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Phase I study of the porcupine (PORCN) inhibitor RXC004 in patients with advanced solid tumours

N. Cook¹, S. Blagden², J. Lopez³, D. Sarker⁴, A. Greystoke⁵, N. Harris⁵, F. Kazmi², A. Naderi², G. Nintos⁴, A. Ortego Franco¹, R. Pihlak¹, R. Shinde³, L. Goodwin⁶, C. Phillips⁶, J. Robertson⁶, A. Saunders⁶, C. Tilston⁶, S. Woodcock⁶, R. Plummer⁷

¹ Experimental Cancer Medicine Centre, The University of Manchester and the Christie NHS Foundation Trust, Manchester, UK, ² Early Phase Clinical Trials Unit, Churchill Hospital, Oxford University Hospitals NHS Foundation Trust, Oxford, UK, ³ Phase 1 Drug Development Unit, Royal Marsden Hospital, London, UK, ⁴ Medical Oncology, Guy's Hospital NHS Trust, London, UK, ⁵ Sir Bobby Robson Cancer Trials Research Centre, The Freeman Hospital (NHS Foundation Trust) Northern Centre for Cancer Care, Newcastle-upon-Tyne, UK, ⁶ Oncology, Redx Pharma Plc, Cheshire, UK ⁷ Sir Bobby Robson Cancer Trials Research Centre, The Freeman Hospital (NHS Foundation Trust) Northern Centre for Cancer Care, Newcastle-upon-Tyne, Tyne and Wear, UK

Background

Dysregulated Wnt signalling drives several cancers through effects on proliferation, fibrosis and immune evasion. RXC004 is a novel small molecule inhibitor of the protein-serine O-palmitoyltransferase, PORCN, which is required for post-translational modification of Wnt ligands and downstream signaling. RXC004 has potential for monotherapy efficacy in Wnt pathway activated tumours: ~5% pancreatic and ~8% microsatellite stable colorectal (CRC) cancers with RNF-43 mutations or R-Spondin fusions, and thymus and biliary tract (BTC) cancers with high Wnt ligand activity.

Methods

This open label, 3+3 dose escalation study was one module of a multi-modular adaptive design protocol (NCT03447470). Following a single dose with a 7-day washout, patients received RXC004 once daily in 21-day cycles. The primary objectives were to assess safety and tolerability and define a recommended phase 2 dose of RXC004. Secondary objectives were PK and RECIST response. Pharmacodynamic markers included skin Wnt pathway (Axin2) suppression.

Results

Between 05/02/2018 and 21/06/2021, 25 patients with advanced cancers received RXC004. The first patient, who received 10mg daily, discontinued due to diarrhoea and an asymptomatic clavicle fracture was found on follow up. The half-life ($T_{1/2}$) and exposure were higher than predicted from preclinical models. The study was paused and restarted at 0.5mg. Subsequently, 1mg, 1.5mg, 2mg and 3mg doses were evaluated. Patients received denosumab 120 mg s.c monthly to prevent bone adverse events [AEs]. For doses <3mg, the most common treatment related AEs were fatigue, nausea, dysgeusia, vomiting and anorexia. No grade 4/5 AEs or bone fragility events were reported. Exposure was dose proportional and median $T_{1/2}$ was 14.5h. Exposures above the preclinical model IC_{50} were observed at all doses, as was Axin2 suppression. Five patients, all with Wnt pathway activated tumours [2 BTC, 1 Thymus, 1 mutRNF43 CRC and 1 RSPO fusion CRC] had stable disease, in one case for up to 26 weeks.

Conclusions

In patients with unselected cancers, RXC004 was safe and tolerated at doses up to 2mg/day, supporting phase 2 development in selected patients with Wnt pathway activated tumours. Studies will open in 2021.

Clinical trial identification

EudraCT 2017-000720-98.

Legal entity responsible for the study

Redx Pharma Plc.

Funding

Redx Pharma Plc.

Disclosure

N. Cook: Financial Interests, Personal and Institutional, Advisory Board: Redx Pharma; Financial Interests, Personal, Advisory Board: Roche; Financial Interests, Institutional, Research Grant, research finding: AstraZeneca, Orion, F. Hoffmann-La Roche Ltd, Taiho, GSK, Novartis, Starpharma, Bayer, Eisai, UCB, RedX Pharmaceuticals, Stemline Therapeutics, Boehringer Ingelheim,

Merck, Tarveda Therapeutics. S. Blagden: Financial Interests, Institutional, Research Grant, Research funding: Nucana PLC, Sierra Oncology, Astex, Incyte, Tesaro, Redx, MSD, Roche, UCB.; Financial Interests, Personal, Advisory Role, Consulting: Ellipses, Amphista; Financial Interests, Personal, Member of the Board of Directors, Director: RNA Guardian Ltd. D. Sarker: Financial Interests, Personal, Advisory Board: Novartis, Ipsen, Surface Oncology and Eisai; Financial Interests, Personal, Invited Speaker: MSD, Pfizer, Ipsen, Bayer, AstraZeneca and Eisai; Financial Interests, Personal, Funding, Travel payments: Ipsen, Eisai, Bayer and MiNA Therapeutics. A. Greystoke: Financial Interests, Institutional, Research Grant, Research funding: AstraZeneca; Financial Interests, Personal and Institutional, Invited Speaker: AstraZeneca, Amgen, Boehringer-Ingelheim, Bristol-Myers Squibb, Janssen/ J and J, MSD, Novartis, Pfizer, Lilly, Takeda and Roche. L. Goodwin: Financial Interests, Personal, Full or part-time Employment: Redx Pharma. C. Phillips: Financial Interests, Personal, Full or part-time Employment: Redx Pharma. J. Robertson: Financial Interests, Personal, Full or part-time Employment: Redx Pharma. A. Saunders: Financial Interests, Personal, Full or part-time Employment: Redx Pharma. C. Tilston: Financial Interests, Personal, Full or part-time Employment: Redx Pharma. R. Plummer: Financial Interests, Personal and Institutional, Advisory Board: Pierre Faber, Genmab, Bayer, Octimet, Clovis Oncology, Novartis, Karus Therapeutics, Biosceptre, BMS Sanofi Aventis, Ellipses, CV6 Therapeutics, Cybrexa; Financial Interests, Personal, Invited Speaker: AstraZeneca, Novartis, Bayer, Tesaro BMS and Expert Medical Events. All other authors have declared no conflicts of interest.

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