The Wnt Pathway drives Tumour Growth and Immune Evasion

**Clinical Safety Results**

Safety of RXC004 in combination with nivolumab is similar to monotherapy

**Preliminary Clinical Efficacy results**

Clinical Activity by Dose Cohort

Changes in immune cells and cytokines on treatment

**Study Design**

**PK Profile of RXC004 in combination with nivolumab is similar to monotherapy**

**Patient Characteristics and Pharmacokinetics**

**Phase 1 study of the Porcupine (PORCN) inhibitor RXC004 in combination with the PD-1 inhibitor Nivolumab in patients with advanced solid tumours**


**Case Study 1**

**Case Study 2**

**Conclusions**

**References**

Poster No. 719

Impact of Wnt-Pathway inhibition on circulating tumor cells and adaptive resistance to immune checkpoint inhibitors (ICI) therapy

- Wnt-signalling is inhibited with: 
  - Reduced CD279 (PD-1) expression
  - Increased number of immune suppressive Tg cells
  - CD45+ viability

- Inhibition of Wnt-signalling can enhance efficacy by: 
  - Increasing anti-tumoral infiltration
  - Decreasing generation of Tg cells
  - Reversing dendritic cell tolerization

- An increase in CD8+ T cells and a decrease in monocytes was observed in patients with RNF43 LoF mt CRC.

- Discreet increases in peripheral Tg cells were observed in patient blood following combination treatment (A) and are consistent with preclinical observations in Clinical observations in multiple cancers - Case Study 1.

- The combination of RXC004 + anti-PD-1 showed a statistically significant increase in the ratio of Cytotoxic T cells: Regulatory T cells in patient blood as measured by flow cytometry (mean + SD).

- In patients with RNF43 LoF mt CRC there was a significant increase in the ratio of Cytotoxic T cells: Regulatory T cells in patient blood as measured by flow cytometry (mean + SD).

- 16/13 patients had RECIST- evaluable disease
  - 4/13 patients with RECIST- evaluable disease and a validated PD-L1 expression of at least 1% on tumour cell (C0D1) and peripheral blood (C1D15) sample, C1D15 = Cycle 1 Day 15, C2D1 = Cycle 2 Day 1.

- 4/13 patients in the 1.5 mg cohort had RECIST stable disease as best response
  - 4/13 patients had RECIST- evaluable disease
  - 3/13 patients with RECIST- evaluable disease and a validated PD-L1 expression of at least 1% on tumour cell (C0D1) and peripheral blood (C1D15) sample, C1D15 = Cycle 1 Day 15, C2D1 = Cycle 2 Day 1.

- In patients with RNF43 LoF mt CRC there was an increase in the ratio of Cytotoxic T cells: Regulatory T cells in patient blood as measured by flow cytometry (mean + SD).

- The recommended Phase 2 dose of RXC004 is 2mg in combination:
  - Both RXC004 1.0mg and 1.5 doses were safe and tolerable in combination with nivolumab
  - No local or systemic treatment related non-haematological grade 5 events were reported
  - No dose limiting toxicities were reported
  - No treatment related discontinuations were reported

- No treatment related serious adverse events were reported
- No treatment related deaths were reported

- No deterioration in Karnofsky Performance Status was observed

- Nivolumab combination Module 1 and is a known adverse effect of immune checkpoint inhibitors.

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  - RXC004 1.5 mg in the selected Phase 2 dose is combination with nivolumab
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