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Original article

# Potential roads for reaching the summit: an overview on target therapies for high-grade gliomas

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**Abstract.** *Background:* The tailored targeting of specific oncogenes represents a new frontier in the treatment of high-grade glioma in the pursuit of innovative and personalized approaches. The present study consists in a wide-ranging overview of the target therapies and related translational challenges in neuro-oncology. *Methods:* A review of the literature on PubMed/MEDLINE on recent advances concerning the target therapies for treatment of central nervous system malignancies was carried out. In the Medical Subject Headings, the terms "Target Therapy", "Target drug" and "Tailored Therapy" were combined with the terms "High-grade gliomas", "Malignant brain tumor" and "Glioblastoma". Articles published in the last five years were further sorted, based on the best match and relevance. The ClinicalTrials.gov website was used as a source of the main trials, where the search terms were "Central Nervous System Tumor", "Malignant Brain Tumor", "Brain Cancer", "Brain Neoplasms" and "High-grade gliomas". *Results:* A total of 137 relevant articles and 79 trials were selected. Target therapies entailed inhibitors of tyrosine kinases, PI3K/AKT/mTOR pathway, farnesyl transferase enzymes, p53 and pRB proteins, isocitrate dehydrogenases, histone deacetylases, integrins and proteasome complexes. The clinical trials mostly involved combined approaches. They were phase I, II, I/II and III in 33%, 42%, 16%, and 9% of the cases, respectively. *Conclusion:* Tyrosine kinase and angiogenesis inhibitors, in combination with standard of care, have shown most evidence of the effectiveness in glioblastoma. Resistance remains an issue. A deeper understanding of the molecular pathways involved in gliomagenesis is the key aspect on which the translational research is focusing, in order to optimize the target therapies of newly diagnosed and recurrent brain gliomas. (www.actabiomedica.it)

**Key words:** Glioblastoma; Malignant Brain Tumors; Neuro-Oncology; Target Therapy; Tyrosine Kinase Inhibitors.

## Background

High-grade gliomas, with glioblastoma (GBM) being the progenitor, are the most lethal primary brain tumors of all because of the certainty of recurrence and mortality.[1-4] As a matter of fact, the median overall survival is no longer than 15 months, despite current multimodality treatment including surgery, radiotherapy and chemotherapy.[5,6]

The significant resistance of GBM to therapy is related to the heterogeneous genetic landscape of the tumor. High-grade gliomas harbor recurrent molecular abnormalities which are involved in the maintenance of the cell's cycle and growth, the tumor

microenvironment, pathological angiogenesis, DNA repair and apoptosis.[7-10]

Advances in genetics and the studies of epigenetics in many pathologies affecting the central nervous system (CNS) have allowed the molecular characterization, as well as the identification of the anomalies in the cellular signaling pathways[11-14]. The same insights have been of utmost importance also in neuro-oncological field, GBM first, where they led to a better understanding of tumor progression and cancer drug escape.[15-20] A deeper understanding of the malignant GBM phenotype has recently improved the knowledge about the biology of cancer, which is the starting point for identifying specific biomarkers and for developing new agents for targeting specific steps in the transduction pathways of glioma cells.[21] Novel tailored therapies include drugs aimed at counteracting the effects of the neoplastic genetic deregulation, pathological angiogenesis and growth factor receptors; the latter with their downstream signaling pathways.

An overview of the target therapeutic strategies and challenges in developing effective agents is reported as follows.

## Methods

The search of the literature was performed on the PubMed/MEDLINE (https://pubmed.ncbi.nlm.nih.gov) search engine, with combinations of Medical Subject Headings (MeSH) terms and text words, and on the ClinicalTrials.gov website (https://clinicaltrials.gov). The MeSH terms "Target Therapy", "Target drug" and "Tailored Therapy" were combined with the MeSH terms "High-grade gliomas", "Malignant brain tumor" and "Glioblastoma". In addition to original articles, our research involved reviews and editorials. The sorting of articles was carried out focusing on the most relevant studies chosen according to titles and abstracts.

On the ClinicalTrials.gov database the texts words "Central Nervous System Tumor", "Malignant Brain Tumor", "Brain Cancer", "High-grade gliomas" and "Brain Tumor" were used for the field "condition/disease". Only trials regarding target therapies, without restrictions for localization, study phase and recruitment status were selected. Filtering included articles published in the last five years, in English or translated into English. A descriptive analysis was provided.

## Results

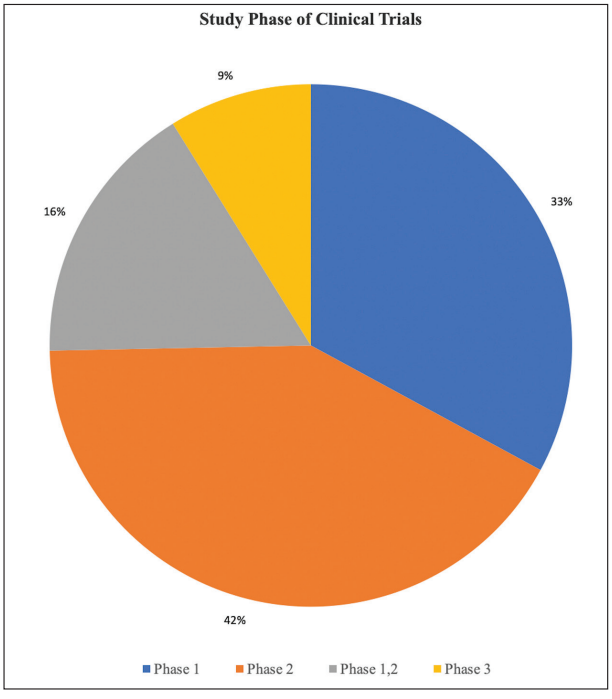
### 1. *Volume of the Literature*

The search retrieved a total of 178 articles and 148 clinical trials. After the implementation of the exclusion criteria and removal of duplicates, 137 articles and 79 randomized and non-randomized clinical trials were collected.

About the clinical trials, 33% were phase I, 42% phase II, 16% phase I/II and 9% phase III (Graph 1). Table 1 summarizes the most relevant clinical trials on target therapies for high-grade gliomas (Table 1).

### 2. *Classification of The Target Therapies*

The target therapies are mostly categorized according to the targets, which, in their turn, include molecular alterations and oncogenic signaling. The




**Graph 1.** Pie graph showing the distribution of the selected clinical trials according to the study phase.

**Table 1.** Clinical Trials on Target Therapies for High-Grade Gliomas.

| # | ClinicalTrials.gov Identifier | Conditions | # of Patients Enrollment | Interventions | Study Phase | Status | Locations |
|---|---|---|---|---|---|---|---|
| 1 | NCT00025675 | Brain and Central Nervous System Tumors | 105 | Gefitinib | 2 | Completed | USA |
| 2 | NCT00016991 | Brain and Central Nervous System Tumors | 53 | Gefitinib | 2 | Completed | USA |
| 3 | NCT00238797 | Glioblastoma Multiforme | 36 | Gefitinib | 2 | Completed | SW |
| 4 | NCT00027625 | Brain and Central Nervous System Tumors | n/a | Gefitinib, Temozolomide | 1 | Completed | USA |
| 5 | NCT00418327 | Malignant Brain Tumor | 48 | Erlotinib | 1 | Completed | FR |
| 6 | NCT00301418 | Glioblastoma Multiforme<br>Anaplastic Astrocytoma | 11 | Erlotinib | 1, 2 | Completed | USA |
| 7 | NCT00086879 | Brain and Central Nervous System Tumors | 110 | Carmustine, Erlotinib, Temozolomide | 2 | Completed | BE, FR, IT, NL, UK |
| 8 | NCT01591577 | Newly Diagnosed Glioblastoma Multiforme | 50 | Lapatinib, Temozolomide, Radiotherapy | 2 | Completed | USA |
| 9 | NCT00099060 | Brain and Central Nervous System Tumors | 24 | Lapatinib | 1, 2 | Completed | CN |
| 10 | NCT02423525 | Brain Cancer | 24 | Afatinib | 1 | Completed | USA |
| 11 | NCT00977431 | Glioblastoma Multiforme | 36 | Afatinib, Temozolomide, Radiotherapy | 1 | Completed | UK |
| 12 | NCT01520870 | Glioblastoma Multiforme<br>Brain Tumor, Recurrent | 49 | Dacomitinib | 2 | Completed | ES |
| 13 | NCT01112527 | Glioblastoma Multiforme | 58 | Dacomitinib | 2 | Completed | USA |
| 14 | NCT00463073 | Malignant Gliomas | 32 | Cetuximab, Bevacizumab, Irinotecan | 2 | Completed | DK |
| 15 | NCT01800695 | Glioblastoma Multiforme | 202 | Depatuxizumab mafodotin (ABT-414) , Temozolomide, Whole Brain Radiation | 1 | Completed | AU |
| 16 | NCT02573324 | Glioblastoma Multiforme | 691 | Depatuxizumab mafodotin (ABT-414) , Temozolomide | 3 | Active, not recruiting | USA |
| 17 | NCT04083976 | Advanced Solid Tumor | 280 | Erdafitinib | 2 | Recruiting | USA |
| 18 | NCT00049127 | Recurrent Adult Brain Neoplasm | 64 | Imatinib | 1, 2 | Completed | USA |
| 19 | NCT00613054 | Glioblastoma Multiforme | 27 | Imatinib, Hydroxyurea | 1 | Completed | USA |
| 20 | NCT01331291 | Glioblastoma Multiforme | 36 | Bosutinib | 2 | Completed | USA |
| 21 | NCT00601614 | Glioblastoma Multiforme<br>Gliosarcoma | 119 | Temozolomide, Vandetanib | 1.2 | Completed | USA |

| # | ClinicalTrials.gov Identifier | Conditions | # of Patients Enrollment | Interventions | Study Phase | Status | Locations |
|---|---|---|---|---|---|---|---|
| 22 | NCT00427440 | Advanced Malignant Glioma | 61 | AMG 102 | 2 | Completed | USA |
| 23 | NCT01632228 | Glioblastoma Multiforme | 135 | Onartuzumab, Bevacizumab | 2 | Completed | CN, FR, DE, IT, ES, SW, UK , USA |
| 24 | NCT01113398 | Glioblastoma Multiforme<br>Gliosarcoma | 36 | AMG 102, Bevacizumab | 2 | Completed | USA |
| 25 | NCT01632228 | Glioblastoma Multiforme | 135 | Bevacizumab, Onartuzumab | 2 | Completed | USA |
| 26 | NCT00606879 | Advanced Cancer | 46 | SGX523 | 1 | Terminated | USA |
| 27 | NCT00607399 | Advanced Cancer | 46 | SGX523 | 1 | Terminated | USA |
| 28 | NCT00784914 | Brain and Central Nervous System Tumors | 12 | Temsirolimus | 1 | Completed | USA |
| 29 | NCT00016328 | Adult Glioblastoma Multiforme<br>Adult Gliosarcoma<br>Recurrent Adult Brain Tumor | 33 | Temsirolimus | 2 | Completed | USA |
| 30 | NCT00047073 | Brain and Central Nervous System Tumors | 13 | Sirolimus, Surgery | 1, 2 | Completed | USA |
| 31 | NCT00672243 | Glioblastoma Multiforme<br>Gliosarcoma | 32 | Erlotinib, Sirolimus | 2 | Completed | USA |
| 32 | NCT00553150 | Brain and Central Nervous System Tumors | 122 | Everolimus, Temozolomide, Radiotherapy | 1.2 | Completed | USA |
| 33 | NCT00085566 | Brain and Central Nervous System Tumors<br>Prostate Cancer | 61 | Everolimus, Gefitinib | 1.2 | Completed | USA |
| 34 | NCT01339052 | Glioblastoma Multiforme | 65 | Buparlisib, Surgery | 2 | Completed | USA |
| 35 | NCT01473901 | Glioblastoma Multiforme | 38 | Buparlisib, Temozolomide, Radiotherapy | 1 | Completed | USA |
| 36 | NCT01349660 | Glioblastoma Multiforme | 88 | Buparlisib, Bevacizumab | 1, 2 | Active, not recruiting | USA |
| 37 | NCT00590954 | Malignant Gliomas<br>Brain Cancer | 32 | Perifosine | 2 | Completed | USA |
| 38 | NCT00005859 | Brain and Central Nervous System Tumors | 136 | Tipifarnib | 1.2 | Completed | USA |
| 39 | NCT00049387 | Adult Giant Cell Glioblastoma<br>Adult Glioblastoma<br>Adult Gliosarcoma | 19 | Tipifarnib, Temozolomide, Radiotherapy | 1 | Completed | USA |
| 40 | NCT00015899 | Brain and Central Nervous System Tumors | 53 | Lonafarnib | 1 | Completed | USA |

| # | ClinicalTrials.gov Identifier | Conditions | # of Patients Enrollment | Interventions | Study Phase | Status | Locations |
|---|---|---|---|---|---|---|---|
| 41 | NCT00038493 | Glioblastoma Multiforme | 23 | Temozolomide, Lonafarnib | 2 | Completed | USA |
| 42 | NCT01748149 | Pediatric BRAFV600E-mutant Gliomas | 40 | Vemurafenib | 1 | Active, not recruiting | USA |
| 43 | NCT02345824 | Glioblastoma<br>Glioma | 3 | Ribociclib | 1 | Active, not recruiting | USA |
| 44 | NCT02896335 | Metastatic Malignant Brain Tumors | 30 | Palbociclib | 2 | Recruiting | USA |
| 45 | NCT03834740 | Glioblastoma Multiforme<br>Brain Gliomas | 24 | Ribociclib, Everolimus | 1 | Recruiting | USA |
| 46 | NCT03224104 | Astrocytoma, Grade III<br>Glioblastoma | 81 | Zotiraciclib, Temozolomide, Radiotherapy | 1 | Recruiting | SW |
| 47 | NCT02942264 | Brain Tumors<br>Astrocytoma, Astroglioma<br>Glioblastoma<br>Gliosarcoma | 152 | Zotiraciclib, Temozolomide | 1, 2 | Recruiting | USA |
| 48 | NCT02073994 | Cholangiocarcinoma<br>Chondrosarcoma<br>Glioma<br>Other Advanced Solid Tumors | 170 | Ivosidenib | 1 | Active, not recruiting | USA, FR |
| 49 | NCT02481154 | Glioma | 150 | Vorasidenib | 1 | Active, not recruiting | USA |
| 50 | NCT00884741 | Glioblastoma Multiforme<br>Gliosarcoma<br>Supratentorial Glioblastoma | 637 | Bevacizumab, Temozolomide, Radiotherapy | 3 | Completed | USA |
| 51 | NCT00731731 | Adult Glioblastoma | 125 | Temozolomide, Vorinostat | 1, 2 | Active, not recruiting | USA |
| 52 | NCT00128700 | Brain and Central Nervous System Tumors | 20 | Temozolomide, Vatalanib, Radiotherapy | 1, 2 | Completed | BE, DE, IT, NL, SW |
| 53 | NCT00108056 | Glioma | 26 | Enzastaurin | 1 | Terminated | USA |
| 54 | NCT00190723 | Malignant Glioma | 120 | Enzastaurin | 2 | Completed | USA |
| 55 | NCT00503724 | Brain and Central Nervous System Tumors<br>Neuroblastoma | 32 | Enzastaurin | 1 | Completed | USA |
| 56 | NCT00006247 | Brain and Central Nervous System Tumors | 33 | Semaxanib | 1 | Terminated | USA |
| 57 | NCT01229644 | Glioma | 10 | Crenolanib | 2 | Terminated | USA |
| 58 | NCT01393912 | Diffuse Intrinsic Pontine Glioma<br>Progressive or Refractory High-Grade Glioma | 55 | Crenolanib | 1 | Completed | USA |

| # | ClinicalTrials.gov Identifier | Conditions | # of Patients Enrollment | Interventions | Study Phase | Status | Locations |
|---|---|---|---|---|---|---|---|
| 59 | NCT00305656 | Adult Giant Cell Glioblastoma<br>Adult Glioblastoma<br>Adult Gliosarcoma<br>Recurrent Adult Brain Tumor | 31 | Cediranib | 2 | Completed | USA |
| 60 | NCT00326664 | Recurrent Glioblastoma | 55 | Cediranib | 1 | Completed | USA |
| 61 | NCT00503204 | Brain Tumor | 20 | Cediranib, Lomustine | 1 | Completed | USA, UK |
| 62 | NCT00704288 | Glioblastoma Multiforme | 222 | Cabozantinib | 2 | Completed | USA |
| 63 | NCT00960492 | Glioblastoma Multiforme<br>Gliosarcoma | 26 | Cabozantinib, Temozolomide, Radiotherapy | 1 | Completed | USA |
| 64 | NCT00337207 | Brain and Central Nervous System Tumors | 55 | Bevacizumab | 2 | Completed | USA |
| 65 | NCT01740258 | Malignant Glioma<br>Grade IV Malignant Glioma<br>Glioblastoma<br>Gliosarcoma | 69 | Bevacizumab, Temozolomide, Radiotherapy | 2 | Completed | USA |
| 66 | NCT00271609 | Recurrent High-Grade Gliomas<br>Malignant Gliomas | 88 | Bevacizumab | 2 | Completed | USA |
| 67 | NCT01290939 | Glioblastoma Multiforme<br>Cognition Disorders<br>Disability Evaluation | 433 | Bevacizumab, Lomustine | 3 | Unknown | USA |
| 68 | NCT01860638 | Glioblastoma Multiforme | 296 | Bevacizumab, Lomustine | 2 | Completed | AU |
| 69 | NCT00884741 | Glioblastoma Multiforme<br>GliosarcomaSupratentorial | 637 | Bevacizumab, Chemiotherapy, Radiotherapy | 3 | Completed | USA |
| 70 | NCT00943826 | Glioblastoma Multiforme | 921 | Bevacizumab, Temozolomide, Radiotherapy | 3 | Completed | USA |
| 71 | NCT00895180 | Adult Glioblastoma Multiforme | 80 | Olaratumab, Ramucirumab | 2 | Completed | USA |
| 72 | NCT00369590 | Adult Anaplastic Astrocytoma<br>Adult Anaplastic Oligodendroglioma<br>Adult Giant Cell Glioblastoma<br>Adult Gliosarcoma<br>Recurrent Adult Brain Tumor | 58 | Aflibercept | 2 | Completed | USA |
| 73 | NCT00093964 | Glioblastoma Multiforme | 81 | Cilengitide | 2 | Completed | USA |

| # | ClinicalTrials.gov Identifier | Conditions | # of Patients Enrollment | Interventions | Study Phase | Status | Locations |
|---|---|---|---|---|---|---|---|
| 74 | NCT00085254 | Adult Giant Cell Glioblastoma<br>Adult Glioblastoma<br>Adult Gliosarcoma | 112 | Cilengitide, Temozolomide, Radiotherapy | 1, 2 | Completed | USA |
| 75 | NCT00689221 | Glioblastoma Multiforme | 545 | Cilengitide, Temozolomide, Radiotherapy | 3 | Completed | USA, DE |
| 76 | NCT00165477 | Glioblastoma Multiforme<br>Gliosarcoma<br>Malignant Gliomas | 23 | Lenalidomide, Radiotherapy | 2 | Completed | USA |
| 77 | NCT03345095 | Newly Diagnosed Glioblastoma | 750 | Marizomib, Temozolomide, Radiotherapy | 3 | Recruiting | AU, BE |
| 78 | NCT00006773 | Adult Anaplastic Astrocytoma<br>Adult Anaplastic Oligodendroglioma<br>Adult Giant Cell Glioblastom<br>Adult Glioblastoma<br>Adult Gliosarcoma<br>Recurrent Adult Brain Tumor | 42 | Bortezomib | 1 | Terminated | USA |
| 79 | NCT00998010 | Brain and Central Nervous System Tumors | 25 | Bortezomib, Temozolomide, Radiotherapy | 2 | Completed | USA |

AU: Austria; BE: Belgium; CA: Canada; DE: Germany; DK: Denmark; ES: Spain; FR: France; IT: Italy; NL: Netherlands; SW: Switzerland; UK: United Kingdom; USA: United States of America

majority of approaches are directed against signaling pathways related to cell proliferation and glioma invasion, angiogenesis and inhibition of apoptosis.[22-25] Table 2 reports the classification of the target therapies used for malignant brain tumors (Table 2).

### *2.1. Tyrosine Kinase Inhibitors*

Tyrosine kinase receptors consist in an extracellular ligand-binding and a transmembrane tyrosine kinase domain containing sites for autophosphorylation. Upon the binding of its ligand, the receptors undergo dimerization and phosphorylation of specific tyrosines, those become binding sites, recruit proteins and activate downstream intracellular pathways, ultimately resulting in tumor maintenance and proliferation.[26-28] The most widely studied tyrosine kinase receptors are the epidermal growth factor receptor (EGFR), the platelet-derived growth receptor (PDGFR), the fibroblast growth factor receptor (FGFR) and the hepatocyte growth factor receptor (HGFR). All of them are constantly overexpressed or mutated in GBMs. Tyrosine kinase inhibitors (TKIs) are molecules which bind the aforementioned receptors, blocking their downstream signals.

#### *2.1.1 EGFR*

The EGFR gene is amplified or overexpressed in 40% to 60% of the primary GBMs, whereas loss of exons 2 to 7 (EGFRvIII) is present in 40-50% of the cases.[29-31]

**Table 2.** Classification of Target Therapies for Malignant Brain Tumors

| Target Therapy | | |
|---|---|---|
| Candidate Drugs | Target | Biological Role in GBM |
| TKIs | EGFRvIII | Proliferation, migration, invasion, and resistance to apoptosis |
| | PDGFR | |
| | FGFR | |
| | HGFR | |
| PI3K/AKT/ mTOR Is | PI3K | Growth, metabolism, proliferation, migration |
| | AKT | |
| | mTORC1 | |
| FTIs | RAS/MAPK | Cell cycle maintenance and proliferation |
| | BRAF V600E | |
| p53Is | MDM2/ MDM4 | Cell cycle progression and resistance to apoptosis |
| pRBIs | CDK4/CDK6 | |
| IDHIs | IDH1 | Metabolism, proliferation, invasion, angiogenesis |
| HDACIs | Histones | Dysregulation DNA transcription, expansion of gene mutations |
| AIs | VEGF-A | Blood vessel formation, proliferation, therapeutic resistance |
| | VEGFR1 | |
| | PKC | Tumor microenvironment maintenance |
| IIs | Integrins | Cell adhesion, migration, metastasis |
| PIs | Proteasome complex | Homeostasis, growth and resistance to apoptosis |

AIs Angiogenesis Inhibitors, EGFR: Epidermal Growth Factor Receptor; FGFR: Fibroblast Growth Factor Receptor FTIs: Farnesyl Transferase Inhibitors; HDACIs: Histone Deacetylases Inhibitors; HGFR: Hepatocyte Growth Factor Receptor; IDH1: Isocitrate Dehydrogenase 1; IDHIs: Isocitrate Dehydrogenase Inhibitors; IIs: Integrin Inhibitors; mTOR: Mammalian Target of Rapamycin; mTORC1: Mammalian Target of Rapamycin Complex 1; PDGFR: Platelet- Derived Growth Receptor; PI3K: Phosphatidylinositol 4,5-Bisphosphate–3; PIs: Proteasome Inhibitors; PKC: Protein Kinase C; TKIs: Tyrosine Kinase Inhibitors; VEGF-A: Vascular Endothelial Growth Factor A; VEGFR1: Vascular Endothelial Growth Factor Receptor 1

EGFRvIII mutation leads to a ligand-independent kinase activity and, accordingly, an EGFR-pathway overactivation, resulting in increased cell proliferation, invasiveness and resistance to chemotherapeutic agents.[32, 33] Gefinitib (Iressa®) and erlotinib (Tarceva®) are approved TKIs directed against EGFRvI-II. Three phase II clinical trials (#NCT00025675, #NCT00238797, #NCT00016991) highlighted the efficacy of gefinitib, pointing out a progression-free survival at 6 months (PFS-6) of 13%.[34] Erlotinib lacked success as a monotherapy, but enhanced the efficacy of chemo-radiotherapy, especially if associated with temozolomide (TMZ) and carmustine at a dose of 150 or 300 mg/daily.[35, 36] Similar results have been reported for lapatinib, afatinib and dacomitinib.[37]

In addition, two monoclonal antibodies (MAbs) are under observation. Cetuximab, a chimeric murine-human IgG1 Mab that binds the extracellular EGFR domain inducing tumor apoptosis.[38] As a monotherapy, it demonstrated a PFS-6 of 9.2% and an increased overall survival (OS) of 5 months. In combination with bevacizumab and irinotecan cetuximab, it showed a PFS-6 of 30% and a median OS of 7.2 months.[39] ABT-414, an EGFR-directed MAb conjugated to an anti-microtubulin agent, had a PFS-6 of 28.3% in monotherapy or when combined with standard temozolomide chemoradiotherapy (#NCT02573324).[40]

### *2.1.2. PDGFR*

PDGFR gene amplification is found in nearly 15% of GBMs, and the receptor's overexpression, which leads to tumor growth and angiogenesis, is frequently associated with transition from low- to high-grade glioma.[30] Imatinib is the most famous PDGFR inhibitor, used in many hematological tumors for its activity against the mast/stem cell growth factor receptor (c-KIT), and oncogene fusion protein BCR-ABL.

Many phase II clinical trials have proven that imatinib monotherapy failed to improve PFS-6 or OS in patients with GBM,[41] but resulted in a good response in combination with hydroxyurea.[42]

Sorafenib, vandetanib, dasatinib and bosutinib are other PDGFR inhibitors. However, many clinical trials have failed to demonstrate the efficacy of dasatinib,

both as monotherapy and combined with radiotherapy, TMZ and lomustine.[43, 44]

### *2.1.3. FGFR*

Erdafitinib, a selective FGFR TKI, showed promising results in patients with GBM harboring oncogenic FGFR-TACC fusion.[45, 46]

### *2.1.4. HGFR/c-MET*

HGFR, also known as c-Met, amplification/mutation has a role in promoting gliomagenesis and drug resistance.[47, 48] Crizotinib, specifically designed against c-Met, has given some results in combination with dasatinib.[49, 50] Analogous results have been reported for SGX523[51, 52] (#NCT00606879, #NCT00607399). Conversely, onartuzumab and rilotumumab (AMG102) basically demonstrated no clinical benefits.[53, 54] Two phase II clinical trials have been completed, one with AMG102 as monotherapy (#NCT00427440), and the other with AMG102 plus bevacizumab (#NCT01113398), both for patients with recurrent high-grade gliomas.

## *2.2. PI3K/AKT/mTOR Inhibitors*

The Cancer Genome Atlas analysis highlighted the presence of PI3K/AKT/ mTOR signaling pathway dysregulation in 50-60% of GBMs.[55, 56] The activation of phosphatidylinositol 4.5-bisphosphate-3 (PI3K) regulates the activity of many kinase proteins, such as AKT. It transduces the signals to many downstream intracellular effectors, like the mammalian target of rapamycin (mTOR). A fundamental intracellular protein is mTOR, involved in cell growth signaling and tumorigenesis. It is composed of two subunits, mTORC1-2, with different roles, and mTORC1, particularly involved in the transition of the cell cycle from G1 to S. The Food and Drug Administration (FDA) approved three mTORC1 inhibitors: sirolimus (Rapamycin, Rapamune®), everolimus® and temsirolimus®.

Temsirolimus has been evaluated in some significant clinical trials; one of these was a phase II study involving 65 patients with recurrent GBM. It demonstrated a radiographic improvement in 36% of the patients, a PFS-6 of 7.8% and median OS of 4.4 months.[57]

Sirolimus has been tested in combination with surgery (#NCT00047073), gefitinib in 34 recurrent glioma patients, and erlotinib (#NCT00672243), demonstrating moderate effectiveness.[58]

Everolimus was studied in combination with gefitinib (#NCT00085566), bevacizumab or chemioradiotherapy. A phase II clinical trial tested the combination of everolimus, TMZ and radiotherapy versus conventional standard of care (#NCT00553150).

However, mTOR inhibitors have not demonstrated significant clinical activity, if not in combination with other treatments. This is due to their selectivity for mTORC1 and not mTORC2, ensuring only a partial blocking of the mTOR function.

In fact, two novel ATP-competitive mTORC2 inhibitors (CC214-1 and CC214-2) are under investigation, in order to overcome the resistance of mTOR inhibitors.[59]

Other promising strategies involve the selective PI3K inhibitor, buparlisib, which has an antitumor activity, especially when associated with bevacizumab in patients with recurrent GBM.[59]

Perifosine is a novel selective AKT inhibitor, currently tested in some ongoing trials. A phase II study investigated perifosine as a monotherapy for recurrent malignant gliomas[60] (#NCT00590954).

## *2.3. Farnesyl Transferase Inhibitors*

Following the activation of TK receptors, the intracellular RAS protein family undergoes post-translational modifications and triggers multiple effector pathways, including the RAF and MAP kinases (MAPK) involved in cell proliferation, differentiation and survival.

However, translocation of RAS to the cell membrane requires a post-translational alteration catalyzed by the farnesyl transferase enzyme.[30, 61]

Farnesylation is the limiting step in RAS activities and the specific farnesyl transferase inhibitors (FTIs) lock all its functions upstream, and consequently the intracellular RAS-RAF-MEK-MAPK pathway.[62]

Among these, tipifarnib (Zarnestra®), exhibited in a phase II trial, had modest efficacy as a monotherapy or after radiotherapy, in patients with newly diagnosed and recurrent malignant gliomas.[63, 64]

Lonafarnib, an FTI, was tested in a phase I clinical trial in combination with TMZ and radiotherapy, with promising results[65] (#NCT00049387).

#### *2.3.1. BRAF V600E*

RAF kinases, also triggered by the RAS system, are involved in intracellular growth pathways and stimulation.

Several studies reported the presence of BRAF V600E mutation, especially in infant gliomas.[66] Vemurafenib, a BRAF inhibitor, is under investigation in a phase I ongoing trial, for children with recurrent BRAFV600E-Mutant gliomas[67] (#NCT01748149).

### *2.4. MDM2/MDM4/p53 inhibitors*

The dysregulation of p53 signaling pathways is found in more than 80% of high-grade gliomas. The p53 is fundamental in cell-cycle arrest and apoptosis; mutation results in clonal expansion of tumor cells and genetic instability.[68, 69]

In 20% of the patients, the p53 inactivity is due to the MDM2 or MDM4 overexpression. MDM2/MDM4 inactivates p53 and consequently leads to loss of cancer suppression.[30, 70]

Therefore, an effective strategy rationale is to restore the p53 activity, by molecules targeting MDM2 or MDM4. Preclinical studies demonstrated the successful suppression of GBM growth with several MDM2 inhibitors, including RG7112,[71] RG7388 and AMG232 as well as many others in progress (#NCT03107780).

### *2.5. CDK4/CDK6/pRB inhibitors*

The altered function of retinoblastoma protein (pRB) contributes to gliomagenesis in 78% of the cases and the overexpression of CDK4/CDK6 plays a fundamental role in the modulation of this pathway, involved in cell growth.[72-74]

Novel agents directed to CDK4 and CDK6 demonstrated strong antitumor efficacy in RB1-wild-type GBM, such as ribociclib and palbociclib.

Ribociclib was tested in a phase I trial for recurrent glioblastoma or anaplastic glioma[75] (#NCT02345824); palbociclib was employed as a monotherapy for brain metastases[76] (#NCT02896335).

Zotiraclib, a multi-CDK inhibitor, has been explored in clinical trials for newly diagnosed or recurrent gliomas (#NCT02942264, #NCT03224104).

### *2.6. Isocitrate dehydrogenase-1 inhibitors*

Isocitrate dehydrogenase-1 (IDH1) mutation is one of the most frequent abnormalities found in high-grade gliomas, and according to the World Health Organization, is a new classification of brain tumors also having predictive value of treatment response. This mutation consists in the gain-of-function with the production of D-2-hydroxyglutarate, which interferes with cellular metabolism [77, 78]. Ivosidenib, an IDH1 inhibitor, is being evaluated in a phase I ongoing trial, as a monotherapy, for advanced solid tumors including IDH-mutated gliomas (#NCT02073994).

### *2.7. Histone deacetylases inhibitors*

Histone deacetylases (HDAC) are enzymes involved in the regulation of histones, which are proteins that organize the DNA structure and regulate gene transcription.

HDAC inhibitors have an emerging role in the treatment of GBMs, potentially promoting the apoptosis of the cancer cells.[79]

Vorinostat, an oral quinolone HDAC inhibitor, is being studied in phase I/II clinical trials, as a monotherapy in recurrent GBM,[80] and in combination with TMZ, showing good tolerance and giving promising results[81] (#NCT00731731).

Panobinostat, Romidepsin and other HDAC inhibitors are still under evaluation.

### *2.8. Angiogenesis inhibitors*

The tumor's microenvironment, together with pathological angiogenesis and neovascularization, play

a fundamental role in the development and progression of high-grade gliomas.

Acting as managers for the angiogenesis process, as well as for a wide range of CNS vascular pathologies, they are mainly vascular growth factors of all the vascular endothelial growth factor-A (VEGF-A) and its receptors, VEGFR1 and VEGFR2, found on the glioma's endothelial cells.[82-85]

Efforts to downregulate this pathway have been pursued through the development of agents directed to VEGF/VEGFR, which not only block neoangiogenesis, but also have an effect on the vascular phenotype.

The inhibition of VEGF signaling also changes the vessels' diameter, permeability and tortuosity, decreasing tumor hypoxia and consequently disrupting the survival mechanism in glioma cells as well as increasing chemotherapy delivery and radiosensitivity.[83-85]

### *2.8.1. VEGFR*

Several studies evaluated VEGFR inhibitors for patients with newly diagnosed, as well as recurrent GBM.

Vatalanib has been tested in phase I/II studies in combination with TMZ and radiotherapy (#NCT00128700). Cediranib demonstrated no clinical benefits in a phase II clinical trial as a monotherapy (#NCT00305656), yet there was greater benefit together with lomustine in a randomized phase III study[86] (#NCT00503204).

Cabozantinib is a promising agent against VEGFR and MET signaling, evaluated in two phase II studies involving newly diagnosed (#NCT00960492) and recurrent GBM (#NCT00704288). Ramucirumab and icrucumab are new MAbs under evaluation, directed to VEGFR-2 and VEGFR-1, respectively.[87]

### *2.8.2. VEGF*

The most relevant of the VEGF inhibitors is bevacizumab, a humanized IgG1 monoclonal antibody against VEGF-A, which in 2009 received FDA-approval for the treatment of recurrent GBM, after the high radiographic response rates (ranging from 28% to 59%) achieved in two clinical trials.[88, 89]

The significant antitumor potential of bevacizumab has been proven in many studies, using it as a monotherapy or in combination with lomustine (#NCT01290939) and radiochemiotherapy.[90, 91]

Combinations of bevacizumab with the standard of care were examined in two phase III clinical trials, AVAglio[92] (#NCT00943826) and RTOG- 0825[93] (#NCT00884741), and although both demonstrated encouraging results in PFS survival benefit, bevacizumab remains only an alternative treatment in the recurrent setting.

Another promising agent is aflibercept, known as VEGF-trap, a recombinant product fusion protein which has been studied in phase II trials with a PFS-6 of 7.7% and median OS of 3 months.[94, 95]

### *2.8.3. Protein kinase C*

Protein kinase C (PKC) is implicated in activation of the angiogenesis process, cell proliferation and constitution of the microenvironment, therefore, it is a potentially attractive therapeutic target.

Enzastaurin, a potent PKC inhibitor, demonstrated in a phase I/II trial a 25% radiographic response and a PFS-6 of 7% in GBM.[96]

Tamoxifen, a modulator of the estrogen receptor, has been described as a PKC inhibitor and was tested in GBM therapy with a median OS of 9.7 months.[97, 98]

## *2.9. Integrin inhibitors*

The integrins are transmembrane proteins which bind multiple extracellular ligands and mediate cell adhesion and migration. They are expressed at a high level in malignant glioma cells and play a central role in the angiogenesis, development, invasion and metastasis of the tumor.[99, 100] Integrin inhibitors are being investigated as a means of reducing this mechanism.

Cilengitide, which competitively inhibits integrin ligand binding,[101] has been evaluated in a phase I/II study stand-alone;[102] or in a phase III trial, associated to TMZ and radiotherapy, resulting in a good improvement of PFS-6[103] (#NCT00689221).

Thalidomide and lenalidomide, which interfere with the expression of integrin receptors and have an

antiangiogenic effect, are being studied for GBM therapy, with results that are still unsatisfactory.[104-106]

### *2.10. Proteasome inhibitors*

Proteasomes are proteins with enzymatic activities involved in the regulation of homeostasis, cell growth and apoptosis.

Bortezomib (Velcade®), the most used proteasome inhibitor in the oncological field, has also been tested for GBM therapy in combination with chemioradiotherapy[107] (#NCT00006773).

The pan-proteasome inhibitor, Marizomib, is currently undergoing phase III evaluation in newly diagnosed GBMs[108] (#NCT03345095).

## Discussion

The present literature review highlights the current role of a series of target therapies, especially tyrosine kinase and angiogenesis inhibitors, in the treatment of malignant CNS tumors.

Several steps forward have been done in the recent years toward a deep understanding of complex pathophysiologic pathways associated with a wide spectrum of neurological and neuro-oncological pathologies of adulthood and pediatric age. [109-111] Nevertheless, the lack of success of the standard of care and the still largely dismal prognosis of patients affected by high-grade gliomas dictate the urgent need of new and more effective therapeutic approaches.

In this scenario, the improved understanding of genome mutations underlying the GBM phenotype has led to greater insight into the biology of the tumor, at the same time providing the opportunity for designing novel and personalized treatment strategies.[82, 112, 113]

Data from the Cancer Genome Atlas project [55] revealed the complicated genetic profile of GBMs and recognized the core signaling and transduction pathways commonly involved in the growth, proliferation, angiogenesis and spreading of the tumor.[114]

A further tangible aspect of these advances is the latest World Health Organization's classification of brain tumors, which integrates data from traditional histological analysis with biomolecular connotation obtained by specific genetic analysis and characterizations.[115]

Accordingly, the target therapies developed on the basis of the above have detected molecular abnormalities, and have made use of pharmacological agents tailored to specific mutations, specific to tumor subtypes.

Typical genetic alterations of GBMs are the overexpression of the tyrosine kinase receptors, especially the EGFR, PDGFR, FGFR and HGFR, dysregulation of PI3K/AKT/mTOR and RAS/MAPK pathways, as well as p53 or pRB mutations.[30, 116, 117]

TKIs have long been investigated in several clinical trials with disappointing results. Despite the extreme specificity of these agents, they were not efficacious as a monotherapy, thus the current approach consists in the combination of multiple molecular agents within the same targets or between separate pathways.[33, 118, 119]

PI3K/AKT/mTOR pathway and farnesyltransferase inhibitors show low tolerability and safe profiles during clinical studies, but have a synergistic effect only in combination with standard of care.[58, 120]

Likewise, agents directed at restoring p53 and pRB activity gave encouraging results in association with chemotherapy and whole brain radiotherapy.[76, 121] The newly discovered alterations in metabolic pathways, including IDH1 and HDAC enzymes, seem to be up-and-coming targets. Currently, anti-angiogenetic drugs are among the most promising. They focused on the blocking of VEGF/VEGFR,[122, 123] along with components of the tumor microenvironment, such as protein kinase C, integrins and proteasome complexes.[89, 124, 125]

Despite the rationale of the target therapies, the vast intratumoral heterogeneity and GBM cell plasticity have caused a rapid shift toward resistant tumor phenotypes, the latter responsible for the failure of the therapy.[126-128]

Additionally, the route of drug administration still presents a limitation for the efficacy of these therapies. Recent progress has been made through the use of stereotactic or endoscopic techniques for the intrathecal administration of pharmacological agents directly into the tumor site, also benefiting from the minimal invasiveness of these approaches, well evident also for other neurosurgical pathologies.[129-131]

Last but not least, the immunological tumor microenvironment, composed of glia cells and lymphocytes, consistently modulates tumor sensitivity to treatment.[132-134]

## Conclusion

The improved knowledge of the biology of tumors has recently made it possible to transform the molecular alterations at the base of the high malignancy of GBM, into different treatment strategies.

Good results came from tyrosine kinase inhibitors, primarily erlotinib and gefinitinb. Similarly, PI3K/AKT/mTOR inhibitors and p53 restoring agents proved their efficacy in several clinical trials. Bevacizumab, in association with TMZ and radiotherapy, has been approved for recurrent GBMs.

An in-depth identification of driver molecular alterations may make it possible to appropriately select those patients who are candidates for a target therapy.

The greatest challenge of the near future consists in overcoming the issue of escape of GBM that is present in all of these therapies.

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