# DDR Inhibitors Summit 2023

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

# Adding On to Monotherapy:
## Combining DDR Inhibitors

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.

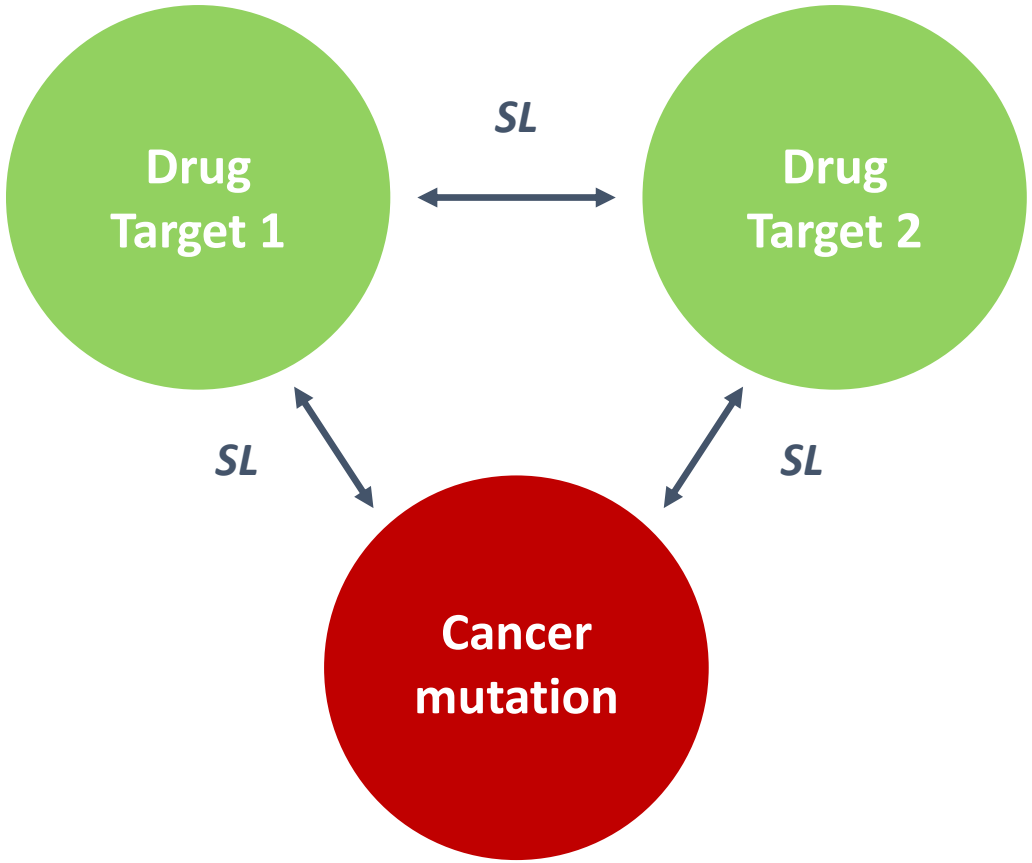
# Combinations to combat emerging resistance:

identifying combination agents

# Potential Benefits For Combination Therapy:

- Overcome Resistance
- Increase Efficacy
- Reduce Toxicity
- Indication Expansion

## Drug Combination SL Approach



# Combining DDR Inhibitors with PARPi:

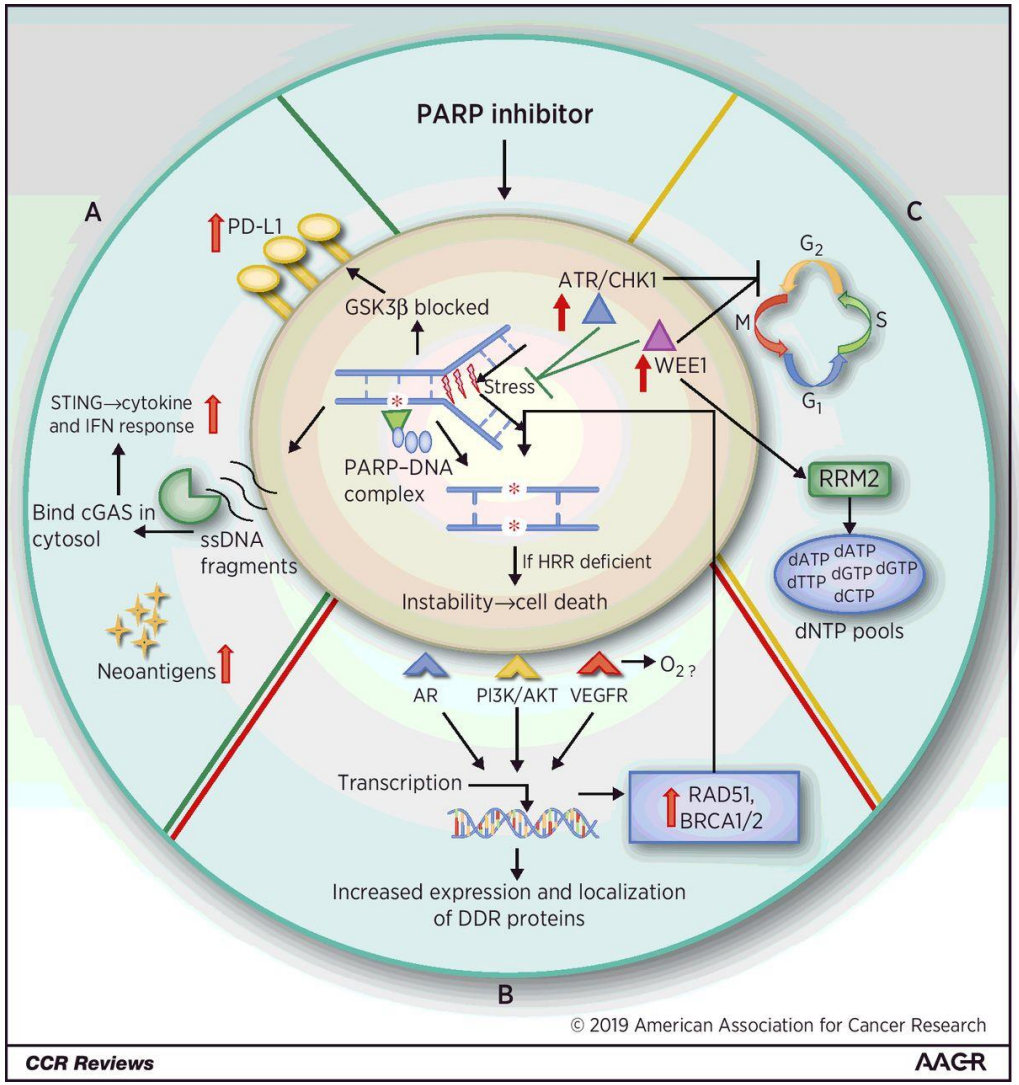
Standard of Care

CA CANCER J CLIN 2011;61:31–49

## Poly(ADP-Ribose) Polymerase (PARP) Inhibitors: Exploiting a Synthetic Lethal Strategy in the Clinic

Timothy A. Yap, BSc, MB BS[1,2]; Shahneen K. Sandhu, MB BS[1,2]; Craig P. Carden, MB BS[1,2]; Johann S. de Bono, MB ChB, MSc, PhD[1,2]

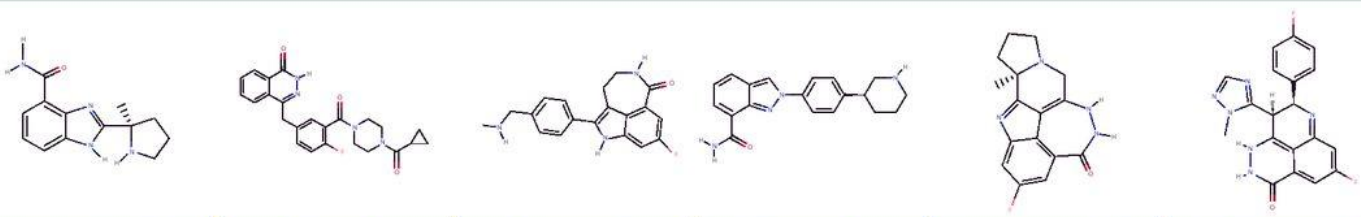
# PARP inhibitor–based combination treatment strategies
# Broad categories of PARP inhibitors: combination treatment strategies






Pilié et al., Clin Cancer Res. 2019;25(13):3759-3771

# Comparison of PARP inhibitors under clinical development Including toxicity profile



| | Veliparib[E] | Olaparib | Rucaparib | Niraparib | Pamiparib[F] | Talazoparib |
|---|---|---|---|---|---|---|
| Relative PARP-trapping capacity[A] (refs. 23–28) | - | ++ | ++ | ++ | ++ | +++ |
| Single-agent dose | 400 mg PO BID | 300 mg PO BID | 600 mg PO BID | 300 mg PO QD | 60 mg PO BID | 1 mg PO QD |
| Toxicities[B] Most frequent | Nausea (30%)/ fatigue (25%)/ lymphopenia (16%) | Nausea (58%–76%)/ fatigue (29%–66%)/ vomiting (30%–37%)/ diarrhea (21%–33%)/ dysgeusia (27%)/ headache (20%–25%) | Nausea (75%)/fatigue (69%)/vomiting (37%)/ diarrhea (32%)/ dysgeusia (39%)/LFT elevation (34%) | Nausea (74%)/fatigue (59%)/LFT elevation (36%)/vomiting (34%)/ headache (26%)/insomnia (24%)/HTN (19%) | Limited early-phase trial data from abstracts only: nausea (56%)/fatigue (40%)[F] | Nausea (49%)/fatigue (50%)/headache (33%)/ vomiting (25%)/alopecia (25%)/diarrhea (22%) |
| Grade ≥3 hematologic toxicities in ≥5% of study population | NTD | Anemia (16%–19%), neutropenia (5%–9%) | Anemia (19%), neutropenia (7%) | Thrombocytopenia (34%), anemia (25%), neutropenia (20%) | Limited early-phase trial data from abstracts only: anemia (10.3%), neutropenia (8.8%)[F] | Anemia (39%), neutropenia (21%), thrombocytopenia (15%) |
| Clinical benefit[C] | NTD | OlympiAD (Her2–breast), HR 0.50, PFS benefit<br>SOLO2 (relapsed ovarian maintenance), HR 0.30, PFS benefit<br>SOLO1 (ovarian maintenance), HR 0.30, PFS benefit | ARIEL2 (relapsed ovarian), HR 0.27, PFS benefit<br>ARIEL 3 (relapsed ovarian maintenance), HR 0.23, PFS benefit | NOVA (relapsed ovarian maintenance), HR 0.27, PFS benefit | Ongoing, data not mature (NCT03427814) | EMBRACA (Her2–breast), HR 0.54, PFS benefit |
| Approvals[D] | NTD | Ovarian<br>Breast | Ovarian | Ovarian | NTD | Breast (FDA) |



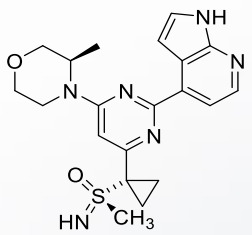
CCR Reviews AACR



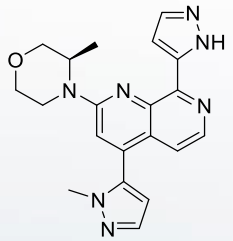
Pilié et al., Clin Cancer Res. 2019;25(13):3759-3771

# ATR Landscape: Current ATRs Structurally Similar in Backbone, and Toxicity Profile

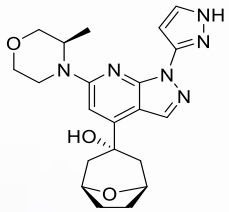
## Potential *overlapping toxicity in combination with other agents may limit therapeutic affect*



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%)<br><br>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%)<br><br>**Neutropenia** (1/2, 50%) | **Anemia** (23/95, 24%)<br><br>**Neutrophil count decreased** (10/95, 11%)<br><br>**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

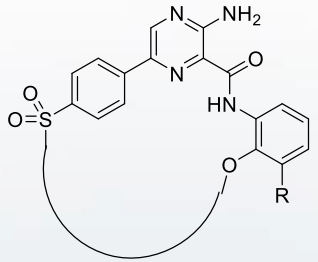
(2) Poster CT084: A Phase I dose-escalation study of ATR inhibitor monotherapy with AZD6738 in advanced solid tumors (PATRIOT Part A), AACR 2017

(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



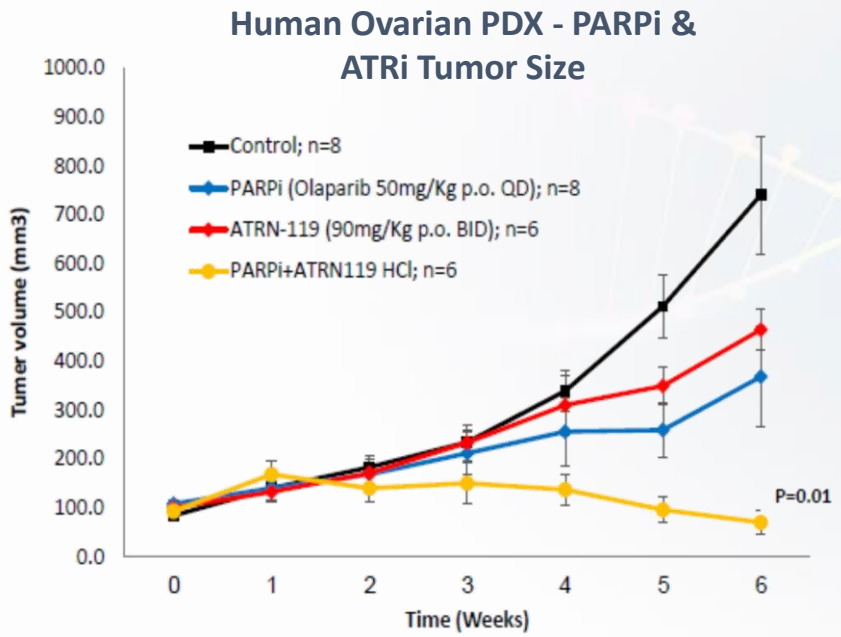

| Parameter | ATRN-119 (1) |
|---|---|
| Route Of Administration | Oral |
| Clinical Studies Chosen (MTD/RP2D), Dose Schedule | continuous once-daily dosing (dose TBD in Phase 1) (1) |
| Hematological toxicities in preclinical studies | **Pre-Clinical, Toxicology Studies:**<br>• In 28-day GLP tox study in dogs, hematological changes were of small magnitude with complete recovery<br>• 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

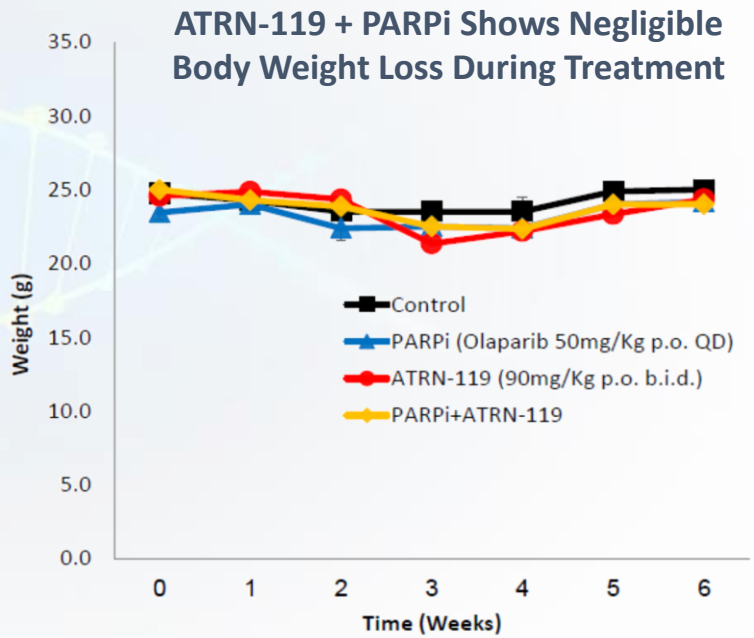
# ATRN-119 + Olaparib (Lynparza®):
## Regression of BRCA2-Deficient Ovarian (HGSOC) Tumors

### ATRN-119 + PARPi Inhibits Ovarian Tumor Growth Over Time




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

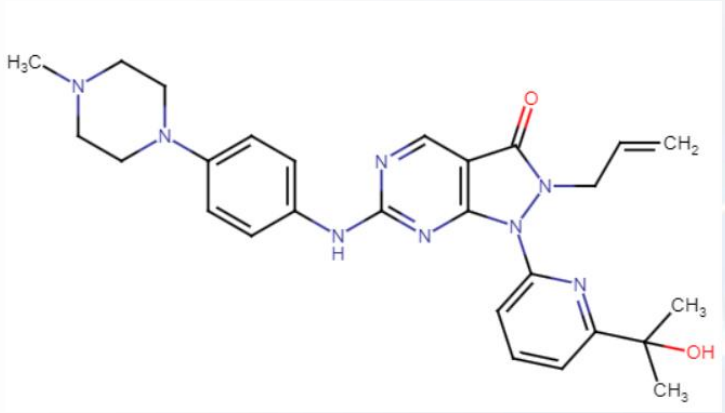
### ATRN-119 + PARPi Shows Negligible Weight Loss Over Time



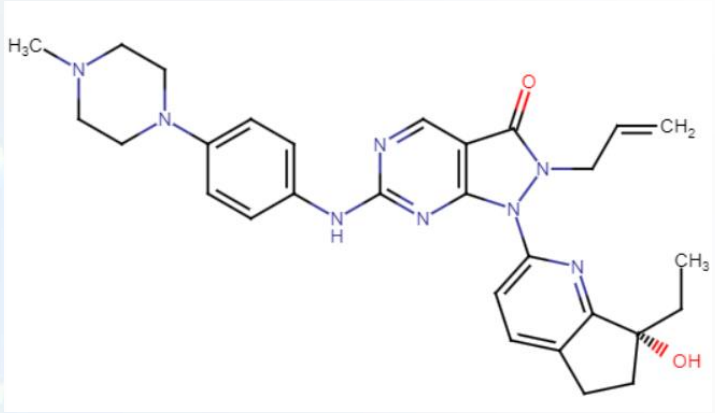

Based on pre-clinical results to date, the combination of ATRN-119 and PARPi potentially appears to be well tolerated

# Leading WEE1i are potent but off-target PLK1, PLK2 and PLK3

Leading WEE1i are potent but off-target PLK1, PLK2 and PLK3



AZD-1775[1]



ZN-c3

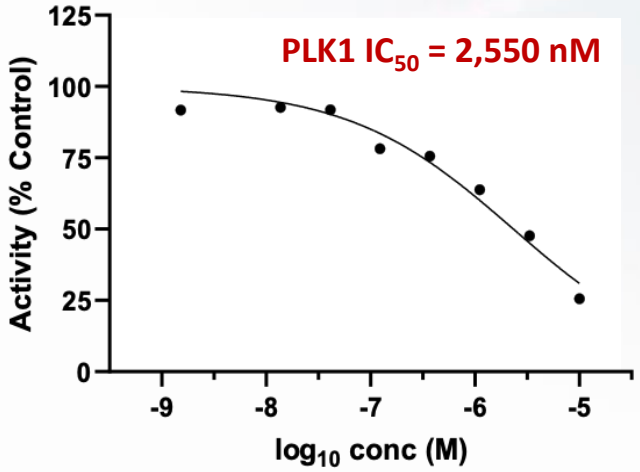
| | On-Target $IC_{50}$ (nM) | Off-Target Inhibition at 1 μM (%) | | |
|---|---|---|---|---|
| | WEE1 | PLK1 | PLK2 | PLK3 |
| ZN-c3 [1] | 3.8 | 79 | 96 | 92 |
| AZD-1775 [1,2] | 3.9 | 70 | 101 | 91 |

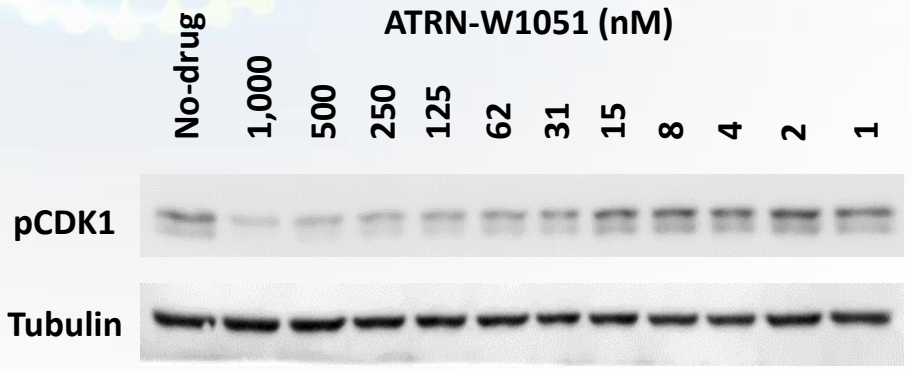
1. Huang et al, *J Med Chem*, 2021
2. AstraZeneca announced discontinuation of AZD-1775 development on June 29, 2022

# ATRN-W1051 is potentially differentiated from other WEE1 inhibitors

| | On-Target $IC_{50}$ (nM) | Off-Target Inhibition at 1 μM (%) | | |
|---|---|---|---|---|
| | WEE1 | PLK1 | PLK2 | PLK3 |
| ATRN-W1051 | 2.2 | 17 | 33 | 12 |
| ZN-c3 (1) | 3.8 | 79 | 96 | 92 |
| AZD-1775 (1) | 3.9 | 70 | 101 | 91 |

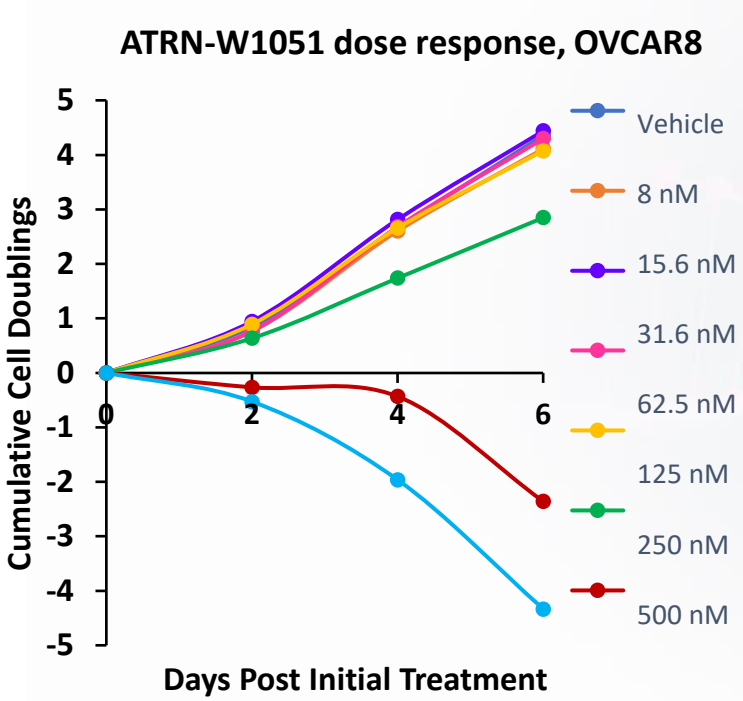
## ATRN-W1051 IC50 for PLK1 inhibition is >1000-fold higher than for WEE1 inhibition

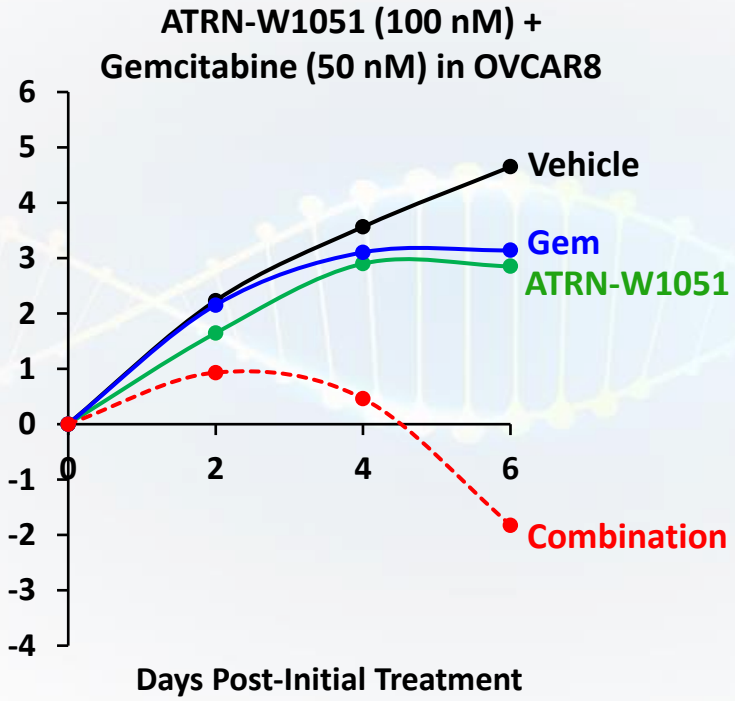


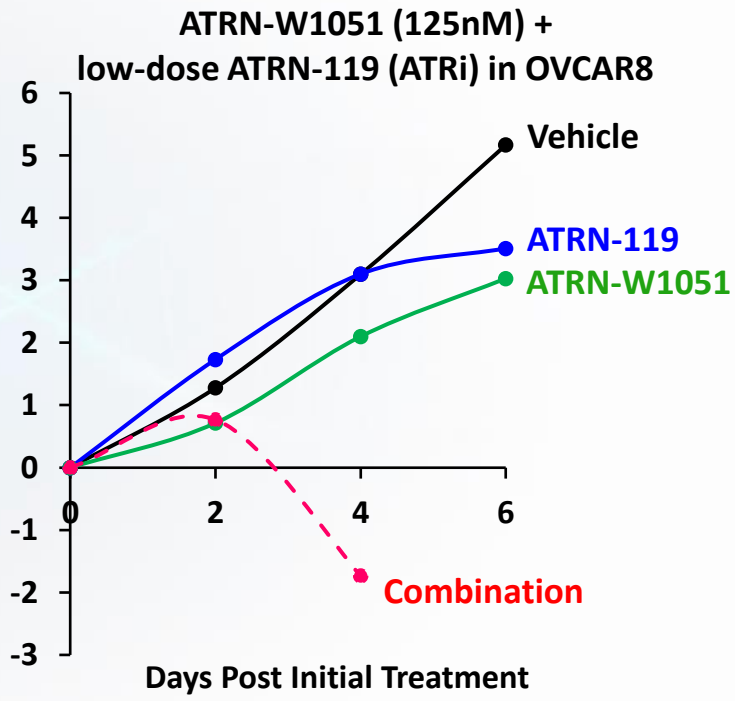




(1) Head-to-head studies have not been conducted.
(2) Huang et al, J Med Chem, 2021

# ATRN-W1051 potently inhibits OvCa cell proliferation both alone and in combination



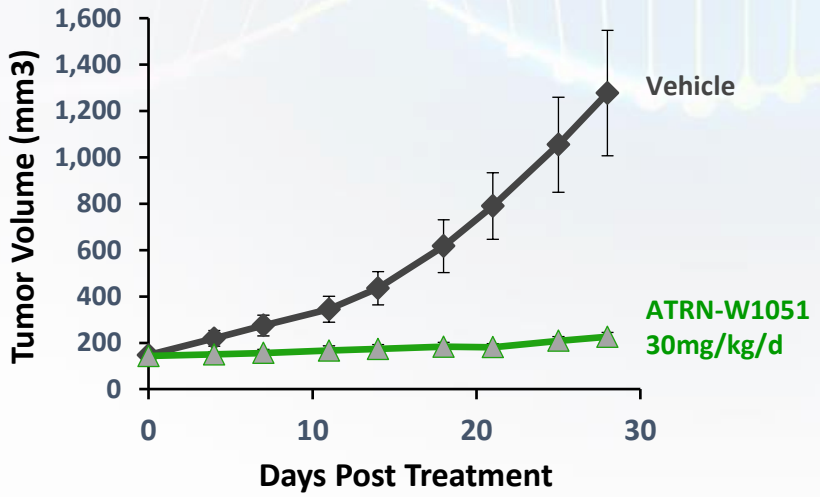
# ATRN-W1051 has potentially compelling PK and anti-tumor activity

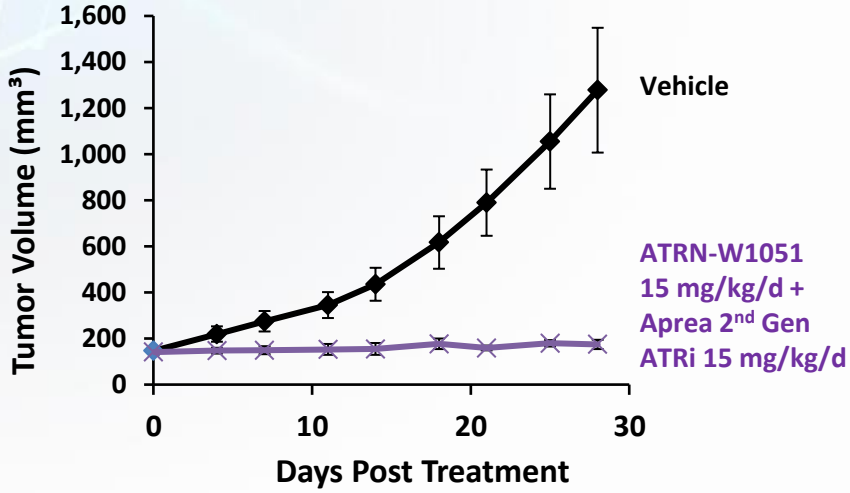
**Preclinical data highlight potentially favorable PK properties of ATRN-W1051**

| | ATRN-W1051 (1,2) | ZN-c3 (1,3) | | | AZD-1775 (1,3) | | |
|---|---|---|---|---|---|---|---|
| Dose (mg/kg/d) | 10 | 20 | 40 | 80 | 20 | 40 | 80 |
| $C_{max}$, ng/mL | 1219 | 1167 | 1997 | 5100 | 635 | 2460 | 4703 |
| $T_{max}$, hr | 2 | 1 | 1 | 1 | 1 | 1 | 1 |
| $AUC_{0-24}$, ng*hr/mL | 14,211 | 4863 | 17,088 | 39,722 | 1494 | 6,313 | 13,408 |
| Tumor concentration, ng/mL | 9000 ng/gr (@ 15 mg/kg/d) | 10.5 | 48 | 811 | BQL | BQL | 6.95 |

**Anti-tumor activity of ATRN-W1051 – Oral administration**

OVCAR3 CCNE1-amplified xenograft model



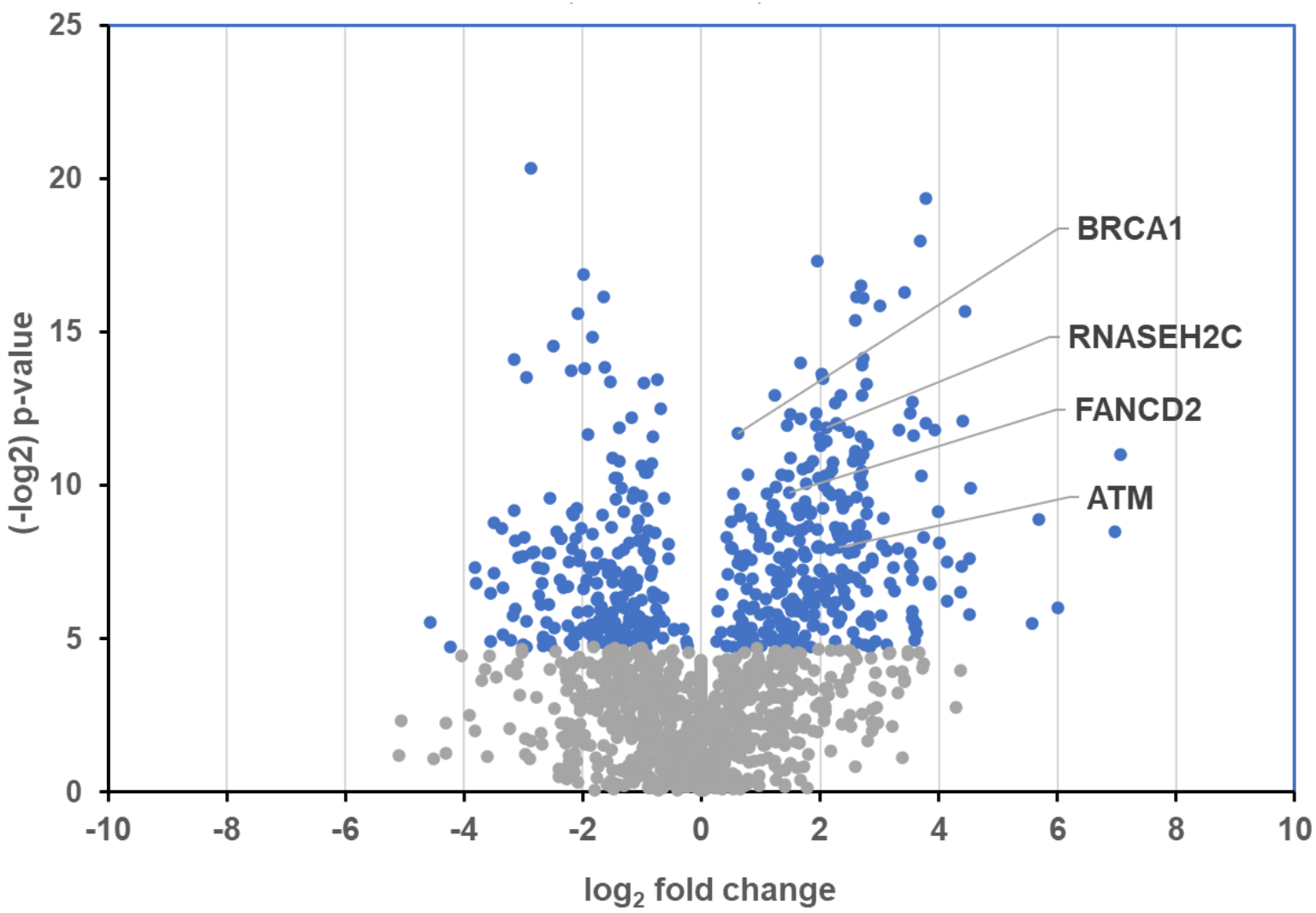




1. Head-to-head studies have not been conducted.
2. Data from study in normal mice
3. Data from study in A-427 NSCLC xenograft model as reported in Zentalis Corporate Overview, March 2022

# Summary

- Numerous ongoing trials investigating inhibitors in Synthetic Lethality and DDR as monotherapy or in combination
- PARP inhibitors are approved as standard of care
- Toxicity remains a major challenge in the development of new therapies as single agents and in combination
- ATRN-119's 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
- ATRN-W1051 is a potent WEE1i (2.2 nM IC50) with low off-target inhibition of PLK1, PLK2 and PLK3
- ATRN-W1051 has the potential to become a promising therapeutic candidate as a singly agent and in combination with ATRi.

# ATRN-119 causes recruitment of factors previously shown to be SL with ATRi




*In collaboration with Aprea Therapeutics*


Yap et al., *Cancer Discov*ery, 2021
Ngoi et al., *Trends Cancer*, 2021
Chen et al., *Molecular Cancer*, 2009
Wang et al., *Oncogene*, 2019
Zimmerman et al., Cell Report, 2022