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Discovering Targeted Medicines

Phase 1 Study of the Porcupine (PORCN) Inhibitor RXC004 in Patients with Advanced Solid Tumours

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University of Manchester and Christie NHS
Foundation Trust at ESMO 2021 on
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AIM:REDX



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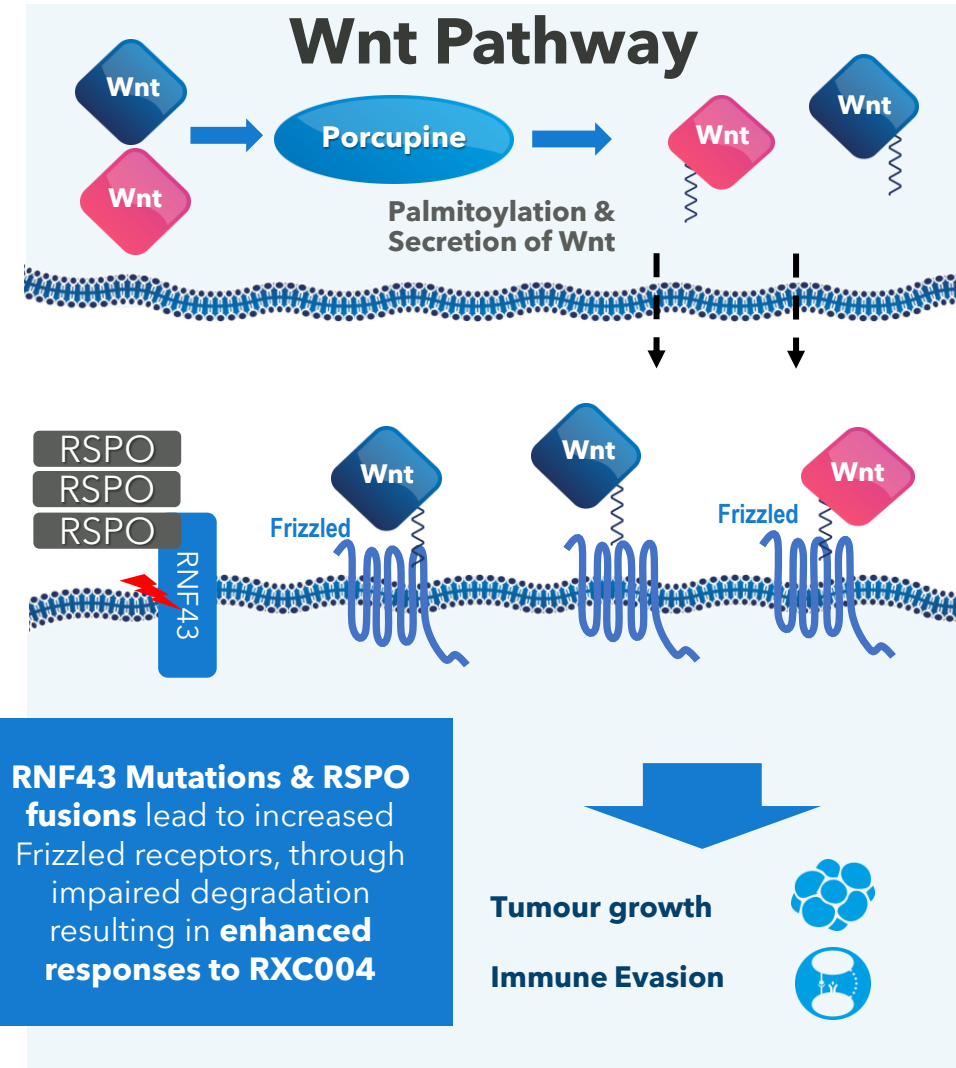
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Porcupine Inhibition and RXC004 Background

Porcupine is a Clinically Relevant Target for Wnt-Ligand Driven Cancers

- **RXC004 is a highly potent, orally active Porcupine inhibitor**
- **Porcupine is a key enzyme in the Wnt pathway - aberrations in Wnt pathway are a known driver of multiple cancers**
- **Inhibition of Porcupine blocks the release of all Wnt ligands from cells, preventing both tumour growth and tumour immune evasion**
- **Wnt-ligand driven tumours should respond to Porcupine inhibition**
 - pre-clinical activity in genetically-selected tumours with RNF43 mutations or RSPO fusions
 - high Wnt-ligand driven cancers e.g. Biliary tract cancers and Thymus cancers



RNF43: Ring Finger Protein 43; RSPO: R-Spondin; Wnt: Wingless/integrated

First in Human Phase 1 Study of RXC004



Open Label, Multi-Module, 3+3 Dose Escalation Study in Adults with Unselected Advanced Solid Tumours

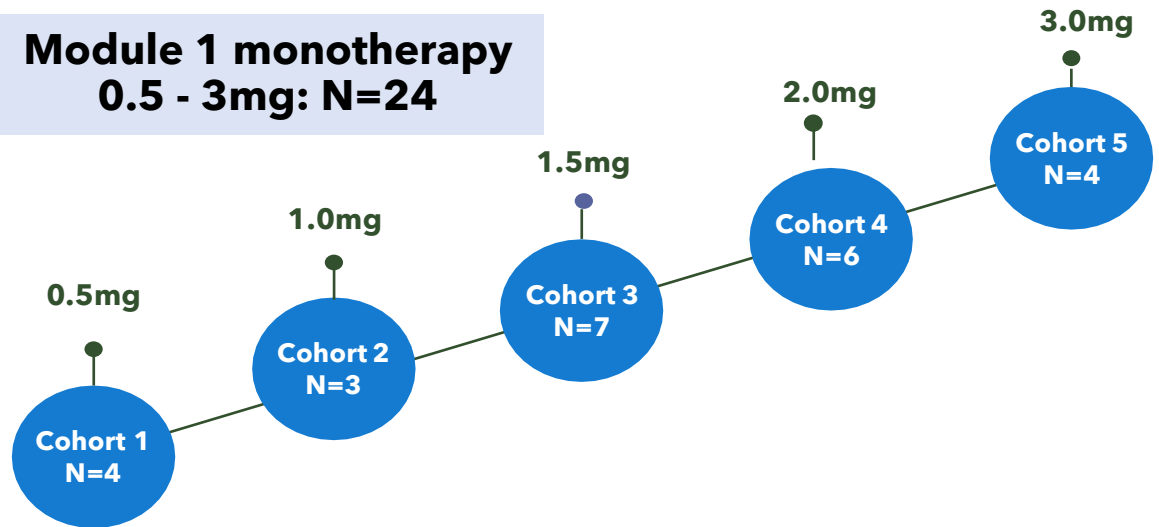
Module 1: Monotherapy Continuous Dosing

Module 2: Combination with PD-1 Inhibitor

Module 3: Intermittent Dosing Schedules

Module 1 Complete and reported here

- opened with 10mg dose
 - 1 patient - dose was not tolerated - diarrhoea, colitis and bone fragility fractures - on-target effect of Wnt inhibition
 - Exposure significantly higher than predicted pre-clinically
- re-started with a 0.5mg dose
 - Five dose levels studied to determine RP2D



- **Patient Population:** Adults with unselected advanced solid tumours, ECOG Performance Status 0-1
- Endpoints: Safety, PK, PD, and Preliminary efficacy
- Data cut-off July 30th 2021

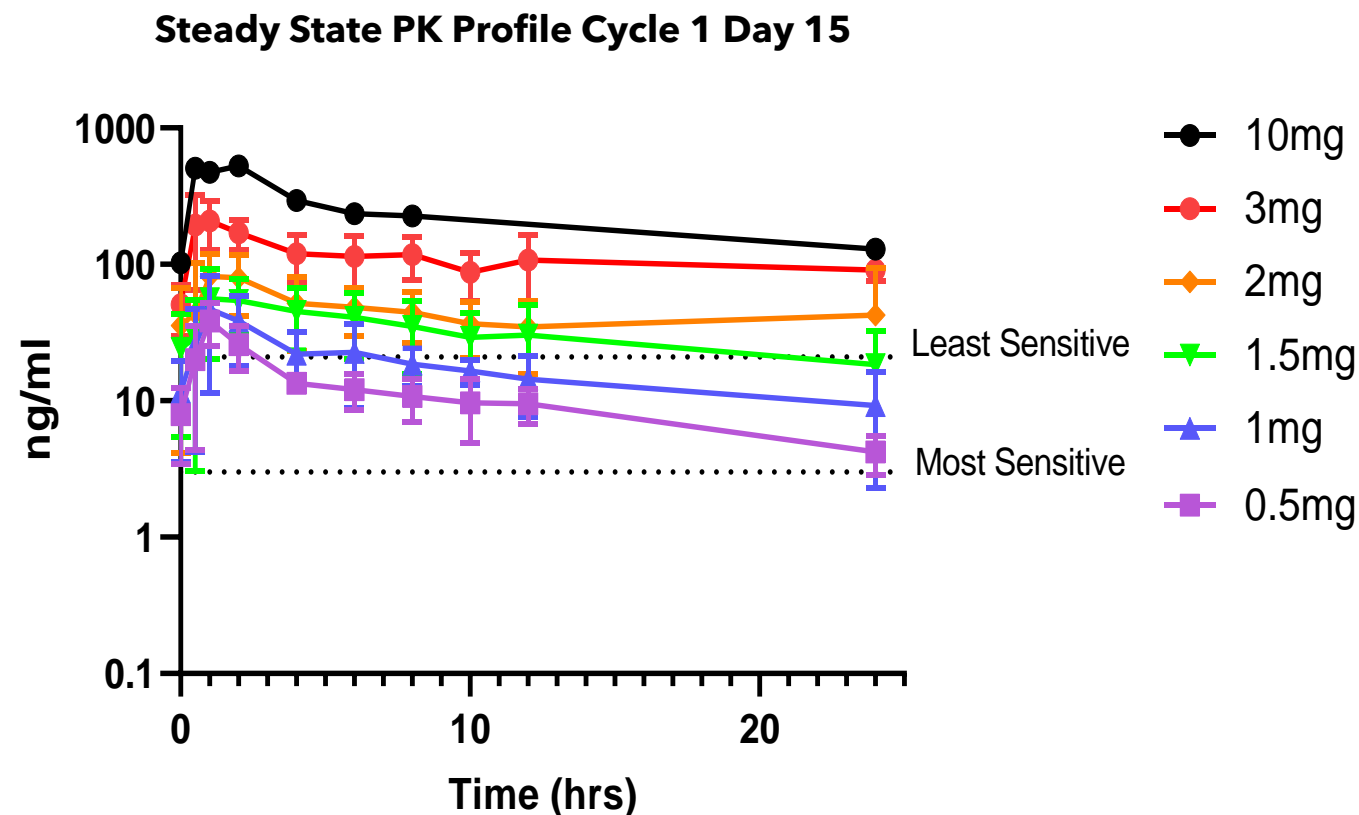
RP2D: Recommended Phase 2 Dose; PD-1: Programmed Death-1 receptor; PK: Pharmacokinetic

Patient Characteristics and Pharmacokinetic Profiles



Proportional Increases in Exposure from 0.5mg to 2mg with a Half-life of 14.5 Hours

Patient Characteristics		N=25
Age (median, range) yrs		65 (44-77)
Men		14 (56%)
Women		11(44%)
ECOG Performance Status	0	10 (40%)
	1	15 (60%)
Colorectal Cancer		15 (60%)
Biliary Tract Cancer		4 (16%)
Pancreatic Cancer		3 (12%)
Other Tumour Type		3 (12%)
Prior lines of systemic therapy (median, range)		3 (1-5)



ECOG: Eastern Cooperative Oncology Group; PK: Pharmacokinetic; Other tumours: Thymus cancer, High grade serous fallopian tube cancer and squamous cell anal cancer
 Dotted lines represent the minimum efficacious concentration (Cmin) from preclinical oncology models. These range from Cmin cover of >1x IC50 (most sensitive model) for 24hrs to >7x IC50 (least sensitive model) for 24hrs.

Treatment-Related Adverse Events*

RXC004 is Safe and Well Tolerated at Doses of up to 2mg



Number of Patients	0.5mg cohort N=4	1.0mg cohort N=3	1.5mg cohort N=7	2.0mg cohort N=6	3.0mg cohort N=4	10.0mg cohort N=1	TOTAL N=25
Any TEAEs	4 (100)	3 (100)	5 (71)	5 (83)	4 (100)	1 (100)	22 (88)
Fatigue	2 (50)	1 (33)	4 (57)	3 (50)	2 (50)	1 (100)	13 (52)
Nausea	1 (25)	2 (67)	3 (43)	1 (17)	3 (75)	1 (100)	11 (44)
Decreased appetite	1 (25)	1 (33)	2 (29)	2 (33)	3 (75)	1 (100)	10 (40)
Dysgeusia	0 (0)	0 (0)	2 (29)	4 (66)	3 (75)	1 (100)	10 (40)
Vomiting	0 (0)	1 (33)	2 (29)	1 (17)	1 (25)	1 (100)	6 (24)

Dose Limiting Toxicities in 4 pts: Diarrhoea, Colitis and fragility fractures (10mg) Colitis (3mg) Ileitis (3mg) Pancreatitis (2mg)

Denosumab prophylaxis successfully prevented increases in bone turnover marker β CTX and spontaneous fractures

* All treatment related adverse events (any grade) occurring in at least 20% patients

Efficacy Results



Patients Unselected however Clinical Activity Appeared Greater in Tumours with Wnt-Ligand Dependence

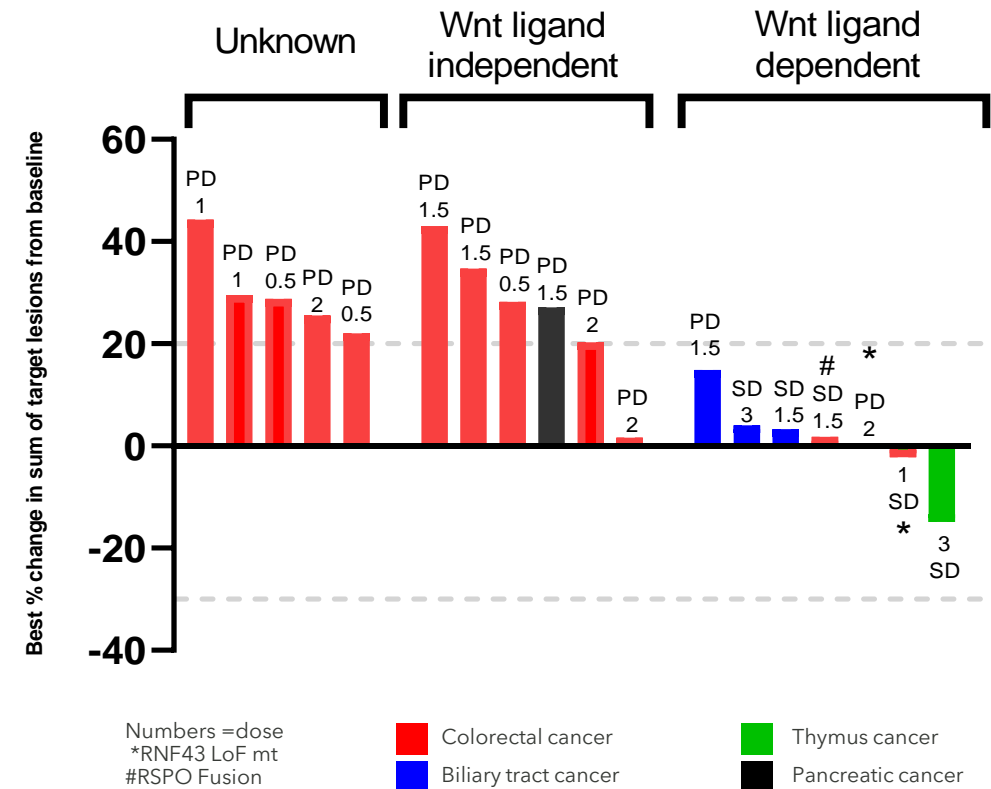
18 patients had RECIST - evaluable disease

- 7 patients had **Wnt-ligand dependent** tumours defined as: detectable LoF RNF43 / RSPO fusion, Biliary tract cancers, Thymus cancer
- 6 patients had **Wnt-ligand independent** tumours defined as: no detectable LoF RNF43 / RSPO fusion; CRC with detectable downstream APC mutations
- 5 patients had unknown Wnt-ligand dependence

5/7 patients with Wnt-ligand dependent tumours had durable RECIST SD

- 2/7 patients with Wnt-ligand dependent tumours had SD in target lesions but disease progression overall
- 0/11 patients with unknown or Wnt ligand independent tumours had RECIST SD
- Median treatment duration was 13.1 wks (6.4 - 25.4) for patients with Wnt-ligand dependent tumours vs 6.6 wks (5.4-7.3) for patients with unknown or Wnt-ligand independent tumours

Clinical Activity by Wnt-Ligand Dependence Group



APC: Adenomatous Polyposis Coli Gene; CRC: Colorectal Cancer; LoF: Loss of Function; RNF43: Ring Finger Protein 43; RSPO: R-Spondin; Wnt: Wingless/integrated

- **RXC004 monotherapy demonstrated manageable toxicity in targeting the Wnt pathway via Porcupine**
 - Lower doses and denosumab prophylaxis averted bone toxicity associated with Wnt inhibition
- **PK profile of RXC004 supports once daily dosing**
- **Target engagement evident at all doses with doses of 1.5mg and higher achieving exposures that demonstrated efficacy in all preclinical models tested**
- **Based on the safety, PK, PD and efficacy data, the recommended dose for Phase 2 monotherapy studies is 2mg QD**
- **Efficacy data supports hypothesis that RXC004 will be most effective in Wnt-ligand dependent tumours**
 - Phase 2 studies in patients with Wnt-ligand dependent tumours will open in 2H 2021 (biliary tract cancers or genetically selected MSS-mCRC and Pancreatic cancers with RNF43 mutations or RSPO fusions)