# Final results of the first-in-human study of the porcupine (PORCN) inhibitor zamaporvint (RXC004) in patients with advanced solid tumors

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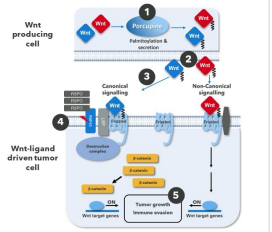
Poster CT101

## Introduction




Overview of Porcupine and the Wnt pathway

Dysregulated Wnt signaling drives several cancers through effects on proliferation, fibrosis and immune evasion **[1]**. Signaling through the Wnt pathway is highly regulated at the level of ligand (Wnt), receptor (Fzd/LRP) and downstream components (Destruction complex components - e.g. APC/Axin/GSK3β).

Zamaporvint (RXC004), a potent and selective inhibitor of the Wnt pathway regulator PORCN **[2]**, is being investigated in phase 2 studies in patients with advanced cancers, (NCT04907851 and NCT04907539). Zamaporvint has potential for efficacy in Wnt ligand dependent tumor subgroups: ~5% pancreatic cancer and ~8% microsatellite stable colorectal (CRC) cancer with RNF43 loss-of-function mutations or RSPO2/3-fusions **[1,3]**, and tumors with high Wnt ligand expression (e.g. Biliary Tract and Thymus cancers).

1. Porcupine adds a lipid chain to all 19 Wnt ligands (palmitoylation)
2. Palmitoylation is a prerequisite of Wnt ligand secretion from the cell
3. Palmitoylated Wnt ligands bind to Frizzled receptor complexes and activate canonical (β-catenin dependent) & non-canonical signaling pathways
4. In tumor cells with RSPO fusions or RNF43_LoF mutations, Wnt signaling is upregulated due to increased levels of surface Frizzled receptors
5. Wnt signaling drives tumor growth in genetically selected tumors and drives immune evasion in over 25 cancer types

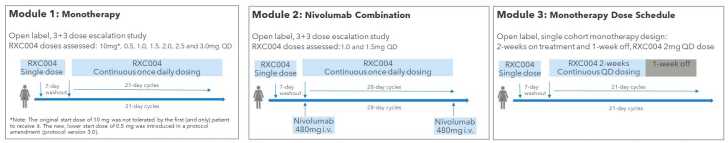
## Study Design

**Phase 1 Objective:** Assess safety and tolerability of RXC004 in cohorts of advanced cancer patients **(NCT03447470)**

**Module 1:** Monotherapy, 10mg* then 0.5-3.0 mg RXC004 , N=25

**Module 2:** Nivolumab Combination, 1.0-1.5 mg RXC004, N=14

**Module 3:** Monotherapy Dose Scheduling, 2 mg in patients with Wnt-ligand signaling tumors, N=7

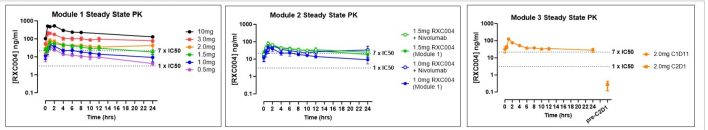



**Modules 1 and 2 assessed safety and tolerability in unselected all-comers, retrospective genetic analysis was performed where feasible; Module 3 assessed patients with Wnt ligand signaling tumors**

**All patients in Module 1 (from 1.5mg onwards) and in Modules 2 and 3 received prophylactic denosumab (120mg s.c. monthly)**

## Patient Characteristics and Pharmacokinetic Results

| Patient Characteristics | Module 1 (N=25) | Module 2 (N=14) | Module 3 (N=7) |
|---|---|---|---|
| Age (median, range) yrs | **66** (44-77) | **60.5** (30-75) | **63** (42-84) |
| Men | **14** (56%) | **7** (50%) | **3** (43%) |
| Women | **11** (44%) | **7** (50%) | **4** (57%) |
| **Race:** | | | |
| White | **21** (84%) | **12** (86%) | **7** (100%) |
| Asian/Asian British | **1** (4%) | **0** | **0** |
| Black/African/Caribbean/Black British | **2** (8%) | **1** (7%) | **0** |
| Other | **0** | **0** | **0** |
| Not reported | **1** (4%) | **1** (7%) | **0** |
| ECOG Performance Status 0 | **10** (40%) | **6** (43%) | **3** (43%) |
| ECOG Performance Status 1 | **15** (60%) | **8** (57%) | **4** (57%) |
| **Primary Location:** | | | |
| Anal | **1** (4%) | **0** | **0** |
| Biliary | **4** (16%) | **1** (7%) | **5** (71%) |
| Bladder | **0** | **0** | **1** (14%) |
| Colon | **12** (48%) | **4** (29%) | **1** (14%) |
| Gastric | **0** | **1** (7%) | **0** |
| Lung | **0** | **3** (21%) | **0** |
| Ovarian | **1** (4%) | **1** (7%) | **0** |
| Pancreatic | **3** (12%) | **0** | **0** |
| Rectal | **3** (12%) | **2** (14%) | **0** |
| Other | **1** (4%) | **2** (14%) | **0** |
| Prior lines of therapy (median, range) | **3** (1-5) | **3** (1-6) | **2** (1-2) |
| Received an immune checkpoint inhibitor | **1** (4%) | **1** (7%) | **0** |




**Plasma Pharmacokinetic Profiles of zamaporvint (RXC004) at steady state (M1 and M2: Cycle 1 Day 15, M3: Cycle 1 Day 11)**

Total Mean±SEM plasma concentrations of zamaporvint (RXC004) are shown over time at steady state during Cycle 1. Dotted lines represent the equivalent minimum efficacious plasma concentration ($C_{min}$) from preclinical oncology models, ranging from $C_{min}$ cover of ≥1x cellular $IC_{50}$ (most sensitive model) to ≥7x cellular $IC_{50}$ (least sensitive model) for 24hrs.

- Pharmacokinetic profile supports once daily dosing (~14.5hr half-life)
- Potential best-in-class clinical PK profile, providing target coverage whilst limiting $C_{max}$
- Doses ≥1.5mg achieved exposures that demonstrated efficacy in all preclinical models tested
- Combination with nivolumab did not significantly alter RXC004 exposures
- Scheduling of zamaporvint demonstrates 1-week off treatment gives a break from cellular $IC_{50}$ cover

| PK parameter (RXC004) | Module 1 2mg (N=6) | Module 2 1.5mg (N=8) | Module 3 2mg (N=7) |
|---|---|---|---|
| $AUC_{0\text{-}24}$ (GeoMean; h.ng/mL) | **941.3** | **740.4** | **719.3** |
| $C_{max}$ (Median; ng/mL) | **82.5** (C1D15) | **71.3** (C1D15) | **109.0** (C1D11) |
| $C_{24}$ (Median; ng/mL) | **18.2** (C1D15) | **10.6** (C1D15) | **10.9** (C1D11) |
| | **24.4** (C2D1) | **15.2** (C2D1) | **0.2** (pre-C2D1) |

**Table of zamaporvint steady state PK parameters per module/dose indicated**

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## Clinical Safety Results

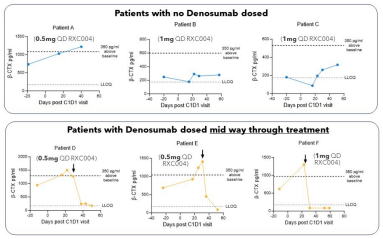
**Safety of RXC004 is similar as monotherapy and in combination with nivolumab**

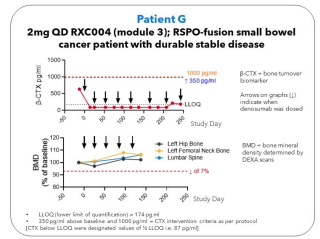
| | | Module 1 (N=25) | | Module 2 (N=14) | | Module 3 (N=7) | |
|---|---|---|---|---|---|---|---|
| | TRAEs* | All grades: N (%) | Grade ≥3: N (%) | All grades: N (%) | Grade ≥3: N (%) | All grades: N (%) | Grade ≥3: N (%) |
| | Patients with any TRAE* | 22 (88) | 6 (24) | 13 (93) | 5 (36) | 6 (86) | 0 |
| Most common TRAEs* | Decreased appetite | 11 (44) | 0 | 4 (29) | 0 | 0 | 0 |
| | Fatigue | 11 (44) | 0 | 5 (36) | 2 (14) | 4 (57) | 0 |
| | Nausea | 10 (40) | 1 (4) | 7 (50) | 0 | 1 (14) | 0 |
| | Dysgeusia | 9 (36) | 0 | 5 (36) | 0 | 5 (71) | 0 |
| | Vomiting | 6 (24) | 1 (4) | 2 (14) | 0 | 1 (7) | 0 |
| | Diarrhoea | 6 (24) | 2 (8) | 3 (21) | 0 | 1 (14) | 0 |
| | Lipase increased | 4 (16) | 0 | 0 | 0 | 2 (29) | 0 |
| | C-telopeptide increased | 3 (12) | 0 | 0 | 0 | 0 | 0 |
| | Anaemia | 2 (8) | 0 | 1 (7) | 1 (7) | 0 | 0 |
| | Constipation | 2 (8) | 0 | 3 (21) | 1 (7) | 0 | 0 |
| | Weight decreased | 2 (8) | 1 (4) | 4 (29) | 0 | 0 | 0 |
| | Blood bilirubin increase / hyperbilirubinaemia | 2 (8) | 0 | 3 (21) | 0 | 1(7) | 0 |
| | Other RXC004 related Grade ≥ AEs | Enteritis: 1, pancreatitis: 1, procitis: 1, subdural haematoma: 1, hyponatraemia: 2 | | DILI**: 1, transaminase increase: 1, hypomagnesaemia: 1 | | 0 | |

*Treatment-related (RXC004) Adverse Events, **Drug Induced Liver Injury - this was a DLT (Dose limiting toxicity)

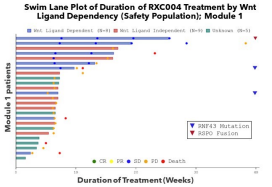
Recommended Phase 2 dose (RP2D) of RXC004 is **2mg** in monotherapy **[4]**, and **1.5mg** in combination with anti-PD-1 **[5]**

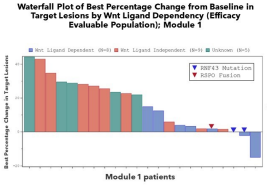
- Both RXC004 2.0mg monotherapy, and 1.5mg in combination with nivolumab were well tolerated
  - In Module 1, there were no DLTs in the lowest 3 dose cohorts (0.5, 1.0 and 1.5mg); 4 patients had a DLT at higher dose cohorts (1 patient at 2mg with pancreatitis, 2 patients at 3mg with colitis and enteritis, and 1 patient at 10mg with diarrhoea)
  - In Module 2, there was 1 patient with a DLT in the 1.5mg cohort (DILI)
  - At the monotherapy RP2D (2mg) in Module 1, 3 patients (50%) had dose interruptions and 1 patient (17%) had a dose reduction, whilst in Module 3, 2 patients (29%) had dose interruptions and there were no dose reductions
  - At the anti-PD-1 combination RP2D (1.5mg) in Module 2, 6 patients (75%) had dose interruptions and 3 patients (38%) had dose reductions
- Use of prophylactic denosumab prevented rises in the bone turnover marker β-CTX, and prevented reductions in bone mineral density, known side effects of Wnt pathway inhibition **[6]**

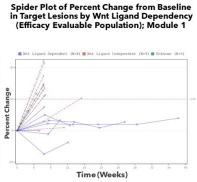


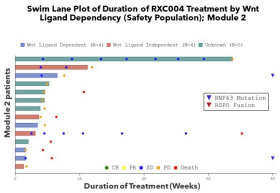



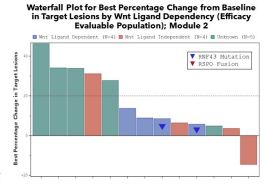

## Clinical Efficacy Results

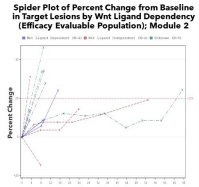


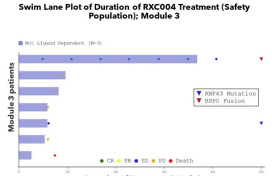



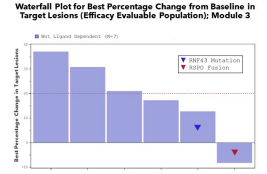



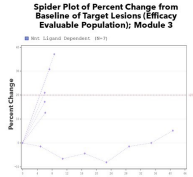



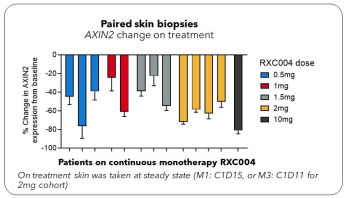



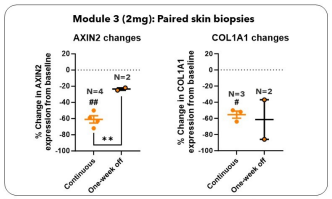



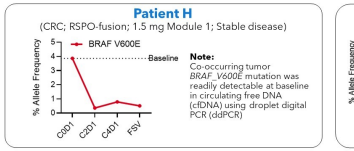

## Biomarker Results

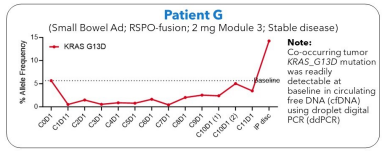



*On treatment skin was taken at steady state (M1: C1D15, or M3: C1D11 for 2mg cohort)*

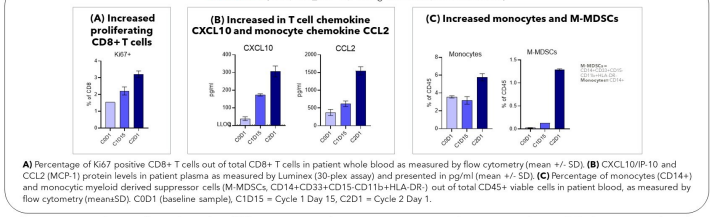



- Zamaporvint demonstrates robust Wnt pathway inhibition (decrease in AXIN2 expression) in paired skin biopsies at all continuous dose levels tested
- Whilst Module 3 patients (2mg) exhibit robust Wnt pathway inhibition following 11 days of continuous zamaporvint treatment, after 1 week off treatment Wnt signaling returns to near baseline, consistent with the break in cellular $IC_{50}$ cover measured in PK profiles




- In RSPO-fusion patients, zamaporvint monotherapy substantially decreases the circulating tumour DNA (ctDNA) levels of co-occurring MAPK mutants (BRAF and KRAS), genes that frequently co-occur with RNF43/RSPO **[3]**




**A)** Percentage of Ki67 positive CD8+ T cells out of total CD8+ T cells in patient whole blood as measured by flow cytometry (mean +/- SD). **(B)** CXCL10/IP-10 and CCL2 (MCP-1) protein levels in patient plasma as measured by Luminex (30-plex assay) and presented in pg/ml (mean +/- SD). **(C)** Percentage of monocytes (CD14+) and monocytic myeloid derived suppressor cells (M-MDSCs, CD14+CD33+CD15-CD11b+HLA-DR-) out of total CD45+ viable cells in patient blood, as measured by flow cytometry (meanSD). C0D1 (baseline sample), C1D15 = Cycle 1 Day 15, C2D1 = Cycle 2 Day 1.

- Consistent with pre-clinical studies **[2]**, treatment of zamaporvint in combination with anti-PD-1 increases levels of circulating immune cells (e.g. CD8+ T-cells, monocytes & M-MDSCs) and chemokines (e.g. CXCL10 & CCL2)

## Conclusions

- In patients with advanced solid tumors, zamaporvint (RXC004) was safe and well tolerated at doses up to and including the RP2Ds of 2mg QD as monotherapy and 1.5mg QD in combination with anti-PD-1 (nivolumab)
- Zamaporvint's PK profile indicates potential best-in-class, suitable for once-daily oral dosing that demonstrates robust target engagement
- Zamaporvint demonstrated differential disease control in Wnt-ligand signaling tumors:
  - In patients with Wnt-ligand signaling tumors: In Module 1, 5/8 patients (**63%**) had a best overall response (BOR) of Stable Disease (SD); in Module 2, 2/4 patients (**50%**) had a BOR of SD; whilst in Module 3, 2/6 (**33%**) had a BOR of SD
  - Across the study, out of the 7 patients with RNF43/RSPO genetic aberrations, 6 (**86%**) had a BOR of SD
- Intermittent zamaporvint dosing was well tolerated with no apparent detrimental impact on efficacy
- Prophylactic denosumab prevented increases in bone turnover biomarkers and successfully prevented loss of bone mineral density (BMD) and any bone related adverse events at or below the RP2Ds
- Two phase 2 studies assessing zamaporvint in prospectively selected Wnt ligand dependent GI cancers as a monotherapy or in combination with anti-PD-1 are ongoing
  - **PORCUPINE (NCT04907539)** – Genetically-selected RNF43/RSPO aberrant Microsatellite Stable (MSS) metastatic Colorectal Cancer (mCRC)
  - **PORCUPINE2 (NCT04907851)** – All comer Biliary Tract Cancer or RNF43_LoF mutant Pancreatic Cancer

## References

**[1] Flanagan et.al.** (2022), Pharmacology & Therapeutics; **[2] Phillips et.al.** (2022), Cancer Research Communications; **[3] Cook et.al.** (2023), Annals of Oncology; **[4] Cook et.al.** (2021), Annals of Oncology; **[5] Cook et.al.** (2022), Journal for ImmunoTherapy of Cancer; **[6] Rodon et.al.** (2021), British Journal of Cancer.

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