Poster No. 719

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

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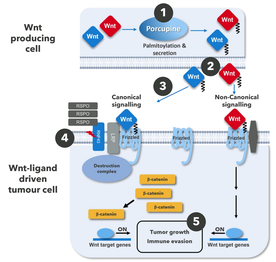
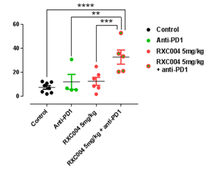
The Wnt Pathway drives Tumour Growth and Immune Evasion



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 tumour cells with RSPO fusions or RNF43 mutations the Wnt pathway is upregulated (due to an increased number of Frizzled receptors)
5. Wnt signalling drives tumour growth in genetically selected tumours and drives immune evasion in over 25 cancer types,

- Tumour-derived Wnt-ligand signaling reprograms the immune microenvironment causing intrinsic and adaptive resistance to Immune Checkpoint Inhibitor (ICI) therapy.
- Wnt signaling is correlated with:
  - reduced CD8+ve T-cell infiltration[1]
  - increased number of immune suppressive Treg cells [2]
  - ICI resistance in multiple cancers[3,4]
- Inhibition of Wnt-ligand signaling can enhance ICI efficacy by
  - (i) reversing dendritic cell tolerization
  - (ii) decreasing generation of Treg cells
  - (iii) reducing the recruitment of myeloid-derived suppressor cells[5,6]

RXC004 in combination with anti-PD-1



The combination of RXC004 + anti-PD-1 showed a statistically significant increase in the ratio of Cytotoxic T cells: Regulatory T cells, compared to either monotherapy alone in PD(L)-1 axis dominated CT26 CRC model[6]

Study Design

This is the second module of a Phase 1 protocol (NCT03447470; EUdraCT2017-000720-98).

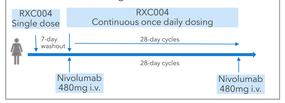
The first (monotherapy) module was reported at ESMO in 2021

Module 1: Monotherapy

- RXC004 well tolerated in patients at doses up to 2mg QD
  - Most common AEs: fatigue, decreased appetite, nausea, dysgeusia, vomiting
  - Dysgeusia was dose-related; did not lead to discontinuations
  - DLTs of colitis at higher doses
- 2mg selected as Phase 2 monotherapy dose

Module 2: Nivolumab Combination

Open label, 3+3 dose escalation study
Initial RXC004 dose:1mg QD



Patients received denosumab 120 mg s.c monthly to prevent bone adverse events [AEs] which are a known consequence of Wnt pathway inhibition.

The primary objectives of Module 2 were to assess safety and tolerability with nivolumab and to define a RP2D for this combination. Secondary objectives were PK and RECIST response.

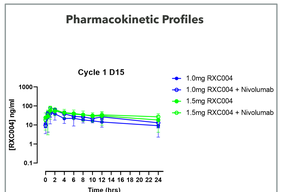
Exploratory objectives included on-treatment changes in circulating immune subsets and cytokines

Patient Characteristics and Pharmacokinetics

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

Patient Characteristics		N=13
Age (median, range) yrs		63 (30-74)
Men		7(54%)
Women		6(46%)
ECOG Performance Status	0	6 (46%)
	1	7 (54)
Colorectal Cancer		5 (38%)
Biliary Tract Cancer		2 (15%)
Ovarian Cancer		1 (8%)
Gastric Cancer		1 (8%)
Epithelioid Mesothelioma		1 (8%)
Squamous Vulval Cancer		1 (8%)
Other rare tumour types		2 (15%)
Prior lines of therapy (median, range)		3 (1-8)
Received an immune checkpoint inhibitor		1

Pharmacokinetic Profiles



Clinical Safety Results

Safety of RXC004 in combination with nivolumab is similar to monotherapy

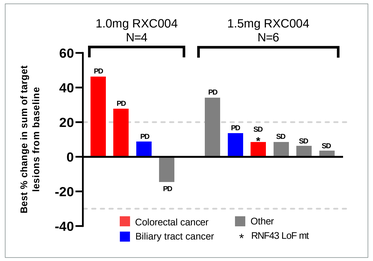
	1.0mg monotherapy N=3	Phase 2 doses: 1.0mg nivolumab combination N=5	1.5mg monotherapy N=7	Phase 2 doses: 1.5mg nivolumab combination N=8	2.0mg monotherapy N=6	3.0mg monotherapy N=4	TOTAL N=33*
Any TRAEs*	3 (100)	5 (100)	5 (71)	8 (100)	5 (83)	4 (100)	**30 (91)**
Fatigue	1 (33)	2 (40)	4 (57)	3 (38)	3 (50)	2 (50)	**15 (45)**
Nausea	2 (67)	2 (40)	3 (43)	4 (50)	1 (17)	3 (75)	**15 (45)**
Dysgeusia	0 (0)	1 (20)	2 (29)	4 (50)	4 (67)	3 (75)	**14 (41)**
Decreased appetite	1 (33)	1 (20)	2 (29)	3 (38)	2 (33)	3 (75)	**12 (36)**

- The recommended Phase 2 dose of RXC004 is 2mg in monotherapy
- Both RXC004 1.0mg and 1.5 doses were safe and tolerable in combination with nivolumab
- RXC004 1.5mg is the selected Phase 2 dose in combination with nivolumab
  - RXC004 doses higher than 1.5mg were not explored in Module 2 because of the potential for overlapping toxicity of colitis, which was reported in RXC004 monotherapy Module 1 and is a known adverse effect of immune checkpoint inhibitors.

*Treatment-related Adverse Events

Preliminary Clinical Efficacy results

Clinical Activity by Dose Cohort



Source: RedX internal data
2 Additional patients in 1.5mg group did not have RECIST data available in the database at the time of data cut off: 1 patient with adenocarcinoma descending colon RNF43 LOF mt and one patient with mucinous adenocarcinoma hepatic flexure

10/13 patients had RECIST-evaluable disease

- 4/5 at1mg [1 patient non-evaluable as discontinued treatment in Cycle 1 due to unrelated adverse event]
- 6/8 at 1.5mg [2 patients without RECIST data on database at time of data cut off]

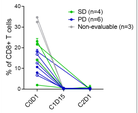
4/6 patients in the 1.5mg cohort had RECIST stable disease as best response

- Signet cell rectal cancer (LoF mt RNF43)
- Pleural epithelioid mesothelioma
- Malignant pulmonary cylindroma
- Recurrent solitary fibrous tumour of pleura

One additional patient with RNF43 LoF mt CRC did not yet have RECIST data on database, received 4 cycles of study treatment

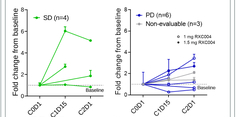
Changes in immune cells and cytokines on treatment

(A) PD-1+CD8+ T cells



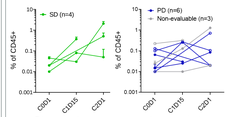
- Decrease in detection of circulating PD-1 positive CD8+ T cells evidence of target engagement for nivolumab
- Confirmed *in vitro* using Jurkat cells

(B) Ki67+CD8+ T cells



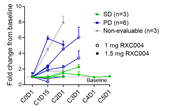
- CD8 T-cell proliferation increased in some patients and was more pronounced in patients with stable disease. This observation is reported to correlate with improved response to immune checkpoint inhibitors[8,9,10]

(C) M-MDSCs



- Circulating monocytic myeloid derived suppressor cells (M-MDSCs) increased in some patients and in all patients with stable disease. This is consistent with pre-clinical observations in the B16 syngeneic model following RXC004 treatment[6] , in which increased circulating M-MDSCs correlated with reduced tumour M-MDSCs

(D) CXCL10

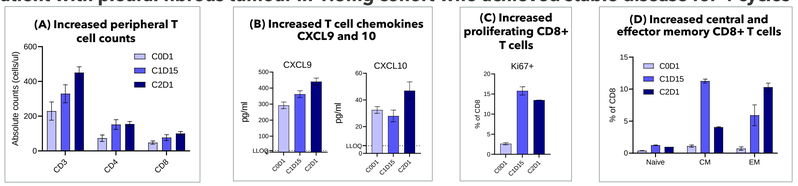


- Increased CXCL10 (T cell chemoattractant) was observed in the circulation of many patients – however this did not appear to correlate with clinical activity

(A) Percentage of PD-1 (CD279) positive cells out of total CD8+ T cells in patient blood as measured by flow cytometry (mean + SD). **(B)** Percentage of Ki67 positive CD8+ T cells in patient whole blood as measured by flow cytometry. Data is expressed as fold change from baseline C0D1 cycle 0, day 1 sample (mean + SD). **(C)** Percentage of monocytic myeloid derived suppressor cells (M-MDSCs - CD14+CD33+CD15-CD11b+HLA-DR-) in patient whole blood, plotted as a percentage of total CD45+ viable cells. **(D)** CXCL10/IP-10 protein expression in patient plasma as measured by Luminex (30-plex assay) and presented in pg/ml (mean + SD). Each line represents an individual patient. SD = stable disease, PD = progressive disease. C0D1 = Cycle 0 Day 1 (baseline sample), C1D15 = Cycle 1 Day 15, C2D1, C3D1, C4D1, C5D1 = Cycle 2,3,4,5 Day 1 (on treatment samples).

Case Study 1

Patient with pleural fibrous tumour in 1.5mg cohort who achieved stable disease for 4 cycles

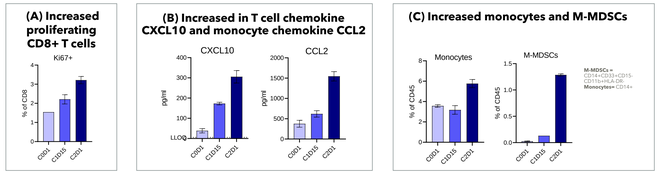


Notes: **CM+ central memory T cells** - CD45RO+CD45RA-CD62L+CCR7+; **EM+ effector memory T cells** - CD45RO+CD45RA-CD62L-CCR7-

(A) Absolute cell counts (cells/uL) for CD3+ T cells, CD3+CD4+ T cells and CD3+CD8+ T cells as measured in patient blood by flow cytometry (mean +/- SD). **(B)** CXCL9/MIG and CXCL10/IP-10 protein levels in patient plasma as measured by Luminex (30-plex assay) and presented in pg/ml (mean +/- SD). **(C)** Percentage of Ki67 positive CD8+ T cells out of total CD8+ T cells in patient whole blood as measured by flow cytometry (mean +/- SD). **(D)** Percentage of naïve (CD45RA+CD45RO-CD62L+CCR7+), central memory (CM; CD45RO+CD45RA-CD62L+CCR7+) and effector memory (EM; CD45RO+CD45RA-CD62L-CCR7-) CD8+ T cells out of total CD8+ T cells in patient blood, as measured by flow cytometry (mean +/- SD). C0D1 = Cycle 0 Day 1 (baseline sample), C1D15 = Cycle 1 Day 15, C2D1 = Cycle 2 Day 1.

Case Study 2

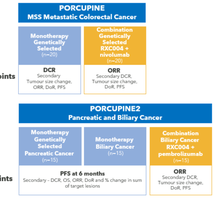
Patient with LoF RNF43mt CRC in 1.5mg cohort who remained on treatment for 4 cycles



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 (mean +/- SD). C0D1 = Cycle 0 Day 1 (baseline sample), C1D15 = Cycle 1 Day 15, C2D1 = Cycle 2 Day 1.

Conclusions

- RXC004 at doses of 1mg and 1.5mg QD in combination with standard dose nivolumab demonstrated a manageable tolerability profile
- The PK profile of RXC004 supports once daily dosing in combination with nivolumab
- Preliminary efficacy data supports the continued clinical investigation of this combination
- Preliminary observations in peripheral immune cell compartments for some patients on treatment are consistent with pre-clinical data, and suggest an anti-tumour immune response
- The recommended dose of RXC004 for Phase 2 combination studies with anti-PD-1 therapies is 1.5mg QD
- Ongoing Phase 2 studies or RXC004 in patients with Wnt ligand dependent tumours will now open enrolment into Combination Cohorts, where RXC004 is combined with immune checkpoint inhibitors



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