Identification of an RNF43 mutated gastric cancer patient population with potential sensitivity to porcunine inhibitor RXC004 and development of a complimentary ctDNA liquid biopsy assay for patient screening

M. Bingham1, I. Bhamra1, R. Armer1, B. Thompson1, S. Woodcock1, A. Thomason1, C. Phillips1, H. Mckeever1, J. Bradford2, B. Chaffey3, L. Little4, G. Clack5
1Oncology and Immunology, Redx Pharma Plc, Manchester, UK, 2Department of Oncology and Metabolism, University of Sheffield, Sheffield, UK, 3Bioscience Building, NewGene Ltd, Newcastle-Upon-Tyne, UK, 4Faculty of Medicine, University of Sheffield, Sheffield, UK

**Background:** RXC004 is a small molecule PORCN inhibitor, entering first-in-human trials in 2017. PORCN inhibition has been shown to have potential for the treatment of molecularly selected pancreatic and colorectal cancers, as well as the ability to synergise with anti-PD1 checkpoint inhibition. The aim of this study was to identify additional patient segments predicted to benefit from treatment with a PORCN inhibitor.

**Methods:** Mutation incidence for the WNT pathway gene RNF43 was analysed in 674 gastric cancer samples. RXC004 was profiled in gastric, pancreatic and biliary PDX models carrying the RNF43 mutations and growth inhibition was correlated with WNT pathway inhibition. To support the clinical trial a patient selection strategy, based on detection of RNF43 mutations from a liquid biopsy, was developed using MassArray mass spectrometry technology is described.

**Results:** Bioinformatic analysis of TCGA identified that the prevalence of RNF43 mutation in gastric cancer is 14-16%. A specific hot spot mutation (G659Vfs*41) has been identified, which accounts for ~70% of the RNF43 mutations. Profiling of RXC004 in RNF43 mouse models of gastric and pancreatic cancer shows the potential for monotherapy efficacy. In order to translate our findings to the clinic, we developed an assay suitable for detection of RNF43 mutations in circulating tumour DNA (ctDNA) from patient plasma. Multiplexed assays for RNF43 mutations, including the G659Vfs*41 hotspot, have been developed using MassArray technology. By converting to UltraSeek MassArray methodology we are targeting a sensitivity of 0.1% allelic frequency and specificity >99% in patient ctDNA.
Conclusions: RXC004 is entering first-in-human trials in 2017 with a modular phase I/Ila clinical protocol design which allows for phase Ila expansion arms in molecularly selected patient segments including gastric cancer. We demonstrate that there is an RNF43 mutated patient segment which may benefit from therapy with RXC004, and that these patients have the potential to be identified by a ctDNA screening approach.

Clinical trial identification: EudraCT Number 2017-000720-98

Legal entity responsible for the study: Redx Pharma Plc

Funding: Redx Pharma Plc