Facciamo il punto su...

"Homologous Recombination Deficiency (HRD) e biopsia liquida"

Dialogo tra oncologo e anatomo-patologo

Quali Nuovi Agenti?

Laura Cortesi

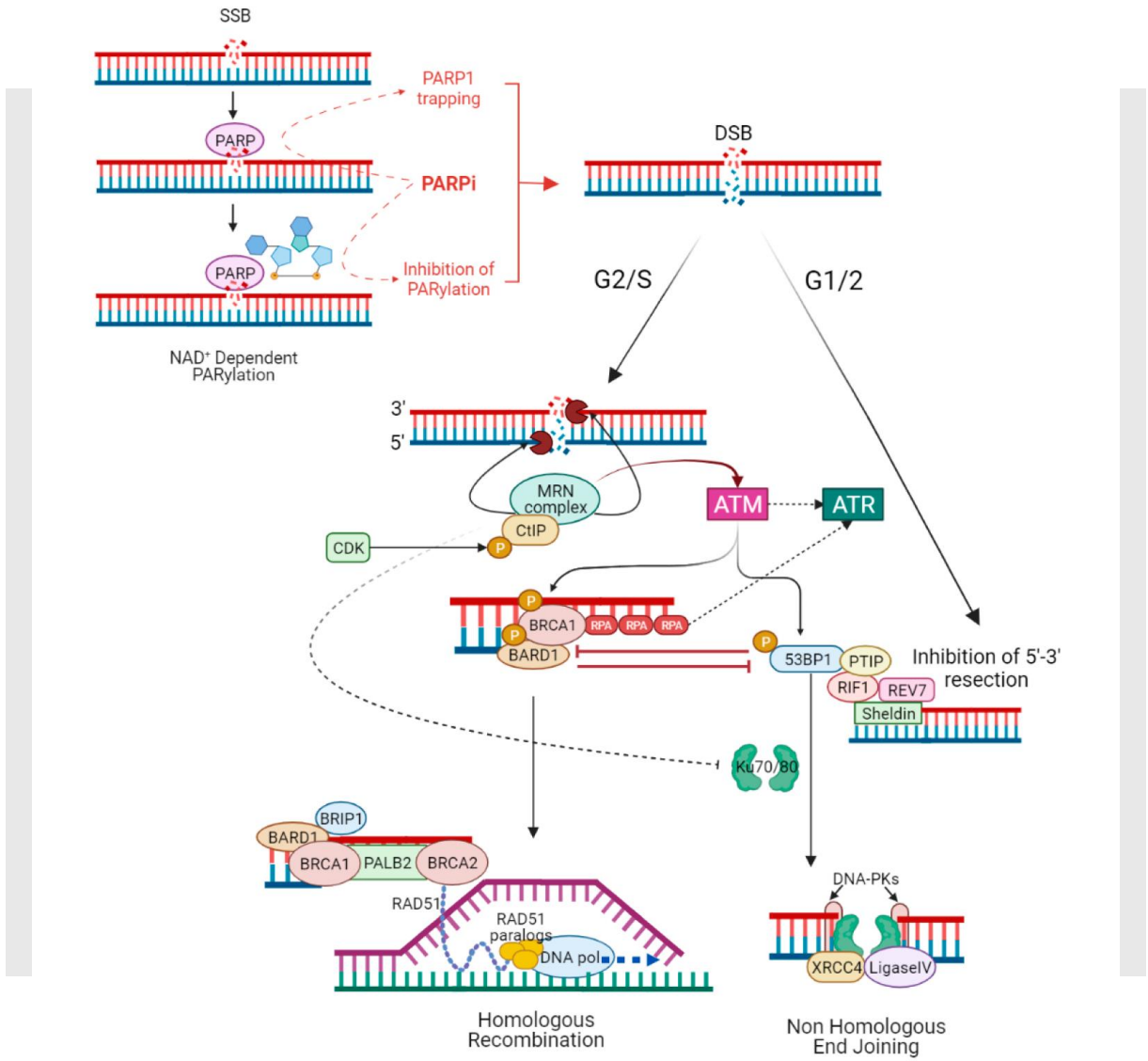
SS Genetica Oncologica

AOU Policlinico Modena

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero-Universitaria di Modena
Policlinico

CTF MO

DNA double-strand break repair mechanisms

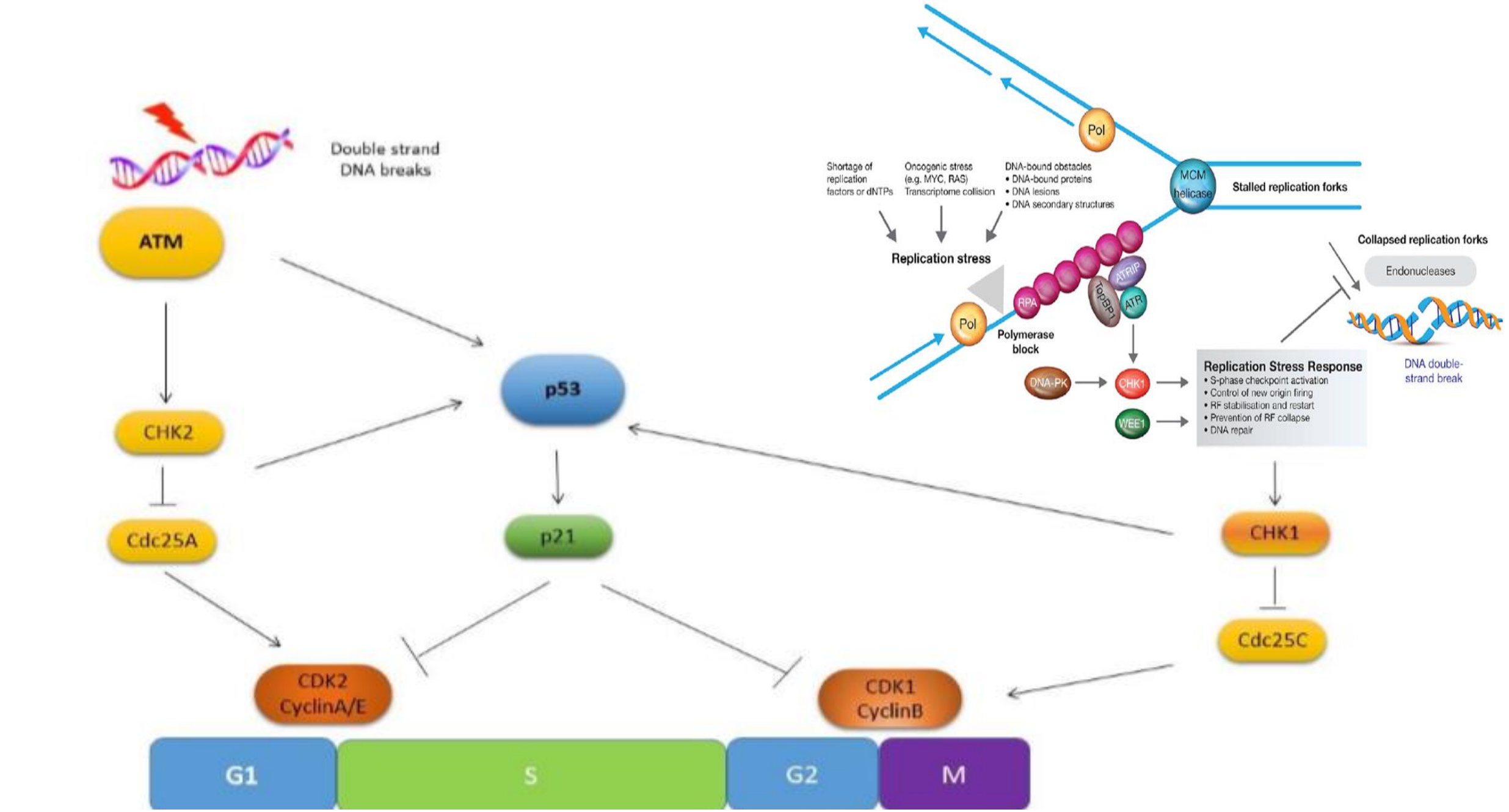


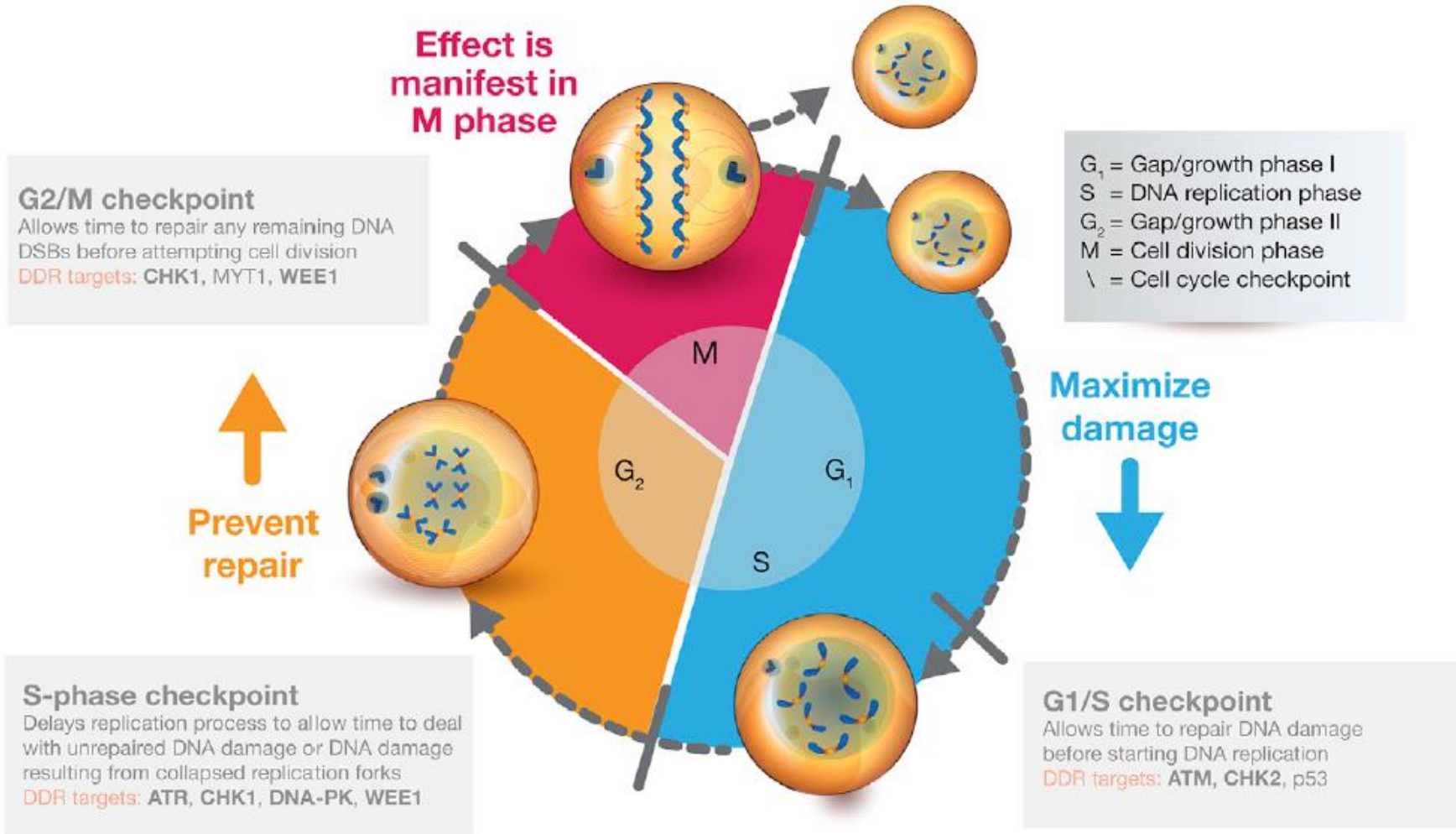
GENOMIC INSTABILITY

Cell death

Piombino C, Cortesi L. *Cancers* 2022

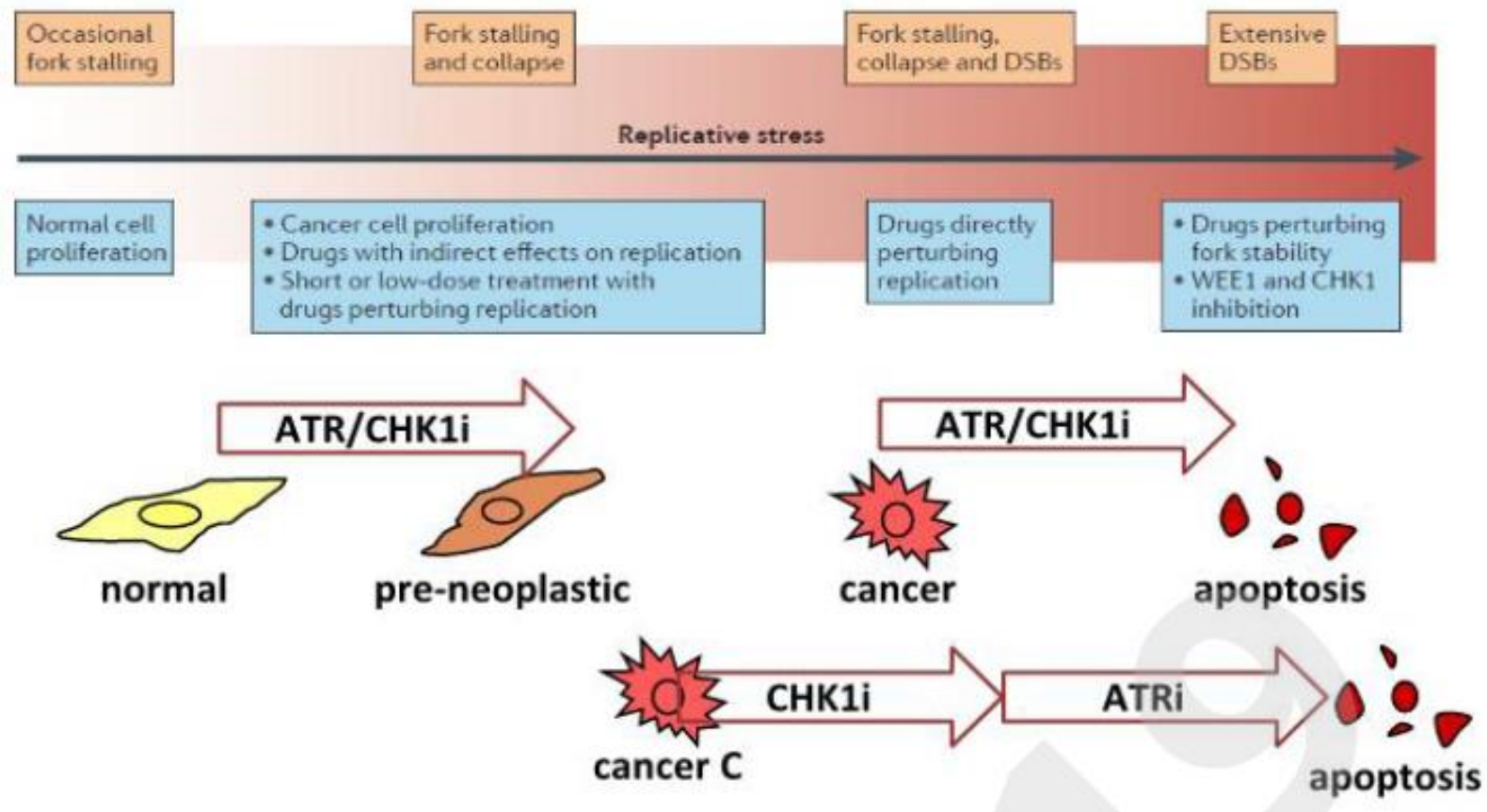
Figure 1. DNA Damage Response signaling through ATM and ATR



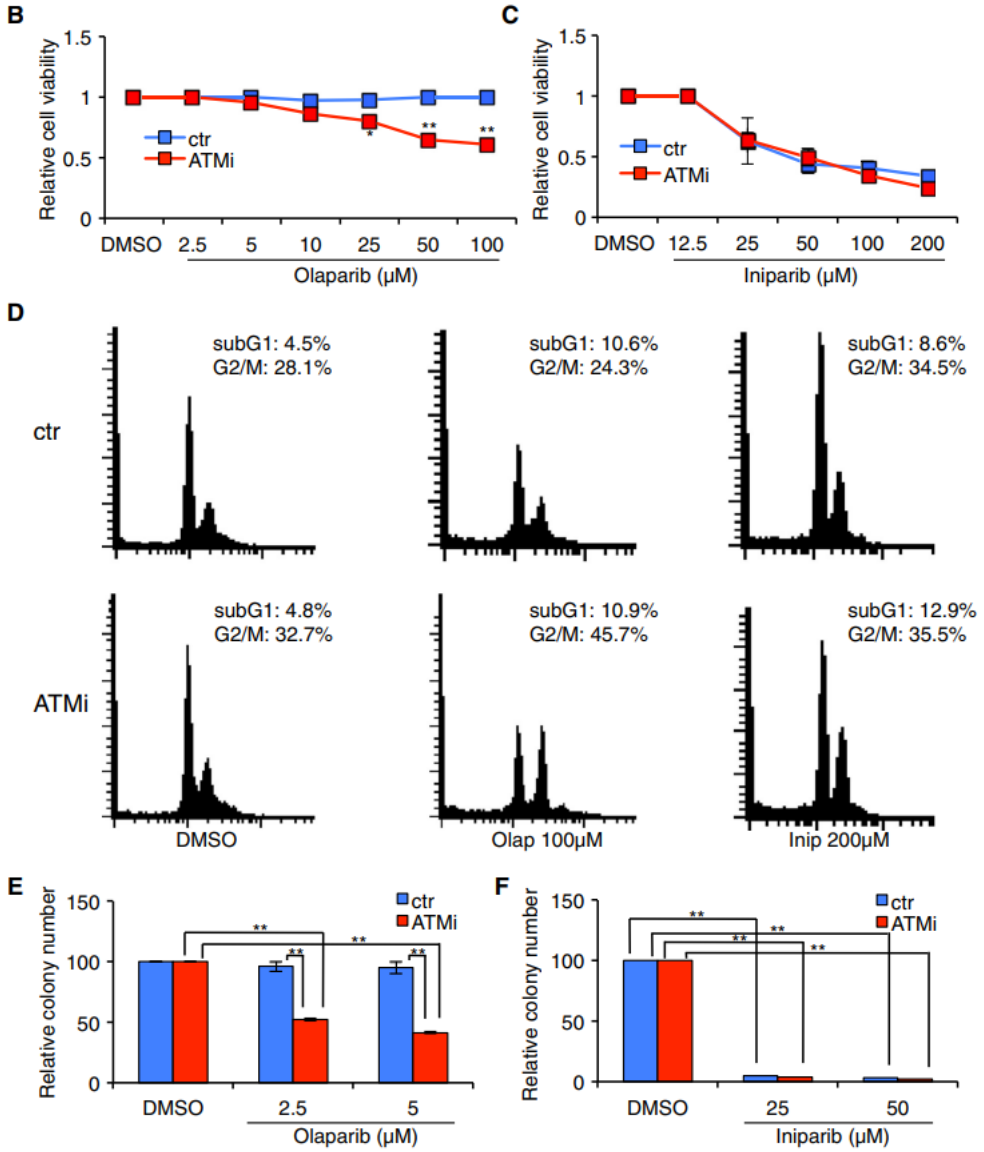


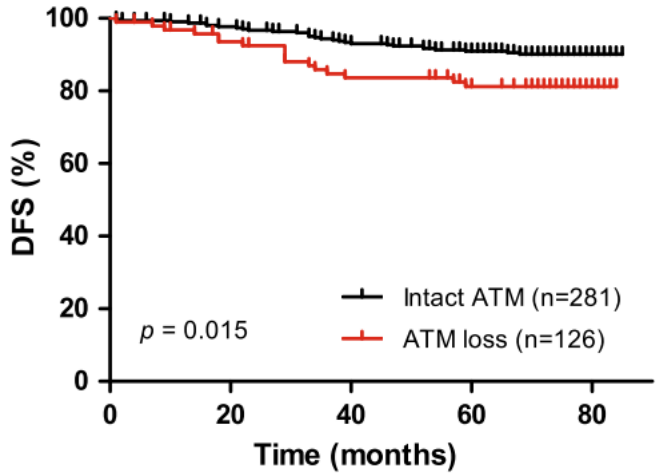
Combinations with immunotherapy may achieve immune-mediated cell death at lower DNA damage thresholds

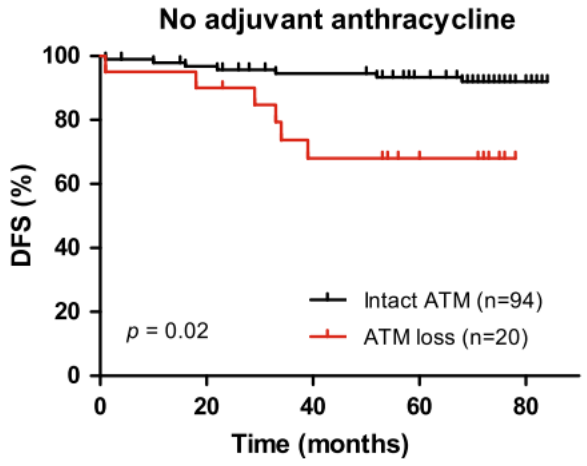
Cancers with replication stress are sensitive to ATR, CHK1 and WEE1 inhibitors

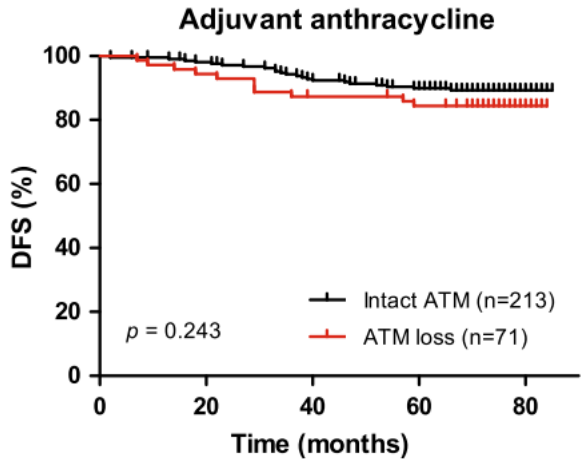


ATM-depletion in breast cancer cells confers sensitivity to PARPi and anthracycline



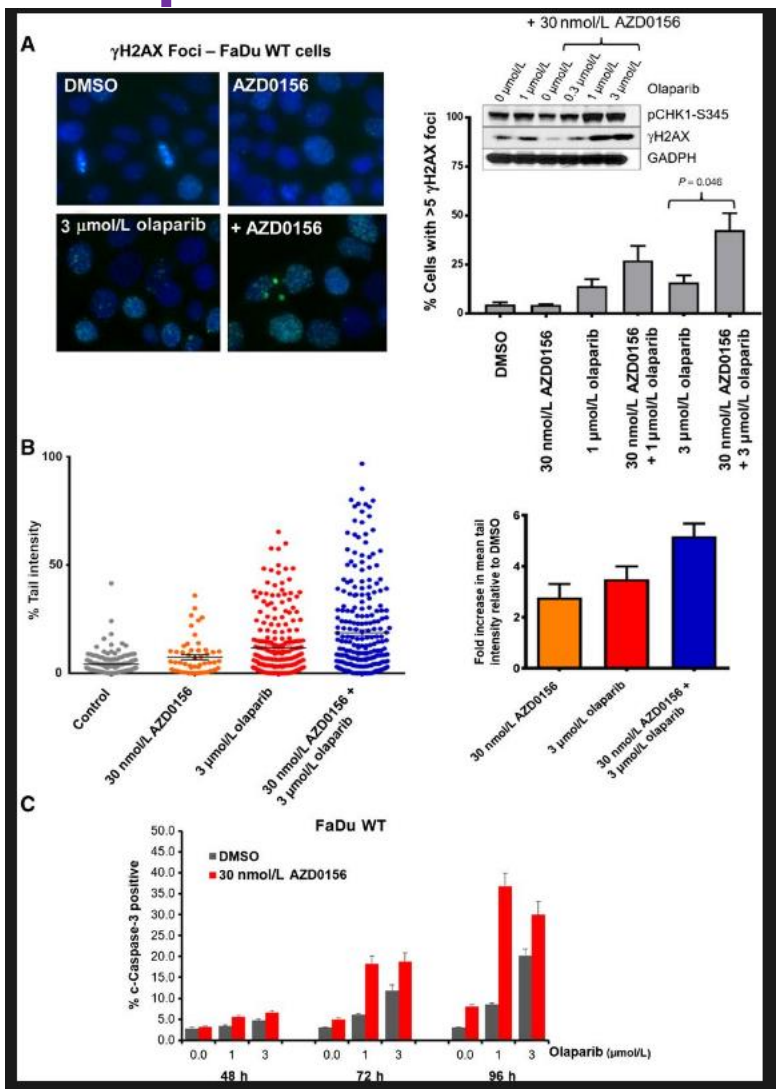






- Gilardini Montani MS, J Exp Clin Cancer Res. 2013; Suh KJ, Breast Cancer Res Treat. 2016

ATM Inhibitor AZD0156 Potentiates Preclinically Olaparib Responses

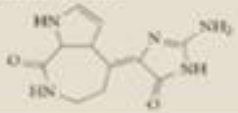
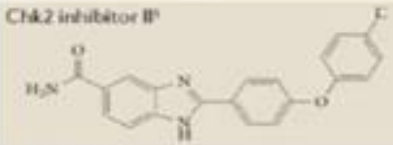
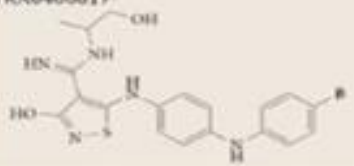
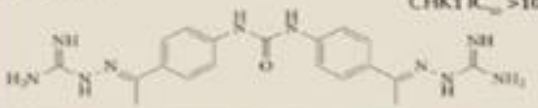


A Phase I, Open-Label Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of Ascending Doses of AZD0156 Monotherapy Or in Combination With irinotecan/FOLFIRI or Olaparib in Patients With Advanced Malignancies (NCT02588105)

Recruitment Completed

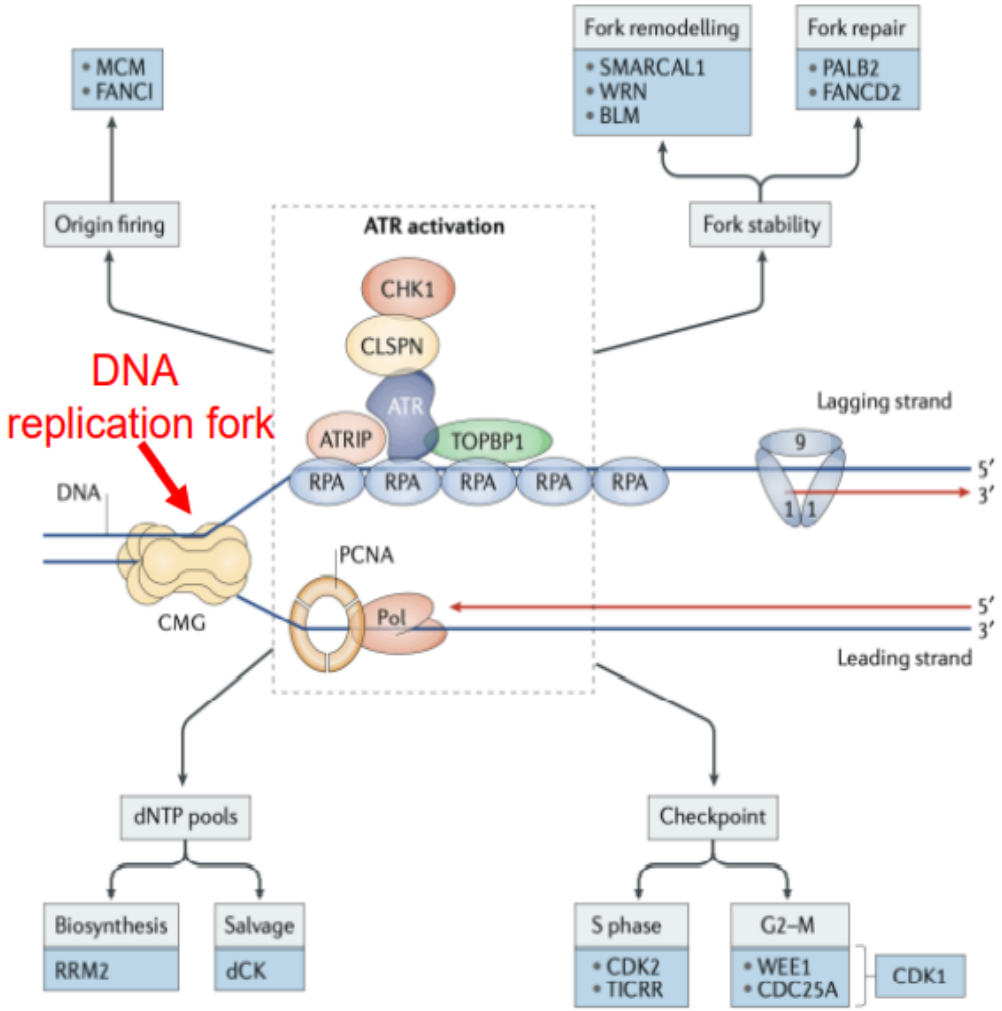
- Riches LC, Mol Cancer Ther. 2020 ;

Function	CHK1	CHK2
Involved in the response to DNA damage	Yes	Yes
Phosphorylates CDC25 phosphatases and p53	Yes	Yes
Structure	Distinct from CHK2	Distinct from CHK1
Protein half-life	<2 hours	>6 hours
Activated by single-strand DNA breaks only	Yes	No
Phosphorylates BRCA1, PML1 and E2F1	No	Yes
Knockout mice	Embryonic lethal	Viable
Knockout mouse embryonic fibroblasts	Defects in G2 checkpoint	No detectable defects in the G2 checkpoint
Mutations identified in the germline	None	Rare founder mutations identified in different populations with varying frequencies

Inhibitor	CHK2 potency and selectivity versus CHK1	Cell lines investigated	Inhibitor effects	Refs
Go6976 	Equipotent at CHK2 and CHK1*	MDA-MB-231 breast cancer (p53 mutant) MCF-10A breast cancer (p53 wild type)	Abrogation of the G_2/S phase arrest induced by the topoisomerase I inhibitor SN38 No effect on the SN38-induced G_2/S phase arrest in p53 wild-type cells	112
Debromohymeniialdisine 	CHK2 IC_{50} = 183 nM‡ CHK1 IC_{50} = 725 nM	14-3-3δ-deficient HCT116 colon cancer Syncytia arrested in G_2 from fusion of asynchronous HeLa cervical cancer cells	Chemosensitized cells to doxorubicin Provoked mitotic catastrophe	46
EXEL-9844 (structure not disclosed)	CHK2 K_i = 0.07 nM CHK1 K_i = 2.2 nM	PANC-1 pancreatic cancer AsPC1 pancreatic cancer HeLa cervical cancer SKOV-3 ovarian cancer	Abrogation of the G_2 arrest induced by the antimetabolite gemcitabine Chemosensitization of PANC-1 xenografts to gemcitabine	113
Chk2 inhibitor II§ 	CHK2 K_i = 37 nM CHK1 IC_{50} >10,000 nM	$CD4^+$ and $CD8^+$ T cells from human blood	T cells rescued from γ-irradiation-induced apoptosis (inhibitor EC_{50} 3–7 μM)	118
VRX0466617‖ 	CHK2 K_i = 11 nM CHK1 IC_{50} >10,000 nM	HCT116 colon cancer (p53 wild type) Bj-hTERT fibroblasts EBV-immortalized lymphoblastoid LCL-N cells Isolated mouse thymocytes	Prevented CHK2-dependent, γ-radiation-induced degradation of MDMX protein Protected thymocytes from γ-radiation induced apoptosis	117
NSC 109555¶ 	CHK2 IC_{50} = 240 nM CHK1 IC_{50} >10,000 nM	MCF-7 breast cancer (p53 wild type) HT29 (p53 mutant)	No cellular effects when used in combination with topotecan or camptothecin — attributed to confounding off-target activities and poor cell permeability	115

*Inhibition determined in a cell-based assay; enzyme inhibition parameters not described. ‡Inhibition data from REF. 149. §Systematic name: 2-(4-(4-chlorophenoxy)phenyl)-1H-benzo[d]imidazole-5-carboximidamide. ‖Systematic name: 5-(4-(4-bromophenylamino)phenylamino)-3-hydroxy-N-(1-hydroxypropan-2-yl)isothiazole-4-carboximidamide. ¶Systematic name: (2E,2'E)-2,2'-(1,1'-(4,4'-carbonylbis(azanediyl)bis(4,1-phenylene))bis(ethan-1-yl-1-ylidene))bis(hydrazinec

What is ATR and why inhibit it?



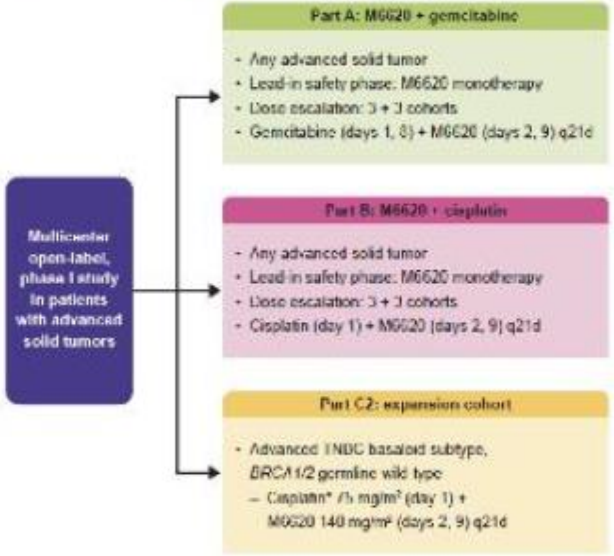
- ATR is a druggable kinase
- Central to the response to DNA replication fork arrest

- DNA Replication Stress response
- S and G2/M checkpoints
- Replication fork remodelling/repair

- Many oncogenes and therapies cause Replication Stress
- Cyclin E amplification / TP53 / ATM mutations sensitise to ATRi in vitro

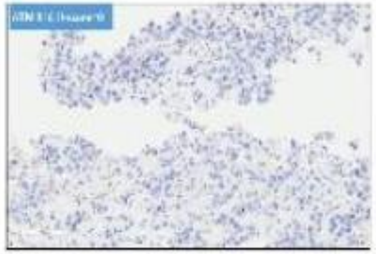
Adapted from Lecona et al Nat Rev Cancer Vol. 18, Iss. 9, 586-595

Early clinical development of ATR inhibitors

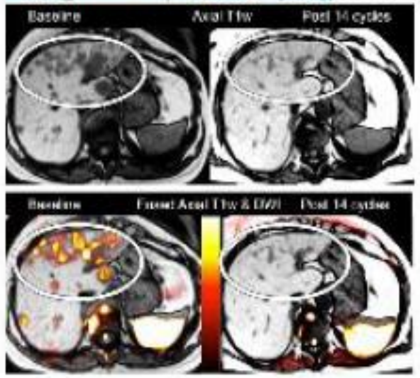


Clinical case: patient #1

- ATM / ER / HER2 platinum refractory breast cancer with 11 prior lines of therapy
- PR (−54%), duration of treatment 356 days
- BAY 1895344 dose 60 mg BID reduced to 40 mg BID (escalation cohort)



DDR: tumor specimen with ATM protein loss and an ATM_T2333fs*40 (71% allele frequency)



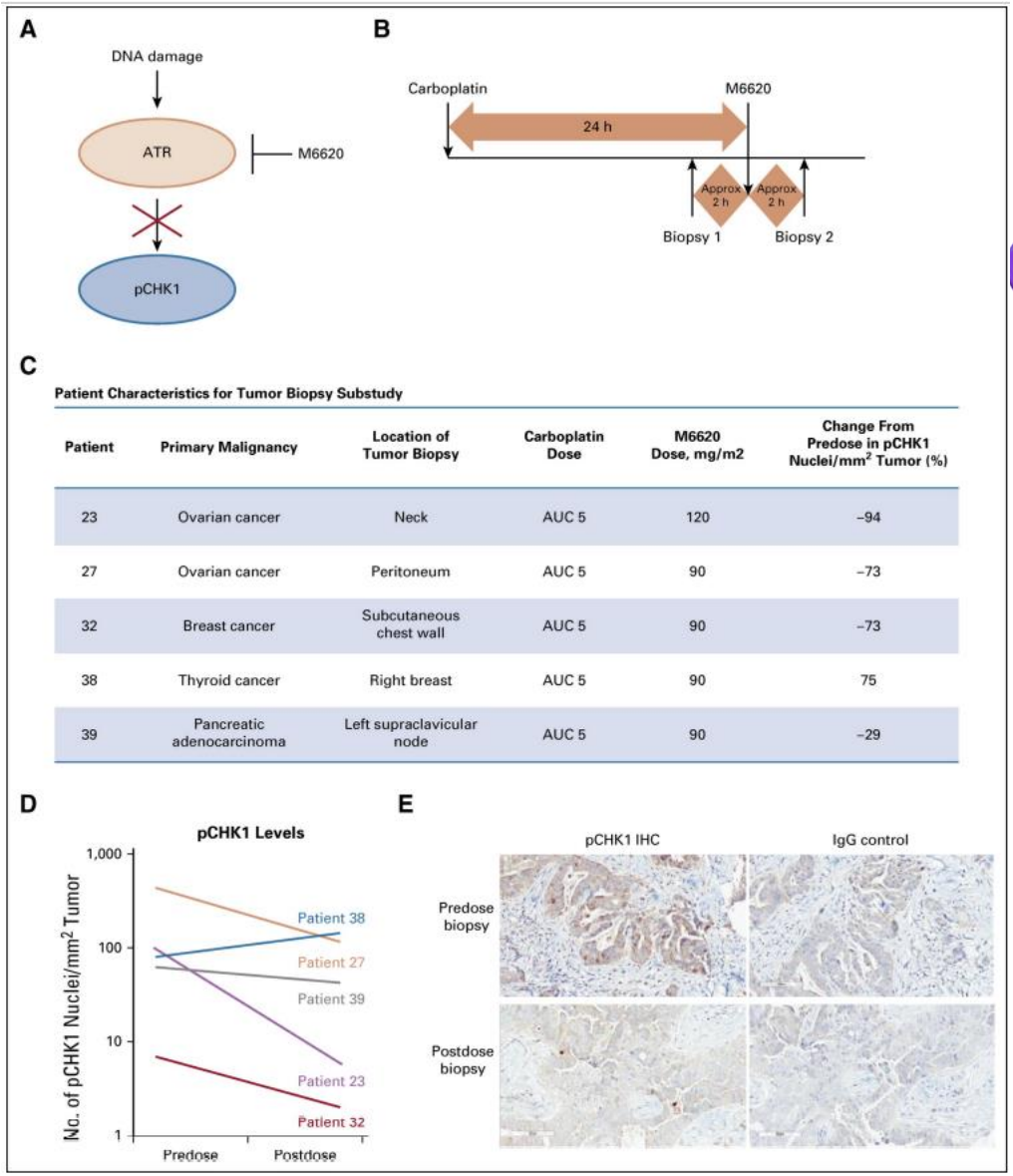
- **Cisplatin + M6620 (VX-970) in 1st-3rd line BRCA1/2 wild-type mTNBC**
  - Selection of PAM50 basal subtype as surrogate for TP53 deficiency
- **ORR 32% 1st – 3rd line**
- **ORR 44% 1st line**

- **BAY1895344 monotherapy phase I in advanced solid tumors**
  - Selection for DDR alterations or ATM loss by IHC
- **ORR 30.7% at MTD or above**
- **Responses durable**

Telli ML, et al. ESMO 2017
DeBono J, et al. ASCO 2019

Phase I Trial of First-in-Class ATR Inhibitor M6620 (VX-970) as Monotherapy or in Combination With Carboplatin in Patients With Advanced Solid Tumors

Part A (n = 17) M6620 monotherapy		Part B (n = 23)* M6620 + carboplatin
Dose level 1 (n = 1) M6620 60 mg/m^2 once weekly	**Dose level 5 (n = 6)** M6620 240 mg/m^2 twice weekly	**Dose level 1 (n = 3)** M6620 240 mg/m^2 once weekly + carboplatin AUC 5
Dose level 2 (n = 2) M6620 120 mg/m^2 once weekly	Twice-weekly RP2D: 240 mg/m^2 twice weekly	**Dose level 2 (n = 3)** M6620 120 mg/m^2 once weekly + carboplatin AUC 5
Dose level 3 (n = 1) M6620 240 mg/m^2 once weekly		**Dose level 3 (n = 3)** M6620 120 mg/m^2 once weekly + carboplatin AUC 4
Dose level 4 (n = 7) M6620 480 mg/m^2 once weekly		**Dose level 4 (n = 14)** M6620 90 mg/m^2 once weekly + carboplatin AUC 5
RP2D: 240 mg/m^2 once weekly		RP2D: M6620 90 mg/m^2 once weekly + carboplatin AUC 5



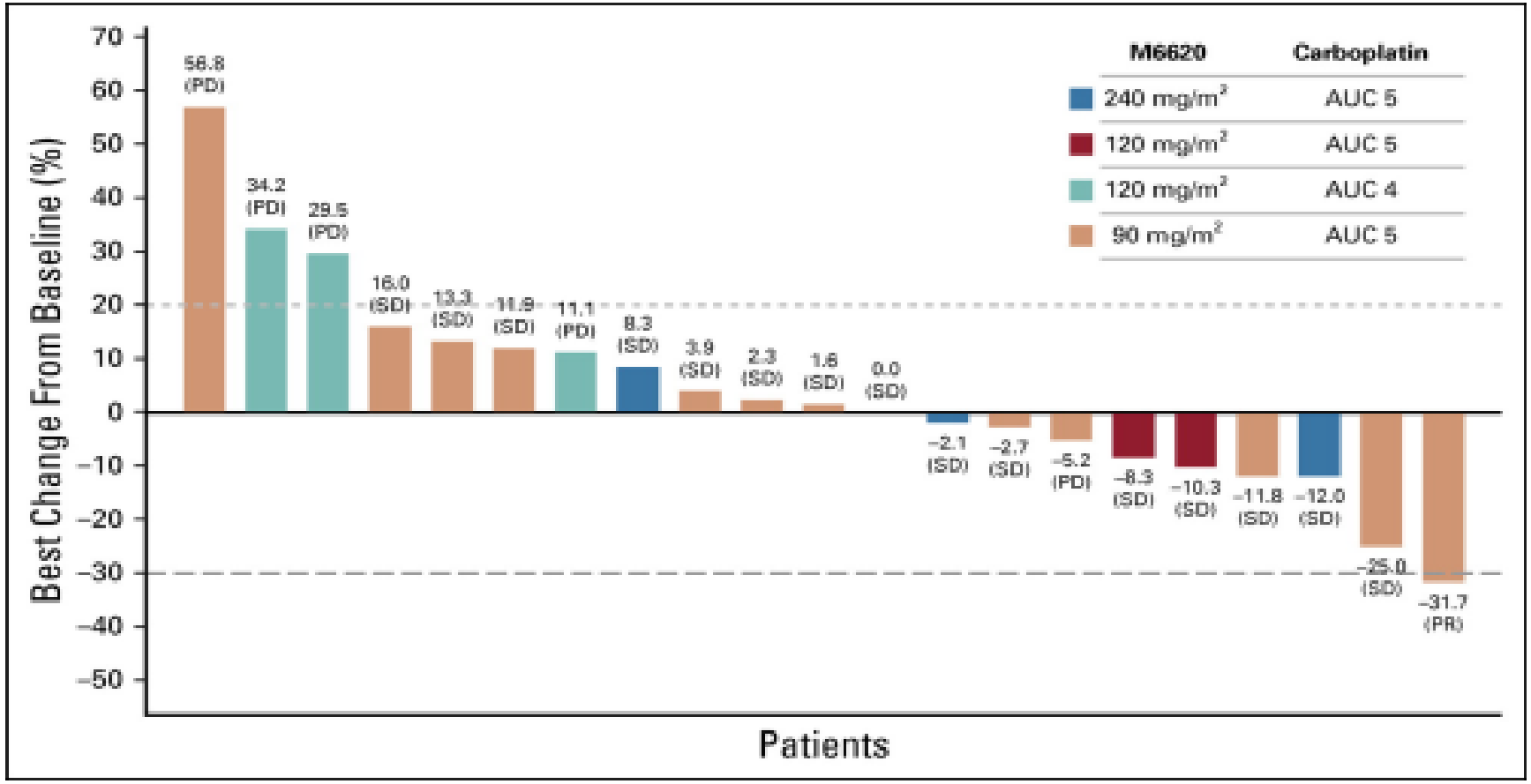
C

Patient Characteristics for Tumor Biopsy Substudy

Patient	Primary Malignancy	Location of Tumor Biopsy	Carboplatin Dose	M6620 Dose, mg/m2	Change From Predose in pCHK1 Nuclei/mm^2 Tumor (%)
23	Ovarian cancer	Neck	AUC 5	120	−94
27	Ovarian cancer	Peritoneum	AUC 5	90	−73
32	Breast cancer	Subcutaneous chest wall	AUC 5	90	−73
38	Thyroid cancer	Right breast	AUC 5	90	75
39	Pancreatic adenocarcinoma	Left supraclavicular node	AUC 5	90	−29

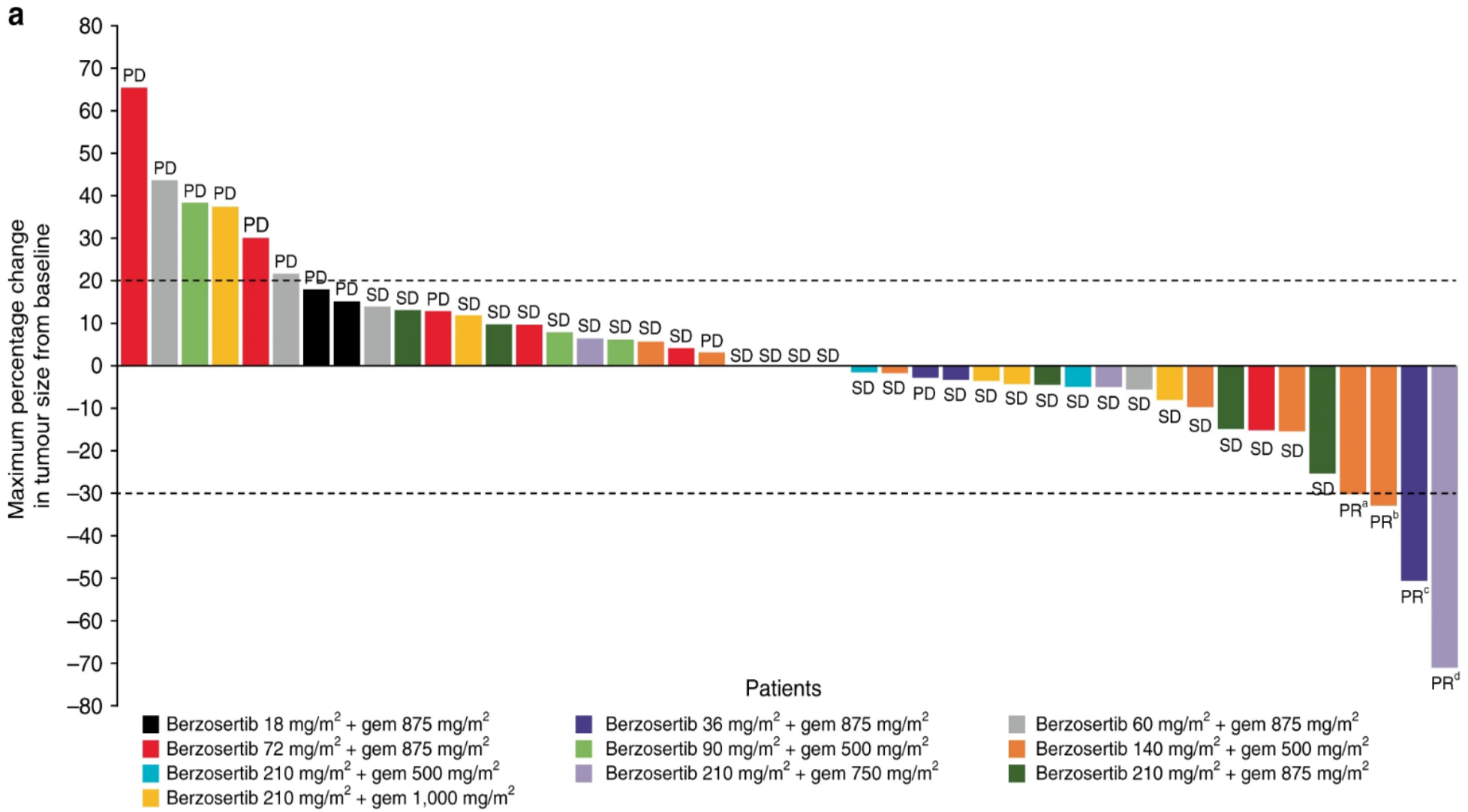
- Yap T, JCO 2020

Phase I Trial of First-in-Class ATR Inhibitor M6620 (VX-970) as Monotherapy or in Combination With Carboplatin in Patients With Advanced Solid Tumors



- Yap T, JCO 2020

Phase 1 study of the ATR inhibitor berzosertib (formerly M6620, VX-970) combined with gemcitabine ± cisplatin in patients with advanced solid tumours



- Middleton MR, BJC 2021

Combination cisplatin D1 and IV ATRi D2/9 inTNBC?

ARTICLE OPEN

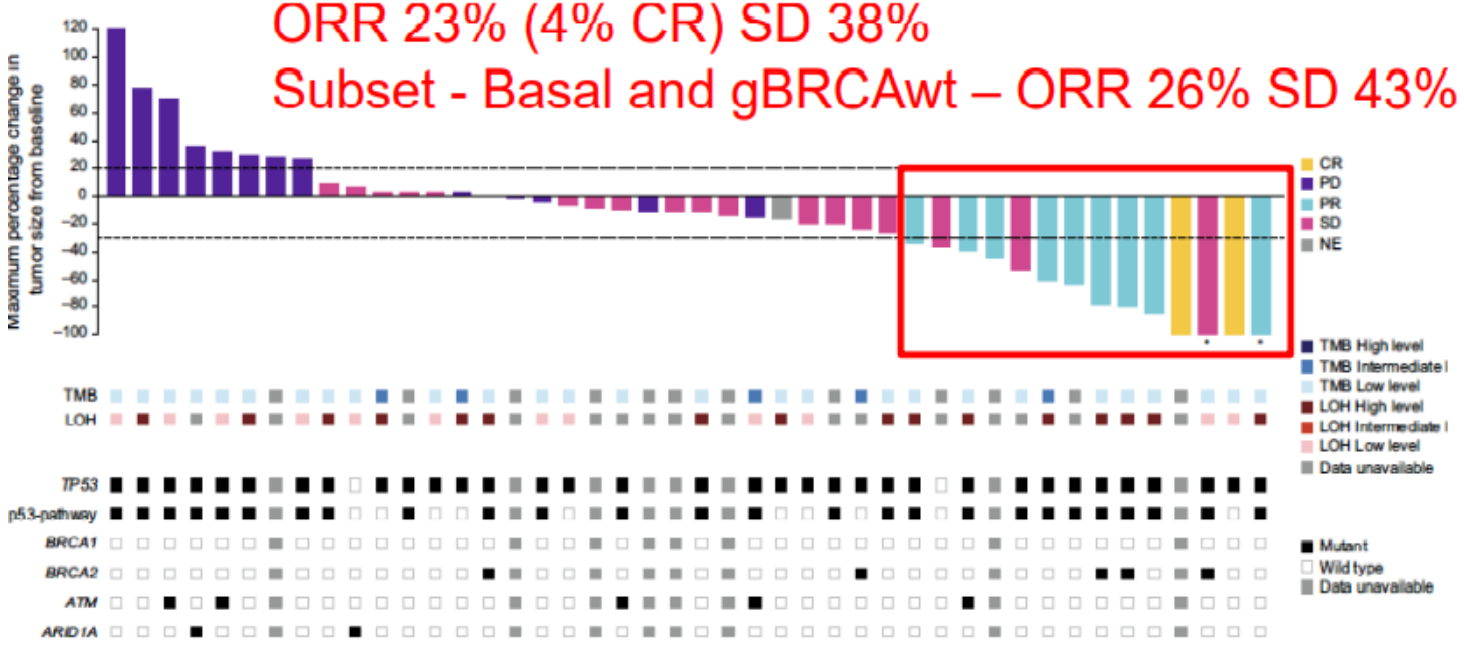
Check for updates

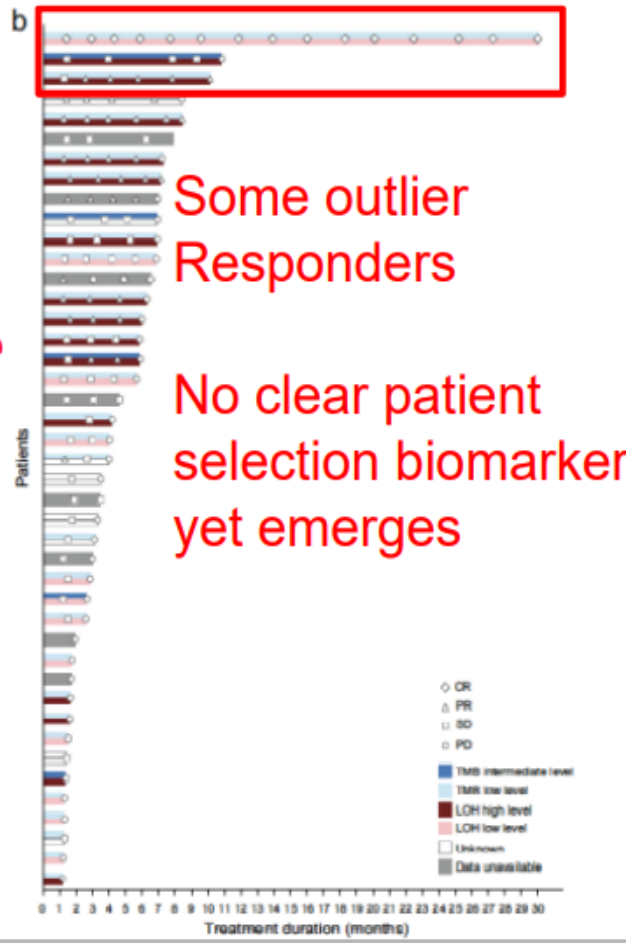
Phase 1b study of berzosertib and cisplatin in patients with advanced triple-negative breast cancer

Melinda L. Telli[1], Sara M. Tolaney[2], Geoffrey I. Shapiro[2], Mark Middleton[3], Simon R. Lord[3], Hendrik Tobias Arkenau[4,5], Andrew Tutt[6,7], Vandana Abramson[8], Emma Dean[9,16], Tufia C. Haddad[10], Robert Wesolowski[11], Jordi Ferrer-Playan[12], Thomas Goddemeier[13], Thomas Grombacher[13], Jennifer Dong[14], Patricia Fleuranceau-Morel[14], Ivan Diaz-Padilla[12,17] and Ruth Plummer[15]

ORR 23% (4% CR) SD 38%

Subset - Basal and gBRCAwt – ORR 26% SD 43%





Some outlier Responders

No clear patient selection biomarker yet emerges

Ceralasertib + olaparib demonstrate clinical activity in patients with PARPi resistance

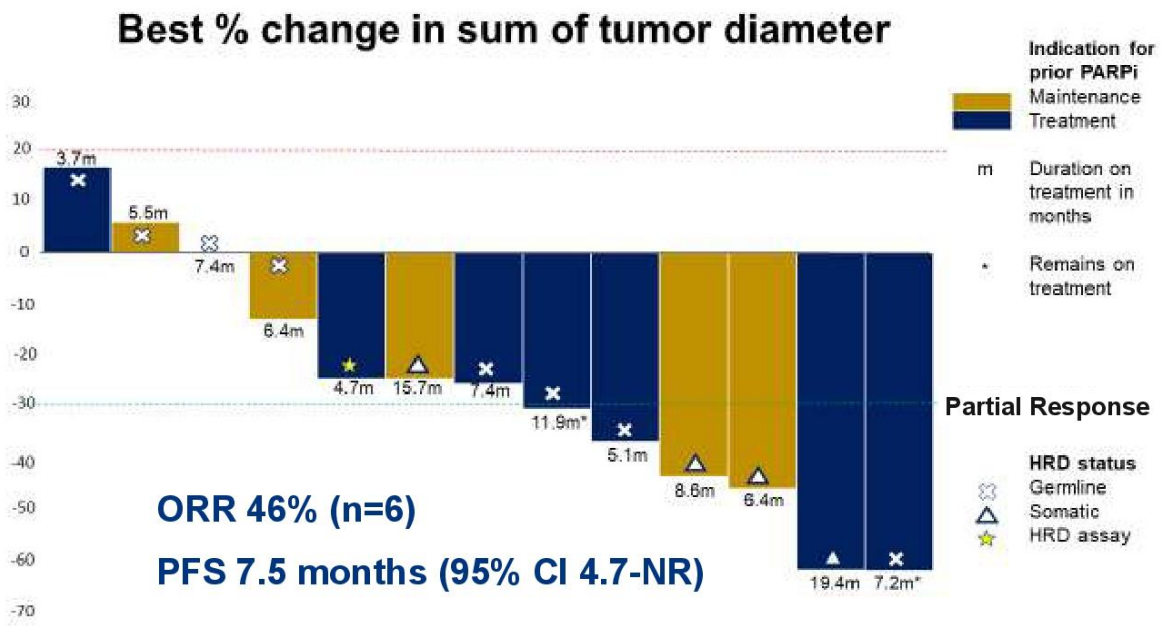
13 subjects

BRCA/HRD

- Germline BRCA^{MUT} 69% (n=9)
- Somatic BRCA^{MUT} 23% (n=3)
- Positive HRD score 8% (n=1)

Prior PARPi

- 1st line maintenance 8% (n=1)
- 2nd line maintenance 38% (n=5
- Treatment 54% (n=7)



ORR 46% (n=6)

PFS 7.5 months (95% CI 4.7-NR)

Genomic and pathologic determinants of response to RP-3500, an ataxia telangiectasia and Rad3-related inhibitor, in patients with DNA damage repair loss-of-function mutant tumors in the Phase 1/2 TRESR trial

Timothy A. Yap,[1] Ian M. Silverman,[2] Elisa Fontana,[3] Elizabeth Lee,[4] David R. Spigel,[5] Martin Højgaard,[6] Stephanie Lheureux,[7] Niharika Mettu,[8] Benedito A. Carneiro,[9] Louise Carter,[10] Ruth Plummer,[11] Joseph D. Schonhoft,[2] Danielle Ulanet,[2] Parham Nejad,[2] Peter Manley,[2] Jorge S. Reis-Filho,[12] Yi Xu,[2] Victoria Rimkunas,[2] Maria Koehler,[2] Ezra Rosen[12]

	5d on/2d off (N=25)			3 d on/4 d off (N=95)		
Preferred Term	Grade 3 N (%)	Grade 4 N (%)	All Grade N (%)	Grade 3 N (%)	Grade 4 N (%)	All Grade N (%)
Any TRAE	14 (56.0)	1 (4.0)	22 (88.0)	28 (29.5)	4 (4.2)	81 (85.3)
Anemia	13 (52.0)	0	20 (80.0)	**23 (24.2)**	**0**	**58 (61.1)**
Fatigue	1 (4.0)	0	7 (28.0)	2 (2.1)	0	26 (27.4)
Neutrophil count decreased	3 (12.0)	0	6 (24.0)	10 (10.5)	3 (3.2)*	25 (26.3)
Nausea	0	0	3 (12.0)	0	0	22 (23.2)
Platelet count decreased	2 (8.0)	1 (4.0)	7 (28.0)	5 (5.3)	1 (1.1)**	17 (17.9)
Decreased appetite	0	0	4 (16.0)	0	0	14 (14.7)
Diarrhea	0	0	0	0	0	13 (13.7)
Vomiting	0	0	3 (12.0)	0	0	9 (9.5)
White blood cell count decreased	0	0	1 (4.0)	4 (4.2)	0	11 (11.6)
Dyspnea	0	0	5 (20.0)	0	0	6 (6.3)

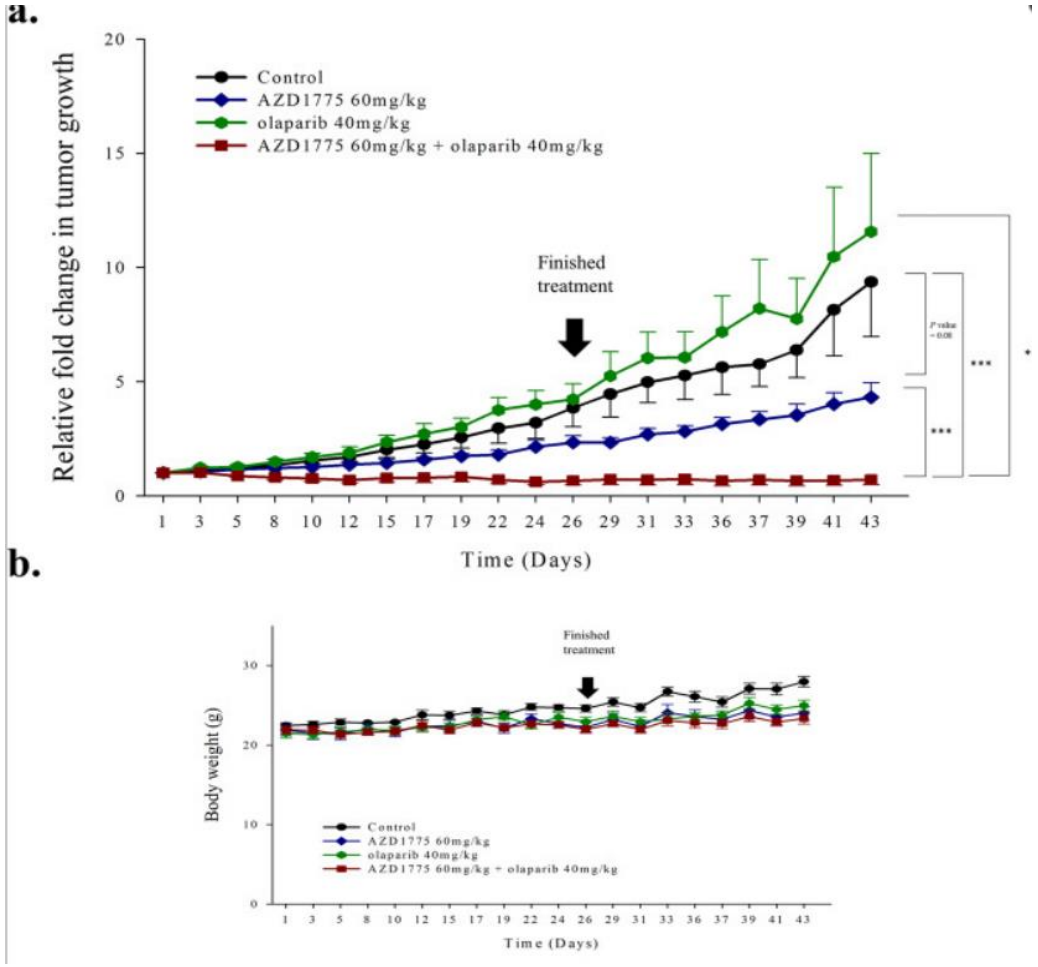
Other ATRi also focusing on HRD and Replication Stress

Tumor Types, n	
Ovarian	22
Prostate	21
Breast	17
Pancreas	13
Other[1]	47
Most Common Genotypes, n	
ATM	44
BRCA1	25
BRCA2	15
CDK12	9
RNAseH2	5
PALB2	5
SETD2	5
Other[2]	12

Molecular responses (≥50% ctDNA decline)

AACR American Association for Cancer Research ANNUAL MEETING

Antitumor effect of a WEE1 inhibitor and potentiation of olaparib sensitivity by DNA damage response modulation in triple-negative breast cancer



- Dong-Jeon H, Sci Rep 2020

Clinical efficacy and molecular response correlates of the WEE1 inhibitor adavosertib combined with cisplatin in patients with metastatic triple-negative breast cancer (mTNBC)

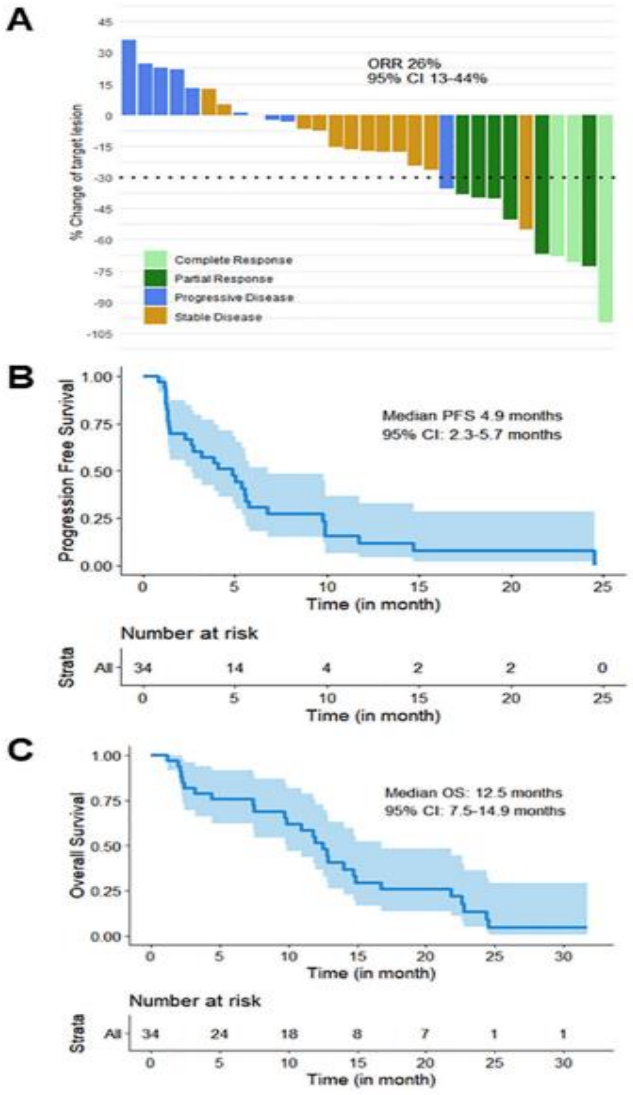


Table 3.

Treatment-Related Adverse Events (> 20% of patients)

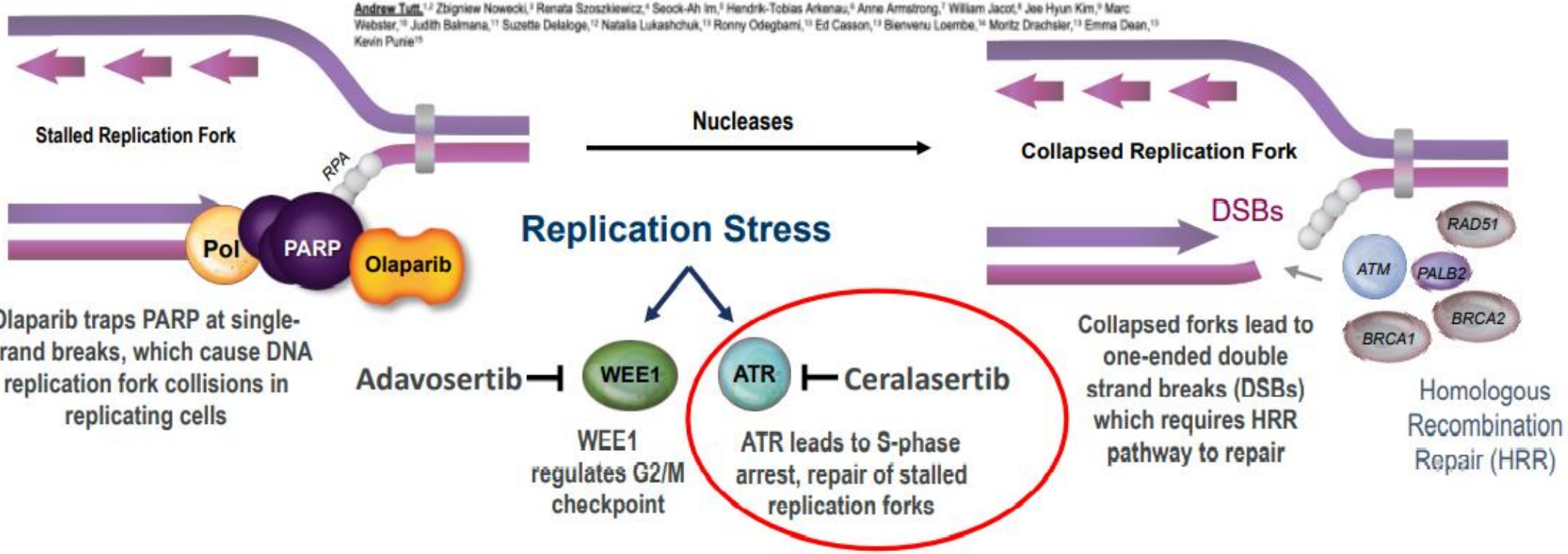
Adverse Event	All Grades n (%)	Grade 3–5* n (%)
Any	31 (91)	18 (53)
Nausea	17 (50)	2 (6)
Diarrhea	12 (35)	7 (21)
Anemia	10 (29)	4 (12)
Neutropenia	10 (29)	6 (18)
Fatigue	9 (26)	0 (0)
Vomiting	7 (21)	0 (0)
Tinnitus	7 (21)	0 (0)

*1 death occurred from sepsis possibly related to study therapy.

- Keenan TAE, Clin Cancer Res 2021

VIOLETTE: A RANDOMISED PHASE 2 STUDY OF OLAPARIB + CERALASERTIB OR ADAVOSERTIB VS OLAPARIB ALONE IN PATIENTS WITH METASTATIC TRIPLE-NEGATIVE BREAST CANCER (NCT03330847)

Andrew Tutt,[1,2] Zbigniew Nowecki,[3] Renata Szoszkiewicz,[4] Seock-Ah Im,[5] Hendrik-Tobias Arkenau,[6] Anne Armstrong,[7] William Jacot,[8] Jee Hyun Kim,[9] Marc Webster,[10] Judith Balmana,[11] Suzette Delaloge,[12] Natalia Lukashchuk,[13] Ronny Odegbami,[13] Ed Casson,[13] Bienvenu Loembe,[14] Moritz Drachsler,[13] Emma Dean,[13] Kevin Punie[15]

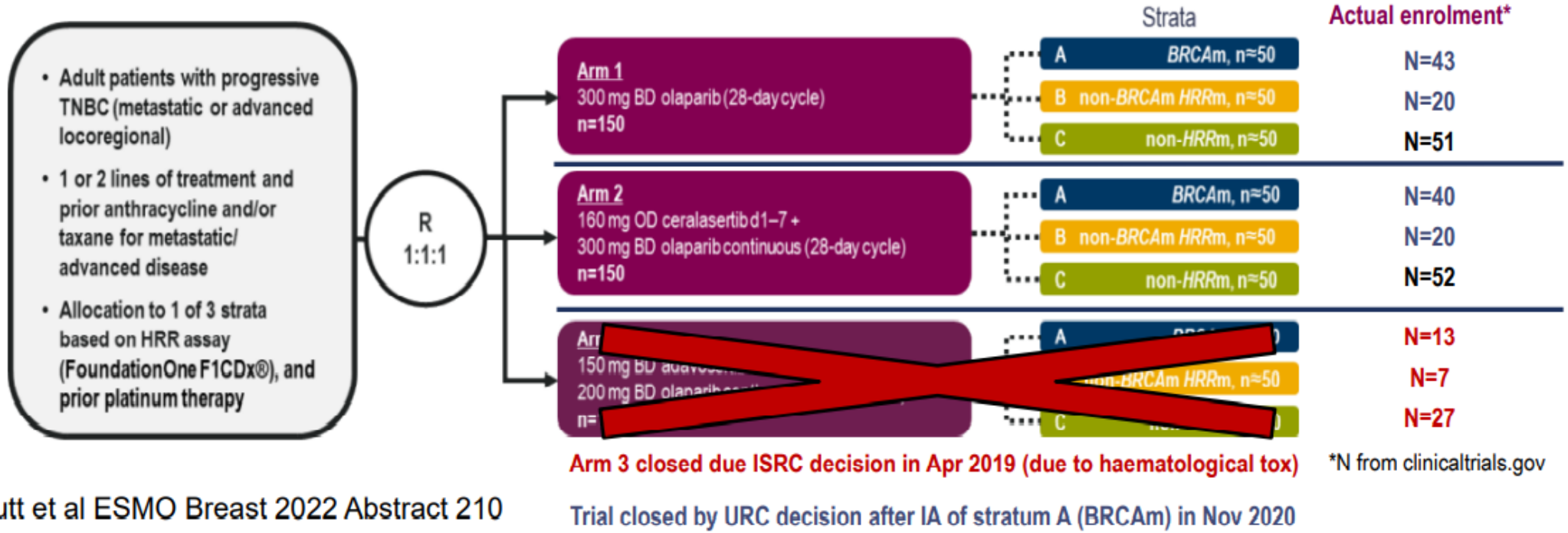


Hypothesis: Inhibition of key kinases in replication stress—ATR and WEE1—would enhance efficacy of Olaparib

Abbreviations: *ATM*, ataxia-telangiectasia mutated; ATR, ataxia telangiectasia and RAD3-related protein; *BRCA1/2*, breast cancer susceptible gene 1/2; DSB, double-strand break; PARP, poly (adenosine diphosphate-ribose) polymerase; *PALB2*, partner and localizer of *BRCA2*; Pol, polymerase; WEE1, mitosis inhibitor protein kinase; RPA, Replication protein A.

VIOLETTE (NCT03330847): STUDY DESIGN AND ACTUAL ENROLMENT

- Open-label, multicentre, phase 2 study: Patients were randomised in the three arms and stratified within each arm by pathogenic or likely pathogenic mutations in genes involved in the HRR pathway, and prior platinum therapy



Tutt et al ESMO Breast 2022 Abstract 210

Slide adapted by discussant Professor Valentina Guarneri

*n shown here depict planned enrolment. The 3 strata were to be capped to achieve ~150 patients within each stratum (~50 patients per treatment arm).
Abbreviations: BD, twice daily; *BRCA*m, *BRCA1/2*-mutated; *HRR*m, homologous recombination repair pathway mutation; OD, once daily; TNBC, triple-negative breast cancer.

PRIMARY ENDPOINT: PFS (BICR)

	Number (%) of PFS Events[a]		Median PFS, Months (90% CI)		HR (90% CI)	*P*-value
	Olaparib	Ceralasertib + Olaparib	Olaparib	Ceralasertib + Olaparib		
All	72/114 (63.2)	73/112 (65.2)	3.6 (2.9–5.4)	5.3 (3.7–5.5)	0.79 (0.59–1.04)	0.1822
*BRCA*m	23/43 (53.5)	25/40 (62.5)	7.3 (5.5–8.1)	7.4 (5.3–7.8)	1.02 (0.63–1.66)	0.9403
Non-*BRCA*m *HRR*m	15/20 (75.0)	14/20 (70.0)	1.9 (1.8–3.6)	3.9 (1.9–7.4)	0.54 (0.28–1.03)	0.1274
Non-*HRR*m	34/51 (66.7)	34/52 (65.4)	1.9 (1.8–2.9)	3.6 (2.7–3.8)	0.76 (0.50–1.14)	0.2959

[a]Progressive disease according to RECIST v1.1.

Stratum A (*BRCA*m) and Stratum B (Non-*BRCA*m *HRR*m) data were analysed prior to the planned primary analysis due to early closure of the study.
Abbreviations: *BRCA*m, *BRCA1/2*-mutated; CI, confidence interval; HR, hazard ratio; *HRR*m, homologous recombination repair pathway mutation; PFS, progression-free survival.

Marginal improvement in ORR and duration in non-HRRmut TNBC

- No significant difference in ORR with olaparib and ceralasertib + olaparib in *BRCA*m or non-*BRCA*m *HRR*m
- ORR was significantly higher in non-*HRR*m for ceralasertib + olaparib; the clinical significance of this finding is limited due to a lack of benefit in PFS

n/N (%)	Objective Response Rate		OR	90% CI	*P*-value
	Olaparib	Ceralasertib + Olaparib			
All	24/114 (21.1)	32/112 (28.6)	1.50	0.90–2.51	0.1932
*BRCA*m	19/43 (44.2)	20/40 (50.0)	1.25	0.61–2.61	0.6090
Non-*BRCA*m *HRR*m	3/20 (15.0)	4/20 (20.0)	1.42	0.36–6.02	0.6769
Non-*HRR*m	2/51 (3.9)	8/52 (15.4)	4.45	1.30–21.20	0.0425

		Arm 1: Olaparib	Arm 2: Ceralasertib + Olaparib
Median DoR	*BRCA*m	20.0 (16.0, 32.1)	32.0 (16.1, 56.4)
	Non-*BRCA*m *HRR*m	16.8 (16.3, 17.3)	17.1 (12.3, NC)
	Non-*HRR*m	11.4 (7.1, 15.7)	24.1 (15.1, 24.1)

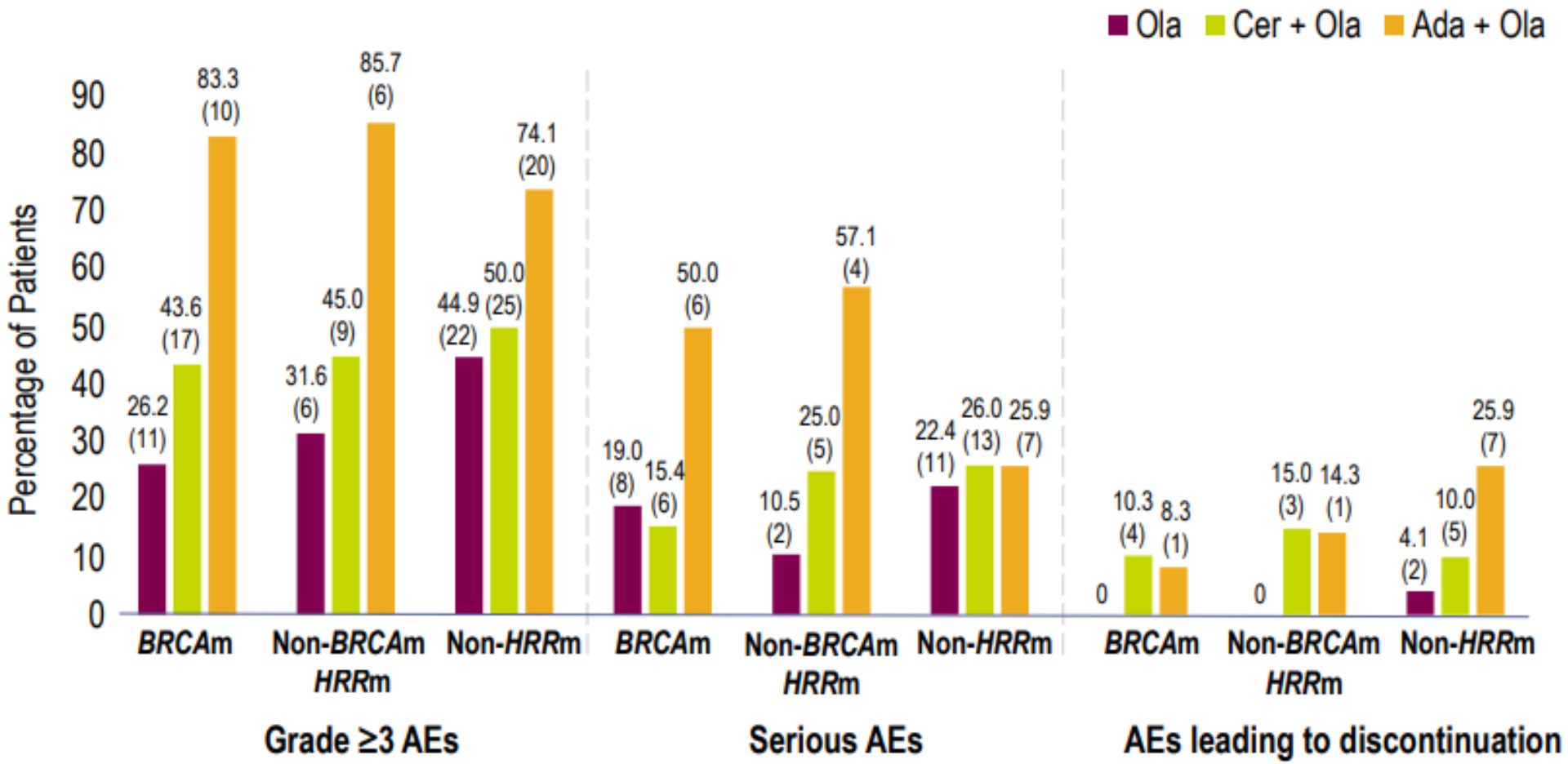
(wks, 25th percentile, 75th percentile)

Adapted Tutt et al ESMO Breast 2022 Abstract 210

ESMO BREAST CANCER

Abbreviations: CI, confidence interval; *BRCA*m, *BRCA1/2*-mutated; DoR, duration of response; *HRR*m, homologous recombination repair pathway mutation; OR, odds ratio; ORR, objective response rate; NC, not calculable.

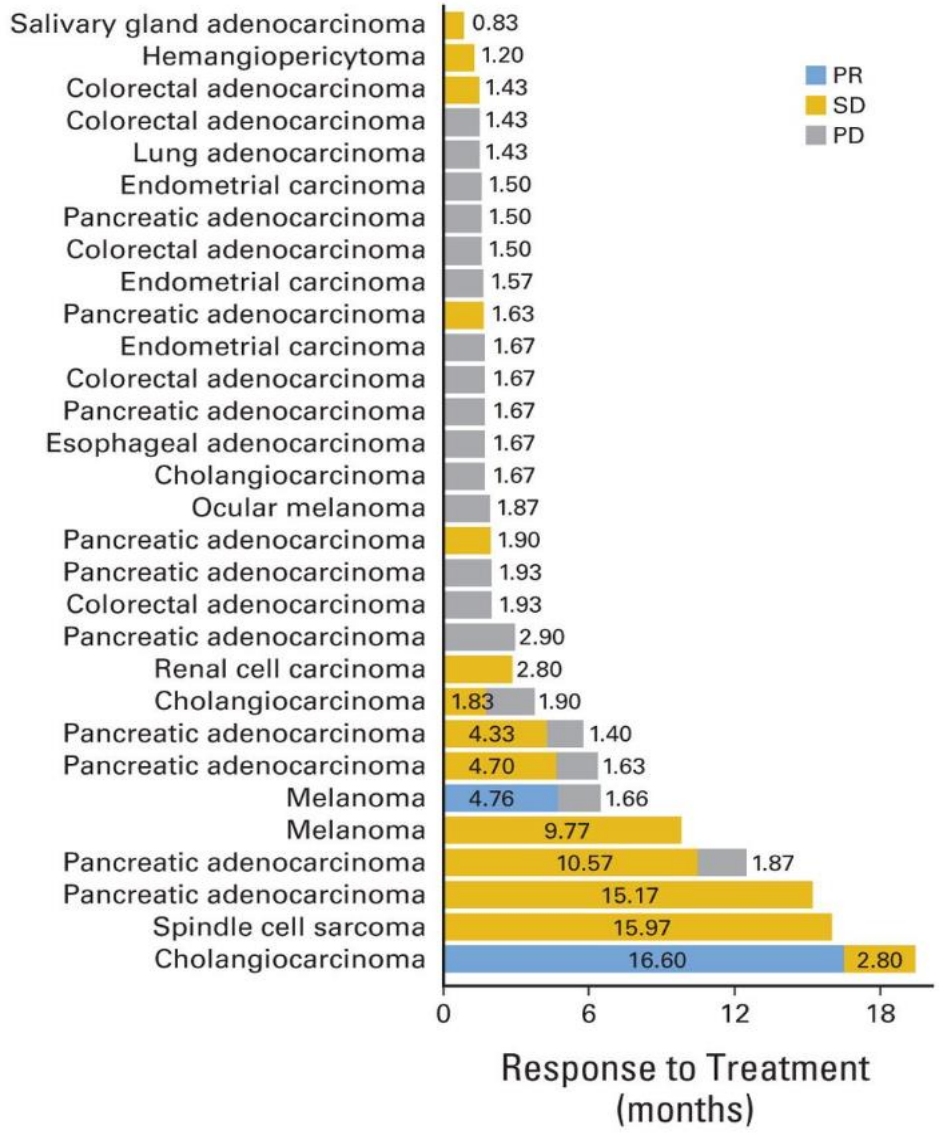
SECONDARY ENDPOINT: SAFETY AND TOLERABILITY BY STRATUM



Data shown as % (n).

Abbreviations: AE, adverse event; *BRCA*m, BRCA1/2-mutated; *HRR*m, homologous recombination repair pathway mutation.

Phase I Dose-Escalation Trial of Checkpoint Kinase 1 Inhibitor MK-8776 As Monotherapy and in Combination With Gemcitabine in Patients With Advanced Solid Tumors

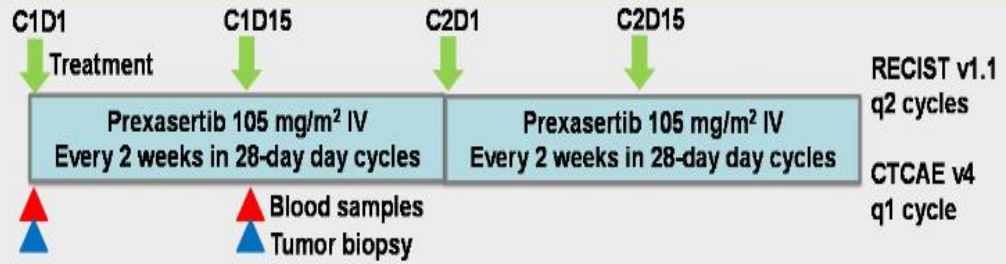


- Daud AJ, JCO 2015

Background

- HGSOC is the deadliest gynecologic malignancy in industrialized countries. Approximately 25-30% of HGSOC are deficient in homologous recombination (HR) repair due to *BRCA1* or *BRCA2* (BRCA1/2) germline or somatic mutations leading to sensitivity to PARP inhibitors (PARPis). However, they eventually progress on PARPis leaving unmet clinical need for novel therapeutic strategies.
- ATR/CHK1-mediated G2/M cell cycle checkpoint is necessary for coordination between DNA damage response and cell cycle control. Targeting of cell cycle signaling is a rational approach to induce DNA damage and tumor cell death.
- Preclinical data suggest ATR or CHK1 inhibitors (CHK1i) induce cell death in *BRCA* mutant HGSOC by causing replication stress and dysregulation of DNA damage responses. Furthermore, both CHK1i monotherapy and combination with PARPi have shown therapeutic activity against PARPi-resistant *BRCA1*-mutant HGSOC preclinical models.
- We hypothesized that prexasertib (LY2606368), the second generation CHK1i, would result in clinical activity in *BRCA* mutated HGSOC patients.

Study design



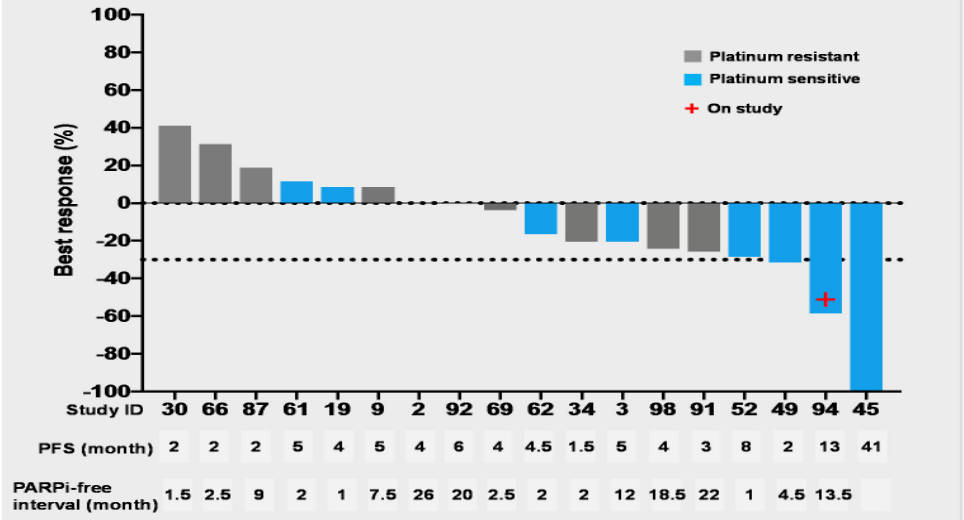
- Open label, single arm phase II trial of prexasertib
- RP2D dose 105 mg/m² IV prexasertib every 2 weeks in 28-day cycles
- Patients receive treatment until progression of disease, unacceptable toxicity, or withdrawal of consent

Table 2. Clinical response

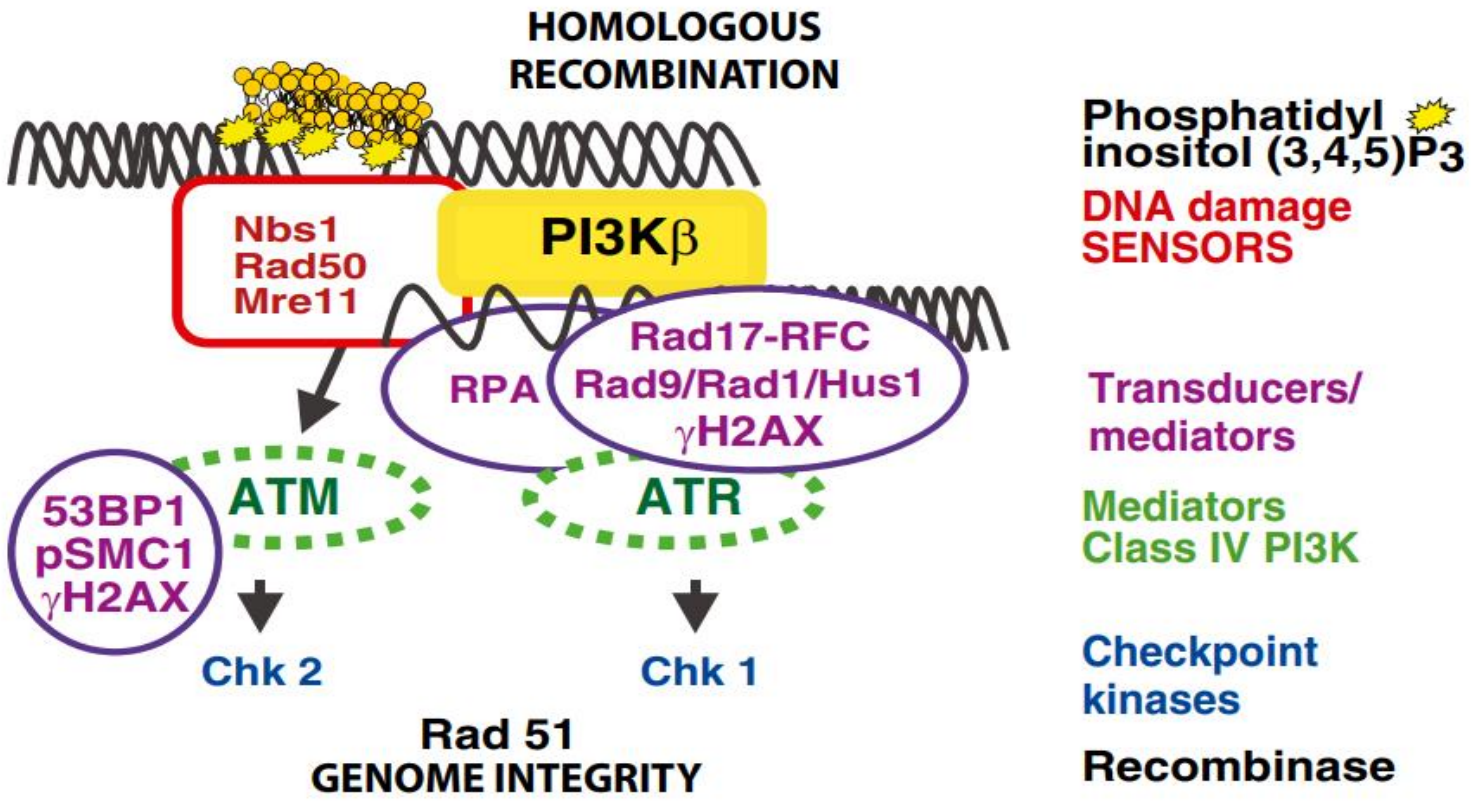
Best response	Number of patients (n = 18 evaluable)
CR	1 (5.5%) [41 months]
PR	1 (5.5%) [13+ months]
SD	12 (66.6%)
PD	4 (22.2%)
Response Rate (CR+PR)	2 (11%)
Clinical Benefit Rate (CR+PR+SD ≥ 4 months)	12 (66.6%)

CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease

Figure 2. Best response (n=18 evaluable)

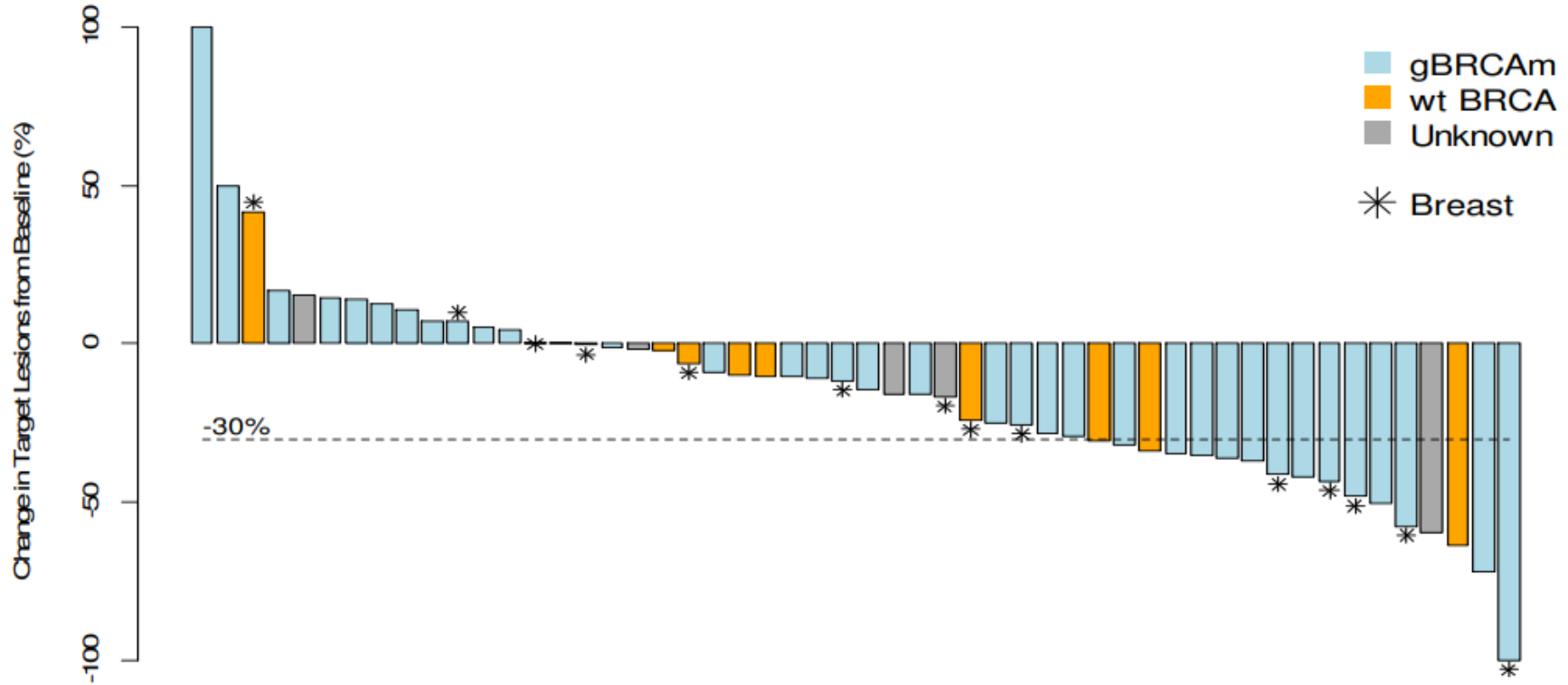


PRIMARY RESISTANCE: PI3K/AKT ACTIVATION IN BRCA1-/-



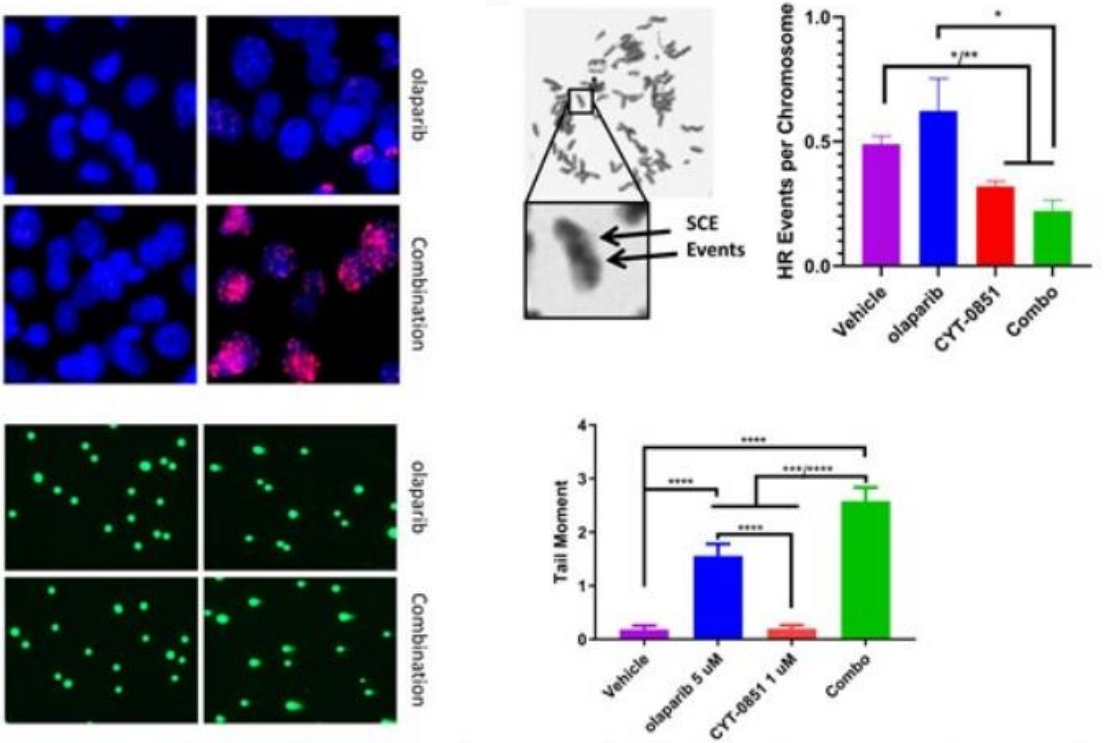
Kumar A, PNAS 2010

Phase I dose escalation study of the PI3kinase pathway inhibitor BKM120 and the oral poly (adp ribose) polymerase (PARP) inhibitor olaparib for the treatment of high grade serous ovarian and breast cancer



Matulonis U., Ann Oncol 2017

Rad51 inhibition using CYT-0851, shows anti-cancer activity in cellular models of breast cancer and acts synergistically with PARP inhibitors



igure 3: Combination of CYT-0851 and olaparib prevents homologous recombination and promotes DNA damage in 4T1 ells (mouse model triple negative breast cancer). (A) Immunofluorescent analysis after ionizing radiation showed ccumulation of γH2AX foci (red) in the nuclei (blue) of combination treated 4T1 cells. (B) Sister chromatid exchange (SCE) ssay was used to examine homologous recombination activity. Images show an example of a metaphase spread with bservable SCE events (blow up image). A reduction in events was observed with CYT-0851 (0.625μM) alone and in ombination with olaparib (2.5μM). (C) Neutral Comet assay performed under non-denaturing conditions resulted in increased ail moment in combination treated cells. Error bars represent SEM * p< 0.05; ** p< 0.01; *** p< 0.001; **** p< 0.0001

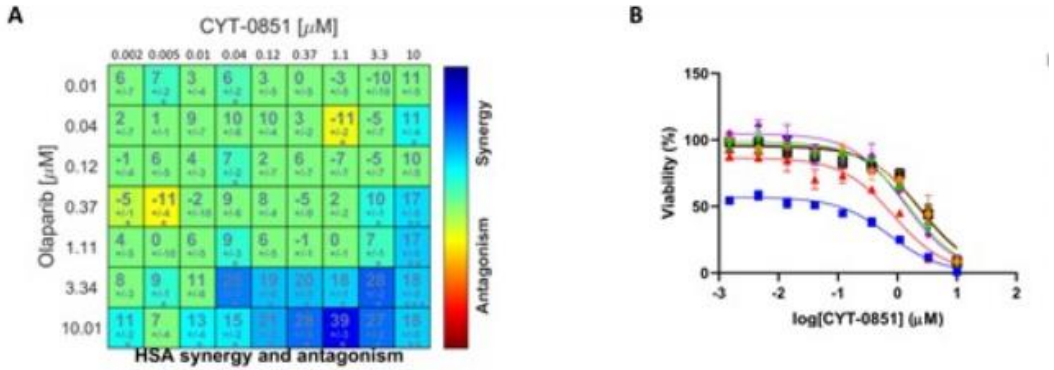


Figure 5: CYT-0851 and olaparib act synergistically in an *in vitro* model of human breast cancer. A matrix study was CYT-0851 and olaparib in an ER+, BRCA wildtype breast cancer cell line, T47D. (A) Synergy score was calculated with th biological replicates using the highest single agent (HSA) model. Synergy is represented in blue and antagonism is rep (B) Dose response curves that correspond with the synergy analysis. Concentration of CYT-0851 is plotted on the concentration of olaparib is an individual curve. Error bars represent SEM.

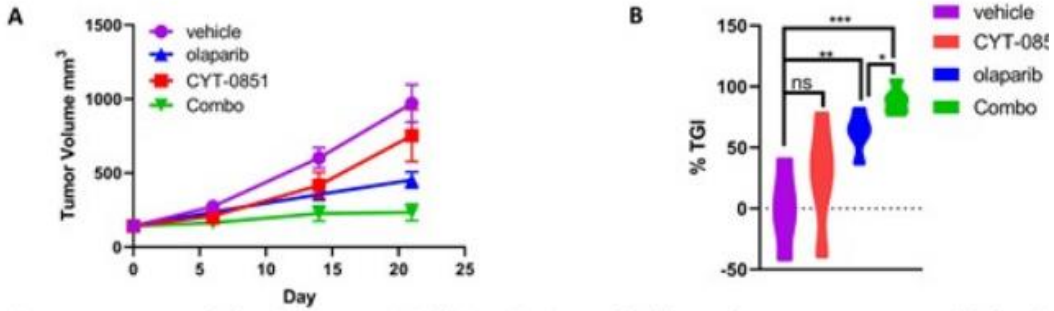
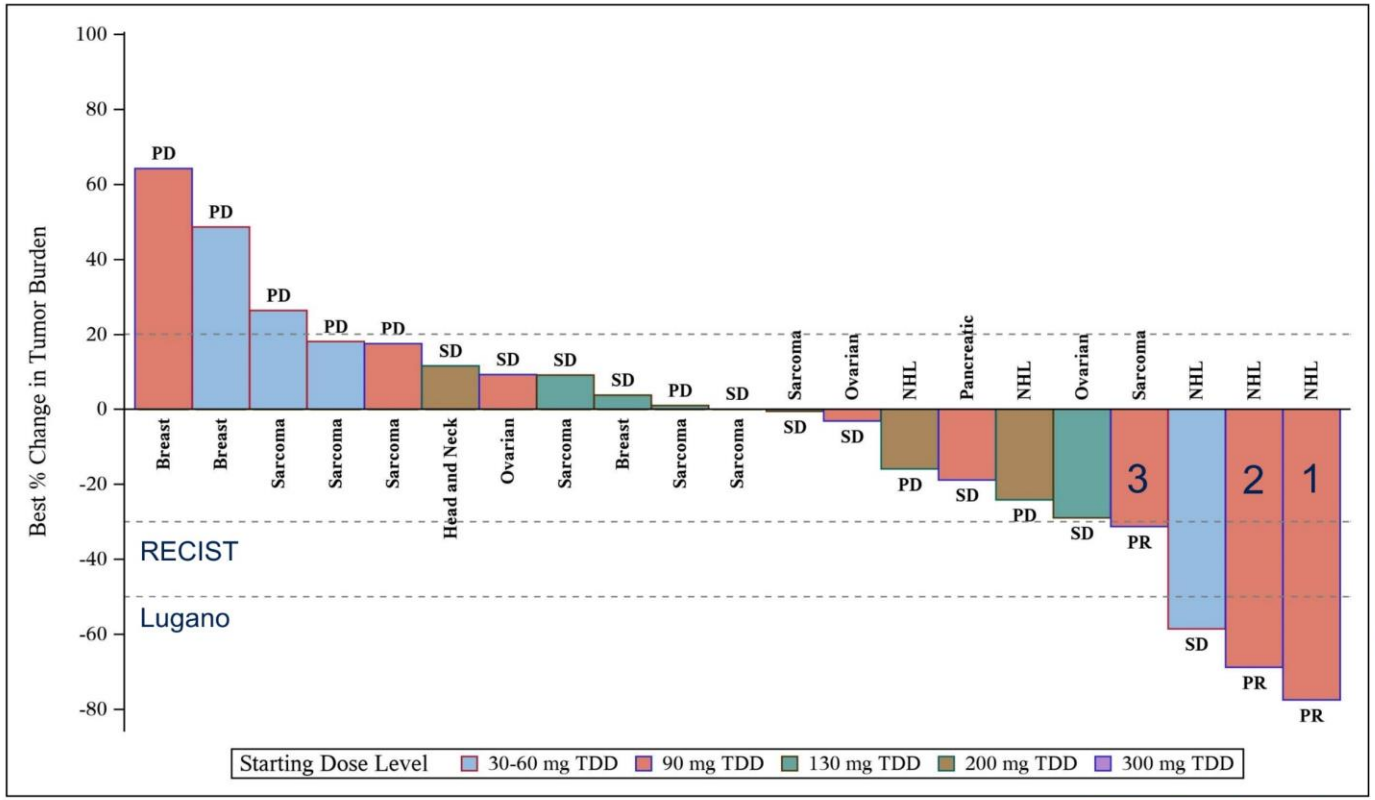


Figure 6: CYT-0851 and olaparib act synergistically in an *in vivo* model of human breast cancer. A PDX model of triple cancer (homozygous BRCA mutation/HRD +, RAD51 high expression) was subcutaneously engrafted onto the flanks mice. The tumors were allowed to reach a volume of about 150 mm³ prior to the animals being randomized into groups (vehicle, olaparib 100 mg/kg QD, CYT-0851 80 mg/kg QD, and olaparib + CYT-0851) of five animals each. (A) were measured weekly and graphed over time. (B) Percent tumor growth inhibition was calculated using the mean t

- *Joey L Guy, P2-05-05*

CYT-0851 Efficacy: Change in Tumor Burden



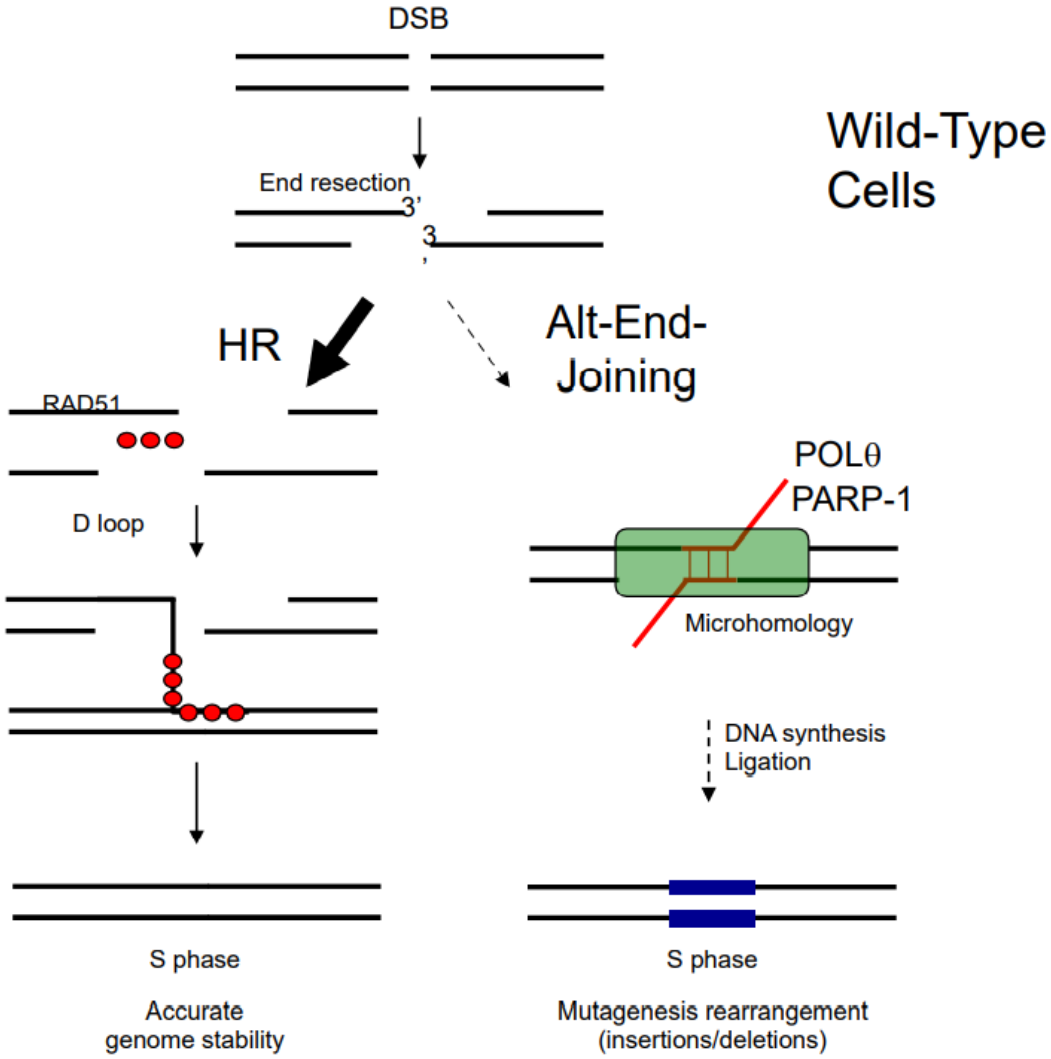
TDD = Total Daily Dose

21 patients were response-evaluable

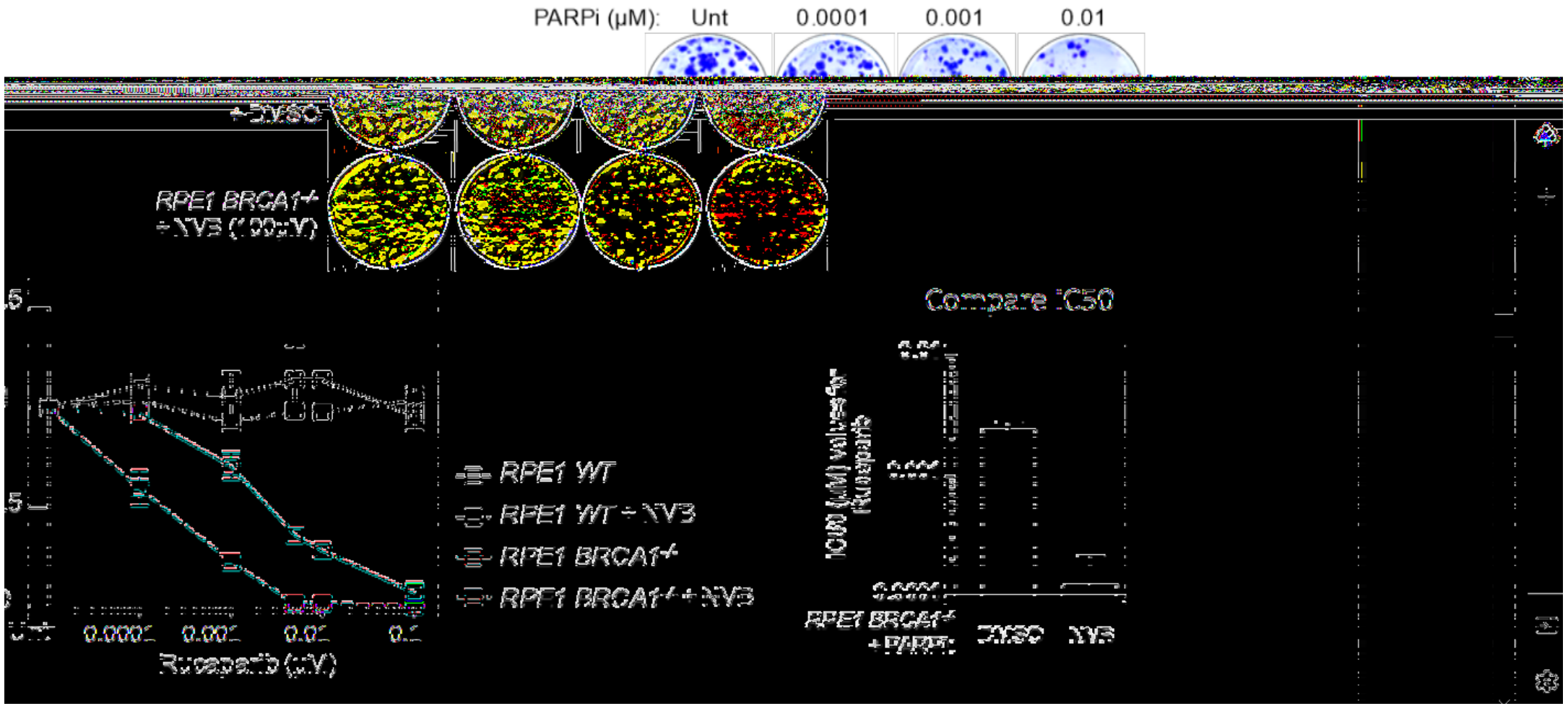
3 partial responses
1) DLBCL (Pt 013)
2) Follicular lymphoma (Pt 021)
3) Soft-tissue sarcoma (Pt 006) (unconfirmed)

- 10 patients had stable disease

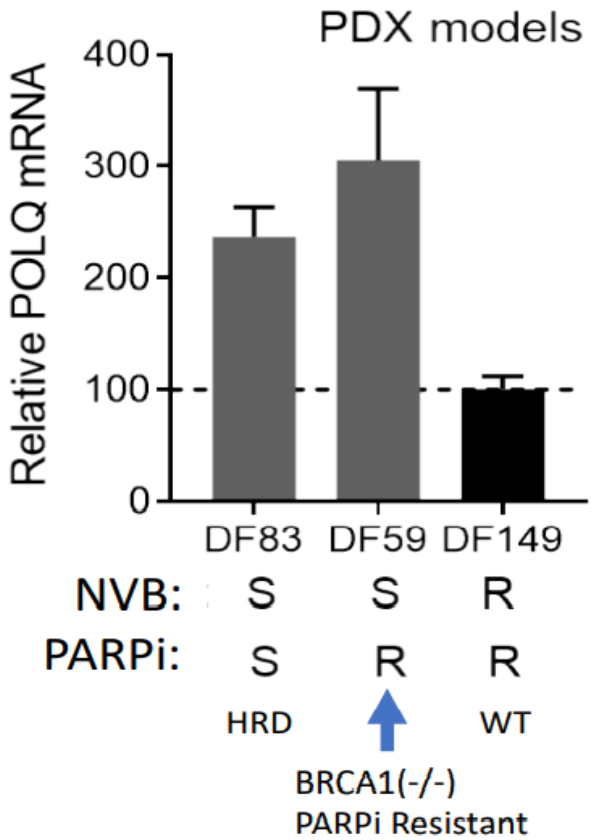
Two Pathways Repair Double Strand Breaks during S phase



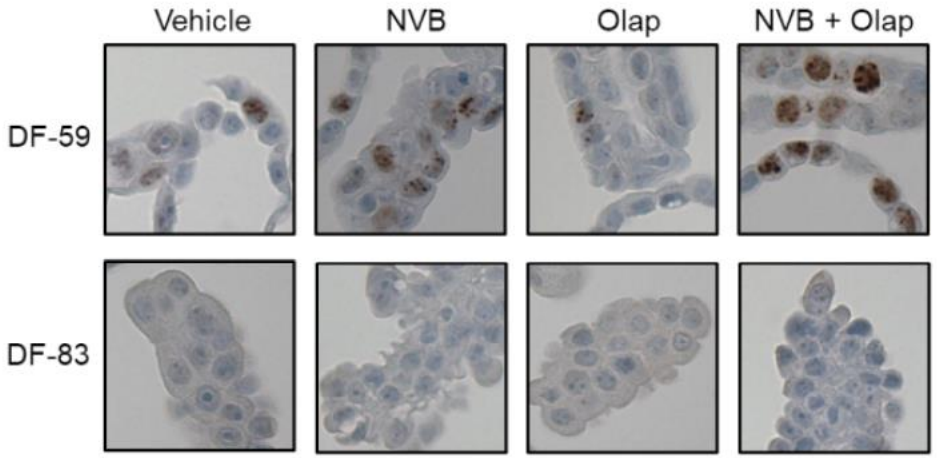
Synergistic effect of a combination of PARPi and NVB



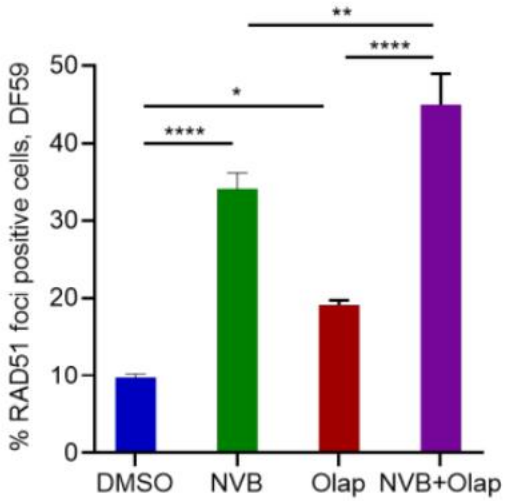
High POLθ expression is a predictive biomarker for NVB sensitivity.



Mechanism of Action: Inhibition of POLQ with NVB results in increased DSB end resection and increased toxic RAD51 levels



RAD51 IHC



High DSB end resection is a PD biomarker for POLQi response
Zatreanu et al, Nat Com 12: 3636, 2021

Predictive Biomarkers for Response to a POLQ inhibitor

BIOMARKERS	
ATM	LOSS
ATR	
BRCA1	
BRCA2	
FA Pathway	
53BP1	
TP53	
SHIELDIN complex	
REV7	
DYNL1	
TRIP13	Up Regulation
POLQ LEVEL	

Targeting DNA Repair with Combined Inhibition of NHEJ and MMEJ Induces Synthetic Lethality in *TP53*-Mutant Cancers

Jeffrey Patterson-Fortin[1,2], Arindam Bose[2,3], Wei-Chih Tsai[2], Carter Grochala[2], Huy Nguyen[2,3], Jia Zhou[2], Kalindi Parmar[2,3], Jean-Bernard Lazaro[2,3], Joyce Liu[1], Kelsey McQueen[2,3], Geoffrey I. Shapiro[1,3], David Kozono[2], and Alan D. D'Andrea[1,2,3]

Cancer Research 20, 3815, 2022

Summary:

1.Peposertib is a specific inhibitor of DNA-PK and NHEJ

2.CRISPR Screen: sgRNAs to POLQ and other MMEJ genes Results in Synthetic lethality with DNA-PK inhibitors

3.Cancer cells become resistant to DNA-PK inhibitors by Downregulating p53

4.Downregulation of p53 results in increased sensitivity to NVB. Provides rationale for combination of DNA-PKi and NVB

Conclusions

- ATMi provides sensitivity to PARPi inducing synthetic lethality in BC cells (Phase I study completed)
- CHEK2 inhibitors abrogate the G1/S cell cycle arrest induced by topoisomerase I inhibitor and gemcitabine
- ATRi bezosertib in addition with gemcitabine +/- cisplatin induces 26 % ORR and 43% SD in BRCAWT TNBC
- ATRi RP-3500 provides ≥ 50% ctDNA decline in 41% of pts in phase I (mostly ATM,BRCA1/2, CDK12 and PALB2m)
- Ceralasertib + Olaparib show a significant improvement in ORR and DoR in non HRR mutated TNBC
- Adavosertib + Olaparib show toxicity grade ≥ 3 in 53% (mostly haematological)
- CHEK1i plus gemcitabine in phase I trial provide ORR in pancreatic and cholangiocarcinomas
- PI3Ki + Olaparib overcome resistance to PARP in BRCA mutated and wtBRCA
- RAD51i in phase I provides SD in about 50% of patients (mostly lymphoma and sarcome)
- Novobiocin inhibits POLQ inducing increased DSB end resection and toxic RAD51 levels
- Novobiocin plus DNA-PK inhibitors induce synthetic lethality in p53 mutant cells