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Translational Gap in Ongoing Clinical Trials for Glioma

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Abstract

Despite the vast amounts of information gathered about gliomas, the overall survival of glioma patients has not improved in the last four decades. This could partially be due to an apparent failure to include basic concepts of glioma biology into clinical trials. Specifically, attempts to overcome the limitations of the blood brain barrier (BBB) and the chemoresistance of glioma stem cells (GSCs) were seldom included (a phenomenon known as the translational gap, TG) in a study involving 29 Phase I/II clinical trials (P2CT) published in 2011. The aim of this study was to re-evaluate this finding with a new series of 100 ongoing, but still unpublished, P2CT in order to determine if there is a TG reduction. As indicators, we evaluated in each P2CT the number of drugs tested, concomitant radiotherapy, and the ability of drugs to pass the BBB and to target GSCs. Compared to clinical trials published in 2011, we found that while in OCT there is an increase in the number of P2CT using two drugs (from 24.1% to 44.9%), and an increase in the number of drugs able to pass the BBB (7.14% versus 64.29%) and target GSCs (0% versus 16.3%), there was a decrease in the number of P2CT using concomitant radiotherapy (34.5% versus 18.37%). Overall our results suggest that there is only a modest improvement regarding reducing the TG because the vast majority of ongoing P2CT are still not including well known concepts of glioma biology important for a successful treatment.

Keywords

Brain Cancer; Gliomas; Translational Gap; Clinical Trial; Cancer Stem Cells; Blood Brain Barrier

1. Introduction

Gliomas are some of the most aggressive brain tumors, and despite the vast amounts of research and resources allocated to find a cure, there has been a lack of progress in improving the survival of cancer patients. The prognosis for glioma patients is exceptionally low, especially for glioblastoma multiforme (GBM), the most common form of glioma in

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humans. Currently, the standard treatment for patients with GBM involves surgery, followed by radiotherapy and the administration of Temozolomide (TMZ). In the best scenario, this treatment only extends patient survival by about 22 months, but only for a select few individuals whose tumor contained a methylated MGMT promoter [1]. The average median survival time for GBM ranges from 12 to 16 months [2].

Gliomas, like most solid tumors, contain a subpopulation of cancer-stem like cells (GS-LCs) that have been associated with chemoresistance and tumor relapse [3]. GS-LCs have been isolated in 2003 and 2004 [4, 5], and are known to be resistant to Temozolomide and other conventional anticancer drugs [6–8], partially explaining the poor success of current treatments.

Another factor that has limited glioma treatment success is the blood brain barrier (BBB), which prevents the diffusion of anticancer drugs into the central nervous system [9]. It is expected then that newly developed therapeutic interventions should take in consideration these two factors, which have been known for decades to impact the outcome of clinical trials. However, by analyzing 29 clinical trials published during 2011, we found an important “translational gap” in glioma research: our study provided evidence supporting that there was no attempt by the sample clinical trials to utilize drugs that target GSCs in 2011, and only two of the twenty-nine studies published in 2011 included attempts to overcome the limitation imposed by the BBB. This lack of information translation results in repeated treatment failures, and will continue to be a significant waste of time and resources for researchers if the translational gap is not eliminated or reduced. In this study, we have analyzed about 100 ongoing (but still not published) clinical trials in order to evaluate if there has been an improvement in the design of glioma clinical trials regarding the translational gap.

2. Materials and Methods

Ongoing clinical trials (OCT) for glioma were retrieved from (www.clinicaltrials.gov) through the search phrase “phase II glioma” (last accessed December 2016). The search was filtered to “completed trials”, “studies with results”, “interventional studies”, the “adult” age group, and “phase II” clinical trials. 100 OCT were identified following this search, and all pertinent information pertaining to them were cataloged in Table I.

To characterize and classify the drugs being tested in each OCT, the PubMed (www.pubmed.com) database was applied. To determine whether or not a particular drug was capable of traversing the BBB, the search phrase “[drug name(s)] blood brain barrier” was used and relevant search results were read. To determine the GSC targeting capability of a particular drug, the search phrase “[drug name(s)] glioma stem cells” was inputted, and relevant search results were also read. The drug was then cataloged in Table II with a “Yes”, “No”, or “NK” (Not Known) classification for each capability. If the PubMed database supplied “No results” for either search phrase, than the drug in question received a “NK” classification.

3. Results & Discussion

3.1 Number of Drugs Tested per Clinical Trial

Our search results following the criteria described in 2. Materials and Methods identified 100 OCT from www.clinicaltrials.gov (Table I). Two studies were excluded from evaluation because no drugs were tested. From this group (98 studies), we first assessed the number of drugs tested in each study as a potential indicator of the future success of the treatment. The rationale for this assumption is supported by the fact that combination chemotherapy is more effective than single-agent treatments [10], and that gliomas display high intratumoral heterogeneity [11], making probable that within a single tumor there are subpopulations of cells with different sensitivities, some of which are resistant to particular anticancer drugs. Therefore, an increase in the number of drugs being tested per clinical trial can be considered promising. Our data indicated that 46 (46.94%), 44 (44.9%), 7 (7.14%) and 1 (1.02%) OCT tested 1, 2, 3 and >3 drugs respectively. Compared to a similar study using 29 clinical trials published in 2011, there is a decrease in clinical trials that use only one drug (from 65.5% to 46.94%) and an increase in the number of clinical trials using 2 drugs (from 24.1% to 44.9%). The percentage of studies that utilize 3 drugs remained nearly the same (6.9% and 7.14%). Regarding clinical trial using >3 drugs, the percentage of such studies were very low for both groups (3.4% and 1.02%) (Figure 1). These data suggest that there may be a reduction in the translational gap related to an increased awareness that combination chemotherapy is more effective than monotherapy.

3.2 Radiation Therapy in Combination with Chemotherapy

Since radiotherapy is an important component of glioma treatment that is shown to improve survival [12], we evaluated the number of clinical trials that incorporated radiotherapy as an element of intervention. In OCT, it was found that only 18 studies (18.37%) included radiotherapy in conjunction with chemotherapy, and 80 studies (81.63%) did not include radiotherapy at all. Compared to the clinical trials published in 2011, we found an important decrease in the use of radiotherapy (34.5% versus 18.37%) (Figure 2). This result is unexpected and discouraging, considering the therapeutic precedent of radiation as an effective means of limiting tumor proliferation in combination with chemotherapy and other treatments [12]. It is also well documented that Temozolomide plus radiotherapy provides better survival compared to Temozolomide alone [13, 14].

3.3 Ability of Tested Drugs to Traverse the Blood Brain Barrier

The blood brain barrier (BBB) is a key factor that limits the availability of drugs in the central nervous system and therefore the effectiveness of therapeutics [9, 15]. Hence, to be successful, any anticancer drugs used to treat gliomas should be able to pass the BBB and reach a concentration considerable enough to prevent glioma cell proliferation. Following this rationale, we evaluated the ability of the drugs used in OCT to overcome the BBB (Table II). In OCT, we found that 63 studies (64.29%) included at least one drug able to pass the BBB, but 35 studies (35.71%) included drugs that are known not to pass the BBB, or, at present, its ability to do so is unknown (Figure 3). However, regarding this issue, our present data indicated there may be an improvement in the translational gap, considering that more OCT are using drugs able to pass the BBB compared to the clinical trials published in 2011

(7.14% versus 64.29%). It is important to notice that there are strategies to improve the delivery of anticancer drugs across the BBB to treat brain tumors [16], but are seldom included in clinical trials, as evident in our data.

3.4 Ability of Tested Drugs to Target Glioma Stem Cells

Cancer stem cells in glioma have been associated with tumor relapse in part because of their high resistance to conventional chemotherapy. In fact, glioma stem cells (GSCs) are highly resistant to Temozolomide, which is considered the most effective drug to treat this disease. It is necessary, then, to incorporate new drugs with the ability to eliminate GSCs into newly designed clinical trials. For this reason, we evaluated the ability of drugs used in OCT to target GSCs. Unexpectedly, we found that only 16 (16.3%) OCT included at least one drug known to target GSCs. The vast majority of OCT (82, 83.67%) did not include any drug with documented ability to inhibit GSCs viability or proliferation (Figure 4). These data represent a slight improvement from the status of glioma clinical trials published in 2011 (0% versus 16.3%), but it is clearly a poor development in reducing the translational gap.

4. Impact of the translational gap

Raising awareness about the translational gap has crucial implications for both clinical trial designers and for patients. Clinical trials designers should take into consideration well documented factors that are known to affect drug delivery (the BBB) and chemoresistance (GCS-LCs, and CSC in general) when designing new interventional clinical trials. Without strategies to overcome the BBB with at least one drug capable of targeting GCS-LCs, it is likely that the clinical trial will ultimately fail. On the other hand, due to the large quantity of available ongoing clinical trials for glioma, it is difficult for patients and oncologists looking for experimental treatments to determine which one may be the most beneficial to enroll in. It is clear that at least three questions should be answered: 1) Is there any evidence that at least one drug will target GCS-LCs? 2) If the drug(s) is (are) delivered by systemic infusion, is there any evidence that it (they) will traverse the BBB and reach effective concentrations? And 3). If only one drug is used, is there any evidence that it will target both GCS-LCs and non-GCS-LCs?

The economic implications of the present study are immense considering the cost of clinical trials. We previously proposed an algorithm to guide the decision to run a Phase I/II clinical study using a particular drug [17]. According to this algorithm, a drug should only enter a Phase I/II clinical trial when there is evidence in animal models that it can at least reach effective antitumoral concentrations *in vivo* (either by locally or systemic delivery), and if there is *in vitro* evidence that it can eliminate the majority (ideally 100 %) of glioma cells.

5. Conclusions

Despite an increase in the number of studies that utilize more than one drug, as well as drugs able to pass the BBB, there is only a modest increase in the number of studies that included drugs known to target GCS-LCs. In addition, we found a decrease in the number of OCT using radiotherapy. Overall, the results confirm our previous finding that there is an evident

translational gap in the designs of clinical trials for glioma that needs to be reduced or eradicated.

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Highlights

- In this this study we reviewed 100 ongoing, but still unpublished Phase I/II clinical trials (P2CTs) in order to determine if there is a reduction in the translational gap (TG) previously reported in glioma research.
- We found in ongoing P2CTs there are more studies testing 2 drugs as well as an increase in the use of drugs able to pass the blood brain barrier compared to P2CTs published in 2011. However, less studies tested concomitant radiotherapy and only a small percentage of studies tested drugs known to target glioma stem cells.
- Our data suggest that there is only a modest improvement regarding reducing the TG.

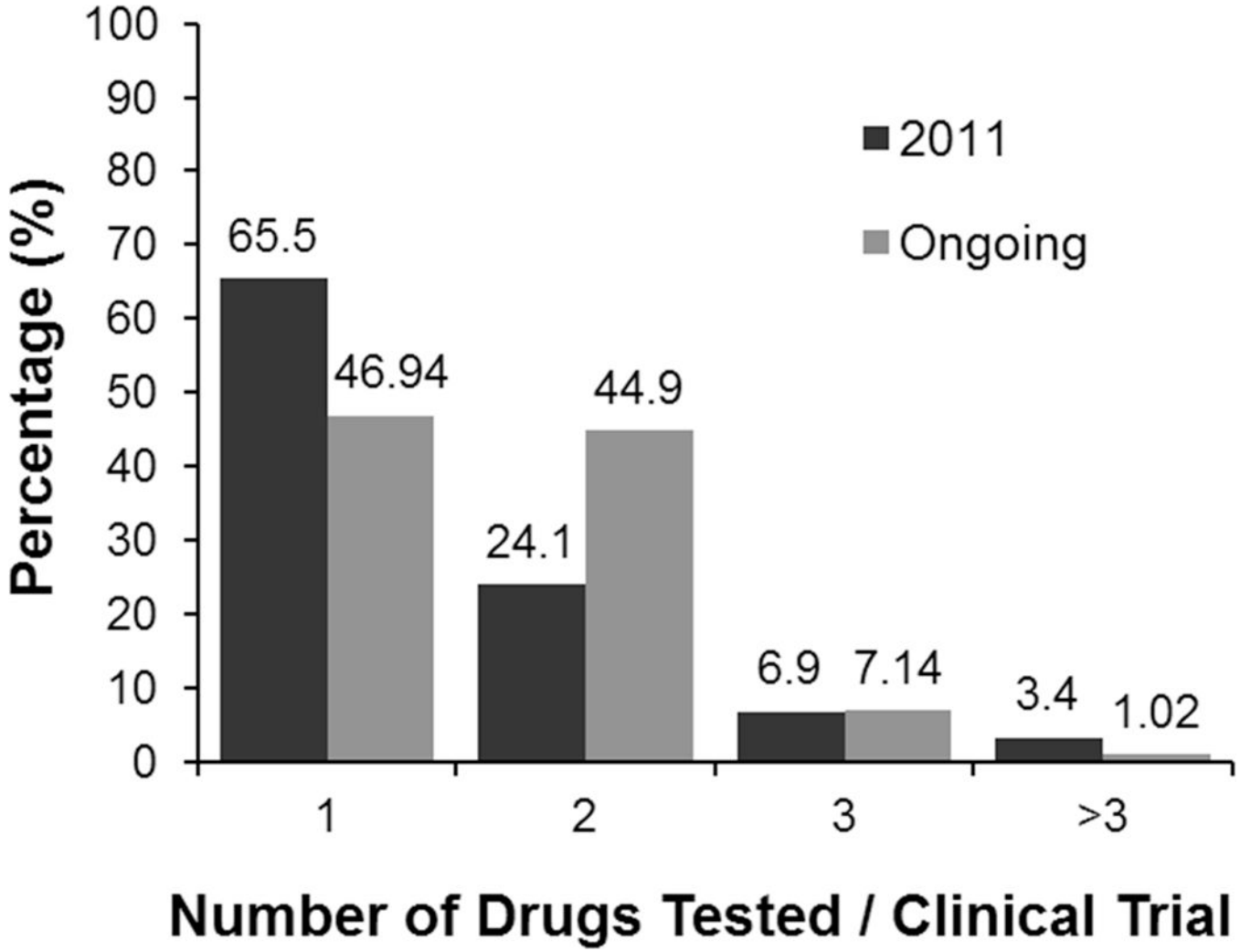

Figure 1.
Number of drugs tested per clinical trial in ongoing clinical trials (Ongoing; n=98) compared to clinical trials published in 2011 (2011; n=29).

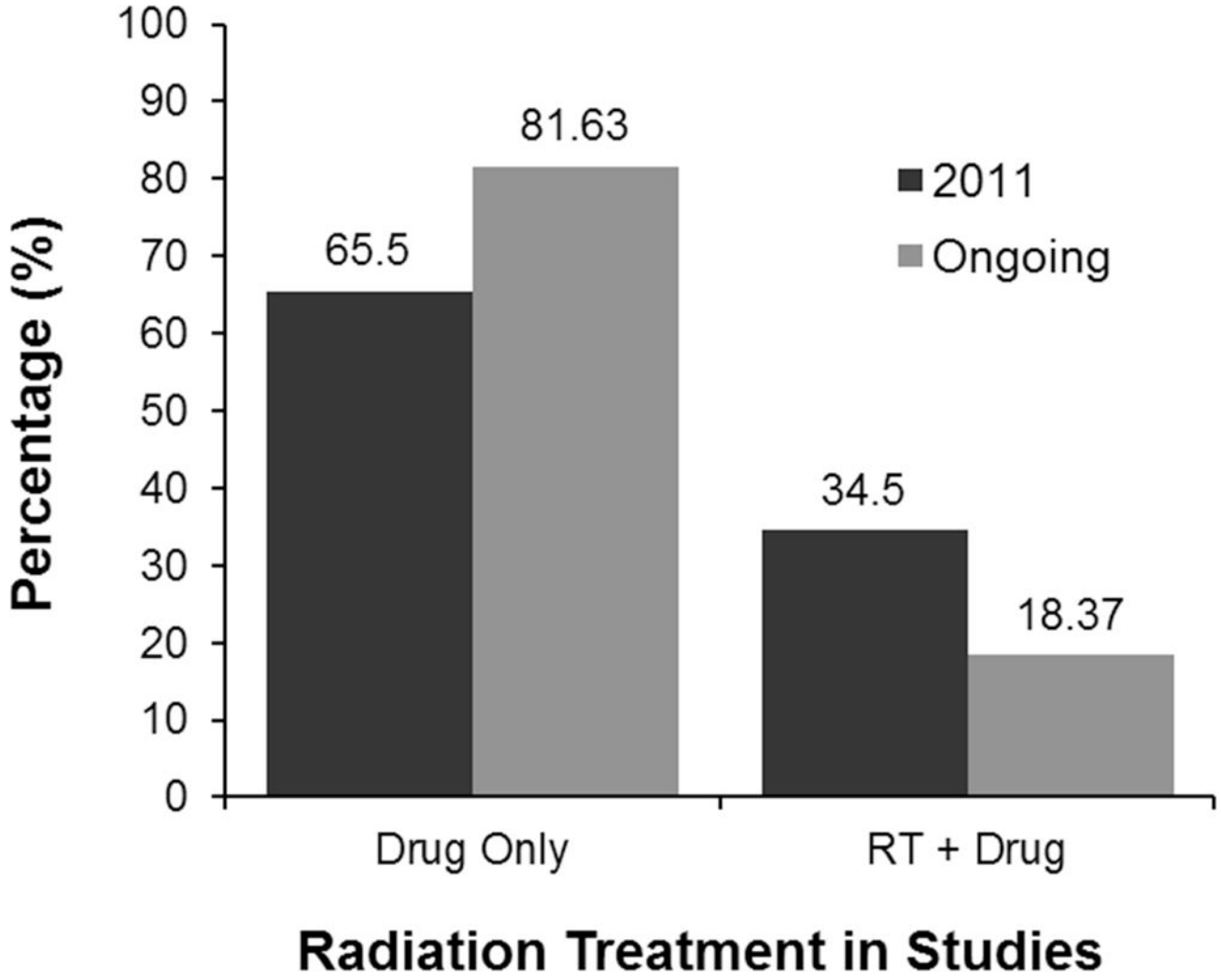

Figure 2.

Use of chemotherapy alone (drug only) or chemotherapy + radiotherapy (RT + Drug) in ongoing clinical trials (Ongoing; n=98) compared to clinical trials published in 2011 (2011; n=29).

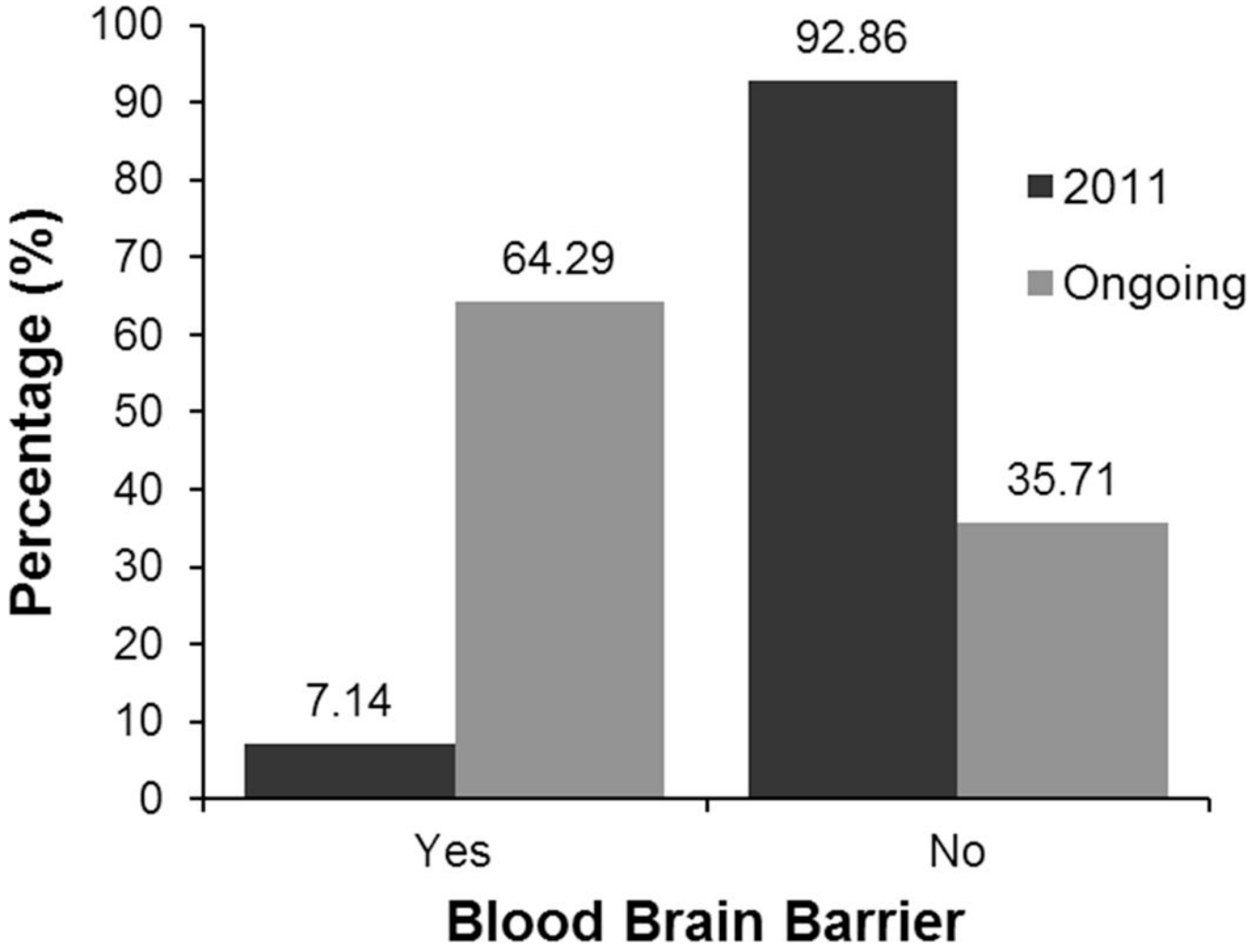

Figure 3.

Use of drugs with known (Yes) or unknown (No) ability to cross the BBB in ongoing clinical trials (Ongoing; n=98) compared to clinical trials published in 2011 (2011; n=29).

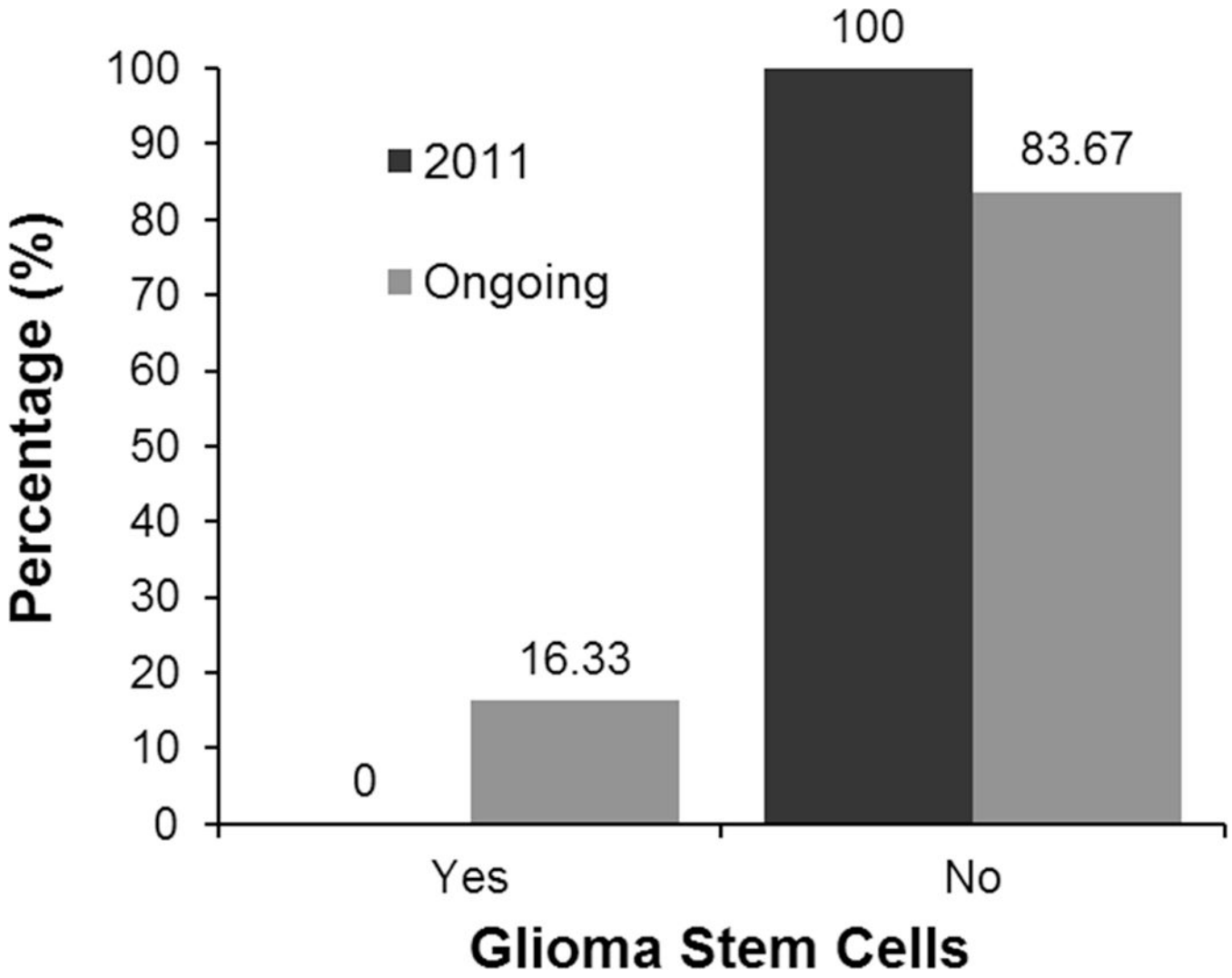

Figure 4.

Use of drugs with known (Yes) or unknown (No) ability to target GCS-LCs in ongoing clinical trials (Ongoing; n=98) compared to clinical trials published in 2011 (2011; n=29).

Table I

List of 100 ongoing Phase I/II and II Glioma Clinical Trials collected from www.clinicaltrials.gov by searching “phase II gliomas” and refining the study results to “Interventional Studies”, the “Adult” age range, “Completed” studies “With Results”, and “Phase II.”

Result #	Clinical Trials ID	Condition/ Type of Glioma	Participants	Drug (s)	Age (Groups)	BBB	GSC Targeting	RT	Other Intervention	Endpoints	Start Date	Duration in Months (End Date)
1	NCT00047879	Recurrent	7	Pegylated Interferon Alfa 2b + Thalidomide	18+ (Adult, Senior)	Pegylated Interferon Alfa 2b: NK; Thalidomide: NK	Pegylated Interferon Alfa 2b: NK; Thalidomide: NK	No	No	PFS	2002	84 (2009)
2	NCT01663012	Bevacizumab -Resistant, High Grade, GBM, AA, AO	20	Etirinotecanpegol/NKTR -102	18+ (Adult, Senior)	Yes	No	No	No	PFS	2012	36 (2015)
3	NCT00036569	Diffuse Intrinsic Pontine	32	Pegylated Interferon Alfa 2b	up to 21 (Child, Adult)	NK	NK	No	No	2YS, MTTP	2002	120 (2012)
4	NCT00611325	Recurrent, Malignant, GB, GSC	56	Avastin/Bevacizumab + Bortezomib	18+ (Adult, Senior)	Avastin/Bevacizumab: No; Bortezomib: Yes	Avastin/Bevacizumab: No; Bortezomib: No	No	No	6mPFS, MPFS, OS	2008	60 (2013)
5	NCT00995007	Recurrent, High Grade, GBM, GSC, AA, AO, AMO	112	ZD6474/Vandetanib +/− Carboplatin	18 – 100 (Adult, Senior)	ZD6474/Vandetanib: No; Carboplatin: NK	ZD6474/Vandetanib: NK; Carboplatin: No	No	No	6mPFS, OS	2009	72 (2015)
6	NCT00615927	Recurrent, Progressive, Grade II, Low Grade, GB, GSC	64	Imatinib Mesylate + Hydroxyurea/Hydroxycarbamide	18+ (Adult, Senior)	Imatinib Mesylate: No; Hydroxyurea/ Hydroxycarbamide: Yes	Imatinib Mesylate: No; Hydroxyurea/ Hydroxycarbamide: NK	No	No	12mPFS, MPFS, OS	2006	72 (2012)
7	NCT00727506	Recurrent, Malignant	151	BIBW 2992/Afatinib +/− TMZ	18+ (Adult, Senior)	BIBW 2992/Afatinib: Yes; TMZ: Yes	BIBW 2992/Afatinib: NK; TMZ: No	No	No	6mPFS, OBR	2008	96 (2016)
8	NCT00387790	Pontine	64	Motexafin Gadolinium/Xcytrin	Up to 21 (Child, Adult)	No	NK	Yes	No	EFS, OS	2007	36 (2010)
9	NCT00900757	Malignant	57	PALO + TMZ	18 – 90 (Adult, Senior)	PALO: NK; TMZ: Yes	PALO: NK; TMZ: No	Yes	No	Change in FLIE Score From Baseline - Each Week of RT and TMZ Treatment	2009	36 (2012)
10	NCT00085540	AO, AA, Recurrent, GSC, Giant Cell GB	50	FR901228/Depsipeptide/Romidepsin	18+ (Adult, Senior)	NK	NK	No	No	6mPFS, OBR	2005	48 (2009)
11	NCT00501891	GBM	32	Avastin/Bevacizumab + TMZ	18+ (Adult, Senior)	Avastin/Bevacizumab: No; TMZ: Yes	Avastin/Bevacizumab: No; TMZ: No	No	Metronomic treatment (TMZ)	6mPFS, OBR, Incidence/ Severity ofCNS/Systemic Hemorrhage	2007	24 (2009)
12	NCT00275002	Brain/CNS Tumors, Recurrent, Progressive	41	O^6-Benzylguanine + TMZ	Up to 21 (Child, Adult)	O^6-Benzylguanine: Yes; TMZ: Yes	O^6-Benzylguanine: Yes; TMZ: No	No	No	OBR, # of Patients with Grades 3 to 4 Adverse Events (Possibly Related to O^6-Benzylguanine +TMZ)	2006	48 (2010)
13	NCT00392171	GB, AC, OLDG	120	TMZ	19 – 70 (Adult, Senior)	Yes	No	No	Continuous 28-day Therapy (Patient who failed Conventional 5-day)	6mPFS	2006	36 (2009)
14	NCT00369590	AA, AO, Giant Cell GB, GSC, Recurrent	58	VEGF Trap/Ziva flibercept	18+ (Adult, Senior)	NK	NK	No	No	6mPFS, OS, PFS, Safety Profiles	2006	72 (2012)
15	NCT00939991	GB, Recurrent, Malignant	48	Vorinostat/SAHA + Avastin/Bevacizumab + TMZ	18+ (Adult, Senior)	Vorinostat/SAHA: Yes; Avastin/Bevacizumab: No; TMZ: Yes	Vorinostat/SAHA: Yes; Avastin/Bevacizumab: No; TMZ: No	No	Daily TMZ	6mPFS, Radiographic Response, MPFS, OS	2009	48 (2013)
16	NCT00619112	Recurrent, CNS Neoplasm, High Grade	60	TMZ	18+ (Adult, Senior)	Yes	No	No	No	6mPFS	2007	36 (2012)

Result #	Clinical Trials ID	Condition/ Type of Glioma	Participants	Drug (s)	Age (Groups)	BBB	GSC Targeting	RT	Other Intervention	Endpoints	Start Date	Duration in Months (End Date)
17	NCT01462695	Cerebellar AA, Cerebral AC, OLDG, Infratentorial/Supratentorial Ependymoma, Subependymal Giant Cell AC, Recurrent, Progressive, Refractory	30	Sunitinib Malate	1 – 21 (Child, Adult)	Yes	No	No	No	OBR	2012	24 (2014)
18	NCT00859222	Recurrent, Malignant, High Grade	51	LBH589/Panobinostat + Avastin/Bevacizumab	18+ (Adult, Senior)	LBH589/Panobinostat: Yes; Avastin/ Bevacizumab: No	LBH589/Panobinostat: NK; Avastin/ Bevacizumab: No	No	No	MTD (LBH589), 6mPFS, OS, PFS, Best Radiographic Response	2009	72 (2015)
19	NCT00498927	Recurrent, GBM, Malignant	47	TMZ	18 – 120 (Adult, Senior)	Yes	No	No	Immunoenzyme technique	6mPFS, OS	2007	72 (2013)
20	NCT01137604	Recurrent, Malignant	151	Lenvatinib + Avastin/Bevacizumab	18 – 99 (Adult, Senior)	Lenvatinib: NK; Avastin/Bevacizumab: No	Lenvatinib: NK; Avastin/Bevacizumab: No	No	No	6mPFS, OBR Rate, PFS, OS, DCR, CBR	2010	48 (2014)
21	NCT00990652	Brain/CNS Tumors, Recurrent, Malignant	10	Avastin/Bevacizumab + TMZ	18+ (Adult, Senior)	Avastin/Bevacizumab: No; TMZ: Yes	Avastin/Bevacizumab: No; TMZ: No	No	Pre-op Avastin/Bevacizumab, Post-op Avastin/Bevacizumab + TMZ	6mPFS, MacDonald Criteria Treatment Response, 6mOS, Adverse Events, OS (days)	2009	36 (2012)
22	NCT00003473	Mixed Glioma, Refractory, Recurrent	20	Atengenal/A 10 + Astugenal/A S2-1 (Antineoplaston therapy)	18 – 99 (Adult, Senior)	Atengenal/A10: NK; Astugenal/AS2-1: NK	Atengenal/A10: NK; Astugenal/A S2-1: NK	No	No	OBR, OS	1996	132 (2007)
23	NCT00302159	High Grade, Brain Tumors	43	Valproic Acid/Valproate + TMZ	18 – 90 (Adult, Senior)	Valproic Acid/ Valproate: Yes; TMZ: Yes	Valproic Acid/ Valproate: Yes; TMZ: No	Yes	Adjuvant Therapy	MPFS, 6,12,24mP FS, OS, 6,12,24m OS, Adverse Events, Best Response	2006	96 (2014)
24	NCT00499473	AA, Diffuse AC, Giant Cell GB, GB, GSC, Mixed Glioma, OLDG, Pineal Gland AC, Recurrent, Malignant	31	Sunitinib Malate	18+ (Adult, Senior)	Yes	No	No	No	6mPFS, MTD, OBR, 12mPFS, OS	2007	84 (2014)
25	NCT00124657	Brain/CNS Tumors, Newly Diagnosed	62	Erlotinib	3 – 21 (Child, Adult)	Yes	NK	Yes	No	DLT, MTD, PFS	2005	108 (2014)
26	NCT00953121	Malignant	104	Avastin/Bevacizumab + Irinotecan/CPT-11 + Carboplatin	18+ (Adult, Senior)	Avastin/Bevacizumab: No; Irinotecan/CPT-11: Yes; Carboplatin: NK	Avastin/Bevacizumab: No; Irinotecan/CPT-11: NK; Carboplatin: No	No	No	6mPFS, OBR, MPFS, OS	2009	48 (2013)
27	NCT00271609	Recurrent, High Grade, Malignant	88	Avastin/Bevacizumab	18+ (Adult, Senior)	No	No	No	No	6mPFS, Adverse Events	2005	108 (2014)
28	NCT00042991	Newly Diagnosed AA, AO, Giant Cell GB, Brain Stem, GB, GSC, OLDG, Gliomatosis Cerebri	69	Gefitinib	3 – 21 (Child, Adult)	Yes	No	Yes	No	MPFS, MS, Change in Tumor Volume	2002	96 (2010)
29	NCT00108069	Recurrent, Brain Tumors	43	Bortezomib + TAM	18+ (Adult, Senior)	Bortezomib: Yes; TAM: NK	Bortezomib: No; TAM: NK	No	No	OBR, Adverse Events	2005	96 (2013)
30	NCT00671970	Malignant, Recurrent, GB, GSC	57	Avastin/Bevacizumab + Erlotinib	18+ (Adult, Senior)	Avastin/Bevacizumab: No; Erlotinib: Yes	Avastin/Bevacizumab: No; Erlotinib: NK	No	No	6mPFS, Radiographic Response, Association of Biomarkers and 1yS	2007	36 (2010)
31	NCT01738646	Recurrent, GBM, Malignant, Brain Tumors	48	Vorinostat/SAHA + Avastin/Bevacizumab	18 – 120 (Adult, Senior)	Vorinostat/SAHA: Yes; Avastin/Bevacizumab: No	Vorinostat/SAHA: Yes; Avastin/Bevacizumab: No	No	No	6mPFS, Radiographic Response, MPFS, OS	2013	24 (2015)
32	NCT00424554	Glioma (not specified)	40	TMZ	18 – 75 (Adult, Senior)	Yes	No	No	Low Dose for 2 weeks on Brain Tumor Enzyme	MGMT Activity from Tumor Tissue, Adverse Events, TMZ Concentrations	2006	60 (2011)
33	NCT00782626	Refractory, Progressive, Recurrent, Low Grade, AC	23	Everolimus/RAD001	3 – 21 (Child, Adult)	NK	NK	No	No	OR	2009	36 (2012)
34	NCT00301873	Brain Tumors, CNS Malignancies, Osteoporosis	60	Zoledronate/IV Zometa	18+ (Adult, Senior)	NK	NK	No	No	Combined BMD T-Score, Mean Change in BMD	2006	72 (2012)

Result #	Clinical Trials ID	Condition/ Type of Glioma	Participants	Drug (s)	Age (Groups)	BBB	GSC Targeting	RT	Other Intervention	Endpoints	Start Date	Duration in Months (End Date)
35	NCT00112736	AA, AO, Diffuse AC, Giant Cell GB, GB, GSC, Mixed Glioma, Pilocytic AC, Pineal Gland AC, Subependymal Giant Cell AC, Recurrent, Brain Tumors	69	Erlotinib + Torisel/Temsirolimus	18+ (Adult, Senior)	Erlotinib: Yes; Torisel/ Temsirolimns: NK	Erlotinib: NK; Torisel/ Temsirolimus: NK	No	Therapeutic Conventional Surgery	6mPFS	2006	72 (2012)
36	NCT01113398	Recurrent, Malignant, GBM, GSC	36	Avastin/Bevacizumab + AMG 102/Rilotumumab	18+ (Adult, Senior)	Avastin/Bevacizumab: No; AMG 102/ Rilotumumab: NK	Avastin/Bevacizumab: No; AMG 102/ Rilotumumab: NK	No	No	Radiographic Response, OS, 6mPFS, CNS Hemorrhage, Non-Hematologic Toxicities	2010	60 (2015)
37	NCT00350727	Relapsed, Malignant	75	Pazopanib/Votrient + Lapatinib Ditosylate	18+ (Adult, Senior)	Pazopanib/Votrient: NK; Lapatinib Ditosylate: Yes	Pazopanib/Votrient: NK; Lapatinib Ditosylate: Yes	No	No	Mean Change from Baseline to Maximum Value (various indicators), PFS, OS, OR, 6mPFS, MTTP	2006	36 (2009)
38	NCT01380782	Recurrent, High Grade, GB, GSC, AA, AO, AOLGAC	37	BIBF 1120/Nintedanib	18+ (Adult, Senior)	NK	NK	No	No	3mPFS, 6mPFS, Radiographic Response, OS, MTTP, Safety Profile	2012	24 (2014)
39	NCT00003459	Brain Stem Glioma	40	Atengenal/A 10 + Astugenal/A S2-1 (Antineoplaston therapy)	6m – 99 (Child, Adult, Senior)	Atengenal/A10: NK; Astugenal/AS2-1: NK	Atengenal/A10: NK; Astugenal/A S2-1: NK	No	No	OBR, OS	1996	84 (2007)
40	NCT00095940	Recurrent, Refractory, CNS Tumors, AA, Brain Stem, Ependymoma, Giant Cell GB, GB, GSC, Medulloblastoma, OLDG	52	Lapatinib Ditosylate	Up to 21 (Child, Adult)	Yes	Yes	No	Therapeutic Conventional Surgery	Molecular Biology Objective, OBR	2004	72 (2010)
41	NCT00672243	Recurrent, Malignant, GBM, GSC, GB	32	Erlotinib + Torisel/Temsirolimus	18+ (Adult, Senior)	Erlotinib: Yes; Torisel/ Temsirolimus: NK	Erlotinib: NK; Torisel/ Temsirolimus: NK	No	No	MPFS, 6mPFS, OS, Radiographic Response, Non-Hematologic Toxicities	2007	24 (2009)
42	NCT00412542	GBM	78	Thalidomide +/−TMZ or Irinotecan/CPT-11	Not specified (Child, Adult, Senior)	Thalidomide: NK; TMZ: Yes; Irinotecan/ CPT-11: Yes	Thalidomide: NK; TMZ: No; Irinotecan/ CPT-11: NK	No	No	6mPFS	2003	72 (2009)
43	NCT00612430	GB, GSC, Malignant, Recurrent	59	Etoposide/To posar + Avastin/Bevacizumab	18+ (Adult, Senior)	Etoposide/Toposar: NK; Avastin/ Bevacizumab: No	Etoposide/Toposar: No; Avastin/Bevacizumab: No	No	No	6mPFS, OBR, MPFS, OS	2007	48 (2011)
44	NCT00679354	Recurrent, Progressive, High Grade, Cerebellar AC, Cerebral AC, AA, AO, AOLGAC, Brain Tumors, Visual Pathway, Hypothalamic	30	Cilengitide/EMD 121974	Up to 21 (Child, Adult)	NK	NK	No	No	OBR, MTTP, TTD, TTF	2008	36 (2011)
45	NCT00404495	Medulloblastoma, Brain Tumors	83	TMZ + Irinotecan/CPT-11	6m – 18 (Child, Adult)	TMZ: Yes; Irinotecan/ CPT-11: Yes	TMZ: No; Irinotecan/ CPT-11: NK	No	No	OBR, TTF, MTTP, OS	2007	48 (2011)
46	NCT00079339	Untreated, Brain Stem	51	Tipifarnib/Zarnestra/R1 15777	3 – 21 (Child, Adult)	NK	NK	Yes	No	PFS, Change from Baseline to: Perfusion Ratio, Diffusion Ratio; Mean Tumor to: Gray, White Matter	2004	60 (2009)
47	NCT00187226	CNS Tumors, Brain Tumors	202	No Drug Tested	8m – 25 (Child, Adult)	N/A	N/A	Yes	Image Guided RT	Local Tumor Control	1997	96 (2005)
48	NCT00667394	GB, GSC, AA, AO, AMOLGAC	42	Tandutinib M LN-518 + Avastin/Bevacizumab	18+ (Adult, Senior)	Tandutinib/ML N-518: NK; Avastin/ Bevacizumab: No	Tandutinib/MLN-518: NK; Avastin/ Bevacizumab: No	No	No	6mPFS, Adverse Events	2008	36 (2011)
49	NCT00520936	Osteosarcoma, Medulloblastoma, Ewing's Sarcoma, Neuroblastoma, Rhabdomyosarcoma, Ependymoma, High Grade	72	Pemetrexed	Up to 22 (Child, Adult)	No	NK	No	No	OR, Adverse Events, Pharmacogenomics	2007	36 (2010)

Result #	Clinical Trials ID	Condition/ Type of Glioma	Participants	Drug (s)	Age (Groups)	BBB	GSC Targeting	RT	Other Intervention	Endpoints	Start Date	Duration in Months (End Date)
50	NCT00763750	Newly Diagnosed, Brain Tumors	25	PPX/CT-2103 + TMZ	18+ (Adult, Senior)	PPX/CT-2103: NK; TMZ: Yes	PPX/CT-2103: No; TMZ: No	Yes	No	# Patients Assessed for Toxicity (CTC Ver. 3.0)	2008	48 (2012)
51	NCT01303835	Malignant	110	Naltrexone	18+ (Adult, Senior)	No	NK	No	No	Change in QoL	2011	48 (2015)
52	NCT00717197	Recurrent, High Grade, Malignant	30	Capecitabine/Xeloda	18+ (Adult, Senior)	Yes	NK	No	No	PFS	2008	60 (2013)
53	NCT00766467	Malignant	81	Armodafinil	18+ (Adult, Senior)	NK	NK	No	No	Change from Baseline in Fatigue, QoL; Side Effects	2008	72 (2014)
54	NCT00565721	High Grade	33	Fluciclatide Injection/AH111585 (F18)	18+ (Adult, Senior)	NK	NK	No	PET Imaging	Drug Uptake Magnitude/ Retention, Expression of Various Integrins	2007	60 (2012)
55	NCT00612339	GB, GSC, Unresectable, Multifocal	41	Avastin/Bevacizumab + TMZ	18+ (Adult, Senior)	Avastin/Bevacizumab: No; TMZ: Yes	Avastin/Bevacizumab: No; TMZ: No	No	No	Response Rate	2007	60 (2012)
56	NCT00979017	GB, GSC, Unresectable, Multifocal	41	Avastin/Bevacizumab + TMZ + Irinotecan/CPT-11	18+ (Adult, Senior)	Avastin/Bevacizumab: No; TMZ: Yes; Irinotecan/CPT-11: Yes	Avastin/Bevacizumab: No; TMZ: No; Irinotecan/CPT-11: NK	No	No	Response Rate, CNS and Systemic Hemorrhage, MPFS, Hematologic and Non-hematologic Toxicities, OS	2009	48 (2013)
57	NCT00575887	GB, AC, OLDG, Brain Tumors, Recurrent, Progressive	25	TMZ	18+ (Adult, Senior)	Yes	No	No	Protract ed TMZ	6mPFS	2006	36 (2009)
58	NCT01751308	Malignant, Solid Tumor, CNS Neoplasm, Refractory	39	Cabazitaxel/XRP6258	2 – 18 (Child, Adult)	NK	NK	No	No	OBR, DOR, Adverse Events, PFS, OS, PK Parameters of Cabazitaxel	2013	36 (2016)
59	NCT00492089	Primary Brain Tumors, Meningioma, Head and Neck Cancer	11	Avastin/Bevacizumab	18+ (Adult, Senior)	No	No	No	Patients have undergo ne RT previously	Response from Baseline to 6wks Post-Treatment	2007	36 (2010)
60	NCT00404248	Recurrent, High Grade, Brain Tumors, CNS Tumor	35	Tetra-O-Methyl Nordihydroguaiaretic Acid/Terameprocol	18+ (Adult, Senior)	NK	NK	No	No	PK Endpoints, OR, OS	2007	60 (2012)
61	NCT00504660	GBM, Brain Tumors, Anaplastic	75	6-Thioguanine/6-TG + Capecitabine/Xeloda + Celecoxib/ Celebrex + TMZ or Lomustine/CCNU	12+ (Child, Adult, Senior)	6-Thioguanine/6-TG: Yes; Capecitabine/ Xeloda: Yes; Celecoxib/Celebrex: NK; TMZ: Yes; Lomustine/CCNU: Yes	6-Thioguanine/6-TG: NK; Capecitabine/ Xeloda: NK; Celecoxib/Celebrex: NK; TMZ: No; Lomustine/CCNU: NK	No	No	12mPFS (Anaplastic Tumors), 6mPFS (GBM)	2003	84 (2010)
62	NCT01125800	Medulloblastoma, Rhabdomyosarcoma, Neuroblastoma, Hepatoblastoma, AC, Recurrent, Refractory	76	Sonidegib/LDE225	12m – 18 (Child, Adult)	NK	Yes	No	No	MTD, OBR, Adverse Events, DOR	2011	36 (2014)
63	NCT00597402	GBM, Brain Tumors, GSC	125	Avastin/Bevacizumab + TMZ + Irinotecan/CPT-11	18+ (Adult, Senior)	Avastin/Bevacizumab: No; TMZ: Yes; Irinotecan/CPT-11: Yes	Avastin/Bevacizumab: No; TMZ: No; Irinotecan/CPT-11: NK	Yes	No	16mOS, 12mPFS, CNS and Systemic Hemorrhage, Hematologic and Non-Hematologic Toxicities	2007	72 (2013)
64	NCT00597493	Recurrent, GBM	32	Sorafenib/Nexavar + TMZ	18+ (Adult, Senior)	Sorafenib/Nexavar: No; TMZ: Yes	Sorafenib/Nexavar: Yes; TMZ: No	No	Protracted TMZ	6mPFS, Safety/Toxicity of Combination, PK Factors	2007	36 (2010)
65	NCT00106353	Solid Brain Tumors, Adenocarcinoma, Neoplasms, Relapsed, Refractory	71	Torisel/Temsirolimus	1 – 21 (Child, Adult)	NK	NK	No	No	Adverse Events, Number of Patients who Died, MTD, 3mPFS, PCI Changes in Vital Signs, Plasma Concentration	2005	84 (2012)
66	NCT00684567	Newly Diagnosed, GBM, GB	30	TMZ	18 – 70 (Adult, Senior)	Yes	No	Yes	No	Adverse Events, Adverse Reactions, 12mPFS, OBR	2005	24 (2007)

Result #	Clinical Trials ID	Condition/ Type of Glioma	Participants	Drug (s)	Age (Groups)	BBB	GSC Targeting	RT	Other Intervention	Endpoints	Start Date	Duration in Months (End Date)
67	NCT00606008	Recurrent, AA, GB,	30	Sunitinib Malate	18+ (Adult, Senior)	Yes	No	No	No	6mPFS, OR, Adverse Events	2007	60 (2012)
68	NCT00323115	Newly Diagnosed, GBM	11	Dendritic Cell Vaccine	18+ (Adult, Senior)	NK	Yes	No	No	Cytotoxic T-cell Response, PFS, OS	2006	84 (2013)
69	NCT00187486	Newly Diagnosed, Brain Tumors, GBM, GSC	66	Erlotinib + TMZ	18+ (Adult, Senior)	Erlotinib: Yes; TMZ: Yes	Erlotinib: NK; TMZ: No	Yes	No	OS, PFS	2004	84 (2011)
70	NCT00085254	Newly Diagnosed, GBM, Giant Cell GB, GB, GSC	112	Cilengitide/EMD 121974 + TMZ	18+ (Adult, Senior)	Cilengitide/EMD 121974: NK; TMZ: Yes	Cilengitide/EMD 121974: NK; TMZ: No	Yes	No	DLT, MTD, OS, Hematologic and Non-Hematologic Adverse Events	2005	84 (2012)
71	NCT00544817	GBM	47	Sorafenib/Nexavar + TMZ	18+ (Adult, Senior)	Sorafenib/Nexavar: No; TMZ: Yes	Sorafenib/Nexavar: Yes; TMZ: No	Yes	No	PFS, OS, OBR	2007	36 (2010)
72	NCT00973739	Neurofibromatosis 2, Vestibular Schwannoma	21	Lapatinib Ditosylate	4 – 80 (Child, Adult, Senior)	Yes	Yes	No	No	12mPFS, Toxicities	2009	36 (2012)
73	NCT00305864	Giant Cell GB, GB, GSC, GBM	118	TMZ + Motexafin Gadolinium/Xcytrin	18+ (Adult, Senior)	TMZ: Yes; Motexafin Gadolinium/Xcytrin: No	TMZ: No; Motexafin Gadolinium/Xcytrin: NK	Yes	No	MTD, OS, PFS	2006	60 (2011)
74	NCT00939484	Recurrent, Refractory, Medulloblastoma	31	Vismodegib/Erivedge	22+ (Adult, Senior)	NK	NK	No	No	OBR, PFS, PK, DOBR	2009	72 (2015)
75	NCT01239316	Recurrent, Refractory, Medulloblastoma, Pediatric	12	Vismodegib/Erivedge	3 – 21 (Child, Adult)	NK	NK	No	No	OBR, PK, PFS, DOBR	2010	60 (2015)
76	NCT01402063	GB, GBM without Methylation, Newly Diagnosed	63	PPX/CT-2103 + TMZ	18+ (Adult, Senior)	PPX/CT-2103: NK; TMZ: Yes	PPX/CT-2103: No; TMZ: No	Yes	No	PFS, PPX/RT vs. TMZ/RT	2011	48 (2015)
77	NCT00641706	Giant Cell GB, GB, GSC, Recurrent, Brain Tumors	44	Vorinostat/SAHA + Bortezomib	18+ (Adult, Senior)	Vorinostat/SAHA: Yes; Bortezomib: Yes	Vorinostat/SAHA: Yes; Bortezomib: No	No	Therapuetic Conventional Surgery	6mPFS, OS, MTTP, CTR, PTR, REGR	2008	24 (2010)
78	NCT00238303	Recurrent, Progressive, GBM, Giant Cell GB, GSC, Brain Tumors	103	Vorinostat/SAHA	18+ (Adult, Senior)	Yes	Yes	No	Therapuetic Conventional Surgery	PFS, CTR, OS, MTTP	2010	48 (2014)
79	NCT00445588	Giant Cell GB, GB, GSC, Recurrent, Brain Tumors	56	Erlotinib + Sorafenib/Nexavar	18+ (Adult, Senior)	Erlotinib: Yes; Sorafenib/Nexavar: No	Erlotinib: NK; Sorafenib/Nexavar: Yes	No	No	OS, 6mPFS	2007	24 (2009)
80	NCT00433381	GB, GSC, Recurrent, Brain Tumors, Refractory	123	Avastin/Bevacizumab + TMZ + Irinotecan/CPT-11	18+ (Adult, Senior)	Avastin/Bevacizumab: No; TMZ: Yes; Irinotecan/CPT-11: Yes	Avastin/Bevacizumab: No; TMZ: No; Irinotecan/CPT-11: NK	No	No	6mPFS, OBR, Degree of Cerebral Blood Volume, RTDis	2007	48 (2011)
81	NCT00805961	GBM	68	TMZ + Avastin/Bevacizumab + Everolimus/RAD001	18+ (Adult, Senior)	TMZ: Yes; Avastin/ Bevacizumab: No; Everolimus/RA D001: NK	TMZ: No; Avastin/ Bevacizumab: No; Everolimus/RAD001: NK	Yes	No	PFS, OS, CTR, Toxicities	2009	48 (2013)
82	NCT01115491	GBM	32	Avastin/Bevacizumab + TMZ	18+ (Adult, Senior)	Avastin/Bevacizumab: No; TMZ: Yes	Avastin/Bevacizumab: No; TMZ: No	No	Extended Treatment of TMZ	PFS, 6mPFS, OS, OR, PTR, CTR	2010	24 (2012)
83	NCT00525525	GB, GSC	74	Avastin/Bevacizumab + Erlotinib + TMZ	18+ (Adult, Senior)	Avastin/Bevacizumab: No; Erlotinib: Yes; TMZ: Yes	Avastin/Bevacizumab: No; Erlotinib: NK; TMZ: No	No	No	OS, PFS, Unexpected Toxicities	2007	72 (2013)
84	NCT00354913	GB, GSC, Recurrent, Progressive, Meningioma	21	Imatinib Mesylate + Hydroxyurea/Hydroxycarbamide	18+ (Adult, Senior)	Imatinib Mesylate: No; Hydroxyurea/ Hydroxycarbamide: Yes	Imatinib Mesylate: No; Hydroxyurea/ Hydroxycarbamide: NK	No	No	6mPFS, OS, OBR	2005	60 (2010)
85	NCT00004146	Supratentorial GBM, Giant Cell GB, GB, GSC	55	Carboxyamidotriazole	18+ (Adult, Senior)	NK	NK	Yes	No	OS, Toxicity When Combined with RT, PK	2000	120 (2010)

Result #	Clinical Trials ID	Condition/ Type of Glioma	Participants	Drug (s)	Age (Groups)	BBB	GSC Targeting	RT	Other Intervention	Endpoints	Start Date	Duration in Months (End Date)
86	NCT00253448	GBM, Brain Tumors, CNS Tumor	35	No Drug Tested	18+ (Adult, Senior)	N/A	N/A	Yes	Stereotactic Radiosurgery	OS	2002	108 (2011)
87	NCT00262730	Newly Diagnosed, GBM	97	Hiltonol/Poly ICLC + TMZ	18+ (Adult, Senior)	Hiltonol/Poly ICLC: No; TMZ: Yes	Hiltonol/Poly ICLC: NK; TMZ: No	Yes	No	OS	2006	48 (2010)
88	NCT00813943	Newly Diagnosed, GBM, Unmethylated Gene Promoter Status, GB	265	Cilengitide/EMD 121974 + TMZ	18+ (Adult, Senior)	Cilengitide/EM D 121974: NK; TMZ: Yes	Cilengitide/EMD 121974: NK; TMZ: No	Yes	No	OS, PFS, Plasma Concentrations, Adverse Events, Clinically Significant Abnormal Electrocardiogram, Thromboembolic Events and Hemorrhage	2009	48 (2013)
89	NCT00613028	GB, GSC, Patients Who Have Failed Avastin/Bevacizumab + Irinotecan/CPT-11	23	Avastin/Bevacizumab +/− Etoposide/To posar or TMZ	18+ (Adult, Senior)	Avastin/Bevacizumab: No; Etoposide/Toposar: NK; TMZ: Yes	Avastin/Bevacizumab: No; Etoposide/Toposar: No; TMZ: No	No	No	6mPFS, MPFS, OS, Non-Hematologic Toxicities	2008	36 (2011)
90	NCT01474239	Recurrent, GB, GBM	91	Fotemustine/Mustoforan + Avastin/Bevacizumab	18+ (Adult, Senior)	Fotemustine/ Mustoforan: Yes; Avastin/Bevacizumab: No	Fotemustine/ Mustoforan: Yes; Avastin/Bevacizumab: No	No	No	6mOS, OS, 6mPFS, PFS, 9mOS, 12mOS, CTR, PTR, Corticosteroid Initiation, KPS Deterioration, WHO PS Deterioration	2011	24 (2013)
91	NCT01856933	GBM, GSC	6	PSMA/BrUOG 263/Prostate Specific Membrane Antigen	18+ (Adult, Senior)	NK	NK	No	No	OBR, Adverse Events	2013	24 (2015)
92	NCT00301418	AA, Recurrent, Residual, GBM	11	Erlotinib	18+ (Adult, Senior)	Yes	NK	No	No	Safety of 150mg Twice Daily Dose, 6mPFS, OS	2006	96 (2014)
93	NCT00918281	Solid Tumor, High Grade, Head and Neck Cancer	70	Fluciclatide Injection/AH111585 (F18)	18+ (Adult, Senior)	NK	NK	No	Intravenous Administration, PET Imaging	Test Image and Retest Image Reproducibility of F18 Uptake, Administration Safety	2009	24 (2011)
94	NCT00657267	Recurrent, GB, GSC	58	TMZ	18+ (Adult, Senior)	Yes	No	No	Dose-Intense TMZ	6mPFS, OS, MTTP, Radiographic Response	2008	60 (2013)
95	NCT01331291	Recurrent, GB	36	Bosutinib	18+ (Adult, Senior)	Yes	NK	No	No	PFS, Intratumoral Concentration, Safety Profile, Anti-Tumor Response	2011	36 (2014)
96	NCT00050986	Recurrent, Progressive, GBM	55	TMZ + Tipifarnib/Zarnestra/R1 15777	Not specified (Child, Adult, Senior)	TMZ: Yes; Tipifarnib/ Zarnestra/R115 777: NK	TMZ: No; Tipifarnib/ Zarnestra/R 115777: NK	No	No	MTD, PFS	2002	72 (2008)
97	NCT01280552	GBM	124	Dendritic Cell Vaccine	18 – 80 (Adult, Senior)	NK	Yes	No	No	OS, PFS	2011	48 (2015)
98	NCT00085566	Brain Tumors, CNS Tumors, GBM, Progressive	61	Everolimus/RAD001 + Gefitinib	18 – 120 (Adult, Senior)	Everolimus/RA D001: NK; Gefitinib: Yes	Everolimus/RAD001: NK; Gefitinib: No	No	No	OBR	2004	48 (2008)
99	NCT00967330	GBM	182	Avastin/Bevacizumab + Irinotecan/CPT-11 vs. TMZ	18 – 70 (Adult, Senior)	Avastin/Bevacizumab: No; Irinotecan/CPT-11: Yes; TMZ: Yes	Avastin/Bevacizumab: No; Irinotecan/CPT-11: NK; TMZ: No	No	TMZ Radiochemistry	6mPFS, PFS, OS, CTR, PTR, OR, Change From Baseline, TTF	2010	48 (2014)
100	NCT00411619	Subependymal Giant Cell AC, Tuberous Sclerosis Complex	28	Everolimus/RAD001	3+ (Child, Adult, Senior)	NK	NK	No	No	Adverse Side Effects, Reduction in Tumor Volume	2007	84 (2014)
Average Treatment Duration (in months):												56.52

Abbreviations: NK – Not Known; *Endpoints:* RT - Radiation therapy; PFS – Progression Free Survival; 3mPFS – 3 month Progression Free Survival; 6mPFS – 6 month Progression Free Survival; 12mPFS – 12 month Progression Free Survival; 24mPFS – 24 month Progression Free Survival; MPFS - Median Progression Free Survival; OS - Overall Survival; 6mOS – 6 month Overall Survival; 9mOS – 9 month Overall Survival; 12mOS – 12 month Overall Survival; 16mOS – 16 month Overall Survival; 24mOS – 24 month Overall Survival; 2YS - 2

Year Survival; MTTP - Median Time to Progression; OBR - Objective Tumor Response; DOBR – Duration of Objective Tumor Response; EFS – Event Free Survival; FLIE - Functional Living Index – Emesis; MTD – Maximum Tolerated Dose; DCR – Disease Control Rate; CBR – Clinical Benefit Rate; DLT – Dose Limiting Toxicity; MS – Median Survival; TTD – Time to Death; TTF – Time to Treatment Failure; 1yS – One Year Survival; OR – Overall Response; BMD – Bone Mass Density; QoL – Quality of Life; DOR – Duration of Response; PCI – Potentially Clinically Important; PK – Pharmacokinetic Parameters; CTR – Confirmed/Complete Tumor Response; PTR – Partial Tumor Response; REGR – Regression; RTDis – Rate of Treatment Discontinuation; KPS - Karnofsky Performance Status; WHO – World Health Organization; PS – Performance Status; *Glioma:* GBM – Glioblastoma Multiforme; GB – Glioblastoma; CNS – Central Nervous System; AC – Astrocytoma; AA - Anaplastic Astrocytomas; OLDG – Oligodendrogliomas; AO - Anaplastic Oligodendrogliomas; AMO - Anaplastic Mixed Oligodendrogliomas; GSC – Gliosarcoma; OLGAC – Oligoastrocytoma; AOLGAC – Anaplastic Oligoastrocytoma; AMOLGAC – Anaplastic Mixed Oligoastrocytoma; *Drugs:* TMZ – Temozolomide; PPX – Paclitaxel Poliglumex; PALO – Palonosetron; SAHA - Suberoylanilide Hydroxamic Acid; TAM – Tamoxifen; MGMT - Methylguanine-DNA MethylTransferase; PSMA - Prostate Specific Membrane Antigen

Table II

List of anticancer drugs used in the ongoing clinical trials cataloged in Table I. Using PubMed (www.pubmed.com), each drug and alternate drug name was searched in order to find studies pertaining to whether the particular drug is shown to cross the blood brain and/or target glioma stem cells. Search criteria: "[drug name] glioma stem cells" and "[drug name] blood brain barrier". The typical routes of administration for each drug were also compiled utilizing the Google search engine (Note: a lack of data access has prevented two drugs from having their typical routes of administration recorded).

Drug Name (s)	Type of Drug	Typical Administration Method (Injection, I.V., I.A., I.C., I.N., I.M., Oral [Capsule or Pill], etc.)	Ability to Pass the BBB	GSC Sensitivity to Drug (High, Resistant, Minimal/Insensitive, Moderate)	References
Pegylated Interferon Alfa 2b	Pegylated Interferon	Local Injection: (Outer) Upper Arm, (Outer) Thigh, Stomach	NK (No studies)	NK (No studies)	–
Thalidomide	Immuno mo dulatory drug	Oral (Capsule)	NK (No studies)	NK: No single agent data	[18]
Etirinotecanpegol/NKTR-102	Topoisomerase 1 inhibitor	Injection	Yes	NK (No studies)	[19]
Avastin/Bevacizumab	Monoclonal Antibody (Angiogenesis inhibitor)	Injection	Yes: SLNs No: single-agent	Minimal/Insensitive (indirectly) Resistant	[20], [21], [22], [23]
Bortezomib	Proteasome inhibitor	I.V., Subcutaneous Injection	Yes	High: Stem-like cells and TMZ resistant cell lines; Stimulates stem-like cell VEGF production Resistant: single agent	[24], [25], [26]
ZD6474/V andetanib	VEGFR, RET, EGFR inhibitor	Oral (Pill)	No	NK (No studies)	[27], [28]
Carboplatin	Platinum-based antineoplastic	Injection	Yes: liposomal encapsulation and I.A. infusion NK: single agent	NK (No studies) Resistant	[29], [7]
Imatinib Mesylate	Multi-Targeted Tyrosine-kinase inhibitor	Oral (Pill)	No: enhances BBB integrity	Minimal/Insensitive	[30], [31], [32]
Hydroxyurea/Hydroxycarbamide	Ribonucleotide reductase inhibitor (deoxyribonucleotide suppression)	Oral (Capsule)	Yes	NK (No studies)	[33]
BIBW 2992/Afatinib	EGFR and HER2 inhibitor	Oral	Yes	NK (No studies)	[34]
Temozolomide	Alkylating antineoplastic agent	I.V., Oral (Capsule)	Yes	Minimal/Insensitive Resistant	[6], [8], [7]
Motexafin Gadolinium/Xcytrin	Ribonucleotide reductase inhibitor (deoxyribonucleotide suppression), thioredoxin reductase inhibitor	Injection	No	NK (No studies)	[35]
Palonosetron	5-HT_3 antagonist	I.V.	NK (No studies)	NK (No studies)	–
FR901228/Depsipeptide/Romidepsin	Peptide with both peptide and ester linkages in proximity to the same amino-acid containing molecule/chain	I.V.	NK (No studies)	NK (No studies)	
O^6-Benzylguanine	Antineoplastic agent (O6-alkylguanine-DNA alkyltransferase inhibitor)	I.A.	Yes	Moderate	[36], [37]

Drug Name (s)	Type of Drug	Typical Administration Method (Injection, I.V., I.A., I.C., I.N., I.M., Oral [Capsule or Pill], etc.)	Ability to Pass the BBB	GSC Sensitivity to Drug (High, Resistant, Minimal/Insensitive, Moderate)	References
VEGF Trap/Ziv-aflibercept	VEGFR inhibitor	Injection	NK: not specific	NK (No studies)	[38]
Vorinostat/Suberoylanilide Hydroxamic Acid	HDAC inhibitor	Oral (Capsule)	Yes: single agent Yes: triple combination formulation	NK: synergistically enhances lethality when used in combination treatments High	[39], [40], [41], [42], [43], [44]
Sunitinib Malate	Multi-targeted tyrosine-kinase inhibitor	Oral (Capsule)	Yes: low penetration	Resistant	[45], [46], [47]
LBH589/Panobinostat	Non-selective/pan-HDAC inhibitor	Oral (Capsule)	Yes	NK: no single agent data	[48], [49], [50]
Lenvatinib	VEGFR 1, 2, 3 inhibitor	Oral (Capsule)	NK (No studies)	NK (No studies)	–
Atengenal/A10	Synthetic animo acid derivative (Antineoplaston)	I.V., Injection	NK (No studies)	NK (No studies)	–
Astugenal/AS2-1	Synthetic animo acid derivative (Antineoplaston)	I.V., Injection	NK (No studies)	NK (No studies)	–
Valproic acid/Valproate	Histone deacetylase inhibitor; Anticonvulsant (anti-seizure)	Oral (Capsule, Pill), I.V., I.N.	Yes: I.N. infusion	Moderate: Most cell lines High: Long term exposure	[51], [52], [53]
Erlotinib	EGFR inhibitor	Oral (Pill)	Yes: low penetration Yes	NK: Moderate in combination treatments	[54], [55] [56]
Irinotecan/CPT-11	Plant alkaloid; Topoisomerase-1 inhibitor	I.V.	Yes	NK (No studies)	[57], [58]
Gefitinib	EGFR inhibitor	Oral (Pill), Dispersion (Drink)	Yes: liposomal encapsulation Yes	Resistant	[59], [60], [61]
Tamoxifen	Estrogen receptor antagonist, Antineoplastic agent	Injection, Oral (Pill)	NK: enhances delivery of drugs when used in liposomal carrier membranes	NK: increases radiosensitivity	[62], [63]
Everolimus/RAD001	mTOR inhibitor	Oral (Pill)	NK (No studies)	NK (No studies)	–
Zoledronate/IV Zometa	Bisphosphonate derivative	I.V.	NK (No studies)	NK (No studies)	–
Torisel/Temsirolimus	mTOR inhibitor, Antineoplastic agent	Injection, I.V.	NK (No studies)	NK (No studies)	–
AMG 102/Rilotumumab	Anti-HGF monoclonal antibody	I.V.	NK (No studies)	NK (No studies)	–
Pazopanib/Votrient	Multi-Targeted Tyrosine-kinase inhibitor	Oral (Pill)	NK: varied brain deposition	NK (No studies)	[64]
Lapatinib Ditosylate	EGFR and HER2 inhibitor	Oral (Pill)	Yes	Yes	[65], [66]
BIBF 1120/Nintedanib	FGFR, PDGFR, VEGFR inhibitor	Oral (Capsule), I.V.	NK (No studies)	NK (No studies)	–
Etoposide/Toposar	Plant alkaloid; Topoisomerase-2 inhibitor	Injection, Oral (Capsule, Pill), I.V.	Yes: SLNs NK: single agent	Resistant	[67], [68], [69], [7]
Cilengitide/EMD 121974	Angiogenesis inhibitor	I.V.	NK (No studies)	NK (No studies)	–
Tipifarnib/Zarnestra/R 115777	Farnesyltransferase inhibitor	Oral (Pill)	NK (No studies)	NK (No studies)	–

Drug Name (s)	Type of Drug	Typical Administration Method (Injection, I.V., I.A., I.C., I.N., I.M., Oral [Capsule or Pill], etc.)	Ability to Pass the BBB	GSC Sensitivity to Drug (High, Resistant, Minimal/Insensitive, Moderate)	References
Tandutinib/MLN-518	FLT3, PDGFR, c-KIT inhibitor	Oral (Pill)	NK (No studies)	NK (No studies)	–
Pemetrexed	TS, DHFR, GARFT inhibitor	I.V.	No	NK (No studies)	[70]
Paclitaxel Poliglumex/CT-2103	Plant alkaloid	Injection, I.V.	NK (No studies)	Resistant	[7]
Naltrexone	MOR, KOR, DOR antagonist	I.V., Oral (Pill)	No	NK (No studies)	[71]
Capecitabine/Xeloda	Metabolizes to 5-FU, a thymidylate synthase inhibitor	Oral (Pill)	Yes: low penetration Yes	NK (No studies)	[72], [73]
Armodafinil	Enantiopure of the eugeroic Modafinil (Provigil)	Oral (Pill)	NK	NK (No studies)	[74]
Fluciclatide Injection/AH111585 (F18)	Peptide, Radiopharmaceutical diagnostic	Injection, I.V.	NK (No studies)	NK (No studies)	–
Cabazitaxel/XRP6258	Semi – synthetic derivative of a natural taxoid	I.V.	NK (No studies)	NK (No studies)	–
Tetra-O-Methyl Nordihydroguaiaretic Acid/Terameprocol	Synthetic tetra-methylated derivative of NDGA; Sp1 transcriptional inhibitor	I.V., I.M., I.D., I.P., subcutaneous	NK (No studies)	NK (No studies)	–
6-Thioguanine/6-TG	Thio analogue of guanine; utilizes HGPRTase to be converted to 6-TGMP, which may hamper guanine nucleotide synthesis	Oral (Pill), I.V.	Yes	NK (No studies)	[75]
Celecoxib/Celebrex	NSAID	Oral (Capsule)	NK (No studies)	NK (No studies)	–
Lomustine/CCNU	Alkylating antineoplastic agent	Oral (Capsule)	Yes: MET nanoparticles Yes	NK	[76], [77], [78]
Sonidegib/LDE225	Hedgehog signaling pathway inhibitor via smoothened antagonist	Oral (Capsule)	NK (No studies)	Moderate	[79], [80]
Sorafenib/Nexavar	VEGFR, PDGFR, C-Raf, B-Rafinhibitor, Antineoplastic agent	Oral (Pill)	No	Moderate High	[81], [82], [83], [84]
Dendritic Cell Vaccine	Immunotherapeutic	Injection, I.V., I.D.	NK: not specific	High	[85], [86], [87]
Vismodegib/Erivedge	Hedgehog signaling pathway inhibitor, Antineoplastic agent	Oral (Capsule)	NK: not specific	NK: not specific	[88], [80]
Carboxyamidotriazole	Calcium channel blocker, Angiogenesis inhibitor	?	NK (No studies)	NK (No studies)	–
Hiltonol/Poly ICLC	Immunostimulant	I.M., Injection	No: enhances BBB integrity	NK (No studies)	[89]
Fotemustine/Mustoforan	Nitrosourea alkylating agent	I.V.	Yes Yes: rapidly	NK (No studies)	[90], [91]
BrUOG 263/Prostate Specific Membrane Antigen	Glycoprotein enzyme	?	NK (No studies)	NK (No studies)	–
Bosutinib	ATP-competitive Tyrosine-kinase inhibitor	Oral (Pill)	Yes	NK (No studies)	[92]

Abbreviations: NK - Not Known; SLNs – solid lipid nanoparticles; NSAID - Nonsteroidal anti-inflammatory drug; MET - Molecular Envelope Technology; HGF - hepatocyte growth factor; EGFR – epidermal growth factor receptor; VEGFR – vascular endothelial growth factor receptor; PDGFR – platelet derived growth factor receptor; FGFR - fibroblast growth factor receptor; MOR - μ-opioid receptor; KOR - κ-opioid receptor; DOR - δ-opioid receptor; I.V. – intra-venous I.A. – intra-arterial; I.C. – intra-carotid; I.N. – intra-nasal; I.M. – intra-muscular; I.D. – intra-dermal; I.P. – intra-peritoneally; FLT3 – FMS-like tyrosine kinase 3; HER2 - erbB2; HDAC - histone deacetylases; TS - thymidylate synthase; DHFR - dihydrofolate reductase; GARFT - glycinamide ribonucleotide formyltransferase; NDGA - nordihydroguaiaretic acid; HGPRTase - hypoxanthine-guanine phosphoribosyltransferase; TGMP - 6-thioguanosine monophosphate