Background Tumour-derived Wnt-ligand signalling leads to a reprogramming of the immune microenvironment and is implicated in intrinsic and adaptive resistance to Immune Checkpoint Inhibitor (ICI) therapy. Specifically, Wnt-ligand signaling is correlated with reduced CD8+ve T-cell infiltration,1 and ICI resistance2 in multiple cancers.3 Inhibition of Wnt-ligand signalling can enhance ICI efficacy by (i) reversing dendritic cell tolerization, (ii) decreasing generation of Treg cells, and (iii) reducing the recruitment of myeloid-derived suppressor cells in tumor models.4 RXC004 is a novel small molecule inhibitor of PORCN, a protein-serine-O-palmitoyltransferase [5]. PORCN is essential for post-translational modification of Wnt ligands which is required for downstream Wnt signaling. RXC004 thus has potential for monotherapy efficacy in Wnt-ligand driven tumors i.e. cancers with RNF43 mutations or R-Spondin fusions, or with high Wnt-ligand activity. Furthermore, RXC004 can reverse immune evasion in mouse models,5 and may therefore restore ICI sensitivity in ICI resistant tumors when co-administered.

This abstract reports the second module of a multi-modular adaptive design protocol (NCT03447470). The first module was previously reported6 and the recommended Phase 2 dose (RP2D) for RXC004 monotherapy was 2mg QD.

Methods This was an open label, 3+3 dose escalation study. Following a single dose with a 7-day washout, patients received RXC004 QD in 28-day cycles, and nivolumab 480mg i.v every 4 weeks.

The primary objectives were to assess safety and tolerability and define a RP2D of RXC004 to combine with ICIs. Secondary objectives were Pharmacokinetics (PK) and RECIST response. Exploratory objectives included changes in circulating immune subsets by flow cytometry, and cytokines by a bead-based multiplexed immunoassay.

Results Between 24/03/2021 and 30/06/2022, 14 patients with unselected advanced solid tumors received RXC004 at doses of 1mg and 1.5mg QD, in combination with nivolumab. The AE profile for the combination was broadly similar to nivolumab monotherapy. The most common treatment-related AEs were nausea, dysgeusia, fatigue, anorexia and weight loss. No grade 4/5 AEs, bone events or immune-related AEs were reported.

RXC004 PK exposure in the combination did not exceed the 2mg QD monotherapy exposure. Disease control was observed in some patients in the 1.5mg QD combination cohort.

Conclusions In patients with unselected cancers, RXC004 was safe and tolerated at doses up to 1.5mg QD in combination with standard dose nivolumab. The RP2D was 1.5mg QD. RXC004+ICI combinations will now be investigated in selected patients with Wnt-ligand driven tumors.

Trial Registration EudraCT No: 2017-000720-98

REFERENCES

Ethics Approval This study was approved by West Midlands-Edgbaston Research Ethics Committee and Health Research Authority in UK; approval number 222362 (IRAS ID).


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