Proof-of-Mechanism Based on Target Engagement and Modulation of Gene Expression Following Treatment with SY-1365, a First-in-Class Selective CDK7 Inhibitor in Phase 1 Patients with Advanced Cancer

Dejan Juric[1], Kyriakos P. Papadopoulos[2], Anthony Tolcher[2], Erika Hamilton[3], Khanh T. Do[4], David Orlando[5], William Zamboni[5], Graeme Hodgson[5], Emmanuelle di Tomaso[5], Kristin Stephens[5], David A. Roth[5], Geoffrey I. Shapiro[4]

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Conflicts of Interest

Dr. Juric reports personal fees as Scientific Advisory Board member for:

- Novartis

- Genentech

- Eisai

- Ipsen

- EMD Serono

CDK7 Has Emerged as a Potentially Important Target Across a Range of Solid Tumors and Blood Cancers

Transcription

CDK7

Cell Cycle

Certain cancers hijack transcriptional machinery to drive increased expression of oncogenic transcription factors and anti-apoptotic proteins

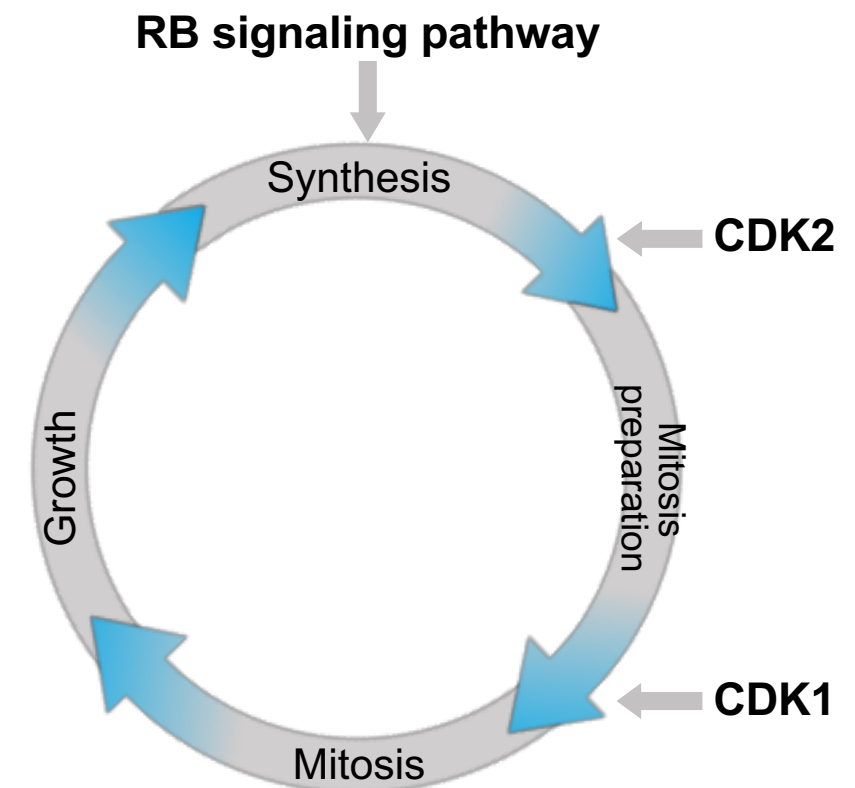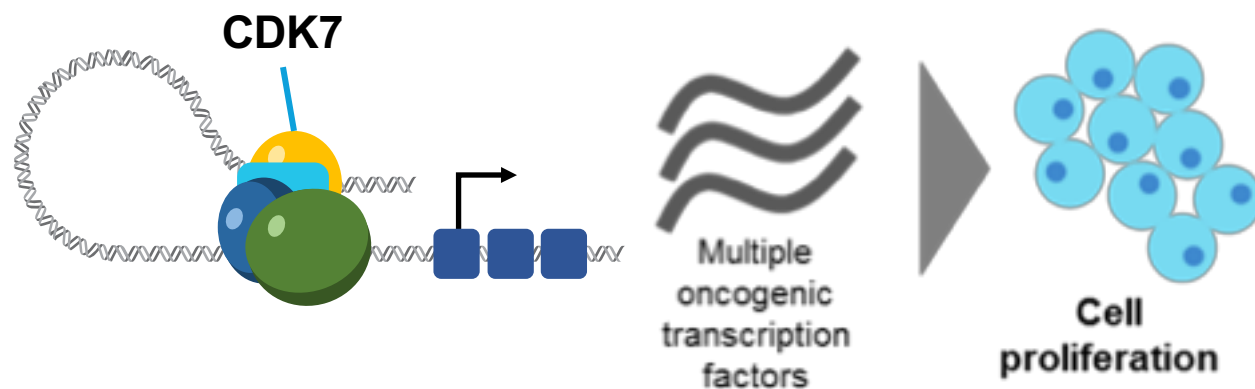Certain cancers develop adaptations to progress through the cell cycle despite damaged DNA and genomes

CDK7 is an essential component in regulating transcription

CDK7 regulates the cell cycle as a cell cycle activating kinase (CAK)

CDK7

Multiple oncogenic transcription factors

Cell proliferation

RB signaling pathway

Synthesis

CDK2

Growth

Mitosis preparation

CDK1

Mitosis

SY-1365 is a First-in-Class Potent and Selective CDK7 Inhibitor

- Covalent

- Highly potent

- Highly selective
  - Only binds to 7 out of 468 kinases screened at >90% binding
  - Does not significantly bind to CDK9 or cell cycle CDKs

- Preclinical models demonstrated sustained CDK7 occupancy levels >50% maximized antitumor effects, and supported intermittent dosing

- Durable tumor responses in *in vivo* models
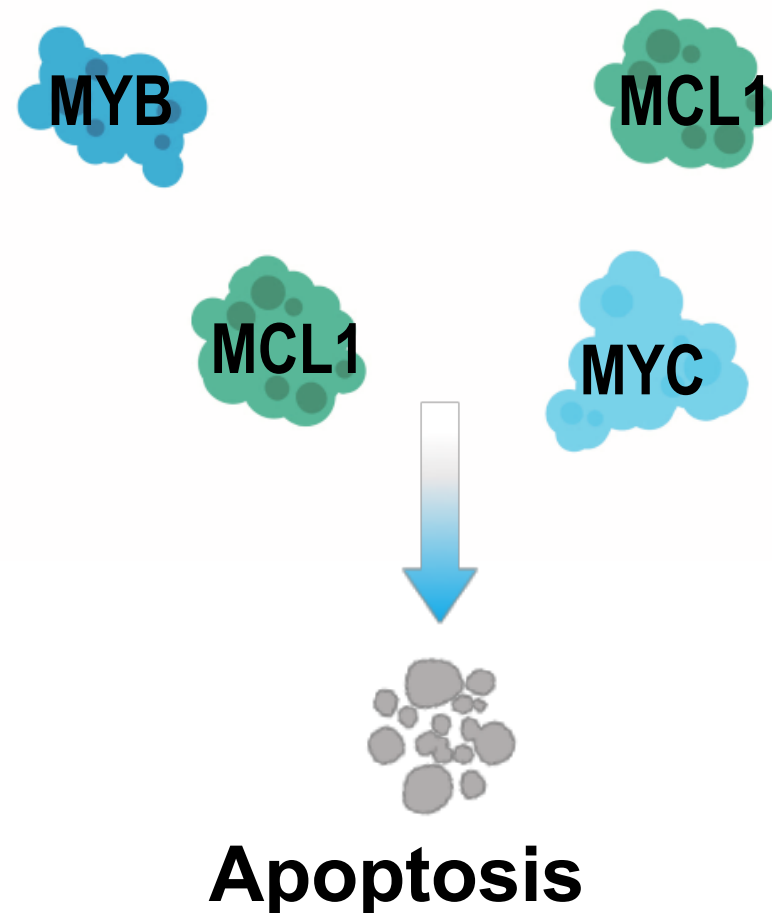
DiscoveRx kinome scan at 1µM SY-1365
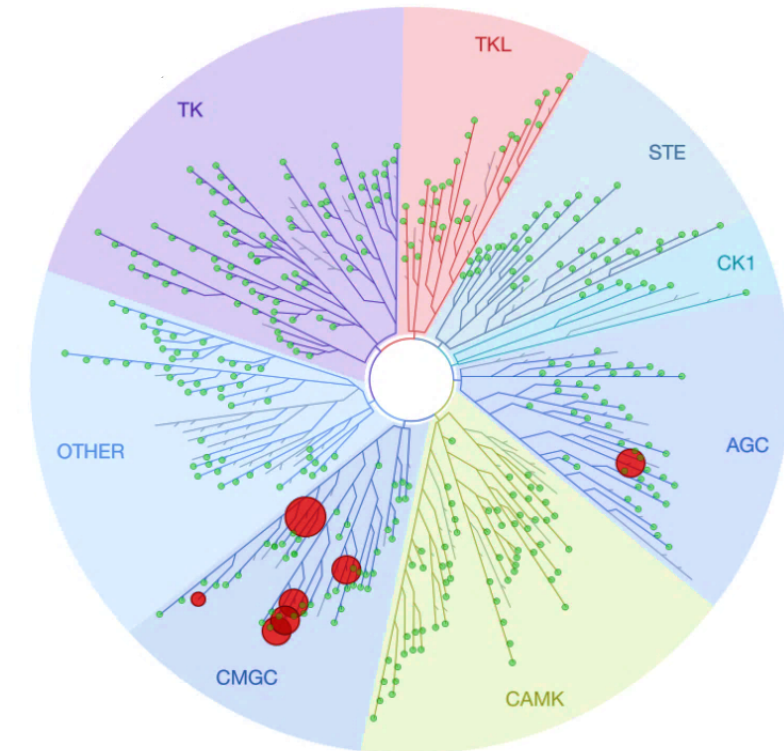
Gene	% Control
CDK7	0.25
RSK4	2
DYRK1B	2.6
JNK3	2.7
JNK1	2.8
JNK2	3
CDK15	10

SY-1365 Has Dual Effect on Transcription and Cell Cycle, Preferentially Killing Cancer Cells in Preclinical Studies

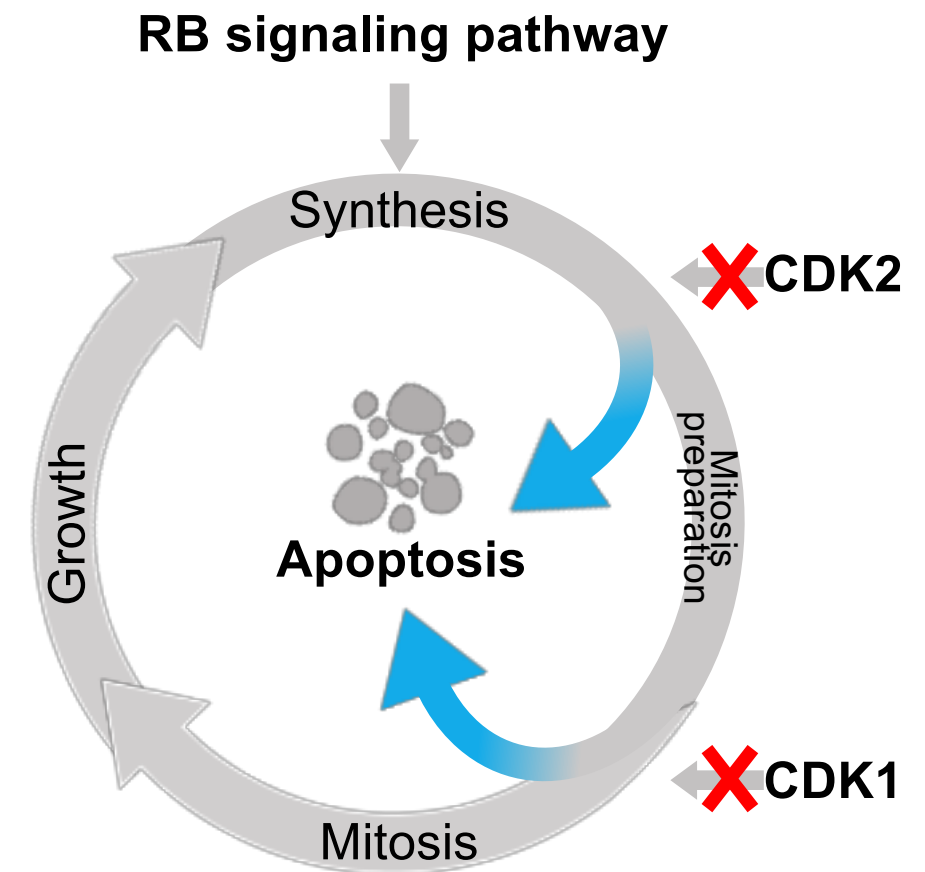| Transcription	SY-1365	Cell Cycle

SY-1365 has been shown to down-regulate oncogenic transcription factors and anti-apoptotic proteins

SY-1365 is thought to interfere with multiple points in the cell cycle, promoting the induction of apoptosis

MYB **MCL1**

MCL1 **MYC**

Apoptosis

RB signaling pathway

Synthesis

✗ **CDK2**

Growth

Mitosis preparation

Apoptosis

✗ **CDK1**

Mitosis

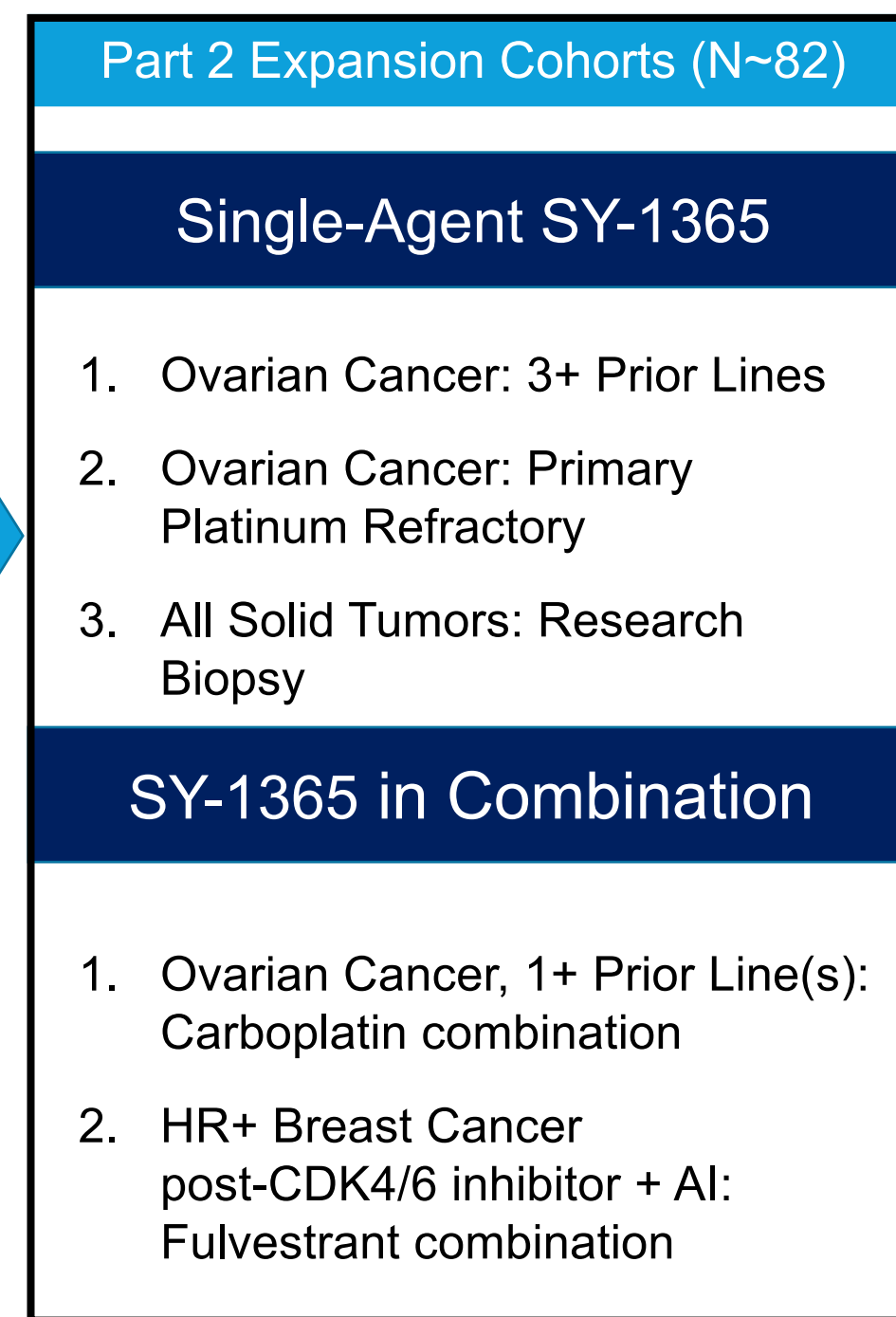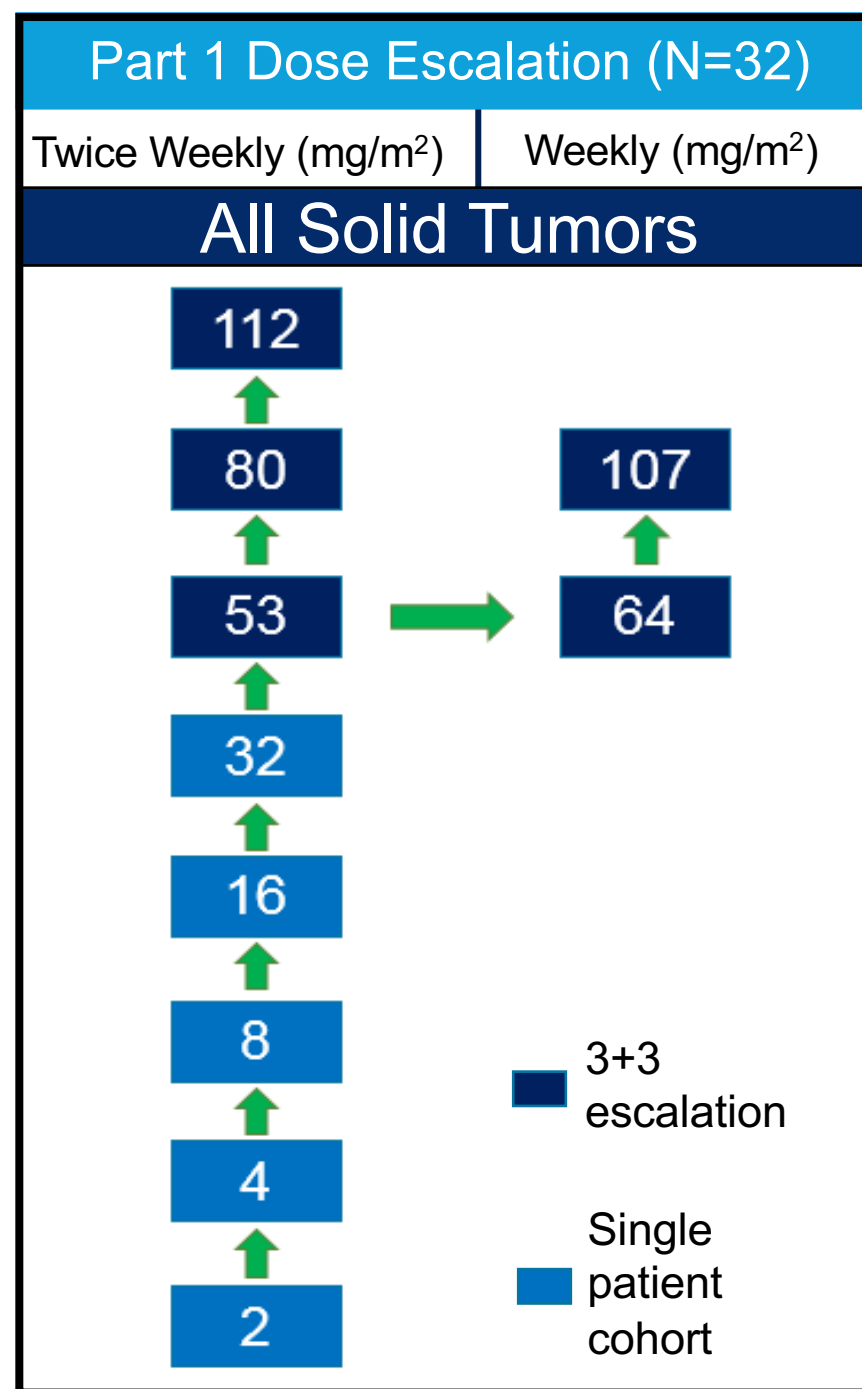# Study SY-1365-101: A Multi-center, Open-label Phase 1 Trial

Dosing
- IV dosing over one hour
  - 3 weeks every 4 weeks

Trial Endpoints
- **Primary:** DLTs and safety
- **Secondary:** PK and PD
- **Exploratory:** Anti-tumor activity

Data presented for Part 1
- Data snapshot: Oct. 15, 2018

Part 1 Dose Escalation (N=32)

Twice Weekly (mg/m^2)	Weekly (mg/m^2)

All Solid Tumors

112 ← 80 ← 53 → 64, 107; 53 ← 32 ← 16 ← 8 ← 4 ← 2

3+3 escalation

Single patient cohort

Part 2 Expansion Cohorts (N~82)

Single-Agent SY-1365
1. Ovarian Cancer: 3+ Prior Lines
2. Ovarian Cancer: Primary Platinum Refractory
3. All Solid Tumors: Research Biopsy

SY-1365 in Combination
1. Ovarian Cancer, 1+ Prior Line(s): Carboplatin combination
2. HR+ Breast Cancer post-CDK4/6 inhibitor + AI: Fulvestrant combination

SY-1365 Patient Baseline Characteristics

Characteristics N(%)	N=32
Median Age, years (range)	63 (25-87)
Female sex, n (%)	25 (78.1)
≥4 Prior Lines of Therapy	28 (87.5)
Median Number Prior Lines (range)	5 (1-13)
Cancer Type	
Breast	8 (25)
Ovarian	8 (25)
Endometrial	5 (16)
Pancreatic	2 (6)
Adrenal	1 (3)
Biliary Tract Adenocarcinoma	1 (3)
Cervical	1 (3)
Clival Chordoma	1 (3)
Colon	1 (3)
Non-Small Cell Lung Cancer	1 (3)
Periorbital SCC	1 (3)
Prostate	1 (3)
Sarcoma	1 (3)

SY-1365 Patient Disposition

Number of Patients Enrolled By Dose Level											N
Dose (mg/m^2)	2	4	8	16	32	53	64	80	107	112	Total
Safety Population	1	2	1	1	1	6	7	6	6	1	32
Response Evaluable	1	1	1	1	1	3	5	3	3	0	19

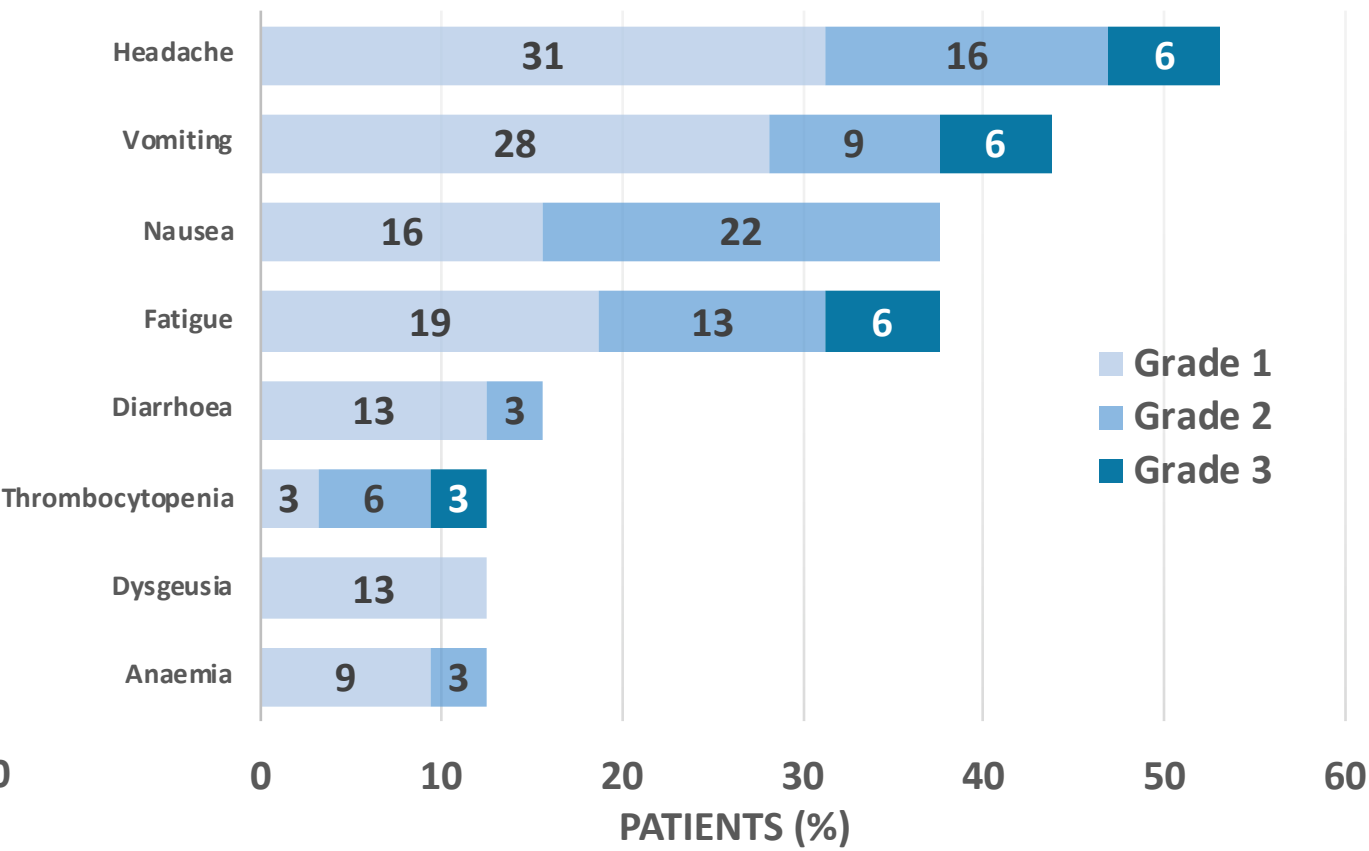| Number of Patients Enrolled	N (%)
Duration of Treatment: Median days (range)	46.5 (2 – 147)
Patients withdrawn from treatment	28 (87.5)
Progressive Disease per RECIST 1.1	16 (50.0)
Clinical Progression	7 (21.9)
Withdrawal of Consent	4 (12.5)
Death*	1 (3.1)

*Due to progression of disease

SY-1365 Safety Overview: Part 1 Dose Escalation (N=32)
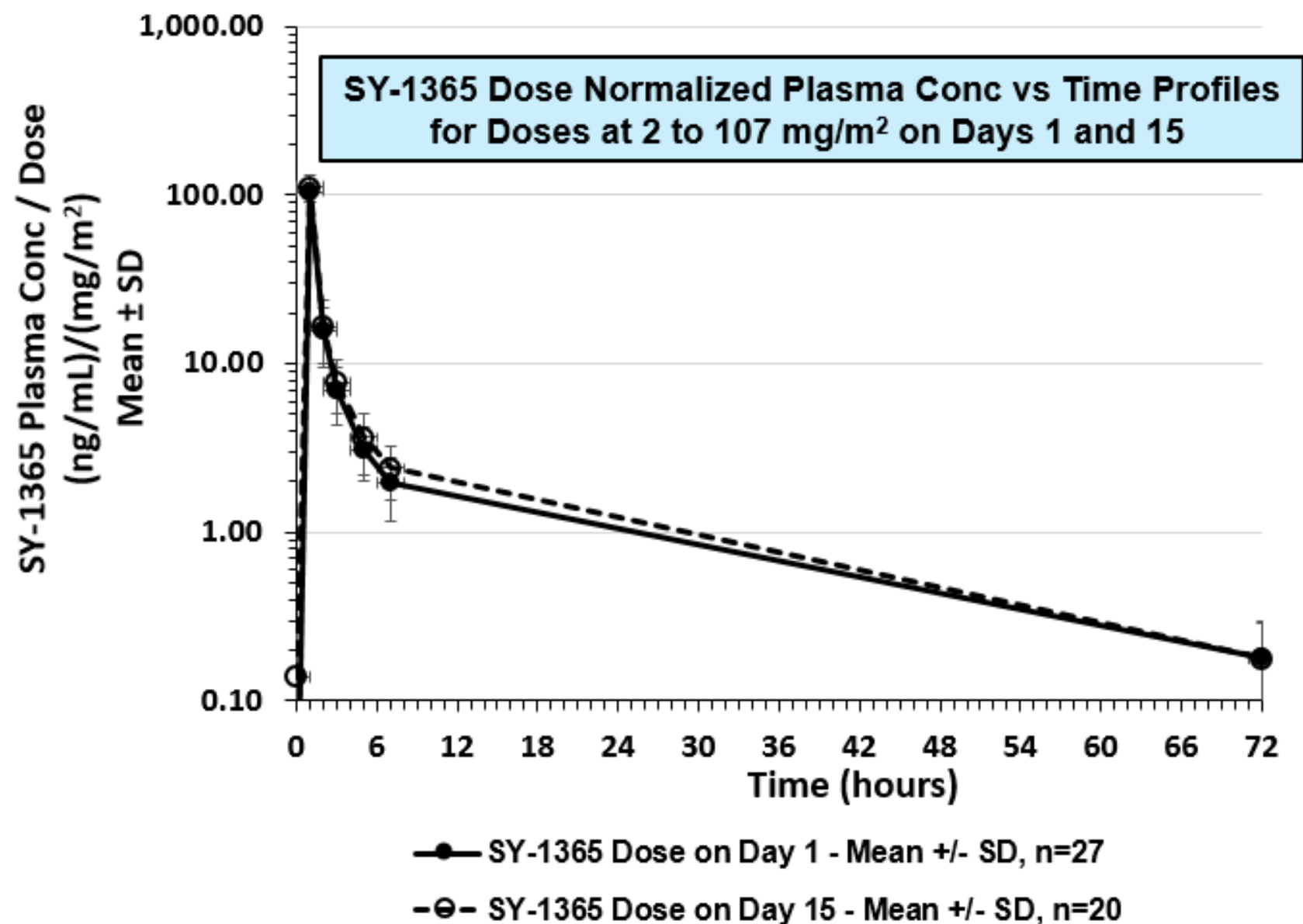
ADVERSE EVENTS (≥15%), ALL CAUSALITY

Adverse Event	Grade 1	Grade 2	Grade 3
Headache	31	19	6
Vomiting	31	16	9
Nausea	13	25	
Fatigue	19	13	6
Hyponatraemia	16		6
Diarrhoea	16	3	
Decreased appetite	16	3	
Anaemia	6	9	3
Hypoalbuminaemia	3	13	
Dizziness	13	3	
ALT increased	16		

PATIENTS (%)
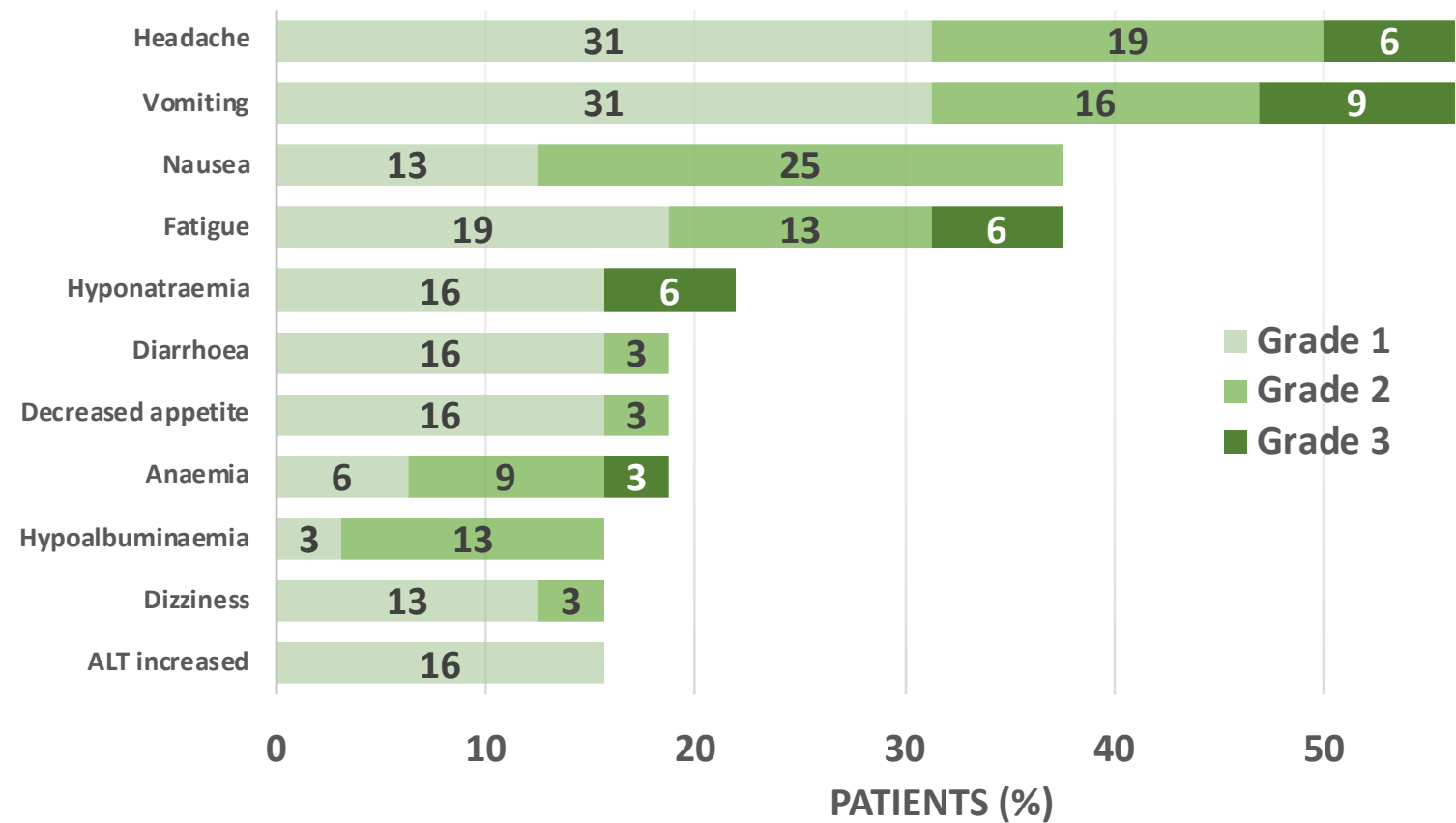
RELATED ADVERSE EVENTS (≥10%)

Adverse Event	Grade 1	Grade 2	Grade 3
Headache	31	16	6
Vomiting	28	9	6
Nausea	16	22	
Fatigue	19	13	6
Diarrhoea	13	3	
Thrombocytopenia	3	6	3
Dysgeusia	13		
Anaemia	9	3	

PATIENTS (%)

- Predominantly low grade, reversible, and generally manageable
- Most frequent related AEs include headache, nausea, vomiting, and fatigue
- No reports of neutropenia
- DLTs: headache (64 mg/m^2), coronary vasospasm (80 mg/m^2), and fatigue (112 mg/m^2)
- MTD not defined

SY-1365 Plasma Pharmacokinetics

SY-1365 Dose Normalized Plasma Conc vs Time Profiles for Doses at 2 to 107 mg/m^2 on Days 1 and 15

Y-axis: SY-1365 Plasma Conc / Dose (ng/mL)/(mg/m^2) Mean ± SD

X-axis: Time (hours)

— SY-1365 Dose on Day 1 - Mean +/- SD, n=27

- o - SY-1365 Dose on Day 15 - Mean +/- SD, n=20

- Plasma PK exposures (Cmax, AUC) are linear from doses of 2 to 107 mg/m^2

- No SY-1365 accumulation with repeat dosing

- SY-1365 Day 1 PK Parameters at 80 mg/m^2

  – Cmax: 7,498 ± 1,116 ng/mL

  – AUC: 11,696 ± 2,848 ng/mL·h

  – Half-life: 17.9 ± 4.2 h

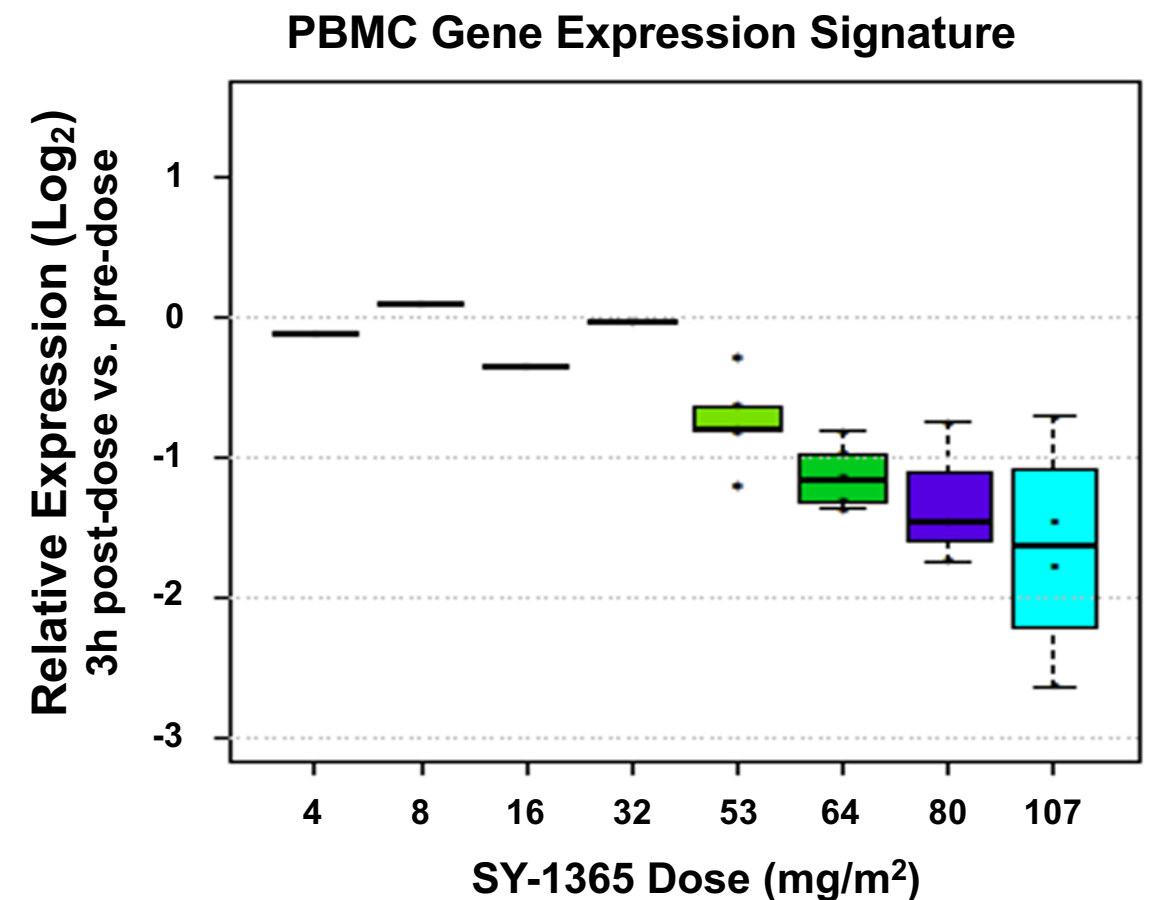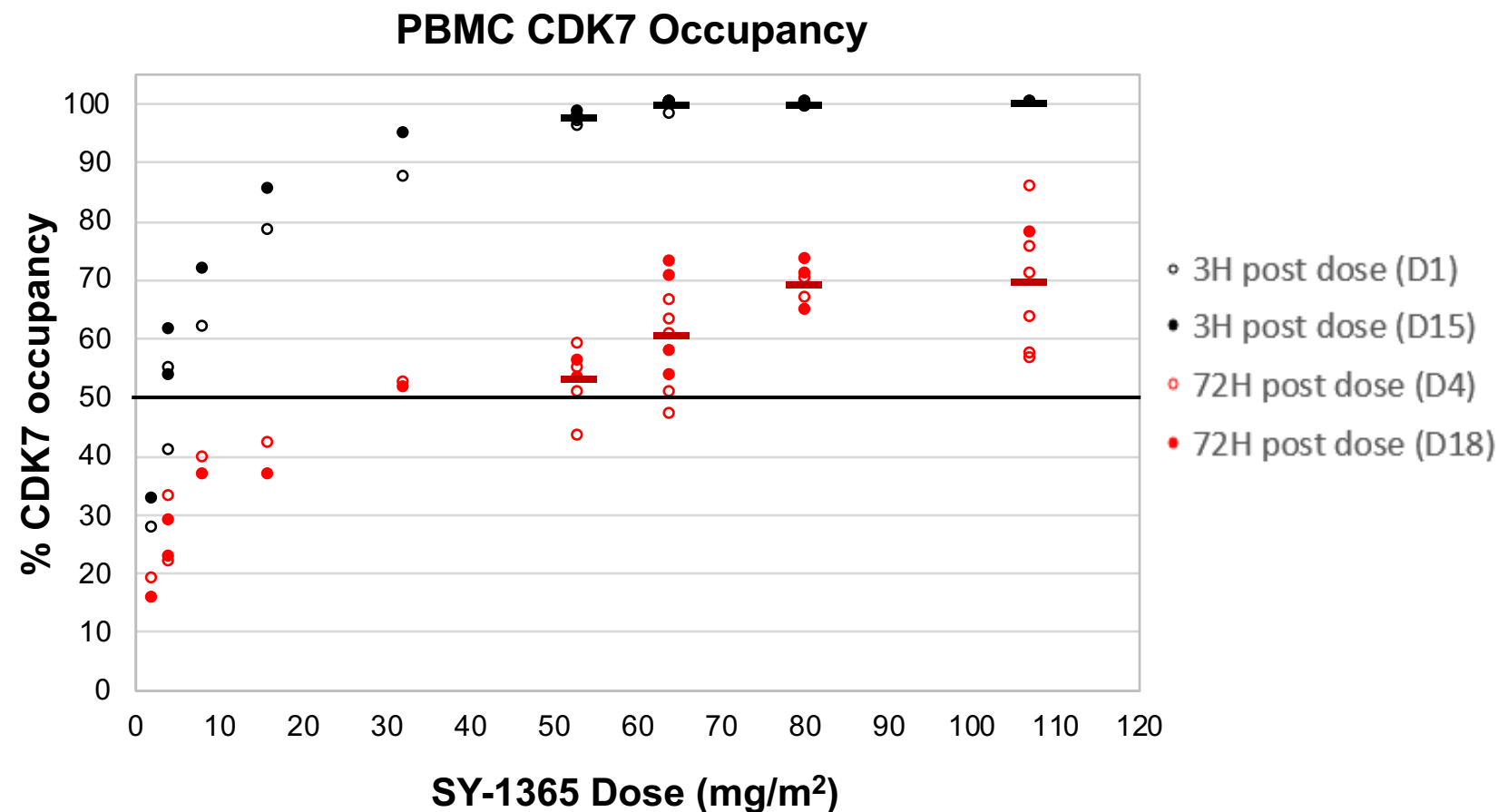# SY-1365 PD Effects Evaluated by CDK7 Occupancy and Transcriptional Assays

- CDK7 Occupancy: relative measure of free CDK7 to total CDK7
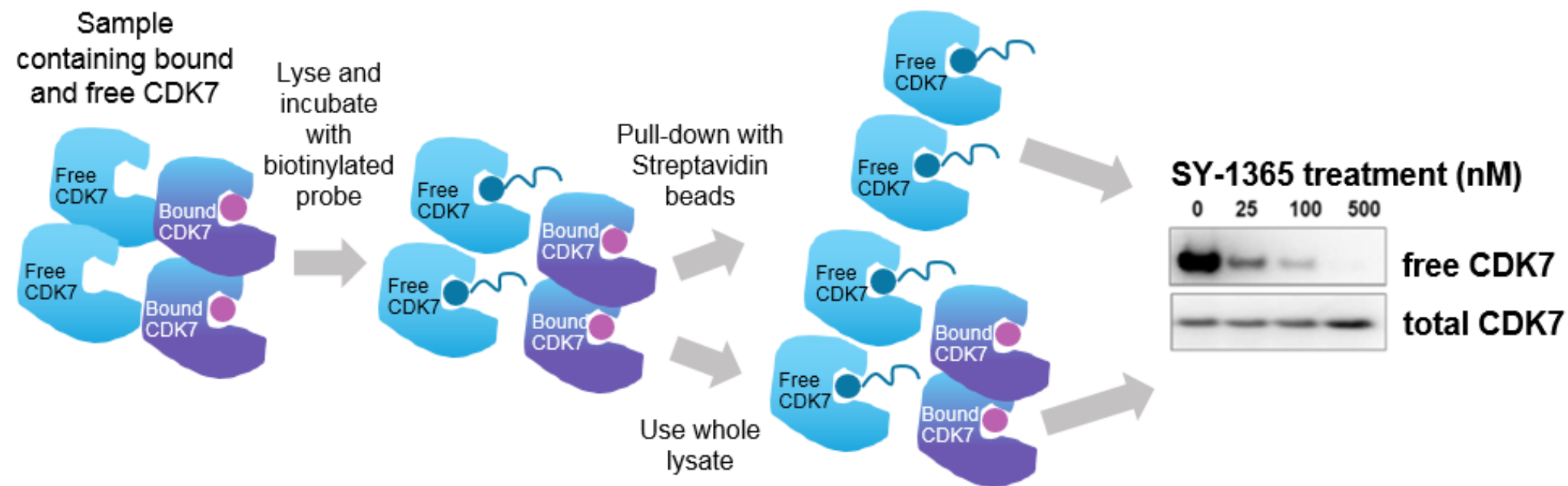
- SY-1365-biotin probe molecule to capture unbound/free CDK7
- MSD format for high-throughput assessment

- Transcriptional assay: gene expression signature
  - SY-1365 dose-response gene signature developed in PBMCs in vitro
  - ~25 early response genes (3-5 hrs post treatment)
  - Custom Nanostring codeset to evaluate a subset of response and control genes in patient PBMCs

SY-1365 Demonstrates Dose-Dependent Effects on CDK7 Occupancy and Gene Transcription

PBMC CDK7 Occupancy

- 3H post dose (D1)
- 3H post dose (D15)
- 72H post dose (D4)
- 72H post dose (D18)

PBMC Gene Expression Signature

- SY-1365 binding to CDK7 over the dosing interval exceeded target levels from preclinical efficacy models at doses ≥ 32 mg/m² with plateauing at 80 mg/m² and above

- Similar %CDK7 occupancies observed between PBMCs and xenograft tissues in syngeneic mouse studies, and between PBMCs and tumor biopsies collected from patients (n=2)

- Transcriptional assay demonstrated SY-1365 dose response relationship with gene expression changes

Early Evidence of SY-1365 Clinical Activity

- CT images of 52 year old woman with relapsed ovarian cancer on SY-1365 80 mg/m^2 BIW

Before treatment   **After 2 months**   **After 6 months**
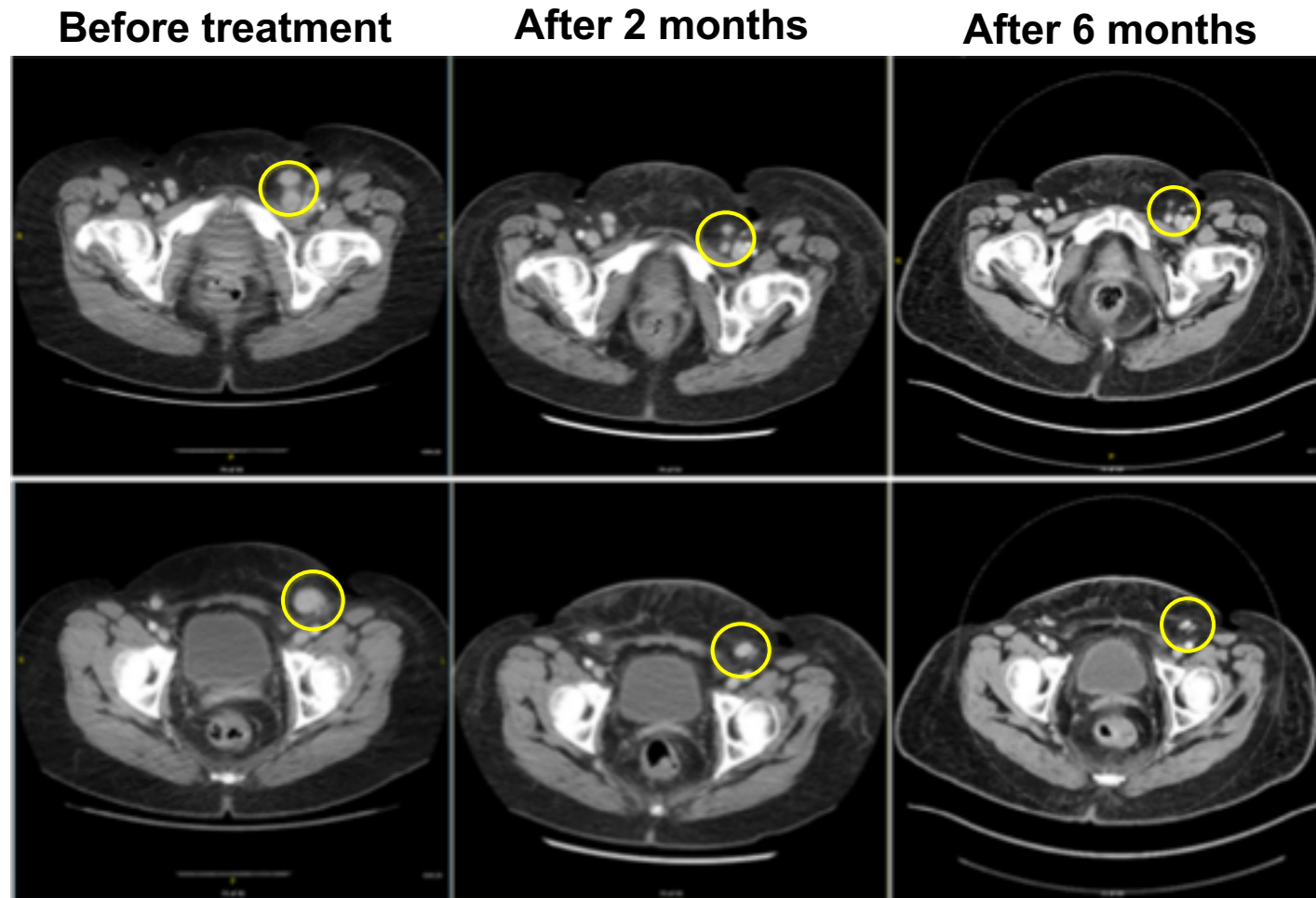
- Stage IV Clear cell in 4th relapse
  - ARID1A, PIK3CA, NF1 mutations

- Best response to prior lines of therapy: SD

- Confirmed PR after 2 cycles
  - 31.8% reduction (C3D1)

- Remains on study in PR in 7th month of SY-1365 treatment
  - 49% reduction at last scan (C7D1)

- 6 additional patients with SD, mostly at higher doses (≥ 32 mg/m^2 BIW)
  - Duration on treatment ranging 50 - 127 days
  - Disease Control Rate (CR+PR+SD) = 36.8% (7 out of 19 response evaluable patients)

Conclusions

- SY-1365, a first-in-class selective CDK7 inhibitor, showed dose-dependent effects on CDK7 occupancy and gene expression demonstrating proof of mechanism in patients with advanced solid tumors

- Adverse events were predominantly low grade, reversible, and generally manageable

- PK/PD analyses of exposure and drug target binding coupled with anti-tumor activity supported selection of 80 mg/m^2 dose for further evaluation

- Expansion cohorts to evaluate SY-1365 as a single-agent and in combination in patients with ovarian and breast cancer are currently ongoing (NCT03134638)