

**AZD1390, OR A PHARMACEUTICALLY ACCEPTABLE SALT THEREOF,
IN COMBINATION WITH RADIATION FOR USE IN A METHOD OF
TREATMENT OF A CNS TUMOUR**

The present disclosure relates to methods of treatment of CNS tumours.

5 Background

- Glioblastoma (also known as GBM) is the most common primary brain malignancy in adults (48.6% of all malignant CNS tumors) with an average incidence rate of 3.23 per 100000 population in the United States (Ostrom 2020). It is the most lethal primary brain tumor and less than 10% of patients survive 5 years post diagnosis (Ajaz 2014, Cloughesy 2014,
- 10 Delgado-Lopez and Corrales-Garcia 2016, Ostrom 2020). Glioblastoma is a very aggressive and infiltrative tumor. Its ability to rapidly invade surrounding brain parenchyma with an intact BBB, and its intrinsic resistance to radio-and chemotherapies significantly limit the curative intent of surgery and other therapeutic interventions (Cuddapah 2014).
- 15 The standard of care for GBM has not changed in over a decade and consists of maximal-safe surgical resection, followed by radiotherapy (RT) with or without temozolamide (TMZ), which is given concomitantly with and after RT (NCCN 2022, Stupp 2005). Standard irradiation regimens in GBM vary based on the age of patients but are typically delivered by intensity-modulated radiation therapy (IMRT) with daily fractions of 2 Gy over 4 to 6 weeks.
- 20 O⁶methylguanine-DNA methyl-transferase promoter methylation has been found to be a favourable prognostic and predictive factor of response to TMZ in GBM patients (Alnahhas 2020, Hegi 2005). Epigenetic silencing of the MGMT gene by promoter methylation results in decreased expression of MGMT, a protein that mediates DNA repair in response to DNA damage caused by alkylating agents such as TMZ (Ochs and Kaina 2000). In a meta-
- 25 analysis of 10 Phase III studies in patients with newly diagnosed GBM treated with RT+TMZ, mean overall survival (mOS) was 14.11 months for those with MGMT unmethylated tumors versus 24.59 months for patients harbouring MGMT promoter methylation (Alnahhas 2020).

- With first-line treatment, most GBM patients experience local disease recurrence with a
- 30 median progression free survival of 5 months in MGMT unmethylated and 9.5 months in methylated tumors (Alnahhas 2020). For patients who relapse, there is no established standard of care. Possible salvage therapies include re-resection, chemotherapy, bevacizumab monotherapy, and a second course of RT (NCCN 2022). Given the typical infiltrative nature of GBM, the preferred irradiation regimen in the recurrent setting is IMRT,
- 35 with cumulative doses varying based on the time interval between re-irradiation and the original irradiation courses. One of the most commonly used regimens of RT in this setting is 35 Gy in 10 fractions. Despite all efforts, survival in recurrent GBM remains poor with a mOS

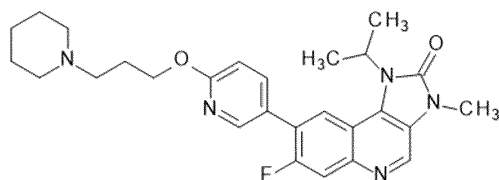
of 6 to 9 months with palliative systemic treatments, and 9.5 to 11.3 months following re-irradiation, highlighting the high unmet need in this disease (Minniti 2021, Tsien 2023, Wick and Kessler 2018).

- 5 The average annual age-adjusted incidence rate (AAAIR) of all malignant and non-malignant brain and other CNS tumors was 23.79 per 100000 population in the United States (Malignant AAAIR=7.08, non-Malignant AAAIR=16.71) (Ostrom 2020). The most common non-malignant tumor was meningioma (38.3% of all tumors). There is also an unmet need in the treatment of these CNS tumours.

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AZD1390 is an ATP-competitive kinase inhibitor with a cellular IC_{50} of 0.78 nM and is highly selective against other phosphatidylinositol 3-kinase-related kinases (PIKKs) including ATR (ataxia- and Rad3-related), DNA-PK (DNA-dependent protein kinase, and mTOR (mammalian target of rapamycin). It was disclosed in WO2017/046216 (example 2) and has

- 15 the structure:



- and the chemical name, 7-fluoro-1-isopropyl-3-methyl-8-[6-[3-(1-piperidyl)propoxy]-3-pyridyl]imidazo[4,5-c]quinolin-2-one. AZD1390 has been disclosed as having blood brain barrier penetrance in pre-clinical models (Durant 2018) and in human microdosing studies (Jucaite 2021) and has been shown to significantly prolong the survival of patient-derived xenograft and syngeneic models of adult malignant gliomas and brain metastases in pre-clinical studies (Durant 2018). Similarly to adult (brain) tumours, AZD1390 has also been shown to enhance the efficacy of radiation *in vivo* in both *TP53* wild-type and *TP53* mutant paediatric xenograft models of paediatric high-grade gliomas (pHGG) (Xie 2023).

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To deliver AZD1390 to patients with CNS tumours, safe and effective dosing regimens need to be developed with the aim of providing a more efficacious cancer treatment compared with currently approved treatments.

30 Summary

In some embodiments, disclosed is a method of treating a CNS tumour in a subject in need thereof comprising administering to the subject a total daily dose of about 300 mg of AZD1390, optionally in the form of a pharmaceutically acceptable salt thereof, and an

amount of radiation therapy. AZD1390 may be administered as a pharmaceutically acceptable salt thereof, where the daily dosage is that of AZD1390 not in a salt form.

5 In some embodiments, disclosed is a method of treating a CNS tumour in a subject in need thereof comprising administering to the subject a total daily dose of about 400 mg of AZD1390, optionally in the form of a pharmaceutically acceptable salt thereof, and an amount of radiation therapy. AZD1390 may be administered as a pharmaceutically acceptable salt thereof, where the daily dosage is that of AZD1390 not in a salt form.

10 In some embodiments, disclosed is AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour, wherein said treatment comprises the separate, sequential or simultaneous administration of i) a total daily dose of about 300 mg of AZD1390, optionally in the form of a pharmaceutically acceptable salt thereof and ii) radiation therapy, to said subject.

15 In some embodiments, disclosed is AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour, wherein said treatment comprises the separate, sequential or simultaneous administration of i) a total daily dose of about 400 mg of AZD1390, optionally in the form of a pharmaceutically acceptable salt thereof and ii) radiation therapy, to said subject.

20 In some embodiments, disclosed is the use of AZD1390, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of treatment a CNS tumour, wherein said treatment comprises the separate, sequential or simultaneous administration of i) a total daily dose of about 300 mg of said AZD1390, optionally in the form of a pharmaceutically acceptable salt thereof, and ii) radiation therapy, to said subject.

25 In some embodiments, disclosed is the use of AZD1390, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of treatment a CNS tumour, wherein said treatment comprises the separate, sequential or simultaneous administration of i) a total daily dose of about 400 mg of said AZD1390, optionally in the form of a pharmaceutically acceptable salt thereof, and ii) radiation therapy, to said subject.

30 In some embodiments, disclosed is a pharmaceutical product, such as a tablet, comprising AZD1390 in a dose of 50 mg or 100 mg or 200 mg, where AZD1390 may be present as a pharmaceutically acceptable salt, and a pharmaceutically acceptable excipient, carrier or diluent.

In some embodiments, the CNS tumour is selected from glioblastoma, IDH mutant glioma (WHO Grade 2-4), ependymoma, high grade meningioma, paediatric high-grade glioma, adult and/or paediatric medulloblastoma and metastatic CNS tumour. In some of these
5 embodiments, the CNS tumour is glioblastoma.

In some embodiments, the CNS tumour is selected from glioblastoma, IDH mutant glioma (WHO Grade 2-4), ependymoma, high grade meningioma, paediatric high-grade glioma, Diffuse Intrinsic Pontine Glioma (DIPG), choroid plexus carcinoma, astrocytoma (such as
10 Grade 4 astrocytoma), adult and/or paediatric medulloblastoma and metastatic CNS tumour (such as leptomeningeal disease). In some of these embodiments, the CNS tumour is glioblastoma, Grade 4 astrocytoma or leptomeningeal disease.

In some embodiments, the CNS tumour is newly diagnosed glioblastoma, also known as
15 primary glioblastoma. In some of these embodiments, the glioblastoma has unmethylated MGMT (O⁶-methylguanine-DNA methyltransferase). In other of these embodiments, the glioblastoma has methylated MGMT.

In some embodiments, the CNS tumour is recurrent glioblastoma. In some of these
20 embodiments, the glioblastoma has unmethylated MGMT. In other of these embodiments, the glioblastoma has methylated MGMT.

Figures

25 Fig. 1 shows time from 1st AZD1390 treatment to discontinuation, death or first data cut-off for 6 patients with recurrent GBM treated with a combination of 400 mg QD AZD1390 and radiation therapy.

Fig. 2A shows time from 1st AZD1390 treatment to discontinuation, death or second data cut-
30 off for 6 patients with recurrent GBM treated with a combination of 400 mg QD AZD1390 and radiation therapy.

Fig. 2B shows time from 1st AZD1390 treatment to discontinuation, death or second data cut-
35 off for a further 3 patients with recurrent GBM treated with a combination of 400 mg QD AZD1390 and radiation therapy.

Fig. 3 shows time from 1st AZD1390 treatment to discontinuation, death or second data cut-off for 6 patients with recurrent GBM treated with a combination of 200 mg QD AZD1390 and radiation therapy.

- 5 Fig. 4 shows time from 1st AZD1390 treatment to discontinuation, death or second data cut-off for 6 patients with recurrent GBM treated with a combination of 150 mg QD AZD1390 and radiation therapy.

- 10 Fig. 5 shows time from 1st AZD1390 treatment to discontinuation, death or second data cut-off for 6 patients with newly diagnosed GBM treated with a combination of 400 mg QD AZD1390 and radiation therapy.

- 15 Fig. 6 shows time from 1st AZD1390 treatment to discontinuation, death or second data cut-off for 6 patients with newly diagnosed GBM treated with a combination of 300 mg QD AZD1390 and radiation therapy.

- 20 Fig. 7 shows time from 1st AZD1390 treatment to discontinuation, death or second data cut-off for 6 patients with newly diagnosed GBM treated with a combination of 120 mg QD AZD1390 and radiation therapy.

Fig. 8 shows an X-Ray Powder Diffraction Pattern of Form B of AZD1390.

Fig. 9 shows a DSC Thermogram of Form B of AZD1390.

25 Detailed Description

AZD1390

- In some embodiments, a free base AZD1390 is administered to a subject. In some embodiments, a pharmaceutically acceptable salt of AZD1390 is administered to a subject. In some embodiments, crystalline free base AZD1390 or a crystalline pharmaceutically acceptable salt of AZD1390 is administered to a subject. In some embodiments, Form B of AZ1390 is administered to a subject. Form B of AZ1390 is described in WO2017/046216 in Table 2 and Figures 3 and 4. It has the following characteristic peaks in X-ray powder diffraction: (2 θ): 3.4, 11.7, 13.1, 13.5, 17.5, 18.1, 19.0, 22.7, 23.4, and 24.0.
- 30
- 35 Form B is characterised in providing an X-ray powder diffraction pattern substantially as shown in Figure 8. Ten X-Ray powder diffraction peaks are shown in Table 1.

Table 1: Characteristic X-Ray powder diffraction peaks for Form B, 7-Fluoro-1-isopropyl-3-methyl-8-[6-[3-(1-piperidyl)propoxy]-3-pyridyl]imidazo[4,5-c]quinolin-2-one

Angle 2- Theta (2θ)	Intensity %
3.4	42
11.7	67
22.7	100
13.5	64
13.1	45
19.0	42
23.4	30
24.0	21
17.5	18
18.1	15

- 5 X-ray powder diffraction spectra were determined (using a Bruker D4 Analytical Instrument) by mounting a sample of the crystalline material on a Bruker single silicon crystal (SSC) wafer mount and spreading out the sample into a thin layer with the aid of a microscope slide. The sample was spun at 30 revolutions per minute (to improve counting statistics) and irradiated with X-rays generated by a copper long-fine focus tube operated at 40kV and
- 10 40mA with a wavelength of 1.5418 angstroms. The collimated X-ray source was passed through an automatic variable divergence slit set at V20 and the reflected radiation directed through a 5.89mm antiscatter slit and a 9.55mm detector slit. The sample was exposed for 0.03 seconds per 0.00570° 2-theta increment (continuous scan mode) over the range 2 degrees to 40 degrees 2-theta in theta-theta mode. The running time was 3 minutes and 36
- 15 seconds. The instrument was equipped with a Position sensitive detector (Lynxeye). Control and data capture was by means of a Dell Optiplex 686 NT 4.0 Workstation operating with Diffrac+ software.

- Form B displays a melting endotherm with an onset of 144.7°C and a peak at 145.8°C when
- 20 analysed by differential scanning calorimetry (DSC) at a scanning rate of 10°C/mins (Figure 3).

Differential Scanning Calorimetry was performed on a TA Instruments Q1000 DSC.

Typically, less than 5 mg of material contained in a standard aluminium pan fitted with a lid

was heated over the temperature range 25°C to 300°C at a constant heating rate of 10°C per minute. A purge gas using nitrogen was used at a flow rate 50ml per minute.

The pharmaceutical compositions may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing), or as a suppository for rectal dosing. The compositions may be obtained by conventional procedures well known in the art. Compositions intended for oral use may contain additional components, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

The excipient(s) selected for inclusion in a particular composition will depend on factors such as the mode of administration and the form of the composition provided. Suitable pharmaceutically acceptable excipients are well known to persons skilled in the art and are described, for example, in the *Handbook of Pharmaceutical Excipients*, Sixth edition, Pharmaceutical Press, edited by Rowe, Ray C; Sheskey, Paul J; Quinn, Marian. Pharmaceutically acceptable excipients may function as, for example, adjuvants, diluents, carriers, stabilisers, flavourings, colorants, fillers, binders, disintegrants, lubricants, glidants, thickening agents and coating agents. As persons skilled in the art will appreciate, certain pharmaceutically acceptable excipients may serve more than one function and may serve alternative functions depending on how much of the excipient is present in the composition and what other excipients are present in the composition.

In some embodiments, AZD1390 or a pharmaceutically acceptable salt thereof are administered in a treatment cycle. In some embodiments, AZD1390 or a pharmaceutically acceptable salt thereof is continuously administered in the treatment cycle.

The term “continuous” or “continuously” refers to administration of a therapeutic agent, e.g. AZD1390, at regular intervals without stopping or interruption, i.e., no void day. By “void day”, it is meant a day when a therapeutic agent is not administered. Administration once daily or twice daily is a form of continuous administration.

A “cycle”, “treatment cycle” or “dosing schedule”, as used herein, refers to a period of treatment that is repeated on a regular schedule. For example, the treatment can be given

for one week, two weeks, or three weeks wherein AZD1390 is administered. In some embodiments, a treatment cycle is about 1 week to about 3 months. In some embodiments, a treatment cycle is about 5 days to about 1 month. In some embodiments, a treatment cycle is about 1 week to about 3 weeks. In some embodiments, a treatment cycle is about 1 week, about 10 days, about 2 weeks, about 3 weeks, about 4 weeks, about 2 months, or about 3 months.

In some embodiments, AZD1390 or a pharmaceutically acceptable salt thereof is administered to the human subject in one or more treatment cycles, e.g., a treatment course.

10 A "treatment course" comprises one or more treatment cycles, which can be repeated on a regular schedule, or adjusted as a tapered schedule as the patient's disease progression is monitored. For example, a patient's treatment cycles can have longer periods of treatment and/or shorter periods of rest at the beginning of a treatment course (e.g., when the patient is first diagnosed), and as the cancer enters remission, the rest period lengthens, thereby

15 increasing the length of one treatment cycle. The period of time for treatment and rest in a treatment cycle, the number of treatment cycles, and the length of time for the treatment course can be determined and adjusted throughout the treatment course by the skilled artisan based on the patient's disease progression, treatment tolerance, and prognosis. In some embodiments, the method comprises 1 to 10 treatment cycles. In some embodiments,

20 the method comprises 1 to 5 treatment cycles.

In some embodiments, AZD1390 or a pharmaceutically acceptable salt thereof is administered for 28 days in a 28-day treatment cycle.

25 In some embodiments, AZD1390 or a pharmaceutically acceptable salt thereof is administered before the start of radiotherapy. In some of these embodiments, a single dose of AZD1390 or a pharmaceutically acceptable salt thereof is administered before the start of radiotherapy. This single dose may be administered 1 to 7 days, or 2 to 4 or 6 hours before the first dose of radiotherapy.

30 In some embodiments, AZD1390 or a pharmaceutically acceptable salt thereof is administered continuously (i.e. every day) whilst radiotherapy is being administered.

Where AZD1390 or a pharmaceutically acceptable salt thereof is administered on the same

35 day as a fraction of radiotherapy, the (or the first) dose may be administered at least two hours before the fraction. The (or the first) dose may be administered no more than six hours before the fraction, or no more than four hours before the fraction.

Where a second dose of AZD1390 or a pharmaceutically acceptable salt is administered on the same day, this may be administered at least eight hours after the first dose. This second dose may be administered no more than fourteen hours after the first dose.

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In some embodiments, whilst radiotherapy is being delivered, the AZD1390 or a pharmaceutically acceptable salt thereof is administered only on the days that radiotherapy is administered.

10 In some embodiments, AZD1390 or a pharmaceutically acceptable salt thereof is administered after the last dose of radiotherapy in a cycle. This adjuvant phase may last for at least 1 day, at least 3 days, at least 5 days, or at least 1 week. This adjuvant phase may last up to 4 weeks, up to 3 weeks, or up to 2 weeks.

15 In some embodiments, AZD1390 or a pharmaceutically acceptable salt thereof is administered orally. In some embodiments, AZD1390 or a pharmaceutically acceptable salt thereof is in tablet dosage form.

AZD1390 Total daily dose of about 300 mg

20 In some embodiments, AZD1390 is administered, optionally as a pharmaceutically acceptable salt, in a total daily dose (QD) of about 300 mg to treat primary GBM.

In some embodiments, AZD1390 is administered, optionally as a pharmaceutically acceptable salt, in a total daily dose (QD) of about 300 mg. The total daily dose may be up
25 to 340 mg, 330 mg, 320 mg, 310 mg, or 300 mg. The total daily dose may be at least 250 mg, 260 mg, 270 mg, 280 mg, 290 mg, or 300 mg.

In some embodiments, AZD1390 is administered, optionally as a pharmaceutically acceptable salt, in a total daily dose (QD) of 250 mg, 260 mg, 270 mg, 280 mg, 290 mg, 300
30 mg, 310 mg, 320 mg, 330 mg, or 340 mg.

In some embodiments, AZD1390 is administered, optionally as a pharmaceutically acceptable salt, in a total daily dose (QD) of 300 mg.

35 In some embodiments, AZD1390 is administered, optionally as a pharmaceutically acceptable salt, once a day (OD). In some embodiments, AZD1390 is administered in a once daily dose (OD) of about 300 mg. The once daily dose may be up to 340 mg, 330 mg,

320 mg, 310 mg, or 300 mg. The once daily dose may be at least 250 mg, 260 mg, 270 mg, 280 mg, 290 mg, or 300 mg.

In some embodiments, AZD1390 is administered, optionally as a pharmaceutically acceptable salt, in a once daily dose (OD) of 250 mg, 260 mg, 270 mg, 280 mg, 290 mg, 300 mg, 310 mg, 320 mg, 330 mg, or 340 mg.

In some embodiments, AZD1390 is administered, optionally as a pharmaceutically acceptable salt, in a once daily dose (OD) of 300 mg.

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In some embodiments, AZD1390 is administered, optionally as a pharmaceutically acceptable salt, twice a day (BID). In some embodiments, AZD1390 is administered in a twice daily dose (BID) of about 150 mg. The twice daily dose may be up to 170 mg, 165 mg, 160 mg, 155 mg, or 150 mg. The twice daily dose may be at least 125 mg, 130 mg, 135 mg, 140 mg, 145 mg, or 150 mg.

In some embodiments, AZD1390 is administered, optionally as a pharmaceutically acceptable salt, in a twice daily dose (BID) of 125 mg, 130 mg, 135 mg, 140 mg, 145 mg, 150 mg, 155 mg, 160 mg, 165 mg, or 170 mg.

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In some embodiments, AZD1390 is administered, optionally as a pharmaceutically acceptable salt, in a twice daily dose (BID) of 150 mg.

AZD1390 Total daily dose of about 400 mg

In some embodiments, AZD1390 is administered, optionally as a pharmaceutically acceptable salt, in a total daily dose (QD) of about 400 mg to treat recurrent GBM.

In some embodiments, AZD1390 is administered, optionally as a pharmaceutically acceptable salt, in a total daily dose (QD) of about 400 mg. The total daily dose may be up to 450 mg, 440 mg, 430 mg, 420 mg, 410 mg, or 400 mg. The total daily dose may be at least 350 mg, 360 mg, 370 mg, 380 mg, 390 mg or 400 mg.

In some embodiments, AZD1390 is administered, optionally as a pharmaceutically acceptable salt, in a total daily dose (QD) of 350 mg, 360 mg, 370 mg, 380 mg, 390 mg, 400 mg, 410 mg, 420 mg, 430 mg, 440 mg or 450 mg.

In some embodiments, AZD1390 is administered, optionally as a pharmaceutically acceptable salt, in a total daily dose (QD) of 400 mg.

5 In some embodiments, AZD1390 is administered, optionally as a pharmaceutically acceptable salt, once a day (OD). In some embodiments, AZD1390 is administered in a once daily dose (OD) of about 400 mg. The once daily dose may be up to 450 mg, 440 mg, 430 mg, 420 mg, 410 mg, or 400 mg. The once daily dose may be at least 350 mg, 360 mg, 370 mg, 380 mg, 390 mg or 400 mg.

10 In some embodiments, AZD1390 is administered, optionally as a pharmaceutically acceptable salt, in a once daily dose (OD) of 350 mg, 360 mg, 370 mg, 380 mg, 390 mg, 400 mg, 410 mg, 420 mg, 430 mg, 440 mg or 450 mg.

15 In some embodiments, AZD1390 is administered, optionally as a pharmaceutically acceptable salt, in a once daily dose (OD) of 400 mg.

In some embodiments, AZD1390 is administered, optionally as a pharmaceutically acceptable salt, twice a day (BID). In some embodiments, AZD1390 is administered in a twice daily dose (BID) of about 200 mg. The twice daily dose may be up to 225 mg, 220 mg, 215 mg, 210 mg, 205 mg, or 200 mg. The twice daily dose may be at least 175 mg, 180 mg, 185 mg, 190 mg, 195 mg or 200 mg.

25 In some embodiments, AZD1390 is administered, optionally as a pharmaceutically acceptable salt, in a twice daily dose (BID) of 175 mg, 180 mg, 185 mg, 190 mg, 195 mg, 200 mg, 205 mg, 210 mg, 215 mg, 220 mg or 225 mg.

In some embodiments, AZD1390 is administered, optionally as a pharmaceutically acceptable salt, in a twice daily dose (BID) of 200 mg.

30 *Radiation therapy*

Radiation therapy is a therapy using ionizing radiation. The radiation therapy may involve the use of x-rays, gamma rays, or charged particles.

35 The radiation therapy may be external beam radiation therapy or internal radiation therapy (also called brachytherapy). Systemic radiation therapy, using radioactive substances, such as radioactive iodine, may also be employed. External-beam radiation therapy includes 3D conformational radiation therapy, intensity-modulated radiation therapy, image-guided

radiation therapy, tomotherapy, stereotactic radiosurgery, proton therapy, or other charged particle beams.

In some embodiments, the radiotherapy is intensity-modulated radiation therapy (IMRT).

- 5 In some embodiments, the radiotherapy is whole brain radiation therapy (WBRT) or partial brain radiation therapy (PBRT).

- 10 In some embodiments, the radiation therapy is fractionated radiation therapy, wherein the total dose of radiation is split into a number of smaller doses, i.e. fractions. The number of fractions may be at least 2, at least 3, at least 4, at least 5, at least 6 or at least 7. The number of fractions may be less than 40, less than 35, less than 30, less than 25, less than 20 or less than 15.

- 15 In some embodiments, the radiation therapy fractions are administered in sequential days. In other embodiments, the radiation therapy fractions are administered for some days sequentially, with some rest days. In some of these embodiments, the radiation therapy fractions are administered for five days sequentially, followed by two rest days, which administration pattern is repeated until all fractions have been administered.

- 20 In some embodiments, the total dose of radiotherapy is at least 20 Gy, at least 30 Gy, at least 40 Gy, or at least 50 Gy. In some embodiments, the total dose of radiotherapy is less than 70 Gy, less than 60 Gy, less than 50 Gy, or less than 40 Gy.

In some embodiments, the total dose of radiotherapy is 60 Gy.

- 25 In some embodiments, the total dose of radiotherapy is 35 Gy.

- 30 In some embodiments, the radiotherapy is delivered by IMRT with daily fractions of 2.0 Gy over 4 to 6 weeks (on 5 days out of 7, such as weekdays only), i.e. with a total dose of 40 Gy to 60 Gy. This may be used to treat primary GBM, such as primary GBM with unmethylated MGMT.

- In some embodiments, the radiotherapy is delivered by IMRT with daily fractions of 3.5 Gy over 2 weeks (on 5 days out of 7, such as weekdays only), i.e. with a total dose of 35 Gy. This may be used to treat recurrent GBM.

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In some embodiments, the radiotherapy is delivered by PBRT/WBRT with daily fractions of 3.0 Gy over 2 week (on 5 days out of 7, such as weekdays only), i.e. with a total dose of 30

Gy. This may be used to treat CNS metastases of solid tumors who are not candidates for stereotactic radiosurgery (SRS).

5 In some embodiments, the radiotherapy is delivered by IMRT with daily fractions of 2.0 Gy over 4 to 6 weeks (on 5 days out of 7, such as weekdays only), i.e. with a total dose of 40 Gy to 60 Gy, and AZD1390 is administered, optionally as a pharmaceutically acceptable salt, in a total daily dose of about 300 mg on the same days as radiotherapy, followed by a 2 week adjuvant phase of dosing AZD1390 at 300 mg QD. This may be used to treat primary GBM, such as primary GBM with unmethylated MGMT.

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In some embodiments, the radiotherapy is delivered by IMRT with daily fractions of 3.5 Gy over 2 weeks (on 5 days out of 7, such as weekdays only), i.e. with a total dose of 35 Gy and AZD1390 is administered, optionally as a pharmaceutically acceptable salt, in a total daily dose of about 300 mg on the same days as radiotherapy, followed by a 2 week adjuvant phase of dosing AZD1390 at 300 mg QD. This may be used to treat recurrent GBM.

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In some embodiments, the radiotherapy is delivered by PBRT/WBRT with daily fractions of 3.0 Gy over 2 weeks (on 5 days out of 7, such as weekdays only), i.e. with a total dose of 30 Gy and AZD1390 is administered, optionally as a pharmaceutically acceptable salt, in a total daily dose of about 300 mg on the same days as radiotherapy. This may be used to treat CNS metastases of solid tumors who are not candidates for stereotactic radiosurgery (SRS).

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In some embodiments, the radiotherapy is delivered by IMRT with daily fractions of 2.0 Gy over 4 to 6 weeks (on 5 days out of 7, such as weekdays only), i.e. with a total dose of 40 Gy to 60 Gy, and AZD1390 is administered, optionally as a pharmaceutically acceptable salt, in a total daily dose of about 400 mg on the same days as radiotherapy, followed by a 2 week adjuvant phase of dosing AZD1390 at 400 mg QD. This may be used to treat primary GBM, such as primary GBM with unmethylated MGMT.

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30 In some embodiments, the radiotherapy is delivered by IMRT with daily fractions of 3.5 Gy over 2 weeks (on 5 days out of 7, such as weekdays only), i.e. with a total dose of 35 Gy and AZD1390 is administered, optionally as a pharmaceutically acceptable salt, in a total daily dose of about 400 mg on the same days as radiotherapy, followed by a 2 week adjuvant phase of dosing AZD1390 at 400 mg QD. This may be used to treat recurrent GBM.

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In some embodiments, the radiotherapy is delivered by PBRT/WBRT with daily fractions of 3.0 Gy over 2 weeks (on 5 days out of 7, such as weekdays only), i.e. with a total dose of 30

Gy and AZD1390 is administered, optionally as a pharmaceutically acceptable salt, in a total daily dose of about 400 mg on the same days as radiotherapy. This may be used to treat CNS metastases of solid tumors who are not candidates for stereotactic radiosurgery (SRS).

- 5 The language “treat,” “treating” and “treatment” includes the reduction of size or mass of the CNS tumour, the slowing or delaying of progression of the CNS tumour, and/or prolonging the survival of the patient. The language “treat,” “treating” and “treatment” also includes the reduction or inhibition of the growth of the CNS tumor.
- 10 The language “inhibit,” “inhibition” or “inhibiting” includes a decrease in the baseline activity of a biological activity or process.

The term “subject” includes warm-blooded mammals, for example, primates, dogs, cats, rabbits, rats, and mice. In some embodiments, the subject is a primate. In some

- 15 embodiments, the subject is a human.

- Ranges may be expressed herein as from “about” one particular value, and/or to “about” another particular value. When such a range is expressed, another embodiment includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by the use of the antecedent “about,” it will be understood that the particular value forms another embodiment. The term “about” in relation to a numerical value is optional and means for example +/- 10%, or +/- 5%.
- 20

Preclinical studies

- 25 Nonclinical in vitro pharmacology studies have shown that AZD1390 at concentrations <10 nM led to ≥50% inhibition of ATM kinase enzyme and radiosensitized a panel of GBM cell lines. In vivo, radiosensitization mediated by AZD1390 was confirmed in a series of pre-clinical mouse models of GBM and lung carcinoma (orthotopic and subcutaneous PDX grown in immunocompromised mice, as well as murine immunocompetent syngeneic GBM
- 30 models), showing dose-dependent tumor growth inhibition (Durant 2018). The unbound brain to plasma partition coefficient $K_{p,uu}$ ($C_{u,brain}/C_{u,plasma}$) was calculated using the following equation:

$$K_{p,uu} = \frac{f_{u,brain}}{f_{u,plasma}} \times V_T$$

and was found to be 0.33 in cynomolgus macaques.

Early clinical studies

AZD1390 was radiolabeled with carbon-11 and a microdose (mean injected mass 1.21 µg) was injected in 8 male subjects (21–65 years old). The radioactivity concentration of [¹¹C]AZD1390 in brain was measured using a high resolution PET system. Radioactivity in
5 arterial blood was measured to obtain a metabolite corrected arterial input function for quantitative image analysis. The brain radioactivity concentration of [¹¹C]AZD1390 was 0.64 SUV (standard uptake value) and reached maximum 1.00% of injected dose at $T_{\max[\text{brain}]}$ of 21 minutes (time of maximum brain radioactivity concentration) after i.v. injection. The whole brain total distribution volume was 5.20 mL*cm⁻³. This led to the $K_{p,uu}$ ($C_{u,\text{brain}}/C_{u,\text{plasma}}$) in
10 humans to be calculated as 0.24. No adverse events related to [¹¹C] AZD1390 were reported.

Predicted clinically efficacious doses

The original predicted clinically efficacious daily dose for AZD1390 was 11mg based on (1)
15 early PK-PD-efficacy data in a very sensitive model, (2) K_{puu} delivered in primates and (3) predictions of human PK.

This changed to 60-80 mg with progressing understanding of the drug clearance, and particularly the discovery of metabolism of AZD1390 by aldehyde oxidase (AO).
20

Examples

The methods and use of the application will now be further explained by reference to the following non-limiting examples.

25 Example 1 – ex vivo RT protocol

An *ex vivo* RT protocol was run at the Ivy Brain Tumour Center at the Barrow Neurological Institute (BNI, Phoenix, US) as part of a Pilot Study and then Phase 0 Window of Opportunity (WoO) (NCT05182905) surgical study to evaluate AZD1390 tumor PK and PD in
30 samples resected from GBM patients treated pre-surgically with AZD1390. This approach overcomes significant challenges in obtaining tumor biopsies for assessing tumor PK and PD measurements, particularly in the context of RT combination treatment posed by the anatomical location and treatment sequence for GBM. In addition, this approach resolves the known disconnect between systemic and brain exposures caused by the BBB which limits the value of considering plasma PK and peripheral PD as an effective measure of
35 brain tumor exposure.

Specifically, patients undergoing resection for a WHO Grade 4 glioma were treated with AZD1390 for 3 days prior to surgical resection. Brain tumor samples were collected intraoperatively between 2 to 6 hours (corresponding to C_{max}) and ~24h (corresponding to C_{min}) following the last dose of AZD1390 for PK and PD analysis along with blood and CSF.

5

Resected GBM tumor tissue is immediately transferred to the laboratory, sliced into sections, and incubated in neuronal stem cell media before, during and after *ex vivo* radiation. No radiation (0Gy/sham radiation therapy, control) or a single dose of radiation (5Gy) is delivered to individual parts of the tumor, which are then incubated for 30 minutes before the samples are formalin-fixed, paraffin-embedded and ATM pathway activity assessed by evaluating the level of phosphorylated RAD50 biomarker by immunohistochemistry.

10

All recurrent GBM patients (n = 13) on study as of 15 March 2023 were dosed with 400 mg QD and AZD1390 in plasma and tumor PK samples were measured and K_{p,uu} was calculated (= 0.405). Pathology review identified AZD1390 in both gadolinium enhancing and non-enhancing samples, suggesting penetration of AZD1390 across an intact BBB.

15

In all patients (n = 13) dosed in the WoO study with 400 mg QD, tumor PK exceeded exposures anticipated to result in significant TE in gadolinium enhancing and non-enhancing regions at the early time point (2 to 6 hours, n = 12, near C_{max}) and late time point (~24 hours, n = 1 at 27 hours near C_{min}). PD calculated from 7 AZD1390 dosed patient samples following *ex vivo* irradiation vs 5 control samples from the pilot study was: 93.7%, 90.0%, 96.3%, 95.6%, 97.5%, 99.0%, and 88.3%* pRAD50 inhibition (mean 95.3% 2 to 6 hours; 94.3% including ~24 hour [27 hours] sample). PD calculated from 12 AZD1390 dosed patient samples following *ex vivo* irradiation vs control samples from the pilot study was: 94.7% (range 90 to 97.5%, n = 6) at 2-4 hours, 97.6% (range 96.3 to 99%, n = 4) at 4-6 hours, and 93.4% (range 88.3-98.4%, n = 2) at ~24 hours.

20

25

The clinical pRAD50 biomarker data in recurrent GBM tumors analyzed in the surgical Ph0 WoO study (NCT05182905) demonstrates up to 99% (90% to 99%) of pRAD50 inhibition at the early timepoint (2 to 6 hours post-dose near C_{max}) in 6 out of 6 evaluable samples from patients treated with AZD1390 at 400 mg QD and radiotherapy compared to those treated with radiotherapy alone.

30

In an extension of the study, 9 new diagnosed GBM patients were dosed with 120 mg QD for 3 days prior to surgical resection. The mean pRAD50 inhibition measured was 98.9%

35

(range 94.3 to 99.9%, n = 6) at 4 to 6 hours and 87.4% (range 63.5 to 99.6%, n = 3) at 24 hours.

Combining the data for both 120 mg QD and 400 mg QD shows that the pRAD50 biomarker
5 induction by ex vivo RT is suppressed by ~ 90% (n = 21) over 24 hours. Based on this data, it is projected that 300 mg will achieve adequate target engagement in the brain tumor.

All GBM patients (n = 39) on study as of 24 January 2024 were dosed with either 120 or 400
mg QD and AZD1390 in plasma and tumor PK samples were measured and $K_{p,uu}$ was
10 calculated (= 0.575).

Example 2 – Clinical trial

Study D6940C00002 is a Phase I, multicenter study to assess the safety, tolerability, and PK
of ascending doses of AZD1390 in combination with RT in patients with GBM and brain
15 metastases from solid tumors. The study comprises 3 arms, each of which provides
standard of care IMRT for the disease setting indicated, with AZD1390 being administered in
escalating dose cohorts. Arm A enrolled patients with recurrent GBM, Arm B enrolled
patients with brain metastases from solid tumors, but was closed due to poor recruitment,
and Arm C is enrolling patients with newly diagnosed GBM harbouring unmethylated MGMT
20 promoter.

Inclusion/exclusion criteria

All patients (Arm A, B and C)

For inclusion in the study, patients must fulfil all of the following criteria:

- 25 1. Provision of signed and dated, written informed consent prior to any study specific
procedures, sampling and analyses. If a patient declines to participate in any voluntary
exploratory research component of the study, there will be no penalty or loss of benefit to the
patient and he/she will not be excluded from other aspects of the study.
- 30 2. All patients must agree to provide a formalin-fixed paraffin embedded (FFPE) tissue
sample from their primary or metastatic disease. If archival tissue from a prior resection or
biopsy is unavailable, patient participation must be discussed with the Medical Monitor for
potential inclusion on a case-by-case basis.
3. Aged at least 18 years.
- 4 Karnofsky Performance Score (KPS) of ≥ 60 .
- 35 5 Adequate organ system functions, as outlined below:
- Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$ /L.
 - Platelets $\geq 100 \times 10^9$ /L.

- Hemoglobin ≥ 9 g/dL.
 - Activated partial thromboplastin time (aPTT) ≤ 1.5 times the upper limit of normal (ULN).
 - Total bilirubin ≤ 1.5 times the ULN.
- 5 • Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 times the ULN if no liver involvement or ≤ 5 times the ULN with liver involvement with metastatic disease.
- Creatinine < 1.5 times ULN concurrent with creatinine clearance > 50 mL/min (measured or calculated by Cockcroft and Gault equation); confirmation of creatinine
- 10 clearance is only required when creatinine is > 1.5 times ULN.
- Amylase and lipase within normal limits (WNL).
6. Females of childbearing potential must have a negative pregnancy test during screening and must not be breastfeeding or intending to become pregnant during the study.
7. Male patients with female partners of child-bearing potential must be willing to use two
- 15 forms of acceptable contraception, including one barrier method, during their participation in this study and for 16 weeks following the last dose of the study drug .
8. Ability to swallow and retain oral medication.

Additional inclusion criteria specific for Arm A

- 20 9. Patients must have a histologically proven diagnosis of GBM. Patients who have had RT for low-grade glioma (LGG) or grade 3 glioma and have subsequently relapsed to histologically confirmed GBM can be considered for inclusion in Arm A after discussion with the Medical Monitor.
10. Patients must have a radiological diagnosis of recurrent/relapsed or progressive disease
- 25 according to RANO criteria (Ellingson 2015, Ellingson 2017, Wen 2010).
11. Patients must have completed first-line radiation at least 6 months prior to Cycle 1 Day 1.
12. Patients with tumor-induced seizures must be well controlled on a stable anti-epileptic treatment.
13. Patients must be willing to receive prophylaxis with levetiracetam for the duration of
- 30 study drug administration (or alternative anti-epileptic if agreed with the Medical Monitor).

Additional inclusion criteria specific for Arm B

14. Patient with histologically proven diagnosis of solid tumor malignancy and MR imaging documenting brain lesions.
- 35 15. Patient is not eligible for SRS treatment of brain tumor.

16. Patient has not received any previous brain RT to the area that is to be irradiated. Prior PBRT may be allowed after discussion with the Medical Monitor who may consult with a radiation oncologist to ensure that there is not significant overlap between the prior and new radiation fields, specifics of which are provided in the radiation manual.

- 5 17. Non-CNS malignant disease must be sufficiently controlled so that patients can be without additional systemic therapy for the required washout period before starting therapy until 5 days after the end of RT.

Required washout period before starting the first dose of AZD1390 (Cycle 1) is:

- 28 days for immune checkpoint inhibitors.
- 10 • 7 days for all other agents.

18. Patient has not received radiation to the lung fields within the past 8 weeks.

19. Patient has no history of seizures related to the brain metastases or LMD.

20. Patient receiving PBRT (rather than WBRT) during Cycle 1 as standard of care for brain metastases are eligible for this arm.

15

Additional inclusion criteria specific for Arm C

21. Patients must have a histologically proven primary diagnosis of GBM with unmethylated MGMT. Grade 4 astrocytoma or histology with molecular features of GBM can be considered for inclusion in Arm C after discussion with the Medical Monitor.

- 20 22. Determination of MGMT promoter status by methylation-specific PCR or pyrosequencing per local institutional guidelines is required to assess eligibility for this arm.

23. Patients will have to undergo mutational testing for isocitrate dehydrogenase 1 (IDH1) on a tumor specimen before entering study. Immunohistochemistry is sufficient for enrolment, although DNA sequencing may also be performed based on local institutional guidelines.

- 25 Patients are eligible for Arm C regardless of their IDH1 mutational status.

24. Patient has no history of uncontrolled seizures after surgery for primary GBM (despite adequate antiepileptic therapy) or with need for concurrent administration of more than 2 antiepileptic drugs.

- 25 Patients must be willing to receive prophylaxis with levetiracetam for the duration of
30 study drug administration (or alternative anti-epileptic if agreed with the Medical Monitor).

Exclusion criteria

All patients (Arms A, B and C)

Patients must not enter the study if any of the following exclusion criteria are fulfilled:

- 35 1. Life expectancy less than 12 weeks.
2. Confusion or altered mental state that would prohibit understanding and giving of informed consent.

3. Concomitant treatment with the following medicines: Sensitive substrates of BCRP, OATP1B1, MATE1, MATE2K and P-gp such as prazosin, cimetidine, simvastatin, dofetilide, metformin, dabigatran, digoxin and fexofenadine; Other anticancer agents and investigational agents; Live virus and bacterial vaccines.
- 5 4. Administration of chemotherapy or any investigational drug in the 28 days or carmustine (BCNU) or lomustine (CCNU) in the 6 weeks prior to receiving the first dose of treatment in Arms A and C. Administration of checkpoint inhibitors within 28 days prior to first dose of treatment and any other agent within 7 days of beginning study treatment in Arm B. Hormonal therapies are allowed during study treatment for patients in Arm B.
- 10 5. History of severe brain-injury, or stroke.
6. Patient not eligible for sequential MRI evaluations are not eligible for this study.
7. History of epileptic disorder or any seizure history unrelated to tumor.
8. Treatment with any of the following:
- Strong inhibitors or inducers of CYP3A4 within 2 weeks before the first dose of study treatment (Boceprevir; clarithromycin; conivaptan; elvitegravir/ RIT; fluconazole; grapefruit juice; indinavir; itraconazole; ketoconazole; lopinavir/ RIT; mibefradil; nefazodone;
 - Nelfinavir; osaconazole; ritonavir; saquinavir; telaprevir; telithromycin; tipranavir/ RIT; troleandomycin; voriconazole; avasimibe; carbamazepine; enzalutamide; mitotane;
 - Nevirapine; phenobarbital; phenytoin; rifabutin; rifampin; rifapentine (3 weeks for St John's Wort)
 - Concurrent therapy with other seizurogenic medications
9. Past medical history of interstitial lung disease (ILD), drug-induced ILD, radiation pneumonitis which required steroid treatment, or any evidence of clinically active interstitial lung disease.
10. Evidence of established ILD on screening chest CT scan with a resolution of at least 1 mm slice thickness.
11. Concurrent severe and/or uncontrolled medical condition (e.g., severe COPD). Grade 2 unresolved toxicities may be eligible following discussion with the Medical Monitor.
12. Prior treatment with pneumotoxic drugs, e.g., busulfan, bleomycin, within the past year. If prior therapy in lifetime, then excluded if history of pulmonary toxicities from administration. Patients who have received treatment with nitrosoureas (e.g., BCNU, CCNU) in the year before study entry without experiencing lung toxicity are allowed on study.
13. History or presence of myopathy or raised CK >5 x ULN on 2 occasions at screening. CK should not be measured following strenuous exercise or in the presence of a plausible alternative cause of CK increase, which may confound interpretation of the results. If CK

levels are significantly elevated at baseline ($>5 \times \text{ULN}$) a confirmatory test should be carried out within 5 –7 days. If the repeat test confirms a baseline CK $>5 \times \text{ULN}$, treatment should not be started.

14. Cardiac dysfunction defined as: Myocardial infarction within six months of study entry,
5 NYHA Class II/III/IV heart failure, unstable angina or unstable cardiac arrhythmias.
15. Evidence of severe pulmonary infections, as judged by the Investigator, based on clinical findings and investigations, i.e., significant findings on chest X-ray, significantly raised c-reactive protein (CRP) and/or white cell count, raised temperature, production of purulent sputum, etc.
- 10 16. As judged by the Investigator, any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension, atrial fibrillation, active bleeding diatheses, or active infection including hepatitis B, hepatitis C and human immunodeficiency virus (HIV). Screening for chronic conditions is not required.
17. Any of the following cardiac criteria:
- 15 • Mean resting corrected QT interval (QTcF) > 470 ms obtained from 1 triplicate ECG (set of 3 consecutive 12-lead ECGs) (QTc interval will be calculated using Fridericia's formula) – QT interval is the ECG interval measured from onset of QRS complex to end of the T wave.
- Any clinically important abnormalities in rhythm, conduction or morphology of resting
20 ECG, e.g., complete left bundle branch block, type 2 second degree atrioventricular block, third degree heart block.
- Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalemia, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years-of-age. Patients
25 stable on concomitant medications known to prolong the QT interval may be allowed to participate in the study provided that their mean resting corrected QT interval (QTcF) is < 470 msec at baseline and after discussion with the Medical Monitor
18. History of hypersensitivity to AZD1390 and excipients or drugs with a similar chemical structure or class to AZD1390.
- 30 19. Judgment by the Investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions and requirements.
20. With the exception of alopecia, any unresolved toxicities from prior therapy greater than National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v4.03) Grade 1 at the time of starting study treatment and patients with chronic Grade 2
35 unresolved toxicities may be eligible following discussion with the Medical Monitor.

Additional exclusion criterion for Arm A

21. Have previously received an ATM inhibitor concurrently with RT, including AZD1390.

Dosing Schedules5 *Arm A – Combination with 35 Gy IMRT*

AZD1390 is administered as a single dose (in the amount of the tested daily dose) to allow for PK measurements in the week prior to starting radiation treatment (Cycle 0).

10 Concomitant therapy with photon beam RT is given at the tested daily dose for the duration of radiation treatment (2 weeks: 3.5 Gy IMRT each day for 5 days followed by 2 rest days (Cycle 1 Week 1) which is repeated (Cycle 1 Week 2)).

Following the RT, AZD1390 is given daily at the tested dose for 14 days (Cycle 2).

15 *Arm B – Combination with 30 Gy WBRT/PBRT*

Concomitant therapy with RT is given at the tested daily dose for the duration of radiation treatment (2 weeks: 3.0 Gy WBRT/PRBT each day for 5 days followed by 2 rest days (Cycle 1 Week 1) which is repeated (Cycle 1 Week 2)). Partial Brain Radiation Treatment (PBRT) is allowed for patients in Arm B with lesions localized to the posterior fossa and all other
20 eligible patients receiving PBRT as standard of care.

Arm C – Combination with 60 Gy IMRT

AZD1390 is administered as a single dose (in the amount of the tested daily dose) to allow for PK measurements in the week prior to starting radiation treatment (Cycle 0). This may
25 be omitted.

Concomitant therapy with photon beam RT is given at the tested daily dose for the duration of radiation treatment (6 weeks: 2 Gy IMRT each day for 5 days followed by 2 rest days (Cycle 1 Week 1) which is repeated 5 times (Cycle 1 Weeks 2 to 6)).

30 Following the RT, AZD1390 is given daily at the tested dose for 14 days (Cycle 2).

Dose escalation

The trial involves dose escalation such that a number of different daily dosages of AZD1390
35 are tested. In particular, the trial seeks to establish the maximum tolerated dose (MTD) in each setting, followed by further assessment of the safety, tolerability and efficacy at this dose, or a dose lower than the MTD.

Selected doses in each arm tested are:

Arm A: 150 mg, 200 mg, 400 mg, 600 mg, 900 mg

Arm C: 120 mg, 300 mg, 400 mg

5

Dose-limiting toxicity (DLT)

A DLT is defined as any toxicity not attributable to the disease, an extraneous cause or disease-related processes under investigation, which occurs after initiation of therapy during Cycle 0, 1, and 2 for Arms A and C or Cycle 1 only for Arm B during treatment and before
10 the end of the DLT assessment period. The DLT assessment period ends at the end of Cycle 2 (1 week after the end of AZD1390 treatment) for Arms A and C and 5 days after the end of treatment in Arm B. Toxicity is graded according to the NCI CTCAE v4.03.

DLTs include:

- 15 1. Neutropenia $\geq$ CTCAE Grade 4 present for more than 7 days, or febrile neutropenia.
2. Thrombocytopenia $\geq$ CTCAE Grade 4, or $\geq$ CTCAE Grade 3 associated with bleeding.
3. Anemia $\geq$ CTCAE Grade 4.
4. Non-hematological toxicity $\geq$ CTCAE Grade 3 including but not limited to:
 - Infection, including febrile neutropenia
 - 20 • Nausea, vomiting, and diarrhoea that does not respond to supportive care within 48 hours. Any Grade 4 nausea, vomiting, and diarrhea will be considered a DLT.
 - An increase in AST or ALT $\geq$ 3 times the ULN and total bilirubin (TBL) $\geq$ 2 times the ULN.
 - Amylase and/or lipase abnormalities $\geq$ CTCAE Grade 3 with associated symptoms of
25 pancreatitis.
5. Any neurological AE $\geq$ CTCAE Grade 2 lasting > 7 days.
6. CNS haemorrhage $\geq$ CTCAE Grade 2 of any duration.
7. Any other toxicity that is new or greater than that at baseline, is clinically significant and/or unacceptable, does not respond to supportive care, results in a disruption of dosing
30 schedule of more than 14 days, or is judged to be a DLT by the Investigator in collaboration with the Medical Monitor, or by the SRC.

The following will be considered a DLT in relation to a seizure:

- Before declaring DLT due to the study drug, other possible causes of new onset or
35 worsening of seizures should be excluded (e.g., tumor progression, severe brain injury, hypoglycemia, encephalitis/meningitis, acute stroke, etc.)

- Increased frequency or severity (based on CTCAE) of seizures compared to status of seizures at baseline (prior to starting AZD1390) which is judged by the Investigator to be hazardous, incapacitating, or unacceptable to the patient or caregiver.
- Any Grade 4 seizure (e.g., prolonged repetitive seizures) or Grade 3 seizure with increased severity or frequency above baseline.
- Recurrence of Grade 2 after appropriate pharmacological management (see Table 5).

The following will be considered a DLT in relation to lung toxicity:

- Before declaring DLT due to the study drug, other possible causes of pulmonary adverse events (AEs) or toxicity should be excluded (e.g., congestive heart failure, pulmonary embolism, pneumonia, pulmonary hypertension).

In patients with lung metastases, if the Investigator, in consultation with the SRC, believes that findings are due to disease progression, this won't constitute DLT. However, patients who progress will still be withdrawn from treatment if the risk benefit becomes unfavourable.

- Grade 3 or higher Dyspnea.
- Grade 3 or higher Cough.
- Grade 3 or higher Hypoxia.
- A significant reduction (Grade 3 CTCAE) in carbon monoxide diffusing capacity.
- Pulmonary toxicity in the absence of infections or non-infectious etiology (that includes pulmonary embolism, etc.) with:
 - Oxygen saturation on room air <88% at rest (if supported by pulmonary consultation and SRC evaluation).
- OR
- New or increased lung symptoms (e.g., dyspnea, severe dry cough, inspiratory crackles, fever) suggestive of pneumonitis/ILD.
- AND
- CT compatible with ILD.
- OR
- Negative CT and lung criteria changes (oxygen saturation, or new or increased lung symptoms) without improvement for more than 2 weeks.

The following will be considered a DLT in relation to discontinuation of radiation therapy:

- For Arm A, and Arm B, a dose of AZD1390 that prevents patients from receiving at least 75% of their scheduled course of RT is considered a DLT.

- For Arm C, a dose of AZD1390 that prevents patients from receiving at least 85% of their scheduled course of RT is considered a DLT. Particular attention should be placed on the timing of RT daily doses that are missed on the treatment plan due to toxicities caused by AZD1390. Even if the amount of RT completed is >85%, a toxicity may be considered a DLT if the Investigator and Medical Monitor determine that radiation treatment was compromised by toxicities related to AZD1390.

A DLT excludes:

- Grade 3 or 4 laboratory abnormalities which are not considered clinically significant and which resolve within 48 hours.
- Alopecia of any grade.

Maximum Tolerated Dose

In each arm, the MTD is defined as the highest dose at which the predicted probability of a DLT is less than 25% in that specific RT setting. Due to the differences in patient populations and RT cumulative dose, each arm may be determined to have a distinct MTD.

Radiation therapy adverse effects

Radiation therapy AEs are classified as follows:

20

Acute

Expected acute radiation-induced toxicities include hair loss, fatigue, and erythema or soreness of the scalp. Potential acute toxicities include nausea and vomiting as well as temporary aggravation of brain tumor symptoms such as headaches, seizures, and weakness.

Reactions in the ear canals and on the ear should be observed and treated symptomatically; these reactions could result in short-term hearing impairment. Dry mouth and altered taste have been occasionally reported.

30

Early Delayed

Possible early delayed radiation effects include lethargy and transient worsening of existing neurological deficits occurring 1 to 3 months after radiotherapy treatment.

35 *Late Delayed*

Possible late delayed effects of radiotherapy include risk of radiation necrosis, and endocrine dysfunction. In addition, neurocognitive deficits, which could lead to mental slowing and behavioural change, are possible. Permanent hearing impairment and visual damage are rare. Cataracts can be encountered.

5

For patients in Arms A and C assessment for evidence of radiation necrosis is required at the first follow up and every 8 weeks until disease progression. Following disease progression, any standard of care imaging will be assessed for radiation necrosis as part of the post-progression follow-up visits. The post-progression follow-up visits will be performed according to the schedule of standard of care brain scans (or every 3 months by telemedicine visit if brain scans are not being performed) until death, withdrawal of consent or the end of the study, whichever is sooner.

For patients in Arm B, assessment for evidence of radiation necrosis is required at 4 weeks after the end of RT and at every standard of care follow up safety visit.

Adverse events

Definition of adverse events

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

Any deterioration of the disease under study and associated symptoms or findings should not be regarded as an AE as far as the deterioration can be anticipated.

The term AE is used generally to include any AE whether serious or non-serious.

Definitions of serious adverse events

A serious AE (SAE) is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death.
- Is immediately life-threatening.

- Requires in-patient hospitalization or prolongation of existing hospitalization.
 - Results in persistent or significant disability/ incapacity or substantial disruption of the ability to conduct normal life functions.
 - Is or results in a congenital anomaly or birth defect.
- 5 • Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above.

Pharmacokinetics (PK) and Pharmacodynamics (PDc)

The following samples will be taken a pre-determined times during the study:

- 10 • Venous blood samples (2 mL) for determination of concentrations of AZD1390 in plasma Blood samples to measure the induction biomarker 4-β-hydroxycholesterol (4-β-OH-Chol)
- Urine, including samples for determination of AZD1390 concentrations
- 15 The timing of the PK samples may be adjusted during the study, dependent on emerging data, in order to ensure appropriate characterization of the plasma concentration-time profiles.

- A PDc sample will be collected immediately before administration of AZD1390 or RT, and 1
- 20 hour after AZD1390 or RT, In addition there will be PK samples collected at the same time as PDc samples post AZD1390. This will allow deriving exposure/PDc relationships.

- Peripheral blood mononuclear cells (PBMCs) will be isolated from whole blood and analysed for protein levels and post-translational modifications of pharmacodynamic biomarkers,
- 25 PBMCs may also be stimulated *ex vivo* to induce DNA damage prior to protein analysis.

All patients will be required to provide a sample of their archival tumor blocks, if available.

The analysis of archival tumor tissue may include, but is not limited to:

- DNA sequencing of archival tumor tissue for mutant p53.
- 30 • IHC staining of archival tumor tissue for ATM.
- Gene expression analysis of the archival tumor tissue.

Whole blood will also be collected for ctDNA analysis or analysis of other peripheral Biomarkers.

35

Tumor assessments

Brain tumors will be assessed by brain MRI. Patients in Arm A and C will undergo MRI at screening and every 8 weeks until progression, starting 4 weeks after the end of RT. For patients in Arm A and C, standard of care brain MRI scans will be assessed for radiation necrosis until death, withdrawal of consent or the end of the study, whichever is sooner.

5

Brain MRI scans performed outside the study can be used as the baseline evaluation for all arms, provided that they are performed within 3 weeks of the patient starting treatment (Cycle 0 or Cycle 1 [RT] if Cycle 0 is omitted).

10 In Arm A and C, if the first on treatment scan appears to show progression and the Investigator believes the patient can safely continue on study, another scan to verify tumor growth and progression should be acquired at the next planned 8-week interval, or a minimum of 4 weeks later.

15 Patients in Arm B will undergo brain MRI at screening and at 4 weeks after the end of RT. Subsequent MRI measurements performed as part of standard of care will be used to assess radiation necrosis until one year after the end of RT or until re-irradiation of the brain, whichever is sooner.

20 Patients in Arm B will also undergo assessment of their systemic disease (CT or MRI Scans as appropriate) at baseline and at 4 weeks after the end of RT which will be evaluated by RECIST criteria. In Arm B, the results of any serological tumor markers (e.g., CEA, CA 19-9, CA-125, PSA) for patients with tumors that have correlative tumor markers that are measured as part of standard of care will be recorded in the eCRF.

25

The response criteria to evaluate treatment for CNS disease are based on The Response Assessment in Neuro-Oncology (RANO) Working Group for GBM (Arms A and C) and RANO-Brain Metastases (Arm B).

30 Results up to 18 May 2023

In Arm A, dose limiting toxicities manifesting as a constellation of low-grade gastrointestinal AEs, fatigue and confusion were reported at 900 mg QD dose level (n = 4 evaluable, 3 DLTs).

35 A summary of common AZD1390 related Adverse Events for Arm A at 400 mg QD and 600 mg QD is shown below:

System Organ Class Preferred Term	400 mg (N=9)		600 mg (N=10)	
	Any grade	G3/4	Any grade	G3/4
Gastrointestinal disorders				
Nausea	2 (22.2)	0	5 (50.0)	2 (20.0)
Vomiting	2 (22.2)	0	6 (60.0)	1 (10.0)
Diarrhoea	2 (22.2)	0	2 (20.0)	1 (10.0)
Laboratory abnormalities				
Lipase increased	0	0	5 (50.0)	1 (10.0)
Alanine aminotransferase incr	0	0	3 (30.0)	2 (20.0)
Amylase incr	1 (11.1)	0	3 (30.0)	0
Blood creatine phosphokinase incr	3 (33.3)	1 (11.1)	5 (50.0)	2 (20.0)
Aspartate aminotransferase incr	2 (22.2)	0	3 (30.0)	2 (20.0)
Neutrophil count decr	0	0	3 (30.0)	0
General disorders				
Fatigue	3 (33.3)	0	1 (10.0)	1 (10.0)
Headache	0	0	1 (10.0)	0
Eye disorders				
Asthenopia	2 (22.2)	0	0	0

400 mg QD was determined as the MTD for Arm A.

A summary of common AZD1390 related Adverse Events for Arm C at 300 mg QD is shown below:

5

System Organ Class Preferred Term	300 mg (N=6)	
	Any grade	G3/4
Gastrointestinal disorders		
Nausea	2 (33.3)	0
Diarrhoea	3 (50.0)	0
Laboratory abnormalities		
Alanine aminotransferase incr	2 (33.3)	0
Aspartate aminotransferase incr	2 (33.3)	0

Nervous system disorders		
Dizziness	2 (33.3)	0
Skin disorders		
Radiation Dermatitis	2 (33.3)	0
General disorders		
Fatigue	1 (16.7)	0

The 400 mg QD dose in Arm C is open for enrolment.

Fig. 1 shows time from 1st AZD1390 treatment to discontinuation, death or data cut-off (18 May 2023) for the initial 6 patients dosed at 400 mg QD in Arm A.

The symbols at the right-hand end of the bars show the patient disposition status:

◆	End of study: death
▼	End of study: withdrawal
►	Ongoing

The symbols inside the bars (labelled by duration in months) who the RANO assessment:

△	Not evaluable (NE)
▽	Progressive Disease (PD)
□	Stable Disease (SD)
◇	Partial Response (PR)

The circles for patient 5 indicate that at 1.5 months the investigator considered the disease to be stable disease and at 3.3 months, progressive disease.

The circle for patient 6 indicates that at 1.4 months the investigator considered the disease to be stable disease.

Results up to 6 February 2024

In Arm A (Recurrent GBM), a summary of the adverse effects at 150 mg QD, 200 mg QD and 400 mg QD is shown below:

n (%)	Recurrent GBM		
	150 mg (N = 6)	200 mg (N = 6)	400 mg (N = 9)
Any AE	6 (100)	6 (100)	9 (100)
Any AE related to AZD1390 and/or radiotherapy (RT)	6 (100)	6 (100)	9 (100)
Any AE related to AZD1390	6 (100)	5 (83.3)	8 (83.3)
AE Grade $\geq$ 3	5 (83.3)	4 (66.7)	4 (44.4)
AZD1390 and/or RT Related	3 (50)	2 (33.3)	3 (33.3)
AZD1390 Only Related	3 (50)	1 (16.7)	2 (22.2)
AE with outcome death	0	0	0
Any SAE	4 (66.7)	4 (66.7)	3 (33.3)
AZD1390 and/or RT Related	0	1 (16.7)	1 (11.1)
AZD1390 Only Related	0	0	1 (11.1)
Any AE leading to dose modification of AZD1390	0	0	1 (11.1)
AZD1390 and/or RT Related	0	0	1 (11.1)
AZD1390 Only Related	0	0	1 (11.1)
Any AE leading to dose modification of RT	0	0	0
AZD1390 and/or RT Related	0	0	0
AZD1390 Only Related	0	0	0

Fig. 2A shows time from 1st AZD1390 treatment to discontinuation, death or data cut-off for the initial 6 patients dosed at 400 mg QD in Arm A, and Fig. 2B shows time from 1st AZD1390 treatment to discontinuation, death or data cut-off for the additional patients dosed at 400 mg QD in Arm A.

Fig. 3 shows time from 1st AZD1390 treatment to discontinuation, death or data cut-off for the 6 patients dosed at 200 mg QD in Arm A.

Fig. 4 shows time from 1st AZD1390 treatment to discontinuation, death or data cut-off for the 6 patients dosed at 150 mg QD in Arm A.

In Arm C (Newly Diagnosed GBM), a summary of the adverse effects at 120 mg QD, 300 mg QD and 400 mg QD is shown below:

n (%)	Newly Diagnosed GBM		
	120 mg (N = 3)	300 mg (N = 11)	400 mg (N = 6)
Any AE	3 (100)	10 (90.9)	6 (100)
Any AE related to AZD1390 and/or radiotherapy (RT)	2 (66.7)	8 (72.7)	6 (100)
Any AE related to AZD1390	1 (33.3)	7 (63.6)	5 (83.3)
AE Grade $\geq$ 3	0	2 (18.2)	4 (66.7)
AZD1390 and/or RT Related	0	1 (9.1)	4 (66.7)
AZD1390 Only Related	0	0	2 (33.3)
AE with outcome death	0	0	0
Any SAE	0	3 (27.3)	3 (50)
AZD1390 and/or RT Related	0	1 (9.1)	3 (50)
AZD1390 Only Related	0	0	0
Any AE leading to dose modification of AZD1390	0	1 (9.1)	2 (33.3)
AZD1390 and/or RT Related	0	1 (9.1)	1 (16.7)
AZD1390 Only Related	0	0	0
Any AE leading to dose modification of RT	0	0	2 (33.3)
AZD1390 and/or RT Related	0	0	1 (16.7)
AZD1390 Only Related	0	0	0

300 mg QD was determined as the MTD for Arm C.

- 5 Fig. 5 shows time from 1st AZD1390 treatment to discontinuation, death or data cut-off for the initial 6 patients dosed at 400 mg QD in Arm C.

Fig. 6 shows time from 1st AZD1390 treatment to discontinuation, death or data cut-off for the 11 patients dosed at 300 mg QD in Arm C.

10

Fig. 7 shows time from 1st AZD1390 treatment to discontinuation, death or data cut-off for the 2 patients dosed at 120 mg QD in Arm C.

The symbols at the right-hand end of the bars show the patient disposition status:

◆	End of study: death
▼	End of study: withdrawal
►	Ongoing

The symbols inside the bars (labelled by duration in months) who the RANO assessment:

△	Not evaluable (NE)
♥	Progressive Disease (PD)
□	Stable Disease (SD)
◇	Partial Response (PR)

Results up to 27 May 2024

- 5 15 additional primary GBM patients were enrolled sine the 6 Feb 2024 data cut off: 8 at 200mg and 6 at 300mg.

In Arm C (Newly Diagnosed GBM), a summary of the adverse effects at 120 mg QD, 300 mg QD and 400 mg QD is shown below:

10

n (%)	Newly Diagnosed GBM			
	120 mg (N = 3)	200 mg (N = 8)	300 mg (N = 15)	400 mg (N = 6)
Any AE	3 (100)	7 (87.5)	15 (100)	6 (100)
AE Grade ≥ 3	0	2 (25)	9 (60)	4 (66.7)
AZD1390 and/or RT Related	0	2 (25)	5 (33.3)	4(66.7)
AE with outcome death	0	-	0	0
Any SAE	0	1 (12.5)	7 (46.7)	3 (50)
AZD1390 and/or RT Related	0	1 (12.5)	5 (33.3)	2 (33.3)
Dosing Limiting Toxicities	0	-	1*	3 (50)
Treatment related AEs leading to discontinuation of AZD1390	0	0	2 (13.3)	3 (50)

Example 3 – Further clinical trial

Further to the Phase 0 Window of Opportunity (WoO) (NCT05182905) surgical study described in Example 1, this study has been extended to a Phase 1 study treating patients with both recurrent GBM (Arm A) and primary GBM (Arm C).

5

In Arm A patients are treated with 400mg AZD1390 QD and 35 Gy IMRT. The median progression free survival and overall survival for 15 patients treated was reported as 11.3 months and 15.4 months, respectively (Sanai et al 2024).

In Arm C patients are treated with either 120mg or 300mg AZD1390 QD and 60 Gy IMRT.

10

References

A number of publications are cited above. Full citations for these references are provided below. The entirety of each of these references is incorporated herein.

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Numbered Statements for a total daily dose of about 300 mg of AZD1390

1. A method of treating a CNS tumour in a subject in need thereof comprising administering to the subject a total daily dose of about 300 mg of AZD1390, optionally in the form of a pharmaceutically acceptable salt thereof, and an amount of radiation therapy.
- 5 2. The method according to statement 1, wherein AZD1390 or a pharmaceutically acceptable salt thereof is administered before the start of radiotherapy.
3. The method according to statement 2, wherein a single dose of AZD1390 or a pharmaceutically acceptable salt thereof is administered before the start of radiotherapy.
4. The method according to statement 3, wherein said single dose is administered 1 to
10 7 days, or 2 to 6 hours before the first dose of radiotherapy.
5. The method according to any one of statements 1 to 4, wherein AZD1390 or a pharmaceutically acceptable salt thereof is administered continuously whilst radiotherapy is being administered.
6. The method according to any one of statements 1 to 4, wherein, whilst radiotherapy
15 is being delivered, AZD1390 or a pharmaceutically acceptable salt thereof is administered only on the days that radiotherapy is administered.
7. The method according to any one of statements 1 to 6, wherein when AZD1390 or a pharmaceutically acceptable salt thereof is administered on the same day as a fraction of radiotherapy, the, or the first, dose is administered at least two hours before the fraction.
- 20 8. The method according to any one of statements 1 to 7, wherein when AZD1390 or a pharmaceutically acceptable salt thereof is administered on the same day as a fraction of radiotherapy, the, or the first, dose is administered no more than six hours before the fraction.
9. The method according to statement 8, wherein the, or the first, dose of AZD1390 or a
25 pharmaceutically acceptable salt thereof is administered no more than four hours before the fraction.
10. The method according to any one of statements 1 to 9, wherein AZD1390 or a pharmaceutically acceptable salt thereof is administered after the last dose of radiotherapy in a cycle as an adjuvant phase.
- 30 11. The method according to statement 10, wherein the adjuvant phase lasts for at least 1 day, at least 3 days, at least 5 days, or at least 1 week.
12. The method according to either statement 10 or statement 11, wherein the adjuvant phase lasts up to 4 weeks, up to 3 weeks, or up to 2 weeks.
13. The method according to any one of statements 1 to 12, wherein the AZD1390 or a
35 pharmaceutically acceptable salt thereof is administered orally.

14. The method according to any one of statements 1 to statement 13, wherein the AZD1390 or a pharmaceutically acceptable salt thereof is in tablet form.
15. The method according to any one of statements 1 to 14, wherein the total daily dose of AZD1390 is up to 340 mg, 330 mg, 320 mg, 310 mg, or 300 mg.
- 5 16. The method according to any one of statements 1 to 15, wherein the total daily dose of AZD1390 is at least 250 mg, 260 mg, 270 mg, 280 mg, 290 mg, or 300 mg.
17. The method according to any one of statements 1 to 14, wherein the total daily dose of AZD1390 is 300 mg.
18. The method according to any one of statements 1 to 14, wherein AZD1390 is
10 administered once a day.
19. The method according to statement 18, wherein the once daily dose of AZD1390 is up to 340 mg, 330 mg, 320 mg, 310 mg, or 300 mg.
20. The method according to either statement 18 or statement 19, wherein the once daily dose of AZD1390 is at least 250 mg, 260 mg, 270 mg, 280 mg, 290 mg, or 300 mg.
- 15 21. The method according to any one of statements 1 to 14, wherein the once daily dose of AZD1390 is 300 mg.
22. The method according to any one of statements 1 to 14, wherein AZD1390 is administered twice a day.
23. The method according to statement 22, wherein the twice daily dose of AZD1390 is
20 up to 170 mg, 165 mg, 160 mg, 155 mg, or 150 mg.
24. The method according to either statement 22 or statement 23, wherein the twice daily dose of AZD1390 is at least 125 mg, 130 mg, 135 mg, 140 mg, 145 mg, or 150 mg.
25. The method according to any one of statements 1 to 14, wherein the twice daily dose of AZD1390 is 150 mg.
- 25 26. The method according to any one of statements 1 to 25, wherein the CNS tumour is selected from glioblastoma, IDH mutant glioma (WHO Grade 2-4), ependymoma, high grade meningioma, paediatric high-grade glioma, Diffuse Intrinsic Pontine Glioma (DIPG), choroid plexus carcinoma, astrocytoma (such as Grade 4 astrocytoma), adult and/or paediatric medulloblastoma and metastatic CNS tumour (such as leptomeningeal disease).
- 30 27. The method according to statement 26, wherein the CNS tumour is glioblastoma.
28. The method according to statement 27, wherein the CNS tumour is primary glioblastoma.
29. The method according to statement 28, wherein the glioblastoma has unmethylated MGMT (O⁶-methylguanine-DNA methyltransferase).
- 35 30. The method according to statement 28, wherein the glioblastoma has methylated MGMT.

31. The method according to any one of statements 1 to 30, wherein the radiotherapy is intensity-modulated radiation therapy (IMRT).
32. The method according to any one of statements 1 to 30, wherein the radiotherapy is whole brain radiation therapy (WBRT) or partial brain radiation therapy (PBRT).
- 5 33. The method according to any one of statements 1 to 32, wherein the radiation therapy is fractionated radiation therapy.
34. The method according to statement 33, wherein the radiation therapy fractions are administered in sequential days.
35. The method according to statement 33, wherein the radiation therapy fractions are
10 administered for some days sequentially, with some rest days.
36. The method according to statement 35, wherein the radiation therapy fractions are administered for five days sequentially, followed by two rest days.
37. The method according to any one of statements 33 to 36, wherein the total dose of radiotherapy is at least 20 Gy, at least 30 Gy, at least 40 Gy, or at least 50 Gy.
- 15 38. The method according to any one of statements 33 to 37, wherein the total dose of radiotherapy is less than 70 Gy, less than 60 Gy, less than 50 Gy, or less than 40 Gy.
39. The method according to any one of statements 33 to 36, wherein the total dose of radiotherapy is 60 Gy.
40. The method according to any one of statements 33 to 36, wherein the total dose of
20 radiotherapy is 35 Gy.
41. The method according to any one of statements 1 to 30, wherein the radiotherapy is delivered by IMRT with daily fractions of 2.0 Gy over 4 to 6 weeks on 5 days out of 7, such as weekdays only.
42. The method according to any one of statements 1 to 30, wherein the radiotherapy is
25 delivered by IMRT with daily fractions of 3.5 Gy over 2 weeks on 5 days out of 7, such as weekdays only.
43. The method according to any one of statements 1 to 30, wherein the radiotherapy is delivered by PBRT/WBRT with daily fractions of 3.0 Gy over 2 weeks on 5 days out of 7, such as weekdays only.
- 30 44. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour, wherein said treatment comprises the separate, sequential or simultaneous administration of i) a total daily dose of about 300 mg of said AZD1390, optionally in the form of a pharmaceutically acceptable salt thereof, and ii) radiation therapy, to said subject.
- 35 45. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to statement 44, wherein the AZD1390 or a pharmaceutically acceptable salt thereof is administered before the start of radiotherapy.

46. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to statement 45, wherein a single dose of AZD1390 or a pharmaceutically acceptable salt thereof is administered before the start of radiotherapy.
47. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of
5 treatment of a CNS tumour according to statement 45, wherein the single dose is administered 1 to 7 days, or 2 to 6 hours before the first dose of radiotherapy.
48. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of statements 44 to 47, wherein AZD1390 or a pharmaceutically acceptable salt thereof is administered continuously whilst
10 radiotherapy is being administered.
49. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of statements 44 to 47, wherein, whilst radiotherapy is being delivered, AZD1390 or a pharmaceutically acceptable salt thereof is administered only on the days that radiotherapy is administered.
- 15 50. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of statements 44 to 49, wherein when AZD1390 or a pharmaceutically acceptable salt thereof is administered on the same day as a fraction of radiotherapy, the, or the first, dose is administered at least two hours before the fraction.
- 20 51. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of statements 44 to 50, wherein when AZD1390 or a pharmaceutically acceptable salt thereof is administered on the same day as a fraction of radiotherapy, the, or the first, dose is administered no more than six hours before the fraction.
- 25 52. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to statement 51, wherein the, or the first, dose of AZD1390 or a pharmaceutically acceptable salt thereof is administered no more than four hours before the fraction.
- 30 53. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of statements 44 to 52, wherein AZD1390 or a pharmaceutically acceptable salt thereof is administered after the last dose of radiotherapy in a cycle as an adjuvant phase.
54. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to statement 53, wherein the adjuvant phase lasts for
35 at least 1 day, at least 3 days, at least 5 days, or at least 1 week.

55. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to either statement 53 or statement 54, wherein the adjuvant phase lasts up to 4 weeks, up to 3 weeks, or up to 2 weeks.
56. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of
5 treatment of a CNS tumour according to any one of statements 44 to 55, wherein the AZD1390 or a pharmaceutically acceptable salt thereof is administered orally.
57. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of statements 44 to 56, wherein the AZD1390 or a pharmaceutically acceptable salt thereof is in tablet form.
- 10 58. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of statements 44 to 57, wherein the total daily dose of AZD1390 is up to 340 mg, 330 mg, 320 mg, 310 mg, or 300 mg.
59. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of statements 44 to 58, wherein the total
15 daily dose of AZD1390 is at least 250, 260 mg, 270 mg, 280 mg, 290 mg, or 300 mg.
60. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of statements 44 to 57, wherein the total daily dose of AZD1390 is 300 mg.
61. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of
20 treatment of a CNS tumour according to any one of statements 44 to 57, wherein AZD1390 is administered once a day.
62. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to statement 61, wherein the once daily dose of AZD1390 is up to 340 mg, 330 mg, 320 mg, 310 mg, or 300 mg.
- 25 63. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to either statement 61 or statement 62, wherein the once daily dose of AZD1390 is at least 250 mg, 260 mg, 270 mg, 280 mg, 290 mg, or 300 mg.
64. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of
30 treatment of a CNS tumour according to any one of statements 44 to 57, wherein the once daily dose of AZD1390 is 300 mg.
65. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of statements 44 to 57, wherein AZD1390 is administered twice a day.
- 35 66. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to statement 65, wherein the twice daily dose of AZD1390 is up to 170 mg, 165 mg, 160 mg, 155 mg, or 150 mg.

67. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to either statement 65 or statement 66, wherein the twice daily dose of AZD1390 is at least 125 mg, 130 mg, 135 mg, 140 mg, 145 mg, or 150 mg.
- 5 68. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of statements 44 to 57, wherein the twice daily dose of AZD1390 is 150 mg.
69. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of statements 44 to 68, wherein the CNS
- 10 tumour is selected from glioblastoma, IDH mutant glioma (WHO Grade 2-4), ependymoma, high grade meningioma, paediatric high-grade glioma, Diffuse Intrinsic Pontine Glioma (DIPG), choroid plexus carcinoma, astrocytoma (such as Grade 4 astrocytoma), adult and/or paediatric medulloblastoma and metastatic CNS tumour (such as leptomeningeal disease).
70. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of
- 15 treatment of a CNS tumour according to statement 69, wherein the CNS tumour is glioblastoma.
71. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to statement 70, wherein the CNS tumour is primary glioblastoma.
- 20 72. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to statement 71, wherein the glioblastoma has unmethylated MGMT (O⁶-methylguanine-DNA methyltransferase).
73. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to statement 71, wherein the glioblastoma has
- 25 methylated MGMT.
74. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of statements 44 to 73, wherein the radiotherapy is intensity-modulated radiation therapy (IMRT).
75. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of
- 30 treatment of a CNS tumour according to any one of statements 44 to 73, wherein the radiotherapy is whole brain radiation therapy (WBRT) or partial brain radiation therapy (PBRT).
76. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of statements 44 to 75, wherein the
- 35 radiation therapy is fractionated radiation therapy.

77. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to statement 76, wherein the radiation therapy fractions are administered in sequential days.
78. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of
5 treatment of a CNS tumour according to statement 76, wherein the radiation therapy fractions are administered for some days sequentially, with some rest days.
79. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to statement 78, wherein the radiation therapy fractions are administered for five days sequentially, followed by two rest days.
- 10 80. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of statements 76 to 79, wherein the total dose of radiotherapy is at least 20 Gy, at least 30 Gy, at least 40 Gy, or at least 50 Gy.
81. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of statements 76 to 80, wherein the total
15 dose of radiotherapy is less than 70 Gy, less than 60 Gy, less than 50 Gy, or less than 40 Gy.
82. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of statements 76 to 81, wherein the total dose of radiotherapy is 60 Gy.
- 20 83. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of statements 76 to 81, wherein the total dose of radiotherapy is 35 Gy.
84. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of statements 44 to 73, wherein the
25 radiotherapy is delivered by IMRT with daily fractions of 2.0 Gy over 4 to 6 weeks on 5 days out of 7, such as weekdays only.
85. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of statements 44 to 73, wherein the radiotherapy is delivered by IMRT with daily fractions of 3.5 Gy over 2 weeks on 5 days out
30 of 7, such as weekdays only.
86. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of statements 44 to 73, wherein the radiotherapy is delivered by PBRT/WBRT with daily fractions of 3.0 Gy over 2 weeks on 5 days out of 7, such as weekdays only.
- 35 87. Use of AZD1390, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of treatment a CNS tumour, wherein said treatment comprises the separate, sequential or simultaneous administration of i) a total daily dose of

about 300 mg of said AZD1390, optionally in the form of a pharmaceutically acceptable salt thereof, and ii) radiation therapy, to said subject.

88. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to statement 87, wherein AZD1390 or a pharmaceutically acceptable salt thereof is

5 administered before the start of radiotherapy.

89. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to statement 88, wherein a single dose of AZD1390 or a pharmaceutically acceptable salt thereof is administered before the start of radiotherapy.

90. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to
10 statement 89, wherein the single dose is administered 1 to 7 days, or 2 to 6 hours before the first dose of radiotherapy.

91. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to any one of statements 87 to 90, wherein AZD1390 or a pharmaceutically acceptable salt thereof is administered continuously whilst radiotherapy is being administered.

15 92. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to any one of statements 87 to 90, wherein, whilst radiotherapy is being delivered, AZD1390 or a pharmaceutically acceptable salt thereof is administered only on the days that radiotherapy is administered.

93. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to any one
20 of statements 87 to 92, wherein when AZD1390 or a pharmaceutically acceptable salt thereof is administered on the same day as a fraction of radiotherapy, the, or the first, dose is administered at least two hours before the fraction.

94. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to any one
25 of statements 87 to 93, wherein when AZD1390 or a pharmaceutically acceptable salt thereof is administered on the same day as a fraction of radiotherapy, the, or the first, dose is administered no more than six hours before the fraction.

95. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to statement 94, wherein the, or the first, dose of AZD1390 or a pharmaceutically acceptable salt thereof is administered no more than 4 hours before the fraction.

30 96. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to any one of statements 87 to 95, wherein AZD1390 or a pharmaceutically acceptable salt thereof is administered after the last dose of radiotherapy in a cycle as an adjuvant phase.

97. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to statement 96, wherein the adjuvant phase lasts for at least 1 day, at least 3 days, at least 5
35 days, or at least 1 week.

98. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to either statement 96 or statement 97, wherein the adjuvant phase lasts up to 4 weeks, up to 3 weeks, or up to 2 weeks.
99. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to any one of statements 87 to 98, wherein the AZD1390 or a pharmaceutically acceptable salt thereof is administered orally.
100. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to any one of statements 87 to statement 99, wherein the AZD1390 or a pharmaceutically acceptable salt thereof is in tablet form.
101. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to any one of statements 87 to 100, wherein the total daily dose of AZD1390 is up to 340 mg, 330 mg, 320 mg, 310 mg, or 300 mg.
102. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to any one of statements 87 to 101, wherein the total daily dose of AZD1390 is at least 250 mg, 260 mg, 270 mg, 280 mg, 290 mg, or 300 mg.
103. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to any one of statements 87 to 100, wherein the total daily dose of AZD1390 is 300 mg.
104. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to any one of statements 87 to 100, wherein AZD1390 is administered once a day.
105. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to statement 104, wherein the once daily dose of AZD1390 is up to 340 mg, 330 mg, 320 mg, 310 mg, or 300 mg.
106. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to either statement 104 or statement 105, wherein the once daily dose of AZD1390 is at least 250, 260 mg, 270 mg, 280 mg, 290 mg, or 300 mg.
107. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to any one of statements 87 to 100, wherein the once daily dose of AZD1390 is 300 mg.
108. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to any one of statements 87 to 100, wherein AZD1390 is administered twice a day.
109. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to statement 108, wherein the twice daily dose of AZD1390 is up to 170 mg, 165 mg, 160 mg, 155 mg, or 150 mg.
110. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to either statement 108 or statement 109, wherein the twice daily dose of AZD1390 is at least 125 mg, 130 mg, 135 mg, 140 mg, 145 mg, or 150 mg.
111. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to any one of statements 87 to 100, wherein the twice daily dose of AZD1390 is 150 mg.

112. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to any one of statements 87 to 111, wherein the CNS tumour is selected from glioblastoma, IDH mutant glioma (WHO Grade 2-4), ependymoma, high grade meningioma, paediatric high-grade glioma, Diffuse Intrinsic Pontine Glioma (DIPG), choroid plexus carcinoma, astrocytoma (such as Grade 4 astrocytoma), adult and/or paediatric medulloblastoma and metastatic CNS tumour (such as leptomeningeal disease).
113. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to statement 112, wherein the CNS tumour is glioblastoma.
114. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to statement 113, wherein the CNS tumour is primary glioblastoma.
115. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to statement 114, wherein the glioblastoma has unmethylated MGMT (O⁶-methylguanine-DNA methyltransferase).
116. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to statement 114, wherein the glioblastoma has methylated MGMT.
117. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to any one of statements 87 to 116, wherein the radiotherapy is intensity-modulated radiation therapy (IMRT).
118. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to any one of statements 87 to 116, wherein the radiotherapy is whole brain radiation therapy (WBRT) or partial brain radiation therapy (PBRT).
119. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to any one of statements 87 to 118, wherein the radiation therapy is fractionated radiation therapy.
120. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to statement 119, wherein the radiation therapy fractions are administered in sequential days.
121. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to statement 119, wherein the radiation therapy fractions are administered for some days sequentially, with some rest days.
122. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to statement 121, wherein the radiation therapy fractions are administered for five days sequentially, followed by two rest days.
123. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to any one of statements 119 to 122, wherein the total dose of radiotherapy is at least 20 Gy, at least 30 Gy, at least 40 Gy, or at least 50 Gy.
124. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to any one of statements 119 to 123, wherein the total dose of radiotherapy is less than 70 Gy, less than 60 Gy, less than 50 Gy, or less than 40 Gy.

125. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to any one of statements 119 to 122, wherein the total dose of radiotherapy is 60 Gy.
126. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to any one of statements 119 to 122, wherein the total dose of radiotherapy is 35 Gy.
- 5 127. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to any one of statements 87 to 116, wherein the radiotherapy is delivered by IMRT with daily fractions of 2.0 Gy over 4 to 6 weeks on 5 days out of 7, such as weekdays only.
128. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to any one of statements 87 to 116, wherein the radiotherapy is delivered by IMRT with daily fractions of
- 10 3.5 Gy over 2 weeks on 5 days out of 7, such as weekdays only.
- 129 Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to any one of statements 87 to 116, wherein the radiotherapy is delivered by PBRT/WBRT with daily fractions of 3.0 Gy over 2 weeks on 5 days out of 7, such as weekdays only.

Numbered Statements for a total daily dose of about 400 mg of AZD1390

1. A method of treating a CNS tumour in a subject in need thereof comprising administering to the subject a total daily dose of about 400 mg of AZD1390, optionally in the form of a pharmaceutically acceptable salt thereof, and an amount of radiation therapy.
- 5 2. The method according to statement 1, wherein AZD1390 or a pharmaceutically acceptable salt thereof is administered before the start of radiotherapy.
3. The method according to statement 2, wherein a single dose of AZD1390 or a pharmaceutically acceptable salt thereof is administered before the start of radiotherapy.
4. The method according to statement 3, wherein said single dose is administered 1 to
10 7 days, or 2 to 6 hours before the first dose of radiotherapy.
5. The method according to any one of statements 1 to 4, wherein AZD1390 or a pharmaceutically acceptable salt thereof is administered continuously whilst radiotherapy is being administered.
6. The method according to any one of statements 1 to 4, wherein, whilst radiotherapy
15 is being delivered, AZD1390 or a pharmaceutically acceptable salt thereof is administered only on the days that radiotherapy is administered.
7. The method according to any one of statements 1 to 6, wherein when AZD1390 or a pharmaceutically acceptable salt thereof is administered on the same day as a fraction of radiotherapy, the, or the first, dose is administered at least two hours before the fraction.
- 20 8. The method according to any one of statements 1 to 7, wherein when AZD1390 or a pharmaceutically acceptable salt thereof is administered on the same day as a fraction of radiotherapy, the, or the first, dose is administered no more than six hours before the fraction.
9. The method according to statement 8, wherein the, or the first, dose of AZD1390 or a
25 pharmaceutically acceptable salt thereof is administered no more than four hours before the fraction.
10. The method according to any one of statements 1 to 9, wherein AZD1390 or a pharmaceutically acceptable salt thereof is administered after the last dose of radiotherapy in a cycle as an adjuvant phase.
- 30 11. The method according to statement 10, wherein the adjuvant phase lasts for at least 1 day, at least 3 days, at least 5 days, or at least 1 week.
12. The method according to either statement 10 or statement 11, wherein the adjuvant phase lasts up to 4 weeks, up to 3 weeks, or up to 2 weeks.
13. The method according to any one of statements 1 to 12, wherein the AZD1390 or a
35 pharmaceutically acceptable salt thereof is administered orally.

14. The method according to any one of statements 1 to statement 13, wherein the AZD1390 or a pharmaceutically acceptable salt thereof is in tablet form.
15. The method according to any one of statements 1 to 14, wherein the total daily dose of AZD1390 is up to 450 mg, 440 mg, 430 mg, 420 mg, 410 mg, or 400 mg.
- 5 16. The method according to any one of statements 1 to 15, wherein the total daily dose of AZD1390 is at least 350 mg, 360 mg, 370 mg, 380 mg, 390 mg or 400 mg.
17. The method according to any one of statements 1 to 14, wherein the total daily dose of AZD1390 is 400 mg.
18. The method according to any one of statements 1 to 14, wherein AZD1390 is
10 administered once a day.
19. The method according to statement 18, wherein the once daily dose of AZD1390 is up to 450 mg, 440 mg, 430 mg, 420 mg, 410 mg, or 400 mg.
20. The method according to either statement 18 or statement 19, wherein the once daily dose of AZD1390 is at least 350 mg, 360 mg, 370 mg, 380 mg, 390 mg or 400 mg.
- 15 21. The method according to any one of statements 1 to 14, wherein the once daily dose of AZD1390 is 400 mg.
22. The method according to any one of statements 1 to 14, wherein AZD1390 is administered twice a day.
23. The method according to statement 22, wherein the twice daily dose of AZD1390 is
20 up to 225 mg, 220 mg, 215 mg, 210 mg, 205 mg, or 200 mg.
24. The method according to either statement 22 or statement 23, wherein the twice daily dose of AZD1390 is at least 175 mg, 180 mg, 185 mg, 190 mg, 195 mg or 200 mg.
25. The method according to any one of statements 1 to 14, wherein the twice daily dose of AZD1390 is 200 mg.
- 25 26. The method according to any one of statements 1 to 25, wherein the CNS tumour is selected from glioblastoma, IDH mutant glioma (WHO Grade 2-4), ependymoma, high grade meningioma, paediatric high-grade glioma, Diffuse Intrinsic Pontine Glioma (DIPG), choroid plexus carcinoma, astrocytoma (such as Grade 4 astrocytoma), adult and/or paediatric medulloblastoma and metastatic CNS tumour (such as leptomeningeal disease).
- 30 27. The method according to statement 26, wherein the CNS tumour is glioblastoma.
28. The method according to statement 27, wherein the CNS tumour is recurrent glioblastoma.
29. The method according to statement 28, wherein the glioblastoma has unmethylated MGMT (O⁶-methylguanine-DNA methyltransferase).
- 35 30. The method according to statement 28, wherein the glioblastoma has methylated MGMT.

31. The method according to any one of statements 1 to 30, wherein the radiotherapy is intensity-modulated radiation therapy (IMRT).
32. The method according to any one of statements 1 to 30, wherein the radiotherapy is whole brain radiation therapy (WBRT) or partial brain radiation therapy (PBRT).
- 5 33. The method according to any one of statements 1 to 32, wherein the radiation therapy is fractionated radiation therapy.
34. The method according to statement 33, wherein the radiation therapy fractions are administered in sequential days.
35. The method according to statement 33, wherein the radiation therapy fractions are
10 administered for some days sequentially, with some rest days.
36. The method according to statement 35, wherein the radiation therapy fractions are administered for five days sequentially, followed by two rest days.
37. The method according to any one of statements 33 to 36, wherein the total dose of radiotherapy is at least 20 Gy, at least 30 Gy, at least 40 Gy, or at least 50 Gy.
- 15 38. The method according to any one of statements 33 to 37, wherein the total dose of radiotherapy is less than 70 Gy, less than 60 Gy, less than 50 Gy, or less than 40 Gy.
39. The method according to any one of statements 33 to 36, wherein the total dose of radiotherapy is 60 Gy.
40. The method according to any one of statements 33 to 36, wherein the total dose of
20 radiotherapy is 35 Gy.
41. The method according to any one of statements 1 to 30, wherein the radiotherapy is delivered by IMRT with daily fractions of 2.0 Gy over 4 to 6 weeks on 5 days out of 7, such as weekdays only.
42. The method according to any one of statements 1 to 30, wherein the radiotherapy is
25 delivered by IMRT with daily fractions of 3.5 Gy over 2 weeks on 5 days out of 7, such as weekdays only.
43. The method according to any one of statements 1 to 30, wherein the radiotherapy is delivered by PBRT/WBRT with daily fractions of 3.0 Gy over 2 weeks on 5 days out of 7, such as weekdays only.
- 30 44. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour, wherein said treatment comprises the separate, sequential or simultaneous administration of i) a total daily dose of about 400 mg of said AZD1390, optionally in the form of a pharmaceutically acceptable salt thereof, and ii) radiation therapy, to said subject.
- 35 45. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to statement 44, wherein the AZD1390 or a pharmaceutically acceptable salt thereof is administered before the start of radiotherapy.

46. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to statement 45, wherein a single dose of AZD1390 or a pharmaceutically acceptable salt thereof is administered before the start of radiotherapy.
47. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of
5 treatment of a CNS tumour according to statement 45, wherein the single dose is administered 1 to 7 days, or 2 to 6 hours before the first dose of radiotherapy.
48. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of statements 44 to 47, wherein AZD1390 or a pharmaceutically acceptable salt thereof is administered continuously whilst
10 radiotherapy is being administered.
49. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of statements 44 to 47, wherein, whilst radiotherapy is being delivered, AZD1390 or a pharmaceutically acceptable salt thereof is administered only on the days that radiotherapy is administered.
- 15 50. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of statements 44 to 49, wherein when AZD1390 or a pharmaceutically acceptable salt thereof is administered on the same day as a fraction of radiotherapy, the, or the first, dose is administered at least two hours before the fraction.
- 20 51. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of statements 44 to 50, wherein when AZD1390 or a pharmaceutically acceptable salt thereof is administered on the same day as a fraction of radiotherapy, the, or the first, dose is administered no more than six hours before the fraction.
- 25 52. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to statement 51, wherein the, or the first, dose of AZD1390 or a pharmaceutically acceptable salt thereof is administered no more than four hours before the fraction.
- 30 53. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of statements 44 to 52, wherein AZD1390 or a pharmaceutically acceptable salt thereof is administered after the last dose of radiotherapy in a cycle as an adjuvant phase.
54. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to statement 53, wherein the adjuvant phase lasts for
35 at least 1 day, at least 3 days, at least 5 days, or at least 1 week.

55. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to either statement 53 or statement 54, wherein the adjuvant phase lasts up to 4 weeks, up to 3 weeks, or up to 2 weeks.
56. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of
5 treatment of a CNS tumour according to any one of statements 44 to 55, wherein the AZD1390 or a pharmaceutically acceptable salt thereof is administered orally.
57. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of statements 44 to 56, wherein the AZD1390 or a pharmaceutically acceptable salt thereof is in tablet form.
- 10 58. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of statements 44 to 57, wherein the total daily dose of AZD1390 is up to 450 mg, 440 mg, 430 mg, 420 mg, 410 mg, or 400 mg.
59. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of statements 44 to 58, wherein the total
15 daily dose of AZD1390 is at least 350, 360 mg, 370 mg, 380 mg, 390 mg or 400 mg.
60. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of statements 44 to 57, wherein the total daily dose of AZD1390 is 400 mg.
61. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of
20 treatment of a CNS tumour according to any one of statements 44 to 57, wherein AZD1390 is administered once a day.
62. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to statement 61, wherein the once daily dose of AZD1390 is up to 450 mg, 440 mg, 430 mg, 420 mg, 410 mg, or 400 mg.
- 25 63. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to either statement 61 or statement 62, wherein the once daily dose of AZD1390 is at least 350, 360 mg, 370 mg, 380 mg, 390 mg or 400 mg mg.
64. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of
30 treatment of a CNS tumour according to any one of statements 44 to 57, wherein the once daily dose of AZD1390 is 400 mg.
65. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of statements 44 to 57, wherein AZD1390 is administered twice a day.
- 35 66. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to statement 65, wherein the twice daily dose of AZD1390 is up to 225 mg, 220 mg, 215 mg, 210 mg, 205 mg, or 200 mg.

67. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to either statement 65 or statement 66, wherein the twice daily dose of AZD1390 is at least 175 mg, 180 mg, 185 mg, 190 mg, 195 mg or 200 mg.
- 5 68. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of statements 44 to 57, wherein the twice daily dose of AZD1390 is 200 mg.
69. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of statements 44 to 68, wherein the CNS
- 10 tumour is selected from glioblastoma, IDH mutant glioma (WHO Grade 2-4), ependymoma, high grade meningioma, paediatric high-grade glioma, Diffuse Intrinsic Pontine Glioma (DIPG), choroid plexus carcinoma, astrocytoma (such as Grade 4 astrocytoma), adult and/or paediatric medulloblastoma and metastatic CNS tumour (such as leptomeningeal disease).
70. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of
- 15 treatment of a CNS tumour according to statement 69, wherein the CNS tumour is glioblastoma.
71. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to statement 70, wherein the CNS tumour is recurrent glioblastoma.
- 20 72. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to statement 71, wherein the glioblastoma has unmethylated MGMT (O⁶-methylguanine-DNA methyltransferase).
73. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to statement 71, wherein the glioblastoma has
- 25 methylated MGMT.
74. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of statements 44 to 73, wherein the radiotherapy is intensity-modulated radiation therapy (IMRT).
875. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of
- 30 treatment of a CNS tumour according to any one of statements 44 to 73, wherein the radiotherapy is whole brain radiation therapy (WBRT) or partial brain radiation therapy (PBRT).
76. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of statements 44 to 75, wherein the
- 35 radiation therapy is fractionated radiation therapy.

77. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to statement 76, wherein the radiation therapy fractions are administered in sequential days.
78. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of
5 treatment of a CNS tumour according to statement 76, wherein the radiation therapy fractions are administered for some days sequentially, with some rest days.
79. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to statement 78, wherein the radiation therapy fractions are administered for five days sequentially, followed by two rest days.
- 10 80. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of statements 76 to 79, wherein the total dose of radiotherapy is at least 20 Gy, at least 30 Gy, at least 40 Gy, or at least 50 Gy.
81. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of statements 76 to 80, wherein the total
15 dose of radiotherapy is less than 70 Gy, less than 60 Gy, less than 50 Gy, or less than 40 Gy.
82. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of statements 76 to 81, wherein the total dose of radiotherapy is 60 Gy.
- 20 83. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of statements 76 to 81, wherein the total dose of radiotherapy is 35 Gy.
84. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of statements 44 to 73, wherein the
25 radiotherapy is delivered by IMRT with daily fractions of 2.0 Gy over 4 to 6 weeks on 5 days out of 7, such as weekdays only.
85. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of statements 44 to 73, wherein the radiotherapy is delivered by IMRT with daily fractions of 3.5 Gy over 2 weeks on 5 days out
30 of 7, such as weekdays only.
86. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of statements 44 to 73, wherein the radiotherapy is delivered by PBRT/WBRT with daily fractions of 3.0 Gy over 2 weeks on 5 days out of 7, such as weekdays only.
- 35 87. Use of AZD1390, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of treatment a CNS tumour, wherein said treatment comprises the separate, sequential or simultaneous administration of i) a total daily dose of

about 400 mg of said AZD1390, optionally in the form of a pharmaceutically acceptable salt thereof, and ii) radiation therapy, to said subject.

88. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to statement 87, wherein AZD1390 or a pharmaceutically acceptable salt thereof is

5 administered before the start of radiotherapy.

89. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to statement 88, wherein a single dose of AZD1390 or a pharmaceutically acceptable salt thereof is administered before the start of radiotherapy.

90. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to
10 statement 89, wherein the single dose is administered 1 to 7 days, or 2 to 6 hours before the first dose of radiotherapy.

91. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to any one of statements 87 to 90, wherein AZD1390 or a pharmaceutically acceptable salt thereof is administered continuously whilst radiotherapy is being administered.

15 92. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to any one of statements 87 to 90, wherein, whilst radiotherapy is being delivered, AZD1390 or a pharmaceutically acceptable salt thereof is administered only on the days that radiotherapy is administered.

93. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to any one
20 of statements 87 to 92, wherein when AZD1390 or a pharmaceutically acceptable salt thereof is administered on the same day as a fraction of radiotherapy, the, or the first, dose is administered at least two hours before the fraction.

94. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to any one
25 of statements 87 to 93, wherein when AZD1390 or a pharmaceutically acceptable salt thereof is administered on the same day as a fraction of radiotherapy, the, or the first, dose is administered no more than six hours before the fraction.

95. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to statement 94, wherein the, or the first, dose of AZD1390 or a pharmaceutically acceptable salt thereof is administered no more than 4 hours before the fraction.

30 96. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to any one of statements 87 to 95, wherein AZD1390 or a pharmaceutically acceptable salt thereof is administered after the last dose of radiotherapy in a cycle as an adjuvant phase.

97. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to statement 96, wherein the adjuvant phase lasts for at least 1 day, at least 3 days, at least 5
35 days, or at least 1 week.

98. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to either statement 96 or statement 97, wherein the adjuvant phase lasts up to 4 weeks, up to 3 weeks, or up to 2 weeks.
99. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to any one of statements 87 to 98, wherein the AZD1390 or a pharmaceutically acceptable salt thereof is administered orally.
100. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to any one of statements 87 to statement 99, wherein the AZD1390 or a pharmaceutically acceptable salt thereof is in tablet form.
101. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to any one of statements 87 to 100, wherein the total daily dose of AZD1390 is up to 450 mg, 440 mg, 430 mg, 420 mg, 410 mg, or 400 mg.
102. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to any one of statements 87 to 101, wherein the total daily dose of AZD1390 is at least 350, 360 mg, 370 mg, 380 mg, 390 mg or 400 mg.
103. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to any one of statements 87 to 100, wherein the total daily dose of AZD1390 is 400 mg.
104. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to any one of statements 87 to 100, wherein AZD1390 is administered once a day.
105. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to statement 104, wherein the once daily dose of AZD1390 is up to 450 mg, 440 mg, 430 mg, 420 mg, 410 mg, or 400 mg.
106. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to either statement 104 or statement 105, wherein the once daily dose of AZD1390 is at least 350, 360 mg, 370 mg, 380 mg, 390 mg or 400 mg.
107. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to any one of statements 87 to 100, wherein the once daily dose of AZD1390 is 400 mg.
108. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to any one of statements 87 to 100, wherein AZD1390 is administered twice a day.
109. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to statement 108, wherein the twice daily dose of AZD1390 is up to 225 mg, 220 mg, 215 mg, 210 mg, 205 mg, or 200 mg.
110. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to either statement 108 or statement 109, wherein the twice daily dose of AZD1390 is at least 175 mg, 180 mg, 185 mg, 190 mg, 195 mg or 200 mg.
111. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to any one of statements 87 to 100, wherein the twice daily dose of AZD1390 is 200 mg.

112. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to any one of statements 87 to 111, wherein the CNS tumour is selected from glioblastoma, IDH mutant glioma (WHO Grade 2-4), ependymoma, high grade meningioma, paediatric high-grade glioma, Diffuse Intrinsic Pontine Glioma (DIPG), choroid plexus carcinoma, astrocytoma (such as Grade 4 astrocytoma), adult and/or paediatric medulloblastoma and metastatic CNS tumour (such as leptomeningeal disease).
113. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to statement 112, wherein the CNS tumour is glioblastoma.
114. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to statement 113, wherein the CNS tumour is recurrent glioblastoma.
115. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to statement 114, wherein the glioblastoma has unmethylated MGMT (O⁶-methylguanine-DNA methyltransferase).
116. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to statement 114, wherein the glioblastoma has methylated MGMT.
117. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to any one of statements 87 to 116, wherein the radiotherapy is intensity-modulated radiation therapy (IMRT).
118. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to any one of statements 87 to 116, wherein the radiotherapy is whole brain radiation therapy (WBRT) or partial brain radiation therapy (PBRT).
119. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to any one of statements 87 to 118, wherein the radiation therapy is fractionated radiation therapy.
120. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to statement 119, wherein the radiation therapy fractions are administered in sequential days.
121. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to statement 119, wherein the radiation therapy fractions are administered for some days sequentially, with some rest days.
122. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to statement 121, wherein the radiation therapy fractions are administered for five days sequentially, followed by two rest days.
123. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to any one of statements 119 to 122, wherein the total dose of radiotherapy is at least 20 Gy, at least 30 Gy, at least 40 Gy, or at least 50 Gy.
124. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to any one of statements 119 to 123, wherein the total dose of radiotherapy is less than 70 Gy, less than 60 Gy, less than 50 Gy, or less than 40 Gy.

125. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to any one of statements 119 to 122, wherein the total dose of radiotherapy is 60 Gy.
126. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to any one of statements 119 to 122, wherein the total dose of radiotherapy is 35 Gy.
- 5 127. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to any one of statements 87 to 116, wherein the radiotherapy is delivered by IMRT with daily fractions of 2.0 Gy over 4 to 6 weeks on 5 days out of 7, such as weekdays only.
128. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to any one of statements 87 to 116, wherein the radiotherapy is delivered by IMRT with daily fractions of
- 10 3.5 Gy over 2 weeks on 5 days out of 7, such as weekdays only.
129. Use of AZD1390, or a pharmaceutically acceptable salt thereof, according to any one of statements 87 to 116, wherein the radiotherapy is delivered by PBRT/WBRT with daily fractions of 3.0 Gy over 2 weeks on 5 days out of 7, such as weekdays only.

Claims

1. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour, wherein said treatment comprises the separate, sequential or simultaneous administration of i) a total daily dose of about 300 mg of said AZD1390,
5 optionally in the form of a pharmaceutically acceptable salt thereof, and ii) radiation therapy, to said subject.
2. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to claim 1, wherein AZD1390 or a pharmaceutically acceptable salt thereof is administered continuously whilst radiotherapy is being
10 administered.
3. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to either claim 1 or claim 2, wherein, whilst radiotherapy is being delivered, AZD1390 or a pharmaceutically acceptable salt thereof is administered only on the days that radiotherapy is administered.
- 15 4. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of claims 1 to 3, wherein AZD1390 or a pharmaceutically acceptable salt thereof is administered after the last dose of radiotherapy in a cycle as an adjuvant phase.
5. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of
20 treatment of a CNS tumour according to any one of claims 1 to 4, wherein the AZD1390 or a pharmaceutically acceptable salt thereof is administered orally.
6. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of claims 1 to 5, wherein the AZD1390 or a pharmaceutically acceptable salt thereof is in tablet form.
- 25 7. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of claims 1 to 6, wherein the total daily dose of AZD1390 is up to 340 mg, 330 mg, 320 mg, 310 mg, or 300 mg.
8. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of claims 1 to 7, wherein the total daily
30 dose of AZD1390 is at least 250, 260 mg, 270 mg, 280 mg, 290 mg, or 300 mg.
9. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of claims 1 to 6, wherein the total daily dose of AZD1390 is 300 mg.
10. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of
35 treatment of a CNS tumour according to any one of claims 1 to 9, wherein AZD1390 is administered once a day.

11. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of claims 1 to 9, wherein AZD1390 is administered twice a day.
12. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of
5 treatment of a CNS tumour according to any one of claims 1 to 11, wherein the CNS tumour is selected from glioblastoma, IDH mutant glioma (WHO Grade 2-4), ependymoma, high grade meningioma, paediatric high-grade glioma, Diffuse Intrinsic Pontine Glioma (DIPG), choroid plexus carcinoma, astrocytoma (such as Grade 4 astrocytoma), adult and/or paediatric medulloblastoma and metastatic CNS tumour (such as leptomeningeal disease).
- 10 13. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to claim 12, wherein the CNS tumour is glioblastoma.
14. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to claim 13, wherein the CNS tumour is primary glioblastoma.
- 15 15. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of claims 1 to 14, wherein the radiotherapy is intensity-modulated radiation therapy (IMRT).
16. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of
20 treatment of a CNS tumour according to any one of claims 1 to 14, wherein the radiotherapy is whole brain radiation therapy (WBRT) or partial brain radiation therapy (PBRT).
17. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of claims 1 to 16, wherein the radiation therapy is fractionated radiation therapy.
18. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of
25 treatment of a CNS tumour according to claim 17, wherein the radiation therapy fractions are administered in sequential days.
19. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to claim 17, wherein the radiation therapy fractions are administered for some days sequentially, with some rest days.
- 30 20. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to claim 19, wherein the radiation therapy fractions are administered for five days sequentially, followed by two rest days.
21. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of claims 17 to 20, wherein the total dose
35 of radiotherapy is at least 20 Gy, at least 30 Gy, at least 40 Gy, or at least 50 Gy.

22. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of claims 17 to 21, wherein the total dose of radiotherapy is less than 70 Gy, less than 60 Gy, less than 50 Gy, or less than 40 Gy.
23. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of
5 treatment of a CNS tumour according to any one of claims 17 to 20, wherein the total dose of radiotherapy is 60 Gy.
24. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of claims 17 to 20, wherein the total dose of radiotherapy is 35 Gy.
- 10 25. AZD1390, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a CNS tumour according to any one of claims 1 to 14, wherein the radiotherapy is delivered by IMRT with daily fractions of 2.0 Gy over 4 to 6 weeks on 5 days out of 7, such as weekdays only.