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Phase I study of sapacitabine and seliciclib in patients with advanced solid tumors.

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Background: Sapacitabine is an oral nucleoside analogue; the active metabolite CNDAC generates ssDNA breaks that are converted to dsDNA breaks (DSB) during subsequent replication, resulting in cell death. CNDAC-induced DSB repair is dependent on homologous recombination (HR). Seliciclib is an oral CDK2, 7 and 9 inhibitor, and sensitizes cells to CNDAC by decreasing DSB repair via compromise of HR protein activation. This phase I study evaluates sequential and concomitant sapacitabine and seliciclib treatment. **Methods:** Dose escalation was conducted in patients with incurable solid tumors with sapacitabine b.i.d. x 7 consecutive days (d 1-7) followed by seliciclib b.i.d. x 3 consecutive days (d 8-10) or sapacitabine q.d. concomitantly with seliciclib q.d. x 5 days per week x 2 weeks (d 1-5, 8-12). MTD was the highest dose level at which less than one-third of at least 6 patients experienced cycle 1 DLT. Skin biopsies were obtained to assess DNA damage following sapacitabine and seliciclib treatment. **Results:** 67 patients were treated including 45 BRCA mutation carriers (BRCA +ves). MTDs are sapacitabine 50 mg b.i.d./seliciclib 1200 mg b.i.d. and sapacitabine 250 mg q.d./seliciclib 200 mg q.d. respectively. DLTs were reversible elevations in transaminase and bilirubin, neutropenia/febrile neutropenia and pneumonia. The most frequent grade 3/4 adverse events included elevations in ALT (10%), AST (13%), bilirubin (6%) and alkaline phosphatase (7%), neutropenia (21%),

febrile neutropenia (6%), hyperglycemia (6%), hypokalemia (6%), and abdominal pain (7%). Skin biopsies showed a 2.3-fold increase in gH2AX staining post-sapacitabine (n = 16; p = 0.007) and a further 0.58-fold increase post-seliciclib (n = 12; p = 0.069). Six confirmed PRs occurred in BRCA +ves with pancreatic, ovarian and breast cancer. Response durations range from 49 to > 224 weeks in 4 ovarian and breast patients. SD was observed in 10 additional BRCA +ves with durations ranging from 26 to 81 weeks in 5 ovarian and breast cancer patients. **Conclusions:** Sequential and concomitant sapacitabine and seliciclib is safe with preliminary antitumor activity (35% PR + SD) in BRCA +ves, the status of which may be a potential biomarker for response across multiple tumor types. Clinical trial information: NCT00999401

A phase 1 study of sapacitabine and seliciclib in patients with advanced solid tumors

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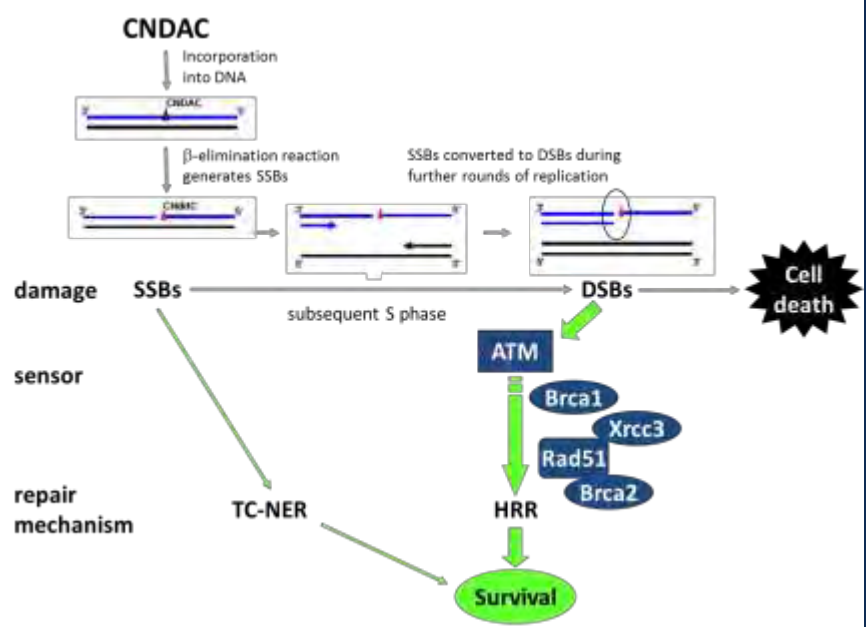
PRESENTED AT ASCO ANNUAL MEETING '16

Background: Sapacitabine



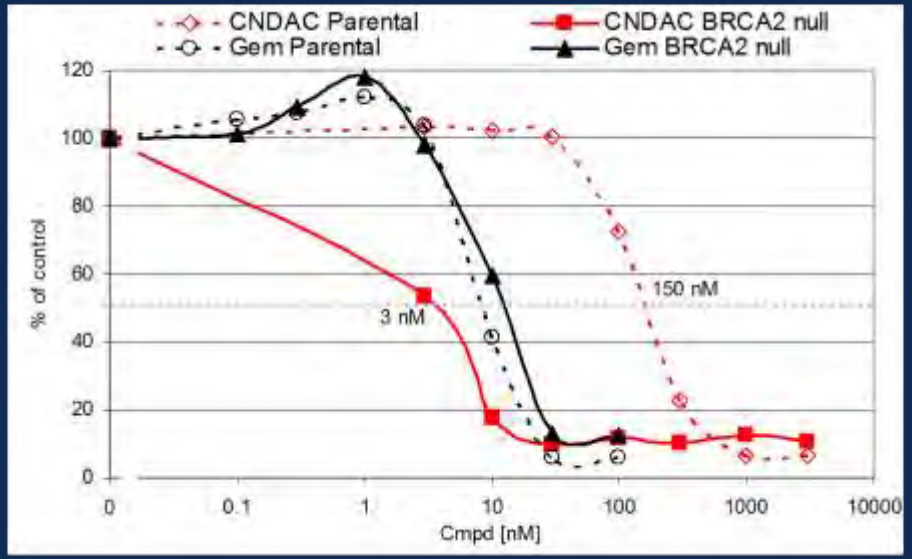
- Orally available 2'-deoxycytidine analogue, converted to CNDAC *in vivo*
- Incorporated into DNA during replication or repair, resulting in ssDNA breaks via a covalent rearrangement
- During further rounds of replication, ssDNA breaks converted to dsDNA breaks, resulting in cell death

Source: Adapted from Liu, X. et al. Expert Opin Investig Drugs 2012

Background: HR-deficient cells are highly sensitive to sapacitabine

- Unlike Ara-C or gemcitabine, repair of sapacitabine-induced DNA damage is dependent on the homologous recombination (HR) repair pathway

- *BRCA2* loss enhances sapacitabine (CNDAC) sensitivity 50-fold but does not alter gemcitabine sensitivity

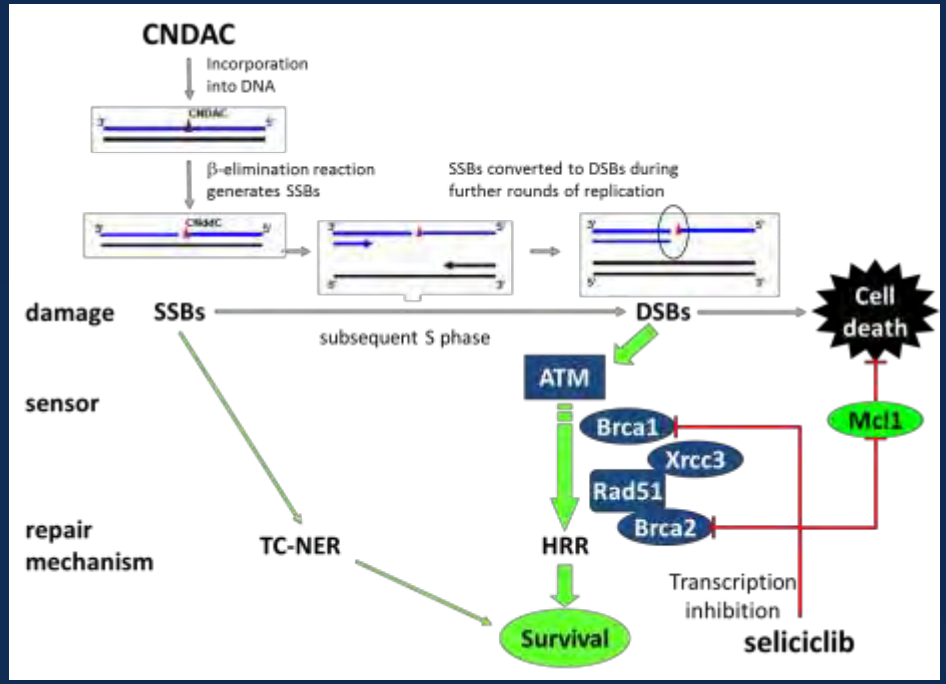


Colony forming assay in *BRCA2* WT and null isogenic DLD-1 colorectal cell lines

Frame et al. AACR 2010, Abs 3502.

Background: Seliciclib and synergy

- Seliciclib is a CDK2 and CDK9 inhibitor
- CDK9 inhibition results in reduced levels of MCL1 and other anti-apoptotic proteins with short half-lives enhancing sapacitabine-induced cell death
- CDK9 inhibition reduces expression of components of DNA repair pathways (e.g. BRCA proteins and RAD51)
- CDK2 inhibition disrupts both HR and NHEJ repair pathways



Background: Patient populations of interest for combined sapacitabine and seliciclib

BRCA wild type cancers (i.e. HR-proficient)

- Seliciclib will disrupt HR and sensitize cells to sapacitabine

BRCA-mutated cancers

- HR-deficient cancers may be sensitive to sapacitabine alone; apoptosis may be augmented by seliciclib
- *BRCA*-mutated cancers with residual or restored HR (i.e. after platinum or PARP inhibitor exposure) may be rendered HR-deficient with seliciclib and sensitized to sapacitabine

Background: Synergy *in vitro*

Tissue of origin	Cell line	CNDAC then seliciclib			seliciclib then CNDAC		
		ED50	ED75	ED90	ED50	ED75	ED90
NSCLC	ABC-1	1.01	0.94	0.87	0.67	0.61	0.56
	A549	0.98	0.84	0.74	0.79	0.76	0.76
	H23	1.01	1.00	1.00	0.90	0.82	0.78
	H358	0.35	0.52	0.91	0.37	0.23	0.37
	H441	0.77	0.63	1.12	0.39	0.41	1.14
	H460	2.20	1.28	0.79	0.60	0.54	0.50
	H520	0.71	0.74	0.78	0.59	0.59	0.61
	H1581	0.60	0.66	0.74	0.68	0.67	0.67
	H1944	0.28	0.21	0.23	0.73	0.49	0.42
	H2122	0.60	0.68	0.78	0.37	0.34	0.40
	LU99A	0.59	0.65	0.73	0.42	0.45	0.50
	SW1573	0.81	0.78	0.76	0.71	0.69	0.74
colon	HCT116	0.88	0.78	0.70	0.75	0.70	0.65
ovarian	PEO1	0.62	0.59	0.56	0.74	0.72	0.70
	PEO4	0.75	0.65	0.56	0.68	0.42	0.26

CI value	< 0.9	0.9 - 1.1	> 1.1
Drug Interaction	synergistic	additive	antagonistic

Sequential sapacitabine (CNDAC) and seliciclib are broadly synergistic in either order

Two Schedules

Sequential

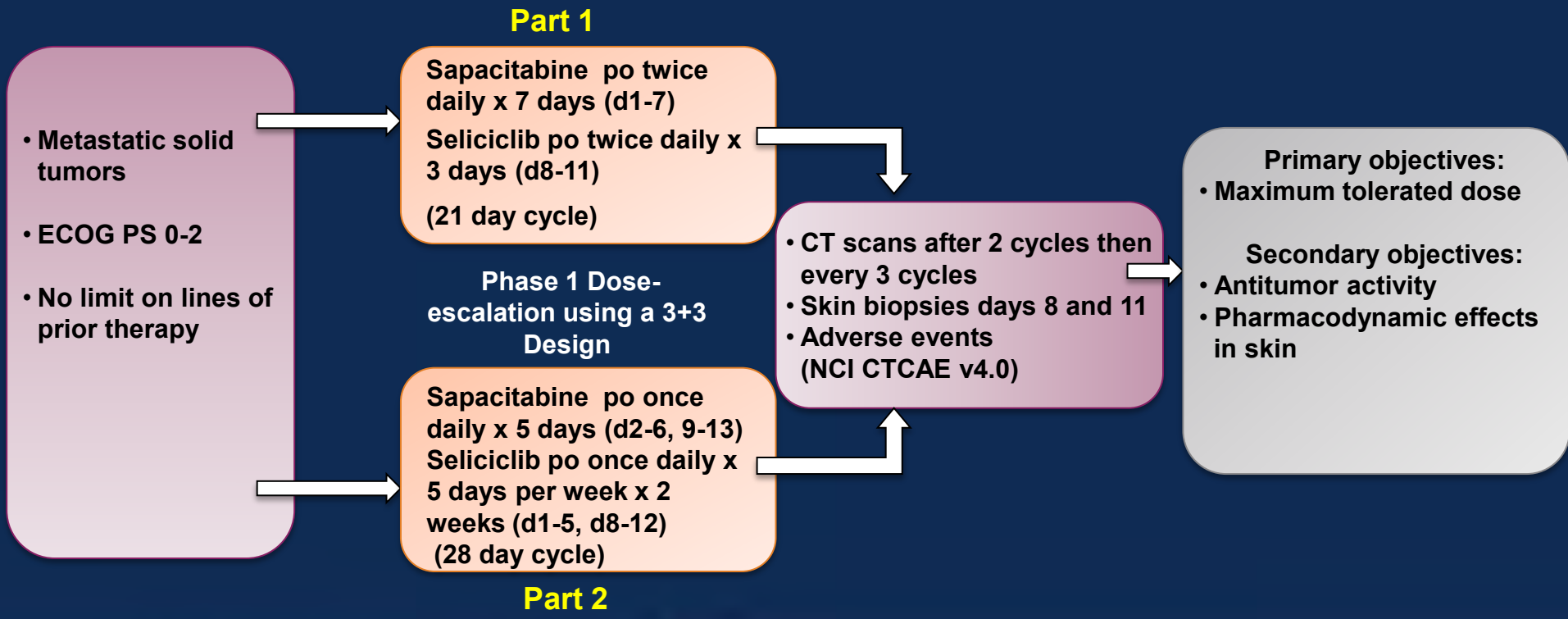
- Sapacitabine twice-daily for 7 days
- Subsequently, seliciclib twice-daily for 3 days, followed by an 11-day rest period
- Twice-daily administration of each drug based on short half-life and designed to achieve continuous exposure over the dosing interval

Interleaved

- Higher dose of sapacitabine given once daily to increase C_{max} and maximize DNA damage
- Seliciclib given once daily and alternated with sapacitabine at 12-hour intervals
- 5 days per week for two weeks followed by 2 weeks off

In each case, seliciclib given to disrupt HR repair, increase DNA damage and augment apoptosis

Study Design: Phase 1 Trial



Key Eligibility Criteria

- Incurable advanced solid tumor
- ECOG PS 0-2
- Evaluable Disease
- Adequate Organ Function
  - Absolute Neutrophil Count $\geq 1.5 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L
  - Total bilirubin $\leq$ ULN, ALT $\leq 1.5 \times$ ULN, Creatinine $\leq$ ULN

Dose Limiting Toxicity: Definition

The occurrence of any of the following events during cycle 1 (for Part 1) or during the first 2 cycles (Part 2) when judged to be clinically significant and related to sapacitabine and/or seliciclib

- **Grade 3 or 4 non-hematological toxicity (except alopecia, inadequately treated nausea, vomiting and diarrhea)**
- **Neutropenic fever or grade 4 neutropenia lasting longer than 5 days**
- **Grade 3 thrombocytopenia associated with bleeding or grade 4 thrombocytopenia**
- **Treatment delay > 2 weeks due to drug-related adverse events**

MTD is the dose level at which at least 2/3 or 3/6 patients experience DLT in cycle 1

Accrual per Dose Level

Sapacitabine b.i.d x 7days (mg)	Seliciclib b.i.d x 3 days (mg)	# Treated (n=38)	
50	400	10	PART 1
75	400	3	
50	800	6	
50	1200	19	
Sapacitabine q.d x 5 days (mg)	**Seliciclib q.d. x 5 days (mg)**	**# Treated (n=29)**	
150	200	6	PART 2
200	200	6	
250	200	10	
250	400	7	

Patient Characteristics

	PART 1		PART 2	
	BRCA carriers (n=16)	Others (n=22)	BRCA carriers (n= 28)	Others (n= 1)
Median age (range)	55 (31-75)	56 (32-80)	53 (33-66)	36
Gender				
Male	-	15	1	-
Female	16	7	27	1
ECOG PS				
0	7	5	16	1
1	9	17	12	-

Disease Characteristics

	PART 1		PART 2	
	BRCA carriers (n=16)	Others (n=22)	BRCA carriers (n= 28)	Others (n=1)
Tumor Type				
Breast	8	-	12	1
Colorectal	-	3	-	-
Non-small cell lung	-	6	-	-
Ovary	7	1	12	-
Pancreas	1	3	4	-
Other	-	9	-	-
Prior Systemic Therapy				
1-3	4	6	7	1
≥4	12	16	21	-
Prior Therapies				
Gemcitabine	7	13	12	-
PARP inhibitor	5	-	9	-
Platinum	5	9	20	-

Dose-Limiting Toxicities: Part 1

Sapacitabine bid x 7days (mg)	Seliciclib bid x 3 days (mg)	# Treated	DLT
50	400	10	Gr 3 elevation in AST* and Gr 4 neutropenia**(n=1)
75	400	3	Gr 4 neutropenia** (n=1) Gr 3 febrile neutropenia** (n=1)
50	800	6	-
50	1200	19	Gr 4 neutropenia** (n=1) Gr 4 AST and T. bili * (n=1) Gr 3 ALT/AST * (n=1) Gr 3 AST, ALT and T.bili* (n=1) Gr 3 Abdominal Pain* (n=1)

RP2D

*related to seliciclib
**related to sapacitabine

Dose-Limiting Toxicities: Part 2

Sapacitabine qday x 5 days (mg)	Seliciclib qday x 5 days (mg)	# Treated	DLT
150	200	6	Gr 3 ALT* (n=1)
200	200	6	Gr 3 ALT * (n=1) Gr 3 pneumonia** (n=1)
250	200	10	Gr 3 febrile neutropenia** (n=2)
250	400	8	Gr 3 AST * (n=1) Gr 3 AST/ALT * (n=1)

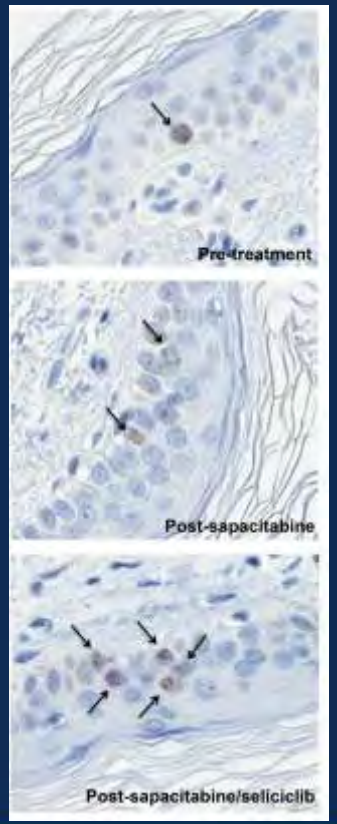
RP2D

*related seliciclib
**related to sapacitabine

Common Adverse Events

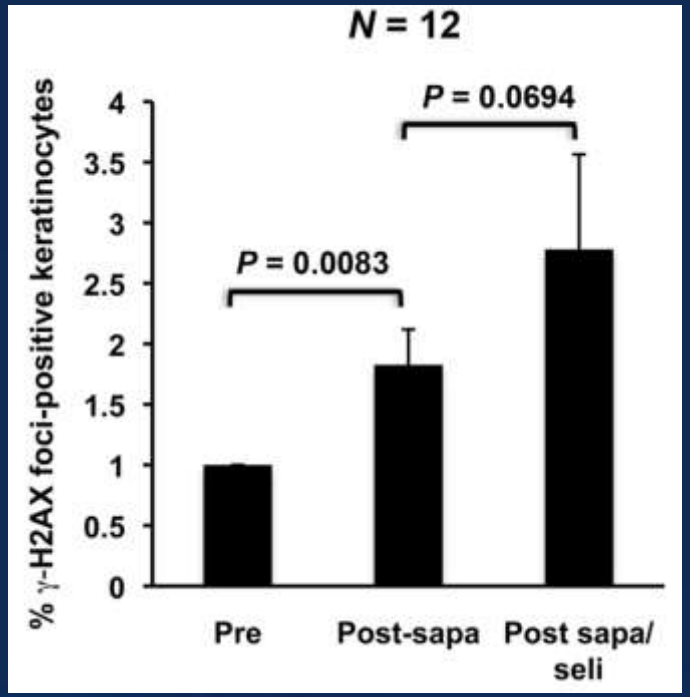
	PART 1 (n=38)		PART 2 (n= 29)	
Adverse Event	Grade 1-2 (%)	Grade 3-4 (%)	Grade 1-2 (%)	Grade 3-4 (%)
Anemia	15 (39.5)	-	5 (17.2)	-
Neutropenia	3 (7.9)	6 (15.8)	7 (24.1)	8 (27.6)
Constipation	11 (28.9)	2 (5.3)	6 (20.7)	-
Diarrhea	17 (44.7)	-	10 (34.5)	1 (3.4)
Nausea	22 (57.9)	1 (2.6)	17 (58.6)	1 (3.4)
Vomiting	16 (26.3)	-	12 (41.4)	1 (3.4)
AST elevation	6 (15.8)	6 (15.8)	2 (6.9)	3 (10.3)
Fatigue	18 (47.4)	2 (5.3)	17 (58.6)	1 (3.4)
Decreased Appetite	14 (36.8)	-	7 (24.1)	-

Treatment-mediated DNA damage



Patient 16

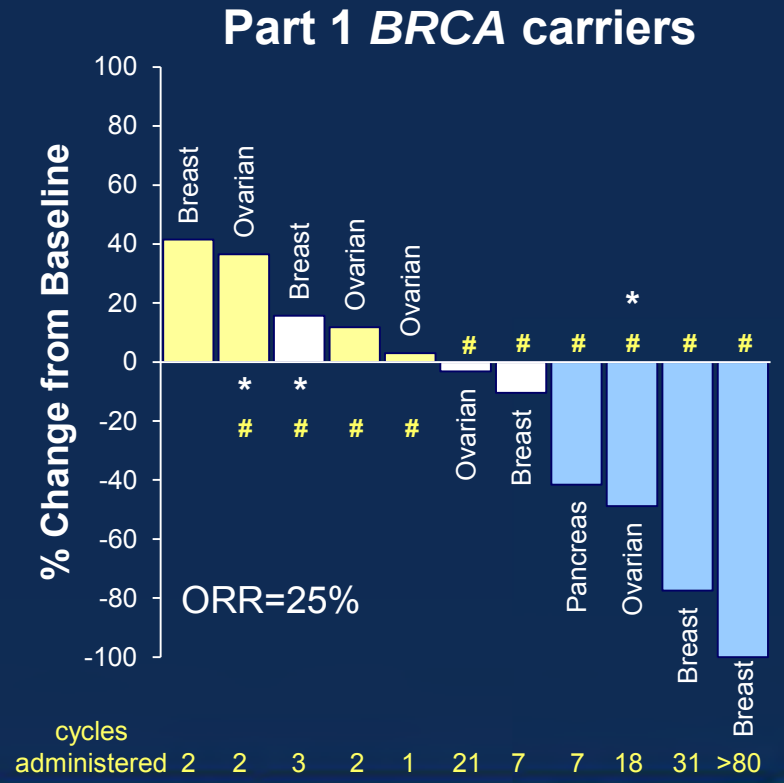
γ–H2AX foci

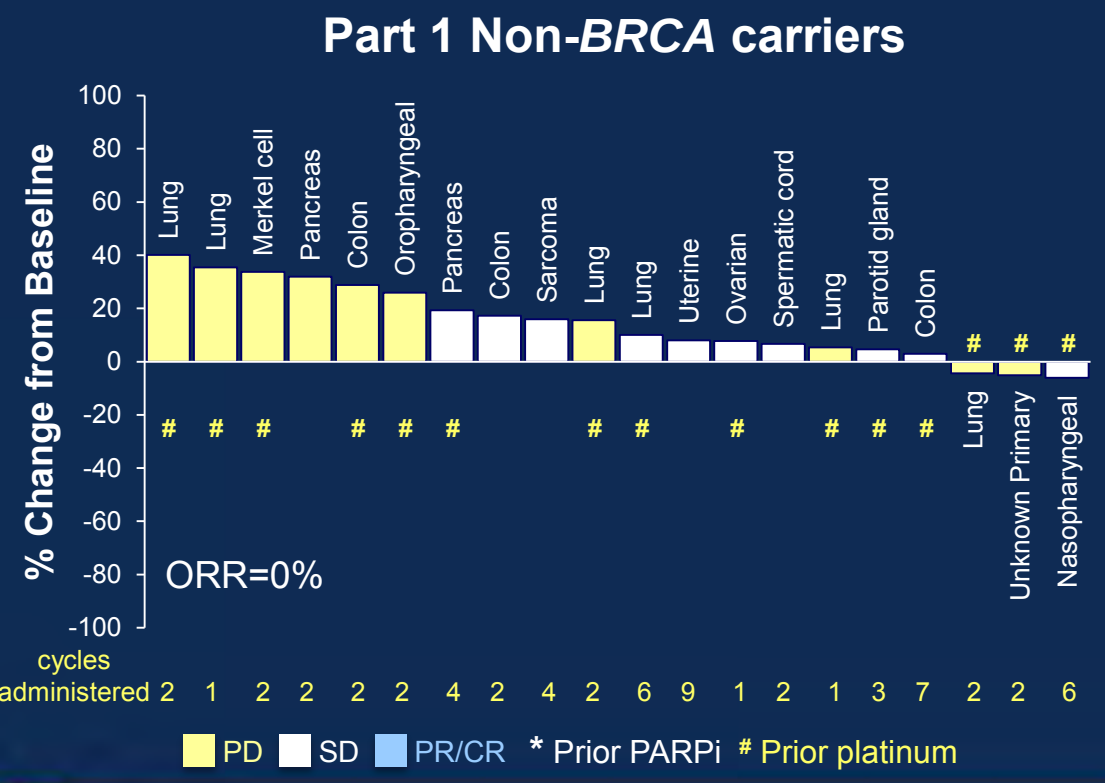


Best Response

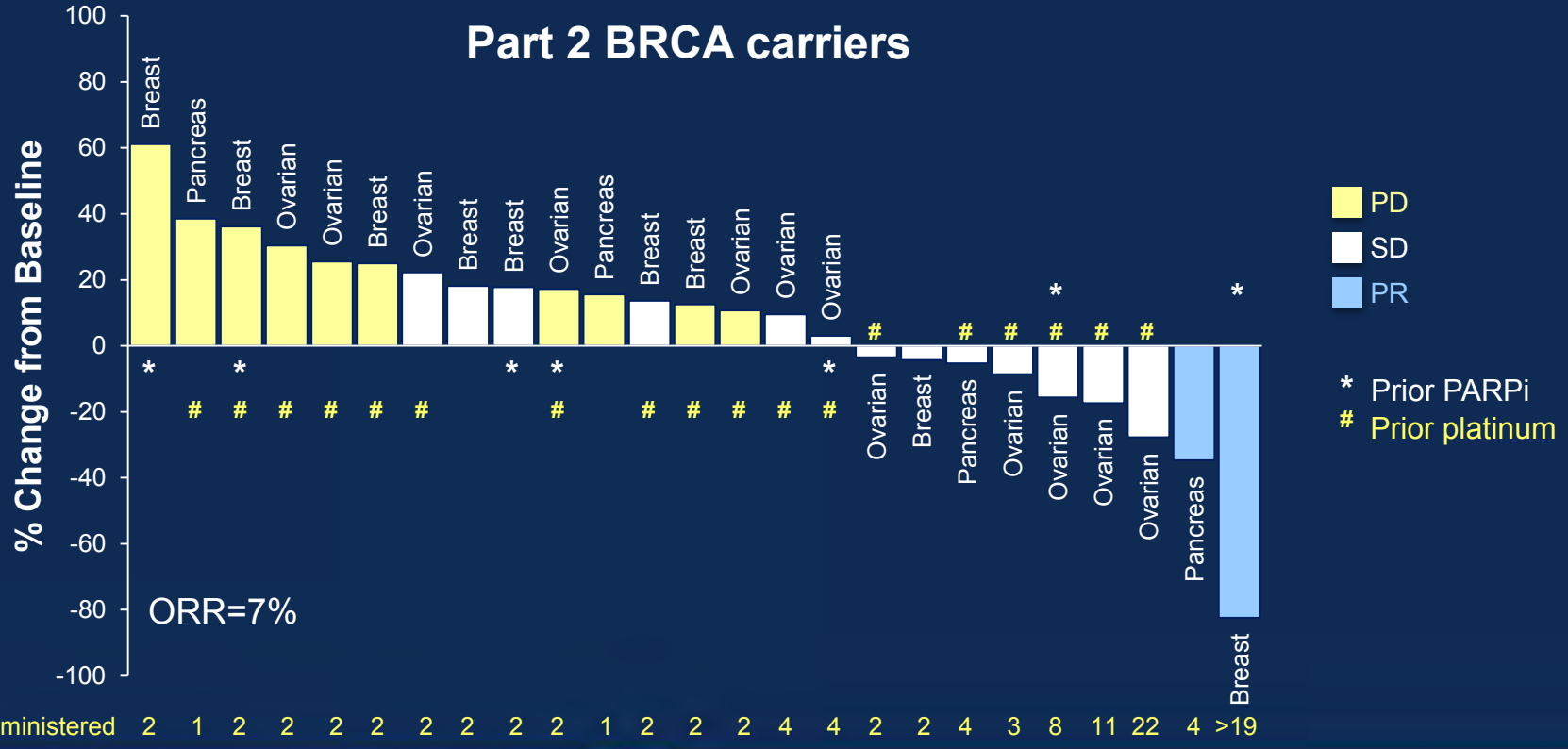
	PART 1		PART 2	
	BRCA carriers (n=16)	Others (n=22)	BRCA carriers (n= 28)	Others (n=1)
CR	1	-	-	-
PR	3	-	2	-
SD	2	6	7	1
ORR	25%	0%	7%	0%
Disease Control (CR/PR/SD)	6 (37.5%)	6 (27.3%)	9 (32.1%)	1 (100%)

Best Response (all cycles)





Best Response (all cycles)



RECIST Evaluable BRCA Carriers

Cancer	*Best Response*	*Prior Treatment*	*Total cycles*
Part 1	*(n=16)*		
Breast	CR	adriamycin, cyclophosphamide, paclitaxel, cisplatin	>80
Breast	PR	adriamycin, cytoxan, paclitaxel, carboplatin	31
Ovary	SD	paclitaxel, carboplatin, gemcitabine	21
Ovary	PR	paclitaxel, carboplatin, gemcitabine, topotecan, iniparib	18
Breast	SD	tamoxifen, raloxifene, anastrozole, adriamycin, Cytoxan, paclitaxel, carboplatin, navelbine	7
Pancreas	PR	gemcitabine, 5-FU, oxaliplatin	7
Part 2	*(n=28)*		
Breast	PR	adriamycin, cytoxan, paclitaxol, capecitabine, irinotecan, ABT-888 (PARP inhibitor), MPDL3280A	>19
Ovary	SD	paclitaxel, carboplatin, doxil	22
Breast	SD	adriamycin, cytoxan, capecitabine, faslodex	12
Ovary	SD	paclitaxel, carboplatin, doxil, gemcitabine, topotecan, cytoxan, avastin	11
Ovary	SD	paclitaxel, carboplatin, doxil, olaparib (PARP inhibitor), cediranib	8
Ovary	SD	paclitaxel, carboplatin	4
Ovary	SD	paclitaxel, carboplatin, doxil, gemcitabine, alimta, cytoxan, avastin, olaparib (PARP inhibitor)	4
Pancreas	PR	gemcitabine, abraxane, docetaxel	4
Pancreas	SD	gemcitabine, cisplatin, abraxane, folfox, TH-302	4

Conclusions

- Recommended Phase 2 dose of sapacitabine and seliciclib
  - Sapacitabine 50 mg b.i.d d1-7, seliciclib 800 mg b.i.d. d8-10 (21 day cycle)

  OR
  - Sapacitabine 250 mg q.d. d 2-6, 9-13, seliciclib 200 mg q.d. d1-5,8-12 (28 day cycle)

- Pharmacodynamic effect of sapacitabine and augmentation by seliciclib observed in skin biopsies

Conclusions

- Stable disease was the best response among patients who are non-*BRCA* carriers
- Partial responses and prolonged stable disease observed in *BRCA* carriers, including some who had already progressed through a PARP inhibitor or platinum
- The seliciclib dose in the Part 2 schedule may be too low to effectively enhance the activity of sapacitabine

Ongoing and Future Plans

- Further evaluation in *BRCA* carriers is warranted
  - Ongoing expansion in *BRCA* mutation carriers with metastatic breast cancer using Part 1 dosing schedule
- Ultimately, randomization of sapacitabine to the combination will help assess contribution of seliciclib

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