Modern Synthetic Lethal Strategies in Clinical Drug Development

2025 Ochsner Multidisciplinary Cancer Update

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THE UNIVERSITY OF TEXAS
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Disclosures

Timothy A. Yap

- **Employee of:** University of Texas MD Anderson Cancer Center, where I am VP, Head of Clinical Development in the Therapeutics Discovery Division, which has a commercial interest in drug discovery and development
- **Consultant for:** AbbVie, Acrivon, Adagene, Aeneid Therapeutics, Almac, Alterome Therapeuticcs Inc., Aduro, Amgen Inc., Amphista, Artios, Astex, AstraZeneca, Atavistik, Athena, Atrin, Avenzo, Avoro, Axiom, Baptist Health Systems, Bayer, Beigene, Bicycle, BioCity Pharma, Bloom Burton, Blueprint, Bluestar Bio, Boxer, BridGene Biosciences, Bristol Myers Squibb, C4 Therapeutics, Calithera, Cancer Research Horizons, Cancer Research UK, Carrick Therapeutics, Circle Pharma, Clasp, Clovis, Cybrexa, Daiichi Sankyo, DAiNA, Dark Blue Therapeutics, Dawn Manco, Debiopharm, Diffusion, Duke Street Bio, 858 Therapeutics, EcoR1 Capital, Eikon, Ellipses Pharma, EMD Serono, Entos, Flagship Pioneering, Forbion, FoRx Therapeutics AG, F-Star, Genesis Therapeutics, Genmab, Glenmark, GLG, Globe Life Sciences, Grey Wolf Therapeutics, GSK, Guardant, Guidepoint, Ideaya Biosciences, Idience, Ignyta, I-Mab, ImmuneSensor, Impact Therapeutics, Institut Gustave Roussy, Intellisphere, Jansen, Jazz Pharma, Joint Scientific Committee for Phase I Trials in Hong Kong, Kyn, Kyowa Kirin, Lumanity, MEI pharma, Mereo, Merck, Merit, Monte Rosa Therapeutics, Natera, Nested Therapeutics, Nexys, Nimbus, Novocure, Odyssey Therapeutics, OHSU, OncoSec, Ono Pharma, Onxeo, PanAngium Therapeutics, Pegascy, PER, Pfizer, Piper-Sandler, Pliant Therapeutics, Plexium Inc., Prelude Therapeutics, Prolynx, Protai Bio, PSIM, Radiopharma Theranostics, Repare, resTORbio, Roche, Ryvu Therapeutics, SAKK, Sanofi, Schrodinger, Servier, Stablix, Synnovation, Synthis Therapeutics, Tango, TCG Crossover, TD2, Techspert.io, Terremoto Biosciences, Tessellate Bio, Theragnostics, Terns Pharmaceuticals, Thryv Therapeutics, Tolremo, Tome, Trevarx Biomedical, Varian, Veeva, Versant, Vibliome, Vivace, Voronoi Inc, Xinthera, Zai Labs and ZielBio
- **Grant/Research support from:** 858 Therapeutics, Accent, Aprea Therapeutics, Artios, AstraZeneca, Bayer, Beigene, BioNTech, Blueprint, BMS, Boundless Bio, BridGene BioScience, circle Pharma, Clovis, Constellation, CPRIT, Cyteir, Department of Defense, Eisbach Bio, Eli Lilly, EMD Serono, Exelixis, Forbius, F-Star, Gilead, GlaxoSmithKline, Genentech, Gilead, Golfers against Cancer, Haihe, Ideaya, ImmuneSensor, Insilico Medicine, Ionis, Ipsen, Jounce, Karyopharm, KSQ, Kyowa, Loxo Oncology, Merck, Mirati, Novartis, NIH/NCI, Pfizer, Pliant, Prelude, Ribon Therapeutics, Regeneron, Repare, Roche, Rubius, Sanofi, Scholar Rock, Seattle Genetics, SpringWorks, Synnovation, Tango, Tesaro, V Foundation, Vivace, Zenith and Zentalis.

What is synthetic lethality?

- Theodore Dobzhansky coined the term "synthetic lethality" in 1946
- This was a concept and now a bona fide antitumor strategy
- Strategy to target tumor suppressor gene aberrations, e.g. PARP inhibitors and *BRCA1/2* mutation cancers

Gene X	Gene Y	Cell viability
+	+	No effect
-	+	No effect
+	-	No effect
-	-	Death

Mutation in either gene individually has no effect, but combining the mutations leads to cell death.

Ashworth, JCO 2008

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PARP inhibitor	BRCA1/2 mutation carrier	Cell viability
No PARP inhibitor	Normal tissue	No effect
No PARP inhibitor	*BRCA1/2* mutation tumor	No effect
PARP inhibitor	Normal tissue	No effect
PARP inhibitor	*BRCA1/2* mutation tumor	**Death**

Efficacy in BRCA1/2 mutation tumor with minimal normal tissue toxicity

Ashworth, JCO 2008

Normal cells in BRCA carrier (functioning HR)

Courtesy of Dr Andrew Tutt

Normal cells in BRCA carrier

PARP inhibitor

Courtesy of Dr Andrew Tutt

Normal cells in BRCA carrier

Courtesy of Dr Andrew Tutt

Normal cells in BRCA carrier

Tumor cells in BRCA carrier (non-functioning HR)

Courtesy of Dr Andrew Tutt

Normal cells in BRCA carrier

Tumor cells in BRCA carrier

Courtesy of Dr Andrew Tutt

Normal cells in BRCA carrier

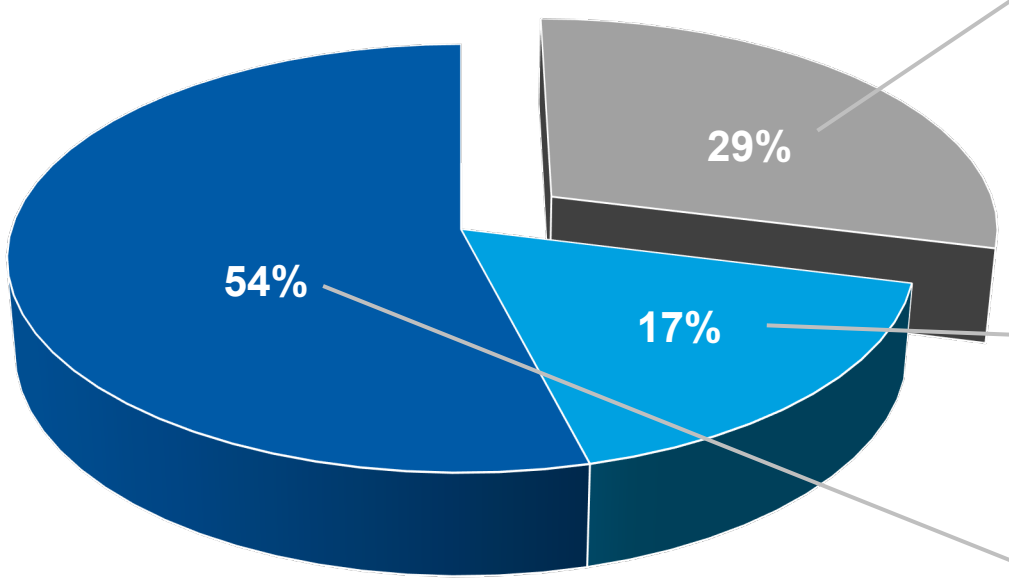
Tumor cells in BRCA carrier

Targeted inhibition → selective therapy

Courtesy of Dr Andrew Tutt

The importance of synthetic lethality in targeting untapped cancer lesions

Tapped and untapped cancer lesions



Focus of precision oncology for 20 years:

Gain of function (targetable, e.g. EGFR)

Gain of function (untargetable, e.g. CCNE1)

Loss of function (e.g. going beyond BRCA1/2)

Untapped space (71%)

The NEW ENGLAND JOURNAL of MEDICINE

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

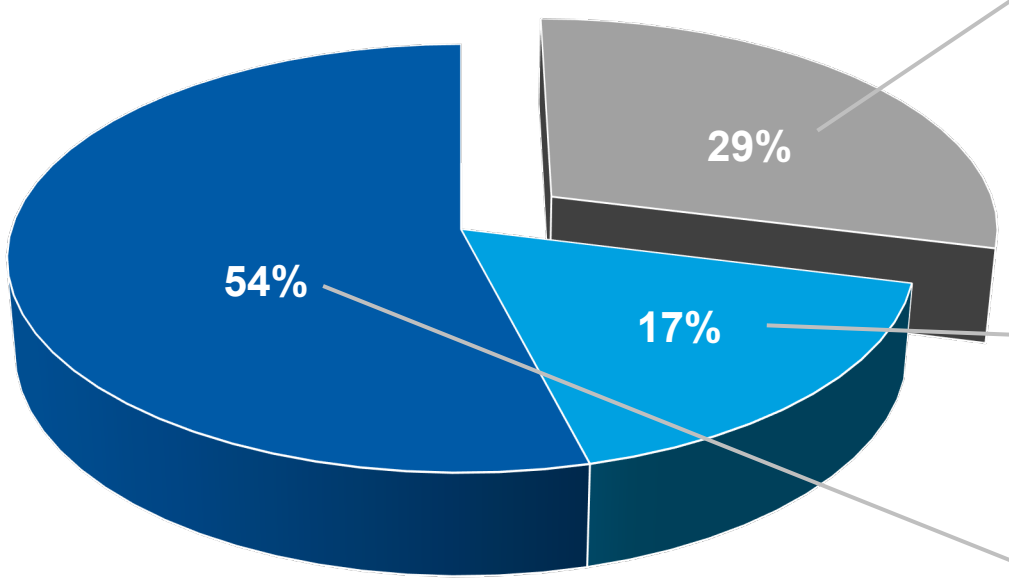
"…known cancer targets represent a small minority of strong cancer dependencies … synthetic lethal targets are particularly attractive as new targets…"

Courtesy of Dr. Mike Zinda

William C. Hahn, NEJM 2019

The importance of synthetic lethality in targeting untapped cancer lesions

Tapped and untapped cancer lesions



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Gain of function (targetable, e.g. EGFR)

Gain of function (untargetable, e.g. CCNE1)

Loss of function (e.g. going beyond BRCA1/2)

Untapped space (71%)

Synthetic Lethal Strategies	
Tumor alteration	Drug
HRR mutations (BRCA1/2, PALB2, RAD51C/D)	PARP inhibitors
ATM LOF alterations	ATR inhibitors
CCNE1 amplification	PKMYT1 inhibitors
MSI/dMMR	WRN inhibitors
SMARCA4 mutations	SMARCA2 inhibitors
MTAP loss	MTA-Cooperative PRMT5 inhibitors

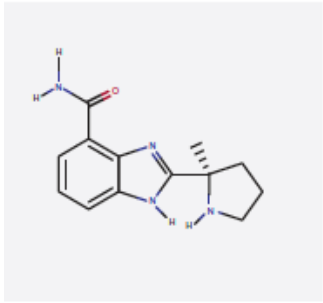
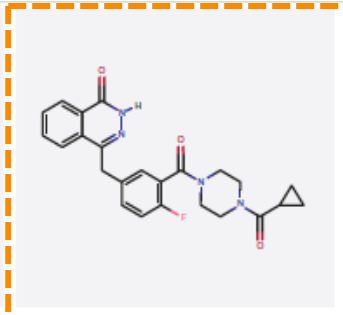
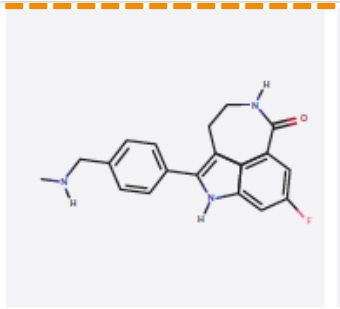
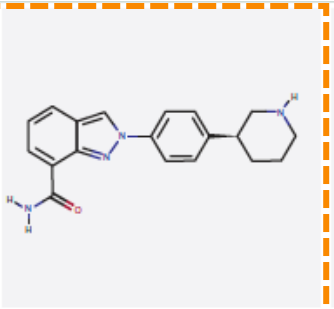
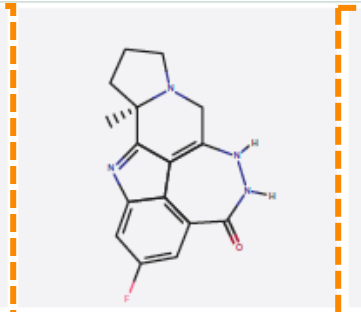
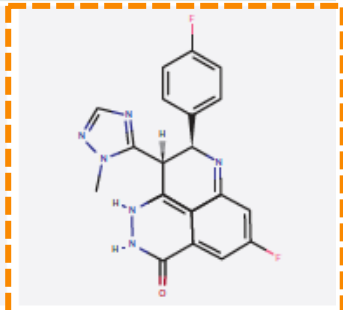
Allows biomarker-driven patient selection strategies
to guide clinical development of multiple anti-tumor agents

Overview

- BRCA1/2 mutated cancers and PARP1 inhibitors
- MTAP loss of function and PRMT5/MAT2A inhibitors
- MSI cancers and Werner Helicase inhibitors
- CCNE1 amplified cancers and PKMYT1 inhibitor combinations

Overview

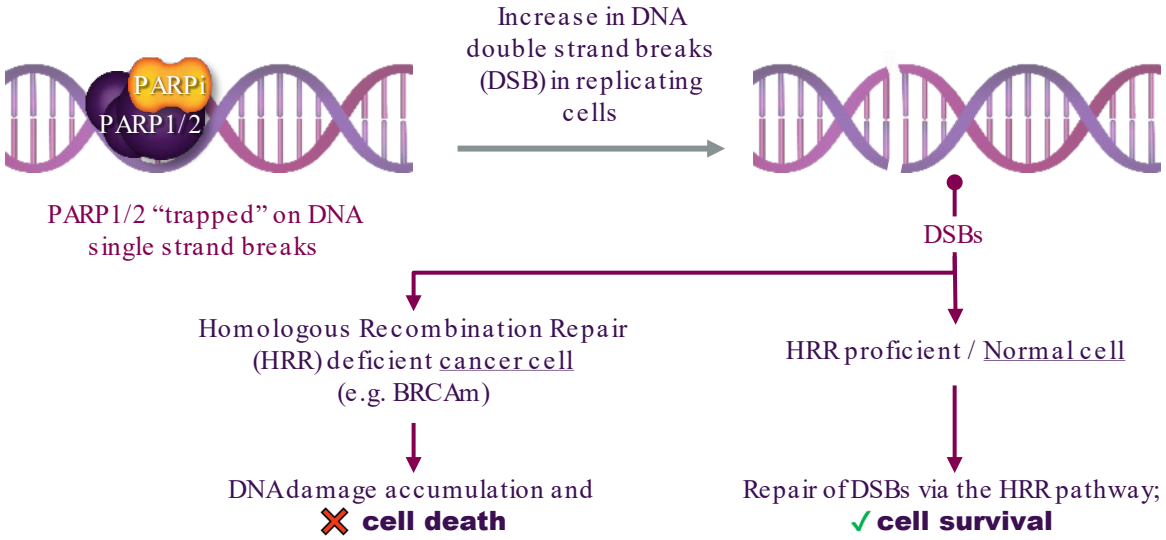
- **BRCA1/2 mutated cancers and PARP1 inhibitors**
- **MTAP loss of function and PRMT5/MAT2A inhibitors**
- **MSI cancers and Werner Helicase inhibitors**
- **CCNE1 amplified cancers and PKMYT1 inhibitor combinations**

	 Veliparib	 Olaparib	 Rucaparib	 Niraparib	 Pamiparib	 Talazoparib
Relative PARP-trapping capacity (nM)	-	**Proof of concept for a synthetic lethal approach in oncology**				
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 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%) diarrhea (32%) dysgeusia (39%) LFT elevation (34%)	nausea (74%) fatigue (59%) LFT elevation (36%) vomiting (34%) headache (26%)	Limited early-phase trial data from abstracts only: nausea (56%) fatigue (40%)	nausea (49%) fatigue (50%) headache (33%) vomiting (25%) alopecia (25%) diarrhea (22%)
Grade ≥3 hematological toxicities in ≥5% of study population	NTD	anemia (16-19%) neutropenia (5-9%)	anemia (19%) neutropenia (7%)	thrombocytopenia (34%) anemia (25%) neutropenia (34%)	anemia (10%) neutropenia (9%)	anemia (39%) neutropenia (21%) thrombocytopenia (15%)
Clinical benefit	Ongoing monotherapy arm BROCADE3 (HER- breast; NCT02163694) VELIA (Velaparib+Chemo in ovarian as first-line), HR 0.44, PFS benefit	OlympiAD (HER2- breast), HR 0.50, PFS benefit OlympiA (HER2- breast), HR 0.58, IDFS benefit SOLO2 (relapsed ovarian maintenance), HR 0.30, PFS benefit SOLO1 (ovarian maintenance), HR 0.30, PFS benefit	ARIEL2 (relapsed ovarian maintenance), HR 0.27, PFS benefit ARIEL 3 (relapsed ovarian maintenance), HR 0.27, PFS benefit TRITON2 (BRAC1/2 relapsed pancreas), ORR 43.9% Ongoing - TRITON3 (mCRPC	NOVA (relapsed ovarian maintenance), HR 0.27, PFS benefit PRIMA (advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer maintenance), HR 0.43, PFS benefit Ongoing - QUADRA	PARALLEL 303 (advanced gastric cancer maintenance), PFS benefit not statistically significant Ongoing - Phase 2 (metastatic HER2- breast; NCT03575065)	EMBRACA (HER2- breast), HR 0.54, PFS benefit

- 1st generation PARP inhibitors are associated with and are limited by toxicities
- Not all patients with *BRCA1/2* mutated cancers will respond
- Drug resistance is nearly inevitable
- Potential to deepen responses and to increase durability of response
- Potential to widen the application of PARP and other DDR inhibitors

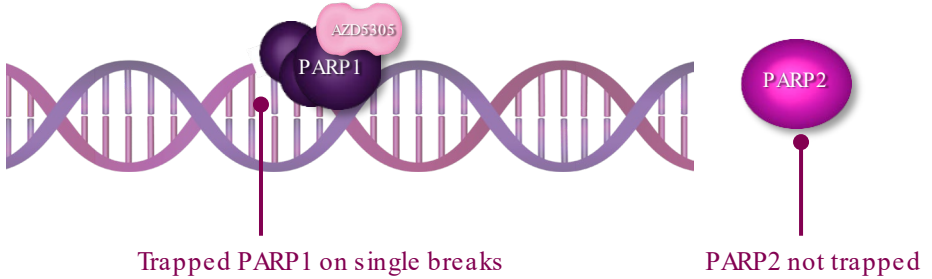
Development of next generation PARP1-selective inhibitors

PARP inhibitors trap PARP1 and PARP2 on ssDNA breaks and selectively kill cancer cells



- First generation PARP inhibitors are approved in multiple indications and are dual PARP1-PARP2 inhibitors/DNA-trappers
- The main clinical adverse events observed with 1st generation PARPi are hematological toxicities
- Pre-clinically, PARP2 is essential for erythropoiesis[2]

Only PARP1 inhibition/ trapping is required for synthetic lethality in HRR deficient settings

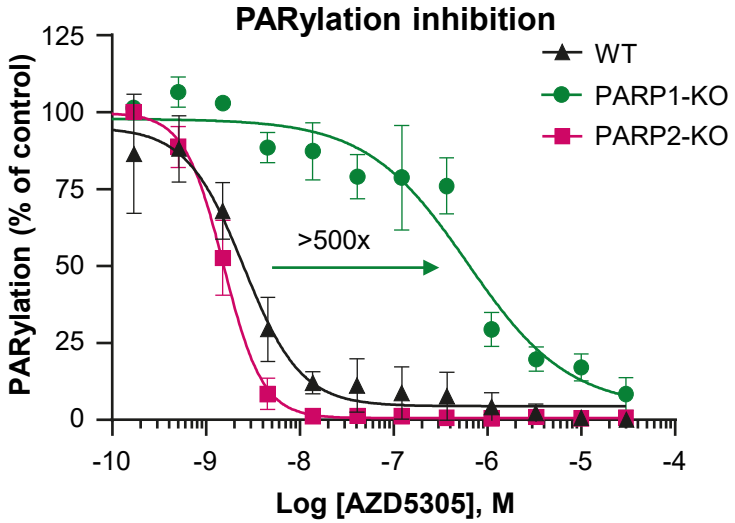


- Hypothesized that PARP1-selective inhibitor will:
  - Have a favourable tolerability profile
  - Enable higher drug exposure over target
  - Achieve greater and more durable target inhibition
  - Achieve greater antitumor efficacy
  - Enable broader combination options

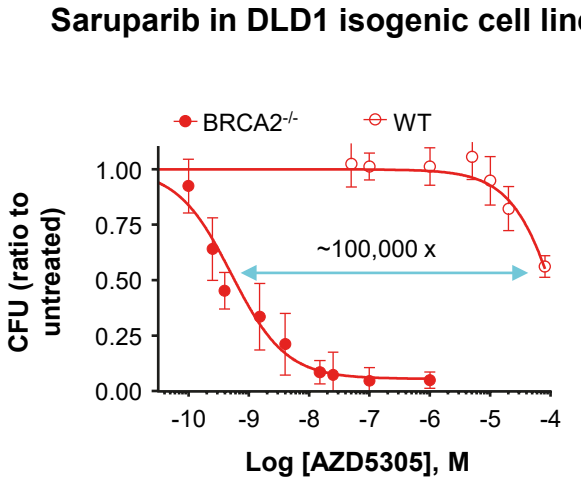
Farrés J, et al, Blood 2013; Murai J, et al. Cancer Res 2012;
Ronson, GE, et al. Nat Commun. 2018
Yap et al, AACR 2022

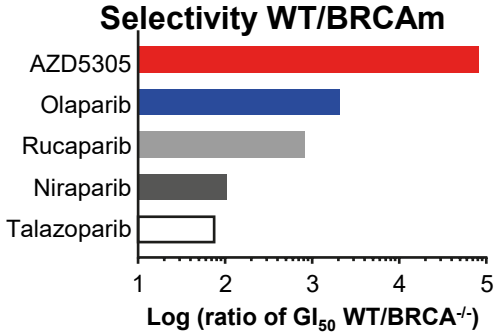
Development of next generation PARP1-selective inhibitors

Saruparib is highly selective (>500-fold) for PARP1 vs PARP2

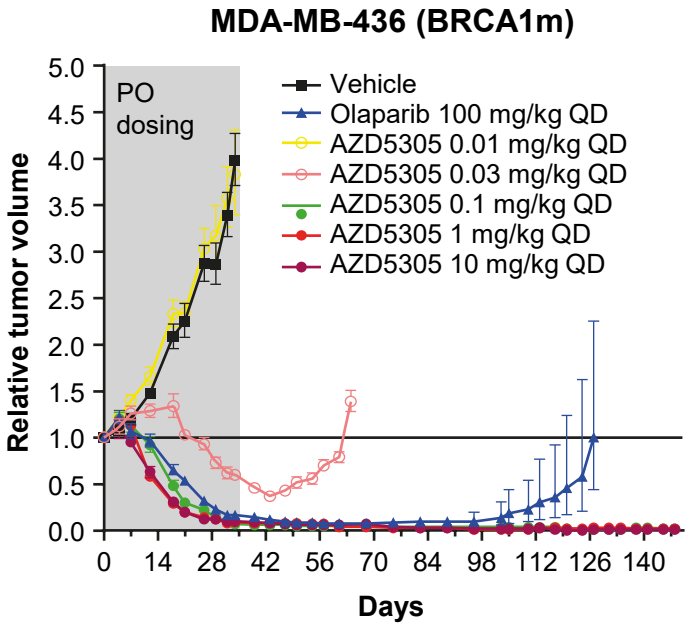


HRR-deficient cells are 100,000-fold more sensitive to **saruparib** than normal cells





Durable regression observed following cessation of **saruparib** dosing



Johannes JW, et al. J Med Chem 2021
Johannes J & Leo E. AACR 2021
Illuzzi G, et al. AACR 2021
Staniszewska AD, et al. AACR 2021

Yap et al, AACR 2022

Next generation PARP1-selective inhibitor landscape

PARP1 inhibitor	Sponsor	Phase	Route
Saruparib (AZD5305)	AstraZeneca	I - III	PO
AZD9574	AstraZeneca	I-II	PO
IMP1734	Eikon Therapeutics & Impact	I/II	PO
HS-10502	Jiangsu Hansoh Pharmaceutical	I	PO
SNV1521	Synnovation Therapeutics	I	PO
GS-0201	Gilead Sciences	I	PO
DSB-2455	Duke Street Bio	Ib	PO
M9466 (HRS-1167)	EMD Serono/Hengrui	I	PO
NMS-293	Nerviano/EMD Serono	I	PO

PETRA Module 1: a first-in-human, Phase 1/2a study of saruparib monotherapy (NCT04644068)

Part A: dose escalation

Part B: dose expansion*

Key inclusion criteria:
***BRCA1, BRCA2, PALB2, RAD51C*, or *RAD51D* mutations**
ECOG PS 0–2
Hemoglobin ≥9 g/dL†
Platelets ≥100 x 10^9/L
ANC ≥1.5 x 10^9/L

Advanced / metastatic **HER2– breast, ovarian, pancreatic, or prostate cancer**

≤1 prior line PARP inhibitor permitted

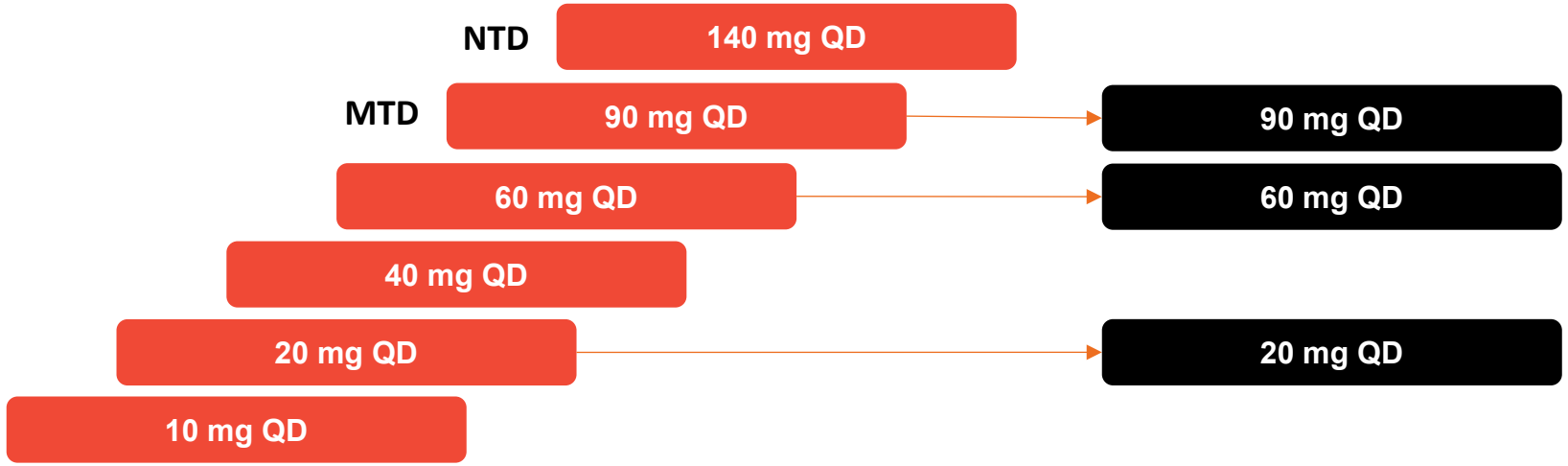
B1: HER2– breast cancer

PARP inhibitor-naïve

No limit on prior chemotherapy lines in metastatic setting

Primary endpoint:
- Safety and tolerability

Other endpoints:
- Pharmacokinetics
- Pharmacodynamics in PBMCs and paired tumor samples
- Preliminary efficacy
- ctDNA analysis



*Part B also included patients with ovarian, pancreatic, and prostate cancers; efficacy results from only patients with HER2– breast cancer are reported here. †In the absence of transfusions ≤14 days prior to the first dose of saruparib.
ANC, absolute neutrophil count; *BRCA1/2*, breast cancer gene 1/2; ctDNA, circulating tumor DNA; ECOG PS; Eastern Cooperative Oncology Group performance status; HER2–, human epidermal growth factor receptor 2 negative; MTD, maximum tolerated dose; NTD, non-tolerated dose; *PALB2*, partner and localizer of *BRCA2*; PARP, poly adenosine diphosphate-ribose (ADP-ribose) polymerase; PBMCs, peripheral blood mononuclear cells; QD, once daily; *RAD51C/D*, RAD51 recombinase homolog C/D

Yap et al, AACR 2024

Saruparib has a favorable safety profile at higher pharmacological target coverage compared with approved PARP inhibitors*

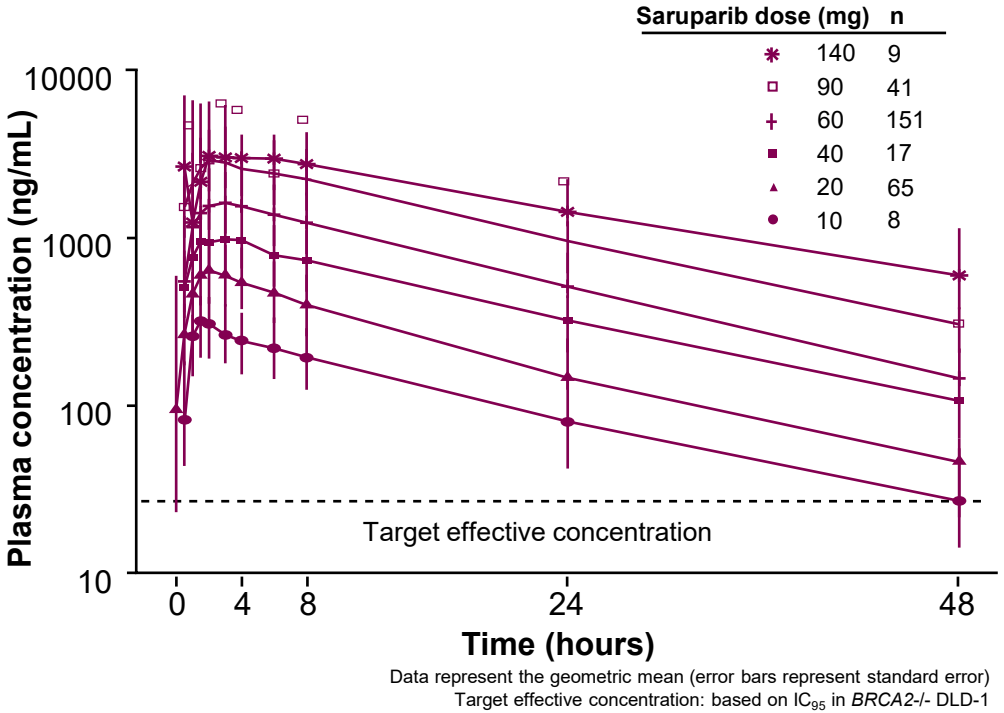
- Safety of saruparib was favorable despite a heavily pretreated patient population.

	Niraparib[1]		Talazoparib[2]		Rucaparib[3]		Olaparib[4]		Saruparib†	
Trial phase (number of patients who received PARP inhibitor therapy)	Phase 2 (N=289)		Phase 3 (N=286‡)		Phase 2 (N=115)		Phase 3 (N=205)		Phase 1/2a (N=141)	
Study tumor type(s)	Prostate		Breast		Prostate		Breast		Breast, ovarian, pancreatic, prostate	
Hemoglobin eligibility	≥9 g/dL		≥9 g/dL		≥10 g/dL		≥10 g/dL		≥9 g/dL	
Number of prior chemotherapy lines	Prior taxane		0–2		Prior taxane		0–2		Not limited§	
Selective for PARP1 vs PARP2	**No**		**No**		**No**		**No**		**Yes**	
Fold coverage over target effective concentration¶	**0.36**		**0.50**		**2.44**		**3.21**		**31.71**	
Gastrointestinal toxicity (%), any Grade										
Nausea	58		49		52		58		34	
Vomiting	38		25		22		32		11	
Hematological toxicity (%) by Grade	**≥3**	**All**	**≥3**	**All**	**≥3**	**All**	**≥3**	**All**	**≥3**	All
Anemia‖	33	54	39	53	25	44	16	40	15	36
Neutropenia‖	10	19	21	35	7	10	9	27	11	23
Thrombocytopenia‖	16	34	15	27	10	25	NR	NR	6	23
Tolerability (%)										
Dose reduction due to any TEAE	44		53		41		25		16	
Discontinuation due to any TEAE	14		6		8		5		5	

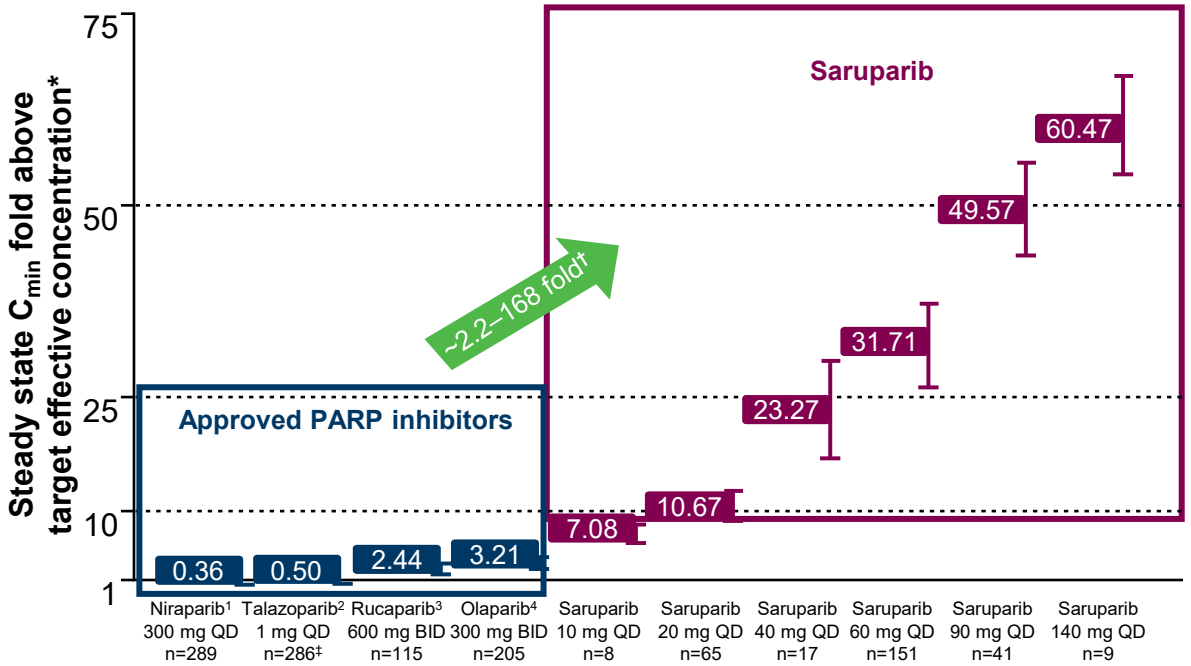
[1]Smith MR, et al. *Lancet Oncol* 2022;23:362–73;
[2]Litton JK, et al. *NEJM* 2018;379:753–63;
[3]Abida W, et al. *J Clin Oncol* 2020;38:3763–72;
[4]Robson ME, et al. *Ann Oncol* 2019;30:558–66

Yap et al, AACR 2024

Saruparib once-daily dosing shows linear PK and achieves higher pharmacological target coverage versus approved PARP inhibitors



Data represent the geometric mean (error bars represent standard error)
Target effective concentration: based on IC_{95} in *BRCA2-/-* DLD-1



Data represent the mean (error bars represent 95% CI)
Target effective concentration: based on IC95 in *BRCA2-/-* DLD-1

- PK was linear with a dose-proportional increase in exposure across 10–140 mg dose cohorts.
- Saruparib had an optimal pharmacological profile with once-daily dosing and no food interaction.
  - Quick onset (T_{max} 1.03–1.95 hours) with mean terminal elimination half-life of 13.81–17.64 hours.

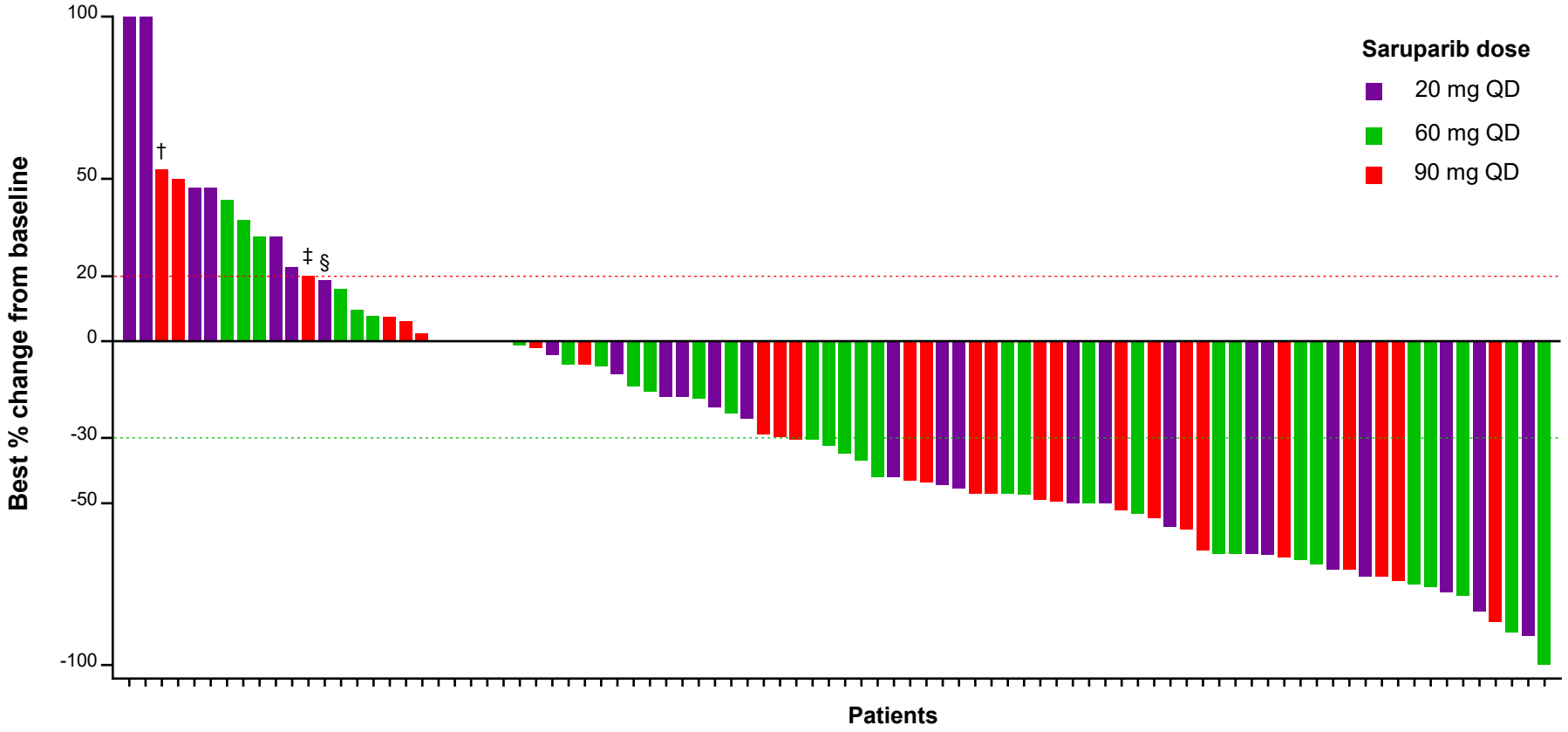
Data cutoff for PETRA was 2 September 2023. *Calculated as free $C_{min,ss}/IC_{95}$. †Ratio of saruparib fold coverage relative to PARP inhibitors (niraparib, talazoparib, rucaparib and olaparib) at approved doses. ‡Number of patients in the safety population.
BID, twice daily; *BRCA-/-* DLD-1, breast cancer gene-deficient colorectal cancer cell line; CI, confidence interval; $C_{min,ss}$, steady state trough concentration; IC_{95}, 95% inhibitory concentration; PARP, poly adenosine diphosphate-ribose (ADP-ribose) polymerase; PK, pharmacokinetics; QD, once daily; T_{max}, time to peak drug concentration

[1]Smith MR, et al. *Lancet Oncol* 2022;23:362–73;
[2]Litton JK, et al. *NEJM* 2018;379:753–63;
[3]Abida W, et al. *J Clin Oncol* 2020;38:3763–72;
[4]Robson ME, et al. *Ann Oncol* 2019;30:558–66

Tumor responses observed across saruparib doses in heavily pretreated HER2– breast cancer (Part B1)*

Key eligibility criteria:

- No limit on prior chemotherapy lines
- *BRCA1/2*m, *PALB2*m, or *RADC51C/D*m



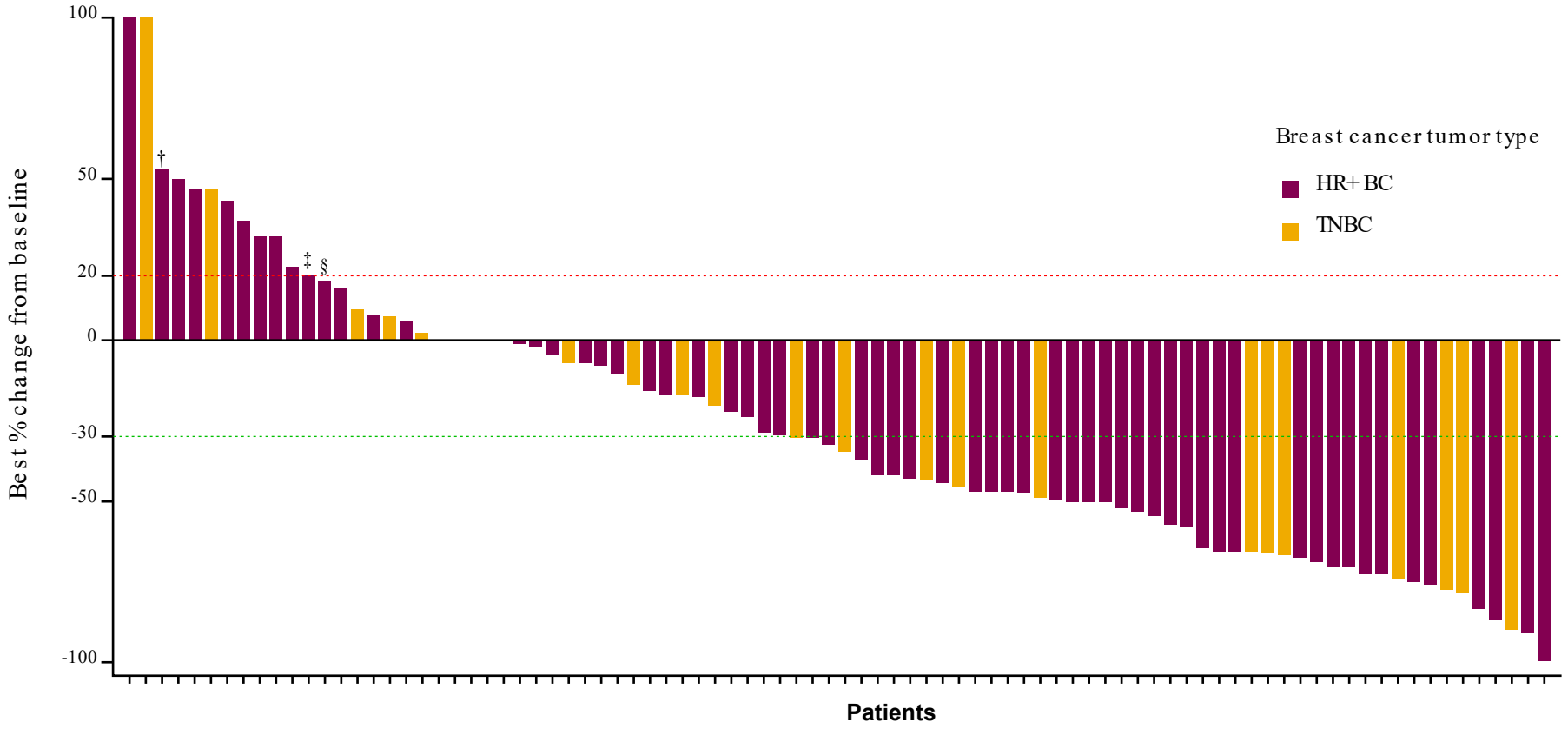
Response based on RECIST version 1.1 (response and progression defined as -30% and +20% change from baseline, respectively).
*Interim analysis set: defined as all dosed patients who had measurable disease at baseline and who received first dose of saruparib at least 17 weeks prior to data cutoff (2 June 2023). †Patient had *BRCA2*m by local test but unconfirmed by central assessment. ‡Imputed value for best percent change from baseline in target lesion size; patient died due to progression prior to first RECIST scan. §Patient had *CHEK2*m but no other eligible mutation.
*BRCA1/2*m, breast cancer gene 1/2 mutation; *CHEK2*m, checkpoint kinase 2 mutation; HER2–, human epidermal growth factor receptor 2 negative; *PALB2*m, partner and localizer of *BRCA2* mutation; QD, once daily; *RAD51C/D*m, RAD51 recombinase homolog C/D mutation; RECIST, Response Evaluation Criteria in Solid Tumors

Yap et al, AACR 2024

Tumor responses observed in both HR+ and triple-negative breast cancer (Part B1)*

Key eligibility criteria:

- No limit on prior chemotherapy lines
- *BRCA1/2*m, *PALB2*m, or *RADC51C/D*m



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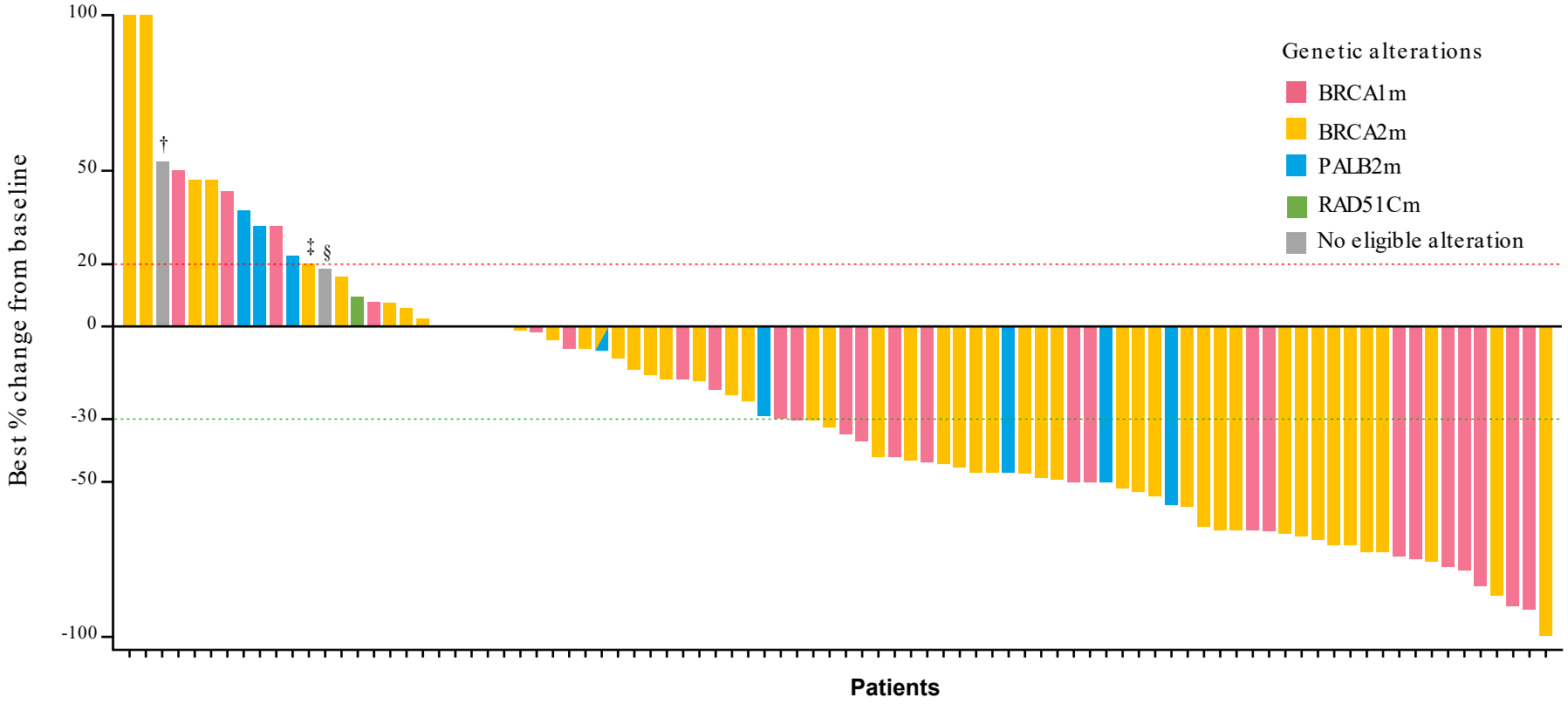
*BRCA1/2*m, breast cancer gene 1/2 mutation; *CHEK2*m, checkpoint kinase 2 mutation; HR+ BC, hormone receptor positive breast cancer; *PALB2*m, partner and localizer of *BRCA2* mutation; *RAD51C/D*m, RAD51 recombinase homolog C/D mutation; RECIST, Response Evaluation Criteria in Solid Tumors; TNBC, triple-negative breast cancer

Yap et al, AACR 2024

Tumor responses observed in mutation-defined subgroups in heavily pretreated HER2– breast cancer (Part B1)*

Key eligibility criteria:

- No limit on prior chemotherapy lines
- *BRCA1/2*m, *PALB2*m, or *RADC51C/D*m



Response based on RECIST version 1.1 (response and progression defined as -30% and +20% change from baseline, respectively).
*Interim analysis set: defined as all dosed patients who had measurable disease at baseline and who received first dose of saruparib at least 17 weeks prior to data cutoff (2 June 2023). †Patient had *BRCA2*m by local test but unconfirmed by central assessment. ‡Imputed value for best percent change from baseline in target lesion size; patient died due to progression prior to first RECIST scan. §Patient had *CHEK2*m but no other eligible mutation.
*BRCA1/2*m, breast cancer gene 1/2 mutation; *CHEK2*m, checkpoint kinase 2 mutation; HER2–, human epidermal growth factor receptor 2 negative; *PALB2*m, partner and localizer of *BRCA2* mutation; QD, once daily; *RAD51C/D*m, RAD51 recombinase homolog C/D mutation; RECIST, Response Evaluation Criteria in Solid Tumors

Yap et al, AACR 2024

Efficacy of saruparib 60 mg QD shows improved benefit (ORR, DoR, and PFS) over saruparib 20 mg QD in patients with HER2– breast cancer (Part B1)

	Part B1*		
	Saruparib 20 mg QD (n=28)	Saruparib 60 mg QD (n=31)	Saruparib 90 mg QD (n=30)
Objective response rate (80% CI)†‡	35.7 (23.5–49.6)	48.4 (35.7–61.3)	46.7 (33.8–59.9)
Median DoR, months (80% CI)§¶	6.1 (3.8–7.4)	7.3 (5.6–7.6)	5.6 (5.6–7.4)
Median TTR from first dose, months (80% CI)¶	1.9 (1.7–1.9)	3.5 (1.9–3.6)	1.8 (1.8–1.9)
PFS			
Number of events, n/N (%)	28/28 (100)	22/31 (71.0)	18/31 (58.1)
Median PFS, months (80% CI)¶	4.6 (3.7–5.4)	9.1 (5.7–9.3)	NA
Median follow-up in censored subjects, months (range)	NE	9.5 (9.0–14.9)	NA

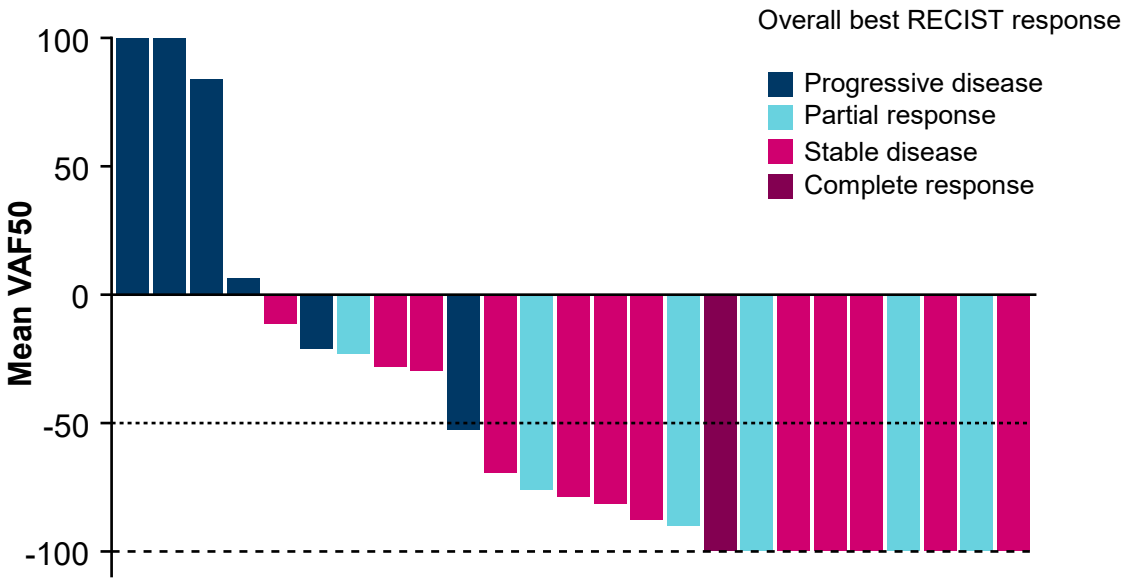
- The saruparib 60 mg QD B1 cohort is still immature: 6 patients remain on treatment at DCO and data collection for PFS is ongoing.
- Patients in the B1 saruparib 90 mg QD cohort had shorter follow-up and data are immature. However, current data do not show improved ORR and DoR at 90 mg QD.
- **Saruparib 60 mg QD was established as the RP2D.**

Yap et al, AACR 2024

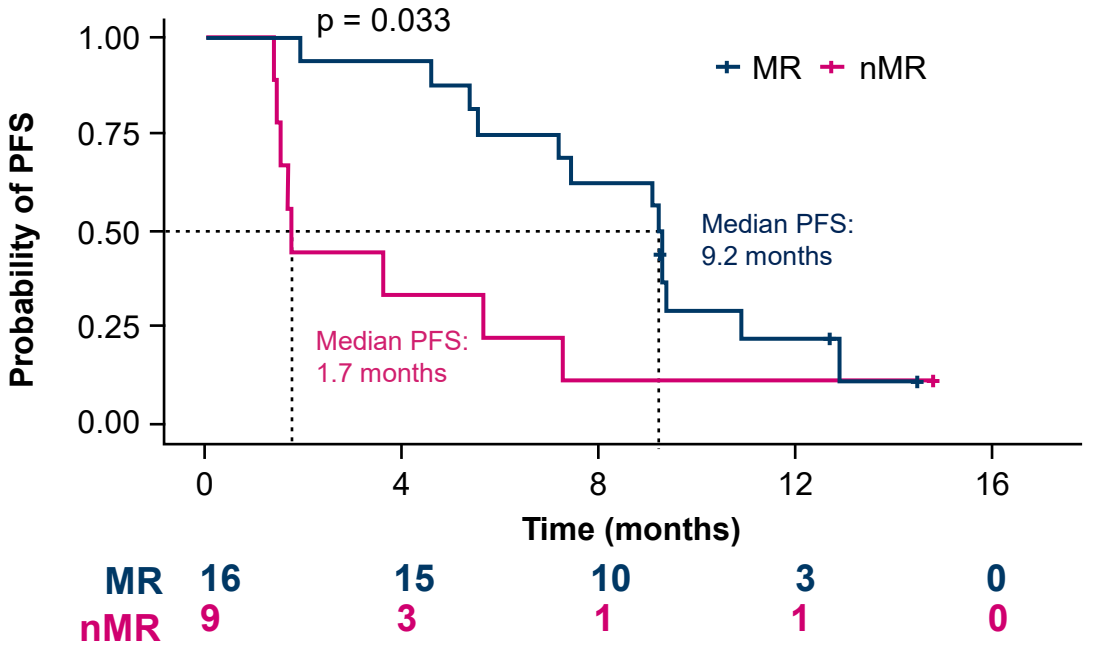
Exploratory analysis of ctDNA indicates an association with PFS in patients treated with saruparib (B1 60 mg cohort)

- Molecular responses (~50% or greater decrease in mean VAF) were observed in 16/25 patients (64%).
- ctDNA molecular responses correlate with improved PFS (p=0.033).
- ctDNA kinetics is a promising early treatment response biomarker in patients with breast cancer.

ctDNA molecular responses in patients treated in B1 60 mg cohort



Association of ctDNA molecular responses with PFS in B1 60 mg cohort



The detection limit was ≥0.3% mean VAF for response-evaluable patients. MR was defined as either complete response (reduction to below detection limit) or partial response (>50% reduction but residual ctDNA above detection limit). nMR was defined as <50% reduction or induction.

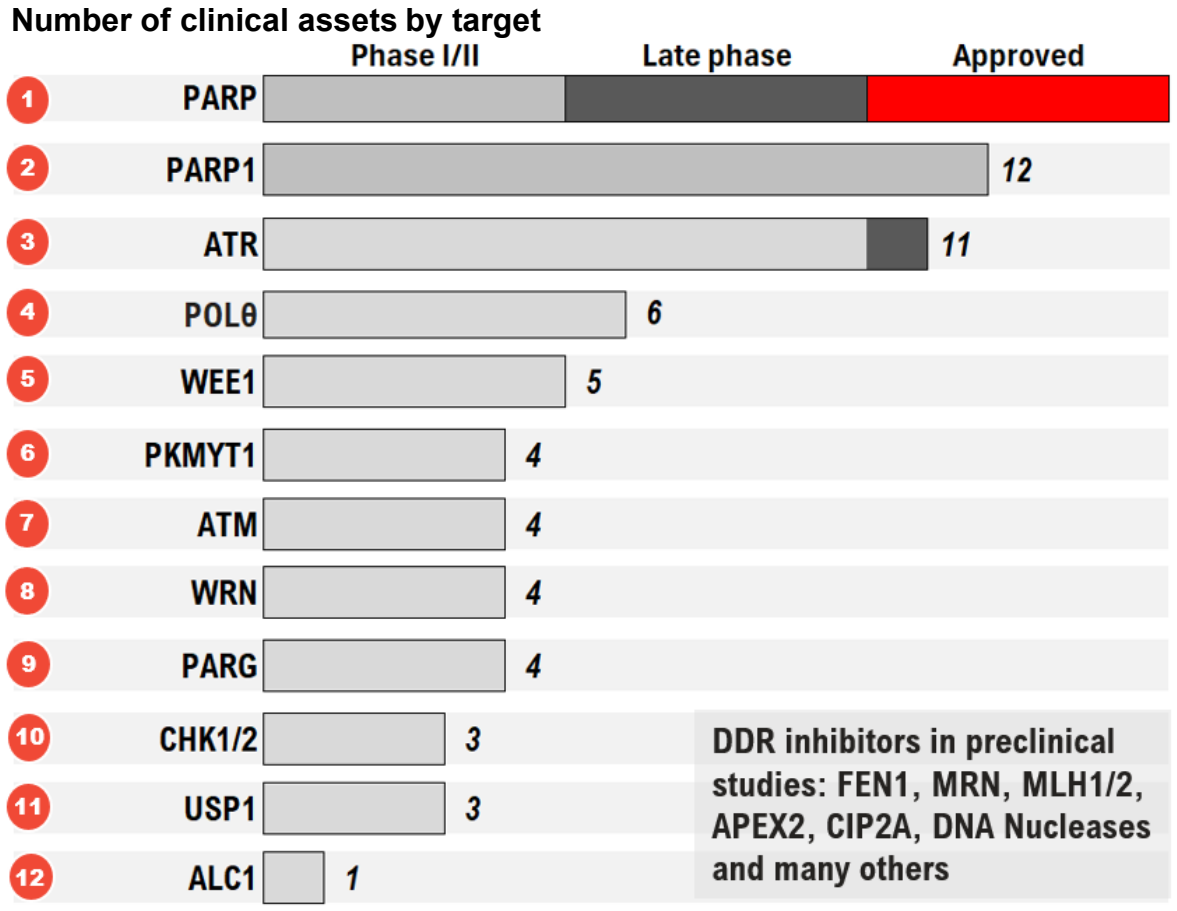
ctDNA, circulating tumor DNA; MR, molecular response; nMR, no molecular response; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; VAF, variant allele frequency; VAF50, variant allele frequency 50%

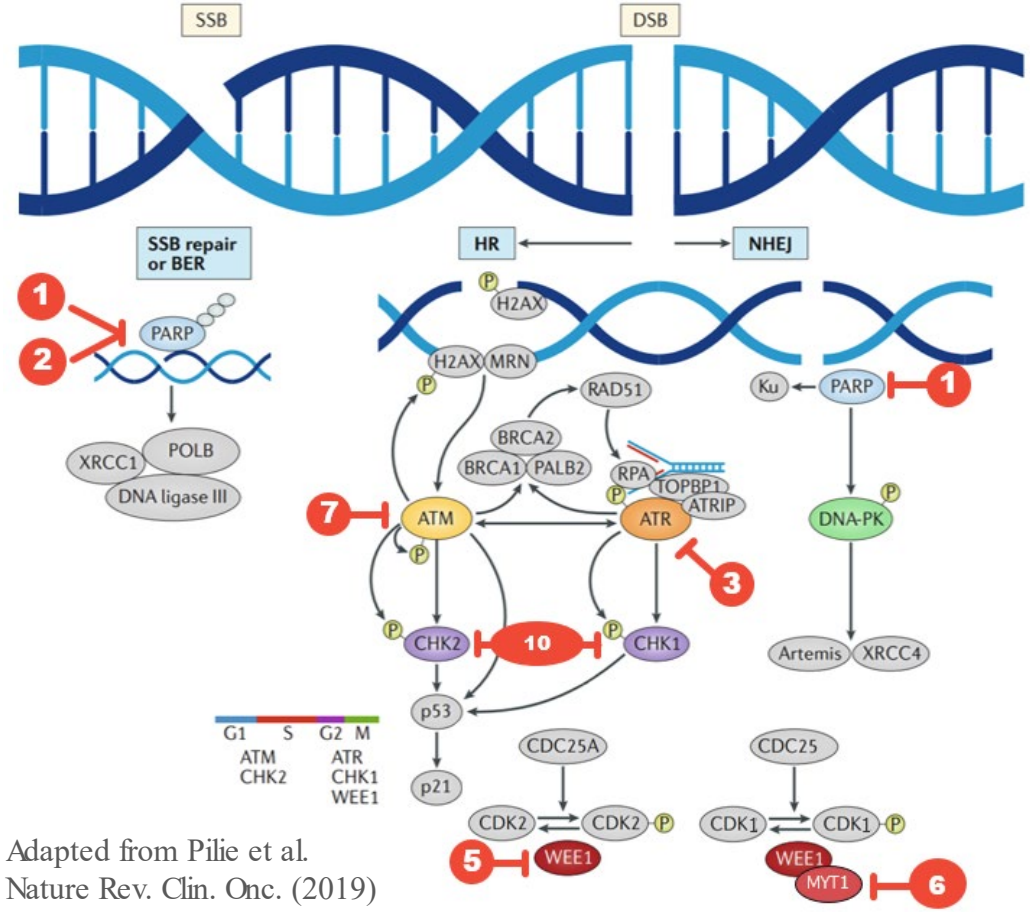
Overview

- BRCA1/2 mutated cancers and PARP1 inhibitors
- **MSI cancers and Werner Helicase inhibitors**
- MTAP loss of function and PRMT5/MAT2A inhibitors
- CCNE1 amplified cancers and PKMYT1 inhibitor combinations

Beyond PARP: Multiple novel Inhibitors across the DDR landscape

- The DNA damage response (DDR) therapeutic landscape has rapidly expanded beyond PARP inhibitors
- Discovery of novel, precision targets enabled by cancer genome sequencing and CRISPR
- Biomarker-driven patient selection to guide clinical development and rational combinations



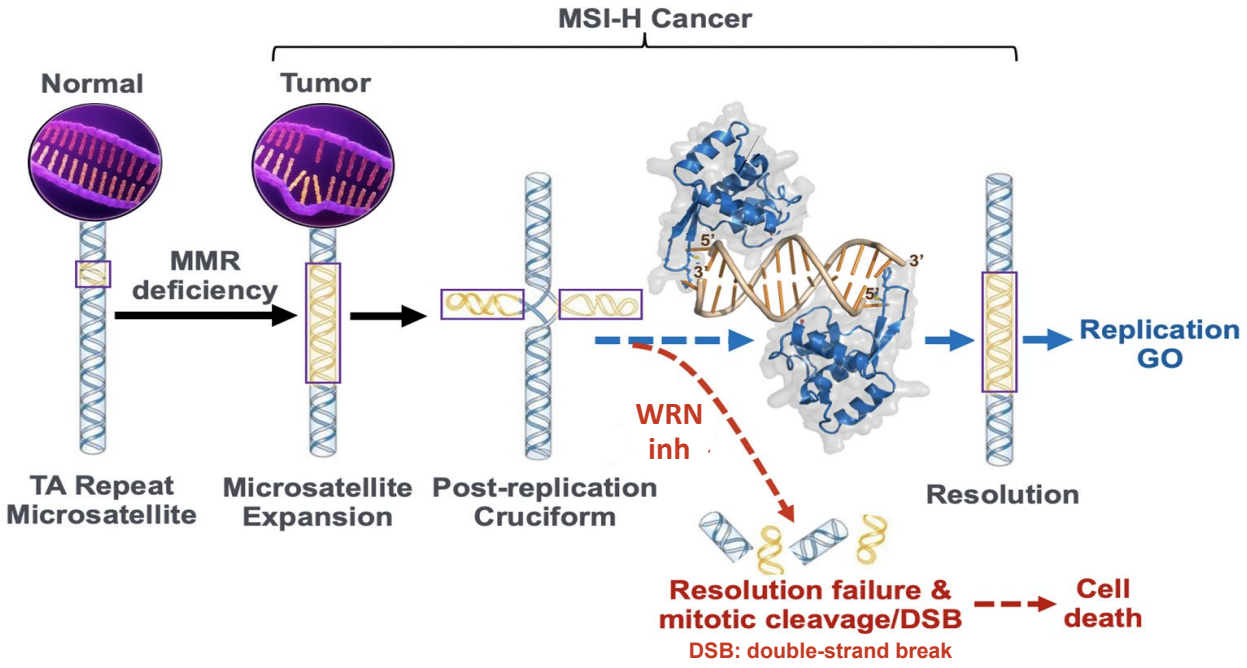


Adapted from Pilie et al. Nature Rev. Clin. Onc. (2019)

WRN inhibitor in patients with Microsatellite Instable (MSI) and/or Mismatch Repair Deficient (dMMR)

- WRN is a helicase enzyme that belongs to the RECQ family and plays a crucial role in the maintenance of genome integrity.
- WRN serves as a DNA caretaker enzyme, playing a critical role in unwinding non-canonical secondary DNA structures formed in response to DNA damage or during the repair processes.

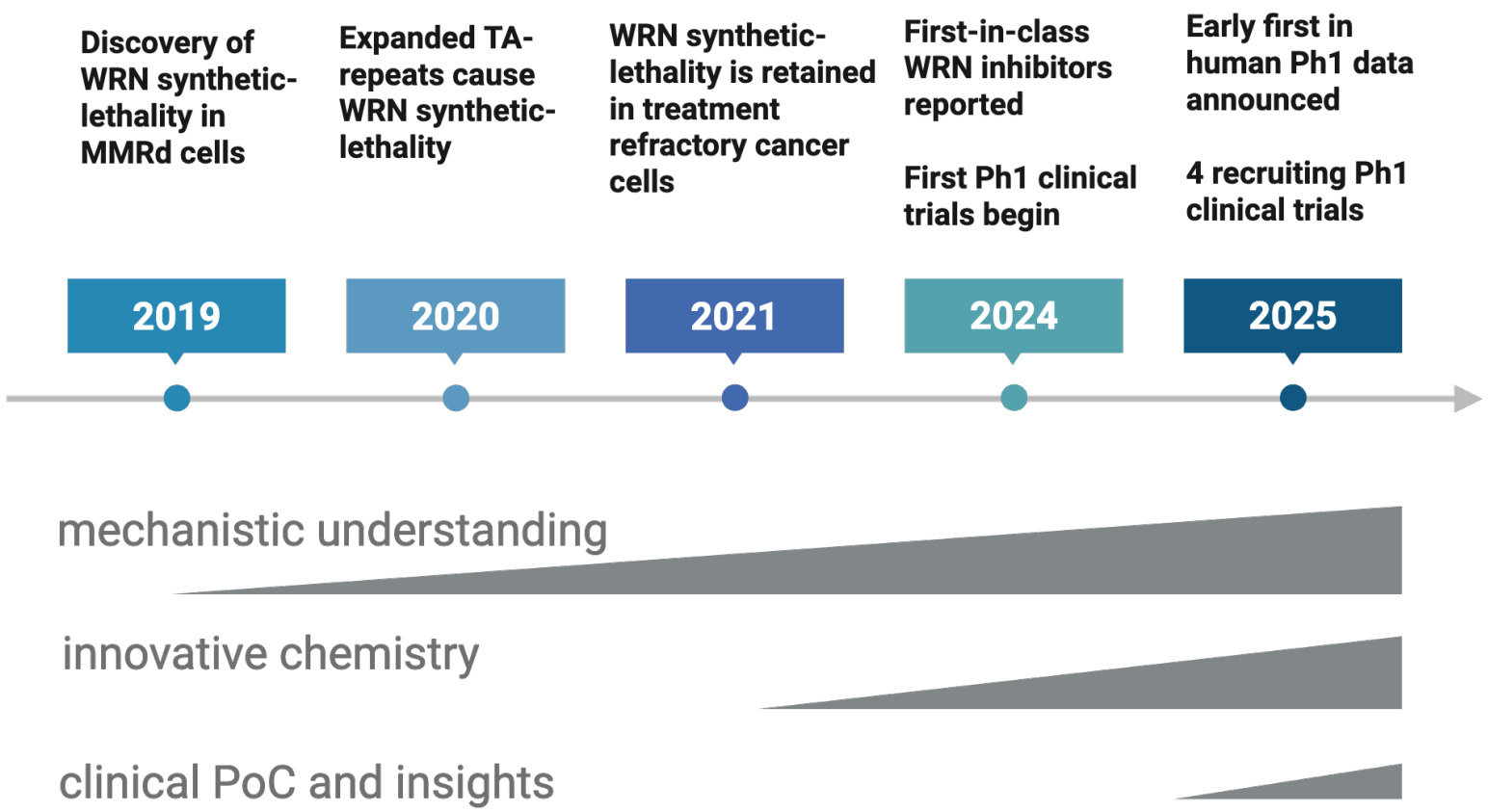
WRN inhibition represents a synthetic lethal vulnerability in cancers with microsatellite instability (MSI)



Kikuchi S & Pettazzoni P, AACR Annual meeting, 2024
Baltgalvis KA et al, Nature, 2024

Behan FM et al.,. Nature, 2019
Chan EM et al., Nature, 2019

Timeline from discovery to clinical data



Garnett et al, AACR (2025)

RO7589831: First In Class covalent WRN inhibitor

nature

Article | Published: 24 April 2024

Chemoproteomic discovery of a covalent allosteric inhibitor of WRN helicase

Kristen A. Baltgalvis, Kelsey N. Lamb, Kent T. Symons, Chu-Chiao Wu, Melissa A. Hoffman, Aaron N. Snead, Xiaodan Song, Thomas Glaza, Shota Kikuchi, Jason C. Green, Donald C. Rogness, Betty Lam, Maria E. Rodriguez-Aguirre, David R. Woody, Christie L. Eissler, Socorro Rodiles, Seth M. Negron, Steffen M. Bernard, Eileen Tran, Jonathan Pollock, Ali Tabatabaei, Victor Contreras, Heather N. Williams, Martha K. Pastuszka, ... Todd M. Kinsella

Drug: RG6457/RO7589831
Clinical trial ID: NCT06004245
Monotherapy and combo with ICI

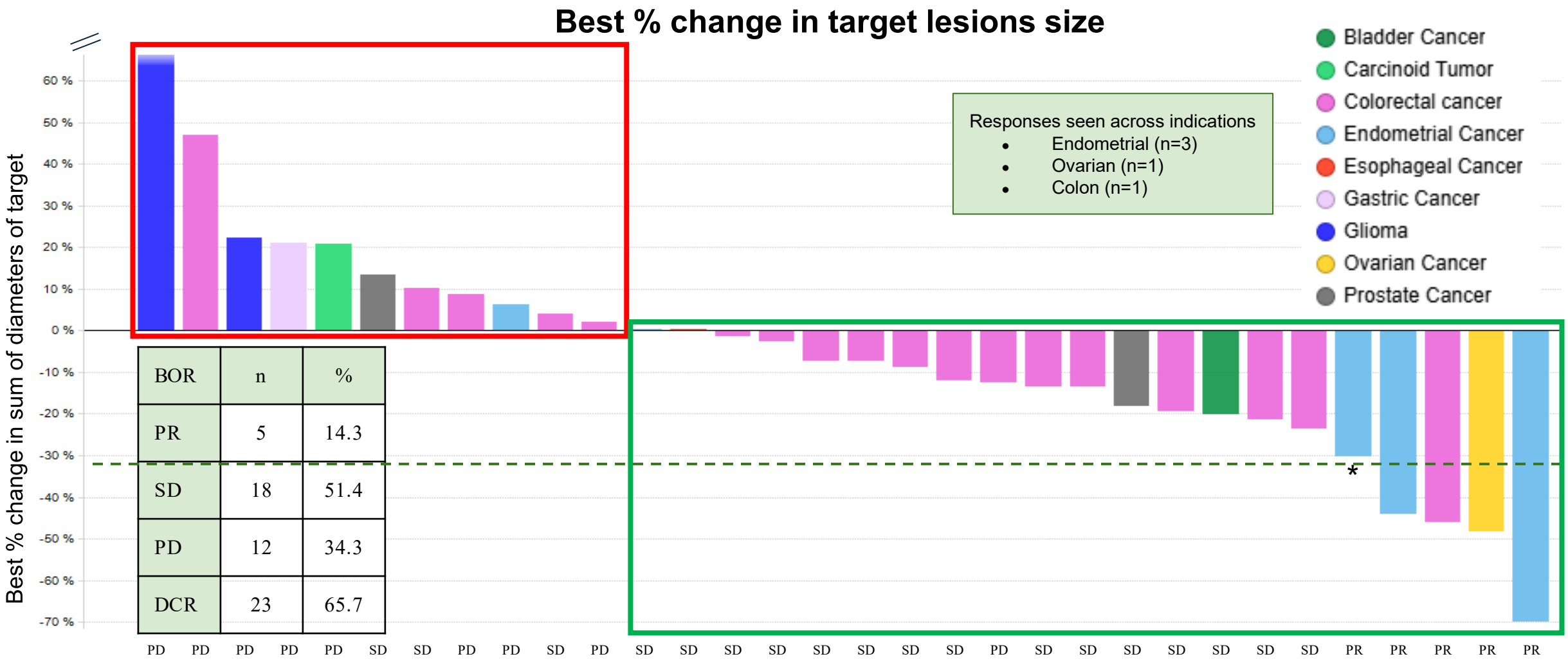
Roche

Kikuchi S & Pettazzoni P, AACR Annual meeting, 2024
Baltgalvis KA et al. Nature, 2024

WRN inhibitor landscape

WRN inhibitor	Sponsor	Phase	Route
IDE275 (GSK4418959)	IDEAYA Biosciences/GSK	I	PO
HRO761	Novartis	I	PO
RO7589831 (VVD-133214)	Hoffmann-La Roche (Vividion Therapeutics)	I	PO
NDI-219216	Nimbus Therapeutics	I	PO

RO7589831 well tolerated with responses in post-ICI MSI patients across different cancer types



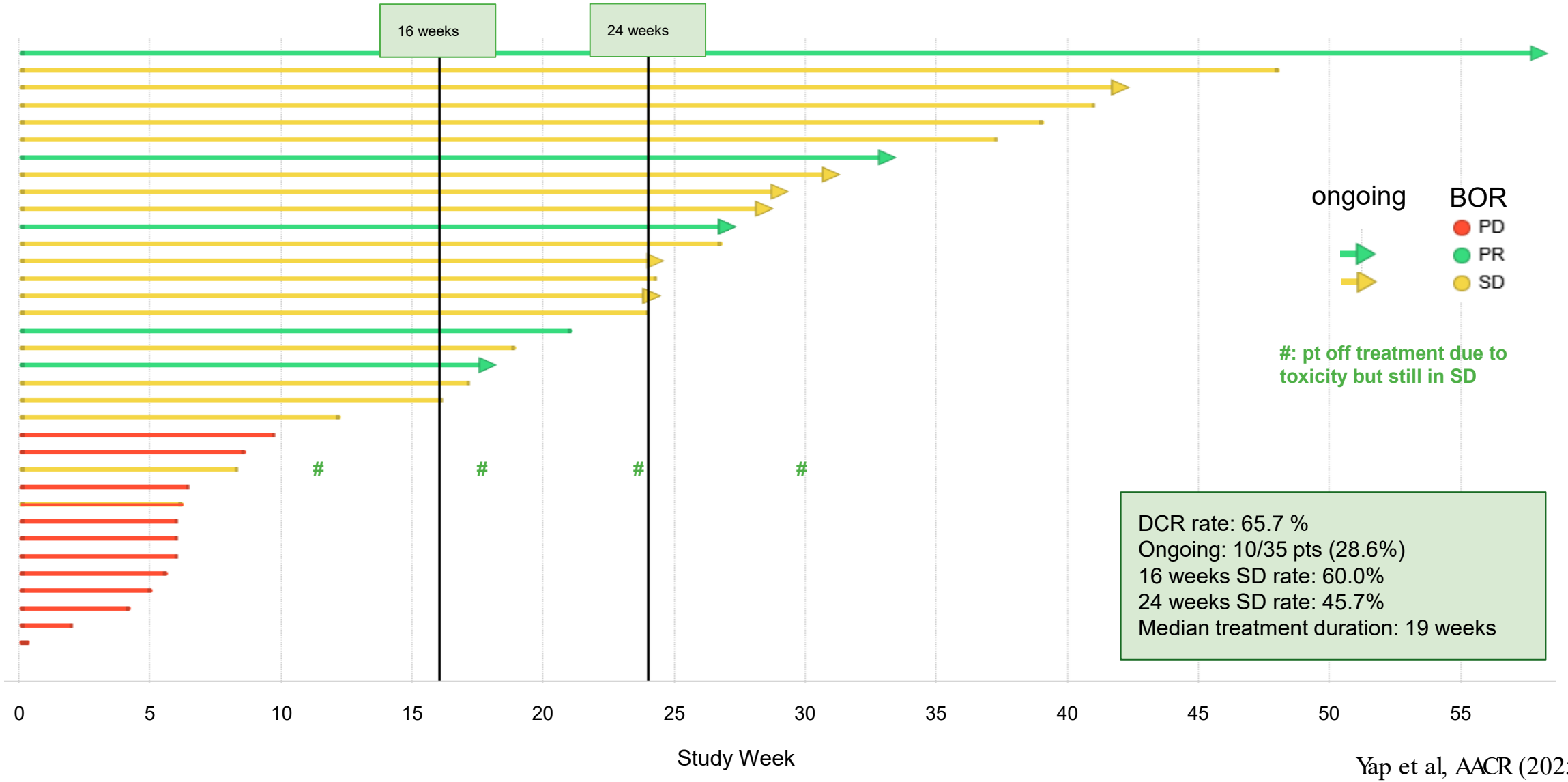
BOR	n	%
PR	5	14.3
SD	18	51.4
PD	12	34.3
DCR	23	65.7

*3 PD pts are not displayed in the plot due to non-evaluable target lesions

*unconfirmed PR, ongoing

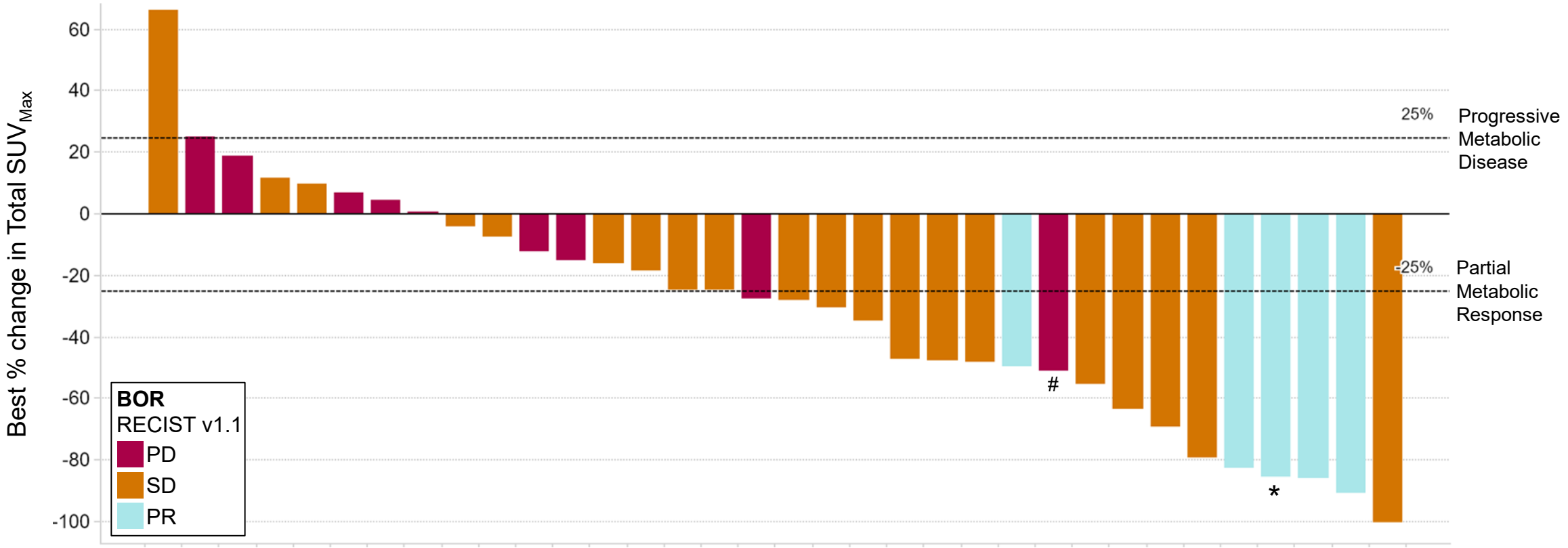
Yap et al, AACR (2025)

Radiological responses or durable disease stabilization in majority of post-ICI MSI patients



Yap et al, AACR (2025)

FDG-PET scans show metabolic responses in 50% of MSI patients across all dose levels

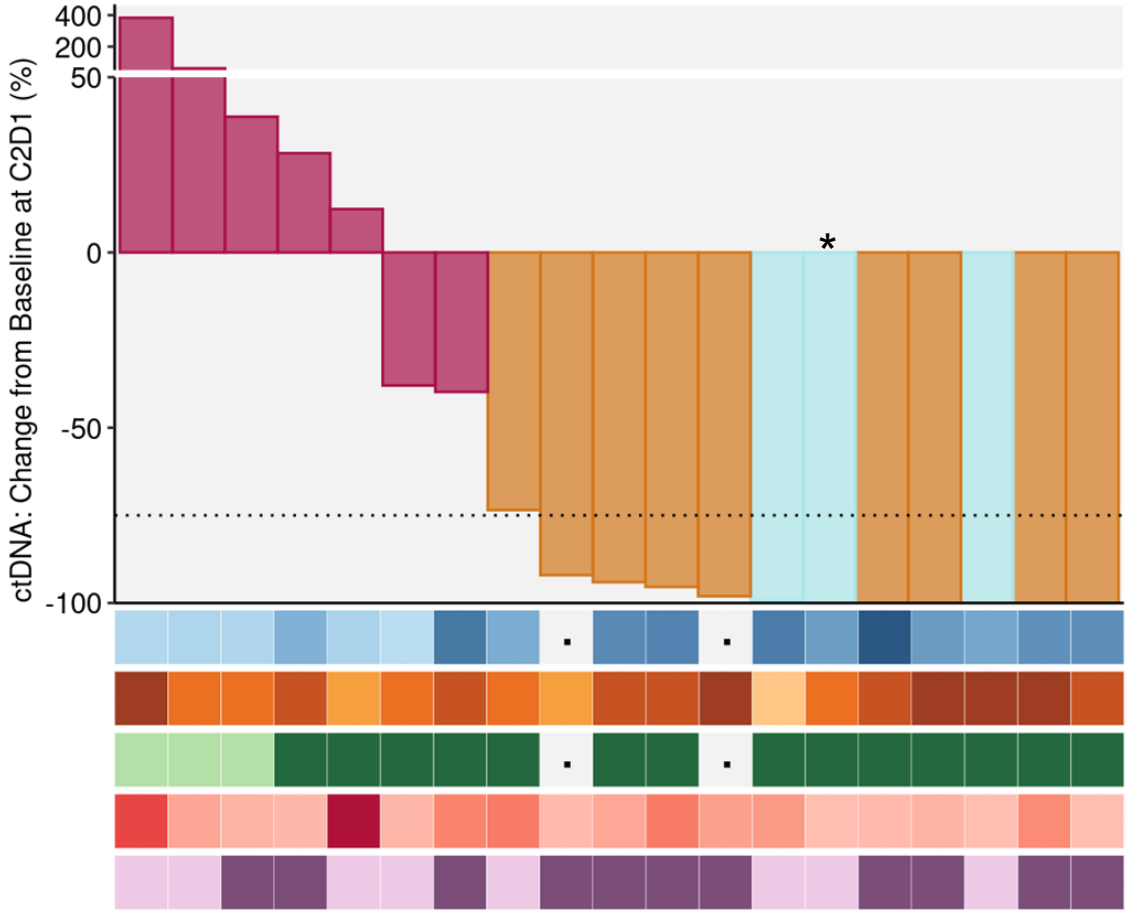


- Reduction of metabolic activity was observed in 76% (26/34) of MSI patients across all dose levels
- Early metabolic responses during treatment are associated with RECIST PR and durable RECIST SD (median duration >28 weeks) (p-value = 0.001**)

*unconfirmed PR, ongoing
Progressive metabolic disease (new lesion)
** Test for association between Partial Metabolic Response and either PR or treatment duration > median

Yap et al, AACR (2025)

ctDNA response across different tumor types and doses in patients achieving PR or SD

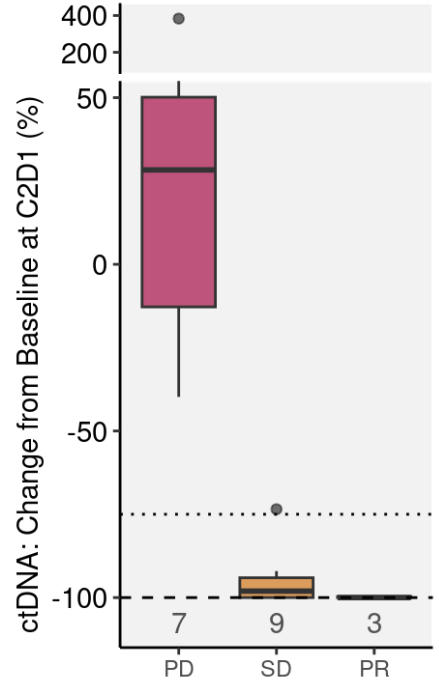


BOR
RECIST v1.1
PD
SD
PR

*unconfirmed PR, ongoing

MS-score (%) 2 4 6
Daily Dose (mg) 150 300 600 1200 2000
TMB INTERMEDIATE HIGH
BL ctDNA conc(100#/ml) 1 2 3 4
Indication Other CRC

ctDNA available in 19/35 MSI pts



p-value 0.005

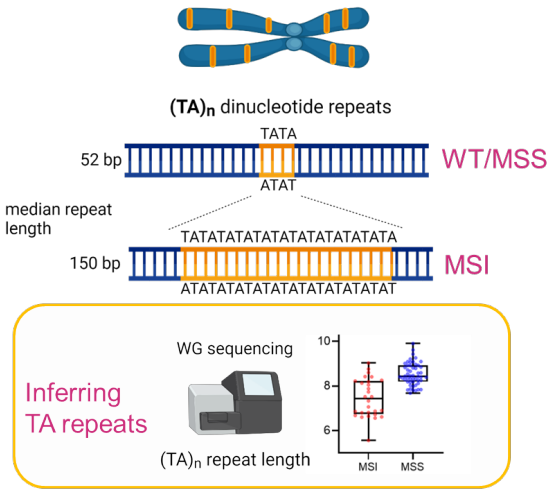
p value: disease control vs significant ctDNA change from baseline (<-75%)

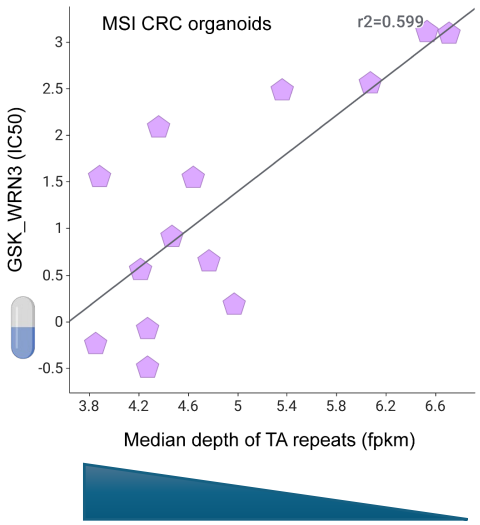
Early ctDNA reduction clearly delineates PR and SD from PD in ctDNA-evaluable patients

Yap et al, AACR (2025)

Challenge: Need improved understanding of predictive biomarkers and resistance to WRN inhibitors

TA repeats expansions as predictive biomarkers of response

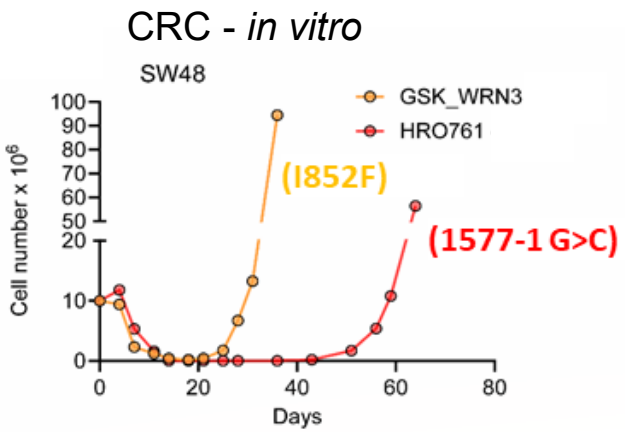


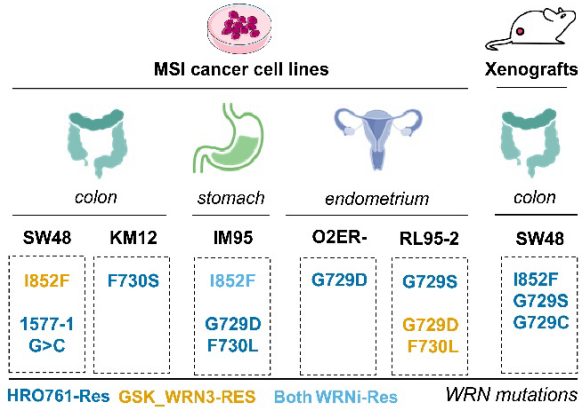


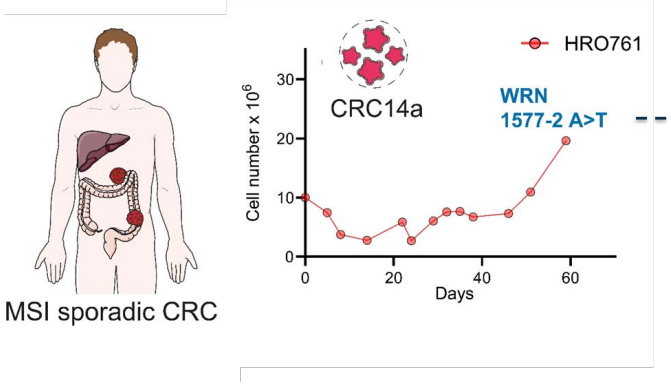
Expanded TA repeats

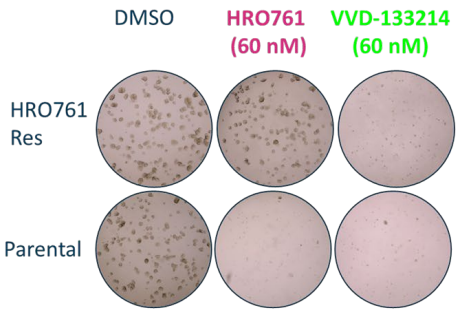
- WGS required
- Long-read needed (?)
- 5k+ regions to profile

On-target mutations confer resistance to WRN inhibitors in MSI Cancer Cells







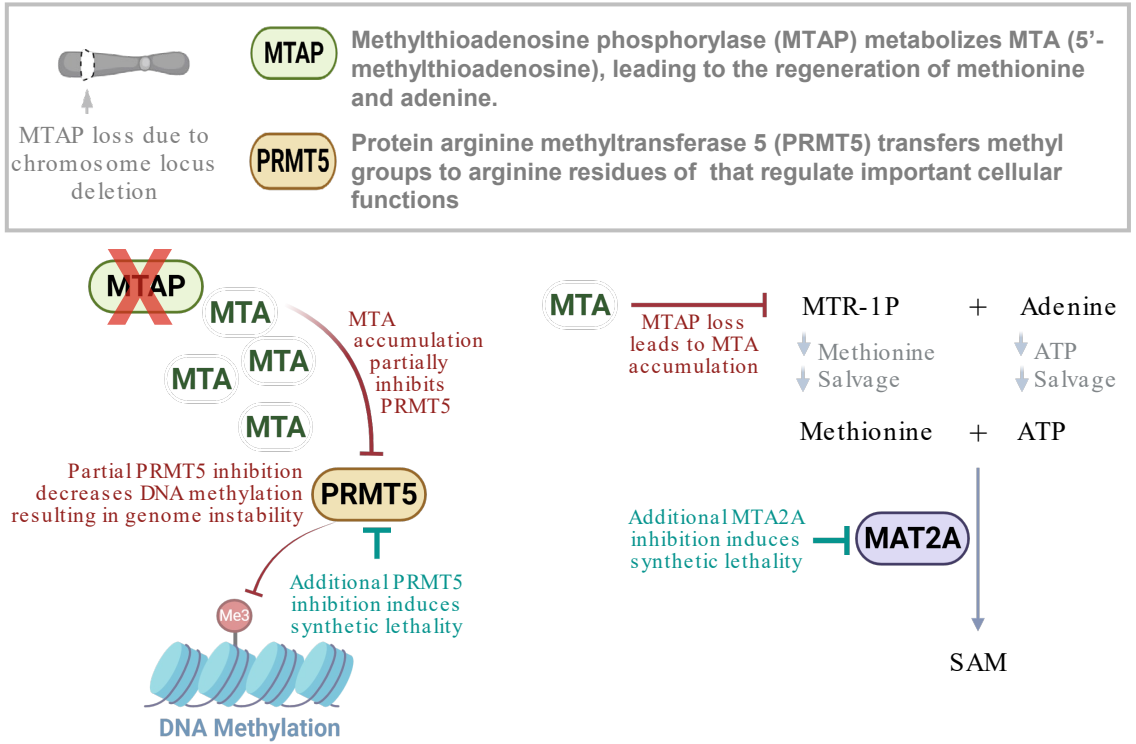


Picco et al., Cancer Discovery 2021 and 2024

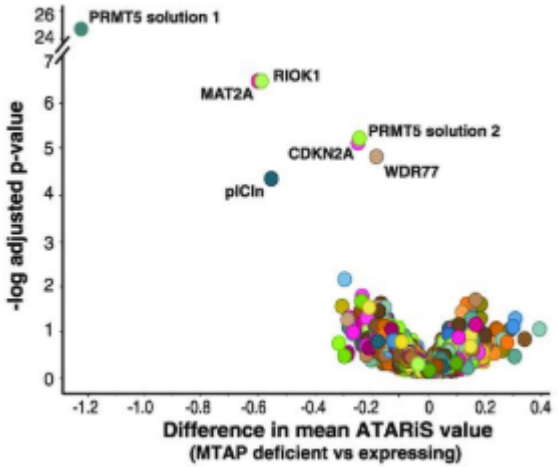
Overview

- BRCA1/2 mutated cancers and PARP1 inhibitors
- MSI cancers and Werner Helicase inhibitors
- **MTAP loss of function and PRMT5/MAT2A inhibitors**
- CCNE1 amplified cancers and PKMYT1 inhibitor combinations

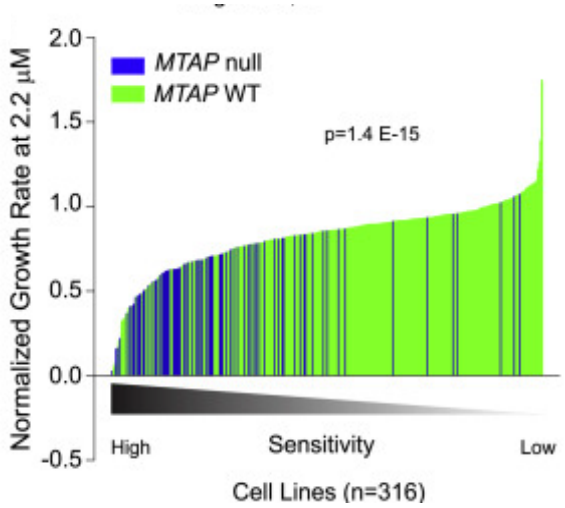
PRMT5 and MAT2A inhibition is synthetically lethal with MTAP loss



shRNA screen analysis of 390 cancer lines to selectively identify genes required for proliferation of MTAP loss cells



Cell lines with MTAP loss (null) are more sensitive to MAT2A inhibition than cell lines with wild-type MTAP



- MTAP is a key enzyme in the methionine salvage pathway that metabolizes MTA, a metabolite that partially inhibits PRMT5, a methyltransferase whose activity regulates several proliferative and biosynthetic processes, including expression of cell-cycle genes.
- Tumors with MTAP loss accumulate MTA, inducing partial inhibition of PRMT5. An MTA-cooperative PRMT5 inhibitor further suppresses PRMT5, targeting cancer cells with MTAP loss selectively.
- MTAP loss occurs frequently in glioblastoma, melanoma, pancreatic, urothelial/bladder cancer, and NSCLC.

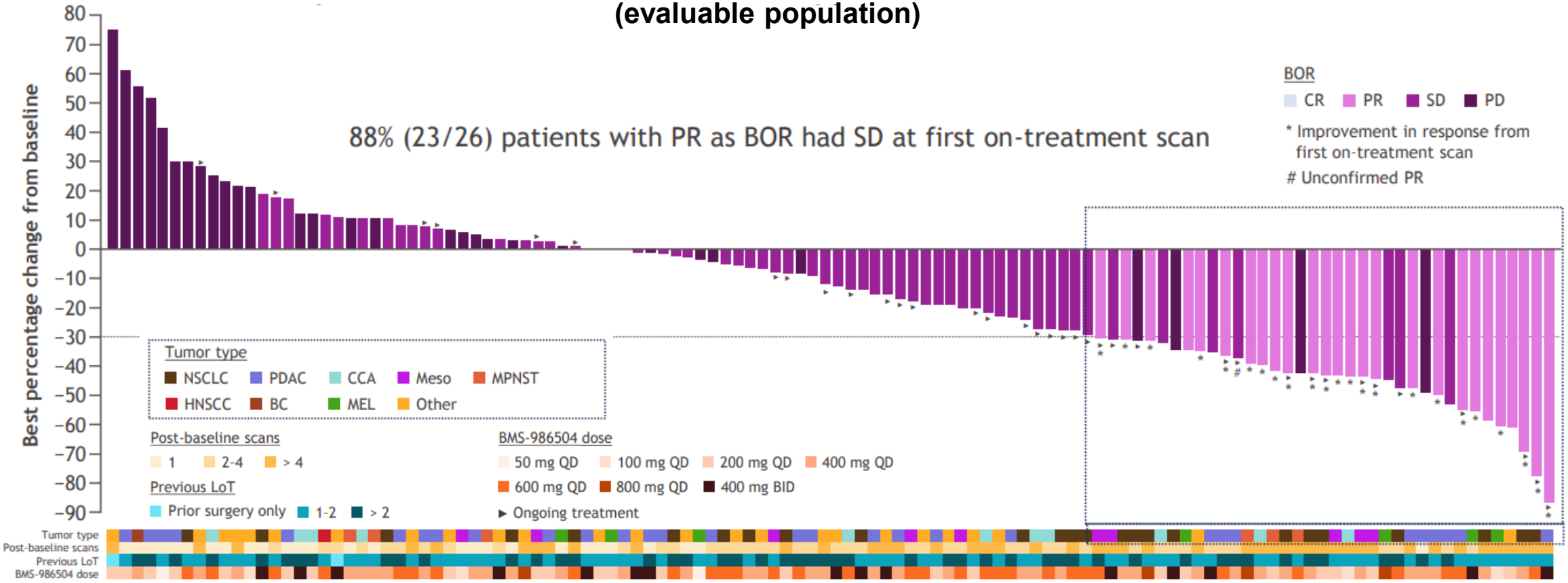
Kryukov, G.V., et. al., Science (2016); Briggs, K.J., et. al., Cancer Res (2021); Han, G., et. al., Nature (2021); Chang., et al., Immunology (2022); Kalev P., et al., Cancer Cell (2021)

PRMT5 inhibitor landscape

PRMT5 inhibitor	Sponsor	Phase	Route
AMG 193	Amgen Therapeutics	I	PO
MRTX1719	Mirati Therapeutics	I	PO
PRT811 + PRT543	Prelude Therapeutics	I	PO
TNG908	Tango Therapeutics	I	PO
JBI-778	Jubilant Therapeutics	I	PO
SKL-27969	SKLife Science	Preclinical	PO

MTAP loss as a therapeutic biomarker for PRMT5 inhibitors

Best percentage response of MTAP loss patients treated with MRTYX1719 (evaluable population)



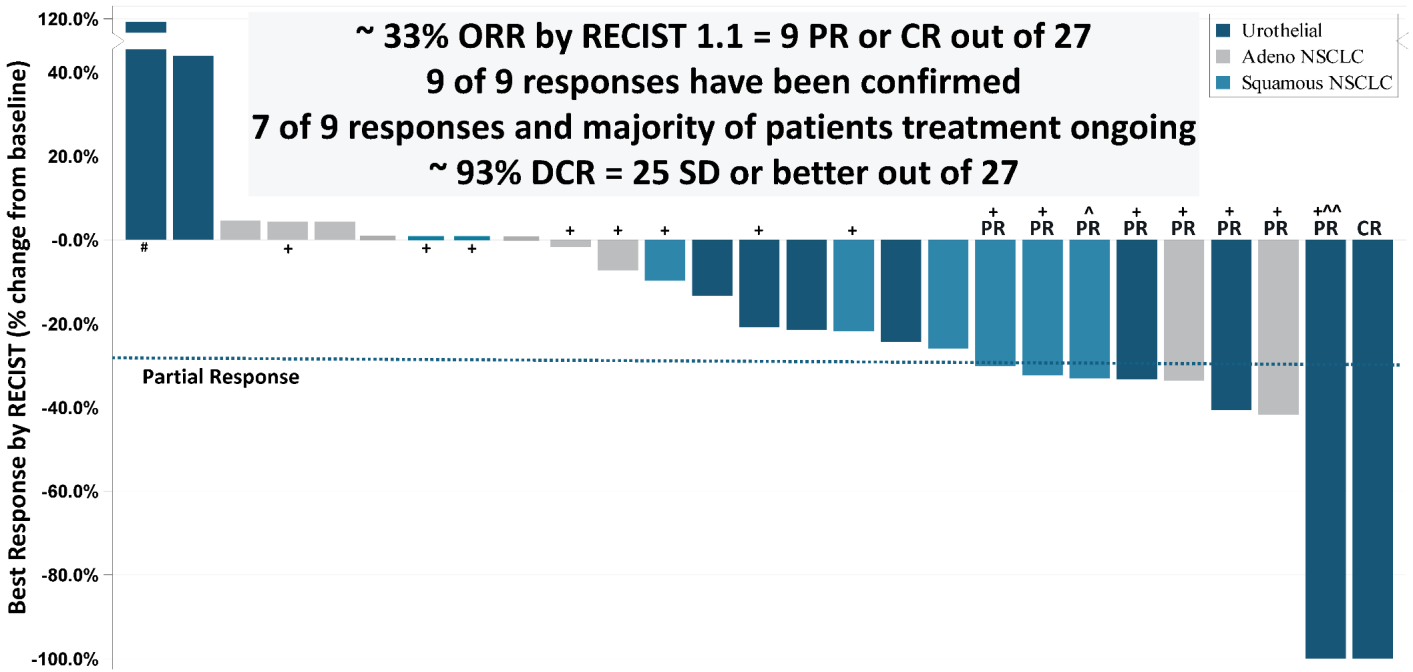
Rodon, J. et. al., ENA, (2024)

MAT2A inhibitor landscape

MAT2A inhibitor	Sponsor	Phase	Route
IDE397	Ideaya/GSK	I	PO
S095033 (AG-270)	Servier	I	PO
ISM3412	InSilico Medicine	I	PO
SYH2039	ZhongQi Pharmaceutical Technology	I	PO

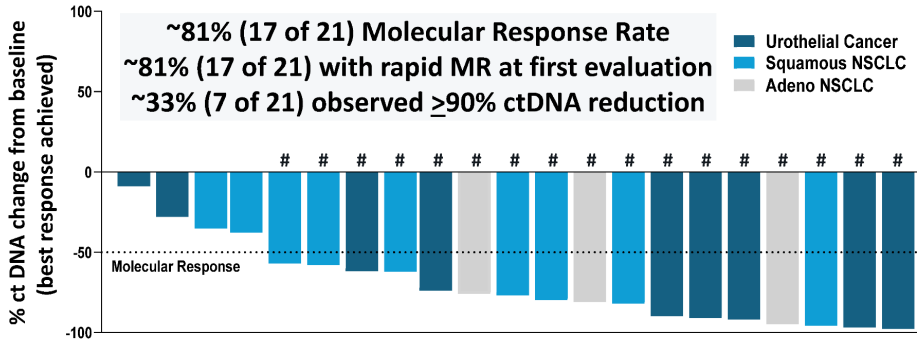
FIH trial of MAT2A inhibitor IDE397

Best Response by RECIST 1.1 at 30mg QD Phase 2 expansion dose*



Efficacy by RECIST 1.1*	
Evaluable Pts	27
Best Response, n (%)	
CR	1 (4)
PR	8 (30)
SD	16 (59)
PD	2 (7)
ORR, n (%)	9 (33)
Confirmed, n^^	9
ORR, n (%), by Tumor (n)	
Squam NSCLC (8)	3 (38)
Adeno NSCLC (9)	2 (22)
Urothelial (10)	4 (40)
DCR, n (%)	25 (93)

ctDNA Molecular Response (MR) Analysis (n=21)*, IDE397 30mg QD



Patient achieved MR at first evaluation
* Patients with available baseline and at least one on-treatment ctDNA sample

- ctDNA reduction was observed in all subjects with evaluable samples.
- Rapid molecular response was observed at the first evaluation in 81% of patients.
- ~33% of patients had a robust reduction of ctDNA (+90%)

Herzberg B, et. al., EORTC-NCI-AACR Symposium (ENA 2024)

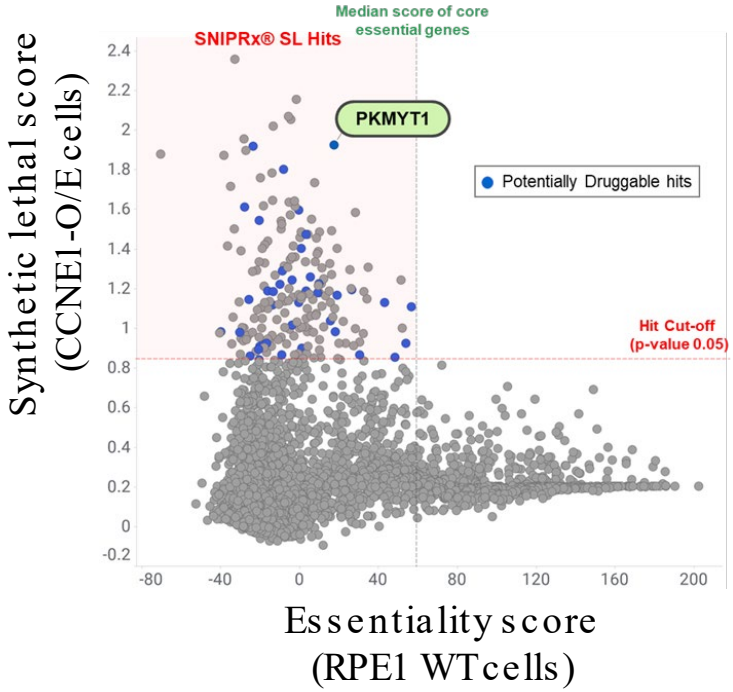
Overview

- BRCA1/2 mutated cancers and PARP1 inhibitors
- MSI cancers and Werner Helicase inhibitors
- MTAP loss of function and PRMT5/MAT2A inhibitors
- **CCNE1 amplified cancers and PKMYT1 inhibitor combinations**

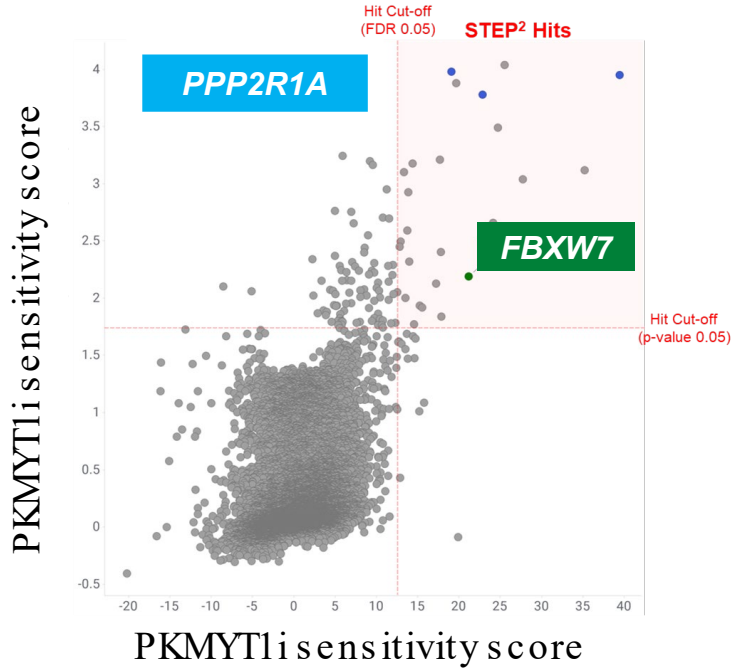
PKMYT1 was identified as a strong synthetic lethal partner to *CCNE1* amplification

Cyclin E overexpression (O/E) drives premature S-phase entry, overloads the DNA replication machinery, resulting in genome instability

Genome-wide CRISPR-Cas9 screen



Chemogenomic screen then identified additional novel sensitizers to PKMYT1 inhibition



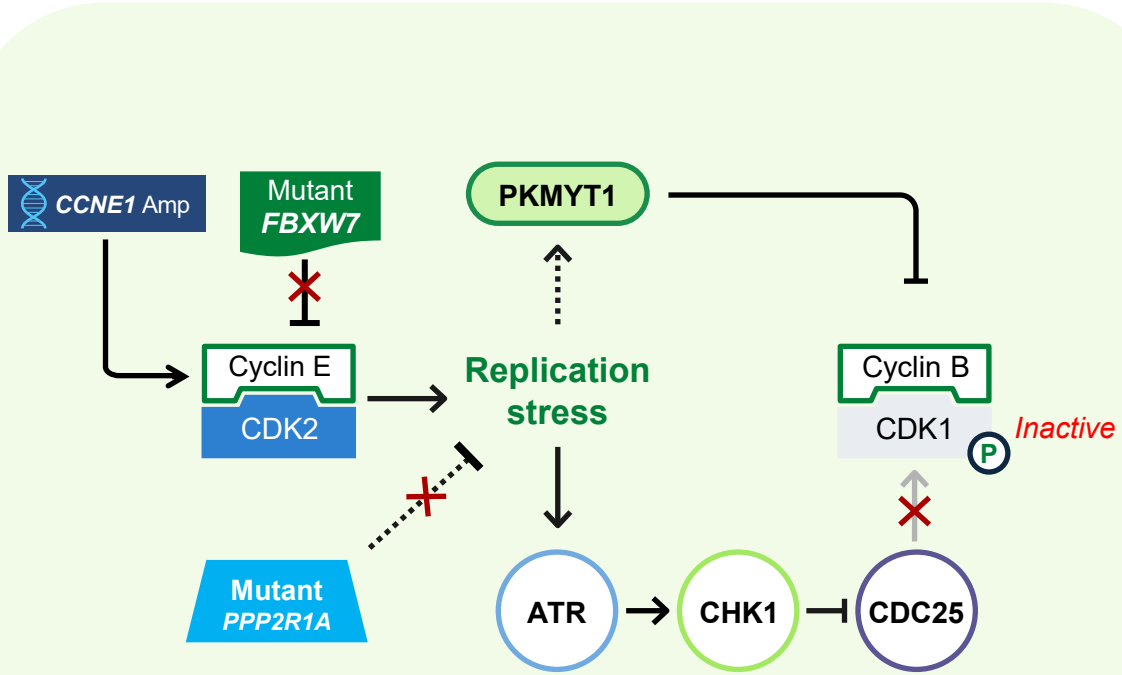
FBXW7 — Inactivating mutations in *FBXW7*, E3 ubiquitin ligase, increase cyclin E levels and replication stress.

PPP2R1A — Hotspot inactivating mutations in PP2A phosphatase increase replication stress.

Challenge: PKMYT1 inhibition through lunresertib monotherapy showed TGI but not tumor regression preclinically and limited clinical activity

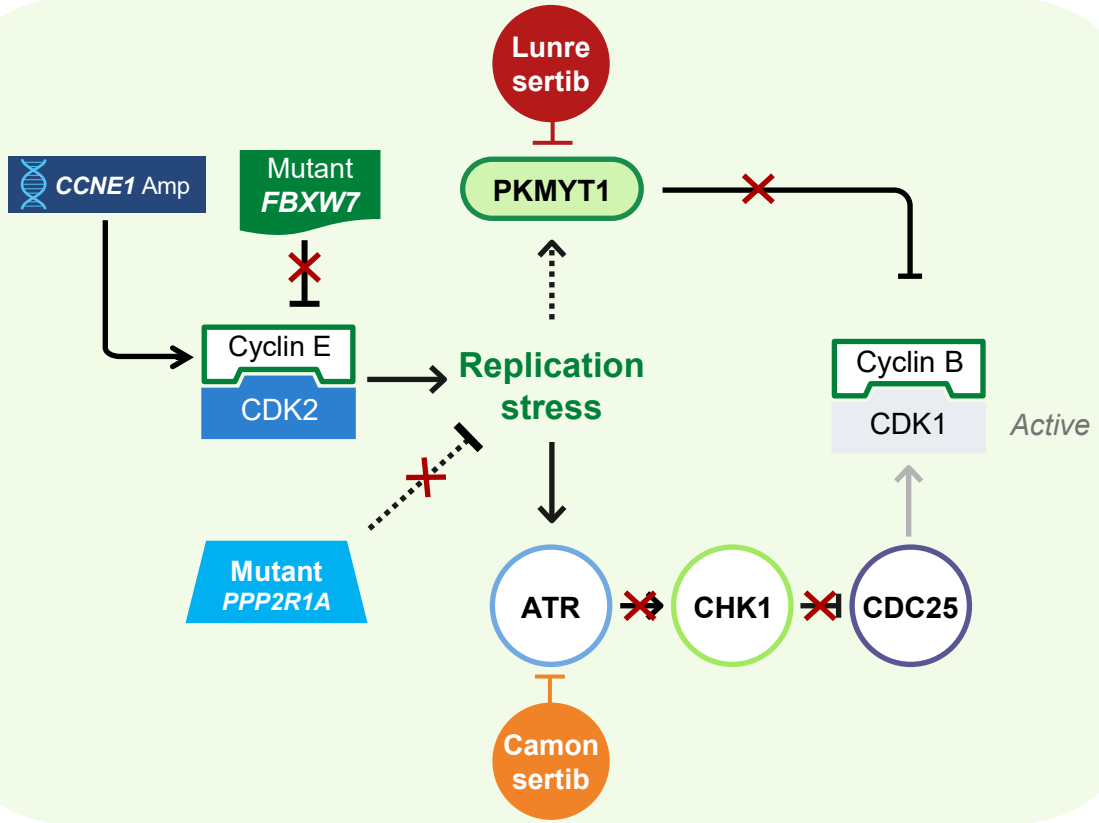
PKMYT1 and ATR inhibitors synergize to enhance anti-tumor activity

Lunresertib-sensitizing alterations (*CCNE1/FBXW7/PPP2R1A*) engage ATR through replication stress



ATR activation (through CHK1-mediated inhibition of CDC25) results in inactive CDK1

Combination of ATR and PKMYT1 inhibition enhances CDK1 activation and premature mitosis



Yap et al, AACR-NCI-EORTC (2023)

PKMYT1 inhibitor landscape

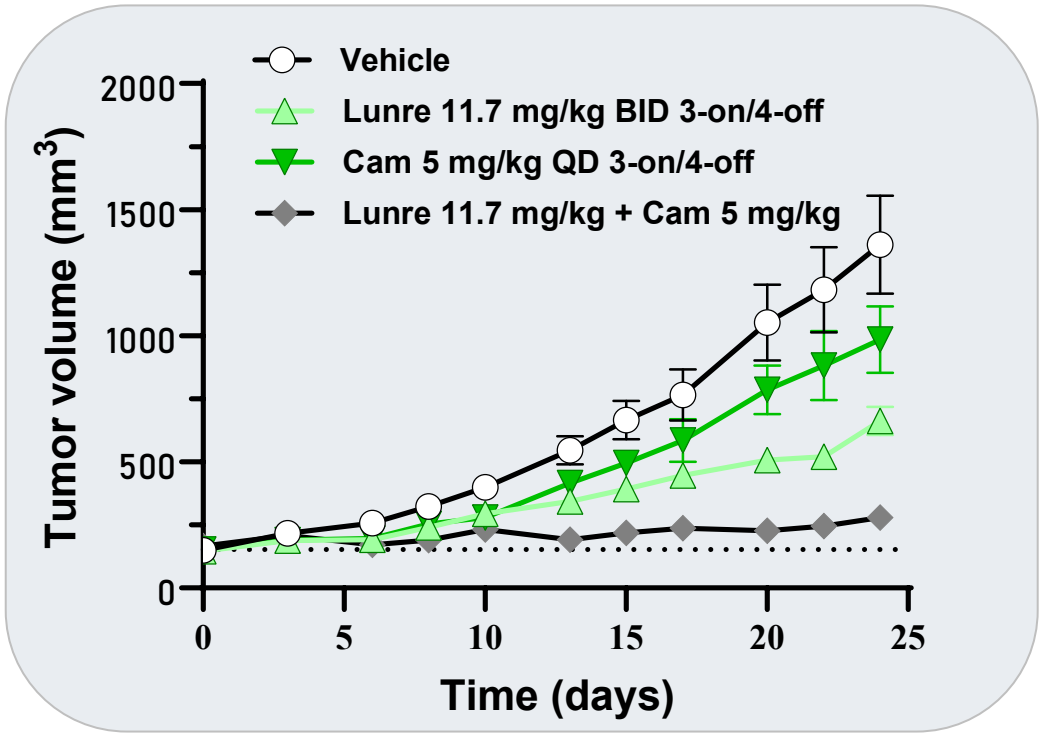
PKMYT1 inhibitor	Sponsor	Phase	Route
Lunresertib (RP-6306)	Repare Therapeutics	I	PO
ACR-2316 (PKMYT1/WEE1 inhibitor)	Acrivon Therapeutics	I	PO
SGR-3515 (WEE1 and PKMYT1 dual inhibitor)	Schrödinger	I	PO
XL495	Exelisis	I	PO

PKMYT1i Lunresertib and ATRi camonsertib combination is active in *CCNE1* amplified or *FBXW7* altered tumor models

Combination treatment drives tumor regressions at sub-efficacious single-agent doses

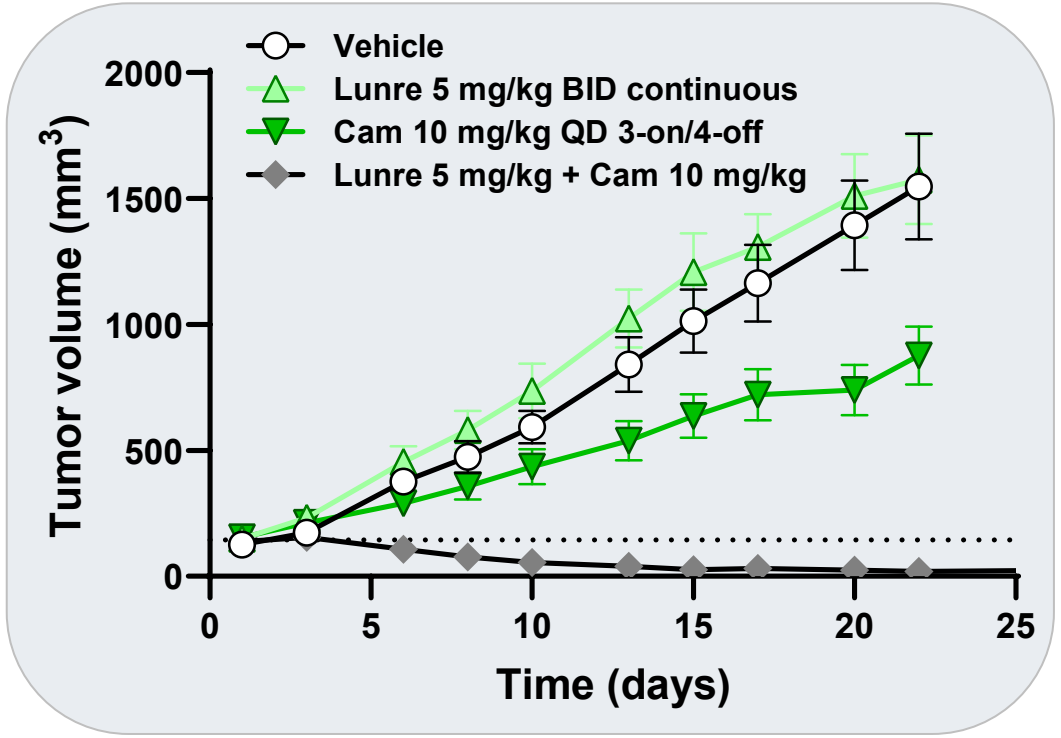
OVCAR3 Ovarian Cancer

CCNE1 amplified CDX model



DLD1 Colorectal Cancer

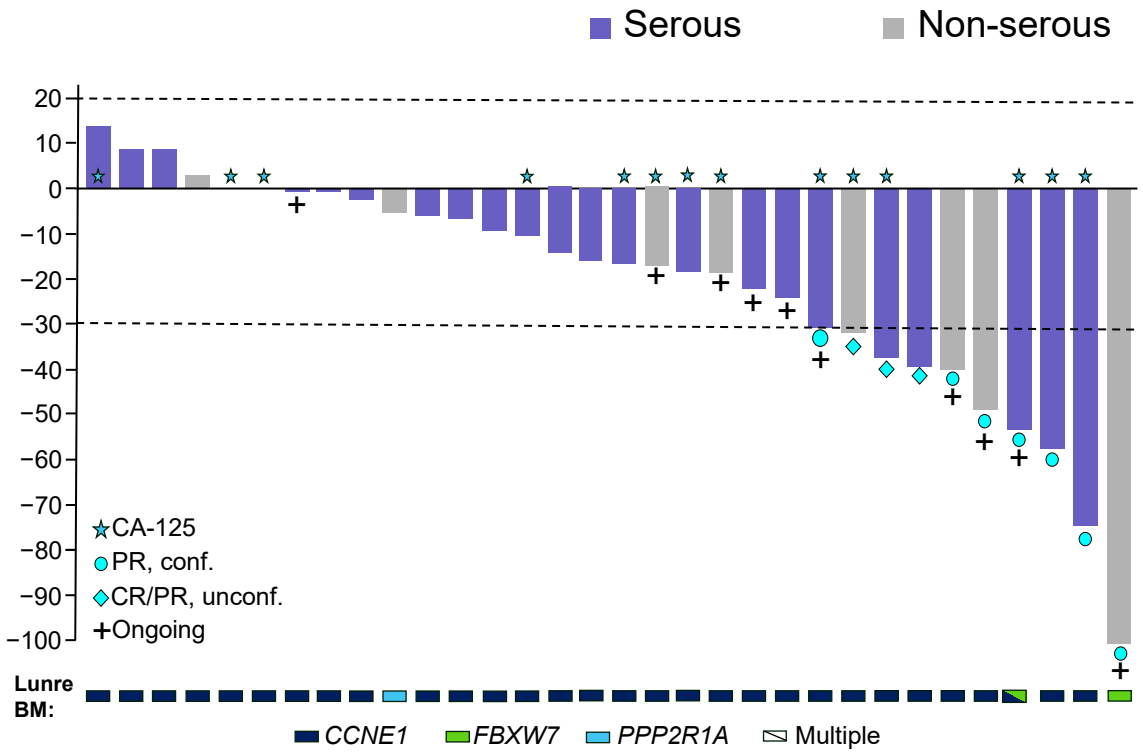
FBXW7 Knockout CDX model

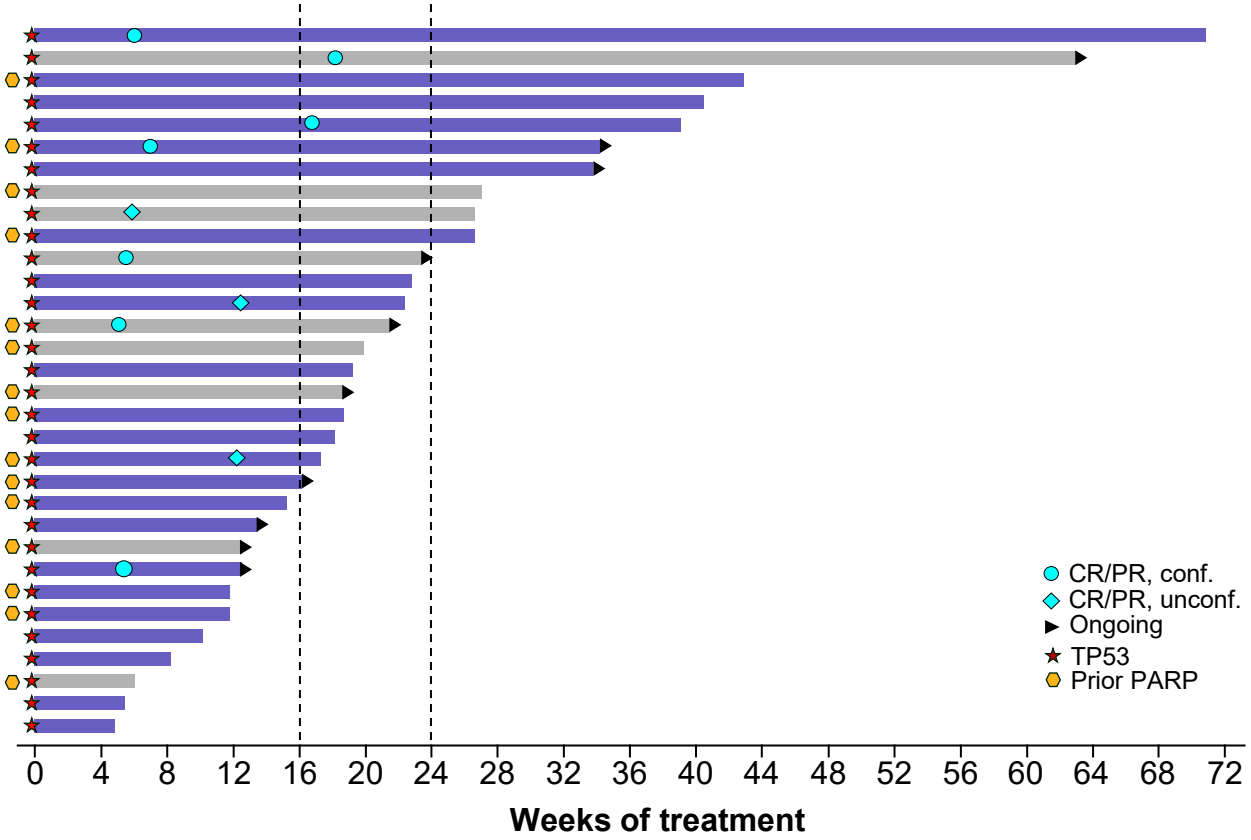


Yap et al, AACR-NCI-EORTC (2023)

Combination of PKMYT1 + ATR inhibition

Clinical benefit observed across ovarian cancer histological subtypes and genotypes





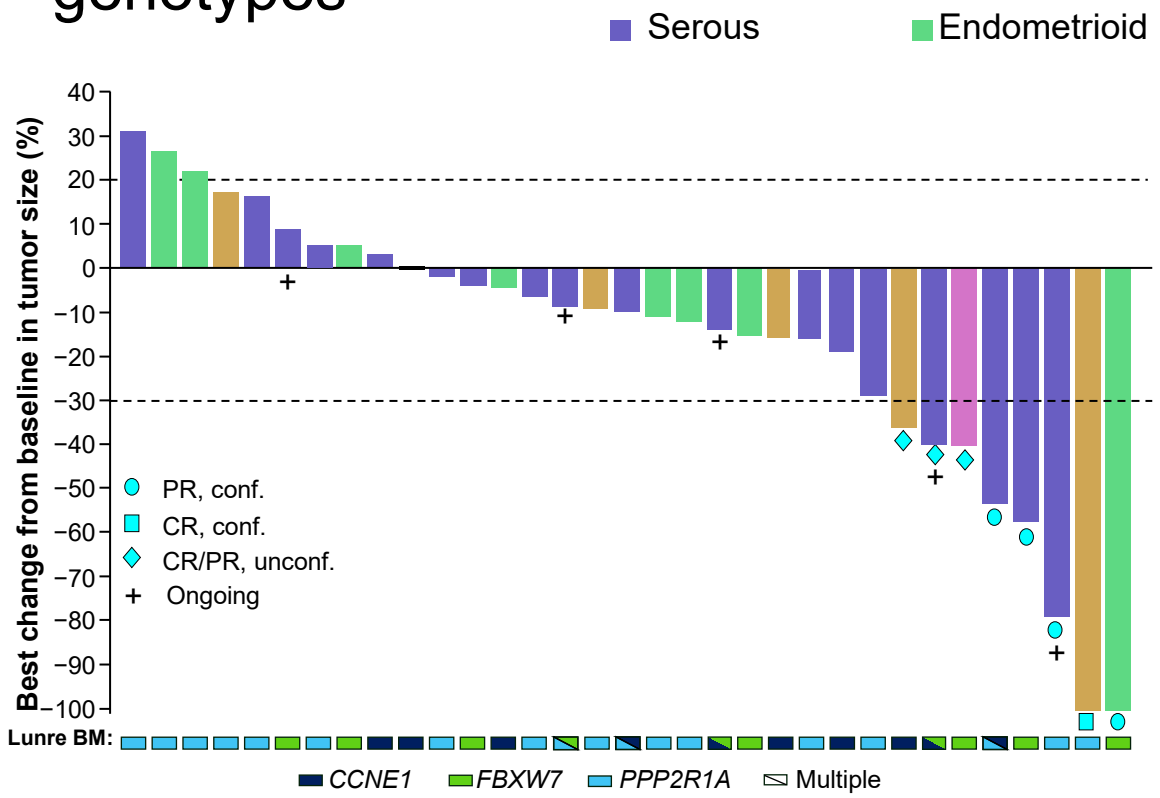
RECIST (conf.+unconf.), %	31.3% (16.1-50.0)
RECIST (conf.), %	21.9% (9.3-40.0)

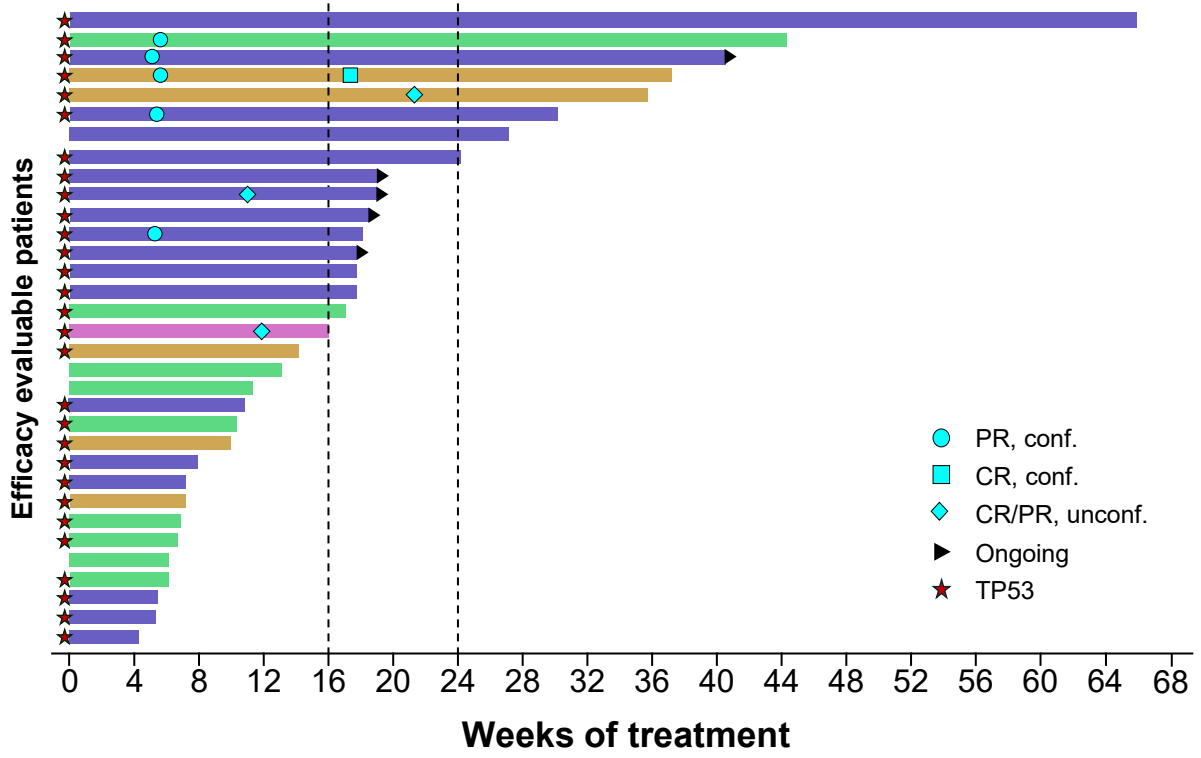
CBR[a], % (95% CI)	68.8% (50.0-83.9)
Time to response (w), median (range)	6.9w (5.1-18.1)
PFS at 24w, % (95% CI)	41.2% (21.8-59.7)

Schram et al, AACR (2025)

Combination of PKMYT1 + ATR inhibition

Clinical benefit observed across endometrial cancer histological subtypes and genotypes





RECIST (conf.+unconf.), %	24.2% (11.1-42.3)
RECIST (conf.), %	15.2% (5.1-31.9)

CBR[a], % (95% CI)	48.5% (30.8-66.5)
Time to response (w), median (range)	5.6w (5.1-21.3)
PFS at 24w, % (95% CI)	38.3% (18.5-57.9)

Schram et al, AACR (2025)

Ongoing and future synthetic lethality (SL) development opportunities

1. Developing **predictive biomarkers** beyond established ones e.g. *BRCA1/2* mutations: SL Functional biomarkers (e.g. phosphoproteomic signatures)

2. **Minimizing toxicities**: Development of more selective and potent SL inhibitors, e.g. PARP1-selective inhibitors; creative dosing/scheduling for combinations

3. Understanding **resistance** mechanisms with SL agents (likely multifactorial)

4. Developing **rational SL combinations** to overcome drug resistance to monotherapy

Acknowledgments

Patients and caregivers

Investigational Cancer Therapeutics (Phase I Program)

Funda Meric-Bernstam
David Hong
Stephane Champiat
Cathy Dumbrava
Siqing Fu
Aung Naing
Sarina Piha-Paul
Jordi Rodon
Tin-Yun Tang
Lia Tsimberidou
Paula Pohlmann

Therapeutics Discovery: Institute for Applied Cancer Science (IACS) & TRACTION

Tim Heffernan
Joe Marszalek
Virginia Giuliani
Mick Soth
Giulio Draetta

Precision Oncology Decision Support

Amber Johnson
Jia Zeng
Michael Kahle
Vijay Holla

Industry Partners

DDR Grants

NIH/NCI Ovarian SPORE (1P50 CA281701-01)
NIH/NCI R01 Grant (1R01CA255074-01)
NIH/NCI PDX Grant (1U54CA224065-01)
NIH/NCI TEX CTN Grant (2UM1CA18688-06)
DOD Ovarian Cancer Grant (OC200482)
DOD Breast Cancer Grant (FP00014873)
V Foundation Scholar Grant (VC2020-001)
CPRIT Grant (RP230135)
AZ, Bayer, EMD Serono, Pfizer, Repare and Mirati Grants

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