Recursion

Overcoming Traditional Design Limitations With AI-Based Discovery

REC-617: Interim Phase 1 Monotherapy Dose Escalation Clinical Data

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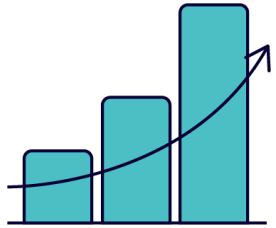
Summary of ELUCIDATE initial clinical data

- REC-617 is an **orally active, highly selective, reversible CDK7 inhibitor**
- Precision designed using the Recursion OS platform, REC-617 is optimized **for rapid oral absorption** and a **half-life tailored to enable optimal dosing regimens** for patients
- **Robust PK exposure** (IC_{80} and above) and **strong target modulation in the clinic (~80-90%),** with **high oral bioavailability** and **superior target coverage** amongst oral investigational CDK7 inhibitors
- REC-617 is preliminarily observed to be **well tolerated with predominately Grade 1-2 AEs**
  - **No treatment discontinuations to date due to AEs,** with reduced GI side-effects compared to published data on CDK7 inhibitors
  - Dose escalation still on-going
- **Encouraging interim monotherapy antitumor activity** at tolerable dose
  - **1 confirmed partial response (PR) with a durable response** ongoing after more than 6 months of treatment
  - **Four additional patients achieved durable (up to 6 months of treatment) stable disease (SD) as best response**
- **MTD has not been reached**
- **Next steps: Continue monotherapy dose escalation** (QD and BID) and **initiate combination studies in H1, 2025**

Issues we must collectively address

>90%

Clinical attrition rate



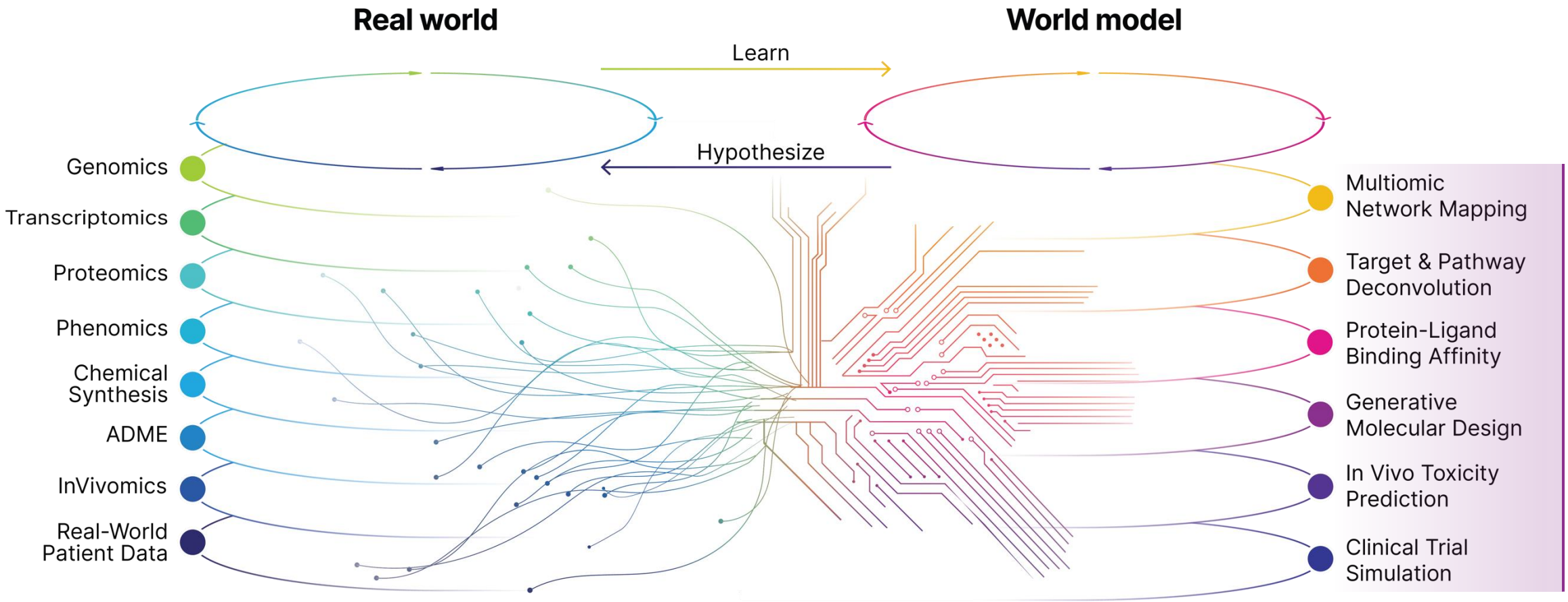
$2.4+ billion

Cost of failure
(attrition weighted)

10-15 years

To commercial launch

Recursion OS: End-to-end AI tech stack for drug discovery



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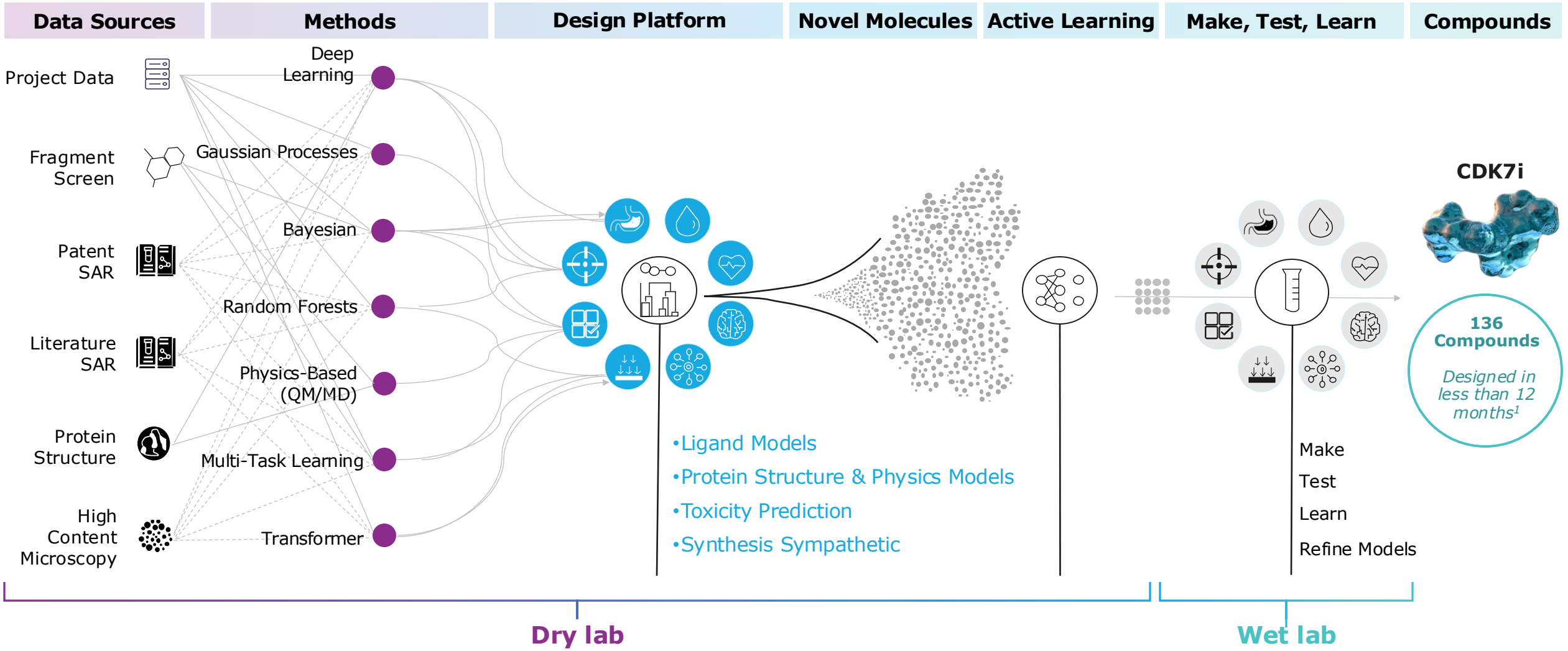
Recursion's precision design platform



1. 11 months from hit to candidate identification

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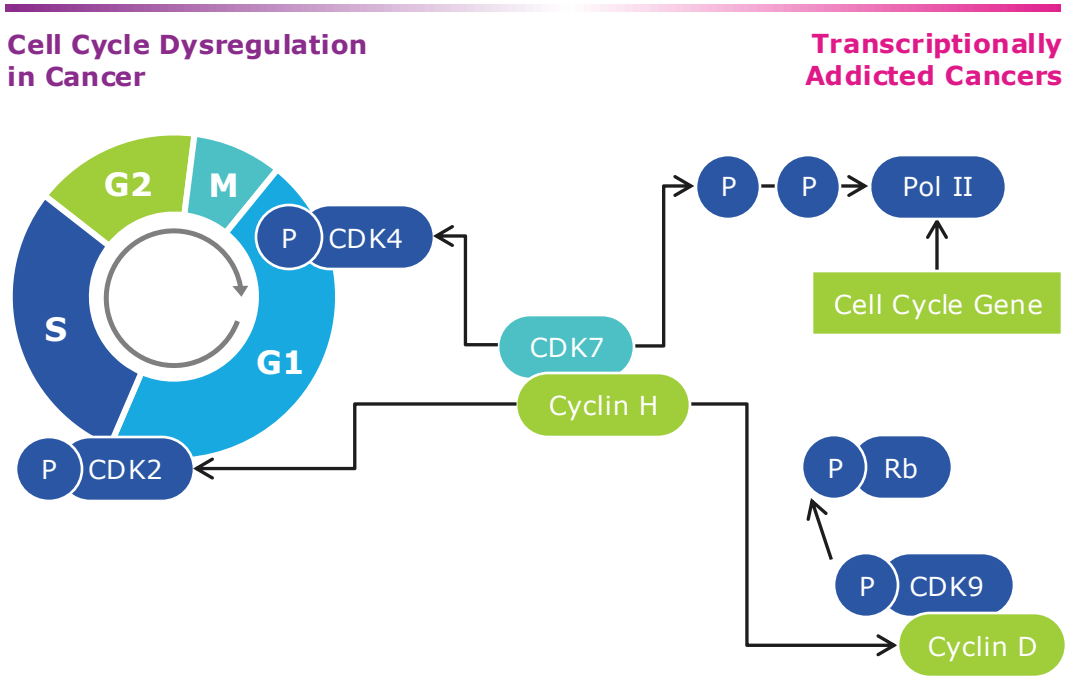
CDK7: A multi-pronged therapeutic strategy

Cell cycle dysregulation and transcriptional "addiction" are both hallmarks of many aggressive cancers

- Simultaneous inhibition of both mechanisms should allow CDK7i to be both effective and overcome common adaptations
- Cell lines resistant to CDK4/6i respond to CDK7i
- CDK7 phosphorylates multiple targets including ER

Combining CDK7 inhibitors with agents targeting complementary pathways may achieve a more comprehensive antitumor response



The design challenge

- CDK7 is indispensable for cell proliferation[1]
- High turnover cells (neutrophils, intestinal, and gastric epithelia) need to be managed

1. Gunuza, M., Sáiz-Ladera, C., Cañamero, M. et al, EMBO J, 31, 2498 (2012). https://doi.org/10.1038/emboj.2012.94; Sources: Zhang M et al,Am J Cancer Res. 2021 May 15;11(5):1913-1935; Schachter and Fisher, Cell Cycle 12:20, 3239–3240; October 15, 2013; © 2013 landes Bioscience; Patel et al (2016) Clin Cancer Res (2016) 22 (23): 5929–5938; Sava GP et al, Ali S. Cancer Metastasis Rev. 2020 Sep;39(3):805-823.; Xu et al. 2020 Nature

Precision design for optimizing therapeutic index with CDK7

In an oral molecule, how do we look to achieve a therapeutic index (TI) >1?

Highly selective for CDK7

Rapid oral absorption to reduce GI tissue exposure (highly permeable with minimal transporter interactions)

Reversible MOA allows fine control of target engagement

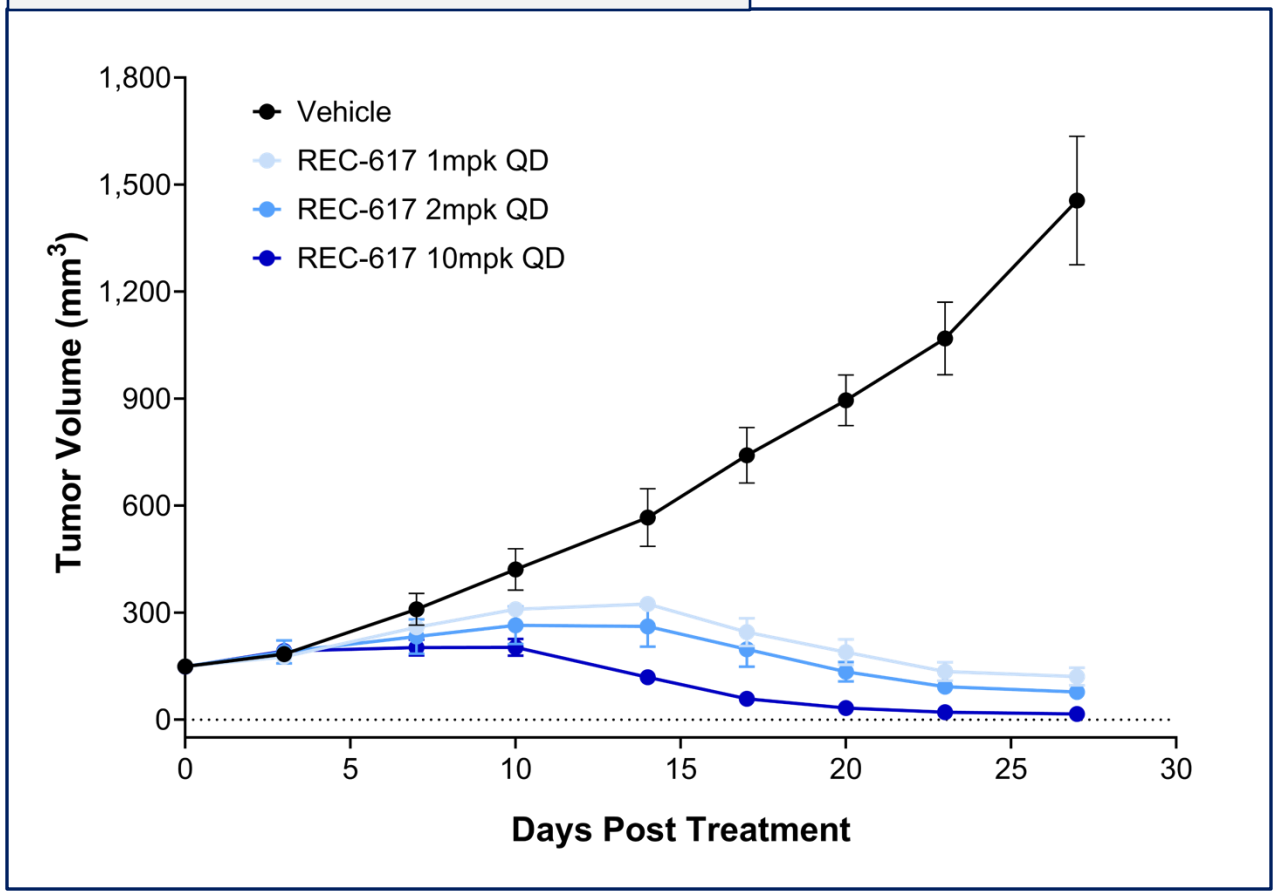
Manage time on target while limiting drug holidays

Short human half-life to enable clinical team to optimize dosing regimen

Select tumors with high dependency on CDK7

In vivo: REC-617 demonstrates potent tumor regressions in *CCNE1*-amp CDX model

OVCAR3 CDX (*CCNE1*-amplified)



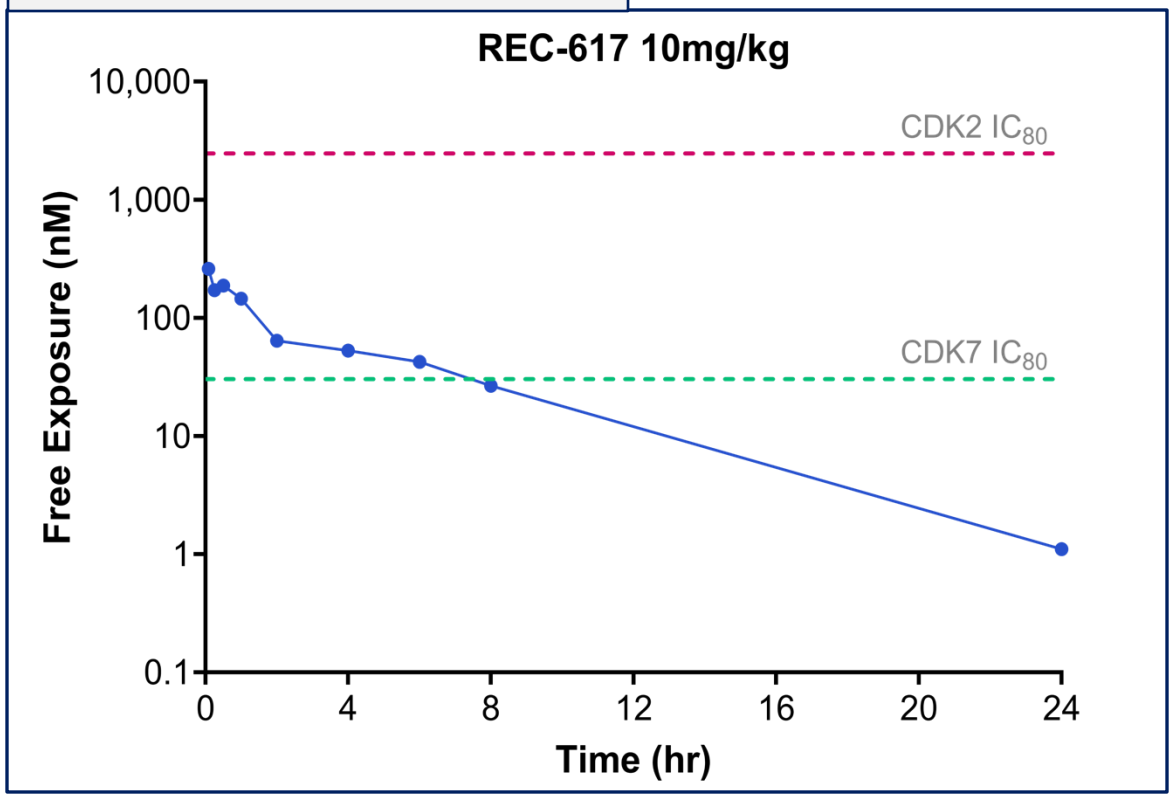
- N = 8
- 28-day treatment
- REC-617 administered QD PO

- **No significant body weight loss** seen across treatment arms
- **8/8 mice in 10mpk arm had complete tumor regression at Day 27**

QD: once a day; PO: by mouth

In vivo: REC-617 is a potent and selective CDK7 inhibitor with favorable PK

Mouse PK for REC-617



- Day 1 PK samples
- **~6-hour coverage over CDK7 biochemical IC_{80}** lead to complete tumor regression
- 82-fold window over nearest off-target

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REC-617 has Best-in-Class potential

Designed to be selective, rapidly absorbed, reduce interaction with GI transporters and result in better AE management

Category	Assay	*SY-5609*	*Samuraciclib*	**REC-617**
Potency & Selectivity	CDK7 IC_{50} (nM)			
	CDK family selectivity			
	HCC70 (breast cancer) IC_{50} (nM)			
ADME	Caco-2 A2B (efflux) 10^{-6} cm/s			
	Human half-life (hr)			

Meets or exceeds criteria | Minor deviation | Major deviation

CDK7 IC_{50}: green <10nM; yellow 10-30nM; red >30nM
CDK7 selectivity: green >100-fold; yellow 30-100-fold; red <30-fold
HCC70 IC_{50}: green <100nM; yellow 100-500nM; red >500 nM
Caco-2 A2B (efflux): green >3(<5); yellow >1.5(<10); red <1.5(>30)
Half-life: green <15, yellow <24, red >24

- REC-617 has **high permeability, low efflux** – consistent with **rapid absorption**
- Other compounds preclinically:
  - Low permeability and higher efflux suggesting slower absorption
  - Will take significantly longer to reach steady state
  - Long half-life and persistent inhibition of CDK7 potentially driving AEs

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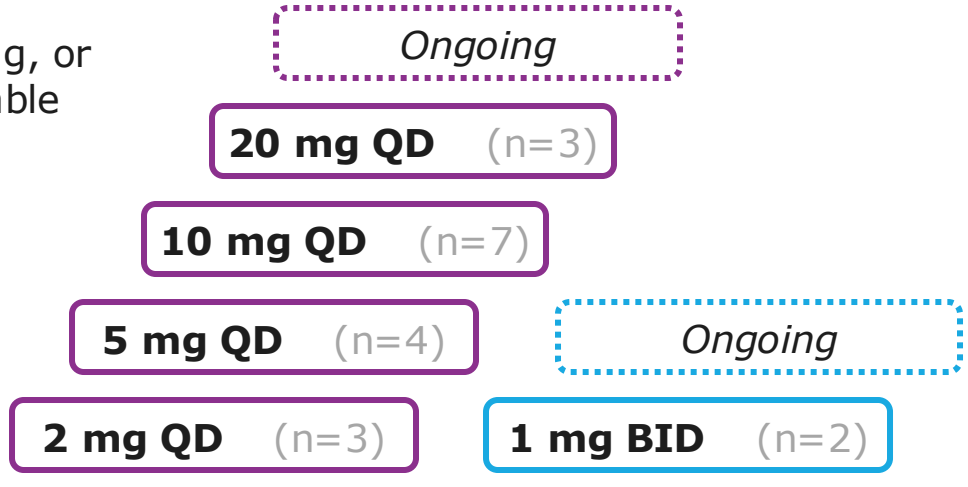
ELUCIDATE: FIH Phase 1/2 clinical trial of REC-617 in advanced solid tumors

Phase 1 Monotherapy Dose-Escalation

REC-617 advanced solid tumors

Enrollment commenced July 2023

- Unresectable, locally recurrent, or metastatic cancer
- Progressed following, or intolerant to, available standard of care treatments
- ECOG PS 0-1



- 18 of 19 response evaluable patients[1]
- PK/PD
- MTD not reached
- Parallel dose escalation ongoing
- Prophylaxis for N/V/D[2] not mandated

1. 19 patients are enrolled, 18 patients are evaluable
2. N/V/D = nausea, vomiting, diarrhea

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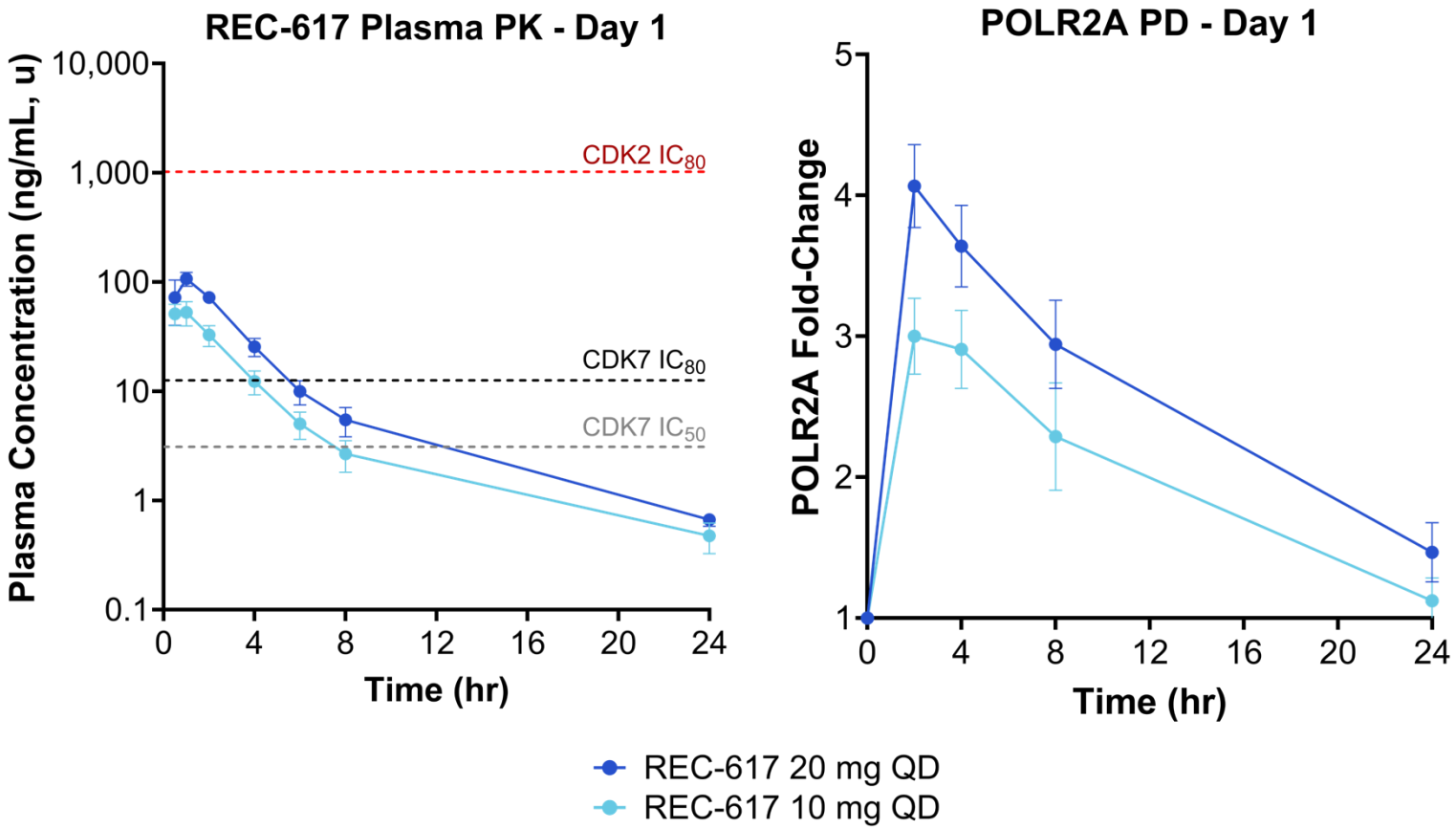
Patient population: Heavily pre-treated with ~4 median prior lines of anti-cancer treatment

Patient Characteristic	All Patients (N=19)[1] 18 of 19 response evaluable patients	Prior Lines of Therapy in the Advanced Setting (median)[3]
Age, Median (range), Years	60 (30, 79)	
Female	9 (48%)	
Tumor Type		
Colorectal Adenocarcinoma	10 (53%)	4
$HR^+/HER2^-$ Breast Adenocarcinoma[2]	3 (16%)	4
Epithelial Ovarian Carcinoma	3 (16%)	4
NSCLC	2 (10%)	3
Pancreatic Adenocarcinoma	1 (5%)	3

1. Data-cut off : 15 November 2024. All data shown as n (%) unless otherwise specified
2. All patients received CDK4/6 inhibitors in prior lines
3. Advanced setting: Locally advanced pre-metastatic and metastatic setting - includes adjuvant and neo-adjuvant treatment regimens as 1 line of therapy

REC-617 achieves dose dependent PK/PD and strong target modulation in the clinic

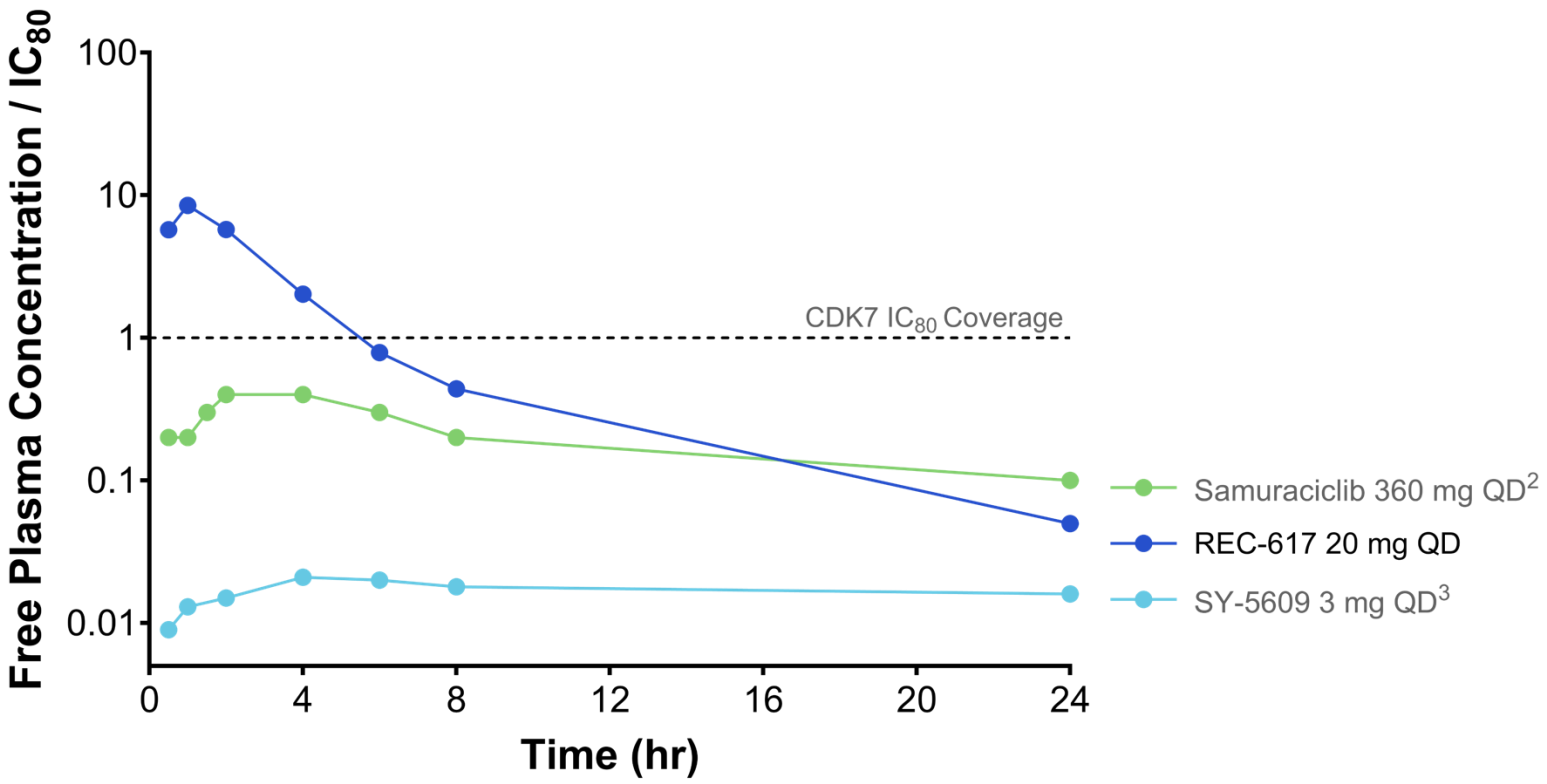


PK/PD Summary

- **Dose-Linear PK**: REC-617 exceeds CDK7 IC_{80} with rapid absorption (Tmax 0.5–2h) and short t½ (5–6h)
- **Robust Target Engagement:** Early POLR2A 3-4x modulation suggests ~80–90% target engagement[1]
- **Rapid Transient Modulation:** Quick, time-limited target engagement with POLR2A normalization in 24h
- **BID Evaluation:** Twice-daily dosing under investigation

1. Papadopoulos KM, et al. ENA (2020)

REC-617 offers a differentiated profile that potentially improves the therapeutic index



Competitive Differentiation

- Data suggests **superior target coverage for REC-617**[1] compared to two clinical CDK7 inhibitors
- REC-617 is **more rapidly absorbed** (earlier Tmax) compared to reported PK from two CDK7 inhibitors[2,3] suggesting **a reduction in localized GI residence time**
- **A shorter half-life** would allow for flexible target modulation, which may **improve the therapeutic index** in the clinic

1. CDK7 IC_{80} reflects biochemical in vitro potencies on file
2. Coombes, RC, Nat Comms (2023)
3. Papadopoulos KM, et al. ENA (2020)

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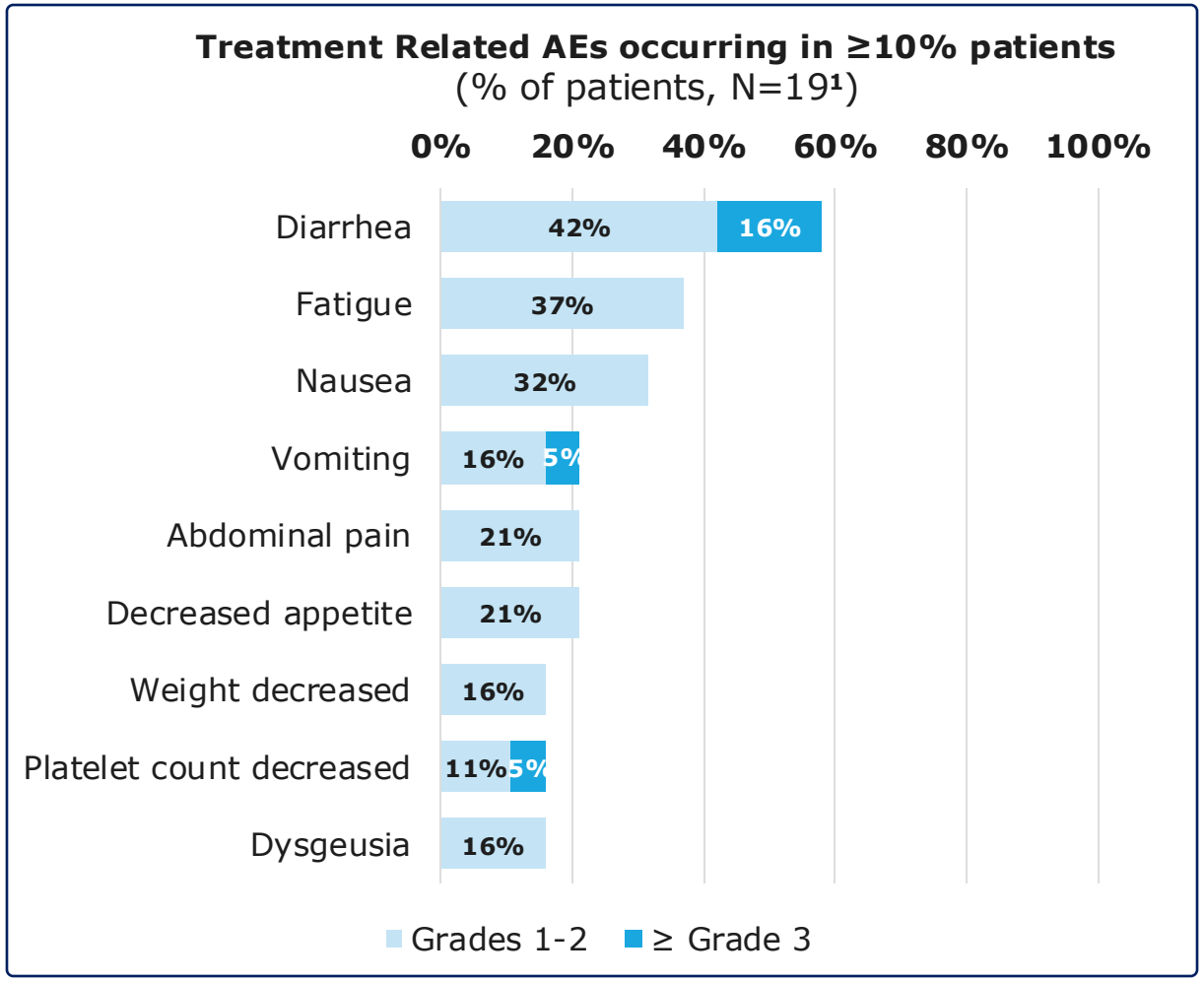
Preliminary safety data suggests potential Best-in-Class oral CDK7 inhibitor



- **Adverse events (AEs) were predominantly low grade**, on-target, and **reversible upon treatment cessation**
- **Early data indicates a favorable safety profile – Maximum tolerated dose (MTD) not reached**
  - **No treatment discontinuations due to AEs** compared to competitor (~14%)[2]
  - **Lower drug-related diarrhea** (58%) than competitor (82%) [2]
- **3 treatment related SAEs** reported in 2/19 patients; enterocolitis (G2, C1), diarrhea (G3, C2), nausea/vomiting (G3, C1)
  - Events resolved and treatment continued after dose reduction
- **Antiemetics, anti-diarrheals not mandated prophylaxis for nausea / vomiting / diarrhea**

1. Data-cut off : 15 November 2024. All data shown as n (%) unless otherwise specified.
2. Coombes, RC, Nat Comms (2023), Phase 1 monotherapy dose escalation data (N=44)

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Monotherapy response: Confirmed durable PR observed in heavily pre-treated metastatic ovarian cancer

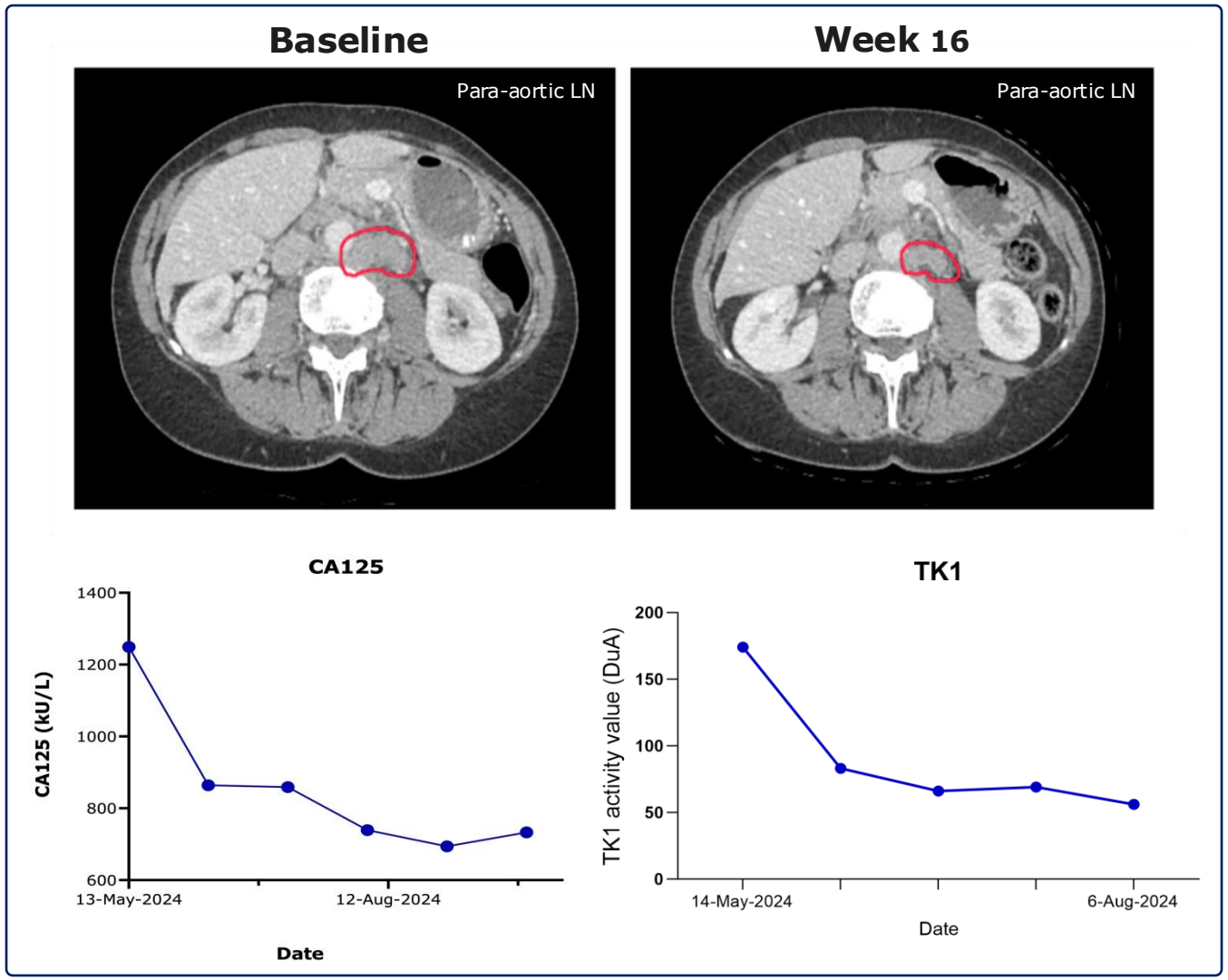
- **One confirmed, durable partial response (PR)** by RECIST 1.1[1]
  - 69-year-old woman with **platinum resistant ovarian cancer**, who had **progressed following 4 lines of prior therapy in advanced setting** with **metastatic disease to lungs and lymph nodes**
    - Patient was diagnosed with Stage IIIc ovarian cancer in 2019
  - No BRCA1/2 mutation, low tumor mutational burden, and small TP53 variant (VAF 8%)
  - Initiated therapy at 20mg QD, dose reduced at Week 4 to 10mg QD due to transient Grade 3 nausea

- **Four additional patients achieved durable (up to 6 months of treatment) response of stable disease (SD)** as best response across multiple dose levels
  - All four patients progressed prior to entering the study
  - Three CRC patients (6L-7L) and one NSCLC patient (4L)
  - One patient on 2mg QD and three patients on 10mg QD

1. Response evaluation criteria in solid tumors, PR: decrease of more than 30% in the sum of the longest diameters of target lesions + no new lesions + no progression of non target lesions

Monotherapy response vignette

- **One confirmed, durable partial response (PR)** by RECIST 1.1[1]
  - **Partial response (-34%) achieved with reduction in 2 lymph nodes** (para-aortic and mesenteric) **at Week 16** with **normalization of LDH**
  - **Reduction of tumor marker CA125 from 1249 to 694 kU/L (-44%)**
  - **Reduction of tumor marker TK1 from 174 to 56 DuA (-68%)**
  - **Response ongoing after more than 6 months of treatment.** Patient continues study therapy without need for antiemetics



1. Response evaluation criteria in solid tumors, PR: decrease of more than 30% in the sum of the longest diameters of target lesions + no new lesions + no progression of non target lesions

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Advancement of REC-617

- **Parallel dose escalation (QD and BID) of monotherapy** ongoing
  - BID dosing schedule may provide optimal coverage
- **Combination studies expected to initiate for ELUCIDATE in H1, 2025**
- ELUCIDATE and preclinical updates to be presented at future medical conferences
- Patient selection to leverage Recursion's multimodal RWD and Casual AI models

Acknowledgements

ELUCIDATE Investigators

- Prof Ruth Plummer, Northern Centre for Cancer Care
- Dr Donna Graham and Prof Fiona Thistlethwaite, The Christie NHS Foundation Trust
- Associate Prof Simon Lord, Churchill Hospital
- Prof Martin Forster, University College London Hospital
- Prof Jeff Evans, Beatson West of Scotland Cancer Centre
- Dr Louseberg, C.H.U. Liege
- Dr Rachel Galot, Cliniques Universitaires Saint-Luc

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- Olivier Barbeau
- Jérémy Besnard
- Ross Paveley
- Elena Fonfria
- Andy Bell
- Anitha Jeyanthan
- Aude Echalier
- Angeline Gavard
- Maria Dominguez
- Tom Wilde
- Ash Willson
- Joanna Harding
- Eric Helmer
- Nieves Diaz
- Holly Garratt
- Emma Matthews
- Cheryl Ruiz
- Jenny Lee
- Marie-Louise Fjaellskog
- Mike Krams
- Tiago Ferronha
- Mani Mudaliar
- Beatrice Li
- Greg Vladimer
- Christophe Boudesco
- Máté Somlyay
- Jérémy Le Coz
- Martin Senekowitsch
- Bekir Ergüner
- Erika Durinikova
- Christina Taubert
- Claudia Baumgärtler
- Maja Stulic
- Robert Sehlke
- Venu Thatikonda
- Thomas Winkler-Penz
- Iva Navratilova
- Sean Robinson
- Katarina Ekelund
- Bimpe Shitta-Bey
- Meghna Das
- Mercedes de Rink
- Aniko Gertner
- Eileen Brandenburger
- Eva Borger

GT Apeiron

- Wang Tao
- Fred Aswad
- Xiao-Hui Gu
- Yangfeng Zhou
- Vivi Gao
- Qiushi Li
- Mingxi Li
- Haiyun Bai
- James Joseph

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Acknowledgements

We would like to thank all of the patients and their families involved in the ELUCIDATE study

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What's next?

International Stroke Conference Late Breaker

"The SYCAMORE Study Results: First Randomized, Placebo-Controlled Phase 2 Trial in Symptomatic Cerebral Cavernous Malformation (CCM) Evaluating REC-994"

Presented by:

Dr. Jan-Kar Burkhardt

University of Pennsylvania Division Head, Cerebrovascular Surgery

Associate Professor of Neurosurgery at the Hospital of the University of Pennsylvania

Late Breaking Science Oral Abstract Session:

5 Feb 2025

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