Introduction

Signalling through the Wnt pathway is highly regulated at the level of ligand (Wnt), receptor (Fzd/LRP) and downstream components (e.g. destruction complex – APC/Axin/GSK3β). Post-translational modification of Wnt ligands via porcine (PORCN; a membrane bound O-acyltransferase) is essential for secretion of active Wnt®. Activity of RNFL43/ZNF93 (E3-ubiquitin ligases) results in ubiquitination and membrane clearance of Fzd, whilst RNFL43/ZNF93 levels are kept in check via GIRQ and secreted RPS24 ligands (Fig. 1). The potent and selective porcine (PORCN) inhibitor RXC004 is being investigated in a Phase 1 clinical trial (NCT03447470), and has the potential to treat tumours dependent on Wnt-ligand.

Upstream Wnt pathway aberrations, including RXC004/ZNF93 mutations and RPSO fusions, result in high levels of surface Fzd receptors and increased Wnt signalling (Fig. 1). These aberrations are implicated in pancreatic, gastric and colorectal cancer (CRC). Dysregulated Wnt signalling initiates oncogenic pathways involved in tumour initiation, growth and metastasis®, and is more recently linked to tumour immune evasion® (see also abstract §506).

Results

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

In vitro pathway inhibition by RXC004 in genetically-defined tumour cell line

RXC004 efficacy and pathway inhibition translates in vivo

RXC004 arrests the G1/S and G2/M cell cycle checkpoints

In vivo pathway inhibition by RXC004 in genetically-defined tumour cell line

Efficacy and sustained Wnt pathway inhibition by low and scheduled RXC004

Summary

RXC004 inhibits tumour proliferation and increases differentiation

References