ABSTRACT

Purpose: Meningiomas are the most common primary central nervous system tumor. Many studies have investigated systemic therapy agents for treating meningiomas, but no study has systematically evaluated these agents in a comparative or comprehensive manner. Our goal was to investigate the recent systemic therapy agents used to treat meningioma and to compare outcomes such as progression-free survival and overall survival.

Methods: A systematic literature review was performed to investigate systemic therapy agents that are being used to treat meningioma tumors. The PubMed database was used for this review and articles published from 7/4/2011 to 7/4/2021 were evaluated. The exclusion criteria were animal and cell line studies, case reports, review articles, articles in a foreign language, and articles not related to meningioma or to systemic therapy agents.

Results: 163 articles were initially evaluated. After excluding 152 articles that did not fit the inclusion criteria, 11 articles exploring 14 different systemic therapy agents were included and compared, focusing on the outcomes of progression-free survival and overall survival. According to our findings, Bevacizumab has the most promising results as it is associated with reducing peri-tumoral edema and has the highest progression-free survival at six months of 86%.

Conclusion: This article evaluated systemic therapy agents used to treat meningioma tumors. Bevacizumab has the most promising results overall. However, further studies are needed to evaluate its efficacy and possible side effects among a larger population of patients with different grades, locations, and responses of the meningioma tumors to Bevacizumab.

Keywords: Meningioma, systemic therapy, Bevacizumab, central nervous system tumors

Introduction

Meningiomas are the most common primary central nervous system (CNS) tumor. There are three grades of meningiomas: Grade I is benign, Grade II is “atypical,” and Grade III is “anaplastic.” There is a gap in the literature about approaching meningioma with systemic therapy. To our knowledge, at the time of writing this article, there is no recent systematic review that has examined systemic therapy agents for the treatment of meningiomas. Several different systemic therapy agents have been examined for treating meningiomas and other CNS tumors, including Bevacizumab, hydroxyurea, interferon alpha, Everolimus, tyrosine kinase inhibitors and immunotherapy agents.

Because meningiomas naturally overexpress somatostatin receptors (SSTRs), radiolabeling somatostatin analogs can be used as an imaging tool or therapeutic agent. The process of formation of a new blood vessel is called angiogenesis, which is mainly mediated by vascular endothelial growth factor (VEGF). Developing evidence supports the role of VEGF-mediated angiogenesis among meningiomas, so targeting VEGF can lead to decreased tumor vascularity and has an antitumor effect. Bevacizumab is a humanized monoclonal antibody that counteracts the activity of VEGF. The Food and Drug Administration (FDA) approved Bevacizumab to be used clinically in recurrent glioblastoma, metastatic colorectal cancer, metastatic colorectal cancer, and several other cancers. Another systemic therapy agent, hydroxyurea, was used historically primarily...
as a chemotherapy agent to treat diverse solid tumors and leukemias\textsuperscript{11,12} due to its early effectiveness as an antineoplastic agent. Over the next several decades, hydroxyurea use expanded to chronic myelogenous leukemia, psoriasis, melanoma, ovarian cancer, polycythemia vera, and even HIV\textsuperscript{13-14}. Hydroxyurea acts as an inhibitor of DNA synthesis,\textsuperscript{14} inhibiting the growth of meningioma cells and inducing apoptosis.\textsuperscript{15,16}

The therapy agent interferon alfa (INF-a) is a pleiotropic immune modulator that has also demonstrated antiproliferative activity in preclinical studies.\textsuperscript{17} It works primarily via angiostatic mechanisms in tumors by inhibiting the growth of tumor cells and inducing apoptosis.\textsuperscript{18-23} INFs show remarkable results in treating certain hematological malignancies and solid tumors, such as craniopharyngiomas.\textsuperscript{19,20} There are some reports that it affects meningiomas in vivo and in vitro as well.\textsuperscript{21,22}

Furthermore, Everolimus is an immunosuppressive macrolide that inhibits the kinase activity of mammalian target of rapamycin (mTOR) and reduces Vascular Endothelial Growth Factor (VEGF) production and therefore reducing tumor angiogenesis.\textsuperscript{23,24} This mechanism of action may be relevant to meningiomas because prospective clinical trials have demonstrated that inhibition of VEGF has therapeutic efficacy in meningioma tumors.\textsuperscript{25,26}

There are multiple different tyrosine kinase inhibitors, some of which have been studied in the context of treatment of meningioma tumors, including Vatalanib, Sunitinib and Imatinib. Tyrosine kinase inhibitors act by inhibiting receptor signaling, which eventually also inhibits cell growth, proliferation, differentiation, and angiogenesis of tumor cells.\textsuperscript{27} Vatalanib is a novel oral, small antiangiogenic molecule belonging to the chemical class of aminophthalazines.\textsuperscript{28} In addition to its ability to inhibit VEGF receptors (VEGFRs), it also inhibits three other kinases belonging to the family of protein tyrosine kinases.\textsuperscript{29,29} This mechanism of action could carry antitumor activity. Sunitinib is approved for the treatment of renal cancer, pancreatic neuroendocrine tumors, and the treatment of imatinib-resistant gastrointestinal stromal tumors.\textsuperscript{30} It has a low molecular weight with a multi-target tyrosine kinase inhibitor (TKI) activity that does inhibit platelet-derived growth factor receptors (PDGF-Rs) and vascular endothelial growth factor receptors (VEGFRs). Tumor vascularity decreases by inhibiting these pathways, leading to cancer cell apoptosis, and inducing a tumor shrinkage.\textsuperscript{31} Imatinib was introduced in 2001 as a BCR-ABL1 tyrosine kinase inhibitor and was approved for the treatment of Chronic Myeloid Leukemia (CML).\textsuperscript{32} Its kinase inhibiting profile was known to include platelet-derived growth factor receptor (PDGFR); imatinib has been researched as a potential therapeutic alternative for recurrent meningiomas.\textsuperscript{33,33}

Meningiomas constitutively overexpress somatostatin receptors (SSTRs),\textsuperscript{4,34,42} so radiolabeled somatostatin analogs can be used for both imaging\textsuperscript{35,36} and therapy.\textsuperscript{7,23} Octreotide is a Somatostatin analog that has shown antitumor activity.\textsuperscript{38,39} Combining Everolimus with Octreotide LAR might enhance antitumor efficacy by simultaneously targeting upstream and downstream components of the mTOR pathway.\textsuperscript{40,41}

Targeting the programmed death 1 (PD-1) signaling axis is another approach for treating multiple malignancies.\textsuperscript{42} Nivolumab is an anti-programmed death-1 antibody\textsuperscript{43} approved for treating some types of cancers by targeting the PD-1 receptor. There is an association between tumor programmed death-ligand 1 (PD-L1) expression and the increased probabilities of therapeutic benefits from anti-PD-1 therapy for some cancers.\textsuperscript{44,45} In the meningioma tumor microenvironment, tumor cells and immune cells showed an expression of PD-L1,\textsuperscript{46} which is associated with meningioma grade and outcome.\textsuperscript{47,48}

Many studies have investigated individual systemic therapy agents used to treat meningioma, but to our knowledge no study has systematically evaluated the various agents used and compared the outcomes between the different systemic therapy agents. Our goal in this systematic literature review is to investigate the systemic therapy agents used to treat meningioma and to compare outcomes such as progression-free survival and overall survival.

Materials and Methods

A systematic literature review was performed to investigate systemic therapy agents that are being used to treat meningioma tumors. The PubMed database was used for this review and articles published from 7/4/2011 to 7/4/2021 were evaluated. The specific search terms used included the terms “meningioma”, “systemic therapy”, and relevant synonyms. The full search terms are listed in Supplementary Table 1.

The exclusion criteria were animal and cell line studies, case reports, review articles, articles in a foreign language (other than English), articles not related to meningioma, and articles not related to systemic therapy of meningioma. Outcomes of the included studies were compared, including progression-free survival (PFS), 6-month progression-free survival (PFS-6), 9-month progression-free survival (PFS-9), overall survival (OS), median survival, and 12-month overall survival (OS-12).

Results

One hundred and sixty-three articles were initially evaluated as part of this systematic review. After excluding 152 articles that did not fit the inclusion criteria, eleven articles exploring fourteen different systemic therapy agents were included (see PRISMA diagram in Figure 1).

Included studies

Eight of the eleven included studies are retrospective studies, while the remaining three studies are prospective. The total number of patients involved in this review from all of the included studies is 238 patients. Not all articles specify the gender of participants, but a total of 79 males and 102 females were included, as well as 57 patients with no gender listed. The ages of the patients ranged from 16 to 89 years, and there was a median follow-up time of 24 months. Fourteen systemic therapy agents were described and compared in this review. Table 1 summarizes the included studies.

Most studies evaluated included Bevacizumab as a therapeutic agent for meningioma tumors. Starting with the Bevacizumab article by Lou et al.,\textsuperscript{2} the authors retrospectively reviewed data for 14 patients diagnosed with recurrent meningioma who were managed with Bevacizumab either as a single systemic therapy agent (29% of patients) or as a combination with chemotherapy (etoposide, temozolomide plus sirolimus and temozolomide; 71% of patients). The PFS-6 was 86%.

Nunes and colleagues' retrospectively analyzed 15 patients with neurofibromatosis 2 (NF2) with 48 intracranial meningiomas, who were managed with Bevacizumab every two weeks with response determined by brain magnetic resonance imaging (MRI). The median follow-up time was 18 months. Radiographic response was seen in 29% of meningioma tumors (14/48
tumors). However, the anti-tumor effect was not durable in all tumors, with only 5/14 responding meningiomas maintaining a radiographic response at the last follow-up. The PFS-6 was 85%. Furtner et al. 49 examined Bevacizumab along with cytotoxic chemotherapy, somatostatin analogs, and tyrosine kinase inhibitors in 34 patients with a total of 57 meningioma lesions. Twenty-three patients (68%) had atypical meningiomas, and eleven patients (32%) had anaplastic meningiomas. Measurements of maximum tumor diameter and tumor volume were represented as average growth rates and further subdivided into values for pre-therapeutic lesions, therapeutic lesions, and post-therapeutic lesions. Overall, the mean tumor growth rates decreased by 51% for tumor diameter and 14% for tumor volume in the therapeutic period compared with the pretherapeutic period. Comparing the growth rates between the different therapy types, they found that the highest decrease of growth rate from the pre-therapeutic to the therapeutic period in patients treated with Bevacizumab (diameter: -80%, volume: -59%), followed by the subgroup of patients treated with chemotherapy (Hydroxyurea, Doxorubicin, Cyclophosphamide, Carboplatin, Etoposide, Vincristine; diameter: -54%, volume: +7%) and tyrosine kinase inhibitors (diameter: -40%, volume: -29%).

The fourth study that examined Bevacizumab was authored by Nayak and colleagues 50 and retrospectively studied 15 patients diagnosed with a typical or anaplastic meningiomas. These patients failed surgical and radiotherapeutic interventions before undergoing therapy with Bevacizumab. Treatment outcomes were assessed by analyzing the radiographic response according to response assessment in neuro-oncology (RANO) criteria as a standard, along with PFS-6, which was 43.8%, and the median OS, which was 15 months. Two of 15 patients demonstrated minor improvement in the enhancing component of the tumor, without reaching partial response. The remaining 13/15 patients had stable disease as their best response.

The next most frequent systemic therapy option that was evaluated in the studies in our review was tyrosine kinase inhibitors (TKIs). There were three TKIs included in our review: Vatalanib, 51 Sunitinib, 52 and Imatinib mesylate. 53 The total number of patients in all three studies was 74 patients: 25 patients examined with Vatalanib with ages ranging from 30 to 89 years, 11 patients with Sunitinib with ages ranging from 28 to 88 years and 18 patients with Imatinib with ages ranging from 42 to 74 years. Grade 2 meningiomas treated with Vatalanib had a PFS-6 of 64.3% and OS of 26 months, while the grade 3 meningiomashada PFS-6 of 37.5% and OS of 23 months. For Sunitinib, the median PFS was 9.1 months and median OS was 29.5 months. Finally, for Imatinib mesylate, the PFS-6 was 66.7% and median survival was 42 months.

The remaining systemic therapy agents, hydroxyurea, INF-a, nivolumab, and Everolimus/octreotide, were mentioned in a single study each. Hydroxyurea was studied by Mazza et al.; 24 in this study, hydroxyurea was investigated among 15 patients aged 18-75 years diagnosed with meningioma, without therapeutic indication for surgery, radiotherapy, or stereotactic radiosurgery. Patients received hydroxyurea either as a single systemic therapy agent (arm A: 8/15 patients) or as a combination with Imatinib (arm B: 7/15 patients). Arm A patients had a median PFS of 4 months, a PFS-9 of 0%, and median OS of 6 months. Arm B patients had a median PFS of 19.5 months, a PFS-9 of 75%, and median OS of 27.5 months. All patients were evaluated for response using MacDonald’s criteria; no objective response was observed in either arm. The best response was stable disease in 4 patients in arm A and 8 patients in arm B. This study showed that the combination of Imatinib with hydroxyurea resulted in the best outcomes.

Interferon alfa (INF-a) was retrospectively investigated among 35 patients aged 34 to 86 years old diagnosed with grade 2 or grade 3 recurrent meningiomas. 55 All patients had previous surgical or radiotherapeutic interventions and hydroxyurea before entering this study. INF-a was administered to all patients with the same dose and evaluated. The PFS-6 was 17%, and the median OS was 2 to 16 months.

Nivolumab was studied by Wenya et al.; 42 in this study, nivolumab was investigated among 25 patients aged 25 to 88 years old diagnosed with grade 2 or 3 meningiomas that had progressed after a surgical resection of the tumor. PFS-6 was 42.4% and median OS was 31 months.

The article by Andre et al. 52 examined 31 patients with ages ranging from 25 to 88 years old, diagnosed with grade 2 or 3 meningiomas that were managed with Sunitinib in 11 patients, or by a combination of Everolimus/octreotide in 14 patients. The PFS of patients treated with the combination of Everolimus/octreotide was 12.1 months and the OS was 36 months. Finally, Olivia et al. 56 examined various different types of systemic therapy agents. In this article, 11 patients with mean age of 39 years old (standard deviation of 12 years), with confirmed NF2 and multiple meningiomas were managed by radiolabeled somatostatin analogs. The PFS was 12 months and median OS was 37 months.

**Discussion**

After reviewing the literature, we identified various systemic therapy agents and treatment approaches for meningioma tumors. Some were examined for use as primary management, while other agents were used as adjuvant therapy. However, the data is limited, and more clinical trials are needed to illustrate the efficacy, outcomes, and possible side effects of systemic therapy agents among a larger population and different grades, locations, and responses of the meningioma tumors.

Bevacizumab is the systemic therapy agent that has been studied the most in our reviewed articles (in four included studies). 3, 23, 40, 50 The PFS-6 ranged from 43.8% to 86%, while the OS was 15 months in one study 50 and not mentioned for the other studies. One study 2 found that 12/14 patients with meningioma had a partial response or stable disease after treatment with Bevacizumab. Another study 1 of 15 patients with 48 meningiomas found that a radiographic response was seen in 29% of tumors (14/48 tumors). An additional study 49 of Bevacizumab and 3 other systemic therapy agents showed that in 34 patients, the mean tumor growth rates decreased by 51% for tumor diameter and 14% for tumor volume, and only Bevacizumab was associated with the shrinking of peritumoral edema volumes compared to other therapies. Thus, Bevacizumab treatment may be of particular clinical benefit in meningioma patients with symptomatic peritumoral edema and may help to decrease the symptomatic burden and corticosteroid need.

Three independent articles investigated three agents belonging to the tyrosine kinase inhibitor class: 49 Vatalanib, 51 Sunitinib, 52 and Imatinib. 53 There were overall a wide range of outcomes, with a PFS-6 ranging from 9.1% to 66.7% in the studies and with various degrees of response rates depending on whether the
TKIs were used individually or in combination with other agents such as Everolimus and octreotide. The wide range of outcomes could be clarified in the future if there were a greater number of patients with different tumor grades and sizes included in further studies.

From all of the evaluated systemic therapy agents, the highest PFS-6 recorded was 86% with Bevacizumab in the study by Lou et al. The highest median survival recorded was 42 months with Imatinib mesylate by Horak et al. Interestingly, the second highest median OS was 37 months with radiolabeled somatostatin analogs in the study by Olivia et al., with 6 out of 11 patients achieving disease stabilization with the use of this systemic therapy agent.

This review has several limitations. First, PubMed was the only database used to search the literature. Second, regarding the included systemic therapy agents, only Bevacizumab was explored in 4 recent studies, while the remaining systemic therapy agents were investigated in a single study each. Also, several studies have limited outcomes to compare; some studies are missing the PFS-6, others are missing the OS or median follow-up time. Limitations acknowledged, this systematic review provides a wide variety of outcomes and systemic agents to compare in the treatment of meningioma tumors, including PFS, PFS-6, PFS-9, OS, median survival & OS-12. This review article could therefore provide a basis for further research on this topic.

**Conclusion**

Meningiomas are the most common primary CNS tumor. Therefore, providing new, alternative approaches to the current guidelines for treatment is crucial. Systemic therapy agents are suitable for surgically inaccessible tumors or patients who cannot tolerate surgery or as adjuvant systemic therapy, to provide better outcomes for patients with meningioma. According to our findings in this review, Bevacizumab has the most promising results overall. It has the highest reported PFS-6 of 86% and helps to reduce peritumoral edema, which may help decrease the symptomatic burden of meningioma tumors and corticosteroid use and their associated side effects. However, further studies are needed to evaluate its efficacy and possible side effects among a larger population of patients with different grades, locations, and responses of meningioma tumors to Bevacizumab.

**Table 1 Summary of included studies**

<table>
<thead>
<tr>
<th>Authors, Year</th>
<th>Study design</th>
<th>No. patients/ gender</th>
<th>Median age (y) (range)</th>
<th>Type of systemic therapy</th>
<th>Median follow-up time (mo)</th>
<th>Outcome</th>
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<tr>
<td></td>
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<td>Sunitinib (11 patients)</td>
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<td>Median PFS: 12.1 months</td>
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<td>OS: 36 months</td>
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<td>Median PFS: 9.1 months</td>
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<td>OS: 29.5 months</td>
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<td>P</td>
<td>15 patients:</td>
<td>Group A: 68 (28-73)</td>
<td></td>
<td>Hydroxyurea (HU) with imatinib (7 patients) arm A</td>
<td>N/A</td>
<td>Arm A patients:</td>
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<td>(Arm A) 7 patients: M: 4 F: 3</td>
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<td>Group B: 68.5 (50-79)</td>
<td></td>
<td>Hydroxyurea (HU) (8 patients) arm B</td>
<td></td>
<td>Median PFS: 4 months</td>
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<tr>
<td>(Arm B) 8 patients M: 3 F: 5</td>
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<td>PFS-9: 0%</td>
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<td>Median OS: 6 months</td>
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<td>Arm B patients:</td>
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<td>Median PFS: 19.5 months</td>
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<td>PFS-9: 75%</td>
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<td>Median OS: 27.5 months</td>
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<tr>
<td>Authors, Year</td>
<td>Study design</td>
<td>No. patients / gender</td>
<td>Median age (y) (range)</td>
<td>Type of systemic therapy</td>
<td>Median follow-up time (mo)</td>
<td>Outcome</td>
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<tr>
<td>Emil Lou et al.² (2012)</td>
<td>R</td>
<td>14 patients: Gender not specified</td>
<td>53.5 (20–70)</td>
<td>Bevacizumab (29% of patients) Bevacizumab with chemotherapy (71% of patients)</td>
<td>21.8</td>
<td>PFS-6: 86% OS: N/A</td>
</tr>
<tr>
<td>Fabio P. Nunes et al.² (2013)</td>
<td>R</td>
<td>15 patients: M: 7 F: 8</td>
<td>29.5 (16-63)</td>
<td>Bevacizumab</td>
<td>18</td>
<td>PFS-6: 85% OS: N/A</td>
</tr>
<tr>
<td>Jeffrey J. Raizer et al.¹ (2014)</td>
<td>P</td>
<td>25 patients: M: 15 F: 10</td>
<td>59 (30-89)</td>
<td>Tyrosine kinase inhibitor PTK787/ ZK 222584 (PTK787)</td>
<td>N/A</td>
<td>Grade II Patients: PFS-6: 64.3% OS: 26 months</td>
</tr>
<tr>
<td>Julia Furtner et al.⁰ (2016)</td>
<td>R</td>
<td>34 patients: Gender not specified</td>
<td>N/A</td>
<td>Bevacizumab Cytotoxic chemotherapy Somatostatin analogues Tyrosine kinase inhibitors</td>
<td>N/A</td>
<td>PFS-6: N/A Median OS: N/A</td>
</tr>
<tr>
<td>Lakshmi Nayak et al.⁰ (2012)</td>
<td>R</td>
<td>15 patients: M: 8 F: 7</td>
<td>55 (34-81)</td>
<td>Bevacizumab</td>
<td>N/A</td>
<td>PFS-6: 43.8% Median OS: 15 months</td>
</tr>
<tr>
<td>Marc C Chamberlain et al.⁵ (2013)</td>
<td>R</td>
<td>35 patients: M: 16 F: 19</td>
<td>63 (36-86)</td>
<td>IFN-a</td>
<td>N/A</td>
<td>PFS-6: 17% Median OS: 2-16 months</td>
</tr>
<tr>
<td>Peter Horak et al.⁵² (2012)</td>
<td>R</td>
<td>18 patients: M: 4 F: 5</td>
<td>54 (42-74)</td>
<td>Imatinib mesylate</td>
<td>N/A</td>
<td>PFS-6: 66.7% Median survival: 42 months</td>
</tr>
</tbody>
</table>

**Abbreviations:** F = Female; INF-a = Interferon alfa; M = Male; MO = months; N/A = not applicable; OS = overall survival; OS-12 = 12-month overall survival; P = prospective; PFS = progression-free survival; PFS-6 = 6-month progression-free survival; PFS-9 = 9-month progression-free survival; PTK787/ZK222584 = Vatalanib; R = retrospective; Y = years.
Figure 1: PRISMA diagram of studies selected for review

Supplementary Table 1: Full list of search terms for systematic review search on PubMed

<table>
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<th>Search Date</th>
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<th>Filters applied</th>
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<td>07/04/2021</td>
<td>Syntax: (&quot;Meningioma&quot;[Mesh] OR &quot;Meningioma*&quot; OR &quot;meningeal tumor*&quot; OR &quot;Atypical Meningioma*&quot; OR &quot;Grade 2 Meningioma*&quot; OR &quot;Grade II Meningioma*&quot;) AND (&quot;immunotherap*&quot; OR &quot;Systemic therap*&quot; OR &quot;Systemic treatment&quot; OR &quot;Antibod*&quot; OR &quot;Monoclonal&quot; OR &quot;Humanized&quot; OR &quot;Biological therap*&quot; OR &quot;Biological Response&quot; OR &quot;modifier therap*&quot;) AND (&quot;Therapeutics&quot;[Mesh] OR &quot;Therap*&quot; OR &quot;medical treatment*&quot; OR &quot;treatment*&quot; OR &quot;management*&quot; OR &quot;intervention*&quot; OR &quot;effect*&quot;)</td>
<td>10-year filter</td>
</tr>
</tbody>
</table>
Author contributions: All authors contributed to the study conception and design. Material preparation, data collection and analyses were performed by Khalid Taleb and Anna Brown. The first draft of the manuscript was written by Khalid Taleb and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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24. Lane HA, Wood JM, McSheehy PMJ, et al. mTOR inhibitor RAD001 (everolimus) has antiangiogenic/vascular properties distinct from a VEGFr tissue kinase inhibitor. Clin cancer Res an Off J Am Assoc Cancer Res. 2013.02.010


