
# Targeting the DNA Damage Response: Lessons Learned and the Path Forward

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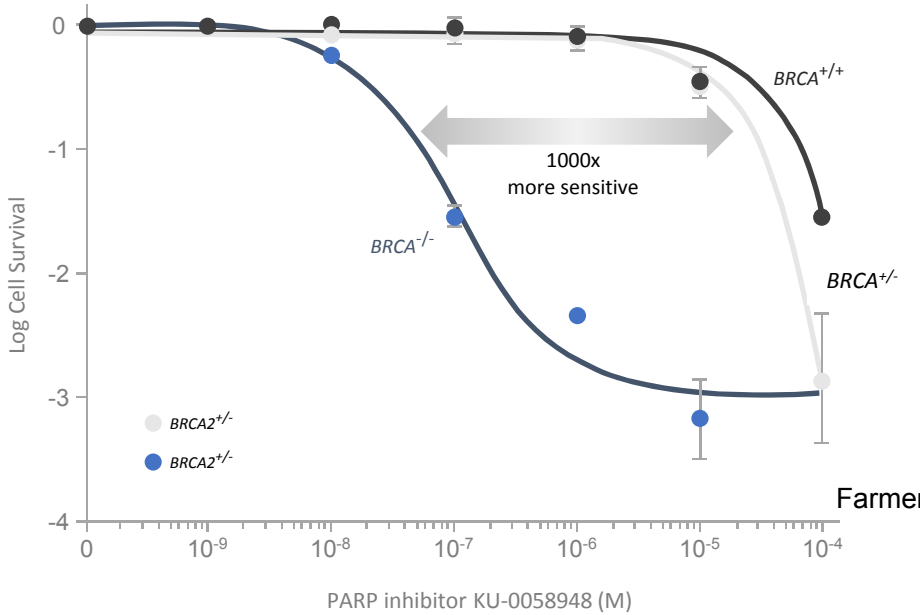
# Increased sensitivity of *BRCA1/2*$^{-/-}$ cells to PARP inhibition vs *BRCA1/2*$^{+/+}$ and *BRCA1/2*$^{+/-}$

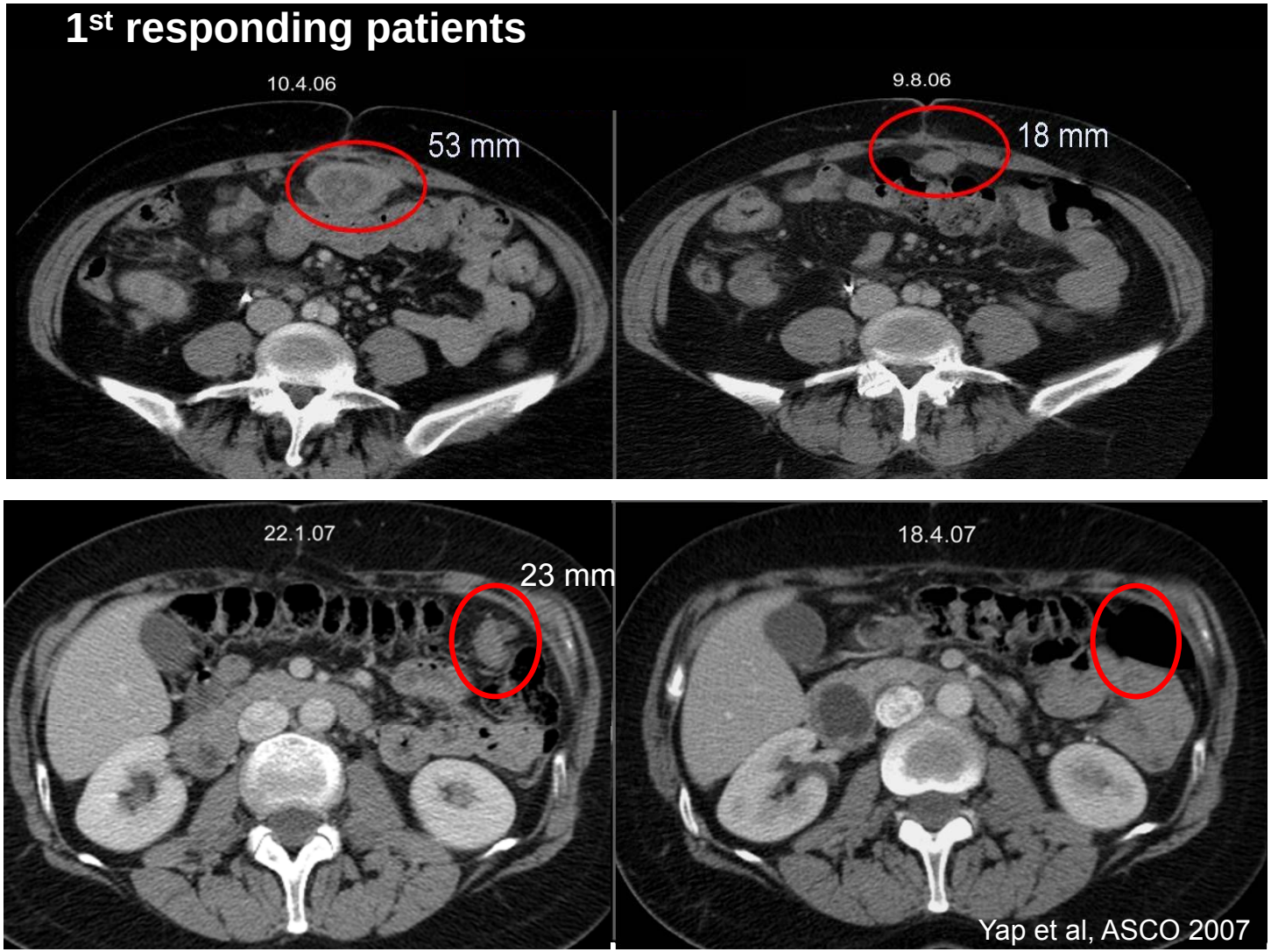



Back-to-back Nature papers from Ashworth and Helleday Groups

Farmer et al, Nature 2005

No difference in sensitivity between heterozygous and wild-type BRCA cells

**PARP inhibition → effective and well tolerated therapy in *BRCA1/2* mutant tumors**


1st responding patients
10.4.06
53 mm
9.8.06
18 mm
22.1.07
23 mm
18.4.07
Yap et al, ASCO 2007

# FDA Approval status of PARP inhibitors

**Olaparib (AstraZeneca)**

- Capsules (2014) and tablets (2017): FDA approved for **advanced** *BRCA1/2* mutant **ovarian** cancer patients ≥ 3 lines of chemotherapy
- Tablets approved for **maintenance** therapy in **ovarian** cancer (2017)
- Germline ***BRCA* mutant metastatic breast cancer** who previously received chemo (Jan 2018)

**Niraparib (Tesaro)**

- FDA approved as **maintenance** treatment in recurrent **ovarian**, fallopian tube, or primary peritoneal cancer for patients who are in complete or partial response to platinum-based chemotherapy (2017)

**Rucaparib (Clovis)**

- FDA approved as monotherapy for **advanced** *BRCA1/2* mutant **ovarian** cancer patients who have received ≥ 2 lines of chemotherapy (2016)
- Positive ARIEL 3 Phase III trial in **maintenance** $2^{nd}/3^{rd}$ line **ovarian** cancer setting

**Talazoparib (Pfizer)**

- Phase 3 EMBRACA **advanced g*BRCA1/2* mutant breast** trial (Litton et al, NEJM 2018)

**Other PARP inhibitors in clinical trials:** pamiparib; veliparib

Brown, O'Carrigan, Jackson and Yap, Cancer Discovery 2017

# Disclosures

**Employment:**

- Medical Director of the Institute for Applied Cancer Science at the University of Texas MD Anderson Cancer Center
- Associate Director for Translational Research of the Institute for Personalized Cancer Therapy at the University of Texas MD Anderson Cancer Center.
- Previous employee of the Institute of Cancer Research, London, England.

**Research support**: AstraZeneca, Bayer, Pfizer, Tesaro, Jounce, Eli Lilly, Seattle Genetics, Kyowa, Constellation, and Vertex Pharmaceuticals

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**Travel support:** AstraZeneca, Merck, Janssen, BMS, Vertex Pharmaceuticals, GSK, EMD Serono, Pfizer

**Speaker bureau**: AstraZeneca, Merck, Pfizer, and Tesaro.

# Overview

- Background and current DDR landscape
- Not all PARP inhibitors are equal
- Lessons learned to date
- The path forward
  - Patient selection
  - Resistance mechanisms
  - Novel combination strategies

# Nobel prize for discovery of cancer therapy by inhibition of negative immune regulation

**Jim Allison** **Tasuku Honjo**

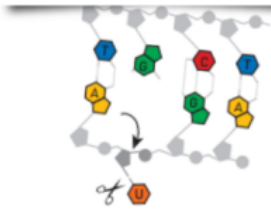
# Nobel prize for DNA repair

## Tomas Lindahl

- Swedish citizen
- Born 1967
- Emeritus group leader at Francis Crick Institute and Emeritus director of Cancer Research UK

**Base excision repair**

Constantly counteracts the collapse of our DNA

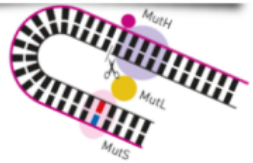


## Paul Modrich

- U.S. citizen
- Born 1946
- Howard Hughes Medical Institute and Duke University School of Medicine

**Mismatch repair**

How the cell corrects errors that occur when DNA is replicated during cell division

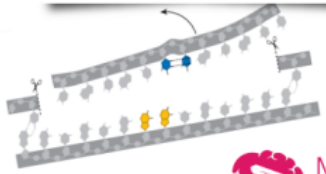



## Aziz Sancar

- U.S. and Turkish citizen
- Born 1946
- University of North Carolina School of Medicine

**Nucleotide excision repair**

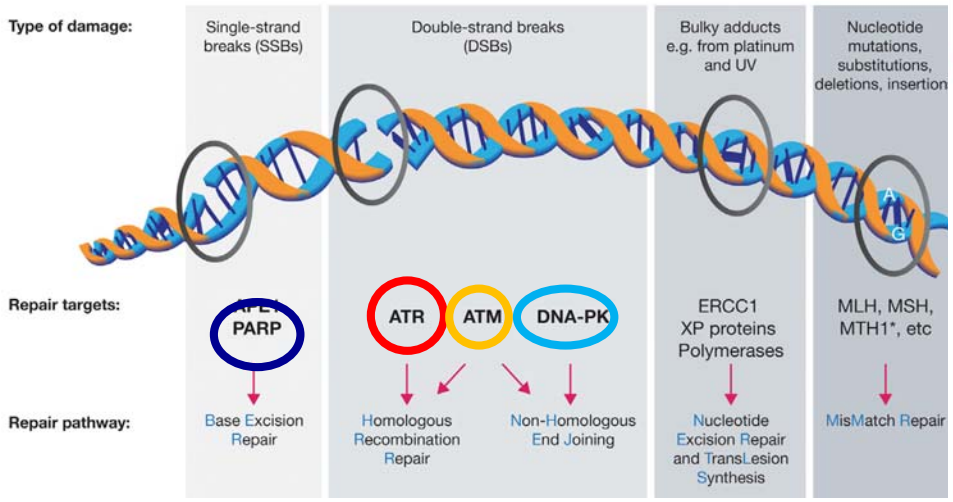
The mechanism that cells use to repair UV damage to DNA



MIND THE GRAPH

# Targeting the DNA damage response in the Clinic

## DDR pathway targets



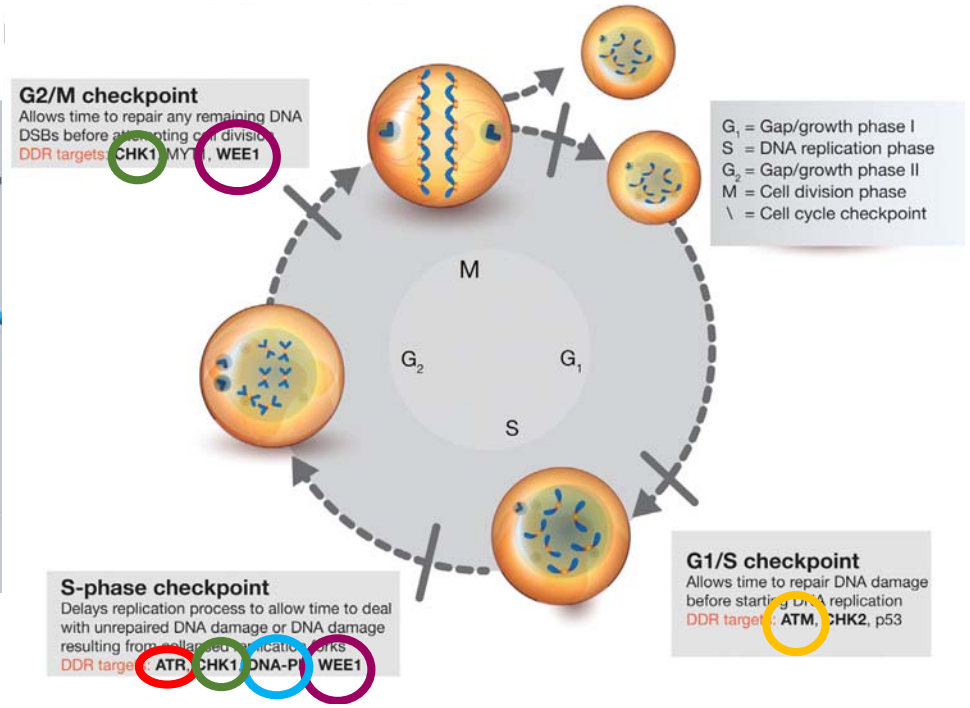

**DDR Inhibitors**

**Phase I:** ATM, DNA-PK

**Phase II:** ATR, WEE1, CHK1

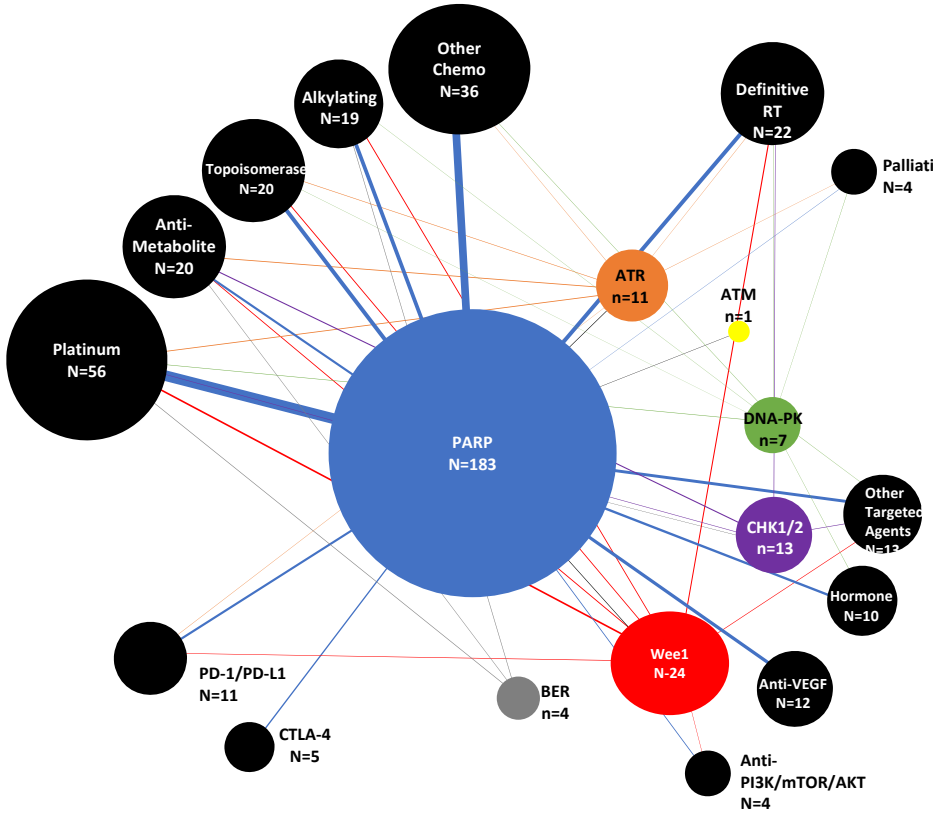
**FDA Approved:** PARP

## DDR cell-cycle targets



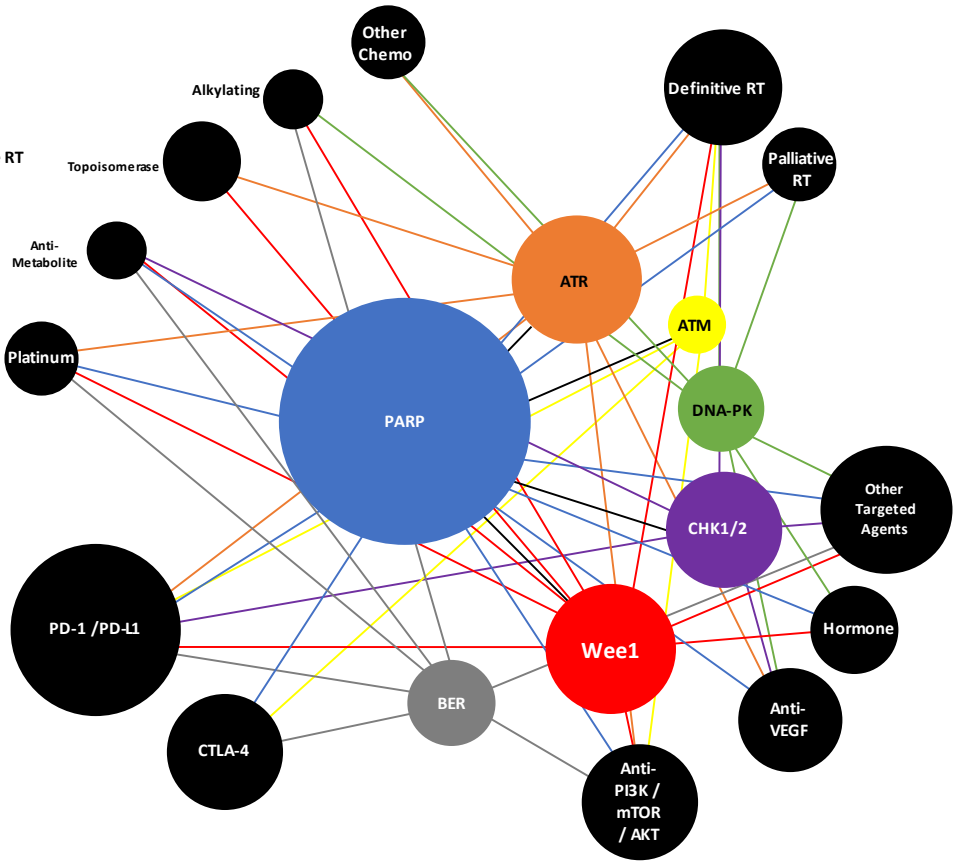

O'Connor, Molecular Cell 2015

## Current landscape of ongoing DDR inhibitor clinical trials




**Done to scale (www.clinicaltrials.gov)**

## Anticipated landscape of future DDR inhibitor clinical trials




**My prediction**

Pilie, Tang, Mills and Yap, Nature Reviews Clinical Oncology 2018 in press

# Targeting PARP

# Differentiating between PARP inhibitors

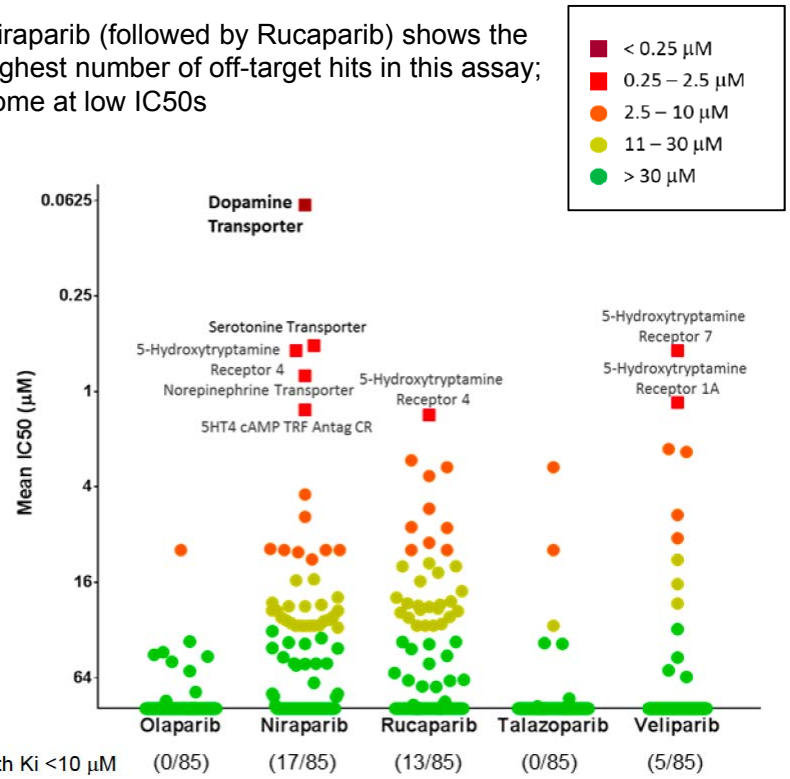
- **PARP inhibitors have similar capacity** to inhibit PARP catalytic activity
- **PARP trapping:**
  - Major mechanism by which PARP inhibitors kill cancer cells by trapping PARP1/2 to sites of DNA damage.
  - PARP enzyme-inhibitor complex "locks" onto damaged DNA and prevents DNA repair, replication, and transcription, leading to cell death.
- **Preclinical ability to trap PARP:** talazoparib >> niraparib > olaparib = rucaparib >> veliparib
- **Preclinical cytotoxic potency:** talazoparib active at nM concentrations ➔➔➔➔➔ veliparib inactive at 100 mM

Murai et al, Cancer Research 2012

# PARP inhibitor Clinical Data and potential mechanisms for off-target toxicities

| | OVARIAN | | | BREAST | |
|---|---|---|---|---|---|
| **EFFICACY DATA** | | | | | |
| | SOLO2 Olaparib (N=295) | NOVA Niraparib (N=203) | ARIEL3 Rucaparib (N=196) | OlympiAD Olaparib (N=302) | EMBRACA Talazoparib (N=431) |
| PFS in g*BRCA*m population (hazard ratio) | | | | | |
| Investigator-assessed PFS | 0.30* | 0.27 | 0.23†* | 0.50 | N/R |
| BICR-assessed PFS | 0.25 | 0.27* | 0.20† | 0.58* | 0.54* |
| **SAFETY AND TOLERABILITY DATA** | | | | | |
| | SOLO2 Olaparib (N=195) | NOVA Niraparib (N=367) | ARIEL3 Rucaparib (N=372) | OlympiAD Olaparib (N=205) | EMBRACA Talazoparib (N=287) |
| Dose adjustments and modifications (%) | | | | | |
| Dose interruptions | 45 | 69¶ | 64¶ | 35 | N/R |
| Dose reductions | 25 | 67¶ | 55¶ | 25 | N/R |
| Dose discontinuations | 11 | 15¶ | 13¶ | 5 | 8 |
| Grade ≥3 haematological adverse events presented in ≥ 5% of patients in any trial‡ (%) | | | | | |
| Anaemia§ | 19 | 25 | 19 | 16 | 39 |
| Neutropenia§ | 5 | 20 | 7 | 9 | 21 |
| Thrombocytopenia§ | 1 | 34 | 5 | 2 | 15 |
| MDS/AML | 2 | 1 | 0.8 | 0 | 0 |
| All grade non-haematological adverse events of special interest (%) | | | | | |
| Nausea | 76 | 74 | 75 | 58 | 49 |
| Fatigue and asthenia | 66 | 59 | 69 | 29 | 50 |
| Vomiting | 37 | 34 | 37 | 30 | 25 |
| Diarrhoea | 33 | 19 | 32 | 21 | 22 |
| Dysguesia | 27 | 10 | 39 | N/R | N/R |
| Headache | 25 | 26 | 18 | 20 | 33 |
| Hypertension | 3 | 19 | N/R | N/R | N/R |
| ALT increased/AST increased | 5 / 2 | 36 / 28 | 34 | 11 / 9 | N/R |
| Alopecia | N/R | N/R | N/R | 3 | 25 |
| Insomnia | 6 | 24 | 14 | N/R | N/R |

Niraparib (followed by Rucaparib) shows the highest number of off-target hits in this assay; some at low IC50s



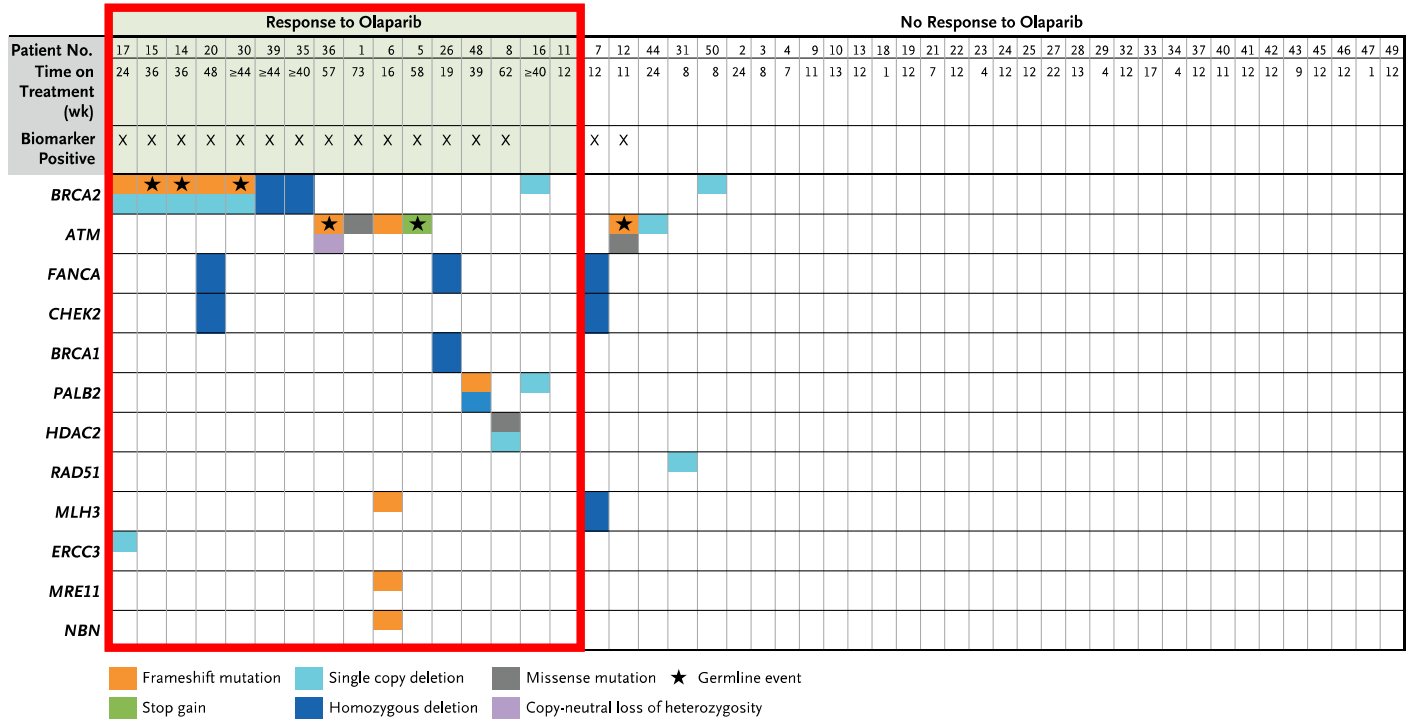

*For patients to be eligible for niraparib 300 mg as a starting dose, screening actual body weight ≥ 77 kg and screening platelet count ≥ 150,000 u/L is necessary

Leo et al, AACR 2018

# Important lessons we have learnt about PARP inhibitors

- Not all PARP inhibitors are made equally
- Most effective in a platinum sensitive population; Platinum-PARPi interval also important
- Concurrent combinations with DNA-damaging chemo is and will be challenging
- Activity is not tumor-type specific
- Antitumor activity not limited to BRCA mutations – other mutations resulting in HR deficiency also result in PARPi sensitivity – ‘BRCAness’

# Monotherapy activity beyond *BRCA1/2* mutant cancers
# Other aberrations result in HR deficiency – 'BRCAness'




- Responses to olaparib in CRPC enriched in patients with DDR mutations
- Still patients with deleterious DDR variants that did not respond; mechanistic reasons unclear

Mateo et al, NEJM 2015

# The path forward for PARP inhibitors

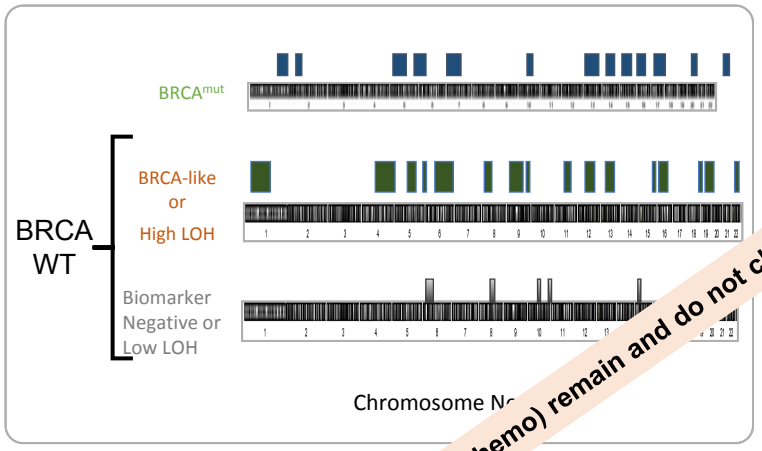
**Want more non-responders to respond**
**Want more responders to become super-responders**

## The path forward for PARP inhibitors

Want more non-responders to respond
Want more responders to become super-responders

- Need an HR deficiency assay.

# Homologous recombination deficiency (HRD) assay
## - Do we have one? E.g. Genomic Scarring LOH assay

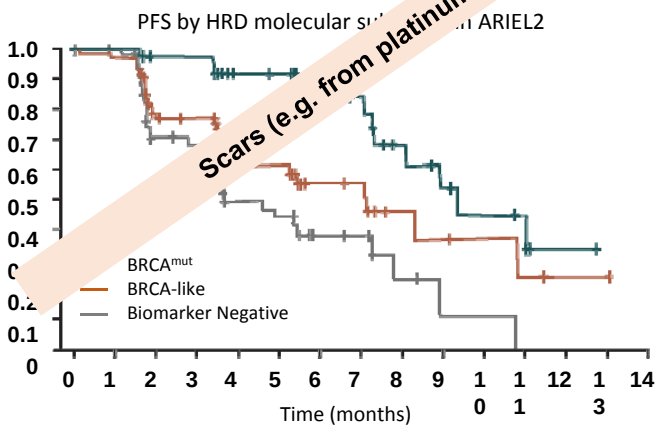



- HRD causes genome wide loss of heterozygosity (LOH) or 'genomic scars' which can be measured by tumour profiling using NGS

  Algorithm developed to identify BRCA WT pts who are BRCA-like (high LOH) or biomarker-neg (low LOH)

- Assay clinically qualified in ARIEL2 Phase II trial with rucaparib (n=204)

**Scars (e.g. from platinum chemo) remain and do not change with clonal evolution**




| HRD Subgroup | Median PFS, mo (90% CI) | Overall Response Rate, % (N) | |
|---|---|---|---|
| | | RECIST | RECIST + CA-125 |
| BRCA^mut | 9.4 (7.3, NR) | 69 (27/39) | 82 (32/39) |
| BRCA^wt: BRCA-like | 7.1 (3.7, 10.8) | 30 (22/74) | 45 (33/74) |
| BRCA^wt: Biomarker Negative | 3.7 (3.5, 5.5) | 13 (8/62) | 21 (13/62) |

**ARIEL3 Phase III trial with rucaparib:** PFS improvement versus placebo was also seen in BRCA wild-type and high LOH or low LOH groups.

Swisher et al, Lancet Oncology 2017; Coleman et al, Lancet 2017

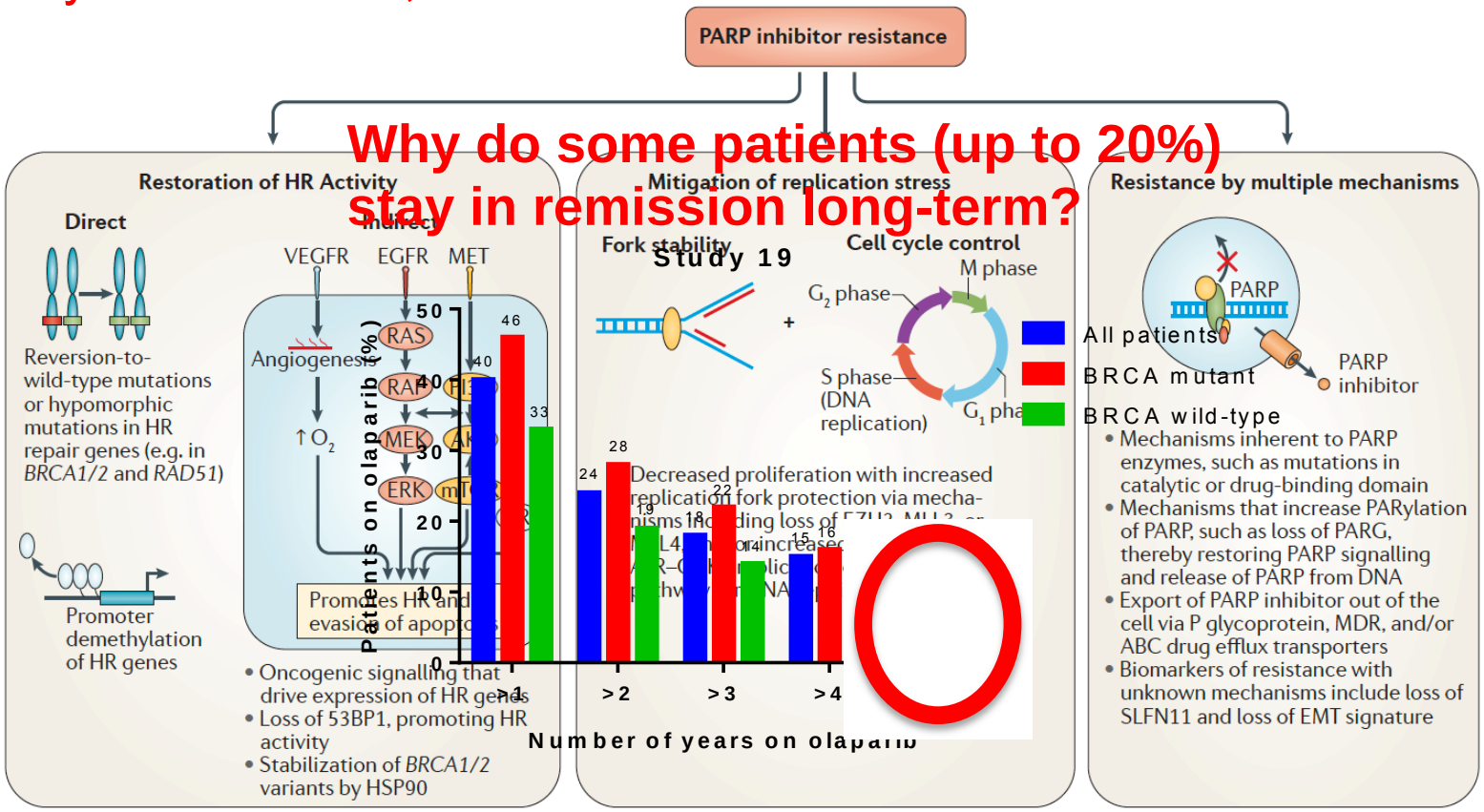
# The path forward for PARP inhibitors

Want more non-responders to respond
Want more responders to become super-responders

- Need an HR deficiency assay.
- PARP inhibitor resistance.

# Resistance to PARP inhibitors

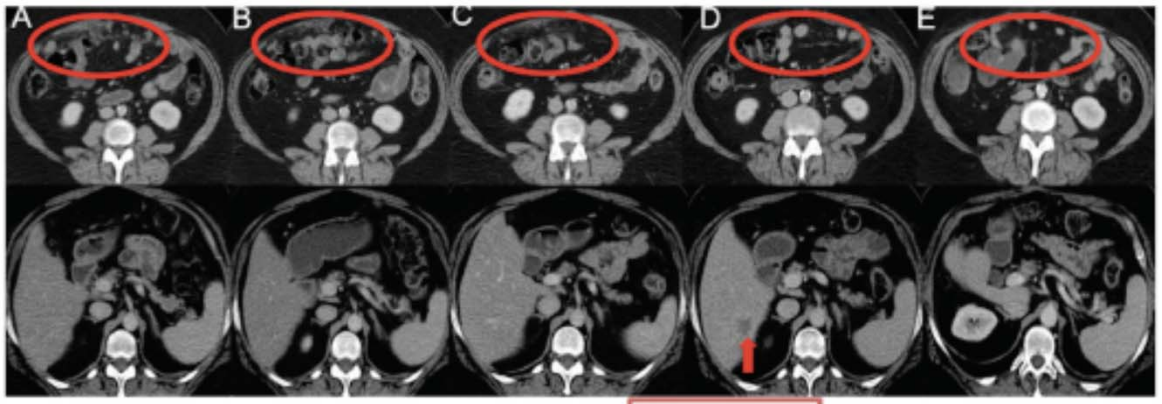
## Likely multifactorial; factors to consider

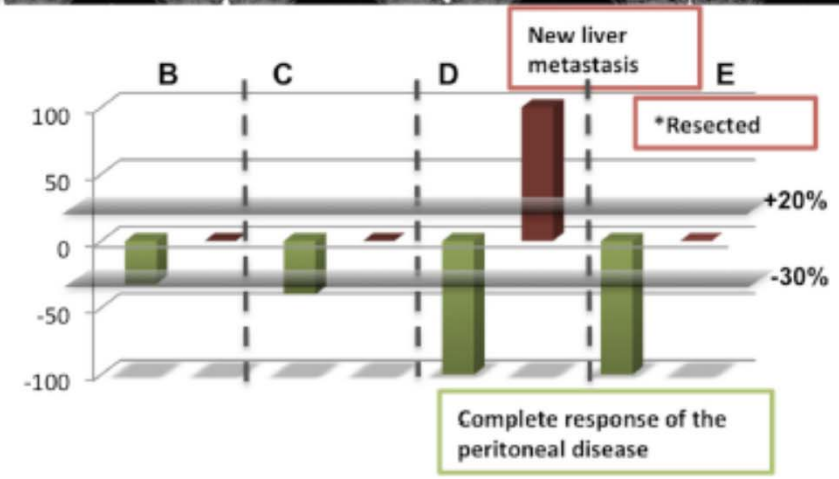



**Why do some patients (up to 20%) stay in remission long-term?**

Pilie, Tang, Mills and Yap, Nature Reviews Clinical Oncology 2018 in press

# Extending the patient journey despite PARPi resistance




- 52yr Advanced *gBRCA2* mutant HGSOC
- Multiple lines of chemotherapy

- RECIST CR after 3 months of olaparib
- After 81 months: CT new solitary liver metastasis; otherwise CR.
- Liver metastasectomy: *BRCA2* reversion

- Restarted on olaparib
- After another 15 months: CT new liver lesion and enlarged retrocaval lymph note; otherwise CR.
- Chemoembolization and radiotherapy

- Restarted on olaparib
- **Remains on treatment for 9yrs+**

Lopez et al, Oncotarget 2017

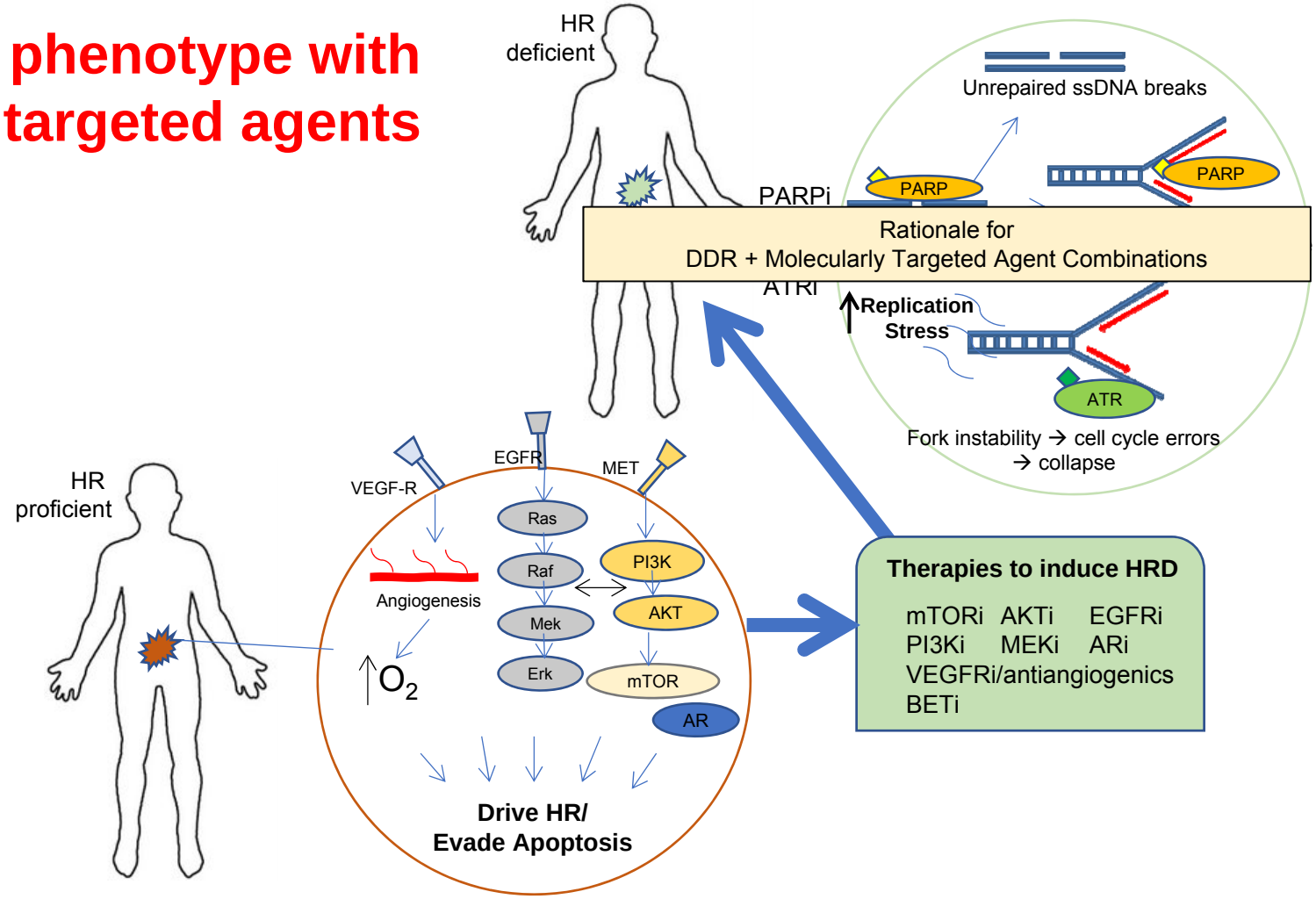
# The path forward for PARP inhibitors

Want more non-responders to respond
Want more responders to become super-responders

- Need an HR deficiency assay.
- Understanding PARPi resistance.
- Novel combination strategies.
  - Molecularly Targeted Agents
  - DDR agents, e.g. ATR inhibitors
  - Immunotherapy, e.g. PD-1/PD-L1 inhibitors

# Combining PARP and Molecularly Targeted Agents

# Induce HRD phenotype with molecularly targeted agents




Pilie, Tang, Mills and Yap, Nature Reviews Clinical Oncology 2018 in press

# Strategies to create a "chemical BRCAness"

## A few examples (there are many more…)

**Aim: Enhance sensitivity to PARPi by inducing HRD phenotype in HR proficient tumors**

**Preclinical +/- clinical data with:**

- **Antiangiogenic agents** e.g. cediranib + olaparib
  - Hypoxia leads to impaired HR by down-regulating HR genes (Bindra et al, Mol Cell Bio 2004)
  - PFS 5.7m olaparib vs 23.7m combo (HR 0.32, p=0.002) in non-BRCA pts (Liu et al, ASCO 2017)
- **MEK inhibitors** (Sun et al, STM 2017)
  - Phase I trial of selumetinib + olaparib in cancers with RAS pathway aberrations (ongoing)
- **BET inhibitors** (Yang et al, STM 2017)
- **PI3K/AKT pathway inhibitors** e.g. AZD5363 + olaparib (Michelarea et al, AACR 2016**)**

# Combining PARP and other DDR agents, e.g. ATR inhibitors

# Can ATR inhibition overcome PARP inhibitor resistance?

- **ATR is apical signaling kinase along DDR pathway**
  - ATR has a key role in the DNA replication stress response pathway by facilitating the recovery from stalled DNA replication forks and prevent premature mitosis.

## Resistance to PARP inhibitors by SLFN11 inactivation can be overcome by ATR inhibition

**Junko Murai[1], Ying Feng[2], Guoying K. Yu[2], Yuanbin Ru[2], Sai-Wen Tang[1,3], Yuqiao Shen[2] and Yves Pommier[1]**

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[2] BioMarin Pharmaceutical Inc., Novato, CA, USA

[3] Current affiliation: Division of Blood and Marrow Transplantation, Department of Medicine, Stranford University School of Medicine, Stanford, CA, USA

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***Keywords:*** PARP-trapping, ATR, PARP inhibitor, BRCA, homologous recombination

***Received:*** *August 25, 2016* ***Accepted:*** *August 26, 2016* ***Published:*** *September 27, 2016*

**ABSTRACT**

**Poly(ADP-ribose) polymerase inhibitors (PARPIs) kill cancer cells by trapping PARP1 and PARP2. Talazoparib, the most potent PARPI inhibitor (PARPI), exhibits remarkable selectivity among the NCI-60 cancer cell lines beyond BRCA inactivation. Our genomic analyses reveal high correlation between response to talazoparib and *Schlafen 11* (*SLFN11*) expression. Causality was established in four isogenic *SLFN11*-positive and -negative cell lines and extended to olaparib. Response to the talazoparib-temozolomide combination was also driven by SLFN11 and validated in 36 small cell lung cancer cell lines, and in xenograft models. Resistance in *SLFN11*-deficient cells was caused neither by impaired drug penetration nor by activation of homologous recombination. Rather, SLFN11 induced irreversible and lethal replication inhibition, which was independent of ATR-mediated S-phase checkpoint. The resistance to PARPIs by SLFN11 inactivation was overcome by ATR inhibition, mechanistically because *SLFN11*-deficient cells solely rely on ATR activation for their survival under PARPI treatment. Our study reveals that SLFN11 inactivation, which is common (~45%) in cancer cells, is a novel and dominant resistance determinant to PARPIs.**

## ATR inhibition disrupts rewired homologous recombination and fork protection pathways in PARP inhibitor-resistant BRCA-deficient cancer cells

**Stephanie A. Yazinski,[1] Valentine Comaills,[1,6] Rémi Buisson,[1,6] Marie-Michelle Genois,[1,6] Hai Dang Nguyen,[1] Chu Kwen Ho,[1] Tanya Todorova Kwan,[1,2] Robert Morris,[1] Sam Lauffer,[1,3] André Nussenzweig,[4] Sridhar Ramaswamy,[1] Cyril H. Benes,[1] Daniel A. Haber,[1,2] Shyamala Maheswaran,[1] Michael J. Birrer,[1,3] and Lee Zou[1,5]**

[1]Massachusetts General Hospital Cancer Center, Harvard Medical School, Charlestown, Massachusetts 02129, USA; [2]Howard Hughes Medical Institute, Massachusetts General Hospital, Charlestown, Massachusetts 02129, USA; [3]Massachusetts General Hospital Gillette Center, Massachusetts General Hospital, Boston, Massachusetts 02115, USA; [4]Laboratory of Genome Integrity, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892, USA; [5]Department of Pathology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts 02115, USA

**Poly-(ADP-ribose) polymerase (PARP) inhibitors (PARPis) selectively kill BRCA1/2-deficient cells, but their efficacy in BRCA-deficient patients is limited by drug resistance. Here, we used derived cell lines and cells from patients to investigate how to overcome PARPi resistance. We found that the functions of BRCA1 in homologous recombination (HR) and replication fork protection are sequentially bypassed during the acquisition of PARPi resistance. Despite the lack of BRCA1, PARPi-resistant cells regain RAD51 loading to DNA double-stranded breaks (DSBs) and stalled replication forks, enabling two distinct mechanisms of PARPi resistance. Compared with BRCA1-proficient cells, PARPi-resistant BRCA1-deficient cells are increasingly dependent on ATR for survival. ATR inhibitors (ATRis) disrupt BRCA1-independent RAD51 loading to DSBs and stalled forks in PARPi-resistant BRCA1-deficient cells, overcoming both resistance mechanisms. In tumor cells derived from patients, ATRis also overcome the bypass of BRCA1/2 in fork protection. Thus, ATR inhibition is a unique strategy to overcome the PARPi resistance of BRCA-deficient cancers.**

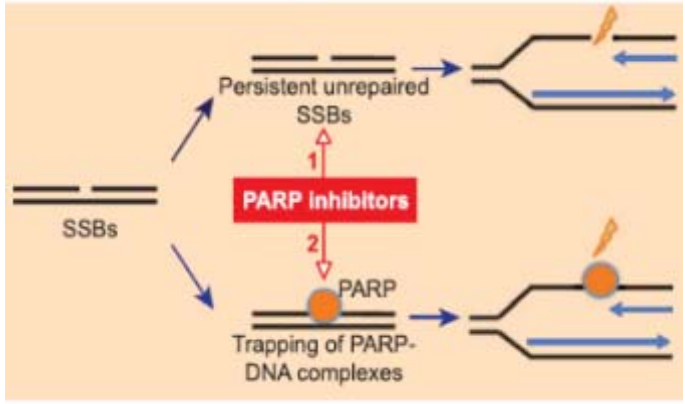
**Suggest use of ATR inhibitors in PARP inhibitor resistance setting and/or as combination strategies**

Murai et al, Oncotarget 2016; Yazinski et al, Genes & Development 2017

# Olaparib induces replication fork stalling/stress

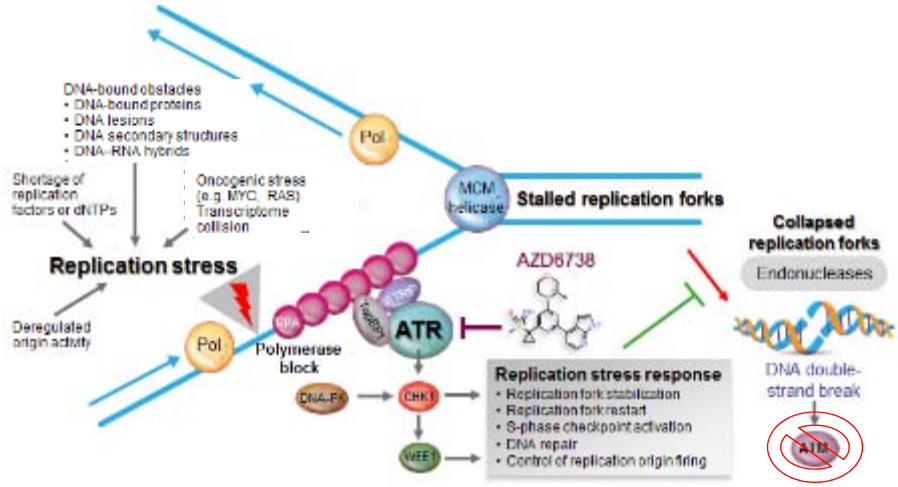
## Mechanistic rationale for combination with ATR inhibitor AZD6738

1. **PARP inhibitors cause increased DNA adducts which stall replication forks**




Murai et al, Cancer Research 2012

2. **ATR is required for repair of such stalled replication forks**

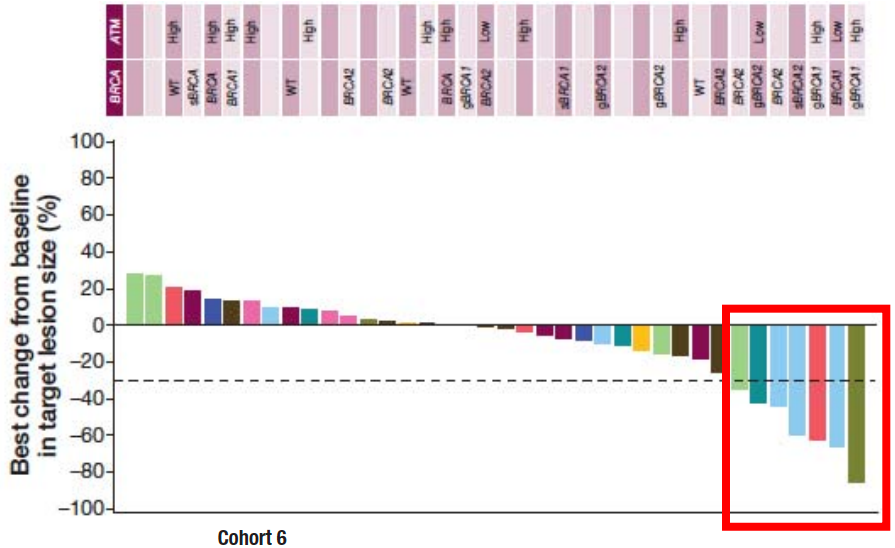


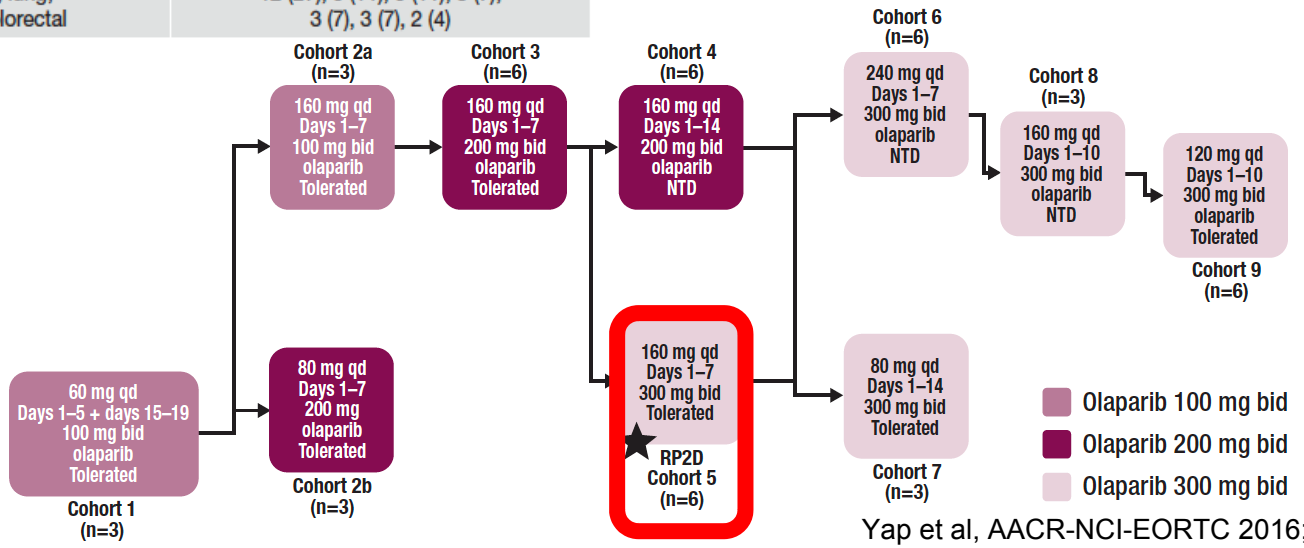

3. **In conjunction with ATM-deficiency, PARP + ATR inhibition will lead to increased DNA damage and cell death**

Yap et al, AACR-NCI-EORTC 2016

# Phase I trial of AZD6738 and olaparib

| Clinical characteristic | AZD6738 + ola |
|---|---|
| Gender: male/female, n (%) | 21/24 (47/53) |
| Median age, years (range) | 52 (31–76) |
| ECOG performance status, n (%)<br>0<br>1 | <br>23 (51)<br>22 (49) |
| Disease classification,* n (%)<br>Locally advanced<br>Metastatic<br>Both<br>Missing | <br>0<br>23 (51)<br>21 (47)<br>1 (2) |
| Recurrence of earlier cancer, n (%) | 18 (40) |
| Median number of prior regimens of chemotherapy (range) | 3.0 (1–≥6) |
| Primary tumor location,† n (%)<br>Breast, ovary, prostate, lung, pancreas, stomach, colorectal | <br>12 (27), 5 (11), 5 (11), 3 (7), 3 (7), 3 (7), 2 (4) |




Yap et al, AACR-NCI-EORTC 2016; Krebs et al, AACR 2018

# Phase I trial of AZD6738 and olaparib - Adverse events of all causes

| Patients with an AE, n (%) | AZD6738 + ola (N=45) | |
|---|---|---|
| | Any grade | Grade ≥3 |
| Fatigue | 29 (64) | 1 (2) |
| Nausea | 26 (58) | 0 |
| Anemia | 25 (56) | 7 (16) |
| Decreased appetite | 14 (31) | 1 (2) |
| Constipation | 12 (27) | 0 |
| Thrombocytopenia* | 12 (27) | 5 (11) |
| Vomiting | 12 (27) | 0 |
| Diarrhea | 10 (22) | 0 |
| Neutropenia† | 10 (22) | 6 (13) |
| Cough | 9 (20) | 0 |
| Ascites | 2 (4) | 2 (4) |
| Urinary tract infection | 5 (11) | 2 (4) |
| Syncope | 2 (4) | 2 (4) |
| White blood cell count decreased | 5 (11) | 2 (4) |

*Includes preferred term of decreased platelet count; †Includes preferred term of neutrophil count decreased

Yap et al, AACR-NCI-EORTC 2016; Krebs et al, AACR 2018

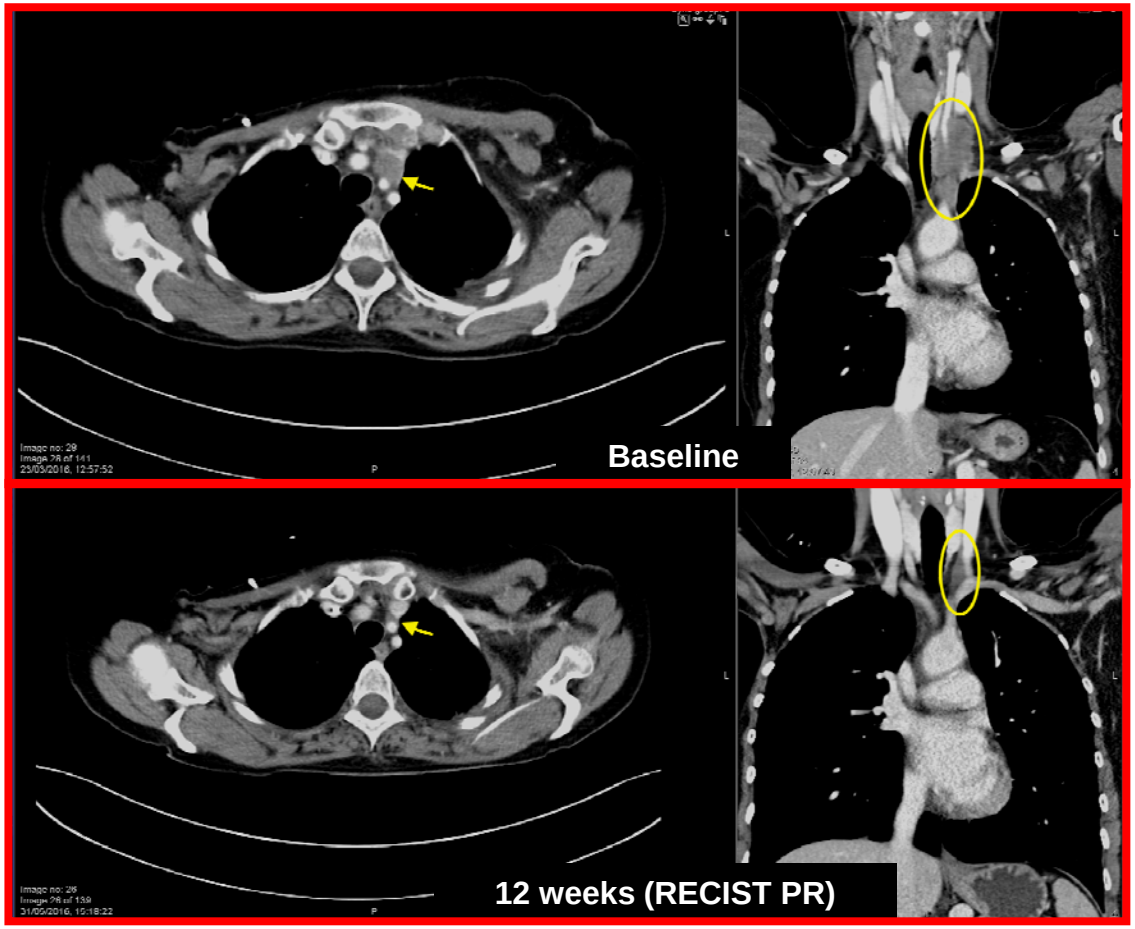
# Phase I trial: AZD6738 + olaparib – clinical responses

***BRCA1* mutant TNBC responder:**

- 42 year old female
- *BRCA1* mutant TNBC
- AZD6738 80mg d1-d7 + 200mg Olaparib BD

- Bilateral mastectomy for prophylaxis
- Adjuvant FEC-T
- Palliative Carboplatin; Eribulin; Paclitaxel + Bevacizumab

- **70% RECIST PR on 1st scan**
- **Remains on trial at 9 months+**




Yap et al, AACR-NCI-EORTC 2016

# Combining DDR and immune checkpoint inhibition

# PD-1/PD-L1 inhibitor drug development
# 20 Agents, 803 Trials, and 166,736 patient slots

PD-1 inhibitors are like the chocolate of oncology

Chocolate makes everything better

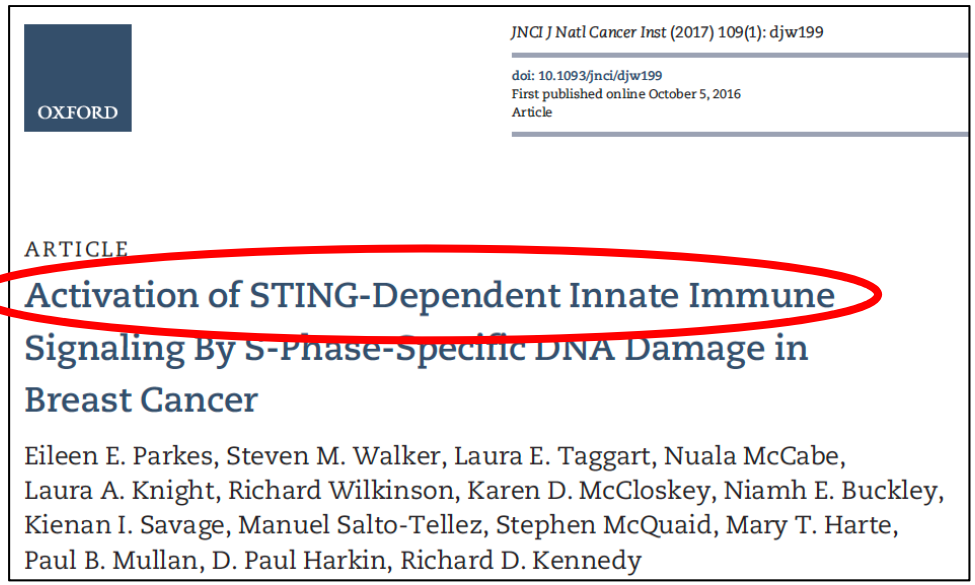
Need to stop serendipitous development of PD-1 combos
Biology should be driving development

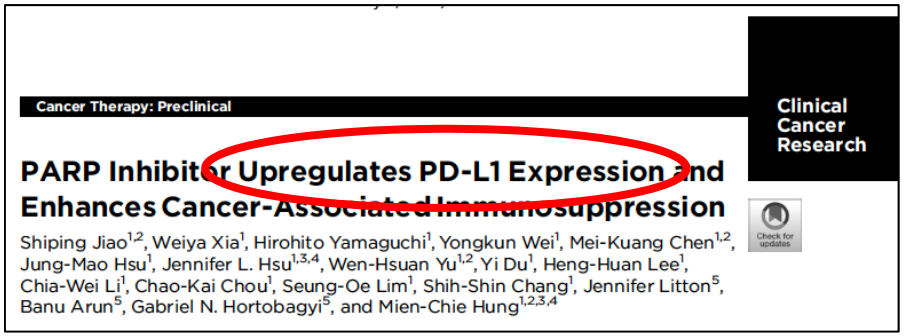
Yap et al, ASCO 2016

# Increasing evidence linking DDR and IO

Initial hypothesis: PARPi ➡ DNA damage ➡ Increased neoantigen expression ➡ more antigenic immune microenvironment
(Higuchi et al, Cancer Immunol Res 2016)

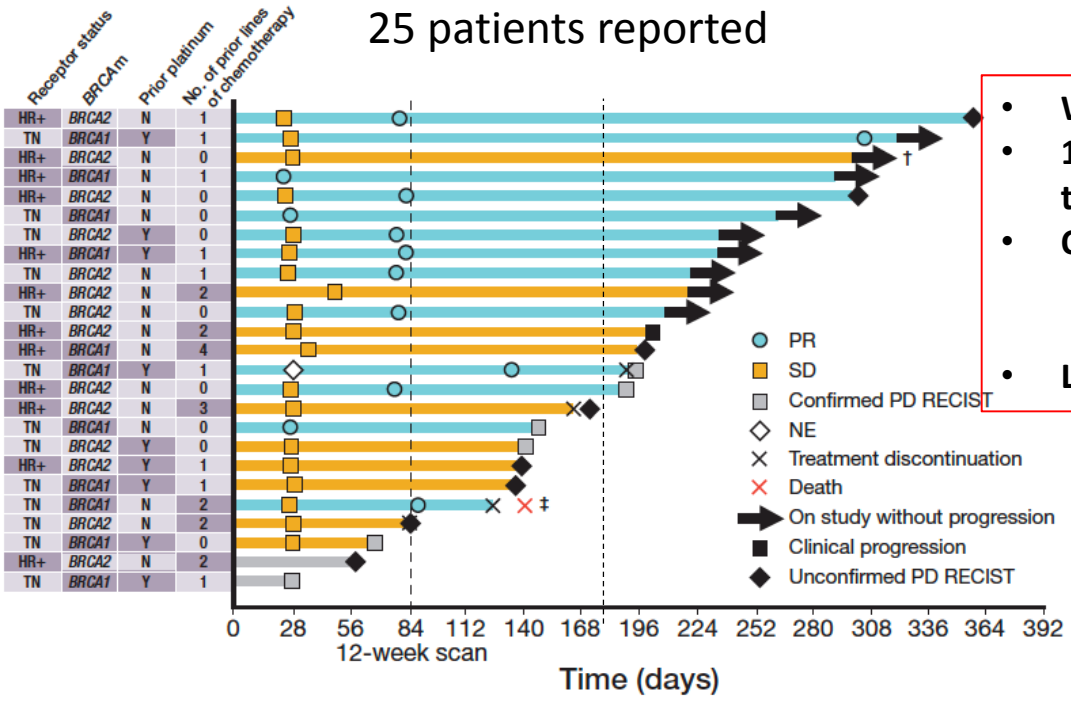
- S phase-specific DNA damage leads to accumulation of cytosolic DNA, which activates STING-dependent innate immune response, priming of antitumor T-cells, and associated upregulation of PD-L1 expression (Parkes et al, PNAS 2017)
- PARP inhibition inactivates GSK3$\beta$, leading to PD-L1 upregulation; *in vivo* synergy (Jiao et al, CCR 2017)




Combining DDR and PD-1/PD-L1 inhibitors is a rational antitumor strategy

# Phase 1/2 MEDIOLA trial of olaparib + durvalumab
# Advanced germline *BRCA1/2* mutant breast cancers




25 patients reported

- **Well tolerated; no overlapping tox**
- **12-week DCR (80%) exceeded the pre-specified target (75%)**
- **ORR of 52% was lower than OlympiAD of 60%:**
  - Later-line patients (≥2 prior chemo)
  - Small sample size
- **Limited paired tumor biopsies**

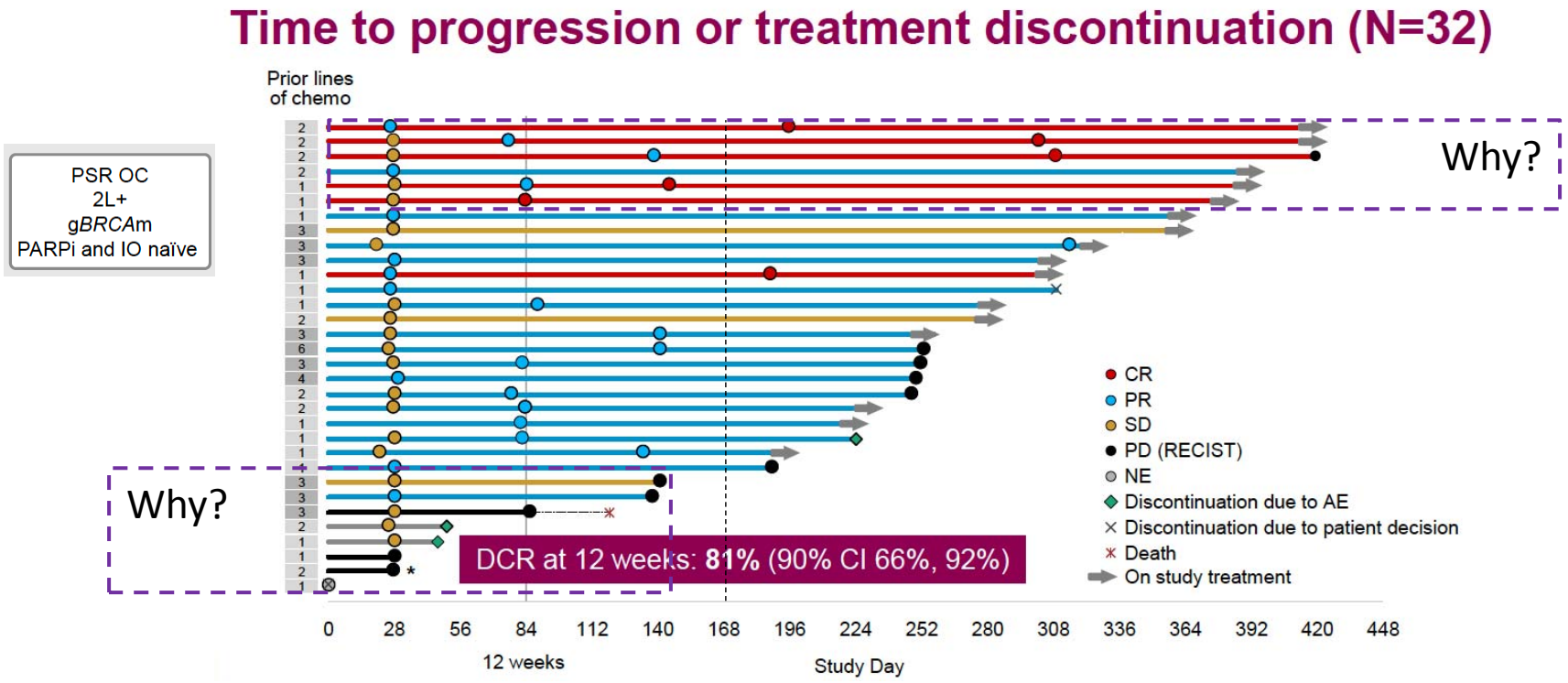
*Whichever occurred first; †Patient had bone-only disease; ‡Patient discontinued treatment because of dyspnea, which was attributed to clinical progression. HR+, hormone receptor positive; NE, not evaluable; PD, progressive disease; TN, triple negative

**Key questions:**

- Better than single agent olaparib?
- Will going earlier improve ORR?

Domchek et al, SABCS Dec 2017

# Phase 1/2 MEDIOLA trial of olaparib + durvalumab
# Platinum-sensitive recurrent *BRCA1/2* mutant ovarian cancers



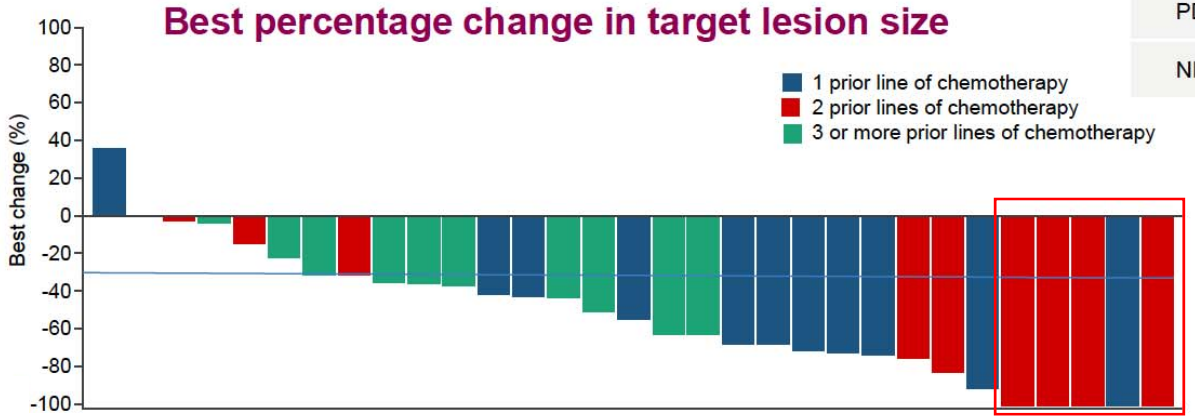

Drew et al, SGO March 2018

# Phase 1/2 MEDIOLA trial of olaparib + durvalumab
# Platinum-sensitive recurrent *BRCA1/2* mutant ovarian cancers

## Tumor responses

| | 1 prior (2L) | 2 prior (3L) | 3+ prior (4L) | All lines |
|---|---|---|---|---|
| **ORR** | 10/13=**77%** | 6/9=**67%** | 7/10=**70%** | 23/32=**72%** |
| **95% CI** | (46%, 95%) | (30%, 93%) | (35%, 93%) | (53%, 86%) |

| Best Response | N (%) |
|---|---|
| **CR** | **6 (19)** |
| **PR** | **17 (53)** |
| SD | 3 (9) |
| PD | 3 (9) |
| NE | 3 (9) |




Global Phase 3 Durvalumab-olaparib (DUO-O) Trial in 1L OC

Drew et al, SGO March 2018

# Phase 1/2 MEDIOLA trial of olaparib + durvalumab
# Platinum-sensitive recurrent *BRCA1/2* mutant ovarian cancers

## Safety (N=34)

| Adverse events* (grade ≥3) | Patients n (%) |
|---|---|
| Anemia | 4 (12) |
| Increased lipase | 3 (9) |
| Decreased lymphocyte count | 2 (6) |
| Fatigue | 2 (6) |
| Hyponatremia | 2 (6) |
| Increased amylase | 2 (6) |
| Neutropenia | 2 (6) |
| Neuralgia | 2 (6) |

*The following AEs were found in N=1 patient (3% of population): Decreased neutrophil count, device-related infection, erythema, hypoalbuminemia, hypotension, ileus, infusion-related reaction, maculo-papular rash, peripheral edema, pleural effusion, pulmonary embolism, sepsis, small bowel obstruction, vomiting, hypokalemia, encephalitis autoimmune, pneumonitis, ascites, constipation, blister, weight decreased, fibula fracture

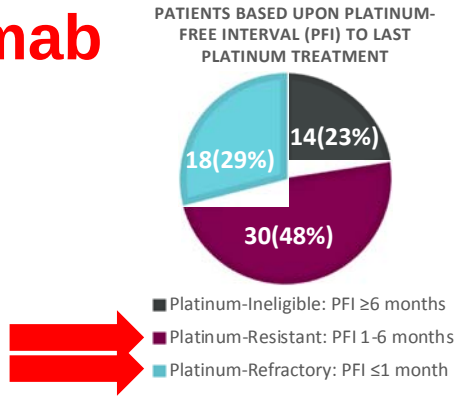
| Immune-mediated adverse events* (all grades) | Patients n (%) |
|---|---|
| Hypothyroidism | 5 (15) |
| Rash | 4 (12) |
| Adrenal insufficiency | 2 (6) |
| Amylase increase | 2 (6) |
| Blood testosterone decreased | 2 (6) |
| Diarrhea | 2 (6) |
| Hyperthyroidism | 2 (6) |
| Lipase increased | 2 (6) |
| Myalgia | 2 (6) |

*The following AEs were found in N=1 patient (3% of population): ALT increase, blood TSH increased, diplopia, dry skin, dyspnea, dyspnea exertional, encephalitis autoimmune, headache, influenza-like illness, lethargy, muscular weakness, peripheral sensorimotor neuropathy, photosensitivity reaction, pneumonia, pneumonitis, pruritus, maculo-papular rash, stomatitis, thyroiditis, tremor, vomiting, blood uric acid increased

Drew et al, SGO March 2018

# TOPACIO: Phase 1/2 Niraparib + Pembrolizumab in Platinum-Resistant Ovarian Cancer

**Monotherapy activity cheat sheet**
Olaparib in BRCAmut platinum-resistant patients: ORR 25-30%
**Olaparib in BRCAwt platinum-resistant patients: ORR ~5%**
**Olaparib in BRCAmut platinum-refractory patients: ORR 0-14%**
Nivolumab: ORR 15%
Pembrolizumab: ORR 11%




| Platinum status | Response | All (%) | tBRCA mut (%) | HRD-pos* (%) | tBRCA wt (%) | HRD-neg (%) |
|---|---|---|---|---|---|---|
| Evaluable platinum-resistant and -refractory patients | **ORR** | **11/46 (24)** | **2/7 (29)** | **4/15 (27)** | **9/34 (26)** | **7/24 (29)** |
| | DCR | 31/46 (67) | 4/7 (57) | 10/15 (67) | 23/34 (68) | 15/24 (63) |

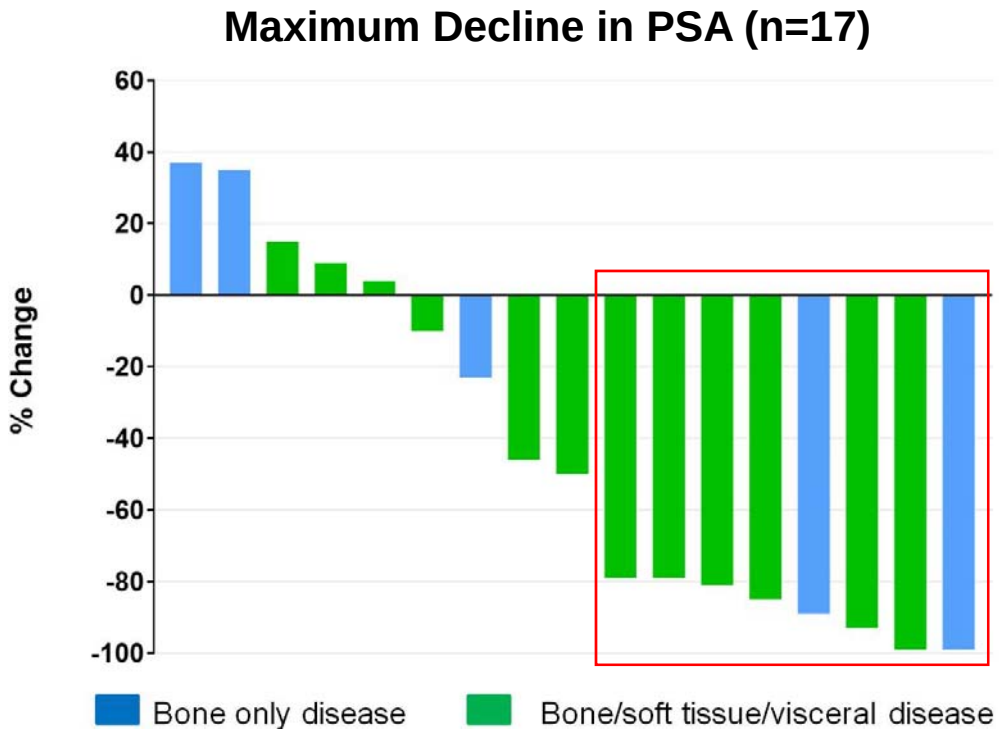
- Addition of pembrolizumab to niraparib in tBRCAwt and HRD-neg led to ORR similar to PARPi monotherapy efficacy in tBRCAmut population
- HRD status does not correlate with response to this combo in platinum resistant/ refractory disease

*HRD-pos includes BRCA mutation or HRD score ≥42 per Myriad assay.
Patients with inconclusive biomarker results were not included in the biomarker subpopulations.

Konstantinopoulos et al, SGO 2018

# Castration-Resistant Prostate Cancer

Phase 2 trial of olaparib + durvalumab

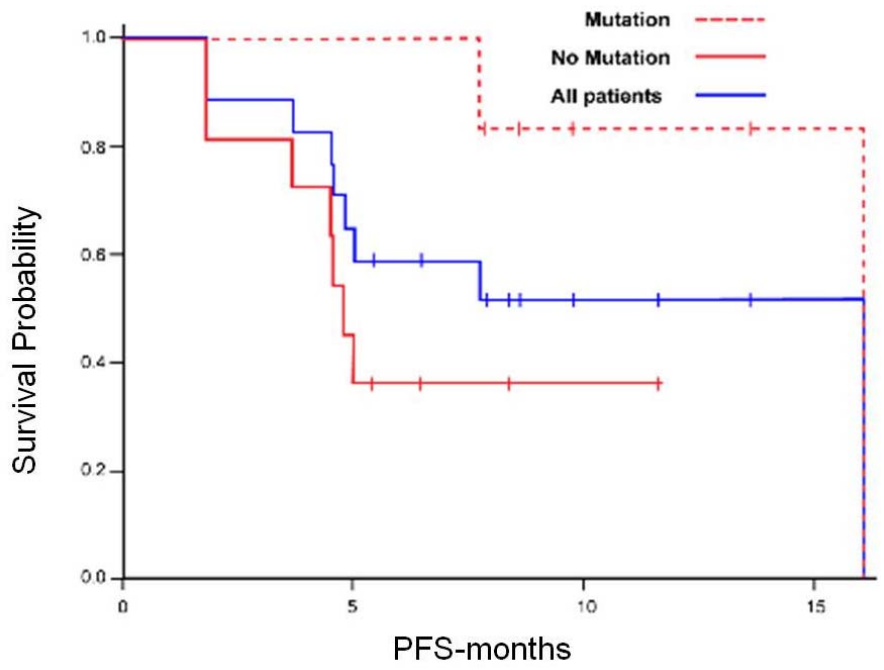



Karzai et al, GU ASCO 2018

# Castration-Resistant Prostate Cancer

## Phase 2 trial of olaparib + durvalumab

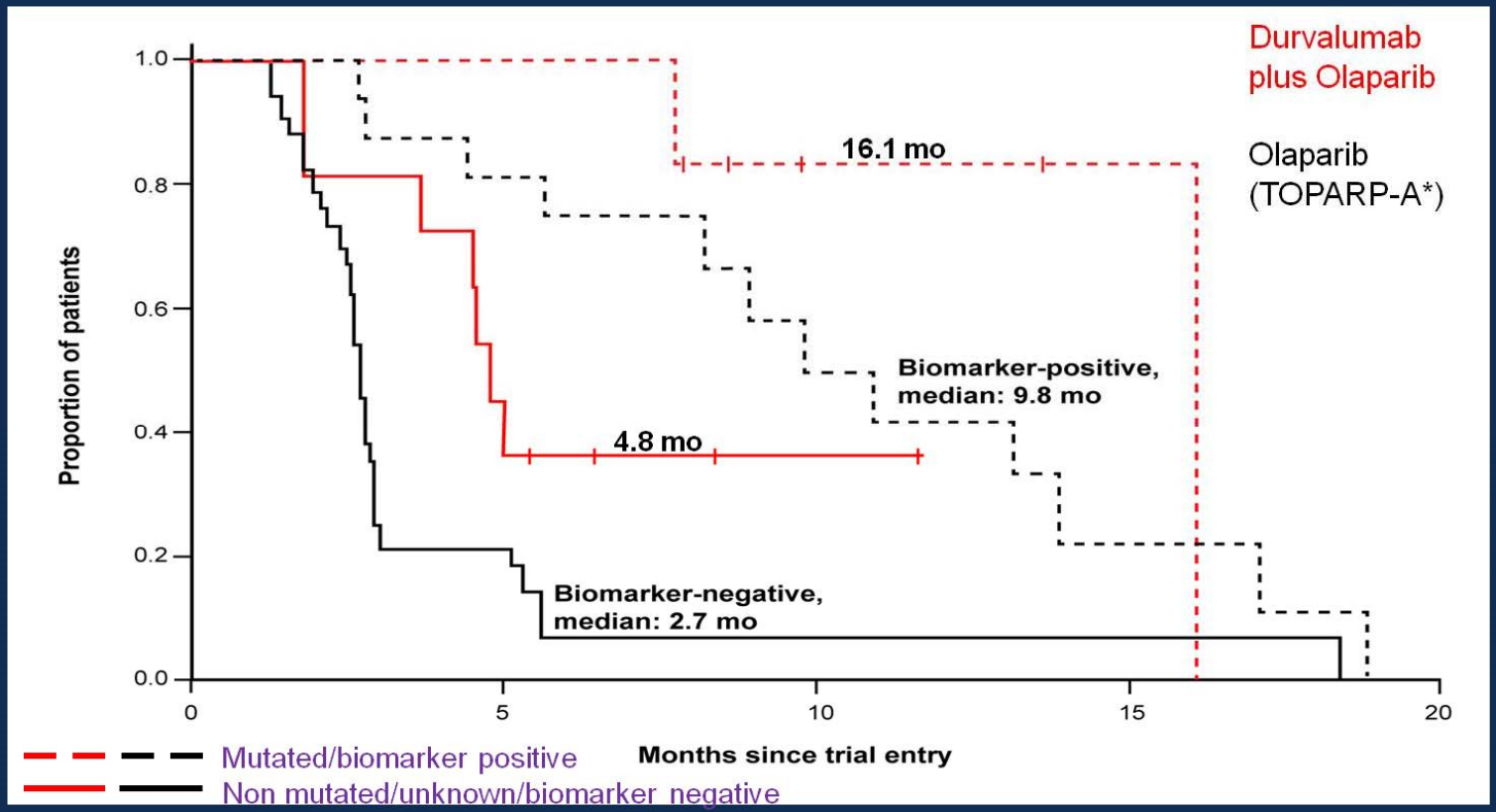
**Median Radiographic PFS**




- **DDR mutated:** 16.1 months (95% CI: 7.8-18.1 months)
- **All patients:** 16.1 months (95% CI: 4.5-16.1 months)
- **Non-DDR mutated/unknown:** 4.8 months (95% CI: 1.8 months – cannot be calculated)

Karzai et al, GU ASCO 2018

# Radiographic PFS of TOPARP-A and Durvalumab plus Olaparib




*Mateo J et al. N Engl J Med. 2015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# Take home points

- Ovarian cancer has served as poster child for PARP inhibitors; clear opportunities in other tumor and molecular subtypes
- Need to better understand mechanisms of tumor response and resistance involved in targeting DDR
- Combinatorial strategies will widen breadth of application of DDR inhibitors

# Thank you

Department of Investigational Cancer Therapeutics (A Phase I Program)

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