A Multi-Arm, Open Label, Phase 2 Study to Assess the Efficacy of RXC004 as Monotherapy and in Combination with Nivolumab, in Patients with RNF43 or RSPO Aberrated, Metastatic, MSS Colorectal Cancer, Following Standard Treatments.

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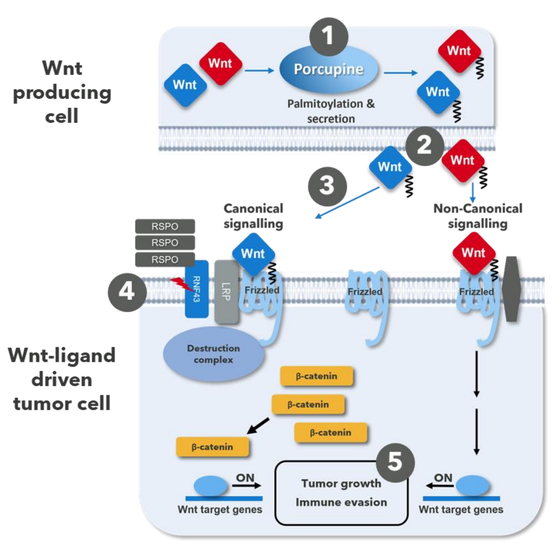
The Wnt Pathway is a critical driver in CRC

- Colorectal Cancer (CRC) is the 4th most common cancer globally with 2 million new cases and 1 million deaths annually.
- Immune Checkpoint Inhibitors (ICI) have not demonstrated efficacy in MSS CRC and response rates with standard third line treatments are <5%(1).
- The Wnt pathway is a critical driver of CRC and plays a central role in immune evasion and unresponsiveness to ICI(2,3).
- Loss of function (LoF) RNF43 mutations and RSPO gene fusions increase expression of the Wnt receptor Frizzled (Fzd) on tumor cells, driving Wnt-ligand dependent signalling.
- These alterations are present in ~8% of colorectal cancers (CRC) and are associated with poor prognosis in CRC (4,5).

The Wnt pathway drives tumor growth and immune evasion in cancer

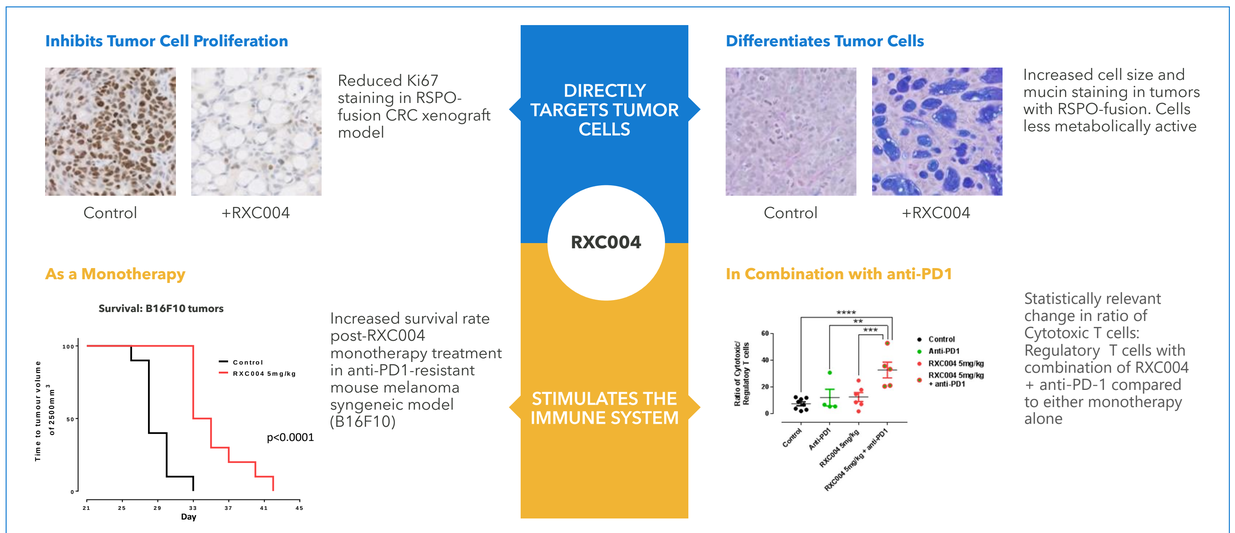


1. Porcupine adds a lipid chain to all 19 Wnt ligands (palmitoylation)
2. Palmitoylation destines Wnt ligands for secretion from the cell
3. Wnt ligands bind to Frizzled receptor complexes and activate canonical (β-catenin dependent) & non-canonical signalling pathways
4. In tumor cells with RSPO fusions or RNF43 mutations the Wnt pathway is upregulated (due to an increased number of Frizzled receptors)
5. Wnt ligand drives tumor immune evasion in over 25 cancer types and drives tumor growth in genetically selected patients

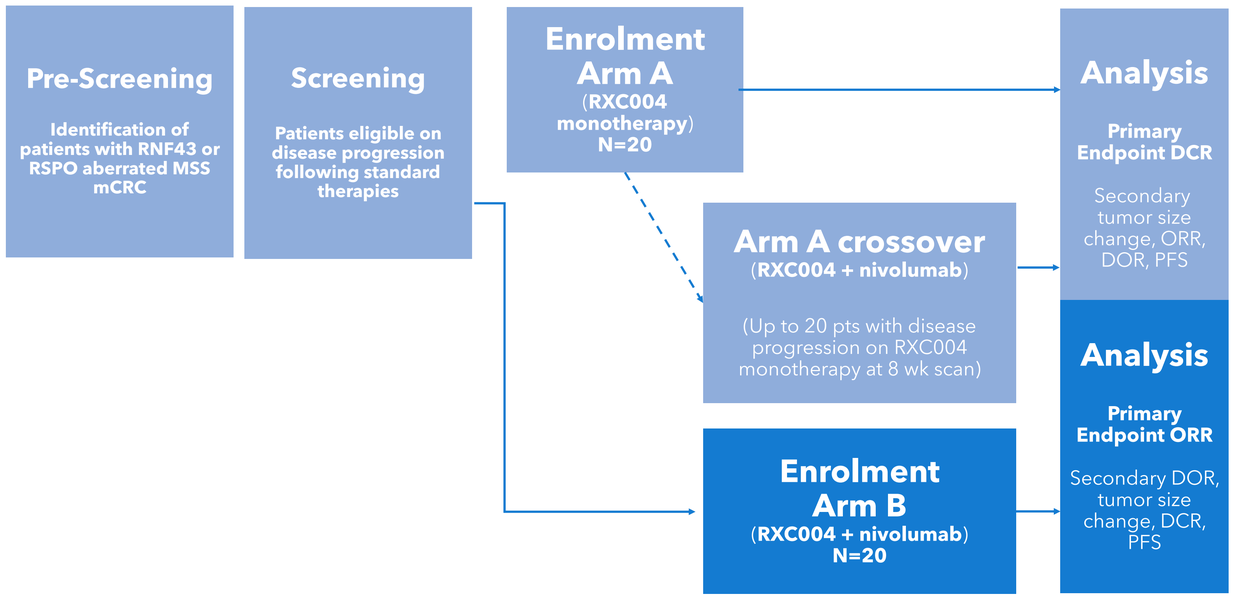
RNF43: Ring finger protein 43; RSPO: R-spondin; Wnt: Wingless/integrated

The Porcupine inhibitor RXC004 has direct anti-tumor effects and prevents tumor immune evasion

- RXC004 is a potent, selective, orally available inhibitor of the key Wnt pathway regulator, Porcupine.
- Inhibition of Porcupine blocks the release of all Wnt ligands, preventing both tumor growth and tumor immune evasion.
- In preclinical models, RXC004 has a dual mechanism of action, targeting tumor cells and reversing immune evasion(6,7).
- In Phase 1 study (NCT03447470), RXC004 was safe and tolerable at doses up to 2mg daily and showed differential activity in Wnt-dependent tumors(8).



The PORCUPINE trial will explore the dual MoA of RXC004



- **The PORCUPINE (NCT04907539) trial** is a Phase 2 study with two arms to explore RXC004 monotherapy (2mg p.o. daily) and in combination with nivolumab (480mg i.v. q4 weeks).
- Patients in monotherapy Arm A may go on to receive RXC004 + nivolumab if there is progressive disease at 1st RECIST scan.
- Patients must have metastatic MSS CRC that has progressed following standard therapies.
- Tumors must have a LoF RNF43 mutation, or an RSPO2/3 fusion, identified by central testing or local testing if the test meets validation requirements.
- As Wnt inhibition can affect bone metabolism, patients must have low risk of fragility fractures and receive prophylactic denosumab 120mg s.c. q4 wks throughout the treatment period.
- The primary endpoint for monotherapy Arm A is the proportion of patients with disease control (CR+PR+SD) at 16 weeks, and for combination Arm B is response rate.

Correlative Studies

- Changes from baseline in FDG-PET SUVmax at week 6
- Changes from baseline in protein and gene expression in tumor biopsies in Cycle 1
- Changes from baseline in circulating tumor DNA

Current Status

- The PORCUPINE study is open in USA, UK, Spain and South Korea
- Recruitment commenced in November 2021
- A second RXC004 study, PORCUPINE 2 (NCT04907851) in Biliary Tract and RNF43m Pancreatic Cancers, is open in UK and Australia

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