Redx Pharma
(AIM:REDX)
Compelling opportunity to take targeted oncology and fibrosis medicines into the clinic

Corporate Presentation
June 2020
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Redx Pharma Overview

Biotech focused on small molecule, targeted medicines in oncology and fibrosis

• Targeting compelling opportunities in disease areas with high unmet need and strong scientific rationale

• Highly experienced in-house research team with proven track record built on medicinal chemistry expertise
  - 2017 Sale to Loxo Oncology/Eli Lilly of BTK inhibitor (now LOXO-305) for $40M cash; promising Ph 1/2 results
  - 2019 Sale to Jazz Pharmaceuticals of pan-RAF inhibitor for $3.5M with up to $203M in milestones, plus royalties

• In oncology, RXC004 has opportunity to unlock potential of the Wnt pathway in genetically selected patients
  - RXC004 Phase 1 monotherapy dose-escalation study completing in 2020, building on compelling animal efficacy data
  - Targeted at tumours driven by Wnt pathway in multiple cancers – both monotherapy and immuno-oncology combination
  - Therapeutic window for class now evident (120+ patients in clinical trials) with early signs of efficacy in targeted patients

• In fibrosis, ROCK2 is an exciting target in multiple fibrotic diseases with RXC007 planned to enter clinic in 2021
  - RXC007 as a ROCK2 selective inhibitor was nominated as a preclinical development candidate in H1 2020
  - Promising preclinical efficacy and targets significant commercial markets (IPF, NASH, diabetic nephropathy) with limited competition in ROCK2 pathway
  - ROCK2 inhibitor belumosudil (KD025) by Kadmon is well tolerated in >450 patients in clinical trials, with clinical anti-fibrotic activity in IPF and compelling efficacy in cGvHD demonstrated

• Beyond delay to ongoing clinical trial due to COVID-19, there is limited impact on other Redx programme activities to-date
Redx Executive Management Team
Ambitious Management team in place with strong scientific, clinical and commercial experience

Lisa Anson,
Chief Executive Officer
20-year career at AstraZeneca plc. Significant leadership experience including President of AstraZeneca UK, President of the Association of British Pharmaceutical Industry

Dr Richard Armer,
Chief Scientific Officer
Significant experience in both small biotech and large pharmaceutical companies through roles in Pfizer, Organon, Ardana, Oxagen & Lectus Therapeutics. Successful in generating and progressing multiple clinical candidates

Dr Andrew Saunders,
Chief Medical Officer
Oncology focus since 1992 both in clinical practice and pharmaceutical/biotech industry. Including senior roles at Eli-Lilly and Roche (Rituximab)

Dr James Mead,
Chief Financial Officer
Finance leadership roles with 16 years at AstraZeneca, including CFO AstraZeneca Netherlands and Investor Relations; PhD in molecular biology
## Redx Pipeline

Highly selected, targeted, small molecules for oncology and fibrosis

<table>
<thead>
<tr>
<th>Target / Product</th>
<th>Indication(s)</th>
<th>Research</th>
<th>Preclinical</th>
<th>Clinical Phase 1/2</th>
<th>Targeted Milestones</th>
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<tr>
<td><strong>Porcupine Inhibitor</strong></td>
<td>Monotherapy in solid tumours (genetically selected mCRC and pancreatic cancer; biliary cancer)</td>
<td></td>
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<td></td>
<td>Phase 1 mono safety completion – H2 2020</td>
</tr>
<tr>
<td>(RXC004)</td>
<td>Combination with anti-PD-(L)1 (genetically selected MSS mCRC)</td>
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<td>Phase 2 start – H1 2021</td>
</tr>
<tr>
<td><strong>ROCK2 Selective Inhibitor</strong></td>
<td>Lung fibrosis (IPF)</td>
<td></td>
<td></td>
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<td>Preclinical development candidate – H1 2020</td>
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<tr>
<td>(RXC007)</td>
<td>Liver fibrosis (NASH)</td>
<td></td>
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<td></td>
<td>Entering clinic – H2 2021</td>
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<td></td>
<td>Kidney fibrosis (DN)</td>
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<tr>
<td><strong>Porcupine Inhibitor</strong></td>
<td>Lung fibrosis (IPF)</td>
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<td></td>
<td>Entering clinic – 2021</td>
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<tr>
<td>(RXC006)</td>
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<tr>
<td><strong>GI-targeted ROCK</strong> Inhibitor</td>
<td>Fibrosis associated with Crohn’s disease</td>
<td></td>
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<td>Preclinical development candidate – 2021</td>
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<tr>
<td>Collaboration</td>
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<td><strong>Pan-RAF inhibitor Collaboration</strong></td>
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<td>Partnered with Jazz Pharmaceuticals</td>
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<td><strong>Research Targets</strong></td>
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<td>In-house Research Teams investigating oncology and fibrosis targets</td>
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Oncology: RXC004 (Porcupine Inhibitor)
Potentially a best-in-class, small molecule drug against a validated cancer target in clinical development

• RXC004 is a potent, oral porcupine inhibitor (PORCNi) in Phase 1/2
  - Significant tumour growth inhibition demonstrated in preclinical models
  - Composition of matter patent granted in US, Europe, China, Singapore, Eurasia and Australia
  - Phase 1/2 clinical trial ongoing with first two patient cohorts completed

• PORCN regulates secretion of Wnt ligands
  - PORCN is a validated drug target
  - Wnt pathway is critical driver of tumour cell proliferation and immune evasion

• RXC004 has promising dual tumour targeting and immuno-oncology combination potential, in genetically selected tumours
  - RXC004 has demonstrated robust direct tumour-targeting efficacy as a monotherapy in preclinical models (human tumour cell lines with upstream Wnt pathway aberrations e.g. RNF43 mutation or RSPO fusion)
  - In genetically selected patients, RXC004 will have a dual effect by halting tumour growth and stimulating the immune system, both as monotherapy and in combination with immune checkpoint inhibitors (ICIs)

“Evidence of RXC004 safety combined with immune cell changes will command interest”
- Immuno-oncology Advisor – Prof. Aurélien Marabelle, Gustave Roussy
Oncology: RXC004 (Porcupine Inhibitor)
Phase 1 clinical trial ongoing with first two cohorts completed as of May 2020

**RXC004 - Phase 1 - Dose Escalation**
Monotherapy, Single Ascending Dose/Multiple Ascending Dose (3+3 design)

- **Starting Dose**: 0.5mg
- **Cohort N=3**
- **Cohort 1.0mg N=3**
- **Cohort 1.5mg N=3**
- **Cohort 2.0mg N=3**
- **Cohort 2.5mg N=3**
- **Cohort 3.0mg N=3**

**Phase 1 Objective**
Dose escalation cohorts: Assess safety and tolerability of RXC004 in an all-comers cohorts of advanced cancer patients.
5 UK sites; 12-18 months duration

**Lead Principal Investigator**
- **Dr Natalie Cook**, Christie Hospital, Manchester, UK

**Other Investigators:**
- **Dr Juanita Lopez**, Royal Marsden Hospital, Institute of Cancer Research, London, UK
- **Dr Debasish Sarker**, Guy’s Hospital, London, UK
- **Prof Ruth Plummer**, Northern Institute of Cancer Research, Newcastle, UK
- **Dr Sarah Blagden**, Department of Oncology, University of Oxford, UK

**Multiple decision points (expand/escalate) based on**
- Emerging safety data (Dose Limiting Toxicity, DLT)
- Pharmacodynamic markers
- Clinical efficacy

*At May 2020*
Oncology: RXC004 Clinical Summary*
RXC004 is well tolerated in patients in first two cohorts in Phase 1

- Completed dose-limiting toxicity (DLT) periods of cohort one (0.5mg QD, n=4)** and two (1.0mg QD, n=3) of Phase 1 dose escalation
  - Median treatment duration to date - 7 weeks
  - Human PK profile confirmed and exposure as predicted from initial 10mg dose
  - Pharmacodynamic response (Wnt pathway inhibition) demonstrated in patient skin at 0.5mg and 1.0mg RXC004 QD dose

- RXC004 is well tolerated in patients in first two cohorts (0.5mg and 1.0mg QD)
  - No DLTs
  - RXC004-related adverse events (AEs) were only grade 1-2 in all patients; no > grade 3-related AEs; most common related AEs were fatigue and nausea
  - Rises in β-CTX (bone turnover marker) observed, bone loss treatment (denosumab) instituted in 3/6 patients; prophylactic denosumab adopted going forward
  - No fractures observed

- Cohort 3 (1.5mg QD) recruitment ongoing with following cohort to include genetically selected patients only
  - Patient selection assays available (RNF43 mutation and RSPO fusion) and ethics obtained to allow pre-screening of patients to enrich Phase 1 dose escalation
  - Expected completion H2 2020 with risk mitigation plan in place for any further COVID-19 delay

*As of May 2020
**One patient not evaluable, did not complete treatment, therefore n=3 total evaluable patients in cohort one
Ant-Fibrotics: RXC007 (ROCK2 Selective Inhibitor)

ROCK2 selective inhibition is an exciting approach with potential to treat multiple fibrotic diseases

- ROCK2 inhibition is a promising approach to a validated target involved in fibroblast activation
  - RXC007, a novel and orally active selective ROCK2 inhibitor, was nominated as a development candidate in January 2020
  - Robust preclinical efficacy demonstrated in murine liver, lung and kidney fibrosis models*

- Redx aim to take RXC007 into clinical trials in H2 2021

ROCK2 inhibition could target multiple diseases underpinned by fibrosis and with high unmet need

NASH and NAFLD

No therapies currently approved for NASH with few pipeline treatments targeting underlying fibrosis, which is increasingly important for treatment of late-stage disease – estimated 10.5m\(^1\) patients

IPF

Chronic and fatal lung disease with limited effective therapy. Estimated median survival is just 2-5 years from diagnosis\(^2\), resulting in >50,000 annual deaths worldwide\(^3\)

*Preclinical efficacy in murine bleomycin-induced lung fibrosis model and murine CCl\(_4\)-induced liver fibrosis model demonstrated with RXC007. Preclinical efficacy in murine UUO kidney fibrosis model demonstrated with close RXC007 analogue REDX10843

Anti-Fibrotics: RXC007 (ROCK2 Selective Inhibitor)
RXC007 demonstrates compelling efficacy in well-validated preclinical model* of lung fibrosis

RXC007 significantly reduced fibrosis (Ashcroft score) and collagen deposition (Masson’s trichrome)

Ashcroft Score

Masson’s Trichrome

RXC007 significantly reduced pro-fibrotic and pro-inflammatory gene expression of pharmacodynamic (PD) biomarkers in the lung, plasma and bronchoalveolar lavage fluid (BALF)

PD lung gene expression

PD biomarkers

*Redx published data from therapeutic bleomycin-induced IPF mouse model
Anti-Fibrotics: RXC006 (Porcupine Inhibitor)
First-in-class PORCNi in fibrosis aiming to move to clinic

- Scientific evidence suggests porcupine inhibition may be effective in patients with advanced fibrosis
  - Both canonical and non-canonical Wnt pathways involved in fibrosis – suggesting universal suppression of Wnt will be effective
  - Wnt pathway involvement increases with the severity of disease

- PORCNi show robust preclinical efficacy in murine kidney, liver and lung fibrosis models
  - RXC006 potently suppresses Wnt release from human cells relevant to fibrosis
  - RXC006 nominated as development candidate (November 2018)
  - Innovate UK grant awarded to progress fibrosis biomarker project with Medicines Discovery Catapult
  - Composition of matter patent granted in US, Japan, China and Australia (distinct from RXC004)

- Phase I clinical study for RXC006 in IPF anticipated to begin in 2021, subject to ongoing partnering discussions
  - RXC006 has pharmacokinetic properties suitable for once or twice-daily oral dosing
  - Manufacturing and preclinical development studies to support a Phase I IND/CTA have been initiated

Porcupine inhibitor, RXC006 suppresses fibrosis in a bleomycin-induced mouse model of IPF
Image representative of group mean Ashcroft scores. Scale bar indicates 1.2 mm. Small region of dense collagenous connective tissue (fibrosis; black arrows demarcate) and lymphocyte infiltrates/aggregates (*) are present. A bronchiole (Br) and blood vessels (BV) are indicated.
Crohn’s disease affects 1.5m people globally, of which 50% will develop strictures or complications leading to fibrostenosis.

- No treatment is currently available except for invasive surgery, representing considerable unmet medical need
- No experimental therapies have progressed beyond preclinical development for underlying fibrosis

Redx GI-targeted ROCK inhibitor series is a potent, small molecule ROCK 1/2 inhibitor that restricts to the gut - potential to be first-in-class

- ROCK (Rho-associated Kinase) is a target involved in fibroblast activation
- Minimal absorption profile makes it highly and selectively active in gut without risking systemic exposure
- Blocks pro-fibrotic signals and has shown in vivo efficacy in models and ex vivo using tissue from Crohn’s patients
- Composition of matter patents granted

Next milestone: preclinical development candidate selection

1. GlobalData Crohns Disease Dynamic Market Forecast to 2026 report; 2. Chan et al, 2018
## Redx Key Milestones and Value Drivers to 2022

<table>
<thead>
<tr>
<th></th>
<th>2020</th>
<th>2021</th>
<th>2022</th>
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<tr>
<td><strong>PORCN (RXC004)</strong></td>
<td><strong>✓</strong> H1 Ph 1 complete first two dose-escalation cohorts</td>
<td><strong>H1</strong> Ph 2 mono expansion start (mCRC, biliary, pancreatic)</td>
<td>Ph 2 data mono MSS mCRC</td>
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<td></td>
<td><strong>H2</strong> Ph 1 monotherapy safety completion</td>
<td><strong>H1</strong> Ph 1 start - IO combo safety</td>
<td>Ph 2 data mono biliary cancer</td>
</tr>
<tr>
<td><strong>ROCK2 (RXC007)</strong></td>
<td><strong>✓</strong> H1 Development Candidate selected</td>
<td><strong>H1</strong> Ph 1 start</td>
<td><strong>H1</strong> Ph 1 safety data readout</td>
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<tr>
<td></td>
<td><strong>H2</strong> GLP toxicity studies</td>
<td><strong>H2</strong> Ph 2 start - IO combo MSS mCRC</td>
<td><strong>H2</strong> Ph 2 start</td>
</tr>
<tr>
<td><strong>PORCN (RXC006)</strong></td>
<td>Ongoing development</td>
<td>Ph 1 start</td>
<td>Ph 2 start</td>
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<tr>
<td><strong>GI-targeted ROCK</strong></td>
<td>Ongoing research</td>
<td>Development Candidate selected</td>
<td>Ph 1 start</td>
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<tr>
<td><strong>Pan-RAF inhibitor</strong></td>
<td>Progress collaboration</td>
<td>Progress collaboration</td>
<td>Progress collaboration</td>
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<td><strong>Research</strong></td>
<td>Progress discovery activities for Research programmes</td>
<td>Progress discovery activities for Research programmes</td>
<td>Progress discovery activities for Research programmes</td>
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### Key
- **Redx Development**
- **Partnered Programme**
- **Redx Research**
Summary

• Biotech Company focused on developing novel targeted medicines in oncology and fibrosis
  − Ambitious management team with strong scientific, clinical and commercial experience
  − Excellence in drug design validated by asset sales to Loxo Oncology (now Eli Lilly) and Jazz Pharmaceuticals

• Lead oncology asset is opportunity to unlock Wnt pathway potential by targeting Wnt-driven tumours in monotherapy and combination
  − Phase 1 monotherapy safety completion in H2 2020
  − Phase 1 IO combo safety start in H1 2021

• Lead fibrosis treatments target significant commercial markets including IPF and NASH
  − ROCK2 selective inhibitor for fibrosis, ready to enter clinic in H2 2021
  − IPF asset (first in pathway) – progress to clinic in 2021
Oncology: RXC004 (Porcupine Inhibitor)
Clinical stage programme for genetically selected cancers

Additional Programme Information
Oncology: RXC004 (Porcupine Inhibitor) – Summary
Targeting Wnt ligand-driven (RNF43 mutation/RSPO-fusion) tumours in monotherapy & combination

• Recent resurgence of interest in the Wnt pathway, beyond direct tumour targeting
  − Strong preclinical and clinical evidence linking Wnt activation to immune-checkpoint inhibitor resistance across 28 cancer types
  − >90% of CRC patients don’t respond to approved immune-checkpoint inhibitors

• RXC004 in Phase 1 targeting efficacy in a genetically-defined (RNF43 mutation or RSPO-fusion) patient population
  − Potent, selective porcupine inhibitor with robust direct tumour efficacy in preclinical models with upstream Wnt pathway aberrations (RNF43 mutation or RSPO-fusion)
  − RXC004 has monotherapy preclinical efficacy with a proven immune-stimulating mechanism of action in mouse model resistant to immune checkpoint inhibitors
  − Multiple opportunities for life cycle management; RNF43 mutations or RSPO-fusion in est. 8% MSS CRC, 5% pancreatic cancer, 5% squamous NSCLC or 6% CRPC. Additional IO opportunities beyond genetic selection based on recent clinical evidence from Novartis e.g. uveal melanoma
  − Phase 1 clinical trial ongoing with completed DLT periods of first two cohorts, with third cohort ongoing
  − Leading CRC, pancreatic and biliary cancer KOLs share enthusiasm for RXC004 clinical programme from recent meetings

• Porcupine inhibitors represent opportunity to unlock potential of Wnt pathway
  − Class demonstrated acceptable safety both in monotherapy (>120 patients* to date) and combination (ongoing anti-PD1 trials)
  − Other porcupine inhibitors ETC159 (A*STAR) and WNT974 (Novartis) both reported early signs of efficacy in early phase 1 trials. Both reported stable disease (SD), with ETC159 showing the most impressive 28 weeks durable SD in RSPO-fusion CRC patient
  − At AACR 2020, WNT974 + anti-PD1 (spartalizumab) in 32 patients demonstrated acceptable safety and a DCR of 47% with durable SD in anti-PD1-pretreated patients (particularly in uveal melanoma). Other combinations in ongoing investigation include A*STAR’s ETC-159 + pembrolizumab including patients with RSPO-fusions; and Curegenix’ CGX1321 + pembrolizumab

• Limited competition, only four other porcupine inhibitors but not all available for acquisition by large pharma
  − RXC004 composition of matter patent filed October 2015; granted in US, EU, China, Singapore, Australia and Eurasia

*Few genetically selected patients
DCR = Disease Control Rate
CRPC = Castrate-Resistant Prostate Cancer
IO = Immuno-oncology
NSCLC = Non-small Cell Lung Carcinoma
Oncology: RXC004 – Dual Mechanism of Action
RXC004 demonstrates multiple mechanisms to fight cancer directly and via the immune system

**Eliminates Tumour Cell Proliferation**
Abolishes Ki67 staining in RSPO-fusion CRC xenograft model

**Differentiates Tumour Cells**
Increased size and mucin staining of tumour cells with RSPO-fusion

**As a Monotherapy**
Dramatic increase in immune related gene expression post-RXC004 treatment in anti-PD1-resistant B16 mouse syngeneic model

**RXC004**

**Stimulates the Immune System**

**In Combination with anti-PD(L)1**
Improved responses observed when RXC004 combined with anti-PD1 in CT26 syngeneic CRC immune-mediated model
Targeting porcupine by RXC004 offers a unique advantage over other Wnt pathway targets

- Porcupine activates all Wnt ligands for secretion
- Secreted Wnt ligands can activate canonical (β-catenin-dependent) and non-canonical (β-catenin-independent) Wnt signalling pathways; which have roles in driving both tumour growth and immune cell evasion in cancer
- Inhibiting porcupine blocks both canonical and non-canonical Wnt signalling pathways

Genetic selection strategy

- Enabled by targeting patients with upstream Wnt pathway aberrations (RNF43 LoF mutations and RSPO-fusions), that occur in multiple cancers including colorectal and pancreatic
- Patient selection assays developed for ongoing RXC004 clinical trial and available for screening
The Wnt pathway is frequently mutated in the early development of CRC and pancreatic cancers

**Preclinical Evidence**
- RNF43 LoF mutations and RSPO fusions both result in increased Fzd receptor in the cell surface of the tumour cell and a greater dependence on Wnt ligand for survival
- Human tumour cell lines with RNF43 LoF mutation and RSPO fusions have been shown to be sensitive to porcunipe inhibitors, in both in vitro and in vivo preclinical models (Jiang et al. 2013; Li et al. 2018; Redx Pharma in-house models)
- Sensitivity to porcupine inhibition is maintained even in the presence of MAPK pathway mutations (e.g. KRAS, BRAF) which often lead to resistance mechanisms to other targeted agents

**Clinical Evidence**
- Early signs of clinical efficacy have been reported in RSPO-fusion CRC from clinical trial of porcupine inhibitor ETC-159 (A*STAR)
- Wnt pathway activation has been associated with immune evasion in 28 cancer types, including pancreatic and CRC

Proliferation plot across 11 genetically-defined human and mouse cancer models of Wnt pathway aberration. Upstream Wnt pathway mutants (RSPO / RNF43 / ZNFR3) are sensitive to RXC004, whereas downstream Wnt pathway mutants (APC/β-Catenin) are not.
The Wnt pathway is frequently mutated in the early development of certain types of cancer, e.g. CRC, pancreatic and biliary cancers

- Wnt pathway mutations can be classified as upstream (such as LoF RNF43 mutations, or RSPO-fusions), or downstream (such as LoF APC mutations, or GoF β-catenin mutations), and are largely mutually exclusive
- Upstream Wnt pathway mutations are dependent on Wnt ligands to drive the pathway, whereas downstream mutations are not

## Oncology: RXC004 – Addressable Indications Overview

Wnt pathway activation drives tumour growth in multiple cancers with poor long-term prognosis

<table>
<thead>
<tr>
<th>RXC004 Addressable Indications</th>
<th>5-Yr Survival (Metastatic disease)</th>
<th>Annual incidence (new Metastatic cases (7-8MM))</th>
<th>Prevalence of Genetic Mutation of Interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSS mCRC (95% of all mCRC cases are MSS)</td>
<td>14%</td>
<td>150,000+ patients</td>
<td>8% of patients (RNF43 mutations in 3% of population + RSPO fusions in 5% of population)*2</td>
</tr>
<tr>
<td>Pancreatic Cancer</td>
<td>3%</td>
<td>120,000+ patients</td>
<td>5% of patients have RNF43 mutations*1</td>
</tr>
<tr>
<td>Biliary Cancer</td>
<td>2%</td>
<td>60,000+ patients</td>
<td>&gt;70% of patients have high Wnt ligand expression*3</td>
</tr>
<tr>
<td>Squamous NSCLC</td>
<td>6%</td>
<td>85,000+ patients</td>
<td>5% of patients have RSPO fusions*3</td>
</tr>
<tr>
<td>CRPC</td>
<td>31%</td>
<td>16,500+ patients</td>
<td>6% of patients have RNF43/RSPO fusions*4</td>
</tr>
</tbody>
</table>

MSS mCRC = Microsatellite-Stable Metastatic Colorectal Cancer; CRPC = Castrate-resistant Prostate Cancer; NSCLC = Non-small-cell lung carcinoma

RNF43 mutation frequency determined from all relevant studies published on cBioPortal for cancer genomics (updated Jan 2018). Only mutations resulting in functional impairment (LoF) were considered. Gao et al. 2013 & Cerami et al. 2012; *2RSPO fusion prevalence in CRC is a combination of studies (Shesagiri, 2012; Shinmura, 2014; Kleeman, 2019) *3Karhera et al. 2014; *4Murillo-Gorzan & Gupta 2017; *ii) "Precision Panc" initiative data. RNF43 mutations in CRC patients identified by RXC004 clinical investigators; *iii) Loilome et al. 2014, Boulter et al. 2015; *v) https://www.cancer.org | *vi) Incidence data sourced from GlobalData Epidemiology data (MM = Major Markets US, EUS, Japan, China) | *v) Gong et al. March 21, 2017 (ASCO JCO)

**Lead RXC004 indications**

**LCM Opportunities**

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<tr>
<th>Affected event</th>
<th>Gene(s) Involved</th>
<th>Other genetic alterations</th>
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<tr>
<td>Wnt pathway activation</td>
<td>APC, EGFR signaling, TGFβ3 response inactivation, Loss of p53 function</td>
<td>Other genetic alterations</td>
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<tr>
<th>Normal epithelium</th>
<th>Early adenoma</th>
<th>Dysplastic crypt</th>
<th>Intermediate adenoma</th>
<th>Late adenoma</th>
<th>Carcinoma</th>
<th>Metastasis</th>
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Approval of immune checkpoint inhibitors (ICIs) has revolutionised the treatment of cancer
- Yet high population (~90%)\(^1\) of eligible patients do not benefit from treatment with ICI

Exciting potential for RXC004 in combination with ICIs with early validation shown in other porcupine inhibitor trials
- ICIs are ineffective in MSS CRC but combination with RXC004 has potential to reverse this innate resistance
- Novartis PORCNi in combination with ICI in ongoing clinical phase 1 demonstrates acceptable safety and early proof of concept\(^2\)
- Three other PORCNi also in clinical development by A*STAR, Curegenix (both have agents in combination with ICI) and Sinovent

RXC004 preclinical data supports combination rationale (see next slide)
- RXC004 may combine with anti-PD1 to further stimulate immune response in “cold” tumours
- RXC004 has potential to improve immune response in “hot” tumours

2. Janku et al. (2020) AACR, CT034 - Phase I study of WNT974 + spartalizumab in patients (pts) with advanced solid tumors
Efficacious in genetically-defined human tumour models

- Strong inhibition of tumour growth in RNF43 mutant pancreatic cancer model
- Direct tumour targeting in genetically selected populations will lead to sensitivity to RXC004

Efficacious as a monotherapy in a “cold” tumour model

- Improved survival rate observed as monotherapy in B16F10 syngeneic melanoma immune mediated model
- Anti-PD1 had no monotherapy effect on this immunologically “cold” model
- RXC004 has potential to initiate immune response in “cold” tumours

Improves immune response in combination with a checkpoint inhibitor

- Improved responses observed in combination with anti-PD1 in CT26 syngeneic CRC immune-mediated model
- RXC004 has potential to improve immune response in “hot” tumours
Oncology: PORCNi Class – Clinical Development Progress

Published data demonstrates tolerability, target engagement, and signs of efficacy from the class

Currently 5 porcupine inhibitors (PORCNi) are in ongoing Phase 1/2 clinical trials for oncology indications. Data has been reported from PORCNi WNT974 (Novartis) and ETC159 (A*STAR) from >120 patients, over multiple treatment cycles

- Porcupine inhibitors administered as mono and in combo are tolerated in patients and have a manageable safety profile
  - MTD was not reached with WNT974 and dysgeusia (impaired taste) was reported as the main AE
  - ETC159 resulted in bone effects and fractures at highest test dose. However after instilling bone protection plan (use of prophylactic denosumab), no further fractures were reported
  - WNT974 + anti-PD1 showed that AEs were largely consistent with those observed during treatment with either single agent

- WNT974 and ETC159 have demonstrated target engagement and immune effects at tolerated doses
  - Demonstrated inhibition of AXIN2 expression (Wnt pathway blockade) in patient tumour and skin
  - Changes in dendritic and chemokine expression profiles in tumours
  - Increased immune cell infiltrate by IHC

- ETC159 and WNT974 (mono and combo) have both reported early signs of efficacy to-date, including in genetically selected patients
  - ETC159 demonstrated impressive 28 weeks durable Stable Disease in RSPO fusion CRC patient (see graph below)
  - Monotherapy WNT974 demonstrated Stable Disease with tumour shrinkage of -27% in RNF43 mutation appendiceal cancer patient
  - Combination of WNT974 + anti-PD1 demonstrated DCR in 47% (9/19 patients) whose cancers were refractory to prior anti-PD1 therapy. 5 patients remain on study for >24 weeks, supporting further investigation
Anti-fibrotic: RXC007 (ROCK2 Selective Inhibitor)
Exciting best-in-class approach to treat multiple fibrotic conditions

Additional Programme Information
Selective Inhibition of ROCK2 is an exciting approach to target Fibrosis

- ROCK2 is a nodal point in cell signalling pathways associated with fibrosis, with potential to deliver compelling efficacy across multiple indications with high unmet need
  - Opportunity to target multiple, commercially attractive disease indications, including lung (IPF), liver (NASH) and Kidney (DN)

- Redx ROCK2 chemical series including RXC007 are highly selective in targeting ROCK2
  - Historically, ROCK2 is challenging to drug because of high homology between ROCK1 and ROCK2 isoforms. Furthermore, ROCK1/2 inhibition induces clinically significant hypotension
  - Selective ROCK2 inhibition does not induce hypotensive cardiovascular events in the clinic as demonstrated by sole ROCK2 competitor belumosudil (KD025)

- ROCK2 is a clinically validated target
  - Clinical efficacy demonstrated across multiple organs, with belumosudil (KD025) demonstrating PoC in cGvHD and early PoC in IPF
  - Safe and well tolerated (KD025 in Ph 2 trials in cGvHD and IPF); KD025 DDI study completed in Aug 2019 (NCT03530995) with ongoing hepatic impairment study estimated to complete Aug 2020 (NCT04166942)

- Redx’s highly selective ROCK2 lead compounds show robust preclinical efficacy in murine liver, kidney and lung fibrosis models

- Significant market interest in ROCK2 selective inhibitor concept with potential development pathways validated by KOLs

- RXC007 was nominated in H1 2020 as a ROCK2 selective development candidate and aims to enter clinical trials in H2 2021

DN = Diabetic Nephropathy; cGvHD = chronic graft versus host disease; Belumosudil (KD025): Kadmon Corp’s ROCK2 selective inhibitor
Anti-Fibrotics: RXC007 – Growth Potential
Considerable opportunity for ROCK2 inhibition to tackle multiple diseases associated with fibrosis

- ROCK2 is a nodal point in cell signalling pathways associated with fibrosis
  - Opportunity to target multiple therapy areas, including IPF, NASH and diabetic kidney disease, but also other areas (see right)

- ROCK2 is a clinically safe and well tolerated target
  - Safe and well tolerated (KD025 in Ph II trials in cGVHD and IPF)

- Positive ROCK2 inhibitor (KD025) PoC observed in human cGVHD
  - High response rate observed (ORR 73-75%) in Ph II ROCKstar trial (KD025-213; NCT03640481)

ROCK2 inhibition could address multiple therapy areas

**Respiratory**
- IPF - 140,000+ patients, $4-6bn market by 2025
- Interstitial lung diseases (ILDs) – potential 2-3x size of IPF market

**Gastroenterology**
- NASH/NAFLD – 65m patients, $10bn market by 2026
- Crohn’s disease – 2m patients, $13bn market by 2023

**Cardiovascular**
- PAH - 60,000+ patients, $4.7bn market by 2023
- Diabetic nephropathy – 4.8m patients, £1.8bn market by 2026

**Immunology**
- Scleroderma/Systemic Sclerosis - 100,000 patients, $0.5bn market by 2024
- Plaque Psoriasis – 17m patients, $20bn market by 2023

**CNS**
- Multiple sclerosis - 2.3m patients, $40bn market by 2026
- Alzheimer’s disease – 32m patients, $8.4bn market by 2023

**Oncology/Related**
- GVHD - 60,000+ patients, $0.6bn market by 2023
- Pancreatic cancer - 125,000+ patients, $2.3bn market by 2023
- Breast cancer - 3.5m patients, $10bn market by 2023

*Diseases based on scientific and preclinical evidence available in literature, and other associated ROCK2 inhibitors in clinical trials. Market sizes and patient prevalence data sourced from GlobalData Epidemiology & Forecast reports, Reuters, Acumen Research and Consulting, iHealthcare Analyst
Anti-Fibrotics: ROCK2 inhibition reduces Hypotension Risk
Selective ROCK2 inhibitors can inhibit fibrosis without inducing hypotension

- Pan-ROCK1/2 inhibitors deliver an anti-fibrotic effect in preclinical studies but induce hypotension, limiting further clinical development
- Selective ROCK2 inhibitors can inhibit fibrosis without inducing hypotension
- No cardiovascular events highlighted from Ph I or Ph II clinical trials with selective ROCK2i belumosudil (KD025)

Hypotension is induced by a ROCK1/2 inhibitor in rats

Redx ROCK2i has no impact on mean blood pressure in rats

Data are plotted LS mean±SEM n=6 animals. Statistical effect of treatment analysed by one-way ANOVA with Fisher’s LSD post test, compared to vehicle treated animals, *p<0.05.

Redx in-house data

Effect of a single oral treatment of azaindole 1 (0, 3, 10 mg/kg) on mean arterial blood pressure in normotensive rats. N=6, data are % change from baseline. British Journal of Pharmacology (2007) 152, 1070–1080.
Anti-Fibrotics: RXC007 – Preclinical *(in vivo)* Highlights (Liver)

RXC007 reduces fibrosis and collagen deposition in the liver in murine CCl₄-induced liver model

- RXC007 reduces markers of fibrosis and collagen deposition in murine CCl₄-induced liver model

![Graphs showing hydroxyproline, Ishak Score, and Sirius Red (collagen I&III) levels with different treatment groups](image)

- Hydroxyproline
- Ishak Score
- Sirius Red (collagen I&III)

*No CCl₄*  
*Vehicle BID*  
*RXC007 5 mg/kg BID*  
*RXC007 20 mg/kg BID*  
*RXC007 50 mg/kg BID*
Protection from tubular damage and atrophy and reduced collagen deposition with REDX10843

- Enhanced tubular cell survival and reduced damage as measured by auto-fluorescence
- Reduced collagen deposition as measured by Masson’s trichrome & Sirius red
- Reduction in gene expression markers of tissue injury, inflammation and fibrosis

PD gene expression in kidney

- **MMP2**
- **Nephrin**
- **TNFα**
- **IL-1β**
- **IL-6**
- **MCP-1**

Redx Pharma Corporate Presentation - June 2020

*UUO = Unilateral Ureteral Obstruction