

## **CCF IRB CC879**

### **Full Title**

A Phase I Dose-Escalation Study of XL765 in combination with Temozolomide in Subjects with malignant Gliomas

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## **Objectives**

### **Primary Objectives:**

The primary objectives of this study are:

- To evaluate the safety and tolerability of daily oral administration of XL765 in combination with TMZ in subjects with AG or glioblastoma currently stable on a maintenance TMZ dose of 200 mg/m<sup>2</sup>/day given on Days 1-5 on a 28-Day cycle
- To determine the maximum tolerated dose (MTD) of XL765 in combination with TMZ in subjects with AG or glioblastoma currently stable on a maintenance TMZ dose

## **Eligibility**

### **Inclusion**

1. The subject has a histologically confirmed intracranial Grade III or Grade IV astrocytic tumor (WHO criteria 2007, Louis et al. 2007), anaplastic oligodendroglioma, or anaplastic oligoastrocytoma.
2. The subject has received at least one cycle of TMZ at a dose of 200 mg/m<sup>2</sup>/day administered on Days 1-5 of a 28-day cycle, without unacceptable (ie, requiring a dose interruption or reduction) toxicity and without clinical or radiologic progression of their disease. This may be decreased to 175 mg/m<sup>2</sup>/day if the combinations of TMZ 200 mg/m<sup>2</sup>/day with XL765 are not well tolerated (see Section 3.4.2 and Table 3-2).
3. The subject is expected to receive at least 3 more cycles of TMZ treatment to be given in combination with XL765.
4. The subject has a Karnofsky performance status of 70 or more.

5. The subject has organ and marrow function as follows:
  1. Absolute neutrophil count  $\geq 1500/\text{mm}^3$
  2. Platelets  $\geq 100,000/\text{mm}^3$
  3. Hemoglobin  $\geq 9 \text{ g/dL}$
  4. Bilirubin  $\leq 1.5 \times$  the upper limit of normal
  5. Serum creatinine  $\leq 1.5 \times$  the upper limit of normal or calculated creatinine clearance  $\geq 60 \text{ mL/min}$
  6. Alanine aminotransferase and aspartate aminotransferase  $\leq 1.5 \times$  the upper limit of normal.
  7. Prothrombin time/ International Normalized Ratio (PT/ INR) or partial thromboplastin time (PTT)  $\leq 1.3 \times$  the laboratory upper limit of normal
6. The subject has a fasting plasma glucose (FPG)  $\leq 160 \text{ mg/dL}$  at screening.
7. At least 15 unstained 4-10 micron tissue sections ( $\geq 15$  slides, without coverslips), archival or fresh, or a tissue block, of the subject's tumor are identified and designated for central laboratory analysis where allowed by local regulatory bodies (including Institutional Review Board [IRB]/ Ethics Committee [EC] policies).
8. Sexually active subjects (male and female) must use accepted methods of contraception during the course of the study and for 3 months after the last dose of XL765.
9. Female subjects of childbearing potential must have a negative serum pregnancy test at screening. Females of childbearing potential are defined as sexually mature women without prior hysterectomy or who have had any evidence of menses in the past 12 months. Women who have been amenorrheic for 12 or more months are still considered to be of childbearing potential if the amenorrhea is possibly due to prior therapy such as chemotherapy, anti-estrogens, or ovarian suppression.
10. The subject has not had a diagnosis of non-glioma malignancy other than:
  1. Surgically excised non-melanoma skin cancer or in situ carcinoma of the cervix
  2. A malignancy diagnosed 2 or more years ago if the subject has had no evidence of disease for 2 years prior to screening for this study.
11. A brain magnetic resonance imaging (MRI) must be performed within 14 days prior to the first dose of XL765 and with the subject on a glucocorticoid dose that has been stable for at least 5 days. If the glucocorticoid dose is changed between the date of imaging and the first dose of XL765, a new baseline MRI is required.
12. The subject is  $\geq 18$  years old.

The subject is capable of understanding and complying with the protocol and has signed the informed consent document.

## **Exclusions**

1. Subjects who have progressed on TMZ.
2. Subject has evidence of acute intracranial or intratumoral hemorrhage > Grade 1 either by MRI or CT scan. Subjects with resolving hemorrhage changes, punctate hemorrhage, or hemosiderin may enter the study.
3. The subject has received any of the following:
  1. Cytotoxic chemotherapy other than TMZ (including investigational cytotoxic agents) or biologic agents (antibodies, immune modulators, cytokines) within 4 weeks or has received nitrosoureas or mitomycin C within 6 weeks before the first dose of XL765
  2. A small-molecule kinase inhibitor (including investigational small-molecule kinase inhibitors) or non-cytotoxic hormonal agent within 7 days or 5 half-lives of the drug or active metabolites prior to the first dose of XL765, whichever is longer
  3. Any prior therapy with a PI3K inhibitor
  4. Other investigational therapy within 28 days of the first dose of XL765
  5. Radiation therapy within 28 days before the first dose of XL765
  6. For subjects taking glucocorticoids (eg, prednisone and dexamethasone) to control brain edema, modification to their glucocorticoid dose within 5 days of their first dose of XL765

NOTE: Any questions related to the timing from prior therapies should be discussed and resolved by the investigator and the sponsor prior to the subject entering the study.

4. The subject has not recovered to baseline or CTCAE Grade  $\leq 1$  (except alopecia) due to any prior treatment. Subjects with Grade 2 toxicities from prior therapy deemed irreversible may be eligible if agreed to by the sponsor and investigator.
5. The subject has a history of diabetes mellitus. Subjects who have developed glucose intolerance due to steroid treatment but currently have a FPG  $\leq 160$  mg/dL are eligible.
6. The subject is taking enzyme-inducing anti-convulsants (see Appendix E) within 14 days before the first dose of XL765.
7. The subject is taking valproic acid within 14 days before the first dose of XL765.
8. The subject is receiving anticoagulation with therapeutic doses of warfarin or other coumarin derivatives. NOTE: low-dose warfarin ( $\leq 1$  mg/day), heparin, and low-molecular-weight heparin are permitted.
9. The subject has an uncontrolled intercurrent illness including but not limited to an active infection or hypertension that would limit compliance with study requirements.
10. The subject has had congestive heart failure, unstable angina, or a myocardial infarction within 3 months of entering the study.
11. The subject has a corrected QT interval (QTc) > 460 ms at screening.
12. The subject is pregnant or breastfeeding.

13. The subject is known to be positive for the human immunodeficiency virus.  
(HIV testing is not required for eligibility.)
14. The subject has a previously identified allergy or hypersensitivity to components of the XL765 formulation or TMZ, including the active metabolite 5-(3-methyltriazene-1-yl)-imidazole-4-carboxamide (MTIC).

The subject is unable or unwilling to abide by the study protocol or cooperate fully with the investigator or designee.