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

Presented by Dr Natalie Cook, MD PhD from the University of Manchester and Christie NHS Foundation Trust at ESMO 2021 on 20th September 2021
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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

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RNF43 Mutations & RSPO fusions lead to increased Frizzled receptors, through impaired degradation resulting in enhanced responses to RXC004
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

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

Steady State PK Profile Cycle 1 Day 15

Target engagement: Axin 2 suppression in skin observed at doses of 0.5mg and above

ECOG: Eastern Cooperative Oncology Group; PK: Pharmacokinetin; 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 coverage of >1x IC50 (most sensitive model) for 24hrs to >7x IC50 (least sensitive model) for 24hrs.

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Treatment-Related Adverse Events*
RXC004 is Safe and Well Tolerated at Doses of up to 2mg

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 βCTX 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

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Conclusions

- **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)

MSS-CRC: Microsatellite Stable-Non-Metastatic Colorectal Cancer; PD-1: Programmed Death-1; PK: Pharmacokinetic; QD: Once daily; RNF43: Ring Finger Protein 43; RSPO: R-Spondin; Wnt: Wingless/Integrate