First Dosing in a Phase 1b Combination Trial of the Dynamin II Inhibitor Prochlorperazine and Anti-EGFR Monoclonal Antibody Cetuximab in Head and Neck Squamous Cell Carcinoma Patients.

10/7/2017: The first two patients have been dosed in a phase Ib clinical trial at the Princess Alexandra Hospital (PAH, Brisbane, Australia), evaluating the efficacy of co-treatment of the anti-psychotic / anti-emetic drug prochlorperazine (Stemetil®) with anti-EGFR monoclonal antibody (mAb) cetuximab in head and neck squamous cell carcinoma (HNSCC) patients (HREC/16/QPAH/825)). Prochlorperazine is a potent off-target inhibitor of the enzyme dynamin II.

A total of 10 patients will be evaluated in five successive cohorts of two patients, investigating a fixed dosage of prochlorperazine together with rising doses of cetuximab. The primary endpoint of this trial is safety of prochlorperazine treatment (dynamin inhibition) when combined with cetuximab. This trial is expected to be completed in December 2017.

The trial follows a successful pilot clinical investigation at the PAH in five head and neck HNSCC patients, in which prochlorperazine treatment demonstrated, for the first time, the capacity for a dynamin inhibitor to increase tumour EGFR surface expression. In that study, prochlorperazine treatment was well tolerated and no serious adverse events were recorded.

Trial Background and Rationale

Dynamin II is a GTPase enzyme that mediates the internalisation of cell receptors (e.g., EGFR, HER2, VEGF) by clathrin-mediated endocytosis. In combination with mAb therapy, dynamin II inhibition enriches and clusters receptor-mAb complexes on the tumour cell surface. This profoundly enhances immune system tumour recognition, leading to selective tumour killing via antibody-dependent cellular cytotoxicity (ADCC). When antibodies are Fc silent dynamin inhibition can improve targeting without enhancing ADCC.

At present, the majority of patients receiving mAb therapy receive no benefit. Dynamin II inhibitors are a powerful adjuvant strategy to enhance both the efficacy and response rates of these therapies. Dynamin II inhibitor mAb combination therapy is predicted to significantly improve outcomes and patient response rates.

An Australian drug discovery Alliance, involving the University of Queensland (UQ), Children's Medical Research Institute (CMRI) and University of Newcastle (UON), owns an IP portfolio that protects the therapeutic and diagnostic applications of this technology, and has a drug discovery platform to develop potent first-in-class dynamin II inhibitors.

The Alliance has an active drug discovery program including promising new chemical entity (NCE) drug scaffolds. It is investigating re-purposing of prochlorperazine as an immediate opportunity to clinically evaluate the safety and efficacy of the dynamin immuno-oncology adjuvant strategy, de-risking a novel reformulation of prochlorperazine together with development of a potent and selective NCE.

To learn more about the Dynamin II Drug Discovery Program please click here.