aprea therapeutics
The p53 Reactivation Company

DDR Inhibitors Summit 2023

January 24-26, 2023 | Boston, MA | ddr-inhibitors-summit.com

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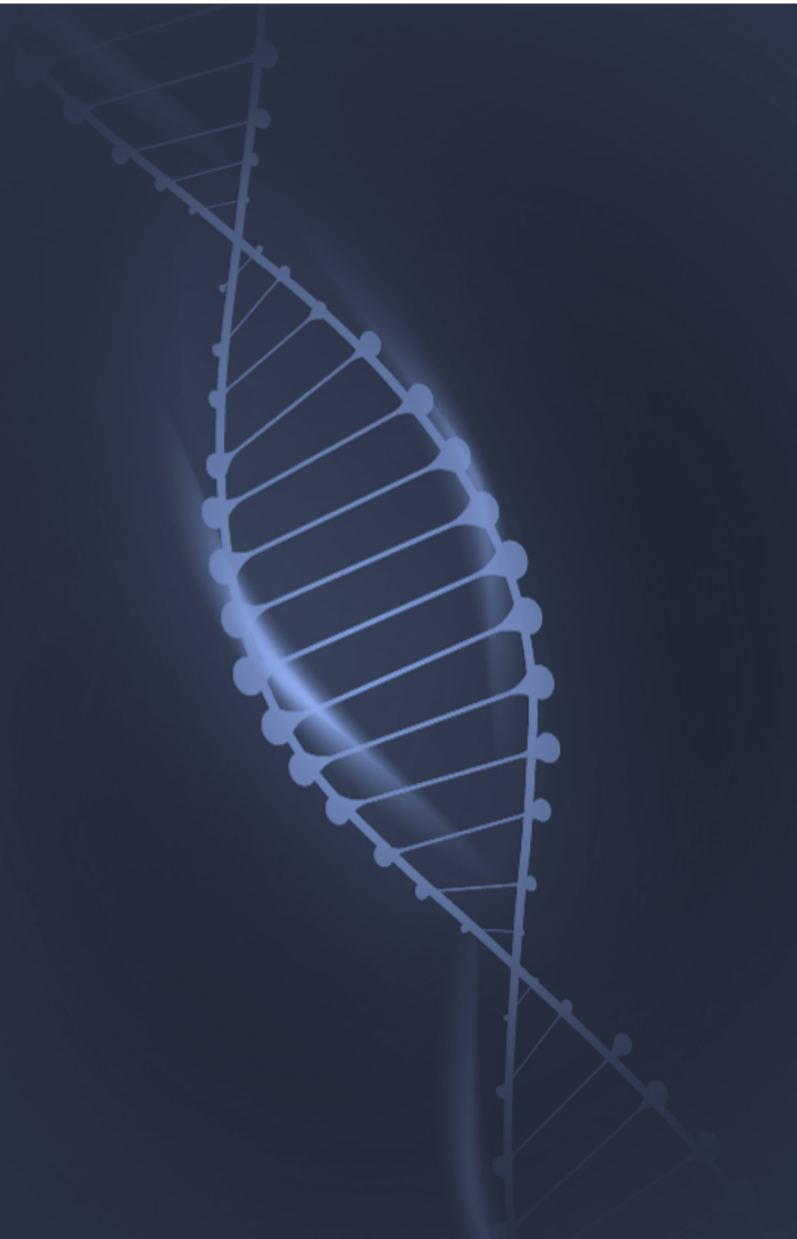
Understanding DDRi's In the Clinic:

Why is Toxicity Such a Big Issue?

January 2023



Forward-Looking Statements

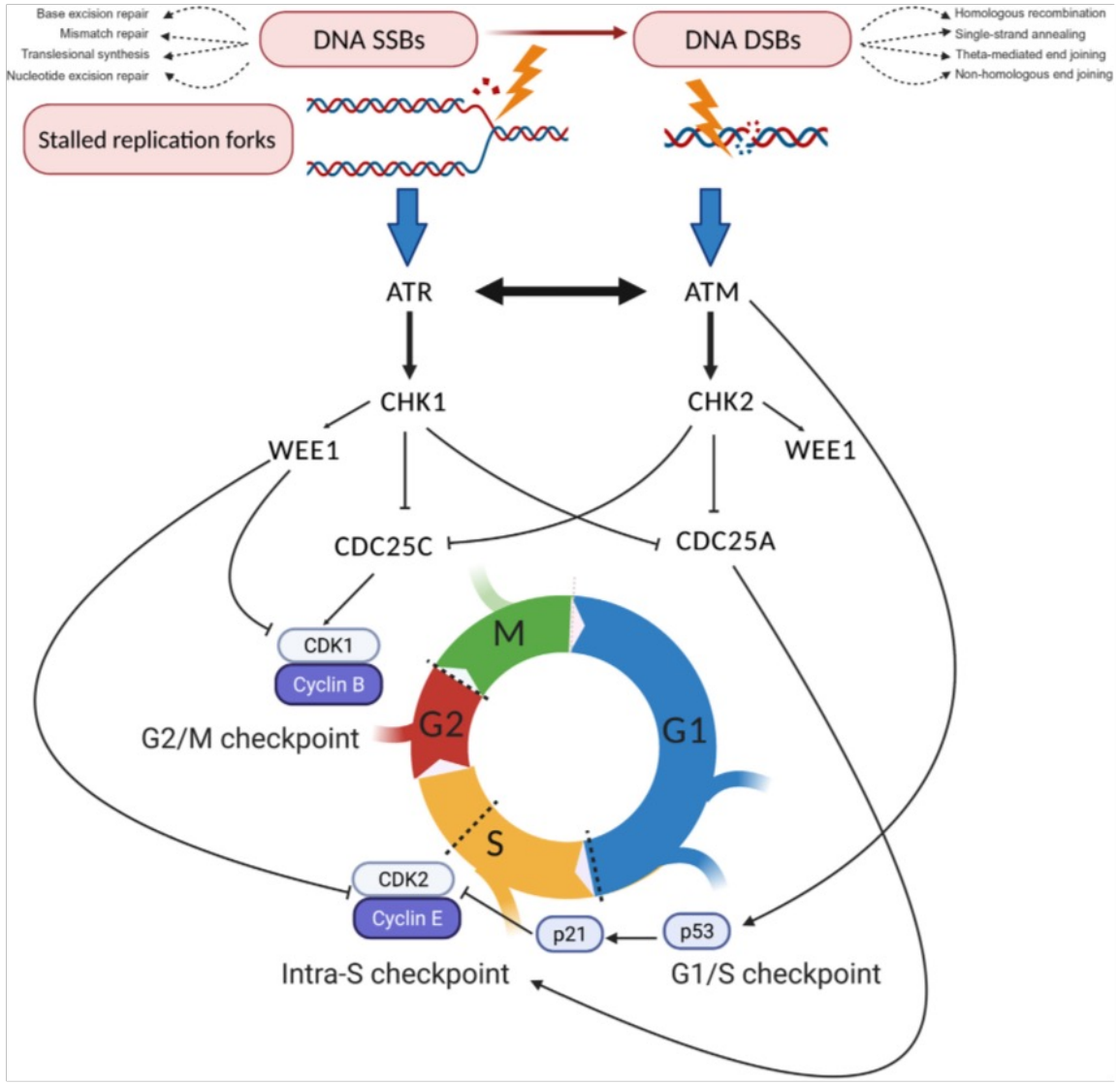
Certain information contained in this presentation includes “forward-looking statements”, within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended, related to our clinical trials, regulatory submissions and strategic plans. We may, in some cases use terms such as “predicts,” “believes,” “potential,” “continue,” “anticipates,” “estimates,” “expects,” “plans,” “intends,” “may,” “could,” “might,” “likely,” “will,” “should” or other words that convey uncertainty of the future events or outcomes to identify these forward-looking statements. The forward-looking statements are based on current beliefs and expectations of our management team that involve risks, potential changes in circumstances, assumptions, and uncertainties. Any or all of the forward-looking statements may turn out to be wrong or be affected by inaccurate assumptions our management team might make or by known or unknown risks and uncertainties. These forward-looking statements are subject to risks and uncertainties including, without limitation, risks related to the success and timing of our clinical trials or other studies and the other risks set forth in our filings with the U.S. Securities and Exchange Commission, including our Annual Reports on Form 10-K and Quarterly Reports on Form 10-Q. Forward-looking statements regarding our product candidates are also subject to additional risks and uncertainties, including without limitation, with respect to: our dependence on additional financing to fund our operations and complete the development and commercialization of our product candidates, and the risks that raising such additional capital may restrict our operations or require us to relinquish rights to our technologies or product candidates; our limited history and preclinical status of the assets we acquired from Atrin Pharmaceuticals Inc.; our business plan or the likelihood of the successful implementation of such business plan; the timing of initiation of planned clinical trials for our product candidates; the future success of such trials; the successful implementation of our research and development programs and collaborations and the interpretation of the results and findings of such programs and collaborations and whether such results are sufficient to support the future success of our product candidates; the success, timing and cost of our anticipated clinical trials for our current product candidates; the timing of initiation, futility analyses, data presentation, reporting and publication and receipt of interim results (including, without limitation, any preclinical results or data); any statements about our understanding of product candidates mechanisms of action and interpretation of preclinical and early clinical results from its clinical development programs and any collaboration studies; and other factors, including legislative, regulatory, political and economic developments not within our control. For all these reasons, actual results and developments could be materially different from those expressed in or implied by our forward-looking statements. You are cautioned not to place undue reliance on these forward-looking statements, which are made only as of the date of this presentation. We undertake no obligation to update such forward-looking statements to reflect subsequent events or circumstances, except to the extent required by law or regulation.

How much inhibition is needed?

On Target Vs Off Target Toxicological Effects:

- Lesson learned from ATR inhibitors

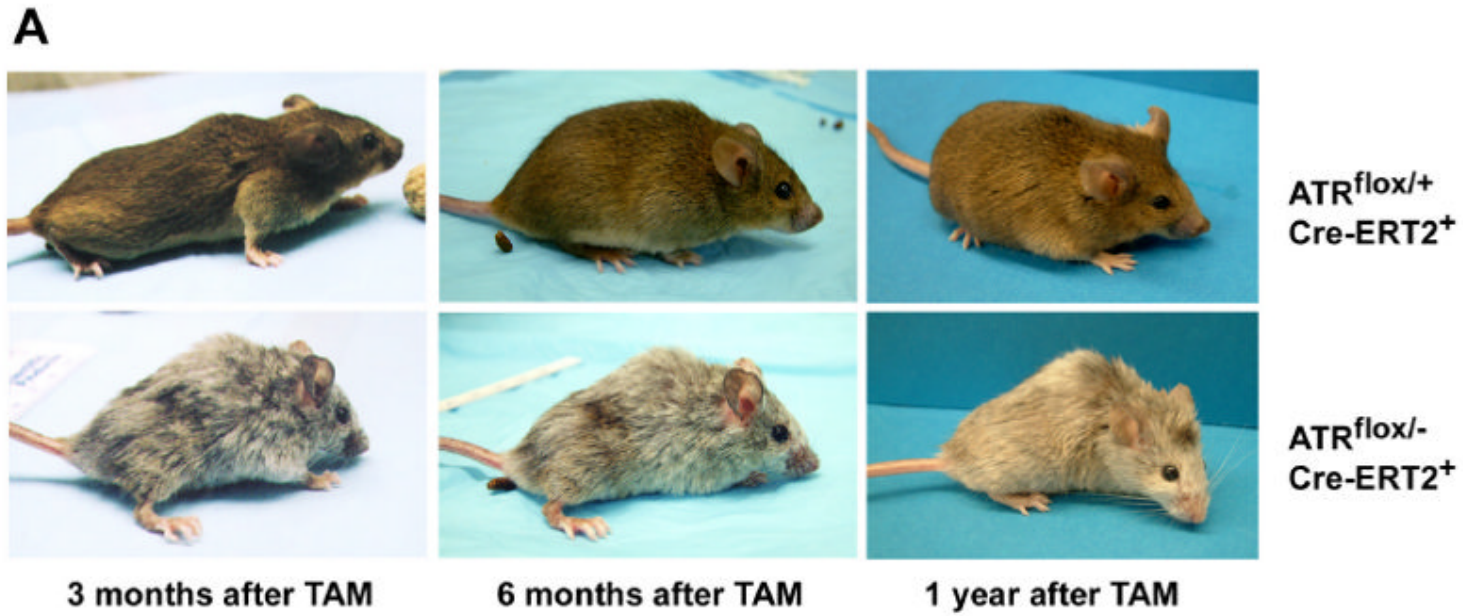
Target Coverage



Ngoi et al., Trends in Cancer, 2021

ATR - On Target Toxicological Effects

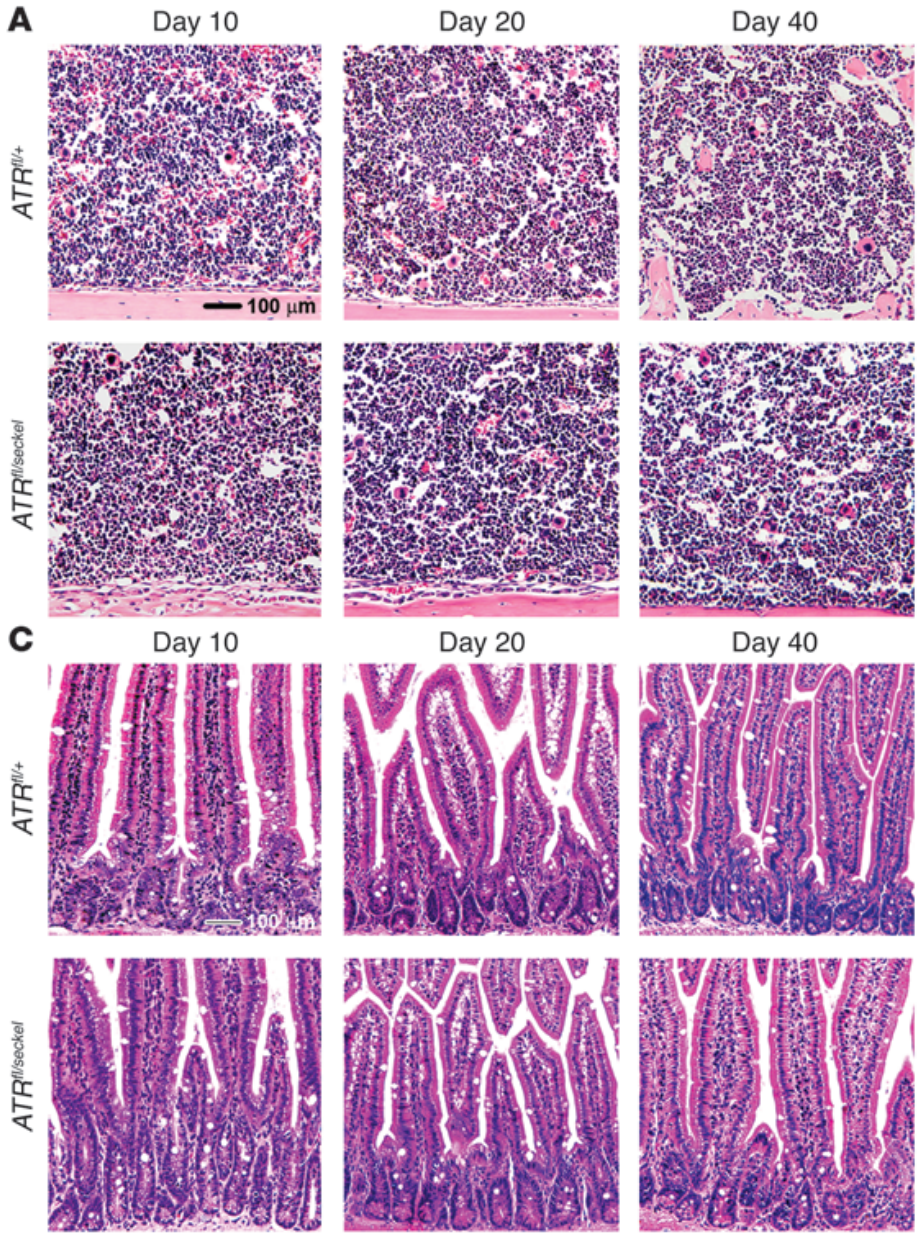
Eliminating ATR in adult mice leads to defects in tissue homeostasis and the rapid appearance of age-related phenotypes, such as hair graying, alopecia, kyphosis, osteoporosis, thymic involution, fibrosis, and other abnormalities.



Ruzankina et al. *Cell Stem Cell*. 2007

ATR - On Target Toxicological Effects

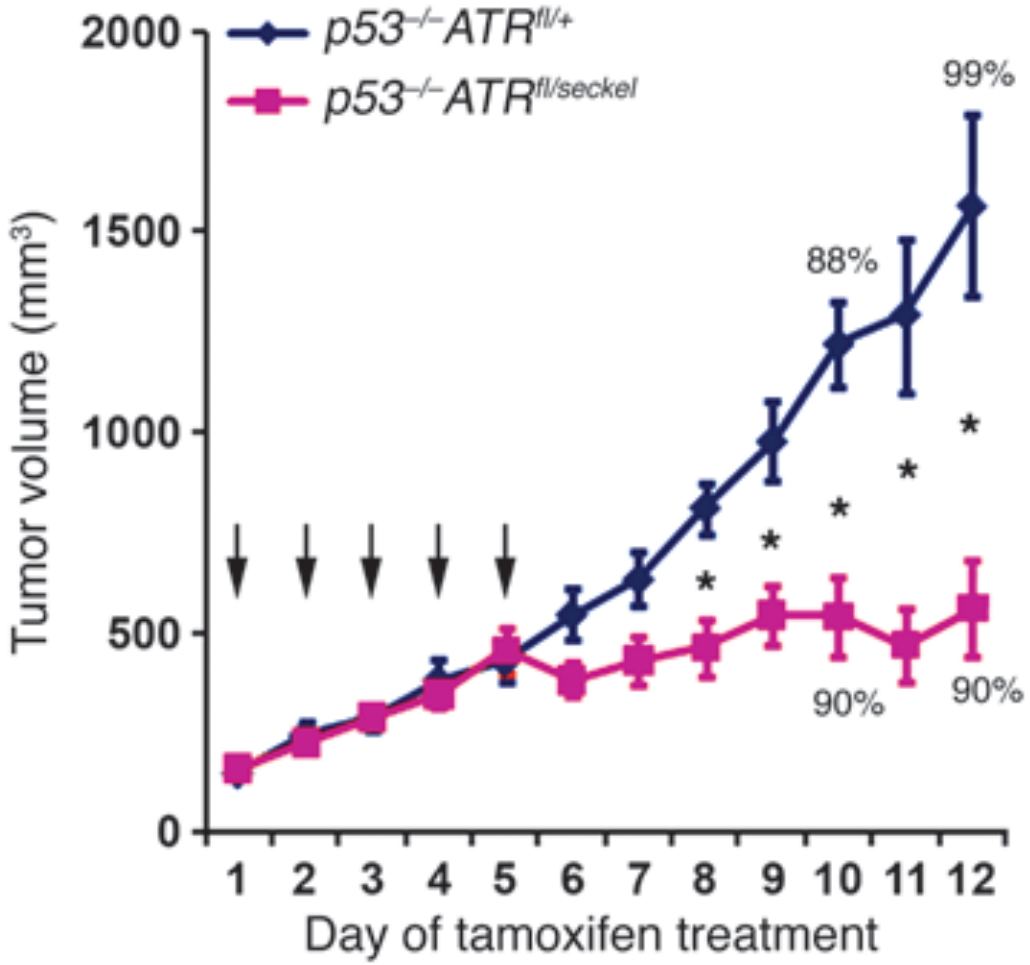
ATR hypomorphic suppression has a minimal impact on normal tissue homeostasis.



Schoppy et al. *J Clin Invest 2012*

ATR - On Target Toxicological Effects

ATR hypomorphic suppression affects tumor growth

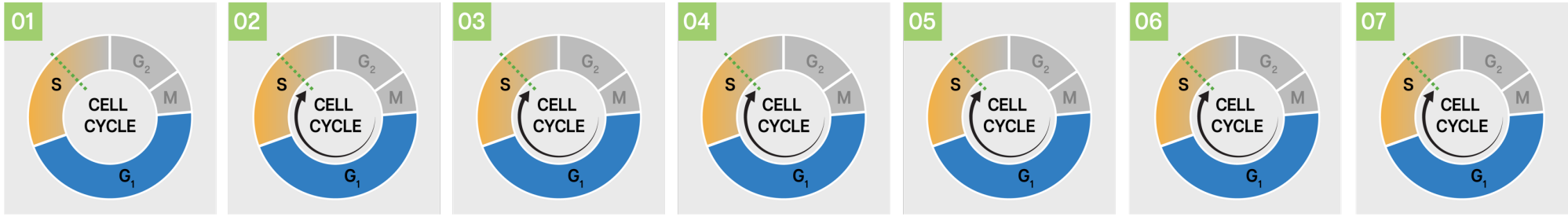


Schoppy et al. *J Clin Invest 2012*

Target Coverage: Daily dosing is desirable

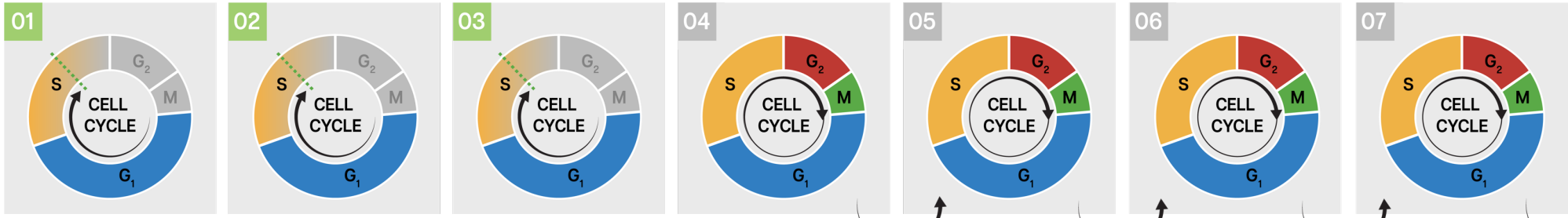
- Assumption: Cancer cells proliferate at an estimated rate of one cell cycle per day

Drug “On”

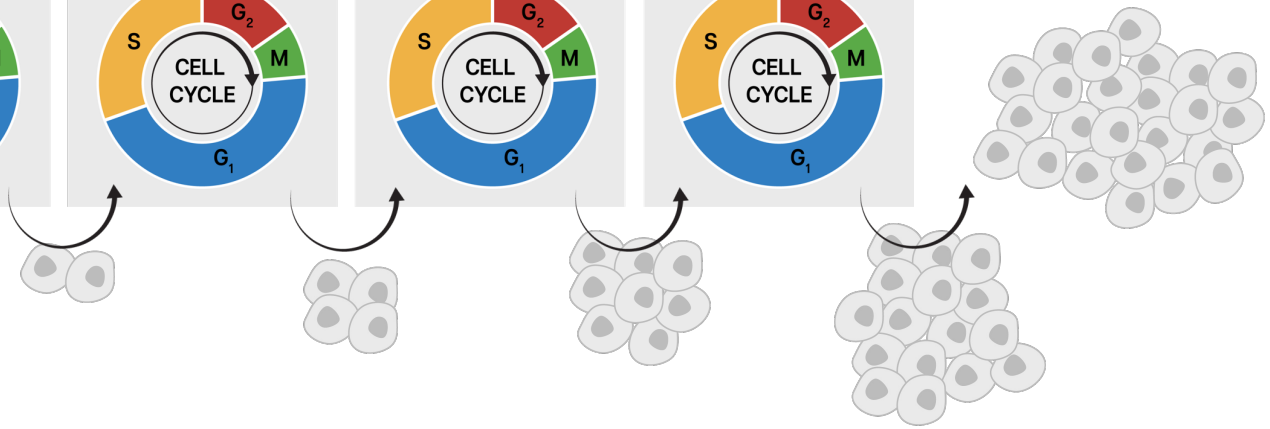


Cancer cell death/ decreased rate of proliferation

Drug “On” Drug “Off”



Cancer cell proliferation



- Lack of daily dosing may contribute to formation of resistance
- Most of the drugs in DDR carry a short half life

Potential Off Target Toxicological Effects

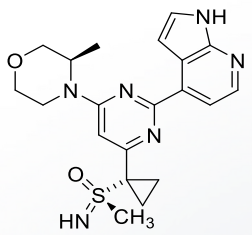
	On-Target Cellular IC_{50} (nM)	Fold Difference in IC_{50} for Off-Target PIKK Inhibition		
	ATRi	ATM	DNA-PK	mTOR
ATRN-119 (1)	4	> 600x	> 2000x	> 2000x
Berzosertib (1)	61	31x	> 200x	> 50x
AZD-6738 (2)	74	> 400x	> 400x	70 – 310x
BAY 1895344 (3)	36	39x	9x	61x
RP3500 (4)	0.33	> 20000x	> 20000x	30x

- Compounds that are highly potent with high selectivity may potentially limit off-target toxicity
- Other targets, outside of PIKK, may also contribute to off target toxicity
- ATRN-119 is highly potent and selective to potentially limit off-target toxicity
- In pre-clinical studies, ATRN-119 has shown potential to have lower hematological toxicity than other ATRi
- M1774 potentially a derivative of Berzosertib

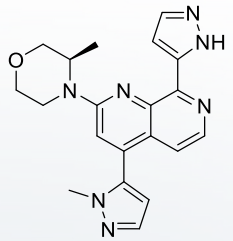
Note: Head-to-head studies with ATRN-119 have not been conducted
(1) Atrin data reported for HCT116 - Bcl/XL cell line;
(2) Foote et al (2018), J Med Chem;
(3) Lücking et al (2020), J Med Chem;
(4) Roulston et al (2022) Mol Cancer Ther

ATR Landscape

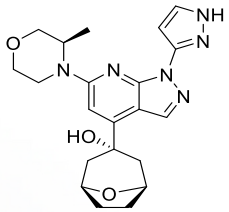
Current ATRs Structurally Similar in Core, Backbone, and Toxicity Profile



AZD-6738



BAY1895344



RP-3500

CAMOSERTIB

Parameter	AstraZeneca AZD6738 (1)(2)	Bayer BAY1895344 (3)	Repare / Roche(4) RP-3500 (5)
Route Of Administration	**Oral**	**Oral**	**Oral**
Clinical Studies Chosen (MTD/RP2D), Dose Schedule	**160mg BID, 2-weeks-on, 2-weeks-off, or: Continuous dosing (1)**	**40mg BID, 3-days-on/4-days-off**	**160mg QD, 3-days-on/4-days-off**
Main Grade ≥3 Hematological toxicities reported at Chosen Dose Schedule (MTD/RP2D), in clinical studies	Patriot 1, Escalation Phase, 160mg, BID (2) : **Anemia** (1/6, 17%) Patriot 2, Expansion Phase (1): **Fatigue, anemia, nausea & thrombocytopenia (not differentiated) (1):** (4/6, 67%) with continuous dosing (3/15, 20%) with 2-week-on, 2-week-off	**Anemia** (2/2, 100%) **Neutropenia** (1/2, 50%)	**Anemia** (23/95, 24%) **Neutrophil count decreased** (10/95, 11%) **Platelet count decreased** (5/95, 5%)

Note: Head-to-head studies with ATRN-119 have not been conducted

(1) Phase I study of ATR inhibitor, AZD6738, as monotherapy in advanced solid tumors (PATRIOT part A, B), Dillon et al, Volume 30, October 2019, Pages v165-v166

(2) Poster CT084: A Phase I dose-escalation study of ATR inhibitor monotherapy with AZD6738 in advanced solid tumors (PATRIOT Part A), AACR 2017

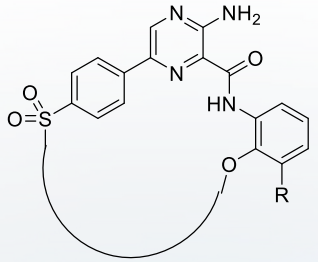
(3) First-in-Human Trial of the Oral Ataxia Telangiectasia and RAD3-Related (ATR) Inhibitor BAY 1895344 in Patients with Advanced Solid Tumors, Yap et al, Cancer Discov 2021;11:80-91 and 2019 ASCO Poster, De-Bono et al.

(4) Repare announced a worldwide license and collaboration agreement with Roche on June 1, 2022

(5) Preliminary Phase 1 Data From Ongoing First-in-Human Phase 1/2 TRESR Study of RP-3500, AACR 2022

ATRN-119: Potential Best-in-Class Oral ATR Inhibitor

With Structurally Differentiated Core, Backbone, and Toxicity Profile



Parameter	ATRN-119 (1)
Route Of Administration	Oral
Clinical Studies Chosen (MTD/RP2D), Dose Schedule	continuous once-daily dosing (dose TBD in Phase 1) (1)
Hematological toxicities in preclinical studies	**Pre-Clinical, Toxicology Studies:** • In 28-day GLP tox study in dogs, hematological changes were of small magnitude with complete recovery • In a head-to-head comparative tolerability study, ATRN-119 demonstrated significantly less toxicity than another oral ATRi that is currently in clinical development

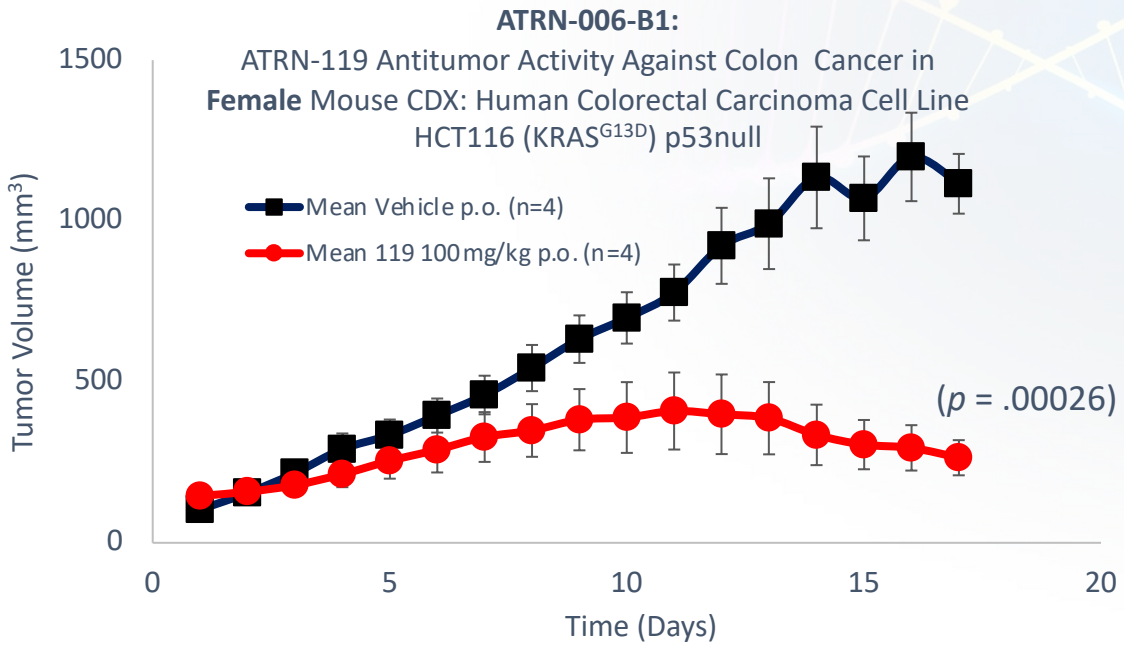
ATRN-119 potential for reduced toxicity could make it a preferred ATR inhibitor as a single agent, as well as a candidate for combination with standard of care therapies

Note: ATRN-119 has not yet been tested clinically
(1) ATRN-119, Phase 1/2a Clinical Study Protocol

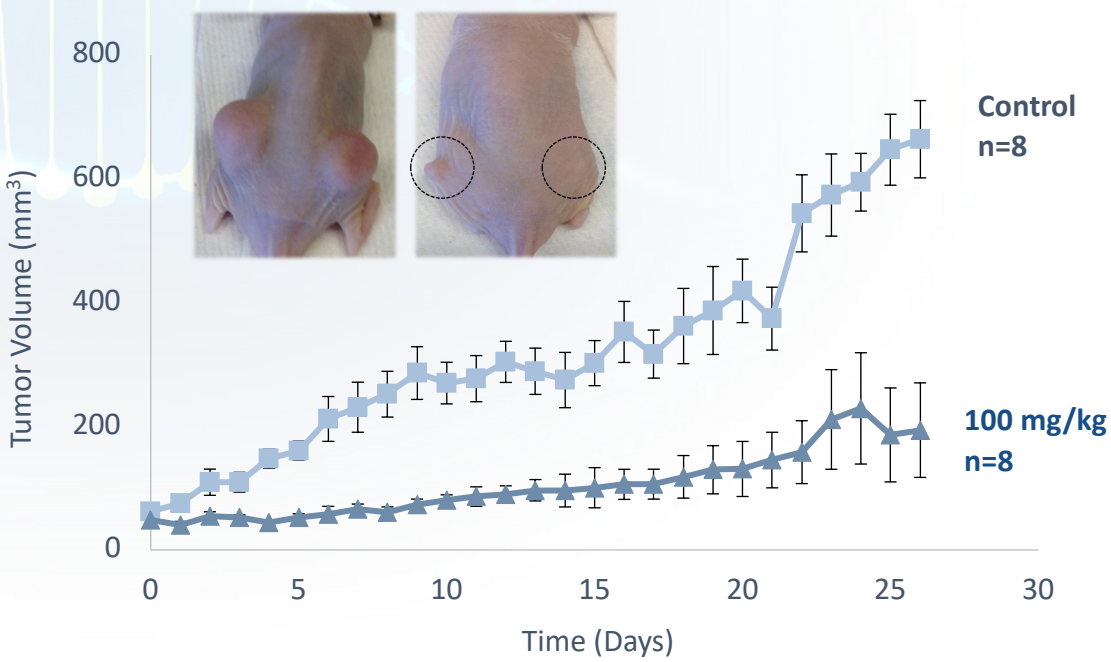
ATRN-119 Preclinical Profile

- Nanomolar potency *in vitro* across a broad spectrum of cancer cell lines
- Based on pre-clinical studies, strong tumor control observed *in vivo*, including in challenging genetic backgrounds

HCT-116 p53 null (KRAS^{mut}, p53)



Pancreatic (CAPAN-1) (KRAS^{mut}, BRCA2)

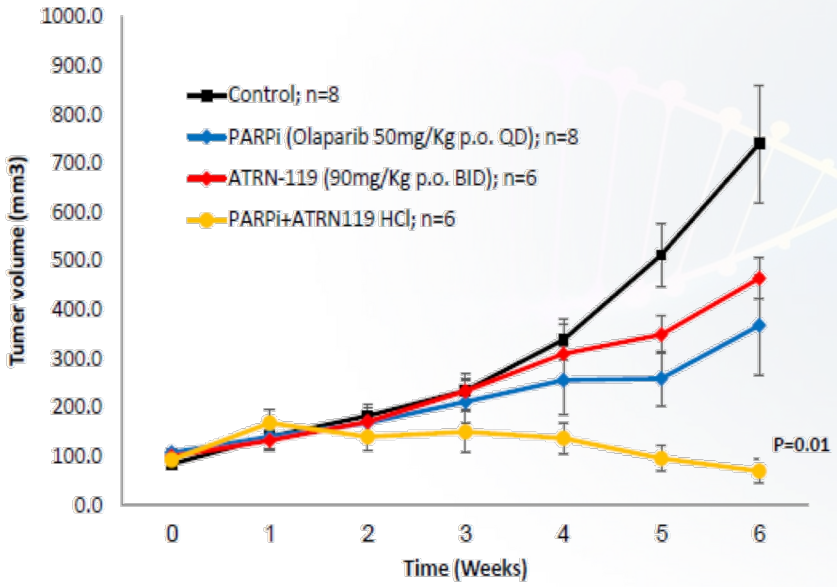


Pre-clinical studies with ATRN-119

ATRN-119 + Olaparib (Lynparza®): Regression of BRCA2-Deficient Ovarian (HGSOC) Tumors

ATRN-119 + PARPi Inhibits Ovarian Tumor Growth Over Time

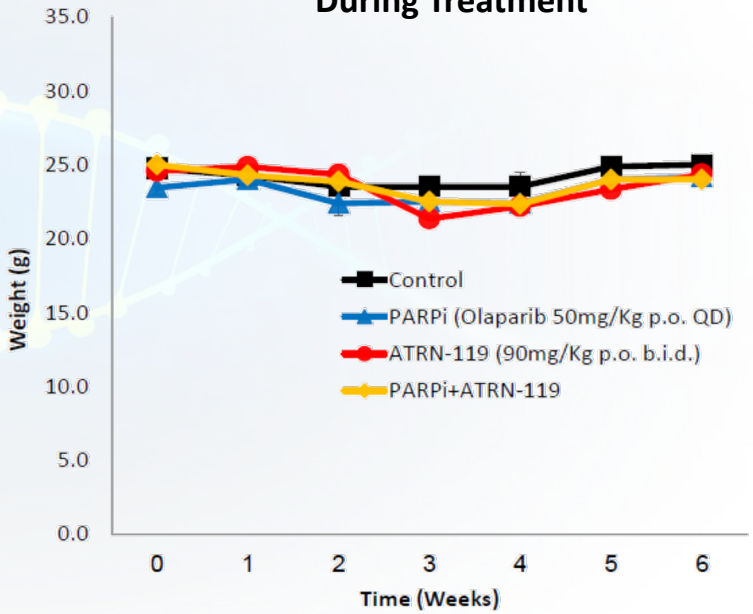
Human Ovarian PDX - PARPi & ATRi Tumor Size



Based on pre-clinical results to date, the combination of ATRN-119 and PARPi has shown potentially compelling tumor growth inhibition

ATRN-119 + PARPi Shows Negligible Weight Loss Over Time

ATRN-119 + PARPi Shows Negligible Body Weight Loss During Treatment



Based on pre-clinical results to date, the combination of ATRN-119 and PARPi potentially appears to be well tolerated

Pre-clinical studies with ATRN-119

Summary

- Multiple DDR inhibitors have been shown to cause hematologic toxicity
- However, genetic models of ATR suppression showed tumor can be targeted with limited toxicity
- This leads to the hypothesis that selectivity can help limit toxicity for ATR inhibitors
- ATRN-119 shows decrease hematologic toxicity yet is therapeutic at allometric concertation in mice
- Phase 1 human clinical trial of ATRN-119 are ongoing