Glioblastoma targeted therapy: updated approaches from recent biological insights

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Glioblastoma (WHO grade IV astrocytoma) is the most frequent primary brain tumor in adults, representing a highly heterogeneous group of neoplasms that are among the most aggressive and challenging cancers to treat. An improved understanding of the molecular pathways that drive malignancy in glioblastoma has led to the development of various biomarkers and the evaluation of several agents specifically targeting tumor cells and the tumor microenvironment. A number of rational approaches are being investigated, including therapies targeting tumor growth factor receptors and downstream pathways, cell cycle and epigenetic regulation, angiogenesis and antitumor immune response. Moreover, recent identification and validation of prognostic and predictive biomarkers have allowed implementation of modern trial designs based on matching molecular features of tumors to targeted therapeutics. However, while occasional targeted therapy responses have been documented in patients, to date no targeted therapy has been formally validated as effective in clinical trials. The lack of knowledge about relevant molecular drivers in vivo combined with a lack of highly bioactive and brain penetrant-targeted therapies remain significant challenges. In this article, we review the most promising biological insights that have opened the way for the development of targeted therapies in glioblastoma, and examine recent data from clinical trials evaluating targeted therapies and immunotherapies. We discuss challenges and opportunities for the development of these agents in glioblastoma.

Key words: glioma, cancer genomics, targeted therapies, precision medicine, personalized medicine, biomarkers

Introduction

Glioblastoma is the most frequent and aggressive primary malignant brain tumor in adults [1], with a median overall survival (OS) between 10 and 20 months [2–4]. Standard of care is maximal safe surgery followed by concomitant radio-chemotherapy and adjuvant chemotherapy with temozolomide, which can be combined with intermediate-frequency alternating electric fields [2, 4, 5]. Once recurrence occurs, therapeutic options are limited, including bevacizumab and nitrosoureas, although bevacizumab is not approved in Europe. Unlike in most other cancers, this lack of progress has been sustained despite growing insight into the biology of the disease [6–11]. Fortunately, these significant advances have continued to stimulate the development and re-purposing of numerous targeted therapies in clinical trials.

Genomic landscape of glioblastoma

Glioblastomas constitute a highly heterogeneous group of invasive malignant brain tumors [12]. It was the first tumor to undergo comprehensive molecular characterization [6–10, 13–15]. Briefly, these studies showed that most tumors harbor recurrent molecular alterations disrupting core pathways involved in regulation of growth (receptor tyrosine kinase [RTK], mitogen-activated protein kinase [MAPK] and phosphoinositide 3-kinase [PI3K] signaling pathways), cell cycle, DNA repair and apoptosis (Retinoblastoma/E2F and p53 tumor suppressor pathways) as well as control of chromatin state and telomere length (Table 1). Frequently, these alterations derive from copy number aberrations (CNAs). The most common amplification events involve chromosomes 7 (EGFR/MET/CDK6), 12 (CDK4 and MDM2) and 4 (PDGFRA), while recurrent...
homologous deletions are found in chromosomes 9 (CDKN2A/B) and 10 (PTEN). In addition, genome-wide sequencing highlighted single nucleotide variants (SNVs) and short insertions and deletions, resulting in recurrent mutations in the TERT promoter, PTEN, TP53, EGFR, PIK3CA, PIK3R1, NFI and RB1 [10].

Most of these recurrent and biologically relevant genomic variants continue to be attractive targets for drug development [16–23] (Table 1). However, none of the recurrent genomic variants in glioblastoma has been strongly associated with clear prognostic and predictive value so far. This challenges the assumption that these variants are necessarily obligate cancer drivers in glioblastoma and suggests that strong cancer cell plasticity and redundancy among alterations that drive tumor growth may contribute to therapy failure more than previously assumed (Figure 1).

Increasingly, it is being recognized that glioblastomas are characterized by significant inter- and intra-tumor genomic heterogeneity, which can exist as temporal or spatial [10, 24–33]. This represents challenges for appropriate driver identification due to glioblastoma being inherently limited in the amount and locations that one can sample, as well as the limited opportunities for reoperation [34–36]. The evidence that such heterogeneity might be relevant comes from multisector genome-wide sequencing of primary and post-treatment tumors, which revealed substantial divergence in the landscape of driver alterations between primary and recurrent tumors [30, 32, 33, 37, 38]. Moreover, heterogeneity at the single cell level can exist as multiple genomic alterations within redundant pathways (e.g. mosaic amplifications of EGFR, MET and PDGFRA) [10, 24, 29, 39, 40], or multiple unique variants of a single gene (e.g. multiple EGFR oncogenic variants in a single cell) [29, 30, 40], which overall results in heterogeneity in drug sensitivity within individual tumor cells [41] (Figure 1).

### Targeting growth factor receptors and their downstream signaling pathways

Drugs directed against alterations that lead to constitutive activation of growth factor RTKs are the most common type of targeted therapy in all types of cancer with successful responses seen in many cancers. These drugs have also been of great interest in glioblastoma because direct alterations in RTKs and/or downstream MAPK/PI3K signaling pathways represent a hallmark of this tumor (Table 1) [10].

### EGFR-targeted therapies

EGFR amplification, rearrangement or point mutations are found in approximately half of glioblastomas and multiple aberrations in EGFR often co-exist within an individual tumor [10, 30, 42–44]. Nearly 20% of glioblastomas harbor deletion of exons 2–7 of EGFR, resulting in EGFRvIII, a constitutively active oncoprotein variant frequently associated with EGFR amplification. Preclinical studies have demonstrated that EGFRvIII-driven tumors are only weakly sensitive to first generation EGFR tyrosine kinase inhibitors (TKI) erlotinib and gefitinib [45, 46]. Indeed, EGFRvIII—as most other EGFR SNVs found in glioblastoma—alters the extracellular domain of EGFR in glioblastoma, while in contrast lung adenocarcinomas typically harbor direct activating mutations in the kinase domain [45].

Rindopepimut is an EGFRvIII peptide vaccine that demonstrated signs of activity in preclinical models of glioblastoma and early phase trials [16, 47, 48]. The recently completed randomized phase II study ReACT evaluated the association of rindopepimut plus bevacizumab in EGFRvIII-positive recurrent glioblastoma.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Alteration or target</th>
<th>Target frequency in glioblastoma (%)</th>
<th>Candidate therapy (drug example)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>Deletion (EGFRvIII), mutation,</td>
<td>55</td>
<td>EGFR vaccine or antibody-drug conjugate (rindopepimut, ABT-414)</td>
</tr>
<tr>
<td></td>
<td>translocation and/or amplification</td>
<td></td>
<td>KIT inhibitor (imatitinib)</td>
</tr>
<tr>
<td>KIT</td>
<td>Amplification, mutation</td>
<td>10</td>
<td>PDGFR inhibitor (dasatinib)</td>
</tr>
<tr>
<td>PDGFRA</td>
<td>Amplification</td>
<td>15</td>
<td>FGFR1/3 inhibitor (JNJ-42756493)</td>
</tr>
<tr>
<td>FGFR1, FGFR3</td>
<td>Translocation (e.g. FGFR3-TACC3)</td>
<td>3</td>
<td>MET inhibitor (cabozantinib)</td>
</tr>
<tr>
<td>MET</td>
<td>Amplification, translocation</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAPK and PI3K/mTOR signaling pathways</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTEN</td>
<td>Deletion, mutation</td>
<td>40</td>
<td>AKT inhibitor, mTOR inhibitor (voxtalisib)</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>Amplification, mutation</td>
<td>10</td>
<td>mTOR inhibitor, PI3K inhibitor (buparlisib)</td>
</tr>
<tr>
<td>NFI</td>
<td>Deletion, mutation</td>
<td>14</td>
<td>MEK inhibitor (trametinib)</td>
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<tr>
<td>BRAF</td>
<td>Mutation (BRAF V600E)</td>
<td>2</td>
<td>BRAF inhibitor (vemurafenib), MEK inhibitor (trametinib)</td>
</tr>
<tr>
<td>Cell cycle pathways</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDM2</td>
<td>Amplification</td>
<td>10</td>
<td>MDM2 inhibitor (AMG232)</td>
</tr>
<tr>
<td>TP53</td>
<td>Wild-type (no mutations)</td>
<td>60</td>
<td>MDM2 inhibitor (AMG232)</td>
</tr>
<tr>
<td>CDK4/6</td>
<td>Amplification</td>
<td>20</td>
<td>CDK4/6 inhibitor (ribociclib)</td>
</tr>
<tr>
<td>RB1</td>
<td>Wild-type (no mutations)</td>
<td>90</td>
<td>CDK4/6 inhibitor (ribociclib)</td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDH1</td>
<td>Mutation</td>
<td>6</td>
<td>IDH1 inhibitor (AGI120)</td>
</tr>
<tr>
<td>MYC, MYCN</td>
<td>Amplification</td>
<td>5</td>
<td>Bromodomain inhibitor (OTX-015)</td>
</tr>
</tbody>
</table>

Table 1. Genomic alterations and example targeted therapies in glioblastoma

*Source: cbioportal.org (glioblastoma TCGA dataset, n = 281 tumor samples with sequencing and CNA data) [10].
Advantage to rindopepimut therapy was reported across multiple endpoints including 2-year OS rate and progression-free survival (PFS), although the trial failed to meet its primary endpoint [49] (Table 2). Preliminary analyses from the phase III randomized study of rindopepimut in newly diagnosed EGFRvIII-positive glioblastoma indicated that its benefit on OS will not reach statistical significance (23 months from diagnosis in both arms), resulting in the closure of the trial [50]. Subgroup analyses suggested that rindopepimut might have failed due to reduced amount of EGFRvIII antigen burden in patients that underwent gross total resection (2-year survival rate of 30% in patients with non-minimal residual disease versus 19% in patients with minimal residual disease), although these results will need confirmation after longer follow-up. Further development of rindopepimut is uncertain.

Other EGFRvIII-targeted therapies are being evaluated. ABT-414 is an antibody drug conjugate (ADC) consisting of an anti-EGFR MAb, conjugated to the tubulin inhibitor monomethylauristatin F. ABT-414 demonstrated cytotoxicity against glioblastoma patient-derived xenograft models expressing either wild-type EGFR or EGFRvIII [51]. Preliminary data from a phase I trial of ABT-414 monotherapy in EGFR-amplified recurrent glioblastoma showed a 6 months PFS rate of 28.3% [52] (Table 2). OS from trial entry was 9 months, which was considered encouraging, as 56% of patients had already undergone two to three prior therapies. No dose-limiting toxicity was reported, although specific ocular toxicities were frequently observed (mostly reversible blurred vision, with some patients presenting with keratitis or corneal epithelial microcysts). The clinical development of ABT-414 is ongoing with randomized phase II/III trials (Table 3).

In addition, several trials have evaluated more broadly effective EGFR-targeted therapies (Table 2). A variety of first and second

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**Figure 1.** Cellular heterogeneity of RTK aberrations in glioblastoma: implications for appropriate drug targeting (adapted from Francis et al. [30]). Dynamics of the glioblastoma genome may generate or select for subclonal populations of tumor cells that are highly resistant to treatment, overall suggesting that comprehensive characterization of tumor heterogeneity is a prerequisite for the success of pharmacological inhibition of RTK alterations. Left, multiple amplifications of distinct RTK genes can be observed in non-overlapping subclonal populations from individual tumors, or within individual tumor cells. In other cases (right), tumor heterogeneity may exist as multiple alterations within a single RTK gene.
Table 2. Recently reported trials of targeted therapies in recurrent glioblastoma

<table>
<thead>
<tr>
<th>Design</th>
<th>Drug regimen</th>
<th>Target(s)</th>
<th>Population, number of patients (n)</th>
<th>Median OS (months)</th>
<th>Median PFS (months)</th>
<th>PFS-6</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Growth factor receptors, MAPK/PI3K signaling pathways</strong></td>
<td></td>
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<tr>
<td>Phase II, randomized</td>
<td>Onartuzumab + bevacizumab (ona/beva) or bevacizumab + placebo (beva/p)</td>
<td>MET (onartuzumab), VEGF (bevacizumab)</td>
<td>First recurrence, n = 64 (ona/beva), n = 65 (beva/p)</td>
<td>8.8 (ona/beva), 12.6 (beva/p)</td>
<td>3.9 (ona/beva), 2.9 (beva/p)</td>
<td>33.9% (ona/beva), 29% (beva/p)</td>
<td>[97]</td>
</tr>
<tr>
<td>Phase II, double-blind, randomized</td>
<td>Bevacizumab + rindopepimut (beva/rindo) or bevacizumab + placebo (beva/p)</td>
<td>VEGF (bevacizumab), EGFRVIII (rindopepimut)</td>
<td>First or second recurrence, bevacizumab-naïve, EGFRVIII-positive, n = 73</td>
<td>11.6 (beva/rindo), 9.3 (beva/p)</td>
<td>NA</td>
<td>33.9% (ona/beva), 29% (beva/p)</td>
<td>[49]</td>
</tr>
<tr>
<td>Phase II, randomized</td>
<td>Temozolomide (TMZ) or afatinib (afa) or afatinib + temozolomide (afa/TMZ)</td>
<td>EGFR (Afatinib)</td>
<td>First recurrence, n = 39 (TMZ), n = 41 (afa), n = 39 (afa/TMZ)</td>
<td>106 (TMZ), 98 (afa), 8 (afa/TMZ)</td>
<td>1.9 (TMZ), 1 (afa), 1.5 (afa/TMZ)</td>
<td>23% (TMZ), 3% (afa), 10% (afa/TMZ)</td>
<td>[62]</td>
</tr>
<tr>
<td>Phase I, single-agent</td>
<td>ABT-414</td>
<td>EGFR, EGFRVIII</td>
<td>Any recurrence, n = 60</td>
<td>90</td>
<td>NA</td>
<td>NA</td>
<td>[52]</td>
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<tr>
<td>Phase II, single-agent</td>
<td>PX-866</td>
<td>PI3K</td>
<td>First recurrence, n = 33</td>
<td>108</td>
<td>NA</td>
<td>NA</td>
<td>[101]</td>
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<tr>
<td>Phase II, single-arm</td>
<td>Buparlisib + bevacizumab</td>
<td>PI3K (buparlisib), VEGF (bevacizumab)</td>
<td>First recurrence, n = 68</td>
<td>5.7</td>
<td>2.5</td>
<td>14%</td>
<td>[71]</td>
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<tr>
<td>Phase II, single-arm</td>
<td>Erlotinib + sorafenib</td>
<td>EGFR (erlotinib), VEGF, PDGFR, Raf kinases (sorafenib)</td>
<td>NA, n = 56</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>[143]</td>
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<tr>
<td><strong>DNA repair and other epigenetic modifiers</strong></td>
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<tr>
<td>Phase II, randomized</td>
<td>Bevacizumab (beva) + vorinostat (beva/vor) or bevacizumab (beva)</td>
<td>Histone deacetylases (vorinostat), VEGF (bevacizumab)</td>
<td>First recurrence, n = 49 (beva/vor), n = 41 (beva)</td>
<td>83 (beva/vor), 70 (beva)</td>
<td>4.2 (beva/vor), 3.6 (beva)</td>
<td>NA</td>
<td>[154]</td>
</tr>
<tr>
<td>Phase II, randomized</td>
<td>Sequential temozolomide + veliparib</td>
<td>PARP (veliparib)</td>
<td>NA, n = 141</td>
<td>103 (beva-naïve), 4.7 (beva-resistant)</td>
<td>20 (beva-naïve), 2.0 (beva-resistant)</td>
<td>17.0% (beva-naïve), 4.4% (beva-resistant)</td>
<td>[129]</td>
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<tr>
<td>Phase II, single-arm</td>
<td>Panobinostat + bevacizumab</td>
<td>Histone deacetylases (panobinostat), VEGF (bevacizumab)</td>
<td>First or second recurrence, n = 24</td>
<td>90</td>
<td>5.0</td>
<td>30.4%</td>
<td>[143]</td>
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<tr>
<td><strong>Antiangiogenics</strong></td>
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<tr>
<td>Phase III, double-blind, randomized</td>
<td>Lomustine + bevacizumab (lom/beva) vs. lomustine (lom)</td>
<td>VEGF (beva)</td>
<td>First recurrence, n = 288 (lom/beva), n = 149 (lom)</td>
<td>9.1 (lom/beva), 8.6 (lom)</td>
<td>4.2 (lom/beva), 1.5 (lom)</td>
<td>NA</td>
<td>[169]</td>
</tr>
<tr>
<td>Phase III, double-blind, randomized</td>
<td>CCNU + placebo (CCNU) or cediranib (ced) or cediranib + CCNU (CCNU/ced)</td>
<td>VEGFR1-3 and PDGFR (ced)</td>
<td>First recurrence, n = 65 (CCNU), n = 131 (ced), n = 129 (CCNU/ced)</td>
<td>98 (CCNU), 8.0 (ced), 9.4 (CCNU/ced)</td>
<td>2.7 (CCNU), 3.1 (ced), 4.2 (CCNU/ced)</td>
<td>24.5% (CCNU), 16% (ced), 34.5% (CCNU/ced)</td>
<td>[155]</td>
</tr>
<tr>
<td>Phase II, randomized</td>
<td>Axitinib (axi) or physician’s choice (lomustine or bevacizumab)</td>
<td></td>
<td>First recurrence, n = 22 (axi), n = 22 (control)</td>
<td>63 (axi), 3.7 (control)</td>
<td>34% (axi), 28% (control)</td>
<td>[165]</td>
<td></td>
</tr>
<tr>
<td>Design</td>
<td>Drug regimen</td>
<td>Target(s)</td>
<td>Population, number of patients (n)</td>
<td>Median OS (months)</td>
<td>Median PFS (months)</td>
<td>PFS-6</td>
<td>Reference</td>
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<tr>
<td>------------------------</td>
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<tr>
<td>Phase II, randomized</td>
<td>Bevacizumab + placebo (beva/p) vs. bevacizumab + dasatinib (beva/dasa)</td>
<td>SRC, c-KIT, EPHA2, PDGFR (dasa), VEGF (beva)</td>
<td>First or second recurrence, n = 38 (beva/p), n = 83 (beva/dasa)</td>
<td>7.9 (beva/p), 7.2 (beva/dasa)</td>
<td>NA</td>
<td>184% (beva/p), 27.2% (beva/dasa)</td>
<td>[164]</td>
</tr>
<tr>
<td>Phase II, single-agent</td>
<td>Dasatinib</td>
<td>SRC, c-KIT, EPHA2, PDGFR</td>
<td>First recurrence, overexpression of at least 2 putative dasatinib targets, n = 50</td>
<td>7.9</td>
<td>1.7</td>
<td>6%</td>
<td>[84]</td>
</tr>
<tr>
<td>Phase II, single-arm</td>
<td>Pazopanib + lapatinib</td>
<td>VEGFR1-3, c-KIT, PDGFR (lapatinib)</td>
<td>NA, n = 41</td>
<td>NA</td>
<td>1.9</td>
<td>75%</td>
<td>[65]</td>
</tr>
<tr>
<td>Phase II, single-agent</td>
<td>Sunitinib</td>
<td>VEGFR1-2, c-KIT, PDGFR, FLT3, CSF-1R, RET</td>
<td>NA, n = 63</td>
<td>9.4 (beva-naive), 4.4 (beva-resistant)</td>
<td>1 (beva-naive), 1 (beva-resistant)</td>
<td>10.4% (beva-naive) 0% (beva-resistant)</td>
<td>[152]</td>
</tr>
<tr>
<td>Phase II, single-agent</td>
<td>Nintedanib</td>
<td>VEGFR1-3, FGFR1-3, PDGFR</td>
<td>First or second recurrence, n = 25</td>
<td>6</td>
<td>1</td>
<td>NA</td>
<td>[157]</td>
</tr>
</tbody>
</table>

**Immune checkpoint inhibitors**

<table>
<thead>
<tr>
<th>Design</th>
<th>Drug regimen</th>
<th>Target(s)</th>
<th>Population, number of patients (n)</th>
<th>Median OS (months)</th>
<th>Median PFS (months)</th>
<th>PFS-6</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase II/III, randomized</td>
<td>Nivolumab (3 mg/kg, nivo1) or nivolumab (1 mg/kg) + ipilimumab (3 mg/kg, nivo1/ipi3) or nivolumab (3 mg/kg) + ipilimumab (1 mg/kg, nivo3/ipi1)</td>
<td>PD1 (nivolumab), CTLA-4 (ipilimumab)</td>
<td>First recurrence, n = 10 (nivo3), n = 10 (nivo1/ipi3), n = 20 (nivo3/ipi1)</td>
<td>10.5 (nivo3), 9.3 (nivo1/ipi3), 7.3 (nivo3/ipi1)</td>
<td>1.9 (nivo3), 2.1 (nivo1/ipi3), 2.4 (nivo3/ipi1)</td>
<td>NA</td>
<td>[183]</td>
</tr>
<tr>
<td>Phase II, single-agent</td>
<td>Durvalumab</td>
<td>PD-L1</td>
<td>First or second recurrence, bevacizumab-naive, n = 30</td>
<td>6.7</td>
<td>3.2</td>
<td>20%</td>
<td>[185]</td>
</tr>
<tr>
<td>Phase Ib, single-agent</td>
<td>Pembrolizumab</td>
<td>PD1</td>
<td>Any recurrence, n = 26</td>
<td>14.0</td>
<td>3.0</td>
<td>44%</td>
<td>[184]</td>
</tr>
</tbody>
</table>

Abbreviations: NA, data not available.
This receptor is highly active in all glioma types and represents a target for therapeutic intervention. A phase II trial evaluated the efficacy of dasatinib, a multikinase inhibitor targeting PDGFR, c-KIT, SRC and EPHA2 [84] (Table 2). Despite the fact that patients were selected on the basis of overexpression of at least 2 putative dasatinib targets, no response was reported. Additional trials evaluated other multikinase inhibitors without showing any consistent clinical activity in glioblastoma [85–89].

Finally, preclinical evidences indicated an oncogenic role for c-MET signaling pathway activation in glioblastoma, notably by promoting tumor growth and invasiveness as well as drug resistance [90–94]. Rare responses have been documented in patients receiving crizotinib, a c-MET/ALK inhibitor and represent some of the first evidence of targeted therapy success [95, 96]. MET amplification or mutation as well as overexpression of c-MET or its ligand, the hepatocyte growth factor (HGF), have been proposed as predictive biomarkers, although efficacy and its molecular determinants remain unclear to date. A recently reported randomized phase II trial investigated the safety and efficacy of bevacizumab plus onartuzumab—a MAb against MET—versus bevacizumab plus placebo in recurrent glioblastoma (Table 2) [97]. Overall, there was no evidence of clinical benefit with bevacizumab plus onartuzumab compared with bevacizumab plus placebo, although exploratory biomarker analyses suggested benefit in patients with unmethylated O6-methylguanine–DNA methyltransferase (MGMT) or high HGF expression in tumor tissue. Further understanding of the role of these RTKs in the disease process is needed to guide the development of novel targeted therapies.

### Table 3. Ongoing randomized phase 3 trials evaluating investigational agents in glioblastoma

<table>
<thead>
<tr>
<th>ClinicalTrials.gov Identifier</th>
<th>Population</th>
<th>Treatment arms</th>
<th>Primary endpoint</th>
<th>Status</th>
<th>Sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT0045968</td>
<td>Sufficient tumor lysate after surgery</td>
<td>Experimental: RT/TMZ followed by TMZ + DCVax-L (dendritic cells vaccine) Comparator: RT/TMZ followed by TMZ + placebo</td>
<td>PFS Accrual completed</td>
<td>Recruiting</td>
<td>ImmunoCellular Therapeutics</td>
</tr>
<tr>
<td>NCT02617589</td>
<td>Unmethylated MGMT promoter</td>
<td>Experimental: RT + nivolumab (anti-PD1 MAb) Comparator: RT/TMZ followed by TMZ</td>
<td>Recruiting</td>
<td>Recruiting</td>
<td>AbbVie</td>
</tr>
<tr>
<td>NCT02546102</td>
<td>HLA-A2 positive patients</td>
<td>Experimental: RT/TMZ followed by TMZ + ICT-107 (dendritic cells vaccine) Comparator: RT/TMZ followed by TMZ + placebo</td>
<td>Recruiting</td>
<td>Recruiting</td>
<td>ImmunoCellular Therapeutics</td>
</tr>
<tr>
<td>NCT02573324</td>
<td>EGFR-amplified</td>
<td>Experimental: RT/TMZ/ABT-414 followed by TMZ + ABT-414 (anti-EGFR ADC) Comparator: RT/TMZ/placebo followed by TMZ + placebo</td>
<td>Recruiting</td>
<td>Recruiting</td>
<td>AbbVie</td>
</tr>
<tr>
<td>NCT02152982</td>
<td>Unmethylated MGMT promoter</td>
<td>Experimental: RT/TMZ + folllowed by TMZ + velparab (PARP inhibitor) Comparator: RT/TMZ followed by TMZ + placebo</td>
<td>Recruiting</td>
<td>Recruiting</td>
<td>National Cancer Institute</td>
</tr>
</tbody>
</table>

**Source:** clinicaltrials.gov (November 2016).

### Targeting other receptor tyrosine kinases

Oncogenic FGFR–TACC fusions are found in nearly 3% of glioblastomas, with promising evidence of actionability provided by preclinical studies [21, 81]. Encouraging evidence of activity was recently reported in a phase I study evaluating JNJ-42756493—a highly selective pan-FGFR TKI—in three patients harboring FGFR3–TACC3-positive glioblastomas [21, 82]. Phase II clinical trials evaluating other selective FGFR inhibitors (e.g. BGJ398 and AZD4547) are currently ongoing [83].

PDGFRA amplification is found in nearly 13% of glioblastomas [10]. This receptor is highly active in all glioma types and represents one of the more underexplored targets for therapy. A recently reported phase II trial evaluated the efficacy of dasatinib, a multikinase inhibitor targeting PDGFR, c-KIT, SRC and EPHA2 [84] (Table 2). Despite the fact that patients were selected on the basis of overexpression of at least 2 putative dasatinib targets, no response was reported. Additional trials evaluated other multikinase inhibitors without showing any consistent clinical activity in glioblastoma [85–89].

Finally, preclinical evidences indicated an oncogenic role for c-MET signaling pathway activation in glioblastoma, notably by promoting tumor growth and invasiveness as well as drug resistance [90–94]. Rare responses have been documented in patients receiving crizotinib, a c-MET/ALK inhibitor and represent some of the first evidence of targeted therapy success [95, 96]. MET amplification or mutation as well as overexpression of c-MET or its ligand, the hepatocyte growth factor (HGF), have been proposed as predictive biomarkers, although efficacy and its molecular determinants remain unclear to date. A recently reported randomized phase II trial investigated the safety and efficacy of bevacizumab plus onartuzumab—a MAb against MET—versus bevacizumab plus placebo in recurrent glioblastoma (Table 2) [97]. Overall, there was no evidence of clinical benefit with bevacizumab plus onartuzumab compared with bevacizumab plus placebo, although exploratory biomarker analyses suggested benefit in patients with unmethylated O6-methylguanine–DNA methyltransferase (MGMT) or high HGF expression in tumor tissue. Further understanding of the role of these RTKs in the disease process is needed to guide the development of novel targeted therapies.

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**Table 3. Ongoing randomized phase 3 trials evaluating investigational agents in glioblastoma**

<table>
<thead>
<tr>
<th>ClinicalTrials.gov Identifier</th>
<th>Population</th>
<th>Treatment arms</th>
<th>Primary endpoint</th>
<th>Status</th>
<th>Sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT0045968</td>
<td>Sufficient tumor lysate after surgery</td>
<td>Experimental: RT/TMZ followed by TMZ + DCVax-L (dendritic cells vaccine) Comparator: RT/TMZ followed by TMZ + placebo</td>
<td>PFS Accrual completed</td>
<td>Recruiting</td>
<td>ImmunoCellular Therapeutics</td>
</tr>
<tr>
<td>NCT02617589</td>
<td>Unmethylated MGMT promoter</td>
<td>Experimental: RT + nivolumab (anti-PD1 MAb) Comparator: RT/TMZ followed by TMZ</td>
<td>Recruiting</td>
<td>Recruiting</td>
<td>AbbVie</td>
</tr>
<tr>
<td>NCT02546102</td>
<td>HLA-A2 positive patients</td>
<td>Experimental: RT/TMZ followed by TMZ + ICT-107 (dendritic cells vaccine) Comparator: RT/TMZ followed by TMZ + placebo</td>
<td>Recruiting</td>
<td>Recruiting</td>
<td>ImmunoCellular Therapeutics</td>
</tr>
<tr>
<td>NCT02573324</td>
<td>EGFR-amplified</td>
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<td>Recruiting</td>
<td>National Cancer Institute</td>
</tr>
</tbody>
</table>

**Source:** clinicaltrials.gov (November 2016).
Targeting PI3K/AKT/mTOR and MAPK signaling pathways

In light of the disappointing activity observed with existing RTK inhibitors, agents designed to interfere with downstream molecules remain attractive. The PI3K/AKT/mTOR signaling pathway is dysregulated in the vast majority of glioblastomas through various molecular alterations (Table 1). mTOR inhibitors such as temsirolimus and everolimus have been FDA-approved to treat various solid cancers including subependymal giant cell astrocytoma, a low grade brain tumor arising in patients with tuberous sclerosis complex, with good response in this special type of astrocytoma. However, when evaluated in glioblastoma as monotherapy, or in combination with either EGFR TKIs, bevacizumab or temozolomide and radiation therapy, these agents have not demonstrated significant clinical activity [66–70, 98–100].

Nonetheless, it has been hypothesized that a subset of patients may benefit from PI3K/AKT/mTOR signaling inhibition, and novel agents with a broader range of activity are currently being evaluated. PX-866 is an oral PI3K inhibitor recently tested in a phase II trial [101]. While the study was negative, durable stabilization was observed in 21% of patients. No association between outcome and PTEN, PIK3CA or PIK3R1 status was observed. The dual PI3K/mTOR inhibitor voxtalisib and the pan-class I PI3K inhibitor buparlisib have been evaluated in other trials. Preliminary results from phase II trials evaluating buparlisib indicated activity in association with bevacizumab [102], while limited efficacy was observed in patients receiving buparlisib as monotherapy, even in the presence of PIK3CA, PIK3R1 or PTEN molecular alterations (Table 2).

Targeting MAPK pathway signaling, activated in all glioblastomas, is also a rational approach. A small subset of patients (3%), especially those with giant cell or epithelioid morphology (11%), harbors the BRAF V600E mutation [103], a well-known targetable oncogene. The BRAF inhibitor vemurafenib has shown promising efficacy in individual patients with BRAF-mutant (V600E) high-grade gliomas of non-glioblastoma types [104, 105]. The RAF multikinase inhibitor sorafenib has been evaluated in several small phase I/II studies as monotherapy or in combination with bevacizumab, temozolomide, temsirolimus [106–110] or radiation therapy and temozolomide [111]. Unfortunately, limited efficacy was observed and has not supported further development of sorafenib in glioblastoma (Table 2). Future preclinical studies and trials should focus on combined inhibition of MAPK and other pathways, as well as identifying predictive biomarkers. The presence of responses in other glioma types with BRAF alterations suggests these agents may be some of the most promising for future success in targeted therapies.

Targeting DNA repair and cell cycle control pathways

Disruption of p53 and Retinoblastoma/E2F tumor suppressor pathways is found in more than 80% of glioblastomas [10]. TP53 encodes the tumor suppressor protein p53 that causes cell-cycle arrest and promotes apoptosis upon DNA damage [112]. TP53 mutation/deletion results in growth advantage and clonal expansion of glioma cells, as well as impairment of DNA repair, promoting overall genetic instability and transformation [113, 114].Besides direct gene mutation or deletion, p53 inactivation may be caused by MDM2 or MDM4 amplification (20% of patient overall) [10, 115]. The first therapeutic strategies targeting p53 were centered on attempting reactivation of the pathway using gene therapy or pharmacological approaches, although these have failed to demonstrate clinical efficacy [116]. A key disadvantage of the original nutlin-based drugs was the low potency and poor blood–brain barrier (BBB) penetration. However, MDM2 inhibition has recently re-emerged as an attractive strategy to restore p53 function with advances in the chemical properties of nutlin-based agents (RG7112, RG7388), as well as other classes of agents recently developed (HDQ201, AMG232). Preclinical studies have demonstrated striking antitumor efficacy in MDM2-amplified glioblastoma models [117, 118]. Most importantly, TP53-wild-type models also showed marked response to these agents and–tumor and blood–brain penetration of the more novel agents has been in a range as feasible for clinical trials. Given that about 50% of glioblastoma patients have TP53-wild-type tumors this represents an attractive strategy for the majority of patients.

Cell cycle progression is frequently deregulated through various recurrent molecular alterations including inactivation of CDKN2A/CDKN2B and RB1 as well as amplification of CDK4 and CDK6 (Table 1) [10, 119]. Novel agents designed to inhibit CDK4 and CDK6 have demonstrated strong antitumor efficacy in RB1-wild-type glioblastoma models [120–123], and have been subsequently evaluated in phase II. Results from this study as well as other trials evaluating newer compounds (NCT02345824) should shed light on the value of CDK inhibitors in glioblastoma, and the biomarker profile of the patients that may respond.

Finally, synthetic lethal approaches have been developed as novel strategies to target tumors harboring alterations disrupting DNA repair and tumor suppressor pathways. WEE1—a nuclear serine/threonine kinase—acts as a gatekeeper against mitotic catastrophe in glioblastoma. Recent preclinical works demonstrated that small-molecule inhibition of WEE1 sensitized glioblastoma to DNA damaging agents including radiation therapy [124–126]. Combination of the WEE1 inhibitor AZD1775 with radiation therapy and temozolomide is currently being evaluated (NCT01849146). Other promising strategies exploiting synthetic lethal interactions include association of DNA repair inhibitors (e.g. the PARP inhibitors veliparib and olaparib) with radiation therapy and/or temozolomide, which have demonstrated antitumor efficacy in animal models [127–128], and are currently evaluated in randomized trials (Table 3) [129].

Targeting epigenetic deregulation and tumor metabolism

Targeting isocitrate dehydrogenase

IDH1 mutations are found in 6% of primary glioblastomas [7, 130–132]. These mutations confer a gain-of-function, resulting in the production of d-2-hydroxyglutarate (D2HG), which interferes with cellular metabolism and epigenetic regulation [132,
Histone deacetylase (HDAC) inhibitors represent an emerging class of therapeutics that has shown activity in hematologic malignancies. Despite encouraging efficacy in preclinical models including histone H3-mutant pediatric glioblastoma [137–139], only modest activity has been observed in clinical trials evaluating HDAC inhibitors as a single agent, or in combination with temozolomide, bortezomib or bevacizumab [140–143] (Table 2). Beyond HDAC inhibitors, other epigenetic modifiers have recently gained interest for the treatment of glial tumors. These include BET bromodomain proteins inhibitors and EZH2 inhibitors, which have recently entered in clinical trials (NCT01897571, NCT02711137), and have both demonstrated antitumor activity in preclinical models [144–147].

Targeting tumor angiogenesis

A multitude of anti-angiogenic targeted therapies have been evaluated in clinical trials of glioblastoma as monotherapy or in combinations with various agents, all with no significant survival benefit to patients [63, 84, 106, 148–168] (Table 2). In 2009, bevacizumab received provisional FDA-approval for the treatment of recurrent glioblastoma on the basis of radiographic response rates ranging from 28% to 59% reported in two single-arm trials [148, 149]. However, subsequent trials failed to demonstrate superiority of bevacizumab alone or combined with lomustine in terms of OS [161, 169]. In newly diagnosed glioblastoma, two recently reported placebo-controlled randomized trials evaluating the benefit from the addition of bevacizumab to standard of care showed no difference in OS, while significant improvement in PFS was demonstrated in both trials (extension of median PFS of 3.4 and 4.6 months) [162, 163].

Given the encouraging preclinical data, what went wrong? The lack of the target being expressed in tumor cells is something that became clearer with time. The level of dependency of the tumor ecosystem on the vasculature now appears to be low. Despite the lack of clear survival benefit of antiangiogenic agents in glioblastoma, prolonged PFS with long-lasting tumor response or stabilization has been proposed to be present in a subset of patients receiving bevacizumab. The identification of biomarkers to predict response of antiangiogenics agents may therefore be warranted. One possibility for this comes from post-hoc analysis from the AVAglio randomized phase III trial [170], which reported significant OS advantage of adding bevacizumab to standard of care in patients with proneural IDH1 wild-type tumors, albeit this needs to be validated further in an independent trial.

Immunotherapies

Immunotherapy for glioblastoma has gained considerable interest over the past years. The concept of the central nervous system (CNS) as an ‘immune privileged site’ has been recently challenged by the discovery of the CNS lymphatic system, which is connected to the deep cervical lymph nodes [171–174]. Therapeutic targeting of immune checkpoint programmed cell death 1 (PD1)/programmed death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated molecule-4 (CTLA-4) using MAbs has been associated with significant clinical benefit in several human malignancies [175, 176]. These treatments aim at enhancing antitumor immune responses, by blocking negative regulatory pathways in T-cell activation. In glioblastoma, PD-L1 is expressed in some patients [177, 178], and preclinical studies have provided rationale for the evaluation of immune checkpoint blockers (ICBs) [179–182].

Several clinical trials evaluating ICBs are ongoing (Tables 2 and 3), including randomized phase III trials of the anti-PD1 nivolumab. Preliminary data on efficacy and safety of ICBs as monotherapy or in combination were recently reported [183–186] (Table 2). Overall, the response rates observed with these agents in recurrent disease were low; however, the observation of a relative increase in 6-month PFS and OS suggested a possible benefit in a subset of patients. Recent studies in non-CNS cancers have indicated that patients whose tumors bear high neoantigen and/or mutation load may derive enhanced clinical benefit from immune checkpoint inhibitors [187–190]. Partial responses to nivolumab were recently reported in two pediatric patients that developed hypermutant glioblastoma in the context of biallelic mismatch repair deficiency [191], suggesting that this subset of patients may be responsive to this strategy.

Beyond targeting of immune checkpoints, other approaches taking advantage of the immune system and the tumor microenvironment are being explored. Dendritic cell and peptide vaccines have entered clinical trials, with promising signs of activity reported in preclinical studies and early phase trials [16, 47, 48, 135, 136, 192–197]. These encouraging results need further confirmation in the ongoing larger randomized trials. Other immune-cells based approaches include engineered chimeric antigen receptor (CAR T)/NK cells re-directed to specific tumor antigens (e.g. EGFRvIII), which have demonstrated promising antitumor efficacy in animal models [198, 199], and are currently evaluated in several phase I/II trials (NCT01109095, NCT02442297, NCT02664363, NCT01454596). However, these novel approached will require further standardization and optimization efforts, and costs and technical issues associated with cell-based therapy will likely limit its widespread application.

Development of targeted therapies in glioblastoma: current state of the art and future directions

Lessons learned from the clinical development of targeted therapies

Unlike the experience in some other human malignancies harboring activating oncogenic alterations (e.g. EGFR or ALK in lung adenocarcinoma), efforts in the field of precision medicine have not yet...
demonstrated consistent clinical activity in glioblastoma. Several factors may explain such disappointing results. A central element of precision medicine is the matching of a selective drug and its mechanism of action using a robust biomarker (e.g., a molecular assay defining a specific biologic subgroup) to select patients that are expected to benefit from the drug (‘selecting the right drug for the right patient’). Before evaluation in large trials, scientists and investigators should provide: (i) strong evidence of antitumor activity in disease-relevant models [200] and (ii) proof-of-concept (i.e. demonstration of the feasibility) as well as evidence of effective target modulation in early phase trials. In glioblastoma, few if any trials that evaluated targeted therapies have met these preliminary requirements.

As far as target relevance and selection are concerned, most of the trials had not implemented molecular enrichment for patient selection. It is likely that most patients have received investigational agents in the absence of the relevant target in their tumor. Defining relevant targets is often challenging. Although early studies suggested that EGFR and PTEN status could predict response to EGFR-targeted therapies [201, 202], outcome was not correlated with the presence of EGFR amplification, EGFRvIII, PTEN loss or other molecular alterations in subsequent studies, and molecular predictors for the efficacy of EGFR targeted therapies remain undetermined. Future precision medicine studies should more largely implement systematic molecular characterization, including assessment of non-invasive biomarkers [203, 204], which will theoretically enable physicians to identify the most relevant targets for each patient, and allow further correlation of molecular profile with outcome (Figure 2).

In trials that have failed despite molecular enrichment [50], other potential sources of failures have to be considered. As previously mentioned, the marked heterogeneity and plasticity of glioblastoma cells are likely major factors mediating the currently observed resistance to targeted therapies [31, 40, 205]. As an illustration, in a phase II trial, analyses of tissues from glioblastoma patients treated with gefitinib before debulking surgery revealed significant intratumoral accumulation of gefitinib associated with dephosphorylation of EGFR, while downstream canonical pathways were not significantly dephosphorylated when compared with untreated controls [31, 40, 206]. This indicated concomitant activation of redundant cell signaling pathways, a resistance mechanism observed in EGFR-driven glioma models [205]. This clearly implies that exploring combinations of targeted therapies to avoid emergence of resistant subclones is needed (Figure 1). Moreover, future studies should explore approaches that have the potential to more broadly inhibit tumor cell growth and survival [207, 208]. Agents that more broadly target pathways rather than single mutation variants have the potential to improve outcome in a much wider population of patients, even in the absence of actionable mutation targets identified by genomic profiling. As an illustration, novel MDM2 inhibitors have been reported to inhibit the growth of TP53-wild-type glioblastoma PDCLs, regardless of the tumor MDM2 amplification status [117, 118]. However, such approaches are expected to go along with more side effects. Other examples include synthetic lethal approaches and immunotherapy, which are investigated in large trials (Table 3).

Regarding drug relevance, most of the tested agents were neither primarily designed to inhibit alterations that are specific to glioblastoma, nor developed for targeting tumors located in the brain. Most currently available agents display inadequate pharmacokinetic properties due to poor crossing of the BBB [209–211]. The BBB is universally disrupted in glioblastomas but not necessarily within more infiltrative non-enhancing areas of the tumor. Given this mixed BBB setting, novel agents should be optimized for brain penetration. Other approaches include the use of tailored regimens (e.g. higher doses in pulsed schedules) and other strategies to actively break down the BBB (e.g. transient opening of the BBB by pulsed ultrasound) [212, 213], which may improve drug delivery and target inhibition using agents that are unlikely to adequately penetrate the tumor. In this

Figure 2. Current implementation of precision medicine in glioblastoma. Practical implications of implementing precision medicine approaches in glioblastoma are depicted in this figure. Appropriate molecular profiling requires analysis of tumor tissue from the relapsed tumor. Further steps include target identification and selection, and treatment selection. Main limitations include difficulties in obtaining tumor tissue from relapse, target prioritization, and availability of optimal drugs in the context of CNS disease and related molecular alterations. This figure features pictures from ‘Servier medical art’ by Servier, used under Creative Commons Attribution 3.0 France.

<table>
<thead>
<tr>
<th>Examples of ongoing precision medicine trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Recurrent glioblastoma: MOSCATO 02 (NCT01566019), MATCH-RR (NCT02517892), NCI-IMPACT (NCT018023784), NCI-MATCH (NCT02465060), IMPACT (NCT00851032), MOST (NCT02029001), SHIVA (NCT01771458)</td>
</tr>
<tr>
<td>• Newly diagnosed glioblastoma: INSIGHT (NCT02977780)</td>
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<table>
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<tr>
<th>Collection of tissue samples</th>
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<tbody>
<tr>
<td>Tumor tissue Liquid biopsies</td>
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<table>
<thead>
<tr>
<th>Molecular characterization</th>
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<tbody>
<tr>
<td>• Favor multiplex genotyping assays to single target analyses</td>
</tr>
<tr>
<td>• Integrate analyses from multi-omics data to reveal potential ‘compound’ driver aberration profiles of relevance</td>
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<table>
<thead>
<tr>
<th>Therapy assignment</th>
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</thead>
<tbody>
<tr>
<td>• Actionable target: clinical trial</td>
</tr>
<tr>
<td>• No actionable target: pathway inhibitor trials or standard of care</td>
</tr>
<tr>
<td>• Efficacy assessment correlated with molecular biomarker analysis during or after the trial</td>
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<tr>
<th>Experimental validation</th>
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<tbody>
<tr>
<td>• Establish stable patient-derived models</td>
</tr>
<tr>
<td>• Validate potential drivers (cell viability assays, in vivo screens), characterize novel variants</td>
</tr>
<tr>
<td>• Predict patient’s response to therapy</td>
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</table>
context, having a molecular assay that confirms effective modulation of the target in the tumor is essential; otherwise conclusions on relevance of the target will remain elusive. Novel trial designs should more often incorporate tissue biomarkers collection during treatment, enabling evaluation of pharmacodynamics markers.

Novel biomarker-driven trial designs

Overall, considering the lack of clear demonstration of the benefit of targeted therapies in glioblastoma, proof-of concept in well molecularly characterized populations should be established in early phase and small-randomized phase II trials before further evaluation in registration trials. Academic groups and industry should collaborate in order to identify: (i) the best targets, drugs/combinations to be tested in clinical trials; (ii) the best population and (iii) the best biomarkers. Within the context of more precise and systematic molecular characterization of glioblastoma and increasing availability of novel targeted therapies, novel trial designs will be essential to more rapidly test agents. Practical implications for such precision medicine studies are represented in Figure 2.

A popular design is the ‘basket trial’ that involves screening of patients with cancer independent of tumor histology, for recruitment of a specific and often molecularly-defined population. A recently reported basket phase II trial evaluating vemurafenib in several BRAFV600E, mutant non-melanoma tumors reported responses in high-grade glioma patients [105]. Similarly, crizotinib is currently investigated in MET-amplified glioblastomas (NCT02034981) as part of a larger trial with 23 molecularly defined cohorts. However, basket trials require robust preclinical studies to identify relevant biomarkers that will predict treatment response with high confidence, and well-established diagnostic assays available in real-time for patient selection [32, 214–220] (listed in supplementary Table S1, available at Annals of Oncology online). Moreover, such trial designs can present a major challenge when the molecular alterations in question are rare, requiring such trials to screen and reject a high number of patients who are then disappointed.

Other new approaches are multi-arm ‘master protocol’ and ‘umbrella’ trials, which most commonly involve screening for multiple targets [221], arms and agents, and yield added benefit that a higher proportion of patients may enter into the trial once screened. Such trials may include randomization between ‘standard’ and ‘molecularly tailored’ treatment arms, allowing assessing the utility of precision medicine approaches. These designs have been aided by translation of modern methods of high-throughput multiplex diagnostic assays, allowing to simultaneously measuring a host of targets using platforms such as targeted exomes or CGH/SNP arrays [208, 222]. These are now commonplace in an increasing number of centers and aid designing novel trials based on systematic molecular screening programs for treatment stratification (Figure 2). As an illustration, personalized medicine trials such as MOSCATO 02 (NCT01566019) and INSIGHT (NCT02977780) studies are currently evaluating the feasibility and the utility of genomic profiling to inform treatment decisions in patients with glioblastoma.

Conclusion

An improved understanding of the molecular pathways that drive malignancy in glioblastoma has led to the development of various biomarkers and several agents targeting specific molecular pathways in malignant cells. The concept of precision medicine driven by molecular stratification for the treatment of glioblastoma is appealing and scientifically sound; however, no evidence has yet demonstrated an improved patient outcome within the context of this disease, likely as a result of both scientific and logistical challenges that have hampered the success of clinical trials. The identification of relevant driver molecular events and highly bioactive and specific drugs remain the biggest challenges. With the recent incorporation in clinical practice of modern methods allowing molecular characterization and appropriate stratification of patients, there is hope that novel trials evaluating targeted therapies may be more effective. Identification of relevant targets, compounds and biomarkers for appropriate patient selection during early phase trials are essential for successful development of novel therapies.

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