Mechanism of action of RXC004, a Wnt pathway inhibitor, in genetically-defined models of cancer

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**Introduction**

Signalling through the Wnt pathway is highly regulated at the level of ligand (Wnt), receptor (Frizzled) and downstream components (e.g. destruction complex). Post-translational modification of Wnt ligands via porcine RXC004 (porcine membrane-bound O-acetyltransferase) is essential for secretion of active Wnt. Activity of RXC004/ZNFR3 (3′-ubiquitin ligases) results in ubiquitination and membrane clearance of Fzd, whilst RXC004/ZNFR3 levels are kept in check via LGR and secreted RSPO ligands (Fig. 1).

The potent and selective PORCN inhibitor RXC004 is being investigated in a Phase 1 clinical trial (NCT03447474), and has the potential to treat tumour types on the Wnt, and is up-regulated in a number of relevant cancer subsets. RXC004 is a small molecule inhibitor that blocks the PORCN/Wnt pathway.

RXC004 reduces tumour volume, eliminates proliferation and differentiates RSPO fusion tumour cells

**Results**

**Anti-proliferative effects of RXC004 in genetically-defined tumour cell lines**

**Study 1A**

SNU-1411 cells were implanted into mice, selected at ~35 mm³ and randomised into two groups:

- **Group 1:** Vehicle treated
- **Group 2:** RXC004 5mg/kg QD

Animals treated for 9 days, tumours were then removed from each group and fragments re-implanted into new, tumour and treatment naive mice in Study 1B.

**RXC004 pre-treatment results in continued growth inhibition even in the absence of continued treatment**

- **Study 1B:** Viable tumour fragments were implanted into tumour naive mice and tumour growth monitored.

- **Group 1:** Tumour fragments from previously vehicle treated (group 1) mice
- **Group 2:** Tumour fragments from previously RXC004 treated (group 2) mice

No drug treatment was given to either group in Study 1B.

**Summary**

- **RXC004 treatment alters metabolic activity of sensitive cells in vitro and in vivo**

  - **Direct tumour targeting**
    - **RXC004 inhibits tumour proliferation and increases differentiation**
    - **Glucose uptake**
    - **ATP release**
    - **Glucose uptake**

  - **Immune-modulatory**
    - **Expansive and infiltration of T-cells**
    - **Enhanced infiltration of T-cells**
    - **Recruitment and activation of regulatory T-cells**

RXC004 treatment is associated with enhanced infiltration and activation of regulatory T-cells, which increases immune-mediated responses to RXC004 and its downstream effects.

**References**

2. Zhu et al.: Oncology, 2017; 87: 676-687

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