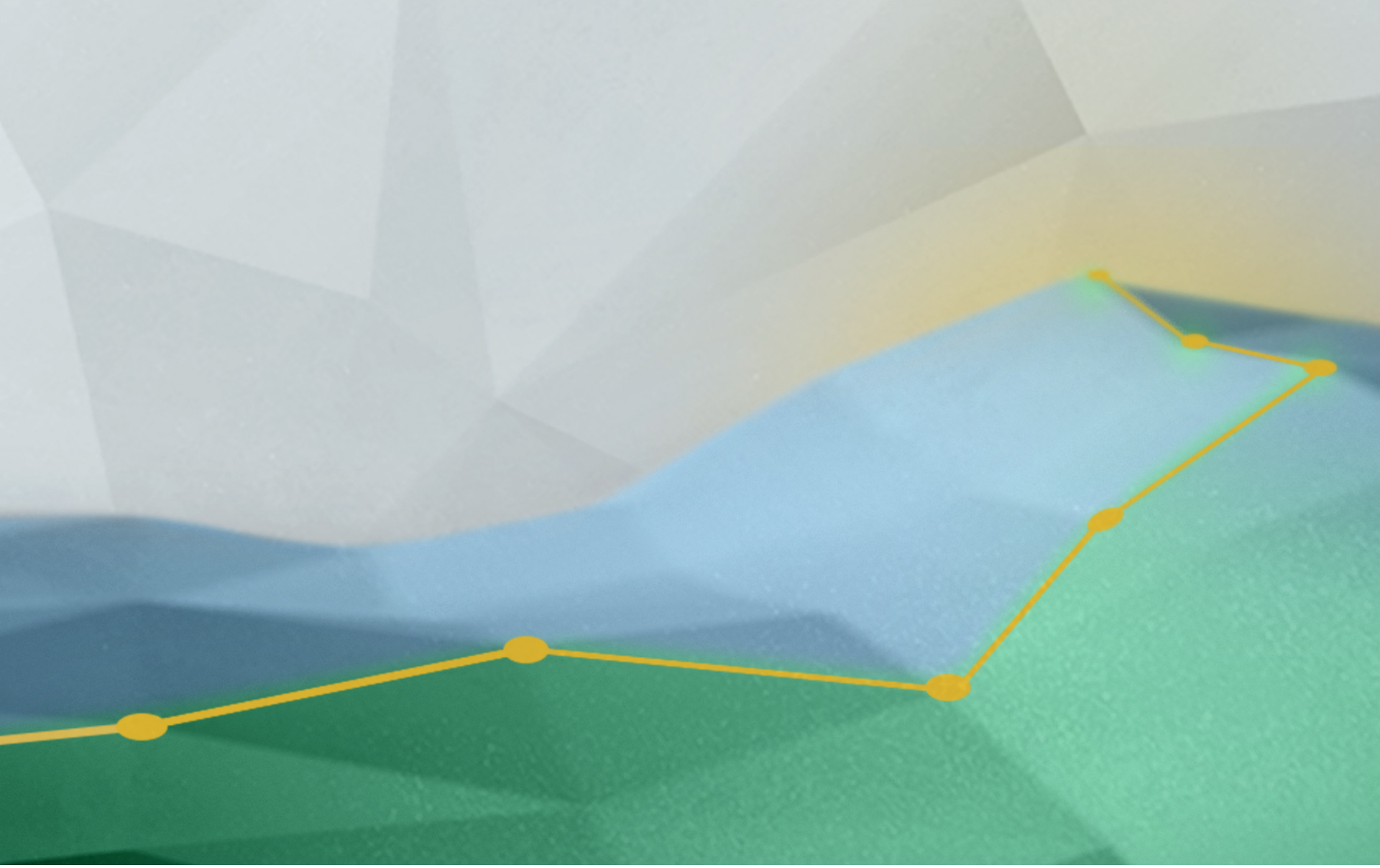

SIERRA ONCOLOGY

Beyond PARP: The Clinical Potential of Next Generation DNA Damage Response Therapeutics

October 12, 2017

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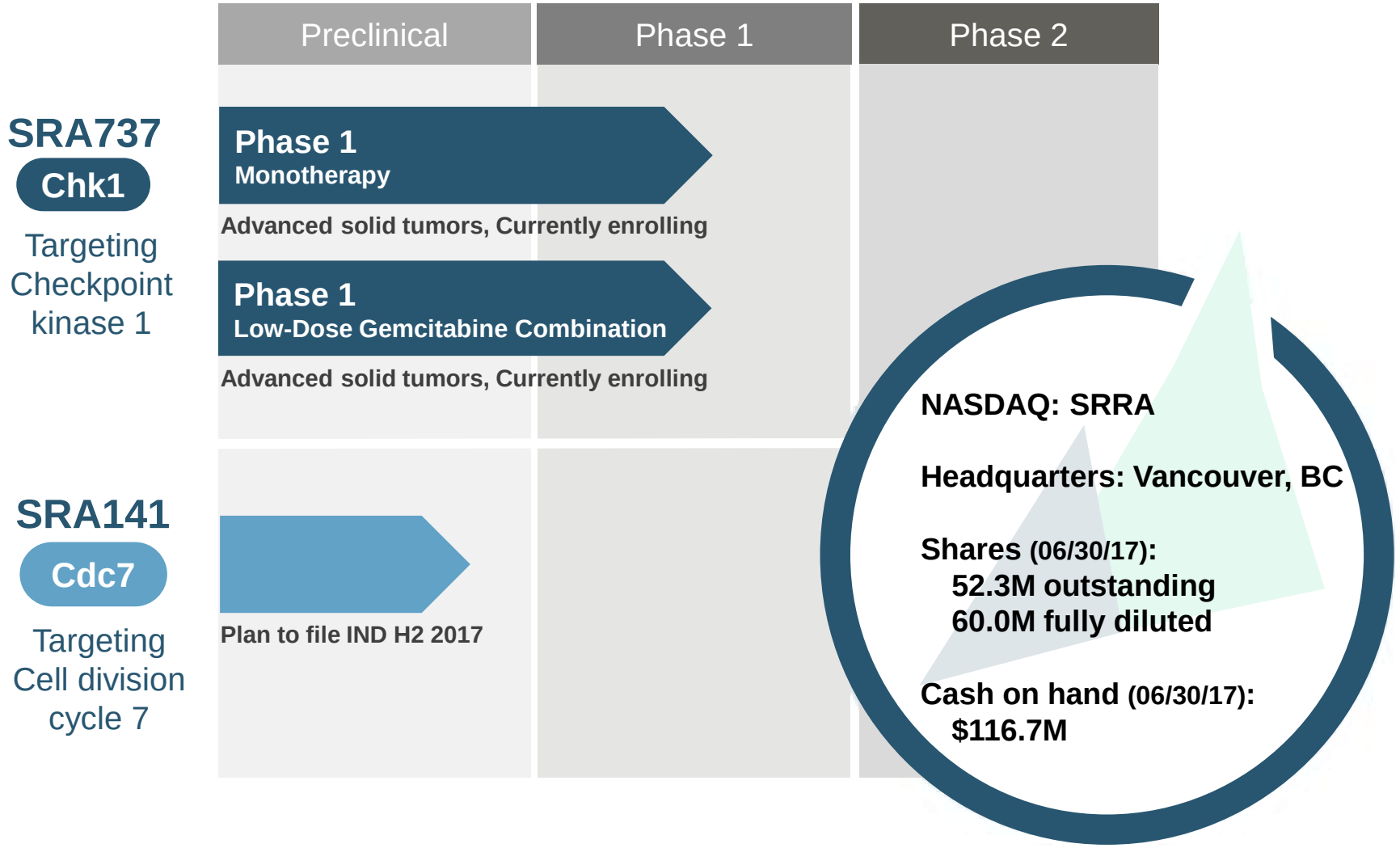
Our Pipeline of ‘Next Generation’ DDR Therapeutics



Monotherapy Phase 1:
Innovative Trial Design to Show Synthetic Lethality

Jan 2017: Sierra assumes sponsorship of SRA737

May 2017: Amendment cleared by regulators

June 2017: Progress update

Dose escalation

Continued dose escalation to MTD

Fall 2016:
CRUK-sponsored Ph1 monotherapy dose escalation initiated (advanced solid tumors)

Prospective patient selection using NGS technology

- Prostate
- Ovarian
- Non-Small Cell Lung
- Head & Neck
- Colorectal

- *Parallel MTD determination and cohort expansion in genetically-defined patient populations.*
- *Continuous daily oral administration.*

Chemotherapy Combination Phase 1: Leverages Potentiation & Synthetic Lethality

Jan 2017: Sierra assumes sponsorship of SRA737

May 2017: Amendment cleared by regulators

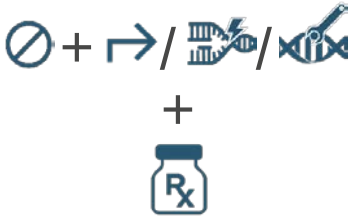
Cis/Gem combo dose escalation

Low-dose gem combo dose escalation

Bladder

Pancreatic

Prospective patient selection using NGS technology



Fall 2016: CRUK-sponsored Ph1 cis-gem combination dose escalation initiated (advanced solid tumors)

- *Intermittent oral dosing following each dose of chemotherapy.*

Breadth of Development Opportunities Reflected in Sierra's Development Strategy

Current Clinical Trials

Monotherapy 

Exploit synthetic lethality in genetically-defined patient populations across five tumor types that have predicted high sensitivity to SRA737.

Low-Dose Gem Combination 

Exploit profound potentiating effects of SRA737 with low-dose gemcitabine plus synthetic lethality in genetically-defined populations in two tumor types.

Potential Clinical Opportunities

PARP Combo 

Exploit synergy between SRA737 + PARP inhibitor to expand/enhance PARP inhibitor sensitivity / overcome resistance.

I/O Combo 

Explore PD-(L)1 combination and its potential to drive neoantigen presentation in "double checkpoint" strategy.

DDR Advisory Committee – Leading DDR Experts

Represented by leading experts in DDR biology, chemistry and medicine; Providing advice on our DDR oriented development programs with a focus on maximizing the potential clinical and commercial deployment of our drug candidates.

- **Eric J. Brown, PhD**
  Associate Professor of Cancer Biology at the Perelman School of Medicine of the University of Pennsylvania.
- **Karlene Cimprich, PhD**
  Vice Chair and Professor of Chemical and Systems Biology at the Stanford University School of Medicine.
- **Alan D. D'Andrea, MD**
  Fuller-American Cancer Society Professor of Radiation Oncology at Harvard Medical School and the Director of the Center for DNA Damage and Repair at the Dana-Farber Cancer Institute.
- **Alan R. Eastman, PhD**
  Professor at the Geisel School of Medicine at Dartmouth and the founding Director of the Molecular Therapeutics Research Program of the Norris Cotton Cancer Center at Dartmouth.
- **Michelle D. Garrett, PhD**
  Professor of Cancer Therapeutics in the School of Biosciences at the University of Kent and Visiting Professor of Cancer Therapeutics at the Institute of Cancer Research, London, UK.
- **Thomas Helleday, PhD**
  The Torsten and Ragnar Söderberg Professor of Translational Medicine and Chemical Biology at Karolinska Institutet, Stockholm, Sweden.
- **Leonard Post, PhD**
  Chief Scientific Officer of Vivace Therapeutics; former CSO of BioMarin Pharmaceuticals.

Leonard Post, PhD

- Chief Scientific Officer of Vivace Therapeutics; serves as an advisor to several biotechnology companies and to venture investors.
- Dr. Post was Chief Scientific Officer of BioMarin Pharmaceuticals, and before that was CSO and co-founder of LEAD Therapeutics which was acquired by BioMarin in 2010.
- His work in DNA repair involved the discovery of the PARP inhibitor talazoparib at LEAD and its development into Phase 3 at BioMarin.
- As Senior Vice President of Research and Development at Onyx Pharmaceuticals, Dr. Post was involved in the clinical development of Nexavar from IND through NDA approval.

Leonard Post, PhD

Chief Scientific Officer of Vivace Therapeutics

Eric J. Brown, PhD

- Dr. Brown's laboratory examines how signaling maintains genome stability during DNA synthesis and how this function is essential to cancer cells.
- The Brown Laboratory is currently identifying predictive biomarkers of therapeutic benefit and the mechanisms of action of these drugs through a combination of genome-wide breakpoint mapping and replication fork proteomics.
- The first to report that oncogenic stress is sufficient to cause selective sensitivity to ATR inhibition, the Brown laboratory seeks both to define the mechanisms of action of ATR/Chk1 inhibitors and to identify their optimal uses in cancer therapies.

Eric J. Brown, PhD

Associate Professor of Cancer Biology at the Perelman School of Medicine of the University of Pennsylvania.

Geoffrey Shapiro, MD, PhD

- Dr. Shapiro runs one of the largest Phase 1 clinical trials programs in the United States and dedicates his time to developing leading cancer treatments.
- He participates in Dana-Farber's Thoracic and Breast Oncology Programs and is a member of the Dana-Farber/Harvard Cancer Center SPORE (Specialized Program of Research Excellence) in Breast Cancer
- Dr. Shapiro contributes to the SU2C Ovarian Cancer Dream Team.
- Dr. Shapiro conducts both basic and translational research on cyclin-dependent kinase inhibitors, with a focus on defining the role of these inhibitors in the cellular response to DNA damage.

Geoffrey Shapiro, MD, PhD

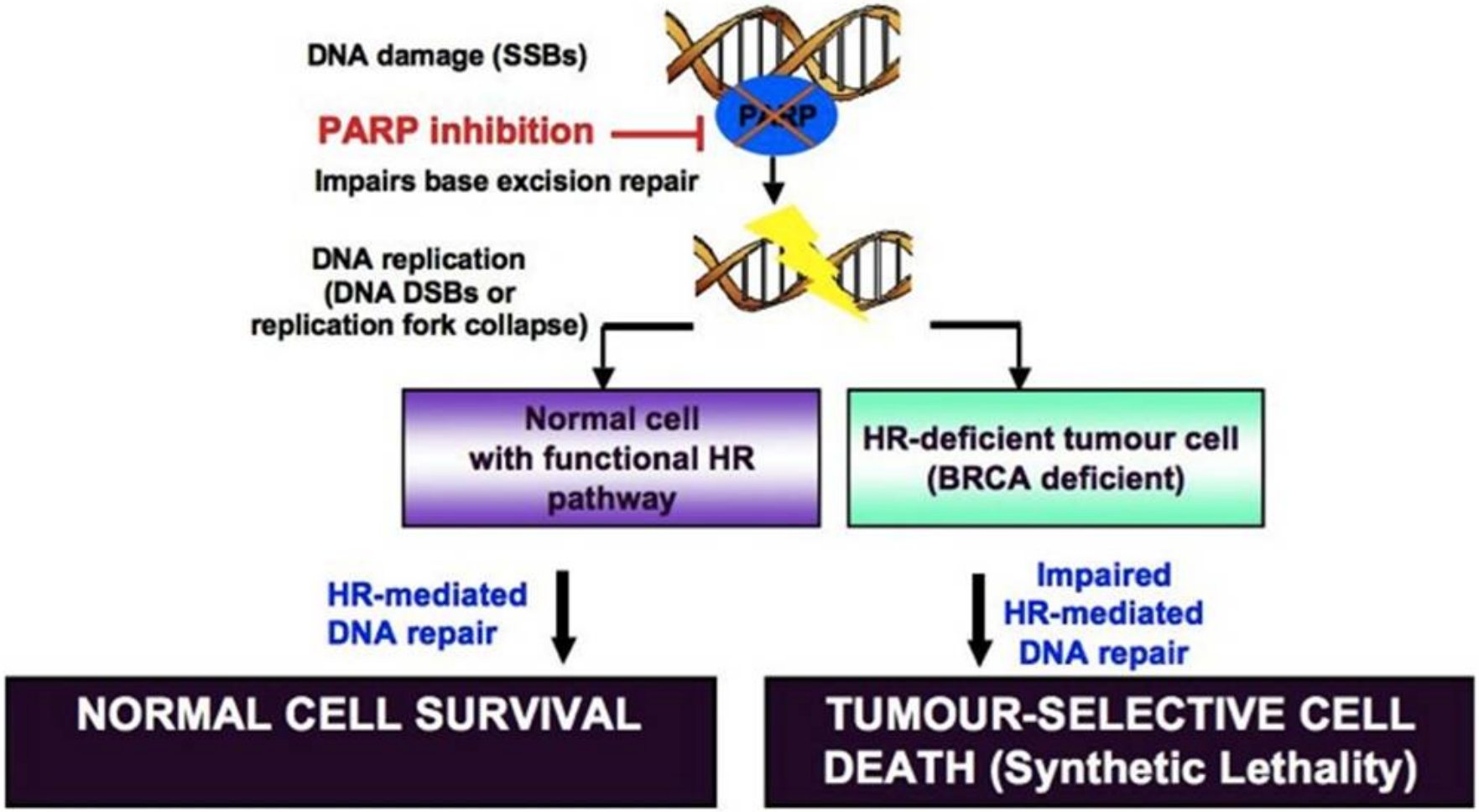
Associate Professor of Medicine at Harvard Medical School, Director of the Early Drug Development Center at the Dana-Farber Cancer Institute, and Clinical Director for Dana-Farber's Center for DNA Damage and Repair.

Lessons Learned From PARP Inhibitor Development

Len Post, PhD

October 12, 2017

Synthetic lethality between PARP inhibition and BRCA 1/2 mutation



Presented By Alan Ashworth at 2015 ASCO Annual Meeting

History of PARP inhibitors

- 1963: Discovery of PARP activity in chicken liver. (Chambon, et al, BBRC, 1963)
- 1980: PARP participates in DNA excision repair. (Durkacz, Schall, et al Nature, 1980)

  First PARP inhibitor: 3-aminobenzamide.
- 2003: First PARP inhibitor clinical trial open. (Plummer, et al Clin Cancer Res 2008)
- 2011: Iniparib (Sanofi) failed Phase 3.
- 2014: December 19. Olaparib received FDA Accelerated Approval for ovarian cancer with germline BRCA mutations.

34 years from discovery that PARP inhibitors inhibit DNA repair to first approval.

No approval yet for combination with DNA damage agents.

We learned a lot during that time!

What was happening over that 34 years?

The field has learned a lot:

1. Discovery of the good specific PARP inhibitors, and understanding how they work.

   - first generation chemistry exhibited inadequate potency and off-target related liabilities.

2. Synthetic lethality: learning which tumors to treat with PARP inhibitors.

3. Rational basis for combinations.

Lessons can be applied to other DDRi development targets (e.g. Chk1)?

History of PARP inhibitors

- 1963: Discovery of PARP activity in chicken liver. (Chambon, et al, BBRC, 1963)
- 1980: PARP participates in DNA excision repair. (Durkacz, Schall, et al Nature, 1980)

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  Rucaparib
- 2011: Iniparib (Sanofi) failed Phase 3.
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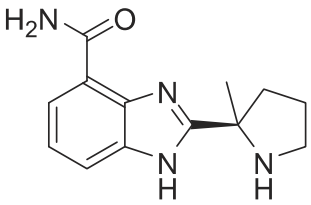
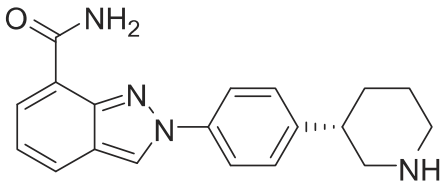
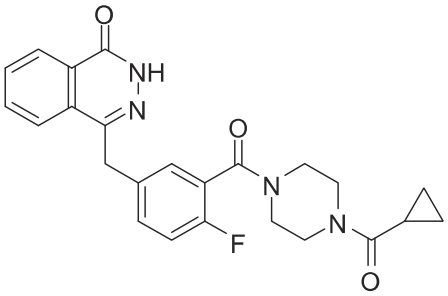
PARP inhibitors approved and in Phase 3 clinical development



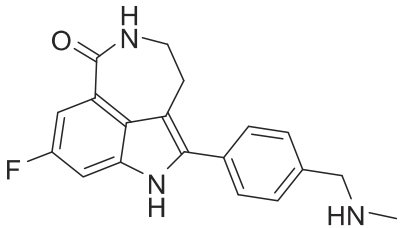
veliparib



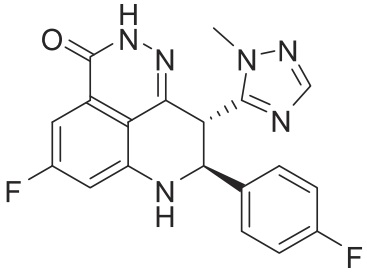
niraparib



olaparib



rucaparib



talazoparib

Summary of *in vitro* PARP inhibitor activities

	PARP-1 Enzyme Inhibition[1] IC_{50} (nM)	Cellular PAR Synthesis[2] EC_{50} (nM)	Temozolomide Potentiation[3] GI_{50} (nM)	Capan-1 (BRCA2-/-) Cytotoxicity[4] IC_{50} (nM)
Veliparib	4.73	5.94	6203	>10,000
Rucaparib	1.98	4.69	144	609
Olaparib	1.94	3.56	237	259
Talazoparib	0.57	2.5	4	5

Shen et. al, Clinical Cancer Research, 19 : 5003-5015 (2013)

- Niraparib shows comparable activity as rucaparib in BRCA-negative cells.

Important Discovery: Not all PARP inhibitors are alike!

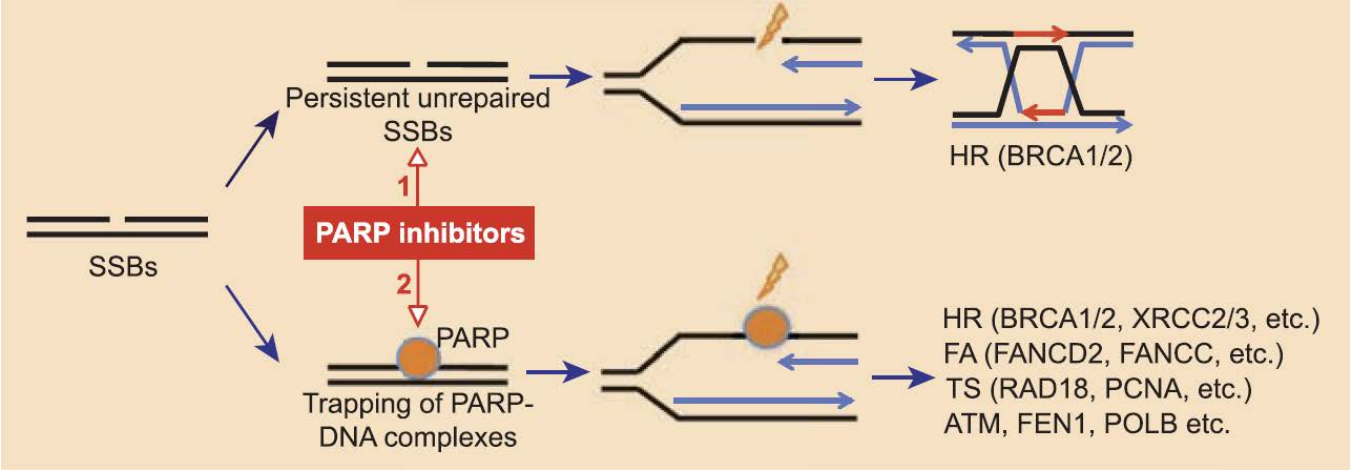
Trapping of PARP1 and PARP2 by Clinical PARP Inhibitors

Junko Murai[1,4], Shar-yin N. Huang[1], Benu Brata Das[1], Amelie Renaud[1], Yiping Zhang[2], James H. Doroshow[1,3], Jiuping Ji[2], Shunichi Takeda[4], and Yves Pommier[1]

Cancer Research 2012

"..PARP inhibitors act in part as poisons that trap PARP enzyme on DNA."

"… the potency in trapping PARP differed markedly among inhibitors…., a pattern not correlated with the catalytic inhibitory properties for each drug."

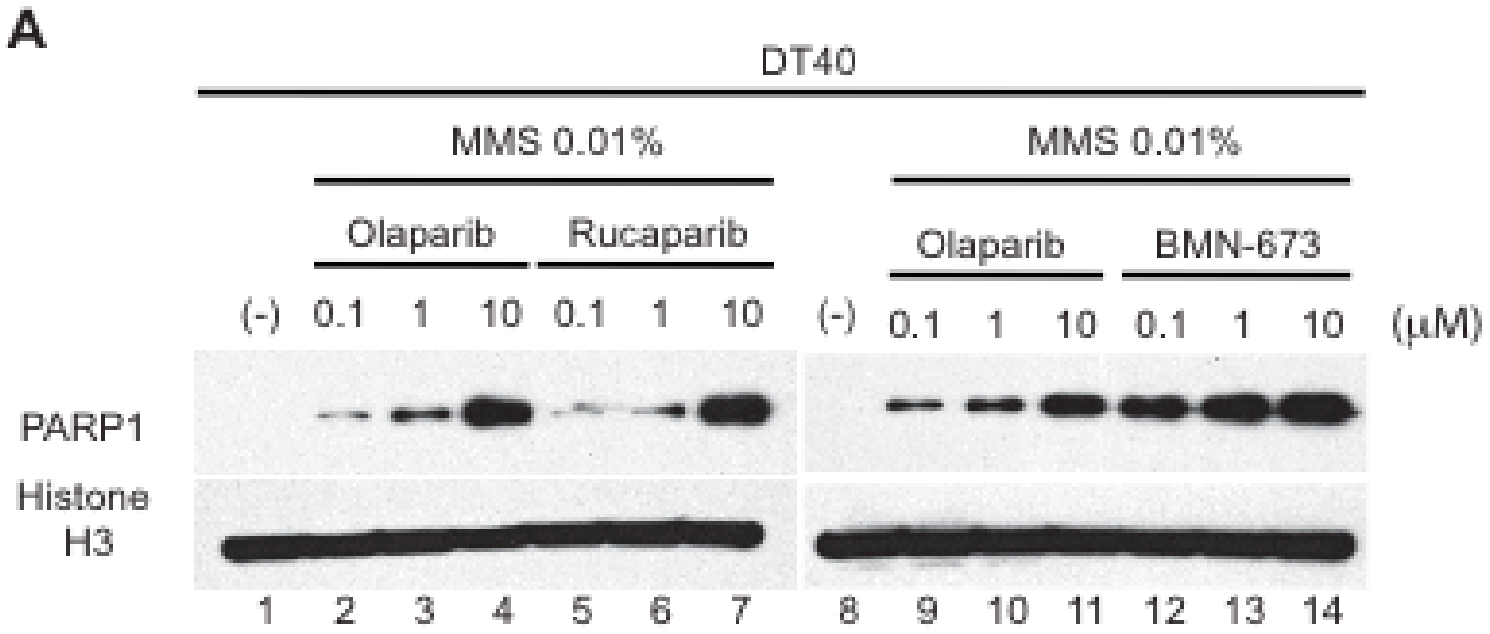


Talazoparib traps PARP-DNA complexes at 100X greater potency than Olaparib and Rucaparib

Mol Cancer Ther. 2014 Feb;13(2):433-43. doi: 10.1158/1535-7163.MCT-13-0803. Epub 2013 Dec 19.

Stereospecific PARP Trapping by BMN 673 and Comparison with Olaparib and Rucaparib.

Murai J[1], Huang SY, Renaud A, Zhang Y, Ji J, Takeda S, Morris J, Teicher B, Doroshow JH, Pommier Y.

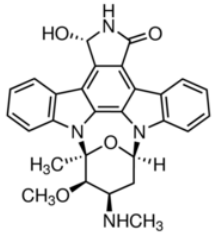


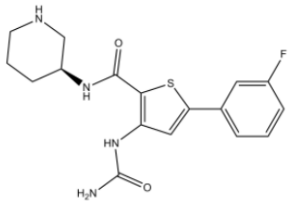
"Talazoparib >> Niraparib > Olaparib = Rucaparib >> Veliparib"

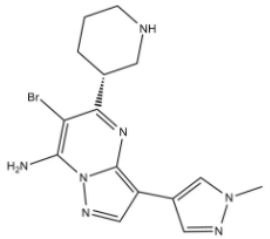
Discontinued first-generation Chk inhibitors

- Similar to PARP first generation, Chki chemistry exhibited structural and target related liabilities.

UCN-01: IV delivered non-selective staurosporine analog	• Discontinued due in part to **poor PK and likely off-target toxicity** (e.g. hyperglycemia 65%, nausea 53% were common AEs).
AZD7762: IV delivered dual Chk1/2 inhibitor	• Discontinued due to **cardiac toxicity** (bradycardia 50%, hypertension 25%).
MK-8776: an IV delivered selective Chk1 inhibitor	• In Phase 2 with no recent development reported displayed; **QTc prolongation** (19%), nausea (16%), fatigue (14%), and constipation (14%) as the most frequent AEs; extremely short half-life.







- Cardiotox **not reported** for clinical trials evaluating current Chk1i >>> effects **are not target-based.**
- First generation Chk inhibitors limited by poor PK, off-target toxicities.

History of PARP inhibitors

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- 1980: PARP participates in DNA excision repair. (Durkacz, Schall, et al Nature, 1980)

  First PARP inhibitor: 3-aminobenzamide.
- 2003: First PARP inhibitor clinical trial open. (Plummer, et al Clin Cancer Res 2008)
- 2005. Ashworth and Helleday labs published landmark Nature papers on synthetic lethality of PARP inhibitors and BRCA mutant tumor cells.
- 2014: December 19. Olaparib received FDA Accelerated Approval for ovarian cancer with germline BRCA mutations.

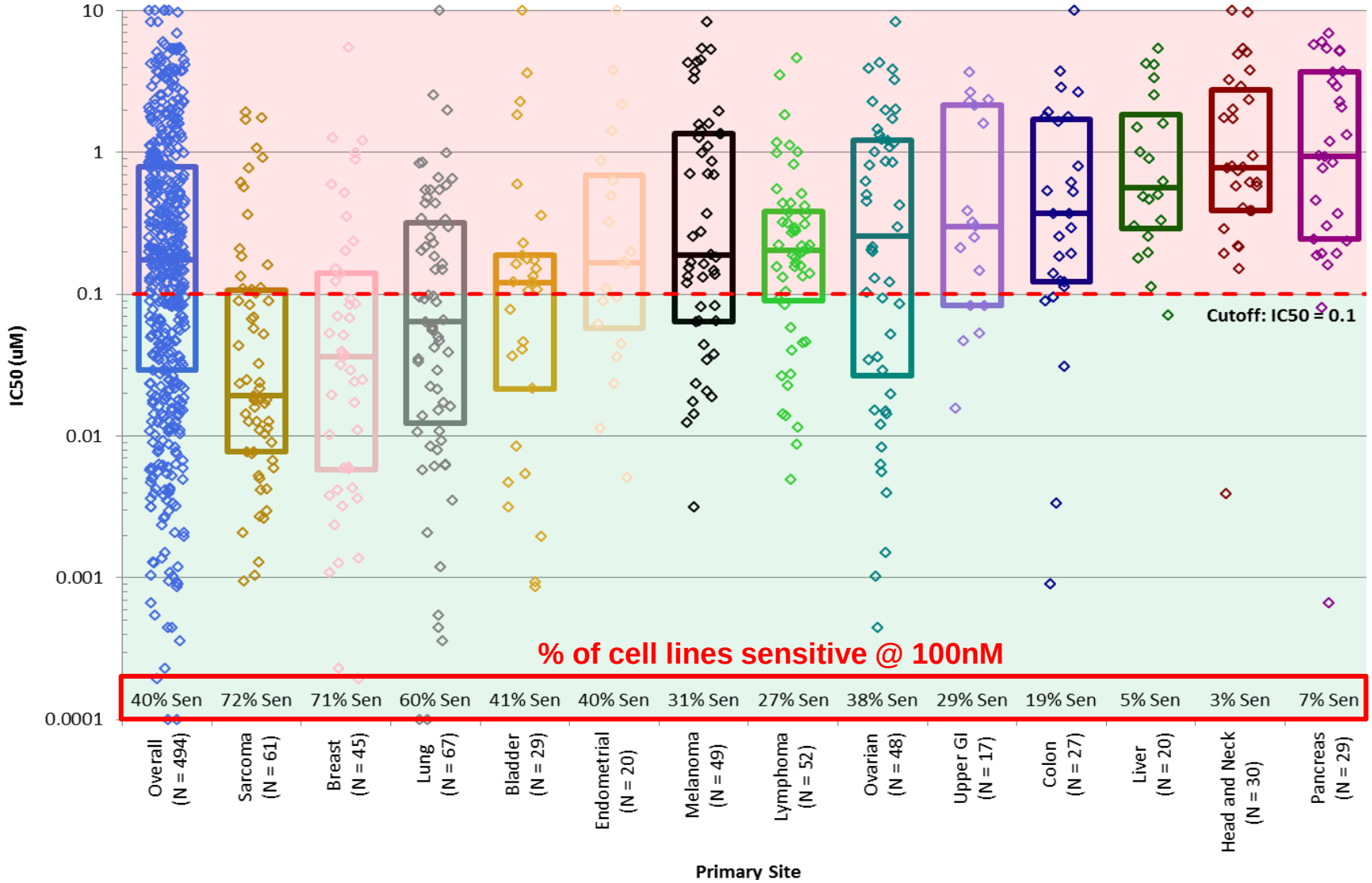
First Report: Clinical response of BRCA mutation carriers ASCO 2007

First in human phase I pharmacokinetic (PK) and pharmacodynamic (PD) study of KU-0059436 (Ku), a small molecule inhibitor of poly ADP-ribose polymerase (PARP) in cancer patients (p), including BRCA1/2 mutation carriers

T. A. Yap , D. S. Boss , P. C. Fong , M. Roelvink , A. Tutt , J. Carmichael , M. J. O'Connor , S. B. Kaye , J. H. Schellens , J. S. de Bono

The Royal Marsden Hospital NHS Trust, Surrey, United Kingdom; The Netherlands Cancer Institute, Amsterdam, The Netherlands; The Institute of Cancer Research, London, United Kingdom; KuDOS Pharmaceuticals Limited, Cambridge, United Kingdom

Talazoparib IC_{50} distribution by cancer type – more than BRCA



Presented by D. Slamon at BioMarin R&D Day, Sept. 2013

Inhibition of Chk1 in tumors harboring replication stress-inducing mutations

Analogy to PARPi sensitization in HR deficient *BRCA* mutant background

Given the essential role for Chk1 (ATR/Chk1 pathway) in managing replication stress (RS), tumor cells with RS-driving genomic alterations become highly reliant on Chk1 for survival and extremely sensitive to Chk1 inhibition.

- Inactivation of ATR or Chk1 inhibits growth of tumor cells with activated ***KRAS*** (Gilad et al., Cancer Res, 2010).

- Chk1 inhibitors, including CCT245737 (SRA737) inhibit ***MYC***-driven lymphoma *in vivo* (Walton et al., *Oncotarget*, 2015; Hoglund et al., *Clin Cancer Res,* 2011).

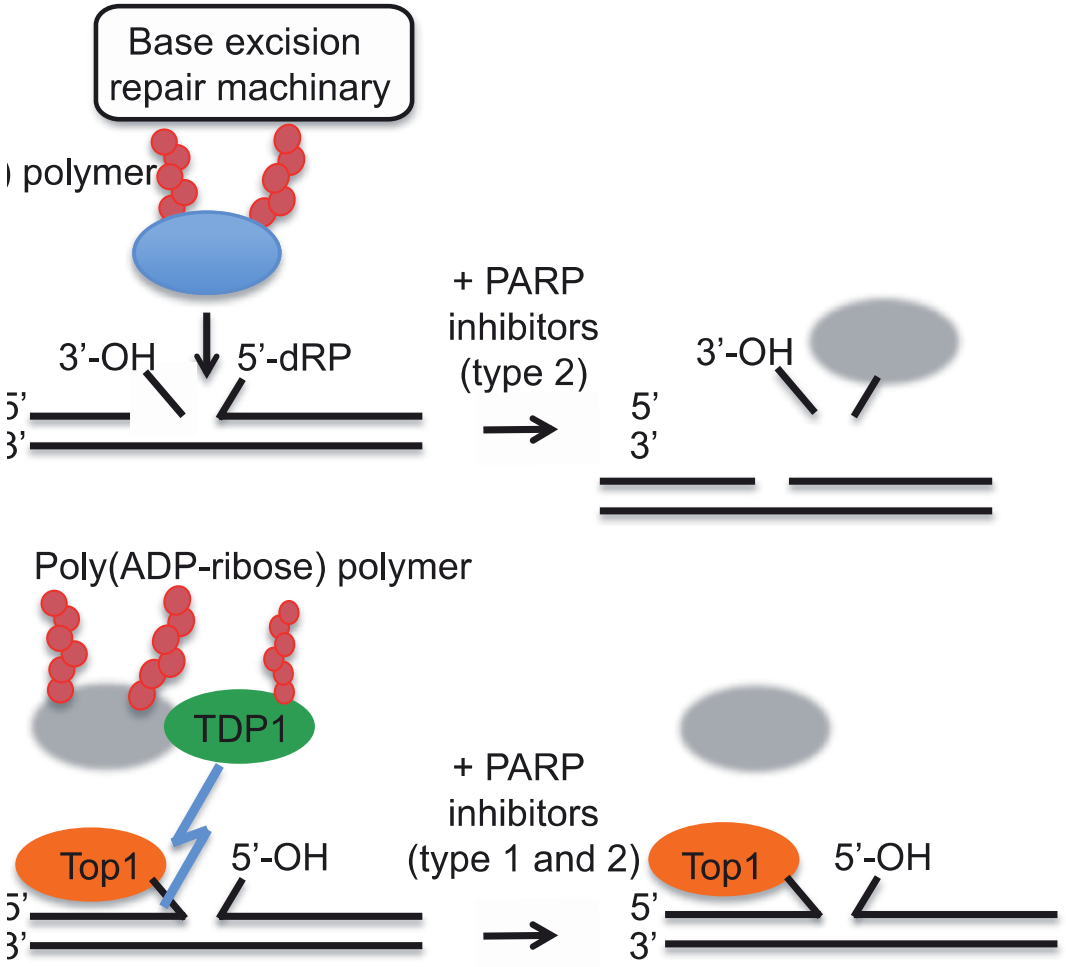
- ***TP53*** activating mutations lead to origin dysregulation, replication stress, increased Chk1 expression, and enhanced sensitivity to Chk1i *in vivo* (Singh et al., *J Clin Invest*, 2017).

Key insights for rational combinations with PARP inhibitors: Use a DNA damaging agent to sensitize to PARP inhibitor

1. Select a combination agent with a mechanistic interaction with PARP inhibitors. Inhibitors that trap PARP will interact differently than those which do not with some types of DNA damage.
2. Cytotoxic administered at less than monotherapy MTD to induce DNA damage. Maximum tolerated dose of a cytotoxic is not tolerable with an agent that increases sensitivity.

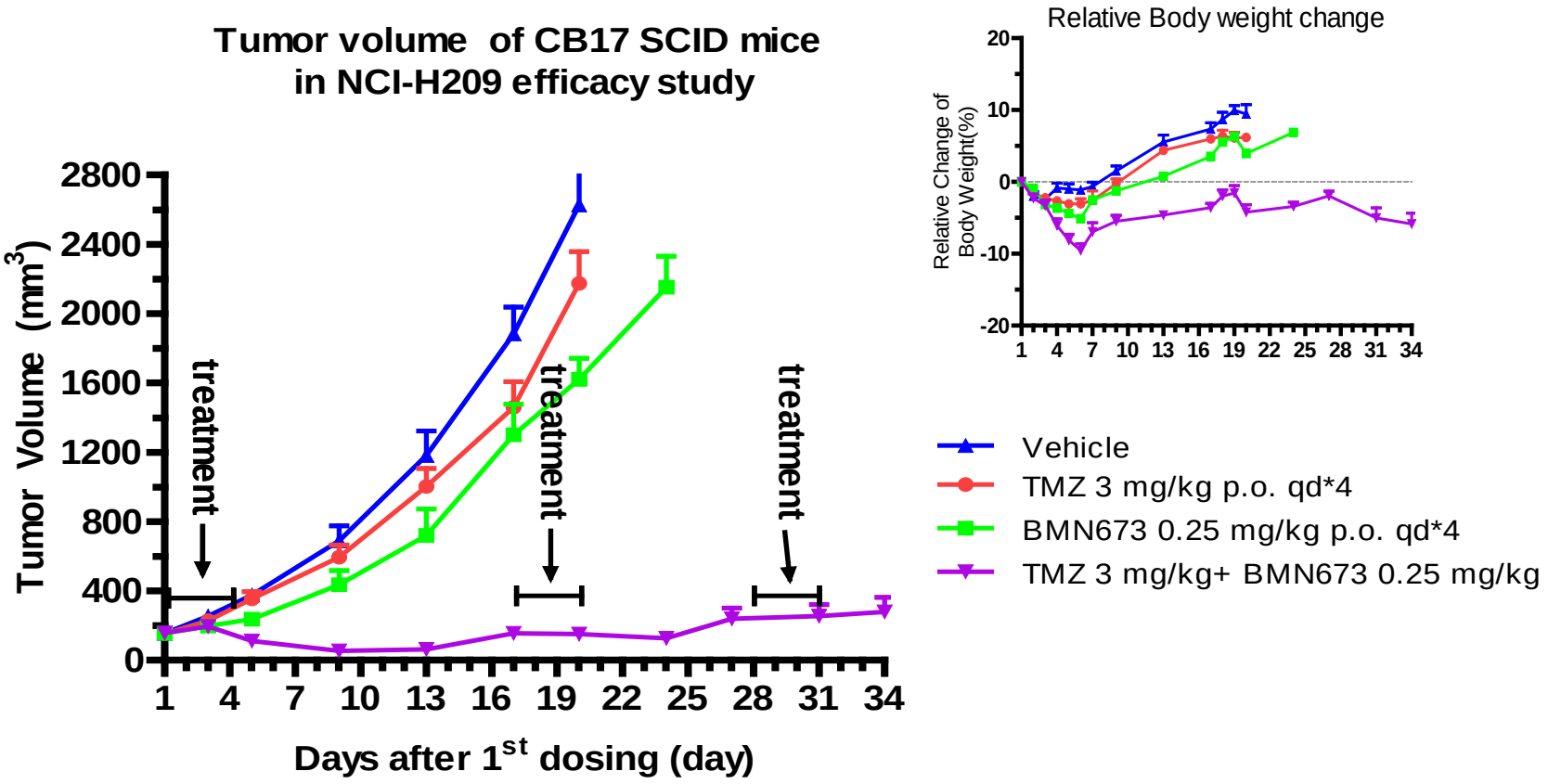
Acknowledgment: Malcolm Smith, Dennis Slamon

Temozolomide creates sites where PARP-trapping inhibitors can stabilize the PARP-DNA complex



Murai and Pommier, 2014

Talazoparib + TMZ combination in H209 Xenografts



Safety and Efficacy Results of a Phase 1 Dose-Escalation Trial of the PARP inhibitor Talazoparib in Combination with either Temozolomide or Irinotecan in Patients with Advanced Malignancies

Zev A. Wainberg[1], J. Randolph Hecht, Gottfried E. Konecny, Bartosz Chmielowski, Arun Singh, Jonathan Goldman, Richard S. Finn, Diego Martinez, Lisa Yonemoto, John Glaspy and Dennis J. Slamon

[1]David Geffen School of Medicine at University of California, Los Angeles, CA

Presented at AACR, 2016

UCLA Talazoparib combination study
Z. Wainberg et al, AACR 2016

- Dose-finding study to determine tolerable temozolomide or irinotecan doses with full dose daily talazoparib.
- MTD:
  - Talazoparib 1 mg PO QD with temozolomide 37.5 mg/m^2 (PO days 1-5) 28 day cycle.
  - Talazoparib 1 mg PO QD with irinotecan 37.5 mg/m^2 IV q 2 wks.
- Study conclusion: "These combination treatments showed anti-tumor activity in heavily pre-treated non-BRCA associated cancers."
  - Temozolomide arm reported two PRs in ovarian (not BRCA carriers).
  - Irinotecan arm reported two PRs in ovarian (not BRCA carriers), 1 PR in triple negative breast cancer (BRCA carrier), 1 PR in small cell lung cancer, 1 PR in cervical adenocarcinoma.

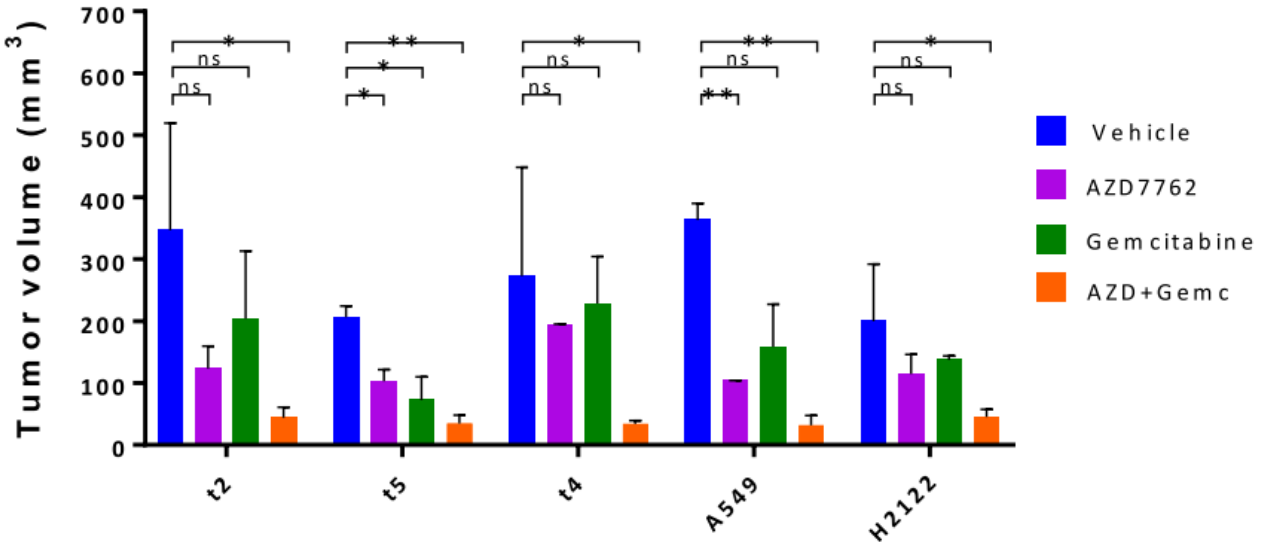
First study demonstrating both tolerability and activity with low dose chemotherapy in combination with full-dose PARP inhibitor.

Chk1 inhibition synergizes with extrinsic inducers of replication stress

- Mutant *p53* cells show synergy between Chk1i and gemcitabine over dynamic range including low doses of gemcitabine where cells suffer extensive markers of RS leading to substantial genomic damage and subsequent cell death (Koh et al., *Cancer Res.,* 2015).
- Low dose gemcitabine (40 mg/kg) resulted in persistent S phase arrest and sensitized tumor cells in vivo to the Chk1i MK-8776, resulting in extensive DNA damage (gH2A.X) and tumor growth inhibition (Montano et al., *Oncotarget*, 2017).

Low Doses (subtherapeutic) of certain chemos (e.g. gemcitabine, possibly PARPi?) induce replication stress without overt cytotoxicity, thereby making rational combination partners with potent and highly selective Chk1i, YET, prior studies have been combining with MTD or near-MTD chemo doses.

Chk1 inhibition synergizes with low dose gemcitabine *in vivo*



Very low doses of gemcitabine (20mpk gem) combo is active in multiple lung xenografts

Chk1i AZD7762 demonstrates robust anti-tumor activity in murine cancer models in combination with very low dose gem (20 mg/kg) (Wong et al., *Cancer Res.* 2017).

Critical lessons that the PARP inhibitor field has learned

The importance of:

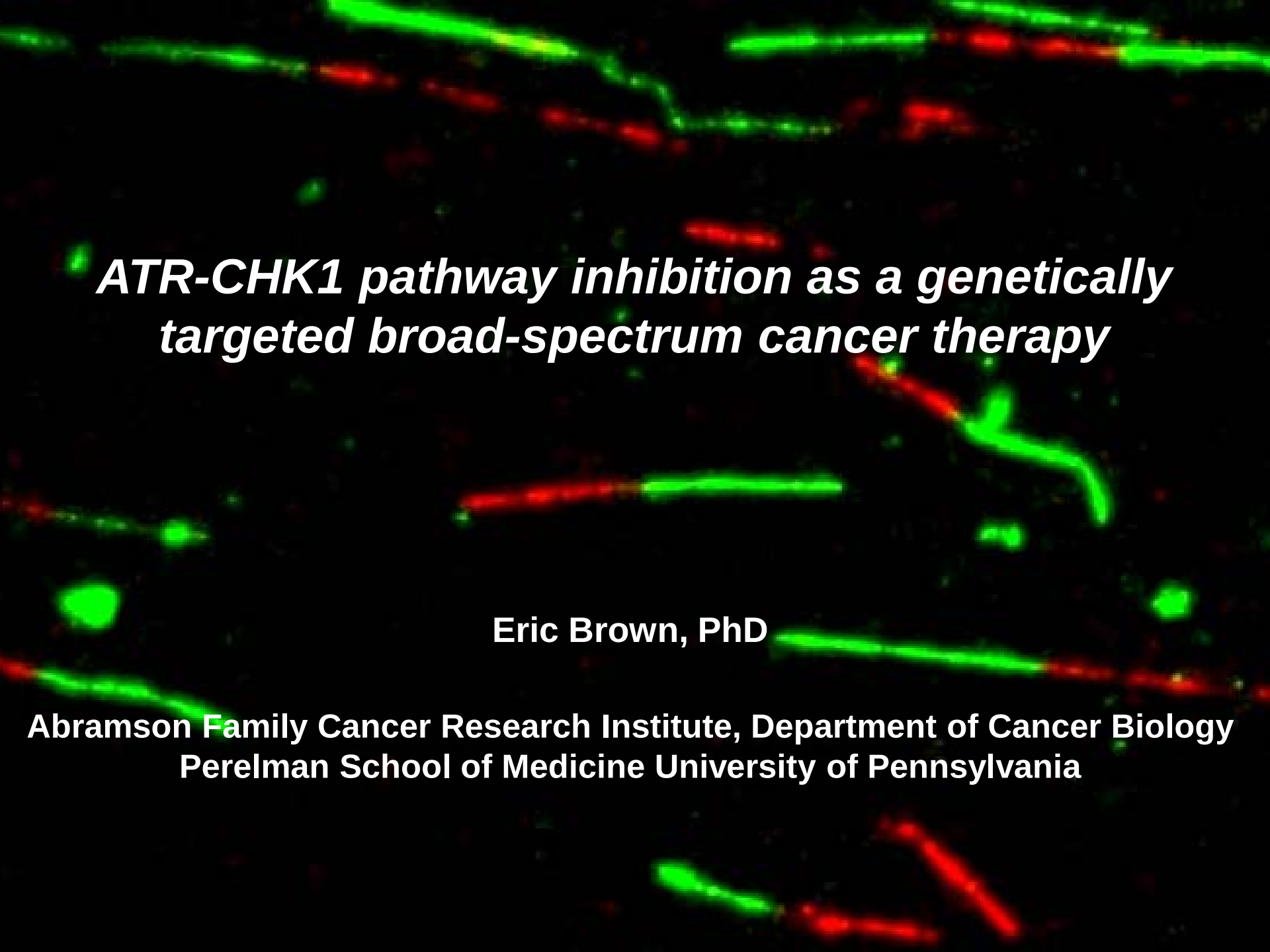
1. Discovery of the good specific PARP inhibitors, and understanding how they work.

   - first generation chemistry exhibited inadequate potency and off-target related liabilities.

2. Synthetic lethality: learning which tumors to treat with PARP inhibitors.

3. Rational basis for combinations.

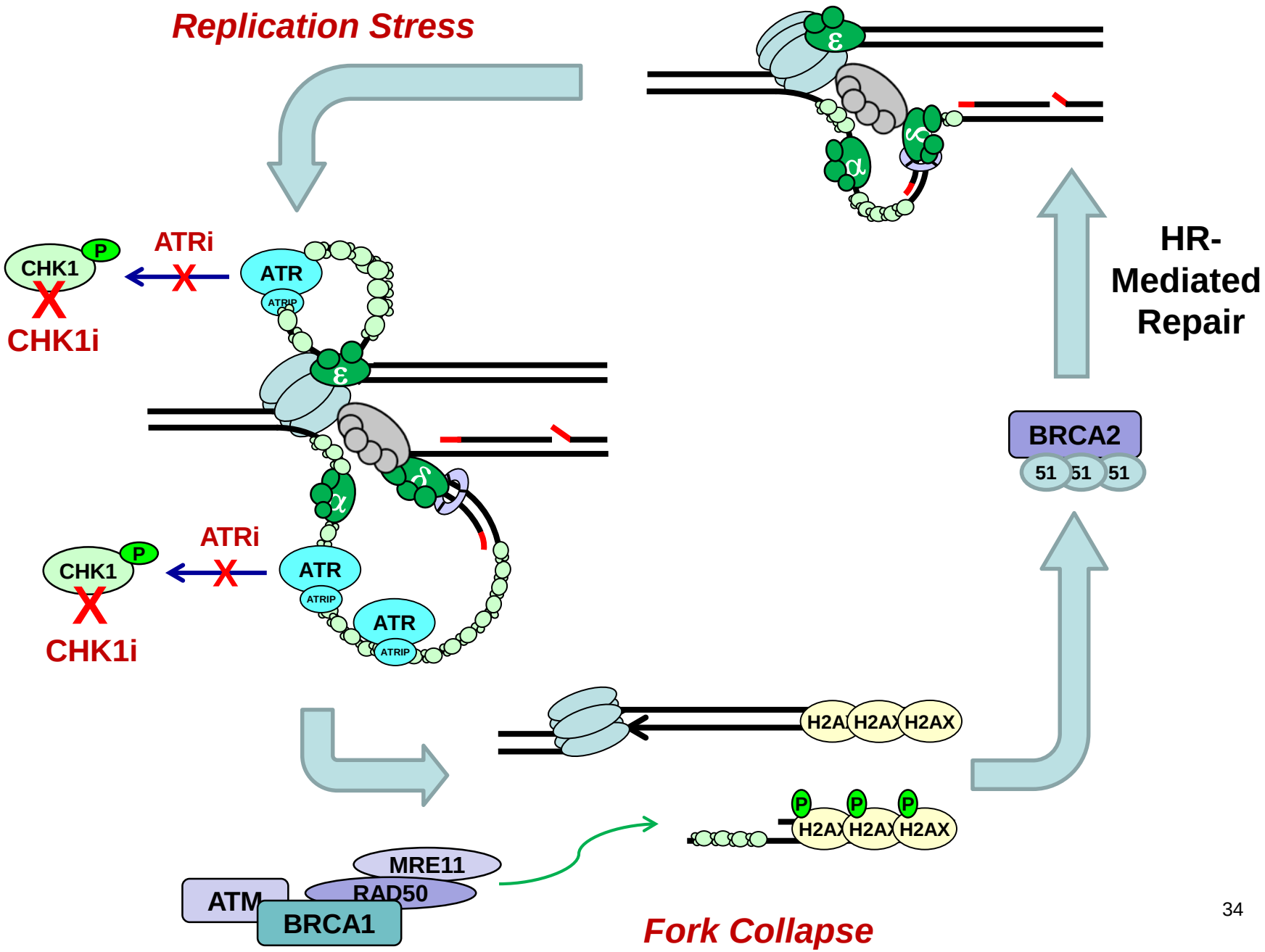
Clear analogies to the Chk1 field!



ATR-CHK1 pathway inhibition as a genetically targeted broad-spectrum cancer therapy

Eric Brown, PhD

Abramson Family Cancer Research Institute, Department of Cancer Biology
Perelman School of Medicine University of Pennsylvania


Replication Stress
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RAD50
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BRCA1
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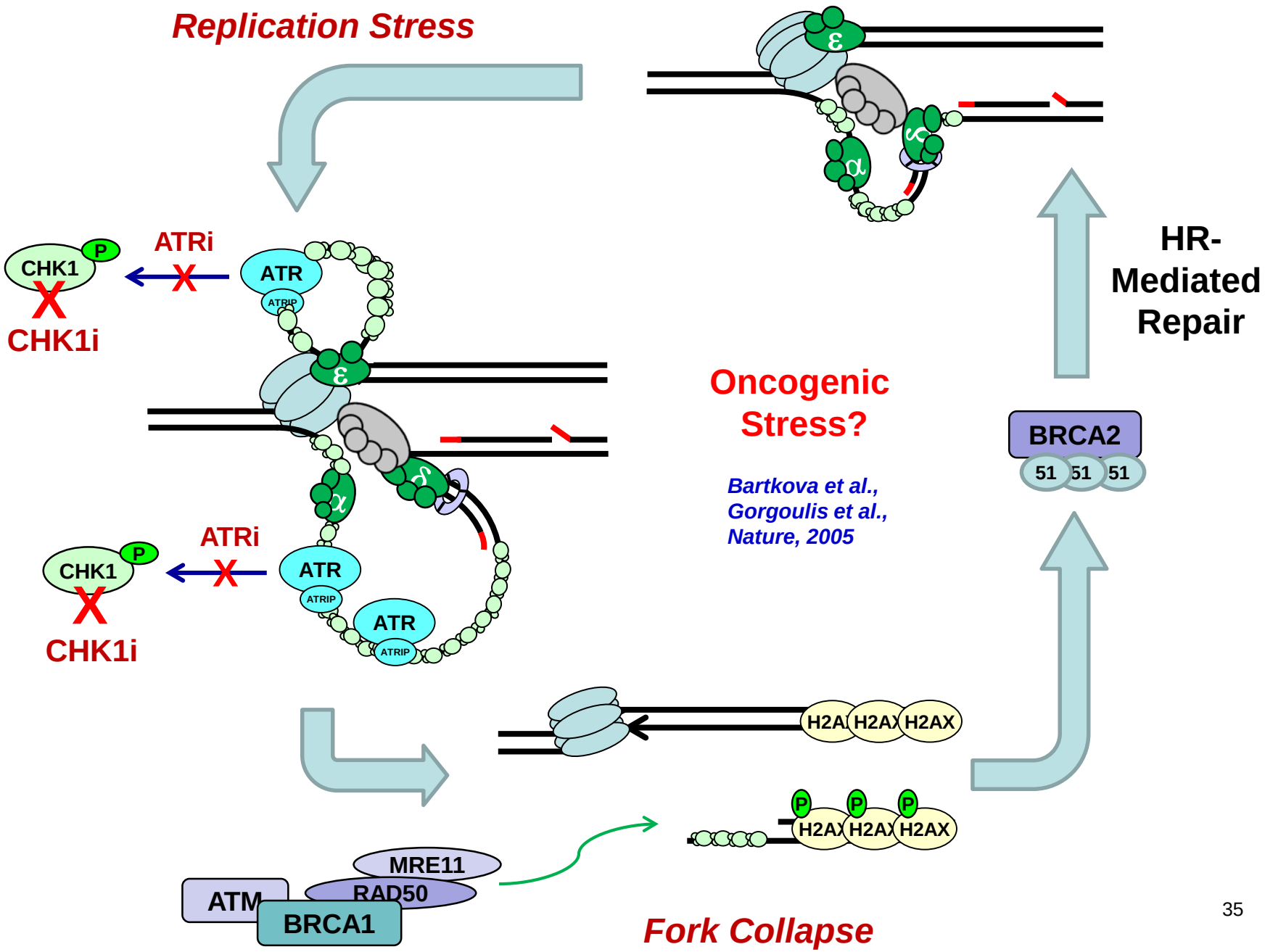
HR-
Mediated
Repair


Replication Stress
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ATR
ATRIP
Oncogenic Stress?
Bartkova et al., Gorgoulis et al., Nature, 2005
ε
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ε
HR-Mediated Repair
BRCA2
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51
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H2A
H2AX
H2AX
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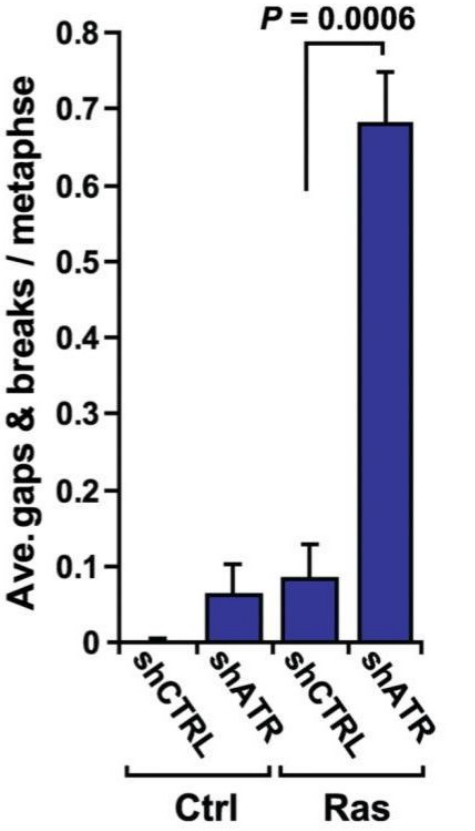
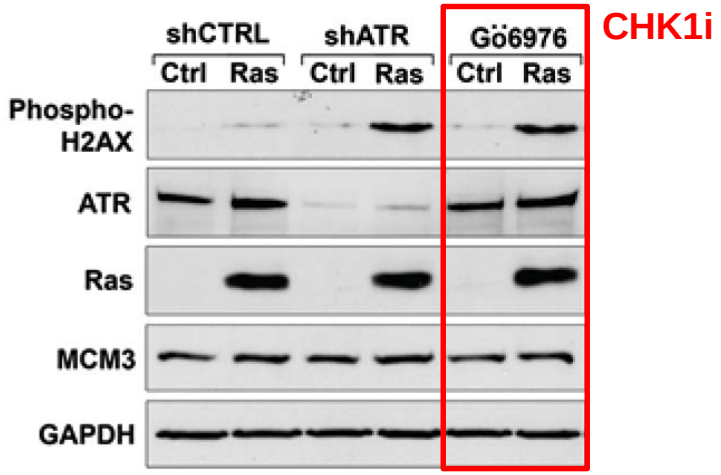
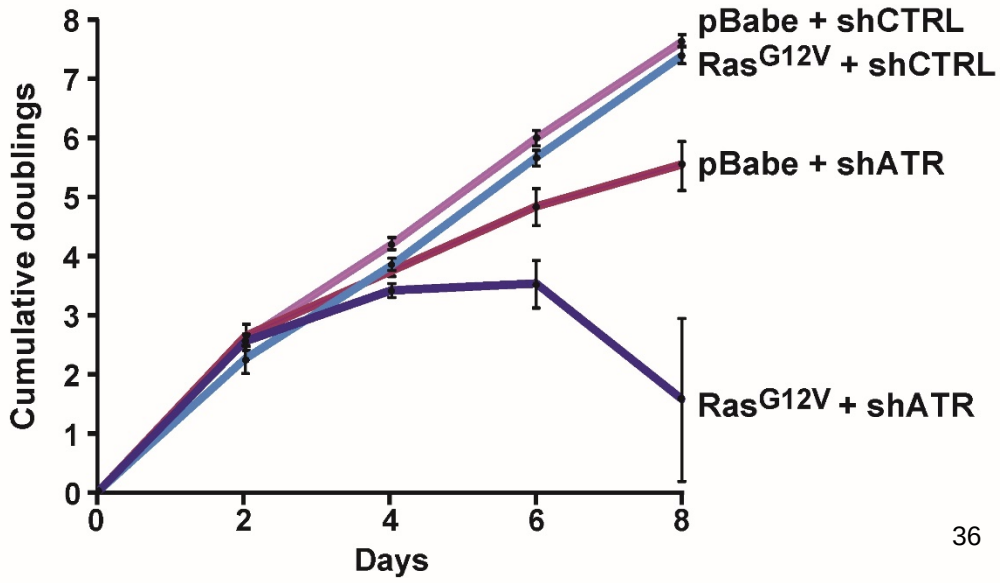
H2AX
MRE11
RAD50
ATM
BRCA1
Fork Collapse

Combining ATR-CHK1 pathway suppression with oncogenic RAS expression is lethal



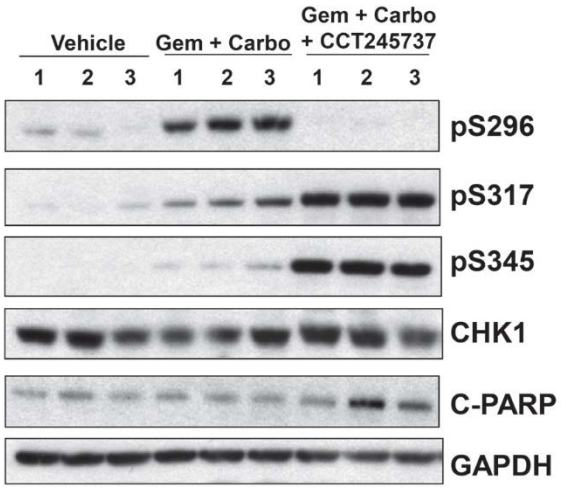


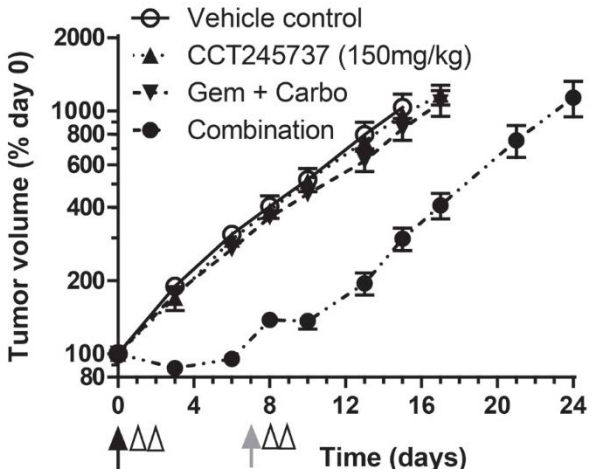


Gilad et al., Cancer Res, 2010

CHK1 inhibition (SRA737, Sierra Oncology) synergizes with chemotherapy and oncogenic stress

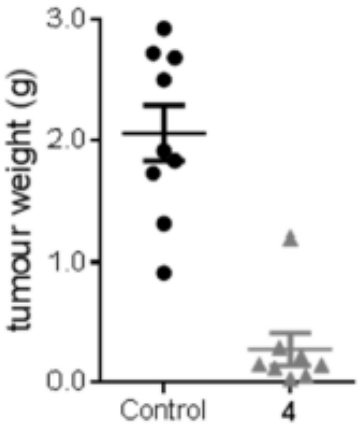
Lung cancer

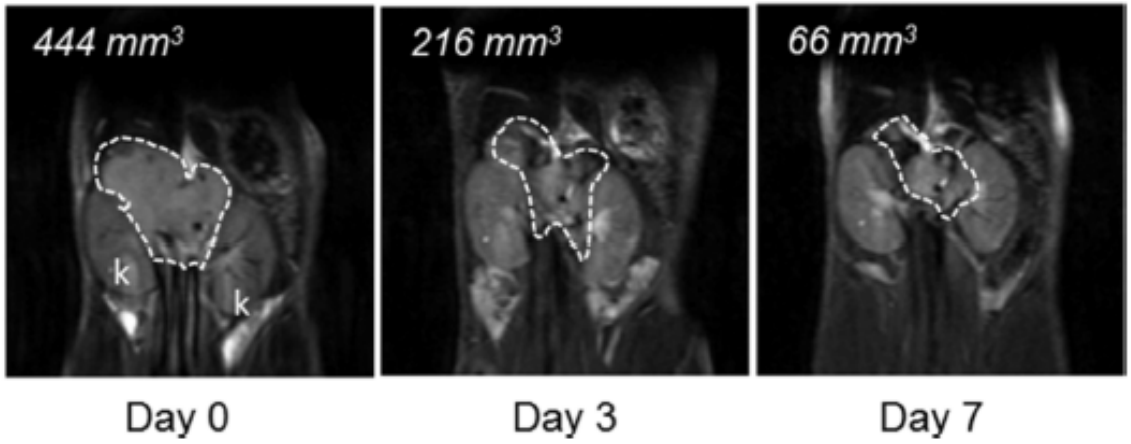




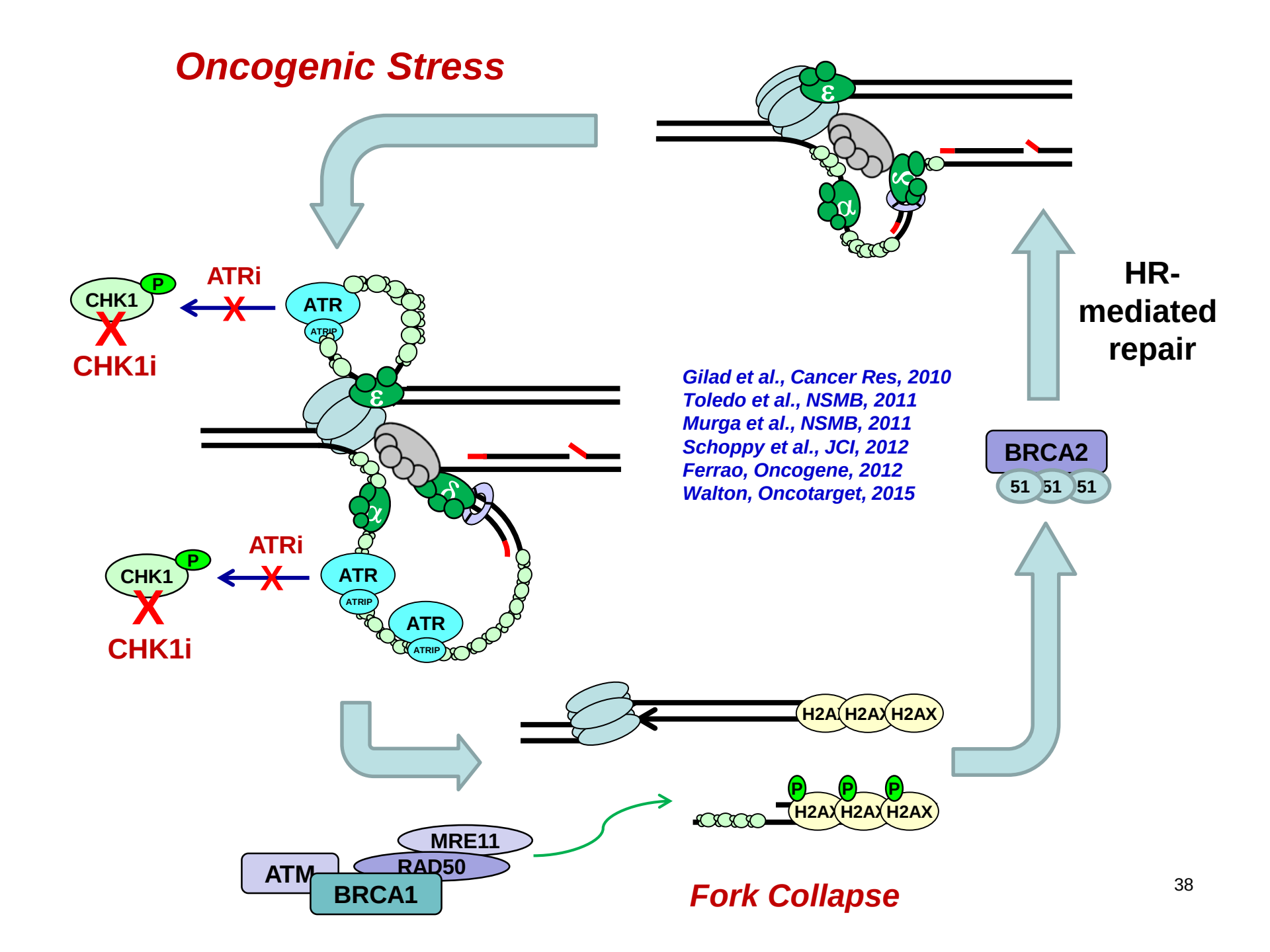
Walton et al., Oncotarget, 2015

Neuroblastoma

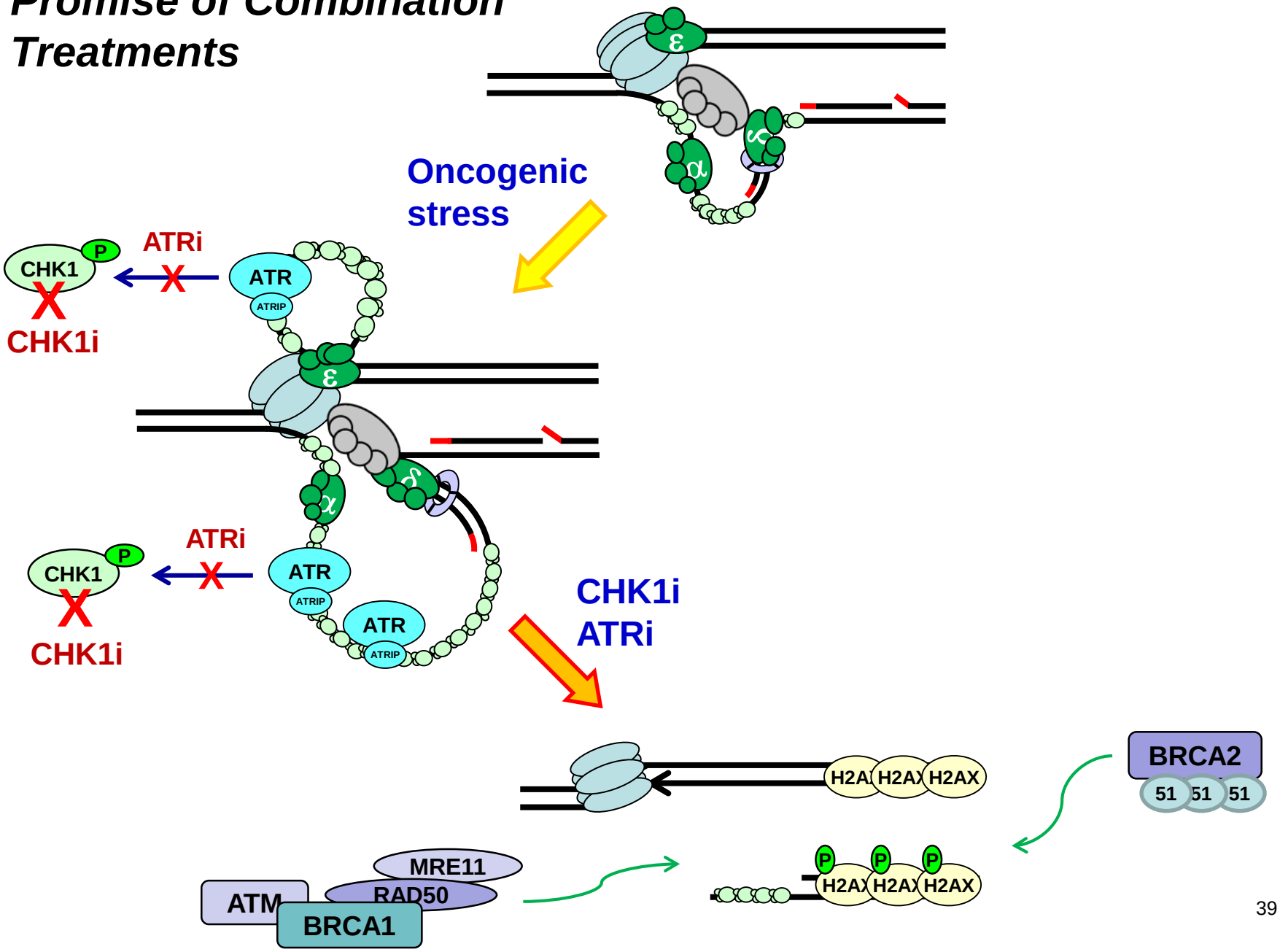




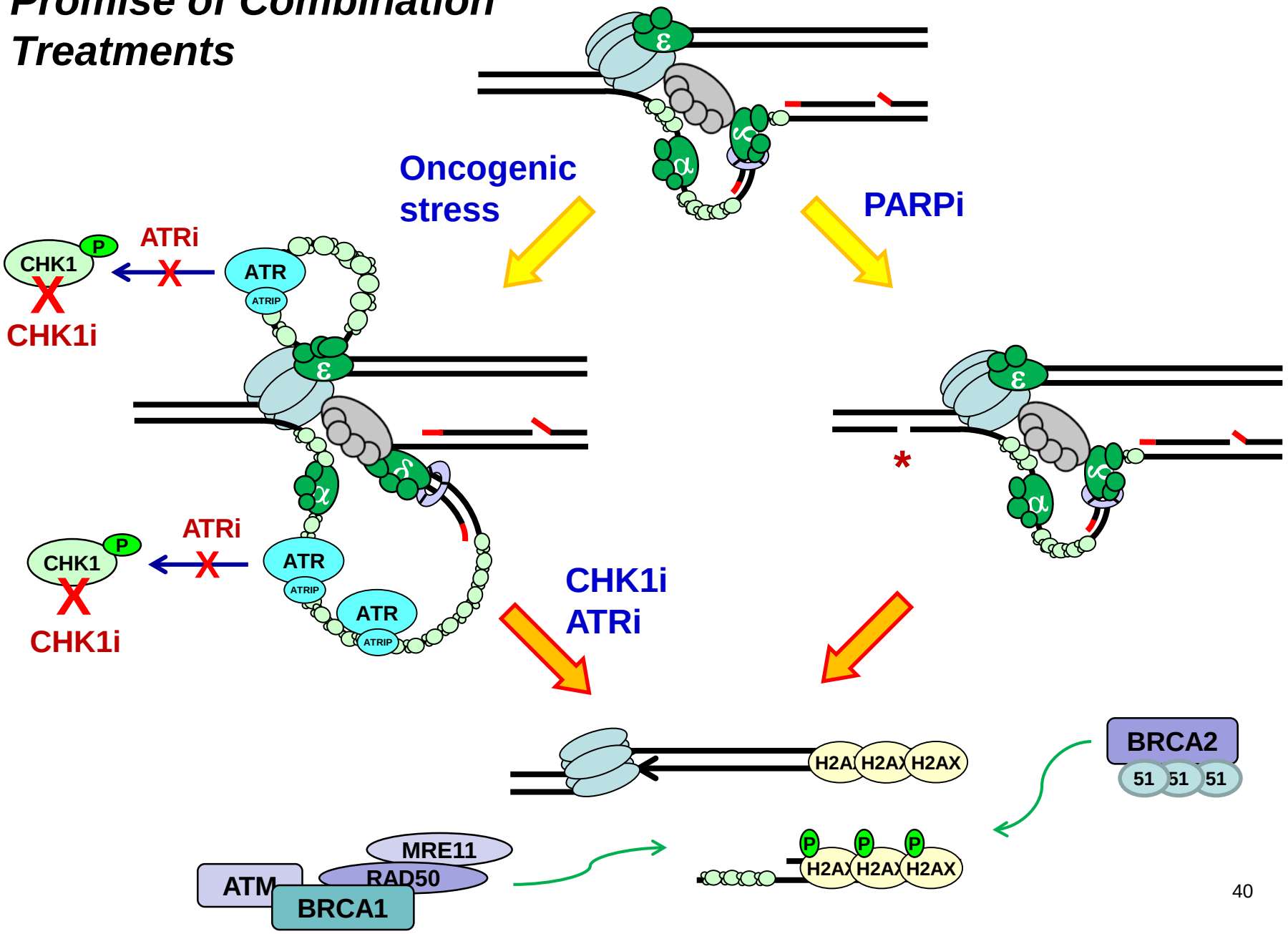
Osborne et al., J Med Chem, 2016


Oncogenic Stress
ATRi
CHK1
P
CHK1i
ATR
ATRIP
ε
α
ATRi
CHK1
P
CHK1i
ATR
ATRIP
ATR
ATRIP
Gilad et al., Cancer Res, 2010
Toledo et al., NSMB, 2011
Murga et al., NSMB, 2011
Schoppy et al., JCI, 2012
Ferrao, Oncogene, 2012
Walton, Oncotarget, 2015
HR-mediated repair
BRCA2
51
51
51
H2A
H2AX
H2AX
P
P
P
H2AX
H2AX
H2AX
MRE11
RAD50
ATM
BRCA1
Fork Collapse

Promise of Combination Treatments

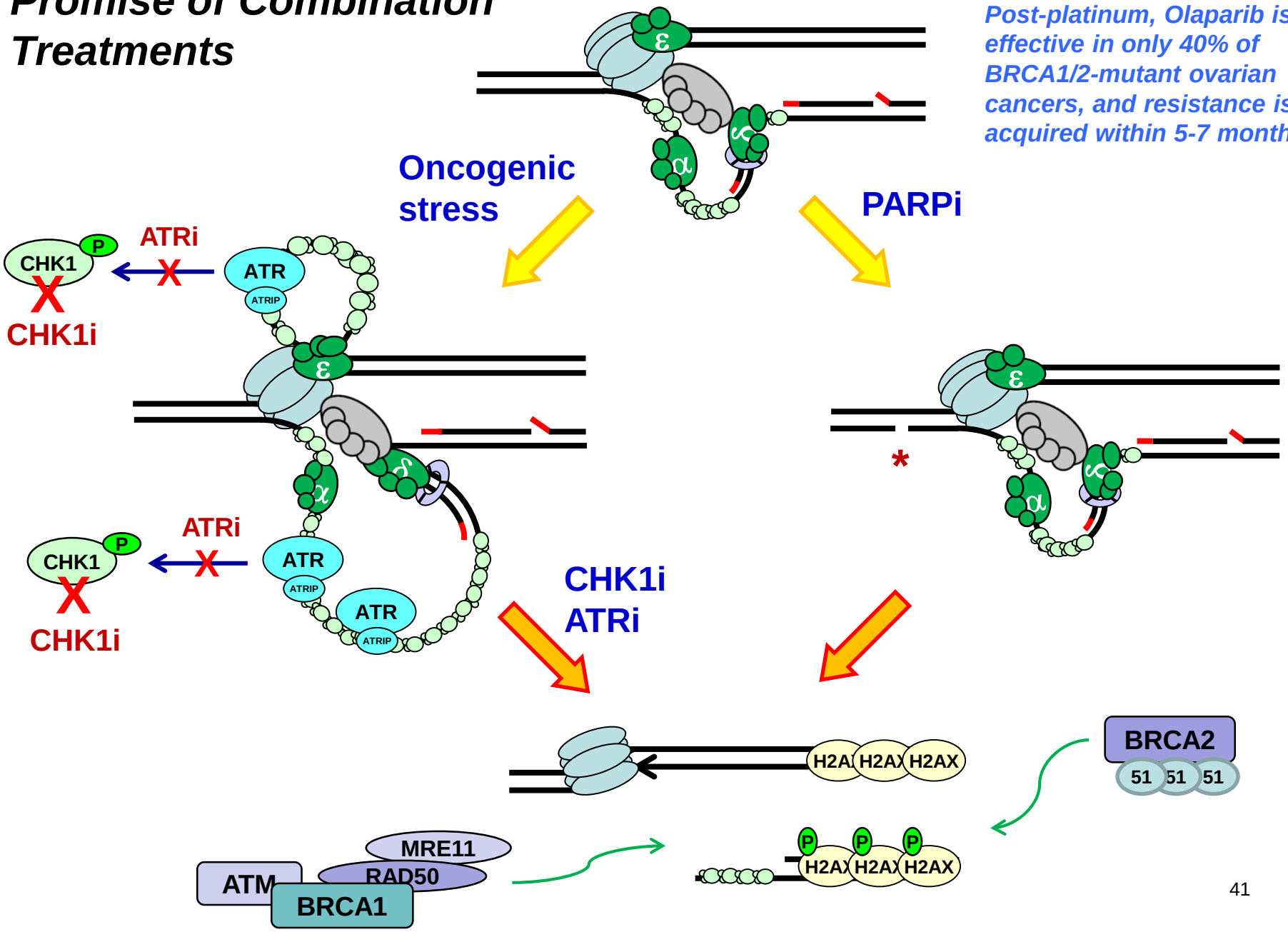


Promise of Combination Treatments



Promise of Combination Treatments

Post-platinum, Olaparib is effective in only 40% of BRCA1/2-mutant ovarian cancers, and resistance is acquired within 5-7 months



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CHK1i/ATRi+PARPi?

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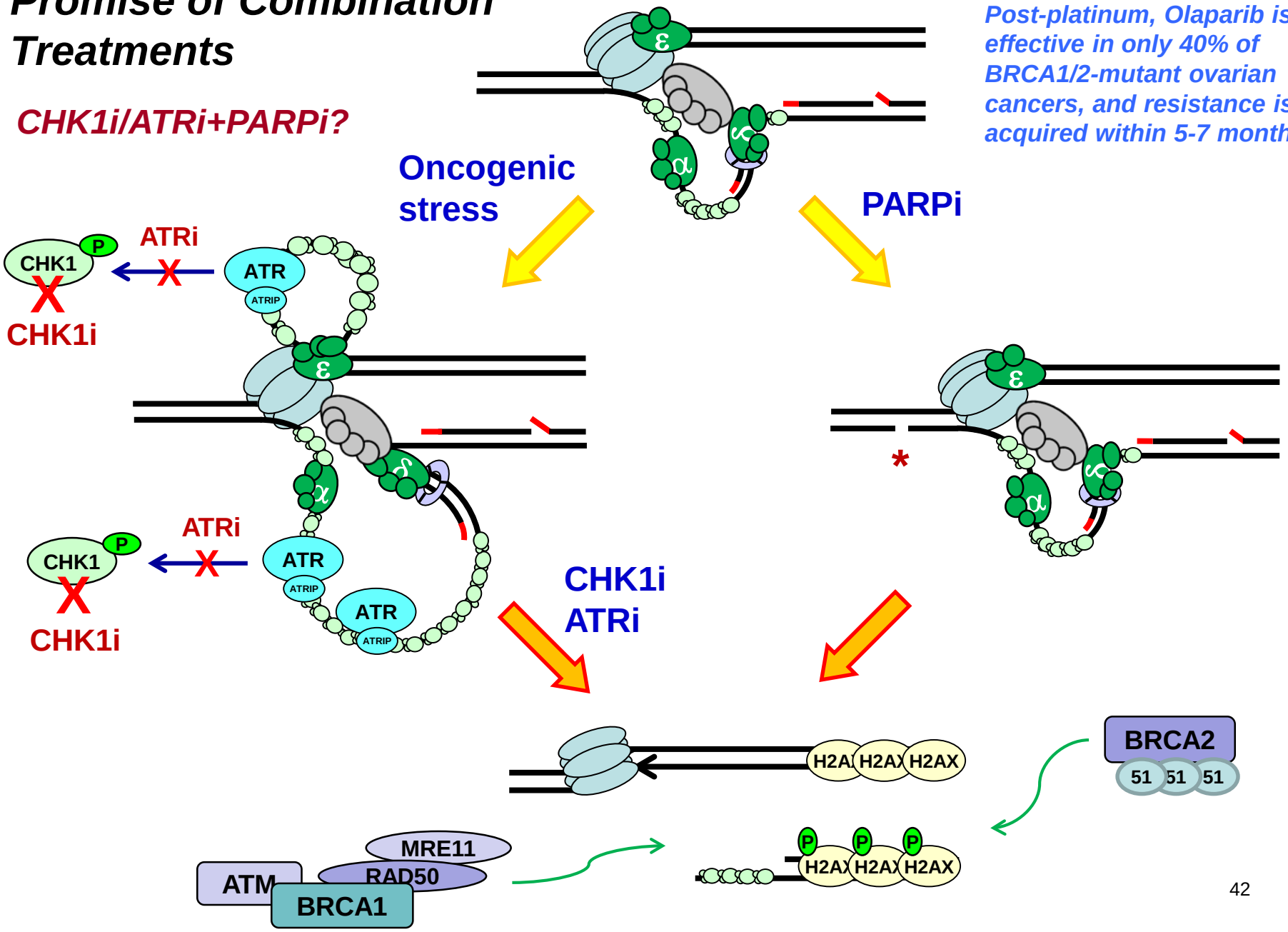
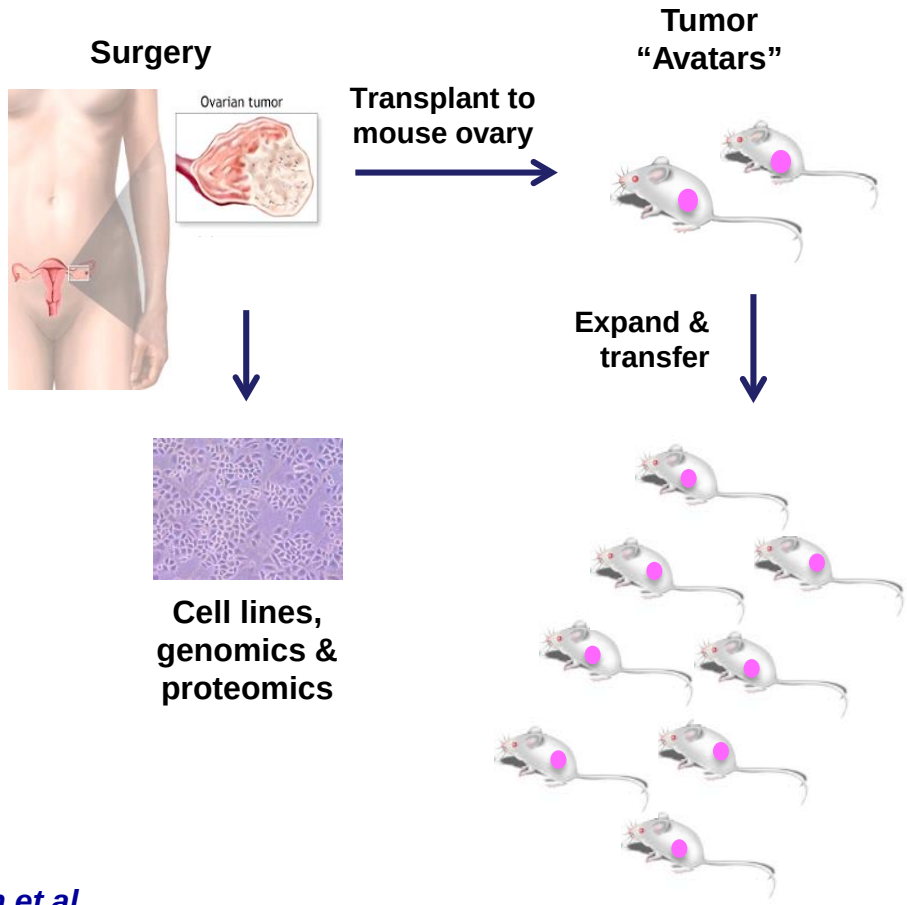


ATRi and PARPi synergize in treating BRCA2^{MUT} ovarian cancer

Personalized treatments using patient-derived xenografts (PDXs)



Kim et al., Clin Cancer Res, 2017
George et al., unpublished results

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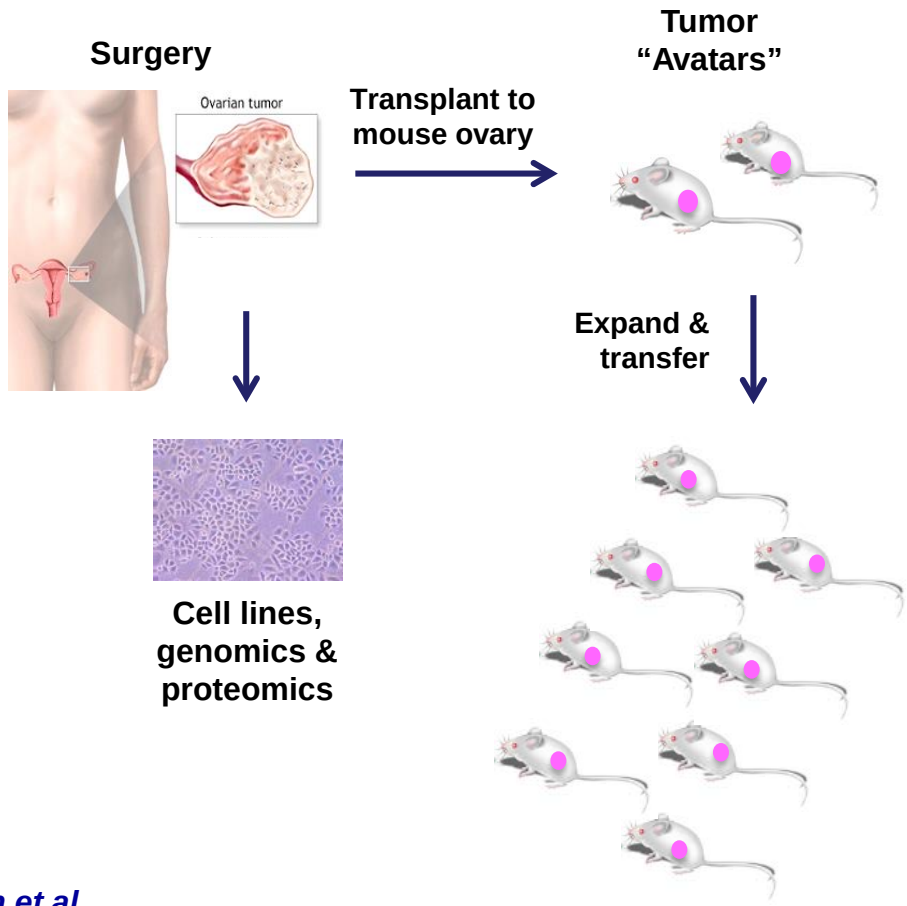

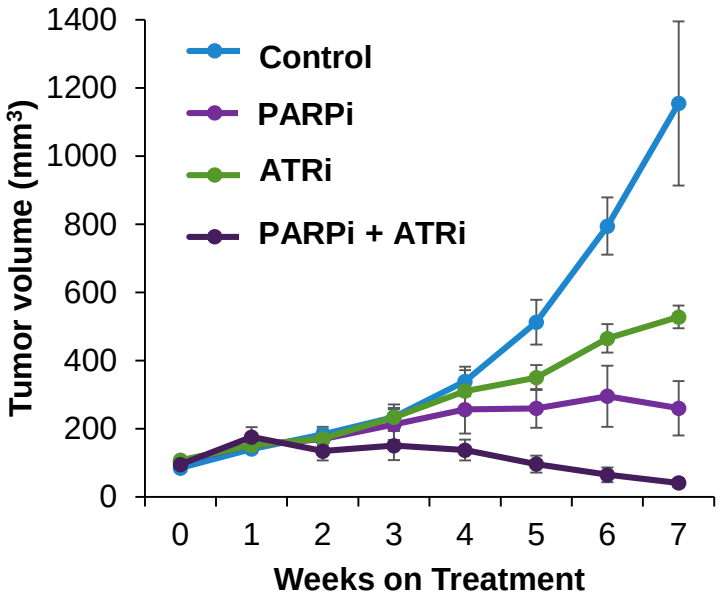

Kim et al., Clin Cancer Res, 2017
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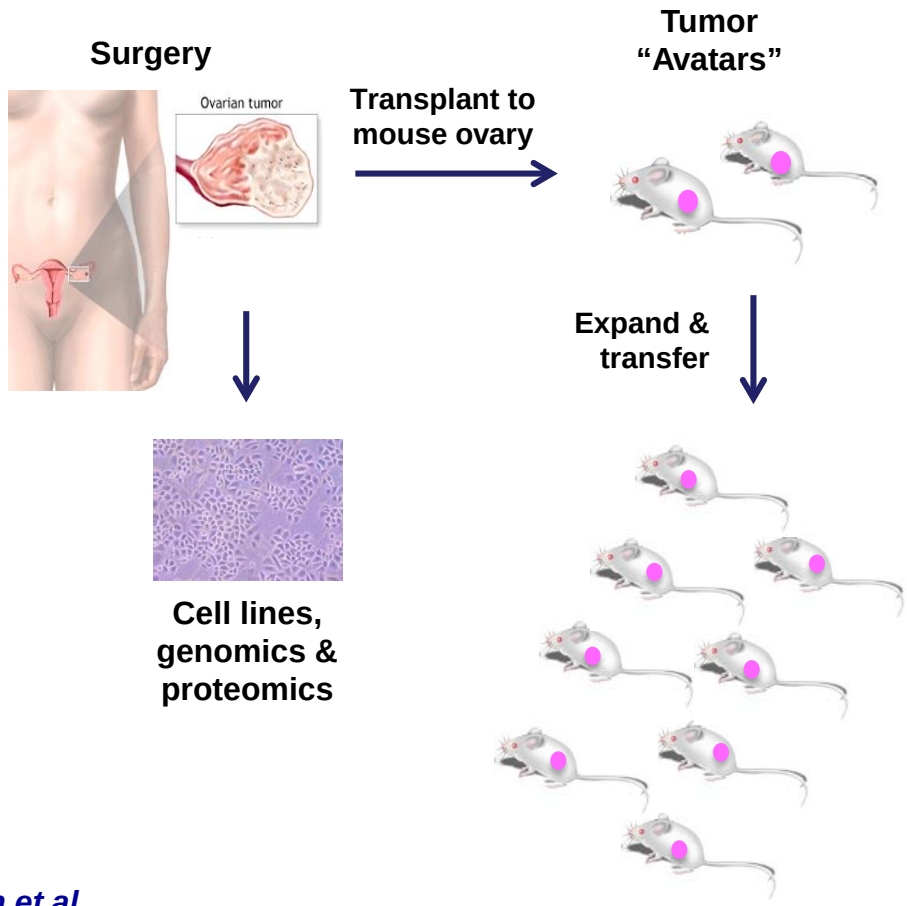
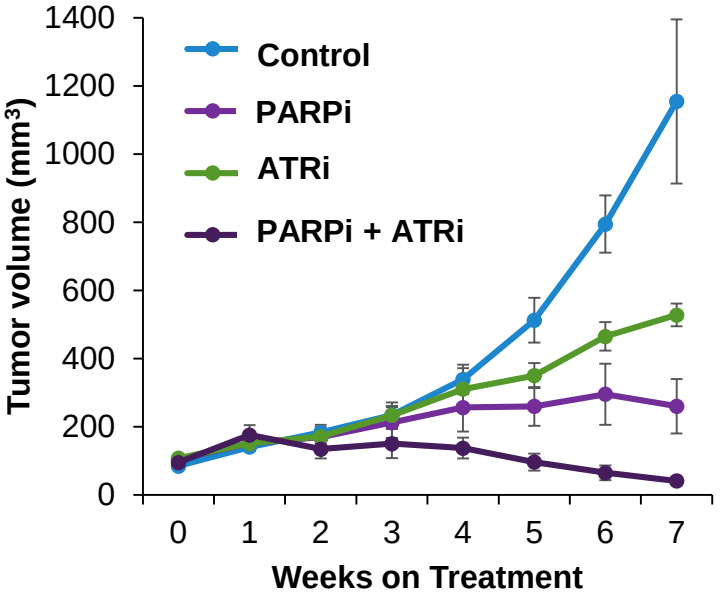
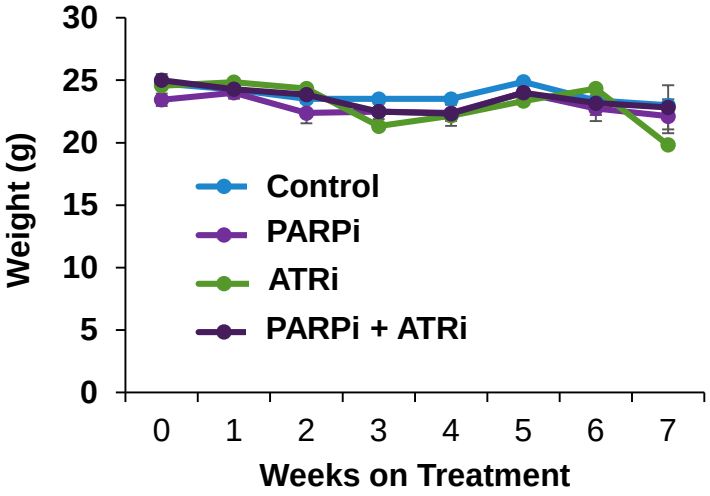
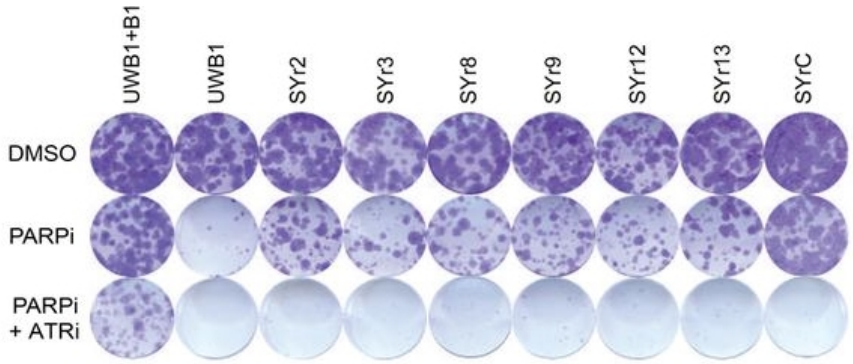


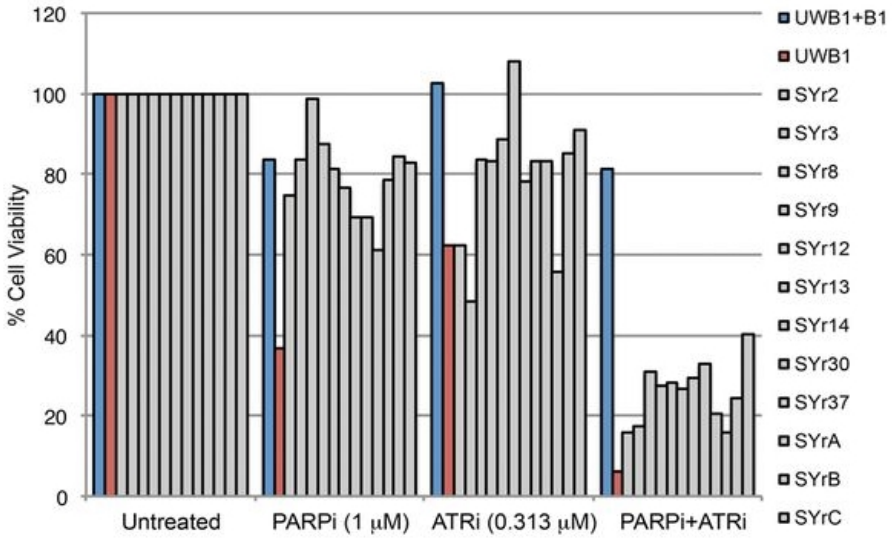




Kim et al., Clin Cancer Res, 2017
George et al., unpublished results

ATRi-PARPi combination kills BRCA^{MUT} PARPi-resistant lines





Yanzinski et al., Genes Dev, 2017

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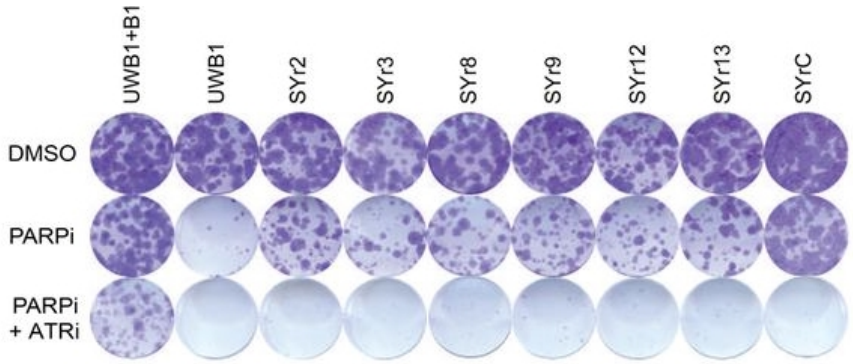
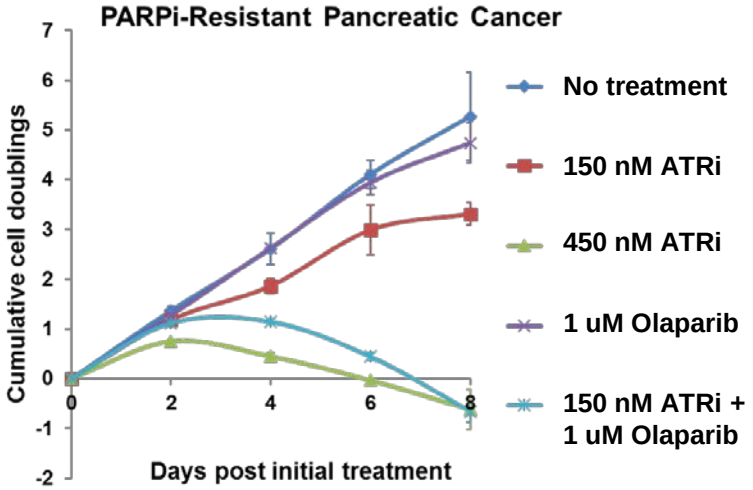
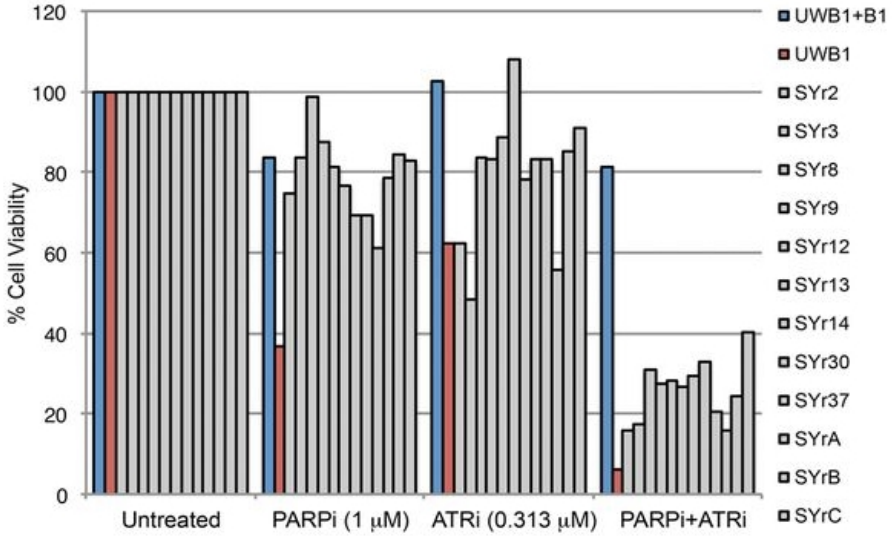
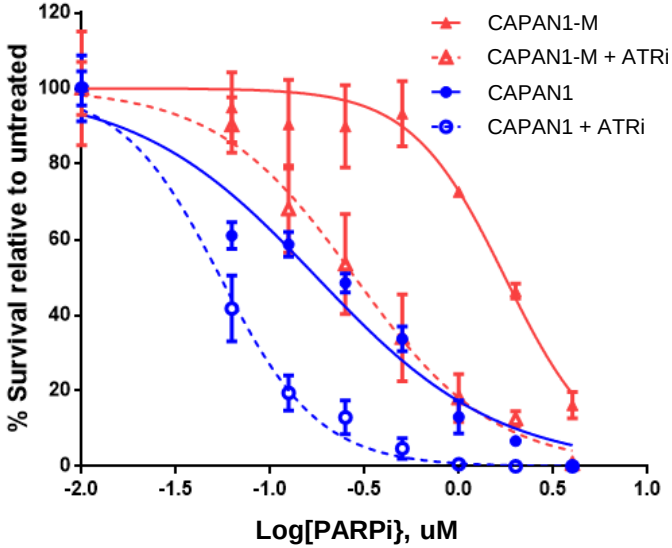




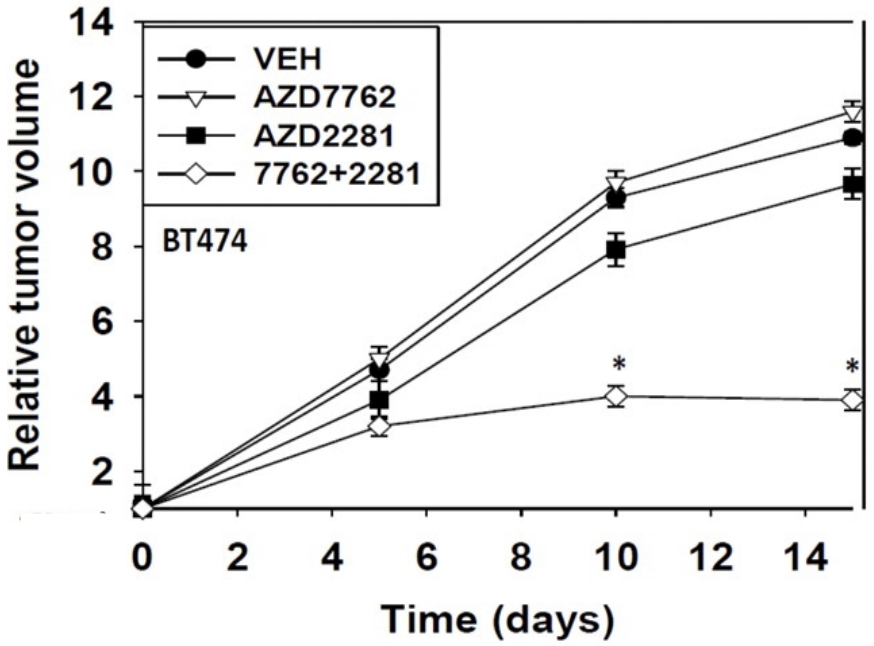


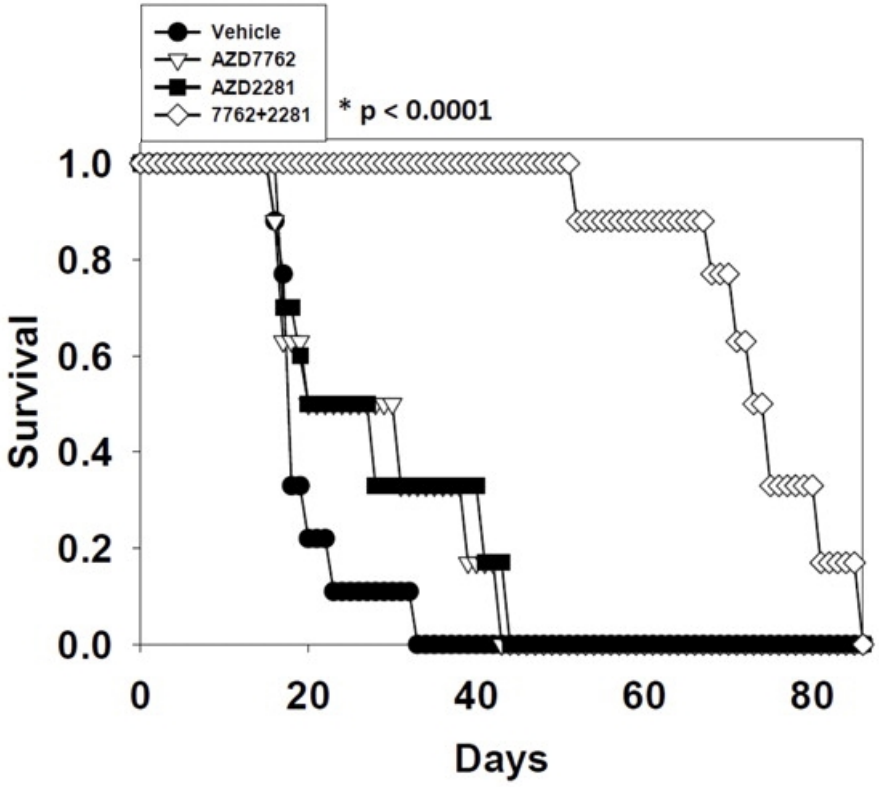
Yanzinski et al., Genes Dev, 2017



Butler et al., unpublished results

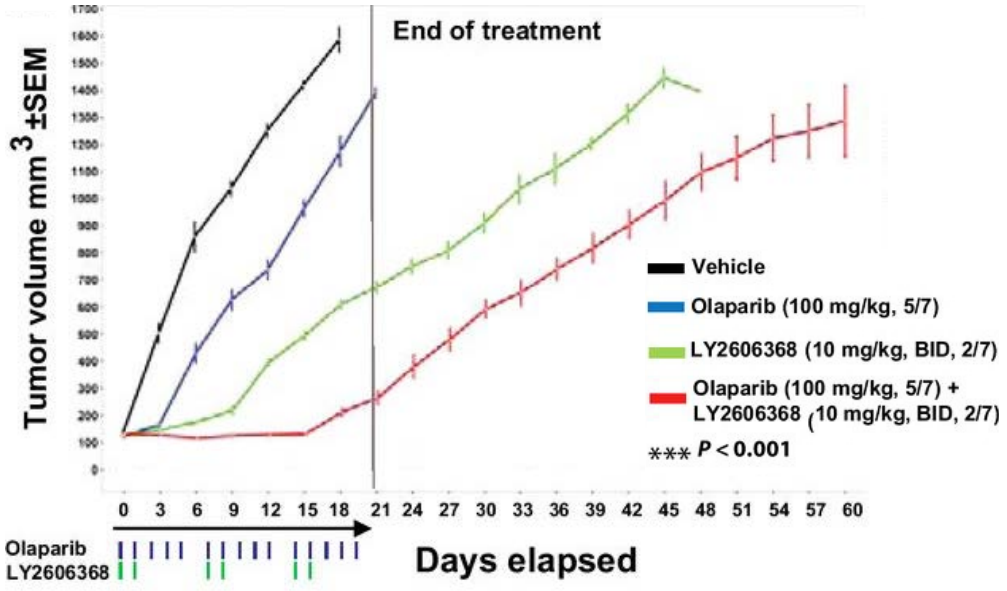
CHK1i and PARPi synergize as a breast cancer treatment

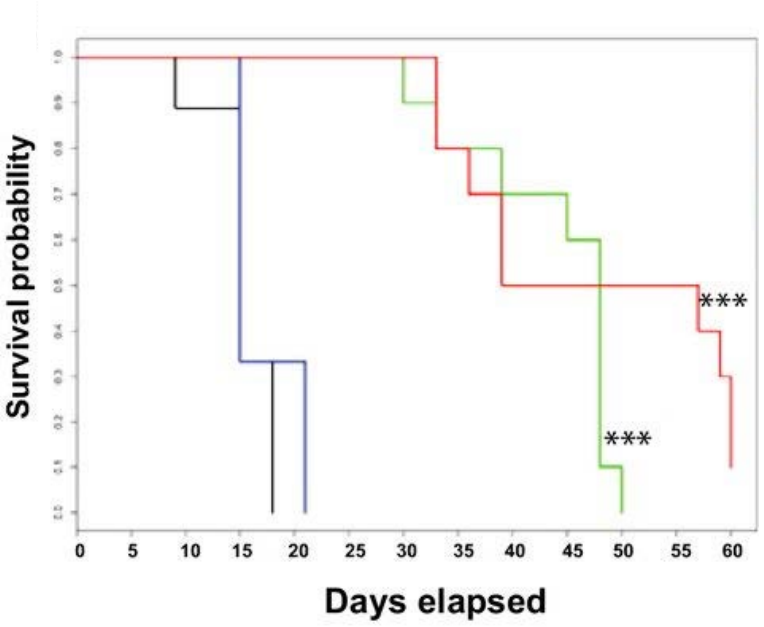




Tang et al., Mol Pharmacol, 2012

PARPi-resistant SCLC tumors respond better to CHK1i-PARPi

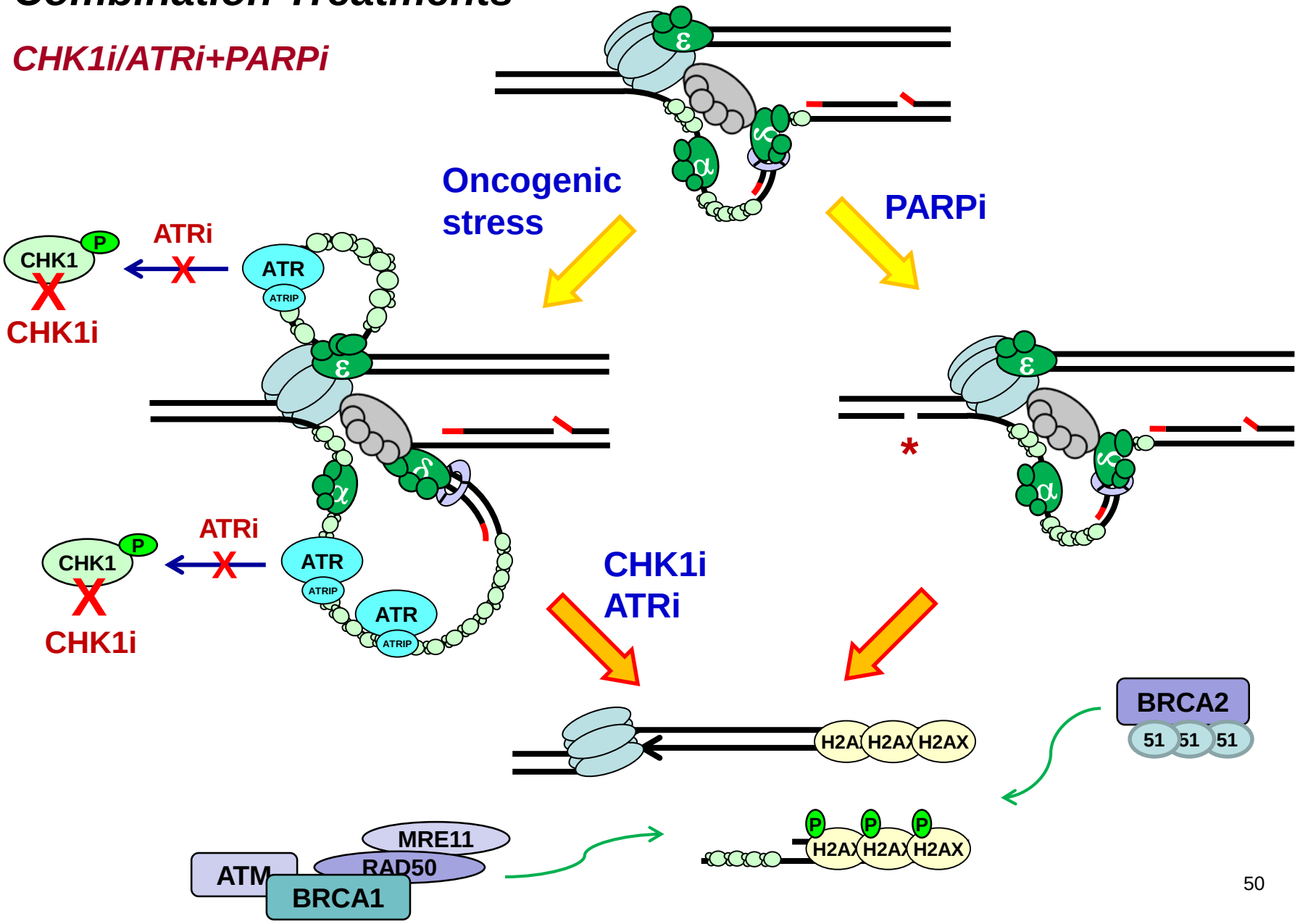




Sen et al., Cancer Res, 2017

Combination Treatments

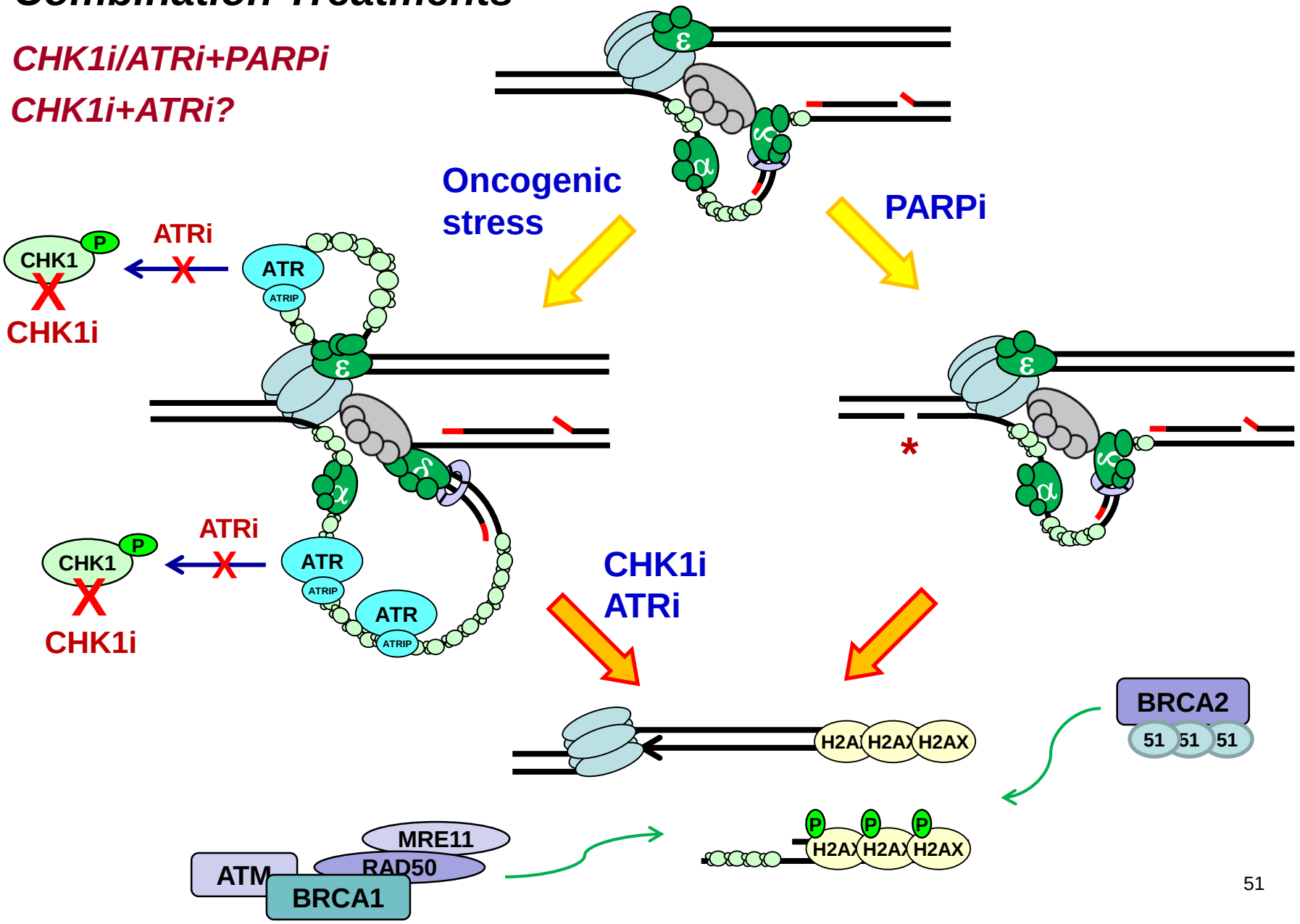
CHK1i/ATRi+PARPi



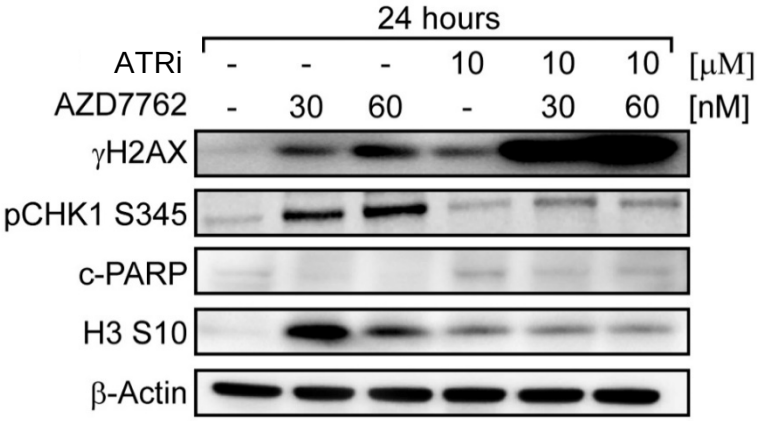
Combination Treatments

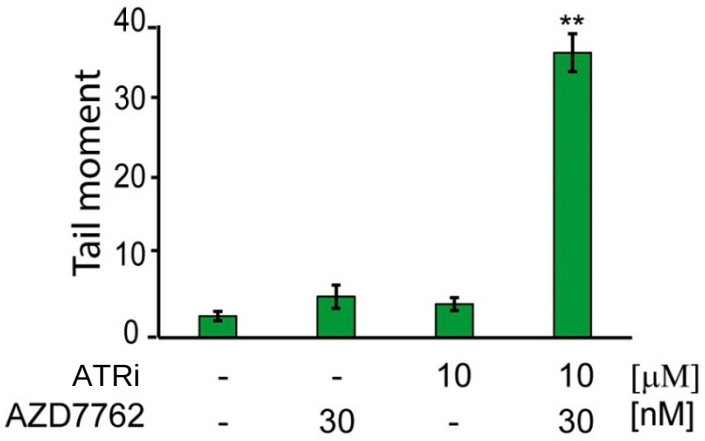
CHK1i/ATRi+PARPi

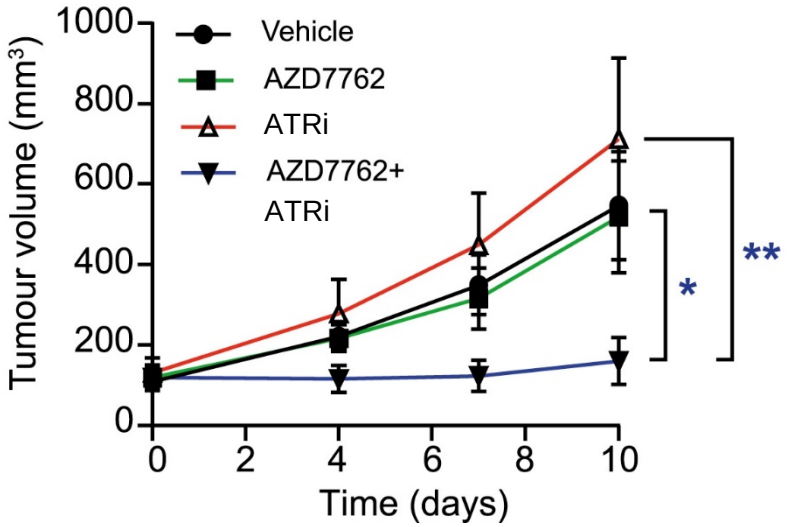
CHK1i+ATRi?

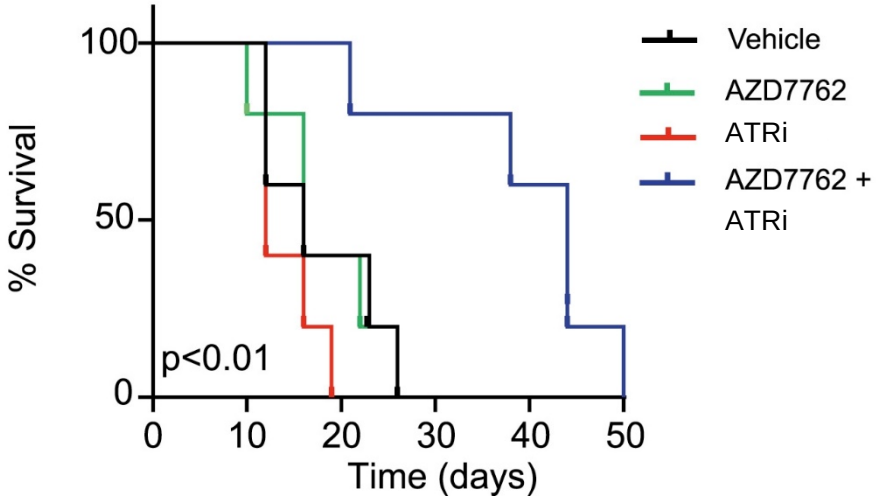


Synergistic therapeutic effects of combining CHK1i with ATRi



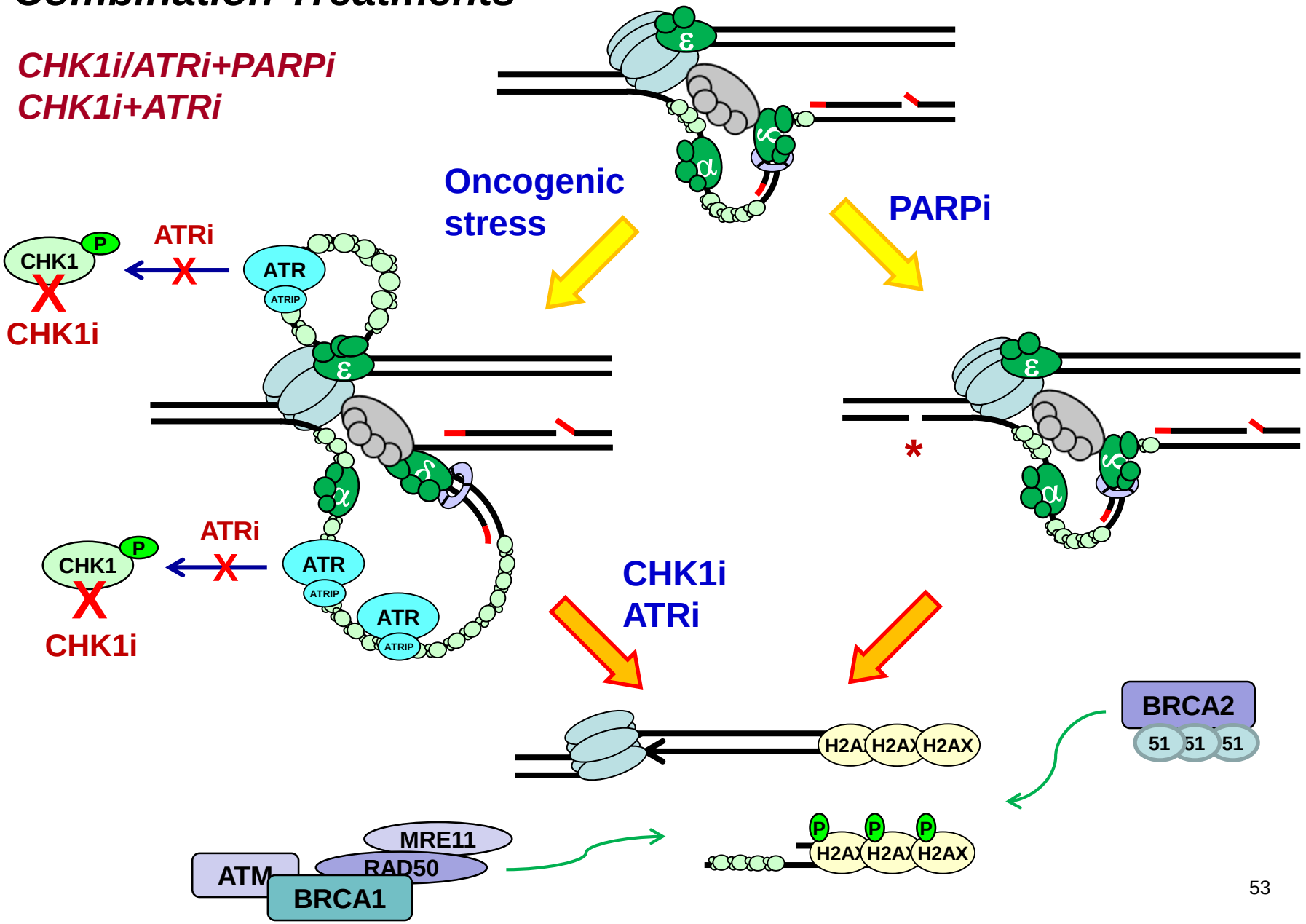




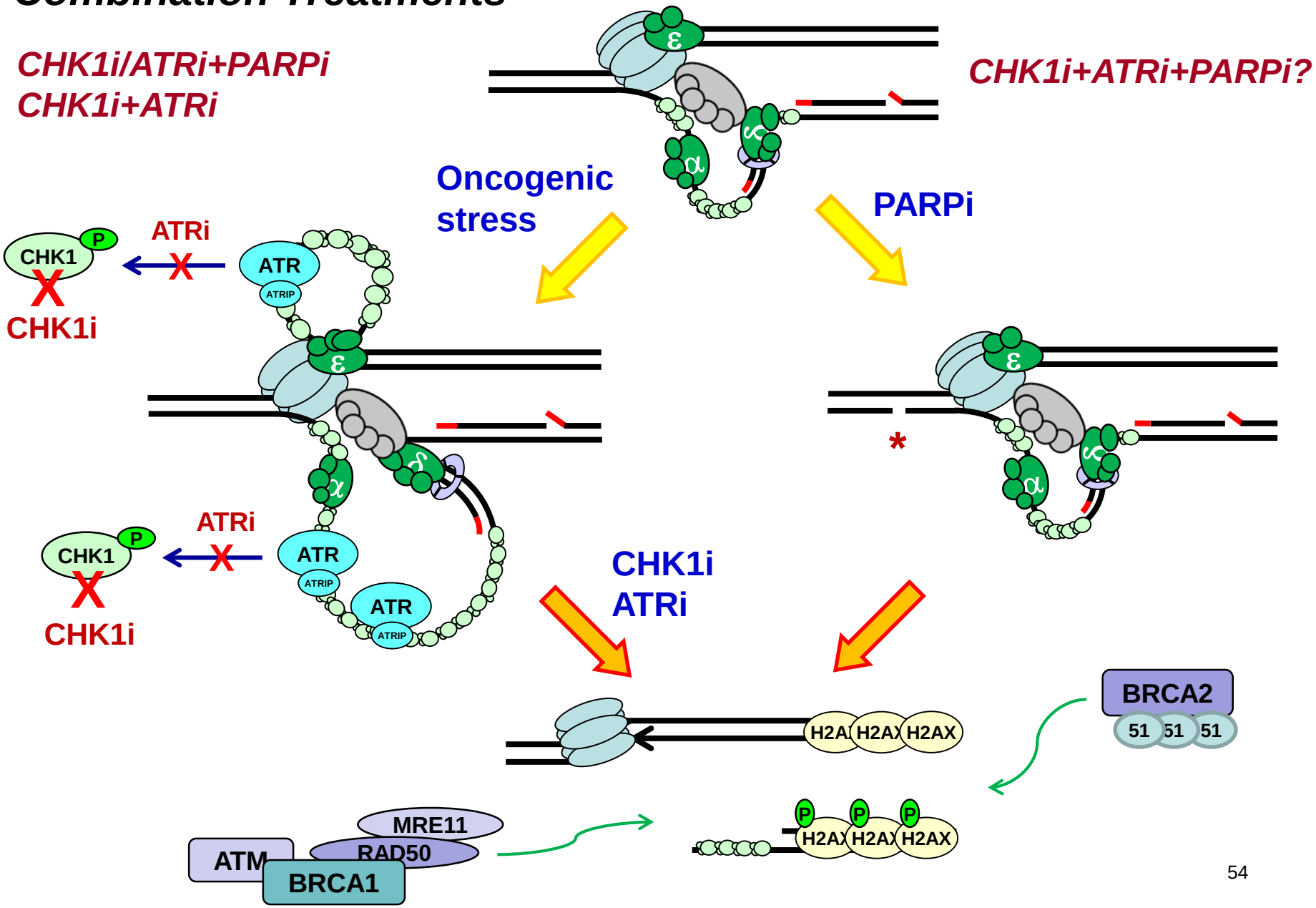


Sanjiv et al., Cell Reports, 2016

Combination Treatments



Combination Treatments



Summary

- Inhibition of ATR-CHK1 pathway is a targeted approach for cancer treatment.
- ATR-CHK1 pathway inhibition synergizes with numerous cancer-associated mutations, including oncogenic stress, making it a relatively broad spectrum treatment.
- There is tremendous promise in combining ATRi/CHK1i inhibition not only with standard chemotherapeutics, but also with other targeted treatments (e.g. PARPi).
- ATR-CHK1 pathway inhibition provides avenues for treatment of PARPi-resistant cancers.
- CHK1i- and ATRi-containing drug combination regimens are well positioned to replace standard-of-care chemotherapeutic treatments as frontline therapies.

Beyond PARP: The Clinical Potential of Next Generation DNA Damage Response (DDR) Therapeutics
October 12, 2017

CHK1 Inhibition in the Anti-Cancer Armamentarium

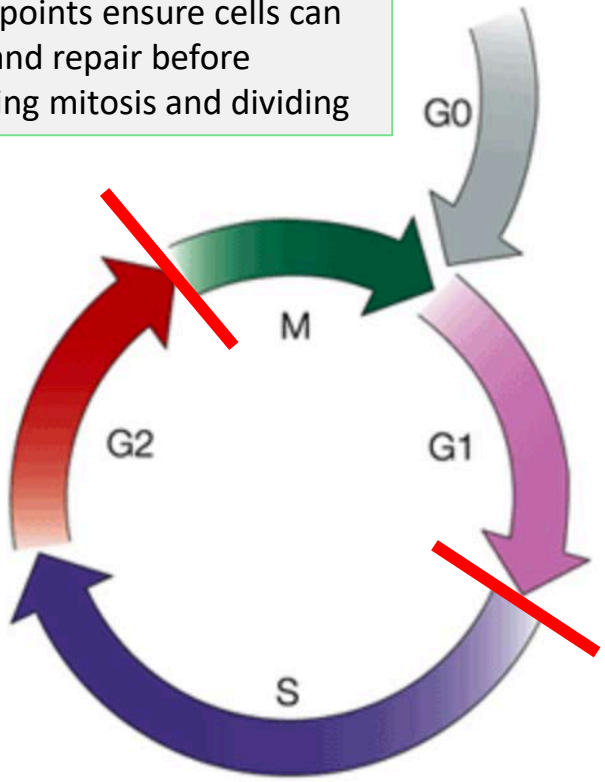
Geoffrey Shapiro, MD, PhD
Director, Early Drug Development Center
Dana-Farber Cancer Institute
Associate Professor of Medicine,
Harvard Medical School

Outline

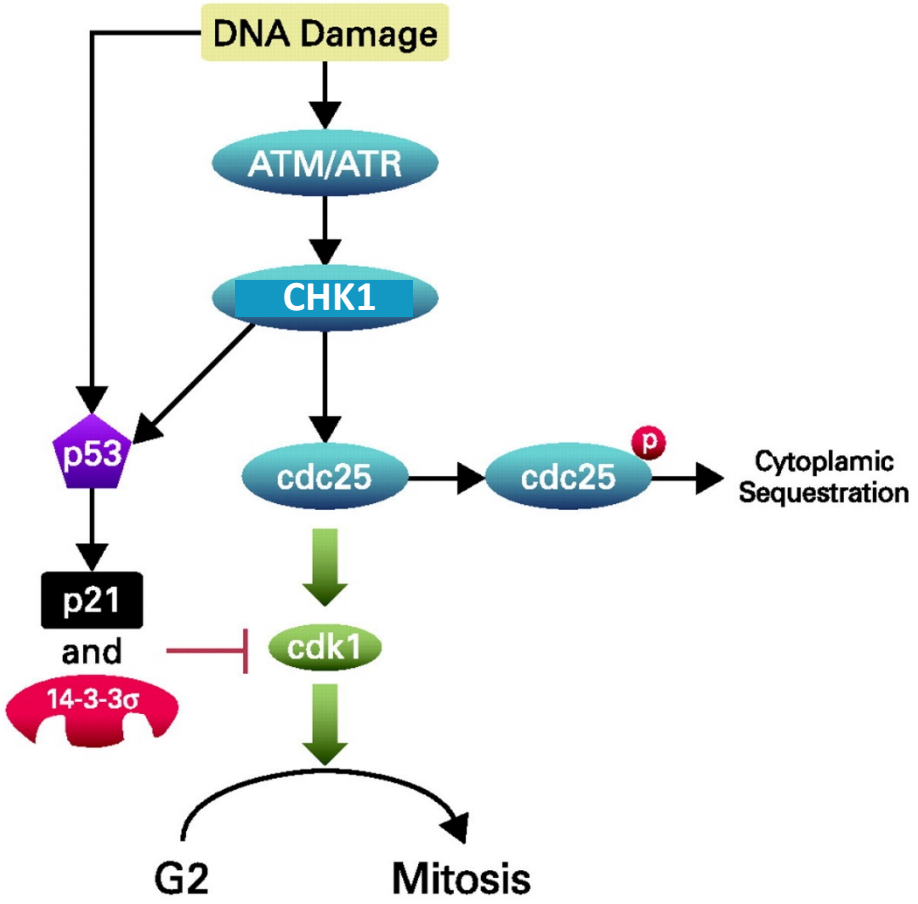
- Augmentation of chemotherapy-induced DNA damage
- Defining monotherapy vulnerability
- Reversal of PARP inhibitor resistance

DNA Damage-Induced Checkpoints

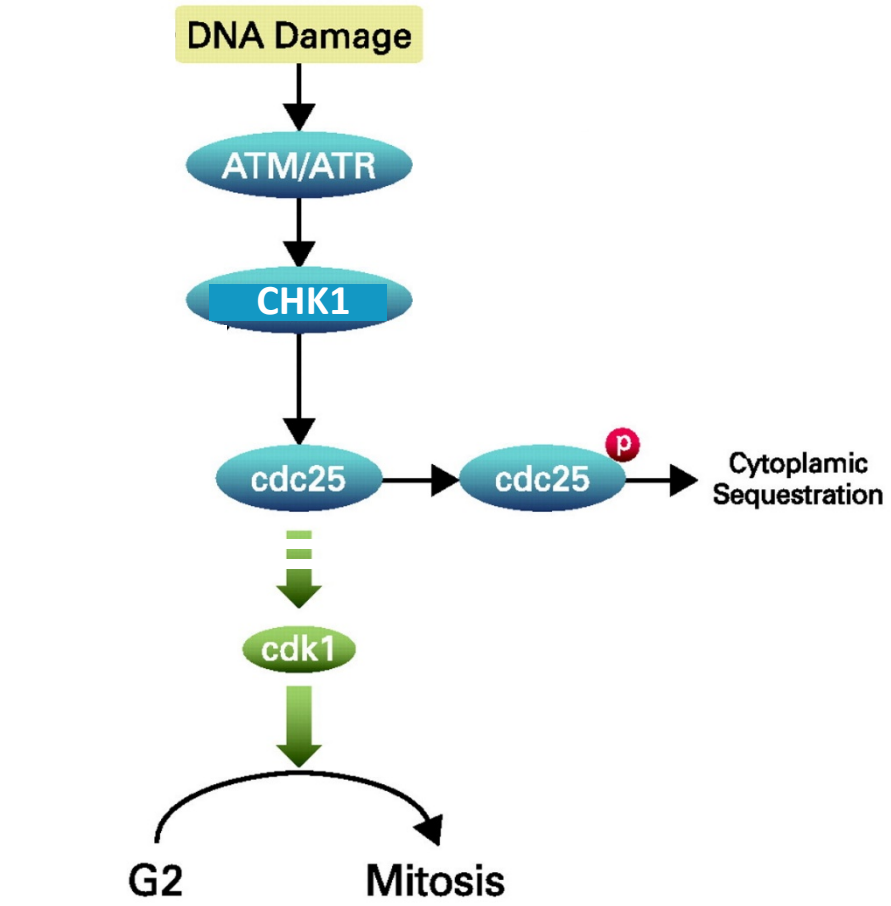
DNA damage-induced checkpoints ensure cells can stop and repair before entering mitosis and dividing



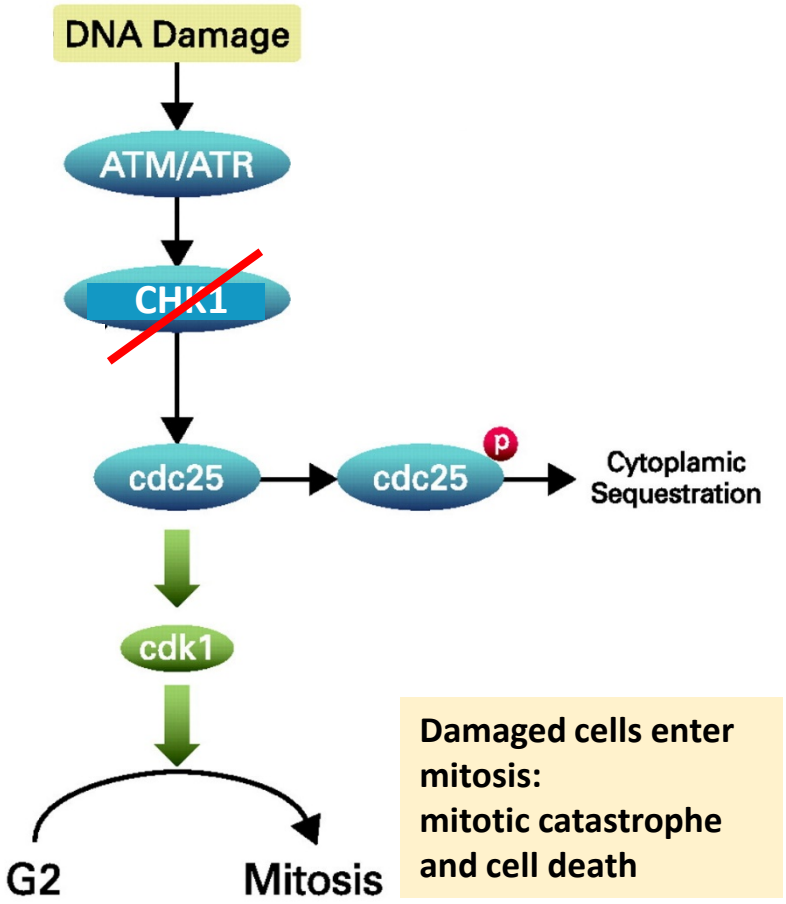
Many chemotherapy agents damage DNA



The CHK1-mediated DNA damage- induced checkpoint is essential in p53 deficiency



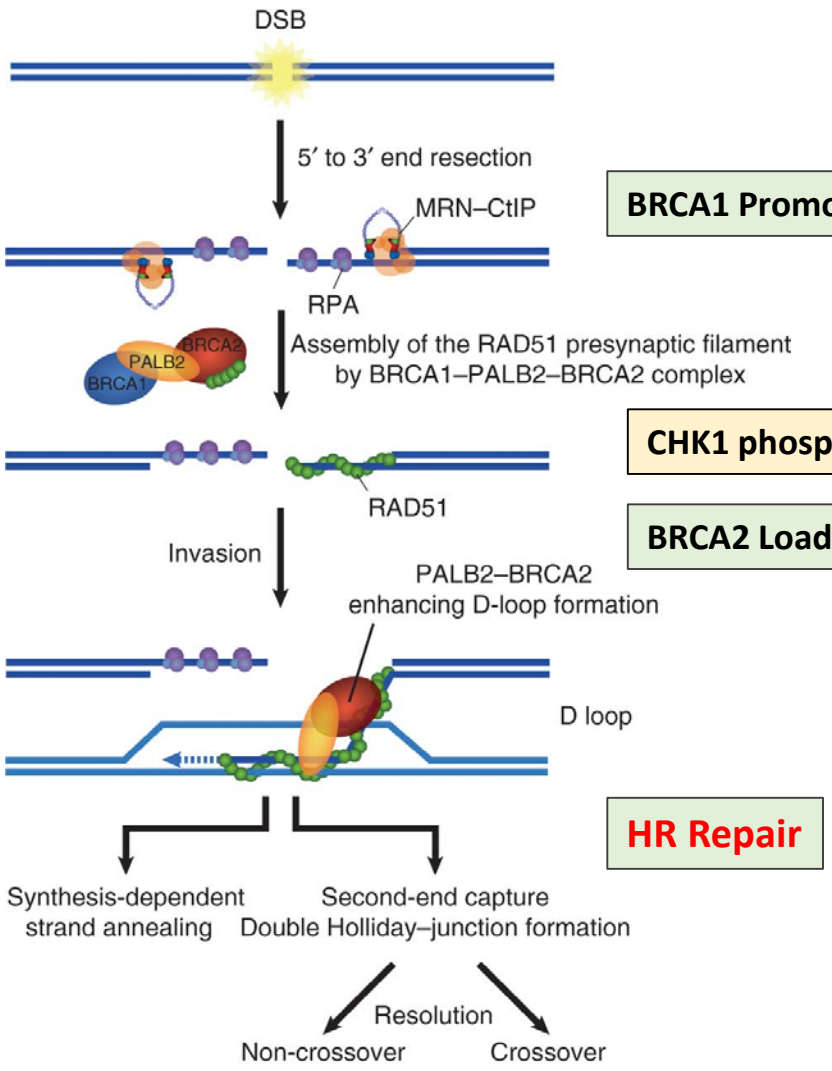
CHK1 inhibition accentuates DNA damage in p53-deficient cells



DNA Damaging agents + CHK1 inhibition

- Gemcitabine + CHK1 inhibitor
- Irinotecan + CHK1 inhibitor
- Selectivity for p53-deficient cells may mitigate toxicity to non-transformed cells
- Combining the Ckh1 inhibitor with subtherapeutic doses of gemcitabine retains the potentiating effect and represents a novel biological strategy
  - Any clinical activity observed can be ascribed to the combination

Understanding CHK1 inhibitor monotherapy: Steps of Homologous Recombination Repair



BRCA1 Promotes End Resection

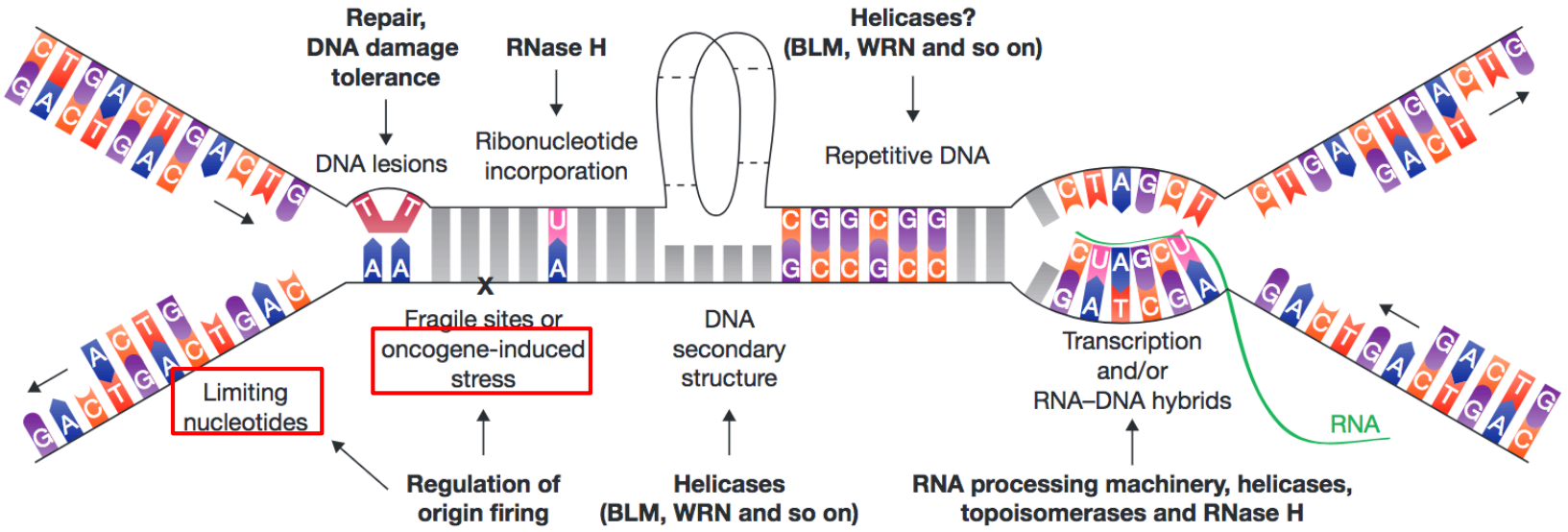
CHK1 phosphorylates RAD51

BRCA2 Loads RAD51

HR Repair

CHK1 is essential for homologous recombination

Understanding CHK1 monotherapy: The replication fork

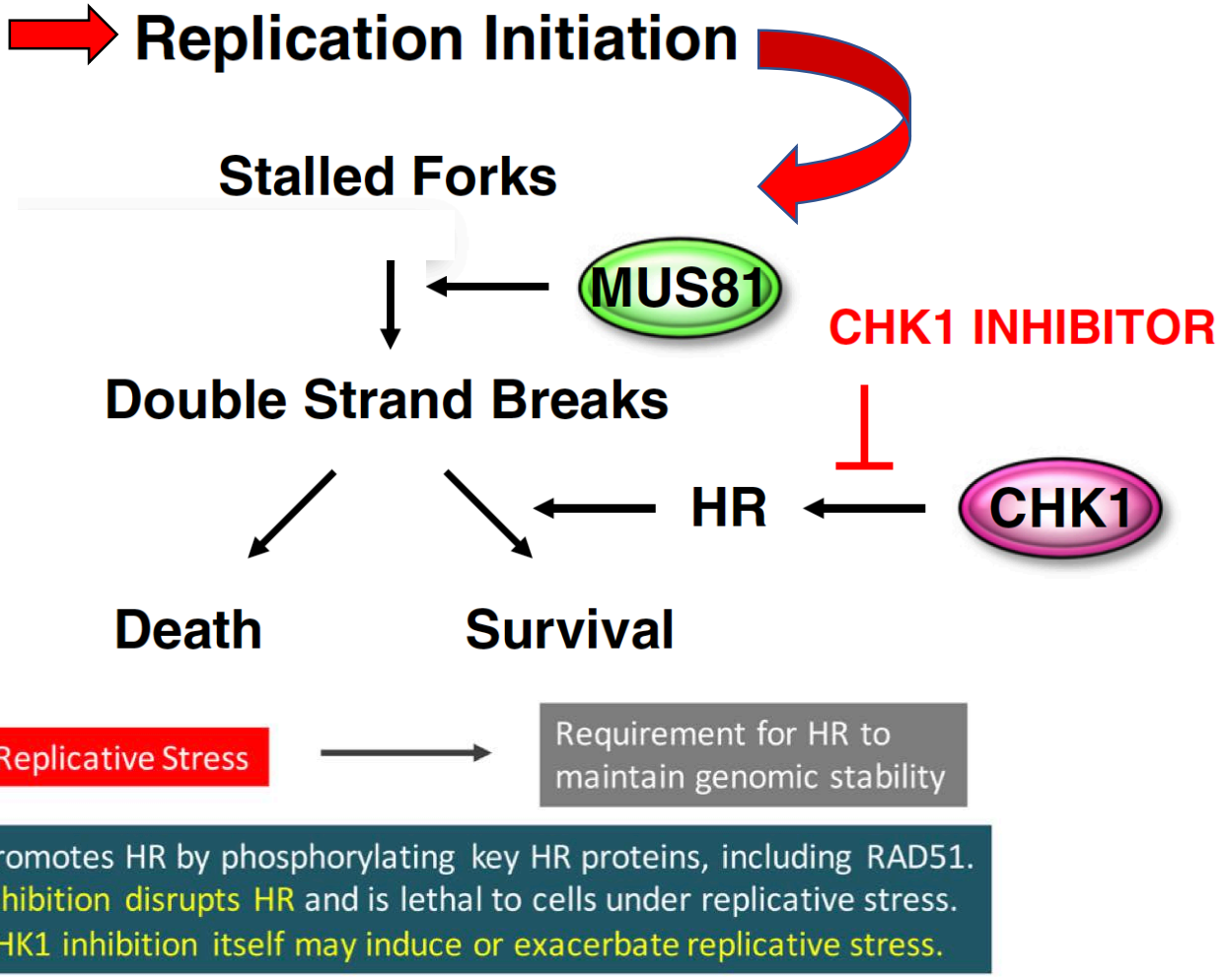


Oncogene-induced stress: increased replication firing; depletion of nucleotide pools and Increased collisions with transcription complexes, and leads to double strand breaks

Zeman and Cimprich, *Nat Cell Biol*, 2014

CHK1 inhibitor monotherapy: Cells in a state of 'replicative stress' are dependent on HR repair

Oncogenic Stress:
- **KRAS**
- **MYC**
- **CCNE1 (cyclin E)**
- **FBXW7**

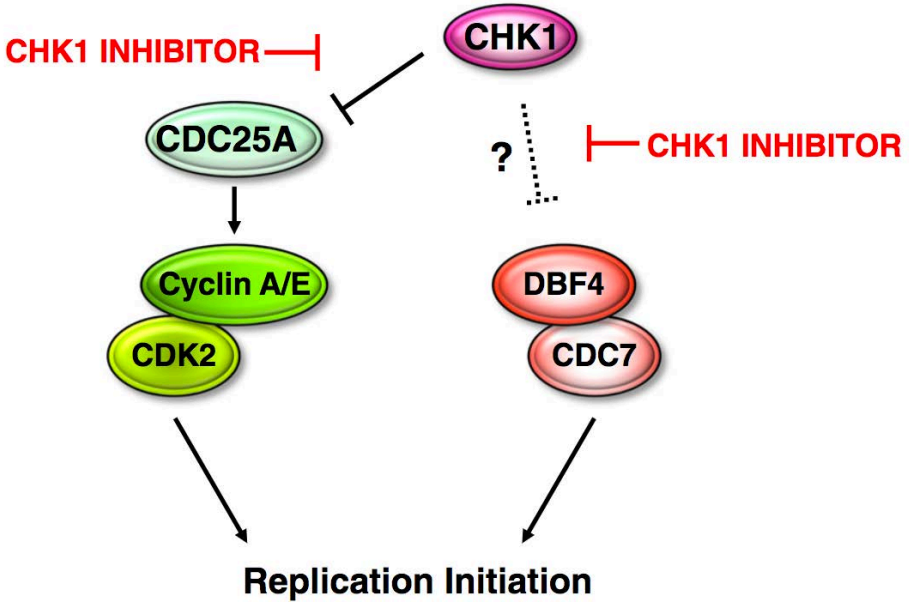


McNeely, Beckmann and Bence Lin, *Pharmacol Ther*, 2014

CHK1 inhibition may itself induce or exacerbate replicative stress

Replicative Stress → Requirement for HR to maintain genomic stability

CHK1 promotes HR by phosphorylating key HR proteins, including RAD51.
CHK1 inhibition disrupts HR and is lethal to cells under replicative stress.
Also, CHK1 inhibition itself may induce or exacerbate replicative stress.

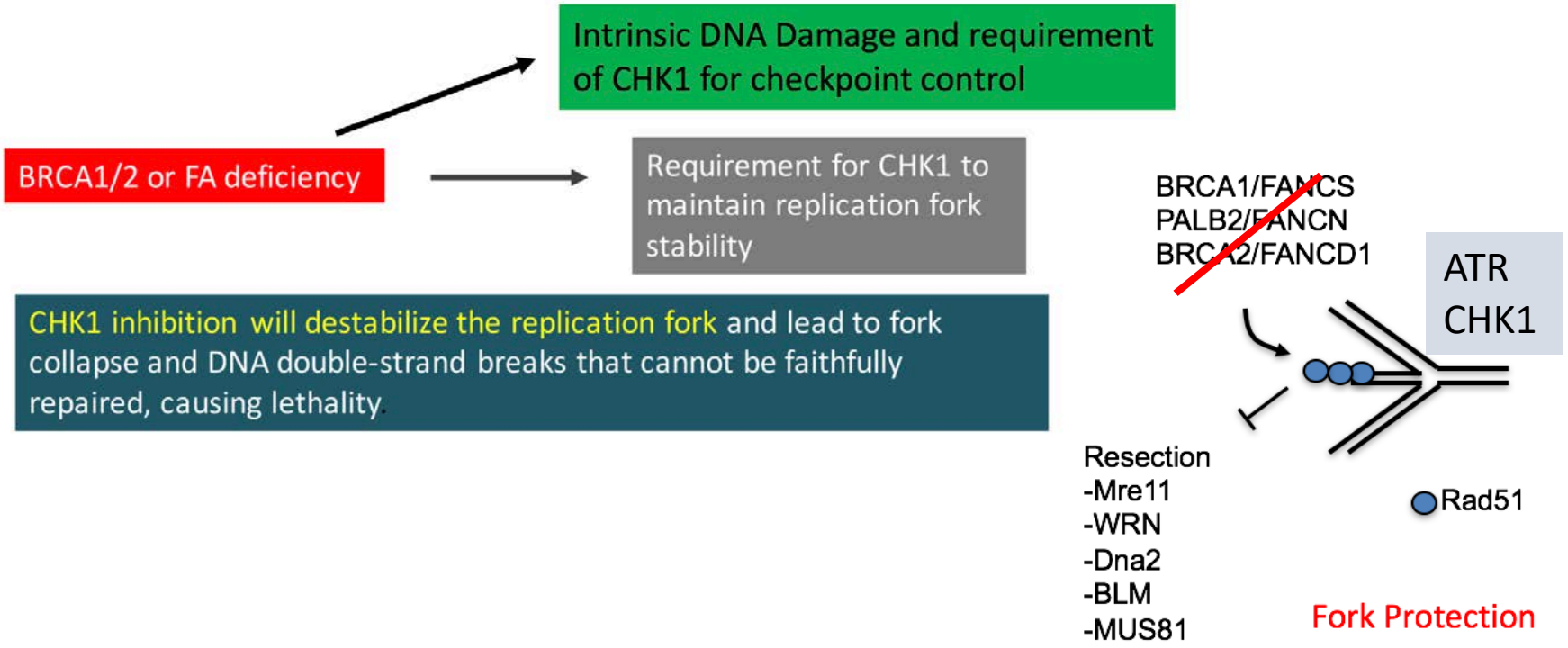


McNeely, Beckmann and Bence Lin, *Pharmacol Ther*, 2014

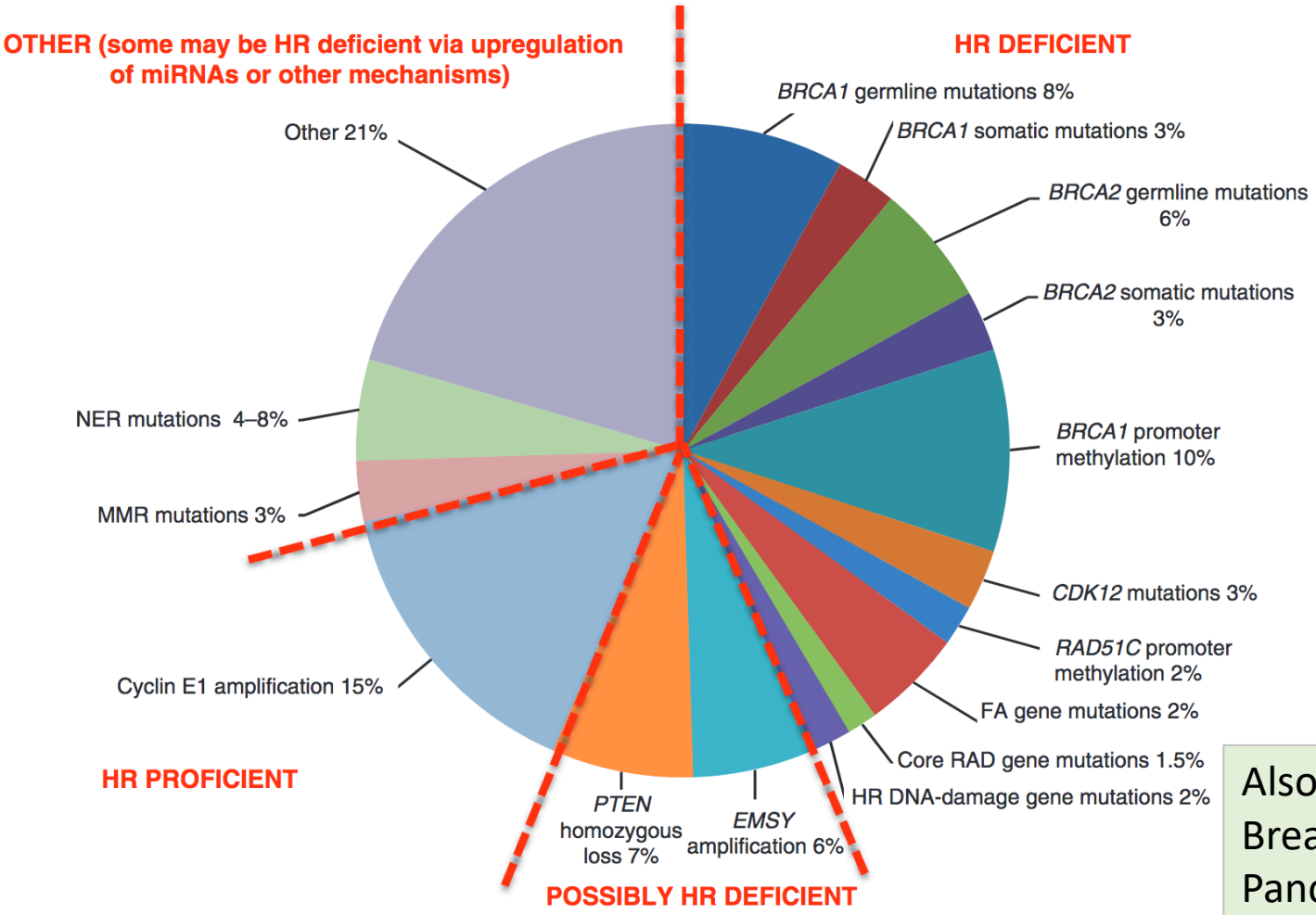
Examples of genomic alterations driving high degree of replicative stress

- **RAS-driven tumors:** non-small cell lung cancer, pancreatic, colorectal, melanoma
- **MYC-driven tumors:** lymphoma, small-cell lung cancer, triple-negative breast cancer
- **CCNE1 (cyclin E)-driven tumors:** ovarian cancer, triple-negative breast cancer
- **FBXW7 mutations:** colorectal, endometrial, head and neck, bladder, and others

HR repair-deficient cancers may also be sensitive to CHK1 inhibitor monotherapy



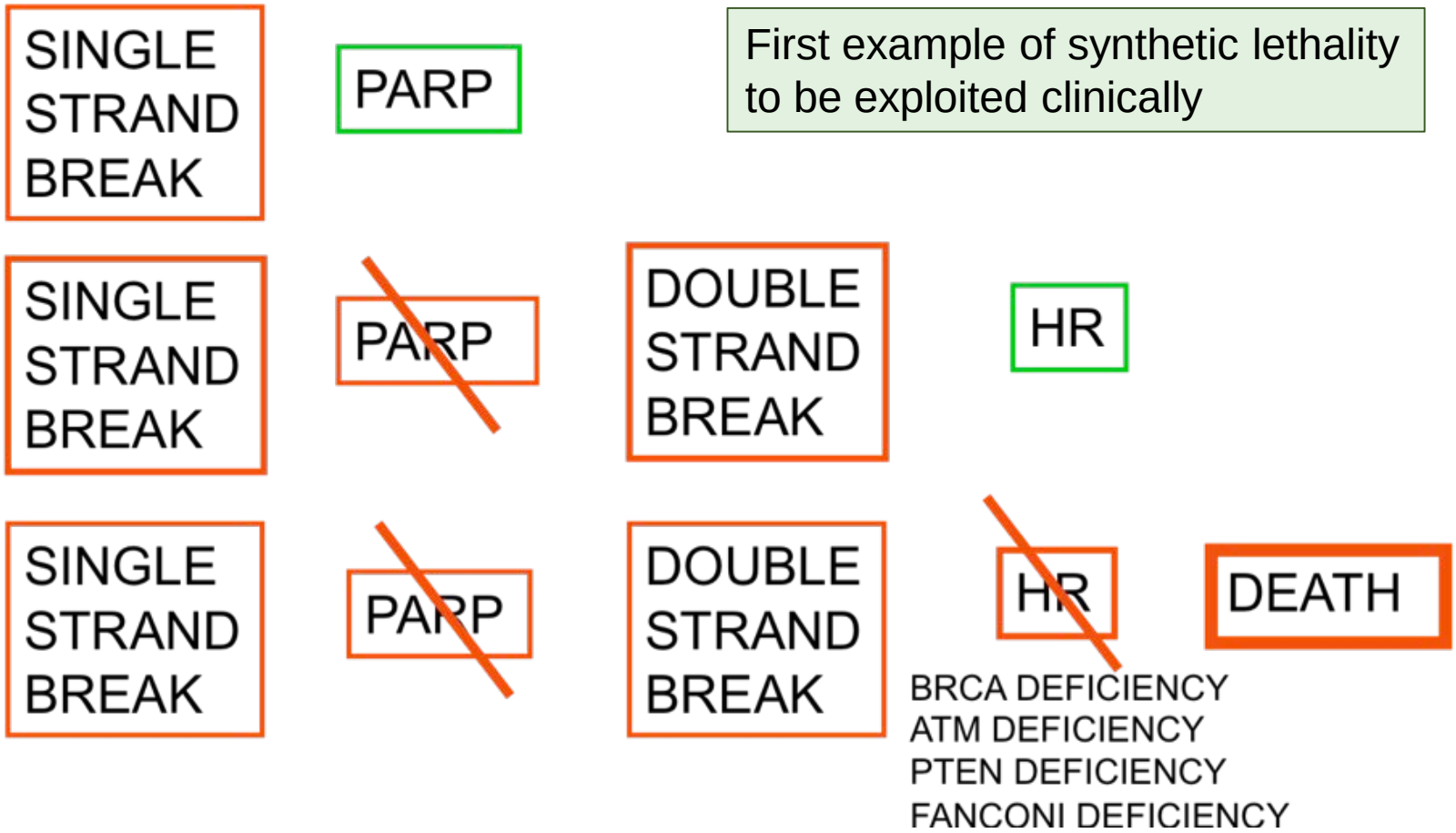
HR-deficient cancers: High-grade serous ovarian cancer



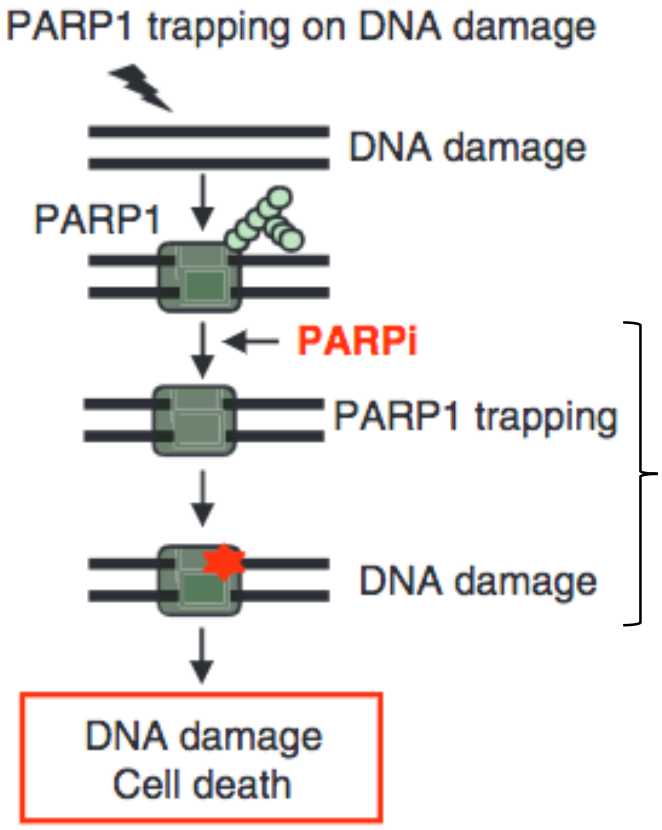
Also BRCA-associated:
Breast Ca
Pancreatic Ca
Prostate Ca

Konstantinopoulos et al., Cancer Discov., 2015

HR-deficient cancers are treated with PARP inhibitors



PARP-DNA Trapping by PARP Inhibitors

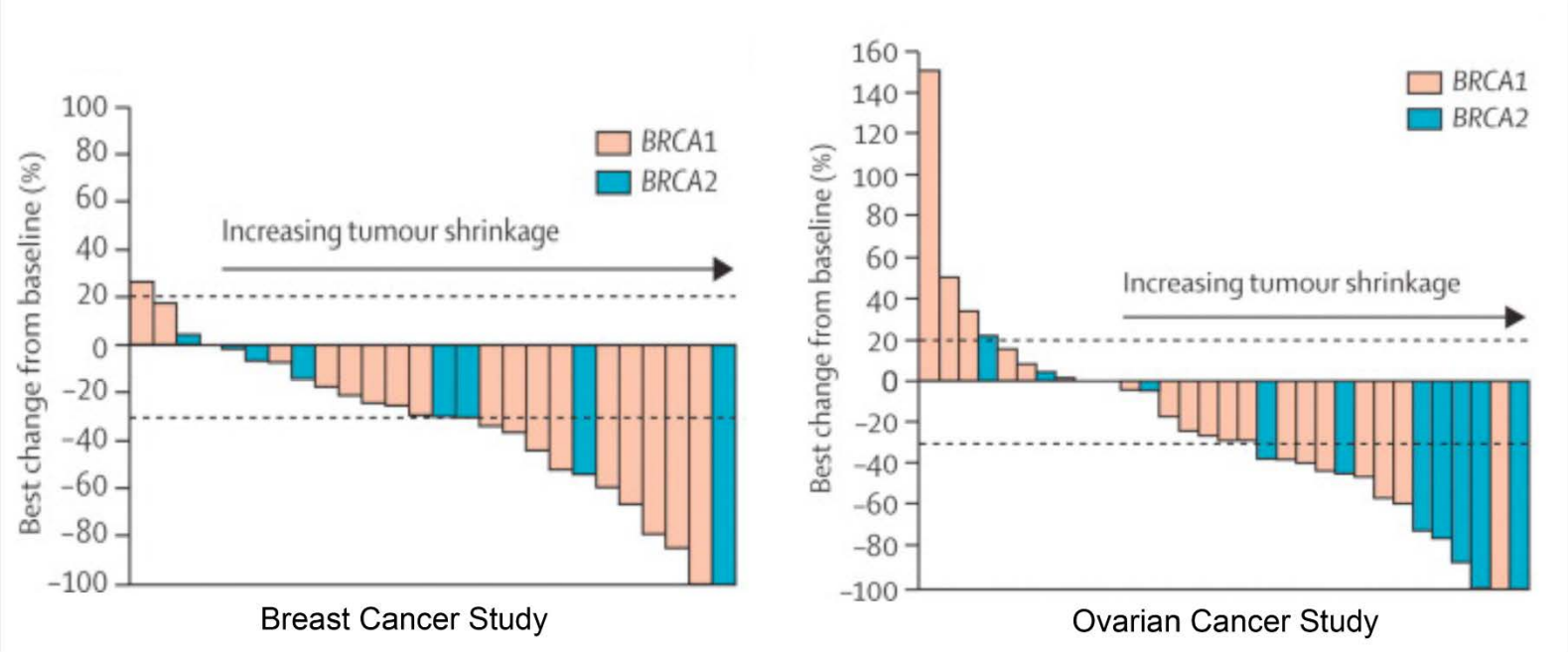


PARP inhibitor traps PARP1 on DNA; Homologous Recombination is required to bypass the lesion; in an HR-deficient cell, the trapped PARP1 causes DNA damage and cell death

Mechanism is reminiscent of the conversion of topoisomerase I into a poison by topoisomerase I Inhibitors.

Konstantinopoulos et al., Cancer Discov, 2015

Olaparib in patients with *BRCA*-associated cancers

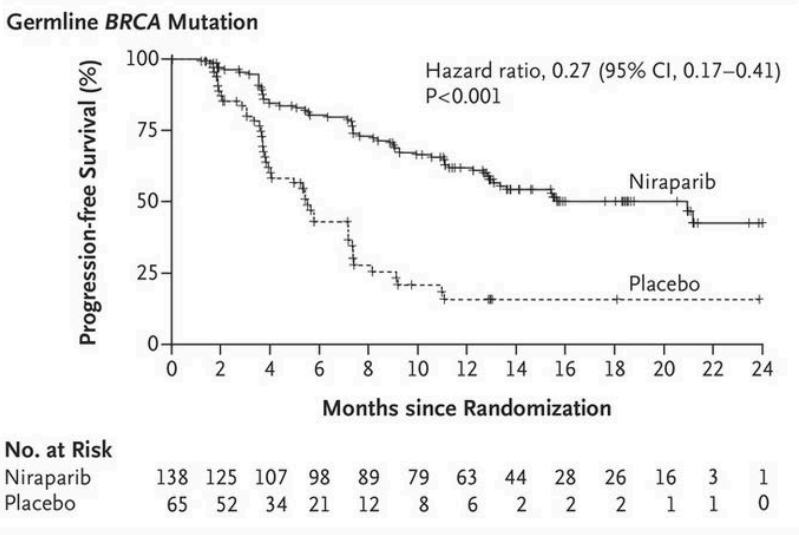


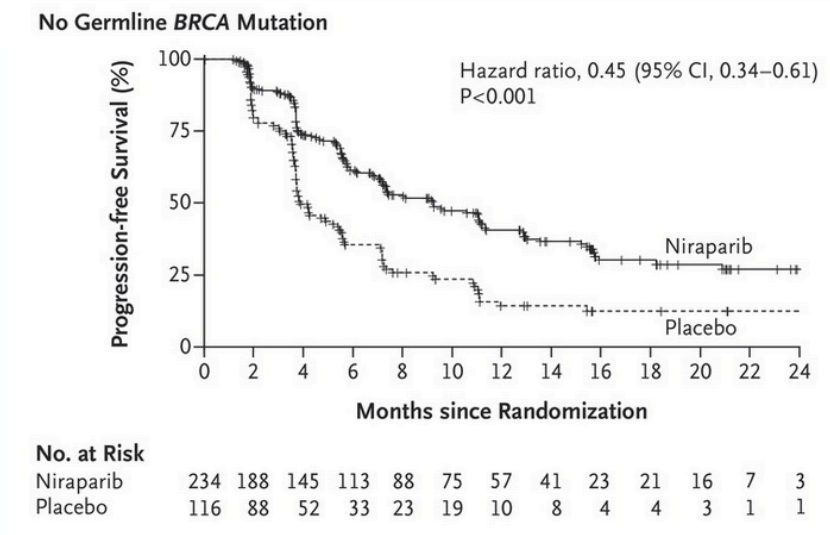
Small Molecule PARP inhibitor
Recommended Phase 2 Dose 400 mg BID
Adverse Events: nausea, vomiting, fatigue, anemia

Tutt et al. Lancet 2010; 376-235-44; Audeh et al. Lancet 2010;376:245-51

PARP Inhibitor Maintenance Treatment in Platinum-Sensitive HGSOG

Niraparib Study



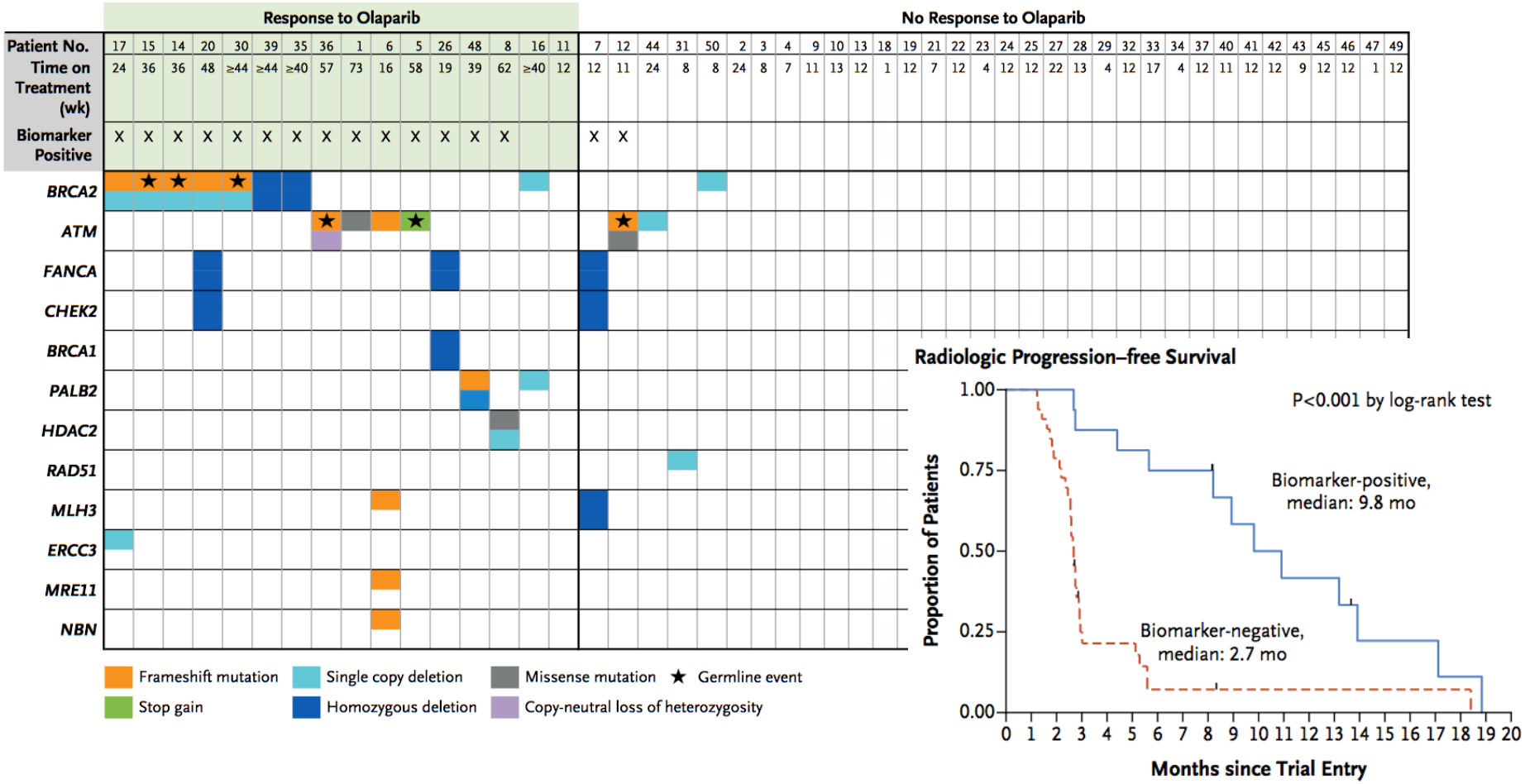


First-line Platinum-Based → Second-line Platinum-Based → Niraparib vs. Placebo*

*Penultimate platinum regimen: Complete or partial response and disease progression > 6 months after completion

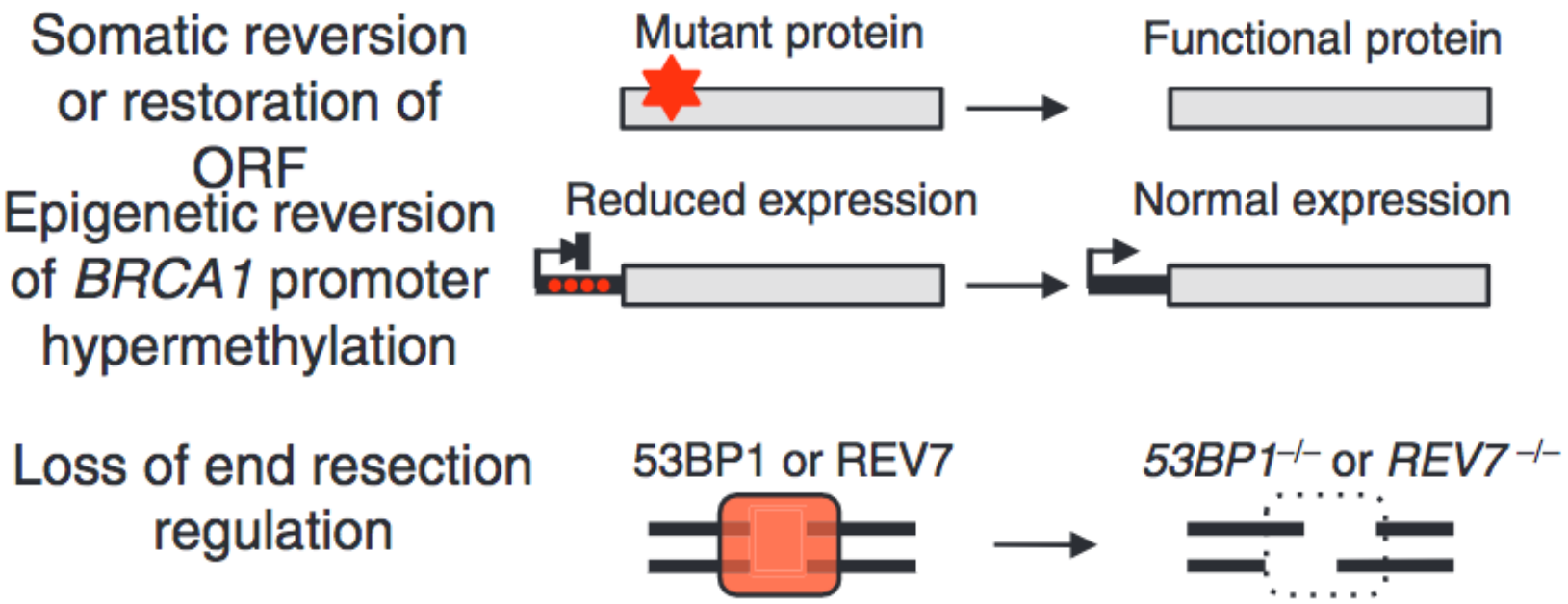
Mirza et al. NEJM, 2016

DNA Repair Defects in Prostate Cancer and Response to Olaparib



Mateo et al., NEJM, 2015

Emerging Clinical Problem: Acquired Resistance



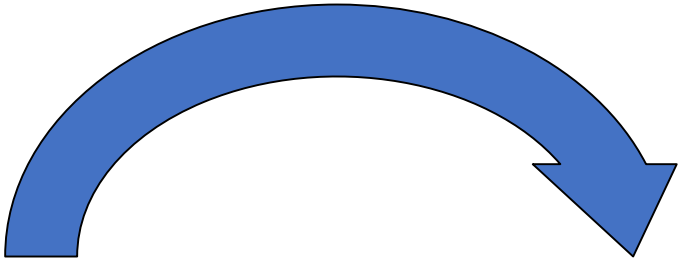
Most common mechanism of PARP inhibitor resistance:
Restored HR

Konstantinopoulos et al., Cancer Discov, 2015

Reversing Acquired PARP Inhibitor Resistance

CHK1 inhibitor

Agents that inhibit HR



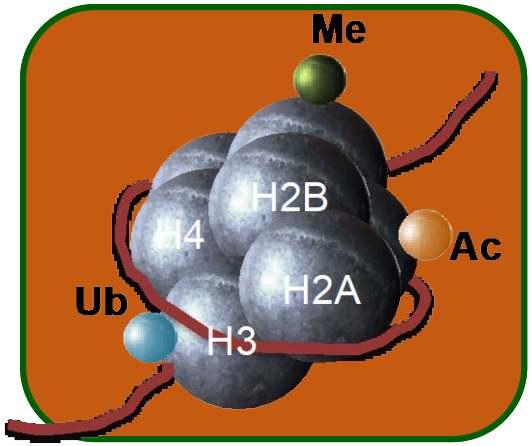
HR proficient

HR deficient

+

PARP Inhibitor

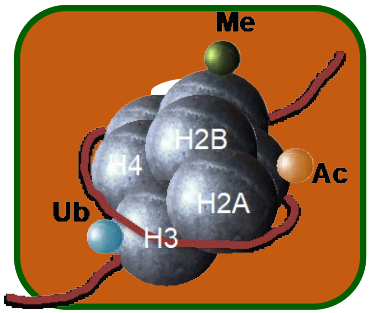
The MLL3-4/PTIP/MRE11 pathway is required for replication fork restart and normal replication velocity



MLL3-4/ PTIP → ***MRE11*** → Fork Restart

Chaudhuri et al., Nature 2016;535:382-7

Knockdown of the MLL3-4/PTIP/MRE11 pathway enhances replication fork stability



H3K4 methylation

MLL3-4/ PTIP → ***MRE11*** → Increased Replication Fork Stability

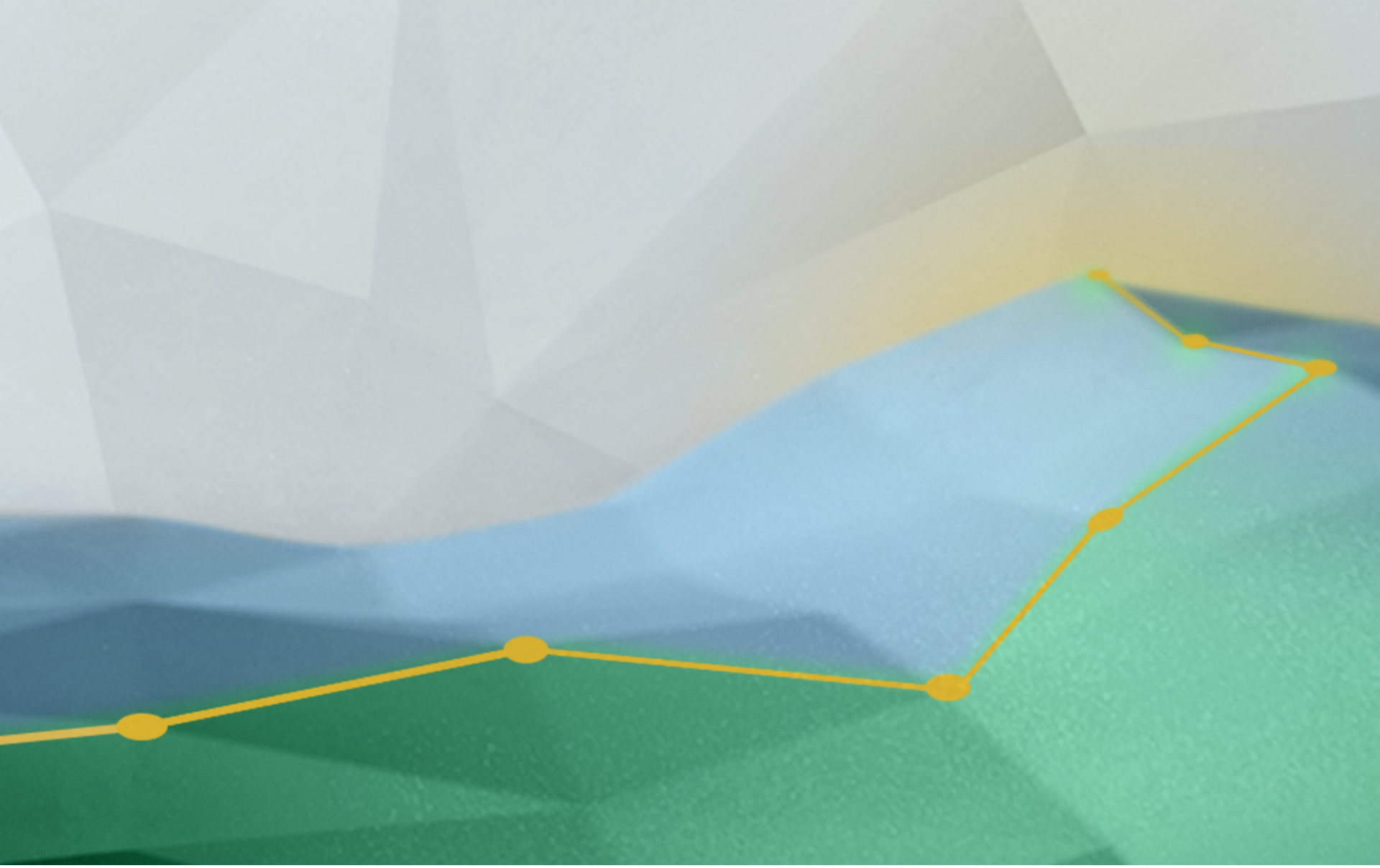
CHK1 inhibition will destabilize the replication fork

Knockdown of this pathway in *BRCA1/2* deficient cells results in PARP inhibitor resistance

Chaudhuri et al., Nature 2016; 585:382-7

Summary

- CHK1 inhibition may augment clinical responses to DNA damaging agents (i.e. chemotherapy) by abrogating DNA damage-induced checkpoint control.
- Tumors that are under replication stress or deficient in homologous recombination (HR) repair may be vulnerable to monotherapy CHK1 inhibition.
- Treating HR-deficient cancers will be an increasing challenge, since they will be approached by PARP inhibition; PARP inhibitor resistance will emerge as a pressing clinical problem.
- CHK1 inhibition may reverse major mechanisms of PARP inhibitor resistance including restoration of HR and replication fork stabilization.



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