

METHODS OF TREATING PEDIATRIC LOW-GRADE GLIOMA**CROSS-REFERENCE**

[0001] This application claims the benefit of US Provisional Application Serial Number 63/599,378 filed on November 15, 2023 and US Provisional Application Serial Number 63/637,875 filed on April 23, 2024, each of which is hereby incorporated by reference herein in its entirety.

BACKGROUND

[0002] 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.

[0003] Pediatric low-grade glioma (pLGG) is the most common brain tumor diagnosed in children, with patients suffering profound tumor and treatment-associated morbidities that can impact their life trajectory. For the vast majority of patients in the relapsed setting, there is no standard of care and no approved therapy. Thus, there exists an unmet need for new and more effective treatment for patients having pLGG.

BRIEF DESCRIPTION OF FIGURES

[0004] FIG. 1. FIREFLY-1 patient disposition/CONSORT diagram. This figure presents efficacy data from the evaluable population (enrolled patients who received at least one dose of tovorafenib and met the prespecified efficacy analyses criteria per each radiological assessment method according to the IRC) in arm 1 (registrational) and the safety data from arms 1 and 2 (safety-analysis set) as of a June 5, 2023 datacut. Patients were enrolled in arm 2 (extension) after arm 1 had fully accrued and closed for enrollment. ^aNot radiologically confirmed. ^bOnly patients with measurable disease at baseline per independent review were included. HGG, high-grade glioma; IRC, independent radiology review committee; LGG, low-grade glioma; RANO, Response Assessment in Neuro-Oncology; RAPNO, Response Assessment in Pediatric Neuro-Oncology.

[0005] FIGs 2A-2C. Maximal change in tumor size for evaluable patients. FIG 2A: Per RANO-HGG, FIG 2B: RAPNO, and FIG 2C: RANO-LGG criteria. Two patients are not shown in the waterfall plots: One patient died due to PD (not tovorafenib-related) before first tumor assessment and one patient with missing T1 Gd+ imaging at baseline was deemed not evaluable. The dashed lines indicate the range of growth/shrinkage of target lesions to be considered as one of the requirements for PD, SD, MR, PR or CR. BRAFi, BRAF inhibitor; CR, complete response; HGG, high-grade glioma; LGG, low-grade glioma; MEKi, MEK inhibitor; MR, minor response; PD, progressive disease; PR, partial response; RANO, Response Assessment in Neuro-Oncology; RAPNO, Response Assessment in Pediatric Neuro-Oncology; SD, stable disease.

[0006] FIGs 3A and 3B. Swimlane plot of time to response and duration of therapy. FIG 3A: Per RANO-HGG, and FIG 3B: RAPNO criteria. In patients with response, symbols indicate the start of response (MR,

PR or CR). If initial responses improved with continued treatment (from MR to confirmed PR, or from PR to confirmed CR), both the timepoint of the initial response and the timepoint that the response initially improved are marked accordingly. BRAFi, BRAF inhibitor; HGG, high-grade glioma; LGG, low-grade glioma; MEKi, MEK inhibitor; RANO, Response Assessment in Neuro-Oncology; RAPNO, Response Assessment in Pediatric Neuro-Oncology.

[0007] FIG 4A illustrates visual acuity assessments for patients. Percents may not add up to 100 due to rounding. LogMAR ranges adapted from Schultz-Bonsel K, et al. Invest Ophthalmol Vis Sci. 2006;47(3):1236-1240 and Gnekow AK, et al. Glioma Klin Padiatr. 2019;231(3):107-135. *Six patients are not included in the analysis; 4 had no visual acuity assessments done due to bilateral blindness, 1 had no baseline assessment, and 1 discontinued treatment and had no follow-up assessment after baseline. logMAR, logarithm of the minimum angle of resolution; RANO, Response Assessment in Neuro-Oncology; RAPNO, Response Assessment in Pediatric Neuro-Oncology-low-grade glioma. FIG 4B illustrates neuro-radiological correlation with visual acuity in the patients. logMAR, logarithm of the minimum angle of resolution; RANO, Response Assessment in Neuro-Oncology; RAPNO, Response Assessment in Pediatric Neuro-Oncology-low-grade glioma.

[0008] FIGs 5A-5C. Best change in tumor size in patients with an OPG who were deemed evaluable for response by the independent radiology review committee according to FIG 5A: RANO-HGG, FIG 5B: RAPNO, and FIG 5C: RANO-LGG criteria. RANO-HGG, RAPNO and RANO-LGG criteria. Data for one patient not included (RANO-HGG and RAPNO assessments). CR, complete response; HGG, high-grade glioma; LGG, low-grade glioma; MR, minor response; OPG, optic pathway glioma; PD, progressive disease; PR, partial response; RANO, Response Assessment in Neuro-Oncology; RAPNO, Response Assessment in Pediatric Neuro-Oncology; SD, stable disease.

[0009] FIG 6. Swimlane plots of time to response and duration of therapy according to RAPNO and RANO-LGG criteria. In patients with confirmed response, symbols indicate the start of response (MR or PR). If initial responses improved with continued treatment (from MR to confirmed PR), both the timepoint of the initial response and the timepoint that the response initially improved are marked accordingly. BRAFi, BRAF inhibitor; LGG, low-grade glioma; MEKi, MEK inhibitor; PR, partial response; MR, minor response; RANO, Response Assessment in Neuro-Oncology; RAPNO, Response Assessment in Pediatric Neuro-Oncology.

[0010] FIGs 7A and 7B. FIG 7A: On study change in visual acuity in best eye. FIG 7B: Visual acuity outcomes in patients with a best overall confirmed radiological response of MR according to RAPNO and RANO-LGG. Best response represents best confirmed VA response with end of treatment/datacut VA status determined by the single final available assessment. EOT, end of treatment; LGG, low-grade glioma; LogMAR, logarithm of the minimum angle of resolution; MR, minor response; RANO, Response Assessment in Neuro-Oncology; RAPNO, Response Assessment in Pediatric Neuro-Oncology.

SUMMARY

[0011] In one aspect, described herein is a method of treating a relapsed or refractory pediatric low-grade glioma (pLGG) in a subject in need thereof, comprising administering to the subject tovorafenib or a salt thereof, wherein the subject is 6 months of age or older. In some embodiments, the pediatric low-grade glioma (pLGG) harbors a BRAF fusion or rearrangement, or BRAF V600 mutation. In certain embodiments, the method comprises administering to the subject a starting dose of tovorafenib or the salt thereof. In certain embodiments, the method comprises administering to the subject a reduced dose of tovorafenib or the salt thereof, and optionally a further reduced dose of tovorafenib or the salt thereof. In certain embodiments, the method comprises withholding the tovorafenib or the salt thereof prior to the administering of the reduced dose or further reduced dose.

[0012] The disclosure provides a method of treating pediatric low-grade glioma (pLGG) in a subject in need thereof, comprising selecting a subject that previously received MAP kinase inhibitor therapy and administering to the subject a type II pan-RAF inhibitor.

[0013] In certain embodiments, the subject had radiographic progression or no progression of the pLGG while receiving the MAP kinase inhibitor therapy. In certain embodiments, the subject had radiographic progression of the pLGG while receiving the MAP kinase inhibitor therapy. In certain embodiments, the subject is relapsed/refractory for pLGG following MAP kinase inhibitor therapy.

[0014] In certain embodiments, the MAP kinase inhibitor therapy is the most recently therapy administered to the subject. In certain embodiments, the MAP kinase inhibitor therapy is not the most recent therapy administered to the subject. In certain embodiments, the most recent therapy administered to the subject is selected from chemotherapy, radiation therapy, and surgery.

[0015] The disclosure also provides a method of treating optic pathway gliomas (OPCs) in a subject in need thereof, comprising selecting a subject that previously received MAP kinase inhibitor therapy and administering to the subject a type II pan-RAF inhibitor.

[0016] In certain embodiments, the subject had radiographic progression or no progression of the OPCs while receiving the MAP kinase inhibitor therapy. In certain embodiments, the subject had radiographic progression of the OPC while receiving the MAP kinase inhibitor therapy. In certain embodiments, the subject is relapsed/refractory for OPC following MAP kinase inhibitor therapy.

[0017] In certain embodiments, the subject previously received one or more additional therapeutic treatments including chemotherapy, radiation therapy, and surgery.

[0018] In certain embodiments, the type II pan-RAF inhibitor is tovorafenib or a salt thereof.

[0019] In certain embodiments, the pLGG has a BRAF mutation or fusion. In certain embodiments, the pLGG has a BRAF mutation. In certain embodiments, the BRAF mutation is a V600E mutation. In certain embodiments, the BRAF mutation is a mutation other than a V600E mutation.

[0020] In certain embodiments, the OPCs has a BRAF mutation or fusion. In certain embodiments, the OPCs has a BRAF mutation. In certain embodiments, the BRAF mutation is a V600E mutation. In certain embodiments, the BRAF mutation is a mutation other than a V600E mutation.

[0021] In certain embodiments, the MAP kinase inhibitor therapy comprises trametinib or a salt thereof.

[0022] In certain aspects, the disclosure provides a method of treating a pediatric low-grade glioma (pLGG) in a subject in need thereof, comprising administering to the subject a type II pan-RAF inhibitor for 2 months or more, wherein the pLGG shows radiographic progression after the initial month of administration.

[0023] In certain embodiments, the pLGG shows radiographic progression after the initial two months of administration. In certain embodiments, the type II pan-RAF inhibitor is administered to the subject for 3 or more, 4 or more, or 5 or more months. In certain embodiments, the type II pan-RAF inhibitor is tovorafenib or a salt thereof.

[0024] In certain embodiments, the pLGG has a BRAF mutation or fusion. In certain embodiments, the pLGG has a BRAF mutation. In certain embodiments, the BRAF mutation is a V600E mutation. In certain embodiments, the BRAF mutation is a mutation other than a V600E mutation.

[0025] In certain embodiments, the subject is selected from a subject that previously received MAP kinase inhibitor therapy. In certain embodiments, the subject had radiographic progression or no progression of the pLGG while receiving the MAP kinase inhibitor therapy. In certain embodiments, the subject had radiographic progression of the pLGG while receiving the MAP kinase inhibitor therapy. In certain embodiments, the subject is relapsed/refractory for pLGG following MAP kinase inhibitor therapy. In certain embodiments, the MAP kinase inhibitor therapy is the most recently therapy administered to the subject. In certain embodiments, the MAP kinase inhibitor therapy is not the most recent therapy administered to the subject. In certain embodiments, the most recent therapy administered to the subject is selected from chemotherapy, radiation therapy, and surgery. In some embodiments, the MAP kinase inhibitor is Vemurafenib. In some embodiments, the MAP kinase inhibitor is Dabrafenib/Trametinib. In some embodiments, the MAP kinase inhibitor is Binimetinib. In some embodiments, the MAP kinase inhibitor is Trametinib.

[0026] In certain aspects, the disclosure provides a method of treating optic pathway gliomas (OPCs) in a subject in need thereof, comprising administering to the subject a type II pan-RAF inhibitor for 2 months or more, wherein the OPC shows radiographic progression after the initial month of administration.

[0027] In certain embodiments, the OPC shows radiographic progression after the initial two months of administration. In certain embodiments, the type II pan-RAF inhibitor is administered to the subject for 3 or more, 4 or more, or 5 or more months. In certain embodiments, the type II pan-RAF inhibitor is tovorafenib or a salt thereof.

[0028] In certain embodiments, the OPC has a BRAF mutation or fusion. In certain embodiments, the OPC has a BRAF mutation. In certain embodiments, the BRAF mutation is a V600E mutation. In certain embodiments, the BRAF mutation is a mutation other than a V600E mutation.

[0029] In certain embodiments, the subject is selected from a subject that previously received MAP kinase inhibitor therapy. In certain embodiments, the subject had radiographic progression or no progression of the OPC while receiving the MAP kinase inhibitor therapy. In certain embodiments, the subject had radiographic progression of the OPC while receiving the MAP kinase inhibitor therapy. In certain

embodiments, the subject is relapsed/refractory for pLGG following MAP kinase inhibitor therapy. In certain embodiments, the MAP kinase inhibitor therapy is the most recently therapy administered to the subject. In certain embodiments, the MAP kinase inhibitor therapy is not the most recent therapy administered to the subject. In certain embodiments, the most recent therapy administered to the subject is selected from chemotherapy, radiation therapy, and surgery.

[0030] In certain embodiments, the subject previously received one or more additional therapeutic treatments including chemotherapy, radiation therapy, and surgery.

[0031] In certain embodiments, the subject is administered from about 350 mg/m² to about 400 mg/m² of tovorafenib or a salt thereof per week. In certain embodiments, the subject is administered about 380 mg/m² of tovorafenib or a salt thereof per week. In certain embodiments, the subject is administered from about 400 mg/m² to about 450 mg/m² of tovorafenib or a salt thereof per week. In certain embodiments, the subject is administered about 420 mg/m² of tovorafenib or a salt thereof per week. In certain embodiments, the subject is administered tovorafenib or a salt thereof for 10 weeks or more. In certain embodiments, the subject is administered tovorafenib or a salt thereof for 16 weeks or more.

[0032] In certain embodiments, the tovorafenib or a salt thereof is administered as a tablet or liquid formulation. In certain embodiments, the tovorafenib or a salt thereof is administered with food.

[0033] In certain embodiments, the tovorafenib or a salt thereof is administered without food.

DETAILED DESCRIPTION

Definitions

[0034] In this application, the use of “or” means “and/or” unless stated otherwise. The terms “and/or” and “any combination thereof” and their grammatical equivalents as used herein, can be used interchangeably. These terms can convey that any combination is specifically contemplated. Solely for illustrative purposes, the following phrases “A, B, and/or C” or “A, B, C, or any combination thereof” can mean “A individually; B individually; C individually; A and B; B and C; A and C; and A, B, and C.” The term “or” can be used conjunctively or disjunctively, unless the context specifically refers to a disjunctive use.

[0035] The term “about” or “approximately” can mean within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on how the value is measured or determined, i.e., the limitations of the measurement system. For example, “about” can mean within 1 or more than 1 standard deviation, per the practice in the art. Alternatively, “about” can mean a range of up to 20%, up to 15%, up to 10%, up to 5%, or up to 1% of a given value. In some embodiments, “about” refers to a range of up to 10% of a given value. In some embodiments, “about” refers to a range of up to 5% of a given value. Alternatively, particularly with respect to biological systems or processes, the term can mean within an order of magnitude, within 5-fold, or within 2-fold, of a value.

[0036] As used in this specification and claim(s), the words “comprising” (and any form of comprising, such as “comprise” and “comprises”), “having” (and any form of having, such as “have” and “has”), “including” (and any form of including, such as “includes” and “include”) or “containing” (and any form

of containing, such as “contains” and “contain”) are inclusive or open-ended and do not exclude additional, unrecited elements or method steps. It is contemplated that any embodiment discussed in this specification can be implemented with respect to any method or composition of the present disclosure, and vice versa. Furthermore, compositions of the present disclosure can be used to achieve methods of the present disclosure.

[0037] Reference in the specification to “some embodiments,” “an embodiment,” “certain embodiment” or “other embodiments” means that a particular feature, structure, or characteristic described in connection with the embodiments is included in at least some embodiments, but not necessarily all embodiments, of the present disclosures.

[0038] As used herein, the terms “treatment,” “treat,” and “treating” are meant to include the full spectrum of intervention for the cancer from which the subject is suffering, such as administration of a compound such as tovorafenib to alleviate, slow, stop, or reverse one or more symptoms of the cancer and to delay the progression of the cancer even if the cancer is not actually eliminated. Treatment can include, for example, a decrease in the severity of a symptom, the number of symptoms, or frequency of relapse, e.g., the inhibition of tumor growth, the arrest of tumor growth, or the regression of already existing tumors.

[0039] The term “therapeutically effective amount” as used herein to refer to an amount effective at the dosage and duration necessary to achieve the desired therapeutic result. A therapeutically effective amount of the composition may vary depending on factors such as the individual's condition, age, sex, and weight, and the ability of the protein to elicit the desired response of the individual. A therapeutically effective amount is also an amount that exceeds any toxic or deleterious effect of the composition that would have a beneficial effect on the treatment.

[0040] The term “subject,” as used herein, means a mammal, and “mammal” includes, but is not limited to a human.

[0041] A “pharmaceutically acceptable salt” suitable for the disclosure may be an acid or base salt that is generally considered in the art to be suitable for use in contact with the tissues of human beings or animals without excessive toxicity, irritation, allergic response, or other problem or complication. Such salts include mineral and organic acid salts of basic residues such as amines, as well as alkali or organic salts of acidic residues such as carboxylic acids. Specific pharmaceutical salts include, but are not limited to, salts of acids such as hydrochloric, phosphoric, hydrobromic, malic, glycolic, fumaric, sulfuric, sulfamic, sulfanilic, formic, toluenesulfonic, methanesulfonic, benzene sulfonic, ethane disulfonic, 2-hydroxyethyl sulfonic, nitric, benzoic, 2-acetoxybenzoic, citric, tartaric, lactic, stearic, salicylic, glutamic, ascorbic, pamoic, succinic, fumaric, maleic, propionic, hydroxymaleic, hydroiodic, phenylacetic, alkanoic such as acetic, $\text{HOOC}-(\text{CH}_2)_n-\text{COOH}$ where n is 0-4, and the like. Similarly, pharmaceutically acceptable cations include, but are not limited to sodium, potassium, calcium, aluminum, lithium and ammonium. Those of ordinary skill in the art will recognize from this disclosure and the knowledge in the art that further pharmaceutically acceptable salts include those listed by Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, PA, p. 1418 (1985). In general, a pharmaceutically acceptable acid or base salt can be

synthesized from a parent compound that contains a basic or acidic moiety by any conventional chemical method. Briefly, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in an appropriate solvent.

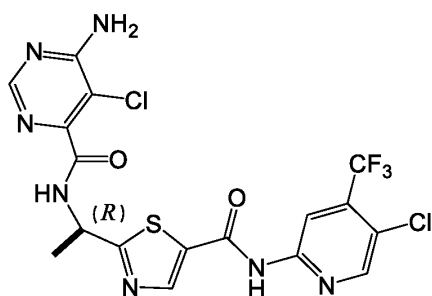
[0042] Ranges provided herein are understood to be shorthand for all of the values within the range. For example, a range of 1 to 50 is understood to include any number, combination of numbers, or sub-range from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50, as well as all intervening decimal values between the aforementioned integers such as, for example, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, and 1.9. With respect to sub-ranges, “nested sub-ranges” that extend from either end point of the range are specifically contemplated. For example, a nested sub-range of an exemplary range of 1 to 50 may comprise 1 to 10, 1 to 20, 1 to 30, and 1 to 40 in one direction, or 50 to 40, 50 to 30, 50 to 20, and 50 to 10 in the other direction.

[0043] Unless otherwise stated, structures depicted herein are meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structure except for the replacement of a hydrogen atom by a deuterium or tritium, or the replacement of a carbon atom by a ^{13}C - or ^{14}C -enriched carbon are within the scope of the disclosure.

[0044] Certain compounds described herein may exist in tautomeric forms, and all such tautomeric forms of the compounds being within the scope of the disclosure. Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms of the structure; i.e., the R and S configurations for each asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the disclosure.

Raf inhibitor

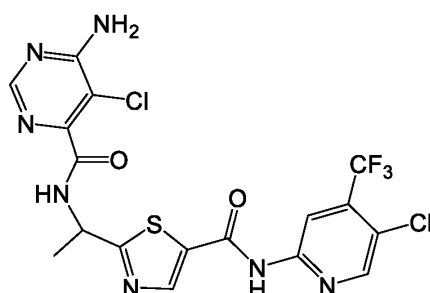
[0045] In some embodiments, described herein is a Raf inhibitor that is (R)-2-(1-(6-amino-5-chloropyrimidine-4-carboxamide)ethyl)-N-(5-chloro-4-(trifluoromethyl)pyridin-2-yl)thiazole-5-carboxamide (Compound A), or a pharmaceutically acceptable salt or solvate thereof. The structure of Compound A is illustrated below:



Compound A. Compound A, or a pharmaceutically acceptable

salt or solvate thereof, is described in US8293752B2. Compound A is also called tovorafenib, DAY101, formally TAK-580, BIIB024, or MLN2480. In some embodiments, the Raf inhibitor is (R)-2-(1-(6-amino-5-chloropyrimidine-4-carboxamide)ethyl)-N-(5-chloro-4-(trifluoromethyl)pyridin-2-yl)thiazole-5-carboxamide. Compound A is also referred to as 6-amino-5-chloro-N-[(1R)-1-[5-[[[5-chloro-4-

(trifluoromethyl)-2-pyridinyl]amino]carbonyl]-2-thiazolyl]ethyl]-4-pyrimidinecarboxamide, and is sold under the trade name OJEMDA. In some embodiments, the Raf inhibitor is Tovorafenib. In some embodiments, the Raf inhibitor is a pharmaceutically acceptable salt of Compound A. In some embodiments, the Raf inhibitor is a solvate of Compound A. In some embodiments, the Raf inhibitor is a crystalline form of Compound A. In some embodiments, the Raf inhibitor is a hydrate of Compound A. In some embodiments, the Raf inhibitor is a crystalline form of Compound A. In some embodiments, the



Raf inhibitor is

[0046] In some embodiments, described herein is a pharmaceutically acceptable salt of tovorafenib. Suitable pharmaceutically acceptable salts include those described in, for example, S. M. Berge et al., d J. Pharmaceutical Sciences, 1977, 66, 1-19, incorporated herein by reference. Pharmaceutically acceptable salts of compounds described herein include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and N+(C1-4 alkyl)₄ salts. The present disclosure also envisions the quaternization of any basic nitrogen-containing groups. Water or oil-soluble or dispersible products may be obtained by such quaternization. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate and aryl sulfonate.

Methods of treatment

[0047] The disclosure provides methods for treating children and young adults with *BRAF*-altered relapsed/refractory pLGG. Specifically, the disclosure provides methods of treating subjects with tovorafenib monotherapy.

[0048] The disclosure provides a method of treating pediatric low-grade glioma (pLGG) in a subject in need thereof, comprising selecting a subject that previously received MAP kinase inhibitor therapy and administering to the subject a type II pan-RAF inhibitor. In one aspect, the disclosure provides a method of treating optic pathway gliomas (OPCs) in a subject in need thereof, comprising selecting a subject that previously received MAP kinase inhibitor therapy and administering to the subject a type II pan-RAF inhibitor. In certain embodiments, the type II pan-RAF inhibitor is tovorafenib. In certain embodiments, the type II pan-RAF inhibitor is a salt of tovorafenib.

[0049] In certain embodiments, the subject had radiographic progression or no progression of the pLGG while receiving the MAP kinase inhibitor therapy. In certain embodiments, the subject had radiographic progression of the pLGG while receiving the MAP kinase inhibitor therapy. In certain embodiments, the subject had partial response of the pLGG while receiving the MAP kinase inhibitor therapy. In certain embodiments, the subject had stable disease of the pLGG while receiving the MAP kinase inhibitor therapy. In certain embodiments, the subject is relapsed/refractory for pLGG following MAP kinase inhibitor therapy. In some embodiments, the MAP kinase inhibitor is Vemurafenib. In some embodiments, the MAP kinase inhibitor is Dabrafenib/Trametinib. In some embodiments, the MAP kinase inhibitor is Binimetinib. In some embodiments, the MAP kinase inhibitor is Trametinib.

[0050] In certain embodiments, the MAP kinase inhibitor therapy is the most recently therapy administered to the subject. In certain embodiments, the MAP kinase inhibitor therapy is not the most recent therapy administered to the subject. In certain embodiments, the most recent therapy administered to the subject is selected from chemotherapy, radiation therapy, and surgery. In certain embodiments, the subject has received 1 line of prior therapy before the administering of the type II pan-RAF inhibitor (such as tovorafenib). In certain embodiments, the subject has received 2 lines of prior therapy before the administering of the type II pan-RAF inhibitor (such as tovorafenib). In certain embodiments, the subject has received 3 lines of prior therapy before the administering of the type II pan-RAF inhibitor (such as tovorafenib). In certain embodiments, the subject has received 4-10 lines of prior therapy before the administering of the type II pan-RAF inhibitor (such as tovorafenib). In certain embodiments, the subject has received 1 line of prior therapy before the administering of the type II pan-RAF inhibitor (such as tovorafenib). In certain embodiments, the subject has received at least 3 lines of prior therapy before the administering of the type II pan-RAF inhibitor (such as tovorafenib).

[0051] In certain embodiments, the subject previously received one or more additional therapeutic treatments including chemotherapy, radiation therapy, and surgery.

[0052] In certain embodiments, the type II pan-RAF inhibitor is tovorafenib or a salt thereof.

[0053] In certain embodiments, the pLGG has a BRAF mutation or fusion. In certain embodiments, the pLGG has a BRAF mutation. In certain embodiments, the BRAF mutation is a V600E mutation. In certain embodiments, the BRAF mutation is a mutation other than a V600E mutation.

[0054] In one aspect, the disclosure also provides methods for treating children and young adults with *BRAF*-altered relapsed/refractory OPCs. In some embodiments, the disclosure provides methods of treating subjects with tovorafenib monotherapy.

[0055] In certain embodiments, the subject had radiographic progression or no progression of the OPC while receiving the MAP kinase inhibitor therapy. In certain embodiments, the subject had radiographic progression of the OPC while receiving the MAP kinase inhibitor therapy. In certain embodiments, the subject is relapsed/refractory for OPC following MAP kinase inhibitor therapy.

[0056] In certain embodiments, the MAP kinase inhibitor therapy comprises trametinib or a salt thereof. In certain embodiments, the MAP kinase inhibitor therapy comprises a MEK inhibitor. In certain embodiments, the MEK inhibitor is trametinib. In certain embodiments, the MEK inhibitor is binimetinib. In certain embodiments, the MEK inhibitor is cobimetinib. In certain embodiments, the MEK inhibitor is selumetinib. In certain embodiments, the MAP kinase inhibitor therapy comprises an EGFR inhibitor. In certain embodiments, the MAP kinase inhibitor therapy comprises a VEGFR inhibitor. In certain embodiments, the MAP kinase inhibitor therapy comprises a PDGFR inhibitor. In certain embodiments, the MAP kinase inhibitor therapy comprises a G-protein inhibitor. In certain embodiments, the MAP kinase inhibitor therapy comprises an RAS inhibitor. In certain embodiments, the MAP kinase inhibitor therapy comprises an RAF inhibitor. In certain embodiments, the MAP kinase inhibitor therapy comprises an MEK1/2 inhibitor. In certain embodiments, the MAP kinase inhibitor therapy comprises an MEK5 inhibitor. In certain embodiments, the MAP kinase inhibitor therapy comprises an p38 inhibitor. In certain embodiments, the MAP kinase inhibitor therapy is a combination therapy. In certain embodiments, the MAP kinase inhibitor therapy is a combination of dabrafenib with trametinib.

[0057] In certain aspects, the disclosure provides a method of treating a pediatric low-grade glioma (pLGG) in a subject in need thereof, comprising administering to the subject a type II pan-RAF inhibitor for 2 months or more, wherein the pLGG shows radiographic progression after the initial month of administration. In certain aspects, the disclosure provides a method of treating optic pathway gliomas (OPCs) in a subject in need thereof, comprising administering to the subject a type II pan-RAF inhibitor for 2 months or more, wherein the OPC shows radiographic progression after the initial month of administration.

[0058] In certain aspects, a radiographic progression or other assessment is determined by RAPNO. In certain aspects, a radiographic progression or other assessment is determined by RANO-LGG. In certain aspects, a radiographic progression or other assessment is determined by RANO-HGG.

[0059] In certain embodiments, the pLGG shows radiographic progression after the initial two months of administration. In certain embodiments, the type II pan-RAF inhibitor is administered to the subject for 3 or more, 4 or more, or 5 or more months. In certain embodiments, the type II pan-RAF inhibitor is tovorafenib or a salt thereof. In certain embodiments, the OPC shows radiographic progression after the

initial two months of administration. In certain embodiments, the type II pan-RAF inhibitor is administered to the subject for 3 or more, 4 or more, or 5 or more months. In certain embodiments, the type II pan-RAF inhibitor is tovorafenib or a salt thereof.

[0060] In certain embodiments, a pLGG has a BRAF mutation or fusion. In certain embodiments, an OPC has a BRAF mutation or fusion. In certain embodiments, the pLGG has a BRAF mutation. In certain embodiments, the OPC has a BRAF mutation. In certain embodiments, the BRAF mutation is a V600E mutation. In certain embodiments, the BRAF mutation is a mutation other than a V600E mutation. In some embodiments, the pLGG has one or more of the following mutations: RAS positive mutation, RAF positive mutation, MEK positive mutation, and ERK positive mutation. In some embodiments, the OPC has one or more of the following mutations: RAS positive mutation, RAF positive mutation, MEK positive mutation, and ERK positive mutation. In embodiments, patients were included to have advance metastatic or respectable melanoma with MAPK mutations. In some embodiments, the pLGG has a BRAF mutation. In some embodiments, the pLGG has a V600E mutation. In some embodiments, the pLGG has a V600D mutation. In some embodiments, the pLGG has a V600K mutation. In some embodiments, the OPC has a V600E mutation. In some embodiments, the OPC has a V600D mutation. In some embodiments, the OPC has a V600K mutation. In some embodiments, the OPC has a non V600E mutation. In some embodiments, the pLGG has a non V600E mutation. In some embodiments, the BRAF mutation is a non V600 BRAF mutation. In some embodiments, 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 embodiments, the subject is identified having a SRGAP3:RAF1 fusion. In some embodiments, the subject is identified having KIAA1549: BRAF fusion. In some embodiments, the subject has a KIAA1549: BRAF fusion. In some embodiments, the subject has a STARD3NL:BRAF fusion. In some embodiments, the subject has a BCAS1:BRAF fusion. In some embodiments, the subject has a KHDRBS2:BRAF fusion. In some embodiments, the subject has a CCDC6:BRAF fusion. In some embodiments, the subject has a FAM131B:BRAF fusion. In some embodiments, the subject has a SRGAP:BRAF fusion. In some embodiments, the subject has a CLCN6:BRAF fusion. In some embodiments, the subject has a GNAI1:BRAF fusion. In some embodiments, the subject has a MRKN1:BRAF fusion. In some embodiments, the subject has a GIT2:BRAF fusion. In some embodiments, the subject has a GTF21:BRAF fusion. In some embodiments, the subject has a FXR1:BRAF fusion. In some embodiments, the subject has a RNF130:BRAF fusion. In some embodiments, the subject has a GTF21:BRAF fusion. In some embodiments, the subject has a BRAF:MACF1 fusion. In some embodiments, the subject has a TMEM106B:BRAF fusion. In some embodiments, the subject has a PPC1CC:BRAF fusion. In some embodiments, the subject has a CUX1:BRAF fusion. In some embodiments, the subject has a SRGAP3:RAF1 fusion. In some embodiments, the subject has a QK1:RAF1 fusion. In some embodiments,

the subject has a FYCO:RAF1 fusion. In some embodiments, the subject has a ATG7:RAF1 fusion. In some embodiments, the subject has a NFIA:RAF1 fusion. In some embodiments, the subject has an AGK:BRAF fusion. In some embodiments, the subject has a ETV6:BRAF fusion. In some embodiments, the subject has an APPL2-RAF1 fusion. In some embodiments, the subject has a BRAF gene fusion. In some embodiments, the subject has a CRAF gene fusion. In some embodiments, a method described herein comprises identifying a BRAF fusion or rearrangement, or BRAF V600 mutation in a subject by a genomic profiling assay. The genomic profiling assay can be any suitable assay known in the art. In some embodiments, the genomic profiling assay is FOUNDATIONONE®, FOUNDATIONONE® HEME, FOUNDATIONONE® CDX™, EXODX®, Guardant360, MSK-IMPACT™, ILLUMINA® TruSight, and any combination thereof. In some embodiments, the genomic profiling assay is a FOUNDATIONONE assay.

[0061] In certain embodiments, the subject is selected from a subject that previously received MAP kinase inhibitor therapy. In certain embodiments, the subject had radiographic progression or no progression of the pLGG while receiving the MAP kinase inhibitor therapy. In certain embodiments, the subject had radiographic progression of the pLGG while receiving the MAP kinase inhibitor therapy. In certain embodiments, the subject is relapsed/refractory for pLGG following MAP kinase inhibitor therapy. In certain embodiments, the MAP kinase inhibitor therapy is the most recently therapy administered to the subject. In certain embodiments, the MAP kinase inhibitor therapy is not the most recent therapy administered to the subject. In certain embodiments, the most recent therapy administered to the subject is selected from chemotherapy, radiation therapy, and surgery.

[0062] In some embodiments, the subject has previously received tovorafenib and is on a drug holiday of tovorafenib. In some embodiments, methods described herein comprises re-initiating the treatment of tovorafenib on a subject who is on a drug holiday. In some embodiments, the subject has been on a drug holiday of at least one month. In some embodiments, the subject has been on a drug holiday of at least three months. In some embodiments, the subject has been on a drug holiday of at least six months. In some embodiments, the subject has been on a drug holiday of at least nine months. In some embodiments, the subject has been on a drug holiday of at least one year. In some embodiments, the subject has been on a drug holiday of at least two years.

[0063] In certain embodiments, the subject previously received one or more additional therapeutic treatments including chemotherapy, radiation therapy, and surgery.

[0064] In certain embodiments, a method disclosed here comprises administering the type II pan-RAF inhibitor (such as tovorafenib or a salt thereof) in combination or concurrently with a second therapeutic agent. The second therapeutic can comprise an anti-infective agent, acne treatment (e.g., agent for management of cutaneous toxicities), a drug for management of brain edema, an antiemetic agent, an anti-convulsant, an agent for treating neurocognitive disorder, or an agent for skin disorder. The second therapeutic can comprise imaging agent, viral vaccine, neurosurgical anesthesia, antiemetics, or pain/fever relief medications.

[0065] In certain embodiments, the subject is administered from about 400 mg/m² to about 450 mg/m² of tovorafenib or a salt thereof per week. In certain embodiments, the subject is administered about 420 mg/m² of tovorafenib or a salt thereof per week. In certain embodiments, the subject is administered tovorafenib or a salt thereof for 10 weeks or more. In certain embodiments, the subject is administered tovorafenib or a salt thereof for 16 weeks or more.

[0066] In certain embodiments, the subject is orally administered from about 400 mg/m² to about 450 mg/m² of tovorafenib or a salt thereof per week. In certain embodiments, the subject is orally administered about 420 mg/m² of tovorafenib or a salt thereof per week. In certain embodiments, the subject is administered tovorafenib or a salt thereof for 10 weeks or more. In certain embodiments, the subject is administered tovorafenib or a salt thereof for 16 weeks or more.

[0067] In certain embodiments, the subject is administered from about 350 mg/m² to about 400 mg/m² of tovorafenib or a salt thereof per week. In some embodiments, the subject is orally administered from about 350 mg/m² to about 400 mg/m² of tovorafenib or a salt thereof per week. In some embodiments, the subject is administered about 380 mg/m² of tovorafenib or a salt thereof per week. In some embodiments, the subject is orally administered about 380 mg/m² of tovorafenib or a salt thereof per week. In some embodiments, the subject is administered about 600 mg of tovorafenib or a salt thereof per week. In certain embodiments, the subject is administered tovorafenib or a salt thereof for 10 weeks or more. In certain embodiments, the subject is administered tovorafenib or a salt thereof for 16 weeks or more.

[0068] In one aspect, disclosed herein is a method of improving visual acuity in a subject in need thereof, wherein the method comprises administering a type II pan-RAF inhibitor (such as tovorafenib or a salt thereof) to the subject. In some embodiments, the subject has pLGG. In some embodiments, the subject has OPCs. In some embodiments, the subject has an optical pathway pLGG. In some embodiments, the tumor size of the subject's pLGG is reduced. In some embodiments, the tumor size of the subject's pLGG is not reduced. In some embodiments, the tumor size of the subject's OPC is reduced. In some embodiments, the tumor size of the subject's OPC is not reduced. The tumor size can be assessed via a radiographic means including RAPNO, RANO-LGG, or RANO-HGG. In some embodiments, the subject has mild impairment of visual acuity before the administering of the type II pan-RAF inhibitor. In some embodiments, the subject has moderate impairment of visual acuity before the administering of the type II pan-RAF inhibitor. In some embodiments, the subject has severe impairment of visual acuity before the administering of the type II pan-RAF inhibitor. In some embodiments, the subject has profound impairment of visual acuity before the administering of the type II pan-RAF inhibitor. In some embodiments, the optical pathway pLGG is an OPC. In some embodiments, the subject has an OPC.

[0069] Described herein is a method of treating cancer such as glioma (e.g., low grade glioma, optic pathway gliomas) that comprises administering tovorafenib, or a pharmaceutically acceptable salt or solvate thereof based on a subject's body surface area (BSA), for example mg/m². BSA can be determined by any suitable calculation method. In some embodiments, the BSA is determined by Mosteller Formula ($\sqrt{(\text{height} \times \text{weight})/3600}$). In some embodiments, the BSA is determined at the start of each cycle of administration.

[0070] In some embodiments, tovorafenib, or a pharmaceutically acceptable salt or solvate thereof, is administered in an amount of up to about 600 mg of per dose. In some embodiments, tovorafenib, or a pharmaceutically acceptable salt or solvate thereof, is administered in an amount of up to about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, or about 1000 mg of per dose. In some embodiments, tovorafenib, or a pharmaceutically acceptable salt or solvate thereof, is administered in an amount of up to about 600 mg of tovorafenib per dose. In some embodiments, tovorafenib, or a pharmaceutically acceptable salt or solvate thereof, is administered in an amount of up to about 800 mg of tovorafenib per dose.

[0071] In some embodiments, tovorafenib, or a pharmaceutically acceptable salt or solvate thereof, is administered in an amount of up to 1200 mg/m² per dose. In some embodiments, tovorafenib, or a pharmaceutically acceptable salt or solvate thereof, is administered in an amount of up to 1000 mg/m² per dose. In some embodiments, tovorafenib, or a pharmaceutically acceptable salt or solvate thereof, is administered in an amount of up to 800 mg/m² per dose. In some embodiments, tovorafenib, or a pharmaceutically acceptable salt or solvate thereof, is administered in an amount of up to 600 mg/m² per dose. In some embodiments, tovorafenib, or a pharmaceutically acceptable salt or solvate thereof, is administered in an amount of up to 500 mg/m² per dose. In some embodiments, tovorafenib, or a pharmaceutically acceptable salt or solvate thereof, is administered in an amount of up to 300 mg/m² per dose. In some embodiments, tovorafenib, or a pharmaceutically acceptable salt or solvate thereof, is administered in an amount of up to 200 mg/m² per dose.

[0072] In some embodiments, the tovorafenib, or a pharmaceutically acceptable salt or solvate thereof is administered at starting dose once a week. In some embodiments, the tovorafenib, or a pharmaceutically acceptable salt or solvate thereof is administered 2, 3, 4, 5, 6, or 7 times a week. In some embodiments, the starting dose is about 825 mg/m² per week. In some embodiments, the starting dose is about 660 mg/m² A per week. In some embodiments, the starting dose is about 530 mg/m² per week. In some embodiments, the starting dose is about 420 mg/m² per week. In some embodiments, the starting dose is about 380 mg/m² per week. In some embodiments, the starting dose is about 410 mg/m² to about 430 mg/m² per week. In some embodiments, the starting dose is about 400 mg/m² to about 450 mg/m² per week. In some embodiments, the starting dose is about 350 mg/m² to about 450 mg/m² per week. In some embodiments, the starting dose is about 350 mg/m² to about 400 mg/m² per week. In some embodiments, the starting dose is about 350 mg/m² per week. In some embodiments, the starting dose is about 280 mg/m² per week. In some embodiments, the initial dose is about 600 mg/m² to about 700 mg/m² per week. In some embodiments, the initial dose is about 500 mg/m² to about 550 mg/m² per week. In some embodiments, the initial dose is about 400 mg/m² to about 450 mg/m² per week. In some embodiments, the initial dose is about 400 mg/m² to about 500 mg/m² per week. In some embodiments, the initial dose is about 100 mg/m² to about 200 mg/m² per week. In some embodiments, the initial dose is about 200 mg/m² to about 300 mg/m² per week. In some embodiments, the initial dose is about 250 mg/m² to about 300 mg/m² per week. In some

embodiments, the dosing is based on the tovorafenib free base. In some embodiments, the dosing is administered once a week.

[0073] In some embodiments, the tovorafenib, or a pharmaceutically acceptable salt or solvate thereof is administered at a maintenance dose once a week. In some embodiments, the tovorafenib, or a pharmaceutically acceptable salt or solvate thereof is administered 2, 3, 4, 5, 6, or 7 times a week. In some embodiments, the maintenance dose is about 825 mg/m² per week. In some embodiments, the maintenance dose is about 660 mg/m² per week. In some embodiments, the maintenance dose is about 530 mg/m² per week. In some embodiments, the maintenance dose is about 420 mg/m² per week. In some embodiments, the maintenance dose is about 350 mg/m² per week. In some embodiments, the maintenance dose is about 280 mg/m² per week. In some embodiments, the maintenance dose is about 600 mg/m² to about 700 mg/m² per week. In some embodiments, the maintenance dose is about 500 mg/m² to about 550 mg/m² per week. In some embodiments, the maintenance dose is about 400 mg/m² to about 450 mg/m² per week. In some embodiments, the maintenance dose is about 420 mg/m² per week. In some embodiments, the maintenance dose is about 410 mg/m² to about 430 mg/m² per week. In some embodiments, the maintenance dose is about 350 mg/m² to about 450 mg/m² per week. In some embodiments, the maintenance dose is about 400 mg/m² to about 500 mg/m² per week. In some embodiments, the maintenance dose is about 200 mg/m² to about 300 mg/m² per week. In some embodiments, the maintenance dose is about 250 mg/m² to about 300 mg/m² per week. In some embodiments, the maintenance dose is the same as the initial dose. In some embodiments, the maintenance dose is higher than the initial dose. In some embodiments, the maintenance dose is lower than the initial dose. In some embodiments, the dosing is based on the tovorafenib free base. In some embodiments, the dosing is administered once a week.

[0074] In some embodiments, tovorafenib, or a pharmaceutically acceptable salt or solvate thereof is administered to a subject based on body surface area (BSA). In some embodiments, about 380 mg/m² of tovorafenib, or a pharmaceutically acceptable salt or solvate thereof is administered once a week. In some embodiments, about 400 mg/m² of Tovorafenib, or a pharmaceutically acceptable salt or solvate thereof is administered once a week. In some embodiments, about 500 mg/m² of Tovorafenib, or a pharmaceutically acceptable salt or solvate thereof is administered once a week. In some embodiments, about 600 mg/m² of Tovorafenib, or a pharmaceutically acceptable salt or solvate thereof, is administered once a week. In some embodiments, about 380 mg/m² of tovorafenib is administered orally once weekly. In some embodiments, about 380 mg/m² of tovorafenib is administered orally once weekly, with a maximum dose of 600 mg orally once weekly. In some embodiments, tovorafenib is administered with a maximum dose of 600 mg orally once weekly. In some embodiments, about 400 mg of tovorafenib is administered orally once weekly. In some embodiments, about 500 mg of tovorafenib is administered orally once weekly. In some embodiments, about 600 mg of tovorafenib is administered orally once weekly. In some embodiments, tovorafenib is administered with or without food. In some embodiments, tovorafenib is administered with food. In some embodiments, tovorafenib is administered without food.

[0075] In some embodiments, about 125 mg of tovorafenib, or a pharmaceutically acceptable salt or solvate thereof is administered orally once weekly. In some embodiments, about 150 mg of tovorafenib, or a pharmaceutically acceptable salt or solvate thereof is administered orally once weekly. In some embodiments, about 175 mg of tovorafenib, or a pharmaceutically acceptable salt or solvate thereof is administered orally once weekly. In some embodiments, about 200 mg of tovorafenib, or a pharmaceutically acceptable salt or solvate thereof is administered orally once weekly. In some embodiments, about 225 mg of tovorafenib, or a pharmaceutically acceptable salt or solvate thereof is administered orally once weekly. In some embodiments, about 275 mg of tovorafenib, or a pharmaceutically acceptable salt or solvate thereof is administered orally once weekly. In some embodiments, about 300 mg of tovorafenib, or a pharmaceutically acceptable salt or solvate thereof is administered orally once weekly. In some embodiments, about 350 mg of tovorafenib, or a pharmaceutically acceptable salt or solvate thereof is administered orally once weekly. In some embodiments, about 375 mg of tovorafenib, or a pharmaceutically acceptable salt or solvate thereof is administered orally once weekly. In some embodiments, about 450 mg of tovorafenib, or a pharmaceutically acceptable salt or solvate thereof is administered orally once weekly. In some embodiments, about 525 mg of tovorafenib, or a pharmaceutically acceptable salt or solvate thereof is administered orally once weekly. In some embodiments, about 600 mg of tovorafenib, or a pharmaceutically acceptable salt or solvate thereof is administered orally once weekly. In some embodiments, tovorafenib or a pharmaceutically acceptable salt or solvate thereof is administered orally once weekly as an oral suspension. In some embodiments, tovorafenib or a pharmaceutically acceptable salt or solvate thereof is administered orally once weekly as an oral suspension at a concentration of about 25 mg/mL. In some embodiments, each bottle of the suspension delivers 300 mg/12 mL. In some embodiments, tovorafenib, or a pharmaceutically acceptable salt or solvate thereof is administered to a subject based on body surface area (BSA).

[0076] In some embodiments, about 125 mg of tovorafenib is administered orally once weekly. In some embodiments, about 150 mg of tovorafenib is administered orally once weekly. In some embodiments, about 175 mg of tovorafenib is administered orally once weekly. In some embodiments, about 200 mg of tovorafenib is administered orally once weekly. In some embodiments, about 225 mg of tovorafenib is administered orally once weekly. In some embodiments, about 275 mg of tovorafenib is administered orally once weekly. In some embodiments, about 300 mg of tovorafenib is administered orally once weekly. In some embodiments, about 350 mg of tovorafenib is administered orally once weekly. In some embodiments, about 375 mg of tovorafenib is administered orally once weekly. In some embodiments, about 450 mg of tovorafenib is administered orally once weekly. In some embodiments, about 525 mg of tovorafenib is administered orally once weekly. In some embodiments, about 600 mg of tovorafenib is administered orally once weekly. In some embodiments, tovorafenib or a pharmaceutically acceptable salt or solvate thereof is administered orally once weekly as an oral suspension. In some embodiments, tovorafenib or a pharmaceutically acceptable salt or solvate thereof is administered orally once weekly as an oral suspension

at a concentration of about 25 mg/mL. In some embodiments, each bottle of the suspension delivers 300 mg/12 mL. In some embodiments, tovorafenib is administered to a subject based on body surface area (BSA).

[0077] In some embodiments, tovorafenib, or a pharmaceutically acceptable salt or solvate thereof is administered to a subject based on the recommended dosage of Table A.

Table A. Recommended tovorafenib tablets dosage based on body surface area

Body Surface Area (m ²)	Recommended Dosage
0.30-0.89	Administer tovorafenib oral suspension once weekly (see Table B)
0.90-1.12	400 mg once weekly
1.13-1.39	500 mg once weekly
≥ 1.40	600 mg once weekly

[0078] The recommended dosage of tovorafenib based on body surface area (BSA) can be 380 mg/m² orally once weekly (the maximum recommended dosage is 600 mg orally once weekly) with or without food until disease progression or intolerable toxicity. Tovorafenib may be administered as an immediate release tablet (see Table A) or as an oral suspension (see Table B).

Table B. Recommended Dosage for tovorafenib for Oral Suspension Based on Body Surface Area

Body Surface Area (m ²)	Dose Volume (mL) ¹	Dosage
0.30-0.35	5	125 mg once weekly
0.36-0.42	6	150 mg once weekly
0.43-0.48	7	175 mg once weekly
0.49-0.54	8	200 mg once weekly
0.55-0.63	9	225 mg once weekly
0.64-0.77	11	275 mg once weekly
0.78-0.83	12	300 mg once weekly
0.84-0.89	14	350 mg once weekly
0.90-1.05	15	375 mg once weekly
1.06-1.25	18	450 mg once weekly
1.26-1.39	21	525 mg once weekly
≥1.40	24	600 mg once weekly

¹ tovorafenib for oral suspension has a concentration of 25 mg/mL. Each bottle of tovorafenib for oral suspension delivers 300 mg/12 mL.

[0079] In some embodiments, tovorafenib or a pharmaceutically acceptable salt or solvate thereof is administered as a liquid formulation (such as a suspension). In some embodiments, the liquid formulation is administered in an amount of about 1 mL to about 50 mL. In some embodiments, the liquid formulation is administered in an amount of about 5 mL to about 25 mL. In some embodiments, about 125 mg of tovorafenib (e.g., about 5 mL), or a pharmaceutically acceptable salt or solvate thereof as a liquid formulation is administered once a week. In some embodiments, about 150 mg of tovorafenib (e.g., about 6 mL), or a pharmaceutically acceptable salt or solvate thereof as a liquid formulation is administered once a week. In some embodiments, about 175 mg of tovorafenib (e.g., about 7 mL), or a pharmaceutically

acceptable salt or solvate thereof as a liquid formulation is administered once a week. In some embodiments, about 200 mg of tovorafenib (e.g., about 8 mL), or a pharmaceutically acceptable salt or solvate thereof as a liquid formulation is administered once a week. In some embodiments, about 225 mg of tovorafenib (e.g., about 9 mL), or a pharmaceutically acceptable salt or solvate thereof as a liquid formulation is administered once a week. In some embodiments, about 275 mg of tovorafenib (e.g., about 11 mL), or a pharmaceutically acceptable salt or solvate thereof as a liquid formulation is administered once a week. In some embodiments, about 300 mg of tovorafenib (e.g., about 12 mL), or a pharmaceutically acceptable salt or solvate thereof as a liquid formulation is administered once a week. In some embodiments, about 350 mg of tovorafenib (e.g., about 14 mL), or a pharmaceutically acceptable salt or solvate thereof as a liquid formulation is administered once a week. In some embodiments, about 375 mg of tovorafenib (e.g., about 15 mL), or a pharmaceutically acceptable salt or solvate thereof as a liquid formulation is administered once a week. In some embodiments, about 450 mg of tovorafenib (e.g., about 18 mL), or a pharmaceutically acceptable salt or solvate thereof as a liquid formulation is administered once a week. In some embodiments, about 525 mg of tovorafenib (e.g., about 21 mL), or a pharmaceutically acceptable salt or solvate thereof as a liquid formulation is administered once a week. In some embodiments, about 600 mg of tovorafenib (e.g., about 24 mL), or a pharmaceutically acceptable salt or solvate thereof as a liquid formulation is administered once a week. In some embodiments, the tovorafenib or a pharmaceutically acceptable salt or solvate thereof is tovorafenib.

[0080] In some embodiments, when the tovorafenib, or a pharmaceutically acceptable salt or solvate thereof is administered as a suspension, a herein-described method of treating pLGG can include one or more of the following steps (a) – (e):

- (a) Prior to first time use of tovorafenib for oral suspension, ensure that caregivers (and if appropriate, patients) read and understand the “Instructions for Use” before preparing, measuring, and administering tovorafenib.
- (b) Reconstitute the powder in each supplied bottle with exactly 14 mL of room temperature water to form the tovorafenib for oral suspension. After reconstitution each mL contains 25 mg of tovorafenib.
- (c) Each bottle delivers 300 mg of tovorafenib in 12 mL. For doses greater than 300 mg, reconstitute two bottles to achieve the dose. Split the dose as equally as possible between the two bottles (e.g., 6 mL and 7 mL for a 325 mg dose).
- (d) Administer tovorafenib for oral suspension using the supplied oral dosing syringe or feeding tube (minimum 12 French) immediately after preparation.
- (e) If the tovorafenib for oral suspension is not administered within 15 minutes after preparation, instruct the patient to discard it.

[0081] In some embodiments, a method described herein comprise a dosage reduction.

[0082] The recommended dosage reductions for adverse reactions for tovorafenib tablets are provided in Table C and tovorafenib for oral suspension in Table D.

Table C. Tovorafenib Tablets: Recommended Dosage Reductions for Adverse Reactions

BSA (m ²)	First Dosage Reduction	Second Dosage Reduction
-----------------------	------------------------	-------------------------

0.30-1.12	Administer the oral suspension once weekly (see Table D)	
1.13-1.39	400 mg once weekly	Administer Tovorafenib oral suspension once weekly (see Table D)
≥1.40	500 mg once weekly	400 mg once weekly

Table D. Tovorafenib for Oral Suspension: Recommended Dosage Reductions for Adverse Reactions

BSA (m ²)	First Dosage Reduction		Second Dosage Reduction	
	Volume (mL)	Dose (mg)	Volume (mL)	Dose (mg)
0.30-0.35	4	100 mg once weekly	3	75 mg once weekly
0.36-0.42	5	125 mg once weekly	4	100 mg once weekly
0.43-0.48	6	150 mg once weekly	5	125 mg once weekly
0.49-0.54	7	175 mg once weekly	6	150 mg once weekly
0.55-0.63	8	200 mg once weekly	6	150 mg once weekly
0.64-0.77	9	225 mg once weekly	8	200 mg once weekly
0.78-0.83	10	250 mg once weekly	8	200 mg once weekly
0.84-0.89	12	300 mg once weekly	10	250 mg once weekly
0.90-1.05	13	325 mg once weekly	11	275 mg once weekly
1.06-1.25	15	375 mg once weekly	13	325 mg once weekly
1.26-1.39	18	450 mg once weekly	15	375 mg once weekly
≥1.40	20	500 mg once weekly	16	400 mg once weekly

[0083] In certain embodiments, for patients with a BSA of:

- ≥0.3 m² but less than 0.9 m² only use the tovorafenib for oral suspension (see Table A)
- ≥0.9 m² use the tablets (see Table A) OR tovorafenib for oral suspension (see Table B)
- Take tovorafenib with or without food.
- Swallow tablets whole with water. Do not chew cut or crush.
- Continue once weekly dosing until disease progression or intolerable toxicity.
- For patients with a BSA ≥0.9, tovorafenib tablets and tovorafenib for oral suspension may be substituted.

[0084] In certain embodiments, if a dose is missed by 3 days or less, the subject can take the missed dose as soon as possible and take the next dose on its regularly scheduled day. In certain embodiments, if a dose is missed by more than 3 days, the subject can skip the dose and take the next dose on its regularly scheduled day. In certain embodiments, if a dose is missed, the subject can take separate doses by a minimum of four days.

[0085] In certain embodiments, vomiting may occur with tovorafenib tablets. In certain embodiments, if vomiting occurs less than 2, 5, 10, 15, 20, 30, 45 or 60 minutes after the tablets have been swallowed, the subject can take another dose. In certain embodiments, if vomiting occurs more than 10, 15, 20, 30, 45, 60, 90, 120, 240 minutes after the tablets have been swallowed, the subject can take the next dose on its regularly scheduled day. In certain embodiments, if vomiting occurs immediately after taking a dose, the subject can repeat that dose. In certain embodiments, vomiting may occur with tovorafenib oral suspension. In certain embodiments, if vomiting occurs less than 15 minutes after the oral suspension has been swallowed, the subject can repeat the dose. In certain embodiments, if vomiting occurs more than 15

minutes after the for oral suspension has been swallowed, the subject will be administered the next dose at the regularly scheduled time.

[0086] In some embodiments, reconstitute each bottle of the supplied tovorafenib for oral suspension with exactly 14 mL of room temperature water to form the tovorafenib for oral suspension. In some embodiments, for doses greater than 300 mg, reconstitute two bottles to achieve the dose. In some embodiments, administer the for oral suspension using the supplied oral dosing syringe or feeding tube (minimum 12 French) immediately after preparation. In some embodiments, if the tovorafenib for oral suspension is not administered within 15 minutes after preparation, discard it.

[0087] In one aspect, disclosed herein is a method of treating a relapsed or refractory pediatric low-grade glioma (pLGG) in a subject in need thereof, comprising administering to the subject tovorafenib or a salt thereof, wherein the pediatric low-grade glioma (pLGG) harbors a BRAF fusion or rearrangement, or BRAF V600 mutation, wherein the subject is 6 months of age or older; and, wherein, (i) when the subject has a Body Surface Area (BSA) of 0.30-0.35 m², the tovorafenib or a salt thereof is administered in a starting dose of about 125 mg once weekly, and if the subject does not tolerate the starting dose, the tovorafenib or a salt thereof is administered in a reduced dose of about 100 mg once weekly, and if the subject does not tolerate the reduced dose, the tovorafenib or a salt thereof is administered in a further reduced dose of about 75 mg once weekly; (ii) when the subject has a Body Surface Area (BSA) of 0.36-0.42 m², the tovorafenib or a salt thereof is administered in a starting dose of about 150 mg once weekly, and if the subject does not tolerate the starting dose, the tovorafenib or a salt thereof is administered in a reduced dose of about 125 mg once weekly, and if the subject does not tolerate the reduced dose, the tovorafenib or a salt thereof is administered in a further reduced dose of about 100 mg once weekly; (iii) when the subject has a Body Surface Area (BSA) of 0.43-0.48 m², the tovorafenib or a salt thereof is administered in a starting dose of about 175 mg once weekly, and if the subject does not tolerate the starting dose, the tovorafenib or a salt thereof is administered in a reduced dose of about 150 mg once weekly, and if the subject does not tolerate the reduced dose, the tovorafenib or a salt thereof is administered in a further reduced dose of about 125 mg once weekly; (iv) when the subject has a Body Surface Area (BSA) of 0.49-0.54 m², the tovorafenib or a salt thereof is administered in a starting dose of about 200 mg once weekly, and if the subject does not tolerate the starting dose, the tovorafenib or a salt thereof is administered in a reduced dose of about 175 mg once weekly, and if the subject does not tolerate the reduced dose, the tovorafenib or a salt thereof is administered in a further reduced dose of about 150 mg once weekly; (v) when the subject has a Body Surface Area (BSA) of 0.55-0.63 m², the tovorafenib or a salt thereof is administered in a starting dose of about 225 mg once weekly, and if the subject does not tolerate the starting dose, the tovorafenib or a salt thereof is administered in a reduced dose of about 200 mg once weekly, and if the subject does not tolerate the reduced dose, the tovorafenib or a salt thereof is administered in a further reduced dose of about 150 mg once weekly; (vi) when the subject has a Body Surface Area (BSA) of 0.64-0.77 m², the tovorafenib or a salt thereof is administered in a starting dose of about 275 mg once weekly, and if the subject does not tolerate the starting dose, the tovorafenib or a salt thereof is administered in a

reduced dose of about 225 mg once weekly, and if the subject does not tolerate the reduced dose, the tovorafenib or a salt thereof is administered in a further reduced dose of about 200 mg once weekly; (vii) when the subject has a Body Surface Area (BSA) of 0.78-0.83m², the tovorafenib or a salt thereof is administered in a starting dose of about 300 mg once weekly, and if the subject does not tolerate the starting dose, the tovorafenib or a salt thereof is administered in a reduced dose of about 250 mg once weekly, and if the subject does not tolerate the reduced dose, the tovorafenib or a salt thereof is administered in a further reduced dose of about 200 mg once weekly; (viii) when the subject has a Body Surface Area (BSA) of 0.84-0.89 m², the tovorafenib or a salt thereof is administered in a starting dose of about 350 mg once weekly, and if the subject does not tolerate the starting dose, the tovorafenib or a salt thereof is administered in a reduced dose of about 300 mg once weekly, and if the subject does not tolerate the reduced dose, the tovorafenib or a salt thereof is administered in a further reduced dose of about 250 mg once weekly; (ix) when the subject has a Body Surface Area (BSA) of 0.90-1.05 m², the tovorafenib or a salt thereof is administered in a starting dose of about 375 mg once weekly, and if the subject does not tolerate the starting dose, the tovorafenib or a salt thereof is administered in a reduced dose of about 325 mg once weekly, and if the subject does not tolerate the reduced dose, the tovorafenib or a salt thereof is administered in a further reduced dose of about 275 mg once weekly; (x) when the subject has a Body Surface Area (BSA) of 1.06-1.25m², the tovorafenib or a salt thereof is administered in a starting dose of about 450 mg once weekly, and if the subject does not tolerate the starting dose, the tovorafenib or a salt thereof is administered in a reduced dose of about 375 mg once weekly, and if the subject does not tolerate the reduced dose, the tovorafenib or a salt thereof is administered in a further reduced dose of about 325 mg once weekly; (xi) when the subject has a Body Surface Area (BSA) of 1.26-1.39m², the tovorafenib or a salt thereof is administered in a starting dose of about 525 mg once weekly, and if the subject does not tolerate the starting dose, the tovorafenib or a salt thereof is administered in a reduced dose of about 450 mg once weekly, and if the subject does not tolerate the reduced dose, the tovorafenib or a salt thereof is administered in a further reduced dose of about 375 mg once weekly; or (xii) when the subject has a Body Surface Area (BSA) of ≥ 1.40 m², the tovorafenib or a salt thereof is administered in a starting dose of about 600 mg once weekly, and if the subject does not tolerate the starting dose, the tovorafenib or a salt thereof is administered in a reduced dose of about 500 mg once weekly, and if the subject does not tolerate the reduced dose, the tovorafenib or a salt thereof is administered in a further reduced dose of about 400 mg once weekly.

[0088] In one aspect, disclosed herein is a method of treating a relapsed or refractory pediatric low-grade glioma (pLGG) in a subject in need thereof, comprising orally administering to the subject tovorafenib or a salt thereof, wherein the pediatric low-grade glioma (pLGG) harbors a BRAF fusion or rearrangement, or BRAF V600 mutation, wherein the subject is 6 months of age or older; and

wherein,

- (i) when the subject has a Body Surface Area (BSA) of 0.30-0.35 m², the method comprises administering a starting dose of tovorafenib or the salt thereof and a reduced dose of tovorafenib

or the salt thereof to the subject, and wherein the method optionally comprises administering a further reduced dose of tovorafenib or the salt thereof to the subject,

wherein the starting dose is equivalent to about 125 mg once weekly or about 380 mg/m² once weekly of tovorafenib,

wherein the reduced dose is equivalent to about 100 mg once weekly of tovorafenib,
and

wherein the further reduced dose is equivalent to about 75 mg once weekly of tovorafenib;

(ii) when the subject has a Body Surface Area (BSA) of 0.36-0.42 m², the method comprises administering a starting dose of tovorafenib or the salt thereof and a reduced dose of tovorafenib or the salt thereof to the subject, and wherein the method optionally comprises administering a further reduced dose of tovorafenib or the salt thereof to the subject,

wherein the starting dose is equivalent to about 150 mg once weekly or about 380 mg/m² once weekly of tovorafenib,

wherein the reduced dose is equivalent to about 125 mg once weekly of tovorafenib,
and

wherein the further reduced dose is equivalent to about 100 mg once weekly of tovorafenib;

(iii) when the subject has a Body Surface Area (BSA) of 0.43-0.48 m², the method comprises administering a starting dose of tovorafenib or the salt thereof and a reduced dose of tovorafenib or the salt thereof to the subject, and wherein the method optionally comprises administering a further reduced dose of tovorafenib or the salt thereof to the subject,

wherein the starting dose is equivalent to about 175 mg once weekly or about 380 mg/m² once weekly of tovorafenib,

wherein the reduced dose is equivalent to about 150 mg once weekly of tovorafenib,
and

wherein the further reduced dose is equivalent to about 125 mg once weekly of tovorafenib;

(iv) when the subject has a Body Surface Area (BSA) of 0.49-0.54 m², the method comprises administering a starting dose of tovorafenib or the salt thereof and a reduced dose of tovorafenib or the salt thereof to the subject, and wherein the method optionally comprises administering a further reduced dose of tovorafenib or the salt thereof to the subject,

wherein the starting dose is equivalent to about 200 mg once weekly or about 380 mg/m² once weekly of tovorafenib,

wherein the reduced dose is equivalent to about 175 mg once weekly of tovorafenib,
and

wherein the further reduced dose is equivalent to about 150 mg once weekly of tovorafenib;

- (v) when the subject has a Body Surface Area (BSA) of 0.55-0.63m², the method comprises administering a starting dose of tovorafenib or the salt thereof and a reduced dose of tovorafenib or the salt thereof to the subject, and wherein the method optionally comprises administering a further reduced dose of tovorafenib or the salt thereof to the subject,

wherein the starting dose is equivalent to about 225 mg once weekly or about 380 mg/m² once weekly of tovorafenib,

wherein the reduced dose is equivalent to about 200 mg once weekly of tovorafenib, and

wherein the further reduced dose is equivalent to about 150 mg once weekly of tovorafenib;

- (vi) when the subject has a Body Surface Area (BSA) of 0.64-0.77 m², the method comprises administering a starting dose of tovorafenib or the salt thereof and a reduced dose of tovorafenib or the salt thereof to the subject, and wherein the method optionally comprises administering a further reduced dose of tovorafenib or the salt thereof to the subject,

wherein the starting dose is equivalent to about 275 mg once weekly or about 380 mg/m² once weekly of tovorafenib,

wherein the reduced dose is equivalent to about 225 mg once weekly of tovorafenib, and

wherein the further reduced dose is equivalent to about 200 mg once weekly of tovorafenib;

- (vii) when the subject has a Body Surface Area (BSA) of 0.78-0.83m², the method comprises administering a starting dose of tovorafenib or the salt thereof and a reduced dose of tovorafenib or the salt thereof to the subject, and wherein the method optionally comprises administering a further reduced dose of tovorafenib or the salt thereof to the subject,

wherein the starting dose is equivalent to about 300 mg once weekly or about 380 mg/m² once weekly of tovorafenib,

wherein the reduced dose is equivalent to about 250 mg once weekly of tovorafenib, and

wherein the further reduced dose is equivalent to about 200 mg once weekly of tovorafenib;

- (viii) when the subject has a Body Surface Area (BSA) of 0.84-0.89 m², the method comprises administering a starting dose of tovorafenib or the salt thereof and a reduced dose of tovorafenib or the salt thereof to the subject, and wherein the method optionally comprises administering a further reduced dose of tovorafenib or the salt thereof to the subject,

wherein the starting dose is equivalent to about 350 mg once weekly or about 380 mg/m² once weekly of tovorafenib,

wherein the reduced dose is equivalent to about 300 mg once weekly of tovorafenib, and

wherein the further reduced dose is equivalent to about 250 mg once weekly of tovorafenib;

(ix) when the subject has a Body Surface Area (BSA) of 0.90-1.05 m², the method comprises administering a starting dose of tovorafenib or the salt thereof and a reduced dose of tovorafenib or the salt thereof to the subject, and wherein the method optionally comprises administering a further reduced dose of tovorafenib or the salt thereof to the subject,

wherein the starting dose is equivalent to about 375-400 mg once weekly or about 380 mg/m² once weekly of tovorafenib,

wherein the reduced dose is equivalent to about 325 mg once weekly of tovorafenib, and

wherein the further reduced dose is equivalent to about 275 mg once weekly of tovorafenib;

(x) when the subject has a Body Surface Area (BSA) of 1.06-1.25m², the method comprises administering a starting dose of tovorafenib or the salt thereof and a reduced dose of tovorafenib or the salt thereof to the subject, and wherein the method optionally comprises administering a further reduced dose of tovorafenib or the salt thereof to the subject,

wherein the starting dose is equivalent to about 400-500 mg (e.g., 450 mg) once weekly or about 380 mg/m² once weekly of tovorafenib,

wherein the reduced dose is equivalent to about 375-400 mg once weekly of tovorafenib, and

wherein the further reduced dose is equivalent to about 325 mg once weekly of tovorafenib;

(xi) when the subject has a Body Surface Area (BSA) of 1.26-1.39m², the method comprises administering a starting dose of tovorafenib or the salt thereof and a reduced dose of tovorafenib or the salt thereof to the subject, and wherein the method optionally comprises administering a further reduced dose of tovorafenib or the salt thereof to the subject,

wherein the starting dose is equivalent to about 500-525 mg once weekly or about 380 mg/m² once weekly of tovorafenib,

wherein the reduced dose is equivalent to about 400-450 mg once weekly of tovorafenib, and

wherein the further reduced dose is equivalent to about 375 mg once weekly of tovorafenib; and

(xii) when the subject has a Body Surface Area (BSA) of $\geq 1.40\text{m}^2$, the method comprises administering a starting dose of tovorafenib or the salt thereof and a reduced dose of tovorafenib or the salt thereof to the subject, and wherein the method optionally comprises administering a further reduced dose of tovorafenib or the salt thereof to the subject,

wherein the starting dose is equivalent to about 600 mg once weekly or about 380 mg/m² once weekly of tovorafenib,

wherein the reduced dose is equivalent to about 500 mg once weekly of tovorafenib, and

wherein the further reduced dose is equivalent to about 400 mg once weekly of tovorafenib.

[0089] In some embodiments, the subject has a Body Surface Area (BSA) of 0.30-0.35 m², and the method comprises administering a starting dose of tovorafenib or the salt thereof and a reduced dose of tovorafenib or the salt thereof to the subject. In some embodiments, the method further comprises administering a further reduced dose of tovorafenib or the salt thereof to the subject. In some embodiments, the starting dose is equivalent to about 125 mg once weekly of tovorafenib. In some embodiments, the starting dose is equivalent to about 380 mg/m² once weekly of tovorafenib. In some embodiments, the reduced dose is equivalent to about 100 mg once weekly of tovorafenib. In some embodiments, the further reduced dose is equivalent to about 75 mg once weekly of tovorafenib. In some embodiments, the tovorafenib or the salt thereof is tovorafenib.

[0090] In some embodiments, the subject has a Body Surface Area (BSA) of 0.36-0.42 m², and the method comprises administering a starting dose of tovorafenib or the salt thereof and a reduced dose of tovorafenib or the salt thereof to the subject. In some embodiments, the method further comprises administering a further reduced dose of tovorafenib or the salt thereof to the subject. In some embodiments, the starting dose is equivalent to about 150 mg once weekly of tovorafenib. In some embodiments, the starting dose is equivalent to about 380 mg/m² once weekly of tovorafenib. In some embodiments, the reduced dose is equivalent to about 125 mg once weekly of tovorafenib. In some embodiments, the further reduced dose is equivalent to about 100 mg once weekly of tovorafenib. In some embodiments, the tovorafenib or the salt thereof is tovorafenib.

[0091] In some embodiments, the subject has a Body Surface Area (BSA) of 0.43-0.48 m², and the method comprises administering a starting dose of tovorafenib or the salt thereof and a reduced dose of tovorafenib or the salt thereof to the subject. In some embodiments, the method further comprises administering a further reduced dose of tovorafenib or the salt thereof to the subject. In some embodiments, the starting dose is equivalent to about 175 mg once weekly of tovorafenib. In some embodiments, the starting dose is equivalent to about 380 mg/m² once weekly of tovorafenib. In some embodiments, the reduced dose is equivalent to about 150 mg once weekly of tovorafenib. In some embodiments, the further reduced dose is equivalent to about 125 mg once weekly of tovorafenib. In some embodiments, the tovorafenib or the salt thereof is tovorafenib.

[0092] In some embodiments, the subject has a Body Surface Area (BSA) of 0.49-0.54 m², and the method comprises administering a starting dose of tovorafenib or the salt thereof and a reduced dose of tovorafenib or the salt thereof to the subject. In some embodiments, the method further comprises administering a further reduced dose of tovorafenib or the salt thereof to the subject. In some embodiments, the starting dose is equivalent to about 200 mg once weekly of tovorafenib. In some embodiments, the starting dose is equivalent to about 380 mg/m² once weekly of tovorafenib. In some embodiments, the reduced dose is equivalent to about 175 mg once weekly of tovorafenib. In some embodiments, the further reduced dose is equivalent to about 150 mg once weekly of tovorafenib. In some embodiments, the tovorafenib or the salt thereof is tovorafenib.

[0093] In some embodiments, the subject has a Body Surface Area (BSA) of 0.55-0.63 m², and the method comprises administering a starting dose of tovorafenib or the salt thereof and a reduced dose of tovorafenib or the salt thereof to the subject. In some embodiments, the method further comprises administering a further reduced dose of tovorafenib or the salt thereof to the subject. In some embodiments, the starting dose is equivalent to about 225 mg once weekly of tovorafenib. In some embodiments, the starting dose is equivalent to about 380 mg/m² once weekly of tovorafenib. In some embodiments, the reduced dose is equivalent to about 200 mg once weekly of tovorafenib. In some embodiments, the further reduced dose is equivalent to about 150 mg once weekly of tovorafenib. In some embodiments, the tovorafenib or the salt thereof is tovorafenib.

[0094] In some embodiments, the subject has a Body Surface Area (BSA) of 0.64-0.77 m², and the method comprises administering a starting dose of tovorafenib or the salt thereof and a reduced dose of tovorafenib or the salt thereof to the subject. In some embodiments, the method further comprises administering a further reduced dose of tovorafenib or the salt thereof to the subject. In some embodiments, the starting dose is equivalent to about 275 mg once weekly of tovorafenib. In some embodiments, the starting dose is equivalent to about 380 mg/m² once weekly of tovorafenib. In some embodiments, the reduced dose is equivalent to about 225 mg once weekly of tovorafenib. In some embodiments, the further reduced dose is equivalent to about 200 mg once weekly of tovorafenib. In some embodiments, the tovorafenib or the salt thereof is tovorafenib.

[0095] In some embodiments, the subject has a Body Surface Area (BSA) of 0.78-0.83 m², and the method comprises administering a starting dose of tovorafenib or the salt thereof and a reduced dose of tovorafenib or the salt thereof to the subject. In some embodiments, the method further comprises administering a further reduced dose of tovorafenib or the salt thereof to the subject. In some embodiments, the starting dose is equivalent to about 300 mg once weekly of tovorafenib. In some embodiments, the starting dose is equivalent to about 380 mg/m² once weekly of tovorafenib. In some embodiments, the reduced dose is equivalent to about 250 mg once weekly of tovorafenib. In some embodiments, the further reduced dose is equivalent to about 200 mg once weekly of tovorafenib. In some embodiments, the tovorafenib or the salt thereof is tovorafenib.

[0096] In some embodiments, the subject has a Body Surface Area (BSA) of 0.84-0.89 m², and the method comprises administering a starting dose of tovorafenib or the salt thereof and a reduced dose of tovorafenib or the salt thereof to the subject. In some embodiments, the method further comprises administering a further reduced dose of tovorafenib or the salt thereof to the subject. In some embodiments, the starting dose is equivalent to about 350 mg once weekly of tovorafenib. In some embodiments, the starting dose is equivalent to about 380 mg/m² once weekly of tovorafenib. In some embodiments, the reduced dose is equivalent to about 300 mg once weekly of tovorafenib. In some embodiments, the further reduced dose is equivalent to about 250 mg once weekly of tovorafenib. In some embodiments, the tovorafenib or the salt thereof is tovorafenib.

[0097] In some embodiments, the subject has a Body Surface Area (BSA) of 0.90-1.05 m², and the method comprises administering a starting dose of tovorafenib or the salt thereof and a reduced dose of tovorafenib or the salt thereof to the subject. In some embodiments, the method further comprises administering a further reduced dose of tovorafenib or the salt thereof to the subject. In some embodiments, the starting dose is equivalent to about 375-400 mg once weekly of tovorafenib. In some embodiments, the starting dose is equivalent to about 375 mg once weekly of tovorafenib. In some embodiments, the starting dose is equivalent to about 400 mg once weekly of tovorafenib. In some embodiments, the starting dose is equivalent to about 380 mg/m² once weekly of tovorafenib. In some embodiments, the reduced dose is equivalent to about 325 mg once weekly of tovorafenib. In some embodiments, the further reduced dose is equivalent to about 275 mg once weekly of tovorafenib. In some embodiments, the tovorafenib or the salt thereof is tovorafenib.

[0098] In some embodiments, the subject has a Body Surface Area (BSA) of 1.06-1.25m², and the method comprises administering a starting dose of tovorafenib or the salt thereof and a reduced dose of tovorafenib or the salt thereof to the subject. In some embodiments, the method further comprises administering a further reduced dose of tovorafenib or the salt thereof to the subject/ In some embodiments, the starting dose is equivalent to about 400-500 mg (e.g., 450 mg) once weekly of tovorafenib. In some embodiments, the starting dose is equivalent to about 400 mg once weekly of tovorafenib. In some embodiments, the starting dose is equivalent to about 450 mg once weekly of tovorafenib. In some embodiments, the starting dose is equivalent to about 500 mg once weekly of tovorafenib. In some embodiments, the starting dose is equivalent to about 380 mg/m² once weekly of tovorafenib. In some embodiments, the reduced dose is equivalent to about 375-400 mg once weekly of tovorafenib. In some embodiments, the reduced dose is equivalent to about 375 mg once weekly of tovorafenib. In some embodiments, the reduced dose is equivalent to about 400 mg once weekly of tovorafenib. In some embodiments, the further reduced dose is equivalent to about 325 mg once weekly of tovorafenib. In some embodiments, the tovorafenib or the salt thereof is tovorafenib.

[0099] In some embodiments, the subject has a Body Surface Area (BSA) of 1.26-1.39m², and the method comprises administering a starting dose of tovorafenib or the salt thereof and a reduced dose of tovorafenib or the salt thereof to the subject. In some embodiments, the method further comprises administering a

further reduced dose of tovorafenib or the salt thereof to the subject. In some embodiments, the starting dose is equivalent to about 500-525 mg once weekly of tovorafenib. In some embodiments, the starting dose is equivalent to about 500 mg once weekly of tovorafenib. In some embodiments, the starting dose is equivalent to about 525 mg once weekly of tovorafenib. In some embodiments, the starting dose is equivalent to about 380 mg/m² once weekly of tovorafenib. In some embodiments, the reduced dose is equivalent to about 400-450 mg once weekly of tovorafenib. In some embodiments, the reduced dose is equivalent to about 400 mg once weekly of tovorafenib. In some embodiments, the reduced dose is equivalent to about 450 mg once weekly of tovorafenib. In some embodiments, the further reduced dose is equivalent to about 375 mg once weekly of tovorafenib. In some embodiments, the tovorafenib or the salt thereof is tovorafenib.

[0100] In some embodiments, the subject has a Body Surface Area (BSA) of $\geq 1.40\text{m}^2$, and the method comprises administering a starting dose of tovorafenib or the salt thereof and a reduced dose of tovorafenib or the salt thereof to the subject. In some embodiments, the method optionally comprises administering a further reduced dose of tovorafenib or the salt thereof to the subject. In some embodiments, the starting dose is equivalent to about 600 mg once weekly of tovorafenib. In some embodiments, the starting dose is equivalent to about 380 mg/m² once weekly of tovorafenib. In some embodiments, the reduced dose is equivalent to about 500 mg once weekly of tovorafenib. In some embodiments, the further reduced dose is equivalent to about 400 mg once weekly of tovorafenib. In some embodiments, the tovorafenib or the salt thereof is tovorafenib.

[0101] In some embodiments, a method described herein comprises withholding the tovorafenib or the salt thereof before the administering of a reduced dose. In some embodiments, a method described herein comprises withholding the tovorafenib or the salt thereof before the administering of a further reduced dose. In some embodiments, a method described herein comprises withholding the tovorafenib or the salt thereof after the administering of a starting dose. In some embodiments, a method described herein comprises withholding the tovorafenib or the salt thereof after the administering of a reduced dose. In some embodiments, tovorafenib or the salt thereof is withheld according to Table E. In some embodiments, the subject is administered to a reduced dose according to Table E. In some embodiments, the subject is administered to a further reduced dose according to Table E.

[0102] In some embodiments, a method described herein comprises evaluating a subject's adverse reactions selected from: Hemorrhage, Skin Toxicity including Photosensitivity; Hepatotoxicity; and Other Adverse Reactions. In some embodiments, an adverse reaction of hemorrhage includes Intolerable Grade 2; Any Grade 3; First occurrence of any Grade 4; and/or Recurrent Grade 4. In some embodiments, when the subject experiences an adverse reaction of hemorrhage, the subject is withheld of tovorafenib or the salt thereof, and optionally, administered a lower dose (e.g., a reduced or further reduced dose) of tovorafenib or the salt thereof. In some embodiments, an adverse reaction of skin toxicity includes Intolerable Grade 2, and/or Grade 3 or 4. In some embodiments, when the subject experiences an adverse reaction of skin toxicity, the subject is withheld of tovorafenib or the salt thereof, and optionally, administered a lower dose

(e.g., a reduced or further reduced dose) of tovorafenib or the salt thereof. In some embodiments, an adverse reaction of hepatotoxicity includes Grade 3 AST or ALT, and/or Grade 3 bilirubin. In some embodiments, an adverse reaction of hepatotoxicity includes First occurrence of any Grade 4 or Recurrent Grade 4. In some embodiments, when the subject experiences an adverse reaction of hepatotoxicity, the subject is withheld of tovorafenib or the salt thereof, and optionally, administered a lower dose (e.g., a reduced or further reduced dose) of tovorafenib or the salt thereof, or administered at the same dose if laboratory abnormality resolves within 8 days. In some embodiments, other adverse reactions include Intolerable Grade 2, Any Grade 3, First occurrence of any Grade 4, and/or Recurrent Grade 4. In some embodiments, when the subject experiences an adverse reaction, the subject is withheld of tovorafenib or the salt thereof, and optionally, administered a lower dose (e.g., a reduced or further reduced dose) of tovorafenib or the salt thereof. In some embodiments, the method further comprises permanently discontinuing tovorafenib or the salt thereof. In some embodiments, the method further comprises monitoring the growth of the subject. In some embodiments, the method further comprises confirming the absence of NF1 in the subject. In some embodiments, the method further comprises determining or confirming BRAF alternation in the subject before the initiation of tovorafenib or the salt thereof.

[0103] In some embodiments, the starting dose is administered to the subject for over 2 years. In some embodiments, the starting dose is administered to the subject for over 1 year. In some embodiments, the starting dose is administered to the subject until disease progression or intolerable toxicity.

[0104] In some embodiments, the starting dose is administered to the subject for 1-4 weeks. In some embodiments, the starting dose is administered to the subject for about 1-20, 1-12, 2-12, 4-8, or 8-20 weeks. In some embodiments, the starting dose is administered to the subject for at least 1, 2, 3, 4, 5, 6, 7, or 8 weeks. In some embodiments, the starting dose is administered to the subject for at most 2, 4, 8, 12, 16, 20, or 56 weeks. In some embodiments, the starting dose is administered to the subject until the subject experienced a treatment-emergent adverse event. In some embodiments, the treatment-emergent adverse event is an event provided in Table 10. In some embodiments, the treatment-emergent adverse event is grade 3 or higher. In some embodiments, the treatment-emergent adverse event is grade 2 or higher. In some embodiments, the starting dose is administered to the subject until the subject experienced a treatment-related adverse event. In some embodiments, the treatment-related adverse event is an event provided in Table 10. In some embodiments, the treatment-related adverse event is grade 3 or higher. In some embodiments, the treatment-related adverse event is grade 2 or higher.

[0105] In some embodiments, the reduced dose is administered to the subject for over 2 years. In some embodiments, the reduced dose is administered to the subject for over 1 year. In some embodiments, the reduced dose is administered to the subject until disease progression or intolerable toxicity.

[0106] In some embodiments, the reduced dose is administered to the subject for 1-4 weeks. In some embodiments, the reduced dose is administered to the subject for about 1-20, 1-12, 2-12, 4-8, or 8-20 weeks. In some embodiments, the reduced dose is administered to the subject for at least 1, 2, 3, 4, 5, 6, 7, or 8 weeks. In some embodiments, the reduced dose is administered to the subject for at most 2, 4, 8, 12, 16, 20,

or 56 weeks. In some embodiments, the reduced dose is administered to the subject until the subject experienced a treatment-emergent adverse event. In some embodiments, the treatment-emergent adverse event is an event provided in Table 10. In some embodiments, the treatment-emergent adverse event is grade 3 or higher. In some embodiments, the treatment-emergent adverse event is grade 2 or higher. In some embodiments, the reduced dose is administered to the subject until the subject experienced a treatment-related adverse event. In some embodiments, the treatment-related adverse event is an event provided in Table 10. In some embodiments, the treatment-related adverse event is grade 3 or higher. In some embodiments, the treatment-related adverse event is grade 2 or higher.

[0107] In some embodiments, the further reduced dose is administered to the subject for over 2 years. In some embodiments, the further reduced dose is administered to the subject for over 1 year. In some embodiments, the further reduced dose is administered to the subject until disease progression or intolerable toxicity.

[0108] In some embodiments, the further reduced dose is administered to the subject for 1-4 weeks. In some embodiments, the further reduced dose is administered to the subject for about 1-20, 1-12, 2-12, 4-8, or 8-20 weeks. In some embodiments, the further reduced dose is administered to the subject for at least 1, 2, 3, 4, 5, 6, 7, or 8 weeks. In some embodiments, the further reduced dose is administered to the subject for at most 2, 4, 8, 12, 16, 20, or 56 weeks. In some embodiments, the further reduced dose is administered to the subject until the subject experienced a treatment-emergent adverse event. In some embodiments, the treatment-emergent adverse event is an event provided in Table 10. In some embodiments, the treatment-emergent adverse event is grade 3 or higher. In some embodiments, the treatment-emergent adverse event is grade 2 or higher. In some embodiments, the further reduced dose is administered to the subject until the subject experienced a treatment-related adverse event. In some embodiments, the treatment-related adverse event is an event provided in Table 10. In some embodiments, the treatment-related adverse event is grade 3 or higher. In some embodiments, the treatment-related adverse event is grade 2 or higher.

[0109] In one aspect, described herein is a method of treating a relapsed or refractory pediatric low-grade glioma (pLGG) in a subject in need thereof, comprising administering to the subject tovorafenib or a salt thereof, wherein the subject is 6 months of age or older. In some embodiments, the tovorafenib or a salt thereof is tovorafenib. In some embodiments, tovorafenib or a salt thereof is administered in an amount of about 380 mg/m² as a starting dose (or in an amount according to Tables A and B), and if the subject does not tolerate the starting dose, the tovorafenib or a salt thereof is administered in a reduced dose, and optionally a further reduced dose according to Tables C and D.

[0110] In one aspect, disclosed herein is a method of treating a relapsed or refractory pediatric low-grade glioma (pLGG) in a subject in need thereof, comprising administering to the subject tovorafenib or a salt thereof, wherein the subject is 6 months of age or older; and wherein, (i) when the subject has a Body Surface Area (BSA) of 0.30-0.89 m², the tovorafenib or a salt thereof is administered as an oral liquid formulation (e.g., a liquid suspension) once weekly (e.g., in an amount of about 380 mg/m²), (ii) when the subject has a BSA of 0.90-1.12 m², the tovorafenib or a salt thereof is administered as an oral liquid

formulation or a solid dosage form once weekly in an amount of about 400 mg, (iii) when the subject has a BSA of 1.13-1.39 m², the tovorafenib or a salt thereof is administered as an oral liquid formulation or a solid dosage form once weekly in an amount of about 500 mg, and (iv) when the subject has a BSA of at least 1.40 m², the tovorafenib or a salt thereof is administered as an oral liquid formulation or a solid dosage form once weekly in an amount of about 600 mg.

[0111] In some embodiments, the pediatric low-grade glioma (pLGG) harbors a BRAF fusion or rearrangement, or BRAF V600 mutation.

[0112] In some embodiments, the method comprises confirming the presence of BRAF fusion or rearrangement, or BRAFV600 mutation prior to initiation of treatment with the tovorafenib or a salt thereof.

[0113] In some embodiments, the method comprises selecting a subject that has PLGG harboring a BRAF fusion or rearrangement, or BRAF V600 mutation. In some embodiments, the method comprises selecting a subject by evaluating liver function tests, including ALT, AST and bilirubin.

[0114] In some embodiments, the tovorafenib or a salt thereof is tovorafenib (i.e., the free base form).

[0115] In some embodiments, the tovorafenib or a salt thereof is administered in an amount of about 380 mg/m².

[0116] In some embodiments, the tovorafenib or a salt thereof is administered at a starting dose of about 380 mg/m².

[0117] In some embodiments, when the subject has a BSA of 0.90-1.12 m², the tovorafenib or a salt thereof is administered as a solid dosage form once weekly in an amount of about 400 mg.

[0118] In some embodiments, when the subject has a BSA of 1.13-1.39 m², the tovorafenib or a salt thereof is administered as a solid dosage form once weekly in an amount of about 500 mg.

[0119] In some embodiments, when the subject has a BSA of at least 1.40 m², the tovorafenib or a salt thereof is administered as a solid dosage form once weekly in an amount of about 600 mg.

[0120] In some embodiments, when the subject has a BSA of about 0.30-0.35 m², the tovorafenib or a salt thereof is administered in an amount of about 125 mg once weekly.

[0121] In some embodiments, when the subject has a BSA of about 0.30-0.35 m², the tovorafenib or a salt thereof is administered as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 125 mg once weekly.

[0122] In some embodiments, when the subject has a BSA of about 0.30-0.35 m², the tovorafenib or a salt thereof is administered as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 5 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.

[0123] In some embodiments, when the subject has a BSA of about 0.36-0.42 m², the tovorafenib or a salt thereof is administered in an amount of about 150 mg once weekly.

[0124] In some embodiments, when the subject has a BSA of about 0.36-0.42 m², the tovorafenib or a salt thereof is administered as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 150 mg once weekly.

[0125] In some embodiments, when the subject has a BSA of about 0.36-0.42 m², the tovorafenib or a salt thereof is administered as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 6 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.

[0126] In some embodiments, when the subject has a BSA of about 0.43-0.48 m², the tovorafenib or a salt thereof is administered in an amount of about 175 mg once weekly.

[0127] In some embodiments, when the subject has a BSA of about 0.43-0.48 m², the tovorafenib or a salt thereof is administered as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 175 mg once weekly.

[0128] In some embodiments, when the subject has a BSA of about 0.43-0.48 m², the tovorafenib or a salt thereof is administered as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 7 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.

[0129] In some embodiments, when the subject has a BSA of about 0.49-0.54 m², the tovorafenib or a salt thereof is administered in an amount of about 200 mg once weekly.

[0130] In some embodiments, when the subject has a BSA of about 0.49-0.54 m², the tovorafenib or a salt thereof is administered as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 200 mg once weekly.

[0131] In some embodiments, when the subject has a BSA of about 0.49-0.54 m², the tovorafenib or a salt thereof is administered as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 8 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.

[0132] In some embodiments, when the subject has a BSA of about 0.55-0.63 m², the tovorafenib or a salt thereof is administered in an amount of about 225 mg once weekly.

[0133] In some embodiments, when the subject has a BSA of about 0.55-0.63 m², the tovorafenib or a salt thereof is administered as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 225 mg once weekly.

[0134] In some embodiments, when the subject has a BSA of about 0.55-0.63 m², the tovorafenib or a salt thereof is administered as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 9 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.

[0135] In some embodiments, when the subject has a BSA of about 0.64-0.77 m², the tovorafenib or a salt thereof is administered in an amount of about 275 mg once weekly.

[0136] In some embodiments, when the subject has a BSA of about 0.64-0.77 m², the tovorafenib or a salt thereof is administered as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 275 mg once weekly.

[0137] In some embodiments, when the subject has a BSA of about 0.64-0.77 m², the tovorafenib or a salt thereof is administered as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 11 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.

[0138] In some embodiments, when the subject has a BSA of about 0.78-0.83 m², the tovorafenib or a salt thereof is administered in an amount of about 300 mg once weekly.

[0139] In some embodiments, when the subject has a BSA of about 0.78-0.83 m², the tovorafenib or a salt thereof is administered as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 300 mg once weekly.

[0140] In some embodiments, when the subject has a BSA of about 0.78-0.83 m², the tovorafenib or a salt thereof is administered as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 12 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.

[0141] In some embodiments, when the subject has a BSA of about 0.84-0.89 m², the tovorafenib or a salt thereof is administered in an amount of about 350 mg once weekly.

[0142] In some embodiments, when the subject has a BSA of about 0.84-0.89 m², the tovorafenib or a salt thereof is administered as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 350 mg once weekly.

[0143] In some embodiments, when the subject has a BSA of about 0.84-0.89 m², the tovorafenib or a salt thereof is administered as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 14 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.

[0144] In some embodiments, when the subject has a BSA of about 0.90-1.05 m², the tovorafenib or a salt thereof is administered in an amount of about 375 mg once weekly.

[0145] In some embodiments, when the subject has a BSA of about 0.90-1.05 m², the tovorafenib or a salt thereof is administered as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 375 mg once weekly.

[0146] In some embodiments, when the subject has a BSA of about 0.90-1.05 m², the tovorafenib or a salt thereof is administered as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 15 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.

[0147] In some embodiments, when the subject has a BSA of about 1.06-1.25 m², the tovorafenib or a salt thereof is administered in an amount of about 450 mg once weekly.

[0148] In some embodiments, when the subject has a BSA of about 1.06-1.25 m², the tovorafenib or a salt thereof is administered as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 450 mg once weekly.

[0149] In some embodiments, when the subject has a BSA of about 1.06-1.25 m², the tovorafenib or a salt thereof is administered as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 18 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.

[0150] In some embodiments, when the subject has a BSA of about 1.26-1.39 m², the tovorafenib or a salt thereof is administered in an amount of about 525 mg once weekly.

[0151] In some embodiments, when the subject has a BSA of about 1.26-1.39 m², the tovorafenib or a salt thereof is administered as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 525 mg once weekly.

[0152] In some embodiments, when the subject has a BSA of about 1.26-1.39 m², the tovorafenib or a salt thereof is administered as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 21 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.

[0153] In some embodiments, when the subject has a BSA of ≥ 1.40 m², the tovorafenib or a salt thereof is administered in an amount of about 600 mg once weekly.

[0154] In some embodiments, when the subject has a BSA of ≥ 1.40 m², the tovorafenib or a salt thereof is administered as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 600 mg once weekly.

[0155] In some embodiments, when the subject has a BSA of ≥ 1.40 m², the tovorafenib or a salt thereof is administered as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 24 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.

[0156] In some embodiments, the tovorafenib or a salt thereof is administered in amount according to Table A or Table B.

[0157] In some embodiments, the method comprises a dosage reduction of tovorafenib or a salt thereof.

[0158] In some embodiments, the dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 5% to 30% less compared to the dose before the dosage reduction.

[0159] In some embodiments, the dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 10% to 20% less compared to the dose before the dosage reduction.

[0160] In some embodiments, the dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, and 20% less compared to the dose before the dosage reduction.

[0161] In some embodiments, the dosage reduction comprising administering tovorafenib or a salt thereof to the subject according to Table C or Table D.

[0162] In some embodiments, when the subject has a BSA of 1.13-1.39 m², the dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 400 mg once weekly.

[0163] In some embodiments, when the subject has a BSA of ≥ 1.40 m², the dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 500 mg once weekly.

[0164] In some embodiments, when the subject has a BSA of 0.30-0.35 m², the dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 100 mg once weekly.

[0165] In some embodiments, when the subject has a BSA of 0.30-0.35 m², the dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 100 mg once weekly.

[0166] In some embodiments, when the subject has a BSA of 0.30-0.35 m², the dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 4 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.

[0167] In some embodiments, when the subject has a BSA of 0.36-0.42 m², the dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 125 mg once weekly.

[0168] In some embodiments, when the subject has a BSA of 0.36-0.42 m², the dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 125 mg once weekly.

[0169] In some embodiments, when the subject has a BSA of 0.36-0.42 m², the dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 5 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.

[0170] In some embodiments, when the subject has a BSA of 0.43-0.48 m², the dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 150 mg once weekly.

[0171] In some embodiments, when the subject has a BSA of 0.43-0.48 m², the dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 150 mg once weekly.

[0172] In some embodiments, when the subject has a BSA of 0.43-0.48 m², the dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 6 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.

[0173] In some embodiments, when the subject has a BSA of 0.49-0.54 m², the dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 175 mg once weekly.

[0174] In some embodiments, when the subject has a BSA of 0.49-0.54 m², the dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 175 mg once weekly.

[0175] In some embodiments, when the subject has a BSA of 0.49-0.54 m², the dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 7 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.

[0176] In some embodiments, when the subject has a BSA of 0.55-0.63 m², the dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 200 mg once weekly.

[0177] In some embodiments, when the subject has a BSA of 0.55-0.63 m², the dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 200 mg once weekly.

[0178] In some embodiments, when the subject has a BSA of 0.55-0.63 m², the dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 8 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.

[0179] In some embodiments, when the subject has a BSA of 0.64-0.77 m², the dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 225 mg once weekly.

[0180] In some embodiments, when the subject has a BSA of 0.64-0.77 m², the dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 225 mg once weekly.

[0181] In some embodiments, when the subject has a BSA of 0.64-0.77 m², the dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 9 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.

[0182] In some embodiments, when the subject has a BSA of 0.78-0.83 m², the dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 250 mg once weekly.

[0183] In some embodiments, when the subject has a BSA of 0.78-0.83 m², the dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 250 mg once weekly.

[0184] In some embodiments, when the subject has a BSA of 0.78-0.83 m², the dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 10 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.

[0185] In some embodiments, when the subject has a BSA of 0.84-0.89 m², the dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 300 mg once weekly.

[0186] In some embodiments, when the subject has a BSA of 0.84-0.89 m², the dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 300 mg once weekly.

[0187] In some embodiments, when the subject has a BSA of 0.84-0.89 m², the dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 12 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.

[0188] In some embodiments, when the subject has a BSA of 0.90-1.05 m², the dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 325 mg once weekly.

[0189] In some embodiments, when the subject has a BSA of 0.90-1.05 m², the dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 325 mg once weekly.

[0190] In some embodiments, when the subject has a BSA of 0.90-1.05 m², the dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 13 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.

[0191] In some embodiments, when the subject has a BSA of 1.06-1.25m², the dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 375 mg once weekly.

[0192] In some embodiments, when the subject has a BSA of 1.06-1.25m², the dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 375 mg once weekly.

[0193] In some embodiments, when the subject has a BSA of 1.06-1.25m², the dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 15 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.

[0194] In some embodiments, when the subject has a BSA of 1.26-1.39m², the dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 450 mg once weekly.

[0195] In some embodiments, when the subject has a BSA of 1.26-1.39m², the dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 450 mg once weekly.

[0196] In some embodiments, when the subject has a BSA of 1.26-1.39m², the dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 18 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.

[0197] In some embodiments, when the subject has a BSA of ≥ 1.40 m², the dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 500 mg once weekly.

[0198] In some embodiments, when the subject has a BSA of ≥ 1.40 m², the dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 500 mg once weekly.

[0199] In some embodiments, when the subject has a BSA of ≥ 1.40 m², the dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 20 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.

[0200] In some embodiments, the method comprises a second dosage reduction of tovorafenib or a salt thereof.

[0201] In some embodiments, the second dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 5% to 30% less compared to the dose before the dosage reduction.

[0202] In some embodiments, the second dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 10% to 20% less compared to the dose before the dosage reduction.

[0203] In some embodiments, the second dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, and 20% less compared to the dose before the dosage reduction.

[0204] In some embodiments, the second dosage reduction comprising administering tovorafenib or a salt thereof to the subject according to Table C or Table D.

[0205] In some embodiments, when the subject has a BSA of $\geq 1.40 \text{ m}^2$, the second dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 400 mg once weekly.

[0206] In some embodiments, when the subject has a BSA of $0.30\text{-}0.35 \text{ m}^2$, the second dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 75 mg once weekly.

[0207] In some embodiments, when the subject has a BSA of $0.30\text{-}0.35 \text{ m}^2$, the second dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 75 mg once weekly.

[0208] In some embodiments, when the subject has a BSA of $0.30\text{-}0.35 \text{ m}^2$, the second dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 3 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.

[0209] In some embodiments, when the subject has a BSA of $0.36\text{-}0.42 \text{ m}^2$, the second dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 100 mg once weekly.

[0210] In some embodiments, when the subject has a BSA of $0.36\text{-}0.42 \text{ m}^2$, the second dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 100 mg once weekly.

[0211] In some embodiments, when the subject has a BSA of $0.36\text{-}0.42 \text{ m}^2$, the second dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 4 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.

[0212] In some embodiments, when the subject has a BSA of $0.43\text{-}0.48 \text{ m}^2$, the second dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 125 mg once weekly.

[0213] In some embodiments, when the subject has a BSA of $0.43\text{-}0.48 \text{ m}^2$, the second dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 125 mg once weekly.

[0214] In some embodiments, when the subject has a BSA of $0.43\text{-}0.48 \text{ m}^2$, the second dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 5 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.

[0215] In some embodiments, when the subject has a BSA of $0.49\text{-}0.54 \text{ m}^2$, the second dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 150 mg once weekly.

[0216] In some embodiments, when the subject has a BSA of $0.49\text{-}0.54 \text{ m}^2$, the second dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 150 mg once weekly.

[0217] In some embodiments, when the subject has a BSA of 0.49-0.54 m², the second dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 6 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.

[0218] In some embodiments, when the subject has a BSA of 0.55-0.63 m², the second dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 150 mg once weekly.

[0219] In some embodiments, when the subject has a BSA of 0.55-0.63 m², the second dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 150 mg once weekly.

[0220] In some embodiments, when the subject has a BSA of 0.55-0.63 m², the second dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 6 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.

[0221] In some embodiments, when the subject has a BSA of 0.64-0.77 m², the second dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 200 mg once weekly.

[0222] In some embodiments, when the subject has a BSA of 0.64-0.77 m², the second dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 200 mg once weekly.

[0223] In some embodiments, when the subject has a BSA of 0.64-0.77 m², the second dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 8 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.

[0224] In some embodiments, when the subject has a BSA of 0.78-0.83 m², the second dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 200 mg once weekly.

[0225] In some embodiments, when the subject has a BSA of 0.78-0.83 m², the second dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 200 mg once weekly.

[0226] In some embodiments, when the subject has a BSA of 0.78-0.83 m², the second dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 8 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.

[0227] In some embodiments, when the subject has a BSA of 0.84-0.89 m², the second dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 250 mg once weekly.

[0228] In some embodiments, when the subject has a BSA of 0.84-0.89 m², the second dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 250 mg once weekly.

[0229] In some embodiments, when the subject has a BSA of 0.84-0.89 m², the second dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 10 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.

[0230] In some embodiments, when the subject has a BSA of 0.90-1.05 m², the second dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 275 mg once weekly.

[0231] In some embodiments, when the subject has a BSA of 0.90-1.05 m², the second dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 275 mg once weekly.

[0232] In some embodiments, when the subject has a BSA of 0.90-1.05 m², the second dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 11 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.

[0233] In some embodiments, when the subject has a BSA of 1.06-1.25 m², the second dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 325 mg once weekly.

[0234] In some embodiments, when the subject has a BSA of 1.06-1.25 m², the second dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 325 mg once weekly.

[0235] In some embodiments, when the subject has a BSA of 1.06-1.25 m², the second dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 13 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.

[0236] In some embodiments, when the subject has a BSA of 1.26-1.39 m², the second dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 375 mg once weekly.

[0237] In some embodiments, when the subject has a BSA of 1.26-1.39 m², the second dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 375 mg once weekly.

[0238] In some embodiments, when the subject has a BSA of 1.26-1.39 m², the second dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 15 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.

[0239] In some embodiments, when the subject has a BSA of ≥ 1.40 m², the second dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 400 mg once weekly.

[0240] In some embodiments, when the subject has a BSA of ≥ 1.40 m², the second dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 400 mg once weekly.

[0241] In some embodiments, when the subject has a BSA of $\geq 1.40 \text{ m}^2$, the second dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 16 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.

[0242] In the some embodiments, the oral liquid formulation is a suspension. In the some embodiments, the oral liquid formulation a reconstituted tovorafenib suspension. In some embodiments, each mL of reconstituted tovorafenib suspension contains 25 mg of tovorafenib and one or more of the following inactive ingredients: artificial strawberry flavor, colloidal silicon dioxide, copovidone, maltodextrin, mannitol, microcrystalline cellulose, simethicone, sodium lauryl sulfate, and/or sucralose. In some embodiments, each mL of reconstituted tovorafenib suspension contains 25 mg of tovorafenib and the following inactive ingredients: artificial strawberry flavor, colloidal silicon dioxide, copovidone, maltodextrin, mannitol, microcrystalline cellulose, simethicone, sodium lauryl sulfate, and sucralose. In some embodiments, each mL of reconstituted, strawberry flavored tovorafenib suspension contains 25 mg of tovorafenib. In some embodiments, each bottle delivers 300 mg of tovorafenib in 12 mL. In some embodiments, a package of tovorafenib comprises a clear glass bottle, co-packaged with a press-in bottle adaptor and a 20 mL oral dosing syringe, and the tovorafenib.

[0243] In some embodiments, the dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation or a solid dosage form once weekly in an amount of about 400 mg when the subject has a BSA of $1.13\text{-}1.39 \text{ m}^2$.

[0244] In some embodiments, the dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation or a solid dosage form once weekly in an amount of about 500 mg when the subject has a BSA of at least 1.40 m^2 .

[0245] In some embodiments, the pLGG has a BRAF mutation or fusion.

[0246] In some embodiments, the pLGG harbors a BRAF fusion, rearrangement, or BRAF V600 mutation.

[0247] In some embodiments, when the subject misses a dose of 3 days or less, the missed dose is administered to the subject and the next dose is administered to the subject on its regularly scheduled day.

[0248] In some embodiments, the missed dose is administered to the subject no more than 3 days after its regularly scheduled day.

[0249] In some embodiments, when the subject misses a dose of more than 3 days, the missed dose is skipped and the next dose is administered to the subject on its regularly scheduled day.

[0250] In some embodiments, when the subject misses a dose, the missed dose and the next dose is administered to the subject by a minimum of four days apart.

[0251] In some embodiments, each dose of the tovorafenib or a salt thereof is administered to the subject by a minimum of four days apart.

[0252] In some embodiments, the pLGG has a BRAF mutation.

[0253] In some embodiments, the BRAF mutation is a V600E mutation.

[0254] In some embodiments, the BRAF mutation is a mutation other than a V600E mutation.

[0255] In some embodiments, the subject is selected from a subject that previously received MAP kinase inhibitor therapy.

[0256] In some embodiments, the subject had radiographic progression or no progression of the pLGG while receiving the MAP kinase inhibitor therapy.

[0257] In some embodiments, the subject had radiographic progression of the pLGG while receiving the MAP kinase inhibitor therapy.

[0258] In some embodiments, the subject is relapsed/refractory for pLGG following MAP kinase inhibitor therapy.

[0259] In some embodiments, the MAP kinase inhibitor therapy is the most recently therapy administered to the subject.

[0260] In some embodiments, the MAP kinase inhibitor therapy is not the most recent therapy administered to the subject.

[0261] In some embodiments, the most recent therapy administered to the subject is selected from chemotherapy, radiation therapy, and surgery.

[0262] In some embodiments, the subject previously received one or more additional therapeutic treatments including chemotherapy, radiation therapy, and surgery.

[0263] In some embodiments, the subject is orally administered from about 400 mg/m² to about 450 mg/m² of tovorafenib or a salt thereof per week.

[0264] In some embodiments, the subject is orally administered about 420 mg/m² of tovorafenib or a salt thereof per week.

[0265] In some embodiments, the subject is orally administered from about 350 mg/m² to about 400 mg/m² of tovorafenib or a salt thereof per week.

[0266] In some embodiments, the subject is orally administered about 380 mg/m² of tovorafenib or a salt thereof per week.

[0267] In some embodiments, the subject is administered tovorafenib or a salt thereof for 10 weeks or more.

[0268] In some embodiments, the subject is administered tovorafenib or a salt thereof for 16 weeks or more.

[0269] In some embodiments, tovorafenib or a salt thereof is administered as a tablet or liquid formulation.

[0270] In some embodiments, tovorafenib or a salt thereof is administered with food.

[0271] In some embodiments, tovorafenib or a salt thereof is administered without food.

[0272] In some embodiments, the tovorafenib or a salt thereof is tovorafenib.

[0273] In some embodiments, the tovorafenib or a salt thereof is administered as an oral liquid suspension.

In some embodiments, when the dosage is less than 400 mg, the tovorafenib or a salt thereof is administered as an oral liquid suspension. In some embodiments, the tovorafenib or a salt thereof is administered as a solid dosage form such as a tablet. In some embodiments, when the dosage is 400 mg or more, the tovorafenib or a salt thereof is administered as a solid dosage form such as a tablet.

[0274] In some embodiments, tovorafenib steady state maximum concentration (C_{max}) is about 6.9 µg/mL (23%) and the area under the concentration-time curve (AUC) is about 508 µg*h/mL (31%), and time to reach steady state of tovorafenib is about 12 days (33%). In some embodiments tovorafenib median (minimum, maximum) time to achieve peak plasma concentration (T_{max}) is about 3 hours (1.5, 4 hours), following a single dose with tablets or oral suspension.

[0275] In one aspect, described herein is a method of treating a relapsed or refractory pediatric low-grade glioma (pLGG) in a subject in need thereof, comprising administering to the subject tovorafenib, wherein the subject is 6 months of age or older, and wherein the tovorafenib is administered in a dosage amount and/or dose reduction amount according to one or more of Tables A, B, C, D and E.

[0276] In some embodiments, the recommended dose modifications of tovorafenib for adverse reactions is provided in Table E.

Table E: Recommended Dosage Modifications for Adverse Reactions	
Severity of ADR ^a	Dose Modification ^b
Hemorrhage	
- Intolerable Grade 2 - Any Grade 3	Withhold tovorafenib. - If improved to Grade 0-1, resume at lower dosage. - If not improved, consider permanent discontinuation of tovorafenib.
First occurrence of any Grade 4	Withhold tovorafenib - If improved to Grade 0-1, resume at lower dosage. OR - Permanently discontinue tovorafenib.
Recurrent Grade 4	Permanently discontinue tovorafenib.
Skin Toxicity including Photosensitivity	
- Intolerable Grade 2 - Grade 3 or 4	Withhold tovorafenib. - If improved to Grade 0-1, resume tovorafenib at a lower dosage. - If not improved, consider permanent discontinuation of tovorafenib.
Hepatotoxicity	
- Grade 3 AST or ALT - Grade 3 bilirubin	Withhold tovorafenib If improved to Grade ≤ 2 or baseline, resume as follows: - If laboratory abnormality resolves within 8 days, resume tovorafenib at the same dose. - If laboratory abnormality does not resolve within 8 days, resume tovorafenib at lower dosage.
First occurrence of any Grade 4	Withhold tovorafenib If improved to Grade 0-1, resume at lower dosage. OR

	Permanently discontinue tovorafenib
Recurrent Grade 4	Permanently discontinue tovorafenib
Other Adverse Reactions	
- Intolerable Grade 2 - Any Grade 3	Withhold tovorafenib. - If improved to Grade 0-1, resume tovorafenib at a lower dosage. - If not improved, consider permanent discontinuation of tovorafenib.
First occurrence of any Grade 4	Withhold tovorafenib - If improved to Grade 0-1, resume at lower dosage. OR - Permanently discontinue tovorafenib.
Recurrent Grade 4	Permanently discontinue tovorafenib.

^a National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0. ^b See Table C and Table D for recommended dosage reductions.

[0277] In some embodiments, about 280 mg/m² of tovorafenib, or a pharmaceutically acceptable salt or solvate thereof is administered once a week. In some embodiments, about 350 mg/m² of Tovorafenib is administered once a week. In some embodiments, about 420 mg/m² of Tovorafenib is administered once a week. In some embodiments, about 530 mg/m² of Tovorafenib is administered once a week.

[0278] In some embodiments, tovorafenib, or a pharmaceutically acceptable salt or solvate thereof can be chronically administered to a subject over the course of 30 days, 60 days, 120 days, 180 days, 240 days, 300 days, 360 days, 720 days, 1440 days, 1880 days, or 3600 days. In some embodiments, tovorafenib, or a pharmaceutically acceptable salt or solvate thereof can be chronically administered to a subject over the course of at least 30 days, at least 60 days, at least 120 days, at least 180 days, at least 240 days, at least 300 days, at least 360 days, at least 720 days, at least 1440 days, at least 1880 days, or at least 3600 days. In some embodiments, tovorafenib, or a pharmaceutically acceptable salt or solvate thereof can be chronically administered to a subject over the course of at most 30 days, at most 60 days, most 120 days, at most 180 days, at most 240 days, at most 300 days, at most 360 days, at most 720 days, at most 1440 days, at most 1800 days, or at most 3600 days. In some embodiments, tovorafenib, or a pharmaceutically acceptable salt or solvate thereof is chronically administered using an amount as disclosed herein.

[0279] In certain embodiments, the tovorafenib or a salt thereof is administered as a tablet or liquid formulation. In certain embodiments, the tovorafenib or a salt thereof is administered with food. In certain embodiments, the tovorafenib or a salt thereof is administered without food.

[0280] In some embodiments, the subject is from about 6 months to 25 years old. In some embodiments, the subject is a child. In some embodiments, the subject is an adolescent. In some embodiments, the subject is an adult. In some embodiments, the subject is from about 1 year to 25 years old. In some embodiments, a subject is 25 years of age or less. In some embodiments, a subject is 20 years of age or less. In some embodiments, a subject is 15 years of age or less. In some embodiments, a subject is 10 years of age or less.

In some embodiments, a subject is 6 months to 5 years of age. In some embodiments, a subject is 6 months to 10 years of age. In some embodiments, a subject is 6 months to 15 years of age. In some embodiments, a subject is 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10 years of age or less. In some embodiments, the subject is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25 years old. In some embodiments, the subject is measured for a performance status. In some embodiments, the performance status is the Karnofsky or Lansky performance status. In some embodiments, the Karnofsky status is greater than or equal to 50. In some embodiments, the Lansky status is greater than or equal to 50. In some embodiments, the subject has low grade glioma. In some embodiments, the subject has failed standard therapy.

[0281] In one aspect, the disclosure provides methods of treatment according to Example 1.

[0282] As illustrated in Example 1 (the FIREFLY-1 trial), tovorafenib monotherapy resulted in clinically meaningful, rapid, and durable tumor responses in children and young adults with *BRAF*-altered relapsed/refractory pLGG.

[0283] *BRAF* genomic alterations are the most common oncogenic drivers in pediatric low-grade glioma (pLGG). Arm 1 ($n=77$) of the ongoing phase 2 FIREFLY-1 (PNOC026) trial investigated the efficacy of the oral, selective, central nervous system-penetrant, type II RAF inhibitor tovorafenib (420 mg/m² once weekly; 600 mg maximum) in patients with *BRAF*-altered, relapsed/refractory pLGG. Arm 2 ($n=60$) is an extension cohort, which provided treatment access for patients with *RAF*-altered pLGG following arm 1 closure. Based on independent review, according to Response Assessment in Neuro-Oncology high-grade glioma criteria (RANO-HGG), the overall response rate (ORR) of 67% met the arm 1 prespecified primary endpoint; median duration of response (DOR) was 16.6 months, and median time to response (TTR) 3.0 months (secondary endpoints). Other select arm 1 secondary endpoints included ORR, DOR, and TTR as assessed by Response Assessment in Pediatric Neuro-Oncology-LGG (RAPNO-LGG) criteria, and safety (assessed in all treated patients and the primary endpoint for arm 2, $n=137$). The ORR according to RAPNO-LGG (including minor responses) was 51%, median DOR 13.8 months, and median TTR 5.3 months. The most common treatment-related adverse events (TRAEs) were hair color changes (76%), elevated creatine phosphokinase (56%), and anemia (49%). Grade ≥ 3 TRAEs occurred in 42% of patients. Nine (7%) patients had TRAEs leading to discontinuation of tovorafenib. These data indicate that tovorafenib could be an effective therapy for *BRAF*-altered, relapsed/refractory pLGG.

[0284] In Example 1, the patients had received a median of three prior lines of systemic therapy, and more than half had previously received RAF and/or MEK inhibitors. Tumor responses can be demonstrated across the three response assessment criteria (RANO-HGG, RAPNO and RANO-LGG), *BRAF* alteration type (mutation versus fusion), and prior MAPKi use, including patients who progressed on a MAPKi as their most recent prior therapy. As illustrated in Example 1, a consistent pattern of improvement of response over time on both T1- and T2-weighted MRI sequences was found.

[0285] Example 1 was designed with IRC-assessed ORR as the primary endpoint, evaluated according to RANO-HGG. These criteria assess tumor response primarily based on T1-weighted, contrast-enhanced

imaging. According to RANO-HGG, the FIREFLY-1 trial met its primary endpoint by rejecting the null hypothesis ORR of 21% observed for single agent vinblastine in this setting.

[0286] For patients with pLGG, decrease in contrast-enhancing tumor may not represent all aspects of antitumor activity. The RAPNO working group recommendations highlighted the lack of standard response criteria in clinical trials of pLGG as well as the biologic difference between pediatric and adult gliomas. RAPNO criteria focus on T2-weighted fluid-attenuated inversion recovery (FLAIR) imaging for assessing response in pLGG rather than changes in contrast-enhancing disease. This can be beneficial as pLGGs have clinical and biological features distinct from adult LGGs, and assessment of the contrast enhancing portion of the tumor may not be the best indicator of response in this population. RAPNO takes into account: changes in tumor-associated cysts; includes an MR category (tumor reduction of 25–<50%); and recommends including visual outcomes in response assessment (optic pathway and hypothalamic pLGGs), given their clinical importance in pLGG. Hence, assessment of tumor response by IRC according to RAPNO and RANO-LGG (both of which assess tumor response primarily based on non-enhancing disease by T2/FLAIR) were included in this trial as secondary and post hoc exploratory endpoints, respectively (see Example 1). Sustained decreases in tumor size were observed in most patients and represent clinically meaningful changes by T2/FLAIR based assessment criteria. ORR and CBR for RAPNO and RANO-LGG were very similar in arm 1. Although in limited numbers of patients, time to response in patients with tumors harboring BRAF V600E mutations appeared to be shorter by both assessment criteria (2.8 and 2.9 months, respectively), compared with patients with tumors harboring *BRAF* fusions (5.5 and 5.5 months).

[0287] While responses to tovorafenib generally occurred early, the kinetic analysis of tumor size over time per RAPNO and RANO-LGG revealed that some patients who remained on treatment following an initial assessment of radiographic PD subsequently had marked tumor shrinkage, suggestive of a delayed response to treatment. It has been suggested that such effects may be related to a transient immune-cell infiltration of the tumor leading to an initial increase in apparent tumor burden. Immune cells, especially microglia, may comprise 40% of all cells in pilocytic astrocytomas and can account for differences in RNA expression profiles between tumor locations and subtypes. The possibility of a late response to tovorafenib after an apparent initial increase in tumor size highlights the challenge of efficacy evaluation in this patient population using established response assessment criteria, and raises the possibility that some patients may benefit from tovorafenib treatment until radiographic progression is confirmed by a second MRI scan. Moving forward, follow-up imaging 8–12 weeks post-initial PD can be suggested for patients receiving tovorafenib with early radiographic progression, in the absence of clinical evidence of progression.

[0288] By utilizing both T1-weighted contrast-enhanced (RANO-HGG) and T2/FLAIR-based (RAPNO and RANO-LGG) approaches, the current trial assessed the impact of tovorafenib on different aspects of pLGG tumor biology and response. Despite the unique challenges of ascertaining an optimal, single set of response assessment criteria for this heterogeneous disease, confirmed responses to tovorafenib over time were observed across three different neuro-oncology response assessment criteria.

[0289] In Example 1, the over 50% ORR reported for tovorafenib using RAPNO and RANO-LGG in the current trial is particularly noteworthy given that over half of patients had previously received MAPKi therapy.

[0290] According to Example 1, regarding the safety and tolerability profile of tovorafenib monotherapy in children and young adults with pLGG, TRAEs were predominantly grade 1 or 2 and only nine (7%) of 137 patients discontinuing due to a TRAE. The most common TRAEs of any grade, excluding laboratory abnormalities, were hair color changes, fatigue, maculopapular rash, dry skin, acneiform dermatitis, pruritus, and paronychia. Although grade 1 and 2 laboratory abnormalities were commonly reported as AEs, most were not associated with any clinical symptoms, or need for clinical intervention or change in therapy. The most common grade ≥ 3 TRAEs included elevated CPK, anemia, and maculopapular rash. Other common grade ≥ 3 TEAEs (not assessed as related to tovorafenib), including seizures, were consistent with effects of the underlying disease.

[0291] Overall, the adverse events were consistent with the tovorafenib phase 1 trial in adults dosed once weekly, and similar to other targeted agents utilized as pLGG therapy, including MAPKIs, with some notable exceptions. Hair color changes, which have been reported in clinical studies of pediatric patients with pLGG treated with other MAPK inhibitors, occurred more often with tovorafenib. However, pyrexia, diarrhea, and weight gain – common adverse reactions for BRAF inhibitor/MEK inhibitor combination therapy – were less often reported as tovorafenib-related and did not significantly disrupt treatment. No signs of ocular toxicity, adverse impact on cardiac function, or abnormal weight gain were observed in children treated with tovorafenib, unlike those observed with MEK inhibitors. Although skin rashes were common in children treated with tovorafenib, no patients experienced life-threatening skin reactions, and the development of squamous cell carcinomas and keratoacanthomas were not observed.

[0292] There were no on-trial treatment-related deaths and TRAEs requiring discontinuation were infrequent. Intratumoral hemorrhage was reported in 15 patients and led to discontinuation of therapy in three patients. However, half (eight of 15) of the patients with intratumor hemorrhage were asymptomatic, with areas of tumor hemorrhage identified on routine trial MRI only. Three of the seven patients with symptomatic tumor hemorrhage had tumor bleeds assessed by the investigator as consistent with the natural history of their underlying tumor and not related to tovorafenib. Of the four patients in which the symptomatic hemorrhage was considered by the investigator to be possibly related to tovorafenib, two patients had a history of tumor hemorrhage prior to starting the study, the third patient had a disseminated tumor with leptomeningeal disease and the fourth patient had bone marrow failure secondary to prior treatment with multiple alkylating agents that was diagnosed prior to the onset of tumor hemorrhage. Although the incidence of intratumoral hemorrhage in this patient population is not well described, case reports suggest that the tumor hemorrhage risk across pLGG tumor types with heterogenous histology, morphology, and prior interventions may be underappreciated.

[0293] Decreases in growth velocity were observed in children treated with tovorafenib. Among patients with complete endocrinology assessments reported, radiographic studies of the wrist supported

conservation of growth potential with no advancement of bone age or evidence of premature fusion of growth plates. Furthermore, patients with available data following discontinuation of tovorafenib in the setting of FIREFLY-1 and prior studies, show various degrees of recovery of growth velocity, including achievement of catch-up growth. A more detailed analysis of growth during and after treatment with tovorafenib is planned. Notably, children with cancer, and with midline CNS tumors such as pLGG, commonly develop endocrine abnormalities that may impact growth trajectories and the likelihood of achieving genetic potential for height. In one report, nearly half of children with hypothalamic/chiasmatic gliomas developed at least one endocrine disorder, most commonly a growth hormone deficiency. Normative data for growth in this patient population is lacking and future studies of targeted therapies in pLGG should include baseline and longitudinal assessments of endocrine function and monitoring of growth velocity during therapy. Long-term follow-up of FIREFLY-1 patients after cessation of treatment is ongoing to assess the impact of transient reduction in growth velocity on final adult height. Collectively, these results show that tovorafenib monotherapy was generally well tolerated and demonstrated encouraging evidence of clinically meaningful, rapid, and durable clinical activity in children and young adults with *BRAF*-altered pLGG. Tovorafenib may consequently offer an important treatment option for *BRAF*-altered, relapsed/refractory pLGG, as the observed safety profile compares favorably to currently available therapies for pLGG with a positive benefit-risk ratio. Notably, the availability of a liquid formulation, a weekly dosing regimen, and lack of food effect allow for better adherence to the prescribed treatment regimen. Management of common adverse reactions was achieved in most patients with only brief dose interruptions. These data provide a strong rationale for the ongoing phase 3 LOGGIC/FIREFLY-2 (NCT05566795) trial of tovorafenib monotherapy versus current standard of care chemotherapy in children and young adults with pLGG requiring primary systemic treatment.

[0294] In another aspect, the disclosure provides methods of treatment according to Example 2.

[0295] As illustrated in Example 2, tovorafenib monotherapy demonstrated antitumor activity in relapsed/refractory *BRAF*-altered OPG across radiological assessment criteria and was generally well tolerated. In some embodiments, a subject's vision remained stable or improved.

[0296] In Example 2, subgroup analysis of the international, multicenter, single-arm phase 2 FIREFLY-1 trial, demonstrated that tovorafenib monotherapy achieved clinically meaningful, rapid and durable tumor responses in children and young adults with *BRAF*-altered sporadic relapsed/refractory OPG. Tumor responses occurred in the OPG subgroup according to all three response assessment criteria, RANO-HGG (ORR, 64%), RAPNO (50%) and RANO-LGG (55%). There was a consistent pattern of improved response over time according to both of the response criteria based on T2/FLAIR-weighted MRI sequences (RAPNO and RANO-LGG). Given that patients had received a median of three prior lines of systemic therapy, and more than two thirds had previously received MEK and/or BRAF inhibitors, the imaging responses of this OPG subgroup support tovorafenib monotherapy.

[0297] In Example 2, VA assessments showed that vision of the best eye improved in 39% of patients, remained stable in 53%, and worsened in only 8%. Vision either improved or remained stable (i.e., was

preserved) in 92% of patients in the OPG subgroup during tovorafenib treatment. The improvement of VA in 40–50% of patients with a best overall response of stable disease (across assessment criteria) suggests that tumor shrinkage was not always needed in order to reach this important functional outcome.

[0298] Preserved VA was seen regardless of *BRAF* alteration type (fusion vs mutation), whether or not patients had previously received MAPKi therapy, and whether they had received ≤ 3 or >3 prior lines of systemic therapy. VA generally remained stable or improved for the majority of patients, regardless of the baseline VA, except for two patients with moderate impairment at baseline and one with profound/worse impairment at baseline (Table 7). Clinically, vision deteriorates with longer time from initial diagnosis. However, the present cohort treated with tovorafenib for OPGs, vision was preserved during tovorafenib treatment (when stratifying patients into quartiles according to time from primary diagnosis).

[0299] A single-institution retrospective study assessed the effect of first-line chemotherapy on vision in 42 patients with NF1-associated (71%) or sporadic OPG (29%). Vision was improved in 14% of evaluable patients (n=35) over the course of therapy and was stable in 77% (preserved in 91%). A further retrospective study in 30 patients from a middle-income country with sporadic (77%) or NF1-associated OPG (23%) showed that vision was preserved after treatment (predominantly chemotherapy) in nine of 10 (90%) evaluable patients. The activity of tovorafenib in relation to improving or preserving vision in patients with heavily pretreated sporadic relapsed/refractory OPG compares favorably with these retrospective studies of the effect of chemotherapy on VA.

[0300] In Example 2, radiological and VA outcomes were fully concordant in 45%, 42%, and 37% of patients, and fully discordant in only 6%, 0%, and 3% of patients (all with radiological response and VA worsened) according to RANO-HGG, RAPNO and RANO-LGG, respectively. Remaining assessments were partially concordant, with the largest group of patients having radiological responses and stable VA. Of note, for both RAPNO and RANO-LGG assessments, large improvements in VA occurred in some patients with only small maximal changes in tumor size.

[0301] The safety profile of tovorafenib monotherapy in the arm 1 OPG subgroup was similar to the previously reported safety profile in the safety analysis set of the combined population of treated patients in FIREFLY-1 arms 1 and 2. Tumor hemorrhage was reported as a TRAE in three patients (7%) in the OPG subgroup.

[0302] According to Example 2, this group of children and adolescents with relapsed/refractory OPG, clinically meaningful, durable and rapid tumor responses were achieved with tovorafenib monotherapy (both according to contrast-enhancement based and T2/FLAIR-weighted sequence-based response criteria). Tovorafenib was well tolerated and treatment discontinued due to TEAEs in only 10% of patients. VA was preserved during treatment for 92% of patients. Tovorafenib may offer an important new treatment option for patients with *BRAF*-altered, relapsed/refractory OPG.

[0303] The disclosure also provides, tovorafenib tablets for oral use and tovorafenib oral suspension. In some embodiments, tovorafenib is administered as a tablet for oral use. In some embodiments, tovorafenib is administered as an oral suspension.

[0304] In certain embodiments, tovorafenib or a salt thereof is a kinase inhibitor used for the treatment of patients 6 months of age and older with relapsed or refractory pediatric low-grade glioma (LGG) harboring a BRAF fusion, rearrangement, or BRAF V600 mutation.

[0305] In certain embodiments, the dosage and administration instructions are: (1) confirm the presence of BRAF fusion, rearrangement, or BRAF V600 mutation prior to initiation of treatment with tovorafenib; (2) recommend dosage of tovorafenib based on body surface area (see Table A); (3) administer tovorafenib orally, once weekly, with or without food; (4) swallow tablets whole with water, do not chew, cut, or crush. In some embodiments, see the full prescribing information for preparation and administration instructions for tovorafenib for oral suspension and dosage modifications for adverse reactions. In some embodiments, the dosage and administration instructions are confirm the presence of BRAF fusion, rearrangement, or BRAF V600 mutation prior to initiation of treatment with tovorafenib. In some embodiments, the dosage and administration instructions are recommend dosage of tovorafenib based on body surface area (see Table A or Table B). In some embodiments, the dosage and administration instructions are administer tovorafenib orally, once weekly, with or without food. In some embodiments, swallow tablets whole with water, do not chew, cut, or crush.

[0306] In certain embodiments, the presence of BRAF fusion, rearrangement, or BRAF V600 mutation prior to initiation of treatment with tovorafenib is confirmed. In some embodiments, tovorafenib (or salt thereof) is administered orally, once weekly, with or without food.. In some embodiments, tovorafenib (or salt thereof) is administered by swallowing the tablets in whole with water.

[0307] In certain embodiments, the dosage forms and strengths are: 100 mg tablet and 25 mg/mL oral suspension. In some embodiments, the dosage form and strength is Tablets: 100 mg. In some embodiments, the dosage and strength is oral suspensions: 25 mg/mL. In certain embodiments, the dose form and strength is tablet: 100 mg. In certain embodiments, the dose form and strength is oral suspension: 25 mg/mL. In certain embodiments, each tablet contains 100 mg tovorafenib and the following inactive ingredients: copovidone, colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, and Opadry®Orange. In certain embodiments, each mL of reconstituted tovorafenib suspension contains 25 mg of tovorafenib and the following inactive ingredients: artificial strawberry flavor, colloidal silicon dioxide, copovidone, maltodextrin, mannitol, microcrystalline cellulose, simethicone, sodium lauryl sulfate, and sucralose.

[0308] In certain embodiments, tovorafenib or a salt thereof is administered in combination with a second therapeutic agent. In some embodiments, the second therapeutic agent prevents or treats hemorrhage. In some embodiments, the second therapeutic agent prevents or treats skin toxicity including photosensitivity. In some embodiments, the second therapeutic agent prevents or treats maculopapular rash and photosensitivity. In some embodiments, the second therapeutic agent promotes growth. In some embodiments, the second therapeutic agent prevents or treats growth reductions. In some embodiments, the second therapeutic agent helps maintain the subject's growth velocity. In some embodiments, the second therapeutic agent prevents or treats embryo-fetal toxicity. In some embodiments, the second therapeutic

agent is selected from an anti-viral therapeutic, an bacterial pneumonia therapeutic, and a sepsis therapeutic. In some embodiments, the second therapeutic agent is selected from an anti-viral and antibacterial. In some embodiments, the antibacterial therapeutic is for pneumonia. In some embodiments, the antibacterial therapeutic is for sepsis. In some embodiments, the anti-viral therapeutic is for a viral infection. In some embodiments, the second therapeutic agent is directed at treating rashes, pyrexia, vomiting, or hemorrhage. In some embodiments, the second therapeutic agent treats or alleviates rash (including erythema multiforme, eczema, rash erythematous, rash macular, rash follicular, rash pruritic, rash maculopapular, rash, rash popular, rash pustular, skin exfoliation, drug eruption, dermatitis, and dermatitis bullous), hair color changes, dry skin, dermatitis acneiform, pruritus, fatigue, pyrexia, edema (including lip edema, periorbital edema, edema peripheral, localized edema, facial edema, and vulval edema), headache, vomiting (including retching and hematemesis), constipation, nausea, abdominal pain, diarrhea (including colitis and enterocolitis), stomatitis (including mouth ulceration, mucosal inflammation, aphthous ulcer, and cheilitis), hemorrhage (including tumor hemorrhage, gastrointestinal hemorrhage, subdural hemorrhage, epistaxis, intracranial tumor hemorrhage, upper gastrointestinal hemorrhage, lower gastrointestinal hemorrhage, vaginal hemorrhage, gingival bleeding, post procedural hemorrhage, hemoptysis, and anal hemorrhage), viral infection (including rhinovirus infection, enterovirus infection, viral upper respiratory tract infection, enterocolitis viral and oral herpes, gastroenteritis viral, influenza, rhinovirus infection, respiratory syncytial virus infection, enterovirus infection, coronavirus infection, herpes simplex, parainfluenza virus infection, adenoviral upper respiratory infection, viraemia, adenovirus infection, conjunctivitis viral, eye infection viral, metapneumovirus infection, parvovirus infection, respiratory syncytial virus bronchiolitis, respiratory tract infection viral, viral pharyngitis, viral rhinitis, and viral tonsillitis), upper respiratory tract infection, paronychia, or combinations thereof. In some embodiments the additional therapeutic agent treats or alleviates an abnormality. In some embodiments, the abnormality is decreased phosphate, increased AST, increased creatine kinase, increased LDH, increased ALT, decreased potassium, increased bilirubin, decreased albumin, decreased sodium, decreased hemoglobin, decreased lymphocytes, or decreased leukocytes, increased lymphocytes, or combinations thereof.

[0309] In some embodiments, the second therapeutic agent is a corticosteroid. In some embodiments, the second therapeutic agent is a nonsteroidal anti-inflammatory drug (NSAIDs). In some embodiments, the nonsteroidal anti-inflammatory drug (NSAIDs) is selected from ibuprofen and acetaminophen. In some embodiments, the second therapeutic agent is an antiemetic. In some embodiments, the second therapeutic agent is an antihistamine. In some embodiments, the antihistamine is bismuth subsalicylate. In some embodiments, the second therapeutic agent is an antiplatelet, an anticoagulant, or an astatin. In some embodiments, the second therapeutic agent is directed at treating rashes or fatigue. In some embodiments, the second therapeutic agent is a stimulant. In some embodiments, the stimulant is selected from modafinil, methylphenidate, amphetamine (dextroamphetamine), amantadine, and dextroamphetamine. In some embodiments, the second therapeutic agent is directed at treating dry skin, constipation, nausea, or upper respiratory tract infection, or combinations thereof. In some embodiments, the second therapeutic agent is

an alpha-hydroxy acid. In some embodiments, the second therapeutic agent is a laxative. In some embodiments, the second therapeutic agent is antiemetic. In some embodiments, the antiemetic is selected from antagonists of dopamine, serotonin, neurokinin, histamine, and acetylcholine. In some embodiments, the second therapeutic agent is an antibiotics directed at upper respiratory tract infection or an antiviral direct at upper respiratory tract infection. In some embodiments, the second therapeutic agent is a vitamin supplement or a mineral supplement. In some embodiments, the vitamin or the mineral supplement is a phosphate salt or a potassium salt. In some embodiments, the second therapeutic agent is a therapeutic directed at treating or alleviating decreased phosphate, decreased hemoglobin, increased creatinine kinase, decreased neutrophils, increased alanine aminotransferase, increased bilirubin, increased aspartate aminotransferase, decreased lymphocytes, and decreased potassium, or combinations thereof. In certain embodiments, the second therapeutic agent is administered at the same time as tovorafenib. In some embodiments, the second therapeutic agent and tovorafenib are administered sequentially. In some embodiments, the second therapeutic agent is administered less frequently than tovorafenib. In some embodiments, the second therapeutic agent is administered more frequently than tovorafenib. In some embodiments, the second therapeutic agent is administered prior than the administration of tovorafenib. In some embodiments, the second therapeutic agent is administered after the administration of tovorafenib.

[0310] In certain embodiments, patients have Karnofsky/Lansky performance status of 80 to 100.

[0311] In certain embodiments, tovorafenib or a salt thereof is not coadministered with a CYP2C8 inhibitor. In certain embodiments, tovorafenib or a salt thereof is not coadministered with a CYP3A4 substrate. In certain embodiments, tovorafenib or a salt thereof is not coadministered with a hormonal contraceptive. In certain embodiments, tovorafenib or a salt thereof is not coadministered with a CYP2C8 inducer. In some embodiments, tovorafenib or a salt thereof is not coadministered with a moderate or strong CYP2C8 inducer.

[0312] In certain embodiments, the recommended dosage of tovorafenib based on body surface area (BSA) is 380 mg/m² orally once weekly (the maximum recommended dosage is 600 mg orally once weekly). In certain embodiments, tovorafenib may be administered as an immediate release tablet (see Table A) or as an oral suspension (see Table B).

[0313] In certain embodiments, the dosage form and strength are tablets at 100 mg. In certain embodiments, the dosage form and strength is powder for oral suspension: 25 mg/mL.

[0314] In certain embodiments, patients received tovorafenib at a dose based on body surface area orally once weekly until disease progression, intolerable toxicity, or loss of clinical benefit. In some embodiments, patients received tovorafenib at a dose based on body surface area orally once weekly. In some embodiments, patients received tovorafenib until disease progression. In some embodiments, patients received tovorafenib until intolerable toxicity. In some embodiments, patients received tovorafenib until loss of clinical benefit.

Examples:

Example 1. Trial design and results

[0315] FIREFLY-1 (PNOC026; NCT04775485) is an ongoing, phase 2, multicenter, open-label study evaluating tovorafenib monotherapy in children, adolescents, and young adults with *RAF*-altered pediatric low-grade gliomas (pLGGs) or advanced solid tumors who have received at least one prior systemic therapy. The trial consists of three treatment arms, with patients enrolled from 32 centers in 11 countries. Arm 1 enrolled patients with relapsed or refractory pLGG harboring an activating *BRAF* alteration, including *BRAF* V600 mutations and *KIAA1549::BRAF* fusions. Arm 2 (pLGG expansion cohort) enrolled patients with relapsed or refractory pLGG harboring an activating *RAF* alteration and arm 3 is enrolling patients with advanced solid tumors harboring an activating *RAF* fusion. *RAF* alterations were identified through molecular assays as routinely performed as part of standard of care diagnostic testing at Clinical Laboratory Improvement Amendments (CLIA) of 1988 certified or other similarly certified laboratories. The classification of *BRAF* fusion included *BRAF* tandem duplication, *BRAF* rearrangement and *BRAF* fusions involving partner genes other than *KIAA1549*.

[0316] Sex and/or gender was not considered in the trial design as no sex differences have been seen in previous clinical trials in pLGG, though in line with rates generally seen in childhood cancer, there is one report of the incidence of pLGG being slightly higher in males than in females. The current trial recruited any patient independent of sex or gender. The sex of the participants was based on either parental or self-report. The gender of patients was not captured or considered as part of this trial as at the time the protocol was written and the FIREFLY-1 trial initiated, there was less of a focus than currently on collecting gender-related information.

[0317] Tovorafenib was administered at the recommended phase 2 dose of 420 mg/m² (not to exceed 600 mg) by mouth (tablet or liquid formulation), once weekly, on days 1, 8, 15, and 22 of 28-day cycles. Treatment cycles were to be repeated every 28 days until radiographic evidence of disease progression as determined by the treating investigator according to RANO-HGG criteria, unacceptable toxicity, decision to enter a drug holiday period, patient withdrawal of consent, or death. Patients who had radiographic evidence of disease progression were allowed to continue tovorafenib treatment if, in the opinion of the investigator and approved by the sponsor, the patient was deriving clinical benefit from continuing trial treatment. Patients were to be treated with tovorafenib for a planned period of 26 cycles (approximately 24 months), after which they could continue on tovorafenib or, at any point, opt to enter a drug holiday period. During this drug holiday period, patients could be re-treated with tovorafenib if there was radiographic evidence of disease progression.

[0318] An independent data safety monitoring board (DSMB) was established prior to initiation of the trial and was in place for the duration of the trial. Medical monitoring of the trial was provided by the sponsor and utilized a safety review committee that included the principal investigator (or their designee) from each active clinical site.

[0319] The protocol, protocol amendments, informed consent form, pediatric assent form, investigator brochure, and other relevant documents were approved by an institutional review board/independent ethics

committee at each trial site. As applicable according to local regulations, the protocol and all protocol amendments were reviewed and approved by each pertinent competent authority.

[0320] This trial was conducted in accordance with the protocol and consensus ethical principles derived from international guidelines including the Declaration of Helsinki, Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines, applicable International Council for Harmonisation Good Clinical Practice Guidelines, and other applicable laws and regulations. All patients and/or their legally authorized representative provided written informed consent and pediatric assent before enrollment in the trial, according to local regulations. No direct compensation was provided to patients or families for participating in the trial.

Data collection

[0321] Clinical data required by the protocol were entered into the Electronic Case Report Forms (eCRF) and used a fully validated secure web-enabled Electronic Data Capture (EDC) System – Medidata Classic Rave® 2022.3.2, which is compliant with 21 CFR Part 11 requirements. Automatic validation edit checks in EDC and offline listings were programmed to capture data discrepancies in the eCRFs and allowed modification and validations of the entered data. The Investigator verified and signed off the eCRFs in EDC to confirm the clinical data captured were complete and accurate. The Sponsor can attest that all data and metadata will be archived in perpetuity. The data are in the EDC (Electronic Data Capture) and TMF (Trial Master File), which are retained in perpetuity. In addition, these data have been filed with the US FDA.

Eligibility

[0322] Full inclusion and exclusion criteria are listed in the trial protocol. Briefly, eligible patients in arm 1 were aged 6 months to 25 years, inclusive, with a histopathologically verified pLGG, which had previously been treated with at least one line of prior systemic therapy with evidence of radiographic progression, a documented known activating *BRAF* alteration and measurable disease as defined by Response Assessment in Neuro-Oncology-high-grade glioma (RANO-HGG) criteria, a Karnofsky (aged ≥ 16 years) or Lansky (aged < 16 years) performance score of ≥ 50 and adequate organ function. Radiation therapy to the measurable lesion(s) must have been completed at least 6 months prior to administration of tovorafenib, and patients must have fully recovered from the acute toxic effects of all prior anticancer chemotherapy and from any prior surgery. Patients must have had adequate bone marrow and organ function including a left ventricular ejection fraction (LVEF) of $\geq 50\%$ as measured by echocardiogram or multiple-gated acquisition (MUGA) scan, or fractional shortening (FS) $\geq 25\%$ as measured by echocardiogram, within 28 days before the first dose of tovorafenib. Tumor tissue (archival) was obtained at enrollment whenever available. Tissue biopsy was required during screening only if an archival tumor tissue sample was not available.

[0323] Patients were excluded if their tumor harbored an additional previously known or expected to be activating molecular alteration, if they had symptoms of clinical progression without radiographically recurrent or radiographically progressive disease, a known or suspected diagnosis of neurofibromatosis type 1 via genetic testing or current diagnostic criteria, a history or current evidence of central serous

retinopathy, retinal vein occlusion, or ophthalmopathy present at baseline that would be considered a risk factor for either, clinically significant active cardiovascular disease or if they were neurologically unstable despite adequate treatment.

Trial endpoints

[0324] The assessment of response was undertaken using three different radiological response assessment criteria: RANO-HGG, which assess tumor response primarily based on T1-weighted, contrast-enhanced imaging and Response Assessment in Pediatric Neuro-Oncology-LGG (RAPNO) and RANO-LGG, both of which assess tumor response primarily based on non-enhancing disease by T2/FLAIR. The characteristics of these different response criteria are summarized in Extended Data Table 1. As per the trial design, patients were initially enrolled based on investigator assessment of eligibility per RANO-HGG. Investigator response assessments per RANO-HGG were also the criteria on which cessation of treatment due to PD were based. Response was subsequently analyzed per all three criteria by blinded independent central review.

Table 1. Patient and baseline characteristics: n=137

Characteristic	Arm 1 n=77	Arm 2 n=60	Total n=137
Age, years			
Median (range)	8 (2–21)	10 (1–24)	9 (1–24)
Gender, n (%)			
Male	40 (52)	33 (55)	73 (53)
Female	37 (48)	27 (45)	64 (47)
Race, n (%) ^a			
White	41 (53)	38 (63)	79 (58)
Asian	5 (6)	5 (8)	10 (7)
Black	2 (3)	1 (2)	3 (2)
Multiple	3 (4)	0	3 (2)
Other	6 (8)	2 (3)	8 (6)
Not specified	20 (26)	14 (23)	34 (25)
Missing	0	0	0
Ethnicity, n (%)			
Hispanic or Latino	3 (4)	1 (2)	4 (3)
Not Hispanic or Latino	51 (66)	47 (78)	98 (72)
Not stated	21 (27)	12 (20)	33 (24)
Missing	2 (3)	0	2 (1)
Primary tumor location, n (%)			
Optic pathway	39 (51)	29 (48)	68 (50)
Deep midline structures	9 (12)	11 (18)	20 (15)
Cerebral hemisphere	6 (8)	5 (8)	11 (8)
Brain stem	6 (8)	2 (3)	8 (6)
Cerebellum	5 (6)	2 (3)	7 (5)
Other ^b	12 (16)	11 (18)	23 (17)
Histology, n (%)			
Astrocytic	72 (94)	55 (92)	127 (93)
Oligodendroglial	0	1 (2)	1 (1)
Mixed glial-neuronal	4 (5)	4 (7)	8 (6)
Other	1 (1)	0	1 (1)
BRAF alteration status, n (%)			
BRAF fusion	64 (83)	51 (85)	115 (84)
KIAA1549::BRAF fusion	56 (73)	45 (75)	101 (74)
Other	8 ^c (10)	6 (10)	14 (10)
BRAF V600E mutation	13 (17)	9 (15)	22 (16)
Baseline Lansky performance score, n/n (%) ^d			

50–70	3/71 (4)	9/51 (18)	12/122 (10)
80–100	68/71 (96)	42/51 (82)	110/122 (90)
Baseline Karnofsky performance score, <i>n</i> / <i>n</i>			
(%) ^d			
50–70	2/6 (33)	0	2/15 (13)
80–100	4/6 (67)	9/9 (100)	13/15 (87)
Prior lines of systemic therapy			
Median (range)	3 (1–9)	3 (1–10)	3 (1–10)
Number of prior lines, <i>n</i> (%)			
1	17 (22)	14 (23)	31 (23)
2	21 (27)	13 (22)	34 (25)
≥3	39 (51)	33 (55)	72 (53)
Prior MAPK pathway targeted therapy, <i>n</i> (%)			
Prior MEK inhibitor	43 (56)	34 (57)	77 (56)
Prior BRAF inhibitor	8 (10)	7 (12)	15 (11)
Prior MEK and BRAF inhibitors	5 (7)	4 (7)	9 (7)
Prior MEK and/or BRAF inhibitor ^e	46 (60)	37 (62)	83 (61)
Any prior surgery for treatment of primary disease, <i>n</i> (%)			
Pre-operative staging			
Localized disease	60 (78)	42 (70)	102 (74)
Disseminated/metastatic disease	9 (12)	11 (18)	20 (15)
Leptomeningeal spread	8 (10)	7 (12)	15 (11)
Post-operative staging			
Gross total resection	1 (1)	0	1 (1)
Subtotal resection	36 (47)	27 (45)	63 (46)
Biopsy only, resection not attempted	40 (52)	33 (55)	73 (53)
Prior radiotherapy for primary disease, <i>n</i> (%)	6 (8)	4 (7)	10 (7)

[0325] The primary endpoint in arm 1 was overall response rate (ORR), defined as the proportion of patients with a confirmed response of CR or PR according to RANO-HGG criteria, as assessed by an independent radiology review committee (IRC). Secondary endpoints for arm 1 included clinical benefit rate (CBR), progression-free survival (PFS), DOR, time to response, as assessed by the IRC using RANO-HGG criteria. The CBR is defined as proportion of patients with a confirmed response or stable disease lasting either any length of time, 6 months or more, or 12 months or more. ORR, CBR, PFS, DOR and time to response were also assessed by the IRC according to Response Assessment in Pediatric Neuro-Oncology (RAPNO) criteria. Secondary endpoints for safety included evaluation of adverse events, laboratory abnormalities, and cardiac function assessments (change from baseline in QTcF, PR interval, QRS interval, heart rate, or electrocardiogram [ECG] waveform morphology). Post hoc exploratory endpoints for arm 1 included ORR and CBR according to RANO-LGG criteria by IRC assessment. For RAPNO and RANO-LGG ORR assessments, patients with confirmed minor responses were considered responders in accordance with published guidelines. Changes in quality of life and health utilities measures were exploratory objectives.

Assessments

[0326] Disease assessments in arm 1 were conducted by MRI of the brain and spine and were performed at screening up to 28 days prior to first dose, at the end of cycle 3, and then at the end of every three cycles thereafter. Spinal scans were only required to be repeated after screening in patients with known or clinically suspected intraspinal disease. Patients who had an optic pathway glioma (OPG) or underlying

visual function deficit related to the primary malignancy had a visual acuity examination every time they had a radiographic disease assessment.

[0327] A central imaging laboratory was used. Imaging Endpoints (IE) (Scottsdale, AZ) is a research and imaging core laboratory providing blinded independent central review of response assessments with dual reader plus adjudication paradigm utilizing neuro-radiologists trained in all three response assessment criteria as readers for the following assessments: RANO-HGG criteria, RAPNO-LGG criteria, and RANO-LGG criteria. All activities at IE meet or exceed GCP standards, and IE underwent GCP audit by the Sponsor. A prospectively designed imaging charter was developed for the FIREFLY-1 study prior to the initiation of the study. This outlined the processes for initial imaging review, data transfers, and data review and queries were followed throughout the study. IE functions as the centralized imaging core lab responsible for the collection, quality control, archival and BICR of imaging for the FIREFLY-1 trial. IE is responsible for management of the image analysis system, reporting methods, implementation of the analysis criteria, and reader management including qualification, training, and oversight.

[0328] Reader performance was assessed by evaluating reader variability at defined and prespecified milestones during ongoing imaging interpretation. Variability metrics included inter- and intra-reader variability to monitor for consistency of reads. If reader acceptance rate fell outside the caution or alert limits, IE determined the appropriate unbiased action(s).

[0329] For this disclosure, safety was assessed in the arm 1 and 2 safety analysis set, which comprised all enrolled patients who received at least 1 dose of trial treatment. The assessment period for AEs was from the first dose of tovorafenib until 30 days after the last dose. For the current trial, an adverse event was defined as treatment emergent if it occurred at any time after the first dose of trial drug until 30 days following the last dose of trial drug. A treatment-related adverse event was any treatment emergent event that the investigator assessed had at least a reasonable possibility of having a causal relationship with the trial drug based on temporal association with initiation of treatment and assessment of other potential etiologies. An adverse event was considered serious if it met one of the following criteria: required or prolonged hospitalization, was life-threatening, caused disability, or was considered a medically important event by the investigator (regardless of symptoms or Common Terminology Criteria for Adverse Events [CTCAE] grade).

[0330] Routine laboratory tests were performed locally and included pregnancy tests for female patients of childbearing potential (at screening and on day 1 of every cycle), assessments of hematology parameters and serum chemistries (at screening, days 1 and 15 of cycle 1, and day 1 of cycle 2 and every cycle thereafter), and thyroid function (at screening, on day 1 of cycles 1–3 and every other cycle thereafter). Scheduled cardiac function assessments included independently centrally reviewed 12-lead resting ECGs (performed in triplicate at baseline, on days 1 and 15 of cycle 1, day 1 of cycles 2 and 4 and day 1 of every third cycle thereafter) and echocardiograms or multiple-gated acquisition scans (conducted throughout by the same technique, on day 1 of cycles 2 and 4 and day 1 of every third cycle thereafter). Creatine

phosphokinase level was assessed at screening, on day 1 of cycles 2 and 4 and day 1 of every fourth cycle thereafter.

[0331] In patients 2 years of age or older, health-related quality of life was assessed using the PedsQL-Core, PedsQL-Cancer, and PROMIS® assessment for the patient or their parent/caregiver every third cycle. The PROMIS® questionnaire was only administered to English-speaking patients enrolled in the U.S., Australia, and U.K.

Statistical considerations

[0332] In terms of the “evaluable” population, patients “evaluable for efficacy” were all patients enrolled in the trial who received at least 1 dose of trial treatment and met the definition for the prespecified efficacy analyses criteria (RANO-HGG, RAPNO, RANO-LGG); those in the “evaluable for DOR” population were patients evaluable for efficacy who had a best overall confirmed response of CR, PR, or minor response (MR; for RAPNO, RANO-LGG). The “safety” population consisted of all patients enrolled in the trial who received at least 1 dose of trial treatment. This disclosure presents efficacy data from the evaluable population in arm 1 and the safety data from arms 1 and 2 as of a June 5, 2023 data cutoff.

[0333] The primary endpoint analysis was performed in the arm 1-evaluable population, which included all enrolled patients who received at least one dose of tovorafenib and had measurable disease at baseline per RANO-HGG criteria as determined by the IRC. A sample size of 60 patients in the evaluable population was considered to provide 88% power to reject the null hypothesis ORR of 21%, at the 2-sided 0.05 level, assuming that the true underlying ORR of tovorafenib was 40% in this disease population. An exact binomial test was used for hypothesis testing. Responses per RAPNO and RANO-LGG criteria were evaluated in evaluable populations, which included all enrolled patients who received at least one dose of tovorafenib and had measurable disease at baseline per RAPNO and RANO-LGG criteria, respectively, as determined by the IRC.

[0334] Prespecified subgroup analysis of the uniformity of the treatment effects for ORR in arm 1 was planned for subgroups defined by *BRAF* alteration (*BRAF* fusion vs. *BRAF* mutation), number of prior lines of therapies, prior MAPKi status (prior MEKi and/or prior BRAFi), sex, age group (6 months to <2 years of age, 2 to <6 years of age, 6 to <12 years of age, 12 to <16 years of age, 16 to ≤25 years of age), and race.

[0335] The ORR and CBR were calculated with 95% CIs determined using the Clopper-Pearson method. PFS and DOR were estimated by the Kaplan-Meier method and were summarized along with the corresponding 2-sided 95% CI. Waterfall plots were generated for each patient’s best percentage change in sum of perpendicular diameters of measurable lesions.

[0336] Safety endpoints were analyzed using descriptive statistics based on the safety population in arms 1 and 2. Adverse events were coded by system organ class and preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.1 and graded according to the National Cancer Institute CTCAE version 5.0.

[0337] Statistical analyses were carried out using SAS v9.4.

Management of cutaneous adverse events

[0338] Guidance for the management of rash/dermatitis was included in the trial protocol, in line with the stepwise approach proposed by Song et al, 2019 for the prevention and treatment of common cutaneous adverse reactions to BRAF, MEK, and mTOR inhibitors in children with CNS tumors. Dermatology assessment was performed at baseline and symptom-directed thereafter. Patients were to be referred to a dermatology department if cutaneous symptoms were impairing function (e.g., if the patient could not sleep, or sit still) or psychosocially bothersome, and/or when management techniques failed to resolve the condition. It was recommended that all trial patients followed a gentle skin care routine comprising short lukewarm showers/baths, the use of unscented, gentle cleansers and the application of unscented thick moisturizers (creams over lotions) immediately following showers. In addition, the prophylactic use of sun protection factor 30+ sunscreen whenever going outside, with this reapplied every 2 hours, and the wearing of sun-protective clothing was recommended for all patients. Specific guidance was also provided to manage mild or moderate/severe follicular, eczematous, paronychia or periungual reactions or hand-foot syndrome.

[0339] In the event of grade 2 macular or papular eruption, erythema with pruritus or other associated symptoms, localized desquamation or other lesions covering <50% of body surface area (BSA), tovorafenib dosage reduction by one dose level once weekly could be considered. In the event of grade 3 or higher severe, generalized erythroderma or macular, papular or vesicular eruption, desquamation covering ≥50% BSA, or generalized exfoliative, ulcerative, or bullous dermatitis, tovorafenib dosing was to be delayed until the condition improved, a dermatologist was to be consulted, and a dosage reduction by two dose levels or holding tovorafenib administration until resolution to grade 1 or baseline could be considered.

[0340] Protocol amendments

[0341] Protocol was amended primarily to add two new arms to the trial, add a powder for reconstitution formulation of tovorafenib, and incorporate other changes based on feedback from regulatory authorities. This version of the full trial protocol (some confidential information redacted) is in the Supplementary Information supporting the article.

[0342] *Version 2.0 October 23, 2020*

[0343] Amended primarily to change the recommended phase 2 dose of tovorafenib from 530 mg/m² to 420 mg/m² and decrease the maximum dose from 800 mg to 600 mg once weekly. The planned number of cycles was reduced from 27 to 26 cycles (patients could continue on trial treatment beyond this if criteria were met), and the upper age limit was increased from 18 to 25 years of age, inclusive.

Clinical Trial registration

[0344] The study is registered on clinicaltrials.gov as NCT04775485 and EudraCT as #2020-003657-30.

Results

[0345] Endpoints

[0346] The primary endpoint in arm 1 was the ORR as assessed by the IRC according to RANO-HGG. Secondary endpoints for arm 1 included ORR by RAPNO per IRC, clinical benefit rate (CBR), progression-

free survival (PFS), DOR, time to response, per IRC by RANO-HGG and RAPNO, and safety and tolerability (primary endpoint in arm 2), assessed by the type, frequency, and severity of adverse events (AEs) and laboratory abnormalities. Additional planned secondary endpoints not reported in this manuscript are described in detail in the full trial protocol in the Supplementary Information and include pharmacokinetics, the effect of tovorafenib on the corrected QT interval by Fredericia (QTcF) and other electrocardiogram parameters, change in visual acuity, and concordance of molecular profiling approaches. The characteristics of the three different radiological response assessment criteria used in the assessment of efficacy in the trial are summarized in Data Table 1.

[0347] Patients and disposition

[0348] Between April 22, 2021 and January 26, 2023, 137 patients were enrolled to arms 1 and 2 and received tovorafenib, 77 in arm 1 and 60 in arm 2. Seven (9%) patients in arm 1 and 21 (35%) in arm 2 received tovorafenib as a liquid formulation; all other patients received the tablet formulation. As of the datacut, 102 patients remained on treatment (Fig. 1). The most common reasons for treatment discontinuation were progressive disease (PD) and AEs. Patient demographics and baseline characteristics are summarized in Table 1 and were similar between arms. In all 137 patients, the median age was 9 years (range 1–24), most patients were white (58%) and most had astrocytic tumors (93%). The most common tumor locations were optic pathway (50%) and deep midline structures (15%). Seventy-four percent of patients had a tumor harboring a *KIAA1549::BRAF* fusion, 10% had a chromosomal rearrangement involving *BRAF* (as detected by fluorescence in situ hybridization or in situ hybridization and presumed to represent a *KIAA1549::BRAF* or other *BRAF* fusion), and 16% had a *BRAF* V600E mutation. Patients had received a median of three lines of prior therapy (range 1–10), with 61% having received a prior MEK and/or *BRAF* inhibitor.

[0349] The IRC deemed 69 patients in arm 1 who received ≥ 1 dose of tovorafenib to have measurable disease at baseline per RANO-HGG. Seventy-six patients in arm 1 were deemed evaluable for efficacy by the IRC per RAPNO and RANO-LGG, which utilize T2-weighted imaging for response assessment. Safety was analyzed in all patients in arms 1 and 2 who received ≥ 1 dose of tovorafenib ($n=137$).

[0350] Patients in arm 1 had received a median of 18 treatment cycles (range 1–26), with median treatment compliance of 100% (range 93–100) (treatment compliance [%] was the total actual dose [mg]/total expected dose [mg] $\times$ 100%). The median duration of treatment (DOT) was 15.8 months (range 0.7–23.7) with 66% ($n=51$) continuing treatment. Two patients had completed 26 treatment cycles and opted to enter a drug holiday period. Neither patient had subsequent imaging following initiation of the drug holiday period. All other patients (except the ones who discontinued drug early) were still on treatment as of the June 5, 2023 datacut. Patients in arm 2 had received a median of 11 treatment cycles (range 2–15), with median treatment compliance of 100% (range 83–100). The median DOT was 9.7 months (range 1.2–13.3) with 85% ($n=51$) continuing treatment. There was no decline from baseline in Karnofsky or Lansky performance status scores during treatment with tovorafenib.

RANO-HGG (primary and secondary endpoints)

[0351] The ORR per RANO-HGG (primary endpoint) in patients with response-evaluable disease was 67% (95% CI 54–78), including 12 (17%) patients with a complete response (CR) and 34 (49%) with a partial response (PR). Eighteen (26%) had a best overall response (BOR) of stable disease (SD), giving a CBR of 93% (Table 2). The ORR was 69% (95% CI 56–81) in patients with tumors harboring *BRAF* fusions and 50% (95% CI 19–81) in patients with tumors harboring BRAF V600E mutations. The ORR was 71% (95% CI 54–84) in the 59% of evaluable patients who had received prior MAPK inhibitor (MAPKi) therapy, and 61% (95% CI 41–78) in those who had not.

[0352] FIG 2A shows the best tumor response from baseline, and FIG 2A shows DOT and timing of response. In 13% ($n=9$) of patients, an initial PR was followed by a CR with continued treatment. The median time to initial response (PR or CR) was 3.0 months (range 2.6–16.6) and the median DOR was 16.6 months (95% CI 11.6–not reached [NR]). The median PFS was 19.4 months (95% CI 16.9–NR). Of the patients who progressed while on therapy per RANO-HGG and continued to receive tovorafenib, 10 had at least one assessment from a scheduled visit post-PD. Tumor kinetics for these patients are shown in Extended Data Fig. 1a, with six having tumor shrinkage close to CR.

RAPNO (secondary endpoints)

[0353] The ORR per RAPNO was 51% (95% CI, 40–63), including 28 (37%; 95% CI 26–49) with a PR ($\geq 50\%$ reduction from baseline by sum of the product of the perpendicular diameters [SPPD]) and 11 (14%; 95% CI 8–24) with a minor response (MR; 25–49% reduction from baseline by SPPD). Twenty-three (30%) had a BOR of SD, resulting in a CBR of 82%. The ORR was similar in patients with tumors harboring *BRAF* fusions (52%; 95% CI 39–64) and BRAF V600E mutations (50%; 95% CI 21–79) and in patients who had received prior MAPKi therapy (49%; 95% CI 34–64), and those who had not (55%; 95% CI 36–73) (Table 2).

Table 2. Response by radiological criteria for patients in arm 1

Response	RANO-HGG		RAPNO ^c		RANO-LGG	
	<i>n</i>		<i>n</i>		<i>n</i>	
ORR, ^a <i>n</i> (%)	69	46 (67)	76	39 (51)	76	40 (53)
<i>BRAF</i> fusion	59	41 (69)	64	33 (52)	64	33 (52)
<i>BRAF</i> mutation	10	5 (50)	12	6 (50)	12	7 (58)
Prior MAPKi	41	29 (71)	45	22 (49)	45	23 (51)
MAPKi-naïve	28	17 (61)	31	17 (55)	31	17 (55)
CBR, ^a <i>n</i> (%) (SD of any length of time)	69	64 (93)	76	62 (82)	76	63 (83)
<i>BRAF</i> fusion	59	55 (93)	64	53 (83)	64	53 (83)
<i>BRAF</i> mutation	10	9 (90)	12	9 (75)	12	10 (83)
Prior MAPKi	41	37 (90)	45	38 (84)	45	38 (84)
MAPKi-naïve	28	27 (96)	31	24 (77)	31	25 (81)
CBR, ^a <i>n</i> (%) (SD ≥ 6 months)	69	57 (83)	76	45 (59)	76	52 (68)
<i>BRAF</i> fusion	59	52 (88)	64	39 (61)	64	43 (67)
<i>BRAF</i> mutation	10	5 (50)	12	6 (50)	12	9 (75)
Prior MAPKi	41	34 (83)	45	26 (58)	45	31 (69)
MAPKi-naïve	28	23 (82)	31	19 (61)	31	21 (68)
CBR, ^a (SD ≥ 12 months)	69	54 (78)	76	43 (57)	76	46 (61)
<i>BRAF</i> fusion	59	49 (83)	64	37 (58)	64	39 (61)
<i>BRAF</i> mutation	10		12	6 (50)	12	7 (58)

Prior MAPKi	41	5 (50)	45	25 (56)	45	26 (58)
MAPKi-naive	28	33 (80)	31	18 (58)	31	20 (65)
		21 (75)				
BOR, ^a n (%)	69		76		76	
CR		12 (17)		0		0
PR		34 (49)		28 (37)		20 (26)
MR		n/a		11 (14)		20 (26)
SD		18 (26)		23 (30)		23 (30)
SD <12 months		10 (14)		19 (25)		17 (22)
SD ≥12 months		8 (12)		4 (5)		6 (8)
PD		4 (6)		13 (17)		11 (14)
NE		1 (1)		1 (1)		2 (3)
Median DOR, months (95% CI) ^b	46	16.6 (11.6–NR)	39	13.8 (11.3–NR)	40	14.4 (11.0–NR)
<i>BRAF</i> fusion	41	16.8 (11.6–NR)	33	13.8 (11.3–NR)	33	16.3 (11.0–NR)
<i>BRAF</i> mutation	5	15.1 (8.3–NR)	6	NR (8.4–NR)	7	12.0 (8.4–NR)
Prior MAPKi	29	15.1 (9.0–16.8)	22	13.8 (11.3–NR)	23	12.0 (8.5–NR)
MAPKi-naive	17	NR (11.6–NR)	17	NR (8.4–NR)	17	16.3 (8.4–NR)
Median TTR, months (range)	46	3.0 (2.6–16.6)	39	5.3 (1.6–11.2)	40	5.5 (1.6–11.3)
<i>BRAF</i> fusion	41	3.0 (2.6–16.6)	33	5.5 (2.3–11.2)	33	5.5 (2.3–11.0)
<i>BRAF</i> mutation	5	2.7 (2.6–16.4)	6	2.8 (1.6–3.0)	7	2.9 (1.6–11.3)
Prior MAPKi	29	2.8 (2.6–16.6)	22	5.4 (1.6–11.2)	23	5.5 (1.6–11.3)
MAPKi-naive	17	5.3 (2.6–11.1)	17	5.3 (2.3–11.0)	17	5.3 (2.3–11.0)

^aORR, CBR, and BOR for RAPNO and RANO-LGG included MRs (ie, ORR=CR+PR+MR; CBR=CR+PR+MR+SD [calculated based on SD of any length of time, SD ≥6 months and SD ≥12 months]). For CR, PR, and MR, confirmation of response by a subsequent scan approximately 3 months after the initial response was required. ^bThe 95% CIs were calculated using Kaplan-Meier method. ^cA subgroup analysis of IRC-assessed ORR based on RAPNO (sex, age group, race, geographical location [US/ex-US]) was conducted. While the small number of patients in some subgroups limits interpretation of these data, responses were observed among all subgroups, with no trends in ORR apparent (Extended Data Fig. 3).

Patients with *BRAF* duplication or rearrangement are considered in the *BRAF* fusion group. BOR, best overall response; CBR, clinical benefit rate; CI, confidence interval; CR, complete response; DOR, duration of response; HGG, high-grade glioma; LGG, low-grade glioma; MAPKi, mitogen-activated protein kinase inhibitor; MR, minor response; n/a, not applicable; NR, not reached; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; RANO, Response Assessment in Neuro-Oncology; RAPNO, Response Assessment in Pediatric Neuro-Oncology; SD, stable disease; TTR, time to response.

[0354] FIG 2B shows the best tumor response from baseline, with most tumors showing some degree of shrinkage. FIG 3B shows DOT and timing of response. In 29% (*n*=22) of patients, an initial MR was followed by a confirmed PR with continued treatment. The median time to initial response (MR or PR) was 5.3 months (range 1.6–11.2) overall, 2.8 months (range 1.6–3.0) in patients with tumors harboring *BRAF* V600E mutations, and 5.5 months (range 2.3–11.2) in patients with tumors harboring *BRAF* fusions. The median DOR was 13.8 months (95% CI 11.3–NR) and the median PFS of the 76 patients was 13.8 months (95% CI 8.3–16.9).

[0355] Thirty-one patients initially had PD according to RAPNO per IRC evaluation, but continued tovorafenib treatment due to the absence of PD by RANO-HGG per investigator, consistent with the trial design and primary endpoint assessment. All but two had no symptoms or signs of clinical progression.

Plots of tumor size (SPPD) over time in several of these patients showed subsequent tumor shrinkage after the initial assessment of PD (Extended Data Fig. 1b).

RANO-LGG (post hoc exploratory endpoints)

[0356] The ORR per RANO-LGG was 53% (95% CI 41–64), including 20 (26%; 95% CI 17–38) patients with a PR and 20 (26%; 95% CI 17–38) with an MR. Twenty-three (30%) had a BOR of SD, giving a CBR of 83%. ORR was similar in patients with tumors harboring *BRAF* fusions and *BRAF* V600E mutations and in patients previously treated with MAPKi or not (Table 2).

[0357] FIG 2C shows the best tumor response from baseline, again with most tumors showing some decrease in size. In 18% ($n=14$) of patients, an initial MR was followed by a confirmed PR with continued treatment. The median time to initial response (MR or PR) was 5.5 months (range 1.6–11.3) overall, 2.9 months (range 1.6–11.3), in patients with tumors harboring *BRAF* V600E mutations and 5.5 months (range 2.3–11.0) in patients with tumors harboring *BRAF* fusions. The median DOR was 14.4 months (95% CI 11.0–NR) and the median PFS was 13.9 months (95% CI 11.1–19.1).

[0358] Similar to the RAPNO analysis, there was a subset of patients who initially had PD according to RANO-LGG per IRC evaluation but who continued on treatment due to the absence of PD according to RANO-HGG. Plots of tumor size (SPPD) over time in several of these patients showed a pattern of subsequent tumor shrinkage after the initial PD assessment.

Response to tovorafenib in patients with progressive disease while on a MAPKi as their most recent prior therapy (post hoc analysis)

[0359] A post hoc analysis was completed using all three radiological criteria to assess responses to tovorafenib in patients who received a MAPKi as their most recent line of therapy and discontinued due to progression. For RANO-HGG, 33% ($n=15$) of those who had progressed on a MAPKi as their most recent prior therapy had a CR or PR to tovorafenib; similar trends were observed for RAPNO and RANO-LGG, which are endpoints that include MRs: 33% ($n=13$) had a PR or MR (31% [$n=12$] with PR) and 30% ($n=12$) had a PR or MR (20% [$n=8$] with PR), respectively (Extended Data Table 2).

Safety

[0360] Among 137 patients (arms 1 and 2), 118 (86%) had been treated for at least 6 months and 67 (49%) for at least 1 year. All patients experienced at least one treatment-emergent AE (TEAE). The most common TEAEs at any grade occurring in $\geq 20\%$ of patients were hair color changes (76%), anemia (59%) and elevated creatine phosphokinase (CPK) (58%) (Table 3). Grade ≥ 3 TEAEs occurred in 63% of patients, the most common were elevated CPK (12%), anemia (11%) and maculopapular rash (8%). The most common treatment-related adverse events (TRAEs) of any grade generally followed a similar trend to the most common TEAEs. Grade ≥ 3 TRAEs occurred in 42% of patients and followed a similar trend as the most common grade ≥ 3 TEAEs, although pyrexia was less often assessed as a related event. Two patients had grade 5/fatal TEAEs, neither of which were assessed as treatment-related (one patient in arm 1 with disease progression, and one patient in arm 2 with a disseminated leptomeningeal mixed-glial-neuronal tumor who

experienced tumor hemorrhage 21 days after their final dose of tovorafenib (discontinued due to disease progression).

Table 3. Treatment-emergent and treatment-related adverse events (safety analysis set, $n=137$)

Preferred term, n , (%)	Treatment-emergent AEs		Treatment-related AEs	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Patients with any AE	137 (100)	86 (63)	134 (98)	58 (42)
Hair color changes	104 (76)	0	104 (76)	0
Anemia	81 (59)	15 (11)	67 (49)	14 (10)
Elevated CPK	80 (58)	16 (12)	77 (56)	16 (12)
Fatigue	76 (55)	6 (4)	60 (44)	6 (4)
Vomiting	68 (50)	6 (4)	28 (20)	3 (2)
Hypophosphatemia	64 (47)	0	48 (35)	0
Headache	61 (45)	2 (1)	29 (21)	0
Maculopapular rash	60 (44)	11 (8)	56 (41)	11 (8)
Pyrexia	53 (39)	5 (4)	17 (12)	1 (1)
Dry skin	49 (36)	0	45 (33)	0
Elevated LDH	48 (35)	0	42 (31)	0
Increased AST	47 (34)	4 (3)	41 (30)	4 (3)
Constipation	45 (33)	0	31 (23)	0
Nausea	45 (33)	0	25 (18)	0
Upper RTI	43 (31)	2 (1)	2 (1)	0
Dermatitis acneiform	42 (31)	1 (1)	41 (30)	1 (1)
Epistaxis	42 (31)	1 (1)	27 (20)	0
Decreased appetite	39 (28)	5 (4)	28 (20)	4 (3)
Paronychia	36 (26)	2 (1)	32 (23)	2 (1)
Pruritus	35 (26)	1 (1)	32 (23)	1 (1)
COVID-19	34 (25)	0	0	0
Weight decreased	30 (22)	2 (1)	21 (15)	0
Cough	30 (22)	1 (1)	2 (1)	0
Increased ALT	29 (21)	7 (5)	24 (18)	7 (5)
Hypokalemia	29 (21)	4 (3)	15 (11)	3 (2)
Diarrhea	29 (21)	2 (1)	14 (10)	1 (1)
Eczema	25 (18)	2 (1)	22 (16)	2 (1)
Erythema	20 (15)	2 (1)	18 (13)	1 (1)
Hypocalcemia	22 (16)	2 (1)	13 (9)	1 (1)
Photosensitivity reaction	19 (14)	1 (1)	19 (14)	1 (1)
Decreased growth velocity	18 (13)	7 (5)	17 (12)	7 (5)
Increased bilirubin	18 (13)	1 (1)	16 (12)	1 (1)
Hyponatremia	17 (12)	3 (2)	4 (3)	1 (1)
Erythematous rash	14 (10)	1 (1)	14 (10)	1 (1)
Decreased WBC count	13 (9)	2 (1)	11 (8)	1 (1)
Tumor hemorrhage	12 (9)	5 (4)	10 (7)	3 (2)
Decreased neutrophil count	12 (9)	4 (3)	9 (7)	3 (2)
Seizure	11 (8)	6 (4)	1 (1)	1 (1)

Weight increased	10 (7)	2 (1)	6 (4)	1 (1)
Lethargy	9 (7)	1 (1)	6 (4)	1 (1)
Pericardial effusion	9 (7)	1 (1)	5 (4)	1 (1)
Decreased phosphorus	7 (5)	1 (1)	5 (4)	1 (1)
Folliculitis	5 (4)	1 (1)	4 (3)	1 (1)
Prolonged APTT	3 (2)	1 (1)	2 (1)	1 (1)
Increased GGT	3 (2)	1 (1)	1 (1)	1 (1)
Systemic infection	2 (1)	2 (1)	1 (1)	1 (1)
Follicular rash	2 (1)	1 (1)	2 (1)	1 (1)
Optic nerve disorder	2 (1)	1 (1)	1 (1)	1 (1)
CSF circulation disorder	1 (1)	1 (1)	1 (1)	1 (1)
Cholecystitis	1 (1)	1 (1)	1 (1)	1 (1)
Eye infection viral	1 (1)	1 (1)	1 (1)	1 (1)
Pruritic rash	1 (1)	1 (1)	1 (1)	1 (1)

TEAEs, TRAEs, and laboratory abnormalities in $\geq 20\%$ of patients and all TRAEs grade ≥ 3 occurring in ≥ 1 patient.

TEAEs, TRAEs, and laboratory abnormalities: Patients are counted only once per event and are shown in the worst CTCAE grade that was reported for each event they experienced.

MedDRA version 23.1; CTCAE version 5.0.

AE, adverse event; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019; CPK, creatine phosphokinase; CSF, cerebrospinal fluid; CTCAE, Common Terminology Criteria for Adverse Events; LDH, lactate dehydrogenase; MedDRA, Medical Dictionary for Regulatory Activities; RTI, respiratory tract infection; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; WBC, white blood cell.

[0361] A decrease in growth velocity was observed in patients treated with tovorafenib. At cycle 13 (n=74), the median decrease in height z-score was 0.7, or less than 1 standard deviation. Eighty percent of these patients remained within 1 standard deviation from baseline height z-score. The remaining patients had a decrease from baseline height z-score of between 1 and 2 standard deviations. At the time of this report, on-treatment bone age results were available for 11 patients. Nine of the 11 were reported as within normal limits for age, one was read as delayed, and one patient with a bone age advanced by 3.5 years prior to the start of treatment had an on-treatment bone age that was reported as advanced by 2.5 years. To date there has been no evidence of bone age advancement or premature closure of growth plates. In patients with available height data off-treatment, growth velocity was recovering.

[0362] Serious TEAEs were reported for 45% of patients, the most common were pyrexia (most cases were confounded by intercurrent infectious disease), seizure, and vomiting (each 5%). Serious TRAEs occurred in 15% of patients, the most common of which were tumor hemorrhage (3%), decreased appetite, hyponatremia, and vomiting (each 2%). Two of four patients with serious tumor hemorrhage TRAEs had a history of intratumor hemorrhage prior to initiating tovorafenib, and in all four, the serious events of tumor hemorrhage resolved.

[0363] Nine (7%) patients had TRAEs leading to tovorafenib discontinuation, the most common were tumor hemorrhage (three patients) and decrease in growth velocity (two patients). TRAEs leading to dosage reduction were seen in 33 (24%), the most common were maculopapular rash (4%) and decreased appetite

(3%). TRAEs leading to dose interruption occurred in 50 (37%), the most common were maculopapular rash (9%), vomiting, fatigue, increased alanine transaminase, and elevated CPK (each 4%). The median duration of dose interruption due to any TEAE was 14 days or two doses.

Example 2. Trial design and results for optic pathway gliomas (OPGs)

[0364] Sporadic optic pathway gliomas (OPGs) are commonly driven by oncogenic genomic alterations affecting *BRAF*, including *KIAA1549::BRAF* fusions and *BRAF* V600E point mutations. The ongoing phase 2 FIREFLY-1 (PNOC026; NCT04775485) trial is assessing the efficacy and safety of the investigational, oral, selective, CNS-penetrant type II RAF inhibitor, tovorafenib, in patients with *RAF*-altered relapsed/refractory pLGG or advanced solid tumors. Tovorafenib monotherapy achieved rapid and durable tumor responses in children and young adults with *BRAF*-altered pLGG, as assessed by an independent radiology review committee (IRC) according to Response Assessment in Neuro-Oncology high-grade glioma (RANO-HGG) Response Assessment in Pediatric Neuro-Oncology-LGG (RAPNO) and RANO-LGG criteria. OPGs are the largest tumor location subgroup in the registrational arm of the FIREFLY-1 trial, representing an important population of patients with sporadic relapsed/refractory pLGG. The efficacy of tovorafenib in the OPG subgroup of FIREFLY-1 arm 1, focusing on both radiological and visual acuity (VA) outcomes was analyzed and the incidence of adverse events (AEs) in this subgroup and ophthalmologic adverse events of special interest (AESI) in the trial safety analysis set of 137 patients with pLGG and the arm 1 OPG subgroup. Arm 1 of the trial enrolled patients with relapsed or refractory pLGG harboring an activating *BRAF* alteration, including *BRAF* V600E mutations and *KIAA1549::BRAF* fusions. Arm 2 of the trial is a pLGG expansion cohort, which provided treatment access for patients with *RAF*-altered pLGG following arm 1 closure. Arm 1 and arm 2 are fully accrued. In the primary registrational analysis, efficacy was assessed in the 77 patients enrolled in arm 1, with safety assessed in all 137 treated patients in arms 1 and 2.

[0365] Tovorafenib was administered at the recommended phase 2 dose of 420 mg/m² (not to exceed 600 mg) by mouth (tablet or liquid formulation), once weekly, in 28-day cycles. Treatment was continued until radiographic evidence of disease progression as determined by the treating investigator according to RANO-HGG criteria, unacceptable toxicity, decision to enter a drug holiday period, patient withdrawal of consent, or death. Patients with disease progression were allowed to continue tovorafenib treatment if they were deemed to be deriving clinical benefit from continuing trial treatment. Patients were treated for a planned period of 26 cycles, after which they could continue on tovorafenib or, at any point, opt to enter a drug holiday period. During this drug holiday period, patients could be retreated with tovorafenib if there was radiographic disease progression.

[0366] The trial was approved by an institutional review board/independent ethics committee at each trial site. The trial was conducted in accordance with current ethical principles and trial standards. All patients and/or their legally authorized representative provided written informed consent and pediatric assent before enrollment in the trial, according to local regulations.

Trial Endpoints

[0367] The assessment of response in the primary analysis and the current subgroup analysis was undertaken using three different radiological response assessment criteria: RANO-HGG, which assess tumor response primarily based on T1-weighted, contrast-enhanced imaging, and RAPNO16 and RANO-LGG, both of which assess tumor response primarily based on non-enhancing disease by T2/fluid-attenuated inversion recovery (FLAIR) sequences. Patients were enrolled based on investigator-assessed measurable disease per RANO-HGG. Investigator response assessments per RANO-HGG were also the criteria on which cessation of treatment due to progressive disease were based. Response was subsequently analyzed according to all three radiological assessment criteria by blinded independent central review.

[0368] The primary endpoint in arm 1 was the ORR, as assessed according to RANO-HGG criteria by an independent radiology review committee (IRC). Secondary endpoints included the ORR, as assessed according to RAPNO criteria by the IRC, and clinical benefit rate (CBR), progression-free survival, duration of response (DOR), and time to response (TTR), as assessed by the IRC using both RANO-HGG and RAPNO criteria. Post hoc exploratory endpoints for arm 1, added to the statistical analysis plan prior to the primary analysis at regulatory authority request, included ORR and CBR according to RANO-LGG criteria by IRC assessment.

Assessments

[0369] Disease was assessed in arm 1 by MRI of the brain and spine at screening (up to 28 days prior to first dose) and at the end of every three cycles thereafter. Safety assessments have been described previously. AEs considered of special interest (AESI) included rhabdomyolysis/myopathy, ventricular arrhythmias, intra-tumoral hemorrhage, secondary primary malignancies, ophthalmologic events, and decrease in growth velocity. They were further reviewed and adjudicated for clinical relevance by the sponsor's senior safety physician, and assessed for clinical relevance to the intended events of interest. Positively adjudicated ophthalmologic AESI are presented in this report. Patients with OPG or underlying visual function deficit related to their tumor had ophthalmology examinations performed at baseline, at the time of each radiographic disease assessment, and at the end of treatment. These examinations were performed by an ophthalmologist or other qualified site clinical personnel and included: a slit-lamp examination, specifically looking for corneal/lens abnormalities; a fundus examination with comment on retinal abnormalities; visual fields to confrontation; optic disc appearance; and best corrected VA, (BCVA) as assessed per local institutional practice.

[0370] Functional VA assessments were age-specific, and included use of Teller Acuity Cards® (all patients), HOTV, or other Early Treatment Diabetic Retinopathy Study charts (in patients developmentally able to perform them). Assessments were done for each eye separately, at a recommended testing distance of 3 meters (or according to local standard practice). If the BCVA data derived at a particular visit were felt to be unreliable due to poor cooperation, testing was to be repeated 1 to 2 weeks later, and only the visit believed to have yielded the most reliable data reported. To reduce variability in scoring, the same BCVA testing methodology was to be used throughout the treatment period. BCVA was reported as a logarithm of

the minimum angle of resolution (logMAR) score, where 0 is normal vision and positive values indicate reduced VA.

[0371] VA response was defined according to outcome in the best eye: i.e., if data for both eyes were available, response and progressive disease determinations were based on the eye with best response. VA status of this eye was used to determine logMAR range group at baseline. If response outcomes for both eyes were the same, baseline logMAR was used to define best eye. A confirmed VA response was defined as a decrease from baseline by at least 0.2 logMAR at two consecutive visits, i.e. every 3 cycles/~12 weeks apart. Confirmed VA progressive disease was defined as an increase from baseline of at least 0.2 logMAR at two consecutive assessments. VA was deemed to be stable if the criteria for VA response or VA progressive disease were not met. To evaluate the degree of clinical-radiological correlation across the different response assessment criteria, concordance between VA in the best eye and radiological outcomes from the start of tovorafenib treatment and last follow-up were analyzed. Full concordance represented concordant outcomes for VA and radiological assessments; partial concordance represented either improvement (positive) or deterioration (negative) of one parameter with the stability of the other; full discordance represented conflicting outcomes.

Statistical Considerations

[0372] In this post hoc subgroup analysis, efficacy was analyzed in all patients in arm 1 with tumors classified as having optic pathway involvement. The evaluable populations for efficacy were as previously described for the primary analysis. Waterfall plots were generated for each patient's best change in sum of perpendicular diameters of measurable lesions. Duration of response was estimated using the Kaplan-Meier method. Patients with responses who had not progressed at data cutoff were censored at the date of their last adequate radiologic disease assessment. Safety assessments were based on the safety population in arms 1 and 2 and the OPG subgroup of arm 1. Statistical analyses were carried out using SAS v9.4. Analyses were based on a 5 June 2023 data cutoff.

Patients and Disposition

[0373] Between April 22, 2021 and January 26, 2023, 42 patients with optic pathway tumor involvement were enrolled in arm 1. Their demographics and baseline characteristics are summarized in Table 4. The median age of patients was 8 years (range 2–16); most patients were male and White (57% each). Tumors of 81% of patients had a *KIAA1549::BRAF* fusion, 7% had a chromosomal rearrangement involving *BRAF* (as detected by fluorescence in situ hybridization and presumed to represent a *KIAA1549::BRAF* or other *BRAF* fusion), and 12% had a *BRAF* V600E mutation. Patients had received a median of 3 lines of prior therapy (range 1–9); 69% had received a prior MEK and/or *BRAF* inhibitor. VA data are not included in the current analysis for six of the 42 patients: four had no VA assessments done due to bilateral blindness, one had no baseline visual assessment, and one patient had no assessment after baseline. Of the remaining 36 patients, baseline VA in the best eye was normal (−0.1 to 0.15) in eight (22%), mildly impaired (0.2 to 0.5) in 15 (42%), moderately impaired (0.6 to 0.9) in seven (19%), severely impaired (1.0 to 1.4) or

profoundly impaired (>1.4) in three (8%) each (logMAR ranges). The median duration of tovorafenib treatment in the OPG subgroup, with 69% of patients (29/42) still on treatment at data cutoff.

Table 4. Patient and baseline characteristics

Characteristic	Arm 1 OPG subgroup <i>n</i> =42
Age, years	
Median (range)	8 (2–16)
Gender, <i>n</i> (%)	
Male	24 (57)
Female	18 (43)
Race, <i>n</i> (%) ^{a,b}	
White	24 (57)
Asian	2 (5)
Black	1 (2)
Multiple	2 (5)
Other	3 (7)
Not specified	10 (24)
Ethnicity, <i>n</i> (%)	
Hispanic or Latino	2 (5)
Not Hispanic or Latino	29 (69)
Not stated	10 (24)
Missing	1 (2)
BRAF alteration, <i>n</i> (%)	
<i>BRAF</i> fusion ^c	37 (88)
<i>KIAA1549::BRAF</i> fusion	34 (81)
Other	3 (7)
<i>BRAF</i> V600E mutation	5 (12)
Baseline Lansky performance score, <i>n/n</i> (%) ^d	
50–70	1/41 (2)
80–100	40/41 (98)
Prior lines of systemic therapy	
Median (range)	3 (1–9)
Number of prior lines, <i>n</i> (%)	
1	5 (12)
2	11 (26)
≥3	26 (62)
Prior MAPK pathway targeted therapy, <i>n</i> (%) ^e	
Prior MEK inhibitor	28 (67)
Prior BRAF inhibitor	3 (7)
Prior MEK and BRAF inhibitors	2 (5)
Prior MEK and/or BRAF inhibitor	29 (69)
Any prior surgery for primary disease, <i>n</i> (%)	
Pre-operative staging	
Localized disease	35 (83)
Disseminated/metastatic disease	4 (10)
Leptomeningeal spread	3 (7)
Post-operative staging ^f	
Subtotal resection	13 (31)

Biopsy only, resection not attempted	29 (69)
Prior radiotherapy <i>n</i> (%)	1 (2)
Visual acuity at enrollment, best eye (logMAR range) (<i>n</i> =36), ^a <i>n</i> (%)	
Normal (-0.1–0.15)	8 (22)
Mild impairment (0.2–0.5)	15 (42)
Moderate impairment (0.6–0.9)	7 (19)
Severe impairment (1.0–1.4)	3 (8)
Profound/worse impairment (>1.4)	3 (8)
Bilateral blindness at enrollment (vision not tested), <i>n</i>	4 ^g

^a There were no Native Hawaiian or other Pacific Islander, American Indian or Alaska Native participants. ^b None were missing. ^c Includes 3 patients with *BRAF* rearrangement per fluorescence in situ hybridization. ^d Denominator for Lansky performance score is the number of patients <16 years of age. There was only one patient ≥16 years of age; their baseline Karnofsky performance score was assessed as 80–100. Baseline is defined as the last available assessment prior to start of tovorafenib on cycle 1 day 1. ^e Patients who had previously received both a MEK inhibitor and also a BRAF inhibitor are recorded in both the “Prior MEK inhibitor” and “Prior BRAF inhibitor” groups. ^f No gross total resections. ^g Patients with visual acuity response data at baseline and at least one other timepoint; six patients are not included in the analysis; four had bilateral blindness and were not tested, one had no baseline assessment and one had no assessment after baseline. **Abbreviations:** OPG, optic pathway glioma; logMAR, logarithm of the minimum angle of resolution; MAPK, mitogen-activated protein kinase.

Imaging Outcomes

[0374] The IRC deemed that 39 of the 42 patients in this analysis had measurable disease at baseline according to RANO-HGG criteria, and were therefore evaluable for response. All 42 patients had measurable disease according to RAPNO and RANO-LGG criteria. The ORR and CBR (stable disease of any length of time) according to the contrast-enhancement based RANO-HGG criteria were 64% and 95%, respectively (Table 5). The ORRs (50% and 55%) and CBRs (88% and 90%) were virtually similar according to the two T2/FLAIR-based RAPNO and RANO-LGG criteria, respectively. Waterfall plots of best tumor response showed that most tumors had some degree of shrinkage as assessed both according to T1-weighted contrast-enhanced (RANO-HGG) and T2/FLAIR-based (RAPNO and RANO-LGG) criteria (FIGs. 5A-5C). Tumor shrinkage occurred both in OPGs harboring BRAF fusions and BRAF V600E mutations, and both in patients who had previously received mitogen-activated protein kinase inhibitor (MAPKi) therapy and patients who had not.

Table 5. Response by radiological assessment criteria and visual acuity response and radiological response correlation

Response (IRC)	RANO-HGG <i>n</i> =39	RAPNO <i>n</i> =42	RANO-LGG <i>n</i> =42
Overall response rate, ^a <i>n</i> (%)	25 (64)	21 (50)	23 (55)
95% CI	47–79	34–66	39–70
Clinical benefit rate, ^a <i>n</i> (%)			
SD of any length of time	37 (95)	37 (88)	38 (90)
SD ≥12 months	31 (79)	25 (60)	28 (67)
Best overall response, <i>n</i> (%)			
CR	7 (18)	0	0

PR	18 (46)	12 (29)	8 (19)
MR	n/a	9 (21)	15 (36)
SD	12 (31)	16 (38)	15 (36)
SD <12 months	6 (15)	12 (29)	10 (24)
SD ≥12 months	6 (15)	4 (10)	5 (12)
PD	2 (5)	5 (12)	3 (7)
NE	0	0	1 (2)
Median DOR, months (95% CI) ^b	16.8 (9.0–NR)	13.8 (11.3–NR)	14.4 (5.8–NR)
Median TTR, months (range)	5.5 (2.6–16.6)	5.5 (2.6–11.2)	5.5 (2.6–11.1)
Visual acuity response/radiological response correlation	RANO-HGG n=33	RAPNO n=36	RANO-LGG n=35
Full concordance ^c	15 (45)	15 (42)	13 (37)
CR/PR/MR ^d + VA improved	8	9	6
SD + VA stable	6	6	6
PD + VA worsened	1	0	1
Partial (positive) concordance ^e	15 (45)	13 (36)	18 (51)
CR/PR/MR ^d + VA stable	11	8	11
SD + VA improved	4	5	7
Partial (negative) concordance ^e	1 (3)	8 (22)	3 (9)
PD + VA stable	1	5	2
SD + VA worsened	0	3	1
Full discordance ^f	2 (6)	0	1 (3)
CR/PR/MR ^d + VA worsened	2	0	1
PD + VA improved	0	0	0

^a ORR and CBRs for RAPNO-LGG and RANO-LGG included MRs (i.e., ORR=CR+PR+MR; CBR=CR, PR, MR, or SD [calculated based on SD of any length of time and SD ≥12 months]). ^b The exact 95% CIs were calculated using Clopper-Pearson method. ^c Full concordance represents concordant outcomes. ^d MR classification only applies to RAPNO and RANO-LGG criteria. ^e Partial concordance represents either improvement (positive) or deterioration (negative) of one parameter with the stability of the other. ^f Full discordance represents conflicting outcomes. **Abbreviations:** BOR, best overall response; CBR, clinical benefit rate; CI, confidence interval; CR, complete response; DOR, duration of response; HGG, high-grade glioma; IRC, independent radiology review committee; LGG, low-grade glioma; MR, minor response; n/a, not applicable; NE, not evaluable; NR, not reached; ORR, overall response rate; PD, progressive disease; PR, partial response; RANO, Response Assessment in Neuro-Oncology; RAPNO, Response Assessment in Pediatric Neuro-Oncology; SD, stable disease; TTR, time to response; VA, visual acuity.

[0375] Duration of therapy and timing of response according to RAPNO and RANO-LGG criteria are shown in FIG. 6. In 11 (26%) patients, an initial minor response per RAPNO criteria was followed by a confirmed partial response with continued treatment. Similarly, per RANO-LGG criteria, an initial minor response in six (14%) patients was followed by a confirmed partial response with continued treatment. Initial responses tended to be rapid, with a median TTR of 5.5 months according to each of the three assessment criteria (Table 5). Responses tended to be durable, with median DORs of 16.8 months (95% CI 9.0–not reached [NR]), 13.8 months (95% CI 11.3–NR), and, 14.4 months (95% CI 5.8–NR) per RANO-HGG, RAPNO, and RANO-LGG, respectively.

Visual Acuity Outcomes

[0376] Among the 36 patients with OPG with VA response data at baseline and at least one other timepoint, VA of the best eye improved in 14 (39%), remained stable (i.e. no improvement or deterioration) in 19 (53%) and deteriorated in three (8%) (Table 6). VA was therefore preserved (i.e., improved or stable) in 92% of patients during treatment with tovorafenib. **FIG 7A** shows a waterfall plot of the best change in VA of the best eye. The proportion of patients with preserved VA was similar in subgroups of patients with OPG harboring *BRAF* fusions and *BRAF* V600E mutations, in those who had received prior MAPKi therapy and those who had not, and in patients who had received ≤ 3 prior lines of systemic therapy, and those who had received >3 (Table 6). The analysis of VA response according to baseline VA showed a consistent pattern of preserved vision in most patients across all subgroups. VA improved in $\geq 43\%$ of patients across subgroups, with no clear correlation to baseline VA (Table 7). Stratifying the 36 patients with VA response data (assessment at baseline and at least one other timepoint) into quartiles according to time from primary diagnosis suggested that vision was preserved across all quartiles, (Table 8).

Table 6. Visual acuity response during treatment according to baseline characteristics (n=36)^a

Visual acuity response (best eye)	Evaluable patients (n=36)	BRAF alteration status		Prior MAPKi targeted therapy		Number of prior lines of systemic therapy	
		Fusion (n=31)	V600E mutation (n=5)	MAPKi-naive (n=12)	Prior MAPKi (n=24)	≤ 3 (n=21)	>3 (n=15)
Preserved ^b	33 (92)	28 (90)	5 (100)	11 (92)	22 (92)	20 (95)	13 (87)
Improved	14 (39)	13 (42)	1 (20)	3 (25)	11 (46)	7 (33)	7 (47)
Stable	19 (53)	15 (48)	4 (80)	8 (67)	11 (46)	13 (62)	6 (40)
Worsened	3 (8)	3 (10)	0	1 (8)	2 (8)	1 (5)	2 (13)

Data are n (%). ^a Six patients are not included in the analysis; four had bilateral blindness and were not tested, one had no baseline assessment and one had no assessment after baseline. ^b Preserved includes patients with improved or stable visual acuity. **Abbreviation:** MAPKi, mitogen-activated protein kinase inhibitor.

Table 7. Visual acuity response best eye by baseline visual acuity status (n=36)^a

Visual acuity response (best eye)	Baseline vision, best eye (logMAR range)				
	Normal vision (-0.1 to 1.5) (n=8)	Mild impairment (0.2 to 0.5) (n=15)	Moderate impairment (0.6 to 0.9) (n=7)	Severe impairment (1.0 to 1.4) (n=3)	Profound/worse impairment (>1.4) (n=3)
Preserved ^b	8 (100)	15 (100)	5 (71)	3 (100)	2 (67)
Improved	0	7 (47)	3 (43)	2 (67)	2 (67)
Stable	8 (100)	8 (53)	2 (29)	1 (33)	0 (0)
Worsened	0	0	2 (29)	0	1 (33)

Data are n (%). ^a Six patients are not included in the analysis; four had bilateral blindness and were not tested, one had no baseline assessment and one had no assessment after baseline. ^b Preserved includes patients with improved or stable visual acuity. **Abbreviation:** logMAR, logarithm of the minimum angle of resolution.

Table 8. Visual acuity response (best eye) by time from primary diagnosis quartiles (n=36)^a

Visual acuity response (best eye)	Quartile: time from primary diagnosis (years)			
	Q1: 0.9–2.9	Q2: 2.9–5.8	Q3: 5.8–8.0	Q4: 8.0–13.8
Preserved ^b	9 (100)	8 (89)	9 (100)	7 (78)
Improved	4 (44)	3 (33)	2 (22)	5 (56)
Stable	5 (56)	5 (56)	7 (78)	2 (22)
Worsened	0	1 (11)	0	2 (22)

Data are n (%). ^a Six patients are not included in the analysis; four had bilateral blindness and were not tested, one had no baseline assessment and one had no assessment after baseline. ^b Preserved includes patients with improved or stable visual acuity. **Abbreviation:** Q, quartile.

Visual Acuity Response-Radiological Response Correlation

[0377] Concordance between VA and radiological outcomes was broadly similar as assessed according to the different response criteria (Table 5). For RANO-HGG, full and partial concordance between these outcomes was 45% and 48%, respectively, with only two cases fully discordant. For RAPNO, full and partial concordance was 42% and 58%, respectively, with no assessments fully discordant, and for RANO-LGG, 37% and 60%, respectively, with one assessment fully discordant.

[0378] Table 9 shows the VA response by best overall response, according to the different radiological assessment criteria. In patients with a radiological response to tovorafenib, vision was improved in 38% of patients according to RANO-HGG, 53% of patients according to RAPNO, and 33% of patients according to RANO-LGG. Vision was also improved in 40%, 36%, and 50% of patients with a best overall response of stable disease per RANO-HGG, RAPNO, and RANO-LGG, respectively. **FIG 7B** shows a Sankey diagram of VA outcomes in patients with a confirmed minor response according to RAPNO and RANO-LGG criteria. In all of these patients, by the end of treatment/data cutoff, VA had either improved or remained stable in relation to baseline category, regardless of response criterion.

Table 9. Visual acuity response (best eye) by best overall response according to different radiological assessment criteria

Visual acuity response (best eye)	Best overall response							
	CR/PR/MR ^a	CR	PR	MR	SD	PD	NE	Total
RANO-HGG, n=33								
Preserved ^b	19 (90)	5 (83)	14 (93)	-	10 (100)	1 (50)	0	30 (91)
Improved	8 (38)	1 (16)	7 (46)	-	4 (40)	0	0	12 (36)
Stable	11 (52)	4 (67)	7 (46)	-	6 (60)	1 (50)	0	18 (55)
Worsened	2 (10)	1 (16)	1 (7)	-	0	1 (50)	0	3 (9)
Total	21	6	15	-	10	2	0	33 (100)
RAPNO, n=36								
Preserved ^b	17 (100)	0	11 (100)	6 (100)	11 (79)	5 (100)	0	33 (92)
Improved	9 (53)	0	6 (55)	3 (50)	5 (36)	0	0	14 (39)
Stable	8 (47)	0	5 (45)	3 (50)	6 (43)	5 (100)	0	19 (53)
Worsened	0	0	0	0	3 (21)	0	0	3 (8)
Total, n	17	0	11	6	14	5	0	36 (100)

RANO-LGG, n=36								
Preserved ^b	17 (94)	0	8 (100)	9 (90)	13 (93)	2 (67)	1 (100)	33 (92)
Improved	6 (33)	0	2 (25)	4 (40)	7 (50)	0	1 (100)	14 (39)
Stable	11 (61)	0	6 (75)	5 (50)	6 (43)	2 (67)	0	19 (53)
Worsened	1 (6)	0	0	1 (10)	1 (7)	1 (33)	0	3 (8)
Total, n	18	0	8	10	14	3	1	36(100)

Data are n (%) unless otherwise stated. ^a MR classification only applies to RAPNO and RANO-LGG criteria. ^b Preserved includes patients with improved or stable visual acuity. **Abbreviations:** CR, complete response; HGG, high-grade glioma; LGG, low-grade glioma; MR, minor response; NE, not evaluable; PD, progressive disease; PR, partial response; RANO, Response Assessment in Neuro-Oncology; RAPNO, Response Assessment in Pediatric Neuro-Oncology; SD, stable disease.

Safety

[0379] The most common treatment-emergent AEs (TEAEs; occurring in $\geq 20\%$ of patients) and treatment-related AEs (TRAEs) occurring at grade ≥ 3 in at least one patient are listed in Table 10. Trends in TEAEs and TRAEs in the arm 1 OPG subgroup were similar to those reported for all patients in arms 1 and 2 (the safety population).

Table 10. Treatment-emergent and treatment-related adverse events (arm 1 OPG subgroup safety analysis set, n=42)

Preferred term, n (%)	Treatment-emergent AEs		Treatment-related AEs	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Patients with any AE	42 (100)	27 (64)	42 (100)	20 (48)
Hair color changes	36 (86)	0	36 (86)	0
Anemia	25 (60)	5 (12)	21 (50)	5 (12)
Fatigue	25 (60)	2 (5)	18 (43)	2 (5)
Elevated CPK	24 (57)	3 (7)	23 (55)	3 (7)
Vomiting	22 (52)	4 (10)	10 (24)	2 (5)
Headache	21 (50)	2 (5)	9 (21)	0
Maculopapular rash	21 (50)	4 (10)	20 (48)	4 (10)
Elevated LDH	17 (40)	0	12 (29)	0
Hypophosphatemia	17 (40)	0	14 (33)	0
Increased AST	16 (38)	2 (5)	14 (33)	2 (5)
Decreased appetite	16 (38)	1 (2)	10 (24)	1 (2)
Epistaxis	16 (38)	0	9 (21)	0
Pyrexia	16 (38)	1 (2)	4 (10)	0
Dry skin	15 (36)	0	14 (33)	0
Paronychia	15 (36)	1 (2)	14 (33)	1 (2)
COVID-19	14 (33)	0	0	0
Constipation	14 (33)	0	7 (17)	0
Nausea	14 (33)	0	5 (12)	0
Upper RTI	14 (33)	0	0	0
Weight decreased	12 (29)	2 (5)	9 (21)	0
Abdominal pain	11 (26)	0	6 (14)	0
Pain in extremity	11 (26)	0	4 (10)	0
Pruritus	11 (26)	0	10 (24)	0
Dermatitis acneiform	10 (24)	1 (2)	10 (24)	1 (2)

Eczema	10 (24)	1 (2)	9 (21)	1 (2)
Face edema	10 (24)	0	7 (17)	0
Increased ALT	9 (21)	0	7 (17)	0
Hypokalemia	9 (21)	3 (7)	6 (14)	2 (5)
Decrease in growth velocity	7 (17)	2 (5)	7 (17)	2 (5)
Increased blood bilirubin	7 (17)	1 (2)	6 (14)	1 (2)
Viral eye infection	1 (2)	1 (2)	1 (2)	1 (2)
Hyponatremia	6 (14)	1 (2)	2 (5)	1 (2)
Lethargy	2 (5)	1 (2)	1 (2)	1 (2)
Erythematous rash	3 (7)	1 (2)	3 (7)	1 (2)
Follicular rash	1 (2)	1 (2)	1 (2)	1 (2)
Tumor hemorrhage	3 (7)	1 (2)	3 (7)	1 (2)

TEAEs, TRAEs, and laboratory abnormalities in $\geq 20\%$ of patients and all TRAEs grade ≥ 3 occurring in ≥ 1 patient are reported. Patients are counted only once per event and are shown in the worst CTCAE grade that was reported for each event they experienced. Adverse events were coded according to MedDRA version 23.1 and graded according to CTCAE version 5.0. **Abbreviations:** AEs, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019; CPK, creatine phosphokinase; CTCAE, Common Terminology Criteria for Adverse Events; LDH, lactate dehydrogenase; MedDRA, Medical Dictionary for Regulatory Activities; RTI, respiratory tract infection; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

[0380] Four patients (10%) had TEAEs leading to discontinuation, which included autoimmune hemolytic anemia, decrease in growth velocity, tumor hemorrhage, and ventricular extrasystoles (one patient each). The autoimmune hemolytic anemia was deemed unrelated to tovorafenib, whereas the other three events were considered to be TRAEs. Fifteen patients (36%) had TRAEs leading to dosage reduction; the most common was decreased appetite (two patients [5%]). Fifteen patients (36%) had TRAEs leading to dose interruption; the most common were increased aspartate aminotransferase, maculopapular rash, and vomiting (two patients [5%] each).

[0381] The incidence of ophthalmologic AESI in the FIREFLY-1 safety population and arm 1 OPG subgroup was also assessed, based on the MedDRA System Organ Class category of “Eye disorders”, excluding selected high-level group terms of “Congenital eye disorders (excl. glaucoma)”, “Ocular neuromuscular disorders”, and “Ocular neoplasms”. Eight (6%) of 137 patients in the overall safety population had positively adjudicated ophthalmologic AESI (all grade 1-2), as detailed in Supplementary Table S5, with the most common being dyschromatopsia (deficiency in the perception of colors), experienced by three (2%) patients. There were no events of uveitis and no events involving the retina. AESI occurred in three (7%) of 42 patients in the OPG subgroup, including dyschromatopsia in two patients (5%; Table 11).

Table 11. Positively adjudicated ophthalmologic AESI* in the safety population

Category Preferred Term, n (%)	Safety analysis set (arm 1 + arm 2, n=137)		Arm 1 OPG subgroup n=42	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Ophthalmologic events	8 (6)	0	3 (7)	0
Vision blurred	1 (1)	0	0	0
Dyschromatopsia	3 (2)	0	2 (5)	0
Corneal edema	1 (1)	0	0	0
Glaucoma	1 (1)	0	1 (2)	0
Photopsia	1 (1)	0	0	0
Episcleritis	1 (1)	0	0	0

*Categorized according to the Medical Dictionary for Regulatory Activities Version 23.1 and graded according to the Common Terminology Criteria for Adverse Events Version 5.0. Note: Only events positively adjudicated as ophthalmologic events are presented. AESI, adverse events of special interest

Example 3

[0382] Methods of the instant disclosure are further illustrated in Clinical Protocol of DAY101-001.

Example 4

[0383] Methods of the instant disclosure are further illustrated in: Clinical Study of DAY101-001 - Statistical Analysis Plan.

CLAIMS

We claim:

1. A method of treating a relapsed or refractory pediatric low-grade glioma (pLGG) in a subject in need thereof, comprising administering to the subject tovorafenib or a salt thereof,
 - wherein the pediatric low-grade glioma (pLGG) harbors a BRAF fusion or rearrangement, or BRAF V600 mutation,
 - wherein the subject is 6 months of age or older; and
 - wherein,
 - (i) when the subject has a Body Surface Area (BSA) of 0.30-0.35 m², the tovorafenib or a salt thereof is administered in a starting dose of about 125 mg once weekly, and if the subject does not tolerate the starting dose, the tovorafenib or a salt thereof is administered in a reduced dose of about 100 mg once weekly, and if the subject does not tolerate the reduced dose, the tovorafenib or a salt thereof is administered in a further reduced dose of about 75 mg once weekly;
 - (ii) when the subject has a Body Surface Area (BSA) of 0.36-0.42 m², the tovorafenib or a salt thereof is administered in a starting dose of about 150 mg once weekly, and if the subject does not tolerate the starting dose, the tovorafenib or a salt thereof is administered in a reduced dose of about 125 mg once weekly, and if the subject does not tolerate the reduced dose, the tovorafenib or a salt thereof is administered in a further reduced dose of about 100 mg once weekly;
 - (iii) when the subject has a Body Surface Area (BSA) of 0.43-0.48 m², the tovorafenib or a salt thereof is administered in a starting dose of about 175 mg once weekly, and if the subject does not tolerate the starting dose, the tovorafenib or a salt thereof is administered in a reduced dose of about 150 mg once weekly, and if the subject does not tolerate the reduced dose, the tovorafenib or a salt thereof is administered in a further reduced dose of about 125 mg once weekly;
 - (iv) when the subject has a Body Surface Area (BSA) of 0.49-0.54 m², the tovorafenib or a salt thereof is administered in a starting dose of about 200 mg once weekly, and if the subject does not tolerate the starting dose, the tovorafenib or a salt thereof is administered in a reduced dose of about 175 mg once weekly, and if the subject does not tolerate the reduced dose, the tovorafenib or a salt thereof is administered in a further reduced dose of about 150 mg once weekly;

(v) when the subject has a Body Surface Area (BSA) of $0.55\text{-}0.63\text{m}^2$, the tovorafenib or a salt thereof is administered in a starting dose of about 225 mg once weekly, and if the subject does not tolerate the starting dose, the tovorafenib or a salt thereof is administered in a reduced dose of about 200 mg once weekly, and if the subject does not tolerate the reduced dose, the tovorafenib or a salt thereof is administered in a further reduced dose of about 150 mg once weekly;

(vi) when the subject has a Body Surface Area (BSA) of $0.64\text{-}0.77\text{ m}^2$, the tovorafenib or a salt thereof is administered in a starting dose of about 275 mg once weekly, and if the subject does not tolerate the starting dose, the tovorafenib or a salt thereof is administered in a reduced dose of about 225 mg once weekly, and if the subject does not tolerate the reduced dose, the tovorafenib or a salt thereof is administered in a further reduced dose of about 200 mg once weekly;

(vii) when the subject has a Body Surface Area (BSA) of $0.78\text{-}0.83\text{m}^2$, the tovorafenib or a salt thereof is administered in a starting dose of about 300 mg once weekly, and if the subject does not tolerate the starting dose, the tovorafenib or a salt thereof is administered in a reduced dose of about 250 mg once weekly, and if the subject does not tolerate the reduced dose, the tovorafenib or a salt thereof is administered in a further reduced dose of about 200 mg once weekly;

(viii) when the subject has a Body Surface Area (BSA) of $0.84\text{-}0.89\text{ m}^2$, the tovorafenib or a salt thereof is administered in a starting dose of about 350 mg once weekly, and if the subject does not tolerate the starting dose, the tovorafenib or a salt thereof is administered in a reduced dose of about 300 mg once weekly, and if the subject does not tolerate the reduced dose, the tovorafenib or a salt thereof is administered in a further reduced dose of about 250 mg once weekly;

(ix) when the subject has a Body Surface Area (BSA) of $0.90\text{-}1.05\text{ m}^2$, the tovorafenib or a salt thereof is administered in a starting dose of about 375 mg once weekly, and if the subject does not tolerate the starting dose, the tovorafenib or a salt thereof is administered in a reduced dose of about 325 mg once weekly, and if the subject does not tolerate the reduced dose, the tovorafenib or a salt thereof is administered in a further reduced dose of about 275 mg once weekly;

(x) when the subject has a Body Surface Area (BSA) of $1.06\text{-}1.25\text{m}^2$, the tovorafenib or a salt thereof is administered in a starting dose of about 450 mg once weekly, and if the subject does not tolerate the starting dose, the tovorafenib or a salt thereof is administered in a reduced dose of about 375 mg once weekly, and if the subject does not tolerate the reduced dose, the

tovorafenib or a salt thereof is administered in a further reduced dose of about 325 mg once weekly;

(xi) when the subject has a Body Surface Area (BSA) of 1.26-1.39m², the tovorafenib or a salt thereof is administered in a starting dose of about 525 mg once weekly, and if the subject does not tolerate the starting dose, the tovorafenib or a salt thereof is administered in a reduced dose of about 450 mg once weekly, and if the subject does not tolerate the reduced dose, the tovorafenib or a salt thereof is administered in a further reduced dose of about 375 mg once weekly; or

(xii) when the subject has a Body Surface Area (BSA) of $\geq 1.40\text{m}^2$, the tovorafenib or a salt thereof is administered in a starting dose of about 600 mg once weekly, and if the subject does not tolerate the starting dose, the tovorafenib or a salt thereof is administered in a reduced dose of about 500 mg once weekly, and if the subject does not tolerate the reduced dose, the tovorafenib or a salt thereof is administered in a further reduced dose of about 400 mg once weekly.

2. A method of treating a relapsed or refractory pediatric low-grade glioma (pLGG) in a subject in need thereof, comprising orally administering to the subject tovorafenib or a salt thereof,

wherein the pediatric low-grade glioma (pLGG) harbors a BRAF fusion or rearrangement, or BRAF V600 mutation,

wherein the subject is 6 months of age or older; and

wherein,

- (i) when the subject has a Body Surface Area (BSA) of 0.30-0.35 m², the method comprises administering a starting dose of tovorafenib or the salt thereof and a reduced dose of tovorafenib or the salt thereof to the subject, and wherein the method optionally comprises administering a further reduced dose of tovorafenib or the salt thereof to the subject,

wherein the starting dose is equivalent to about 125 mg once weekly or about 380 mg/m² once weekly of tovorafenib,

wherein the reduced dose is equivalent to about 100 mg once weekly of tovorafenib, and

wherein the further reduced dose is equivalent to about 75 mg once weekly of tovorafenib;

- (ii) when the subject has a Body Surface Area (BSA) of 0.36-0.42 m², the method comprises administering a starting dose of tovorafenib or the salt thereof and a reduced

dose of tovorafenib or the salt thereof to the subject, and wherein the method optionally comprises administering a further reduced dose of tovorafenib or the salt thereof to the subject,

wherein the starting dose is equivalent to about 150 mg once weekly or about 380 mg/m² once weekly of tovorafenib,

wherein the reduced dose is equivalent to about 125 mg once weekly of tovorafenib, and

wherein the further reduced dose is equivalent to about 100 mg once weekly of tovorafenib;

(iii) when the subject has a Body Surface Area (BSA) of 0.43-0.48 m², the method comprises administering a starting dose of tovorafenib or the salt thereof and a reduced dose of tovorafenib or the salt thereof to the subject, and wherein the method optionally comprises administering a further reduced dose of tovorafenib or the salt thereof to the subject,

wherein the starting dose is equivalent to about 175 mg once weekly or about 380 mg/m² once weekly of tovorafenib,

wherein the reduced dose is equivalent to about 150 mg once weekly of tovorafenib, and

wherein the further reduced dose is equivalent to about 125 mg once weekly of tovorafenib;

(iv) when the subject has a Body Surface Area (BSA) of 0.49-0.54 m², the method comprises administering a starting dose of tovorafenib or the salt thereof and a reduced dose of tovorafenib or the salt thereof to the subject, and wherein the method optionally comprises administering a further reduced dose of tovorafenib or the salt thereof to the subject,

wherein the starting dose is equivalent to about 200 mg once weekly or about 380 mg/m² once weekly of tovorafenib,

wherein the reduced dose is equivalent to about 175 mg once weekly of tovorafenib, and

wherein the further reduced dose is equivalent to about 150 mg once weekly of tovorafenib;

(v) when the subject has a Body Surface Area (BSA) of 0.55-0.63 m², the method comprises administering a starting dose of tovorafenib or the salt thereof and a reduced dose of tovorafenib or the salt thereof to the subject, and wherein the method optionally

comprises administering a further reduced dose of tovorafenib or the salt thereof to the subject,

wherein the starting dose is equivalent to about 225 mg once weekly or about 380 mg/m² once weekly of tovorafenib,

wherein the reduced dose is equivalent to about 200 mg once weekly of tovorafenib, and

wherein the further reduced dose is equivalent to about 150 mg once weekly of tovorafenib;

(vi) when the subject has a Body Surface Area (BSA) of 0.64-0.77 m², the method comprises administering a starting dose of tovorafenib or the salt thereof and a reduced dose of tovorafenib or the salt thereof to the subject, and wherein the method optionally comprises administering a further reduced dose of tovorafenib or the salt thereof to the subject,

wherein the starting dose is equivalent to about 275 mg once weekly or about 380 mg/m² once weekly of tovorafenib,

wherein the reduced dose is equivalent to about 225 mg once weekly of tovorafenib, and

wherein the further reduced dose is equivalent to about 200 mg once weekly of tovorafenib;

(vii) when the subject has a Body Surface Area (BSA) of 0.78-0.83m², the method comprises administering a starting dose of tovorafenib or the salt thereof and a reduced dose of tovorafenib or the salt thereof to the subject, and wherein the method optionally comprises administering a further reduced dose of tovorafenib or the salt thereof to the subject,

wherein the starting dose is equivalent to about 300 mg once weekly or about 380 mg/m² once weekly of tovorafenib,

wherein the reduced dose is equivalent to about 250 mg once weekly of tovorafenib, and

wherein the further reduced dose is equivalent to about 200 mg once weekly of tovorafenib;

(viii) when the subject has a Body Surface Area (BSA) of 0.84-0.89 m², the method comprises administering a starting dose of tovorafenib or the salt thereof and a reduced dose of tovorafenib or the salt thereof to the subject, and wherein the method optionally

comprises administering a further reduced dose of tovorafenib or the salt thereof to the subject,

wherein the starting dose is equivalent to about 350 mg once weekly or about 380 mg/m² once weekly of tovorafenib,

wherein the reduced dose is equivalent to about 300 mg once weekly of tovorafenib, and

wherein the further reduced dose is equivalent to about 250 mg once weekly of tovorafenib;

(ix) when the subject has a Body Surface Area (BSA) of 0.90-1.05 m², the method comprises administering a starting dose of tovorafenib or the salt thereof and a reduced dose of tovorafenib or the salt thereof to the subject, and wherein the method optionally comprises administering a further reduced dose of tovorafenib or the salt thereof to the subject,

wherein the starting dose is equivalent to about 375-400 mg once weekly or about 380 mg/m² once weekly of tovorafenib,

wherein the reduced dose is equivalent to about 325 mg once weekly of tovorafenib, and

wherein the further reduced dose is equivalent to about 275 mg once weekly of tovorafenib;

(x) when the subject has a Body Surface Area (BSA) of 1.06-1.25m², the method comprises administering a starting dose of tovorafenib or the salt thereof and a reduced dose of tovorafenib or the salt thereof to the subject, and wherein the method optionally comprises administering a further reduced dose of tovorafenib or the salt thereof to the subject,

wherein the starting dose is equivalent to about 400-500 mg (e.g., 450 mg) once weekly or about 380 mg/m² once weekly of tovorafenib,

wherein the reduced dose is equivalent to about 375-400 mg once weekly of tovorafenib, and

wherein the further reduced dose is equivalent to about 325 mg once weekly of tovorafenib;

(xi) when the subject has a Body Surface Area (BSA) of 1.26-1.39m², the method comprises administering a starting dose of tovorafenib or the salt thereof and a reduced dose of tovorafenib or the salt thereof to the subject, and wherein the method optionally

comprises administering a further reduced dose of tovorafenib or the salt thereof to the subject,

wherein the starting dose is equivalent to about 500-525 mg once weekly or about 380 mg/m² once weekly of tovorafenib,

wherein the reduced dose is equivalent to about 400-450 mg once weekly of tovorafenib, and

wherein the further reduced dose is equivalent to about 375 mg once weekly of tovorafenib; and

(xii) when the subject has a Body Surface Area (BSA) of $\geq 1.40\text{m}^2$, the method comprises administering a starting dose of tovorafenib or the salt thereof and a reduced dose of tovorafenib or the salt thereof to the subject, and wherein the method optionally comprises administering a further reduced dose of tovorafenib or the salt thereof to the subject,

wherein the starting dose is equivalent to about 600 mg once weekly or about 380 mg/m² once weekly of tovorafenib,

wherein the reduced dose is equivalent to about 500 mg once weekly of tovorafenib, and

3. wherein the further reduced dose is equivalent to about 400 mg once weekly of tovorafenib. The method of claim 1 or 2, wherein the tovorafenib or the salt thereof is tovorafenib.
4. The method of any one of claims 1 to 3, wherein the tovorafenib or the salt thereof is administered as an oral liquid suspension.
5. The method of any one of claims 1 to 3, wherein when the dosage is less than 400 mg, the tovorafenib or a salt thereof is administered as an oral liquid suspension.
6. The method of any one of claims 1 to 3, wherein the tovorafenib or the salt thereof is administered as a solid dosage form such as a tablet.
7. The method of any one of claims 1 to 3, wherein when the dosage is 400 mg or more, the tovorafenib or a salt thereof is administered as a solid dosage form such as a tablet.
8. The method of any one of claims 1 to 7, wherein the tovorafenib or the salt thereof is administered to the subject in an amount not higher than about 600 mg once weekly.
9. The method of any one of claims 1 to 8, wherein the method comprises selecting a subject that has PLGG harboring a BRAF fusion or rearrangement, or BRAF V600 mutation.
10. The method of any one of claims 1 to 9, wherein the subject has previously received a MAP kinase inhibitor therapy.

11. A method of treating pediatric low-grade glioma (pLGG) in a subject in need thereof, comprising selecting a subject that previously received MAP kinase inhibitor therapy and administering to the subject a type II pan-RAF inhibitor.
12. The method of claim 10 or 11, wherein the subject had no progression of the pLGG while receiving the MAP kinase inhibitor therapy.
13. The method of claim 10 or 11, wherein the subject had radiographic progression of the pLGG while receiving the MAP kinase inhibitor therapy.
14. The method of any one of claims 10 to 13, wherein the subject is relapsed/refractory for pLGG following MAP kinase inhibitor therapy.
15. The method of any one of claims 10 to 14, wherein the MAP kinase inhibitor therapy is the most recent therapy administered to the subject.
16. The method of any one of claims 10 to 14, wherein the MAP kinase inhibitor therapy is not the most recent therapy administered to the subject.
17. The method of claim 16, wherein the most recent therapy administered to the subject is selected from chemotherapy, radiation therapy, and surgery.
18. The method of any one of claims 1 to 17, wherein the subject previously received one or more additional therapeutic treatments including chemotherapy, radiation therapy, and surgery.
19. The method of any one of claims 11 to 18, wherein the type II pan-RAF inhibitor is tovorafenib or a salt thereof.
20. The method of any one of claims 10 to 19, wherein the MAP kinase inhibitor therapy comprises trametinib or a salt thereof.
21. A method of treating a pediatric low-grade glioma (pLGG) in a subject in need thereof, comprising administering to the subject a type II pan-RAF inhibitor for 2 months or more, wherein the pLGG shows radiographic progression after the initial month of administration.
22. The method of claim 21, wherein the pLGG shows radiographic progression after the initial two months of administration.
23. The method of claims 21 or 22, the type II pan-RAF inhibitor is administered to the subject for 3 or more, 4 or more, or 5 or more months.
24. The method of any one of claims 21 to 23, wherein the type II pan-RAF inhibitor is tovorafenib or a salt thereof.
25. A method of treating a relapsed or refractory pediatric low-grade glioma (pLGG) in a subject in need thereof, comprising administering to the subject tovorafenib or a salt thereof,

wherein the subject is 6 months of age or older; and

wherein,

(i) when the subject has a Body Surface Area (BSA) of $0.30\text{-}0.89\text{ m}^2$, the tovorafenib or a salt thereof is administered as an oral liquid formulation (e.g., a liquid suspension) once weekly (e.g., in an amount of about 380 mg/m^2),

(ii) when the subject has a BSA of $0.90\text{-}1.12\text{ m}^2$, the tovorafenib or a salt thereof is administered as an oral liquid formulation or a solid dosage form in an amount of about 400 mg once weekly,

(iii) when the subject has a BSA of $1.13\text{-}1.39\text{ m}^2$, the tovorafenib or a salt thereof is administered as an oral liquid formulation or a solid dosage form in an amount of about 500 mg once weekly, and

(iv) when the subject has a BSA of at least 1.40 m^2 , the tovorafenib or a salt thereof is administered as an oral liquid formulation or a solid dosage form in an amount of about 600 mg once weekly.

26. The method of claim 25, wherein the pediatric low-grade glioma (pLGG) harbors a BRAF fusion or rearrangement, or BRAF V600 mutation.

27. The method of any one of claims 1 to 10, 25, or 26, wherein the method comprises confirming the presence of BRAF fusion or rearrangement, or BRAFV600 mutation prior to initiation of treatment with the tovorafenib or a salt thereof.

28. The method of any one of claims 1 to 10, 25, or 26, wherein the method comprises selecting a subject that has PLGG harboring a BRAF fusion or rearrangement, or BRAF V600 mutation.

29. The method of any one of claims 25 to 28, wherein the tovorafenib or a salt thereof is tovorafenib (i.e., the free base form).

30. The method of any one of claims 25 to 29, wherein the tovorafenib or a salt thereof is administered in an amount of about 380 mg/m^2 .

31. The method of any one of claims 25 to 29, wherein the tovorafenib or a salt thereof is administered at a starting dose of about 380 mg/m^2 .

32. The method of any one of claims 25 to 29, wherein when the subject has a BSA of $0.90\text{-}1.12\text{ m}^2$, the tovorafenib or a salt thereof is administered as a solid dosage form once weekly in an amount of about 400 mg.

33. The method of any one of claims 25 to 29, wherein when the subject has a BSA of $1.13\text{-}1.39\text{ m}^2$, the tovorafenib or a salt thereof is administered as a solid dosage form once weekly in an amount of about 500 mg.

34. The method of any one of claims 25 to 29, wherein when the subject has a BSA of at least 1.40 m^2 , the tovorafenib or a salt thereof is administered as a solid dosage form once weekly in an amount of about 600 mg.
35. The method of any one of claims 25 to 29, wherein when the subject has a BSA of about $0.30\text{-}0.35 \text{ m}^2$, the tovorafenib or a salt thereof is administered in an amount of about 125 mg once weekly.
36. The method of any one of claims 25 to 29, wherein when the subject has a BSA of about $0.30\text{-}0.35 \text{ m}^2$, the tovorafenib or a salt thereof is administered as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 125 mg once weekly.
37. The method of any one of claims 25 to 29, wherein when the subject has a BSA of about $0.30\text{-}0.35 \text{ m}^2$, the tovorafenib or a salt thereof is administered as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 5 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.
38. The method of any one of claims 25 to 29, wherein when the subject has a BSA of about $0.36\text{-}0.42 \text{ m}^2$, the tovorafenib or a salt thereof is administered in an amount of about 150 mg once weekly.
39. The method of any one of claims 25 to 29, wherein when the subject has a BSA of about $0.36\text{-}0.42 \text{ m}^2$, the tovorafenib or a salt thereof is administered as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 150 mg once weekly.
40. The method of any one of claims 25 to 29, wherein when the subject has a BSA of about $0.36\text{-}0.42 \text{ m}^2$, the tovorafenib or a salt thereof is administered as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 6 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.
41. The method of any one of claims 25 to 29, wherein when the subject has a BSA of about $0.43\text{-}0.48 \text{ m}^2$, the tovorafenib or a salt thereof is administered in an amount of about 175 mg once weekly.
42. The method of any one of claims 25 to 29, wherein when the subject has a BSA of about $0.43\text{-}0.48 \text{ m}^2$, the tovorafenib or a salt thereof is administered as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 175 mg once weekly.
43. The method of any one of claims 25 to 29, wherein when the subject has a BSA of about $0.43\text{-}0.48 \text{ m}^2$, the tovorafenib or a salt thereof is administered as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 7 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.

44. The method of any one of claims 25 to 29, wherein when the subject has a BSA of about 0.49-0.54 m², the tovorafenib or a salt thereof is administered in an amount of about 200 mg once weekly.
45. The method of any one of claims 25 to 29, wherein when the subject has a BSA of about 0.49-0.54 m², the tovorafenib or a salt thereof is administered as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 200 mg once weekly.
46. The method of any one of claims 25 to 29, wherein when the subject has a BSA of about 0.49-0.54 m², the tovorafenib or a salt thereof is administered as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 8 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.
47. The method of any one of claims 25 to 29, wherein when the subject has a BSA of about 0.55-0.63 m², the tovorafenib or a salt thereof is administered in an amount of about 225 mg once weekly.
48. The method of any one of claims 25 to 29, wherein when the subject has a BSA of about 0.55-0.63 m², the tovorafenib or a salt thereof is administered as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 225 mg once weekly.
49. The method of any one of claims 25 to 29, wherein when the subject has a BSA of about 0.55-0.63 m², the tovorafenib or a salt thereof is administered as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 9 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.
50. The method of any one of claims 25 to 29, wherein when the subject has a BSA of about 0.64-0.77 m², the tovorafenib or a salt thereof is administered in an amount of about 275 mg once weekly.
51. The method of any one of claims 25 to 29, wherein when the subject has a BSA of about 0.64-0.77 m², the tovorafenib or a salt thereof is administered as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 275 mg once weekly.
52. The method of any one of claims 25 to 29, wherein when the subject has a BSA of about 0.64-0.77 m², the tovorafenib or a salt thereof is administered as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 11 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.
53. The method of any one of claims 25 to 29, wherein when the subject has a BSA of about 0.78-0.83 m², the tovorafenib or a salt thereof is administered in an amount of about 300 mg once weekly.

54. The method of any one of claims 25 to 29, wherein when the subject has a BSA of about $0.78\text{-}0.83\text{ m}^2$, the tovorafenib or a salt thereof is administered as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 300 mg once weekly.
55. The method of any one of claims 25 to 29, wherein when the subject has a BSA of about $0.78\text{-}0.83\text{ m}^2$, the tovorafenib or a salt thereof is administered as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 12 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.
56. The method of any one of claims 25 to 29, wherein when the subject has a BSA of about $0.84\text{-}0.89\text{ m}^2$, the tovorafenib or a salt thereof is administered in an amount of about 350 mg once weekly.
57. The method of any one of claims 25 to 29, wherein when the subject has a BSA of about $0.84\text{-}0.89\text{ m}^2$, the tovorafenib or a salt thereof is administered as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 350 mg once weekly.
58. The method of any one of claims 25 to 29, wherein when the subject has a BSA of about $0.84\text{-}0.89\text{ m}^2$, the tovorafenib or a salt thereof is administered as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 14 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.
59. The method of any one of claims 25 to 29, wherein when the subject has a BSA of about $0.90\text{-}1.05\text{ m}^2$, the tovorafenib or a salt thereof is administered in an amount of about 375 mg once weekly.
60. The method of any one of claims 25 to 29, wherein when the subject has a BSA of about $0.90\text{-}1.05\text{ m}^2$, the tovorafenib or a salt thereof is administered as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 375 mg once weekly.
61. The method of any one of claims 25 to 29, wherein when the subject has a BSA of about $0.90\text{-}1.05\text{ m}^2$, the tovorafenib or a salt thereof is administered as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 15 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.
62. The method of any one of claims 25 to 29, wherein when the subject has a BSA of about $1.06\text{-}1.25\text{ m}^2$, the tovorafenib or a salt thereof is administered in an amount of about 450 mg once weekly.
63. The method of any one of claims 25 to 29, wherein when the subject has a BSA of about $1.06\text{-}1.25\text{ m}^2$, the tovorafenib or a salt thereof is administered as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 450 mg once weekly.

64. The method of any one of claims 25 to 29, wherein when the subject has a BSA of about 1.06-1.25 m², the tovorafenib or a salt thereof is administered as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 18 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.
65. The method of any one of claims 25 to 29, wherein when the subject has a BSA of about 1.26-1.39 m², the tovorafenib or a salt thereof is administered in an amount of about 525 mg once weekly.
66. The method of any one of claims 25 to 29, wherein when the subject has a BSA of about 1.26-1.39 m², the tovorafenib or a salt thereof is administered as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 525 mg once weekly.
67. The method of any one of claims 25 to 29, wherein when the subject has a BSA of about 1.26-1.39 m², the tovorafenib or a salt thereof is administered as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 21 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.
68. The method of any one of claims 25 to 29, wherein when the subject has a BSA of ≥ 1.40 m², the tovorafenib or a salt thereof is administered in an amount of about 600 mg once weekly.
69. The method of any one of claims 25 to 29, wherein when the subject has a BSA of ≥ 1.40 m², the tovorafenib or a salt thereof is administered as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 600 mg once weekly.
70. The method of any one of claims 25 to 29, wherein when the subject has a BSA of ≥ 1.40 m², the tovorafenib or a salt thereof is administered as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 24 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.
71. The method of any one of claims 25 to 29, wherein the tovorafenib or a salt thereof is administered in amount according to Table A or Table B.
72. The method of any one of claims 25 to 71, wherein the method comprises a dosage reduction of tovorafenib or a salt thereof.
73. The method of claim 72, wherein the dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 5% to 30% less compared to the dose before the dosage reduction.
74. The method of claim 72, wherein the dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 10% to 20% less compared to the dose before the dosage reduction.

75. The method of claim 72, wherein the dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19% or 20% less compared to the dose before the dosage reduction.
76. The method of any one of claims 72 to 75, wherein the dosage reduction comprising administering tovorafenib or a salt thereof to the subject according to Table C or Table D.
77. The method of any one of claims 72 to 75, wherein when the subject has a BSA of 1.13-1.39 m², the dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 400 mg once weekly.
78. The method of any one of claims 72 to 75, wherein when the subject has a BSA of ≥ 1.40 m², the dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 500 mg once weekly.
79. The method of any one of claims 72 to 75, wherein when the subject has a BSA of 0.30-0.35m², the dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 100 mg once weekly.
80. The method of any one of claims 72 to 75, wherein when the subject has a BSA of 0.30-0.35m², the dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 100 mg once weekly.
81. The method of any one of claims 72 to 75, wherein when the subject has a BSA of 0.30-0.35m², the dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 4 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.
82. The method of any one of claims 72 to 75, wherein when the subject has a BSA of 0.36-0.42 m², the dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 125 mg once weekly.
83. The method of any one of claims 72 to 75, wherein when the subject has a BSA of 0.36-0.42 m², the dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 125 mg once weekly.
84. The method of any one of claims 72 to 75, wherein when the subject has a BSA of 0.36-0.42 m², the dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 5 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.

85. The method of any one of claims 72 to 75, wherein when the subject has a BSA of 0.43-0.48m², the dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 150 mg once weekly.
86. The method of any one of claims 72 to 75, wherein when the subject has a BSA of 0.43-0.48m², the dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 150 mg once weekly.
87. The method of any one of claims 72 to 75, wherein when the subject has a BSA of 0.43-0.48 m², the dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 6 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.
88. The method of any one of claims 72 to 75, wherein when the subject has a BSA of 0.49-0.54 m², the dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 175 mg once weekly.
89. The method of any one of claims 72 to 75, wherein when the subject has a BSA of 0.49-0.54 m², the dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 175 mg once weekly.
90. The method of any one of claims 72 to 75, wherein when the subject has a BSA of 0.49-0.54 m², the dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 7 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.
91. The method of any one of claims 72 to 75, wherein when the subject has a BSA of 0.55-0.63 m², the dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 200 mg once weekly.
92. The method of any one of claims 72 to 75, wherein when the subject has a BSA of 0.55-0.63 m², the dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 200 mg once weekly.
93. The method of any one of claims 72 to 75, wherein when the subject has a BSA of 0.55-0.63 m², the dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 8 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.

94. The method of any one of claims 72 to 75, wherein when the subject has a BSA of 0.64-0.77 m², the dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 225 mg once weekly.
95. The method of any one of claims 72 to 75, wherein when the subject has a BSA of 0.64-0.77 m², the dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 225 mg once weekly.
96. The method of any one of claims 72 to 75, wherein when the subject has a BSA of 0.64-0.77 m², the dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 9 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.
97. The method of any one of claims 72 to 75, wherein when the subject has a BSA of 0.78-0.83 m², the dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 250 mg once weekly.
98. The method of any one of claims 72 to 75, wherein when the subject has a BSA of 0.78-0.83 m², the dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 250 mg once weekly.
99. The method of any one of claims 72 to 75, wherein when the subject has a BSA of 0.78-0.83 m², the dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 10 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.
100. The method of any one of claims 72 to 75, wherein when the subject has a BSA of 0.84-0.89 m², the dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 300 mg once weekly.
101. The method of any one of claims 72 to 75, wherein when the subject has a BSA of 0.84-0.89 m², the dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 300 mg once weekly.
102. The method of any one of claims 72 to 75, wherein when the subject has a BSA of 0.84-0.89 m², the dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 12 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.

103. The method of any one of claims 72 to 75, wherein when the subject has a BSA of $0.90\text{-}1.05\text{m}^2$, the dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 325 mg once weekly.
104. The method of any one of claims 72 to 75, wherein when the subject has a BSA of $0.90\text{-}1.05\text{m}^2$, the dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 325 mg once weekly.
105. The method of any one of claims 72 to 75, wherein when the subject has a BSA of $0.90\text{-}1.05\text{m}^2$, the dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 13 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.
106. The method of any one of claims 72 to 75, wherein when the subject has a BSA of $1.06\text{-}1.25\text{m}^2$, the dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 375 mg once weekly.
107. The method of any one of claims 72 to 75, wherein when the subject has a BSA of $1.06\text{-}1.25\text{m}^2$, the dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 375 mg once weekly.
108. The method of any one of claims 72 to 75, wherein when the subject has a BSA of $1.06\text{-}1.25\text{m}^2$, the dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 15 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.
109. The method of any one of claims 72 to 75, wherein when the subject has a BSA of $1.26\text{-}1.39\text{m}^2$, the dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 450 mg once weekly.
110. The method of any one of claims 72 to 75, wherein when the subject has a BSA of $1.26\text{-}1.39\text{m}^2$, the dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 450 mg once weekly.
111. The method of any one of claims 72 to 75, wherein when the subject has a BSA of $1.26\text{-}1.39\text{m}^2$, the dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 18 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.

112. The method of any one of claims 72 to 75, wherein when the subject has a BSA of $\geq 1.40 \text{ m}^2$, the dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 500 mg once weekly.
113. The method of any one of claims 72 to 75, wherein when the subject has a BSA of $\geq 1.40 \text{ m}^2$, the dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 500 mg once weekly.
114. The method of any one of claims 72 to 75, wherein when the subject has a BSA of $\geq 1.40 \text{ m}^2$, the dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 20 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.
115. The method of any one of claims 25 to 114, wherein the method comprises a second dosage reduction of tovorafenib or a salt thereof.
116. The method of claim 115, wherein the second dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 5% to 30% less compared to the dose before the dosage reduction.
117. The method of claim 115, wherein the second dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 10% to 20% less compared to the dose before the dosage reduction.
118. The method of claim 115, wherein the second dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19% or 20% less compared to the dose before the dosage reduction.
119. The method of any one of claims 115 to 118, wherein the second dosage reduction comprising administering tovorafenib or a salt thereof to the subject according to Table C or Table D.
120. The method of any one of claims 115 to 118, wherein when the subject has a BSA of $\geq 1.40 \text{ m}^2$, the second dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 400 mg once weekly.
121. The method of any one of claims 115 to 118, wherein when the subject has a BSA of $0.30\text{--}0.35 \text{ m}^2$, the second dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 75 mg once weekly.
122. The method of any one of claims 115 to 118, wherein when the subject has a BSA of $0.30\text{--}0.35 \text{ m}^2$, the second dosage reduction comprises administering tovorafenib or a salt

thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 75 mg once weekly.

123. The method of any one of claims 115 to 118, wherein when the subject has a BSA of $0.30\text{-}0.35\text{m}^2$, the second dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 3 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.
124. The method of any one of claims 115 to 118, wherein when the subject has a BSA of $0.36\text{-}0.42\text{m}^2$, the second dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 100 mg once weekly.
125. The method of any one of claims 115 to 118, wherein when the subject has a BSA of $0.36\text{-}0.42\text{m}^2$, the second dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 100 mg once weekly.
126. The method of any one of claims 115 to 118, wherein when the subject has a BSA of $0.36\text{-}0.42\text{m}^2$, the second dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 4 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.
127. The method of any one of claims 115 to 118, wherein when the subject has a BSA of $0.43\text{-}0.48\text{ m}^2$, the second dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 125 mg once weekly.
128. The method of any one of claims 115 to 118, wherein when the subject has a BSA of $0.43\text{-}0.48\text{ m}^2$, the second dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 125 mg once weekly.
129. The method of any one of claims 115 to 118, wherein when the subject has a BSA of $0.43\text{-}0.48\text{ m}^2$, the second dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 5 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.
130. The method of any one of claims 115 to 118, wherein when the subject has a BSA of $0.49\text{-}0.54\text{ m}^2$, the second dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 150 mg once weekly.
131. The method of any one of claims 115 to 118, wherein when the subject has a BSA of $0.49\text{-}0.54\text{ m}^2$, the second dosage reduction comprises administering tovorafenib or a salt

thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 150 mg once weekly.

132. The method of any one of claims 115 to 118, wherein when the subject has a BSA of 0.49-0.54 m², the second dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 6 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.
133. The method of any one of claims 115 to 118, wherein when the subject has a BSA of 0.55-0.63 m², the second dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 150 mg once weekly.
134. The method of any one of claims 115 to 118, wherein when the subject has a BSA of 0.55-0.63 m², the second dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 150 mg once weekly.
135. The method of any one of claims 115 to 118, wherein when the subject has a BSA of 0.55-0.63 m², the second dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 6 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.
136. The method of any one of claims 115 to 118, wherein when the subject has a BSA of 0.64-0.77 m², the second dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 200 mg once weekly.
137. The method of any one of claims 115 to 118, wherein when the subject has a BSA of 0.64-0.77 m², the second dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 200 mg once weekly.
138. The method of any one of claims 115 to 118, wherein when the subject has a BSA of 0.64-0.77 m², the second dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 8 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.
139. The method of any one of claims 115 to 118, wherein when the subject has a BSA of 0.78-0.83 m², the second dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 200 mg once weekly.
140. The method of any one of claims 115 to 118, wherein when the subject has a BSA of 0.78-0.83 m², the second dosage reduction comprises administering tovorafenib or a salt

thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 200 mg once weekly.

141. The method of any one of claims 115 to 118, wherein when the subject has a BSA of 0.78-0.83 m², the second dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 8 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.
142. The method of any one of claims 115 to 118, wherein when the subject has a BSA of 0.84-0.89 m², the second dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 250 mg once weekly.
143. The method of any one of claims 115 to 118, wherein when the subject has a BSA of 0.84-0.89 m², the second dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 250 mg once weekly.
144. The method of any one of claims 115 to 118, wherein when the subject has a BSA of 0.84-0.89 m², the second dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 10 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.
145. The method of any one of claims 115 to 118, wherein when the subject has a BSA of 0.90-1.05 m², the second dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 275 mg once weekly.
146. The method of any one of claims 115 to 118, wherein when the subject has a BSA of 0.90-1.05m², the second dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 275 mg once weekly.
147. The method of any one of claims 115 to 118, wherein when the subject has a BSA of 0.90-1.05m², the second dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 11 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.
148. The method of any one of claims 115 to 118, wherein when the subject has a BSA of 1.06-1.25m², the second dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 325 mg once weekly.

149. The method of any one of claims 115 to 118, wherein when the subject has a BSA of $1.06\text{-}1.25\text{m}^2$, the second dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 325 mg once weekly.
150. The method of any one of claims 115 to 118, wherein when the subject has a BSA of $1.06\text{-}1.25\text{m}^2$, the second dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 13 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.
151. The method of any one of claims 115 to 118, wherein when the subject has a BSA of $1.26\text{-}1.39\text{m}^2$, the second dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 375 mg once weekly.
152. The method of any one of claims 115 to 118, wherein when the subject has a BSA of $1.26\text{-}1.39\text{m}^2$, the second dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 375 mg once weekly.
153. The method of any one of claims 115 to 118, wherein when the subject has a BSA of $1.26\text{-}1.39\text{m}^2$, the second dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 15 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.
154. The method of any one of claims 115 to 118, wherein when the subject has a BSA of $\geq 1.40\text{ m}^2$, the second dosage reduction comprises administering tovorafenib or a salt thereof in an amount of about 400 mg once weekly.
155. The method of any one of claims 115 to 118, wherein when the subject has a BSA of $\geq 1.40\text{ m}^2$, the second dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 400 mg once weekly.
156. The method of any one of claims 115 to 118, wherein when the subject has a BSA of $\geq 1.40\text{ m}^2$, the second dosage reduction comprises administering tovorafenib or a salt thereof as an oral liquid formulation (e.g., a liquid suspension) in an amount of about 16 mL, and wherein the tovorafenib is present in the oral liquid formulation at about 25 mg/mL.

157. The method of any one of claims 1 to 156, wherein each dose of the tovorafenib or a salt thereof is administered to the subject by a minimum of four days apart.
158. The method of any one of the preceding claims, wherein the pLGG has a BRAF mutation.
159. The method of claim 158, wherein the BRAF mutation is a V600E mutation.
160. The method of claim 158, wherein the BRAF mutation is a mutation other than a V600E mutation.
161. The method of any one of claims 1 to 157, wherein the pLGG harbors a BRAF fusion or rearrangement.
162. The method of any one of the preceding claims, wherein the subject is selected from a subject that previously received MAP kinase inhibitor therapy.
163. The method of any one of claims 11-24, wherein the subject is orally administered from about 350 mg/m² to about 400 mg/m² of tovorafenib or a salt thereof per week.
164. The method of claim 163, wherein the subject is orally administered about 380 mg/m² of tovorafenib or a salt thereof per week.
165. The method of any one of the preceding claims, wherein the subject is administered tovorafenib or a salt thereof for 10 weeks or more.
166. The method of claim 165, wherein the subject is administered tovorafenib or a salt thereof for 16 weeks or more.
167. The method of any one of the preceding claims, wherein tovorafenib or a salt thereof is administered as a tablet or liquid formulation.
168. The method of any one of claims 1 to 167, wherein tovorafenib or a salt thereof is administered with food.
169. The method of any one of claims 1 to 167, wherein tovorafenib or a salt thereof is administered without food.
170. The method of any one of claims 1 to 169, further comprising evaluating the subject's liver function (e.g., ALT, AST and/or bilirubin).
171. The method of any one of the preceding claims, wherein the subject has previously received tovorafenib or a salt thereof and is on a drug holiday.