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AACR American Association for Cancer Research®

Overcoming Traditional Design Limitations With AI-Based Discovery

REC-617: Interim Ph 1 monotherapy dose escalation clinical data

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Recursion

The next 20 minutes!

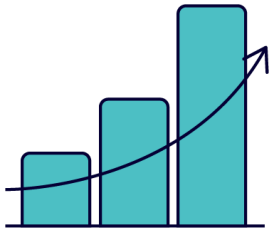
- The real problem
- Recursion OS – precision molecular design
- CDK7 as an oncology drug target
  - Therapeutic index (TI) challenges
- Emerging data from ELUCIDATE
  - Phase 1 monotherapy dose escalation update

REC-617
CDK7i

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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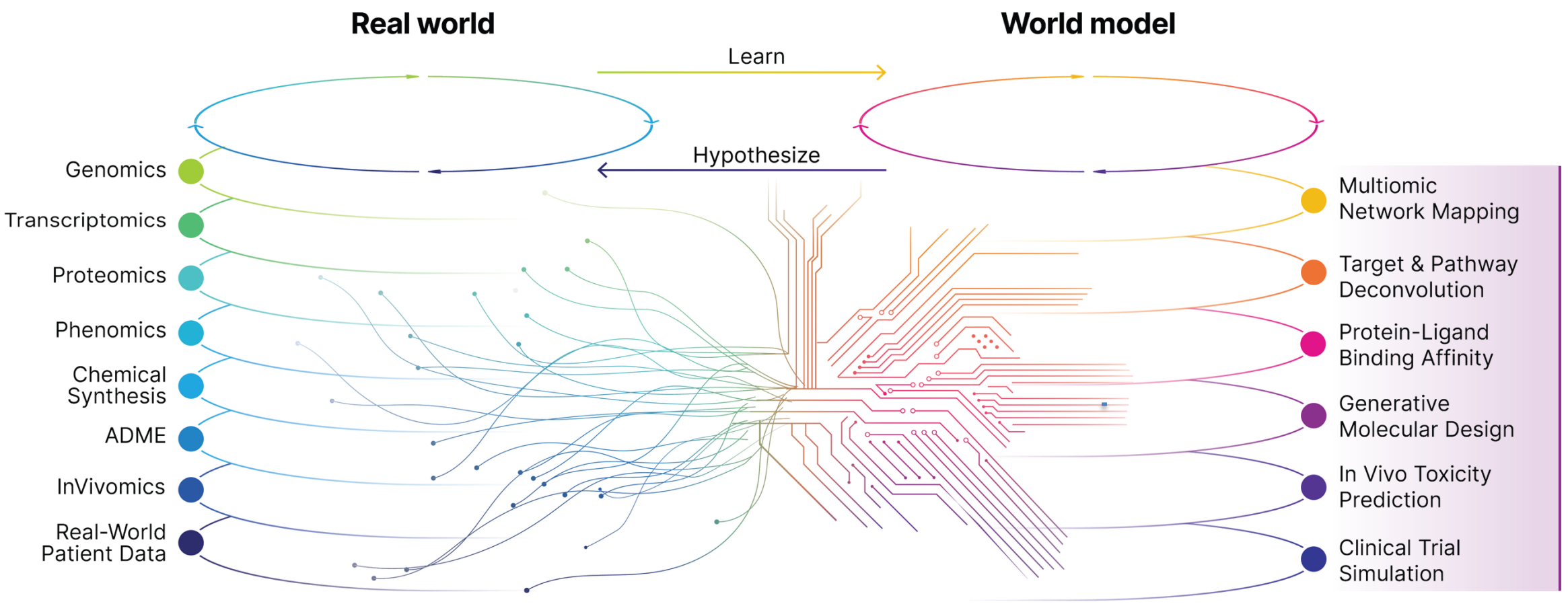
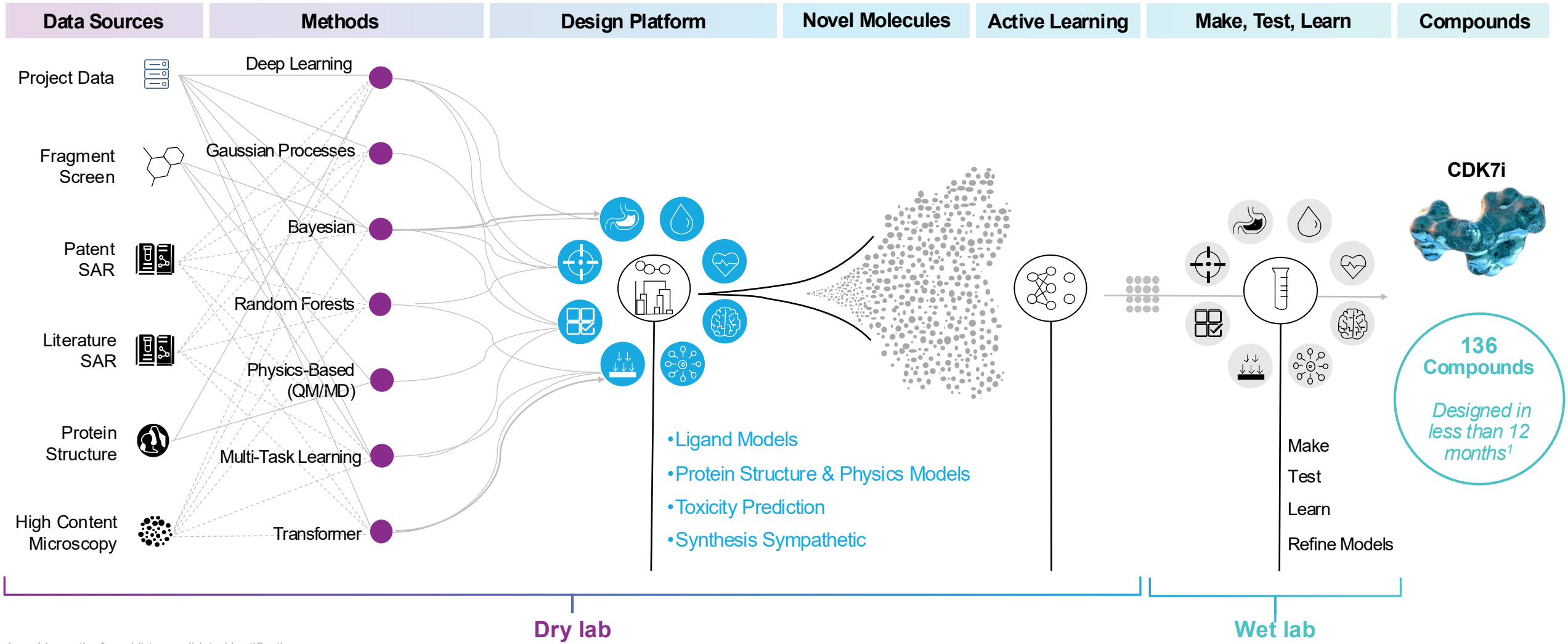


Recursion's precision design platform



1. 11 months from hit to candidate identification

CDK7: A multi-pronged therapeutic strategy

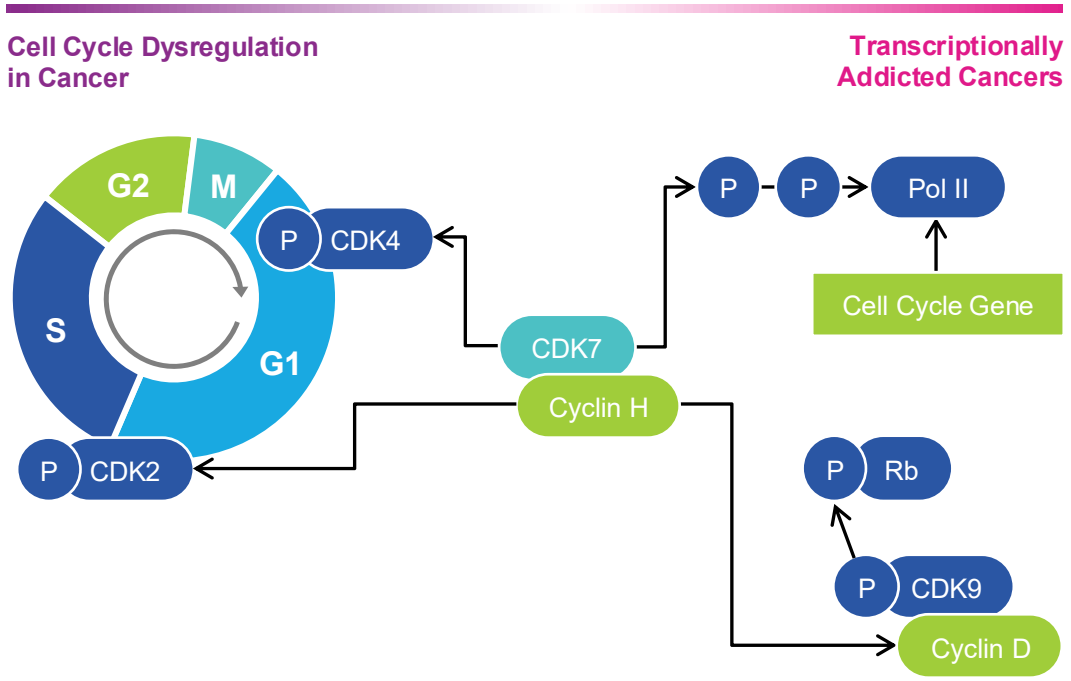
Cell cycle dysregulation and transcriptional "addiction" are both hallmarks of many aggressive cancers

- 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

Suitable 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

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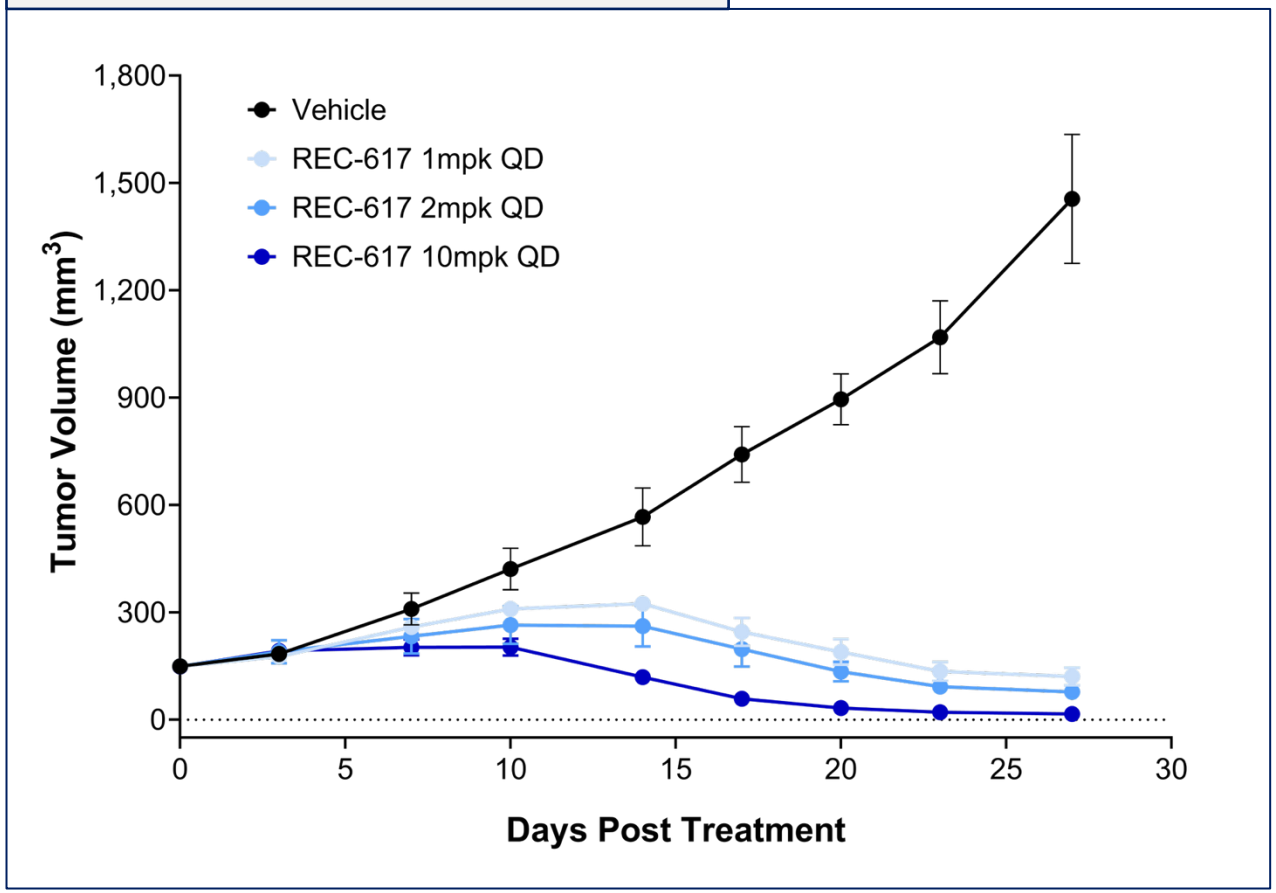
OVCAR3 CDX (*CCNE1*-amplified)



- 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**

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

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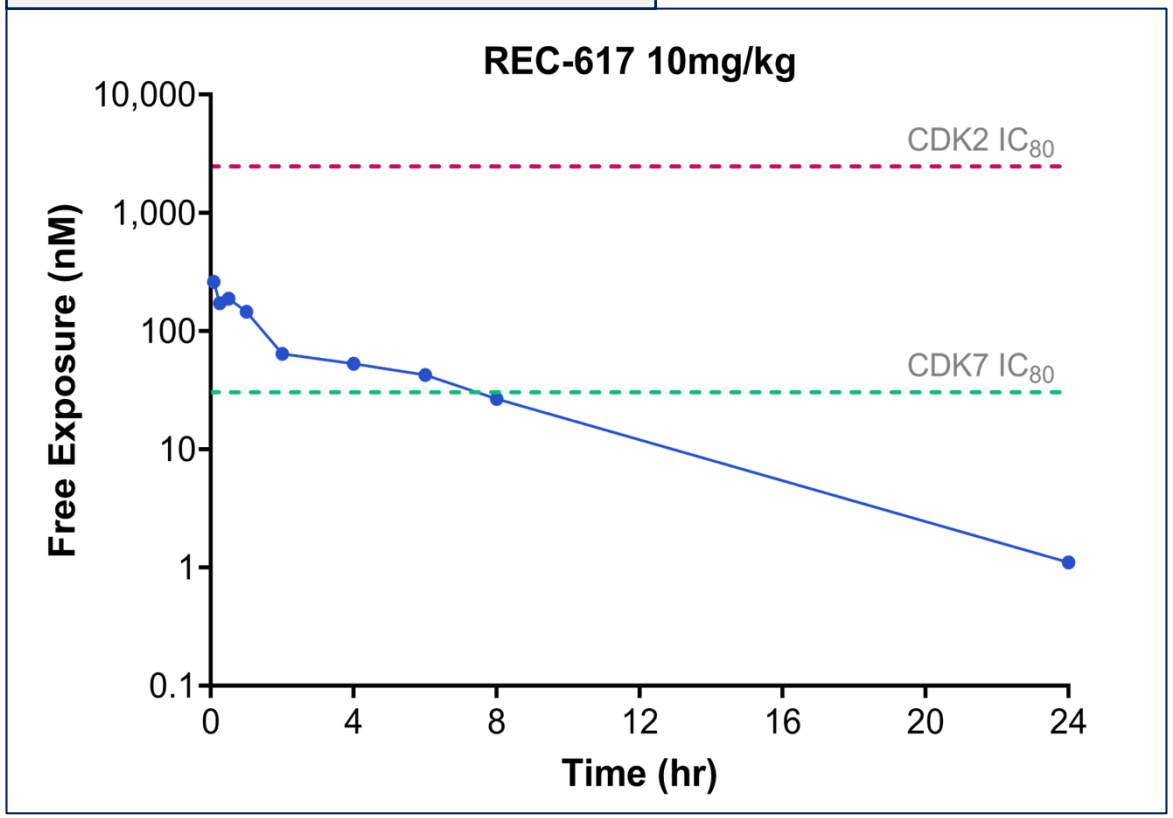
Mouse PK for REC-617



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

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 IC50: green <10nM; yellow 10-30nM; red >30nM
CDK7 selectivity: green >100-fold; yellow 30-100-fold; red <30-fold
HCC70 IC50: 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

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

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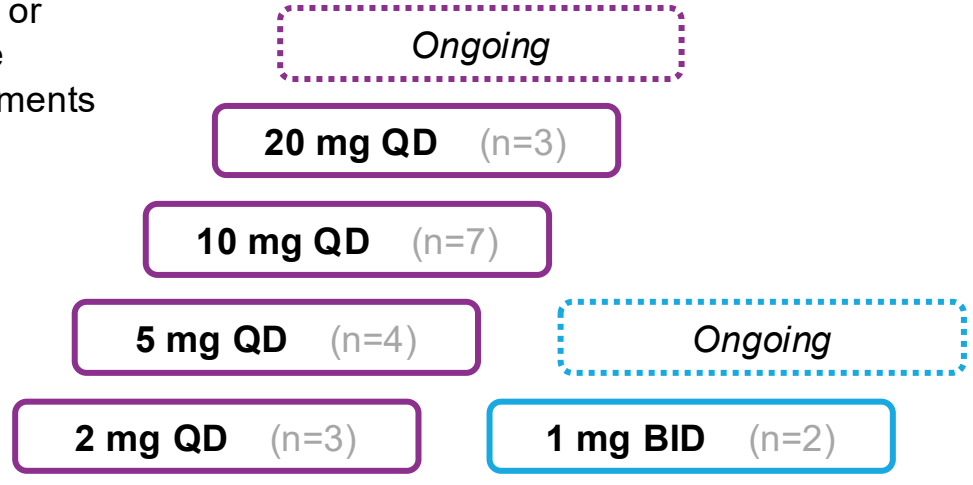
Phase 1 Monotherapy Dose-Escalation

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
- PK/PD
- MTD not reached
- Parallel dose escalation ongoing
- Prophylaxis for N/V/D[1] not mandated

1. N/V/D = nausea, vomiting, diarrhea

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

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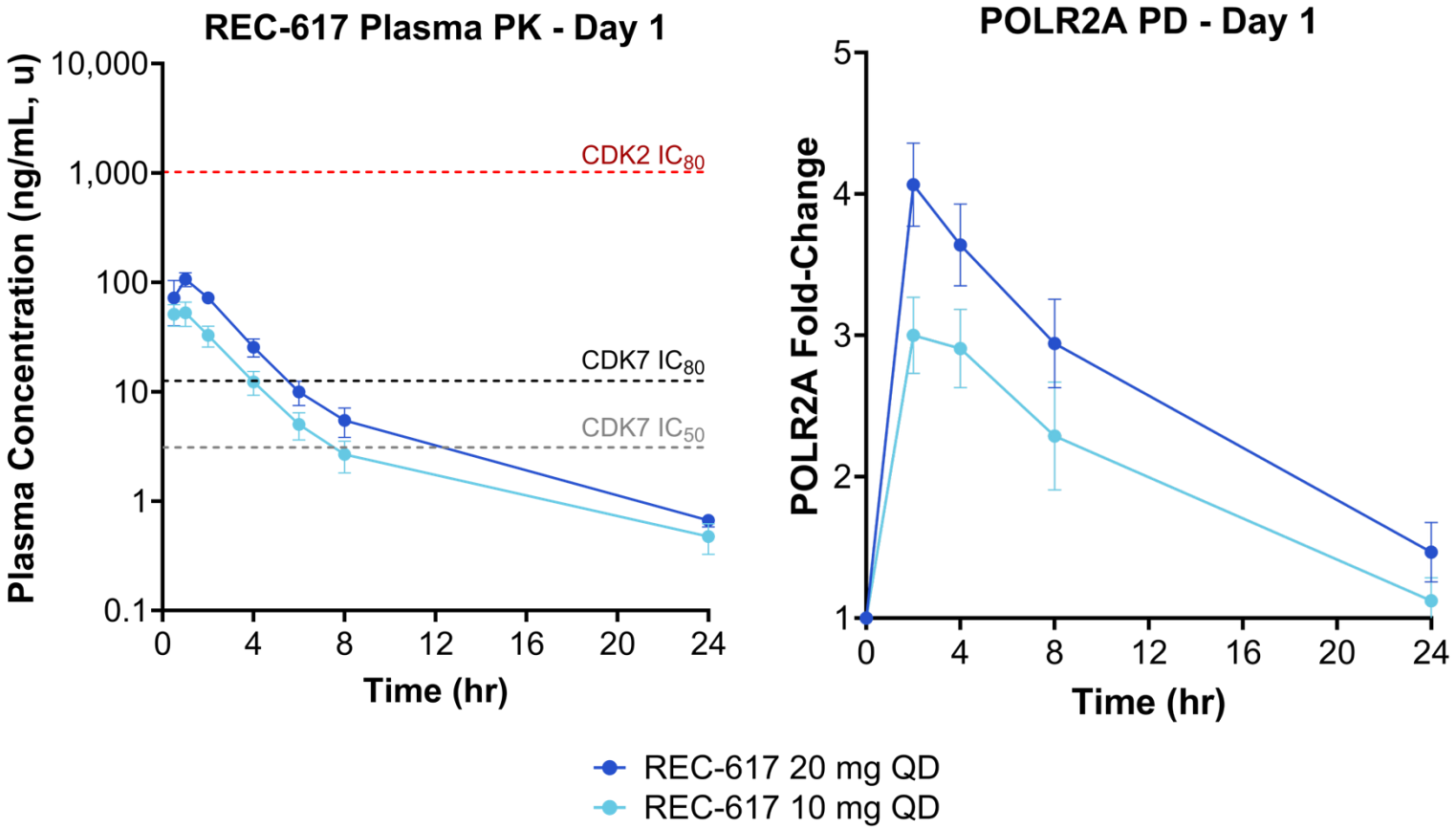
Patient Characteristic	All Patients (N=19)[1] 18 of 19 response evaluable patients	Prior Lines of Therapy in the Advanced Setting (median)[3]
Age, Median (range), Years	60 (30, 79)	
Female	9 (48%)	
Tumor Type		
Colorectal Adenocarcinoma	10 (53%)	4
$HR^+/HER2^-$ Breast Adenocarcinoma[2]	3 (16%)	4
NSCLC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

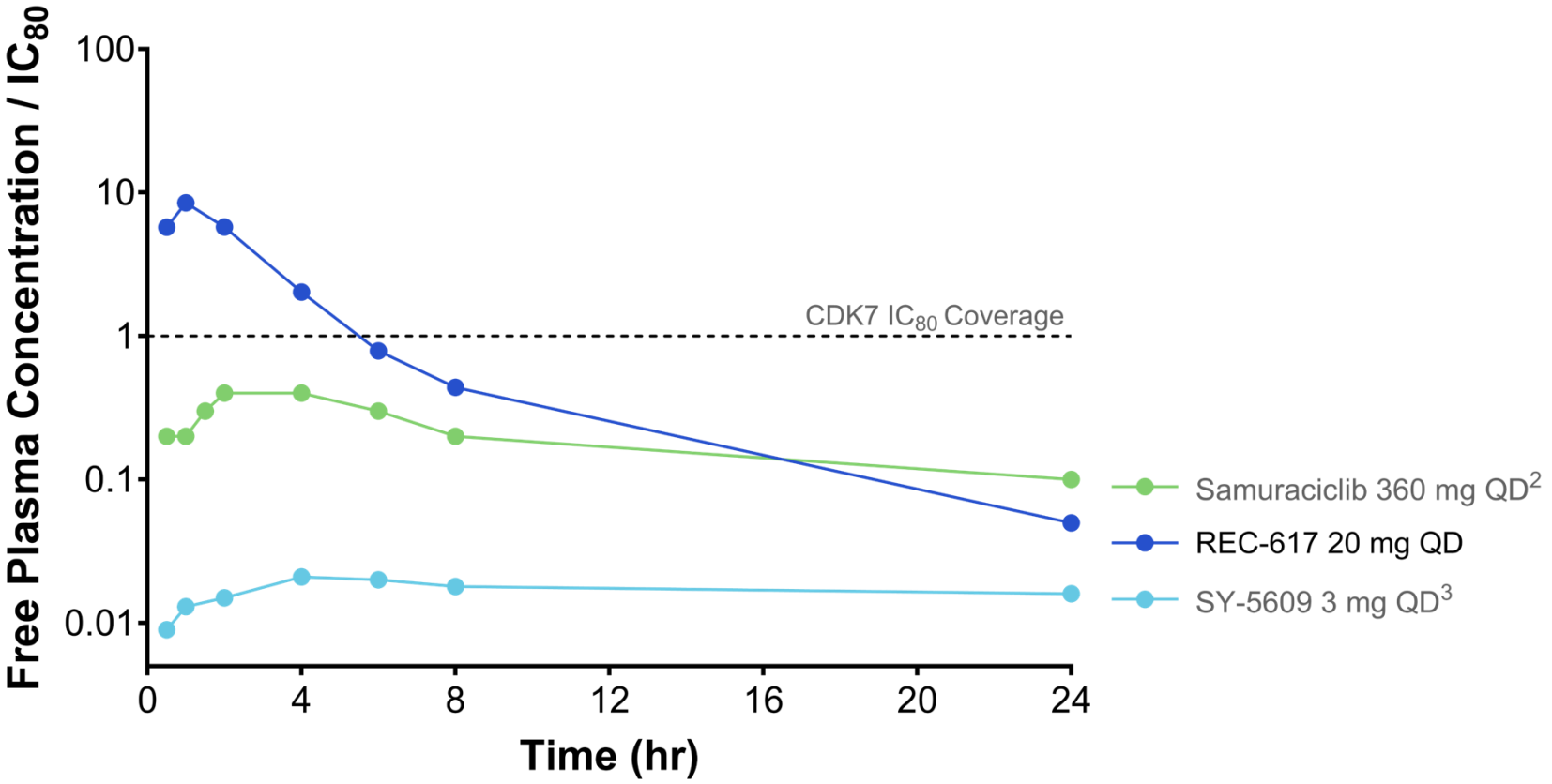


PK/PD Summary

- **Dose-Linear PK**: REC-617 exceeds CDK7 IC_{80} with rapid absorption (T_{max} 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

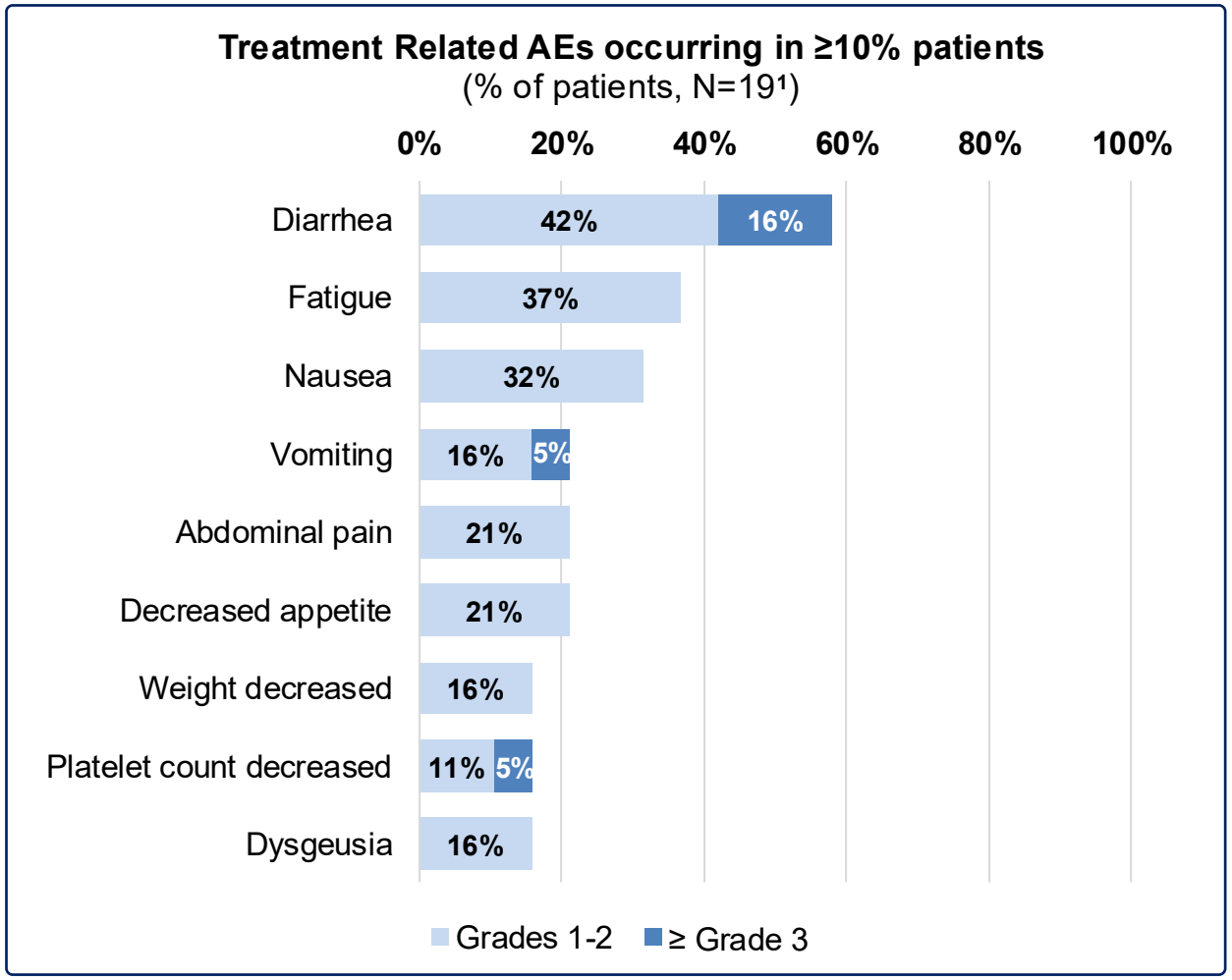


Competitive Differentiation

- 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)

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)

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

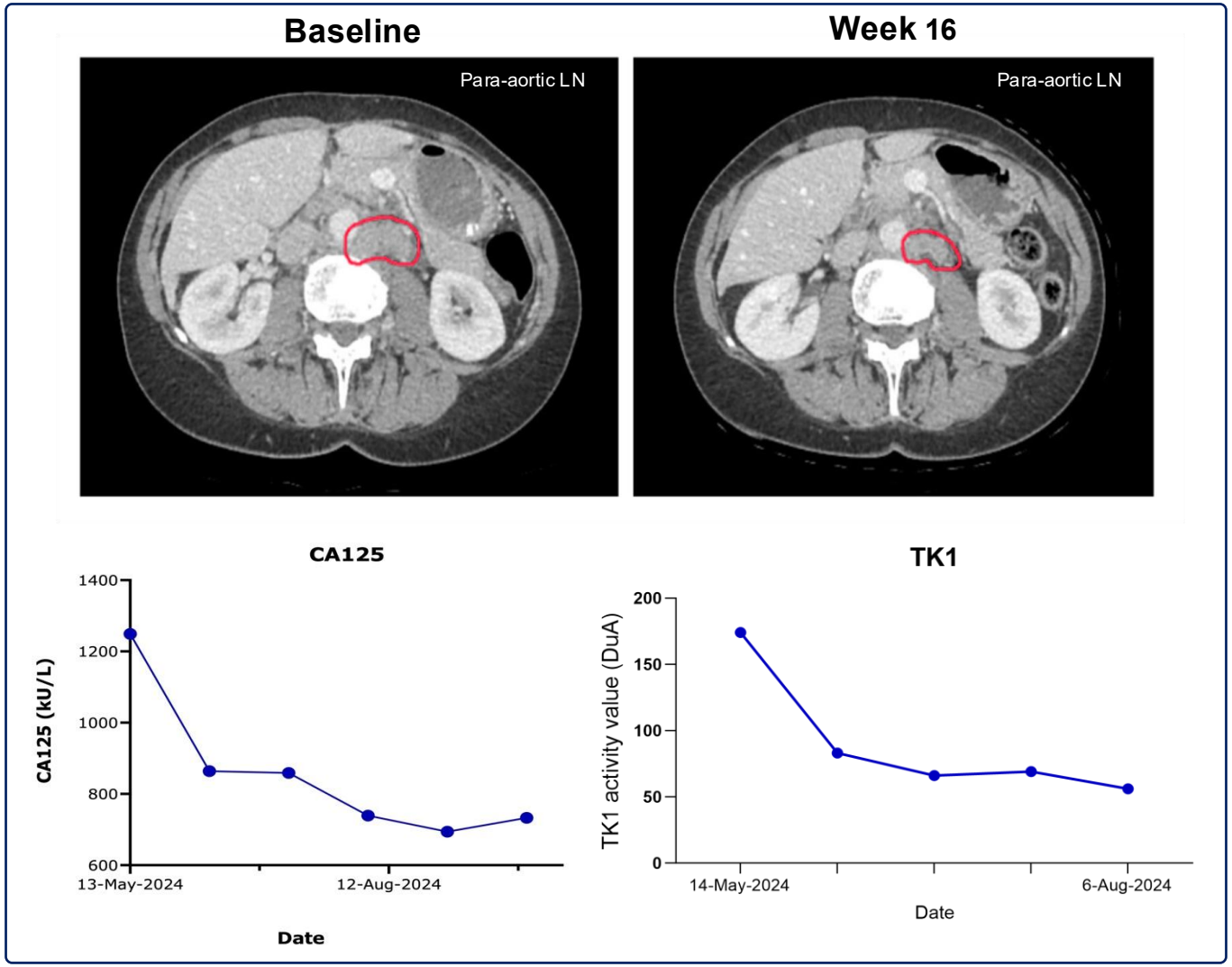
- **One confirmed, durable partial response (PR)** by RECIST 1.1[1]
  - 69-year-old woman with **platinum resistant ovarian cancer**, who had **progressed following 4 lines of prior therapy in advanced setting** with **metastatic disease to lungs and lymph nodes**
    - Patient was diagnosed with Stage IIIc ovarian cancer 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

Summary of interim ELUCIDATE Ph 1 monotherapy clinical data

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- 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, dose escalation continues**

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

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