ying H, Finger DN, Lee PK, *et al*. Vaccination of malignant glioma patients with peptide-pulsed dendritic cells elicits systemic cytotoxicity and intracranial T-cell infiltration. Cancer Res 2001;61:842-7.
337. Yu JS, Liu G, Ying H, Yong WH, Black KL, Wheeler CJ. Vaccination with tumor lysate-pulsed dendritic cells elicits antigen-specific, cytotoxic T-cells in patients with malignant glioma. Cancer Res 2004;64:4973-9.
338. Yung WK, Albright RE, Olson J, Fredericks R, Fink K, Prados MD, *et al*. A phase II study of temozolomide vs. procarbazine in patients with glioblastoma multiforme at first relapse. Br J Cancer 2000;83:588-93.
339. Zhao S, Lin Y, Xu W, Jiang W, Zha Z, Wang P, *et al*. Glioma-derived mutations in IDH1 dominantly inhibit IDH1 catalytic activity and induce HIF-1alpha. Science 2009;324:261-5.
340. Zou P, Xu H, Chen P, Yan Q, Zhao L, Zhao P, *et al*. IDH1/IDH2 mutations define the prognosis and molecular profiles of patients with gliomas: A meta-analysis. PloS One 2013;8:e68782.
341. Zuniga RM, Torcuator R, Jain R, Anderson J, Doyle T, Ellika S, *et al*. Efficacy, safety and patterns of response and recurrence in patients with recurrent high-grade gliomas treated with bevacizumab plus irinotecan. J Neurooncol 2009;91:329-36.