RAF INHIBITOR FOR TREATING LOW GRADE GLIOMA

STATEMENT AS TO FEDERALLY SPONSORED RESEARCH

[0001] This invention was made with government support under award number P50 CA 165962 as part of the SPORE grant for Targeted Therapies in Gliomas by National Cancer Institute of the National Institutes of Health. The government has certain rights in the invention.

CROSS-REFERENCE

[0002] This application claims the benefit of U.S. Provisional Patent Application No. 63/110,724 filed on November 6, 2020, and U.S. Provisional Patent Application No. 63/138,285, filed on January 15, 2021, the entire contents of each of which are incorporated herein by reference.

BACKGROUND

[0003] In 2012, there were an estimated 14.1 million cancer cases around the world. This number is expected to increase to 24 million by 2035. Cancer remains the second most common cause of death in the US, accounting for nearly 1 of every 4 deaths. In 2014, there will be an estimated 1,665,540 new cancer cases diagnosed and 585,720 cancer deaths in the US. Although medical advances have improved cancer survival rates, certain patient populations and particular cancers still require further research. In particular, there is an ongoing need for treatment of cancers in pediatric patients.

[0004] Each year, approximately 15,500 children under the age of 18 in the United States and 300,000 globally are diagnosed with cancer. Moreover, cancer remains the most common cause of death by disease for children in the United States, accounting for over 1,700 deaths per year. Despite the need for safer and more effective therapies for childhood cancers, new drugs for pediatric patients are rare. There are no approved therapies and no standard of care for pediatric patients with relapsed or progressive low-grade glioma, or pLGG, the most common brain tumor diagnosed in children. Thus, there exists an unmet need for new and more effective treatment for pediatric cancer patients.

SUMMARY

[0004a] In an aspect of the present disclosure, there is provided a use of (R)-2-(1-(6-amino-5-chloropyrimidine-4-carboxamido)ethyl)-N-(5-chloro-4-(trifluoromethyl)pyridin-2-yl)thiazole-5-carboxamide (Compound A), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a low grade glioma (LGG) in a subject in need thereof,

wherein the Compound A, or a pharmaceutically acceptable salt thereof, is to be administered to the subject, wherein an initial dose of the Compound A, or a pharmaceutically acceptable salt thereof is equivalent to about 400 mg/m^2 to about 600 mg/m^2 of Compound A per week,

wherein the subject is less than 20 years of age.

[0004b] In another aspect of the present disclosure, there is provided a use of (R)-2-(1-(6-amino-5-chloropyrimidine-4-carboxamido)ethyl)-N-(5-chloro-4-(trifluoromethyl)pyridin-2-yl)thiazole-5-carboxamide (Compound A), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a pediatric low grade glioma (pLGG) in a subject in need thereof,

wherein the Compound A, or a pharmaceutically acceptable salt thereof, is to be administered to the subject, wherein an initial dose of the Compound A, or a pharmaceutically acceptable salt thereof is equivalent to about 420 mg/m^2 of Compound A per week,

wherein the subject is about 6 months to about 25 years old.

[0004c] In a further aspect of the present disclosure, there is provided a use of (R)-2-(1-(6-amino-5-chloropyrimidine-4-carboxamido)ethyl)-N-(5-chloro-4-(trifluoromethyl)pyridin-2-yl)thiazole-5-carboxamide (Compound A), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a low grade glioma (LGG) in a subject in need thereof,

wherein Compound A, or a pharmaceutically acceptable salt thereof, is to be administered to the subject in an amount sufficient to achieve in the subject a maximum observed blood plasma concentration (Cmax) of Compound A of at least 2000 ng/mL,

wherein the subject is less than 20 years of age.

[0004d] In another aspect of the present disclosure, there is provided a use of (R)-2-(1-(6-amino-5-chloropyrimidine-4-carboxamido)ethyl)-N-(5-chloro-4-(trifluoromethyl)pyridin-2-yl)thiazole-5-carboxamide (Compound A), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a low grade glioma (LGG) in a subject in need thereof,

wherein Compound A, or a pharmaceutically acceptable salt thereof, is to be administered to the subject in an amount sufficient to achieve an area under the concentration curve (AUCss) of Compound A of at least about 400,000 ng*h/mL,

wherein the subject is less than 20 years of age.

[0004e] In a further aspect of the present disclosure, there is provided a use of (R)-2-(1-(6-amino-5-chloropyrimidine-4-carboxamido)ethyl)-N-(5-chloro-4-(trifluoromethyl)pyridin-2-yl)thiazole-5-carboxamide (Compound A), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a low grade glioma (LGG) in a subject in need thereof:

wherein Compound A, or a pharmaceutically acceptable salt thereof, is to be administered in combination with one or more therapeutic agents for treating a skin-related condition or disorder,

wherein the subject is less than 20 years of age.

[0005] In one ~~aspect~~example, the present disclosure provides a method of treating a low grade glioma (LGG) in a subject in need thereof comprising, administering (R)-2-(1-(6-amino-5-chloropyrimidine-4-carboxamido)ethyl)-N-(5-chloro-4-(trifluoromethyl)pyridin-2-yl)thiazole-5-carboxamide (Compound A), or a pharmaceutically acceptable salt thereof to the subject, wherein an initial dose of the Compound A, or a pharmaceutically acceptable salt thereof is

equivalent to about 400 mg/m^2 to about 600 mg/m^2 of Compound A per week, and wherein the subject is less than 20 years of age. In some ~~embodiment~~example the initial dose of the Compound A, or a pharmaceutically acceptable salt thereof is equivalent to about 500 mg/m^2 to about 600 mg/m^2 of Compound A per week. In some ~~embodiment~~example, the initial dose of the Compound A, or a pharmaceutically acceptable salt thereof is equivalent to about 400 mg/m^2 to about 500 mg/m^2 of Compound A per week. In some ~~embodiment~~example, the initial dose of the Compound A, or a pharmaceutically acceptable salt thereof is equivalent to about 410 mg/m^2 to about 430 mg/m^2 of Compound A per week. In some ~~embodiment~~example, the initial dose of the Compound A, or a pharmaceutically acceptable salt thereof is equivalent to about 420 mg/m^2 of Compound A per week. In some ~~embodiment~~example, the initial dose of the Compound A, or a pharmaceutically acceptable salt thereof is equivalent to about 530 mg/m^2 of Compound A per week.

[0006] In one ~~aspect~~example, the present disclosure provides a method of treating a low grade glioma (LGG) in a subject in need thereof comprising, administering to the subject (R)-2-(1-(6-amino-5-chloropyrimidine-4-carboxamido)ethyl)-N-(5-chloro-4-(trifluoromethyl)pyridin-2-yl)thiazole-5-carboxamide (Compound A), or a pharmaceutically acceptable salt thereof in an amount sufficient to achieve in the subject a maximum observed blood plasma concentration (Cmax) of Compound A of at least 2000 ng/mL, and wherein the subject is less than 20 years of age. In some ~~embodiment~~example, the Compound A or a pharmaceutically acceptable salt thereof is administered in an amount sufficient to achieve in the subject a Cmax of Compound A of 2000 ng/mL to 8000 ng/mL.

[0007] In one ~~aspect~~example, the present disclosure provides a method of treating a low grade glioma (LGG) in a subject in need thereof comprising, administering to the subject (R)-2-(1-(6-amino-5-chloropyrimidine-4-carboxamido)ethyl)-N-(5-chloro-4-(trifluoromethyl)pyridin-2-yl)thiazole-5-carboxamide (Compound A), or a pharmaceutically acceptable salt thereof in an amount sufficient to achieve an area under the concentration curve (AUCss) of Compound A of at least about 400,000 ng*h/ml, wherein the subject is less than 20 years of age. In some ~~embodiment~~example, the Compound A or a pharmaceutically acceptable salt thereof is administered in an amount sufficient to achieve in the subject an (AUCss) of Compound A of 400,000 ng*h/ml to 1,600,000 ng*h/ml.

[0008] In one ~~aspect~~example, provided herein is a method of treating a low grade glioma (LGG) in a subject in need thereof comprising: administering to the subject (i) (R)-2-(1-(6-amino-5-chloropyrimidine-4-carboxamido)ethyl)-N-(5-chloro-4-(trifluoromethyl)pyridin-2-yl)thiazole-5-carboxamide (Compound A), or a pharmaceutically acceptable salt thereof, in combination with (ii) one or more therapeutic agents for treating a skin-related condition or disorder and wherein

the subject is less than 20 years of age. In some ~~embodiment~~examples, the one or more therapeutic agents are administered on pigmented skin.

[0009] In one ~~aspect~~example, described herein is a method of treating a low grade glioma (LGG) in a subject in need thereof by administering Compound A or a pharmaceutically acceptable salt thereof. In some ~~embodiment~~examples, the LGG is a radiographically recurrent or radiographically progressive disease. In some ~~embodiment~~examples, the Compound A or a pharmaceutically acceptable salt thereof is (R)-2-(1-(6-amino-5-chloropyrimidine-4-carboxamido)ethyl)-N-(5-chloro-4-(trifluoromethyl)pyridin-2-yl)thiazole-5-carboxamide. In some ~~embodiment~~examples, the Compound A or a pharmaceutically acceptable salt thereof is administered as a liquid suspension. In some ~~embodiment~~examples, the Compound A or a pharmaceutically acceptable salt thereof is administered as a tablet. In some ~~embodiment~~examples, the Compound A or a pharmaceutically acceptable salt thereof is administered as a single dose per week. In some ~~embodiment~~examples, the Compound A or a pharmaceutically acceptable salt thereof is administered 2-4 doses a week. In some ~~embodiment~~examples, the Compound A or a pharmaceutically acceptable salt thereof is administered for a period of at least 24 months. In some ~~embodiment~~examples, the subject is 20 years of age or less. In some ~~embodiment~~examples, the subject is 15 years of age or less. In some ~~embodiment~~examples, the subject has a body surface area (BSA) of from 0.5 m^2 to about 2.0 m^2. In some ~~embodiment~~examples, the subject has a BSA of from 0.5 m^2 to about 1.5 m^2. In some ~~embodiment~~examples, the LGG has one or more of the following mutations: RAS positive mutation, RAF positive mutation, MEK positive mutation, and ERK positive mutation. In some ~~embodiment~~examples, the LGG has a BRAF mutation. In some ~~embodiment~~examples, the BRAF mutation is a non-V600 BRAF mutation. In some ~~embodiment~~examples, the subject is identified having one or more of the following wild-type fusions: KIAA1549:BRAF, STARD3NL:BRAF, BCAS1:BRAF, KHDRBS2:BRAF, CCDC6:BRAF, FAM131B:BRAF, SRGAP:BRAF, CLCN6:BRAF, GNAI1:BRAF, MRKN1:BRAF, GIT2:BRAF, GTF21:BRAF, FXR1:BRAF, RNF130:BRAF, BRAF:MACF1, TMEM106B:BRAF, PPC1CC:BRAF, CUX1:BRAF, SRGAP3:RAF1, QK1:RAF1, FYCO:RAF1, ATG7:RAF1, and NFIA:RAF1. In some ~~embodiment~~examples, the subject is identified having KIAA1549:BRAF wild-type fusion.

[0010] In another ~~aspect~~example, the present disclosure provides a method of treating a low grade glioma (LGG) in a subject in need thereof, as described herein, which further comprises the administration of Compound A or a pharmaceutically acceptable salt thereof at a maximum dose. In some ~~embodiment~~examples, the maximum dose of Compound A or a pharmaceutically acceptable salt thereof, is 600 mg. In some ~~embodiment~~examples, the maximum dose of Compound A or a pharmaceutically acceptable salt thereof, is 600 mg orally (PO) once a week.

CLAIMS

WHAT IS CLAIMED IS:

1. Use of (R)-2-(1-(6-amino-5-chloropyrimidine-4-carboxamido)ethyl)-N-(5-chloro-4-(trifluoromethyl)pyridin-2-yl)thiazole-5-carboxamide (Compound A), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for ~~A method of~~ treating a low grade glioma (LGG) in a subject in need thereof ~~comprising~~,

~~administering (R)-2-(1-(6-amino-5-chloropyrimidine-4-carboxamido)ethyl)-N-(5-chloro-4-(trifluoromethyl)pyridin-2-yl)thiazole-5-carboxamide (~~wherein the Compound A~~)~~, or a pharmaceutically acceptable salt thereof, is to be administered to the subject, wherein an initial dose of the Compound A, or a pharmaceutically acceptable salt thereof is equivalent to about 400 mg/m^2 to about 600 mg/m^2 of Compound A per week,

wherein the subject is less than 20 years of age.

2. The ~~method~~use of claim 1, wherein the initial dose of the Compound A, or a pharmaceutically acceptable salt thereof is equivalent to about 500 mg/m^2 to about 600 mg/m^2 of Compound A per week.
3. The ~~method~~use of claim 1, wherein the initial dose of the Compound A, or a pharmaceutically acceptable salt thereof is equivalent to about 400 mg/m^2 to about 500 mg/m^2 of Compound A per week.
4. The ~~method~~use of claim 1, wherein the initial dose of the Compound A, or a pharmaceutically acceptable salt thereof is equivalent to about 420 mg/m^2 of Compound A per week.
5. The ~~method~~use of claim 1, wherein the initial dose of the Compound A, or a pharmaceutically acceptable salt thereof is equivalent to about 530 mg/m^2 of Compound A per week.
6. Use of (R)-2-(1-(6-amino-5-chloropyrimidine-4-carboxamido)ethyl)-N-(5-chloro-4-(trifluoromethyl)pyridin-2-yl)thiazole-5-carboxamide (Compound A), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a pediatric low grade glioma (pLGG) in a subject in need thereof,

wherein the Compound A, or a pharmaceutically acceptable salt thereof, is to be administered to the subject, wherein an initial dose of the Compound A, or a pharmaceutically acceptable salt thereof is equivalent to about 420 mg/m^2 of Compound A per week,

wherein the subject is about 6 months to about 25 years old.

~~6.~~7. Use of (R)-2-(1-(6-amino-5-chloropyrimidine-4-carboxamido)ethyl)-N-(5-chloro-4-(trifluoromethyl)pyridin-2-yl)thiazole-5-carboxamide (Compound A), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for ~~A method of~~ treating a low grade glioma (LGG) in a subject in need thereof ~~comprising~~,

~~administering to the subject (R)-2-(1-(6-amino-5-chloropyrimidine-4-carboxamido)ethyl)-N-(5-chloro-4-(trifluoromethyl)pyridin-2-yl)thiazole-5-carboxamide (~~wherein Compound A~~)~~, or a pharmaceutically acceptable salt thereof, is to be administered to the subject in an amount sufficient to achieve in the subject a maximum observed blood plasma concentration (Cmax) of Compound A of at least 2000 ng/mL,

wherein the subject is less than 20 years of age.

~~7.~~8. The ~~method~~use of claim ~~7~~6, wherein the Compound A or a pharmaceutically acceptable salt thereof is administered in an amount sufficient to achieve in the subject a Cmax of Compound A of 2000 ng/mL to 8000 ng/mL.

~~8.~~9. Use of (R)-2-(1-(6-amino-5-chloropyrimidine-4-carboxamido)ethyl)-N-(5-chloro-4-(trifluoromethyl)pyridin-2-yl)thiazole-5-carboxamide (Compound A), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for ~~A method of~~ treating a low grade glioma (LGG) in a subject in need thereof ~~comprising~~,

~~administering to the subject (R)-2-(1-(6-amino-5-chloropyrimidine-4-carboxamido)ethyl)-N-(5-chloro-4-(trifluoromethyl)pyridin-2-yl)thiazole-5-carboxamide (~~wherein Compound A~~)~~, or a pharmaceutically acceptable salt thereof, is to be administered to the subject in an amount sufficient to achieve an area under the concentration curve (AUCss) of Compound A of at least about 400,000 ng*h/mL,

wherein the subject is less than 20 years of age.

~~9.~~10. The ~~method~~use of claim ~~9~~8, wherein the Compound A or a pharmaceutically acceptable salt thereof is to be administered in an amount sufficient to achieve in the subject an (AUCss) of Compound A of 400,000 ng*h/ml to 1600,000 ng*h/ml.

~~10.~~11. Use of (R)-2-(1-(6-amino-5-chloropyrimidine-4-carboxamido)ethyl)-N-(5-chloro-4-(trifluoromethyl)pyridin-2-yl)thiazole-5-carboxamide (Compound A), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for ~~A method of~~ treating a low grade glioma (LGG) in a subject in need thereof ~~comprising~~:

~~administering to the subject (i) (R)-2-(1-(6-amino-5-chloropyrimidine-4-carboxamido)ethyl)-N-(5-chloro-4-(trifluoromethyl)pyridin-2-yl)thiazole-5-carboxamide (~~wherein Compound A~~)~~, or a pharmaceutically acceptable salt thereof, is to be administered in combination with ~~(ii)~~ one or more therapeutic agents for treating a skin-related condition or disorder~~,~~.

wherein the subject is less than 20 years of age.

~~11.~~12. The ~~method~~use of claim 11~~10~~, wherein the one or more therapeutic agents are to be administered on pigmented skin.

~~12.~~13. The ~~method~~use of any one of claims 1 to ~~11~~12, wherein the LGG is a radiographically recurrent or radiographically progressive disease.

14. The use of any one of claims 1 to 12, wherein the LGG is a relapsed LGG or refractory LGG.

~~13.~~15. The ~~method~~use of any one of claims 1 to ~~12~~14, wherein the Compound A or a pharmaceutically acceptable salt thereof is (R)-2-(1-(6-amino-5-chloropyrimidine-4-carboxamido)ethyl)-N-(5-chloro-4-(trifluoromethyl)pyridin-2-yl)thiazole-5-carboxamide.

~~14.~~16. The ~~method~~use of any one of claims 1 to 15~~13~~, wherein the Compound A or a pharmaceutically acceptable salt thereof is to be administered as a liquid suspension.

~~15.~~17. The ~~method~~use of any one of claims 1 to 15~~13~~, wherein the Compound A or a pharmaceutically acceptable salt thereof is to be administered as a tablet.

~~16.~~18. The ~~method~~use of any one of claims 1 to 17~~15~~, wherein the Compound A or a pharmaceutically acceptable salt thereof is to be administered as a single dose per week.

~~17. The method of any one of claims 1 to 15, wherein the Compound A or a pharmaceutically acceptable salt thereof is administered 2-4 doses a week.~~

~~18.~~19. The ~~method~~use of any one of claims 1 to ~~17~~18, wherein the Compound A or a pharmaceutically acceptable salt thereof is to be administered for a period of at least 24 months.

~~19.~~20. The ~~method~~use of any one of claims 1 to 19~~18~~, wherein the subject is a child~~20 years of age or less~~.

~~20.~~21. The ~~method~~use of any one of claims 1 to 19~~18~~, wherein the subject is an adolescent~~15 years of age or less~~.

~~21.~~22. The ~~method~~use of any one of claims 1 to 21~~20~~, wherein the subject has a body surface area (BSA) of from 0.5 m^2 to about 2.0 m^2.

~~22.~~23. The ~~method~~use of any one of claims 1 to 21~~20~~, wherein the subject has a BSA of from 0.5 m^2 to about 1.5 m^2.

~~23.~~24. The ~~method~~use of any one of claims 1 to 23~~22~~, wherein the LGG has one or more of the following mutations: RAS positive mutation, RAF positive mutation, MEK positive mutation, and ERK positive mutation.

~~24.~~25. The ~~method~~use of any one of claims 1 to ~~22~~23, wherein the LGG has a BRAF mutation.

~~25.~~26. The ~~method~~use of claim 25~~24~~, wherein the BRAF mutation is a non-V600 BRAF mutation.

~~26.~~27. The ~~method~~use of claim 25~~24~~, wherein the BRAF mutation is V600E mutation.

~~27.~~28. The ~~method~~use of any one of claims 1 to 27~~26~~, wherein the subject is identified having one or more of the following wild-type fusions: KIAA1549:BRAF, STARD3NL:BRAF, BCAS1:BRAF, KHDRBS2:BRAF, CCDC6:BRAF, FAM131B:BRAF, SRGAP:BRAF,

CLCN6:BRAF, GNAI1:BRAF, MRKN1:BRAF, GIT2:BRAF, GTF21:BRAF, FXR1:BRAF, RNF130:BRAF, BRAF:MACF1, TMEM106B:BRAF, PPC1CC:BRAF, CUX1:BRAF, SRGAP3:RAF1, QK1:RAF1, FYCO:RAF1, ATG7:RAF1, and NFIA:RAF1.

~~28.~~29. The ~~method~~use of any one of claims 1 to ~~26~~27, wherein the subject is identified having KIAA1549:BRAF wild-type fusion.

~~29.~~30. The ~~method~~use of any one of claims 1 to ~~28~~29, wherein the subject has received one or more therapies selected from surgery, radiation, and chemotherapy before ~~the administering of~~ Compound A, or a pharmaceutically acceptable salt thereof, is to be administered.

~~30.~~31. The ~~method~~use of claim 30~~29~~, wherein the subject has received a complete or partial resection before ~~the administering of~~ Compound A, or a pharmaceutically acceptable salt thereof, is to be administered.

~~31.~~32. The ~~method~~use of any one of the preceding claims, wherein the Compound A or a pharmaceutically acceptable salt thereof is to be administered at a maximum dose of 600 mg per week.

~~32. The method of claim 31, wherein the maximum dose is 600 mg orally (PO) once a week.~~