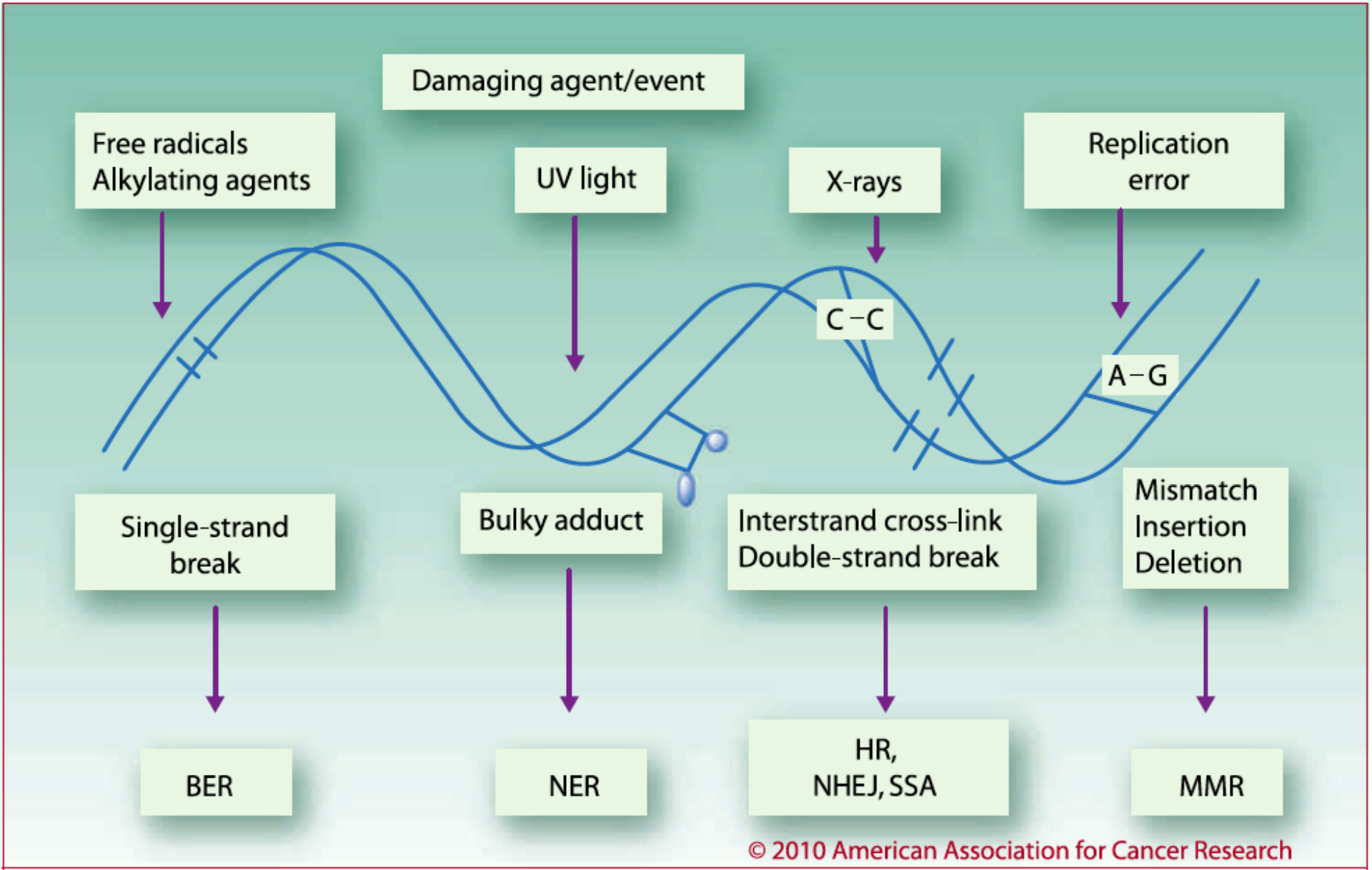
PARP AS A NOVEL THERAPEUTIC TARGET IN CANCER

Christina M. Annunziata, MD, PhD

Medical Oncology Branch, NCI

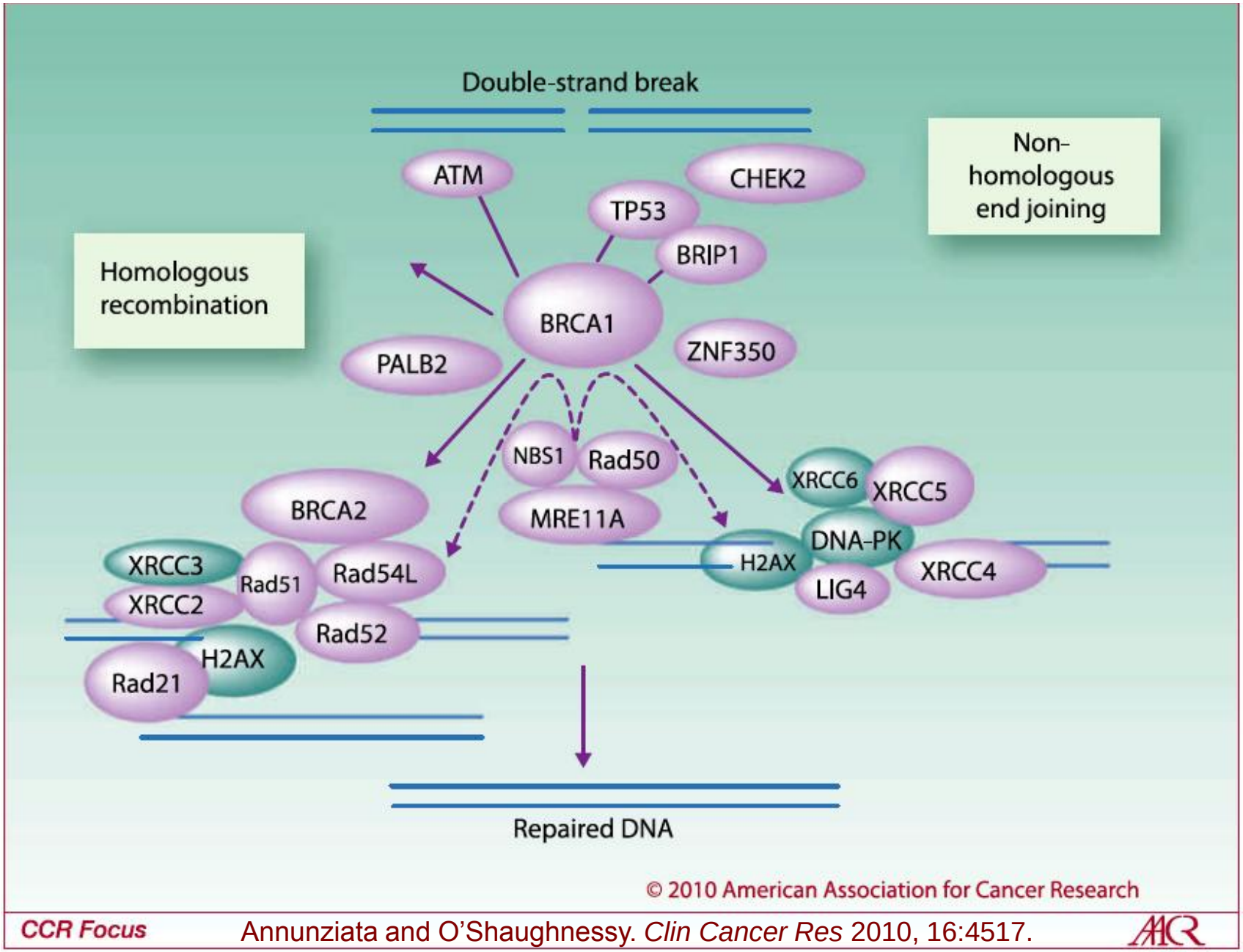
I have no financial disclosures.

DNA Damage and Mechanisms of Repair



Annunziata and O'Shaughnessy. *Clin Cancer Res* 2010, 16:4517.

Mechanisms of DNA Double Strand Break Repair

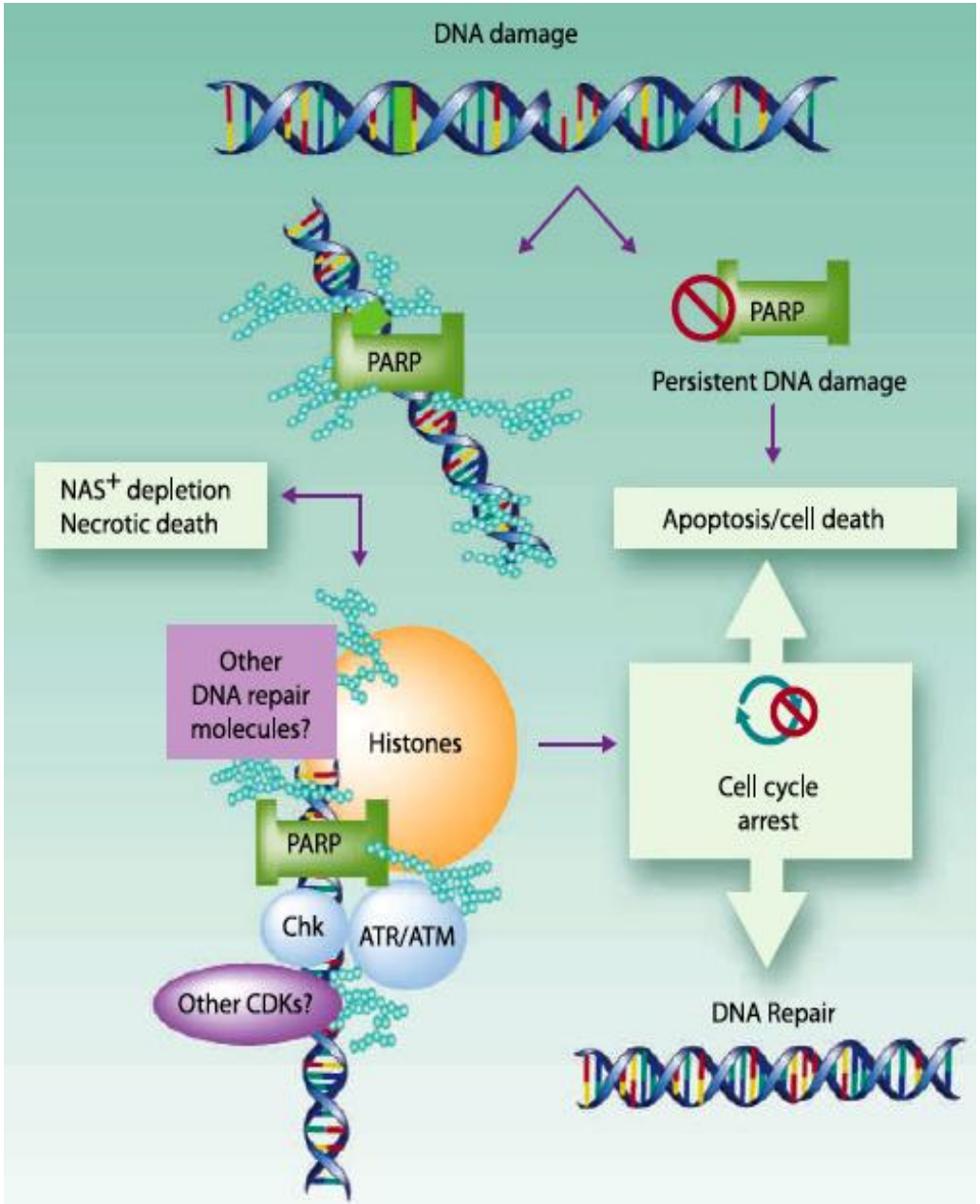


Inherited Defects in Homologous Recombination

Gene mutated	Function(s) affected
BRCA1	Cell-cycle arrest; recruitment of HR repair complex
BRCA2	HR repair complex assembly
PALB2	HR repair complex assembly
BRIP1	DNA helicase activity
MRE11	Assembly and activation of HR and NHEJ repair complexes
RAD50	Assembly and activation of HR and NHEJ repair complexes
NBS1	Assembly and activation of HR and NHEJ repair complexes
ATM	Activation of HR repair complex

Annunziata and O'Shaughnessy. *Clin Cancer Res* 2010, 16:4517.

PARP mechanism of action



- Identifies damaged DNA
- Repairs single-strand DNA breaks
- Involved in NHEJ
- Hyperactive in HR-deficient cells

Annunziata and O'Shaughnessy. *Clin Cancer Res* 2010.

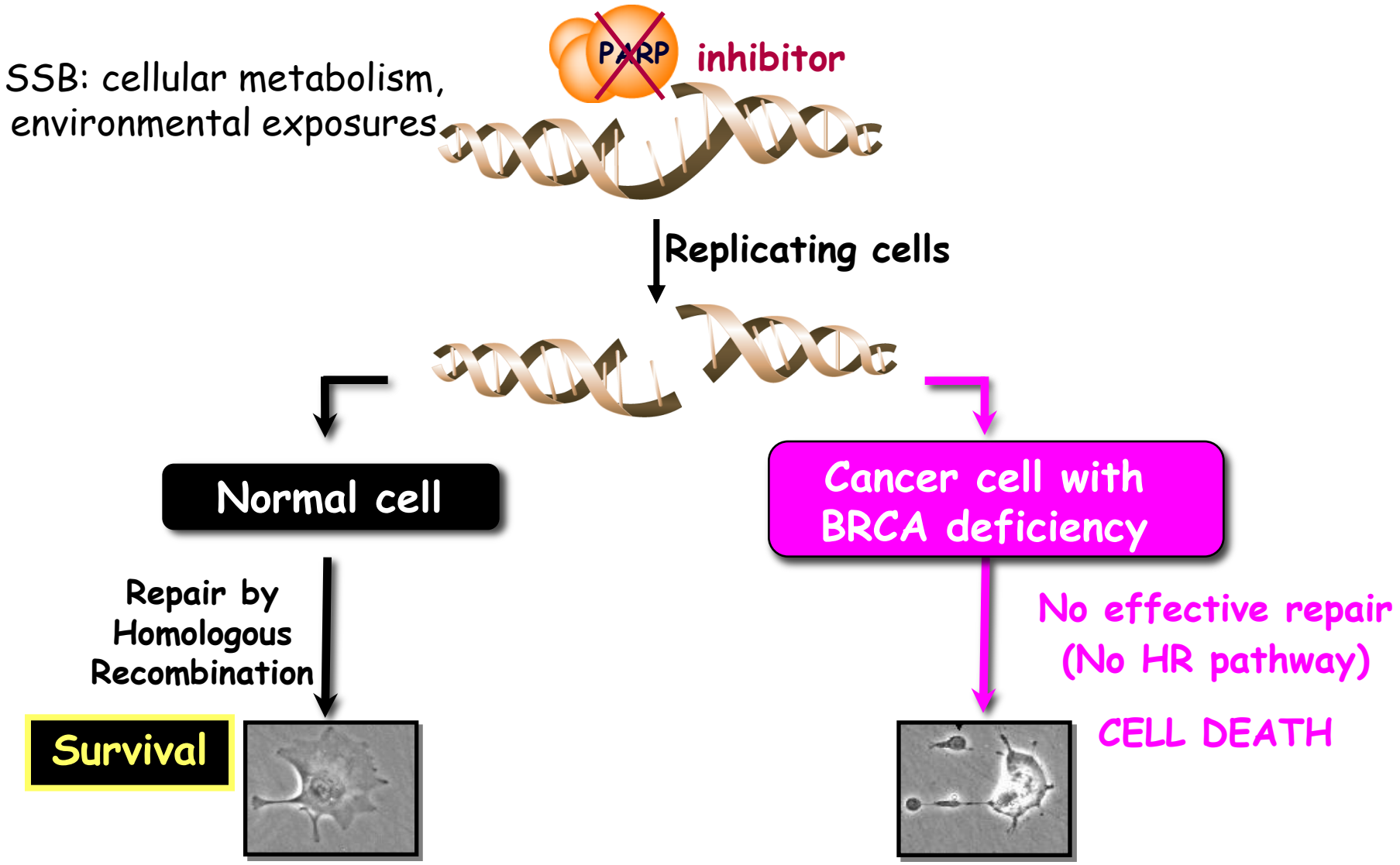
PARP inhibitors in BRCA-mutant cancers

- **PARP is required for repair of single-strand DNA breaks**
- **SSB are converted to double-strand breaks at replication forks**
- **Loss of BRCA function impairs repair of DNA double-strand breaks**
- **Accumulation of DSB overwhelms backup repair mechanisms in BRCA (HR) – deficient cells**
- **This should result in cell lethality**

PARP inhibitors in BRCA-mutant cancers

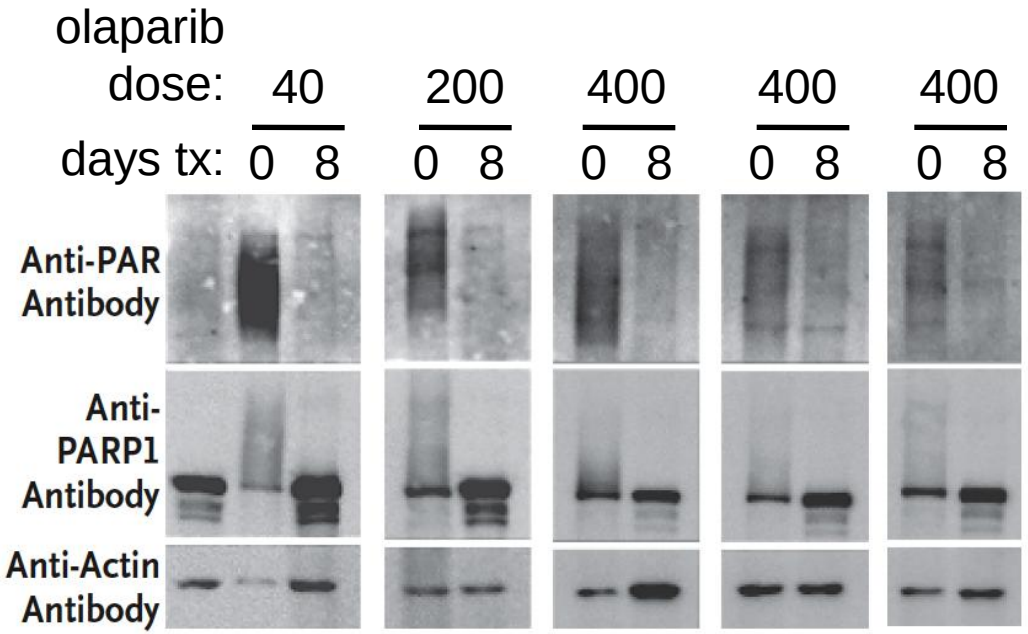
- **Non-cancer cells in carriers retain 1 normal copy of the BRCA gene**
  - Non-carriers have 2 normal copies
- **Some BRCA may result in less susceptibility PARP inhibition death**
- **A validated molecular target in a unique patient population**
  - Testable in clinical trials
  - Side effects may be different in mutation carriers

PARP inhibitors in BRCA-mutant cancers

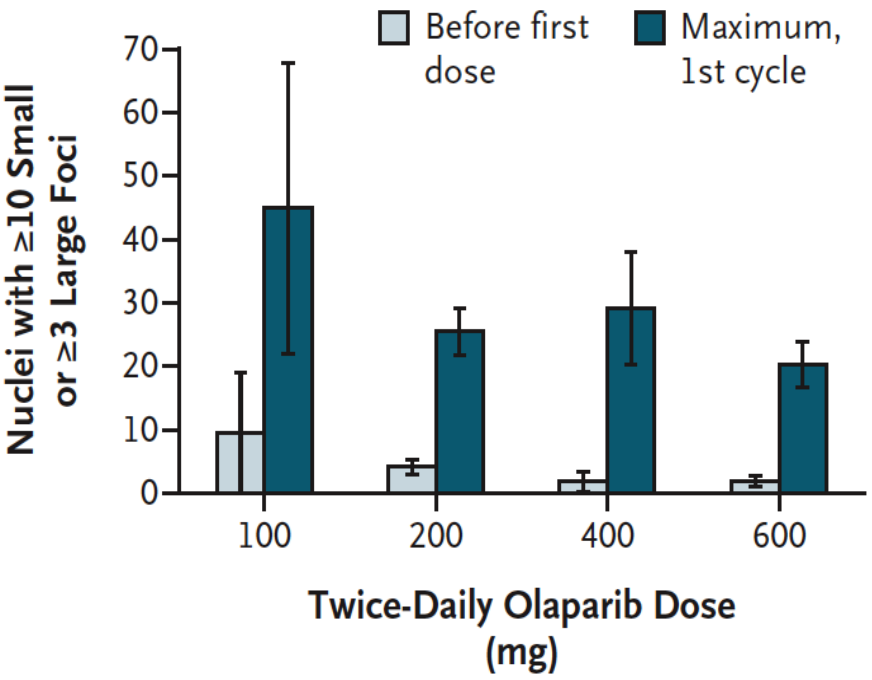


Phase 1 “proof-of-concept” in BRCA-mutant cancers

Loss of PAR in tumors



DNA damage in hair follicles

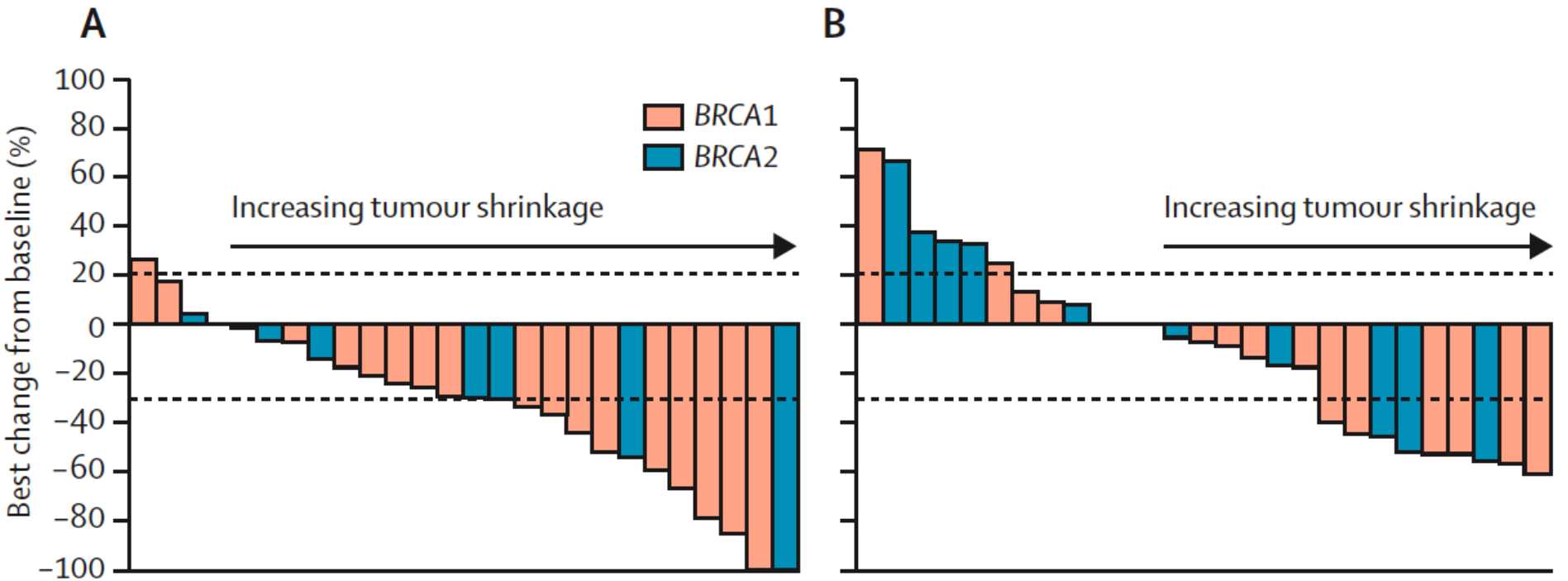


Fong et al, NEJM 361:123, 2009

Phase II - BRCA-Mutated Breast Cancer

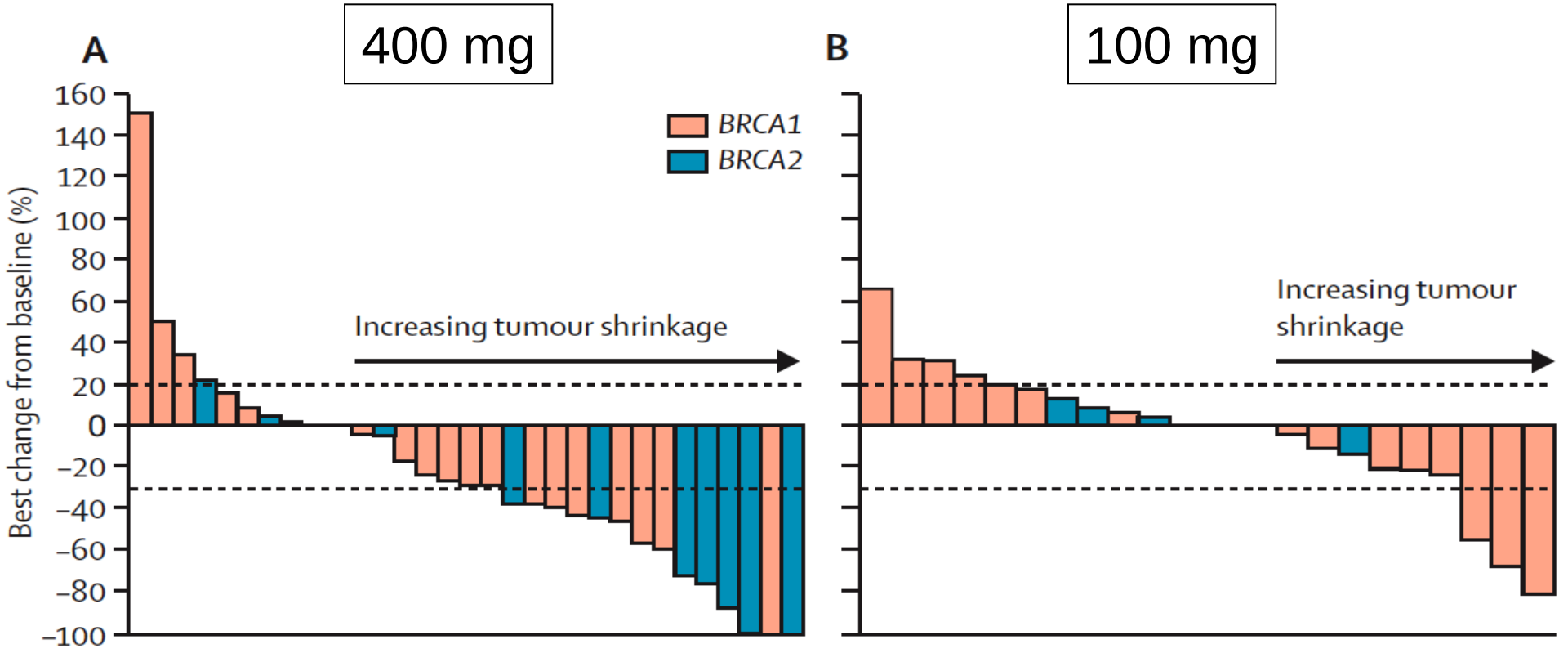
400 mg

100 mg



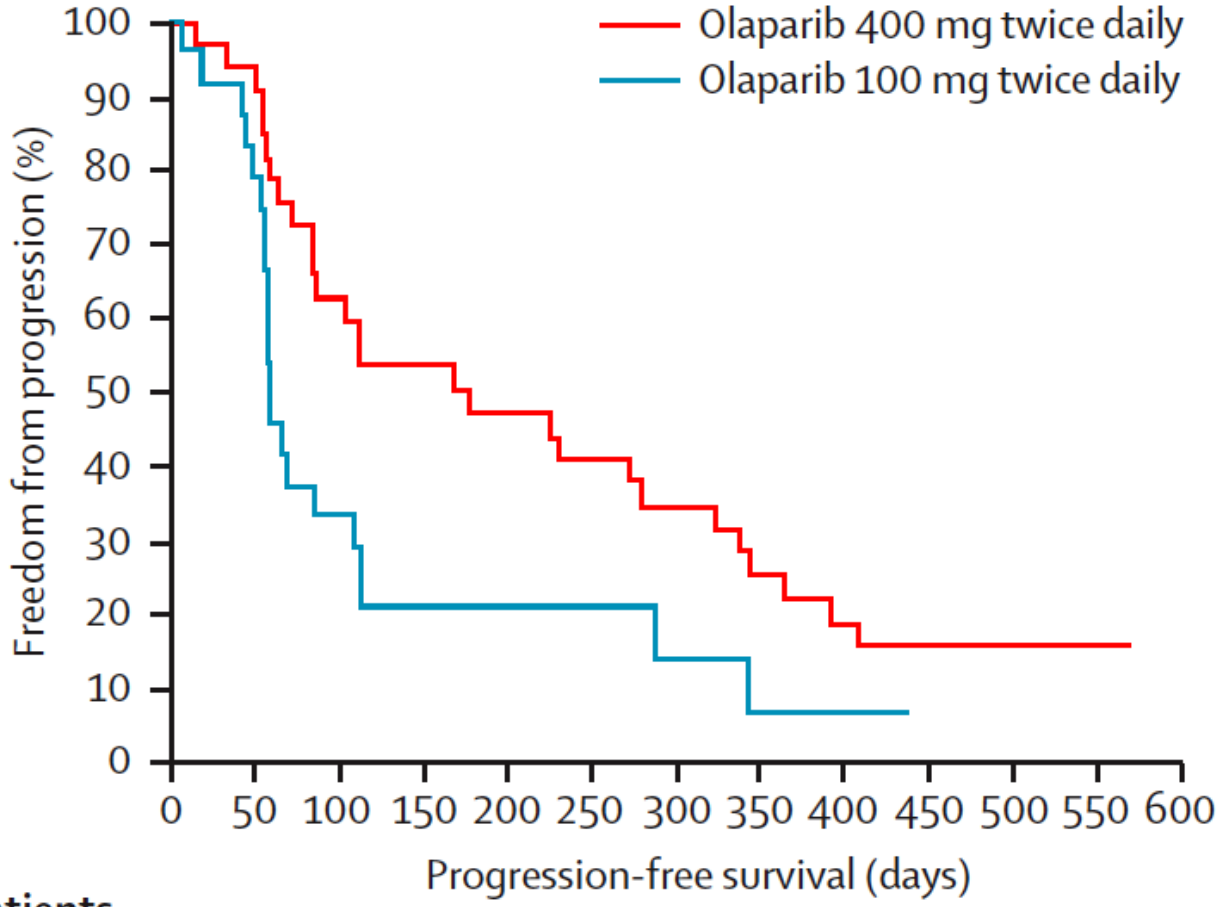
Tutt, et al. *Lancet* 2010

Phase II - BRCA-Mutated Ovarian Cancer



Audeh, et al. *Lancet* 2010

Phase II - BRCA-Mutated Ovarian Cancer



Number of patients

Olaparib 400 mg	33	31	20	17	15	13	11	8	6	4	4	3	0
Olaparib 100 mg	24	19	8	5	4	3	2	1	1	0	0	0	0

Audeh, et al. *Lancet* 2010

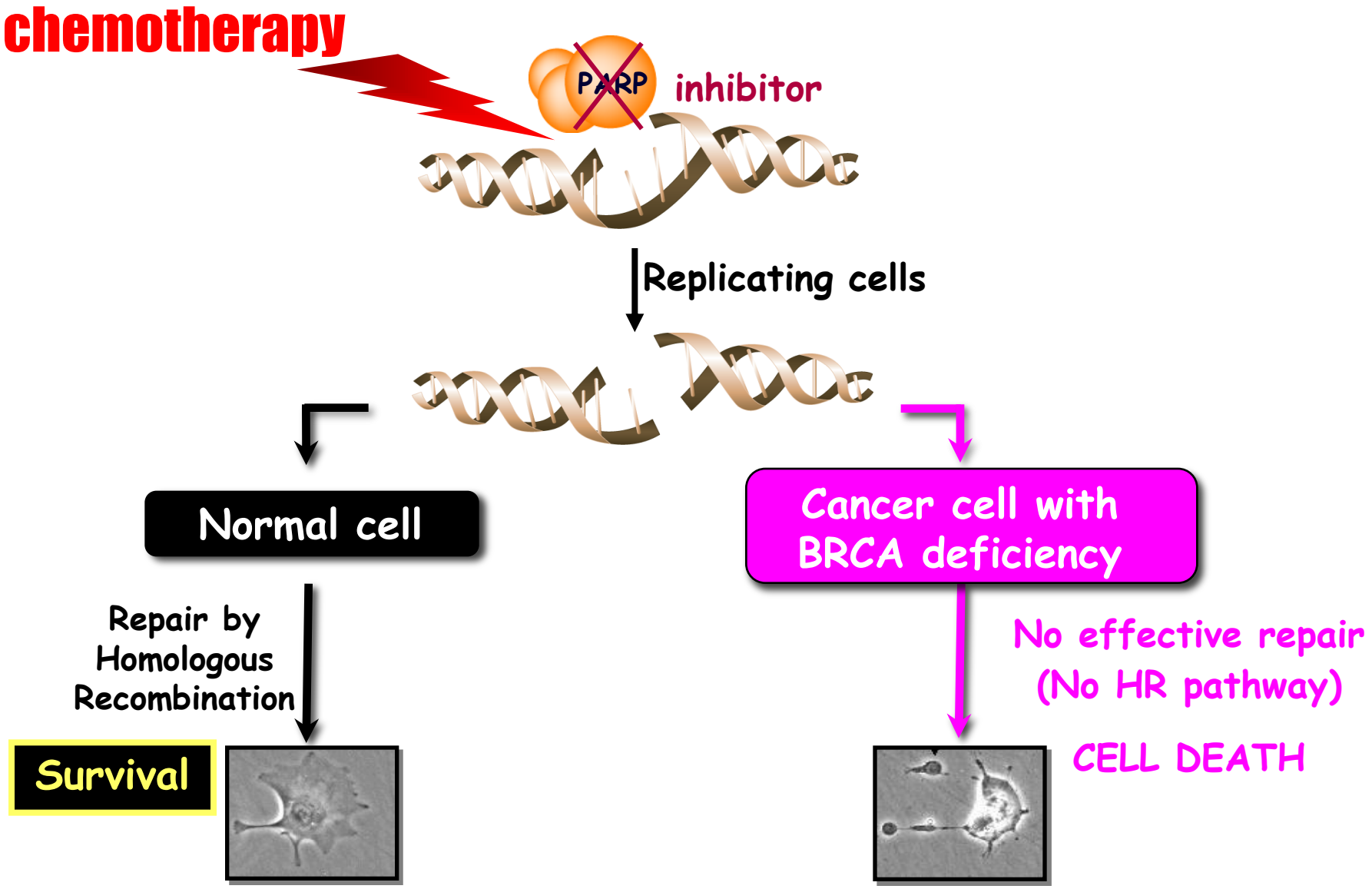
Single agent activity, but not curative

- **PARPi as single agents have not resulted in the expected CR and survival outcome**
  - Can we improve efficacy and duration with combination therapy?
  - Which combinations?

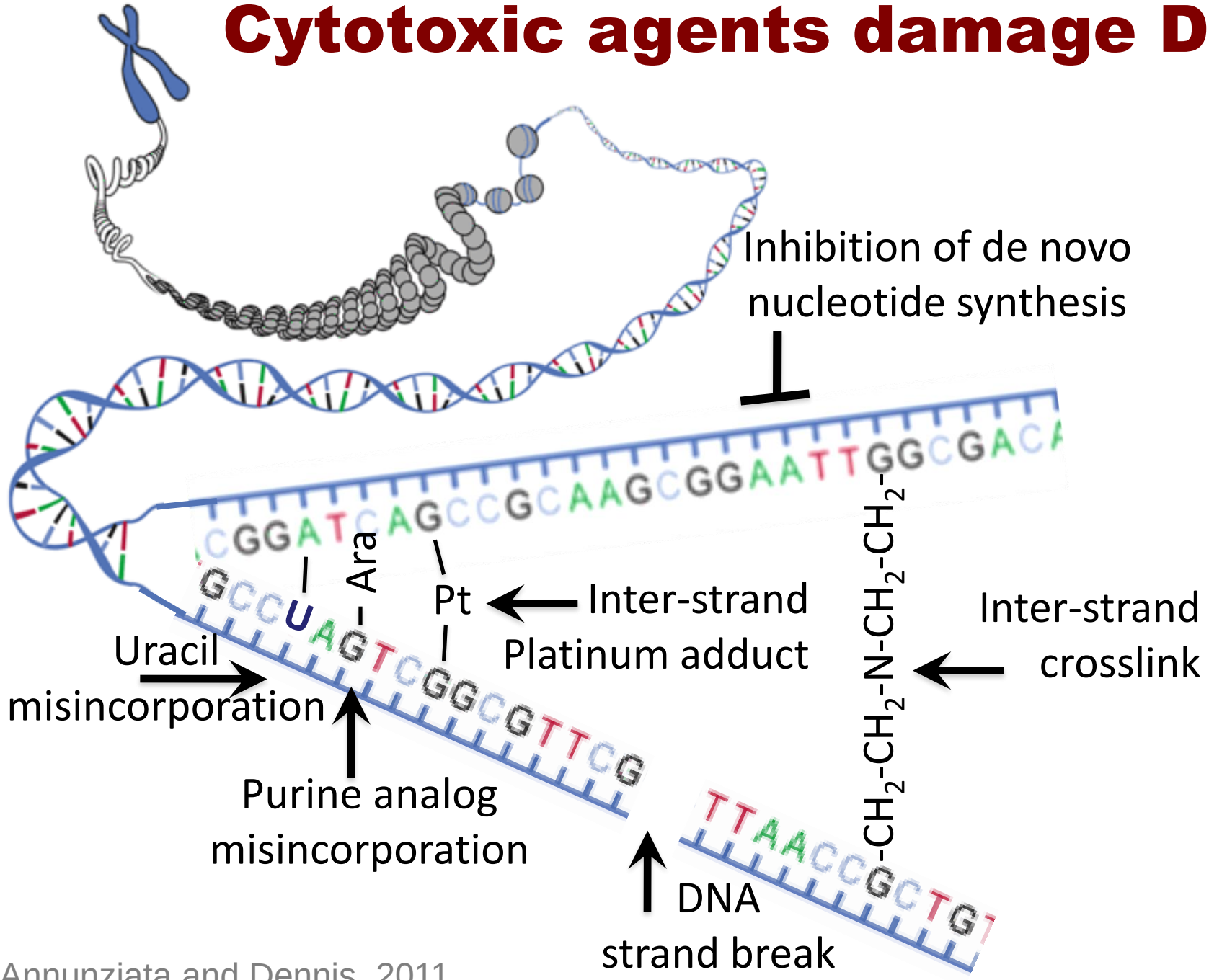
Combinations?

- **Hypothesis: Augmenting DNA damage stress may increase response and outcome**
  - Radiation-therapy for localized cancer with PARP-i sensitization
  - Chemotherapy – systemic therapy, interactive damage

PARP inhibitors in combination



Cytotoxic agents damage DNA



Annunziata and Dennis, 2011

Table 2. Partial list of Poly-ADP ribose polymerase inhibitors and their applications in clinical trials

Drug	Company	Route of administration	Clinical trials	Phase
Iniparib (BSI-201)	BiPar	Intravenous	Non–small cell lung cancer (with gemcitabine-carboplatin)	II
			Ovarian cancer, uterine cancer, and glioblastoma (various combinations)	II
			BRCA1- or BRCA2-mutant tumors	II
			TNBC (with gemcitabine-carboplatin)	III
			Squamous cell lung cancer (with gemcitabine-carboplatin)	III
Veliparib (ABT-888)	Abbott	Oral	Leukemia and lymphoma (with topotecan or irinotecan)	I
			Other solid tumors (various combination)	I
			BRCA1- or BRCA2-mutant tumors	I
			Glioblastoma, melanoma, breast, and colorectal cancers (with temozolomide)	II
Olaparib (AZD2281)	AstraZeneca	Oral	Platinum-sensitive ovarian cancer	II
			BRCA-positive tumors	II
			BRCA1- or BRCA2-mutant tumors	II
			TNBC (single-agent or with carboplatin)	II
AG014699	Pfizer	Intravenous	Advanced solid tumors	I
			BRCA1- or BRCA2-mutant tumors	II
MK-4827	Merck	Oral	Solid tumors, ovarian cancer, and prostate cancer	I
CEP-8933/CEP-9722	Cephalon	Oral	Solid tumors (with temozolomide)	I
INO-1001	Inotek/Genetech	Intravenous	Melanoma (with temozolomide)	I
GPI 21016	MGI Pharma	Oral	Solid tumors (with temozolimide)	N/A

NOTE. Data were obtained from the registry of federally and privately supported clinical trials; http://clinicaltrials.gov.
Abbreviations. N/A, no information available.

Phase II Study of Veliparib Plus Temozolomide in Breast Cancer

	Total (n = 41)	*BRCA1/2* Mutant (n = 8)	*BRCA1/2* Normal/Unknown (n = 33)
Overall Response Rate	7%	37.5%	0
Clinical Benefit Rate[a]	17%	62.5%	6%
Median Progression-Free Survival	1.9 months	5.5 months	1.8 months
		P = .0042	

[a] ORR + stable disease

- **Efficacy appears to be restricted to *BRCA1/2* mutation carriers and further evaluation is ongoing.**

Isakoff et al. *J Clin Oncol* 2010; 28(suppl):118s (abstract 1019).

Phase I/II Study of Olaparib Plus Weekly Paclitaxel for Triple-Negative Breast Cancer

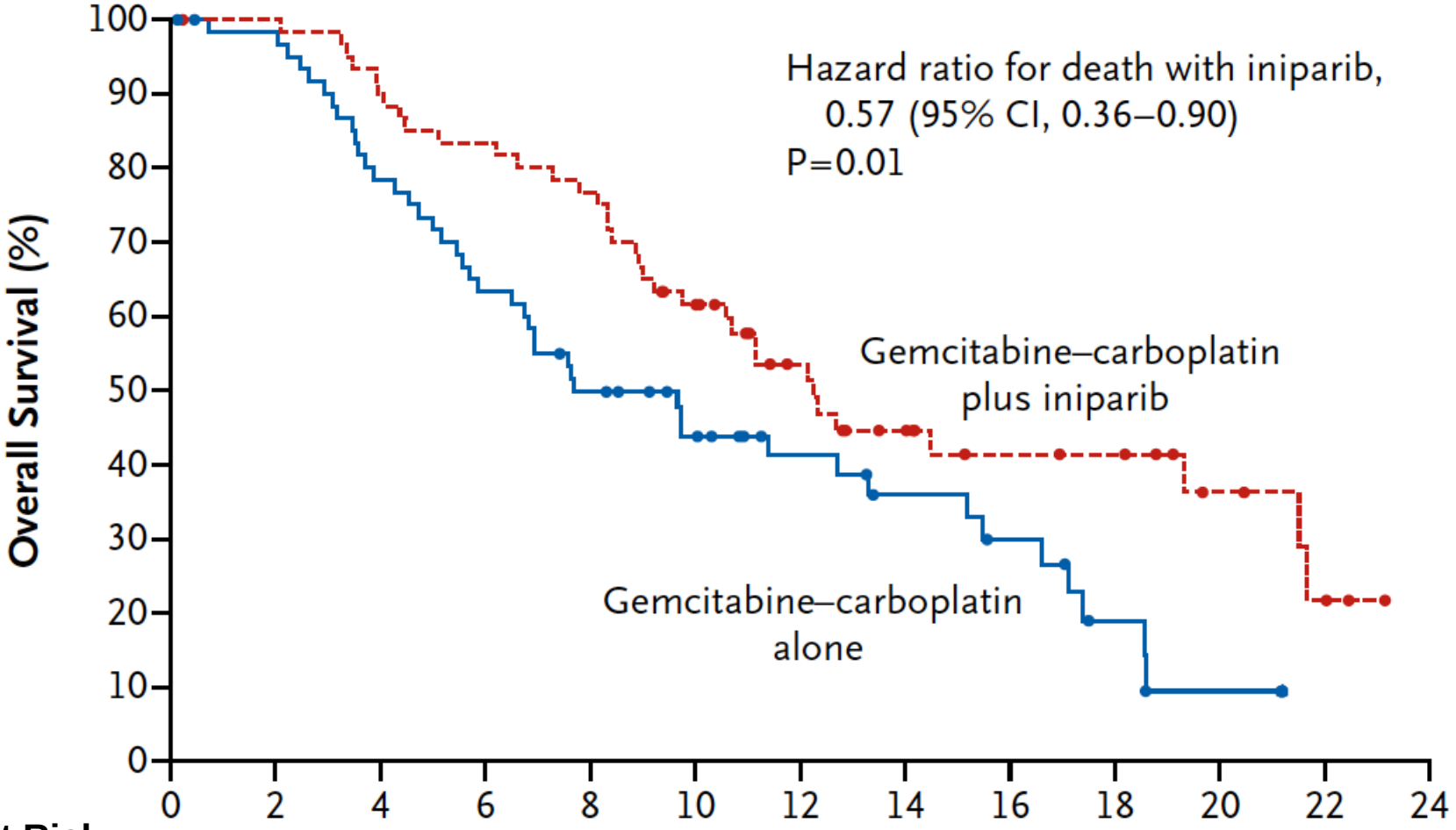
	Cohort 1 (No G-CSF) (n = 9)	Cohort 2 (G-CSF) (n = 10)
Overall Response Rate	33%	40%
Stable Disease ≥ 7 Weeks	33%	40%
Median Progression-Free Survival (95% CI)	6.3 (3.5-8.9) months	5.2 (3.5-NC) months

Abbreviation: NC = not calculable

- **Dose modifications:**
  - **Cohort 1: paclitaxel modified in 89%; olaparib modified in 44%**
  - **Cohort 2: paclitaxel modified in 60%; olaparib modified in 30%**
- **Conclusions:**
  - **Olaparib/paclitaxel is active in triple-negative MBC.**
  - **Associated neutropenia reduced paclitaxel dose intensity and should be carefully monitored.**

Dent et al. *J Clin Oncol* 2010; 28(suppl):118s (abstract 1018).

Phase II Gemcitabine/Carboplatin +/-Iniparib in Triple Negative Breast cancer

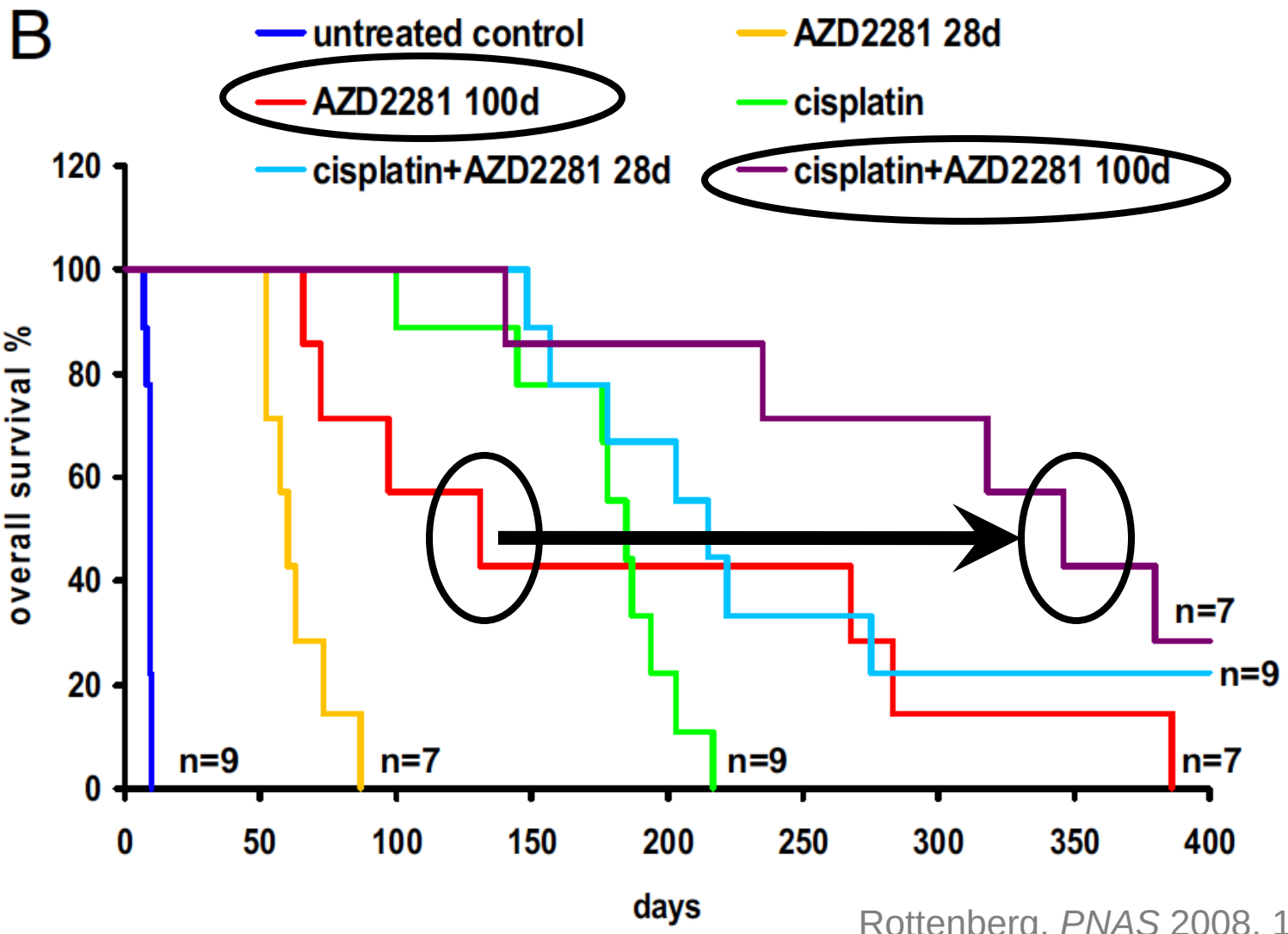


No. at Risk

G/C + Iniparib	61	60	54	50	46	35	24	17	12	11	6	3	0
G/C + alone	62	59	47	38	29	22	16	12	9	4	1	0	0

O'Shaughnessy, NEJM, 2011

PARP inhibition potentiates cisplatin efficacy in a BRCA1 null background



Rottenberg, *PNAS* 2008, 105: 17079

Phase 1 Olaparib + carboplatin at NCI

Cohort 1

Br/Ov cancers
BRCA mutant
BRCApro ≥ 30%

Cohort 2

TNBC
BRCA normal
BRCApro ≤ 10%

Cohort 3

Serous Ovarian
BRCA normal
BRCApro ≤ 20%

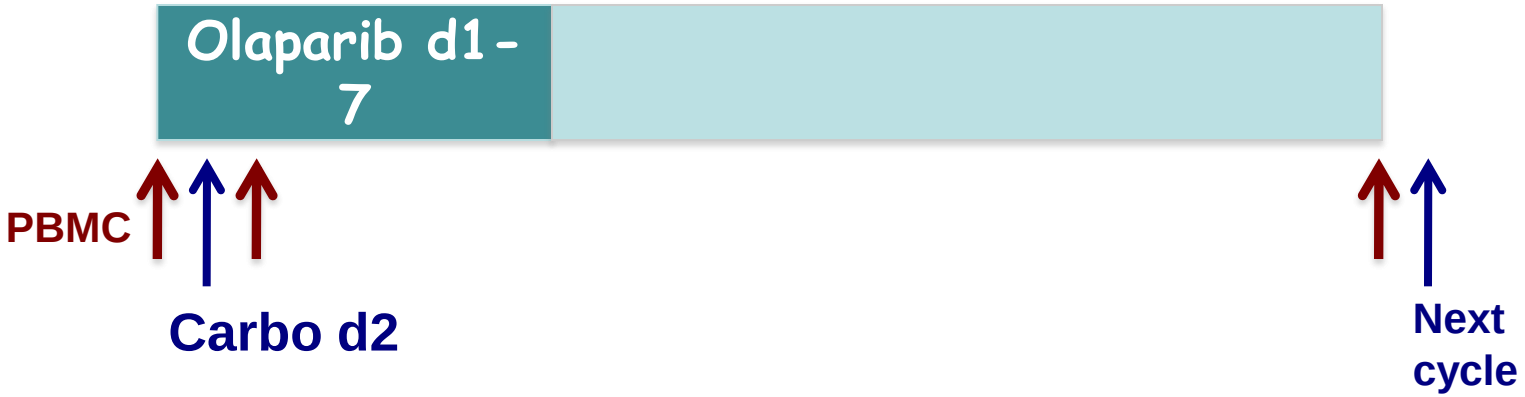
- **Olaparib 200mg twice daily (days 1-21)**
- **Carboplatin AUC 3 (every 21 days)**

- **PBMCs for PAR incorporation pre, d3, d21**
- **Expansion cohorts to examine endpoints in tumor tissue**
- **Biopsy at disease progression for BRCA sequencing**

Phase 1 Olaparib + carboplatin at NCI

- **Initial escalation:**
  - Olaparib twice daily continuously
  - Carboplatin at day 8 (cycle 1) and every 3 weeks
- **N=12 pts, 2 dose levels**
  - Olaparib 100mg + carboplatin AUC 3
  - Olaparib 200mg + carboplatin AUC 3
  - Dose limiting = delayed platelet recovery
- **Clinical benefit:**
  - Ovarian: Stable disease, partial responses 2-18mos
  - Breast: Partial responses, 6-7mos

Phase 1 Olaparib + carboplatin at NCI



- Optimize “synthetic lethality” with DNA damage
  - Interactive toxicity when olaparib used daily
  - Biological benefits with disease regression
- Test BRCAness concept with non-mutation cohorts
- Incorporate biochemical and genetic endpoints to examine mechanisms

Phase 1 Olaparib + carboplatin at NCI

Cohort 1

Br/Ov cancers
BRCA mutant
BRCApro ≥ 30%

Cohort 2

TNBC
BRCA normal
BRCApro ≤ 10%

Cohort 3

Serous Ovarian
BRCA normal
BRCApro ≤ 20%

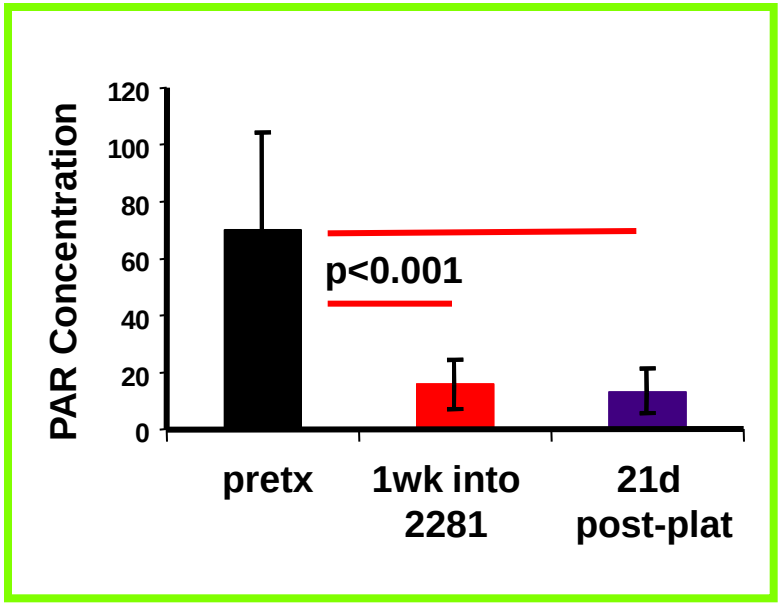
- Olaparib 400mg twice daily (days 1-7)
  - Carboplatin AUC 5 (every 21 days)

- Olaparib 400mg twice daily (days 1-7)
  - Carboplatin AUC 4 (every 21 days)

- Olaparib 400mg twice daily (days 1-7)
  - Carboplatin AUC 4 (every 21 days)

Biomarker of PARP inhibition in PBMCs

08-C-0092 phase I dose levels 1/2:
continuous olaparib with carboplatin AUC 3



(Preliminary data, Doroshow Lab)

PARP inhibitors in BRCA cancers

- **PARP inhibitors are promising inhibitors of HR-deficient cancers carrying BRCA mutations**
- **Combination with different chemotherapies has shown benefit in preclinical and clinical settings**

- **Will sequence specificity matter differentially in BRCA-mutant, “BRCA-like”, and non-HR dependent cancers?**
- **Will tolerance be different in patients carrying BRCA mutation compared to non-hereditary cancers?**

Acknowledgements

- **National Cancer Institute**
  - Elise Kohn
  - Nilofer Azad
  - Jung-Min Lee
  - Medical ovarian cancer research team
- **Baylor-Sammons Cancer Center**
  - Joyce O'Shaughnessy
- **Our Patients**