FPN#3665: First-in-human Dose-Escalation and Expansion Study (MITOPE) to evaluate mitochondrial PRX3 inhibition by RSO-021 in patients with Mesothelioma and other Advanced Solid Tumours

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Background
Tumour cells generate elevated levels of reactive oxygen species (ROS) and therefore exhibit increased expression and activity of critical ROS scavenging pathways, including the mitochondrial peroxide scavenging enzyme peroxiredoxin 3 (PRX3).

**PRX3** is a peroxidase responsible for metabolizing ~ 90% of mitochondrial ROS, primarily H2O2. PRX3 transcript levels are upregulated, compared to normal tissues, in approximately 50% of cancers (data from the GEPiA2 database).

Genetic knock down of PRX3 in human tumour cells results in sensitization to apoptosis. The mitochondria of malignant mesothelioma (MM) cells are structurally and functionally altered leading to disrupted metabolic function that supports tumour growth and can be therapeutically targeted (see figure below).

PRX3 Inhibition in Malignant Pleural Effusion

**Small amounts of pleural effusion in the pleural space is physiologically normal. Mesothelioma and metastatic disease to the lungs often results in build-up of excess fluid (~15% of cancers). Malignant pleural effusion (MPE) is routinely drained using an intrapleural catheter.**

**RSO-021 is a Novel Mitochondrial PRX3 Inhibitor**

RSO-021 is a novel formulation of Thiostronten (TS) for clinical development. RSO-021 is a covalent inhibitor that inactivates PRX3 peroxidase activity through direct adduction of active site cysteine residues, in turn, inducing oxidative stress to levels incompatible with tumour cell survival.

Malignant Pleural Effusion

**Pre-Clinical Rationale**

- **A:** EC50 of RSO-021 in normal mesothelial and various mesothelioma cell lines (varying BAP1 expression).
- **B:** PRX3 knock down with shRNA significantly reduces MM (JM cell line - pleural-pleural pleural) proliferation (red). Co-expression of the H2O2 scavenger catalase rescues proliferation in cells lacking PRX3 expression (green and blue).
- **C:** Weight of residual tumours resected from mice harboring MM xenografts in the peritoneal cavity following 4 weeks of treatment with 20 mg/ml RSO-021 2x weekly. **p<0.01**

**PRX3 Retains activity in patient derived malignant pleural effusions (MPE)**

A) MPE collected from patients with metastatic disease. B) Adherent tumour spheroids and non-adherent immune cells grown in MPE supernatant. C) Relative PRX3 inactivation by RSO-021 in both tumour (adherent) and immune (non-adherent) cells. D) MPE derived tumour cells are equally sensitive to RSO-021 compared to established MM cell lines.

**RSO-021 Local Administration**

RSO-021 will be administered once-a-week via an indwelling intraperitoneal (IPC) catheter until disease progression, unacceptable toxicity, withdrawal of consent or study termination. Prior to each dose patients will have pleural effusion drained to dryness per standard of care. After each administration the IPC is secured until next RSO-021 dosing time point.

1. Drain pleural effusion to dryness
2. Administer RSO-021 via IPC
3. Secure IPC

**MITOPE Phase 1/2 Study Design**

**Primary Objective:** To assess the safety, tolerability and toxicity profile of RSO-021 in patients with MPE from any solid tumor type and mesothelioma

**Secondary Objectives:**
1. Establish systemic and local PK
2. Preliminary anti-tumour activity
3. Evaluate respiratory function
4. Redox status in translational samples

**Key Inclusion/Exclusion Criteria**

**Key Inclusion Criteria**

- Male or female ≥ 18 years old
- Prior systemic anti-cancer or radiation therapy, or surgery within 3 weeks or 5 half-lives. Treatment with investigational product/device within 30 days.
- Histological diagnosis of MPE caused by non-mesothelioma solid tumour (explanatory cohort only) or mesothelioma.
- MPE must be considered the priority for symptom control.
- Received at least 1 prior standard of care treatment regimen, with documented progression and no approved alternative available.
- Resolution of all acute reversible toxic effects of prior therapy to Grade 1.
- Active infection with human immunodeficiency virus (HIV).
- Active infection with hepatitis B or hepatitis C in absence of sustained virologic response
- Adequate organ function as defined by lab values
- Postmenopausal or surgically sterile, or be willing to practice highly effective methods of birth control
- Willingness and ability to comply with schedule/procedures

**Key Exclusion Criteria**

- Pregnant or breast-feeding patients
- Symptomatic/unstable CNS tumour metastases and/or central nervous system malignancies
- Use of systemic corticosteroids within 15 days or other immunosuppressive drugs within 3 weeks.

**Current Study Status**

The MITOPE study initiated first patient treatment in March 2022 and is open for recruitment of patients at the following sites:

- Dr. D. Fennell - Leicester (active - accepts referral patients)
- Dr. S. Lord - Oxford (active - accepts referral patients)
- Dr. P. Salama - St. Bart’s, London (activation in process)
- Dr. J. Spicer - Guy’s Hospital, London (activation in process)
- Dr. R. Thistlethwaite - The Christie, Manchester (activation in process)
- Dr. A. Greystone - Newcastle University (not open - expansion phase only)

Clinicians are encouraged to refer any eligible patients to the open sites. MITOPE trial is supported by Mesothelioma UK (www.mesothelioma.uk.com), NHRI (www.nhr.ac.uk) and clinicaltrials.gov: NCT05278975

For more information scan the QR code or contact: MITOPE@RSOncology.com

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