Phase 2 results of the porcupine (PORCN) inhibitor zamaporvint (RXC004) in genetically-selected microsatellite stable colorectal cancer patients

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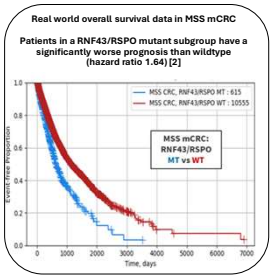
Introduction



Dysregulated Wnt signaling drives many GI cancers through effects on proliferation and immune evasion. ~8% of microsatellite stable colorectal cancers (MSS CRC) are Wnt-ligand dependent, via RNF43 loss-of-function (LoF) mutations or RSPO-fusions **[1]**. This RNF43/RSPO mutant MSS mCRC patient subgroup has an especially poor prognosis **[2]**. Anti-PD-1 treatment alone is ineffective in MSS mCRC patients (0% ORR; mPFS 2.2 months; mOS 5.0 months) **[3]**

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 MSS mCRC tumours to anti-PD-(L)1 by inhibiting Wnt driven immune exclusion in the tumour microenvironment **[4]**.

In Phase 1, RXC004 was well-tolerated up to recommended Phase 2 doses of 2mg QD monotherapy and 1.5mg QD in combination with anti-PD-1. RXC004 demonstrated differential disease control in Wnt-ligand signaling tumours **[5]**.

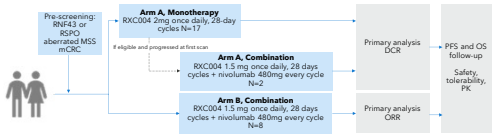
Two Phase 2 studies provide data from small, signal searching cohorts of RXC004 in Wnt-ligand dependent GI cancers as monotherapy or in combination with anti-PD-1:

- PORCUPINE (NCT04907539) in genetically-selected RNF43/RSPO aberrant MSS CRC.
- PORCUPINE2 (NCT04907851; POSTER 391P) in all comer biliary tract cancer or RNF43_LoF pancreatic cancer.

Here we present encouraging data from **PORCUPINE**, in hard to treat, genetically-selected MSS mCRC.

Study Design

Phase 2, open-label, international, multicentre study
Primary objective: Assess anti-tumour activity of RXC004 monotherapy and RXC004 + nivolumab



- International study conducted in 4 countries (US, Republic of Korea, Spain, UK)
- Eligibility: ≥18 yrs with histologically confirmed RNF43/RSPO aberrated MSS metastatic CRC that had progressed on ≥1 prior SoC
- 25 patients planned per arm. Recruitment was closed early resulting in 17 patients in Arm A and 8 patients in Arm B
- Pre-screening for genetic selection performed on >800 patients; 3.3% of those tested were RSPO-fusion positive and 3.5% were RNF43 LoF positive. 40 patients entered screening, and 25 were enrolled (17 in Arm A, 8 in Arm B)
- All patients received prophylactic denosumab 120 mg SC monthly for bone protection.
- PK data are not presented
- DCR=disease control rate, ORR=objective response rate, PFS=progression free survival, PK=pharmacokinetics; OS=overall survival, SoC=standard of care

Patient Characteristics

Patient Characteristics	Arm A (Monotherapy)* (N=17)	Arm B (Combination) (N=8)
Age, yrs		
Range	31-77	53-77
Sex, n (%)		
Male	9 (52.9)	3 (37.5)
Female	8 (47.1)	5 (62.5)
Race, n (%)		
White	15 (88.2)	7 (87.5)
Asian	1 (5.9)	0
Black/African American	1 (5.9)	0
Other	0	1 (12.5)
ECOG Performance Status at Screening, n (%)		
0	6 (35.3)	4 (50.0)
1	11 (64.7)	4 (50.0)
Primary Location, n (%)		
Colon	14 (82.4)	7 (87.5)
Anal/rectal	2 (11.8)	1 (12.5)
Other	1 (5.9)	0
Stage, n (%)		
IV	17 (100.0)	8 (100.0)
Genetics, n (%)		
MSI status – stable	17 (100.0)	8 (100.0)
RNF43 LoF mutation	10 (58.8)	3 (37.5)
RSPO2/3 fusion	7 (41.2)	5 (62.5)
BRAF mutation (co-occurring)	10 (58.8)	5 (62.5)
KRAS mutation (co-occurring)	6 (35.3)	3 (37.5)
Prior Lines of Metastatic Therapy		
Median (range)	2 (1-5)	2.5 (1-4)
Prior BRAF targeted therapy, n (%)	5 (29.4)	4 (50.0)

Full Analysis Set (N=25)
*Includes 2 patients who switched to combination therapy after progressing at the first scan

All data presented are preliminary, based on a data cut-off date of 2 April 2024 for efficacy and 22 March 2024 for safety

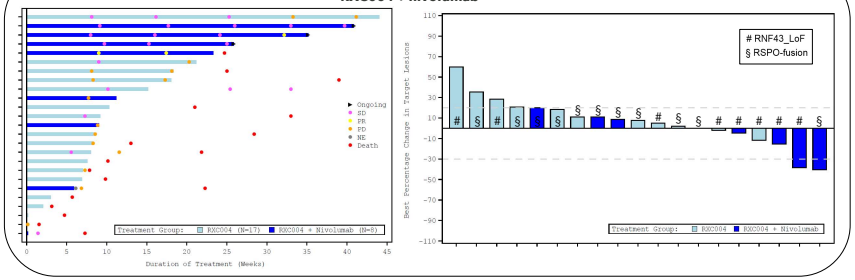
Clinical Efficacy Results

Efficacy endpoints, n (%) patients	Arm A (Monotherapy) (N=13)	Arm B (Combination) (N=7)
Objective response rate (ORR)	0	1 (14.3)
Best objective response (BOR)		
Complete response	0	0
Partial response	0	2 (28.6)
Stable disease	5 (38.5)	2 (28.6)
Progressive disease	6 (46.1)	3 (42.9)
Not evaluable*	2 (15.4)	0
Disease control rate (DCR) ≥ 16 wks	2 (15.4)	4 (57.1)

Evaluable Analysis Set (N=20). *Included in Analysis Set, but no scans available

- Arm A (monotherapy): no responses; 5 patients (38.5%) with stable disease
- Arm B (combination with nivolumab): ORR 14.3%; 2 (28.6%) partial responses (1 confirmed, 1 unconfirmed at time of data cut) and 2 (28.6%) patients with stable disease
- DCR ≥16 weeks numerically higher for RXC004 in combination with nivolumab (Arm B, 57.1%) versus RXC004 monotherapy (Arm A, 15.4%)
- Median PFS 2.0 months, and median OS 4.8 months for Arm A (monotherapy) in Full Analysis Set
- Median PFS 3.8 months, and median OS was not reached for Arm B (combination) in Full Analysis Set
- 3 patients in Arm B remained on treatment at time of study completion (2 April 2024)

Durable disease control (PR and SD) observed in patients with RNF43_LoF and RSPO-fusions treated with RXC004 + nivolumab



Clinical Safety Results

Events, n (%) patients	Arm A (Monotherapy) (N=17)	Arm B (Combination) (N=8)
TEAE	17 (100.0)	8 (100.0)
RXC004 related TEAE	14 (82.4)	8 (100.0)
Nivolumab related TEAE	1 (5.9)#	5 (62.5)
Grade ≥3 TEAE	9 (52.9)	3 (37.5)
RXC004 related grade ≥3 TEAE	3 (17.6)	2 (25.0)
Nivolumab related grade ≥3 TEAE	0	1 (12.5)
Serious TEAE	3 (17.6)	5 (62.5)
RXC004 related serious TEAE	2 (11.8)	4 (50.0)
Nivolumab related serious TEAE	0	2 (25.0)
TEAE leading to		
Death	0	0
Discontinuation of RXC004	2 (11.8)	2 (25.0)
Discontinuation of nivolumab	0	2 (25.0)

Safety Analysis Set (N=25)
#Reported in a patient who switched to combination treatment after progression on monotherapy
TEAE=treatment emergent adverse event

Most frequent treatment related TEAEs (TRAES), n (%) patients	RXC004 TRAEs Arm A (Monotherapy) (N=17)	RXC004 TRAEs Arm B (Combination) (N=8)	Nivolumab TRAEs (N=10*)
Dysgeusia	8 (47.1)	6 (75.0)	0
Decreased appetite	4 (23.5)	4 (50.0)	1 (10.0)
Nausea	4 (23.5)	4 (50.0)	1 (10.0)
Alopecia	2 (11.8)	4 (50.0)	2 (20.0)
Diarrhoea	4 (23.5)	2 (25.0)	0
Total bilirubin increased	2 (11.8)	3 (37.5)	1 (10.0)
Fatigue	2 (11.8)	2 (25.0)	0
Weight decreased	1 (5.9)	3 (37.5)	0
Abdominal pain	1 (5.9)	2 (25.0)	1 (10.0)
AST increased	2 (11.8)	1 (12.5)	0
ALP increased	1 (5.9)	2 (25.0)	0
Nail ridging	2 (11.8)	1 (12.5)	0
Pruritis	0	3 (37.5)	1 (10.0)
Vomiting	2 (11.8)	1 (12.5)	0
Colitis	0	2 (25.0)	2 (20.0)

Safety Analysis Set (N=25)
*8 patients in Arm B and 2 patients from Arm A who crossed over to combination treatment

Overall summary of TEAEs

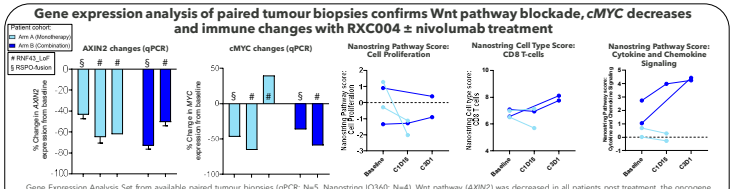
- Most frequent TEAEs across both arms were dysgeusia (56% of patients overall), nausea (52%), decreased appetite (48%) and diarrhoea (36%)
- Colitis events in 3 patients (all treatment related SAEs). Grade 3 enteritis, Grade 3 colitis and Grade 2 colitis (following an accidental RXC004 overdose)
- No bone events - all patients had denosumab to protect against Wnt-related loss in bone density

Treatment related TEAEs

- ≥Grade 3 RXC004 treatment related TEAEs in 5 patients:
  - Arm A: diarrhoea, asthenia and enteritis
  - Arm B: colitis and abdominal pain in 1 patient (both also related to nivolumab) and alanine aminotransferase increased, aspartate aminotransferase increased & blood alkaline phosphatase increased in another patient
- RXC004 treatment related serious TEAEs in 6 patients:
  - Arm A: diarrhoea and enteritis
  - Arm B: colitis (2 patients; both events also related to nivolumab), abdominal pain, and 1 patient with alanine aminotransferase increased, aspartate aminotransferase increased and blood alkaline phosphatase increased

Biomarker Results

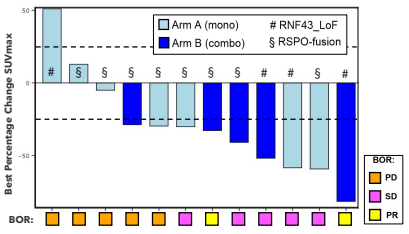
Gene expression analysis of paired tumour biopsies confirms Wnt pathway blockade, *cMYC* decreases and immune changes with RXC004 ± nivolumab treatment



Gene Expression Analysis Set from available paired tumour biopsies (qPCR: N=5, Nanostring (O360: N=4). Wnt pathway (*AXIN2*) was decreased in all patients post treatment, the oncogene cMYC was decreased in 4/5 patients. Nanostring analysis was feasible on 4 patients; cell proliferation showed a trend to decrease on treatment, whilst CD8 T-cells and cytokine/chemokine signalling increased following combination treatment in both patients analysed. Flow cytometry analysis confirmed blockade of PD-1 on CD4 and CD8 T-cells following Nivolumab treatment.

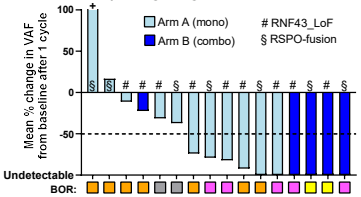
Robust metabolic (FDG-PET) and molecular (ctDNA) responses observed in all patients that achieved disease control (PR + SD) with RXC004 ± nivolumab treatment

Best percentage change in SUVmax from baseline (FDG-PET)



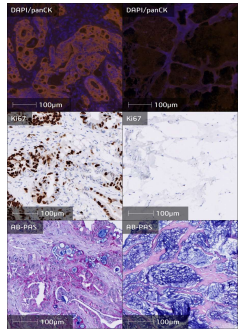
FDG-PET Evaluable Analysis Set (N=12); partial metabolic responses are defined using an empirical 25% reduction in SUVmax as per EORTC criteria **[6]**.

Mean percentage change in VAF from baseline (ctDNA)



ctDNA Evaluable Analysis Set (N=16); molecular responses are defined using an empirical 50% reduction in mean Variant Allele Frequency (VAF) of tumour associated variants detectable at baseline.

Arm B case study patient with cPR



Paired tumour biopsies from baseline and after 2 treatment cycles

- Arm A (monotherapy): 4/7 patients (57%) with partial metabolic response and 6/11 patients (55%) with molecular response
- Arm B (combination): 5/5 patients (100%) with partial metabolic response and 4/5 patients (80%) with molecular response
- Arm B case study shows loss of panCK and a switch from proliferative to mucin phenotype, consistent with preclinical data in RSPO/RNF43 mutant models

Conclusions

- Data from these small, signal searching cohorts show encouraging activity of RXC004 in the extremely hard to treat setting of genetically selected MSS mCRC
  - RXC004 in combination with nivolumab led to durable efficacy in a population where anti-PD-1 alone is not effective. Partial responses seen in 2/7 (28.6%) patients and DCR ≥16 weeks was 57.1%. This activity may offer improvements over current late line SoC* in this setting, if replicated in a larger study
  - RXC004 monotherapy led to stable disease in 38.5% of patients, comparable with late line SoC**
- RXC004 was tolerable both as a monotherapy and in combination with nivolumab
  - Safety profile consistent with the established profile of nivolumab and the emerging safety profile of RXC004 observed in Phase 1
  - Potential for Wnt-related bone events was prevented by prophylactic denosumab co-administration
- Significant Wnt pathway blockade and metabolic responses (FDG-PET) were observed in tumours in both study arms, whilst complete molecular responses (ctDNA) were associated with durable efficacy
- These results support further development of zamaporvint (RXC004) in combination with anti-PD-1, including nivolumab, in genetically-selected GI cancers

*Fruquintinib ORR 1.5% [FRESCO]; trifluridine/tipiracil + bevacizumab ORR 6.1% [SUNLIGHT]) **Regorafenib SD 41% [CORRECT] and TAS-102 SD 44% [RECOURSE]

References

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