

# The “Radioresistance” of Glioblastoma in the Clinical Setting, and the Present Therapeutic Options

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## Radiotherapy: Clinical Historical Landmarks

External Beam Radiotherapy (EBRT) has been the cornerstone of the therapeutic approach to glioblastoma (GBM) for the last 50 years. In the 1970s and early 1980s, data on level-I evidence data became available, thanks to several studies [6, 7], including the prospective phase-III trial conducted by the Brain Tumor Study Group (BTSG 6901) [8]. This study demonstrated the efficacy of radiotherapy (RT) as postoperative treatment. Overall survival (OS) was better in the two arms including RT, compared with surgery alone or chemotherapy alone (BCNU) [8]. In addition, Walker et al. demonstrated a radiation dose–effect relationship in a series of 420 patients treated on Brain Tumor Cooperative Group protocols (BTSG), and the dose of 60 Gy was established as the standard of care [9].

The treatment of GBM dramatically changed after the encouraging findings from a Phase-III

joint EORTC-NCIC trial [5]. This trial, first published by Stupp and colleagues in 2005 and then updated in 2010 with 5-year data, demonstrated a remarkable improvement in median survival (MST) (14.6 months vs. 12.1 months) and 5-year OS (9.8 % vs. 1.9 %; HR, 0.63;  $p < .0001$ ) with the use of concomitant Temozolomide (TMZ) and radiation with adjuvant TMZ [5, 10]. In this study, an acceptable additional toxicity was observed in the combined modality group; concomitant treatment resulted in grade 3 or 4 hematologic toxic effects in 7 % of patients. The benefit of TMZ was particularly striking in patients having the MGMT (O-6-methyl-guanine DNA methyltransferase) DNA-repair gene silenced by promoter methylation [11].

In recent years, literature on the treatment of GBM has been characterized by different promising Phase-II trials unconfirmed in subsequent Phase-III trials.

High-grade gliomas are a very interesting topic for radiation oncologists, but they still represent a frontier to be conquered.

## Dose Escalation and Hypofractionation

GBM is considered one of the most radioresistant solid tumors in humans and has inherent radiation resistance pathways [12, 13]. They are characterized by an extremely high local failure rate

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despite dose escalation, with local recurrence rates approaching 90 % [14, 15]. Resistance may also be induced by some biologic factors within the tumor and some tumor microenvironment features [16, 17]. Moreover, in few cases, the proper doses of radiation can hardly be delivered because of the limited dose tolerance of the surrounding organs at risk. Further dose intensification using higher radiation doses and altered fractionation were pursued, but failed to provide a clear clinical benefit.

In the pre-TMZ era, Nelson et al. reported on the joint study of the Radiation Therapy Oncology Group (RTOG) and the Eastern Cooperative Oncology Group (ECOG). It randomized 253 patients into two treatment groups: whole-brain irradiation (60 Gy) and 60 Gy plus a 10 Gy boost to limited volume. The median survival times were 9.3 months and 8.2 months respectively, with no additional benefit for the group receiving the higher radiation doses [18]. Given these results, 60 Gy has been considered as the standard dose in postoperative radiotherapy and has been adopted in most clinical trials.

However, the poor outcome associated with standard therapy was conditioned by recurrences occurring within the irradiated field. In their renowned paper of 1980, Hochberg and Pruitt reported the use of CT scans to determine that about 90 % of GBM recurrences occurred no farther than 2 cm from the boundary of the primary tumor [19]. Those data were also confirmed by Wallner and associates [20].

For this reason, the role of radiation dose escalation in the management of GBM has been the object of a larger clinical effort. In a multicenter phase-I trial (RTOG 98-03), dose escalation was conducted using 3D-conformal irradiation. Here, a four-step dose escalation strategy from 66 to 84 Gy was studied, but no benefit was detected in progression-free survival (PFS). In fact, even when a dose at 80 Gy was reached, 90 % of patients failed within the high-dose-region [21]. These data have been confirmed in 2002 by a retrospective study by Chan JL et al., where an infield recurrence rate of 80 % also in patients treated to 90 Gy was demonstrated. Chan et al. published the results of 34 patients with GBM

treated using 3D conformal IMRT to a dose of 90 Gy. At a median follow-up of 11.7 months, median survival was 11.7 months, and 1- and 2-year survivals were 47.1 % and 12.9 %, respectively, comparable to historical controls [22].

In the post-TMZ era, dose escalation remains a crucial investigational option, as a pattern of failure, characterized by local progression or recurrence, still exists. Recently, an increase in survival in patients with GBM with no increment in the incidence of severe toxicity has been reported by some dose escalation studies using IMRT [23, 24]. Direct dosimetric comparison of IMRT and 3D-CRT has clearly shown that IMRT improves target dose conformity, reduces doses to organs at risk, and achieves comparable or slightly better target coverage [25, 26]. In a recent study, Tsien et al. demonstrated that doses of 66–81 Gy delivered by IMRT over 6 weeks, with concomitant and adjuvant TMZ, resulted in a lower infield recurrence rate in groups that received higher doses. PFS was 9.0 months (95 % CI, 6.0–11.7) and median OS was 20.1 months [23]. In a recent review by Badiyan et al. all the clinical studies carried out—between 2000 and 2012—using high-dose radiotherapy HDRT (>60 Gy) and TMZ and standard dose radiotherapy (SDRT) (60 Gy at 2 Gy per fraction) with TMZ were considered. OS and PFS rates for patients who received HDRT versus SDRT were 12.4 % versus 13.2 % ( $P=0.71$ ), and 5.6 % versus 4.1 % ( $P=.54$ ), respectively. The result of Badiyan's review was that clinical outcomes for patients with GBM do not seem to be improved by moderate radiation therapy dose escalation above 60 Gy with concurrent TMZ [27]. These data were confirmed by large retrospective series [28].

An advantage in cell-killing of intrinsically radioresistant cancer cells, like the ones in GBM, has been demonstrated in *in vitro* models of [24, 29, 30]. More heavily hypofractionated treatments have therefore been tested for dose escalation to translate to the clinic this advantage in cell-killing. In the Iuchi study, few favorably selected patients were treated with a total dose of 48–68 Gy (260 BEDGy3) and fractional doses of 6–8.5 Gy. Patients treated with tumor BED ranging from 80 to 140 Gy8, obtained the best results

and showed improved local control; local recurrence occurred in only 6/25 patients (25 %). These data and those reported by other groups testing the same strategy are however flawed by the nature of the patient population treated (highly selected) [24].

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## Hyperfractionation

Hyperfractionated schedules were also used by some clinical trials. GBM cells are known to be relatively rapid proliferating cells and a greater number of daily fractions would increase the chance of radiating them during a more sensitive cell-cycle phase. Furthermore, GBM is a very hypoxic tumor: at smaller radiation doses per fraction, cell-killing is less dependent on oxygen, which could be an advantage, especially if the site of the most hypoxic areas is known in advance. Under these circumstances, in several groups hyperfractionated or accelerated regimens have been utilized as a means to escalate dose, using twice, three-times, and even four-times-daily fractionation [31–34]. Unfortunately, in most clinical trials, a statistical benefit in terms of OS was not achieved even by the "low dose per fraction" strategy [31, 33]. Only in the study of Shin et al. was an improvement in survival using three fractions a day shown. In this study, 69 patients were randomized to 61.4 Gy in 69 fractions of 0.89 Gy over 4.5 weeks or to conventional fractionation to 58 Gy in 30 fractions given once daily over 6 weeks. Median survival in the two groups was 39 and 27 weeks, respectively, and the 1-year survival rates were 41 % and 20 %, respectively ( $p < .001$ ) [34]. The prospective, randomized, phase-I/II RTOG 83-02 trial, examined dose escalation using twice-daily fractionation. Patients were randomized to one or four different dose arms (64.8, 72, 76.8, or 81.6 Gy) using twice-daily fractions of 1.2 Gy. Initial results suggested the superiority of the 72 Gy hyperfractionated schedule but, in a subsequent Phase-III trial, no OS improvement was demonstrated [35]. Patients also received chemotherapy with BCNU. In the final report on all 747 patients, there were no significant differences in MST

between the treatment arms. Late toxicities were slightly increased with higher doses. [35]. In a phase-III trial (RTOG 9006), conventional radiotherapy (60 Gy in 30 daily fractions) with hyperfractionated RT to 72 Gy in sixty 1.2 Gy fractions given twice daily were compared. No difference in OS was found [36]. Several other accelerated hyperfractionation regimens to doses over 70 Gy have been investigated, also without significant improvements in survival [37]. Prados and colleagues used a hyperfractionation schedule of 1.6 Gy twice daily to a total dose of 70.4 Gy, also to determine the activity of difluoromethylornithine (DFMO), a compound that inhibits sublethal and potentially lethal damage repair. Unfortunately, survival was not improved by either intervention [38] (Table 2.1).

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## Stereotactic Radiosurgery and Stereotactic Radiation Therapy

Stereotactic Radiosurgery (SRS) and Stereotactic Radiation Therapy (SRT) are types of highly hypofractionated radiotherapy delivery. While achievability and efficacy of the combination of conformal radiotherapy and SRS or SRT have, to date, been confirmed in many retrospective studies, they have only been supported in some prospective studies. Mehta and colleagues reported a 2-year survival rate of 28 % in 31 patients treated with EBRT (54 Gy in 1.8 Gy/fraction) plus SRS boost (15–35 Gy,  $m = 18.75$  Gy), which was significantly superior to the 9.7 % in the previous RTOG study [39]. Loeffler et al reported on 37 patients with GBM treated with fractionated radiotherapy to 59.4 Gy followed by a STR boost to a median dose of 12 Gy. After a median follow-up period of 19 months, a 76 % survival rate was reported [40]. A group of 115 GBM patients who received conformal radiation therapy and a stereotactic boost was described by Sarkaria and colleagues. The median survival time was 96 weeks. It was questioned whether these results represented a real benefit from SRS or simply the effect of a selection bias, since only smaller lesions, in patients with a good performance status, showing a dimensional response after the

**Table 2.1** Hyperfractionation

Authors	Dose fraction	Treatments/day	Total dose	Results
Shin et al. [34]	0.89	3	61.4 Gy	1- and 2-year actuarial survival rate is 54 % and 21 %.
Curran et al. [35]	1.2	2	64.8, 72, 76.8 or 81.6 Gy	Survival rates at 2 and 5 years were: 21 % and 11 %, and 4 %, respectively
Nelson [36]	1.2	2	72 Gy	–
Prados et al. [38]	1.6	2	70.4	OS: 5.7 months PFS 2.7 months

first EBRT phase were usually selected for the SRS boost [41]. Subsequently, in an effort to delineate the role of SRS, a prospective multi-center randomized phase-III trial (RTOG 93-05) was conducted by the RTOG to assess the efficacy of SRS followed by standard adjuvant radiochemotherapy for newly diagnosed GBM. In this trial, 203 patients were randomly assigned to receive either 60 Gy of EBRT at 2 Gy/fraction with BCNU or SRS prior to EBRT and BCNU. The tumor dose was volume-dependent, ranging from 15 to 24 Gy in compliance with the established maximum safely tolerated doses. The median overall survival (OS) was 13.5 months for the SRS group and 13.6 months for the standard treatment group at a median follow-up of 61 months. An improvement of patient survival failed to be demonstrated by the study. Moreover, SRS was not related to a better quality of life, or neurologic function [42].

GBMs are most commonly large, diffusively infiltrative tumors with substantial surrounding edema, known to possibly harbor microscopic disease, reducing the likelihood of success of SRS. Currently the role of SRS in the adjuvant setting for GBM is not well defined. Although adjuvant treatment did not prove to be beneficial, attention still remains focused on SRS for the treatment of recurrent GBM [43–45] (Table 2.2).

## Brachytherapy

Brachytherapy refers to the use of implanted radioactive material at the site of the tumor and is usually used for focal dose escalation. In this field, it is well known that higher radiation doses

**Table 2.2** SRS STR

Authors	EBRT (Gy)	Boost	Results
Mehta et al. [39]	54	SRS boost (15–35 Gy, $m = 18.75$ Gy)	1- and 2-years survival were 38 % and 28 %
Loeffler et al. [40]	59.4	STR boost to a median dose of 12 Gy	–
RTOG 93-05 [42]	60	SRS boost (15 to 24 Gy)	the median survival was 13.5 months

may otherwise significantly increase the risk of brain necrosis [46]. Both permanent and temporary radioactive implants have been placed in the brain of GBM patients. In most studies, including two prospective randomized trials [47, 48], high-dose rate implants (40–70 cGy/h) were used to treat GBM. This approach, however, was associated with a high incidence of radiation-induced changes, requiring treatment with steroids for almost all patients, and repeated surgery rates up to 50 %. Furthermore, no significant survival benefits were achieved by this approach, compared with standard treatment regimens [47, 48]. Another technique is the application of low-dose-rate implants (3–8 cGy/h). It has been demonstrated that this approach was associated with only minimal permanent deficits; radiation-induced changes were almost absent [49, 50].

The results obtained in 56 patients with GBM treated with temporary <sup>125</sup>I interstitial implants were reported by Prados and colleagues. Patients received EBRT (median, 59.4 Gy), in most cases with concomitant chemotherapy (hydroxyurea), followed by interstitial implant. Eight patients (14 %) survived 3 years or longer, and 16 (29 %) sur-

vived 2 years or longer. A second operation was necessary in 50 % of the patients to remove symptomatic localized necrosis produced by the implant. Prolonged steroid use was necessary in many patients [51]. Brachytherapy was used by Laperriere et al. as a boost to conventional radiotherapy in patients with GBM. Patients were randomized to EBRT (50 Gy in 25 fractions) alone ( $n=69$ ) or EBRT plus a temporary stereotactic 125 I implant delivering a minimum peripheral tumor dose of 60 Gy ( $n=71$ ). Median survival was not significantly different in the two arms (13.8 vs. 13.2 months;  $p=.49$ ) [47]. The results of the BTCG—NIH Trial 8701 reported by Selker et al. support these findings. In this randomized, prospective trial, 299 patients with newly diagnosed GBM received surgery, EBRT, and chemotherapy (BCNU) with or without an interstitial radiotherapy boost with 125 I. Survival was not prolonged by treatment with an interstitial boost, compared with conventional treatment [48] (Table 2.3).

## Radiation Volume and the Changing Delineation Concepts

Over the years, the approach of radiotherapy to GBM has evolved. At first, the entire brain volume was covered by means of large opposed lateral fields. In 1989, Shapiro et al. published data from BTCG trial 8001, where the randomization

was altered during the trial to compare partial brain irradiation (PBI) with whole-brain radiotherapy (WBI). No differences in OS or changes in the patterns of failure were observed [52]. Accordingly, WBI is generally not needed to treat GBM. Nowadays, two main practice guidelines for the definition of the volumes and for the dose prescription are enforced: the EORTC and the RTOG.

In EORTC, a single-phase technique is favored, consisting of 30 daily fractions of 2 Gy. The gross tumor volume (GTV) is defined as the region of enhancement in preoperative T1 magnetic resonance imaging (MRI) in patients who underwent biopsy, while in the patients who underwent resection (total/subtotal) GTV corresponds to tumor bed plus any residual enhancing tumor. This is expanded by 2–3 cm to create the clinical target volume (CTV). The planning target volume (PTV) encloses the CTV with a margin of 0.5–0.7 cm, depending on the technique used (3D, IMRT, or others). In RTOG, on the other hand, a cone-down technique is favored, using two different volumes. The GTV in RTOG protocols is similarly defined as in EORTC advice, while the CTV is created including the edema shown on the CT/MRI scan (T2/FLAIR hyperintensity). This is then expanded 2.0 cm to create the PTV1 and it is treated using a total dose of 46 Gy in 23 fractions. The PTV2 is smaller, including GTV with a margin of 2.5 cm (without edema) plus margins related to set up error. PTV2 should be treated with an additional 14 Gy in 7 fractions (total cumulative dose 60 Gy). The mentioned guidelines to PTV margins definition are controversial. The extent of the treated brain volume is associated with the potential development of neurotoxicity; the incidence of these side effects might be reduced by a decrease of the treated volume [53]. RT margin reduction is especially important in treatment regimens that incorporate hypofractionation schedules. Nevertheless, margin reductions could be associated with an increased risk of marginal misses. The pattern of failure in 62 consecutive patients treated with 60 Gy and concurrent TMZ (97 %) was analyzed by McDonald et al. A mean PTV1 margin ranging between 1.05 and 1.3 cm off the GTV was selected, and patients

**Table 2.3** Brachytherapy

Authors	EBRT (Gy)	Boost	Results
Prados et al. [51]	median 59.4	temporary 125I interstitial implants	2-years survival rate 29 %
Laperriere et al. [47]	50	implant delivering a minimum peripheral tumor dose of 60 Gy	Median survival was 13.8 months
Selker et al. [48]	50	temporary stereotactic 125I	The median survival was 9.7 months

were treated with a total PTV boost margin of 1 cm or less. Radiographic tumor progression developed in 43 of 62 patients at 12 months, with a median time to progression (TTP) of 7 months. It was observed that through the use of limited margins, only 5 % and 2 % of patients had respectively a marginal failure and distant failure, with a median follow-up between 12 and 15 months. These data support the notion that limited GTV–CTV margins for GBM do not lead to an increase in local failures [54].

Minniti et al compared relapse patterns in 105 patients planned using the EORTC technique of GTV delineation, encompassing the resection cavity and any residual tumor detected in postoperative T1-weighted MRI with a 2-cm margin to create the CTV. CTV–PTV margin was 3 mm. All the patients were treated with conformal radiotherapy (60 Gy in 30 fractions) plus concomitant and adjuvant chemotherapy (TMZ). The patients were retrospectively rescheduled, when the disease relapsed, using the RTOG guideline and the target radiation coverage (EORTC vs. RTOG) of the site of recurrence was directly compared. No significant difference between the two techniques, in the fraction of “in field” relapses, was documented; however, a significantly greater volume of healthy brain tissue demonstrated to be treated using the RTOG two-phase technique [15].

It was demonstrated by Brandes et al. that patients with MGMT methylation developed fewer recurrences in or close to the radiotherapy treatment field, suggesting a clinically evident radiosensitizing effect of TMZ [55]. Further studies are needed to highlight the relationship between individual molecular variations and patterns of relapse, in order to develop future individualized radiotherapy plans.

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## Radiation Volume and the Use of Advanced Imaging Techniques

Treatment failure for GBM is mainly caused by the invasion of GBM cells into the normal tissue brain. Nowadays, conventional imaging is not able to detect the actual extent of the tumor. Even

the higher spatial resolution of MRI failed to allow direct visualization of the tumor margins. It has been shown, by some postmortem studies, that approximately between 20 and 27 % of GBMs have limited invasion (less than 1 cm from the edge of the gross tumor), 20 % have more extensive invasion (more than 3 cm from the gross tumor), and 8 % show disseminated spread [56, 57]. These groups should be treated differently; however, at present, GBM cannot be treated according to the extent of microscope invasion. The potential of biomarkers for tumor invasion imaging is an active field of research. Biological images are needed in Radiotherapy both to spare normal brain tissue and to better target GBM microscopic extension into the brain parenchyma. Biologic imaging could be referred to as a way to depict physiologic, metabolic, and functional processes, also to noninvasively measure the biologic features of tumors or normal tissues. Significant information on cellular proliferation, angiogenesis, hypoxia, and metabolic activity could be supplied to radiation oncology by functional and molecular imaging techniques (diffusion and perfusion MRI, magnetic resonance spectroscopy (MRS), and positron emission tomography (PET)).

MRS can provide biochemical changes in the brain tissue, particularly when tumors are present. On MRS, the chemical composition (metabolites) of normal brain tissue can be differentiated from the tumor tissue. The metabolites detectable with proton MRS include, among others, N-acetylaspartate (NAA) and choline-containing compounds (Cho), and could act as potential biomarkers for tumor activity. Cho is a membrane component that reflects the metabolism of cellular membrane turnover; NAA is a marker for neuronal density that is decreased in tumors due to neuronal loss. GBM shows an increase in the Cho/NAA ratio due to a marked high resonance in the spectral region of Cho and a low NAA resonance [58]. These data could be significant for radiation oncology to define the CTV in GBM. Ken et al. published a phase-II trial that integrates in 16 patient 3D MRS images in the treatment planning process for GBM, to guide the treatment delivery. A simultaneous boost



technique (SIB) with intensity-modulated radiotherapy (IMRT) was chosen to simultaneously deliver higher doses (72 Gy) to “high-risk” subvolumes; the GTV2 was defined as the MRS abnormality ( $\text{Cho}/\text{NAA} \geq 2.00$ ). No difference in the pattern of recurrences was described [59]. In another prospective Phase-II trial, Einstein et al. reported the results of 35 GBM patients treated with defining high-risk tumor volumes using postoperative MRS (elevated Cho/NAA ratio in excess of 2:1) to deliver a SRS boost (single fraction of 15–24 Gy). All patients received in addition EBRT to a total dose of 60 Gy in 2 Gy daily fractions. Mean Survival Time was 20.8 months, and it equalled the historical control. In this study the local control was not specifically analyzed [60]. MRS is nowadays performed to differentiate brain tumor recurrence from radionecrosis [61].

PET is an imaging modality widely used in oncology for clinical staging, monitoring of treatment efficacy, and follow-up to detect disease recurrence. Conventional (18)F-FDG-PET is of limited relevance for GBM imaging, due to high levels of glucose uptake by normal brain and the resulting unfavourable signal-to-noise ratio. In contrast, 11C-methionine (MET) and 18F-fluoroethyl-L-tyrosine (FET) are more helpful in brain tumor imaging than 18F-FDG [62]. In 2012, Piroth et al. published a prospective phase-II study in which they used postoperative FET-PET to define the CTV receiving a boost dose up to 72 Gy at 2.4 Gy per fraction with IMRT technique. OS and PFS were 14.8 months and 7.8 months, respectively. In this study the authors demonstrated that postoperative tumor volume in FET-PET has an independent significant influence on DFS and OS of patients with GBM [63].

Although some interesting results have been achieved by using sophisticated imaging modalities applied to radiation treatment planning, it has not been possible to develop dose escalation programs that are able to overcome GBM radioresistance. However, better ways to define the target volume could be identified by past research programs and others now in progress, thanks to a more accurate “anatomic” localization of the

tumor biological features. This is particularly relevant to the association of radiation and target therapies to treat a very heterogeneous neoplasm like GBM.

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## Molecularly Targeted Therapies and Radiotherapy

Combinations of different “biologically active” drugs with radiotherapy provide alternative strategies to improve the OS in GBM patients. The main research strategies addressed the possible role of EGFR and VEGF inhibitors.

The *epidermal growth factor receptor (EGFR)* is considered one of the most attractive therapeutic targets for GBM. The gene encoding EGFR is amplified in approximately 40 % of GBMs, especially in the classical subtype (80 %) [64]. EGFR tyrosine kinase inhibitors (TKIs), gefitinib and erlotinib have been used in patients with recurrent GBMs, but only minimal activity and no OS benefit have occurred [65, 66]. A Radiation Therapy Oncology Group (RTOG) phase-I/II trial (RTOG 0211), including 147 patients with newly diagnosed GBM, investigated the combination of gefitinib and radiotherapy followed by gefitinib maintenance until the time of relapse. PFS was 5.1 months and OS was 11 months, which is comparable to historical controls receiving radiotherapy alone [67]. A Phase-II trial by Qaddoumi studied the role of Erlotinib during and after RT in children with newly diagnosed high-grade gliomas. 41 patients were enrolled, 21 with GBM; the 2-year PFS was 19 months. The outcome was not improved by the use of erlotinib during and after RT [68].

Most of the drugs evaluated in clinical trials interfere with the *vascular epidermal growth factor (VEGF)* pathway, blocking directly the receptor or using monoclonal antibody directed against VEGF (bevacizumab). GBM blood vessels are structurally abnormal, contributing to an adverse microenvironment characterized by a low oxygen tension; VEGF inhibitors “normalize” structurally and functionally abnormal tumor vasculature. Radioresistance is promoted by this microenvironment and the delivery of chemo-

therapy is impaired [69]. Two major phase-III trials were performed, one by the RTOG (RTOG-0825) in the USA [70] and one, AVAGlio, mostly run in Centres in Europe [71]. In both studies, in newly diagnosed GBM, a standard “Stupp” regimen was compared to the association of bevacizumab and TMZ plus RT. The results from both trials were presented at the 2013 Meeting of the American Society of Clinical Oncology and subsequently published. PFS was significantly prolonged in both trials and the quality of life was preserved in the AVAGlio trial, but not in RTOG-0825. Unfortunately, OS was not improved. Upon subgroup analysis, it was not possible to identify specific subgroups of patients who particularly benefitted from bevacizumab. Therefore, at present, the use of bevacizumab is approved by the Federal Drug Administration (FDA) as a monotherapy only in recurrent GBM. The approval was based on demonstration of durable objective response rates observed in two single-arm Phase-II trials, AVF3708g and NCI 06-C-0064E [72, 73]. Furthermore, bevacizumab could play an important role in the therapy for CNS radiation necrosis. As a matter of fact, radiation necrosis can be considered an ongoing process from endothelial cell dysfunction to tissue hypoxia and necrosis, accompanied by the release of a vasoactive protein, like the vascular endothelial growth factor (VEGF) that can lead to progressive blood–brain barrier dysfunction and brain edema [74].

Vatalanib is an oral TKI that specifically targets TK signalling of VEGFR. In a Phase I/II trial performed by EORTC, 19 patients with newly diagnosed GBM were treated with vatalanib in combination with standard treatment. The planned randomized phase-II trial was discontinued right at the start due to industry decision not to further develop this agent [75].

Sorafenib is a small molecular inhibitor of several tyrosine protein kinases (VEGFR and PDGFR) (tyrosine kinase inhibitor or TKI) and Raf kinases. A Phase-I dose escalation trial was conducted to evaluate the safety and efficacy of sorafenib in combination with standard treatment (RT+TMZ) in patients with newly diagnosed GMB, or in combination with hypofractionated

stereotactic RT alone in patients with recurrent GMB [76].

Apart from EGFR and VEGF blockade, other biological pathways aroused the interest of clinical researchers as possible targets for the association of radiotherapy and targeted therapy.

Farnesyltransferase inhibitors (FTIs) have been shown to have radiosensitizing properties in preclinical models [77]. The combination of RT and FTI (tipifarnib) was studied in a phase-II clinical trial; the association of tipifarnib with radiotherapy showed promising OS results, but no increase in TTP compared to historical data [78].

Cilengitide is a novel small molecule that selectively blocks the activation of the  $\alpha\upsilon\beta 3$  and  $\alpha\upsilon\beta 5$  integrins and has been studied in GBM. Integrins are a family of cell surface receptors that play different important roles in most biological cells' activity. The  $\alpha\upsilon\beta 3$  and  $\alpha\upsilon\beta 5$  integrins are overexpressed in GBM cells and in tumor vasculature. Integrins, in addition to VEGF, are key mediators of angiogenesis and tumor growth. Unfortunately, the results of two large phase-III trials showed that the addition of cilengitide to RT and TMZ for the treatment of newly diagnosed GBM does not improve PFS and OS compared to RT and TMZ alone [79, 80]. The considerable radiochemoresistance of GBM cells is underlined by these clinical data, and the possible presence of a particular subpopulation of cells responsible for local recurrence is also suggested.

The use of immunotherapy with radiotherapy is one of the modern challenges. No clinical data for GBM have been produced yet by this approach, but it is certainly an exciting future research field. For example, researches and ongoing clinical studies are being conducted to evaluate the role of the programmed death-1 (PD-1)/PD-ligand1 (PD-L1) pathway in cancers. It has been demonstrated by recent preclinical data that a combination of radiosurgery with immunotherapy with anti-PD1 blockade produces long-term survivors in GBM-challenged mice [82]. Ionizing radiation is a potent immune-modulator through several mechanisms: the increased availability and reliability of new drugs that modulate the immune response



**Table 2.4** Targeted therapy

<i>Anti EGFR</i>			
Authors	Drug	Patients	Results
Chakravarti et al. [67]	Gefitinib	147	<i>PFS: 4.9 months</i> <i>OS: 11.1 months</i>
Qaddoumi et al [68]	Erlotinib	21	<i>PFS: 19 months</i>
<i>Anti-VEFG/Anti-VEGFR</i>			
RTOG-0825 [70]	Bevacizumab	637	<i>PFS 10.7 months</i> <i>OS: 15.7 months</i>
Avaglio [71]	Bevacizumab	921	<i>PFS: 10.6 months</i> <i>OS: 16.8 months</i>
Brandes et al. [75]	Vatalanib	19	<i>PFS: 6.8 months</i> <i>OS: 17.3 months</i>
Den et al. [76]	Sorafenib	11	<i>OS: 18 months</i>
<i>Anti <math>\alpha\beta 3</math> and <math>\alpha\beta 5</math> integrins</i>			
Stupp et al. [80]	Cilengitide	52	<i>PFS: 6 months</i> <i>OS: 16.1 months</i>
<i>Other</i>			
Ducassou et al. [79]	Tipifarnib	27	<i>OS 20 months</i>

could represent, in the next future, a powerful synergistic approach. Table 2.4.

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