# Phase 2 results of the porcupine (PORCN) inhibitor zamaporvint (RXC004) in patients with pancreatic and biliary tract cancer

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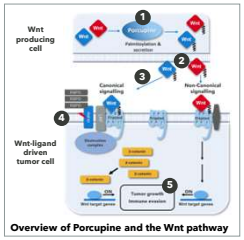
## Introduction




**Overview of Porcupine and the Wnt pathway**

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 tumour 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 tumours and drives immune evasion in over 25 cancer types

Dysregulated Wnt signalling drives many GI cancers through effects on proliferation and immune evasion. Wnt-dependent pancreatic ductal adenocarcinomas (PDAC) are identified by loss of function (LoF) RNF43 mutations, whilst ~70% of biliary tract cancers (BTC) have high Wnt-ligand expression **[1]**. PDAC & BTC have poor prognoses/ outcomes with standard treatments.

Zamaporvint (RXC004), is a potent & selective inhibitor of the Wnt pathway regulator PORCN. In addition to direct tumour targeting effects, RXC004 has the potential to sensitise tumours to anti-PD-(L)1 by inhibiting Wnt driven immune exclusion in the tumour microenvironment **[2]**.

In Phase 1, RXC004 was well-tolerated up to recommended Phase 2 doses of 2mg QD monotherapy and 1.5mg QD in combination with a PD-1 inhibitor. RXC004 demonstrated differential disease control in Wnt-ligand signaling tumours **[3]**.

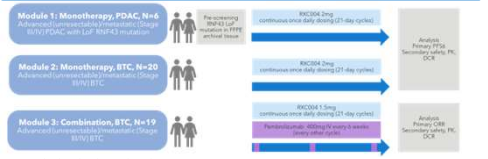
Two Phase 2 studies provide data from small, signal searching cohorts of RXC004 in Wnt-ligand dependent GI cancers as monotherapy or in combination with anti-PD-1:

- PORCUPINE (NCT04907539; POSTER 37P) in genetically-selected RNF43/RSPO aberrant microsatellite stable colorectal cancer
- PORCUPINE2 (NCT04907851) all comer BTC and RNF43_LoF PDAC

Here we present data from **PORCUPINE2.**

## Study Design

**Phase 2, modular, open-label, international, multicentre study**
**Primary objective:** Assess anti-tumour activity of RXC004 as monotherapy and as combination therapy




- International study conducted in UK and Australia.
- Eligibility: ≥18 yrs old, histologically confirmed advanced PDAC (M1) or BTC (M2 & M3) progressed following 1st line SoC.
- 20 patients were planned per cohort to achieve 15 per cohort evaluable for efficacy.
- All patients were dosed within 6 weeks of progression. Note, pembrolizumab is not currently approved in this setting.
- All patients received prophylactic denosumab 120 mg SC monthly for bone protection.
- DCR=disease control rate; ORR=objective response rate; PFS6=progression free survival at 6 months; PK=pharmacokinetics; SoC=standard of care

## Patient Characteristics

| Patient Characteristics | Module 1 (PDAC Monotherapy) (N=6) | Module 2 (BTC Monotherapy) (N=20) | Module 3 (BTC Combination) (N=19) |
|---|---|---|---|
| **Age** | | | |
| Mean (SD) | 65.7 (7.94) | 55.8 (14.72) | 58.1 (10.85) |
| Median (range) | 66.5 (55-73) | 57.5 (27-80) | 60.0 (36-77) |
| **Sex, n (%)** | | | |
| Male | 3 (50.0) | 10 (50.0) | 7 (36.8) |
| Female | 3 (50.0) | 10 (50.0) | 12 (63.2) |
| **Race, n (%)** | | | |
| Asian | 2 (33.3) | 0 | 0 |
| Black/African American | 0 | 0 | 2 (10,5) |
| White | 3 (50.0) | 19 (95.0) | 17 (89.5) |
| Other | 1 (16.7) | 1 (5.0) | 0 |
| **Performance status, n (%)** | | | |
| Karnosky 100 | 1 (16.7) | n/a | n/a |
| 90 | 5 (83.3) | n/a | n/a |
| ECOG 0 | n/a | 4 (20.0) | 6 (31.6) |
| 1 | n/a | 16 (80.0) | 14 (68.4) |
| **Primary location, n (%)** | | | |
| Pancreatic | 6 (100.0) | n/a | n/a |
| Biliary | n/a | 5 (25.0) | 5 (26.3) |
| Gallbladder | n/a | 0 | 1 (5.3) |
| Ampula of Vater | n/a | 12 (60.0) | 10 (52.6) |
| Intrahepatic CCA | n/a | 3 (15.0) | 3 (15.8) |
| Extrahepatic CCA | | | |
| **Stage at study entry, n (%)** | | | |
| III | 0 | 0 | 4 (21.1) |
| IV | 6 (100.0) | 20 (100.0) | 15 (78.9) |
| **RNF43 status, n (%)** | | | |
| Mutant | 6 (100.0) | n/a | n/a |
| **Prior therapy** | | | |
| No lines prior metastatic therapy - 1 | 6 (100.0) | 20 (100.0) | 18 (94.7) |
| - 0 | 0 | 0 | 1 (5.3)* |
| Mean (range) time from progression on prior therapy to first dose of IP, wks | 5.26 (4.3-6) | 5.47 (3.3-6.4) | 5.49 (1.3-7.1) |

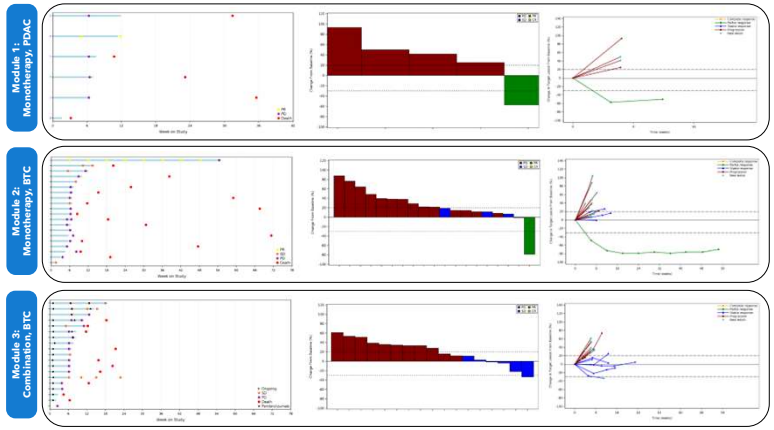
Full Analysis Set (N=45)
*Patient progressed on adjuvant therapy, hence considered 1st line metastatic therapy per protocol
CCA=cholangiocarcinoma

## Clinical Efficacy Results

| Efficacy endpoints | Module 1 (Monotherapy, PDAC) (N=5) | Module 2 (Monotherapy, BTC) (N=18) | Module 3 (Combination, BTC) (N=14) |
|---|---|---|---|
| **Objective response rate** | 1 (20.0) | 1 (5.6) | 0 |
| [90% CI] | [1.0 – 65.7] | [0.3 – 23.8] | [0.0 – 19.3] |
| **Best objective response** | | | |
| CR | 0 | 0 | 0 |
| PR | 1 (20.0) | 1 (5.6) | 0 |
| SD | 0 | 4 (22.2) | 6 (42.9) |
| PD | 4 (80.0) | 13 (72.2) | 8 (57.1) |
| **Disease control rate** | 1 (20.0) | 5 (27.8) | 6 (42.9) |
| [90% CI] | [1.0 – 65.7] | [11.6 – 49.8] | [20.6 – 67.5] |

Evaluable Analysis Set (N=37). CI=confidence interval; CR=complete response; DCR=disease control rate; ORR=objective response rate; OS=overall survival; PD=progressive disease; PFS=progression free survival; PR=partial response; SD=stable disease

- In M1 (PDAC monotherapy):
  - 1 confirmed PR, giving ORR 20%, DCR 20%
  - PFS6 not reached. Median PFS 1.4 months
  - Median OS 5.3 months
- In M2 (BTC monotherapy):
  - 1 confirmed, durable PR (sustained beyond Week 48), ORR 5.6%, DCR 27.8%
  - PFS6 6.5% (90% CI 0.8-21.5). Median PFS 1.5 months
  - Median OS 7.1 months
- In M3 (BTC combination with pembrolizumab):
  - No objective responses, DCR 42.9%
  - PFS6 not reached. Median PFS 1.6 months
  - Median OS 4.7 months (high level of censored data)




Swimmer plots from Full Analysis Set (N=45). Waterfall and spider plots from Evaluable Analysis Set (N=37)

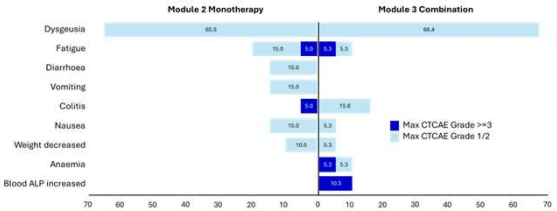
## Clinical Safety and Pharmacokinetics Results

| Events, n (%) patients | Module 1 (Monotherapy, PDAC) (N=6) | Module 2 (Monotherapy, BTC) (N=20) | Module 3 (Combination, BTC) (N=19) |
|---|---|---|---|
| **TEAE** | 6 (100.0) | 20 (100.0) | 19 (100.0) |
| Treatment related TEAE | 4 (66.7) | 17 (85.0) | 18 (94.7) |
| **Grade ≥3 TEAE** | 4 (66.7) | 8 (40.0) | 10 (52.6) |
| Treatment related Grade ≥3 TEAE | 1 (16.7) | 3 (15.0) | 5 (26.3) |
| **Serious TEAE** | 3 (50.0) | 6 (30.0) | 11 (57.9) |
| Treatment related serious TEAE | 0 | 1 (5.0) | 4 (21.1) |
| **TEAE leading to** | | | |
| Death | 0 | 0 | 1 (5.3) |
| Discontinuation of RXC004 | 0 | 2 (10.0) | 6 (31.6) |
| Discontinuation of pembrolizumab | n/a | n/a | 5 (26.3)* |

Full Analysis Set (N=45).
n/a=not applicable; TEAE=treatment emergent adverse event
Related TEAEs: For M1 and 2, RXC004 relation is considered. For M3, RXC004 and/or pembrolizumab is considered.
*1 patient discontinued RXC004 before pembrolizumab started

- Treatment related serious TEAEs in 5/45 patients
  - M2: colitis in 1 patient
  - M3: 1 patient with 3 events (immune mediated myocarditis, immune-mediated adrenal insufficiency and myasthenia gravis), 2 patients with colitis, 1 patient with lacunar stroke
- TEAEs leading to death in 1 patient
  - M3: immune mediated myocarditis and immune-mediated adrenal insufficiency, both treatment related
- TEAEs of colitis in 4 patients, all treatment related
  - M2: 1 with a serious TEAE (Gr 3)
  - M3: 1 with non-serious TEAEs, 2 with serious TEAE (all Gr 2)
- No bone fragility events or BMD loss
- PK assessment: Similar RXC004 exposure whether administered as 2mg monotherapy or 1.5mg in combination with pembrolizumab

**Most common treatment related TEAEs were dysgeusia, diarrhoea, fatigue, vomiting, nausea & colitis**



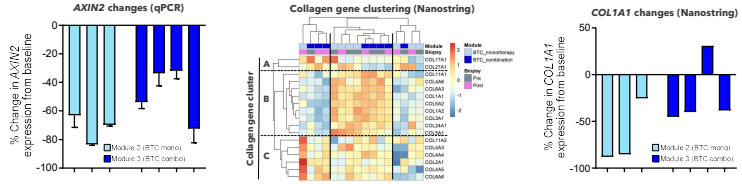

Treatment related TEAEs in BTC Module 2 and Module 3 in >1 patient in either Module. For M2, RXC004 relation is considered. For M3, RXC004 and/or pembrolizumab is considered.
ALP=alkaline phosphatase

≥Gr 3 treatment related TEAEs in 9/45 patients across all modules:

- M1: 1 patient with hyponatraemia
- M2: 3 patients with colitis, fatigue, hypertransaminasaemia
- M3: anaemia (1 patient), fatigue (1 patient), blood ALP increased (2 patients), immune-mediated myocarditis, myasthenia gravis, and immune-mediated adrenal insufficiency (all in 1 patient)

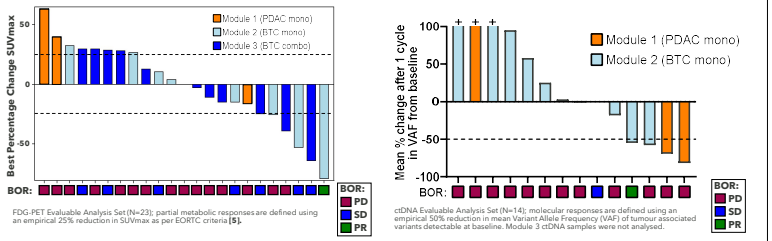
## Biomarker Results

**Gene expression analysis of paired tumour biopsies confirms Wnt pathway blockade (*AXIN2*), and cancer associated fibrosis (*COL1A1*) decreases with RXC004 ± pembrolizumab treatment in BTC**




Gene Expression Analysis Set from available paired tumour biopsies (N=7). Wnt pathway (*AXIN2*) was decreased in all patients post treatment as assessed by qPCR. Nanostring clustering using Z scores indicated 3 distinct collagen gene clusters for BTC tumour samples tested; cluster B contained the majority of collagen genes and showed higher expression levels associated with pre-treatment (63%) versus post-treatment (38%) BTC tumour biopsy samples. Treatment dependent reduction in *COL1A1* expression was confirmed in 6/7 BTC patients; consistent with RXC004-dependent *COL1A1* decreases in paired skin biopsies (Phase 1; **[3]**) and anti-fibrotic RXC004 activity seen in pre-clinical tumour models **[4]**. In addition, flow cytometry analysis confirmed blockade of PD-1 on CD4 and CD8 T-cells following pembrolizumab treatment.

**Metabolic (FDG-PET) and molecular (ctDNA) response rates are consistent with clinical efficacy seen in BTC patients**




FDG-PET Evaluable Analysis Set (N=23); partial metabolic responses are defined using an empirical 25% reduction in SUVmax as per EORTC criteria **[5]**.

ctDNA Evaluable Analysis Set (N=14); molecular responses are defined using an empirical 50% reduction in mean Variant Allele Frequency (VAF) of tumour associated variants detectable at baseline. Module 3 ctDNA samples were not analysed.

- In M1 (PDAC monotherapy); no metabolic responses (0/3 patients)
- In M2 (BTC monotherapy); 3/8 patients (38%) with partial metabolic response
- In M3 (BTC combination); 2/12 patients (17%) with partial metabolic response

- In M1 (PDAC monotherapy); 2/3 patients (67%) with molecular response
- In M2 (BTC monotherapy); 2/11 patients (18%) with molecular response

## Conclusions

- Data from these small, signal searching cohorts provide insight into the potential activity and safety/tolerability of RXC004 in hard-to-treat GI cancers
  - In unselected BTC, a high Wnt-ligand expressing tumour type, some durable clinical benefit was evident. Results are not sufficient to support further clinical development in genetically-unselected patients, a position supported by more recent preclinical data (29% (2/7) RXC004 efficacy in PDX BTC models; **[6]**)
  - In RNF43_LoF PDAC, patient numbers were too low to support any conclusions on efficacy; further investigator-led studies are in the planning stages
- RXC004 was tolerable as monotherapy and in combination with pembrolizumab
  - Safety profile consistent with the established safety profile of pembrolizumab and the emerging safety profile of RXC004 observed in Phase I
  - Potential for Wnt-related bone events prevented by prophylactic denosumab co-administration
- Similar RXC004 exposure was seen whether administered as 2mg monotherapy or as 1.5mg in combination with pembrolizumab
- Significant Wnt pathway blockade (*AXIN2*) and decreases in cancer associated fibrosis (*COL1A1*) were observed in both BTC modules. Metabolic (FDG-PET) and molecular (ctDNA) responses were observed
- Zamaporvint (RXC004) and Wnt pathway inhibition remains of interest in combination with immunotherapies and other agents in genetically-selected GI cancers

## References

**[1] Flanagan et al (2022), Pharmacol Ther; 238:108179. [2] Phillips et al (2022), Cancer Res Commun; 2:914. [3] Cook et al (2024), Cancer Research 84(7, suppl): abstract CT101. [4] Mclean et al (2022), JITC Suppl;1455. [5] Miceli et al (2023). Clinical and Translational Imaging 11:421. [6] Keppel et al (2023), Cancer Research 83(7 suppl): abstract 1654.**

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