CITADEL-123. *TRIAL IN PROGRESS* A Phase I clinical trial to assess the activity of I-123 Poly Adenosine Diphosphate Ribose Polymerase I inhibitor (^{123}I-ATT001) directly administered in subjects with relapsed glioblastoma (rGBM)

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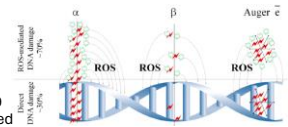
Background

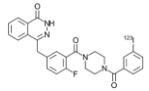
PARP1 is upregulated at levels of mRNA, protein, and enzyme activity in a number of cancers, including ovarian cancer, hepatocellular cancer, colorectal cancer, small cell lung cancer, head and neck and leukemia

PARP1 is consistently over-expressed in GBM but barely detectable in the normal brain (Fulton 2018)

Auger electron emitters exhibit low cellular toxicity during transit in blood or bone marrow.

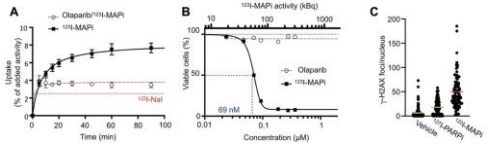
Iodine-123 is a particularly powerful Auger-emitter because it also emits a 159 keV γ-ray, which can be used for SPECT/CT imaging and disease monitoring





^{123}I-ATT001 is an investigational iodine-123 labelled therapeutic PARPi which will be explored in adult patients with PARP1 expressing solid tumours

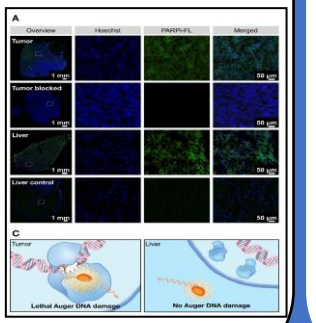
^{123}I-ATT001 *in vitro* effects on cellular uptake and viability



(A) U251 GBM cell line ^{123}I-ATT001 (MAPi) cellular uptake. Blocking with 100-fold Olaparib incubation before treatment. Red line is sodium iodide. Michaelis-Menten curve fitting. (B) Alamar Blue assay comparing ^{123}I-ATT001 with Olaparib at similar molar concentrations. ^{123}I-ATT001 EC50=69 nM. Four-parameter nonlinear fit variable slope. (C) Quantification of γ-H2AX foci in cell nuclei after treatment with ^{123}I-ATT001 (n = 85), 127I-ATT001 (n = 125), and vehicle control (n = 140). ***p-value < 0.001, Kruskal-Wallis test. (Carney 2018)

Subcellular localization of PARPi-FL

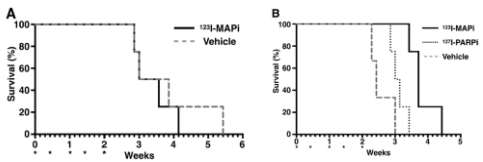
Mouse tissues injected with PARPi-FL and Hoechst were collected. PARPi-FL uptake in tumors was prevented by 100-fold extra Olaparib 1 h before injection. Injecting vehicle IV controlled to liver. (C) Auger radiation-specific toxicity depends on the isotope being near the target DNA, which liver cells do not experience due to lower DNA damage and small continuing DNA repair activities. 2020 (Pirovano).



Preclinical Rationale

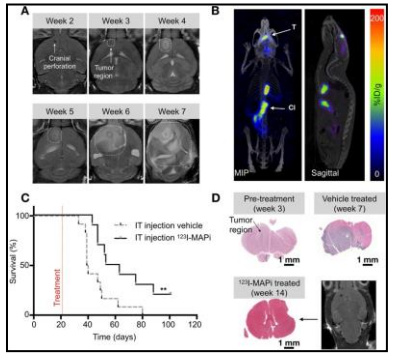
- ^{123}I-ATT00123 has been shown to be efficacious in xenograft models that are known to be strongly positive for PARPi expression
- High tumour uptake and residency time has seen in both intra-tumoural and intravenous administration and no safety concerns reported

Kaplan Meier curves after IV treatment of colon xenografts with ^{123}I-ATT001



(A) HCT116 p53+/+; (B) HCT116 p53−/−; * Represents day of treatment. For each mouse, either vehicle or ^{123}I-ATT001 (2 mCi) or ATT001 (80 μg/kg; only in HCT116 p53-/- animals) was administered intravenously; study endpoints animals' sign of discomfort, pain, significant weight loss, tumour size greater than 800 mm3, or ulceration greater than 5 mm in diameter.

Efficacy of ^{123}I-ATT001 in the TS543 glioblastoma mouse model



(A) MRI monitoring of TS543 xenograft disease progression. (B) SPECT/CT imaging of GBM with ^{123}I-ATT001 (123I-MAPi) single injection. Images were taken at 18 h after local injection. T = tumour, Cl = clearing organs. (C) Kaplan-Meier curve of mice injected with 123I-ATT001 (local single injection 370 kBq - 1.11 MBq, n = 10) compared to vehicle injection (n = 12). Log-Rank (Mantel-Cox) test, **p-value < 0.01. (D) Cytology staining of untreated mice at Weeks 3 and 7 after tumour implantation and cytology staining and MRI imaging of treated mouse brain at 14 weeks post implantation

Clinical Study Methods and Design

- This is a non-randomised, multicentre Phase I study with a dose escalation and expansion (Part 1 – Monotherapy) and a Combination (Part 2) in patients with relapsed glioblastoma

Part 1(Monotherapy): Dose Finding (BOIN design)
Safety, tolerability, PK/PD, clinical utility, PRO endpoints

Part 1 (Monotherapy): Single Arm Expansion
Safety & Efficacy

Part 2 Combination Groups likely to assess both externally directed energy and systemic anticancer therapies in rGBM

- **Part 1, Dose Escalation Phase:** A dose finding study is being conducting using a Bayesian Optimal Interval (BOIN) (Liu and Yuan, 2015) to establish dose-limiting toxicities (DLTs) and a Recommended Dose (RD) for expansion group.
- BOIN: One to four patients per dose level will be assigned to receive intratumoral (IT) of ^{123}ATT001 via an Ommaya reservoir, weekly for up to 4 weeks
- In the Expansion Group, eight weekly doses will be administered at the RD
- At total of 6 dose levels are being evaluated within the BOIN design

Dose Level 1	Dose Level 2	Dose Level 3	Dose Level 4	Dose Level 5	Dose Level 6
500 MBq	800 MBq	1200 MBq	1800 MBq	2400 MBq	3000 MBq
			Pending Approval		

- Part 1 will be completed when 11 consecutive patients have received the recommended dose (RD) as monotherapy

Part 1 Enrolment Criteria

Major Inclusion Criteria

- Men and women over 18 years of age.
- Histologically confirmed recurrent glioblastoma (grade IV) as per WHO criteria 2021 (IDH- wild type only) where the subjects have an Ommaya reservoir in an intralesional cavity of at least 5 mL volume.
- Eastern Cooperative Oncology Group Performance status of 0 or 1
- Documented recurrent disease (radiological, based on RANO v.1.0) within 3 months prior to first study drug administration with no suitable standard of care options available.
- Adequate end organ function

Major Exclusion Criteria

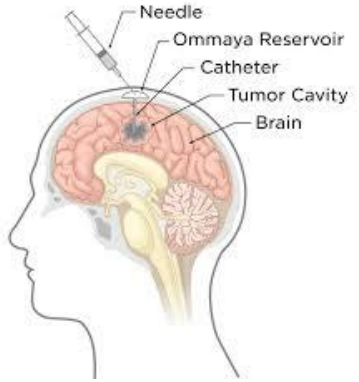
- Diagnosis of immunodeficiency or receiving systemic steroid therapy of greater than 4 mg/ day dexamethasone or equivalent or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment.
- Known additional malignancy that is progressing or requires active treatment excepting basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy, or in situ cervical cancer
- Any condition that precludes the proper performance of SPECT and/or Magnetic Resonance Imaging (MRI) scan.
- Patients with a known allergy to Olaparib or Iodine

Part 1 Objectives and Endpoints

Part 1 - Monotherapy

OBJECTIVES	ENDPOINTS
Primary	
To determine the safety and tolerability of ^{123}I-ATT001. To determine the recommended dose (RD) of ^{123}I-ATT001 via intracavitary direct instillation in subjects with relapsed glioblastoma, both as monotherapy and in combination with other anticancer therapies.	• Frequency and severity of treatment emergent adverse events (TEAEs) and serious adverse events (SAEs) using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0. • Incidence of Dose Limiting Toxicity (DLT).
Secondary	
To determine the biodistribution and pharmacokinetics of ^{123}I-ATT001 in blood and urine. To determine the radiation dosimetry of 123I-ATT001 (exposure of each organ to radiation) To obtain a preliminary assessment of the antitumour activity of ^{123}I-ATT001 To evaluate the effect of ^{123}I-ATT001 on neurological function	• Assessment of organ biodistribution of 123I-ATT001 by single-photon emission computed tomography (SPECT) /computed tomography (CT) and/or whole-body planar imaging at,1 h, 4 h and 24h post-dose. (For the first six participants) • Blood and urine ^{123}I-ATT001 parameters • Clinical benefit (tumour response according to mRANO), change from baseline for applicable tumour markers • Changes from baseline on neurological function, according to the Neurologic Function in Neuro-Oncology (NANO) scale and MDASI-BT questionnaire Outcomes
Exploratory	
To evaluate PARP1expression and other correlated tissue expressions in archive tissue samples and/or fresh frozen tissue and CSF.	• Post treatment change from baseline in levels of applicable tumour markers

^{123}I-ATT001 Administration



Partnering Study Centres and Patient Groups

UCL HOSPITALS CHARITABLE FOUNDATION

NHS University Hospital Southampton NHS Foundation Trust

brainstrust the brain cancer people

NIHR | National Institute for Health Research

Part 2 Expansion Groups

- Combination groups
- Safety run-in for each combo
- Efficacy endpoint
- Safety conformation and exploratory

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5. Image from Barrow Neurological Institute (accessed Apr 2024)

ACKNOWLEDGEMENTS

Special thanks to Dr Paul Mulholland, Prof Jamshed Bomanji and Mr Neil Kitchener at UCL who have worked tirelessly with Theragnostics Ltd (An Ariceum Company) to develop the first human therapy trial. Special thanks also to TCRS team who are our clinical CRO on this study.

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