TLX101 for Brain Cancer
IPAX-1 Study Update

23rd December 2019
Executive summary

• Study recruiting to plan, 5/6 sites open (Australian site open early 2020)
• Both single and multi-dose (fractionated) cohorts are recruiting
• Clear evidence of tumour targeting from imaging
• Well tolerated, no serious adverse events (SAEs)
• Disease stabilisation observed in patients with recurrent glioblastoma in both cohorts (single and fractionated)
• Negligible radiation exposure to the rest of the body
• First study phase / dose-escalation will complete during Q2 2020 with mid-2020 readout that will be used for an FDA/EMA consultation
Glioblastoma multiforme (GBM)

- 300,000 people worldwide diagnosed with brain cancer and 240,000 deaths per year \(^1\)

- With an incidence rate of approx. 3 in 100,000, over half of all brain cancers are GBM – the most common and aggressive primary brain cancer diagnosed in adults

- Initial treatment with surgery, external beam radiation therapy (EBRT), chemotherapy has limited success:
  - Half of all patients survive between 12 – 18 months
  - 25% of patients survive for >12 months, 5% for 5 years
  - Once GBM recurs, most patients have rapid progression of their disease within 2 – 3 months

Reference: (1) Globocan 2018
TLX101 for GBM (\(^{131}\text{I}-\text{IPA}\))

**Targeting Agent:** 4-Iodo-L-phenylalanine (IPA)
- Iodinated synthetic amino acid

**Payload:** \(^{131}\text{I}\) (iodine-131)
- Beta radiation for therapy
- Gamma radiation for imaging

**Target:** LAT-1
- Amino acid transporter
- Highly expressed in GBM
- Expression correlated with grade of GBM

**Description:**
- Small molecule amino acid derivative (L-phenylalanine) taken up by the LAT-1 amino acid transporter for treatment of gliomas
- Both radiation delivery and radiation sensitization

**Technology Origin:**
- SPECT imaging radiotracer (\(^{123}\text{I}-\text{IPA}, \(^{124}\text{I}-\text{IPA}\))
- Pilot clinical use and case series (\(^{131}\text{I}-\text{IPA}\))

**Clinical Status:**
- Phase I/II dose exploration and preliminary efficacy evaluation

**Unmet Need:**
- Orphan drug designation granted, EU and US
### Historical clinical experience

<table>
<thead>
<tr>
<th>Pilot Use (Hellwig 2005)</th>
<th>Case Series</th>
<th>PK and Dosimetry (Samnick 2002)</th>
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<tbody>
<tr>
<td>Tumour targeting and diagnostic usefulness (proof-of-concept) 123I-IPA diagnostic radiotracer for detection of malignant gliomas and other cerebral pathologies in vivo</td>
<td>Named patient use at two sites in Germany Centre for Molecular Radiotherapy and Molecular Imaging, ZBB, Bad Berka (n = 6; Baum 2011) University Hospital Wurzburg (n = 5; Verburg 2013)</td>
<td>Evaluate biodistribution and dosimetry</td>
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#### Objective
- **Patients**: 45
- **IPA dose**: 250 MBq 123I-IPA

#### Results
- **45 y/o male, multiple XRT**
- Treated with 2 GBq 131I-IPA single dose IV
- No acute, sub-acute or delayed toxicity
- Continuous tumour regression over 10 months
- Patient remained professionally active for 24 months
- Survived > 40 months (with further therapy)

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![BL](image1.png) 6 weeks

![c](image2.png) 10 mths

Reference: Baum RP 2011
IPAX-1: A study of ‘IPA’ + external beam radiation therapy (EBRT)

Study Aim
➢ To evaluate the safety and effectiveness of TLX101 combined with EBRT for treating patients with recurrent GBM (rGBM)

Two Active Treatments
➢ $^{131}$I-IPA as a single or divided dose (3 fractions) plus EBRT in 18 x 2 Gy fractions

Main Study Objectives
• Safety:
  ➢ Identify the maximum tolerated dose (MTD) of $^{131}$I-IPA
  ➢ Evaluate feasibility of fractionated (i.e. divided doses) $^{131}$I-IPA administration
  ➢ Evaluate the amount of radiation delivered to the tumour (radiation absorbed dose)
  ➢ Confirm biodistribution and absorbed doses to the rest of the body

• Efficacy:
  ➢ Explore the anti-tumour effect of $^{131}$I-IPA + EBRT combination therapy
IPAX-1 study design

Multi-centre: EU and Australian sites

Open label, single arm: all patients receive TLX101 + EBRT

Dose-finding: increasing doses to find the most suitable dose for further study

Phase I/II: establish safety and then enroll more patients to test efficacy

Patients with rGBM

Phase 1: TLX101 + EBRT

- TLX101 2 GBq single dose or in three fractions (x 3f) n=10
- 4 GBq x 3f
- 6 GBq x 3f
- 8 GBq x 3f

DSMB (3) review
- Safety and efficacy
- Determine Phase 2 dose

Phase 2: TLX101 + EBRT
- n = 12

Expansion cohort (4) n = 10

1) Comparing single vs fractionated dosing at 2GBq
2) Fractionated dosing, n=3 until maximum tolerated dose determined
3) Drug safety monitoring board
4) If evidence of efficacy observed in Phase 2
Six international IPAX-1 sites: leading neuro-oncology centres
Global manufacturing footprint for TLX101

Telix has established a supply chain and manufacturing footprint for TLX101 that will support both further clinical studies and early commercialisation.
Study progress to date

• 5 / 6 sites are recruiting
  • Belgian, Netherlands and Austrian regulatory approvals granted
  • Australian site yet to come online but will commence early 2020. Both TGA CTN and ethics approvals are in place

• Both single and fractionated dose cohorts have recruited patients
  • Disease stabilisation seen in all patients so far
  • First patients enrolled in July are still clinically stable and have not progressed
  • Clear targeting of TLX101 by SPECT imaging
  • Well tolerated, no serious adverse events (SAEs) reported
  • Preliminary data suggests fractionated treatment may be more efficacious than single dose
  • No evidence of hematologic toxicity so far
  • Patients have generally been able to remain off corticosteroids

• Most common adverse events
  • Nausea, fatigue, dry mouth

MRI at baseline (L) and 5 months (R) after TLX101
Biodistribution: imaging by SPECT \(^{(1)}\)

- Well tolerated
- Excellent dose targeting to the brain
- Minimal radiation exposure elsewhere (whole body)
- Brain is the dose-limiting organ

\(^{(1)}\) Single Photon Emission Computed Tomography
Kinetics / clearance (tumour uptake)

SPECT imaging data at 30 minutes (Panel A), 3.5 hours (Panel B) and 48 hours (Panel C) following single administration of TLX101 (1.86 GBq)

There is clear tumour uptake and retention, consistent with previous clinical experience.
2020 study milestones

- **Complete Phase I recruitment (n = 20)**
  - Q1

- **Initiate Phase II**
  - Q2
  - Determine Phase II dose

- **Complete Phase II recruitment (n = 12)**
  - Q3
  - Open Phase II expansion cohort (n = 10)
  - Q4

High awareness among regulators of the significant unmet medical need of GBM

- TLX101 granted orphan drug designation in both the US and EU

The IPAX-1 design – open-label with regular data review – enables “rolling” regulatory consultation

- Mid-2020: present data from Phase I patients to FDA/EMA
- Discuss options for accelerated development and review, including expanded access (pending data outcomes)
Plan beyond IPAX-1

- **US: Strong interest in TLX101 at major tertiary referral centres for GBM**
  - Investigator-initiated trials (IIT) under development with several leading cancer centres
  - Initiate once IPAX-1 Phase I data identifies recommended dose
  - Potential for expanded access program if planned FDA consultation is favourable (planned end-Q2 2020)

- **Multiple indication expansion opportunities:**
  - Pediatric brain cancer
  - Newly-diagnosed GBM
  - Other LAT-1 expressing cancers – brain and other cancer types
See it. Treat it.

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