Systemic Treatment of Recurrent Meningioma

Simo M, Izquierdo C, Bruna J

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Marta Simó, Cristina Izquierdo, Jordi Bruna

Abstract: Meningioma is the most frequently diagnosed primary brain tumour. Although only a subset of meningioma patients suffer recurrence after standard therapy, these patients require further rescue treatment. Owing to the fact that meningioma over-expresses a great number of potential therapeutic targets, some systemic therapies have been evaluated in recurrent meningioma patients. Cytostatic agents, including combined chemotherapeutic regimens, hydroxyurea and temozolomide, are generally ineffective. Immuno-therapy and hormonal therapy with somatostatin analogues have been suggested as potential therapeutic agents, even though studies have presented contradictory results. Recently, several studies using targeted therapies, such as epidermal growth factor receptor (EGFR), platelet-derived growth factor receptor (PDGFR), and vascular endothelial growth factor (VEGF) inhibitors, showed early promising results. However, additional long-term results are still under evaluation. Furthermore, the combination of various medical therapies, such as hydroxyurea and a PDGFR inhibitor, appears to hold some promise. This review provides an overview of the current rationale and evidence base for the various medical therapy approaches tested.

Key words: meningioma, systemic treatment, chemotherapy, immunotherapy, hormonal therapy, targeted therapies

Introduction

Meningioma is the most frequently diagnosed primary brain tumour, accounting for nearly 35.5% of all primary brain tumours [1]. The prevalence of pathologically confirmed meningioma is estimated to be approximately 79.5/100,000 with an incidence rate of 7.1/100,000/year in the United States [1]. Meningioma is more than twice as common in females than in males (female:male ratio: 2.2:1) and it is also more common in the black population (black:white ratio 1.2:1). Moreover, the incidence increases progressively with age [1].

The majority of meningiomas are classified according to the World Health Organization (WHO) as grade I or so-called benign meningioma (nearly 80%). They present a prolonged progression-free survival (PFS) and overall survival (OS) (PFS and OS of 90% at 5 years). In contrast, high-grade meningioma, including atypical or WHO grade II and anaplastic or WHO grade III, differ in important aspects from their benign counterparts [2]. They represent up to 20–35% of all meningiomas, largely WHO grade II (approximately 20–30%). WHO grade-III meningioma represents only approximately 2% of all meningiomas. High-grade meningiomas exhibit an earlier peak incidence, with a small male predominance, and they present a worse PFS (60% and 30% at 5 years, for grades II and III, respectively) and OS (80% and 40% at 5 years for grades II and III, respectively) [3–5]. Atypical meningiomas carry a 7–8-fold increased risk of recurrence and about a 2-fold increased risk of death at 3–5 years compared to benign meningioma [3, 6].

Although there are scarce data regarding meningioma aetiology, 2 risk factors, ionizing radiation and genetic predisposition [7], have been described. Genetic aberrations such as focal chromosomal deletion of the NF2 (type-2 neurofibromatosis) gene on chromosome 22 and other more complex genetic changes have been associated with sporadic meningioma. Moreover, the complexity of genetic aberrations clearly increases with tumour grade [8].

Meningioma results from a clonal outgrowth derived from arachnoid cap cells and it presents some differential facts compared to other brain tumours. First, the natural history of meningioma is relatively unknown. This is due to the fact that meningioma has a prevalence of nearly 3% of subclinical disease as suggested by autopsy studies, and it is frequently discovered incidentally, introducing a detection bias [8]. Second, research regarding the molecular pathogenesis has been limited in comparison to gliomas. All these disadvantages, together with a lack of data from prospective series, make meningioma research a challenging area of study.

Standard therapy for meningioma includes extensive surgical resection for grade I followed by radiation therapy at front line for high-grade meningioma and at recurrence for grade I [9]. Although radiation therapy following surgical resection is the standard and recommended therapy for high-grade meningioma, there is still some controversy among studies [9]. Two currently ongoing phase-II trials (EORTC 22042-26042) are expected to provide better evidence to define optimal therapy in high-grade meningioma patients. Recurrence after completion of both therapies is managed by resection or re-irradiation when feasible [10, 11]. Unfortunately, there is no well-established treatment for meningioma patients with a good performance status who suffer recurrence after completion of these therapies. However, meningiomas have some particularities that make them susceptible and potential good candidates to respond to systemic therapies. The tumour is located outside the blood-brain barrier, it presents high vascularity supply, and it over-expresses a variety of potential therapeutic targets, including growth factors and their receptors, such as PDGF, EGF, and IGF, angiogenesis factors such as VEGF and VEGF receptor, and hormonal receptors such as oestrogen, progesterone, androgen, growth hormone, and somatostatin receptors. In this setting, several approaches have been assessed, although most of them have yielded disappointing results [12]. Nevertheless, 3 of these tested systemic treatments—hydroxyurea, alpha-interferon, and somatostatin analogue—are recommended for the treat-
The aim of the present review is to provide an up-to-date survey of the advances of systemic treatments in recurrent meningioma patients.

### Systemic Therapies

Several systemic therapies have been evaluated in recurrent meningioma patients, especially over the last 10 years. The systemic treatment attempts may be grouped according to the mechanism of action and the targets of the drug or combination of drugs assessed. The most relevant clinical trials are summarized in Table 1.

#### Chemotherapy

Treatment strategy using classic systemic cytostatic drugs has been based on 3 different approaches. First, the drugs and the chemotherapy schedules tested were selected according to the activity and the results obtained in experimental studies. Secondly, assuming that a meningioma has histopathogenic similarities with soft-tissue sarcomas, combined chemotherapeutic regimens used in these patients were reproduced in meningiomas. Lastly, chemotherapy regimens normally employed in glioma treatment have also been explored. Unfortunately, the antineoplastic agents studied, presented very limited results [26–29].

The first evidence from testing chemotherapy in recurrent meningioma came from combined chemotherapeutic regimens, including ifosfamide and mesna [27], cisplatin and doxorubicin [26], cyclophosphamide, adriamycin, and vincristine (CAV [28]), and, more recently, high-dose chemotherapy (carboplatin, etoposide, and thiothepa) followed by mesna, including ifosphamide and mesna [27], cisplatin and mesna [27].

On the other hand, hydroxyurea (HU) is an antineoplastic drug that has demonstrated potent inhibition of cultured meningioma cells by inducing apoptosis in vitro [29]. The first phase-II trial with 4 recurrent meningioma patients resulted in prolonged disease-free survival (PFS at 6 months [PFS6] 100%) with a 50%-partial radiographic response [14]. After these promising preliminary results, several subsequent phase-II clinical trials in recurrent meningioma patients suggested modest efficacy with an acceptable toxicity profile. The interval of PFS6 in these studies was 13–77 months [30–36]. The most important limitation of these studies is that patients were neither previously treated with radiotherapy nor were the drugs administered concomitantly [30–36]. Conversely, a large retrospective case series study with recurrent grade-I and high-grade meningioma treated with HU after surgery and radiotherapy demonstrated a median PFS of 2 months with no radiographic responses [15, 16]. In 2012, a phase-II trial combining HU with imatinib, a PDGF inhibitor, was published [17]. Recurrent grade-I and high-grade meningioma patients were included. Although there were no radiographic responses, median PFS was 7 months (14 and 5.3 months for grade-I and high-grade meningioma, respectively) and median OS was 5.5 and 1.5 years for grade-I and high-grade meningioma, respectively. Thus, although these results are modest and not directly comparable, combined treatment seems better in terms of PFS and OS compared to the studies with HU alone. In addition, another phase-II trial combining HU with verapamil, a calcium channel antagonist, is ongoing (Table 2). Calcium channel blockers block the stimulatory growth effects by inhibiting calcium-dependent secondary messenger pathways of multiple growth factors, and it has been demonstrated that they increase the inhibitory growth

#### Table 1. Summary of the most relevant medical therapies tested in recurrent meningioma patients previously treated with surgery and radiotherapy.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Study design</th>
<th>n</th>
<th>WHO grade</th>
<th>PFS (months)</th>
<th>PFS (%)</th>
<th>OS (years)</th>
<th>RRR (%)</th>
<th>Best RR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxyurea [14]</td>
<td>Phase II</td>
<td>4</td>
<td>3/1</td>
<td>nr</td>
<td>100</td>
<td>nr</td>
<td>75</td>
<td>nr</td>
</tr>
<tr>
<td>Hydroxyurea [15]</td>
<td>Retrospective</td>
<td>60</td>
<td>60/0</td>
<td>2</td>
<td>10</td>
<td>nr</td>
<td>0</td>
<td>SD 35</td>
</tr>
<tr>
<td>Hydroxyurea [16]</td>
<td>Retrospective</td>
<td>35</td>
<td>0/35</td>
<td>2</td>
<td>3</td>
<td>nr</td>
<td>0</td>
<td>SD 43</td>
</tr>
<tr>
<td>Hydroxyurea and imatinib [17]</td>
<td>Phase II</td>
<td>21</td>
<td>8/13</td>
<td>7</td>
<td>62</td>
<td>5.5</td>
<td>0</td>
<td>SD 67</td>
</tr>
<tr>
<td>CPT-11 [18]</td>
<td>Phase II</td>
<td>16</td>
<td>16/0</td>
<td>5</td>
<td>0</td>
<td>nr</td>
<td>0</td>
<td>SD 81</td>
</tr>
<tr>
<td>Mifepristone [19]</td>
<td>Phase III</td>
<td>160</td>
<td>160/0</td>
<td>10</td>
<td>nr</td>
<td>nr</td>
<td>2</td>
<td>nr</td>
</tr>
<tr>
<td>Interferon-[20]</td>
<td>Phase II</td>
<td>35</td>
<td>35/0</td>
<td>7</td>
<td>54</td>
<td>0.7</td>
<td>0</td>
<td>SD 74</td>
</tr>
<tr>
<td>Octeotride [21]</td>
<td>Phase II</td>
<td>16</td>
<td>8/8</td>
<td>5</td>
<td>44</td>
<td>0.6</td>
<td>31</td>
<td>PR 31</td>
</tr>
<tr>
<td>Octeotride [22]</td>
<td>Phase II</td>
<td>12</td>
<td>3/9</td>
<td>4</td>
<td>17</td>
<td>2.7</td>
<td>0</td>
<td>SD 75</td>
</tr>
<tr>
<td>Imatinib [23]</td>
<td>Retrospective</td>
<td>9</td>
<td>1/8</td>
<td>16</td>
<td>67</td>
<td>3.5</td>
<td>0</td>
<td>SD 78</td>
</tr>
<tr>
<td>Bevacizumab [24]</td>
<td>Retrospective</td>
<td>15</td>
<td>0/15</td>
<td>6.5</td>
<td>44</td>
<td>1.3</td>
<td>0</td>
<td>SD 87</td>
</tr>
<tr>
<td>Bevacizumab and chemotherapy [25]</td>
<td>Retrospective</td>
<td>14</td>
<td>6/8</td>
<td>18</td>
<td>86</td>
<td>nr</td>
<td>7</td>
<td>SD 79</td>
</tr>
</tbody>
</table>

WHO: World Health Organization; PFS: median progression-free survival; PFS6: progression-free survival rate at 6 months; OS: median overall survival; RRR: rate of radiographic response; Best RR: best radiographic response; nr: not reported; SD: stable disease; PR: partial response.
In summary, all cytostatic-agent studies in recurrent meningioma patients have proved ineffective. Preliminary hydroxyurea phase-II and case series studies obtained the most promising results. However, this benefit has not been demonstrated in further studies. The combination of hydroxyurea and imatinib showed the best results in a well-designed phase-II trial.

**Immunotherapy**

Interferon-α (IFN-α) is a biologic agent with efficacy in a variety of systemic malignancies due to its antiproliferative and antiangiogenic activity [45]. Moreover, preclinical studies have documented that IFN-α inhibits the growth of cultured human meningioma cell lines [46]. Based on this rationale, small clinical studies using IFN-α in patients with recurrent meningioma were conducted, resulting in promisingly long stabilization periods [47, 48]. Hence, in 2008, Chamberlain et al conducted a phase-II trial in grade-I recurrent meningioma patients treated with IFN-α administered subcutaneously every other day. This resulted in moderate toxicity but with promising outcome results. Median PFS was 7 months and PFS6 was 54 %. However, no patients presented a radiographic response and stable disease was the best response in 74 % of patients. Thus, this study demonstrated moderate but noteworthy results in grade-I recurrent meningioma patients [20]. Nevertheless, as mentioned above, due to the unknown natural history of meningioma, especially the growth ratio of recurrent meningiomas, these results have to be interpreted with caution.

**Hormonal Therapy**

Progesterone receptors (PR) are more frequently expressed in grade-I meningioma (in nearly 80 %) and their presence diminishes with higher histological grade. Likewise, the PR status has been associated with specific gene expression located on the long arm of chromosome 22 near the NF2 gene [49]. This means that meningioma patients with a positive PR status have significant up-regulation of these genes and patients with negative PR status are more likely to have a 22q loss [49]. In this setting, several studies have evaluated the efficacy of

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**Table 2.** Summary of the most relevant ongoing trials in recurrent meningioma patients. Source: clinicaltrials.gov

<table>
<thead>
<tr>
<th>Agent</th>
<th>Study</th>
<th>Mechanism of action</th>
<th>Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxyurea</td>
<td>Phase II</td>
<td>Ribonucleotide reductase inhibitor</td>
<td>UNICANCER</td>
</tr>
<tr>
<td>Hydroxyurea plus verapamil</td>
<td>Phase II</td>
<td>Ribonucleotide reductase inhibitor</td>
<td>University of Utah</td>
</tr>
<tr>
<td>Interferon-α</td>
<td>Phase II</td>
<td>Antiproliferative and antiangiogenic activity</td>
<td>M.D. Anderson Cancer Center</td>
</tr>
<tr>
<td>Pasireotide (SOM230B/SOM230C)</td>
<td>Phase II</td>
<td>Somatostatin analogue</td>
<td>National Cancer Institute</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>Phase I, II</td>
<td>EGFR inhibitor</td>
<td>Sidney Kimmel Comprehensive Cancer Center</td>
</tr>
<tr>
<td>Gefinitib</td>
<td>Phase II</td>
<td>EGFR inhibitor</td>
<td>Memorial Sloan-Kettering Cancer Center</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>Phase II</td>
<td>VEGFR and PDGFR inhibitors</td>
<td>Univerity Mageburg</td>
</tr>
<tr>
<td>Imatinib mesylate</td>
<td>Phase II</td>
<td>PDGFR inhibitor</td>
<td>Istituto Scientifico H. San Raffael</td>
</tr>
<tr>
<td>Imatinib mesylate</td>
<td>Phase II</td>
<td>PDGFR inhibitor</td>
<td>Northwestern University</td>
</tr>
<tr>
<td>Hydroxyurea</td>
<td>Phase II</td>
<td>Ribonucleotide reductase inhibitor</td>
<td>Sarah Cannon Research Institute</td>
</tr>
<tr>
<td>Valatanib</td>
<td>Phase II</td>
<td>VEGFR and PDGFR inhibitors</td>
<td>Northwestern University</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Phase II</td>
<td>VEGF antibody</td>
<td>M.D. Anderson Cancer Center</td>
</tr>
<tr>
<td>Everolimus</td>
<td>Phase II</td>
<td>mTOR inhibitor</td>
<td>National Cancer Institute</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Phase II</td>
<td>VEGF antibody</td>
<td>Burzynski Research Institute</td>
</tr>
<tr>
<td>Ispinesib</td>
<td>Phase I</td>
<td>Inhibitor of kinesin spindle protein</td>
<td></td>
</tr>
<tr>
<td>Antineoplasonta</td>
<td>Phase II</td>
<td>Modulates ras oncogene, gene PS3</td>
<td></td>
</tr>
</tbody>
</table>

EGFR: epidermal growth factor receptor; VEGFR: vascular endothelial growth factor receptor; PDGFR: platelet-derived growth factor receptor
Preclinical studies have identified aberrant expression of critical signalling molecules in meningioma cells [66, 67]. Based on this approach, several studies using targeted molecular agents have recently been performed in recurrent meningioma patients. These trials have been classified into 5 groups depending on their main target: (1) cellular signal transduction tyrosine kinases, (2) intracellular signalling kinases, (3) tumour vasculature, (4) other molecular targets, and (5) multitargeted or combined therapies [68].

Targeted Molecular Agents

Targeted molecular agents are drugs against tyrosine kinases or their receptors. Tyrosine kinases are a group of protein kinases that are critical to many cellular signal transduction pathways involved in cell proliferation, growth, survival, adhesion, motility, and differentiation [69]. In addition, receptor tyrosine kinases are transmembrane proteins containing an extracellular binding domain and an intracellular kinase domain that activates intracellular signalling pathways. This group includes the epidermal growth factor receptor (EGFR) and the platelet-derived growth factor receptor (PDGFR).

The EGFR is over-expressed in > 60% of meningiomas and studies in vitro have demonstrated that EGF and TGF-α activate these receptors, thereby stimulating meningioma growth [44, 63, 70–75]. Recently, 2 phase-II trials with 2 EGFR inhibitors, erlotinib and gefitinib, in recurrent grade-I and high-grade meningioma patients did not find any objective radiographic responses. Median PFS of the analysis of pooled data in both studies was 2.5 months with a PFS6 rate of 25% for grade-I and 29% for high-grade meningioma, respectively. These studies concluded that neither gefitinib nor erlotinib alone appeared to have a significant activity against recurrent meningioma [76].

In addition, most meningiomas also express PDGF and PDGF receptor [77–80]. PDGFR is a fundamental driver of cell proliferation in many tumours, thus supporting meningioma cell growth and maintenance. Expression levels of both PDGF and PDGFR are higher in atypical and malignant meningiomas than in benign meningiomas [78]. Moreover, meningioma cell culture studies provide evidence that the administration of PDGF results in the stimulation of tumour growth and activation of intracellular signalling kinases, while proliferation of meningioma cells can be inhibited by anti-PDGF antibodies [81–83]. The first phase-II study with a PDGFR inhibitor, imatinib mesylate, conducted in grade-I and high-grade recurrent meningioma patients, did not show any radiographic response. Median PFS was 2 months and the PFS6 rate was 29% (45% for grade I but 0% for high grade); there was, therefore, minimal activity against recurrent meningiomas [84]. Conversely, a recent retrospective study conducted in preselected recurrent grade-I and high-grade meningioma patients with positive immunohistochemical PDGFR staining confirmation and treated with imatinib showed promising results. Although no complete or even partial radiographic response was observed, median PFS was 16 months with a PFS6 rate of 67% [23].

The second group of targeted therapies includes drugs that interact with intracellular kinases, a family of enzymes involved in the phosphorylation of serine and threonine residues of their substrates. Many of these kinases serve as intermediaries in important signalling pathways. This group includes phosphatidylinositol 3-kinase/AKT PI3K/Akt inhibitors, ras-mitogen-activated protein kinase (MAPK) inhibitors and protein kinase C inhibitors. MAPK and PI3K/Akt path-
way have been demonstrated to play a role in signal transduc-
tion in meningioma, especially in benign meningioma [82,
85–87]. However, no clinical studies have been reported with
drugs concerning these intracellular signalling kinases in
meningioma patients.

The third group of targeted therapies is related to tumour an-
giogenesis. This process is critical for the growth of many
solid tumours and meningiomas, which are highly vascular
tumours that derive their blood supply predominantly from
meningeal vessels [88]. Thus, the inhibition of angiogenesis
is a potentially important approach in treating meningioma
patients. Vascular endothelial growth factor (VEGF) plays a
central role in tumour angiogenesis, and there is increasing
evidence that inhibition of soluble VEGF or VEGFR can lead
to significant anti-tumour effects [89, 90]. VEGF and VEGFR
are expressed in meningiomas and the level of expression in-
creases with the tumour grade [91–93]. VEGF expression is 2-
fold increased in atypical meningiomas and 10-fold in malig-
nant meningiomas compared to benign meningiomas [91]. Af-
ter the first case report of partial remission of a high-grade re-
current meningioma induced by anti-angiogenic therapy, 2
clinical studies using bevacizumab were reported on in 2012
[24, 25, 94]. Bevacizumab is a monoclonal antibody that inhib-
its VEGF with demonstrated activity in other systemic cancers
as well as in glioblastoma [89, 90, 95]. A retrospective case se-
ries study of high-grade recurrent meningioma patients treated
with bevacizumab demonstrated a median PFS of 6.5 months
with a PFS6 rate of 44 %. However, no complete or partial ra-
diographic responses were observed, although minor response
was documented in 2 patients. In terms of toxicity, be-
vacizumab was relatively well-tolerated although 3 patients
(20 %) developed non-fatal intratumoural haemorrhage. These
results suggest that bevacizumab may be an effective thera-
peutic approach for high-grade recurrent meningioma patients
[24]. The second retrospective case series study in recurrent
meningioma patients reported this year also supported the use
of bevacizumab for this indication [25]. In this study, patients
received bevacizumab alone (n = 4) or combined with che-
motherapy (n = 10), including etoposide- (n = 6) or temo-
zolomide-based regimens (n = 4), and demonstrated a median
PFS of 17.9 months with a PFS6 rate of 85.7 %. However, no
complete radiographic responses were observed, although
one patient treated with bevacizumab and etoposide presented
partial response. Despite these promising results, this study
has several limitations. It was retrospective in nature and the
majority of patients received chemotherapy plus bevac-
uzumab.

Following this line, the multtargeted agents sunitinib and
vatalanib, which inhibit several kinases such as VEGFR and
PDGFR, have demonstrated strong cytostatic and anti-migra-
tory effects on human meningioma cells [96]. To date, pre-
liminary results have been published for 2 phase-II trials. The
first study included mostly recurrent high-grade meningioma
patients treated with sunitinib. This study showed a median
PFS of 4.6 months with a PFS6 rate of 36 %, with one patient
demonstrating partial radiographic response. However, pa-
ients presented important toxicities (34 events of grade-3–4
toxicity) [97]. The other phase-II trial tested vatalanib in high-
grade recurrent meningioma patients and observed a median
PFS of 3.7 months with a PFS6 rate of 37.5 %. However, one

patient presented a partial response, and vatalanib seems to
have been better tolerated (10 events of grade-3–4 toxicity) than sunitinib [98].

Finally, other therapies designed to act on new molecular tar-
gets involved in tumourigenesis such as IGFR, histone
deacetylases, ubiquitin-proteasome system, heat shock pro-
teins, cytokines like TGF-β, and DNA repair proteins have not
been evaluated in recurrent meningioma patients so far al-
though one recent report has documented a response in an in-
cidental meningioma of a patient treated with chemotherapy
combined with an IGFR inhibitor [99].

## Conclusions

Recurrent meningioma patients are a relevant although not
very large group of patients who have made recourse to sur-
gery, radiation therapy, and even to radiosurgery. Therefore,
these patients require further treatment options. In this setting,
systemic drugs have a potential role in the therapeutic arma-
mentarium. Up to now, most studies have shown disappointing
or limited results with only one drug tested in phase-III trials.

Clinical trials in meningioma have several unresolved prob-
lems, making it difficult to draw clear conclusions. One limi-
tation is the heterogeneity of the patients included. Almost all
studies assumed that the behaviour of recurrent grade-I me-
nangiomas was similar to grade II or III, though in fact the
natural history and the growth rate of untreated meningioma
is unknown. This point becomes crucial when the endpoint of
the phase-II trial is PFS or the PFS6 rate or when a biological
agent is tested, the main action of which is the slowing down
or blocking of tumour growth. Thus, based on this back-
ground, the radiological response rate would be a more reli-
bable endpoint than PFS.

Alternatively, the use of comparative randomized phase-II de-
signs may be in order. Actually, the control group of the only
phase-III study published showed a better PFS than the most
promising phase-II studies. However, the details of this study
are scarce because it has only been reported in a congress ab-
stract. Moreover, data provided by retrospective studies are
not useful as screening proof, because PFSs of phase-II stud-
ies are clearly worse than the inevitably biased retrospective
studies.

Even though several studies have provided in recent years bet-
ter understanding of the molecular characteristics of meningi-
oma, identifying novel targets for therapy, researching molecu-
lar pathogenesis, and learning about the critical molecular
changes driving tumour growth need to be addressed if we want
to increase the likelihood of success of either single or com-
combined drug selection.

In conclusion, although systemic therapy research on recur-
rent meningioma patients has substantially increased over the
last years, further basic and clinical research is needed to
clearly elucidate the most effective systemic therapy options
for recurrent meningioma patients.

## Conflict of Interest

The authors state that no conflict of interests exists.
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