Precision oncology

Corporate Presentation
April 2021

REPARE THERAPEUTICS

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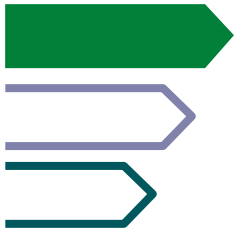
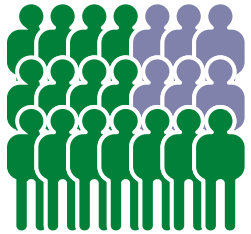
Leading clinical-stage precision oncology company focused on synthetic lethality

Lead clinical-stage candidate RP-3500, a potential best-in-class ATR inhibitor; currently in Ph1/2 monotherapy and combination therapy



Robust pipeline of SL-based therapeutics; including RP-6306, our PKMYT1 inhibitor, expected in clinic Q2 2021, and our Polθ inhibitor

Proprietary **genome-wide CRISPR-enabled SNIPRx platform**, focused on genomic instability and DNA damage repair



Powerful SL-based approach and proprietary platform provides **differentiated patient selection insights**

Cash, restricted cash and marketable securities of $333.9 million at end of 2020

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Experienced team proven in drug discovery and development

Management team

Lloyd M. Segal
President & CEO

McKinsey & Company · CAPRION ACCELERATING PRECISION MEDICINE · PCP

Steve Forte, CPA
Chief financial officer

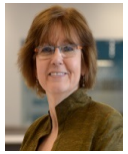
clementia · APTALIS

Michael Zinda, PhD
Chief scientific officer

AstraZeneca · Lilly

Kim A. Seth, PhD
Head, business & corporate development

Pfizer · Goldman Sachs



Maria Koehler, MD, PhD
Chief medical officer

gsk · Pfizer · AstraZeneca

Cameron Black, Ph.D.
Head, discovery

MERCK · aneqpharma

Laurence Akiyoshi, Ed.D.
EVP, Organizational & Leadership Development

CROWDSTRIKE · CISCO

Scientific founders

Daniel Durocher, PhD
- Developed CRISPR SL platform
- Deep DNA repair knowledge
- Lunenfeld-Tanenbaum Research Institute (LTRI) & professor at University of Toronto

Agnel Sfeir, PhD
- DDR and cancer pathway investigator
- Pioneer in Polθ, genome instability
- NYU Langone Medical Center & associate professor, Skirball Institute

Frank Sicheri, PhD
- Globally recognized structural biologist, expert in eukaryotic cell signaling, drug mechanism of action
- LTRI & professor at University of Toronto

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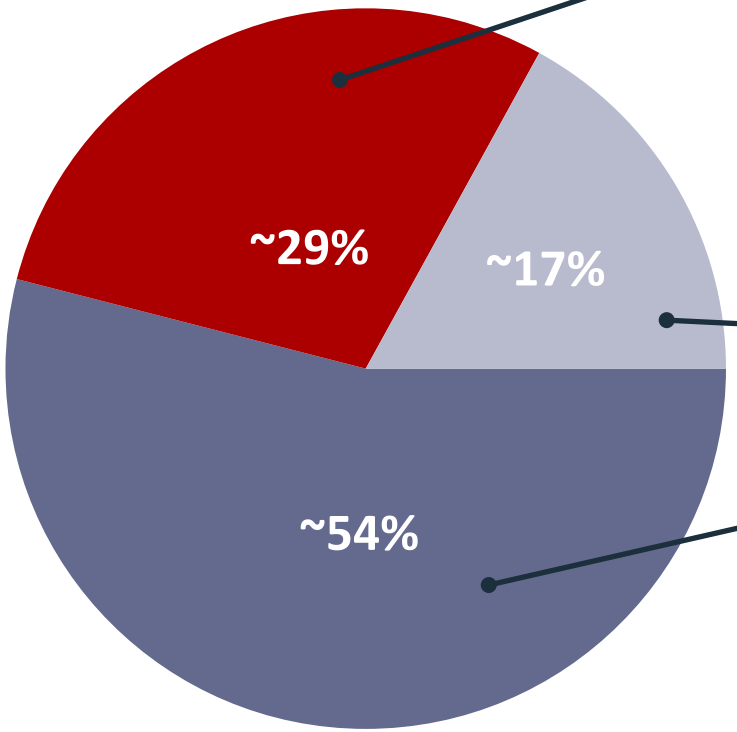
Focused on precision oncology for untapped cancer lesions

Focused on 71% untapped target space
(% of tumors)



Focus of precision oncology for 20 years:
Gain of function (targetable; e.g. EGFR)

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Gain of function (un-targetable; e.g. CCNE1)

Loss of function (no known driver; e.g. BRCA1)

The NEW ENGLAND JOURNAL of MEDICINE

N ENGL J MED 380;25 NEJM.ORG JUNE 20, 2019

"…known cancer targets represent a small minority of strong cancer dependencies … synthetic lethal targets are particularly attractive as new targets…"

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SNIPRx platform

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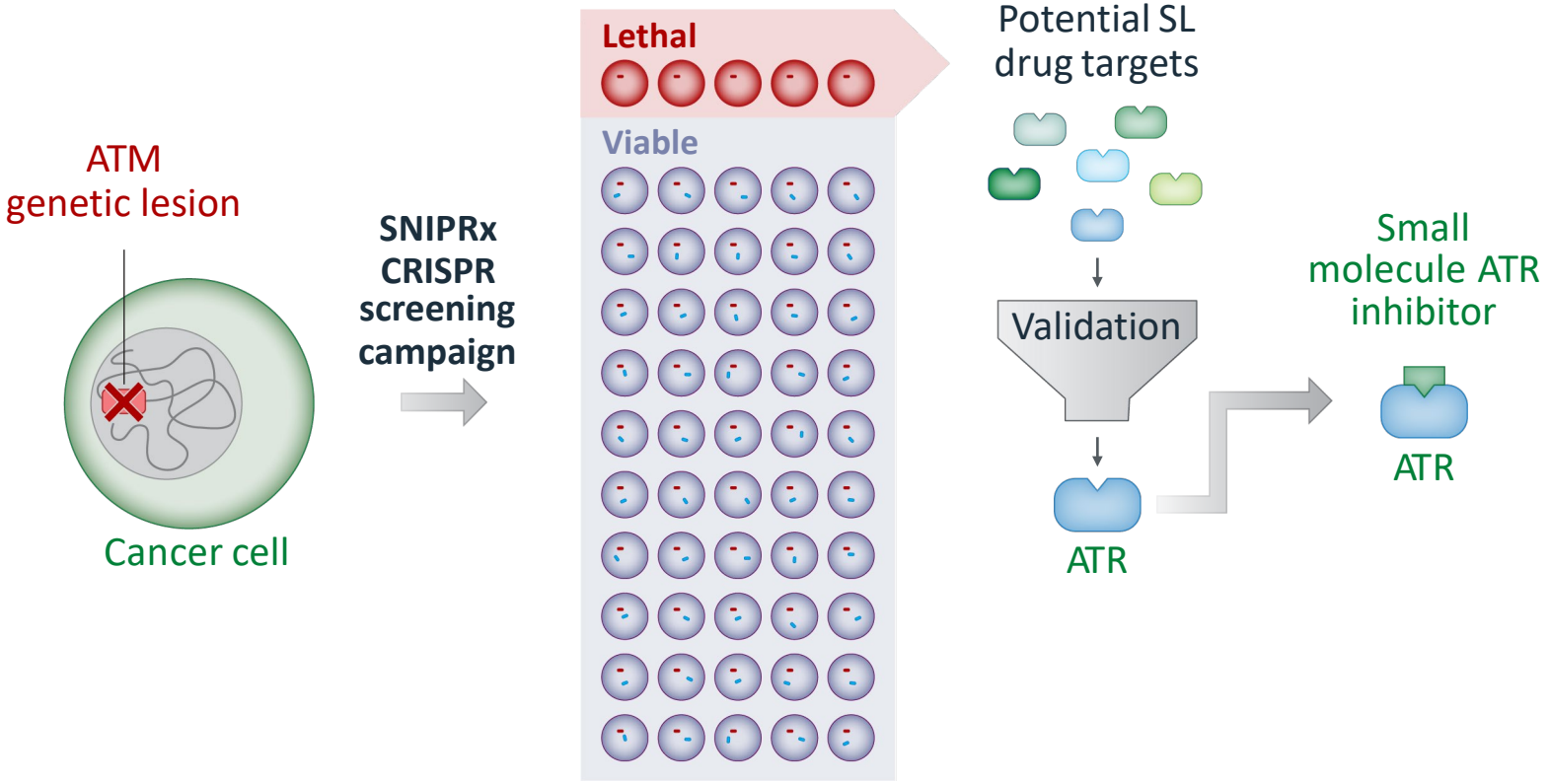
SNIPRx for synthetic lethal ("SL") drug discovery

1. Select tumor lesion of interest
2. Execute SNIPRx® screen campaign
3. Prioritize, select and validate druggable targets
4. Develop potent and selective inhibitors



- **Starts with the patient's unique genetic lesion**
- **Proprietary genome-wide, CRISPR-enabled platform and isogenic cell lines**
  - Optimizes sensitivity, reproducibility
  - Decreases false negatives
- **Finds targets and patient selection markers that others miss**
- **Novel SL targets identified from every campaign completed to-date**

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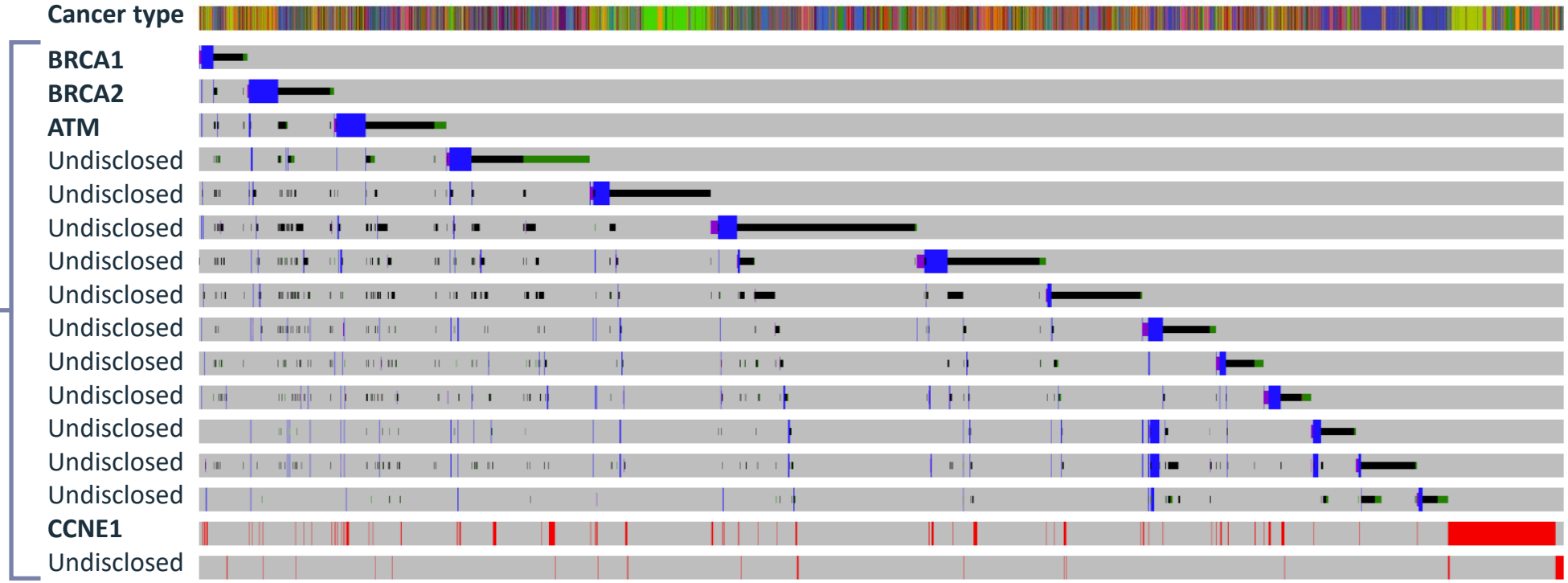
SNIPRx campaigns mine targeted genomic instability lesions

Lesion campaigns completed to-date



We have mined an initial 16 largely mutually exclusive tumor lesions representing ~30% of all tumors

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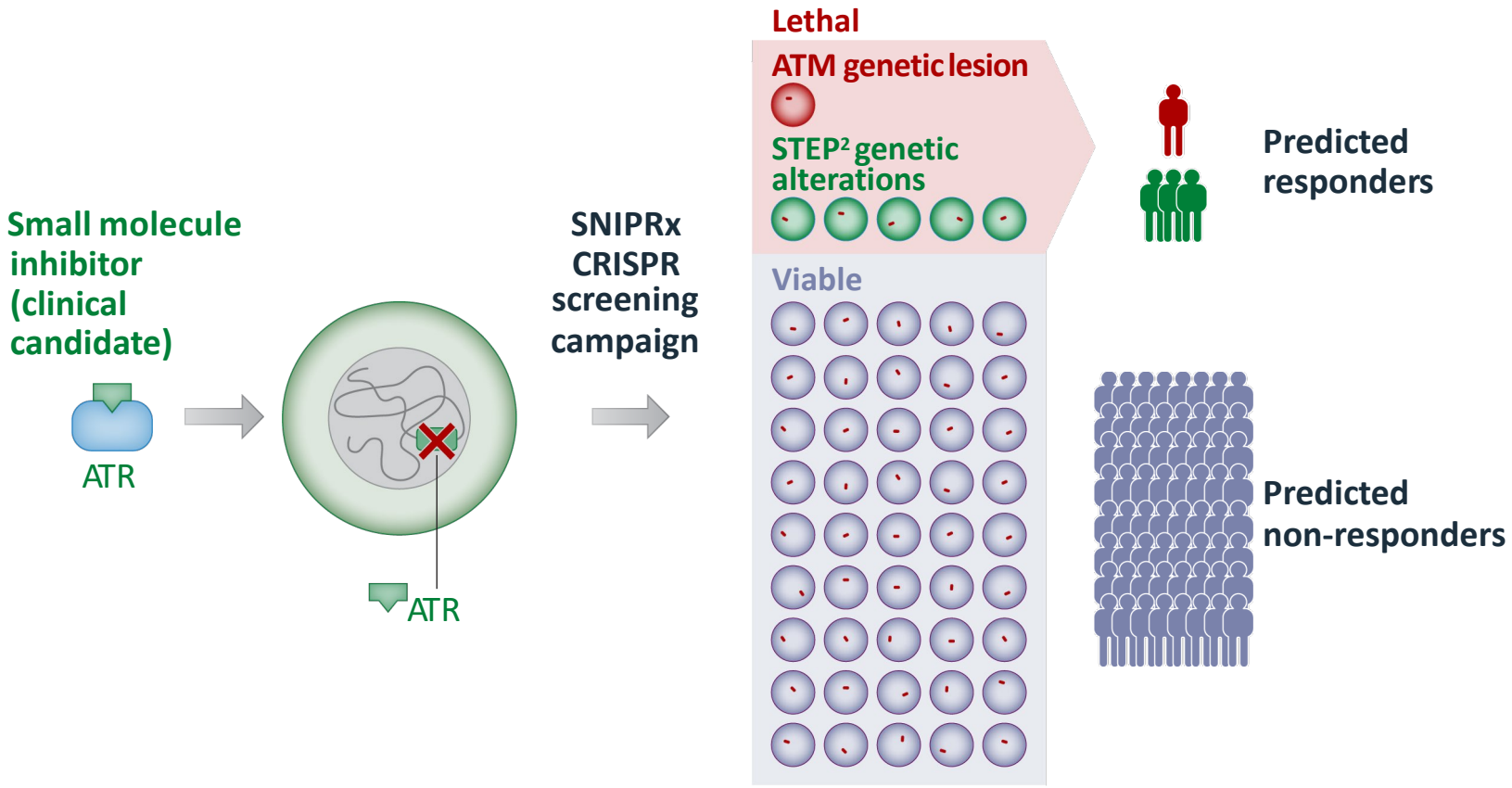
STEP²: Repare's patient selection advantage enabled by SNIPRx discovery

4 Develop potent and selective inhibitors

5 Perform SNIPRx® Targeted Expansion of Patient Populations (STEP²) screens

6 Conduct clinical trials in an enriched patient population



STEP² screens: SNIPRx Targeted Expansion of Patient Populations

- **Expands patient populations** beyond those identified by original SL pair
- STEP² insights **enable precision medicine-driven clinical trials**

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Bristol Myers Squibb – SNIPRx® target discovery collaboration

Multi-target discovery collaboration with Bristol Myers Squibb to leverage Repare's proprietary SNIPRx® synthetic lethal discovery platform to identify multiple oncology drug candidates

~$65M upfront

Including $50M non-dilutive cash and $15M equity investment

~$3 billion

Potential total milestone payments in addition to royalties (~$300M/program)

Target focused

Includes both small molecule SL targets and "undruggable" targets outside our focus

Discovery only

Repare retains all rights to its clinical and pre-clinical pipeline

Robust pipeline of SL-based precision oncology therapeutics

		SL Pair: Tumor lesion	SL Pair: Drug target	Discovery	IND-Enabling	Phase 1/2	Pivotal	Upcoming milestones	Rights
Clinical	ATR inhibitor RP-3500	ATM + 16 STEP[2] lesions	ATR	▶	▶	▶		Early readouts in H2 2021	REPARE THERAPEUTICS
Preclinical	PKMYT1 inhibitor RP-6306	CCNE1, FBXW7 + others	PKMYT1	▶	▶			Initiate Ph1 trial in Q2 2021	REPARE THERAPEUTICS
Preclinical	Polθ inhibitor	BRCA1/2 + others	Polθ	▶				IND-enabling studies in H1 2022	REPARE THERAPEUTICS; ono
Discovery	SNIPRx® platform	8 additional SL targets							REPARE THERAPEUTICS
Discovery	SNIPRx® platform	Discovery and validation of new SL precision oncology targets							REPARE THERAPEUTICS; Bristol Myers Squibb

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ATR inhibitor RP-3500

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RP-3500: Potential best-in-class ATR inhibitor

Oral ATR inhibitor to treat cancers with DNA Damage Response ("DDR") defects and high replication stress

ATR is a critical DDR protein with a central role in regulation of replication stress

Clinical validation of ATR/ATM SL relationship demonstrated at ASCO 2019

Compelling rationale for ATRi combination therapy with PARPi, radiotherapy and PD-1/L1

RP-3500 differentiation driven by:

- **Enhanced chemical properties (potency and selectivity)**
- **Proprietary patient selection insights to expand addressable patient populations**

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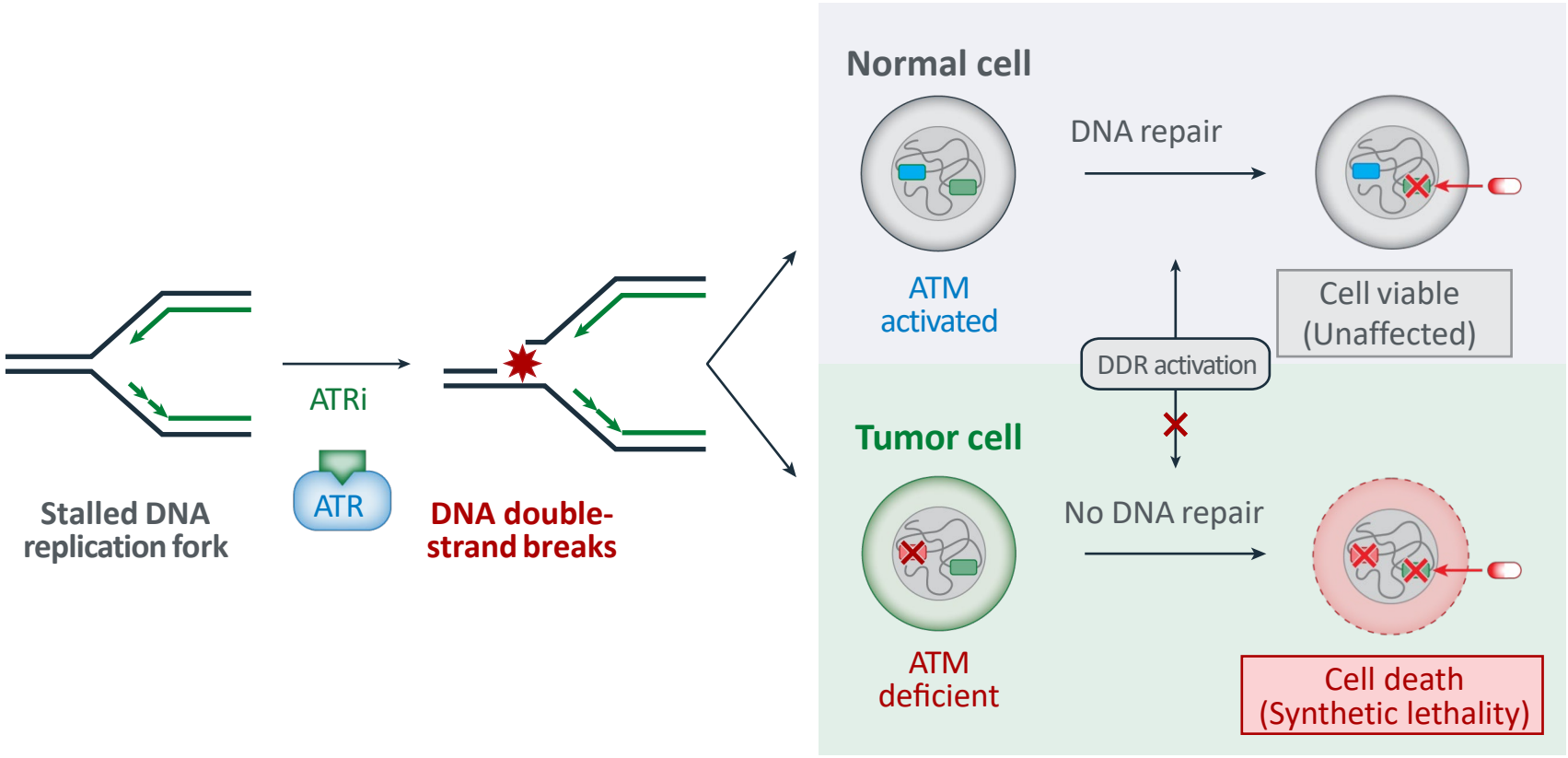
Mechanism of ATM-ATR synthetic lethality



- **Inhibition of ATR:**
  - **Compromises the stabilization of DNA replication forks**
  - **Is associated with increases in DNA double-strand breaks**
- **SL screens have identified that ATR is SL with ATM**

ATR inhibitors induce cell death in ATM-deficient cancer cells

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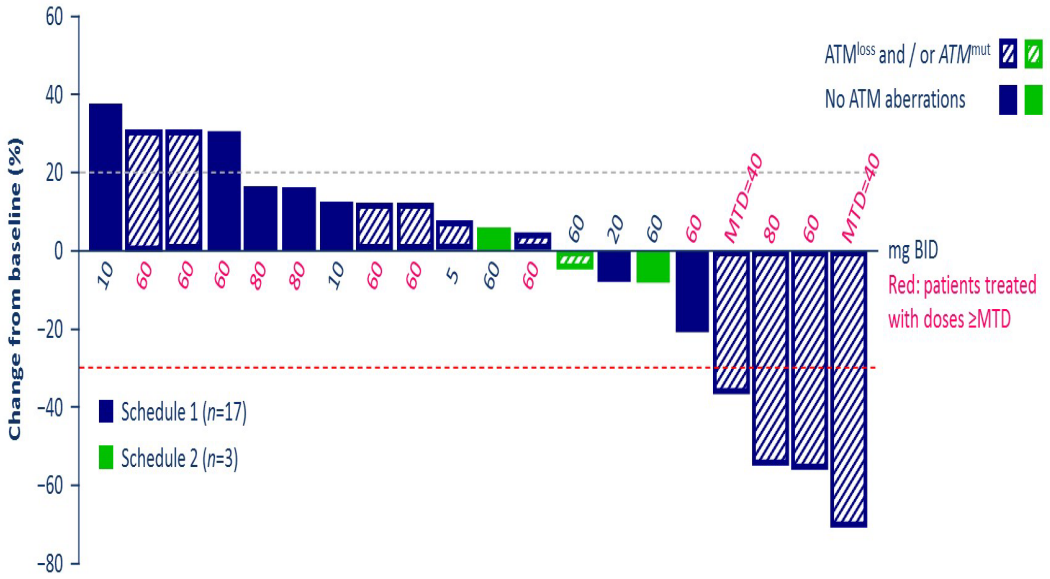
ATRi early human monotherapy POC

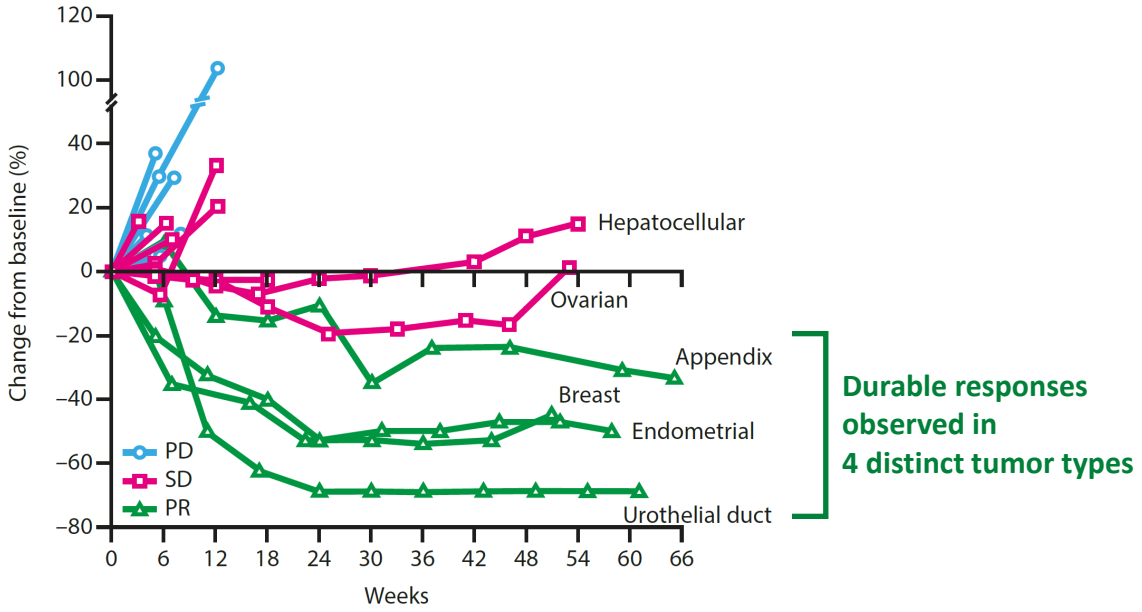
BAY1895344: First in-human dose escalation trial in HRD+ tumors

Tumor Responses



Timothy A. Yap et al, Cancer Discovery 2020, DOI: 10.1158/2159-8290.CD-20-0868

Durability of response across multiple tumor types



Durable responses observed across various tumor types; confirmed responding tumors all had ATM deficiency

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RP-3500: Potential 'best-in-class' ATR inhibitor

	ADME parameter	AZD6738	BAY1895344	M4344 (VX-803)	RP-3500
Potency	ATR Ki (nM)	0.06	3.8	2.9	**0.02**
	ATR Hela cell potency (IC_{50}, nM)	186	2	6	**1**
	Lovo cell viability (IC_{50}, nM)	377	27	86	**22**
	mTor selectivity ratio in Hela cells	6	20	29	**23**
	Kinase activity outside PIKK family	No	No	Yes	**No**
Metabolism	CYP inh (3A4, 2D6, 2C9, 1A2, 2C19)	all >30	12, 28, 12, >30, >30	17, >30, >30, >30, >30	**all >30**
	Liver microsomes: rat, dog, human Cl_{int} (µL/min/mg)	<11.6, <11.6, <11.6	16, 35, 8.6	-	**77, 7.0, 8.0**
	Hepatocytes: rat, dog, human Cl_{int} (µL/min/10^6cells)	<2.9, na, <2.9	<2.9, na, <2.9	<2.9, <2.9, <2.9	**17.3, <1.0, 1.5**

RP-3500 profile offer the potential for:

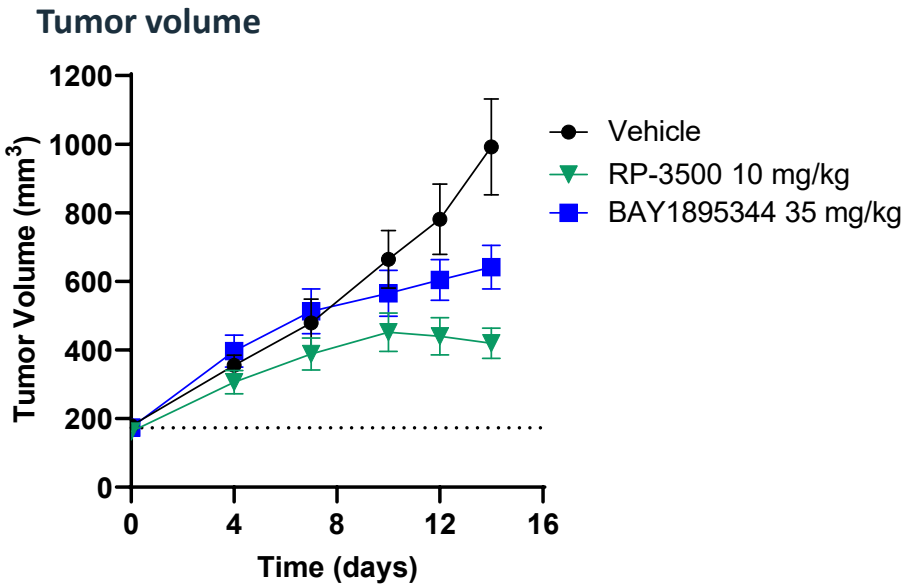
- **Increased potency**
- **Improved/similar selectivity**
- **Favorable pre-clinical PK profile**
- **Low potential for clinical drug-drug interactions**

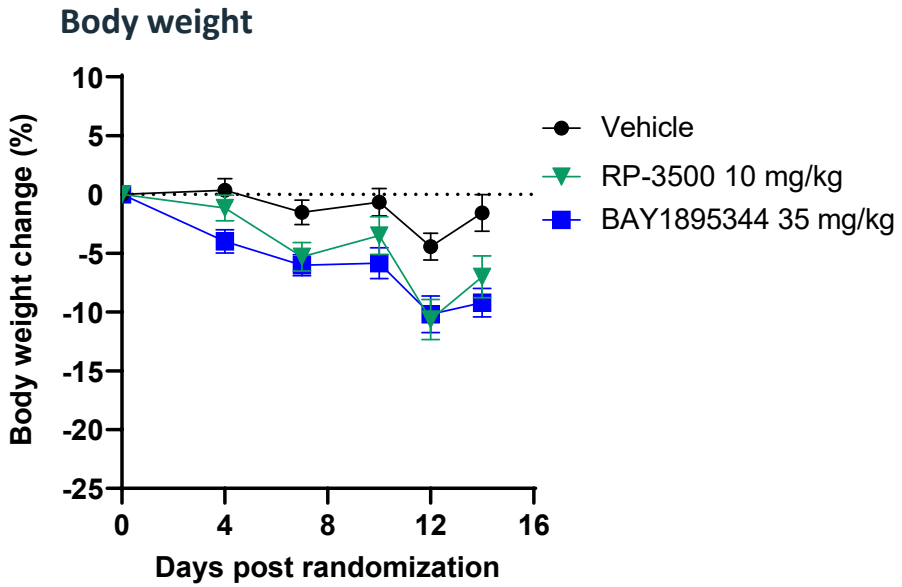
Potential to be best-in-class ATRi*

* RP-3500 has not been assessed in head-to-head preclinical studies with AZD6738 or M4344

Preclinical data: RP-3500 vs competitor in animal models

Statistically significant tumor growth suppression in colon cancer model





Higher suppression of tumor growth was observed with RP-3500 as compared to BAY1895344

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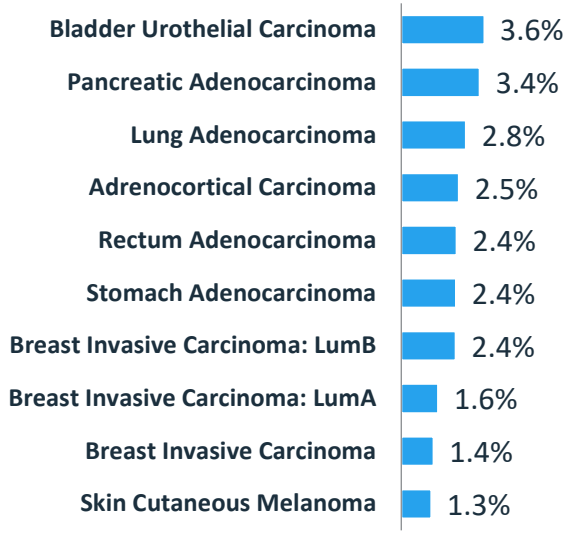
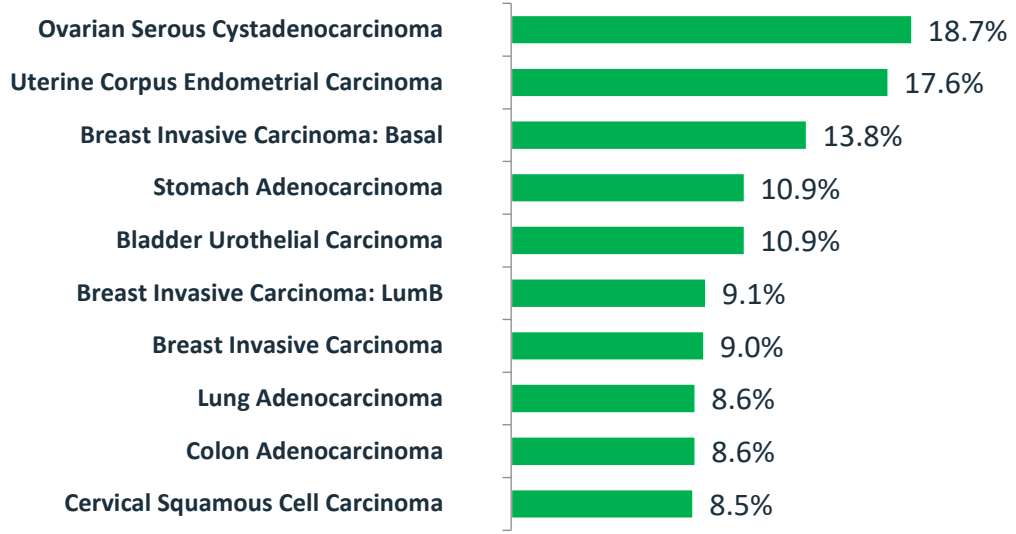
Expanding RP-3500 patient opportunity with STEP² selection tools*

Top 10 tumor types with highest prevalence of ATM deficiency



Top 10 tumor types with highest prevalence of ATM deficiency or STEP² genomic alterations



- Beyond ATM, **16 of 19 additional, mutually exclusive genomic alterations identified as SL with RP-3500 are eligible for recruitment into the ongoing trial**
- Represents **expanded, clinically relevant populations with unmet medical needs**
- **Average prevalence of ~2% (ATM) to ~10% (STEP² genes)** across multiple tumors

*** TCGA; Not weighted for tumor prevalence**

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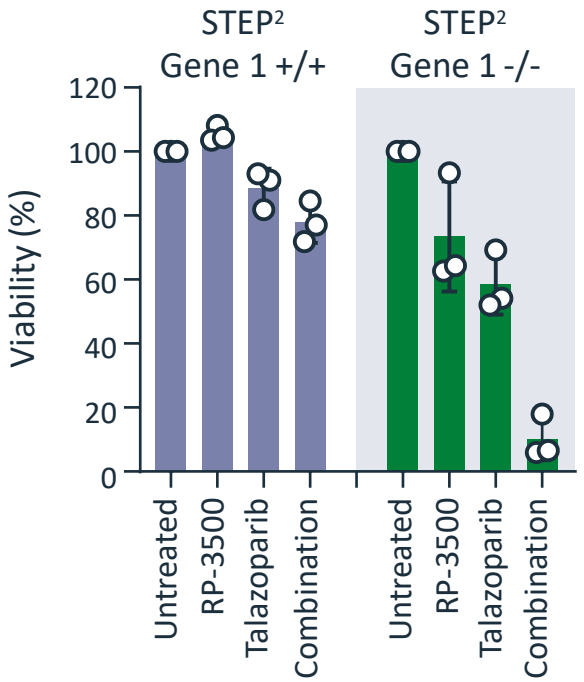
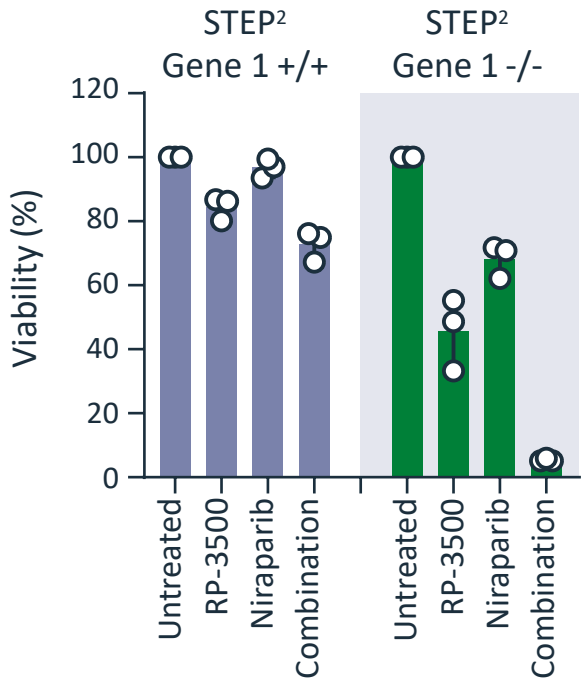
STEP² approach identifies genes to predict combination response

Significant synergy demonstrated by combination of RP-3500 and PARP inhibitors



Talazoparib: 3 nM
RP-3500: 5 nM



Niraparib: 100 nM
RP-3500: 4 nM

- **Identified tumors with STEP² genes sensitive to the combination of RP-3500 and PARP inhibitors**
- **The activity observed at low doses of RP-3500 and PARPi could lead to efficient anti-tumor activity and potentially address known PARPi toxicities**

Significant new approach to select patients for response to combinations

+/+: Wild Type
-/-: Genomically Altered

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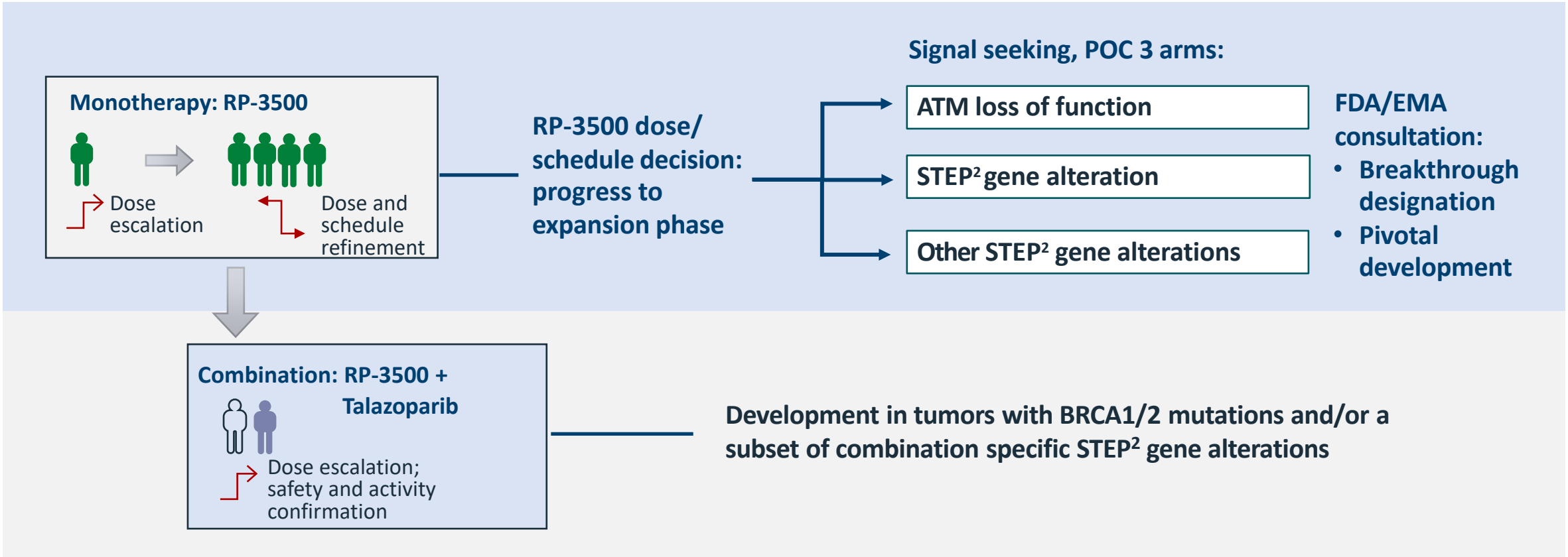
RP-3500 clinical trial design

Global multicenter study designed for patients with:

- Any recurrent tumor with:
  - ATM loss
  - Loss of any of the additional 16 STEP^2 genes



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PKMYT1 inhibitor RP-6306

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RP-6306: First-in-class small molecule program

Oral PKMYT1 inhibitor, serving unmet need in tumors with CCNE1 amplification and other lesions

First in class drug PKMYT1 inhibitor, synthetic lethal in CCNE1 amplified, FBXW7 loss and tumors with other specific alterations

Amplification of CCNE1 drives genome instability; found in many tumor types, including Gyn/GI malignancies

Compelling preclinical anti-tumor activity confirms SL relationship of PKMYT1 and CCNE amplification and FBXW7 alterations

RP-6306 key differentiators include:

- Potent and highly selective
- Proprietary patient selection: CCNE1 amp, FBXW7 loss, other STEP[2] genes
- Combinability with several drug classes

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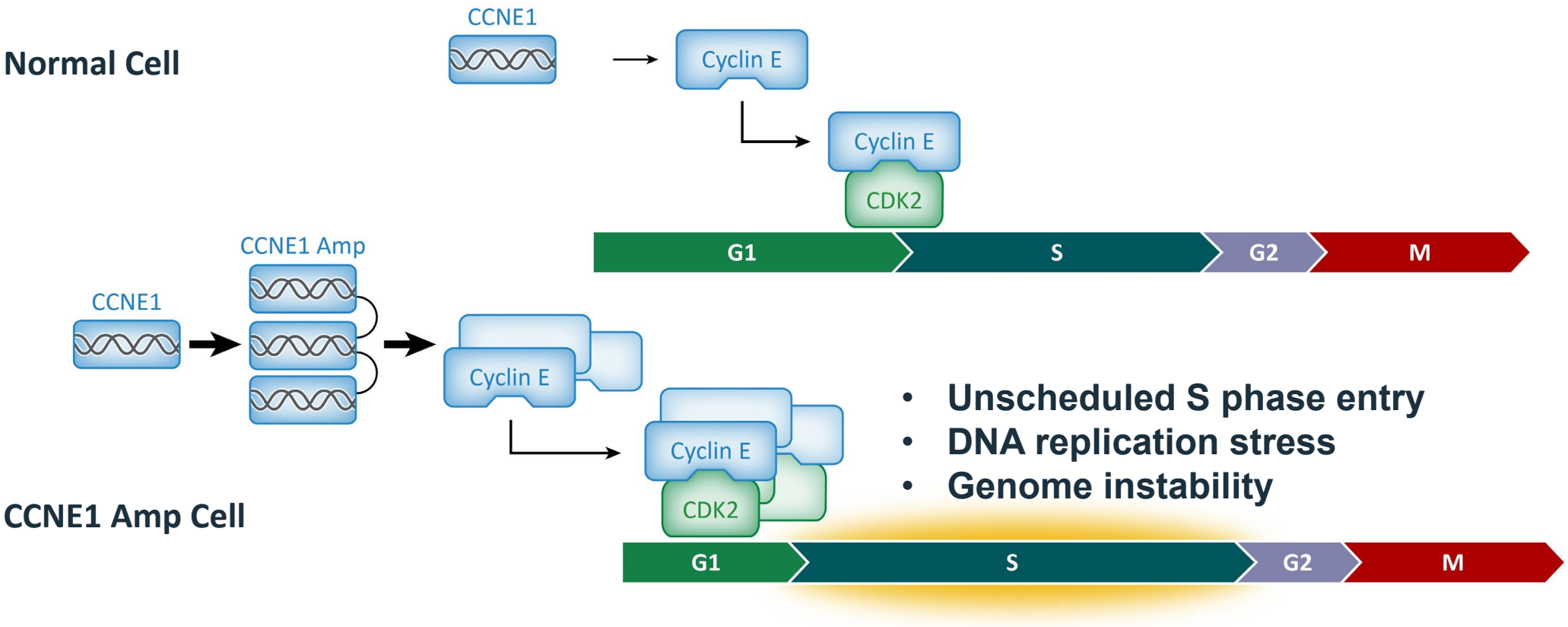
CCNE1 amplification drives genome instability



CCNE1-overexpression drives premature entry into S-phase and overloads the DNA replication machinery, resulting in genome instability

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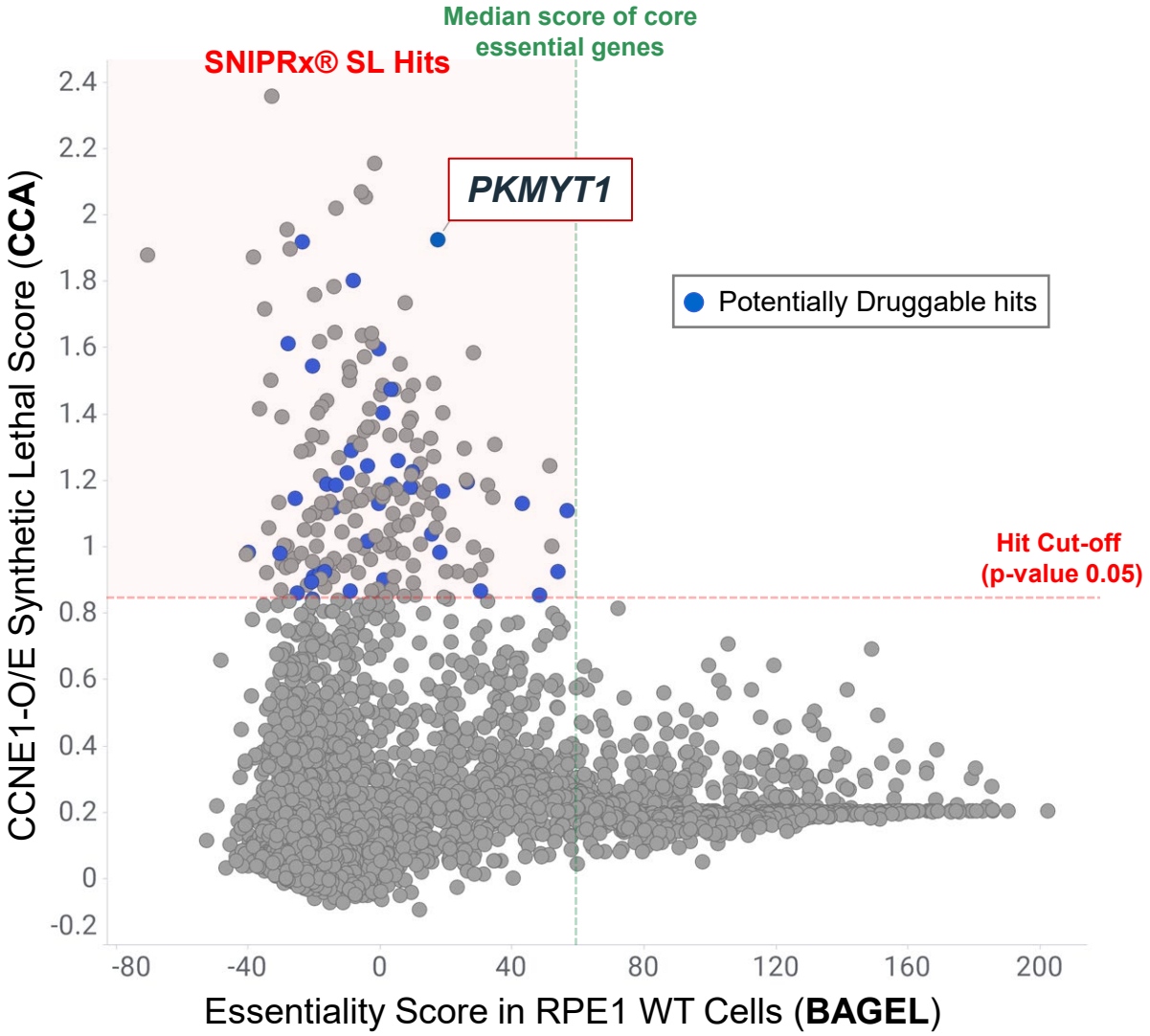
PKMYT1: Strong hit in a CCNE1-overexpression ("O/E") SL screen



- **Genome-wide CRISPR screen**
- **PKMYT1 was the highest scoring druggable hit**
- **PKMYT1 was also a high scoring hit in the DepMap**

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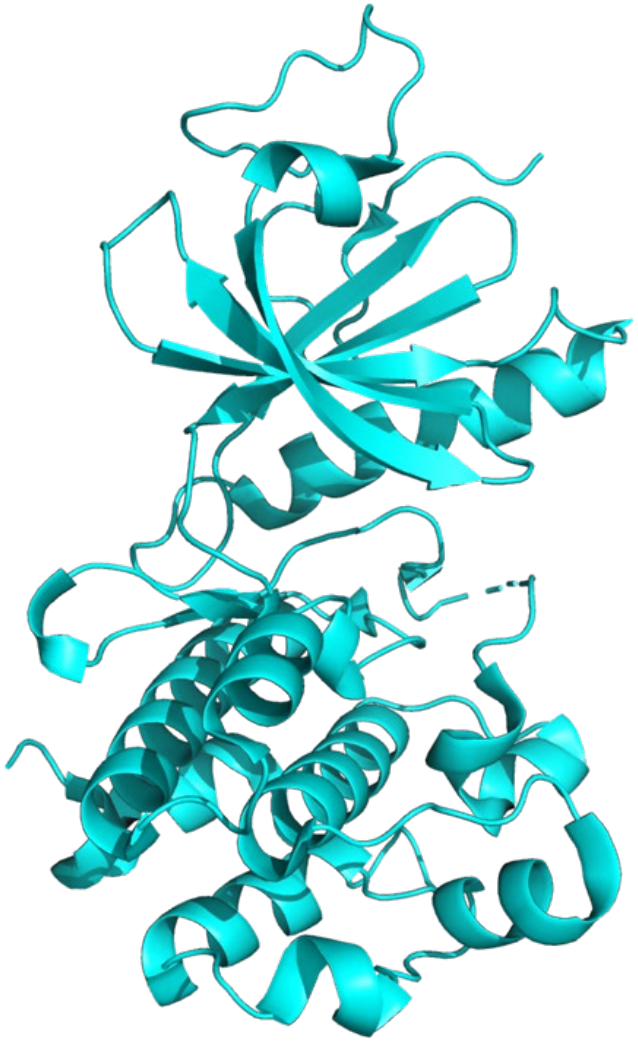
What is PKMYT1?



PKMYT1 (also known as Myt1):

- **Membrane-associated serine/threonine protein kinase**
- **Member of WEE1 protein kinase family**
- **Selectively phosphorylates cyclin-dependent kinase 1 (CDK1) – no other known substrates**
- **Negatively regulates the G2/M transition of the cell cycle by inactivating CDK1**
- **Not previously linked to CCNE1 amplification**

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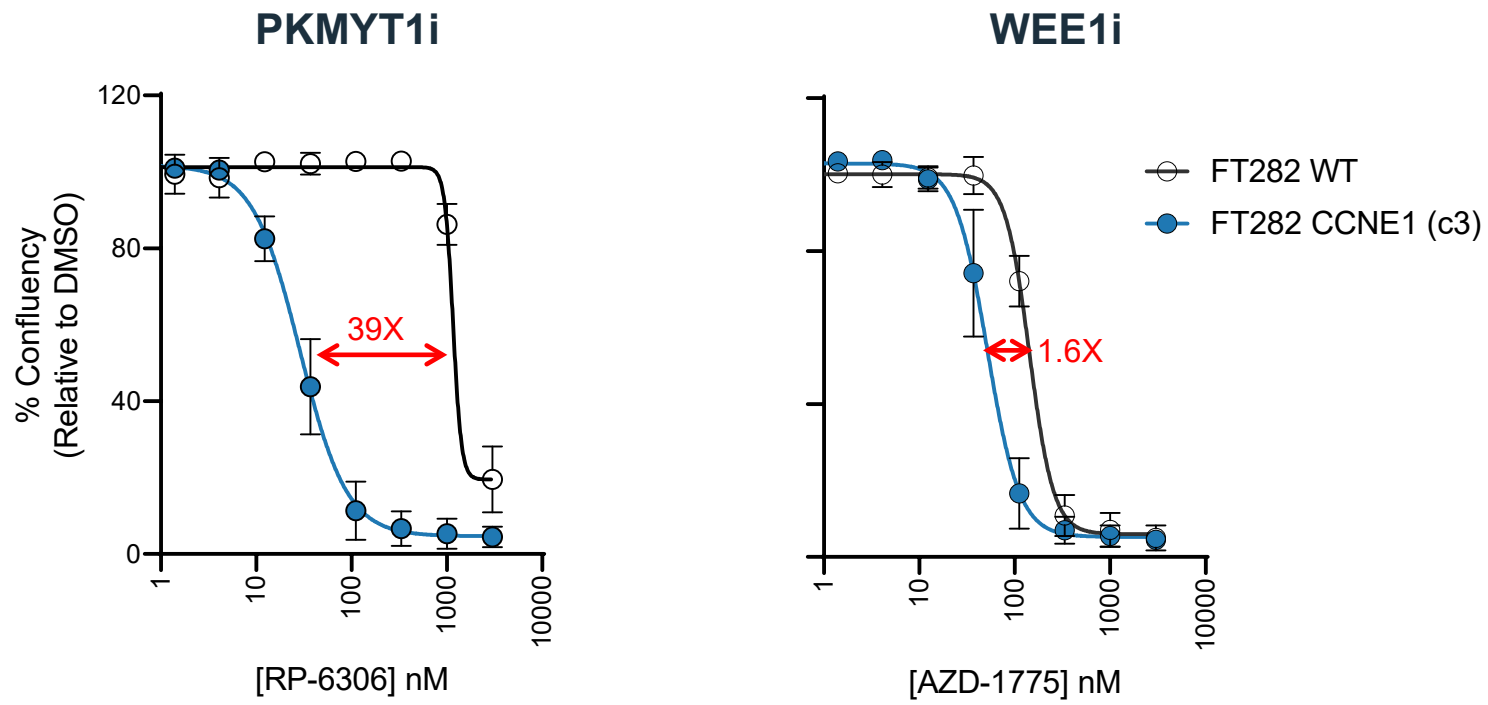
RP-6306: Potent and selective first-in-class PKMYT1 inhibitor

	Parameter	RP-6306
Potency	Enzyme potency (IC_{50}, nM)	3
	HCC1569 CDK1 T14 phosphorylation (IC_{50}, nM)	20
	HCC1569 cell viability (EC_{50}, nM)	19
	PKMYT1 selectivity over WEE1 (cell-based)	>100-fold
ADME Properties	CYP inh (3A4, 2D6, 2C9, 1A2, 2C19)	all >30 µM
	Hepatocytes: rat, dog, human Cl_{int} (µL/min/10^6cells)	28, <6, <6
	Human plasma protein binding	79%
	Rat PK (%F, $t_{1/2}$)	44%, 2.6h
	Dog PK (%F, $t_{1/2}$)	74%, 5.5h

RP-6306 profile:

- Highly potent and selective inhibitor
- PanLabs Lead Profiling screen on 68 assays showed no significant activity at 10 µM
- No activity (>100 µM) in patch clamp assays for hERG, hNaV1.5, and hCaV1.2 ion channels
- Favorable pre-clinical PK profile
- Low potential for clinical drug-drug interactions

RP-6306 Delivers a selective effect on CCNE1-O/E cells vs. WEE1 inhibition



- **PKMYT1 inhibition results in a 39-fold increase in sensitivity in CCNE1-O/E FT282 cells vs. wild type**
- **WEE1 inhibits both wild type and CCNE1-O/E cells**

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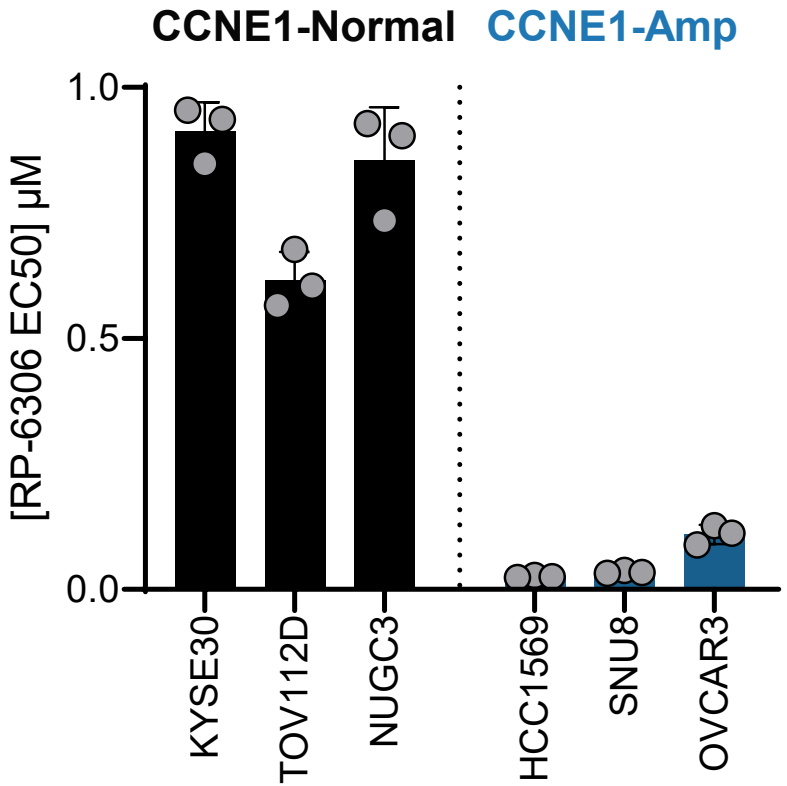
RP-6306 selectively targets CCNE1-amplified tumor cell lines



Tumor cell lines with CCNE1-Amp are hyper-sensitive to PKMYT1 inhibition compared to cells with normal CCNE1 levels

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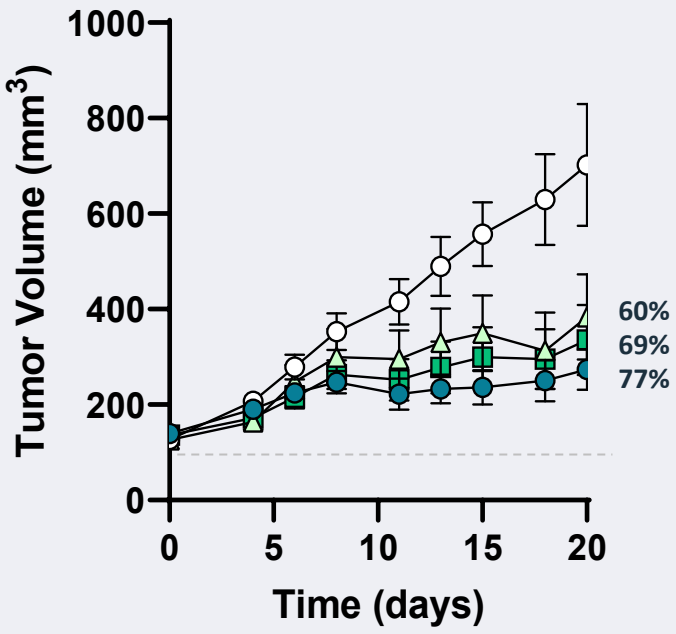
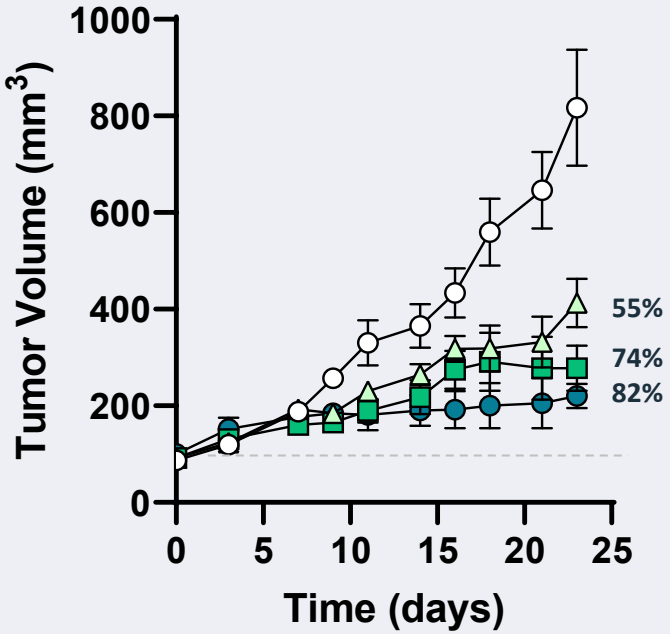
RP-6306 inhibits the growth of multiple CCNE1-amplified xenograft tumors

HCC1569 Breast



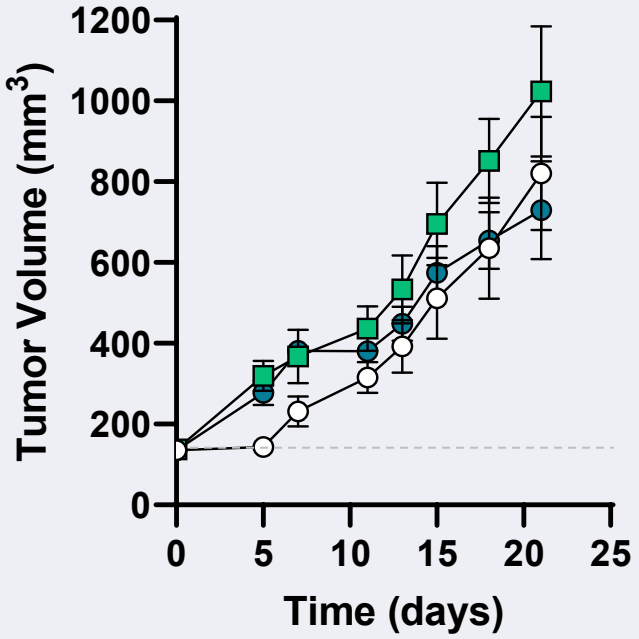
CCNE1 CN = 34

OVCAR3 Ovarian

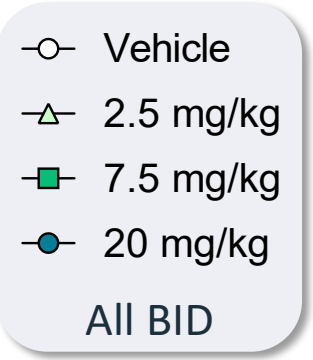


CCNE1 CN = 14

SUM149PT TN Breast



CCNE1 CN = 2 (WT)



RP-6306 demonstrates efficacy in CCNE1-amplified tumors and is efficacious at doses well below MTD

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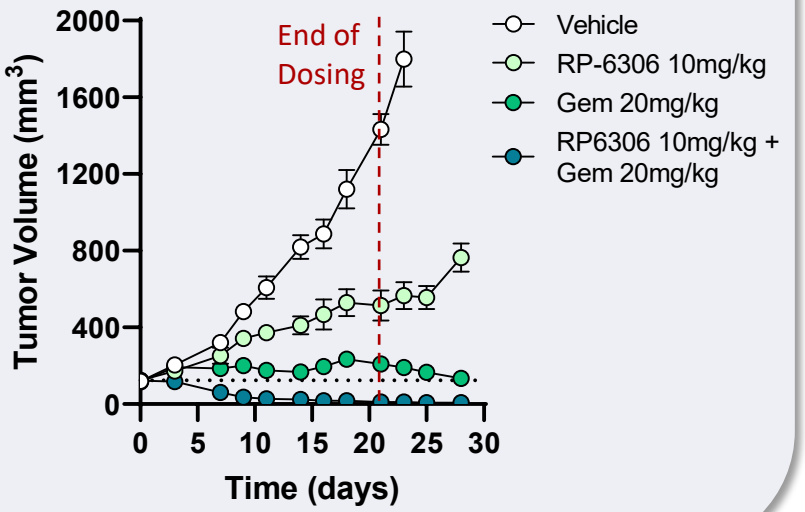
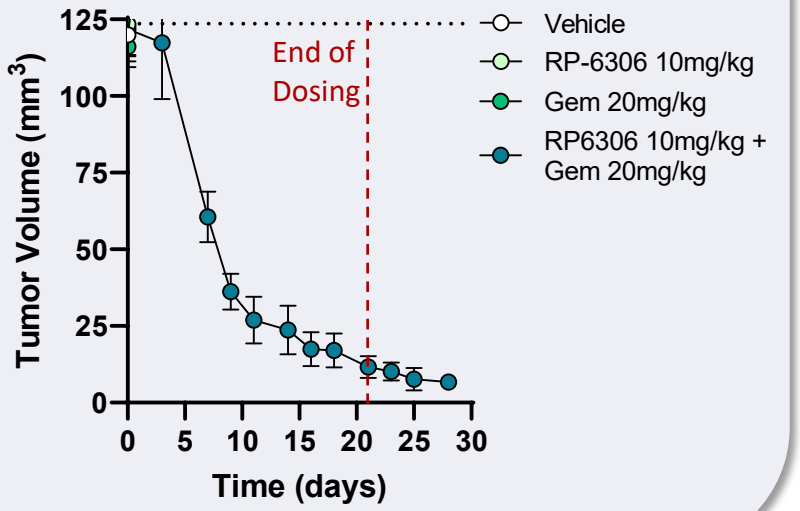
RP-6306 + Gemcitabine drives regression and is well tolerated

Activity (OVCAR3; CCNE1 CN = 14)



Gemcitabine dosed once a week and RP-6306 dosed twice daily

Activity (Robust regression)



Xenograft tumors continue to regress after cessation of dosing with several mice having no measurable tumor detected

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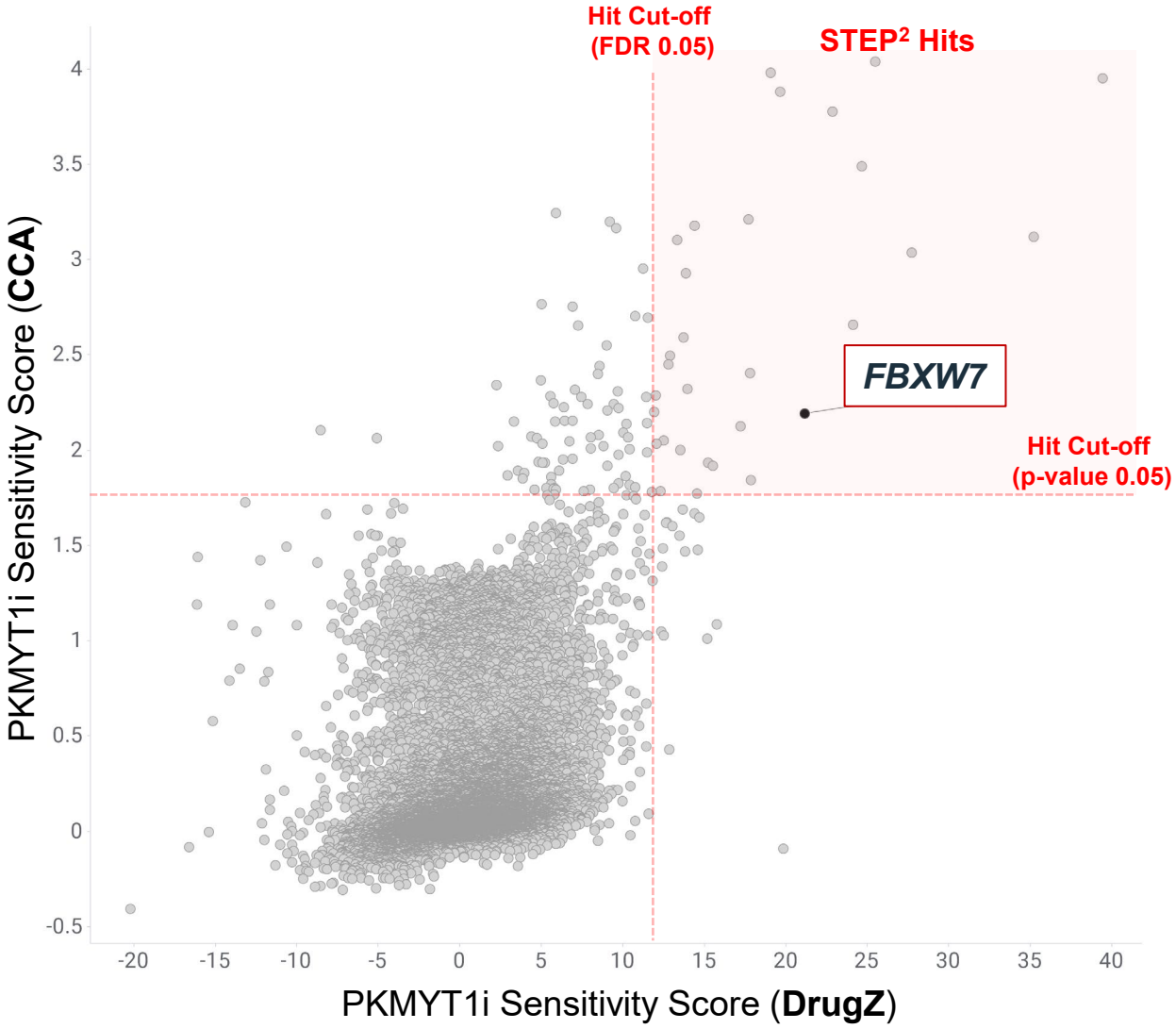
RP-6306 STEP^2 screen identifies FBXW7 tumor population



RP-6306 STEP^2 genome-wide chemical genetic screen identifies novel patient populations, including FBXW7 alterations

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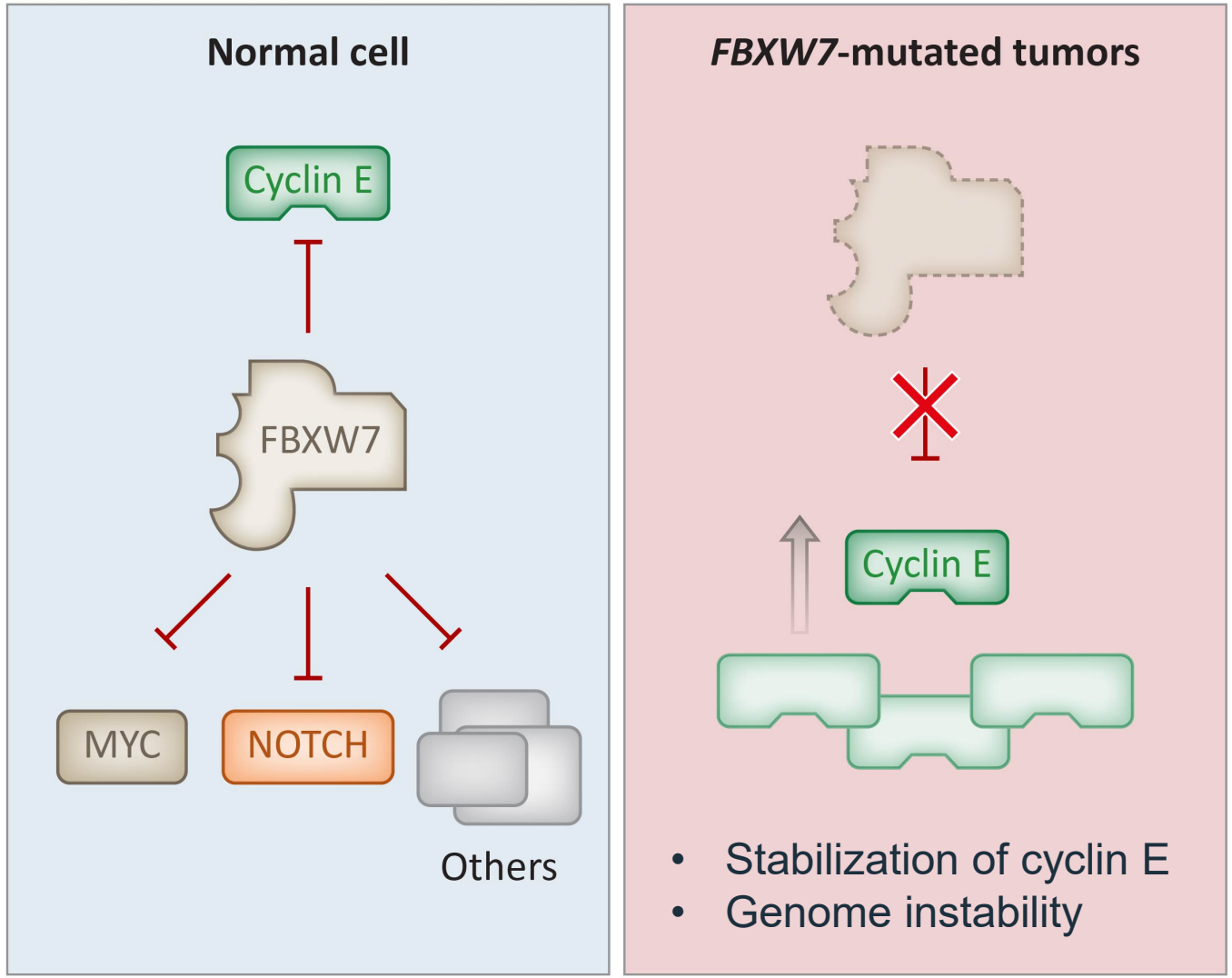
The rationale for targeting FBXW7-mutated tumors with RP-6306



FBXW7:

- **E3 ubiquitin ligase that targets proteins, such as CCNE, for proteasomal degradation**
- **Frequently mutated in tumors**
- **Inactivating mutations can increase CCNE levels**
- **STEP[2] screens show that FBXW7 mutations cause sensitivity to PKMYT1 inhibition**

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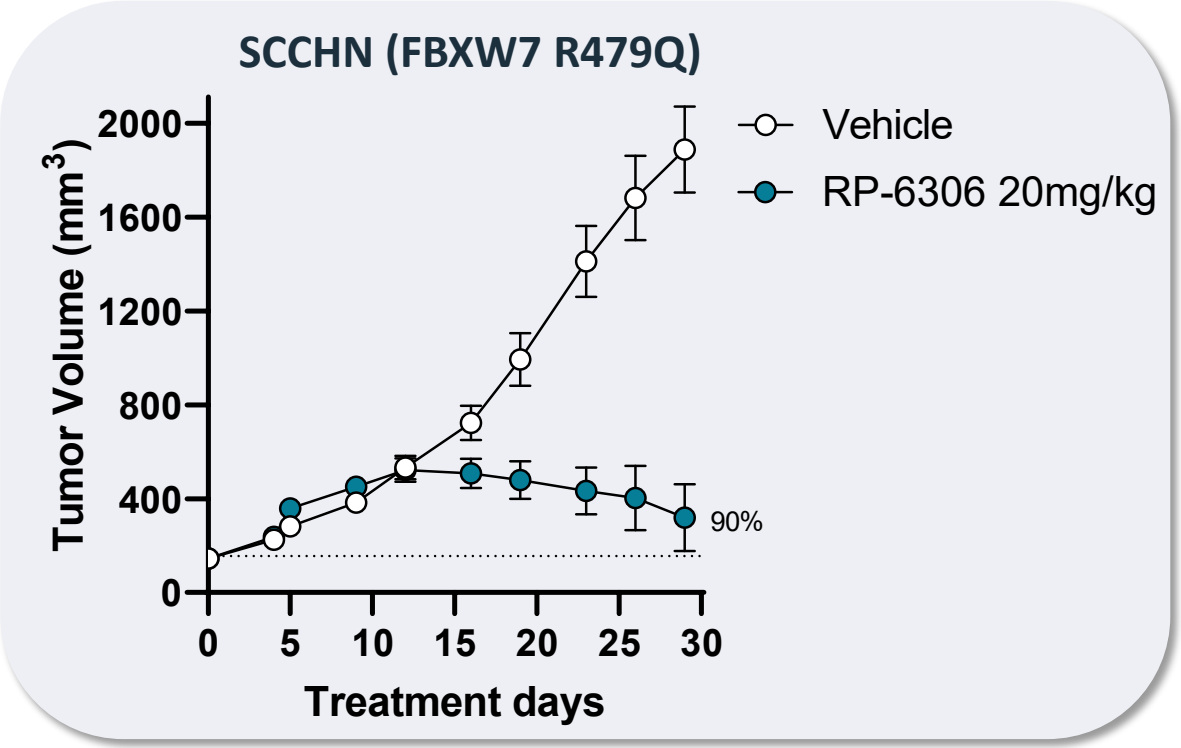
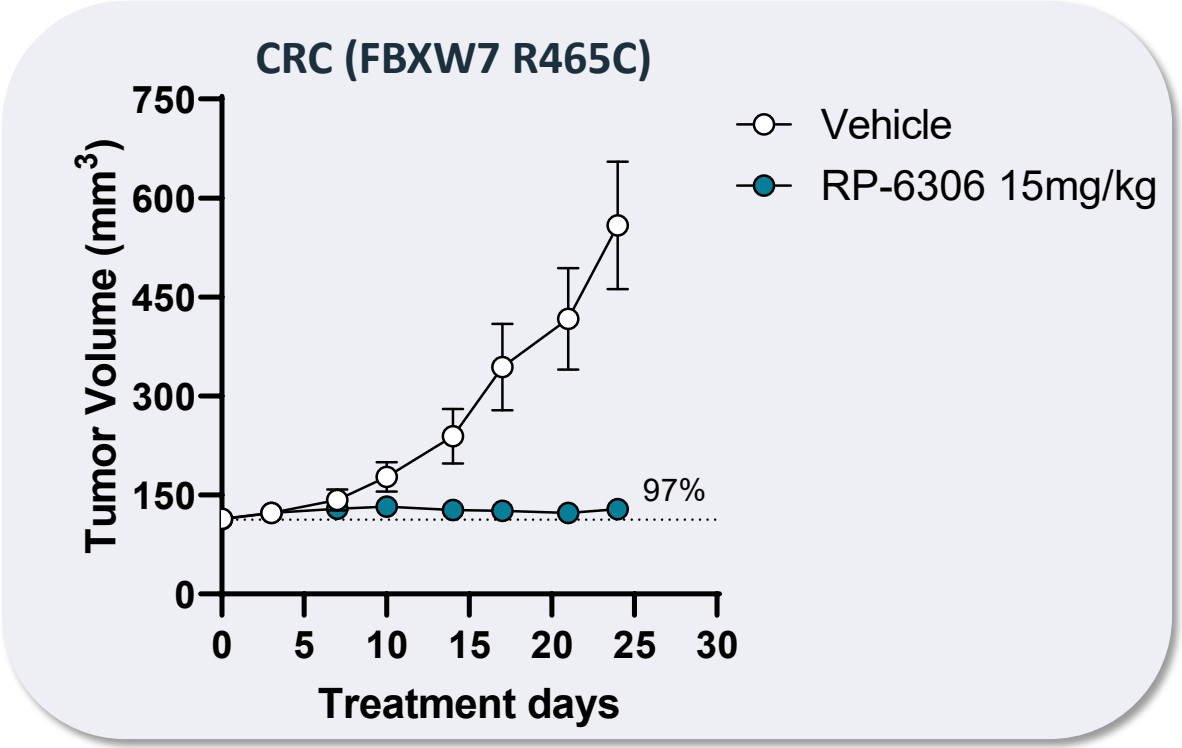
RP-6306 inhibits growth of FBXW7 mutant PDX models





- RP-6306 is active across tumor models with clinically relevant hotspot mutations
- Pre-clinical data supports expanding patient populations for RP-6306

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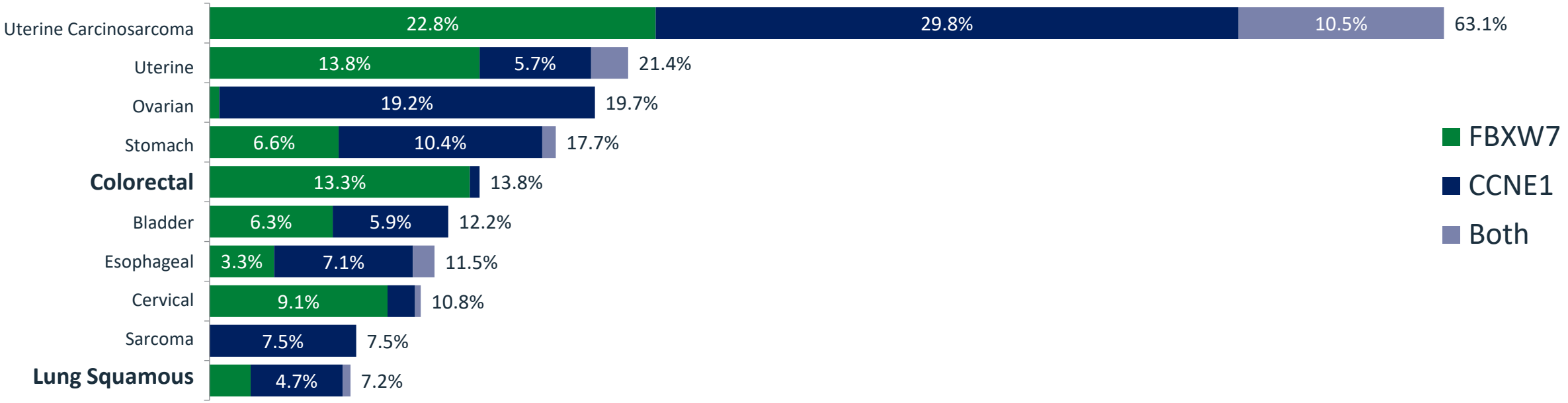
Potential addressable patient populations with RP-6306

Top 10 tumor types with highest prevalence of CCNE1 amplification and FBXW7 mutations deficiency (Source: TCGA)



FBXW7 and CCNE1 Amplification occur in multiple cancers with significant unmet medical need
These lesions are largely mutually exclusive and represent distinct patient populations

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RP-6306 clinical program

Targeting tumors with STEP^2 genomic alterations, including CCNE1 amplification and FBXW7 loss

Trial summary & development objectives:

Eligibility:
Any solid tumors with STEP^2 gene alterations per local NGS or FISH + retrospective central confirmation

Early Program Objectives:
1. Safety, tolerability, dose and schedule Phase 1
2. Efficacy in tumors with STEP^2 gene alterations: several Proof of Concept (POC) studies
3. Multiple RP-6306 based combination POC

Global program: North America and Europe

Designed deliver "go" decisions for broader development

Enrollment start Q2 2021

Preliminary data 2022

RP-6306 profile/plan

- Designed to be an orally available ATP- competitive inhibitor
- Maximized potency and specificity
- Genomically defined, tumor-specific and tumor agnostic indications
- Early combination testing

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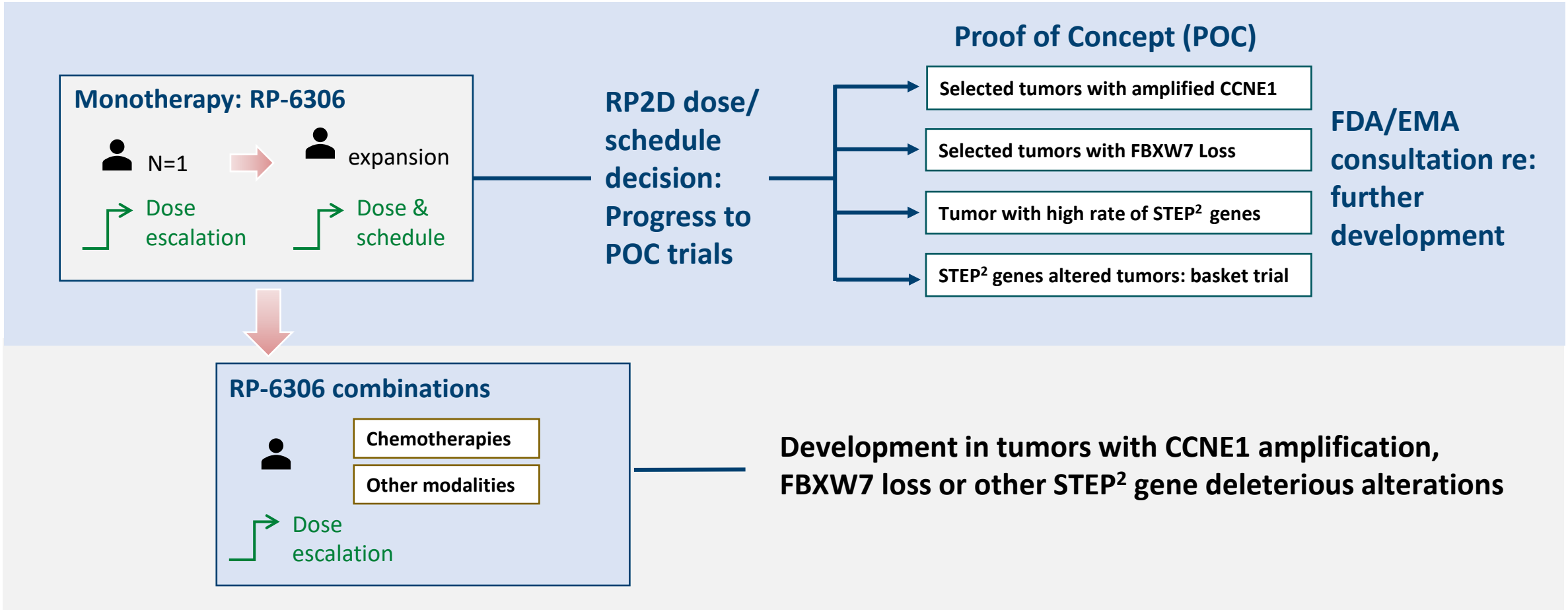
RP-6306 initial global clinical trial program

Key inclusion criteria

- Recurrent solid tumors
- CCNE1 amplification, FBXW7 loss and/or other undisclosed RP-6306 STEP^2 alterations



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Highlights and milestones

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Financial highlights

$333.9M

Cash, restricted cash and marketable securities

Balance sheet 31-Dec-2020

Funded through 2022

Expected runway with cash on hand

36.9M

Basic and fully diluted shares outstanding

Shares outstanding 31-Dec-2020

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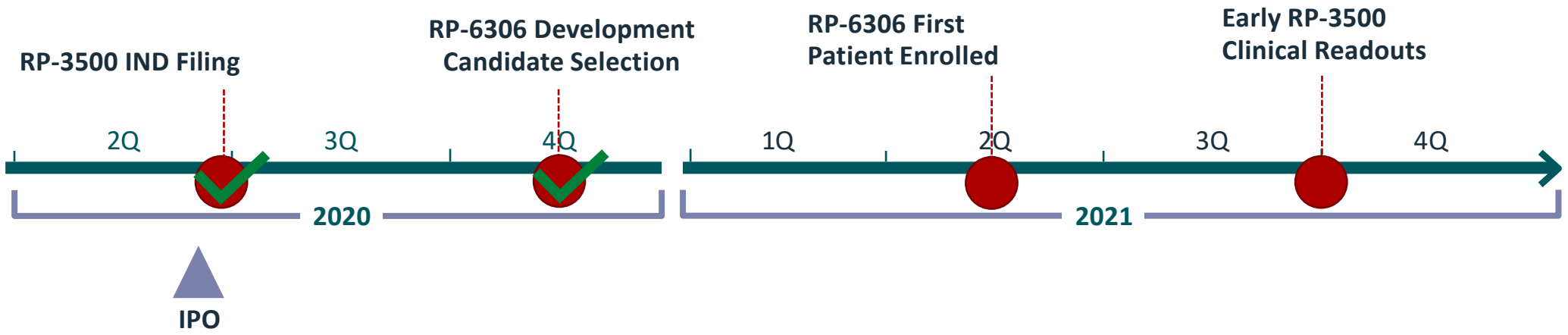
Recent progress and upcoming milestones



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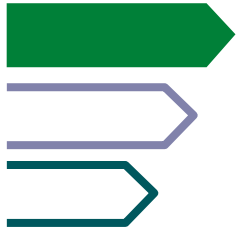
Repare: Summary of key differentiators

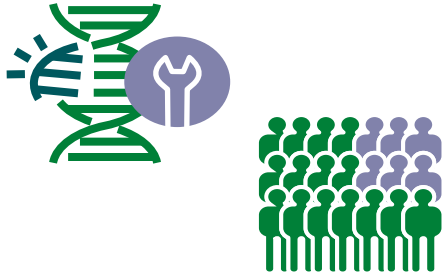
RP-3500 ATR inhibitor

- Enhanced, potential best-in-class compound
- Differentiated, broader STEP^2 patient selection
- Novel PARP combo patient selection



Pipeline

- Portfolio of assets with 2 clinical SL compounds in ’21
- RP-6306, a PKMYT1 inhibitor expected to enter the clinic in Q2 2021



Platform

- SNIPRx platform reveals novel insights
- 16+ tumor lesion campaigns complete
- STEP^2 screens enable expanded patient selection tailored to program

Balance sheet

- Funded for multiple key value-creating milestones

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