A Systematic Review of Glioblastoma-Targeted Therapies in Phases II, III, IV Clinical Trials

Elisabete Cruz Da Silva 1, Marie-Cécile Mercier 1, Nelly Etienne-Selloum 1,2, Monique Dontenwill 1 and Laurence Choulier 1,*

1 CNRS, UMR 7021, Laboratoire de Bioimagerie et Pathologies, Faculté de Pharmacie, Université de Strasbourg, 67401 Illkirch, France; elisabete.silva@unistra.fr (E.C.D.S.); marie.071@hotmail.fr (M.-C.M.); nelly.etienne-selloum@unistra.fr (N.E.-S.); monique.dontenwill@unistra.fr (M.D.)
2 Service de Pharmacie, Institut de Cancérologie Strasbourg Europe, 67200 Strasbourg, France
* Correspondence: laurence.choulier@unistra.fr; Tel.: +33-36885-4114; Fax: +33-36885-4313

Simple Summary: This review describes in a very detailed and exhaustive approach the literature of these last 20 years on glioblastoma targeted therapies in Phases II-IV of 257 clinical trials on adults with newly diagnosed or recurrent GBMs (excluding targeted immunotherapies and therapies targeting tumor cell metabolism, well documented in recent reviews). Divided in four Sections, are provided descriptions and lists (in 12 different tables) of, not only main but all drugs, targets, clinical trials and the results of targeted therapies when they are known.

Abstract: Glioblastoma (GBM), the most frequent and aggressive glial tumor, is currently treated as first line by the Stupp protocol, which combines, after surgery, radiotherapy and chemotherapy. For recurrent GBM, in absence of standard treatment or available clinical trials, various protocols including cytotoxic drugs and/or bevacizumab are currently applied. Despite these heavy treatments, the mean overall survival of patients is under 18 months. Many clinical studies are underway. Based on clinicaltrials.org and conducted up to 1 April 2020, this review lists, not only main, but all targeted therapies in phases II-IV of 257 clinical trials on adults with newly diagnosed or recurrent GBMs for the last twenty years. It does not involve targeted immunotherapies and therapies targeting tumor cell metabolism, that are well documented in other reviews. Without surprise, the most frequently reported drugs are those targeting (i) EGFR (40 clinical trials), and more generally tyrosine kinase receptors (85 clinical trials) and (ii) VEGF/VEGFR (75 clinical trials of which 53 involving bevacizumab). But many other targets and drugs are of interest. They are all listed and thoroughly described, on an one-on-one basis, in four sections related to targeting (i) GBM stem cells and stem cell pathways, (ii) the growth autonomy and migration, (iii) the cell cycle and the escape to cell death, (iv) and angiogenesis.

Keywords: glioblastoma; targeted therapies; biomarkers; clinical trials

1. Introduction

Since 1926, different classifications of brain tumors have been proposed, based mainly on histological and malignancy criteria [1]. Increasing knowledge on glioma molecular characteristics enabled the proposition of a new classification in 2016. Figure 1 recapitulates the main steps of the modern classification of gliomas. Glioblastoma (GBM) is a high-grade glioma (grade IV), the most aggressive and the most frequent glioma. In the 2016 classification, GBMs are divided into three groups according to the status of the isocitrate dehydrogenase (IDH) gene: (i) GBMs IDHwt [this group represents 90% of GBMs and corresponds to primary GBMs], (ii) mutated IDH GBMs [this group represents 10% of GBMs, corresponds to secondary GBMs, occurs in young patients and has a better prognosis], (iii) Not otherwise specified (NOS) GBMs [status could not be evaluated]. When histological data suggest GBM and immunohistochemical analysis of IDHmut is negative,
sequencing is recommended. Sequencing is no longer recommended after the age of 55 [2]. Inhibitors of the mutated IDH proteins are currently evaluated in GBM in Phase I clinical trials (NCT02073994, NCT02273739). They will thus not be further described in this review.

The standard treatment of GBMs is based on surgical resection followed by radiotherapy (RT) and concomitant chemotherapy for 6 weeks. The area around the tumor is irradiated with 2 Gy per day, five days per week for a total dose of 60 Gy. The chemotherapy used is Temozolomide (TMZ) at 75 mg/m² per day. After this radiochemotherapy, TMZ treatment is pursued alone every four weeks at 150–200 mg/m² per day for 5 consecutive days [3]. TMZ is an alkylating agent that causes DNA damage, cell cycle arrest and cell apoptosis. After oral administration, it is spontaneously hydrolyzed into an highly instable metabolite: 3-methyl-(triazen-1-yl)imidazole-4-carboxamide (MTIC) which reacts with water and releases highly reactive 5-aminoimidazole-4-carboxamide and methyl diazonium. The latter induces methylation at the O6 and N7 positions of a guanine and N3 position of an adenine [4]. These mutations cause aberrant repairs.

Despite these aggressive treatments, recurrence generally appears within 6–9 months of diagnosis [5]. In 90% of cases, recurrence is at the edge of the surgical resection. At the appearance of recurrence, patients’ survival is low: 3–6 months [6,7]. No protocol has yet been validated in the management of recurrent GBM. An increase in RT doses does not lead to gain in survival but induces more toxicity, including necrosis of healthy tissue [8]. Long-term side effects of radiation exposure (among which neurocognitive, psychosocial, endocrine . . . ) are present months or years after treatment and cause problems in rare people who survive as the effect of side-effects increases with time [9]. Increasing the doses of TMZ is also not more efficient [10]. In most cases, patients with recurrent GBM are included in clinical trials [11]. If not, several therapeutic molecules are proposed in the second line, mainly alkylating agents (lomustine, carmustine, fotemustine, carboplatin or procarbazine), microtubule destabilizing agent (vincristine) or antiangiogenic drug (bevacizumab). In absence of standard protocols, the therapeutic strategy is discussed for individual patients. In addition, corticosteroids, anticonvulsants (lacosamide, levetiracetam) and anticoagulants are used in the progression of tumors in the event of intracranial pressure, stroke and deep venous thrombosis epilepsy which occurs in 30% of patients with primary brain tumors [12].

Different improvements of the current protocol (surgery, radio and chemo therapies) or new strategies based on the particular microenvironment of GBM are increasingly proposed for the effective care of GBM [13–17]. They are briefly mentioned below, but are not the focus of this review. But regardless of strategies, if new treatments allowed for significantly longer survival, they would require more than improving patients’ survival and would minimize long-term side effects to preserve or even improve patients’ quality of life. Late adverse events induced by administered treatments should be addressed [18].

New strategies are proposed to improve the drug passage through the blood brain barrier (BBB) to achieve a higher therapeutic concentration at the tumor site. Delivering chemotherapy directly into the surgical resection cavity has been proposed. Convection-enhanced delivery (CED) allows chemotherapy to be delivered directly via a catheter in the tissue surrounding the GBM resection cavity. This method increases the volume of distribution but results in unpredictable brain diffusion [19]. It requires the use of several surgical procedures, leading to a high risk of infection or bleeding. Another strategy consists of administrating the therapy directly at the tumor resection bed [20–25]. The use of small lipophilic molecules, able to passively cross the endothelial cells of the BBB, has been tested in combination with standard therapies [26]. Encapsulating therapies in nanoparticles (10–200 nm) not only increases their solubility but also their release time and stability, while reducing side effects [27,28].

GBM has long been considered as a non-immunogenic tumor due to immunosuppressive adaptation mechanisms, low levels of T cells, dendritic cells and monocytes, decreased IgG and IgA and increased regulatory T cells [29]. Many different recent reviews focus on
novel therapies that harness the immune system, including vaccination, T-cell therapies, immune check-point modulators or adaptive immunotherapy [30–33].

Targeting tumor cell metabolism is another option. GBM is a hypoxic tumor. Hypoxia plays a role via different hypoxia inducing factors, HIF-1α and HIF-2α [34]. HIF1-α or factors implicated in the HIFs pathways have been proposed as potential therapeutic targets (as for examples profilin-1 or FIH1) [35–37]. To date, one Phase II clinical trial has been performed via the inhibitor of HIF2α, PT2385 [38] (NCT03216499).

Approaches aiming to exploit the metabolic deregulation of tumor cells compared to healthy cells are also increasing and characterization of specific metabolic pathways and metabolites are under intense investigations. Tumor cells have an increased need for glucose compared to healthy cells [39]. Thus, unlike healthy cells that use mitochondrial oxidative phosphorylation to generate ATP, tumor cells use aerobic glycolysis (the “Warburg effect”) [40]. Based on this concept, reduction of glucose delivery to tumor cells, for example, might influence their growth without influencing normal cells [41].

Delivery of low-intensity, intermediate-frequency (100–300 kHz) alternating electric fields through the TTFields, Optune®, Novocure Inc., Portsmouth, NH USA (tumor treatment fields) device has given an alternative strategy to treat GBM. It was approved by the FDA since 2011 for recurrent GBM. Beside antiproliferative and anti-mitotic effects, this device efficacy might also be related to inhibition of migration, invasion, angiogenesis and DNA repair as well as induction of apoptosis and immune effects [42].

GBMs are characterized by a high molecular and transcriptional inter- and intratumoral heterogeneity [43–46]. Developments in multi-omic analysis have led to identification of specific molecular signatures [47–49] discriminating at least 3 different subclasses (mesenchymal, proneural and classical) but also emphasized a high degree of plasticity between cellular states [50]. Nevertheless, proposition of targeted therapies has increased these last years based on promising preclinical data which supported the initiation of clinical trials. The aim of this paper is to make an exhaustive review of the different clinical trials (completed or under way) focusing on drugs considered as targeted therapeutics. We have divided the topic in 4 different sections considering drugs inhibiting (1) stem cells and stem cell pathways (Section 3.1), (2) the growth autonomy and migration (Section 3.2), (3) the cell cycle and escape to cell death (Section 3.3) and (4) angiogenesis (Section 3.4). Clinical trials of phases I/II, II, III or IV have been considered but not those of Phase I.

**Figure 1.** Timeline showing the principal dates of the histological and molecular classifications of gliomas. Classifying brain tumors has been the subject of many studies for several years. The first classification published in 1926 by Bailey and Cushing was based on histogenetics [51]. According to this classification, the presence of embryonic cells would be at the origin of tumor cells. The second classification proposed in 1949 by Kernohan JW, Mabon [52], includes grades of malignancy. The WHO proposed a new classification of gliomas in 1979 [53], which is internationally recognized and was revised in 1993, 2000, 2007 and 2016 [54–57]. These classifications are based on anatomopathological analysis of a representative glioma fragment (from biopsy or surgical resection) and “grading” elements. The International Society of Neuropathology was held from 1–3 May 2014 in Haarlem, the Netherlands [58]. The meeting reached consensus regarding the incorporation of non-histological data, such as molecular information, into the next WHO classification [55].
2. Methods

1 April 2020 has been set as the end date for data collection for this study. The flowchart (Figure 2) lists the clinical trials included and excluded from this manuscript. Briefly, 1519 clinical trials were listed on www.clinicaltrials.com (accessed on 1 April 2021) for GBM. Restrictions were applied to keep only clinical trials on adults and phases I/II to IV. 788 clinical trials remained (212 Phase I/II, 488 Phase II, 14 Phase II/III, 70 Phase III & 4 Phase IV). They have then been sub-classified: 257 clinical trials concerning targeted therapies are described in this review, and 531 clinical trials were excluded from this analysis as they are related to (i) RT, irradiation, imaging, classic cytotoxic chemotherapy, surgery, (ii) immunotherapy and vaccine therapy, (iii) other tumors than adult brain tumors, and (iv) other studies, such as withdrawal trials, trials which did not retain enough patients or did not pass phase II, studies on hypoxia, metabolism, anti-depressants, vitamins, hormones, molecules for sleep disorders, or cognitive decline, or drugs for which molecular targets are not clearly identified.

Figure 2. Flowchart.

To recapitulate, the 257 clinical trials described in this review cover 20-years of targeted therapies in clinical phases I/II and over, for adult GBM. In addition to GBM, clinical trials including gliomas, high grade gliomas, gliosarcomas, anaplastic astrocytomas, or other brain tumors were retained. Children and young patient brain tumors were excluded.

Twelve tables detail the different clinical trials underway or completed in phases I/II, II, III or IV. The dates mentioned correspond to the start of the clinical trial and the last
date of data update on Clinicaltrials.com. In tables, comparative trials with a significant difference between two treatments are highlighted in green and those with a non-significant difference are highlighted in red.

3. Results-Glioblastoma Targeted Therapies

The different GBM biomarkers targeted in phases I/II, II, III and IV and described in the following paragraphs are presented in Figure 3.

3.1. Targeting Stem Cells and Stem Cell Pathways

The discovery of tumor stem-like cells in solid tumors including glioma [59,60] has changed the landscape of the origin of tumors and their recurrence. These cells also named “GBM initiating cells” (GICs) or “GBM stem cells” (GSC) [61,62] exhibit self-renewal capacity and differentiating ability to form the tumoral mass [63]. The presence of GICs can be explained by the malignant transformation of neural (non-tumor) stem cells [64] and/or by the de-differentiation of tumor cells into tumor stem cells following radiotherapy or chemotherapy [65].

GICs are reported to be more resistant to current treatments than differentiated tumor cells explaining their role in GBM recurrence. This increased resistance can be explained by (1) a quiescent condition, resulting in the ineffectiveness of currently used chemotherapies targeting the cell cycle [66], (2) High expression of efflux transporters, including MRP1 (Multidrug resistance-associated protein 1) and P-gP (Permeability-GlycoProtein), evicting therapeutic molecules and (3) a defective regulation of apoptosis, with higher expression of survival factors and an ability to adapt to a stressful environment [67].

The discovery of GICs has generated hope for new therapeutic targets. Eradicating GICs would prevent the initiation of GBM on the periphery of surgical resection and reduce drug resistance and recurrence [68]. Three strategies are currently being studied to induce apoptosis of GICs: (i) directly targeting the signaling pathways involved in the self-renewal of GICs (Table 1), (ii) inducing their differentiation to sensitize them to therapies, and (iii) inhibiting the pathways that control their resistance.
Figure 3. Principal biomarkers and drugs in GBM targeted therapies. The color code corresponds to the four sections of the Results section. The targeting of stem cells and stem cell pathways is represented in green, the targeting of growth autonomy and migration in blue, the targeting of the cell cycle & escape to cell death in black and the targeting of angiogenesis in red. Acronyms are defined in the text.
### Table 1. Clinical studies analyzing therapies targeting the self-renewal of GICs.

| Molecule       | Date                | Protocol                        | Phase | Patients | Results |
|----------------|---------------------|---------------------------------|-------|----------|---------|
| **Wnt pathway** |                     |                                 |       |          |         |
| Celecoxib      | 06/2005–09/2014     | Combined with TMZ               | I/II  | N        | PFS 10.5 months vs. 13.4 months; TMZ vs. TMZ + celecoxib ($p = 0.97$) [69] |
|                | 01/2003–07/2017     | Combined with thalidomide, etoposide and Cyclophosphamide. Unpublished data | I/II  | R        |         |
|                | 05/2016–10/2019     | Combined with TMZ and eight repurposed drugs. Results: ongoing studies (no recruitment) | I/II  | R        |         |
|                | 09/2003–03/2015     | Combined with RT and anticonvulsant drugs (p450 inhibitor) | II    | N undergoing RT and anticonvulsant treatment | OS 11.5 months vs. 16 months ($p = 0.11$; HR = 2.7); p450 inhibitor vs. no p450 inhibitor [70] |
|                | 10/2002–06/2017     | Thalidomide combined with the Stupp protocol and celecoxib | II    | N        |         |
| **Notch pathway** |                     |                                 |       |          |         |
|                | 11/2010–03/2017     | Monotherapy                     | II    | R        |         |
| **Hedgehog pathway** |                     |                                 |       |          |         |
|                | 09/2009–08/2017     | Monotherapy                     | II    | R resectable |         |
| **STAT3 pathway** |                     |                                 |       |          |         |
|                | 05/2017–02/2020     | Molecularly Matched Targeted Therapies (APG101, alectinib, idasanutin, atezolizumab, vismodegib, temsirolimus, palbociclib) combined with RT [71] | I/II  | N without MGMT promoter methylation |         |
|                | 03/2018–04/2020     | Combined with TMZ               | I/II  | N        |         |
| **Glsdegib (PF-04449913)** |                     |                                 |       |          |         |
|                | 03/2018–04/2020     | Combined with TMZ               | I/II  | N        |         |
| **Napabucasin (BB1608)** |                     |                                 |       |          |         |
|                | 12/2014–10/2019     | Combined with TMZ               | I/II  | R        |         |

R: recurrent GBM; N: newly diagnosed GBM; PFS: progression-free survival; PFS-6: 6-month survival; OS: overall survival. In red, not significant comparative tests. In italics, clinical trials listed in other tables (as mentioned). Results obtained from Clinicaltrials.com (accessed on 1 April 2020) and/or in cited references. Dates correspond to the first posted and last update posted.

### 3.1.1. Targeting the Self-Renewal of GICs

(i) **Wnt pathway**

The Wnt signaling pathway is involved in the development of neural stem cells [72]. Aberrant activation of this pathway is involved in their malignant transformation and the development of brain tumors [73]. The Wnt pathway is also involved in the invasion of GBMs and in the epithelial-mesenchymal transition. Inhibiting the Wnt pathway in GICs leads to the sensitization to TMZ by decreasing the transcription of the transport proteins ABCC2 (MRP2) and ABCC4 (MRP4) [74]. Two proteins are being investigated in the inhibition of the Wnt pathway: β-catenin and GSK3-β. Diclofenac and Celecoxib, non-steroidal anti-inflammatory drugs, respectively, have been shown to inhibit β-catenin and to induce a decrease in the proliferation and migration of GBMs cells [75]. Tested in Phase II in newly diagnosed GBMs, combined with TMZ, Celecoxib had no survival benefit (NCT00112502) [69]. Two GSK3-β inhibitors were assayed in preclinical assays on GBMs cells: AR-A01441 and LiCl. These two agents increase the apoptosis of GBMs cells, decrease neurosphere formation and clonogenicity [76]. Two new selective inhibitors of the Wnt pathway have been synthesized: SEN461 and XAV939 [77]. In vitro, SEN461 is
known to be responsible for the inhibition of GBM cell growth. However no clinical trials have analyzed the efficacy of GSK3-β inhibition [78] in vivo.

(ii) Notch pathway

The Notch pathway is involved in invasion, resistance to anti-VEGF (Vascular endothelial growth factor) therapies and recurrences of GBMs [79–81]. Activation of this pathway induced by one of its ligands (Delta and Jagged) results in the cleavage of the Notch receptor, allowing the release of the receptor’s intracellular domain and its translocation to the nucleus. Notch’s cleavage is mediated by α and γ-secretase [82]. It has been suggested that targeting the Notch pathway via inhibition of γ-secretase [83,84] may be useful. Several inhibitors have been tested in vitro, such as MRK003 [85], GSI (RO4929097) [86], and dnMAML [87]. Only the GSI compound (R04929097) is currently being tested in clinics (Table 1). A Phase I study, investigating the toxicity of GSI combined with Bevacizumab, showed encouraging results (NCT01189240). The study is being pursued in a Phase II study [88].

(iii) Hedgehog (SHH) pathway

The SHH signaling pathway is associated with resistance to radiotherapy and chemotherapy. Two main effectors of this pathway exist: SMO (smoothened) and Gli1 (glioma-associated oncogene homolog 1) [89–91]. SMO inhibition is achievable via two inhibitors, LDE225/Sonidegib and GDC-0449/Vismodegib [92]. The latter is currently in clinical trials (Phase II) in recurrent GBMs (NCT00980343) and (Phase I/II) in patients with newly diagnosed GBM without O6 methylguanine methyl transferase (MGMT) promoter methylation (NCT03158389, referred below as N²M² (NOA-20), NCT Neuro Master Match the umbrella protocol for Phase I/IIa trials of molecularly matched targeted therapies combined with RT) [71].

Glasdegib (PF-04449913), another SMO inhibitor that has demonstrated potent and selective inhibition of Hedgehog signaling in vitro, and significant antitumor efficacy in vivo in various solid and hematologic malignancies [93], is a rational therapeutic agent currently in phase I/II for patients with newly diagnosed GBM, since it inhibits SHH pathway interfering with cancer stem cells and endothelial migration. Gli1 can be inhibited by the cyclopamine. This steroidal alkaloid induces a decrease in the number of GICs and leads to RT sensitization [94]. The optimization of cyclopamine, by addition of a glucuronide group, showed a decrease in the tumor mass without having the toxic effects of Gli1 inhibition in astrocytes. This formulation specifically targets tumor cells expressing the beta-glucuronidase enzyme [95]. Similarly, the formulation of cyclopamine in micelles leads to inhibition of the proliferation and invasion of GBMs cells. This formulation also enhances the cytotoxic effect of TMZ in vivo [96]. No clinical studies have tested Gli1 inhibition.

(iv) STAT3 pathway

The transcription factor STAT3 has an established function in neural stem cell and astrocyte development. It has been found to play dual tumor suppressive and oncogenic roles in glial malignancy depending on the mutational profile of the tumor [97]. Napabucasin (BBI608), a small molecule that blocks stem cell activity in cancer cells by targeting the STAT3 pathway, is currently in clinical Phase I/II in combination with TMZ in adult patients with recurrent or progressed GBM (NCT02315534, Table 1).

3.1.2. Inducing the Differentiation of GICs or Inhibiting Pathways That Control Resistance

Very few clinical trials addressing these points are currently developed although new targets are suggested through preclinical explorations.

As previously mentioned, inducing differentiation of GICs would sensitize them to current therapies. Simulating the BMP (Bone Morphogenetic Proteins) pathway is possible by different mechanisms:
- Activation of an effector of the BMP pathway, such as BMP-7, blocks the tumor progression in vitro [98].
- Using mimic effectors of the BMP pathway: the BMP-2 protein mimicking peptide, GBMP1, has been developed to activate this pathway and is currently being studied [99]. Activation of the BMP pathway is currently tested in clinical trials. A Phase I study is testing the recombinant protein hrBMP4 in recurrent GBMs (NCT02869243).

A new strategy aims to target adenosine, which is involved in GIC chemoresistance [100,101]. Physiologically, adenosine is produced by the degradation of AMP by the factors CD39 and CD73. In GBM cells, CD73 expression is increased and leads to an increase in adenosine levels [102]. An increase in the A3AR adenosine receptor has also been observed in GBM cells. Inhibition of A3AR receptor expression induces a decrease in MRP1 activity and increased sensitivity to chemotherapy [102,103]. CD73/A3AR/MRP1 is a potential therapeutic target, not yet tested in a clinical setting.

Two other adenosine receptors, A1B and A2B, are involved in apoptosis and GIC differentiation. The stimulation of these receptors by agonists helps to sensitize GICs to chemotherapy [104].

3.2. Targeting Growth Autonomy and Migration

Mutations in RAS/MAPK and PI3K/AKT pathways are reported in 88% of GBMs [105]. Their hyperactivation plays a central role in cell survival, growth, angiogenesis and cellular metabolism. It is mainly caused by ligand-induced stimulation of tyrosine kinase receptors (RTKs), such as epidermal growth factor receptor (EGFR) and platelet-derived growth factor receptors (PDGFR). The different RTKs are activated by the autophosphorylation of their tyrosine kinase domain, which results in the binding and activation of PI3K. The activated PI3K transforms PIP2 into PIP3. The latter binds to AKT and transports it to the plasma membrane where residues are phosphorylated by PDK1 (on Thr308) and mTORC2 (on Ser473). The activation of AKT leads to a phosphorylation cascade and to the activation of several proteins involved in cell growth, angiogenesis and apoptosis, including mTOR and its partner mTORC1. One of the main inhibitors of this pathway is PTEN, which prevents the transformation of PIP2 into PIP3 [106].

The RAS/MAPK pathway activation results in the transformation of GDP to GTP, recruitment of RAF to the membrane and its activation, and ERK phosphorylation.

Targeting the different effectors of these pathways would reduce growth autonomy and migration of the GBM.

3.2.1. Inhibition of EGFR and HER2

The ErbB family of proteins contains four receptor tyrosine kinases, structurally related to the epidermal growth factor receptor (EGFR or HER1). EGFR and HER2 are promising anti-tumor targets for the therapy of GBM (Table 2).

i. Inhibition of EGFR

The EGFR signaling drives cancer development. EGFR aberrant expression and signaling promotes cell growth, survival, invasion and angiogenesis, and regulates tumor metabolism and cell stemness [107]. EGFR is a clinical target in solid tumors. In GBM, EGFR is amplified and/or mutated in more than 50% of cases [108]. EGFR and its mutant EGFRvIII are the subjects of extensive research. Several strategies are proposed to inhibit these receptors, including monoclonal antibodies, tyrosine kinase inhibitors (TKI) and anti-tumor vaccines. The first two classes are described in this review (Table 2).
| Target | Molecule | Date | Protocol | Phase | Patients |
|--------|----------|------|----------|-------|----------|
| Cetuximab | EGFR | NCT01044225 01/2010–03/2012 | Combined with RT/TMZ and cilengitide (non-comparative) | II | N with MGMT-promoter unmethylated |
| | | NCT00311857 04/2006–09/2006 | Combined with RT/TMZ | I/II | N |
| | | | Results (77 patients): PFS<sub>n</sub> = 81%; PFS<sub>12</sub> = 37%; OS<sub>12</sub> = 87%; | | |
| | | NCT00463073 04/2007–12/2008 | Combined with bevacizumab and irinotecan | II | R |
| | | NCT02800486 05/2016–01/2017 | Intracranial monotherapy | II | N |
| | | NCT01884740 06/2013–01/2017 | Combined with bevacizumab and intracranial administration | I/II | N aged under 22 |
| | | NCT02861898 08/2016–05/2019 | Intra-arterial combined with STUPP protocol | I/II | N |
| Panitumumab | EGFR | NCT01017653 11/2009–07/2016 | Combined with irinotecan | II | R |
| | | | Results (16 patients): PFS<sub>6</sub> 12.5%; OS 4.6 months | | |
| Nimotuzumab | EGFR | NCT00753246 11/2007–11/2012 | Combined with RT/TMZ vs. RT/TMZ | III | N |
| | | | Results (142 patients): PFS = 7.7 months vs. 5.8 months (p = 0.7989); OS = 22.3 months vs. 19.6 months (p = 0.485) Nimotuzumab + RT/TMZ vs. RT/TMZ | | |
| | | NCT03388372 08/2010–01/2018 | Combined with RT/TMZ | II | N |
| Depatuxizumab-mafodotin | EGFR | NCT03419403 02/2018–04/2020 | Combined with RT/TMZ and ophthalmologic prophylactic treatment | III | |
| | | NCT02573324 10/2015–04/2020 | Combined with RT/TMZ | II/III | N with EGFR amplification |
| | | NCT02590263 10/2015–05/2019 | Monotherapy or combined with RT/TMZ | I/II | N/R |
| | | NCT02343406 01/2015–05/2020 | Monotherapy or combined with TMZ | II | R |
| | | | Results (260 patients): PFS = 2.7 vs. 1.9 vs. 1.9 months; OS = 9.6 vs. 7.9 vs. 8.2 months Depatux-M + TMZ vs. Depatux-M vs. Lomustine or TMZ | | |
| GC1118 | EGFR | NCT03618667 08/2018–08/2018 | Monotherapy | II | R with high EGFR amplification |
| Sym004 | EGFR | NCT02540161 09/2015–08/2019 | Monotherapy | II | R |
| Erlotinib | EGFR | NCT00337883 06/2006–03/2014 | Monotherapy | II | R first |
| | | NCT00039494 01/2003–08/2013 | Combined with TMZ/RT | I/II | N |
| | | NCT00445588 03/2007–03/2016 | Combined with sorafenib | II | R |
Table 2. Cont.

| Target          | Molecule                      | Date               | Protocol                                                        | Phase | Patients | Phase | Patients |
|-----------------|-------------------------------|--------------------|-----------------------------------------------------------------|-------|----------|-------|----------|
| NCT00525525     | Combined with bevacizumab, TMZ in adjuvant therapy | 09/2007–05/2014    | Results (150 patients): PFS 9.2 months; OS 13.6 months [114]   | II    | N        |       |          |
| NCT00187486     | Combined with TMZ during the Stupp protocol | 09/2005–08/2012    | Results (28 patients): PFS 2.8 months; OS 8.6 months [115]      | II    | N        |       |          |
| NCT00720356     | Combined with bevacizumab, in adjuvant therapy after RT/TMZ | 06/2008–10/2018    | Results (48 patients): PFS-12 32%; OS 13.2 months               | II    | N        |       |          |
| NCT00672243     | Combined with sirolimus       | 01/2008–08/2013    | Results (32 patients): PFS 6.9 weeks; OS 33.8 weeks [116]       | II    | R        |       |          |
| NCT00671970     | Combined with bevacizumab     | 01/2008–03/2013    | Results (25 patients): PFS-6 28%; OS = 42 weeks [117]           | II    | R        |       |          |
| NCT00086879     | Monotherapy compared to TMZ or BCNU | 06/2004–09/2017    | Results (110 patients): PFS 1.8 months vs. 2.4 months; OS 7.7 months vs. 7.5 months (No statistical data); Erlotinib vs. BCNU/TMZ [118] | II    | R        |       |          |
| NCT00301418     | Monotherapy                   | 03/2006–02/2016    | Results (11 patients): PFS 1.9 months; OS 6.9 months [119]      | I/II  | R        |       |          |
| NCT00274833     | Combined with TMZ/RT          | 01/2006–12/2012    | Unpublished data                                                | II    | N        |       |          |
| NCT00387894     | Monotherapy                   | 10/2006–06/2013    | Results (6 patients): Terminated because ongoing literature at the time confirmed that the selection process was not likely to enrich for a patient population expected to benefit, and rapid disease progression in the first 6 patients. | II    | R        |       |          |
| NCT00054496     | Monotherapy                   | 02/2003–01/2014    | Results: ongoing studies (recruitment unknown)                  | II    | R        |       |          |
| NCT01112736     | Combined with temsirolimus    | 06/2005–06/2015    | Results (47 patients): PFS-6 13% [120]                          | I/II  | R        |       |          |
| NCT01110876     | Combined with vorinostat and TMZ | 04/2010–11/2014    | Unpublished data                                                | I/II  | R        |       |          |
| NCT00045110     | Monotherapy                   | 01/2003–08/2017    | Results (96 patients): PFS 2 months GBM R; OS 14 months GBM N Post RT [121] | I/II  | R        | R/N  |          |
| NCT00335764     | Sorafenib combined with erlotinib, tipifarnib or temsirolimus  | 04/2006–07/2018    | See Sorafenib                                                   | I/II  | R        |       |          |

**Gefitinib**

| Target          | Molecule                      | Date               | Protocol                                                        | Phase | Patients | Phase | Patients |
|-----------------|-------------------------------|--------------------|-----------------------------------------------------------------|-------|----------|-------|----------|
| NCT00238797     | Combined with RT              | 10/2005–01/2011    | Unpublished data                                                | II    | -        |       |          |
| NCT00250887     | Pre- and post-surgery (second surgery) | 11/2005–10/2007    | Results (22 patients): OS 8.8 months [122]                      | II    | R        |       |          |
| NCT00014170     | Monotherapy                   | 04/2001–07/2013    | Unpublished data                                                | II    | N        |       |          |
| NCT00016991     | Monotherapy                   | 06/2001–06/2013    | Results (53 patients): PFS 8.1 weeks; OS 39.4 weeks [123]       | II    | R first  |       |          |
| NCT00052208     | Combined with RT              | 01/2003–06/2013    | Results (147 patients): PFS 4.9 months; OS 11.0 months [124]    | I/II  | N        |       |          |
| NCT00025675     | Monotherapy                   | 01/2003–06/2018    | No results posted                                               | II    | R        |       |          |
| NCT01310855     | Cediranib combined with gefitinib, compared to cediranib and placebo | 03/2011–05/2017    | See Cediranib                                                  | II    | R        |       |          |
### Table 2. Cont.

| Target | Molecule | Date | Protocol | Phase | Patients |
|--------|----------|------|----------|-------|----------|
| Afatinib | NCT00727506 | 06/2008–06/2017 | Monotherapy ± TMZ and compared with TMZ | II | R |
| | | | | | |
| | Results (119 patients): PFS 0.99 months vs. 1.53 months (p = 0.032) vs. 1.87 months (p = 0.204); 9.8 months vs. 8 months (p = 0.386) vs. 10.6 months (p = 0.119); Afatinib vs. Afatinib + TMZ vs. TMZ [125] |
| Dacomitinib | NCT01520870 | 01/2012–03/2018 | Monotherapy | II | R with EGFR Amplification or EGFRvIII Mutation |
| | | | | | |
| | Results (49 patients): PFS-6 s 10.6%; PFS 2.7 months; OS 7.4 months [126] |
| | NCT0112527 | 04/2010–08/2018 | Monotherapy | II | N |
| Lapatinib | NCT01591577 | 05/2012–09/2016 | Combined with or non-combined with RT/TMZ. Unpublished data | II | N |
| | NCT00099060 | 12/2004–01/2014 | Monotherapy. Unpublished data | I/II | R |
| | NCT00107003 | 04/2005–07/2018 | Pre-operatory monotherapy. Unpublished data | II | R |
| | NCT00350727 | 07/2006–04/2013 | Combined with pazopanib | II | R |
| | Results (41 patients): PFS 62 vs. 56 days; PFS-6 0 vs. 15%; Patients positive vs. negative for EGFRvIII and/or PTEN [127] |
| Neratinib | NCT02977780 | 11/2016–02/2020 | Combined with TMZ vs. TMZ | II | N |
| | | | Results: ongoing studies (recruitment) |

R: recurrent GBM; N: newly diagnosed GBM; PFS: progression-free survival; PFS-6: 6-month survival; OS: overall sur-vival. In red, not significant comparative tests. In italics, clinical trials listed in other tables (as mentioned). Results obtained from Clinicaltrials.com (accessed on 1 April 2020) and/or in cited references. Dates correspond to first posted and last update posted.

### Monoclonal Antibodies

Cetuximab was the first chimeric antibody proposed to target EGFR. Two Phase II studies did not show any therapeutic benefit in patients with recurrent GBM, either as monotherapy [128] or in combination with Bevacizumab and Irinotecan [110].

Panitumumab, the first fully human monoclonal anti-EGFR antibody to enter clinical trials for the treatment of solid tumors, did not prove to be beneficial for GBM patients in a phase II with irinotecan (NCT01017653).

Nimotuzumab, a humanized anti-EGFR antibody, also did not show a gain in overall survival (OS) or progression-free survival (PFS) in patients newly diagnosed and treated with the Stupp protocol (phase III) (NCT00753246) [111]. These results were disappointing compared to an earlier study that showed that the combination of nimotuzumab with RT resulted in prolonged survival [129]. Nimotuzumab remains a potential interesting therapy. Indeed, an enhancement of the cytotoxic activity of TMZ in vivo has recently been observed [130].

GC1118, an anti-EGFR antibody which seems more potent to inhibit EGF binding to EGFR than cetuximab or panitumumab [131] is currently being tested as monotherapy (NCT03618667).

Sym004 is a synergistic antibody combination containing two recombinant mAbs (futuximab and modotuximab) which binds to different non-overlapping epitopes of EGFR and promotes a rapid EGFR internalization and degradation. Sym004 overcame cetuximab resistance in pre-clinical lung cancer cells [132]. However, it did not improve OS in patients with metastatic colorectal cancer [133]. In GBM, it is evaluated as monotherapy (NCT02540161).

Depatuxizumab-mafodotin (ABT-414) is an antibody-drug conjugate (ADC) composed by an anti-EGFR IgG conjugated to the tubulin inhibitor monomethyl auristatin F [134]. Depatuxizumab-mafodotin failed to show survival benefit in newly diagnosed GBM but
used in combination with TMZ in EGFR amplified recurrent GBM presented a possible efficiency [135].

Tyrosine Kinase Activity Inhibitors

Erlotinib is a reversible inhibitor of EGFR tyrosine kinase activity. Two Phase II studies did not show any improvement in OS when combining erlotinib and bevacizumab with TMZ as adjuvant therapy to the Stupp protocol in newly diagnosed patients [114,136]. Similar results were observed in a Phase II study analyzing the efficacy of Erlotinib in combination with sorafenib [113].

Gefitinib is a reversible and specific inhibitor of EGFR tyrosine kinase activity. Combined with RT in newly diagnosed patients, OS is not improved compared to RT alone [124], nor is it improved as adjuvant after RT [137].

Afatinib, an irreversible pan-inhibitor of the ErbB family (including EGFR and EGFRvIII) did not show better results than TMZ in a Phase II study (NCT00727506). Nevertheless, an increase in PFS has been observed in patients with tumors expressing EGFRvIII or with EGFR amplification [125].

Dacomitinib is a pan-HER family inhibitor (EGFR, HER2, and HER4), approved as first-line treatment of EGFR mutant NSCLC. In GBM, dacomitinib was tested as monotherapy in tumors with EGFR amplification or with the presence of the most common EGFR mutation in GBM EGFRvIII, but it provided minimal benefits [126].

ii. Inhibition of HER2

HER2 tends to be activated by forming heterodimers with other members of the family or other receptors, since no activating-ligand is known [138]. HER2 overexpression in breast cancer cells promotes tumor aggressiveness and thus became a therapeutic target combined with a companion test [139]. HER2-targeted antibody trastuzumab in breast cancer is a successful example of a targeted therapy.

Even though HER2 expression is low in GBM cells, multitargeted TKI of HER2, EGFR and VEGFR family are being tested in clinical trials.

Lapatinib and neratinib are two treatments used in HER2-positive breast cancer. In GBM, Lapatinib, a dual EGFR and HER2 kinase inhibitor, did not provide therapeutic gain in patients with recurrent GBMs in a Phase II study [140]. This compound together with TMZ and RT in newly diagnosed patients is in clinical trials (NCT01591577) [141].

3.2.2. Multikinase Inhibitors

Series of multikinase inhibitors have been tested in GBM (Tables 3 and 4). Usually developed initially against one specific target, they proved able to inhibit different RTKs or non-receptor kinases as their ATP/ADP binding pocket revealed similarities. This characteristic may have advantages as simultaneously inhibiting several kinases may limit drug resistance and compensatory pathways [142]. Most of them are able to target EGFR, PDGFR, vascular endothelial growth factor receptors (VEGFR) known targets of GBM or even HER2, a target in breast cancers.

Anlotinib inhibits VEGFR, FGFR, PDGFR and c-kit [143]. Anlotinib is tested in GBM clinical trials as monotherapy or combined with Stupp protocol.

TG02 is an inhibitor of CDKs, JAK2 and FLT3 able to penetrate the blood-brain barrier and is therefore an interesting therapeutic for brain tumors [144]. TG02 is assayed in GBM in combination with TMZ (NCT02942264).

Tesevatinib is an inhibitor of EGFR, HER2, VEGFR and ephrin B4 [145], used in polycystic kidney disease and tested as monotherapy in GBM (NCT02844439).

Vandetanib, an inhibitor of EGFR, VEGFR2 and RET, has shown encouraging preclinical results. A 94% decrease in xenograft tumor size was observed when combined with TMZ and compared to TMZ alone [146]. However, the addition of vandetanib to the Stupp protocol does not prolong the survival of newly diagnosed patients (NCT00441142) [147].
Other multi-kinase inhibitors, such as cabozantinib, TG02, bosutinib are tested in GBM. All clinical trials, ongoing or completed, are listed in Table 3.

Table 3. Clinical studies analyzing multi-kinase inhibitors.

| Molecule            | Date          | Protocol                                                                 | Phase | Patients |
|---------------------|---------------|--------------------------------------------------------------------------|-------|----------|
| Anlotinib           | NCT04157478  | 11/2019–11/2019 Combined with Stupp protocol compared to Stupp protocol alone Not yet recruiting | II    | N        |
|                     | NCT04004975  | 07/2019–07/2019 Monotherapy Results: ongoing studies (recruitment)       | I/II  | R        |
|                     | NCT04119674  | 10/2019–10/2019 Combined with Stupp protocol Results: ongoing studies (recruitment) | I/II  | N        |
| Tesevatinib         | NCT02544439  | 07/2016–02/2020 Monotherapy Unpublished data                              | II    | R        |
| Dacomitinib/Afatinib | NCT01068782  | 02/2010–07/2014 Monotherapy Unpublished data                              | II    | R first or second |
| Cabozantinib        | NCT02942264  | 10/2016–01/2020 Combined with TMZ and compared with TMZW alone Results: ongoing studies (recruitment) | I/II  | R        |
| TG02                | NCT00441142  | 02/2007–03/2019 Combined with TMZ during Stupp protocol compared to Stupp protocol (non-comparative) | I/II  | N        |
|                     | NCT00995007  | 10/2009–03/2016 Combined with carboplatin and then monotherapy compared to carboplatin alone | II    | R        |
|                     | NCT01331291  | 04/2011–07/2016 Monotherapy                                               | II    | R        |

R: recurrent GBM; N: newly diagnosed GBM; PFS: progression-free survival; PFS-6: 6-month survival; OS: overall survival. Results obtained from Clinicaltrials.com (accessed on 1 April 2020) and/or in cited references. Dates correspond to first posted and last update posted.

(i) Inhibition of PDGFR

Similar to EGFR, the PDGF receptor is involved in the activation of the PI3K pathway. It is overexpressed or amplified in 75% of GBMs and thus appears as an interesting therapeutic target [150]. PDGFR inhibition has been largely explored in GBM. However, no specific PDGFR inhibitor exists and inhibitors are multikinase inhibitors (Table 4).

Imatinib was the first inhibitor targeting PDGFRα/β, BCR-Abl, c-kit. Although Imatinib has not shown clinical benefit in combination with hydroxyurea [151], it is currently in clinical trials.

Dasatinib, an inhibitor of PDGFRβ, EPFA2, BCR-Abl, c-kit and SRC, was ineffective in a Phase II study in patients with recurrent GBMs [152].

Tandutinib, an inhibitor of PDGFRβ, FLT3, c-Kit, was tested in a Phase II study with Bevacizumab in patients with recurrent GBMs. The results indicated that this combination does not improve patient survival compared to standard therapy (NCT00667394) [153]. Another Phase II study showed similar results and was stopped [154].
Table 4. Clinical studies analyzing therapies targeting PDGFR, IGFR, FGFR, ALK.

| Target Molecule | Date            | Protocol                                      | Phase | Patients |
|-----------------|-----------------|-----------------------------------------------|-------|----------|
| PDGFR           |                 |                                               |       |          |
| **Imatinib**    |                 |                                               |       |          |
| NCT00290771     | 04/2006–04/2011 | Combined with hydroxyurea                     | II    | R        |
| Results (231 patients): PFS 5.6 weeks; OS 26 weeks [151] |
| NCT00171938     | 09/2005–02/2017 | Monotherapy in case of impossible re-operation | II    | R        |
| Unpublished data |
| NCT00154375     | 09/2005–04/2011 | Combined with hydroxyurea compared with hydroxyurea alone | III    | R        |
| Results (240 patients): PFS 6 weeks vs. 6 weeks (HR = 0.93); OS 21 weeks vs. 19 weeks (HR = 0.92); imatinib + hydroxyurea vs. hydroxyurea alone [155] |
| NCT00010049     | 01/2003–06/2018 | Monotherapy                                   | I/II  | R        |
| Results (34 patients): PFS-6 3% [156] |
| NCT00039364     | 01/2003–07/2012 | Monotherapy                                   | II    | R        |
| Results (51 patients): PFS-6 16% [157] |
| **Dasatinib**   |                 |                                               |       |          |
| NCT00892177     | 05/2009–10/2019 | Combined with bevacizumab and compared with bevacizumab alone | II    | R        |
| Results (121 patients): PFS 3.3 months vs. 3.5 months (p = 0.52; HR = 1.14); OS 7.3 months vs. 7.9 months (p = 0.7; HR = 0.92) bevacizumab + dasatinib vs. bevacizumab + placebo [158] |
| NCT00423735     | 01/2007–04/2017 | Monotherapy                                   | II    | R        |
| Results (77 patients): PFS 1.7 vs. 1.8 months; OS = 6.5 vs. 8.9 months; 200 mg/j vs. 400 mg/j (No statistical data) [152] |
| NCT00948398     | 06/2008–08/2012 | Combined with lomustine                        | I/II  | R        |
| Results (28 patients): PFS 1.35 months; OS 6.4 months [159] |
| NCT00869401     | 03/2009–02/2020 | Combined with RT/TMZ compared to placebo      | I/II  | N        |
| Results (196 patients): OS 15.6 vs. 19.3 months; PFS: 6.2 vs. 7.8 months; dasatinib vs. placebo |
| **Tandutinib**  |                 |                                               |       |          |
| NCT00379080     | 09/2006–04/2017 | Monotherapy                                   | I/II  | R        |
| Results (31 patients): PFS-6 16%; OS 8.8 months [154] |
| NCT00667394     | 04/2008–10/2015 | Combined with bevacizumab                      | II    | R        |
| Results (41 patients): PFS 4.1 months; OS 11 months [153] |
| **Crenolanib** |                 |                                               |       |          |
| NCT02626364     | 11/2015–06/2017 | Monotherapy                                   | II    | R        |
| Results: ongoing studies (recruitment) PDGFRA Gene Amplification |
| **Sunitinib**   |                 |                                               |       |          |
| NCT01100177     | 04/2010–03/2013 | Monotherapy before and during RT              | II    | N unresectable |
| Results:12 patients: PFS 7.7 weeks; OS 12.8 weeks [160] |
| NCT00923117     | 07/2009–09/2015 | Monotherapy with or without bevacizumab       | II    | R        |
| Results (87 patients): PFS-6 0.92 vs. 1.08 months Bevacizumab resistant vs. naive patients |
| NCT00535379     | 09/2007–08/2010 | Monotherapy                                   | II    | R        |
| Results (40 patients): PFS 2.2 months; OS 9.2 months [161] |
| NCT02928575     | 01/2016–10/2016 | Combined with TMZ/RT                           | II    | N        |
| Results: ongoing studies (recruitment unknown) |
| NCT00660608     | 01/2008–11/2012 | Monotherapy                                   | II    | R        |
| Results (16 patients): PFS 1.4 months; OS 12.6 months [162] |
| NCT03025893     | 01/2017–06/2017 | Monotherapy (high dose)                       | II/III| R        |
| Results: ongoing studies (recruitment) |
| NCT00499473     | 07/2007–02/2016 | Monotherapy                                   | II    | R        |
| Results (25 patients): OS 5.7 vs. 12.3 months; Patients non-EIAC (enzyme-inducing anticonvulsants) vs. EIAC |
Table 4. Cont.

| Target | Molecule | Date | Protocol | Phase | Patients |
|--------|----------|------|----------|-------|----------|
| Regorafenib | NCT03970447 | 05/2019–03/2020 | Combined with RT/TMZ | II/III | N/R |
| Results: ongoing studies (recruitment) |
| Regorafenib | NCT04051606 | 08/2019–02/2020 | Monotherapy | II | R |
| Results: ongoing studies (recruitment) |
| Regorafenib | NCT02926222 | 10/2016–09/2018 | Monotherapy | II | R |
| Results: ongoing studies (recruitment) |
| MEDI-575 | NCT01268566 | 12/2010–04/2017 | Monotherapy | II | R |
| Results (56 patients): PFS-6 15.4%; PFS 1.4 months; OS 9.7 months [163] |
| Olaratumab (IMC-3G3) | NCT00895180 | 05/2009–12/2017 | Monotherapy compared to ramucirumab | II | R |
| Results (80 patients): PFS-6 12.5% vs. 7.5%; OS 49.5 vs. 34.3 weeks; ramucirumab vs. olaratumab |
| Ponatinib | NCT02478164 | 06/2015–07/2018 | Monotherapy | II | R Bevacizumab-Refractory |
| Results (15 patients): PFS 28 days; OS 98 days [164] |
| Leflunomide | NCT00003293 | 06/2004–09/2012 | Monotherapy compared to procarbazine | III | R |
| Unpublished data |
| Axl1717 | NCT01721577 | 11/2012–01/2015 | Monotherapy | I/II | R |
| Results (8 patients): PFS 8 weeks; OS 15 weeks [165] |
| FGFR | BGJ398 | NCT01975701 | 11/2013–12/2019 | Monotherapy | II | R |
| Results (26 patients): PFS 1.7 months; OS 6.74 months |
| ALK | Alectinib | NCT03158389 | Molecularly Matched Targeted Therapies (APG101, alectinib, idasanutlin, atezolizumab, vismodegib, temsirolimus, palbociclib) combined with RT [71] | I/II | N without MGMT promoter methylation |
| See Vismodegib |

R: recurrent GBM; N: newly diagnosed GBM; PFS: progression-free survival; PFS-6: 6-month survival; OS: overall sur-vival. In italics, clinical trials listed in other tables (as mentioned). Results obtained from Clinicaltrials.com (accessed on 1 April 2020) and/or in cited references. Dates correspond to first posted and last update posted.

Sunitinib, an inhibitor of PDGFRα/β, c-kit, VEGFR1/2/3, FLT3 and RET, also provided disappointing results. A Phase II study did not show any clinical benefit of sunitinib in patients with recurrent GBMs compared to bevacizumab or conventional chemotherapy [166]. Similar results were observed in newly diagnosed non-operable patients [160].

Regorafenib inhibits a mutant isoform of BRAF (BRAFV600E), KIT, RET, angiopoietin 1 receptor, PDGFRα, VEGFR1/2/3 and FGFR1/2 [167]. In GBM, it is evaluated as monotherapy or together with the Stupp protocol.

Crenolanib, an inhibitor PDGFR and FLT3 is evaluated as monotherapy in recurrent GBM with PDGFRα gene amplification (NCT02626364).

Ponatinib (AP24534), a multi-targeted kinase inhibitor of BCR-Abl, PDGFRα, VEGFR2, FGFR1, and Src [168] but also RET, KIT, and FLT1, is assayed as a monotherapy in recurrent GBM refractory to bevacizumab (NCT02478164).

Leflunomide, an antimetabolite and inhibitor of PDGFR, EGFR and FGFR, is used for the treatment of rheumatoid arthritis. In preclinical trials, the active compound inhibited glioma cell proliferation in vitro and in vivo. Now it is evaluated as monotherapy in GBM (NCT00003293).

Besides these multi-target drugs, specific anti PDGFR antibodies have been designed and tested in GBM. A fully human anti-PDGFR antibody (IMC-3G3) blocks ligand binding and receptor activation and is being tested in different solid tumors [169]. A compara-
tive clinical trial between IMC-3G3 monotherapy and ramucirumab (targeting VEGFR2) monotherapy did not show improved survival (NCT00895180).

Another monoclonal anti-PDGFRα antibody, MEDI-575, was well tolerated but showed limited clinical activity in GBM [163].

(ii) Inhibition of IGFR1 and FGFR

Insulin-like growth factor 1 receptor (IGF1R) activation by its ligand IGF1 promotes GBM cells survival through PI3K/AKT pathway activation. Thus, inhibition of IGF1R may be an interesting strategy to suppress GBM progression [170]. Moreover, IGF1R overexpression in GBM is correlated with a shorter survival and lack of response to TMZ [171]. A phase I/II clinical trial (NCT01721577, Table 4), used AXL1717, an antagonist of IGF1R, as a single agent in the treatment of recurrent malignant astrocytomas. Monotherapy was well tolerated. Further optimizations in dose need to be performed [165].

Mutations of fibroblast growth factor receptor (FGFR) are rare in GBM but signalling through FGFRs impacts GBM progression and patient survival [172]. For example, fusion between FGFR and TACC (transforming acidic coiled-coil containing proteins) enhances tumor-growth and aneuploidy events [173]. FGFR1,2,3 mutations and fusion are targeted by BGJ398 (Table 4) as monotherapy in a phase-II clinical trial in GBM. However, BGJ398 was out licensed and no more studies were performed.

(iii) Inhibition ALK

Anaplastic lymphoma kinase (ALK), a transmembrane receptor tyrosine kinase that belongs to the insulin receptor superfamily, is expressed in about 60% of GBMs and conveys tumorigenic functions. Second-generation ALK inhibitors, such as alecinitib, might be novel therapeutic agents against GBMs, as they induced cell death in various human GBM cell lines with lower concentrations than other ALK inhibitors. The specific anti-tumor mechanism of alecinitib is not yet described [174]. Alecinitib is currently tested in the N2M2 Phase I/IIa clinical trial (NCT 03158389, Table 4) [71].

3.2.3. Inhibition of the PI3K/AKT Pathway

Table 5 describes the clinical trials concerning the inhibition of the PI3K/AKT pathway.

| Target | Molecule | Date | Protocol | Phase | Patients |
|--------|----------|------|----------|-------|----------|
| mTOR   | Temsirolimus | NCT00800917 | 12/2008–01/2010 Combined with bevacizumab | II | R |
|        | Temsirolimus | NCT00016328 | 05/2001–07/2013 Monotherapy | II | R |
|        | Temsirolimus | NCT00329719 | 05/2006–10/2018 Combined with sorafenib ± surgery | I/II | R |
|        | Temsirolimus | NCT01019434 | 11/2009–10/2016 Combined with RT, compared with RT/TMZ | II | N. unmethylated MGMT |
|        | Temsirolimus | NCT00022724 | 01/2003–06/2018 Monotherapy | I/II | R |
|        | Temsirolimus | NCT00112736 | 06/2005–06/2015 Combined with erlotinib | I/II | R |
|        | Temsirolimus | NCT00335764 | 04/2006–07/2018 Sorafenib combined with erlotinib, tipifarnib or temsirolimus | I/II | R |
|        | Temsirolimus | NCT03158389 | 05/2017–02/2020 Molecularly Matched Targeted Therapies (APG101, alecinitib, idasanutlin, atezolizumab, vismodegib, temsirolimus, palbociclib) combined with RT | I/II | N without MGMT methylation |

Table 5. Clinical studies analyzing therapies targeting mTOR, PI3K/mTOR, Akt & protein kinase c.
| Target | Molecule | Date            | Protocol                                      | Phase | Patients |
|--------|----------|-----------------|-----------------------------------------------|-------|----------|
|        |          |                 | Combined with erlotinib                      | II    | R        |
|        | Sirolimus| NCT00672243     | 01/2008–02/2013                               |       |          |
|        |          |                 | Unpublished data                             | II    | R        |
|        | Everolimus| NCT00515086     | 08/2007–09/2011                               |       |          |
|        |          |                 | Combined with AEE788 (inhibitor of the EGFR, HER-2, VEGFR family) | II    | R        |
|        |          |                 | Unpublished data                             |       |          |
|        |          |                 | Combined with sorafenib                      | II    | R        |
|        |          |                 | Results: ongoing studies                      |       |          |
|        |          |                 | Combined with Bevacizumab in adjuvant therapy after RT/TMZ | II    | N        |
|        |          |                 | Results (68 patients): PFS 11.3 months; OS 13.9 months [180] |       |          |
|        |          |                 | Unpublished data                             |       |          |
|        |          |                 | Combined with RT/TMZ, then TMZ/everolimus     | II    | N        |
|        |          |                 | Results (100 patients): PFS-12 6.4 months; OS-12 15.8 months [181] |       |          |
|        |          |                 | Unpublished data                             |       |          |
|        |          |                 | Combined with RT/TMZ                         | I/II  | N        |
|        |          |                 | Results (171 patients): PFS: 8.2 vs. 10.2 months (p = 0.79); OS: 16.5 vs. 21.2 months (p = 0.008); Patients with or without everolimus [182] |       |          |
|        |          |                 | Monotherapy in combination with bevacizumab or RT/TMZ or marizomib, or lomustine |          |          |
|        |          |                 | Results: ongoing studies (recruitment)       | II    | R/N      |
|        | Pictilisib| NCT02430363     | 03/2013–01/2016                               | I/I   | R        |
|        |          |                 | Monotherapy compared with pembrolizumab       |       |          |
|        |          |                 | Unpublished data                             |       |          |
|        | Buparlisib (BKM120) | NCT01349660 | 04/2011–01/2017                               | I/I   | R        |
|        |          | Preliminary data (76 patients): PFS 2.8 vs. 5.3 months; OS 6.5 vs. 10.8 months; buparlisib + bevacizumab vs. bevacizumab alone (No statistical data) |       |          |
|        |          |                 | Combined with bevacizumab                    |       |          |
|        |          |                 | Monotherapy combined or not combined with surgery | II    | R        |
|        |          |                 | Results (65 patients): PFS 1.7 months; OS 9.8 months; Patients not submitted to surgery [165] |       |          |
|        | Sonolisib (PX-866) | NCT01259869 | 04/2015–02/2015                               | II    | R first  |
|        |          | Monotherapy                                             |       |          |
|        |          | Results (17 patients): PFS6 = 17% [183]                 |       |          |
|        | Paxalisib (GDC-0084) | NCT103522298 | 05/2018–03/2020                               | II    | N        |
|        |          | Monotherapy                                             |       |          |
|        |          | Results: ongoing studies (no recruitment)               |       |          |
|        | Bimiralisib (PQR309) | NCT02850744 | 08/2016–10/2018                               | II    | N        |
|        |          | Monotherapy                                             |       |          |
|        | Enzastaurin| NCT00293815 | 02/2006–11/2016                               | III   | R        |
|        |          | Compared with lomustine                                  |       |          |
|        |          | Results (293 patients): PFS 1.51 months vs. 1.64 months (p = 0.08; HR = 1.28); OS 6.60 months vs. 7.13 months (p = 0.25; HR = 1.20) enzastaurin vs. lomustine [184] |       |          |
|        | Akt & protein kinase c | NCT00509821 | 06/2007–04/2016                               | II    | N        |
|        |          | Combined with RT (before, during, after)                |       |          |
|        |          | Results (60 patients): PFS 6.6 months; OS 15.0 months [185] |       |          |
|        |          | Combined with the Stupp protocol                         | II/II | N        |
|        |          | Unpublished Phase II results                             |       |          |
|        |          | Combined with bevacinab                                  | II    | N        |
|        |          | Results (40 patients): PFS 2.0 months; OS = 7.5 months [186] |       |          |
|        |          | Combined with RT/TMZ                                     | II    | N        |
|        |          | Results: ongoing studies (recruitment)                   |       |          |

R: recurrent GBM; N: newly diagnosed GBM; PFS: progression-free survival; PFS-6: 6-month survival; OS: overall sur-vival. In red, not significant comparative tests. In italics, clinical trials listed in other tables (as mentioned). Results obtained from Clinicaltrials.com (accessed on 1 April 2020) and/or in cited references. Dates correspond to first posted and last update posted.
(i) Inhibition of mTOR.

Another target in the PI3K/AKT pathway is mTOR. Several mTOR inhibitors are available and tested in clinical trials.

Among them, temsirolimus, which has recently been shown to target GICs [187], is the subject of many clinical trials. Two Phase II studies did not show clinical benefits when combined with bevacizumab [175] or sorafenib (NCT00800917) [188]. More recently, a Phase II study comparing the combination of temsirolimus with RT in newly diagnosed patients did not show any difference in survival compared to the Stupp protocol (NCT01019434) [178]. It is actually tested in the N\textsuperscript{2}M\textsuperscript{2} (NOA-20) clinical trial (NCT03158389) [71].

Sirolimus (rapamycin) showed promising preclinical results by decreasing 95% tumor mass in vivo [189]. In addition, it also decreased the proliferation of GICs [190] and their differentiation [191]. Despite these results, sirolimus combined with erlotinib is not effective in GBM recurrence (NCT00672243, Table 2) [116].

Similar results were observed with everolimus. A Phase II study showed that the administration of everolimus before the Stupp protocol in newly diagnosed patients does not provide any clinical benefit compared to the standard protocol [181].

ABI-009 is a novel albumin-bound mTOR inhibitor (albumin-bound rapamycin nanoparticles, nab-rapamycin), currently tested as single agent or in combination with standard therapies (NCT03463265) in a Phase II study.

AZD2014, an inhibitor of both mTORC1 and mTORC2, causes radiosensitization of GICs in vitro and in vivo [192]. This compound is currently in a Phase I clinical trial (NCT02619864).

(ii) Inhibition of PI3K

Several PI3K pan-inhibitors have shown promising in vitro and in vivo results, some of which are being tested in clinical trials.

Pictilisib is an isoform inhibitor of PI3K $\alpha/\delta$. Combined with RT and TMZ, it has a pro-apoptotic action, increases autophagy and decreases the migration capacities of GBMs cell lines. In vivo, it increases sensitivity to RT and TMZ [193]. Pictilisib was compared with pembrolizumab in a phase I/II study but data are not published (NCT02430363).

Buparlisib (BKM120) inhibits cell invasive capacities in vitro and reduces tumor invasion in vivo [194,195]. It is currently being tested in two phase I/II and II studies (NCT01349660 NCT01339052). In the Phase II study (NCT01339052), buparlisib achieved significant brain penetration, but had low efficacy in patients with PI3K-activated recurrent GBM, which was explained by incomplete blockade of PI3K pathway in tumor tissue [196].

Sonolisib (PX-866), an isoform inhibitor of PI3K $\alpha, \delta$, and $\gamma$ reduces the invasive and angiogenic capacities of GBM cells in vitro. In vivo, decreased tumor growth and increased survival of xenografted mice [197] were observed. A Phase II study did not show clinical benefit in the case of recurrent GBMs (NCT01259869) [183].

Paxalisib (GDC-0084) is a brain-penetrant small molecule inhibitor of the PI3K/AKT/mTOR pathway. An interim analysis from Kazia Therapeutics reviewed OS of 17.7 months (nine patients) compared to the median OS for patients treated with TMZ (12.7 months). Final data of the phase II trial (NCT03522298) are expected to be presented in the first half of 2021, but FDA has already granted fast track designation to paxalisib.

(iii) Inhibition of AKT

Enzastaurin is an inhibitor of AKT and protein kinase C. This molecule was the first to provide clinical benefit in a subgroup of patients with recurrent GBMs according to their MGMT status [185]. Enzastaurin has been compared to lomustine in a Phase III clinical trial (NCT00295815). Median PFS, 6-month PFS rate and OS did not differ significantly between enzastaurin and lomustine. Enzastaurin was well tolerated, had a better hematologic toxicity profile but did not have superior efficacy compared with lomustine in patients with recurrent GBM [184].

Other AKT inhibitors with promising results are being tested in preclinics or Phase I, such as perifosine [198], nelfinavir [199], MK2206 [200].
3.2.4. Inhibition of RAS/MAPK Pathway

RAS/MAPK pathway is activated by many receptors including tyrosine kinase receptors and involved in cell survival and proliferation. RAS/MAPK has been targeted in GBM (Table 6).

Table 6. Clinical studies analyzing therapies targeting Ras/MAPK/MEK.

| Target | Molecule | Date          | Protocol                                      | Phase | Patients |
|--------|----------|---------------|-----------------------------------------------|-------|----------|
| Ras/MAPK | TLN-4601 | 08/2008–12/2017 | Monotherapy | II    | R        |
|         | NCT00730262 | 08/2008–12/2017 | Results (20 patients): PFS-6 0%; OS 130 days [201] |       |          |
| Sorafenib | NCT00544817 | 10/2007–06/2016 | Combined with the Stupp protocol in adjuvant therapy | II    | N        |
|         | NCT00597493 | 01/2008–03/2013 | Combined with TMZ | II    | R        |
|         | NCT00329719 | 05/2006–11/2016 | Combined with temsirolimus | II    | R        |
|         | NCT00335764 | 04/2006–07/2018 | Combined with erlotinib, tipifarnib or temsirolimus | I/II  | R        |
|         | NCT00445588 | 03/2007–03/2016 | Combined with erlotinib | II    | R        |
|         | NCT00621686 | 02/2008–01/2017 | Combined with bevacizumab | II    | R        |
|         | NCT01434602 | 09/2011–06/2017 | Combined with everolimus | II    | R        |
|         | NCT01817751 | 03/2013–05/2017 | Combined with valproic acid and sildenafil | II    | R        |
|         | NCT02364206 | 02/2015–08/2019 | Combined with the Stupp protocol | II    | N        |
|         | NCT02029573 | 01/2014–08/2017 | Combined with RT/TMZ | II    | /        |
|         | NCT03919071 | 04/2019–03/2020 | Combined with trametinib (MEK inhibitor) post-RT | II    | N        |
|         | NCT04250922 | 01/2020–01/2020 | Combined with RT/TMZ | II    | R        |
| MEK     | NCT03973918 | 06/2019–03/2020 | Combined with encorafenib | II    | R BRAF V600-Mutated HGG |
|         | NCT03919071 | 04/2019–03/2020 | Combined with dabrafenib post-RT | II    | N        |

R: recurrent GBM; N: newly diagnosed GBM; PFS: progression-free survival; PFS-6: 6-month survival; OS: overall sur-vival. In italics, clinical trials listed in other tables (as mentioned). Results obtained from Clinicaltrials.com (accessed on 1 April 2020) and/or in cited references. Dates correspond to first posted and last update posted.

One inhibitor of this pathway, TLN-4601, did not demonstrate therapeutic efficacy in monotherapy in a Phase II study in the event of recurrence [201]. Sorafenib is a Raf-1 and p38 inhibitor, involved in the RAS-MAPK, VEGFR, c-kit and PDGFR pathways [206]. Although sorafenib has been shown to potentiate the pro-apoptotic effect in GBMs cells [207], it does not appear to improve sensitivity to radiotherapy and
chemotherapy in vivo [208]. For clinical trials, the combination of sorafenib and TMZ in recurrent GBMs provides a PFS of 3.2 months and an OS of 7.4 months [209]. Combined with bevacizumab [204], erlotinib [114] and temsirolimus [188], it does not provide clinical benefit. Disappointing results were also observed in newly diagnosed patients treated with sorafenib and combined to the Stupp protocol in adjuvant therapy [202].

Two Ras-MAPK inhibitors are in Phase II clinical trials: LY2228820 and atorvastatin. The latter molecule could potentiate the effects of TMZ in vitro and in vivo [210]. In a Phase II study (NCT02029573) in combination with standard therapy (RT/TMZ) in newly diagnosed GBM patients, preliminary results are encouraging and met criteria for continued accrual [205].

Dabrafenib is a BRAF inhibitor that binds and inhibits the active conformation of the receptor. Dabrafenib is evaluated in combination with the MEK inhibitor trametinib in newly GBM (NCT03919071).

A very recent study includes binimetinib (a MEK inhibitor) with encorafenib (a BRAF inhibitor) in adults with recurrent BRAF V600-Mutated HGG (NCT03973918).

The lipid proliferation switch led to the discovery of a novel anticancer drug target, the tumor repressor protein sphingomyelin synthase 1 (SGMS1). The activation of SGMS1 by 2OHOA, a synthetic hydroxylated fatty acid, modulates the lipid content of cancer cell membranes, regulates the localization of key signalling proteins, including Ras and PKC at the plasma membrane, leading to inactivation of Ras/MAPK, PI3K/Akt and PKC/cyclin/CDK signalling pathways [211]. The clinical trial in Phase I/IIa NCT01792310 demonstrated its safety and efficacy in humans. 2OHOA was designed as orphan drug by the European Medicines Agency (EMA) for the treatment of glioma and is now tested in a Phase IIb study (NCT04250922).

3.3. Targeting the Cell Cycle and Escape to Cell Death

A major reason for the failure of chemotherapy is the resistance of GBM cells to cell death by apoptosis, necrosis or autophagy [212,213].

3.3.1. Therapies Targeting Apoptosis

Apoptosis can be mediated by the extrinsic and the intrinsic pathways. The extrinsic pathway results from the activation of the TNF-R1, FAS and DR4/DR5 death receptors through their respective ligands TNFα, CD95 and TRAIL [214]. The intrinsic pathway is regulated by proteins of the BCL-2 family and of the inhibitor of apoptosis (IAP) family. Pro and anti-apoptotic members of the BCL2 family regulate mitochondria-dependent cell effects. When apoptosis is triggered mitochondria become permeable and release cytochrome C. The two pathways converge on a series of catalytic cascades involving caspases [105]. The tumor suppressor p53 is implicated in several pro-apoptotic pathways and appears mutated in about 30% of GBM. Restoring apoptosis may be obtained by targeting different apoptosis players (Table 7).
Table 7. Clinical studies analyzing therapies targeting apoptosis.

| Target            | Molecule       | Date                  | Protocol                                                                 | Phase | Patients |
|-------------------|----------------|-----------------------|--------------------------------------------------------------------------|-------|----------|
| CD95              | APG101         | Combined with re-irradiation compared to re-irradiation alone       | II R                                       |       |          |
| NCT01071837       | 02/2010–06/2015| Results (91 patients): PFS 2.5 months vs. 4.5 months ($p = 0.0162$; HR = 0.49); OS 11.5 months vs. 11.5 months; reirradiation vs. reirradiation + APG101 [215] |       |          |
| NCT03158389       | 05/2017–02/2020| Molecularly Matched Targeted Therapies (APG101, alectinib, idasanutlin, atezolizumab, vismodegib, temsirolimus, palbociclib) combined with RT [71] | I/II N without MGMT promoter methylation |       |          |
| DRD2/3            | ONC201         | Results: (14 patients): OS 17 weeks; PFS 14 weeks [216]             | II R H3 K27M positive                       |       |          |
| p53               | Gene therapy (SGT-53) | Combined with TMZ Unpublished data | II R                                       |       |          |
| p53-MDM2          | Idasanutlin (RG7388) | Molecularly Matched Targeted Therapies (APG101, alectinib, idasanutlin, atezolizumab, vismodegib, temsirolimus, palbociclib) combined with RT [71] | I/II N without MGMT promoter methylation |       |          |
| Bcl-2             | Gossypol       | Results (56 patients): PFS 1.87 months; OS = 5.9 months             | II R                                       |       |          |
| Farnesyl transferase | Tipifarnib     | Combined with TMZ No published results                              | I/II R                                     |       |          |
|                   | NCT00050986    | 01/2003–08/2012        |                                                                 |       |          |
|                   | NCT00058097    | 04/2003–04/2013        | Results (28 patients): PFS 42 days; OS 234.5 days [217]                 | II N  |          |
|                   | NCT00005859    | 01/2003–06/2018        | Monotherapy                                                               | I/II R |          |
|                   | NCT00335764    | 04/2006–07/2018        | Sorafenib combined with erlotinib. tipifarnib or temsirolimus            | I/II R |          |
|                   | NCT0038493     | 06/2002–10/2018        | Combined with TMZ Unpublished data                                        | II R  |          |

R: recurrent GBM; N: newly diagnosed GBM; PFS: progression-free survival; PFS-6: 6-month survival; OS: overall survival. In red, not significant comparative tests. In green, significant comparative tests. In italics, clinical trials listed in other tables (as mentioned). Results obtained from Clinicaltrials.com (accessed on 1 April 2020) and/or in cited references. Dates correspond to first posted and last update posted.

(i) Activating proteins involved in the extrinsic pathway of apoptosis

The CD95 death receptor is overexpressed in GBMs and mesenchymal GICs. It is also associated with epithelial-mesenchymal transition [219]. APO010 and APG101 are two CD95 agonists. APO010 has significant anti-tumor activity in GICs, increasing their sensitivity to TMZ in vitro. Administered locoregionally, APO010 increases mice survival [220]. A phase II study showed that the combination of the agonist APG101 with re-irradiation in recurrent GBM improves PFS but not OS compared to re-irradiation alone. This therapeutic benefit is more pronounced in mutated IDH tumors [215].

TRAIL/DR5 dependent cell death can be induced by ONC201. ONC201 binds and antagonizes dopamine receptors DRD2 and DRD3 causing p53-independent apoptosis in tumor cells. ONC201 inhibits the phosphorylation of AKT and ERK pathways, leading to the dephosphorylation of transcription factor FOXO3A, and thus transcription of pro-apoptotic death receptor ligand TRAIL. Through a stress response activation ONC201 is involved in EIF2α phosphorylation and increases DR5 expression [221,222] Based on the first results using ONC201 in monotherapy which showed that the treatment was well.
tolerated and that ONC201 may have single agent activity in GBM [223], a phase II clinical trial was started on GBM with H3 K27M mutation (NCT02525692). It showed that ONC201 can be used regardless of age or location [216].

(ii) Activating proteins involved in the intrinsic pathway of apoptosis

The TSPO protein is involved in the permeabilization of the mitochondrial membrane. Its level of expression being correlated with a poor prognosis, it is considered a potential target for apoptosis restoration [224]. Several ligands of TSPO (Translocator protein), derived from pyrazolo[1,5-a]pyrimidine acetamides, are able to specifically reduce the proliferation of GBMs cells [225]. No clinical trials are underway with these new molecules.

(iii) Targeting proteins involved in the regulation of apoptosis

Due to its role in regulating both pathways of apoptosis, targeting the p53 protein has also been suggested to reactivate its pro-apoptotic functions, by gene therapy or by inhibiting its interaction with MDM2 [226,227].

In a recent study, a tumor-targeting p53 nanodelivery system (SGT53) showed sensitization of resistant GBM cells to TMZ in vitro and increase in the survival of xenografted mice [228]. Gene therapy is currently in a Phase II clinical study (NCT02340156).

Inhibition of MDM2-p53 interaction to trigger apoptosis is an approach that showed encouraging preclinical results. Among these, ISA27 inhibits cell growth in vitro and in vivo [229] while nutlin-3a induces apoptosis and senescence of glioma cells [230]. α5β1 integrin-specific inhibition in association with nutlin-3a also triggered a strong apoptosis in glioma cells expressing a functional p53 [231]. Idasanutlin (RG7388) with more potency, selectivity, and better pharmacokinetic profile than other MDM2 inhibitors appears interesting in preclinical assays, is tested in clinical trials for acute myeloid leukemia and recently in the N2M2 (NOA-20) clinical trials in GBM (NCT01358389) [71]. Finally, the AMG-232 inhibitor has shown encouraging results including inhibition of tumor growth in several xenografts (lung, osteosarcoma, etc.) and tumor regression in mouse models [232]. This agent is currently in Phase I clinical trials (NCT03107780, NCT01723020).

Farnesyltransferase inhibitors (FTI) can induce apoptosis, as they revert cells to a state in which cell-substratum attachment is necessary for viability [233]. Inhibition of farnesyltransferase (FT) by tipifarnib blocks the prenylation of the farnesyltransferase tail CAAX motif, thereby preventing Ras binding to the membrane and its activation. Tipifarnib is tested in four clinical studies in monotherapy or combined with RT or TMZ or other targeted therapies (NCT00050986, NCT00058097, NCT00058589 and NCT00335764). Lonafarnib (SCH66336) is a FTI that blocks farnesylation of cell proliferation proteins, such as RhoB, RAS, laminins and CCAX phosphatase [234,235]. It inhibits in vitro [236] and in vivo [237] cell growth in combination with chemo and/or radiotherapy. A phase II was performed in combination with TMZ (NCT00038493).

Simultaneous reactivation of p53 and TSPO proteins appears to be more effective in promoting apoptosis in GBMs cells but also in reducing the risk of resistance [238]. Reactivating these proteins using molecules with irreversible action has been suggested in order to reduce the risk of recurrence [239].

Another potential approach is to target anti-apoptotic proteins from the BCL-2 family. The compound gossypol binds to the common part of proteins Bcl-2, Bcl-XL and Mcl-1 [240]. Its combination with TMZ was shown to inhibit the invasive and proliferative abilities of GBMs cells and angiogenesis in vitro, and to cause apoptosis in vivo [241]. Gossypol was tested as monotherapy in a phase II (NCT00540722).

Finally, a new therapy targeting the Bcl-2 protein consists of the administration of spherical nucleic acid (SNA). SNA-NU-0129, a formulation containing gold nanoparticles and a siRNA targeting BCL2L12, is involved in the inhibition of this protein and in the induction of cellular apoptosis in vitro [242]. A Phase I study is ongoing in recurrent GBMs and gliosarcomas (NCT03020017).
3.3.2. Therapies Targeting Autophagy

Autophagy is a degradation mechanism that can also induce cell death independently of caspases. It is based on the encapsulation of proteins, cytoplasm and organelles in vesicles that will be degraded in lysosomes. The pro- or anti-tumor function of autophagy in the GBM is still uncertain [243]. Molecules inducing autophagy, such as curcubitacin [244], itraconazole [245], rutin [246], givinostat [247] can have different consequences, but none of them are yet tested in Phase I/II or more.

In addition, chloroquine, inhibiting autophagy via lysosomal protease blockade and fusion between lysosomes and autophagosome [248], provoked a decrease in cell proliferation and migration, and an induction of apoptosis in vivo and in vitro [249]. Chloroquine is in Phase I and II clinical trials in combination with TMZ and/or RT (NCT02378532, NCT02432417, NCT00224978 & NCT00486603) (Table 8).

Table 8. Clinical studies analyzing therapies targeting autophagy.

| Target      | Molecule        | Date       | Protocol                        | Phase | Patients |
|-------------|-----------------|------------|---------------------------------|-------|----------|
| Autophagy   | Chloroquine     | NCT02432417| 04/2015–06/2019 Combined with the Stupp protocol | II    | N        |
|             |                 |            | Results: ongoing studies        |       |          |
| Autophagy   | NCT00224978     | 09/2005–11/2009| Monotherapy                      | III   | N        |
|             |                 |            | Results (30 patients): OS 24 vs. 11 months; chloroquine-treated patients vs. controls [250] |       |          |
|             | NCT00486603     | 06/2007–07/2019| Combined with RT/TMZ            | I/II  | N        |
|             |                 |            | Results (76 patients): OS 15.6 months [251] |       |          |

N: newly diagnosed GBM; OS: overall survival. Results obtained from Clinicaltrials.com (accessed on 1 April 2020) and/or in cited references. Dates correspond to first posted and last update posted.

3.3.3. Targeting Multifaceted Pathways and DNA Modifications

Table 9 details all the clinical trials of this section.

Table 9. Clinical studies analyzing therapies targeting the cell cycle (CDK4/6), multifaceted pathways (proteasome, histone deacetylase, TGFβ) and DNA repair (PARP).

| Target      | Molecule          | Date       | Protocol                                                                 | Phase | Patients |
|-------------|-------------------|------------|--------------------------------------------------------------------------|-------|----------|
| CDK4/6      | Palbociclib (PD 0332991) | NCT01227434 | 10/2010–07/2015 Monotherapy combined or not combined to surgery           | II    | R        |
|             |                   |            | Results (22 patients): PFS 5.14 weeks; OS 15.4 weeks [252]               |       | Rb positif |
| CDK4/6      | Abemaciclib       | NCT03158389 | 05/2017–02/2020 Moleularly Matched Targeted Therapies (APG101, alectinib, idasanutlin, atezolizumab, vismodegib, temsirolimus, palbociclib) combined with RT [71] | I/II  | N without MGMT promoter methylation |
| Proteasome  | Bortezomib        | NCT03643549 | 08/2018–02/2020 Combined with TMZ                                     | I/II  | R        |
|             |                   |            | Results: ongoing studies (recruitment)                                  |       | MGMT unmethylated |
|             |                   | NCT00641706 | 03/2008–05/2014 Combined with vorinostat                                  | II    | R        |
|             |                   |            | Results (37 patients): PFS 1.5 mois; OS 3.2 mois [253]                   |       |          |
| Target | Molecule | Date | Protocol | Phase | Patients |
|--------|----------|------|----------|-------|----------|
| NCT00998010 | Combined with TMZ/RT | 10/2009–05/2019 | Unpublished data | II | N |
| NCT00611325 | Combined with bevacizumab | 02/2008–03/2014 | See Bevacizumab | II | R |
| NCT03345095 | Combined with TMZ/RT | 11/2017–06/2019 | Results (749 patients): ongoing studies (recruitment) | III | N |
| NCT03463265 | Monotherapy (ABI-009) or in combination with bevacizumab or RT/TMZ or ABI-009, or lomustine | 08/2018–12/2020 | See ABI-009 | II | R/N |
| NCT02330562 | Combined with bevacizumab | 01/2015–03/2020 | See Bevacizumab | I/II | R |
| NCT00555399 | Combined with isotretinoin and temozolomide | 11/2007–12/2019 | Results: ongoing studies (no recruitment) | I/II | R |
| NCT00731731 | Combined with TMZ/RT | 08/2008–03/2020 | Preliminary results (107 patients): OS-15 months 54.6%; PFS 8.05 months | II | N |
| NCT00238303 | Combined with surgery | 10/2005–05/2014 | Results (68 patients): PFS 1.9 months; OS 5.7 months [254] | II | R |
| NCT01110876 | Combined with erlotinib and TMZ | 04/2010–11/2014 | See Erlotinib | I/II | R |
| NCT00641706 | Combined with bortezomib | 03/2008–05/2014 | See Bortezomib | II | R |
| NCT01266031 | Bevacizumab in monotherapy vs. combined with vorinostat | 12/2010–07/2018 | See Bevacizumab | I/II | R |
| NCT01738646 | Combined with bevacizumab | 11/2012–02/2017 | See Bevacizumab | II | R |
| NCT00939991 | Combined with bevacizumab and TMZ | 07/2009–06/2013 | See Bevacizumab | I/II | R |
| NCT00848523 | Monotherapy | 02/2009–07/2010 | FR901228 | | |
| NCT00855540 | Monotherapy | 06/2004–01/2017 | Results (35 patients): PFS 8 weeks [255] | II | R |
| NCT00431561 | Monotherapy vs. TMZ or PVC (procarbazine/lomustine/vincristine) | 02/2007–12/2013 | Results (145 patients): In GBM patients, response and survival results were comparable among the 3 arms [256] | IIB | R |
| NCT01082269 | Monotherapy or combined with lomustine | 04/2012–12/2019 | Results: ongoing studies (no recruitment) | II | R |
| NCT01220271 | Combined with TMZ/RT vs. TMZ/RT | 10/2010–02/2017 | Results (56 patients): OS 18.2 vs. 17.9 months (HR = 1.2), PFS 7.6 vs. 11.5 months (HR = 1.8), patients treated with galunisertib combined with TMZ/RT vs. TMZ/RT [257] | I/II | N |
| NCT03649464 | Monotherapy | 08/2018–03/2020 | Not yet recruiting | I/II | R |
Table 9. Cont.

| Target | Molecule | Date | Protocol | Phase | Patients |
|--------|----------|------|----------|-------|----------|
| PARP   | Iniparib (BSI-201) | 06/2008–07/2015 | Combined with TMZ | I/II | N |
|        |          |      | Results (81 patients): OS 22 months [258] |       |          |
|        | Veliparib | 06/2014–03/2020 | Combined with TMZ | II/III | N |
|        |          |      | Results: ongoing studies (no recruitment) |       |          |
|        | NCT03581292 | 07/2018–03/2020 | Combined with RT/TMZ | II | N |
|        |          |      | Results: ongoing studies (recruitment) |       |          |
|        | NCT01026493 | 12/2009–07/2017 | Combined with TMZ | I/II | R |
|        |          |      | Results (215 patients): OS 10.3 vs. 10.7 months ($p = 0.95; HR = 0.99$) patients BEV-naïve low vs. high TMZ dose; OS 4.7 vs. 4.7 months ($p = 0.93; HR = 0.93$) patients BEV-failure low vs. high TMZ dose; PFS-6 17 vs. 4.4% patients BEV-naïve vs. BEV-failure [259] |       |          |
|        | NCT02974621 | 11/2016–03/2020 | Cediranib combined with olaparib and compared to bevacizumab | II | R |
|        |          |      | See Cediranib |       |          |
|        | NCT03150862 | 05/2017–11/2019 | Combined with RT/TMZ | I/II | R/N |
|        |          |      | Results: ongoing studies (no recruitment) |       |          |
|        | NCT03914742 | 04/2019–2020 | Combined with TMZ | I/II | R |
|        |          |      | Results: ongoing studies (recruitment) |       |          |

R: recurrent GBM; N: newly diagnosed GBM; PFS: progression-free survival; PFS-6: 6-month survival; OS: overall survival. In red, not significant comparative tests. In italics, clinical trials listed in other tables (as mentioned). Results obtained from Clinicaltrials.com (accessed on 1 April 2020) and/or in cited references. Dates correspond to first posted and last update posted.

(i) CDK4/6 inhibitors

Cyclin-dependent kinases 4 and 6 (CDK4/6) signalling regulates cell cycle, cell differentiation, metabolism and apoptosis. In glioma cells, CDK4 is overexpressed which led to glioma cell proliferation and TMZ resistance [260]. CDK4/6 inhibitors (palbociclib/PD 0332991, abemaciclib) specifically blocked the cell cycle at the G1-to-S transition phase, leading to cell cycle arrest and stopped cell proliferation [261]. These inhibitors are approved in combination with anti-oestrogen therapies for the treatment of hormonal breast cancer, and are being studied in GBM upon surgical resection. Palbociclib is one of the drug tested in the GBM phase I/IIa trial NCT03158389 [71].

(ii) Proteasome inhibitors

The proteasome is a central cellular protein-degradation machinery. It regulates cell homeostasis in normal and cancer cells. Bortezomib, the first-generation proteasome inhibitor, was approved for the treatment of multiple myeloma and mantle cell lymphoma [262]. This therapy is able to increase apoptosis levels in preclinical brain tumor assays. Moreover, clinical trials using proteasome inhibitors in combination strategies are being tested to maximize therapeutic efficacy and limit toxicity [263]. Bortezomib is studied in combination with TMZ and/or radiation, or with an inhibitor of histone deacetylase.

Marizomib, is a second-generation, irreversible proteasome inhibitor with a more lipophilic structure, having the ability to cross the blood-brain barrier [264]. It has been tested in patients with newly diagnosed and recurrent GBM in phase I and phase II studies. In patients with recurrent GBM, marizomib was administered in a Phase I/II study as a single agent or in combination with bevacizumab (NCT02330562) and in a Phase II study as a single agent or in combination with bevacizumab or RT/TMZ or ABI-009, or lomustine (NCT03463265). Based on encouraging observations [265], marizomib combined with RT/TMZ is actually in a Phase III study (NCT0334509).
(iii) Histone deacetylase inhibitors

Epigenetic alterations in histones control chromatin structure and transcriptional activation. Besides their potential role in onset and progression of cancer, they are generally reversible and thus interesting therapeutic targets. Histone acetylation relaxes chromatin and allows access to DNA and transcription activation. On the other hand, histone deacetylases (HDAC) compacts chromatin and represses transcription [266]. HDACs can be essential for cancer cell survival and growth, showing an epigenetic vulnerability of tumor cells. HDAC inhibition can induce tumour cell cycle arrest, apoptosis, reduction of angiogenesis and enhancement of tumor-mediated immunity [266,267]. HDAC inhibitors [268] in GBM tends to re-establish the balance of histone acetylation and sensitizes tumor-mediated immunity. It can also sensitize tumor cells when used in combination, for example, with radiation therapy [267]. Several clinical trials are testing HDAC inhibitors as monotherapy or in combination in GBM. Vorinostat as a monotherapy had modest activity in patients and did not improve PFS or median OS in association with bevacuzimab (NCT01738646) or bortezomib (NCT00085540). Another HDAC inhibitor, FR901228 (Romidepsin), was ineffective for patients with recurrent GBM (NCT00085540).

(iv) TGF-β inhibitors

Transforming growth factor-beta (TGF-β) is a cytokine secreted by immune cells, tumor cells, and stromal cells. TGF-β is overexpressed GBM tissues but inexistet in normal brain. TGF-β signalling regulates GBM proliferation, invasion, angiogenesis, immunosuppression, and GSCs stemness [269]. Targeting TGF-β signaling mechanisms is a promising therapeutic strategy [270]. In GBM clinical trials, TGF-β pathway are targeted by antisens oligonucleotide (trabedersen, NCT004331561) and by small molecules, OKN-007 (NCT03649464) [271], and galunisertib (NCT01582269, NCT01220271). Results are available for galunisertib and trabedersen.

Targeting of TGF-β2 signaling through inhibition of TGF-β mRNA translation by using the antisense oligonucleotides trabedersen, injected in the resection cavity, was tested in GBM in a Phase Ib (NCT00431561) but the first results did not show statistically significant differences among the three arms: trabedersen at doses of 10 or 80 mM or standard chemotherapy (TMZ or procarbazine/lomustine/vincristine) [256].

Galunisertib targets the TGF-β1 receptor and selectively inhibits the serine/threonine activity of the receptor, thereby preventing the phosphorylation of downstream proteins, SMAD2 and SMAD3. It demonstrated antitumor effects in preclinical and radiographic responses [272]. But no differences in efficacy, safety or pharmacokinetic variables were observed in a Phase Ib/IIa clinical trial (NCT01220271) between the two treatment arms (TMZ/RT with and without galunisertib) [257].

(v) PARP inhibitors

Defects in DNA repair pathways are a characteristic feature of cancer cells. They participate in tumour development by promoting genomic instability. For more than 50 years, this characteristic has been exploited as a therapeutic opportunity for the treatment of cancer, with the use of conventional cytotoxic chemotherapies. More recently, the discovery of a synthetic lethality interaction between DNA damage induced by PARP (poly[ADP-ribose] polymerase) inhibitors led to the development of new therapeutic approaches. The PARP proteins use NAD+ as their substrate to modify acceptor proteins with ADP-ribose modifications. Most PARP inhibitors target the NAD+ binding site.

A high expression of PARP-1 mRNA is associated with low survival, particularly in classical GBMs [273]. A few molecules inhibiting PARP-1 are in clinical trials. Among them, iniparib (BSI-201) taken concomitantly with RT and TMZ has shown encouraging results, in human glioma xenografts, resulting in complete tumor regression in 70% of animals [274]. This PARP1 inhibitor plus TMZ was evaluated in a phase I/II in newly-diagnosed GBM (NCT00687765). Other NAD+ mimetics, olaparib (AZD2281), veliparib (ABT-888) and pamiparib (BGB-290) inhibit the catalytic activity of PARP-1 and PARP-2 and are currently being studied in phase I or I/II clinical trials. Only results for veliparib combined with TMZ...
(NCT01026493) are available [259]. The concept of this study was to exploit methylation at positions N3-adenine and N7-guanine, supposedly independent of the MGMT effect and related more to base excision repair with PARP. But the study did not demonstrate any clinical activity.

3.4. Targeting Angiogenesis

Angiogenesis is a complex process regulated by multiple signaling pathways. Due to a high tumor proliferation, access to oxygen and nutrients decreases in some areas of a tumor, leading to hypoxia and necrosis. GBM are highly angiogenic tumors and blocking neo-angiogenesis has represented an interesting therapeutic way for twenty years.

3.4.1. Targeting VEGF/VEGFR Pathway

Clinical trials for VEGF and VEGFR targeting are described in Table 10.

(i) Bevacizumab

VEGF is overexpressed in GBMs and plays a major role in angiogenesis by activating its receptor VEGFR [275]. Since 2009, the food and drug administration (FDA) has approved bevacizumab, an anti-VEGF antibody, as a treatment in recurrent GBMs. Indeed, non placebo-controlled Phase II clinical trials highlighted the bevacizumab anti-tumor activity and this molecule is considered effective alone or in combination with Irinotecan, a topoisomerase I DNA inhibitor [276,277]. Based on encouraging results, few clinical trials were conducted to evaluate the efficacy of bevacizumab in comparative studies. However, results of these trials have been estimated insufficient by EMA to approve bevacizumab use in GBM in Europe. This discrepancy between drug authorities lead to huge off-label use of bevacizumab for GBM, mostly at recurrence, since this antibody is also marketed for the treatment of ovarian, lung, breast and colorectal cancer.

Table 10. Clinical studies analyzing therapies targeting VEGF and VEGFR.

| Target Molecule | Date | Protocol | Phase | Patients |
|----------------|------|----------|-------|----------|
| VEGF | NCT01609790 06/2012–03/2020 | Combined with trebananib | II | R |
| Preliminary results (116 patients): OS 11.5 vs. 7.5 months (p = 0.09; HR = 1.46); PFS 4.8 vs. 4.2% (p = 0.04; HR = 1.51) | |
| NCT00817284 01/2009–11/2011 | Combined with RT/TMZ or RT/irinotecan Unpublished data | II | N |
| NCT01860638 05/2013–04/2018 | Continuous treatment with Stupp, followed with Lomustine in first disease progression (PD1) and with chemotherapy in second progression (PD2) Unpublished data | II | R |
| Results (296 patients): OS 6.4 vs. 5.5 months (HR = 1.04); PFS 2.3 vs. 1.8 months (HR = 0.70) | |
| PD1 lomustine bevacizumab vs. lomustine alone; PFS 2 vs. 2.2 months (HR = 0.70) | |
| PD2 bevacizumab chemotherapy vs. chemotherapy alone. No p values were reported [278] | |
| NCT01115491 05/2010–12/2014 | Combined with TMZ Results (32 patients): PFS 18.29 weeks; OS 31.43 weeks | II | R |
| NCT00590681 01/2008–09/2015 | Combined with TMZ Unpublished data | II | N |
| Results (41 patients): OS 12 months; PFS 8.6 months [279] | |
| NCT00979017 09/2009–03/2014 | Combined with TMZ and irinotecan Unpublished data | II | N unresectable and multifocal |
| Results (41 patients): OS 19.4 months; PFS 11.3 months [279] | |
| NCT01186406 08/2010–02/2019 | Combined with gliadel, TMZ and RT Results (41 patients): OS 19.4 months; PFS 11.3 months | II | N |
| NCT01903330 07/2013–11/2019 | Combined with ERC1671 (vaccine) and granulocyte-macrophage colony-stimulating factor (GM-CSF) compared to combination with placebo Results: ongoing studies (recruitment) | II | R |
| NCT01443676 09/2011–11/2016 | Combined with RT compared to RT alone Results (75 patients): PFS 7.6 vs. 4.8 months (p = 0.003); OS 12.1 vs. 12.2 months (p = 0.77); bevacizumab + RT vs. RT [280] | II | N in elderly |
**Table 10. Cont.**

| Target   | Molecule | Date                  | Protocol                                                                 | Phase | Patients                  |
|----------|----------|-----------------------|--------------------------------------------------------------------------|-------|---------------------------|
| NCT02898012 |          | 09/2016–09/2016       | Combined with TMZ                                                        | II    | N age over 70              |
|          |          |                       | Results (66 patients): OS 23.9 weeks; PFS 15.3 weeks [281]               |       |                           |
| NCT01149850 |          | 06/2010–02/2020       | Combined with TMZ                                                        | II    | N in elderly               |
|          |          |                       | Results: ongoing studies (no recruitment)                               |       |                           |
| NCT01004874 |          | 10/2009–02/2020       | Combined with RT/TMZ followed by combination with TMZ/popotecan         | II    | /                         |
|          |          |                       | Preliminary results (80 patients): OS 17.2 months; PFS 11.1 months       |       |                           |
| NCT00735436 |          | 08/2008–02/2013       | Combined with gliadel and irinotecan                                     | II    | N                         |
|          |          |                       | Results: ongoing studies (18 patients): PFS 8 months; OS 13.5 months     |       |                           |
| NCT02698280 |          | 03/2016–07/2018       | Combined with nimustine                                                  | II    | R                         |
|          |          |                       | Unpublished data                                                         |       |                           |
| NCT01266031 |          | 12/2010–07/2018       | Monotherapy vs. combined with vorinostat                                 | I/II  | R                         |
|          |          |                       | Results (patients): OS 9.24 vs. 7.8 months; bevacizumab vs. bevacizumab + vorinostat |       |                           |
| NCT01013285 |          | 11/2009–01/2016       | Combined with TMZ and RT                                                 | II    | N                         |
|          |          |                       | Results: ongoing studies (recruitment unknown)                          |       |                           |
| NCT01738646 |          | 11/2012–02/2017       | Combined with vorinostat                                                | II    | R                         |
|          |          |                       | Results (38 patients): PFS 3.7 months; OS 10.4 months; PFS-6 30% [282]  |       |                           |
| NCT00939991 |          | 07/2009–06/2013       | Combined with vorinostat and TMZ                                         | I/II  | R                         |
|          |          |                       | Results (39 patients): PFS 6.7 months; OS 12.5 months; PFS-6 53.8%      |       |                           |
| NCT00337207 |          | 06/2006–02/2020       | Monotherapy                                                             | II    | R                         |
|          |          |                       | Results (54 patients): PFS-6 24%                                        |       |                           |
| NCT00268359 |          | 12/2005–07/2014       | Combined with irinotecan                                                 | II    | R                         |
|          |          |                       | Results (32 patients): PFS 23 weeks; PFS-6 38%; OS-6 72% [283]           |       |                           |
| NCT00795665 |          | 11/2008–03/2020       | Combined with carmustine                                                | II    | R                         |
|          |          |                       | Unpublished data                                                         |       |                           |
| NCT02330562 |          | 01/2015–03/2020       | Combined with marizomib                                                 | I/II  | R                         |
|          |          |                       | Results: ongoing studies (no recruitment)                               |       |                           |
| NCT00921167 |          | 06/2009–12/2013       | Combined with irinotecan                                                | II    | R                         |
|          |          |                       | Results: completed, no results posted                                   |       |                           |
| NCT02157103 |          | 06/2014–05/2018       | Subcutaneous monotherapy                                                | II    | R                         |
|          |          |                       | Results (3 patients): 66.7% decrease in radiation-related edema          |       |                           |
| NCT01209442 |          | 09/2010–04/2019       | Combined with hypofractionated RT and TMZ                               | II    | N                         |
|          |          |                       | Results (30 patients): PFS 14.3 months; OS 16.3 months [284]             |       |                           |
| NCT02120287 |          | 04/2014–05/2019       | Combined with radiosurgery                                              | II    | R                         |
|          |          |                       | Results (16 patients): OS 11.73 months                                  |       |                           |
| NCT01102595 |          | 04/2010–08/2015       | Combined with TMZ in neoadjuvant therapy of the Stupp protocol          | II    | N, unresectable            |
|          |          |                       | Results (102 patients): PFS 2.2 vs. 4.8 months (p = 0.10; HR = 0.70); OS 7.7 vs. 10.6 months (p = 0.07; HR = 0.68); TMZ vs. TMZ + bevacizumab [285] |       |                           |
| NCT01022918 |          | 12/2009–09/2012       | Combined with irinotecan in neoadjuvant and adjuvant therapy with TMZ, compared to neoadjuvant TMZ and Stupp | II    | N, unresectable            |
|          |          |                       | Results: (120 patients): PFS = 7.1 vs. 5.2 months (HR = 0.82); OS = 11.1 vs. 11.1 months; bevacizumab/Irinotecan vs. ctrl [286] |       |                           |
| NCT00943826 |          | 07/2009–09/2017       | Combined with TMZ during the Stupp protocol, compared to the Stupp protocol | III   | N                         |
|          |          |                       | Results (921 patients): PFS 10.6 vs. 6.2 months (p < 0.001; HR = 0.64); OS 16.8 vs. 16.7 months (p = 0.1; HR = 0.88); bevacizumab + Stupp vs. Stupp [287] |       |                           |
| Target       | Molecule                          | Date                | Protocol                                                                 | Phase | Patients |
|--------------|-----------------------------------|---------------------|--------------------------------------------------------------------------|-------|----------|
| NCT01067469 | Low dose and combined with lomustine, compared to high dose bevacizumab alone | 02/2010–03/2020     | III R                                                                     |       |          |
| NCT00883298 | Combined with TMZ twice a week     | 04/2009–03/2017     | II R                                                                     |       |          |
| NCT00345163 | Combined with or not combined with irinotecan | 06/2006–05/2017     | II R                                                                     |       |          |
| NCT01474239 | Compared with fotemustine          | 11/2011–03/2016     | II R                                                                     |       |          |
| NCT02761070 | Combined with high-dose TMZ compared to bevacizumab alone | 05/2016–02/2019     | III R                                                                     |       |          |
| NCT02743078 | Combined with Optune®              | 04/2016–11/2019     | II R Beva refractory or resistant to Beva Unpublished data               |       |          |
| NCT01814813 | Combined with vaccination (HSPPC-96) compared to bevacizumab alone | 03/2013–06/2019     | II R                                                                     |       |          |
| NCT01730950 | Combined with re-irradiation, compared to bevacizumab alone | 11/2012–03/2020     | II R                                                                     |       |          |
| NCT00967330 | Combined with RT, then in adjuvant therapy combined with irinotecan compared to the Stupp protocol | 08/2009–11/2015     | II N. MGMT non methylated Results (182 patients): PFS 5.99 vs. 9.7 months (HR = 0.57; p < 0.001); OS 16.6 vs. 17.5 months (HR = 1.02; p = 0.55); TMZ vs. bevacizumab + irinotecan [291] |       |          |
| NCT02343549 | Combined with Optune® and TMZ      | 01/2015–07/2019     | II N                                                                     |       |          |
| NCT01290939 | Combined with lomustine            | 02/2011–02/2018     | III R                                                                     |       |          |
| NCT00611325 | Combined with bortezomib           | 02/2008–03/2014     | II R                                                                     |       |          |
| NCT01269853 | Intracerebral administration       | 01/2011–05/2019     | I/II R                                                                   |       |          |
| NCT01811498 | Intracerebral administration       | 03/2015–03/2019     | I/II N                                                                   |       |          |
| NCT02511405 | Combined with VB-111 (antiangiogenic), compared to bevacizumab alone | 07/2015–10/2018     | III R                                                                     |       |          |
| NCT00612339 | Combined with TMZ                  | 02/2008–05/2013     | II Non resectable                                                       |       |          |
| NCT03149003 | Combined with DSP-7888 (peptide vaccine) compared to bevacizumab alone | 05/2017–01/2020     | II R                                                                     |       |          |
| Target       | Molecule | Date              | Protocol                                                                 | Phase | Patients  |
|--------------|----------|-------------------|--------------------------------------------------------------------------|-------|-----------|
| NCT00501891 |          | 07/2007–05/2013   | Combined with TMZ                                                        | II    | R         |
|              |          |                   | Results (32 patients): PFS 15.8 weeks; OS 37.1 weeks [294]              |       |           |
| NCT00597402 |          | 01/2008–05/2014   | Combined with RT/TMZ, then combined with irinotecan                     | II    | N         |
|              |          |                   | Results (75 patients): PFS 14.2 months; OS 21.2 months [295]            |       |           |
| NCT00433381 |          | 02/2007–09/2018   | Combined with irinotecan or combined with TMZ Unpublished data          | II    | R         |
| NCT00613028 |          | 02/2008–06/2013   | Combined with etoposide or TMZ                                          | II    | R         |
|              |          |                   | Results (22 patients): PFS 4.1 vs. 8.1 weeks; OS 12.6 vs. 19 weeks; PFS-6 0 vs. 7.7%; bevacizumab + TMZ vs. bevacizumab + etoposide |       |           |
| NCT00612430 |          | 02/2008–08/2013   | Combined with etoposide                                                 | II    | R         |
|              |          |                   | Results (27 GBM et 32 grade III glioma patients): PFS6 40.6% & 44.4%; OS 63.1 & 44.4 weeks [296] |       |           |
| NCT00884741 |          | 04/2009–07/2019   | Combined with adjuvant TMZ compared to the Stupp protocol               | III   | N         |
|              |          |                   | Results (621 patients): PFS 10.7 months vs. 7.3 months (HR 0.79; p 0.007); OS 15.7 months vs. 16.1 months (HR 1.13; p 0.21) (bevacizumab + Stupp vs. Stupp + placebo) [297] |       |           |
| NCT00463073 |          | 04/2007–12/2008   | Combined with cetuximab and irinotecan                                  | II    | R         |
|              |          |                   | See Cetuximab                                                           |       |           |
| NCT01884740 |          | 06/2013–01/2017   | Combined with cetuximab and intracranial administration                | I/II  | N         |
|              |          |                   | See Cetuximab                                                           |       | Aged under 22 |
| NCT00525525 |          | 09/2007–05/2014   | Combined with erlotinib, TMZ in adjuvant therapy                        | II    | N         |
|              |          |                   | See Erlotinib                                                            |       |           |
| NCT00720356 |          | 06/2008–10/2018   | Combined with erlotinib, in adjuvant therapy after RT/TMZ               | II    | N         |
|              |          |                   | See Erlotinib                                                            |       |           |
| NCT00671970 |          | 01/2008–03/2013   | Combined with erlotinib                                                 | II    | R         |
|              |          |                   | See Erlotinib                                                            |       |           |
| NCT00892177 |          | 05/2009–10/2019   | Combined with dasatinib and compared with bevacizumab alone             | II    | R         |
|              |          |                   | See Dasatinib                                                            |       |           |
| NCT00667394 |          | 04/2008–10/2015   | Combined with tandutinib                                                | II    | R         |
|              |          |                   | See Tandutinib                                                           |       |           |
| NCT00923117 |          | 07/2009–09/2015   | Sunitinib in monotherapy with or without bevacizumab                    | II    | R         |
|              |          |                   | See Sunitinib                                                            |       |           |
| NCT00800917 |          | 12/2008–01/2010   | Combined with temsirolimus                                              | II    | R         |
|              |          |                   | See Temsirolimus                                                          |       |           |
| NCT00805961 |          | 12/2008–08/2013   | Combined with everolimus in adjuvant therapy after RT/TMZ               | II    | N         |
|              |          |                   | See Everolimus                                                           |       |           |
| NCT03463265 |          | 08/2018–12/2020   | Monotherapy (ABI-009) or in combination with bevacizumab or RT/TMZ or marizomib, or lomustine See ABI-009 | II    | R/N       |
| NCT01349660 |          | 04/2011–01/2017   | Combined with buparlisib                                                | I/II  | R         |
|              |          |                   | See Buparlisib                                                            |       |           |
| NCT00586508 |          | 12/2007–10/2013   | Combined with enzastaurin                                                | II    | N         |
|              |          |                   | See Enzastaurin                                                           |       |           |
| NCT00621686 |          | 02/2008–01/2017   | Combined with sorafenib                                                 | II    | R         |
|              |          |                   | See Sorafenib                                                            |       |           |
| Target | Molecule | Date       | Protocol                                                                 | Phase | Patients       |
|--------|----------|------------|--------------------------------------------------------------------------|-------|----------------|
| NCT01632228 | Onartuzumab combined or not with bevacizumab, compared to bevacizumab alone | 06/2012–02/2018 | II | R |
| NCT01113398 | Rilotumumab combined with bevacizumab | 04/2010–12/2015 | II | R |
| NCT01648348 | TRC105 combined with bevacizumab, compared to bevacizumab alone | 06/2012–05/2018 | II | R |
| NCT01564914 | TRC105 combined with bevacizumab | 03/2012–06/2019 | II | R treated with Bevacizumab |
| NCT01290263 | Trebananib combined or not with bevacizumab | 02/2011–07/2017 | I/II | R |
| NCT02331498 | Combined with the Stupp protocol | 11/2014–07/2019 | I/II | N |
| NCT00459381 | Monotherapy | 04/2007–03/2017 | II | R |
| NCT01931098 | Combined with topotecan | 08/2013–03/2020 | II | R |
| NCT00350727 | Combined with lapatinib | 07/2006–04/2013 | II | R |
| NCT01310855 | Gefitinib, compared to cediranib and placebo | 03/2011–05/2017 | II | R |
| NCT00777153 | Monotherapy or combination with lomustine, compared with lomustine alone | 10/2008–12/2016 | III | R |
| NCT02974621 | Combined with olaparib and compared to bevacizumab | 11/2016–03/2020 | II | R |
| NCT01062425 | Combined with TMZ in the Stupp protocol, compared to the Stupp protocol | 02/2010–03/2020 | II | N |
| NCT00662506 | Combined with TMZ/RT | 04/2008–09/2017 | II | N |
| NCT00305656 | Monotherapy | 03/2006–08/2013 | II | R |
| NCT01251484 | Monotherapy | 12/2010–10/2012 | II | R |
| NCT01666600 | Combined with RT, compared to RT alone | 06/2012–11/2017 | I/II | R |
| NCT01380782 | Monotherapy | 06/2011–08/2014 | II | R whether or not treated with Bevacizumab |

**NCT02331498**

**Results:** ongoing studies (recruitment)

**NCT00459381**

Results (35 patients): PFS 12 weeks; OS 35 weeks; PFS-6 3% [298]

**NCT01931098**

Results (35 patients): OS 42 weeks; PFS 24 weeks; PFS-6 46%; OS-6 77% [277]

**NCT00350727**

Results (31 patients): PFS 117 days; OS 227 days [301]

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**Cediranib**

| Target | Molecule | Date       | Protocol                                                                 | Phase | Patients       |
|--------|----------|------------|--------------------------------------------------------------------------|-------|----------------|
| NCT0305656 | Monotherapy | 03/2006–08/2013 | II | R |

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**Nintedanib**

| Target | Molecule | Date       | Protocol                                                                 | Phase | Patients       |
|--------|----------|------------|--------------------------------------------------------------------------|-------|----------------|
| NCT01251484 | Monotherapy (after treatment with the Stupp protocol or with bevacizumab) | 12/2010–10/2012 | II | R |

Results (25 patients): PFS 1 vs. 1 month; OS 10 vs. 2 months (p < 0.02); previous treatment with Stupp vs. bevacizumab [302]

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**VEGFR**
Table 10. Cont.

| Target Molecule | Date        | Protocol                                               | Phase | Patients |
|-----------------|-------------|--------------------------------------------------------|-------|----------|
| **Dovitinib**   | NCT01753713| 12/2012–12/2017 Monotherapy II                         | II    | R whether or not treated with Bevacizumab |
|                 |             | Results (33 patients): PFS 2 vs. 1.8 months; OS 8 vs. 4.3 months; bevacizumab-naive vs. 1st line with bevacizumab |

**Vandetanib (see Multikinase inhibitors)**

| Target Molecule | Date        | Protocol                                               | Phase | Patients |
|-----------------|-------------|--------------------------------------------------------|-------|----------|
| **Vandetanib**  | NCT00441142| 02/2007–04/2017 Combined with the TMZ of the Stupp protocol I/II | N     | See Multikinase inhibitors |
|                 | NCT00995007| 10/2009–02/2016 Combined with carboplatin and compared to carboplatin alone II | R     | See Multikinase inhibitors |
|                 | NCT00128700| 08/2005–09/2012 Combined with TMZ/RT I/II              | N     | Results (20 patients): PFS 7.2 months; OS 16.2 months [304] |
|                 | NCT01562197| 03/2012–01/2019 Monotherapy or combined with lomustine Unpublished data | II    | R         |
|                 | NCT01508117| 01/2012–09/2017 Combined with RT Results (1 patient): OS 0.2 years | II    | N elderly |
|                 | NCT03660761| 09/2018–04/2019 Combined with TMZ Unpublished data     | II    | R         |
|                 | NCT00562419| 11/2007–10/2010 Combined with irinotecan               | II    | R         |
|                 | NCT00004868| 03/2003–06/2018 Monotherapy Unpublished data           | I/II  | R RT non-responder |
|                 | NCT03856099| 02/2019–03/2020 Monotherapy Results: ongoing studies (recruitment unknown) | II    | R         |
|                 | NCT03033524| 01/2017–01/2017 Monotherapy Results: ongoing studies (recruitment unknown) | II    | R         |

R: recurrent GBM; N: newly diagnosed GBM; PFS: progression-free survival; PFS-6: 6-month survival; OS: overall survival. In red, not significant comparative tests. In green, significant comparative tests. In italics, clinical trials listed in other tables (as mentioned). Results obtained from Clinicaltrials.com (accessed on 1 April 2020) and/or in cited references. Dates correspond to first posted and last update posted.

For other studies presented in Table 10, bevacizumab is usually the reference treatment of the control arm to be compared to combinations of bevacizumab plus other experimental molecules targeting different pathways.

Clinical Trials in Recurrent GBMs

In a Phase II study, the combination of bevacizumab and TMZ did not show a survival benefit compared to bevacizumab alone [294]. Similar results were observed in several other Phase II studies with bevacizumab in combination with temsirolimus [175], Carboplatin and irinotecan [306]. Only the combination of bevacizumab and lomustine appears to provide encouraging results in terms of survival and quality of life in a Phase II study [307,308]. However, these promising results were not demonstrated in a Phase III study, in which the combination therapy resulted in a PFS benefit but no OS improvement (NCT01290939) [292].

The efficacy of bevacizumab was also studied retrospectively in patients exposed to a second irradiation [309]. This study shows that bevacizumab might be a protective
agent against a second irradiation. The improvement in irradiation with an anti-angiogenic agent was explained by the normality of vascularization during VEGFR blockade. Indeed, this “normalization window” allows a temporary increase in tumor oxygenation, which improves the damage induced by irradiation [310].

Clinical Trials in Newly Diagnosed GBMs

No benefit for bevacizumab with or without conventional treatment was obtained in different clinical trials [284,287,297,311,312]. Only one Phase II study, analyzing the combination of RT and bevacizumab followed by an adjuvant therapy combining bevacizumab and irinotecan, showed an improvement in PFS compared to the Stupp protocol in patients with non-methylated MGMT status [291]. A (non-significant) tendency towards an OS gain was also shown when TMZ was combined with bevacizumab in neo-adjuvant Stupp protocol therapy compared to the same protocol without Bevacizumab in non-operable patients [285]. Finally, it was retrospectively shown that proneural GBMs could benefit on the addition of bevacizumab compared to placebo (OS = 17.1 vs. 12.8 months HR = 0.43; \( p = 0.002 \)) [313].

(ii) Molecules targeting VEGFR

Pazopanib, a VEGFR1/2/3, PDGFR-α/β, and c-Kit inhibitor, administered as monotherapy, did not show therapeutic benefit in recurrent GBMs [298].

Cediranib is an oral, highly potent VEGFR inhibitor with similar activity against all three VEGF receptors and c-Kit and partial activity against PDGF receptors [314]. Cediranib, as monotherapy, has provided encouraging results in recurrent GBMs [302]. However, in combination with lomustine, cediranib did not show any therapeutic benefit, due to an increase in EGFR levels. Recently, a survival benefit has been reported with the combination of cediranib and gefitinib in recurrent GBMs [299].

Nintedanib, alone, did not show any survival benefit in recurrent GBMs [302]. Note that nintedanib is an inhibitor of VEGFR1/2/3, FGFR1/2/3 and PDGFRα/β.

Dovitinib, an FGFR, PDGFRβ, VEGFR and c-kit inhibitor, currently in clinical trials, sensitizes GBMs cells to TMZ in vitro [315,316].

Vatalanib is a VEGFR1/2/3, PDGFRβ and c-kit inhibitor. Its tolerance and safety were evaluated in a Phase I/II study (NCT00128700) in newly diagnosed patients [304] and in combination with imatinib and hydroxyurea in patients with glioma [317].

Most of these molecules have multiple targets. A few other molecules for which only a few clinical trials are ongoing and for which few results have been published, are listed in Table 10, such as tivozanib, axitinib, semaxanib, CT-322 (a molecule based on an engineered variant of the tenth type III domain of human fibronectin), and the monoclonal antibody tanibirumab (a specific binder to VEGFR2, thereby preventing the binding of its ligand VEGF).

3.4.2. The secondary Pathways of Angiogenesis

Table 11 shows the clinical trials concerning the secondary pathways of angiogenesis. The failure of anti-VEGF therapies might be explained by compensatory mechanisms, through activation of other factors involved in angiogenesis in response to VEGF inhibition.
### Table 11. Phase I/II clinical studies analyzing therapies targeting c-MET and its ligand HGF, PIGF and Endoglin (CD105).

| Target Molecule | Date          | Protocol                        | Phase | Patients |
|----------------|---------------|---------------------------------|-------|----------|
| **c-MET**      |               |                                 |       |          |
| Onartuzumab    | NCT01632228   | Combined or not with bevacizumab, compared to bevacizumab alone | II    | R        |
| (129 patients): |               |                                 |       |          |
| Results:       |               |                                 |       |          |
| PFS 3.9 months vs. 2.9 months ($p = 0.7444$; HR = 1.06); OS 8.8 months vs. 12.9 months ($p = 0.1389$; HR = 1.45); ornatuzumab + bevacizumab vs. placebo + bevacizumab [318] |       |          |
| Cabozantinib   | NCT00704288   | Monotherapy                     | II    | R        |
| (152 patients): |               |                                 |       |          |
| Results:       |               |                                 |       |          |
| PFS 3.7 vs. 3.7 months; OS 7.7 months vs. 10.4 months; 140 mg/j vs. 100 mg/j (No statistical data) [319] |       |          |
| **HGF**        |               |                                 |       |          |
| Rilotumumab    | NCT01113398   | Combined with bevacizumab       | II    | R        |
| (60 patients): |               |                                 |       |          |
| Results:       |               |                                 |       |          |
| PFS 4 weeks vs. 4.1 weeks (10 mg/kg vs. 20 mg/kg); OS = 3.6 months vs. 3.4 months in patients previously treated with bevacizumab |       |          |
| PFS 4.1 weeks vs. 4.7 weeks; OS 10.9 months vs. 11.4 months in patients previously untreated with bevacizumab [320] |       |          |
| **PIGF**       |               |                                 |       |          |
| Aflibercept    | NCT00369590   | Monotherapy                     | II    | R        |
| (42 patients): |               |                                 |       |          |
| Results:       |               |                                 |       |          |
| PFS 12 weeks; OS 39 weeks [321] |       |          |
| **CD105**      |               |                                 |       |          |
| TRC105         | NCT01648348   | Combined with bevacizumab, compared to bevacizumab alone | II    | R        |
| (101 patients): |               |                                 |       |          |
| Results:       |               |                                 |       |          |
| OS 9.7 vs. 7.4 months (HR = 1.06; $p = 0.82$); PFS-6 25 vs. 30.2% |       |          |
| NCT01564914    | 03/2012–06/2019 | Combined with bevacizumab | II    | R treated with Bevacizumab |
| (22 patients): |               |                                 |       |          |
| Results:       |               |                                 |       |          |
| OS 5.75 months; PFS 1.81 vs. 1.30 patients receiving or not simultaneously bevacizumab |       |          |

R: recurrent GBM; N: newly diagnosed GBM; PFS: progression-free survival; PFS-6: 6-month survival; OS: overall survival. In red, not significant comparative tests. In italics, clinical trials listed in other tables (as mentioned). Results obtained from Clinicaltrials.com (accessed on 1 April 2020) and/or in cited references. Dates correspond to first posted and last update posted.

(i) c-MET pathway

The c-MET pathway is deregulated because of an overexpression of (i) the c-MET receptor via mutation or amplification, or (ii) its HGF ligand [322,323]. Activation of this pathway is particularly important in the transformation of endothelial cells into mesenchymal cells, in the induction of aberrant vascularization and in tumor progression [324]. In addition, its activation is associated with a decrease in VEGFR2 expression, which leads to resistance to anti-VEGF therapies [325,326].

Onartuzumab, a monoclonal antibody targeting c-MET, induced a decrease in the growth of GBMs cells. Combined with bevacizumab in recurrent GBMs, ornatuzumab provides a PFS similar to bevacizumab alone. Nevertheless, this study showed a survival benefit in patients with high HGF expression or non-methylated MGMT status [318].

Other c-MET inhibitors have been developed and are currently being investigated. Among these, crizotinib (a c-MET and ALK inhibitor) causes GBMs cells to become sensitive to TMZ [327]. Crizotinib is currently being tested in combination with TMZ in a Phase I study (NCT02270034). Cabozantinib, a c-MET and VEGFR2 inhibitor, was tested in a Phase I study, combined with TMZ during the Stupp protocol [328] and in two Phase II studies as monotherapy in recurrent GBM (NCT01068782 and NCT00704288).

Targeting the c-MET ligand, HGF, is also being investigated. The anti-HGF antibody, rilotumumubum (AMG 102), did not show therapeutic benefit in monotherapy in a Phase II study in patients with recurrent GBMs [320].

(ii) PIGF pathway

Another factor involved in angiogenesis is PIGF, a member of the VEGF family, binding to VEGFR1 (FLT1) and its neuropilin-1/2 co-receptors (NRP1/2). It is expressed in GBMs and tumor endothelial cells [329]. Aflibercept, also called VEGF-trap, is a recombinant fusion protein mimicking binding domain of VEGFR1 and VEGFR2 and blocking different ligands (VEGF-A, VEGF-B and PIGF). In monotherapy or in combination with bevacizumab in recurrent GBMs, no survival benefit was observed [321,330]. These disappointing
results might be explained by a decrease in PIGF expression during tumor progression, in particular after treatment with TMZ. This new therapeutic option seems more relevant in newly diagnosed patients [331].

(iii) Endoglin

Endoglin (CD105) is strongly expressed in endothelial cells with high proliferation rates [332]. TCR105 is a chimeric antibody targeting endoglin, which enhances the effects of bevacizumab in vivo, tested in two clinical trials (NCT01648348, NCT01564914). The combination of TRC105 and bevacizumab was well tolerated [333], but TRC105 with bevacizumab did not prolong median PFS versus bevacizumab alone in recurrent GBM patients [334].

Endoglin is also studied as a diagnostic marker and to estimate the degree of angiogenesis. The endoglin labelling is more typical of neoplastic endothelial cells and is correlated to Ki67, thus making it specific and sensitive to the evolution of angiogenesis in GBM [335].

3.4.3. Other Pathways of Angiogenesis

Other pathways of angiogenesis are described in Table 12.

| Target | Molecule | Date | Protocol | Phase | Patients |
|--------|----------|------|----------|-------|----------|
| **β-FGF & TN** | | | | | |
| | | | Combined with irinotecan | II | R |
| NCT00412542 | 12/2006–02/2012 | | Thalidomide | | |
| | Results (33 patients): PFS 6.25%; PFS 13 weeks; OS 36 weeks [336] | | | | |
| | | | Combined with irinotecan and RT | II | - |
| NCT0039468 | 06/2002–10/2011 | | | | |
| | Results (26 patients): PFS 619% vs. 40%; recurrent vs. new (No statistical data) [337] | | | | |
| | | | Combined with the Stupp protocol and celecoxib | II | N |
| NCT0047294 | 10/2002–06/2017 | | | | |
| | Results (50 patients): PFS 5.9 months; OS 12.6 months [338] | | | | |
| | | | Combined with TMZ and compared TMZ alone | II | R |
| NCT00521482 | 08/2007–08/2007 | | | | |
| | Results: ongoing studies (recruitment unknown) | | | | |
| | | | Combined with procarbazine | II | R |
| NCT00079092 | 03/2004–04/2017 | | Unpublished data | | |
| | | | Combined with TMZ | II | R |
| NCT00006358 | 05/2004–06/2018 | | | | |
| | Results (44 patients): PFS 15 weeks [339] | | | | |
| | | | combined with celecoxib, etoposide and cyclophosphamide | II | R |
| NCT00047281 | 01/2003–07/2017 | | | | |
| | | | See Celecoxib | | |
| | | | Compared with the Stupp protocol | III | N methylated MGMT status |
| NCT00689221 | 06/2008–11/2014 | | | | |
| | Results (926 patients): PFS 13.5 months vs. 10.7 months; Investigator (p = 0.46; HR = 0.93); PFS 10.6 months vs. 7.9 months (p = 0.41; HR = 0.92); Independent; OS 26.3 months vs. 26.3 months; cilengitide + Stupp vs. Stupp (p = 0.86; HR = 1.02) [340] | | | | |
| | | | Combined with the Stupp protocol | II | N non-methylated MGMT status |
| NCT00813943 | 12/2008–01/2017 | | | | |
| | Results (265 patients): PFS 5.6 vs. 5.9 (HR = 0.822) vs. 4.1 months (HR = 0.794); Independent PFS 6.4 vs. 7.5 (HR = 0.772) vs. 6.0 months (HR = 0.720) Investigator OS 16.3 vs. 14.5 (p = 0.32; HR = 0.686) vs. 13.4 months (p = 0.3771; HR = 0.822); cilengitide 2x/week vs. cilengitide 5x/week vs. Stupp [341] | | | | |
| | | | combined with the Stupp protocol | II | N non-methylated MGMT status |
| NCT01044225 | 01/2010–03/2012 | | | | |
| | | | See Cetuximab | | |
| | | | Combined with the Stupp protocol | II | N non-methylated MGMT status |
| NCT00085254 | 06/2004–02/2016 | | | | |
| | Results (112 patients): OS 19.7 months; OS 17.4 months (cilengitide 500 mg); OS 20.7 months (cilengitide 2000 mg); OS 30 months (methylated MGMT); OS 17.4 months (non-methylated MGMT) [342] | | | | |
Table 12. Cont.

| Target            | Molecule                  | Date              | Protocol                          | Phase | Patients |
|-------------------|---------------------------|-------------------|-----------------------------------|-------|----------|
|                   |                           |                   |                                   |       |          |
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| Target Molecule Date Protocol Phase Patients |
|---------------------------------------------|-------------------------------------------------|
| NCT00112866 10/2004–10/2017 Monotherapy II R | Results (26 patients): PFS-6 12%; PFS 8 weeks |
| NCT01124240 05/2010–07/2011 Combined with TMZ, RT and procarbazine II N | Non Methylated                                      |
| NCT0093964 10/2004–04/2019 Monotherapy II R | Results (81 patients): PFS-6 7.5 vs. 15%; PFS 1.81 vs. 1.91 months; OS 6.54 vs. 9.91 months; Patients receiving 500 mg vs. 2000 mg [343] |
| NCT00006093 01/2003–06/2013 Monotherapy I/II R | Unpublished data |
| NCT00352313 07/2006–05/2012 Combined with carboplatin I/II R | Unpublished data |
| ATN-161 | Trebananib (AMG-386) | NCT01290263 02/2011–07/2017 Combined or not with bevacizumab I/II R | Results (48 patients): OS 285 vs. 341 days; PFS 108 vs. 21 days; AMG-386 + bevacizumab vs. AMG-386 alone |
| PSMA | Prostate Specific Membrane Antigen (PSMA) ADC | NCT01609790 06/2012–03/2020 Combined with bevacizumab II R | See Bevacizumab |
| MMP | Prinomastat | NCT004267978 02/2020–03/2020 Combined with TMZ and irinotecan II R | Results: ongoing studies (recruitment) |

| Target not clearly identified | Recombinant Human Endostatin | NCT04266933 05/2013–04/2019 Monotherapy II R | Results (6 patients): No objective responses noted [344] |
| PSMA | NCT01856933 05/2013–04/2019 Monotherapy II R | Results (6 patients): No objective responses noted [344] |
| MMP | NCT00004200 05/2004–08/2012 Combined with TMZ/RT II N | Unpublished data |

R: recurrent GBM; N: newly diagnosed GBM; PFS: progression-free survival; PFS-6: 6-month survival; OS: overall sur-vival. In red, not significant comparative tests. In italics, clinical trials listed in other tables (as mentioned). Results obtained from Clinicaltrials.com (accessed on 1 April 2020) and/or in cited references. Dates correspond to first posted and last update posted.

Thalidomide is a long-established anti-angiogenic agent that inhibits the angiogenic activity of β-FGF and TNF-α [345]. However, when combined with RT in GBM, no benefit was observed in newly diagnosed GBMs [346]. It has shown limited gastrointestinal toxicity and anti-tumor activity in combination with irinotecan [337], and is currently in clinical trials in combination with the Stupp protocol in newly diagnosed GBMs (NCT00047294).

Integrins αvβ3 and αvβ5 have been proposed as targets of new anti-angiogenic therapies. Promising results have been observed when combining an inhibitor of these integrins, cilengitide, with the Stupp protocol in newly diagnosed patients [342,347]. Nevertheless, in two clinical studies (one phase II and one phase III), this combination did not show survival gains in patients with methylated [340] and non-methylated [341] MGMT status. ATN161 (Ac-PHSCN-NH₂) is a selective antagonist for α5β1 integrin. It is a capped five amino-acid peptide derived from the synergy site of fibronectin, a region which enhances the fibronectin’s RGD-mediated binding to the α5β1 integrin. ATN 161 is antiangiogenic and antimetastatic [348] and was evaluated in a phase I/II trial for recurrent malignant glioma (NCT00352313).

Trebananib (AMG-386) is an angiopoietin neutralizing peptibody comprising a peptide with angiopoietin-binding properties that is fused to the Fc region of an antibody with an antiangiogenic effect in solid tumor. It inhibits the interaction between the ligands angiopoietin-1 and angiopoietin-2 with the Tie-2 receptor [349]. Angiopoietins (Ang1 and Ang2) and their RTK (TIE1 and TIE2) are key mediators of tumor angiogenesis. Angiopoietins are overexpressed in GBM and are involved in GBM tumor growth. Moreover, angiopoietin-2 increased in bevacizumab-treated GBM and thus VEGF and angiopoietin-2 combined therapy may overcome bevacizumab resistance. A phase II study used tre-
bananib as monotherapy on patients with recurrent GBM (NCT01290263). Trebananib was also tested in combination with bevacizumab (NCT01609790). However, combination did not significantly improve outcome over bevacizumab alone. Moreover, angiopoietin recombinant humanized monoclonal antibody, PF-04856884, was enrolled on a phase II as monotherapy in patients with recurrent GBM (NCT01225510). This study, which was withdrawn, was not listed in Tables. Until now no further trials were performed in GBM.

Endostatin is a fragment of type XVIII collagen, and one inhibitor of angiogenesis. Endostatin competitively binds to VEGFR-2 and inhibits MAPK signaling pathway and angiogenesis [350]. Recombinant human endostatin improved chemotherapy efficiency in NSCLC, breast cancer and melanoma [351–353]. Endostatin is actually tested in GBM in a phase II study with TMZ and irinotecan (NCT04267978).

Prostate-specific membrane antigen (PSMA) expression has been demonstrated in the tumor neovasculature of GBM, by immunohistochemical staining [354]. Although its significance has not been fully determined, PSMA may play a functional role in angiogenesis [355]. It is anchored to the cell membrane, which makes it an ideal promising therapeutic target, and can be internalized making it an appropriate candidate for pro-drug activity. Strong reactivity to the antibody component of PSMA antibody-drug conjugate (ADC), BrUOG 263, was observed in the endothelial cells of new tumor blood vessels in GBM. Following binding and internalization of PSMA ADC, the cytotoxic component of PSMA ADC will be released and destroy the neovasculature that supports tumor growth.

Matrix metalloproteinases (MMPs), especially MMP2 & 9, are thought to play a central role in invasion, owing to their ability to degrade the majority of brain ECM components [356]. Prinomastat and COL-3 are two drugs targeting MMPs that may stop the growth of GBM by stopping blood flow to the tumor. They have been tested in two clinical trials. Prinomastat/TMZ compared to TMZ alone did neither improve the one-year survival rate nor PFS (NCT00004200). The clinical trial (NCT00004147) with COL-3 in progressive and recurrent high-grade gliomas did not warrant further studies and did not reach phase II [357].

4. Discussion-Guidance towards Future GBM Targeted Therapies

Out of 257 Phase I/II to III clinical trials on targeted therapies listed in the tables of this manuscript, almost 70% are phase II studies (62 Phase I/II, 177 Phase II, 4 Phase II/III, 14 Phase III). Of the studies for which results are available, only 37 are comparative studies with statistical data. Comparative trials with a significant difference between two treatments are highlighted in color in the tables, in green and red for those showing a significant and non-significant difference between two treatments, respectively. It is clear that the red color dominates over the green one. Only 12 studies showed improvements mainly of PFS. Most of them (11 out of 12) involve therapies targeting VEGF and VEGFR. Although some specific explanations may be proposed for the high degree of these clinical trial failures (see below), improved clinical trial design is also needed. For example, Phase II trials may contain a control arm to assess the efficacy of new therapies and to reduce false positive results which remains difficult to establish in the case of recurrent disease in absence of standard treatment; historical control data became obsolete due to the improvement of patient standard of care in the clinic [358,359]. GBM is a rare disease and enrollment of patients in trials remains too low, promotion of participation must be planned to increase the number of high-quality trials [360]. In addition, the need for stratification of patients at least based on prognostic and predictive biomarkers such as the level of the predictive target is critical. Biomarkers might also help to reduce the development costs through better patient selection. A recent study on the impact of biomarker use in clinical trials shows an overall 5-fold benefit over non-biomarker use by analyzing a collection of 10,000 clinical trials for 745 drugs in four major cancer types (colorectal, lung, melanoma and breast cancer) [361]. The neuro-oncology community must work together to be able to change favorably the guidelines on the treatment of GBM [362].
Many different targeted therapeutic options are investigated. For more recent trials, we identified two main tendencies. First, is underway a clear upward trend towards approaches with multi-kinase inhibitors (i.e., when a kinase inhibitor interacts with multiple members of the protein kinase family). The second trend is towards a multi-targeted therapeutic approach. Drugs able to target multiple critical nodes for GBM development and progression might help to counteract the lack of efficiency and the rapid acquisition of resistance observed with monotherapies [363].

Several factors can explain the therapeutic failure of GBM targeted treatments:

(i) Performing a full surgical resection is impossible. Eliminating tumor cells that have migrated into the healthy parenchyma without causing neurological or cognitive disorders is not feasible. 35% of newly diagnosed patients are estimated to be non-operable due to the location or size of the tumor. In these cases, a biopsy is recommended in order to establish a diagnosis [364]. When surgery is possible, macroscopic resection is described as a good prognostic factor [365]. A recent meta-analysis showed that out of 27,865 patients diagnosed with GBM between 2004 and 2013, a biopsy (non-operable case), partial resection and massive resection accounted for 28.5%, 34.8% and 36.8% of cases [366].

(ii) Crossing the BBB is not a turnkey operation, despite its potential destruction by tumor invasion or RT. New approaches proposed, such as nanoparticles or convection-enhanced delivery (CED), [367,368], show encouraging pre-clinical and clinical results.

(iii) New molecular and genomic data has highlighted the inter- but also intra-tumoral heterogeneity of GBM, with tumors and tumor areas differing in target expression. Intratumoral heterogeneity is described as the root cause of therapy resistance and might explain the failure of targeted therapies specifically targeting tumor biomarkers, including anti-EGFR (cetuximab, gefitinib, erlotinib . . . ), anti-VEGF (bevacizumab) and anti-integrin (cilengitide) therapies. Below, we tried to explain the failure of the therapies targeting these three proteins. These data highlight the need to combine different targeted therapies.

4.1. The Failure of Anti-EGFR Therapies

Besides favourable pre-clinical studies, anti-EGFR therapies barely present any clinical benefit for patients with GBM. Several clinical studies are being carried out in newly diagnosed GBM and recurrent GBM with anti-EGFR therapies as monotherapy or in combination with radiochemotherapy or other targeted agents (Table 2).

Besides the tissue differences between colorectal, head and neck, lung cancers and GBM, EGFR is also molecularly heterogeneous among these cancers. First, EGFR mutations in GBMs (as EGFRvIII) occur within receptor extracellular domain while in lung cancers (as L858R) occur in the kinase domain. Interestingly, EGFRvIII mutation seems to appear at later stages of tumor development. This subclonal EGFR mutation is lost in certain recurrent tumors [369]. However, mutational switch can happen where the initial EGFR mutation is replaced by another in recurrent tumor [370]. EGFRvIII heterogeneity adds another layer of complexity by its location in extrachromosomal double minute structures. Extrachromosomal EGFRvIII loss upon treatment promotes therapy resistance. However, the mutant tends to reappear after TKI withdrawal and resensitizes the tumor [371]. The secondary mutation (T790M) upon TKI treatment provides tumor resistance to therapy, in lung cancer [372]. While, in GBM no EGFR secondary mutation is described as cause of therapy resistance [373].

Tumor heterogeneity can be a reasonable case for GBM resistance to EGFR-targeted therapies. Upregulation of redundant receptor tyrosine kinases and deregulation of EGFR downstream molecules can trigger EGFR therapy resistance.

In GBM, PDGFR and c-MET are also upregulated and contribute to tumor progression. In the same or in other subclones than EGFR, these receptors can mediate an EGFR-inhibition bypass. In vivo, inhibition of EGFR (erlotinib) and c-MET (crizotinib) resulted in decreased tumor growth [374]. Also, in a subcutaneous GBM xenografts, combined
inhibition of EGFR and PDGFRβ signaling suppresses tumor growth [375]. Further clinical multi-targeting is needed to test this hypothesis and try to overcome EGFR-therapy resistance in GBM.

In GBM, an EGFR downstream molecule, PTEN, is often loss. PTEN is a suppressor of PI3K/AKT pathway. Simultaneous expression of EGFRvIII and PTEN was associated with patient response to TKI [376]. However, another study showed that even though PTEN is frequently deleted in GBM, it cannot predict therapeutic efficiency of TKI [140].

Moreover, EGFR therapeutic targeting promotes a switch to an angiogenic and mesenchymal tumor phenotype. Mesenchymal switch is associated with GBM therapy resistance [377,378]. GBM resistance to EGFR therapy is still unclear and further studies are needed to improve EGFR-targeting in clinical trials. Although multi-targeted RTK and combinatorial therapies have been newly proposed (Tables 2–4) [379], there is an urgent need to develop genetic and cellular representative GBM models [380].

4.2. The Failure of Bevacizumab

The lack of efficacy of bevacizumab, a large-size molecule, can be explained by its intravenous route of administration and poor intracerebral bioavailability. Intra-arterial brain administration, after temporary destruction of the BBB by mannitol and followed by intravenous administration, has shown encouraging results in terms of PFS in patients with recurrent GBMs (PFS = 10 months) [381]. Indeed, this route of administration has the advantage of potentiating the cerebral delivery of chemotherapy (local concentration of more than 48.9-fold compared to intravenous administration) [382]. Recent results have confirmed the benefit of this delivery method and are being studied [383,384].

The standard dose of bevacizumab is 10 mg/kg IV, injected every two weeks. Although this dose is clinically well tolerated, it can have adverse biological effects, particularly via the formation of hypoxic areas [321]. The study by Heiland et al., 2016 [385] suggested that a low dose of bevacizumab may decrease the size of cerebral edema and may result in better vascular permeability. This study showed an improvement in PFS when bevacizumab is injected at 5 mg/kg every two weeks and is combined with lomustine, compared to bevacizumab alone at 10 mg/kg every two weeks (PFS = 5 months vs. 3.2 months). This therapeutic benefit was not observed in first-time recurrent patients. Finally, at a dose of 5 mg/kg/week, no gain in PFS or survival was observed [288].

4.3. The Failure of Cilengitide

Although preclinical studies nicely demonstrated that cilengitide may affect both tumoral cells and endothelial cells, failure to improve GBM patient survival of the first antagonist of integrins reaching the clinic was really disappointing. The reasons of this failure can only be guessed, but different factors may be included [386–388].

First, the short half-life (a few hours) and pharmacokinetics of cilengitide restricts its properties in patients. Second, the use of cilengitide at low dose has been shown to stimulate angiogenesis in preclinical models [389]. This point has been addressed in patients [390] where no cilengitide-specific pattern of progression has been detected. Third, no reliable biomarker of cilengitide activity has been identified for stratification of patients. For the CENTRIC assay (the phase III clinical trial), patients were stratified according to the MGMT promoter methylation status, i.e., inclusion concerned only patients with a methylated promoter [340]. A phase II clinical trial (CORE) was conducted concomitantly with patients exhibiting a non-methylated MGMT promoter. Interestingly, a retrospective analysis of both cohorts regarding the expression of the cilengitide targets (αvβ3/β5 integrins) expression, concluded that cilengitide was the most effective in the CORE patients with high level of αvβ3 expression in the tumoral cells and not in the endothelial cells [391]. These results highlight the need for stratification of patients at least based on the level of the predictive target. In line with this, it was recently shown in an elegant work from the Cheresh group, that GBM sensitivity to αvβ3 integrin blockade is not simply related to the overexpression of the integrin but rather to an addiction to glucose uptake by the glucose transporteur
Glut3 [392,393]. A fourth point could be added concerning the redundancy of integrin targets; in fact, other integrins (such as α5β1 integrin) may remain active after cilengitide relaying pro-tumoral effects. The story of cilengitide highlights some pitfalls in the transfer of preclinical results towards the clinic but also the need to stratify patients according to pertinent biomarkers.

(iv) The plasticity of GBM cells complicates heterogeneity. It has been shown a bidirectional plasticity between glioma stem cell and their more differentiated counterparts either to form the tumor mass or in answer to therapies. These two types of cells will have different sensitivity to radio/chemotherapies but also to targeted therapies. Recent data emphasized that differentiated tumoral cells may contribute to GIC-dependent tumor progression [394,395]. These results indicate that targeting both cell populations will be needed to eradicate GBM. In a given tumor, glioma stem cells may vary from a proneuronal to a mesenchymal phenotype with intermediary states and thus acquiring new targets. Plasticity occurs also at the metabolic level when GBM cells adapt to the microenvironment to survive (for example from hypoxic to normoxic area) leading to new resistances. Treatments by themselves induce phenotypic and genomic modifications of tumor areas provoking secondary resistance. For example, bevacizumab has been shown to become ineffective due to the activation of secondary pathways involved in angiogenesis (c-MET, PIGF . . . ).

(v) It is increasingly recognized that preclinical models have to be improved to reflect the clinical reality. In vitro, from 2D long term established cell lines grown on flat surface, 3D spheroids or cells embedded in several matrices, we now go through investigations on patient-derived primary cell lines either as glioma stem cell culture or as organoids. This last model certainly will recapitulate at best the tumoral and environmental heterogeneity of GBM. The deal for the following years will be to test therapies on such personalized models in a time framework which will allow to return towards the patient as rapidly as possible. Majority of in vivo models still are based on nude mice where immunological networks are absent. Even if syngeneic mice models of glioma can be useful, they lack the human specificities and complexities. Success of targeted therapies may be in part dependent on the development of reliable modeling of GBM.

Although targeting the immune system is not the subject of this review, this strategy is also part of many ongoing clinical investigations. Moreover, targeted therapy also mediates immunostimulatory and immunosuppressive effects [396]. While early results of checkpoint inhibitors or others immune-targeting drugs have been disappointing when used as monotherapy, likely because of the overwhelming immunosuppressive contribution of the immune tumor microenvironment (iTME), new combinatorial approach might overcome this issue. Interestingly, targeting microglia which is believed to be a major regulator of this iTME, has been suggested in combination with targeted or antiangiogenic therapies responsible of iTME modulation [397]. Indeed, VEGF and TGF-β signaling and abnormal vasculature, all belonging to the selected targets presented in this review has been implicated in fostering immunosuppression [398]. Their inhibition have been already shown to improved immunotherapies clinical outcomes in various cancer [399]. Although the impact of targeted therapies on iTME is still unclear, ongoing clinical trials combining bevacizumab or others targeted therapies to check-point inhibitors (for instance: NCT03743662, NCT03661723, NCT04704154) open new perspectives for GBM treatment.

5. Conclusions

Within molecular targeted therapies, the most frequently reported are those targeting (i) EGFR, which gene is amplified or over-expressed in more than 50% of GBMs (40 clinical trials), and more generally tyrosine kinase receptors (85 clinical trials) and (ii) VEGF/VEGFR (75 clinical trials of which 53 involving bevacizumab). Besides diagnostic and prognostic relevance, some markers can be of predictive interest (therapeutic decision making) or even constitute a molecular target that can be activated by a specific
therapy (theranostic marker). It seems that new approaches aim to counter heterogeneity by targeting, not specifically certain tumor markers expressed irregularly, but the potential cause of the heterogeneity. New and combined approaches (targeted-, chemo-, immuno-, radiotherapies) may result in reduced secondary resistance because they target the whole tumor. Indeed, the discovery of GBM stem cells gave new hope for the treatment of GBM. Their likely significance in tumor initiation, and therefore in the heterogeneity of the GBM, makes them relevant targets but their differentiated counterparts need to be considered as well as their crosstalk only begin to be understood.

The 257 clinical trials described in tables of this manuscript reveal that many different options are explored and raised questions still unanswered about targeted therapies. However, they led to the accumulation of new fundamental knowledge, which will definitely help to understand the mechanisms of resistance and advance research. The results obtained in recent years highlight the need to better stratify patients, by providing more personalized treatment corresponding to the genetic composition and evolution of GBMs. In that way, initiatives like the N²M² (NOA-20) phase I/II trial (NCT03158389) of molecularly matched targeted therapies plus radiotherapy in GBM patients, with an unmethylated MGMT promoter, appears of great interest [71]. In this trial, molecular profile characterization of tumors allows allocation of patients to first line targeted therapies according to their mode of action. Indeed, complex molecular diagnostics will translate in clinical decision and may be the future for GBM treatment.

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Abbreviations

CNS central nervous system  
GBM glioblastoma  
HR hazard ratio  
OS overall survival  
PFS progression-free survival

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