Precision oncology

Corporate Presentation
January 2021

REPARE THERAPEUTICS

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These forward-looking statements reflect our current beliefs and expectations. Many factors may cause differences between current expectations and actual results, including unexpected safety or efficacy data observed during preclinical or clinical studies, clinical site activation rates or clinical trial enrollment rates that are lower than expected, changes in expected or existing competition, changes in the regulatory environment, and unexpected litigation or other disputes. These and other risks are described more fully in our filings with the Securities and Exchange Commission (“SEC”), including the “Risk Factors” section of our Quarterly Report on Form 10-Q filed with the SEC on November 12, 2020, and other documents we subsequently filed with or furnished to the SEC. All forward-looking statements contained in this presentation speak only as of the date on which they were made. Except as required by law, we assume no obligation to update any forward-looking statements contained herein to reflect any change in expectations, even as new information becomes available.

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Leading precision oncology company focused on synthetic lethality ("SL")

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

Robust pipeline of SL-based therapeutics; including RP-6306, our CCNE1-SL inhibitor, expected in clinic Q3 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 of $348 million at end of Q3 2020

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Experienced team proven in drug discovery and development

Management team

Lloyd M. Segal
President & CEO

McKinsey & Company · CAPRION · PCP

Steve Forte, CPA
Chief financial officer

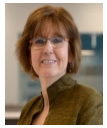
clementia · APTALIS

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

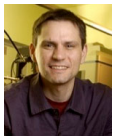
Laurence Akiyoshi, Ed.D.
EVP, Organizational & Leadership Development

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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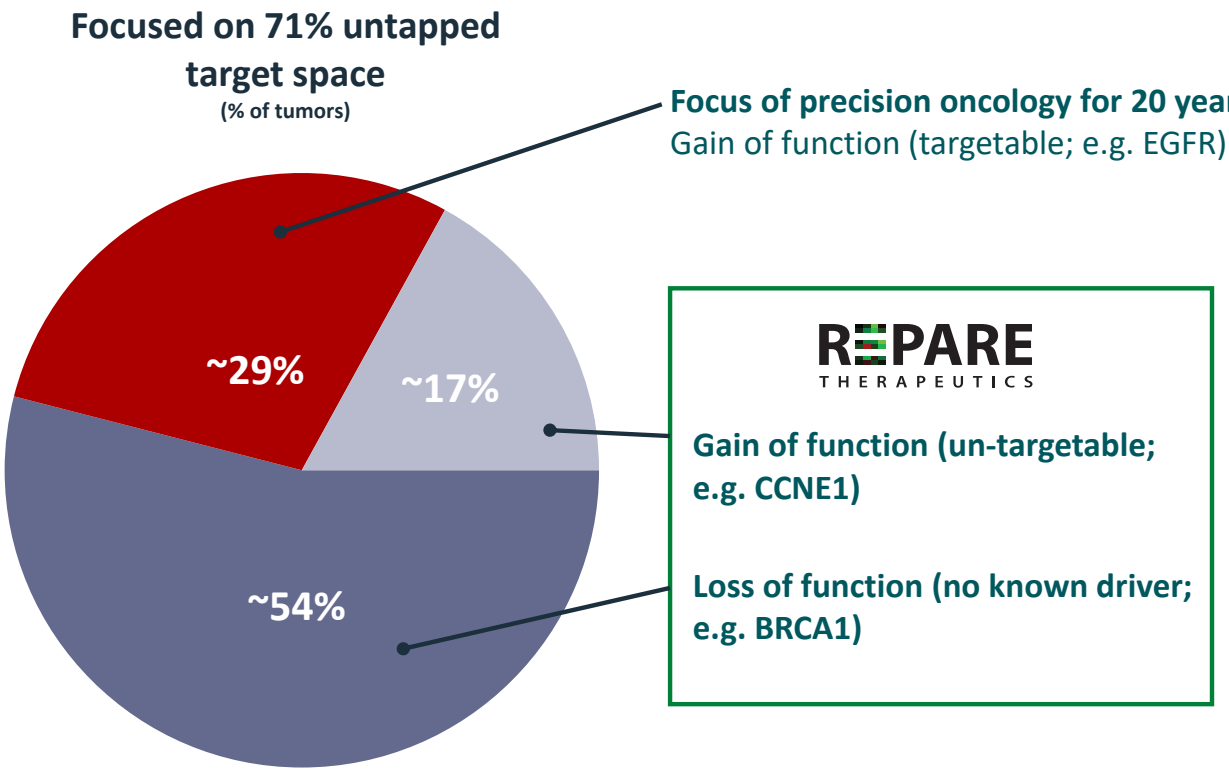
Focused on precision oncology for untapped cancer lesions



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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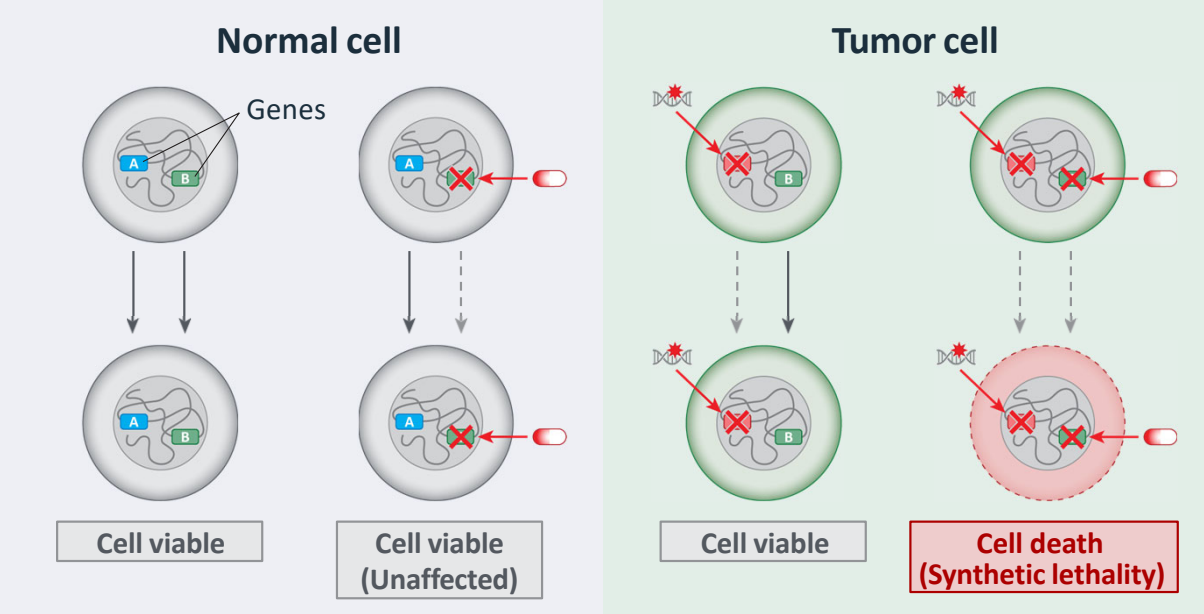
Why we are pursuing synthetic lethality



- The loss of one gene in an SL pair creates a vulnerability in targeting the other:
  - ✓ Intrinsic patient selection in "lost" gene
  - ✓ "Normal" cells without loss are unaffected by drugging the "pair" gene
- Clinical and commercial validation from PARP inhibitors

Our ability to identify new SL pairs allows us to find novel precision therapeutics

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SNIPRx platform

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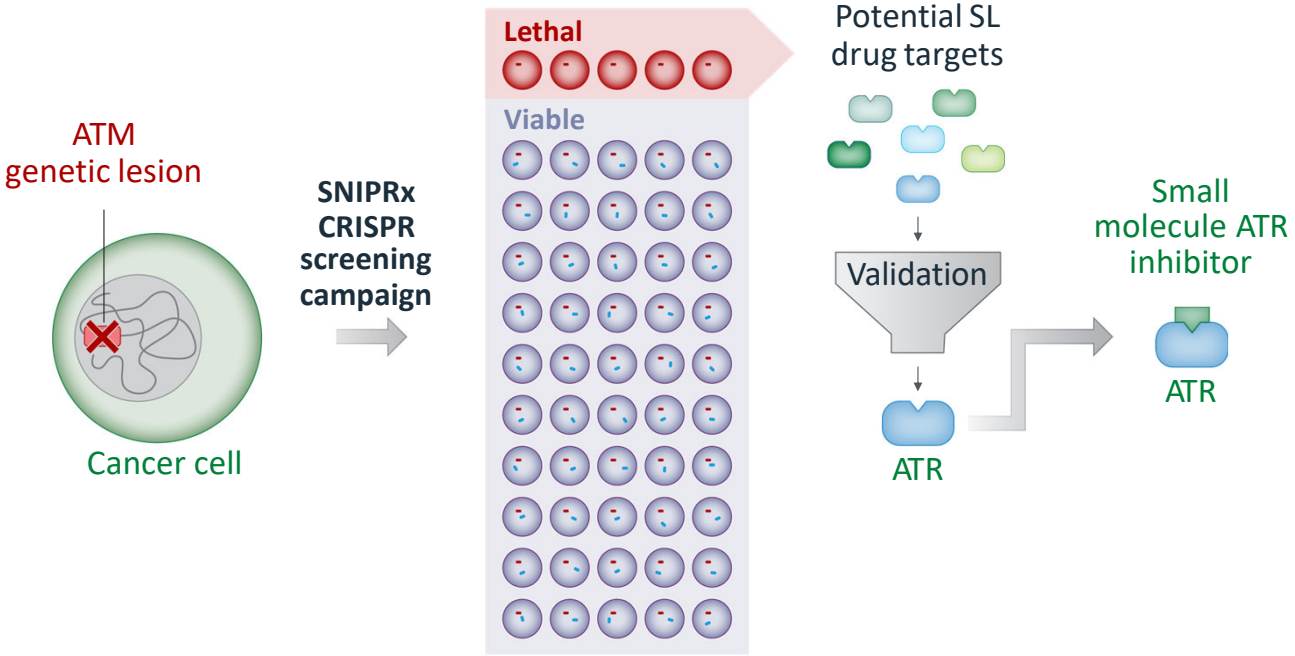
SNIPRx for synthetic lethal drug discovery

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 from every campaign completed to-date**

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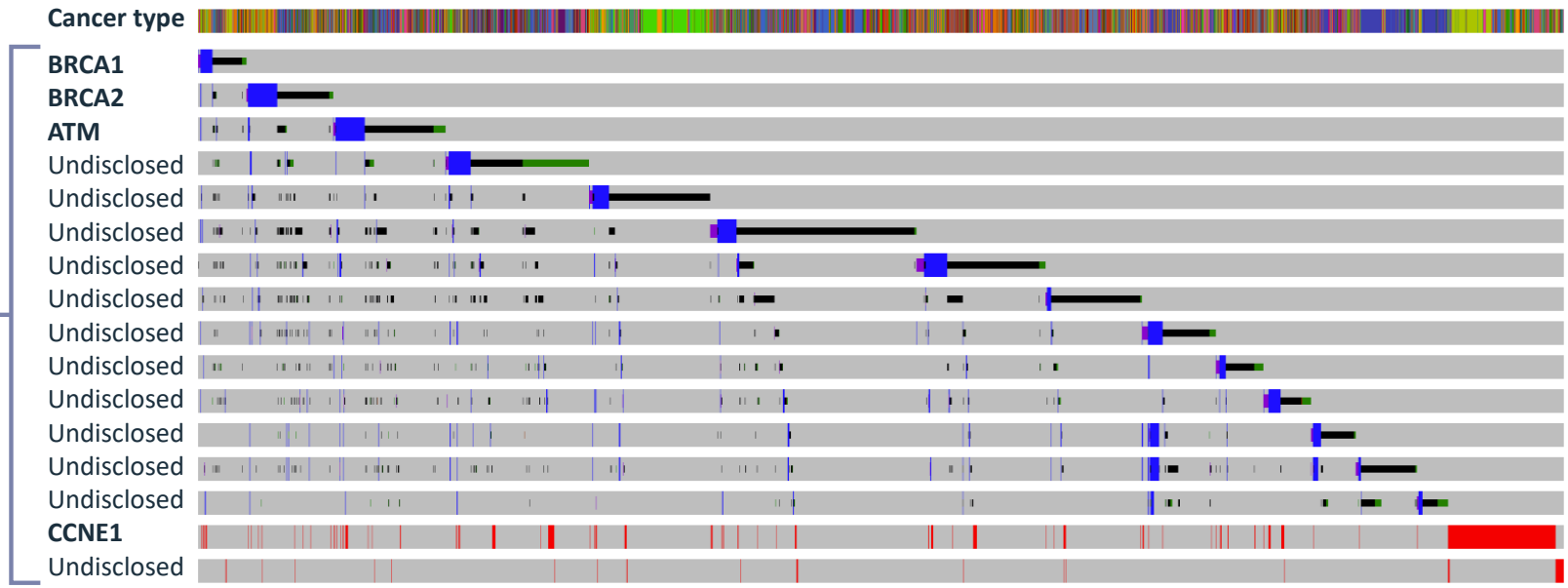
SNIPRx campaigns mine targeted genomic instability lesions

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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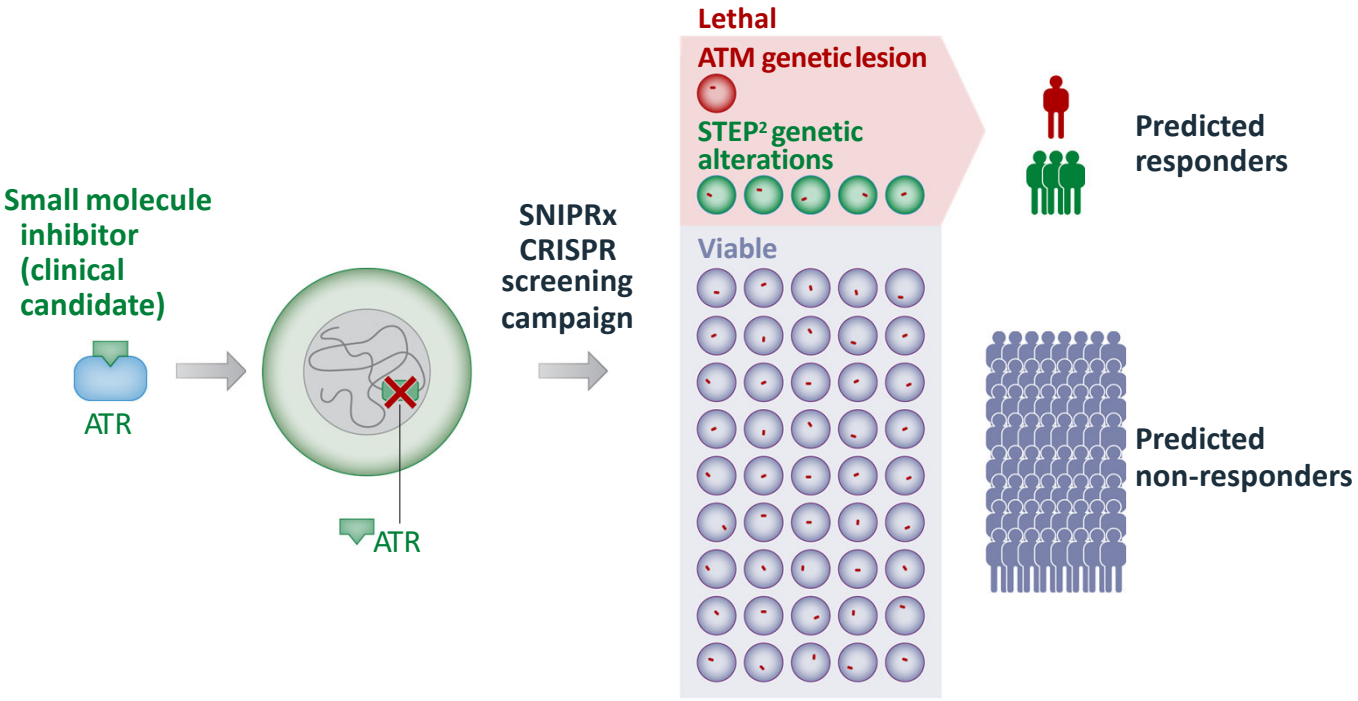
STEP^2: Repare's patient selection advantage enabled by SNIPRx discovery

4 Develop potent and selective inhibitors

5 Perform SNIPRx® Targeted Expansion of Patient Populations (STEP^2) screens

6 Conduct clinical trials in an enriched patient population



STEP^2 screens: SNIPRx Targeted Expansion of Patient Populations

- **Expands patient populations** beyond those identified by original SL pair
- STEP^2 insights **enable precision medicine driven clinical trials**

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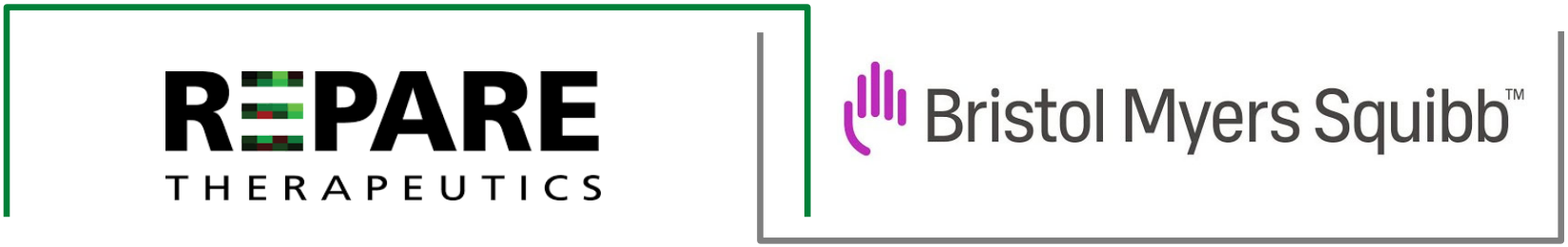
Bristol Myers Squibb – SNIPRx® target discovery collaboration



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 up front

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

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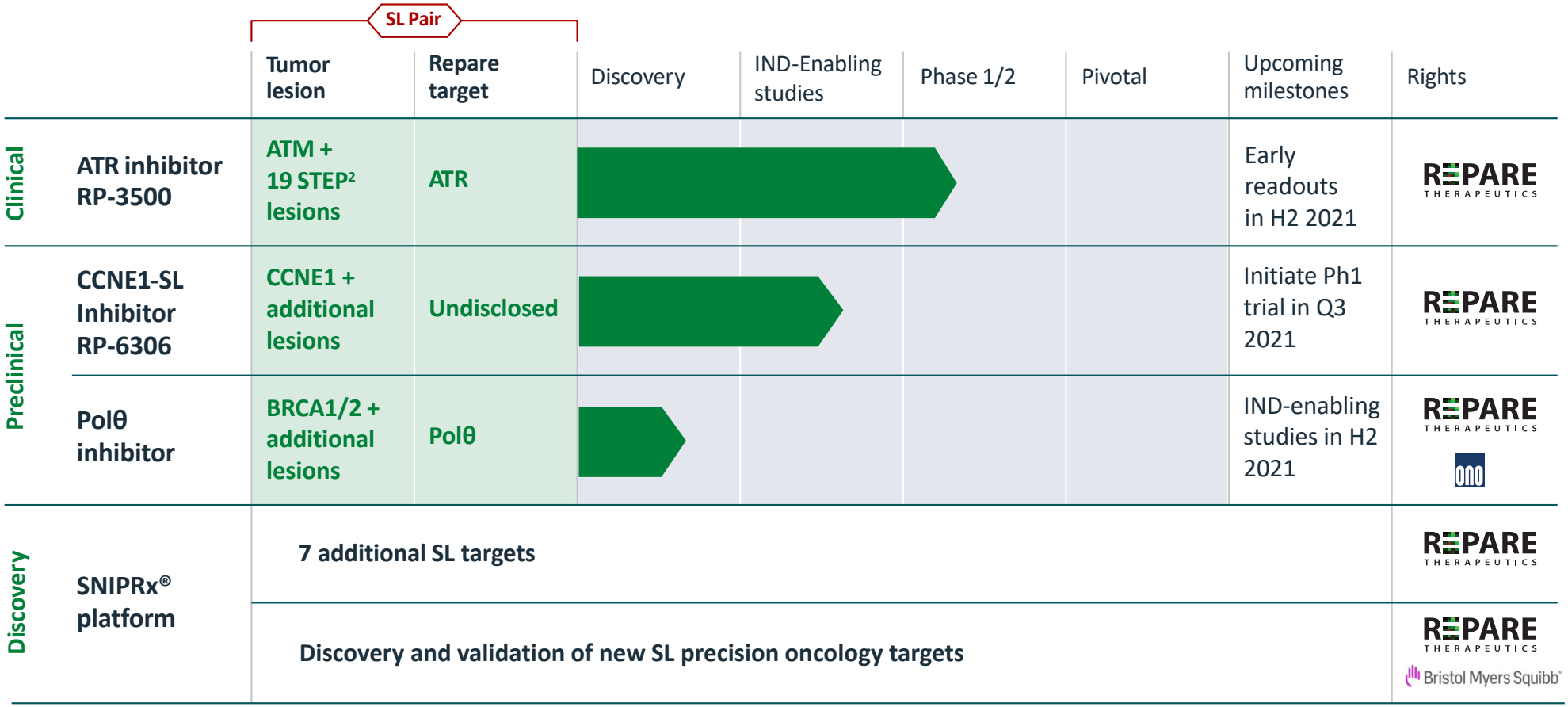
Robust pipeline of SL-based precision oncology therapeutics



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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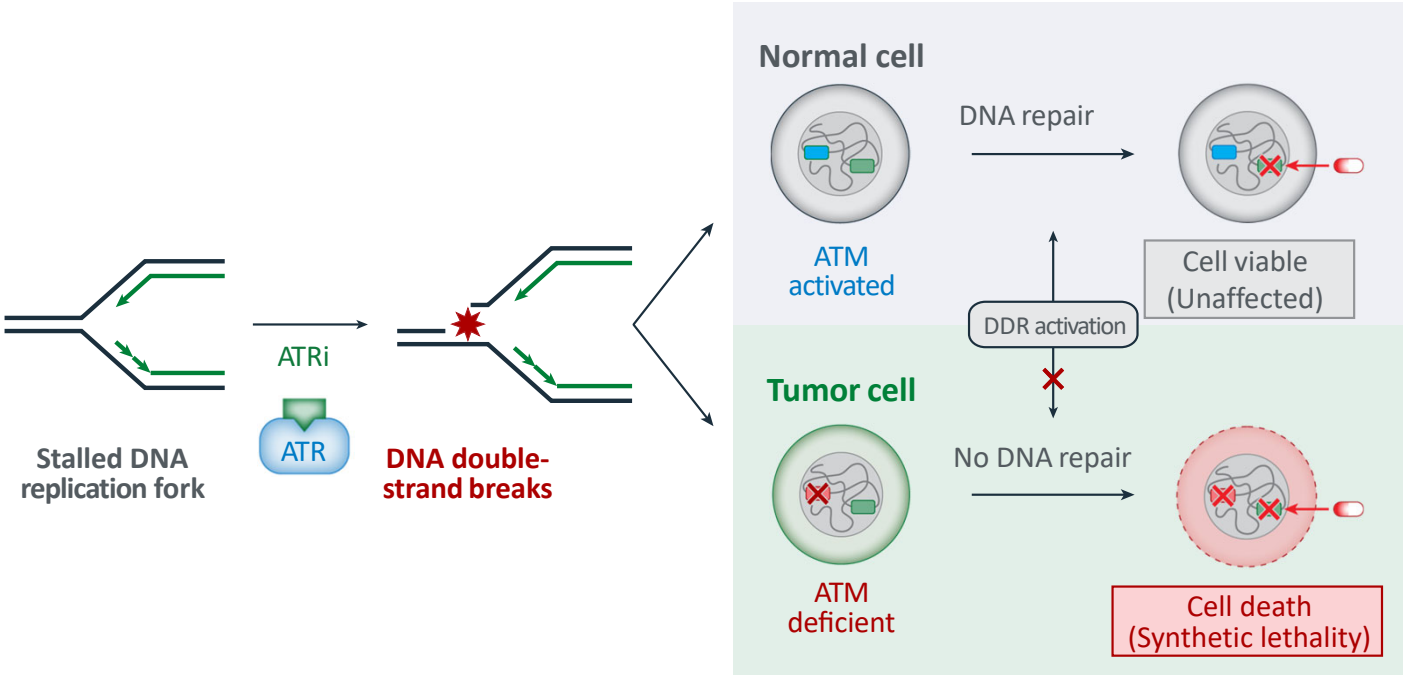
Mechanism of ATM-ATR synthetic lethality



- **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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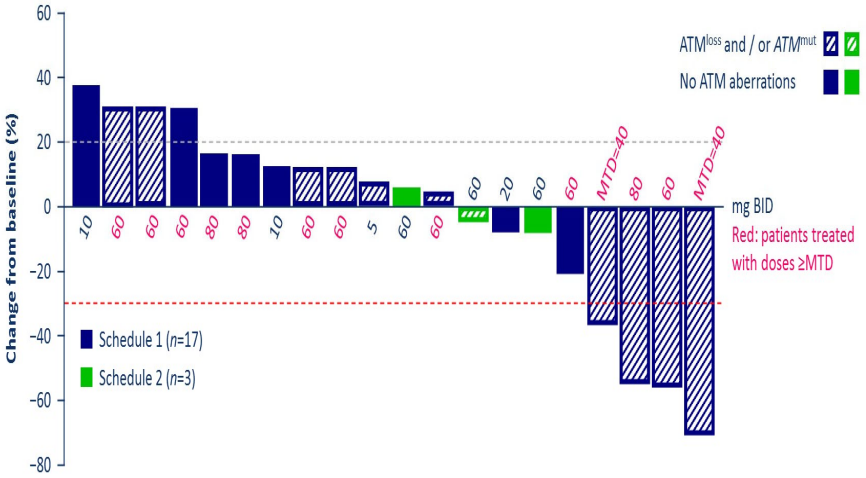
ATRi early human monotherapy POC: ASCO 2019

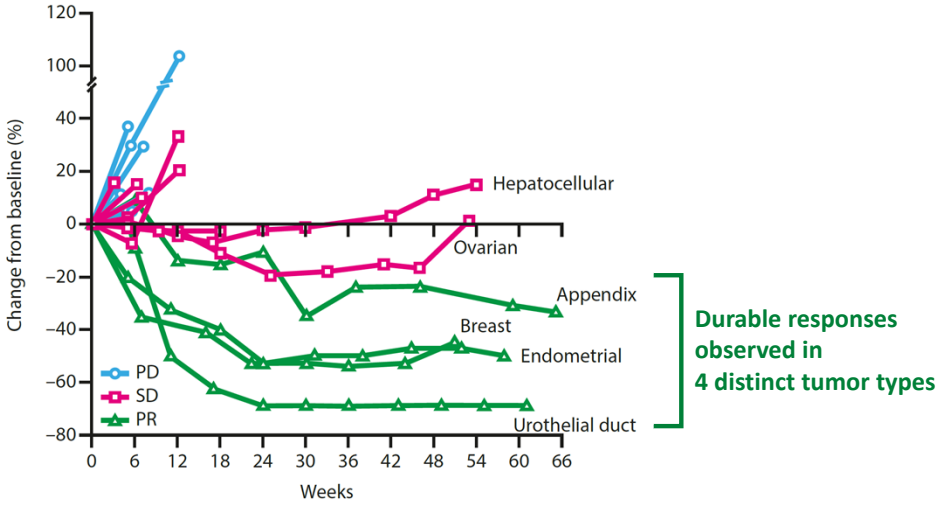
BAY1895344: First in-human dose escalation trial

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; all responding tumors exhibited 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:

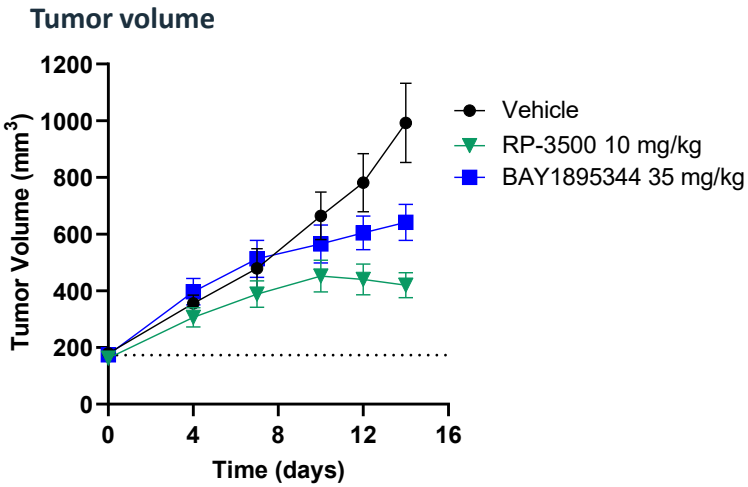
- **Increased potency**
- **Improved/similar selectivity**
- **Favorable pre-clinical PK profile**
- **Low potential for clinical drug-drug interactions**

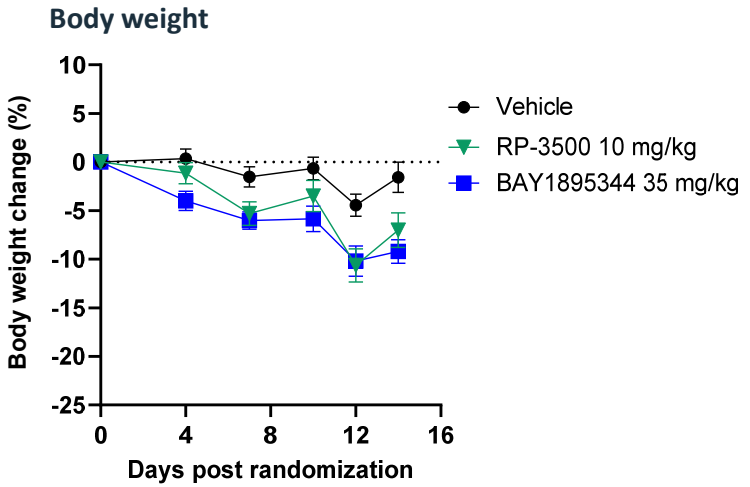
Potential to be best-in-class ATRi*

* 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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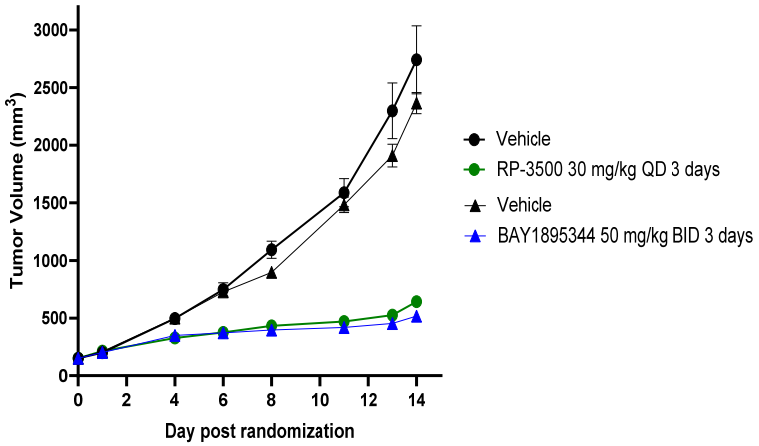
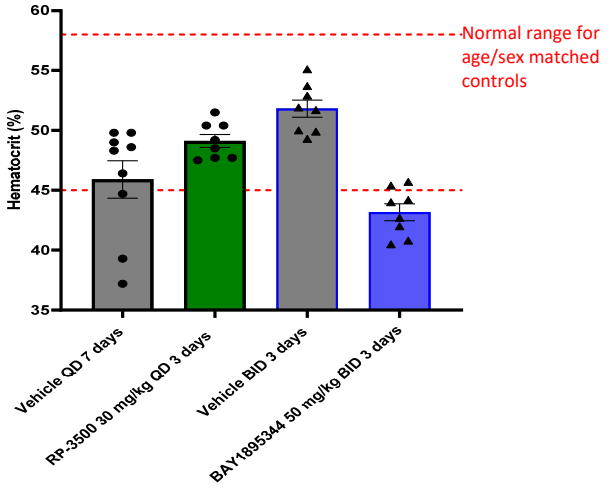
Preclinical data: RP-3500 vs competitor in animal models (cont'd)

RP-3500 exhibits tumor growth suppression without significant anemia measured as hematocrit in mantle cell lymphoma model

Tumor Volume



Hematocrit



Significant anemia (hematocrit reduction) was observed with BAY1985344 but not observed with RP-3500 at MTD

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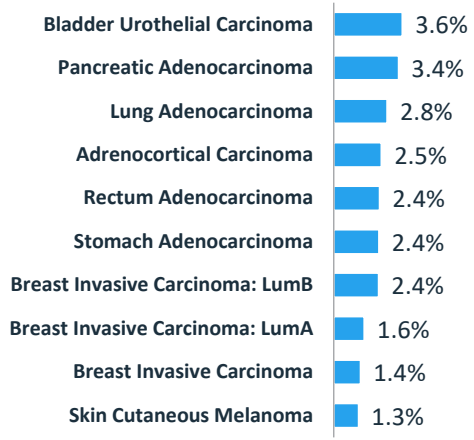
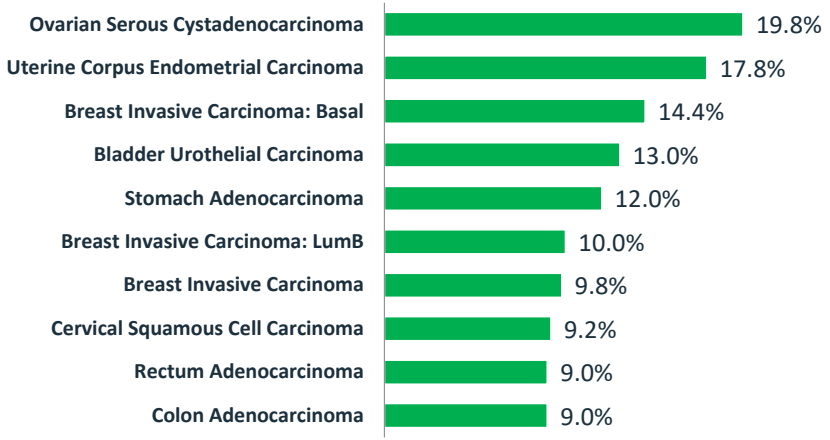
Expanding RP-3500 patient opportunity with STEP2 selection tools*

Top 10 tumor types with highest prevalence of ATM deficiency



Top 10 tumor types with highest prevalence of ATM deficiency or STEP^2 genomic alterations



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

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

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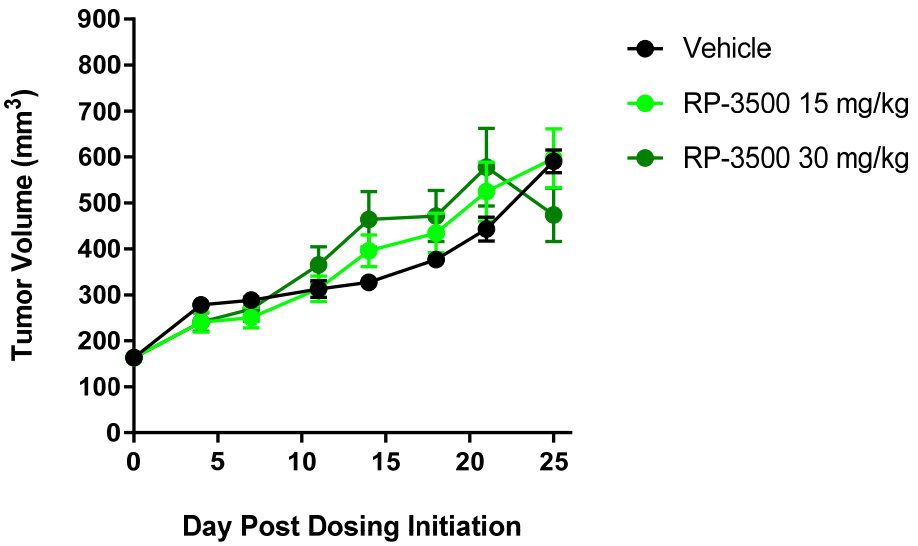
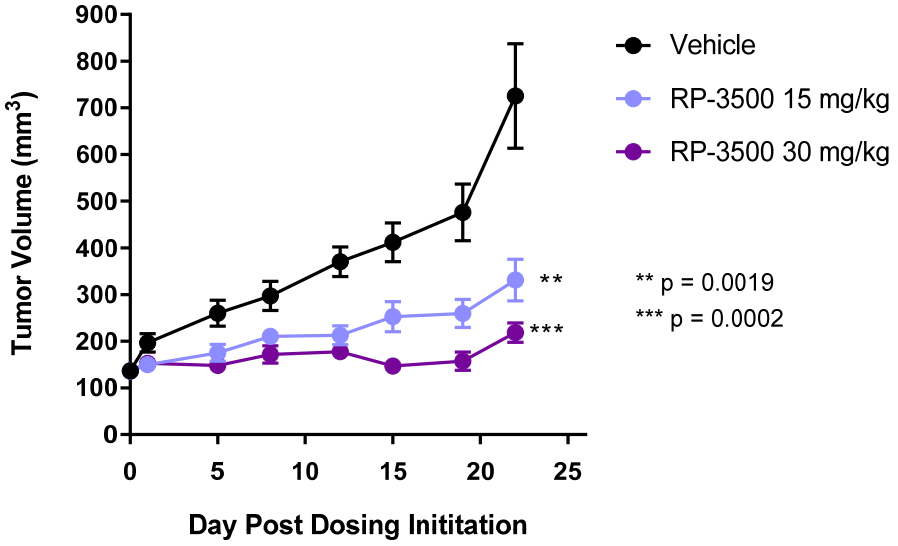
STEP^2 patient selection: in vivo validation of a STEP^2 gene

Tumor growth suppression only in a STEP^2 gene -/- xenograft model

STEP^2 Gene +/+ (Wild Type)



STEP^2 Gene -/- (Gene Deficient)



In vivo efficacy is dependent on loss of novel STEP^2-identified gene

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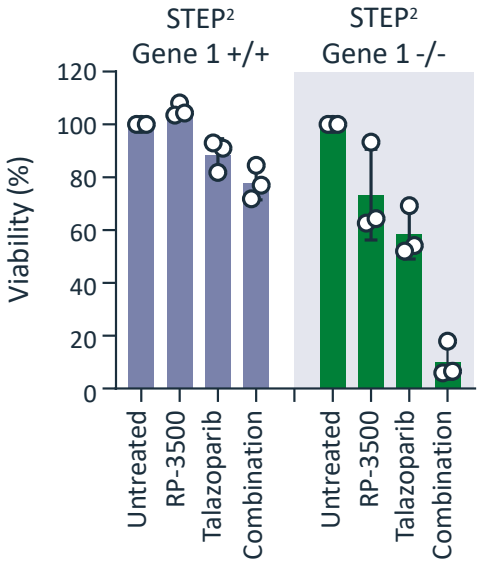
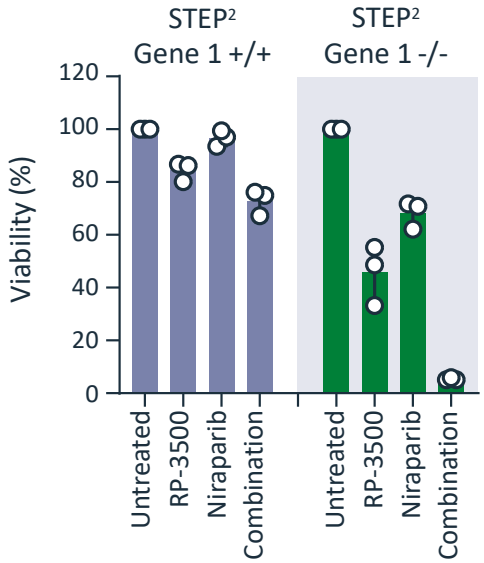
STEP² approach identifies genes to predict combination response

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

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

- **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

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RP-3500 clinical program

Targeting tumors with STEP^2 alterations including ATM -/-

Trial summary & development objectives:

Eligibility:
Any tumor with STEP^2 gene alterations including ATM -/- based on local NGS + central confirmation

Objective:
- Safety, tolerability, dose and schedule
- Determine efficacy in tumors with ATM and other STEP^2 gene alterations (multiple POC)
- PARPi + RP-3500 combination POC

At least 230 patients
Up to 20 sites in North America and the EU

Potential for breakthrough designation and/or "go" decisions for pivotal development

Study enrolling patients

Preliminary data 2H 2021

RP-3500 target product profile

- Designed to be an ATP-site competitive inhibitor with maximized potency and specificity
- Dosing schedule optimized
- Oral, once daily
- Genomically defined, tumor-agnostic indication

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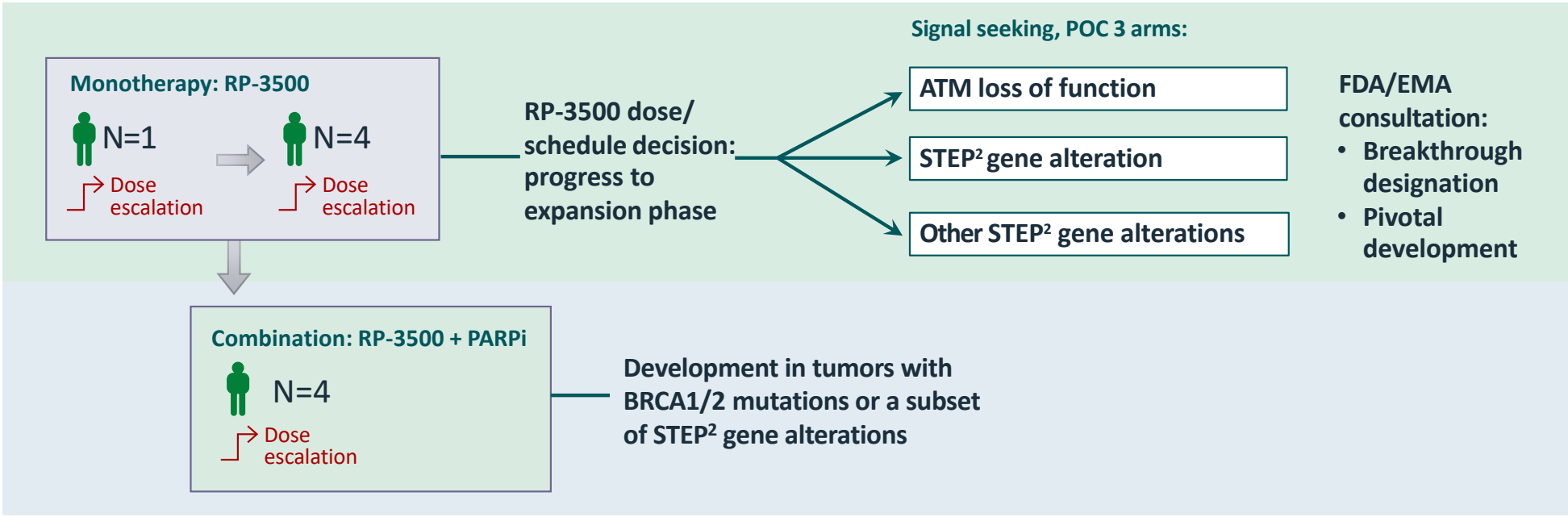
RP-3500 clinical trial design

Key inclusion criteria

- Any recurrent tumor with:
  - ATM loss
  - Loss of any of the additional 19 STEP[2] genes



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Potential patient opportunity for RP-3500 monotherapy

Incidence	Larger	**~2%-10% of all tumors[3]**				Smaller
Mutation	**EGFR[1,2]**	**ATM STEP[2] genes**	**BRACA1/2 HRD genes**	**FGF**	**ALK[1,2]**	**NTRK[1,2]**
Marketed Compounds	TAGRISSO® osimertinib Tarceva® erlotinib	**None**	Lynparza Zejula® niraparib capsules 100 mg TALZENNA® talazoparib 1 mg capsules Rubraca® (rucaparib) tablets	Balversa™ (erdafitinib) 3, 4, 5 mg tablets Pemazyre®	XALKORI® CRIZOTINIB ALECENSA® alectinib 150 mg capsules	ROZLYTREK™ entrectinib 100mg | 200mg capsules VITRAKVI® (larotrectinib) 25 mg/100 mg CAPSULES 25 mg/mL ORAL SOLUTION

1 – No proven combination suitability
2 – Large NSCLC tumor opportunity
3 – Not weighted for prevalence

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CCNE1-SL inhibitor RP-6306

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

Oral inhibitor of CCNE1-SL target to treat tumors with CCNE1 amplification (lesion)

Proprietary drug discovery program for tumors with amplified CCNE1

Amplification of CCNE1 found in many tumor types, including Gyn/GI malignancies

Identification of novel SL gene pair demonstrates the potential of SNIPRx

Novel and selective inhibitors demonstrate compelling preclinical anti-tumor activity

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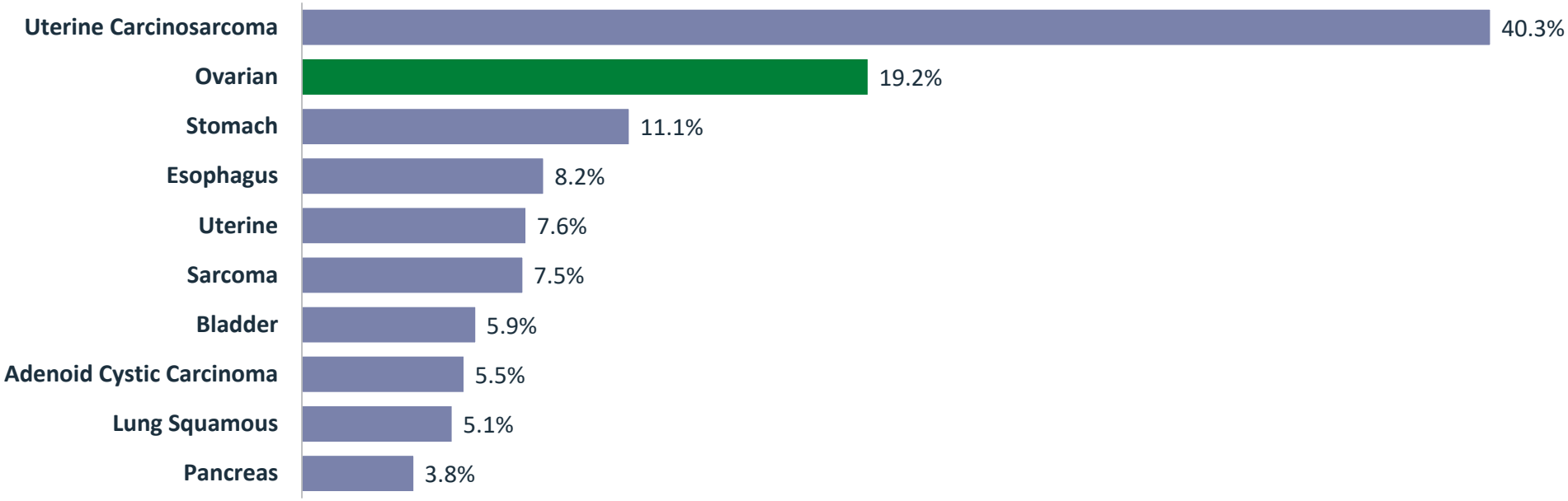
First-in-class oral inhibitor to treat CCNE1 amplified cancers

Top 10 tumor types with highest frequency of CCNE1 amplification

% Frequency of amplification (Source: TCGA)



CCNE1 amplification occurs in multiple cancers with significant unmet medical need

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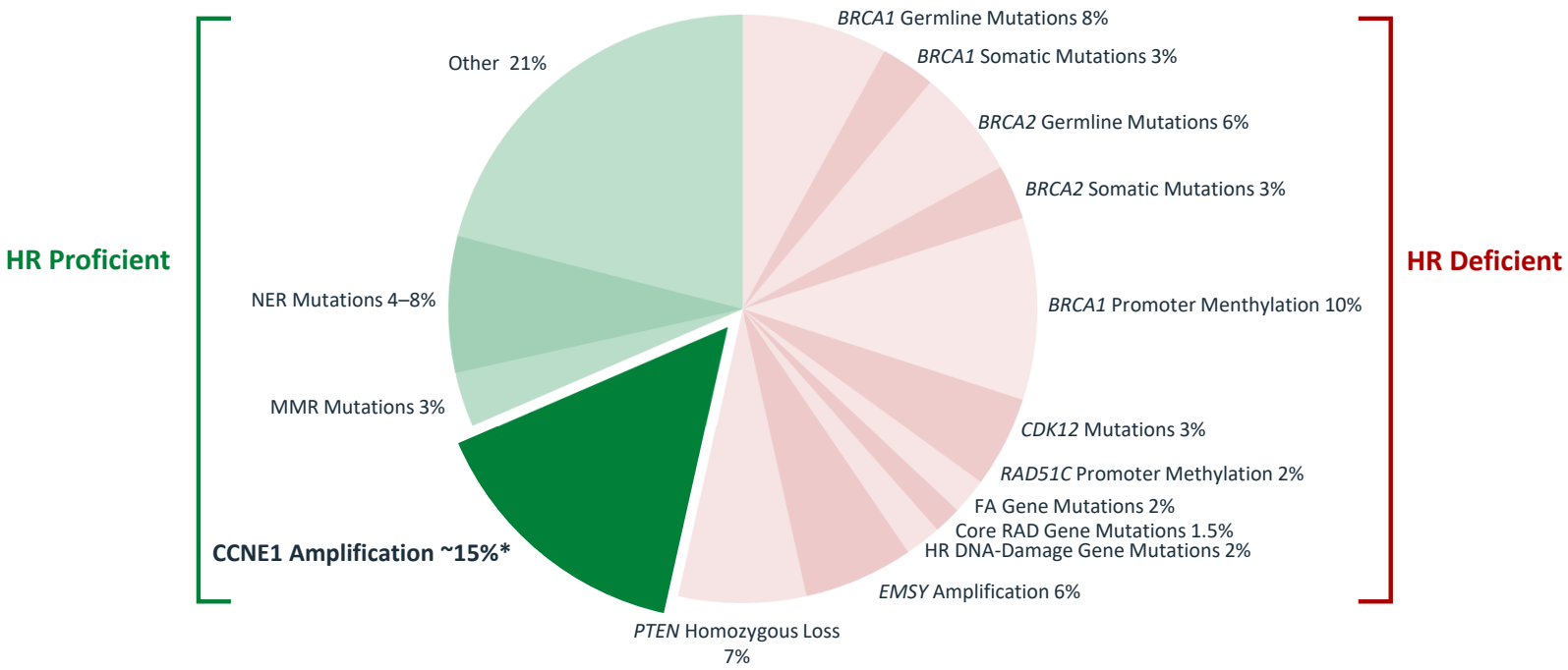
CCNE1 amplification: significant unmet need in ovarian cancer

High-grade Serous Ovarian Carcinoma (HGSOC)



- **CCNE1 amplified in ~15% of HGSOC**
- **These cancers do not respond to platinum or PARPi treatment and represent an area of significant unmet medical need**

* Published ranges of 15% - 19.2%

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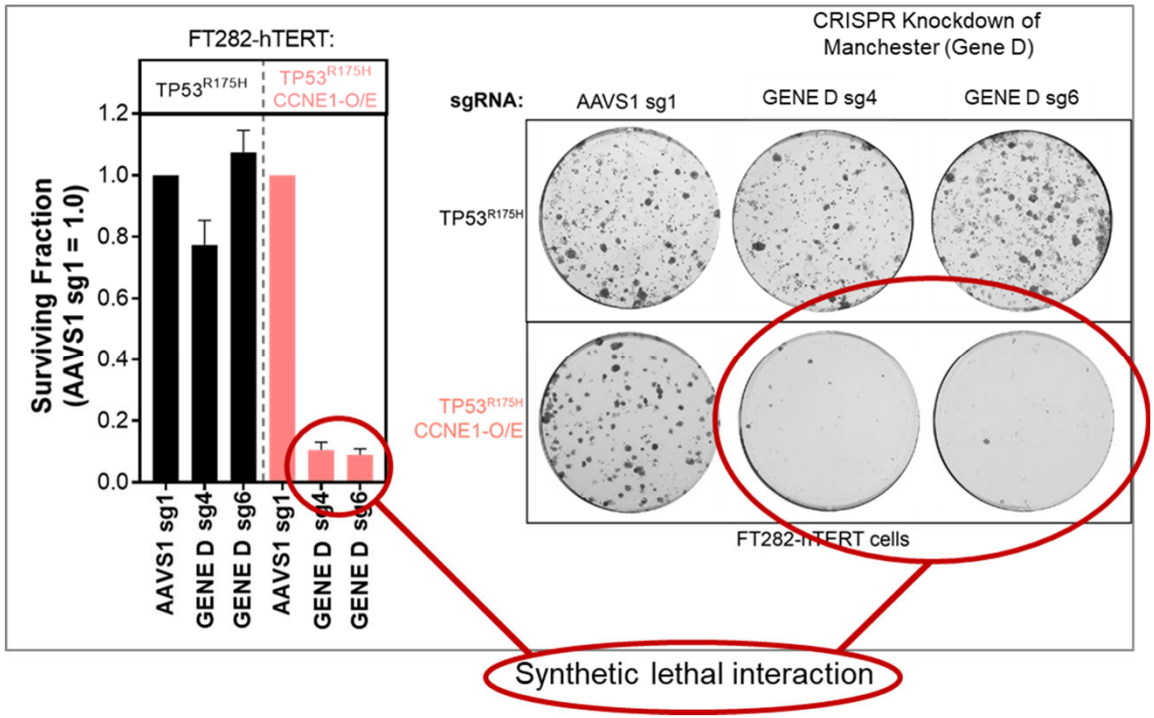
Hit confirmation for SL target of CCNE1 amplification



CCNE1 SL target interaction confirmed in the FT282 fallopian tube cell line

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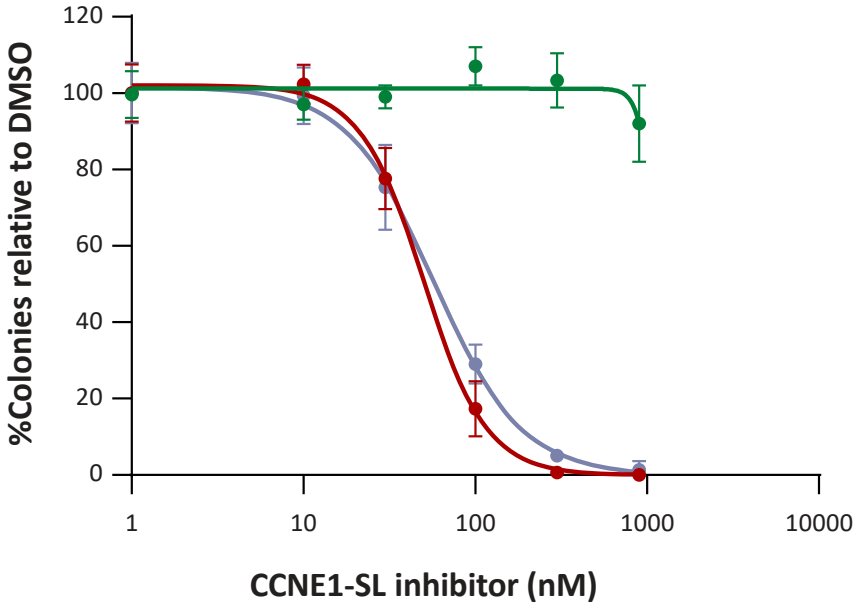
CCNE1-SL target inhibition preferentially kills CCNE1 high cells…



FT282-V1 TP53DN

FT282-C3 (CCNE1 OE) TP53DN

FT282-C3 (CCNE1 OE) TP53DN

IC_{50}: >1 µM

IC_{50}: 0.050 µM

IC_{50}: 0.057 µM

CCNE1-SL inhibition preferentially inhibits the growth of the CCNE1 overexpressing FT282 isogenic cells over WT

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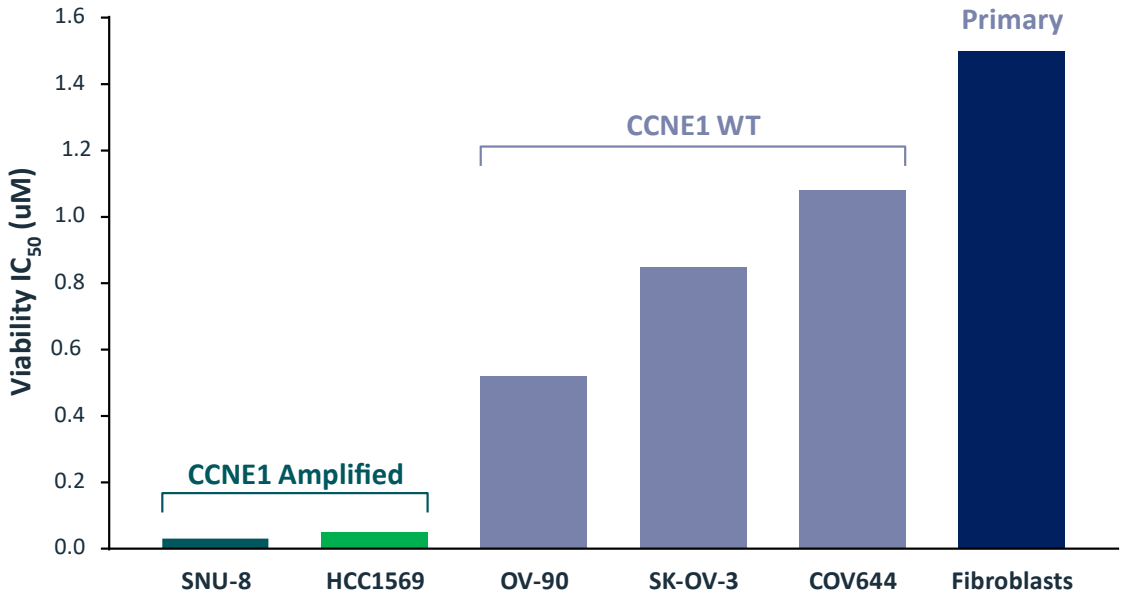
… confirmed in our earliest pharmacology on high expressing CCNE1 cells

CCNE1-SL target inhibition across CCNE1 amplification vs WT cancer lines



CCNE1-amplified cell proliferation potently inhibited by CCNE1-SL target compound

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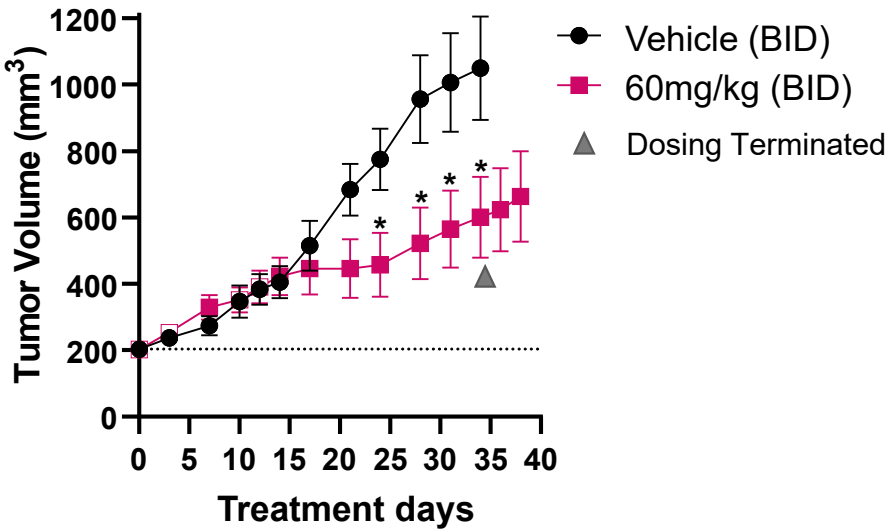
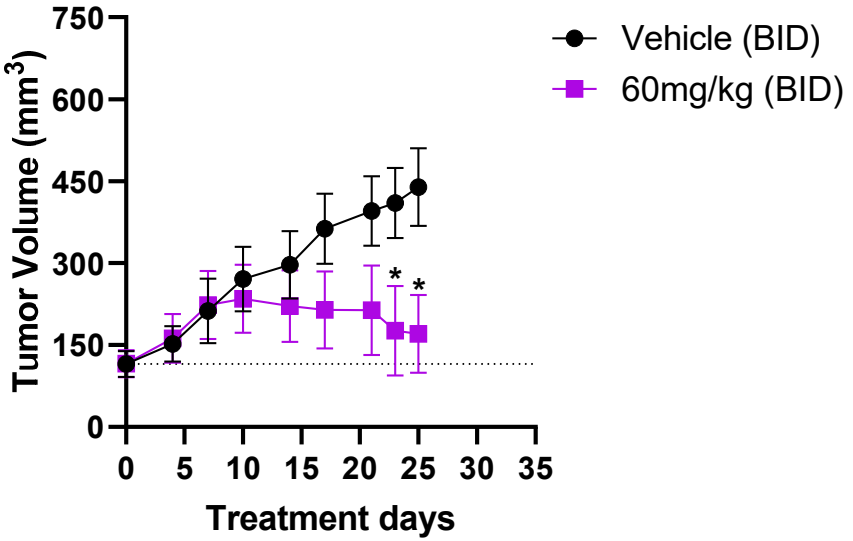
In vivo efficacy demonstrated in CCNE1-amplified PDX models

Colorectal PDX model ~4x amplified



Pancreatic PDX model ~18x amplified



In vivo efficacy observed in both CCNE1-amplified PDX models

REPARE THERAPEUTICS

Polθ inhibitor

REPARE THERAPEUTICS

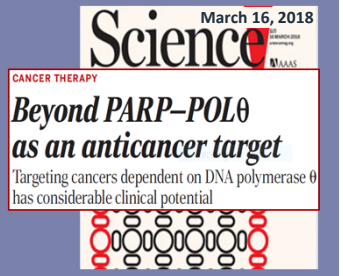
Polθ inhibitor: First-in-class small molecule program

Oral inhibitor of Polθ target to treat cancers in patients with BRCA 1/2 and other lesions

SL relationship between BRCA1/2 and Polθ published in *Nature* in 2016 by Repare co-founder Agnel Sfeir

Proprietary structures enabling chemistry

Preclinical evidence of Polθ inhibition efficacy alone and in combination with PARP inhibitors



Partnered with Ono Pharmaceutical in Asia (ex-China)

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Highlights and milestones

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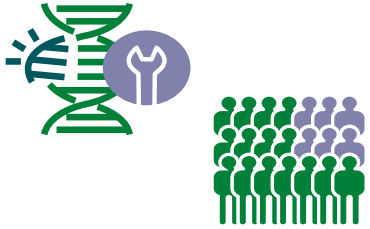
Repare: summary of key differentiators

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 CCNE1-SL inhibitor expected to enter the clinic in Q3 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

REPARE THERAPEUTICS

Financial highlights

$348.1M

Cash and restricted cash

Balance sheet 30-Sep-2020

Funded through 2022

Expected runway with cash on hand

36.8M

Basic and fully diluted shares outstanding

Shares outstanding 30-Sep-2020

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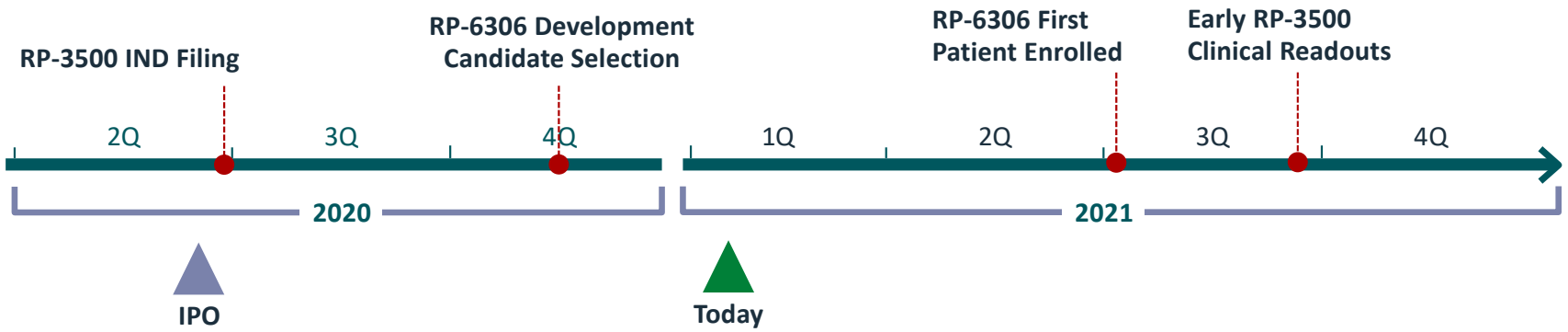
Recent progress and upcoming milestones



Leading precision oncology company focused on synthetic lethality

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

Robust pipeline of SL-based therapeutics; including RP-6306, our CCNE1-SL inhibitor, expected in clinic Q3 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 of $348 million at end of Q3 2020

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