cumulative dose of 30-60 Gy in 2.0-4.0 Gy fractions, or in a cumulative dose of 34 Gy in 3.4 Gy fractions, or in a cumulative dose of 35-45 Gy in 2.5-3.0 Gy fractions, or in a cumulative dose of 50 Gy in 2.5 Gy fractions.

Additional Therapeutic Agents

[0074] As used here, the “one or more additional therapeutic agents” employed in the methods described herein include those agents that are known to be useful for treating brain tumors, i.e., having a therapeutic effect on, alleviating one or more symptoms of, altering the progression of, eradicating, reducing the size of, slowing or inhibiting the growth of, delaying or minimizing one or more symptoms associated with, reducing the malignancy of, or inducing stasis of the brain tumor, or alleviating or minimizing one or more side effects associated with another therapy applied or administered to treat the brain tumor..

[0075] In some embodiments, the one or more additional therapeutic agents include one or more of a DNA-reactive agent, a PARP inhibitor, an anti-emesis agent, an anti-convulsant or anti-epileptic agent, a checkpoint inhibitor, PCV chemotherapy, bevacizumab, and gemcitabine.

[0076] In some embodiments, the one or more additional therapeutic agents is a DNA-reactive agent. As used herein, “DNA-reactive agents” are those agents, such as alkylating agents, cross-linking agents, and DNA intercalating agents, which interact covalently or non-covalently with cellular DNA. For example, DNA-reactive agents include adozelesin, altretamine, bizelesin, busulfan, carboplatin, carboquone, carmustine, chlorambucil, cisplatin, cyclophosphamide, dacarbazine, estramustine, fotemustine, hepsulfam, ifosfamide, improsulfan, irofulven, lomustine, mechlorethamine, melphalan, mitozolomide, nedaplatin, oxaliplatin, piposulfan, procarbazine, semustine, streptozocin, temozolomide, thiotepa, treosulfan, diethylnitrosoamine, benzo(a)pyrene, doxorubicin, mitomycin-C, and the like. Many

clonazepam, clorazepate, diazepam, midazolam, lorazepam, nitrazepam, temazepam, nimetazepam, potassium bromide, felbamate, carbamazepine, oxcarbazepine, eslicarbazepine acetate, valproic acid, sodium valproate, divalproex sodium, vigabatrin, progabide, tiagabine, topiramate, gabapentin, pregabalin, ethotoin, phenytoin, mephenytoin, fosphenytoin, paramethadione, trimethadione, ethadione, beclamide, primidone, brivaracetam, etiracetam, levetiracetam, seletracetam, ethosuximide, phensuximide, mesuximide, acetazolamide, sultiame, methazolamide, zonisamide, lamotrigine, pheneturide, phenacemide, valpromide, valnoctamide, perampanel, stiripentol, pyridoxine, and the like.

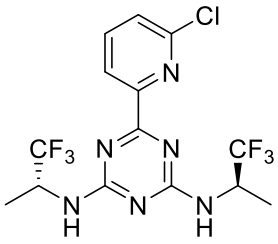
[0081] In some embodiments, the one or more additional therapeutic agents is a checkpoint inhibitor. As used herein, “checkpoint inhibitor” refers to a therapeutic agent that inhibits an immune checkpoint (e.g., CTLA-4, PD-1/PD-L1, and the like) that otherwise would prevent immune system attacks on cancer cells, thereby allowing the immune system to attack the cancer cells. Examples of check point inhibitors include ipilimumab, nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab, BGB-A317, spartalizumab, and the like.

[0082] In some embodiments, the one or more additional therapeutic agents is PCV chemotherapy. As used herein, “PCV chemotherapy” refers to a chemotherapy regimen comprising the combined administration of procarbazine, lomustine (which is sold under the trade name CCNU®), and vincristine (which is sold under the trade name Onocovin®). Typically, the vincristine is administered intravenously, while the procarbazine, and lomustine are administered orally. PCV chemotherapy often is administered in cycles, wherein each cycle comprises a single administration of vincristine and lomustine and a 10-day course of treatment with procarbazine.

[0083] In some embodiments, the one or more additional therapeutic agents is bevacizumab. Bevacizumab, which is sold under the trade name Avastin®, is a recombinant humanized monoclonal antibody.

CLAIMS

1. Use of a compound of formula (I):



(I);

or a pharmaceutically acceptable salt thereof; in the preparation of a medicament for treating glioma characterized by the presence of an IDH1 mutation or an IDH2 mutation, wherein the IDH1 or IDH2 mutation results in accumulation of R(-)-2-hydroxyglutarate, wherein the medicament is to be administered with radiation therapy in amounts effective for treating glioma; wherein said compound of formula (I), or a pharmaceutically acceptable salt thereof and the radiation are to be administered concurrently or sequentially.

2. The use of claim 1, wherein said compound of formula (I), or a pharmaceutically acceptable salt thereof, is to be administered in an amount of from 10 to 50 mg/day.

3. The use of claim 1, wherein said radiation therapy is to be administered in the form of x-ray radiation.

4. The use of claim 1, wherein said radiation therapy is to be administered in a cumulative dose of from 30 to 60 Gy.

5. The use of claim 1, wherein the IDH1 mutation is an R132X mutation.

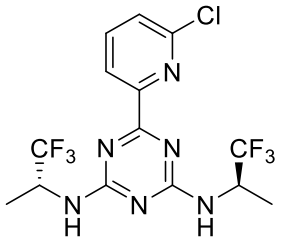
6. The use of claim 5, wherein the IDH1 mutation is an R132H or R132C mutation.

7. The use of claim 1, wherein the IDH2 mutation is an R140X or R172X mutation.

8. The use of claim 7, wherein the IDH2 mutation is an R140Q, R140W, or R140L mutation.

9. The use of claim 7, wherein the IDH2 mutation is an R172K or R172G mutation.

10. Use of a compound of formula (I):



(I);

or a pharmaceutically acceptable salt thereof in the preparation of a medicament for treating a glioma characterized by the presence of an IDH1 mutation or an IDH2 mutation, wherein the IDH1 or IDH2 mutation results in accumulation of R(-)-2-hydroxyglutarate;wherein the medicament is to be administered with one or more additional therapeutic agents; in amounts effective for treating the glioma, wherein said compound of formula (I), or a pharmaceutically acceptable salt thereof, and one or more additional therapeutic agents are to be administered concurrently or sequentially.

11. The use of claim 10, wherein the one or more additional therapeutic agents is a DNA-reactive agent.

12. The use of claim 11, wherein the DNA-reactive agent is temozolomide.

13. The use of claim 12, wherein said temozolomide is to be administered in a daily dose of from 150-200 mg/m^2, based on the patient's body surface area.

14. The use of claim 10, wherein the one or more additional therapeutic agents is a PARP inhibitor.

15. The use of claim 10, wherein the one or more additional therapeutic agents is an anti-emesis agent.

16. The use of claim 10, wherein the one or more additional therapeutic agents is an anti-convulsant or anti-epileptic agent.

17. The use of claim 10, wherein the one or more additional therapeutic agents is a checkpoint inhibitor.

18. The use of claim 10, wherein the one or more additional therapeutic agents is PCV chemotherapy.

19. The use of claim 10, wherein the one or more additional therapeutic agents is bevacizumab.

20. The use of claim 10, wherein the one or more additional therapeutic agents is gemcitabine.

21. The use of any one of claims 10-20, wherein said compound of formula (I), or a pharmaceutically acceptable salt thereof, is to be administered in an amount of from 10 to 50 mg/day.

22. The use of claim 10, wherein the IDH1 mutation is an R132X mutation.

23. The use of claim 22, wherein the IDH1 mutation is an R132H or R132C mutation.

24. The use of claim 10, wherein the IDH2 mutation is an R140X or R172X mutation.

25. The use of claim 24, wherein the IDH2 mutation is an R140Q, R140W, or R140L mutation.

26. The use of claim 24, wherein the IDH2 mutation is an R172K or R172G mutation.

27. The use of claim 10, wherein radiation therapy is also to be administered.

28. The use of any one of claims 1 to 27, wherein said compound of formula (I) is to be administered in non-salt form.