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

Emilie Le Rhun, Sophie Taillibert¹, Marc C. Chamberlain²

Department of Neuro-oncology, Roger Salengro Hospital, University Hospital, Lille, and Neurology, Department of Medical Oncology, Oscar Lambret Center, Lille, France, Inserm U-1192, Laboratoire de Protéomique, Réponse Inflammatoire, Spectrométrie de Masse (PRISM), Lille 1 University, Villeneuve D’Ascq, France, ¹Neurology, Mazarin and Radiation Oncology, Pitié-Salpêtrière Hospital, University Pierre et Marie Curie, Paris-VI, Paris, France, ²Department of Neurology and Neurological Surgery, University of Washington, Fred Hutchinson Cancer Research Center, Seattle, WA, USA

E-mail: Emilie Le Rhun - emilie.lerhun@chru-lille.fr; Sophie Taillibert - sophie.taillibert@gmail.com; Marc C. Chamberlain - chambemc@u.washington.edu

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

 MQTTart 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 currently 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. 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. 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 preferred agent or combination of agents is available. 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
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.[161] 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-RF 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.[100,112,182] 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.[161] 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.[179] The radio- and chemosensitivity of AO appears linked to the presence of the 1p/19q deletion.[25,51,130]

Molecular markers are becoming increasingly important in the management of AG, and may at times assist 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 1p/19q 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).[77,182,320] The frequency and the impact on OS of these markers in Radiation Treatment Oncology Group (RTOG) 9402 trial of anaplastic oligodendrogial 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 predictive factor in AG treated with RT, CT (TMZ or PCV), or both.[22,25,26,30,45,51,52,53,102,112,114,136,271,290,318] 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 sensitivity to treatment.[51]

The IDH1 gene, a cytosolic enzyme, functions as a tumor suppressor when mutationally inactivated contributes to tumorigenesis in part through induction of the hypoxia inducible factor-1 pathway.[319] IDH2
Expression of the DNA repair protein MGMT results in resistance to gliomas to alkylating and methylating agents. Methylation of MGMT promoter methylation can be detected in 55–80% of AO. 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%). In the EORTC 26951 study of AO and AOA, MGMT promoter methylation was observed in 80%. A high level of methylation has been observed in AO up to 88% particularly in 1p/19q codedetated tumors. In the NOA-4 trial, MGMT promoter methylation was associated with 1p/19q loss in AO and AOA but not in AA. In the EORTC 26951 study, the MGMT promoter methylation was also strongly associated with the 1p/19q codeletion.

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

| Anaplastic oligodendroglial tumors AO/AA | 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 oligodendroglial glioma, IDH: Isocitrate dehydrogenase, ATRX: Alpha thalassemia mental retardation X-linked gene, PCV: Procarbazine, lomustine, vincristine

MGMT methylation is of prognostic significance in AG, but there are insufficient data to support a predictive value. In the EORTC 26951 trial, the prognostic significance of MGMT promoter methylation was equally strong in 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. In this study, MGMT promoter methylation had prognostic significance only without any predictive value for response to adjuvant PCV CT. Nevertheless, when IDH1 mutation status was added, the independent prognostic significance of MGMT was lost. 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. In conclusion, MGMT methylation is of prognostic significance in AG, but there are insufficient data to support a predictive value. 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. 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...
ATRX loss has been reported to be rare in oligodendroglial tumors and mutually exclusive with 1p/19q co-deletion. ATRX loss has been detected in 40–73% of AA and 25–77% of mixed AOA, but was infrequent (7%) in AO. ATRX in conjunction with 1p/19q status may be diagnostically useful to classify mixed gliomas as either astrocytic or oligodendroglioma, 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. 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 astrocytomas” and AOA with 1p/19q codeletion and AO as “molecular oligodendroglioma.”

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. Subgroups of AG can also be identified according to their molecular status using an unsupervised analysis of gene expression profiling. Intrinsic glioma subtypes (IGS) have been reported to correlate better with outcome as compared with histology. In conclusion, molecular classification represents a major advance in prognostication of AG. 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 positive (1p19q nondeleted/IDH1 mutated, 1p19q nondeleted/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. 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). 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 management of newly diagnosed anaplastic oligodendrogial 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 day 1, 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. At progression, surgery rates were similar between the treatment arms (45% after PCV/RT vs. 56% after RT alone). Salvage CT rates differed between groups: 41% after PCV/RT arm versus 79% after RT alone ($P < 0.001$).

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. 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 significantly 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.

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%). 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. 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. Initial results of EORTC 26951 were published in 2006, when 217 (59%) of the patients had died. 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. 30.6 months, $P = 0.003$) and OS (43.3 vs. 30.6 months, $P = 0.018$) were both significantly longer in the RT/PCV arm compared with the RT arm.

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 |
|---------------------------------------------------------------|
| RTOG 9402                                                      |
| Whole population ($n=291$)                                    |
| RT alone arm ($n=143$)                                        |
| PCV/RT arm ($n=148$)                                          |
| 1p/19q codeleted patients ($n=126$)                           |
| RT alone arm ($n=67$)                                         |
| PCV/RT arm ($n=59$)                                           |
| Non 1p/19q codeleted patients ($n=137$) (50% of the entire cohort) |
| RT alone arm ($n=61$)                                         |
| PCV/RT arm ($n=76$)                                           |
| EORTC 26951                                                   |
| Whole population ($n=368$)                                    |
| RT alone arm ($n=183$)                                        |
| RT/PCV arm ($n=185$)                                          |
| 1p/19q codeleted patients ($n=80$) (25% of the entire cohort) |
| RT alone arm ($n=37$)                                         |
| RT/PCV arm ($n=43$)                                           |
| Non 1p/19q codeleted patients ($n=236$)                       |
| RT alone arm ($n=122$)                                        |
| RT/PCV arm ($n=114$)                                          |
| PFS                                                                 |
| HR                        | 95% CI                  | OS                        |
|---------------------------|-------------------------|---------------------------|
| 1p/19q codeleted patients  |
| RT alone arm              | HR: 0.68                | 4.7 years                 |
| PCV/RT arm                | 95% CI: 0.53-0.88       | 4.6 years                 |
| 1p/19q codeleted patients  |
| RT alone arm              | HR: 0.47                | 7.3 years                 |
| PCV/RT arm                | 95% CI: 0.30-0.72       | 14.7 years                |
| Non 1p/19q codeleted patients |
| RT alone arm              | HR: 0.81                | 2.7 years                 |
| PCV/RT arm                | 95% CI: 0.56-1.16       | 2.6 years                 |
| EORTC 26951               |
| RT alone arm              | HR: 0.66; 95% CI: 0.52-0.83 | 30.6 months              |
| RT/PCV arm                | 95% CI: 0.52-0.83; 95% CI: 0.52-0.83 | 42.3 months              |
| 1p/19q codeleted patients  |
| RT alone arm              | HR: 0.42; 95% CI: 0.24-0.74 | 111.8 months             |
| RT/PCV arm                | 95% CI: 0.24-0.74; 95% CI: 0.24-0.74 | Not reached              |
| Non 1p/19q codeleted patients |
| RT alone arm              | HR: 0.73; 95% CI: 0.56-0.97 | 21.1 months              |
| RT/PCV arm                | 95% CI: 0.56-0.97; 95% CI: 0.56-0.97 | 25 months              |

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 175 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 oligodendrogial 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 oligodendrogial tumors and currently represents the SOC. The results of both studies suggest that neither the timing of PCV administration (immediately 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 recurrence) versus RT + PCV can spare potential RT-related cognitive deterioration and achieve 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,\(^{[106]}\) 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.\(^{[184,102,191,288,318]}\) 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.\(^{[13,35]}\) 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).\(^{[1219]}\) The main cohort or phase II studies evaluating TMZ in newly diagnosed AG are described in Table 5. An important question is to determine whether the safety and the efficacy 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.\(^{[108,267]}\) The results are reported in Table 4.

Until now, limited data regarding best upfront treatment is available in unii- or noncodeleted 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, \(P < 0.0001\)).\(^{[160]}\) 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,\(^{[25,31]}\) The only exception may be in IDH1 and ATRX mutated tumors. Consequently in unii- or noncodeleted AG, no SOC is currently 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 noncodeleted 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.\(^{[25,31]}\) 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
| 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 | TMZ 200 mg/m²/day 5 days/28 up to 24 cycles | Whole cohort: Clinical improvement: 12 pts (60%), stabilization: 5 pts, progression: 9 pts; Objective response rate: 15 pts (75%); Median TTP: 24 months (3-34) |
| Taliansky-Aronov 2006 | Median age: 47 years (26-65) | | 1p deletion: 58% (7/12) 19q deletion: 83% (10/12) 1p/19q codeletion: Not detailed |
| Mikkelsen 2009 | 36 patients with 1p/19q codeletion | TMZ alone 150-200 mg/m²/day for 5 days every 28 days | 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) |
| Mikkelsen 2009 | Description of the cases with CT | Median age: 46.5 years (22-68) 70% | Median KPS 90 (60-100) |
| Mikkelsen 2009 | 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%) | | Median # of completed cycles: 12 (2-24) |
| Mikkelsen 2009 | | | 1p deletion: 58% (7/12) 19q deletion: 83% (10/12) 1p/19q codeletion: Not detailed |
| Gan 2010 | 40 patients (2203-2006) | TMZ 200 mg/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) |
| Gan 2010 | Median age: 43 years (18-71) ECOG PS: 0=14 (35%); 1=23 (58%); 2=3 (7%) | | 1p/19q codeletion: 47% (18/38) methylation MGMTP: 48% (10/21) |
| Gan 2010 | Total macroscopic resection: 9 pts (22%) Subtotal resection: 27 pts (68%) Biopsy only: 4 pts (10%) | | 1p/19q codeletion: 47% (18/38) methylation MGMTP: 48% (10/21) |
| Gan 2010 | 1p/19q codeletion: 47% (18/38) methylation MGMTP: 48% (10/21) | | 1p/19q codeletion: 47% (18/38) methylation MGMTP: 48% (10/21) |
| Gan 2010 | A0 (n=11) 1p/19q codeletion: 71%; MGMTP methyl 100% | | A0 (n=11) 1p/19q codeletion: 71%; MGMTP methyl 100% |
| Gan 2010 | A0A (n=29) 1p/19q codeletion: 31%; MGMTP methyl 23% | | A0A (n=29) 1p/19q codeletion: 31%; MGMTP methyl 23% |
| Ducray 2011 | 41 patients (2000-2005) | TMZ alone 150 mg/m²/2 day for 5 days every 28 days | Whole cohort: PR: 13 pts (32%), SD: 17 pts (41%), PD: 11 pts (27%); Median PFS: 6.9 months; Median OS: 12.4 months; Median # of completed cycles: 5 (1-13) |
| Ducray 2011 | Median age: 74 years (70-90) | | 1p/19q codeletion: 7% (1/14) |
| Ducray 2011 | Median KPS: 60 (30-100) | | 1p/19q codeletion: 7% (1/14) |
| Ducray 2011 | Complete resection: 2 pts (11%) Partial resection: 9 pts (14%) Biopsy: 33 pts (75%) | | 1p/19q codeletion: 7% (1/14) |
| Ducray 2011 | MGMTP methylation: 50% (38) | | 1p/19q codeletion: 7% (1/14) |
| Ducray 2011 | According to the molecular status | | 1p/19q codeletion: 1p/19q codeletion: 7% (1/14) |
| Ducray 2011 | 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) |

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

**Pt:** 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, **MGMT:** O-6-methylguanine-DNA methyltransferase promoter, **methyl:** Methylation, **codeletion, if:** Number
Table 4: Main cohorts and phase II studies of newly diagnosed anaplastic glioma treated with radiotherapy 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)             | Preradiation TMZ                           | Whole cohort                                                     |
|                 | Median age: 45 (18-71)              | (150 mg/m²/day, 7 on/off) × 6 cycles        | Pre-RT response rate: 32% (CR: 6%; PR: 26%)                        |
|                 | Zubrod PS=0: 27                     | followed by RT (59.4 Gy) + concomitant TMZ | Pre-RT progression rate: 10%                                    |
|                 | AO: 13 pts                          | (75 mg/m²/day)                             | Only and 13 pts had progressed and 8 pts have died at the time of the analysis |
|                 | Mixed glioma oligo-dominant: 13 pts| 32 pts completed RT-TMZ                    |                                                                  |
|                 | Mixed glioma, 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)       |                                            |                                                                  |
| Mikkelsen 2009  | 12 patients without 1p/19q codeletion| Pre-radiation TMZ                           | Whole cohort                                                     |
| Description of  | Median age: 32 (18-81)              | (150-200 mg/m²/day) × 2-4 cycles           | PFS: 13.5 months                                                 |
| the cases with  | Median KPS: 90 (60-100)             | followed by chemo-radiation (RT 60 Gy)     | PFS 6 months: 75% (95% CI 40.8-91.2)                             |
| CT+RT only      | Gross total resection: 3 pts (25%)  | + concomitant TMZ (75 mg/m²/day)           | PFS 12 months: 58.3% (95% CI 27.0-80.1)                           |
|                 | Subtotal resection: 8 pts (66.7%)   |                                            |                                                                  |
|                 | Biopsy: 1 pt (8.3%)                 |                                            |                                                                  |
|                 | AO: 3 pts (25%)                     |                                            |                                                                  |
|                 | AOA: 9 pts (75%)                    |                                            |                                                                  |
| Kim 2011        | 33 patients (2003-2008)             | RT (59.4 Gy) + concomitant TMZ (75 mg/m², | Whole cohort                                                     |
|                 | Median age=41 years (17-60)         | 7 days/week)                               | Response rate: 61%                                               |
|                 | KPS ≥70: 88%                        | followed by adjuvant TMZ (150-200 mg/m²)   | Mean PFS: 48.7 mo (95% CI 36-61.4)                                |
|                 | >75% tumor resection: 58%           | 5 days/28 cycles                           | Mean OS: 66.4 mo (95% CI 0.02-0.73)                               |
|                 | AA: 21 pts (64%)                    | Median # of completed cycles of adjuvant TMZ: 6.2 (2-12) | According to the molecular data                                  |
|                 | AO: 12 pts (36%)                    |                                            | Not done because of the small number of patients                 |
|                 | 1p/19q codeletion: 53% (8/15)       |                                            |                                                                  |
|                 | MGMT promoter methylation: 55% (11/20) |                                            |                                                                  |
| Minniti 2013    | 84 patients (2004-2011)             | RT (59.4 Gy) + concomitant TMZ (75 mg/m², | Whole cohort                                                     |
| Minniti 2014    | Median age: 44 years (22-67)        | 7 days/week)                               | Response rate: 49% (CR: 14%, PR 25%, stabilization 40%)          |
|                 | Complete/subtotal resection: 47 pts (56%) | followed by adjuvant TMZ (150-200 mg/m²)  | Median OS 55.6 mo (95% CI 37-76)                                  |
|                 | Incomplete resection: 29 pts (33%)  | 5 days every 28 days up to 12 cycles       | 5 year survival: 48% (95% CI 35-65)                               |
|                 | Biopsies: 8 pts (11%)               |                                            | 5 year PFS rate: 41% (95% CI 31-53%)                              |
|                 | Median KPS: 90 (60-100)             |                                            | According to the molecular data                                  |
|                 | AO: 59 pts (70%)                    |                                            | Median OS 1p/19q codel: Not reached versus 1p/19q noncodel: 34 mo (P=0.0001) |
|                 | AOA: 25 pts (30%)                   |                                            | IDH1 mutated: Not reached versus IDH1 nonmutated: 31 mo (P=0.0001) |
|                 | Initial grade 2: 24 pts (28.5%)     |                                            | MGMT promoter methylation: 78 mo versus MGMTTP unmethylated promoter: 30 mo (P=0.0001) |
|                 | 1p/19q codel: 57% (48/84)           |                                            | Median PFS 1p/19q codel: Not reached versus 1p/19q noncodel: 16 mo (P=0.0001) |
|                 | IDH1 mutation: 63% (52/82)          |                                            | IDH1 mutated: 76 mo versus IDH1 nonmutated: 23 mo (P=0.0001)       |
|                 | MGMTTP methylated: 74% (57/77)      |                                            | MGMTTP methylated: 65 mo versus MGMTTP unmethylated: 16 mo (P=0.0001) |

Table Contd...
The treatment of recurrent anaplastic glioma 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.\(^{[117]}\) In the EORTC 26971 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.\(^{[23,51]}\)

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.\(^{[155]}\) 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

---

**Table 4: Continue…**

| Authors                  | Patient and tumor’s characteristics | Regimen                            | Response of the whole cohort and according to the molecular status |
|--------------------------|-------------------------------------|-------------------------------------|------------------------------------------------------------------|
| Lassman 2011*            | 528 patients (1981-2007)            | \(CT + RT\) (n=528)                | Whole cohort                                                    |
|                          | Median age: 43 years (20-83)        | CT followed by RT (n=132)          | Median OS: 7.3 years (95% CI: 5.9-8.4)                           |
|                          | KPS ≥70: 453 (80%)                  | \(RT + concurrent CT\) (n=112)     | Median TTP: 4.1 years (95% CI: 3.5-5.4)                          |
|                          | Resection: 466 (80%)                | RT followed by CT (n=281)          |                                                                  |
|                          | AO: 262 pts (50%)                   | Doses not detailed                |                                                                  |
|                          | AOA: 266 pts (50%)                  |                                     |                                                                  |
|                          | Prior LGG: 64 = 12%                 |                                     |                                                                  |
| Shonka 2013              | 1p/19q codeletion: 40% (133/334)    |                                     |                                                                  |
| Description of the cases with concomitant RT+CT only | 52 patients AA (2003-2009) | \(RT (60 \text{ Gy}) + \) | Whole cohort                                                    |
|                          | Median age: 42 years (18-69)        | Concurrent CT drug:                |                                                                 |
|                          | Median KPS: 90 (60-100)             | BCNU: 3 (5.8%)                     |                                                                 |
|                          | Biopsy: 17 (36.2%)                  | TMZ: 49 (94.2%)                    |                                                                 |
|                          | Resection: 30 (63.8%)               |                                     |                                                                 |
|                          | Unknown: 5                          |                                     |                                                                 |

**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**
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. In historical controls, patients with recurrent AG have a median survival of 9–11.8 months and a median PFS 2–6 months. 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, 15–200 mg/m², 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 glosarcoma, GB with oligodendrogial features, and small cell GB. Nonetheless considerable variability in the response to treatment and in prognosis is observed. Molecular markers and gene expression profile now complement 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 alklylation 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 sensitivity to alkylator-induced genotoxic injury. MGMT promoter is methylated in 32–45% in newly diagnosed GB. Additionally, MGMT status appears to be retained in recurrent GB. Various methods for MGMT testing have been evaluated. Methylation-specific PCR is recognized as the method of choice for the evaluation of the MGMT status. The prognostic role of the MGMT promoter methylation status in GB is now well established. The predictive role of MGMT promoter methylation status and response to TMZ has also been established in several studies. 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  | 3.8/8.1            | 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: Chemotheapies
from TMZ alone compared with RT alone.\textsuperscript{[183,321]} In elderly patients considered for treatment with RT or TMZ alone, MGMT testing should be determined to assist in treatment decision making.\textsuperscript{[307]}

Although primary and secondary GBs are histomorphologically identical, these tumors develop through 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%).\textsuperscript{[115,130,209,239,335]} IDH1/2 mutations result in the production of d-2-hydroxyglutarate, a oncometabolite, instead of α-ketoglutarate.\textsuperscript{[35,294]} Furthermore the IDH status does not appear to change during the progression from lower grade glioma to secondary GB.\textsuperscript{[130]} Mutated IDH1 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.\textsuperscript{[155,70,130,307]} IDH1 mutations, or less frequently IDH2 mutations, have been shown to be a prognostic marker in HGG.\textsuperscript{[130,209,239,335,340]} 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 oligodendrogial features and exhibit the longest survival (median OS of 125 months).\textsuperscript{[165]} 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.\textsuperscript{[130,307]} IDH1/2 wild-type GB by contrast undergo further genomic changes at recurrence.\textsuperscript{[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.\textsuperscript{[106,75,225,249,304]}

Other markers are of interest in GB include the ATRX mutation, which is observed in 57% of the secondary GB.\textsuperscript{[119]} 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.\textsuperscript{[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).\textsuperscript{[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 PDGFR-A 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.\textsuperscript{[10,174,246]} In a recent cohort of 941 HGG, 32.7% were proneural, 15.09% neural, 19.77% classical, and 32.41% mesenchymal.\textsuperscript{[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].\textsuperscript{[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/m²/day for 6 weeks) and RT (60 Gy in 30 fractions) and then 6 maintenance cycles of post-RT adjuvant TMZ (150–200 mg/m²/day for consecutive 5 days therapy every 28 days, standard 5/28 TMZ [xdTMZ]) 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 | 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
The role of Genetic/epigenetic profile

Others

Notwithstanding these findings 12/day for 7 consecutive days every 14 days, + there is now general agreement that sdTMZ is the preferable 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. 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. In another study, no benefit of adding BEV to sdTMZ upfront was found. 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 | 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
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 overall 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).

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

### Table 8: Elderly glioblastoma trials

| Author                        | Age (years) | KPS | Number of pts | Treatment | Median survival |
|-------------------------------|-------------|-----|---------------|-----------|----------------|
| Roa 2004                      | ≥ 60 ≥ 50   | 100 | X (n=51)      | X         | 5.1/5.6        |
| Keime Guibert 2007             | ≥ 70 ≥ 70   | 85  | X (n=38)      | X         | 29.1 w/16.9 w  |
| Wick 2013                      | >65 ≥ 60    | 373 | X (n=178)     | X         | 9.6/8.6        |
| Malmström 2013                 | 60-69       | 100 | X (n=59)      | X         | 7.5/7.9        |
|                               | 70+         | 191 | X (n=41)      | X         | 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    | 561 | 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
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 administration 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.\(^{146,189}\) 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 receiving 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 75.3% 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 available.

**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.\(^{146}\) 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 (\(P = 0.05\)) 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 group (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.\(^{227}\) 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 implantation. 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.\(^{43,33,35,39,311,6,151,169,184,185,190,218,257,258,311}\) Several reviews have also been published.\(^{6,31,177,221,255,256}\)

In a review of the literature by Bregy, 19 studies with 795 patients were evaluated in whom carmustine wafers 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 Glial wafers should be used with caution.\(^{146}\) 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. 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%. The randomized (2:1) phase II GLARIUS study compared the combination of BEV/IRI versus TMZ as first-line therapy in MGMT nonmethylated GB. 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.

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 administered 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.

| 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 (PFS6: 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 |
| Gilbert 2014 Phase III (RTOG 0825) | Concomitant RT TMZ BEV followed by adjuvant TMZ | 56 | PFS6: 41.3% | 6 | 14.8 |
| Chinot 2014 Phase III (AVAglio) | Concomitant RT TMZ BEV followed by adjuvant TMZ | 320 | NS | 10.7 | 15.7 |
| | Concomitant RT TMZ followed by adjuvant TMZ | 317 | NS | 7.3 | 16.1 |
| | 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.
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 independent 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. The patterns of radiographic disease progression were similar between treatment arms. At progression, salvage treatment was administered 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, and grade 3 or higher adverse events were more often associated with BEV (32.5% vs. 15.8%).

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.
In both trials, the PFS was prolonged by 3–4 months in the BEV arms, but no difference was observed in OS. 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 received BEV at progression. 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. 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. Despite methodological differences between the two studies, no clear reason was found to explain the divergence in QoL and cognition. 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.

The two trials, RTOG 0825 and AVAglio, were similar in design, patient characteristics, and the primary end points of PFS and OS. Nevertheless, some methodological differences were observed: 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 administrated 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.

In both trials, 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 multilobar GB. A total of 41 patients were included and received up to 4 cycles TMZ at 200 mg/m² 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 7.5 and 7.7 months, respectively, in the these groups, the median OS were 15.1 and 11.8 months, respectively. 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. 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, 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
The expression of EGFRvIII does not significantly affect survival of patients. EGFRvIII, which results from an in-frame deletion of 267 amino acids in the extracellular domain, is a promising target for immunotherapy.

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 well tolerated.

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 available. In arm 1, standard treatment with TMZ (75 mg/m²/day)/RT (30 × 2 Gy) followed by TMZ (150–200 mg/m² 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 that identified a clinical benefit from antiintegrin treatment. OS of this population with methylated MGMT promoter was comparable to previous reports.

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/m²/day)/RT (30 × 2 Gy) followed up by TMZ (150–200 mg/m² 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, 16.5 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 Cilengitide (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.

CENTRIC and CORE trials determined that there is no survival advantage for adding anti-α5β3 integrin therapy (Cilengitide) to SOC for patients with newly diagnosed GB. Nevertheless, other integrin inhibitors (β1, β5…) may represent another promising strategy.

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.

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 available. In arm 1, standard treatment with TMZ (75 mg/m²/day)/RT (30 × 2 Gy) followed by TMZ (150–200 mg/m² 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) concomitantly 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 and encouraging immunogenicity and efficacy. 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. EGFRvIII, a GB TSA is being targeted for vaccination-based therapy in GB. EGFRvIII is present in 20–25% of GB patients and is absent on normal tissues. 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. EGFRvIII expression is only seen in primary GB and is found in nearly 50% of tumors with EGFR amplification. A male predominance has also been reported. The expression of EGFRvIII does not significantly affect survival of patients. 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.\textsuperscript{[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.\textsuperscript{[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\textsuperscript{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 manufactured 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.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[7-9,12,122,172,173,216,229,253,268,297,298,313,329,333,334,336,337]} 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).\textsuperscript{[193]}

In conclusion, available 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 demonstrated 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 | NW Biotherapeutics | Randomized phase 2 | Overall survival | 240 | 10 | Yes |
| Tumor lysate | 2:1 |
| Peptide EGFRvIII | Celldex (Act IV) | Randomized phase 2 | Overall survival | 450 | 6-12 | No |
| DC 6 TAA | Immunocellular Therapeutics (ICT 107) | Randomized phase 2 | Overall survival | 200 | 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.[130]

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 account 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.[72]

Immune check point inhibitors such an anti-CTLA4 and antiprogrammed cell death 1 (anti-PD1) monoclonal antibodies are just beginning 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 more 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.[186] 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.[190] 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.[222] 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.[281] 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.[131] 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.[144,207,222]

The role of the cytomegalovirus (CMV) in GB remains controversial. CMV DNA and proteins are expressed in several types of human cancers,[74,243,236] 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.[222] 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.[231] 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.[220] The VIGAS randomized, double-blind,
placebo-controlled trial was conducted to evaluate the safety and the efficacy of valganciclovir (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 immunohistochemically. Patients could take valganciclovir for compassionate use after the study phase. Trends but no significant differences were observed in tumor volumes in valganciclovir and placebo-treated patients at 3 (3.58 vs. 7.44 cm³, respectively, P = 0.2881) and 6 (3.31 vs. 13.75 cm³, P = 0.2120) months. Median PFS were 5.6 months in the valganciclovir 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 valganciclovir. The authors subsequently collated a subgroup of patients that benefited from valganciclovir 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.[105] 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.[106] 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.[3,16,18,19,37,39,40,42,43,45,66,89,91,95,101,118,142,145,355,356,201,212,222,242,261,203,264,284,285,314,316,322,338] 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/m² every 4 weeks), followed by a 2-week rest. Toxicities included neutropenia, diarrhea, epistaxis, enesis, 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.[100] 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 recurrence, a total 85 patients received BEV alone (10 mg/kg/q2w) and 82 patients BEV (10 mg/kg/q2w) + IRI (125–340 mg/m²/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].[2,5,7,62,65,79,95,96,100,105,106,119,140,159,195,198,204,205,211,235-237,262,275,295,300,301,305] 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%.[27] 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       | Prospective  | Lomustine                      | 65        | 24.5%  | 2.9   | 9.8 |
| Batchelor 2013       | Prospective  | Lomustine                      | 46        | 13%    | ND    | 12  |
| Taal 2013 (BELOB)    |              |                                |           |        |       |     |
| 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

| Authors       | Trial design | Agents                   | Number of patients | PFS-6 | Median PFS (months) | Median OS (months) |
|---------------|--------------|--------------------------|--------------------|-------|--------------------|--------------------|
| Hammond 2011  | Prospective  | TMZ                      | 47                 | 23%   | 2.3                | 13                 |
| Taal 2012     | Retrospective| TMZ                      | 24                 | 29%   | ND                 | 9                  |
| Norden 2013   | Prospective  | TMZ                      | 58                 | 11%   | 1.83               | 11.7               |
| Han 2014      | Prospective  | TMZ                      | 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) |
|------------------|--------------|---------------|--------------------|--------|--------------------|--------------------|
| 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   | 9/122              | 24%    | ND                 | 6.4                |
| Taal 2013        | Prospective  | Bevacizumab   | 50                 | 18%    | ND                 | 12                 |
| Cecchi 2013      | Retrospective| Bevacizumab   | 9                  | 45%    | 5.1                | 6.8                |

Bevacizumab + Irinotecan

| Authors          | Trial design | Agents        | Number of patients | PFS-6  | Median PFS (months) | Median OS (months) |
|------------------|--------------|---------------|--------------------|--------|--------------------|--------------------|
| Stark Vance 2005 | ND           | Bev + iri     | 11                 | ND     | ND                 | ND                 |
| Vredenbrugh CCR 2007 | Prospective | Bev + iri    | 23                 | 30%    | 4.7                | 9.3                |
| Vredenbrugh 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

| Authors          | Trial design | Agents       | Number of patients | PFS-6 | Median PFS (months) | Median OS (months) |
|------------------|--------------|--------------|--------------------|-------|--------------------|--------------------|
| 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

| Authors          | Trial design | Agents        | Number of patients | PFS-6 | Median PFS (months) | Median OS (months) |
|------------------|--------------|---------------|--------------------|-------|--------------------|--------------------|
| Taal 2013        | Prospective  | Bev + Lomustine| 44                 | 42%   | ND                 | 8                  |

Bevacizumab + Fotemustine

| Authors          | Trial design | Agents       | Number of patients | PFS-6 | Median PFS (months) | Median OS (months) |
|------------------|--------------|--------------|--------------------|-------|--------------------|--------------------|
| Soffietti 2014   | Prospective  | Bev + Fotemustine| 44 pts            | 42.6% | 5.2                | 9.1                |

Bevacizumab + Carboplatine

| Authors           | Trial design | Agents             | Number of patients | PFS-6 | Median PFS (months) | Median OS (months) |
|-------------------|--------------|--------------------|--------------------|-------|--------------------|--------------------|
| Mrugala 2012      | Retrospective| Bev + Carboplatine| 14                 | 40%   | 4.75               | 10                 |
| Fields 2013       | Prospective  | Bev + Carboplatine| ND/122             | 26%   | ND                 | 6.9                |

Bevacizumab + Miscellaneous

| Authors           | Trial design | Agents                      | Number of patients | PFS-6 | Median PFS (months) | Median OS (months) |
|-------------------|--------------|------------------------------|--------------------|-------|--------------------|--------------------|
| 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. 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/m² every 6 weeks for 6 cycles), Lomustine (90 mg/m² 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/m², 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. The median OS after progression on BEV is usually poor (average 3–4.6 months) notwithstanding attempted further treatment. Continuation of BEV after progression on BEV is still debated and various conclusions have been offered in retrospective studies. The randomized TAMIGA phase IIIb trial is evaluating the efficacy and safety of continuous 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 RTI, 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; antintegrin inhibitor). 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%. 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...
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. 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 and EGFRvIII-specific immune response were associated with significantly improved outcomes. Patients with both MGMT promoter hypermethylation and EGFRvIII-specific immune response had a median OS of 11.2 months compared to 6.1 months for patients with neither. This suggests that targeting both pathways may be necessary for optimal survival.

**BRAF mutations**
BRAF mutations are another uncommon mutation in GB, which 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.

**Vaccine-based immunotherapy**
ReACT (NCT01498328) a phase II trial with granulocyte-macrophage colony-stimulating factor (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 is 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. 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 MethylLight technology (P = 0.019) and methylation-specific PCR (MSP) analysis (P = 0.046), was associated with better OS. The rate of complications remains unclear in this population, but data in newly diagnosed GB suggest that gliadel wafers should be used with caution.

**Convection-enhanced delivery**
Convection-enhanced delivery (CED) was designed to improve the delivery of drugs that would normally not
Alternating electric fields or tumor treating fields

Two clinical trials have assessed the effect of AEF using the NovoTTF-100A device (Novocure Ltd, Haifa, Israel) 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. 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 was 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.

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 represent 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 1p19q 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 additional...
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 improvement 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 strategy for recurrent HGG. Nevertheless, there is no clear standard recommendation regarding the preferred 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. Adddeo R, Caragli A, De Santi MS, Montella L, Abbruzzese A, Partalo C, et al. A new schedule of fotemustine in temozolomide-pretreated patients with relapsing glioblastoma. J Neurooncol 2011;102:217-24.
4. Affronti PL, Heery CR, Herrndon 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 tamoazolomide plus rotational multiagent chemotherapy. Cancer 2009;115:3501-11.
5. Ali SA, McHayle 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, Tsubawa 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 III 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 II trial comparing conventional adjuvant temozolomide with dose-intensive temozolomide in patients with newly diagnosed glioblastoma. J Clin Oncol 2013;31:4076-84.
11. Arrueta O, Garcia E, Guevara P, Garcia-Navarrete R, Ondarza R, Rombao 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, Mulkerjee D, Datoog O, McGirt MJ, Bohn 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, Hatel J, McLendon RE, Cummings TJ, Sampson JH, Friedman AH, et al. Clinicopathological characteristics and treatment of rhboid 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. Bevacizumab and irinotecan therapy in glioblastoma multiforme: A series of 25 cases. J Neurosurg 2009;110:268-72.
16. Balmaceda C, Peerbooms D, Panullo 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;112:1399-46.
17. Banaszczyk M, Stoczynska-Fidelus E, Wniecka-Klimek M, Bienkowski M, Och W, Rieske P, et al. EGRFvIII—a stable target for anti-EGRFvIII therapy. Anticancer Res 2013;33:5343-8.
18. Batchelor TT, Duda DG, di Tomaso E, Anckiewicz 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, Naboirs 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 Y, Wuf D, 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 EGRFvIII 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, Horowsky A, Schneider S, Bock HC, Mielke D, Rohde V, et al. Concomitant and adjuvant temozolomide of newly diagnosed glioblastoma in elderly patients. Clin Neurosurg 2013;11:2142-6.
24. Van den Bent MJ, Chinito O, Googerd W, Braard Marques J, Taphoorn MJ, Kros MJ, 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, Kourouwen HC, 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.
43. 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. A report of the European Organization for Research and Treatment of Cancer (EORTC) Brain Tumor Group. J Clin Oncol. 2001;19:2079-85.

45. Brandes AA, Tosoni A, Vastola F, Pasetto LM, Coria B, Danieli D, et al. Role of Gliadel wafers in the treatment of high-grade gliomas. Expert Rev Anticancer Ther. 2011;11:1293-303.

46. Brequet A, Shah AH, Diaz MV, Pierce HE, Ames PL, Diaz D, et al. The role of radiation therapy in anaplastic oligodendroglioma and oligoastrocytoma. Neuro Oncol. 2011;13:558-9.

Brem H, Piantadosi S, Burger PC, Walker M, Selker R, Vick NA, et al. Placebo-controlled trial of safety and efficacy of intraoperative controlled drug delivery by biodegradable polymers of chemotherapeutic agents for recurrent gliomas. The Polymer-brain Tumor Treatment Group. Lancet. 1995;345:1008-12.

Brennan C, Monnot H, Hambardzumyan D, Ozawa T, Tandon A, Pedraza A, et al. Glialblomastoma subclones can be defined by activity among signal transduction pathways and associated genomic anomalies. PloS One. 2009;4:e7752.

Breton CW, Verhaak RG, McKenna A, Campos B, Nounmehrin H, Salama SR, et al. The somatic genomic landscape of glioblastoma. Cell. 2013;155:462-77.

Breto R, Aboulafia D, Berti F, Furlan P, Furlan R, et al. Anaplastic oligodendrogliaoma: A hypermethylated phenotype is a better predictor of survival than MGMT methylation in anaplastic oligodendroglial brain tumors. A report from EORTC study 26951. J Clin Oncol. 2011;29:4411-8.

Brock O, Paras A. Heat Shock Protein Peptide Complex-96 (HSPPC-96) Vaccination for Recurrent Glioblastoma:A Phase II, Single Arm Trial. Neuro Oncol. 2014;16:758-9.

Brock HC, Puchner MJA, Lohmann F, Schüzte 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.

Boiardi A, Silvani A, Eoli M, Lamperti E, Salmaschi G, Gaviani P, et al. Treatment of recurrent glioblastoma: Can local delivery of mitoxantrone improve survival? J Neurooncol. 2008;88:105-13.

Bonis D, Bani C, Pompucci A, Fiorentino A, Balducchi M, Chiesa S, et al. Safety and efficacy of Gliadel wafers for newly diagnosed and recurrent glioblastoma. Acta Neurochir (Wien). 2012;154:1371-8.

Borodovsky A, Salmasi V, Turcan S, Favier AWM, Baia GS, Eberhart CG, et al. S-acetylated reduces methylation, promotes differentiation and induces tumor regression in a patient-derived IDH1 mutant glioma xenograft. Oncotarget. 2013;4:1377-47.

Brada M, Hoang-Xuan K, Rampil D, Dietrich PY, Driks L, Macdonald D, et al. Multicenter phase II trial of temozolomide in patients with glioblastoma multiforme at first relapse. Ann Oncol. 2001;12:259-66.

Brada M, Stennert E, Gabe R, Thompson LC, Levy D, Rampil D, et al. Temozolomide versus procarbazine, lomustine, and vincristine in recurrent high-grade glioma. J Clin Oncol. 2010;28:4601-8.

Brandes AA, Ermanni M, Basso U, Amista P, Berti F, Ficienza 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.

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 group Italian cooperative of neuro-oncology (GICNO). Br J Cancer. 2006;95:1155-60.

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.

Brandes AA, Ermanni 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;62:38-41.

Brandes AA, Tosoni A, Franceschi E, Blatt V, Santoro A, Faedi M, et al. Potenzastine 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.

Brandes AA, Tosoni A, Cavallo G, Reni M, Franceschi E, Bontaldi 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.
67. Chauffert B, Feuvret L, Bonnetain F, Taillandier D, Frappaz D, Talilla 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 TEMARIV study from ANOCCEF. Ann Oncol 2014;25:1442-7.

68. Chi AS, Batchelor TT, Kwak EL, Clark JvW, 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, Sasan 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, Hatapoba Kj, Rahkheja D, Kovacs Z, et al. 2-hydroxylipoyd 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 retinal 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. Cobbis 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, Driggers EM, et al. Cancer-associated IDH1 mutations produce 2-hydroxylipoyd. Nature 2009;462:739-44.

76. Darlix A, Baumann C, Lorig V, Ghiringhelli F, Biondi S, 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. Dang L, White DW, Gross S, Bennett BD, Bittinger MA, Driggers EM, 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.

80. De Felice F, Bulzonetti N, Musio D, De’lia A, Saltava M, Tambolini V. Low-dose fotemustine as second-line chemotherapy for recurrent glioblastoma multiforme. Anticancer Res 2012;32:4013-6.

81. Deckeler TA, Propp JM, Group 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.

82. 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.

83. Ducray F, del Rio MS, Carpentier C, Psimaras D, Idbaih A, Dehais C, et al. Combined chemotherapy and post-operative radiotherapy with concomitant fotemustine as second-line chemotherapy for recurrent glioblastoma multiforme. J Neurooncol 2013;106:147-59.

84. Duncan CG, Barbick BG, Jin G, Rago C, Kapoor-Vazirani P, Powell DR, et al. A hypothesis that IDH1 R132H/WT mutation induces genome-wide alterations in DNA methylation. Genome Res 2012;22:2339-55.

85. Lu-Emerson D, Norden AD, Bailey L, 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 oligodendroglioma brain tumors: A report from EORTC study 26951. J Clin Oncol 2013;31:328-36.

86. Esteller M. Epigenetics in cancer. N Engl J Med 2008;358:1148-59.

87. 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.

88. Fabi 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 lystate-dendritic cell vaccination after radiation chemotherapy. J Immunother 2011;34:382-9.

89. De Felice F, Bulzonetti N, Musio D, De’lia A, Saltava M, Tambolini V. Low-dose fotemustine as second-line chemotherapy for recurrent glioblastoma multiforme. Anticancer Res 2012;32:4013-6.

90. Field KM, Simes J, Wheeler H, Hoevey EJ, Nowak AK, Cher L, et al. A randomized phase II study of carmustin 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].

91. Franceschi E, Ouro AB, Lassman AB, Demopoulos A, Nolan C, Abrey LE. Salvage temozolomide for prior temozolomide responders. Cancer 2005;104:2473-6.

92. 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.

93. French PJ, Peeters J, Horsman S, Dujin 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.

94. French PJ, Swagman 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.

95. Frenel JS, Leuix C, Loussouarn D, Le Louppe 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 Neurooncology 2013;114:85-91.

96. Friedman HS, Prados MD, Wen PY, Mikelsens T, Schiff D, Abrey LE, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. J Clin Oncol 2009;27:4733-40.

97. 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 oligodendroglioma/astrocytic features. J Neuropathol Exp Neurol 2003;62:118-28.

98. French PJ, Rose J, St Clair D, Roller M, Petroni JG, Alberc A, Ewing N, et al. Phase II trial of primary temozolomide in patients with grade III oligodendroglioma brain tumors. Neuro Oncol 2010;12:500-7.

99. Gaviani P, Samaggi A, Silvani A. Combined chemotherapy with temozolomide and fotemustine in recurrent glioblastoma patients. J Neurooncol 2011;104:617-8.

100. Gerson SL. MGMT: Its role in cancer aetiology and cancer therapeutics. Nat Rev Cancer 2004;4:296-307.

101. Gil MJ, de Las Peñas R, Reinoso M, Balahá C, Pérez-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 (SEINO). Anticancer Drugs 2012;23:659-65.

102. Gilbert MR, Wang M, Aldape K, Lassman A, Sorensen AG, Mikkelson T, et al. Randomized phase II trial of irinotecan and bevacizumab as neo-adjuvant to temozolomide-based chemoradiation compared to temozolomide-chemoradiation for unresectable glioblastoma: Final results. J Neurooncol 2013;106:147-53.
129. Hofer S, Lassman AB. Molecular markers in gliomas: Impact for the clinician. Target Oncol 2010;5:201-10.
130. Hofer S, Rushing E, Preussler 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. Hofmann M, Rosner GL, Alcorn S, Grossman SA. “Elderly” patients with newly diagnosed glioblastoma deserve optimal care. J Neurooncol 2012;113:334-4.
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, Giamianni C, Arusell RM, Law M, et al. A phase II study of temozolomide and radiotherapy in newly diagnosed glioblastoma and progression after radiation therapy and temozolomide. Neuro Oncol 2010;12:508-16.
137. Jenkins RB, Blair H, Ballman KV, Giamianni C, Arusell RM, Law M, et al. A phase II trial of temozolomide and radiotherapy in newly diagnosed glioblastoma and progression after radiation therapy and temozolomide. Neuro Oncol 2010;12:508-16.
138. Jenkins RB, Blair H, Ballman KV, Giamianni C, Arusell RM, Law M, et al. A phase II trial of temozolomide and radiotherapy in newly diagnosed glioblastoma and progression after radiation therapy and temozolomide. Neuro Oncol 2010;12:508-16.
139. Jenkins RB, Blair H, Ballman KV, Giamianni C, Arusell RM, Law M, et al. A phase II trial of temozolomide and radiotherapy in newly diagnosed glioblastoma and progression after radiation therapy and temozolomide. Neuro Oncol 2010;12:508-16.
140. Jenkins RB, Blair H, Ballman KV, Giamianni C, Arusell RM, Law M, et al. A phase II trial of temozolomide and radiotherapy in newly diagnosed glioblastoma and progression after radiation therapy and temozolomide. Neuro Oncol 2010;12:508-16.
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;3:709-22.
142. Kaslowski SJ, Cho WC, Ertugrul A, Ertugrul A, Ertugrul A, Ertugrul A, et al. Immunomodulatory responses in a patient with glioblastoma multiforme treated with sequential courses of temozolomide and immunotherapy: Case study. Neuro Oncol 2008;10:98-103.
143. Kellela PJ, Rostron GL. OLIG1 and IDH1/2 mutations refine the classification of malignant gliomas. Oncotarget 2014;5:1515-25.
144. Kellela PJ, Rostron GL. OLIG1 and IDH1/2 mutations refine the classification of malignant gliomas. Oncotarget 2014;5:1515-25.
145. Kellela PJ, Rostron GL. OLIG1 and IDH1/2 mutations refine the classification of malignant gliomas. Oncotarget 2014;5:1515-25.
146. Kellela PJ, Rostron GL. OLIG1 and IDH1/2 mutations refine the classification of malignant gliomas. Oncotarget 2014;5:1515-25.
147. Kellela PJ, Rostron GL. OLIG1 and IDH1/2 mutations refine the classification of malignant gliomas. Oncotarget 2014;5:1515-25.
148. Kellela PJ, Rostron GL. OLIG1 and IDH1/2 mutations refine the classification of malignant gliomas. Oncotarget 2014;5:1515-25.
149. Kellela PJ, Rostron GL. OLIG1 and IDH1/2 mutations refine the classification of malignant gliomas. Oncotarget 2014;5:1515-25.
150. Kellela PJ, Rostron GL. OLIG1 and IDH1/2 mutations refine the classification of malignant gliomas. Oncotarget 2014;5:1515-25.
151. Kellela PJ, Rostron GL. OLIG1 and IDH1/2 mutations refine the classification of malignant gliomas. Oncotarget 2014;5:1515-25.
Kleihues P, Ohgaki H. Primary and secondary glioblastomas: From concept to clinical diagnosis. Neuro Oncol 1999;1:44-51.

Kleinberg LR, Weingart J, Burger P, Carson K, Grossman SA, Li K, et al. Clinical course and pathologic findings after Glialdel and radiotherapy for newly diagnosed malignant glioma: Implications for patient management. Cancer Invest 2004;22:1-9.

Kleinschmidt-DeMasters BK, Aisen D, Birks DK, Foreman NK. Epithelioid GMBs show a high percentage of BRAF V600E mutation. Am J Surg Pathol 2013;37:685-98.

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;12:289-93.

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.

Koochekpour S, Jeffers M, Kulung 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.

Kreisl TN, Kim L, Moore K, Ducic R, Royce C, Strood 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.

Kreisl TN, Zhang W, Oda Y, Shih JH, Butman JA, Hammond D, et al. A phase II trial of single-agent bevacizumab in patients with recurrent anaplastic glia. Neuro Oncol 2011;13:114-50.

Kros M, Gorlia T, Kownenovic M, Zheng PP. Prognostic value of molecular markers. J Neurooncol 2014;116:275‑82.

Liau LM, Prins RM, Kierschter 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.

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.

Liu L, Bäcklund LM, Nilsson BR, Grandier 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.

Liu W, Yu 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;18:119-26.

Liu XY, Gerges N, Korshunov A, Sahba 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.

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.

Louis DN, Oghalik H, Wistler 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.

Mallouin N, Chargari C, Forest F, Fottos M, Cartier L, Aubierdies Pet al. Prolonged temozolomide for treatment of glioblastoma: Preliminary clinical results and prognostic value of p53 overexpression. J Neurooncol 2012;106:127-33.

Malmstrom A, Grenberg BH, Marosi C, Stupp R, Frapazz 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.

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.

McDermott U, lafrate A, 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.

McGirt MJ, Than KD, Weingart JD, Chaichana KL, Attinello FJ, Olivi A, et al. Glial (BCNU) wafer plus concomitant temozolomide therapy after primary resection of glioblastoma multiforme. J Neurosurg 2009;110:583-8.

McPherson CM, Gerena-Lewis M, Brenerman 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.

Mehta A, Shervington L, Munje C, Shervington A. A novel therapeutic strategy for the treatment of glioma, combining chemical and molecular targeting of hsp90. Cancers 2011;3:1228-44.

Le Mercier M, Hastir D, Moles Lopez X, De Nève N, Maris C, Trepalt AN, et al. A simplified approach for the molecular classification of glioblastoma. PloS One 2012;7:e45475.

Mesaros EF, Ott GR, Dorsey BD. Anaplastic lymphoma kinase inhibitors as anticancer therapeutics: A patent review. Expert Opin Ther Pat 2014;24:417-42.

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 cohort study. Cancer 2009;115:4783-94.

Migliori P, Bouchekoua M, Rousseau B, Hieu PD, Malhaire JP, Pradier O. Impact of the per-operative 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.

Mikkelsen T, Doyle T, Anderson J, Margolis J, Paleologos N, Gutierrez J, et al. A simplified approach for the molecular classification of glioblastoma. PloS One 2012;7:e45475.
mRNA-transfected dendritic cells in patients with glioblastoma. Cancer Immunol Immunother 2013;62:1499-509.

194. Mölleman M, Wolter M, Feldsberg J, Collins VP, Reifenberger G. Frequent promoter hypermethylation and low expression of the MGMT gene in oligodendrogial 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 tumours and progression after standard therapy. Acta Neurochir 2012;154:797-804.

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, Pedani 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 AR, Fiaro C, García JF, et al. Codetermination of 1p and 19q determines distinct gene methylation and expression profiles in IDH-mutated oligodendrogial tumors. Acta Neuropathol (Berl) 2013;126:277-89.

201. Nabors LB, Mikkelsen T, Hegi ME, Ye X, Batchelor T, Lesser G, et al. Safety, run-in, and randomized phase 2 study of cilengitide combined with chemoradiation for newly diagnosed glioblastoma (NABBTT 0306). Cancer 2012;118:5601-7.

202. Nabors LB, Fink KL, Mikkelsen T, Gruijic 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):S5-64.

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. Ngiemphu PL, Liu W, Lee Y, Tan 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;17:5759-64.

207. Ning J, Wakiimoto H, Rakbin SD. Immunotherapy 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 2012;18:6002-7.

210. Ogbah K, Kleihues P. Genetic pathways to primary and secondary glioblastomas. Am J Pathol 2007;170:1445-53.

211. Okada N, Masunaga Y, Okada Y, Mizughchi H, Iiyama S, Mori N, et al. Dendritic cells transduced with gp100 gene by RGD-fiber-mutant adenovirus vectors are highly efficacious in generating in vitro anti-B16BL6 melanoma immunity in mice. Gene Ther 2003;10:1891-92.

212. Omurow A, DeAngelis LM. Glioblastoma and other malignant gliomas: A clinical review. JAMA 2013;310:1842-50.

213. 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.

214. Panegas KS, Iwamoto FM, Cloughesy TF, Aldape KD, Rivera AL, Eichler AF, et al. Initial treatment patterns over time for anaplastic oligodendrogial tumors. Neuro Oncol 2012;14:761-7.

215. Pérez-Larraga JY, Ducray F, Chinot O, Catry-Thomass 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.

216. Perry J, Chambers A, Spithoff K, Laperruere N. Gliadel wafers in the treatment of malignant gliomas: A systematic review. Curr Oncol 2007;14:189-94.

217. 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 2011;29:2051-7.

218. Phillips HS, Kharbanda S, Chen R, Forrest WS, 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.

219. Piccioni DE, Selfridge J, Mody RR, Chowdhry 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.

220. Platten M, Schumacher T, Bunse L, Sahn F, Pusch S, Quandt J, et al. A vaccine targeting mutant IDH1 induces antitumor immunity. Neurology 2014;81:2324-7.

221. Poulsen HS, Grunnet K, Sorensen M, Olsen P, Hasselbalch B, Nelaeus K, et al. Bevacizumab plus irinotecan in the treatment of patients with progressive recurrent malignant brain tumours. Acta Oncol 2009;48:52-8.

222. Preusser M, Beblz L, Hainfellner J. 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.

223. Preusser M. MGMT analysis as DNA, RNA and protein levels in glioblastoma tissue. Histol Histopathol 2009;24:511-18.

224. Prins RM, Soto H, Koninkkiet 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. Cancer Res 2011;71:1603-15.

225. Putterman HS, Grunnet K, Sorensen M, Olsen P, Hasselbalch B, Nelaeus K, et al. Bevacizumab plus irinotecan in the treatment of patients with progressive recurrent malignant brain tumours. Acta Oncol 2009;48:52-8.

226. Quillien V, Lavenu A, Karayan-Tapon L, Guittier C, Labussière M, 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 methyltransferase in a series of 100 glioblastoma patients. Cancer 2012;118:4201-11.

227. Rahbar A, Orrego I, Peredo I, Dzabic M, Wolmer-Solberg N, Strååt K, et al. Frequent expression of a mutant epidermal growth factor receptor in recurrent malignant glioma: A single-institution experience. Neurology 2009;72:1217-22.

228. Rajpure MN, Zoltick PW, et al. Gene expression-based classification of malignant gliomas correlates better with survival than histological classification. Cancer Res 2003;63:1602-7.

229. O6-methylguanine-DNA methyltransferase expression in glioblastoma multiforme is of clinical relevance. Neuro Oncol 2012;14:761-7.

230. Ozbay G, Shinoura N, et al. Human cytomegalovirus infection levels in glioblastoma multiforme are of clinical relevance. Neuro Oncol 2012;14:761-7.

231. Ozbay G, Shinoura N, et al. Human cytomegalovirus infection levels in glioblastoma multiforme are of clinical relevance. Neuro Oncol 2012;14:761-7.
S42

Salmaggi A, Milanesi I, Silvani A, Gaviani P, Marchetti M, Fariselli L, Sabel M, Giese A. Safety profile of carmustine wafers in malignant glioma: results of a phase II study of sorafenib plus temozolomide in adults with recurrent glioblastoma. J Neurooncol 2011:107:155-64.

Reardon DA, Quinn JA, Rich JN, Desjardins A, Vredenburgh J, Gururangan S, et al. Phase II trial of irinotecan plus temozolomide in adults with recurrent glioblastoma. Cancer 2005;104:109-11.

Reardon DA, Vredenburgh J, Desjardins A, Peters K, Gururangan S, Sampson J, et al. Effect of CYP3A-inducing anti-epileptic drugs on sorafenib exposure: Results of a phase II study of sorafenib plus temozolomide in adults with recurrent glioblastoma. J Neurooncol 2011:107:57-66.

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.

Reithmeier T, Graf E, Piroth T, Tippel M, Pinkser MO, Nikkhah G. BCNU for recurrent glioblastoma multiforme: Efficacy, toxicity and prognostic factors. BMC Cancer 2010:10:30.

Reyes SB, Narayanan AS, Lee HS, Tchaicha JH, Aldape KD, Lang FE, et al. cJ8 integrin interacts with RhoGDI1 to regulate Rac1 and Cdc42 activation and drive glioblastoma cell invasion. Mol Biol Cell 2011:22:474-82.

Reyes-Botero G, Honnorat J, Chinot OL, Taillandier L, Czernichow P, et al. Temozolomide plus bevacizumab in elderly patients with newly diagnosed glioblastoma and poor performance status: An Anocle phase II trial. J Clin Oncol 2013:31. Available from: http://meetinglibrary.asco.org/content/112330-132. [Last accessed on 2014 May 03].

Reynes G, Balalò C, Gallego O, Iglésias 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.

Rehfeldt V, Gietzelt J, Beyer U, Hentschel B, Westphal M, Schackert G, et al. Genomic profiling reveals distinctive molecular subclass patterns in IDH1/2 wild-type glioblastoma. Genes Chromosomes Cancer 2014:53:589-605.

Rivera AL, Pellossi 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.

Roa WB, Brasher PMA, Bauman G, Artes M, Bruea E, Chan A, et al. A randomized course of radiotherapy in older patients with glioblastoma multiforme: A prospective randomized clinical trial. J Clin Oncol 2004;22:1583-8.

Rohle D, Popovic-Muller J, Palakas N, Turcan S, Groneme C, Campos C, et al. An inhibitor of mutant IDH1 delays growth and promotes differentiation of glioma cells. Science 2013:340:626-30.

Roldán Urgoiti S, Singh AJ, Desjardins A, Vredenburgh JJ, McLendon RE, et al. PCV for treatment of newly diagnosed glioblastoma multiforme. J Neurooncol 2012:108:173-7.

Roth P, Sliger M, Goodman SL, Hensbach 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.

Russell SJ, Peng KW, Bell JC. Oncolytic virotherapy. Nat Biotechnol 2008;26:173-8.

Shonka NA, Theeler B, Cahill DJ, Yang 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.

Siesjo B, Klauck 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.

Seestahl K, Wiestler O, Bindsberg T, Hoppold C, Wick W, et al. Bevacizumab alone or in combination with irinotecan in recurrent WHO grade II and grade III gliomas. Eur Neurol 2013:69:95-101.

Shonka NA, Theeler B, Cahill DJ, Yang 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.

Siesjo B, Klauck 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.

Seestahl K, Wiestler O, Bindsberg T, Hoppold C, Wick W, et al. Bevacizumab alone or in combination with irinotecan in recurrent WHO grade II and grade III gliomas. Eur Neurol 2013:69:95-101.

Shonka NA, Theeler B, Cahill DJ, Yang 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.

Siesjo B, Klauck 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.

Seestahl K, Wiestler O, Bindsberg T, Hoppold C, Wick W, et al. Bevacizumab alone or in combination with irinotecan in recurrent WHO grade II and grade III gliomas. Eur Neurol 2013:69:95-101.

Shonka NA, Theeler B, Cahill DJ, Yang 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.

Siesjo B, Klauck 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.
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.

Stupp R, Hegi ME, Nieuwen B, Goldbrunner R, Schlegel U, Clement MJ, et al. Phase II/III study of cetinatide and temozolomide with concomitant radiotherapy followed by cetinatide and temozolomide maintenance therapy in patients with newly diagnosed glioblastoma. J Clin Oncol 2010;28:2712-8.

Stupp R, Hegi ME, Gorilla T, Erridge S, Grujicic D, Steinbach JP, et al. Cetinatide 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].

Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352:987-96.

Stupp R, Wong ET, Kanner AA, Steinberg D, Engelhard H, Heidecker 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.

Stupp R, Wong ET, Scott CB, Taillibert S, Kanner A, Kessari S, Ram Z, et al. Interim analysis of the EP-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.

Taillibert S, Vincent LA, Granger B, Marie Y, Carpentier C, Guillevin R, 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.

Taillibert S, Vincent LA, Granger B, Marie Y, Carpentier C, Guillevin R, et al. Bevacizumab and irinotecan for recurrent oligodendrogliomas. Neurology 2009;72:1601-6.

Taliansky-Aronov A, Bokstein F, Lavon I, Segil T. Temozolomide treatment for newly diagnosed anaplastic oligodendrogliomas: A clinical efficacy trial. J Neurooncol 2006;79:153-7.

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.

Thiessen B, Maguire J, McNeil K, Huntsman D, Martin MA, Horsman D. Loss of heterozygosity for loci on chromosome arms 1p and 10q in oligodendroglioma tumors: Relationship to outcome and chemosensitivity. J Neurooncology 2003;64:271-8.

Turcan S, Rohle D, Goenka A, Walsh LA, Fang FY, Ilmaz E, et al. IDH1 mutation is sufficient to establish the glioma hypermutator phenotype. Nature 2012;483:479-83.

Ueki K, Nakatowa R, Nakazato Y, Hirose T, Kazuto H, et al. Correlation of histology and molecular genetic analysis of IDH1 and IDH2 with long-term outcomes in patients with newly diagnosed glioblastoma multiforme. Neuro Oncol 2009;11:98-105.

Van den Bent MJ, Eisele I, Stupp R, Hegi ME, Stupk R, Haar CP, et al. Bevacizumab and dose-intensive temozolomide in recurrent high-grade glioma. Ann Oncol 2010;21:1723-7.

Villano JL, Letarte N, Yu JM, Abdur S, Bressler LR. Hematologic adverse events associated with temozolomide. Cancer Chemother Pharmacol 2012;69:107-13.

Vollbracht S, Van Calenbergh F, Demerael P, Flamen P, Rutkowski S, Koenig G, Hauw JJ, 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.

Vollbracht S, Sieuw 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;14:3096-104.

Vogelbaum MA, Berkey B, Peerboom 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 B0131. Neuro Oncol 2009;11:167-75.

Vredenburgh JJ, Desjarlins 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.

Vredenburgh JJ, Desjarlins 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.

Vredenburgh JJ, Desjarlins 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. J Clin Cancer Res 2011;17:4119-24.

Wallace GC 4th, Dixon-Mah YN, Vandergrift WA 3rd, Ray SK, Haar CR, Middendorf AM, et al. Targeting oncogenic ALK and MET: A promising therapeutic strategy for glioblastoma. Metab Brain Dis 2013;28:355-66.

Wang F, Travins J, DeLaBarre B, Penard-Lacroix N, Schalm S, Hansen E, et al. Targeted inhibition of mutant IDH2 in leukemia cells induces cellular differentiation. Science 2013;340:622-6.

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.

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.

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 iv:100-8.

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.

Weller M, Wick W. Neuro-oncology in 2013: Improving outcome in newly diagnosed malignant gliomas. Nat Rev Neurol 2014;10:68-70.

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].

Westphal M, Ram Z, Riddle V, Hilt D, Botrye E. Executive Committee of the Glial 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.

Westphal M, Hilt DC, Botrye E, Delvaluat P, Olivesars 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.

Wolff DJ, Kaufman BH, Tsimberidou AM, Weichselbaum RR, Weichselbaum RR, et al. Vaccination elicits correlated immune and clinical responses in glioblastoma multiforme. J Clin Oncol 2007;25:3567-61.

Wolff DJ, Kaufman BH, Tsimberidou AM, Weichselbaum RR, Weichselbaum RR, et al. Vaccination elicits correlated immune and clinical responses in glioblastoma multiforme. J Clin Oncol 2007;25:3567-61.
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;62:113-5.

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 in glioblastoma. Int J Cancer 2014;134:2991-2.

321. Wick W, Meisner C, Hentschel B, Platten M, Wiestler B, et al. Prognostic or predictive value of MGMT promoter methylation in gliomas depends on IDH1 mutation. Neurology 2013;81:1515-22.

322. 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.

323. Wick W, Puduvali VK, Chamberlain MC, van den Bent MJ, Carpenter 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.

324. 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.

325. Wick W, Platten M. Challenging cytomegalovirus data in glioblastoma. Neuro Oncol 2013;14:165.

326. Wick W, Wittel T, Thiel A, Zoch M, et al. ATRX loss refines the classification of anaplastic gliomas and identifies a subgroup of IDH1 mutant astrocytic tumors with better prognosis. Acta Neuropathol (Berl) 2013;126:443-51.

327. Wickström C, 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.

328. Witham TF, Erff ML, Okada H, Chambers WH, Pollack IF. 7-Hydroxy-6-oxo-7,8-dihydro-saframycin A1 induces 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.

329. 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.

330. Wong AJ, Ruppert JM, Bigner SH, Grzeschik KH, 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.

331. Wong ET, Hess KR, Gleason MJ, Jøckel 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.

332. 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.

333. 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.

334. 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.

335. Yu JS,Wheeler CJ, Zeltzer PP, 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.

336. 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.

337. 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.

338. 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.

339. Zou P,Xu H, Chen PYan 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.

340. Zuniga RM, Torcacciar R, Jain R, Anderson J, Doyle T, Ellisia 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.