A Phase 1 Safety and Dose Finding Study of 131I -TLX101 Plus Standard of Care in Patients with Newly Diagnosed Glioblastoma

Published: 18-01-2023
Last updated: 08-02-2025

This study has been transitioned to CTIS with ID 2024-515466-13-00 check the CTIS register for the current data. The purpose of this study is to assess the safety and tolerability of intravenous 131I-TLX101 administered concomitantly and...

Ethical review	Approved WMO
Status	Pending
Health condition type	Nervous system neoplasms malignant and unspecified NEC
Study type	Interventional

Summary

ID

NL-OMON53391

Source
ToetsingOnline

Brief title
IPAX-2

Condition

- Nervous system neoplasms malignant and unspecified NEC
- Nervous system neoplasms malignant and unspecified NEC

Synonym
Glioblastoma - Brain Tumor

Research involving
Human

Sponsors and support

Primary sponsor: Telix Pharmaceuticals (Innovations) Pty Ltd
Source(s) of monetary or material Support: Telix Pharmaceuticals (Innovations) Pty Ltd

Intervention

Keyword: Dose-finding, Glioblastoma, Radiotherapy, Safety

Outcome measures

Primary outcome

- To determine the safety and tolerability of 131I-TLX-101 in combination with standard of care treatment in newly diagnosed Glioblastoma (GBM) patients, by determining the Dose Limiting Toxicities (DLT), Maximum Tolerated Dose (MTD) and Recommended Phase 2 Dose (RP2D). This will be done by assessing TEAEs type (treatment emergent adverse events) type according to MedDRA, frequency, severity according to NCI CTCAE V5.0, seriousness, and relationship of study treatment will be assessed. Laboratory abnormalities will be assessed according to the NCI CTCAE V5.0.
- Incidence rate and the grade (severity) of DLTs based on the occurrence of Adverse Events (AEs) reported according to the NCI CTCAE v5.0. DLTs include any grade >= 3 events considered possibly related to the study drug, but excludes cerebral oedema, and haematological toxicity.

Secondary outcome

- 1-year overall survival rate of patients treated with 131I-TLX-101 plus standard of care treatment.
- 2-year overall survival rate of patients treated with 131I-TLX-101 plus standard of care treatment.

- To determine Progression Free Survival (PFS) from the date of enrolment to the date of progression or death for any cause, whichever comes first, assessed up to 51±1 weeks.

- To determine best Objective Response Rate (ORR) in patients with partial response at weeks 7, 15, 23, 31, 43±1, and 51±1 as defined by modified Response in Neuro-Oncology (mRANO)* criteria.

- To determine ORR in patients with stable disease at weeks 7, 15, 23, 31, 43±1, and 51±1 as defined by mRANO criteria

- To determine safety throughout study completion for each participant, for a minimum of 51±1 weeks

- To determine Quality of Life (QoL) as determined using the EORTC QLQ-C30 questionnaire and Quality of Life Questionnaire - Brain Neoplasm (QLQBN20) questionnaires, and neurocognitive tests: Controlled Oral Word Association Test (COWA test), Hopkins Verbal Learning Test-Revised (HVLT-R test), and Trail Making Test (TMT)

Study description

Background summary

Glioblastoma is the most aggressive, invasive, and frequently occurring type of primary astrocytomas. GBM accounts for over 60% of all central nervous system (CNS) tumours, with extremely poor prognosis. Despite of ideal multidisciplinary treatment, including maximal surgical resection, followed by radiotherapy plus concomitant and maintenance TMZ, almost all patients experience tumor progression. Metabolic reprogramming is vastly identified as a hallmark of malignancy. The proliferation of cancer cells is highly dependent on acquisition of exogenous amino acids, where its uptake and metabolism are aberrantly upregulated in several types of cancer, including GBM. Transmembrane uptake of amino acids is strictly regulated by Amino Acid Transporters (AAT).

Numerous studies have suggested that LAT-1 expression in cancerous tissues is higher than that in normal tissues and LAT-1 expression is correlated with the growth and proliferation of cancer cells, thus making LAT-1 an ideal target for cancer therapy and radio-imaging.
A combined treatment strategy is suggested to advance GBM treatment efficacy, in order to address the following challenges:
i) the infiltrative character of the tumour beyond a safety margin makes it impossible to surgically resect all GBM cells,
ii) systemic chemotherapy reaches the cerebral compartment only to a limited extent, and
iii) hypoxia and an acidotic milieu of the intratumoral and peritumoral microenvironment reduce the efficacy of External Beam Radiation Therapy (EBRT) and chemotherapy.

Currently, Targeted Radiation Therapy (TRT) is considered a potential additive and potent treatment for primary GBM in combination with standard therapy, or as an auxiliary treatment when the tumour tissue seems to be radio and/or chemo-resistant. In the case for EBRT, TRT such as 131I-IPA, causes DNA damage and is therefore likely to be enhanced by combination with chemotherapeutic radiosensitisers such as Temozolomide (TMZ).
Upon intravenous administration,131I-IPA actively crosses the BBB and accumulate specifically in gliomas, presumably via LAT-1 and ASC (Alanine, Serine and Cystine) amino acid transporters, which are overexpressed in malignant glioma cells.
Notwithstanding intense preclinical research and clinical trials, standard therapy has not changed over the past decade. Generally, a combined treatment strategy is suggested to advance GBM treatment efficacy, and to address the following challenges: the infiltrative character of the tumour beyond a safety margin makes it impossible to surgically resect all GBM cells; systemic chemotherapy reaches the cerebral compartment only to a limited extent and hypoxia and an acidotic milieu of the intratumoral and peritumoral microenvironment reduce the efficacy of EBRT and chemotherapy. TRT is considered a potential additive and potent treatment for primary GBM in combination with standard therapy. In addition,
131I-IPA has been well tolerated by the patients to whom it was administered.
The present study aims to investigate the safety and efficacy of 131I-IPA in combination with chemoradiation (consisting of TMZ and EBRT) in newly diagnosed GBM patients

Study objective

This study has been transitioned to CTIS with ID 2024-515466-13-00 check the CTIS register for the current data.

The purpose of this study is to assess the safety and tolerability of intravenous 131I-TLX101 administered concomitantly and sequentially with standard of care in patients newly diagnosed with GBM, to determine the MTD and

the R2PD.

Study design

This is an open label, single arm, parallel-group, multicentre, and dose finding study to evaluate ascending radioactive dose levels of 4-L-[131I] iodo-phenylalanine (c.a.131I-IPA) administered intravenously in combination with best standard of care (SoC) in newly diagnosed Glioblastoma Multiforme patients.
Approximately 12 participants may be enrolled and treated in cohorts according to a *3+3* study design with SoC consisting of radiotherapy of 60 Gy/30 fractions for 6 weeks plus 75 mg/m2 TMZ daily (chemoradiotherapy), followed by 4 weeks of treatment break. Participants will receive a maintenance treatment with 6 maintenance cycles of TMZ 150-200 mg/m2 on Days 1 to 5 q28. 131I-IPA will be administered in 2 fractions corresponding to * full dose activity, via IV infusion. Participants will be admitted to the hospital or research facility at Day 0 and receive their first dose of IP prior to the commencement of chemoradiation therapy and admitted again on Day 56, after completion of chemoradiation therapy, to receive the second dose of IP, and discharged at Day 60±3. The first dose of 131I-IPA must be given at least a week prior to commencement of chemoradiotherapy, and the second dose of 131I-TLX101 must be given 10 days after completion of chemoradiotherapy.

A classic *3+3* study design will be followed to establish DLT, MTD and RP2D. Initially, 3 participants will be enrolled to a cohort, the occurrence of a single drug related, grade >=3 DLT in one these 3 patients will prompt the enrolment of an additional 3 participants to that same cohort. If more than one grade >=3 DLT occurs in <=6 participants in a dosing cohort, dose escalation will be stopped, and this dose level will be identified as the non-tolerated dose. Doses between the non-tolerated dose and the preceding lower dose, where <= 1 grade >=3 DLT occurred, may be explored to more precisely define the MTD.

Intervention

On Day 0 of the study, the patient will receive their first dose of 131-IPA by intravenous infusion. On Day 7 standard treatment will start with chemotherapy (temozolomide=TMZ) and radiotherapy and will last for 6 weeks. TMZ will be administered with a dosage of 75mg/m2 and radiotherapy of 60Gy/30 fractions. On Day 56, the second dose 131I-IPA will be administered, only after completion of the standard treatment on that same day.

Four weeks after completing the chemoradiation (TMZ + EBRT), TMZ is administered for an additional 6 cycles of maintenance treatment. Dosage in Cycle 1 (maintenance) is 150 mg/m2 once daily for 5 days followed by 23 days without treatment. After, that another 5 cycles of each 28 days will follow, during each first 5 days TMZ will be administered. At the start of the 2nd

cycle the dose can be escalated to 200 mg/m2, depending on safety and lab values.

Study burden and risks

Participation in this study can have some risks and cause some burden for each participant. The study consists out of 16 study-visits. These visits can cost extra time compared to regular visits. During the study, 14 times blood samples will be drawn (in total about 150 ml), 5 times an ECG will be done, and several scans will be made (18F-FET PET scan, an MRI and a SPECT), which can cause some discomfort. In addition, during the study each participant will be asked 7 times to complete questionnaires. Also 4 times neurological assessments will be conducted. Seven times a physical examination will be performed.
After administering 131I-IPA (2 times) each participant will have to stay in an isolation room in the hospital for up to 6-7 days.
Administering 131I-IPA can also cause some discomfort and risks. This can be: diarrhea, feeling tired (fatigue), mild allergic reaction (i.e. rash), nausea, vomiting, stomach pain (abdominal pain), higher chance of getting infections, low levels of white blood cells, anemia, coagulation disorders and with it bruising, loss of weight, dizziness, neck pain or stiffness, headache, hiccups, flushing of the skin.

Contacts

Public
Telix Pharmaceuticals (Innovations) Pty Ltd

Suite 401, Flemington Road 55
North Melbourne VIC 3051
AU
Scientific
Telix Pharmaceuticals (Innovations) Pty Ltd

Suite 401, Flemington Road 55
North Melbourne VIC 3051
AU

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Understand and voluntarily sign the informed consent form prior to any study relatedprocedure and/or assessments being conducted.
2. Are Male or Female, and aged 18 and older, at the time of signing the informed consent.
3. Have histologically confirmed intracranial glioblastoma (per WHO 2021 definition) following surgical resection. Tumours primarily localised in the infratentorial compartment will be excluded.
4. Have had prior surgery for glioblastoma, but no systemic therapy or radiation therapy for
GBM.
5. Have a Karnofsky Performance Status >=70.
6. Plan to begin chemoradiation therapy 3-6 weeks after surgical resection with Stupp regimen.
7. Have adequate organ function at Screening:
7.1 Bone marrow:
7.1.1 Leukocytes >=3x10^9/L
7.1.2 Absolute neutrophil count >=1.5x10^9/L
7.1.3 Platelets >=100x10^9/L
7.1.4 Haemoglobin >=9g/dL
7.2 Liver function:
7.2.1 Total bilirubin <=1.5×the upper limit of normal (ULN). For patients with known Gilbert*s Syndrome <=3×ULN is permitted
7.2.2 Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) <=2.5×ULN
7.3 Renal function:
7.3.1 Serum/plasma creatinine <=1.5×ULN or creatinine clearance >=50 mL/min
8. Have at least 6 slides without staining or a tissue block (frozen or paraffin-embedded) available from a previous biopsy or surgery (tumour sample previously archived).
9. Have the capacity to understand the study and be able and willing to comply with all protocol requirements, including compliance with the radiation protection guidelines (including hospital admissions and isolation) that are applied by the treating institution to protect their contacts and the public.
10. Agree to practice adequate precautions to prevent pregnancy to avoid potential problems associated with radiation exposure to the unborn child.
11. Females must have a negative pregnancy test at screening and on dosing day,

must not be lactating.

Exclusion criteria

1. Are unable to provide signed informed consent
2. Have had prior treatment for glioma, excluding surgery.
3. Are unable to undergo contrast-enhanced MRI.
4. Intend to be treated with tumor-treating fields prior to progression.
5. Have a history or evidence of delayed-type hypersensitivity (DTH)-dependent chronic infection (e.g., tuberculosis, systemic fungal or parasitic infection), potentially exacerbating under systemic corticoid therapy.
6. Have a known history of allergy TMZ, any excipient in the study medication or any other intravenously administered human proteins/peptides/antibodies.
7. Have haemostaseologic conditions, precluding catheterisation or invasive procedures.
8. Have phenylketonuria
9. Have any medical condition that in the opinion of the Investigator may interfere with the participant*s ability to adhere to the study or may impose a risk to the participant*s health.
10. Major trauma including major surgery (such as abdominal/cardiac/thoracic surgery) within 3 weeks of administration of study treatment except surgery on primary tumour.
11. Pregnant, breastfeeding or planning to get pregnant during the duration of the study.
12. Requirement of chronic administration of high dose corticosteroids or other immunosuppressant drugs. Limited or occasional use of corticosteroids to treat or prevent acute adverse reactions is not considered an exclusion criterion.
13. Have presence of active and uncontrolled infections or other severe concurrent disease, which, in the opinion of the investigator, would place the participant at undue risk or unable to comply with study requirements. HIV-positive participants may be included in the study if they are on a stable dose of anti-retroviral therapy.
14. Have concurrent malignancies (except: basal cell carcinoma, in situ breast cancer) unless the patient has been disease-free without intervention for at least 2 years.
15. Have taken growth factors or immunomodulatory agents within 7 days prior to the administration of study treatment.
16. Have serious, non-healing wound, ulcer, or bone fracture.
17. Have a requirement of concurrent use of other anti-cancer treatments or agents other than study medication.
18. Have received any other IMP within 90 days prior to the planned administration of study drug.
19. Have uncontrolled Hashimoto*s or Grave*s disease
20. Have on-going and unresolved Grade >= 1 AEs following surgical resection

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-03-2023
Enrollment:	3
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	not available yet
Generic name:	131I-IPA

Ethics review

Approved WMO Date:	18-01-2023
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	28-03-2023
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	09-10-2023
Application type:	Amendment
Review commission:	METC NedMec

Approved WMO Date:	17-10-2023
Application type:	Amendment
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2024-515466-13-00
EudraCT	EUCTR2022-003038-38-NL
ClinicalTrials.gov	NCT0540744/EudraCTnr:2022-003038-38
CCMO	NL82923.041.22