.cáncer. XII FORO DE ovario
Y OTROS TUMORES GINECOLÓGICOS

# ¿Podemos detectar la resistencia a iPARP?: de la preclínica a la clínica

J. Alejandro Pérez Fidalgo
Hospital Clinico Universitario de Valencia
Instituto de investigación INCLIVA
Prof Asociado Universidad de Valencia

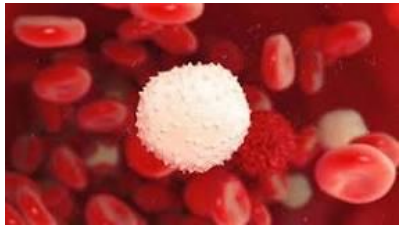
# La paradoja del SS John Harvey

Frederijk Guthrie
Describe el gas mostaza
1859

**1ª Guerra Mundial** → Wilhelm Steinkopf
lo sintetiza a gran escala

**2ª Guerra Mundial**
Bombardeo sobre Bari 1943
“El 2º Pearl Harbour”

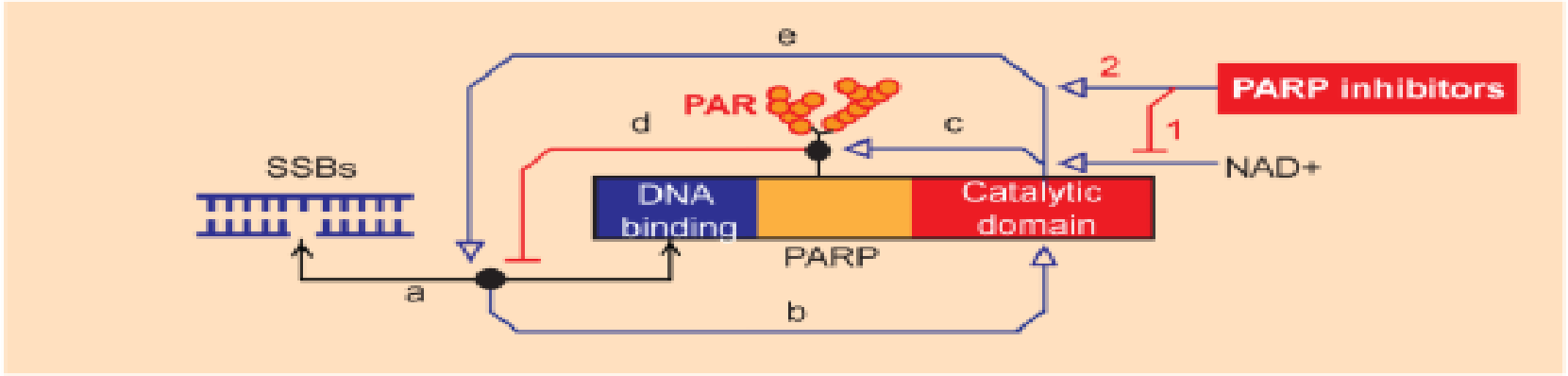
El SS John Harvey se hunde
cargado de gas mostaza

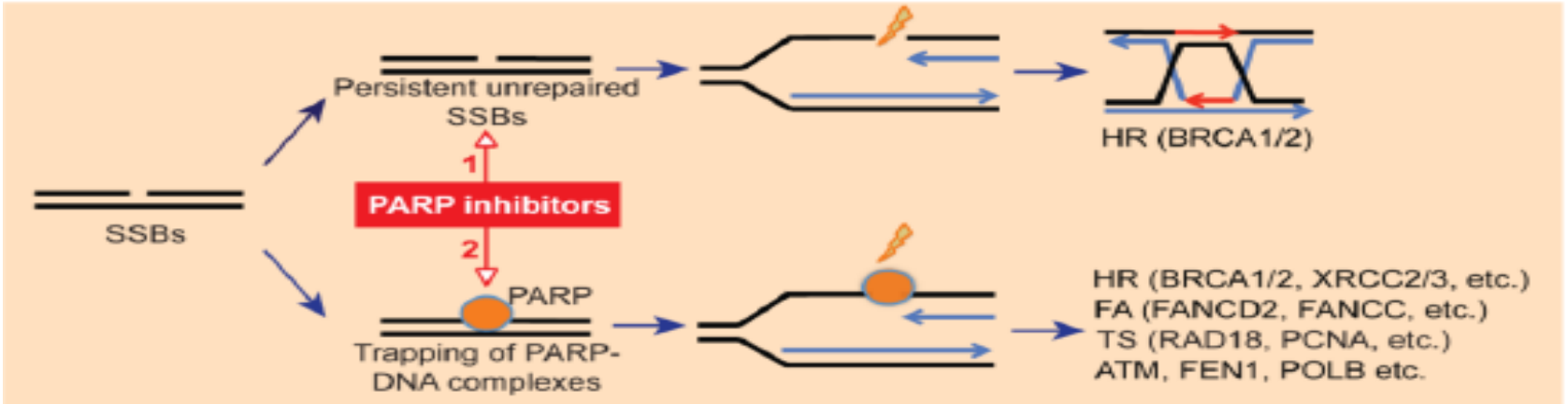


Cientos de habitantes de Bari
fallecen con leucopenia

Se crea la primera
Quimioterapia
**La mostaza nitrogenada**

# La paradoja de los iPARP

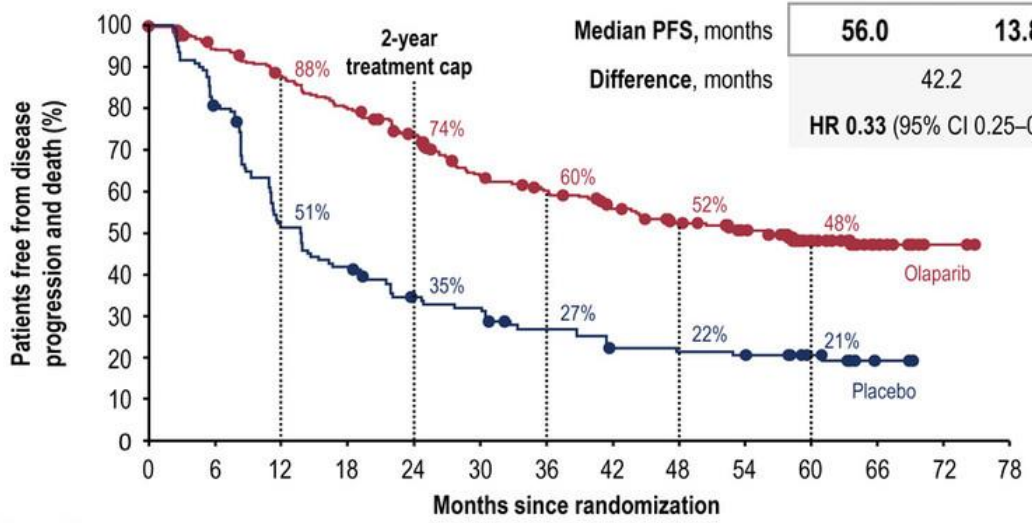



*Murai J et al Cancer Res 2012*

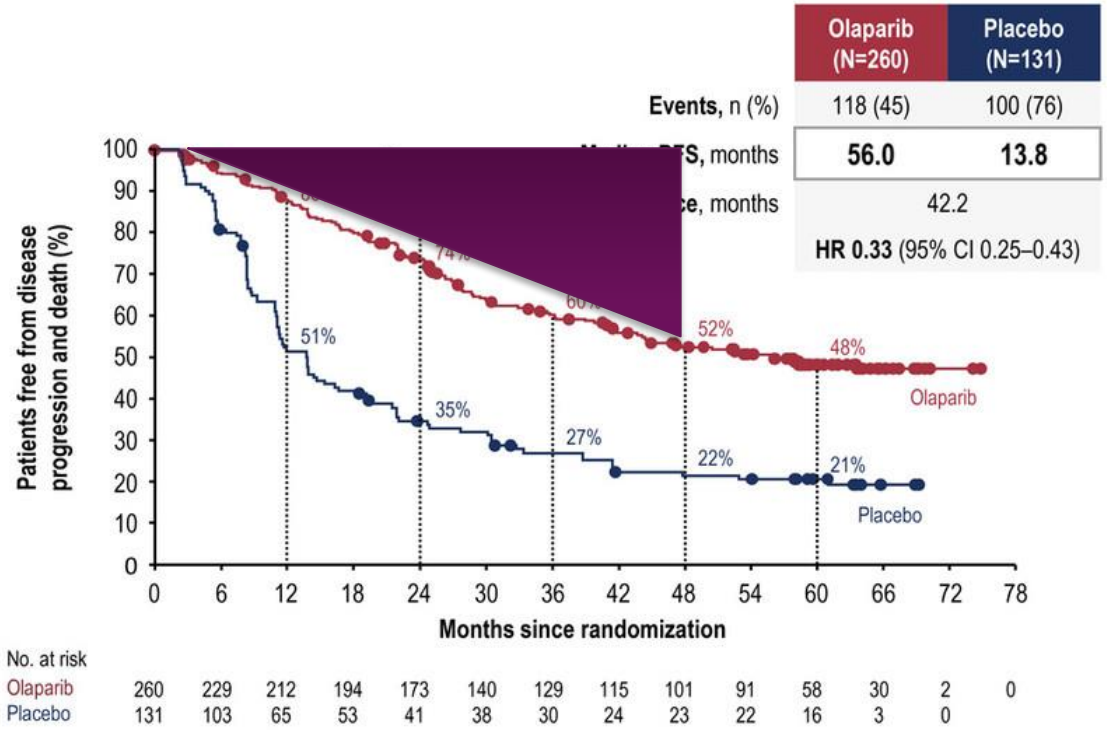
# SOLO-1

| | Olaparib (N=260) | Placebo (N=131) |
|---|---|---|
| **Events**, n (%) | 118 (45) | 100 (76) |
| **Median PFS**, months | **56.0** | **13.8** |
| **Difference**, months | 42.2 | |
| **HR 0.33** (95% CI 0.25–0.43) | | |

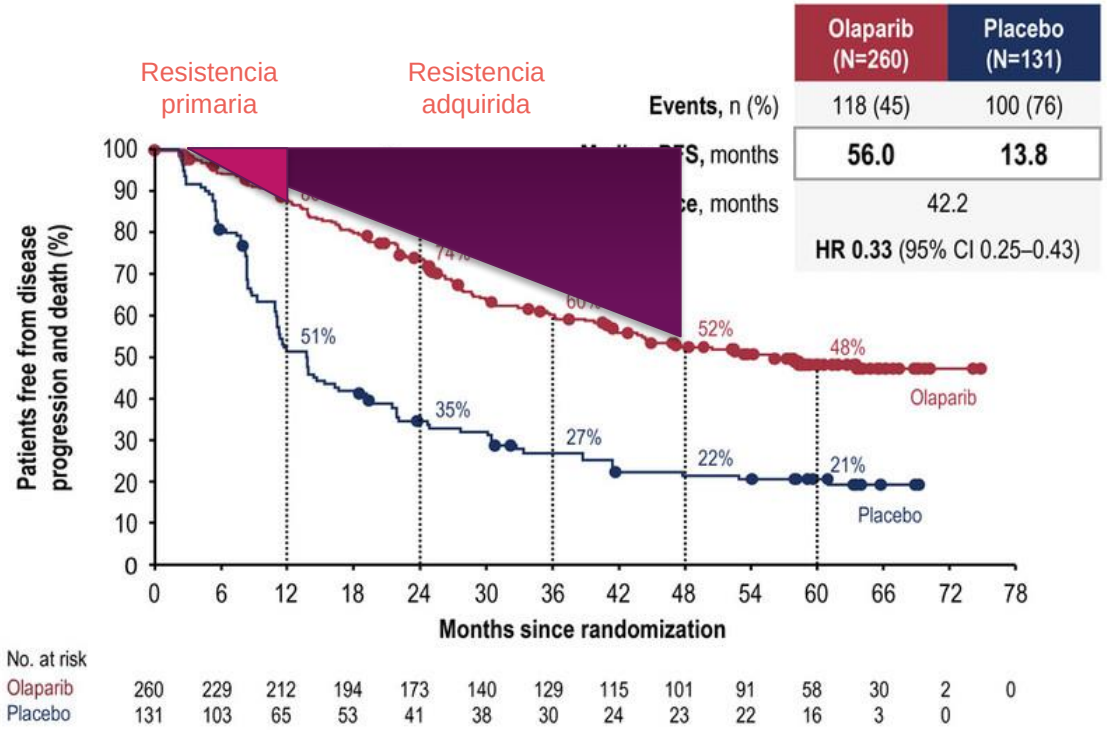



| No. at risk | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Olaparib | 260 | 229 | 212 | 194 | 173 | 140 | 129 | 115 | 101 | 91 | 58 | 30 | 2 | 0 |
| Placebo | 131 | 103 | 65 | 53 | 41 | 38 | 30 | 24 | 23 | 22 | 16 | 3 | 0 | |

# SOLO-1


Olaparib (N=260)
Placebo (N=131)
Events, n (%)
118 (45)
100 (76)
S, months
56.0
13.8
e, months
42.2
HR 0.33 (95% CI 0.25–0.43)
Patients free from disease progression and death (%)
100
90
80
70
60
50
40
30
20
10
0
74%
60%
52%
48%
Olaparib
51%
35%
27%
22%
21%
Placebo
0
6
12
18
24
30
36
42
48
54
60
66
72
78
Months since randomization
No. at risk
Olaparib 260 229 212 194 173 140 129 115 101 91 58 30 2 0
Placebo 131 103 65 53 41 38 30 24 23 22 16 3 0

**SOLO-1**


Resistencia primaria
Resistencia adquirida
Olaparib (N=260)
Placebo (N=131)
Events, n (%)
118 (45)
100 (76)
56.0
13.8
42.2
HR 0.33 (95% CI 0.25–0.43)
Patients free from disease progression and death (%)
100
90
80
70
60
50
40
30
20
10
0
74%
60%
52%
48%
Olaparib
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35%
27%
22%
21%
Placebo
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Months since randomization
No. at risk
Olaparib 260 229 212 194 173 140 129 115 101 91 58 30 2 0
Placebo 131 103 65 53 41 38 30 24 23 22 16 3 0

¿Cuáles son los mecanismos de resistencia a iPARP?

¿Cuáles son las bases biológicas para estrategias que reviertan las resistencias a PARPi?

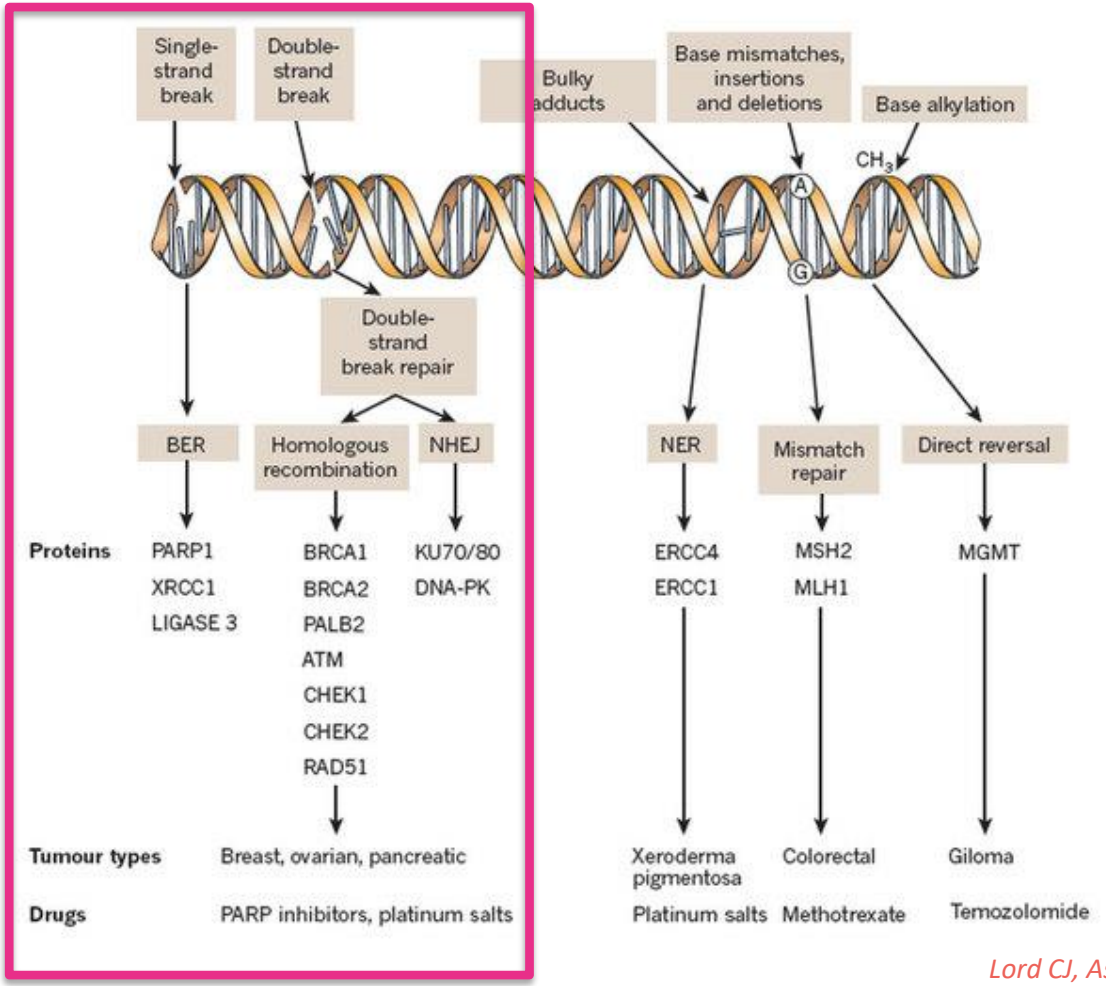
¿Existe una resistencia cruzada PARPi-platino?

¿Cuáles son los mecanismos de resistencia a iPARP?

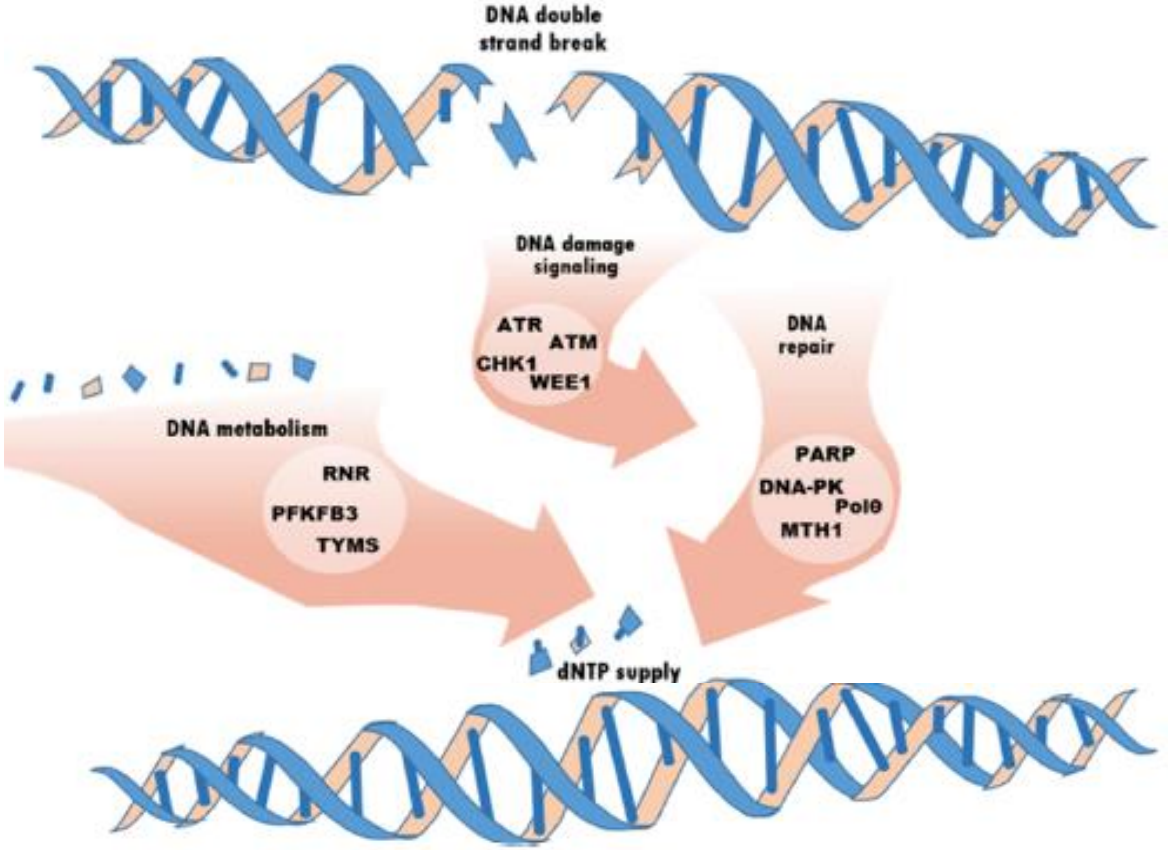
¿Cuáles son las bases biológicas para estrategias que reviertan las resistencias a PARPi?

## Tipos de daño en DNA

## Mecanismos de reparación




*Lord CJ, Ashworth A. Nature 2012*



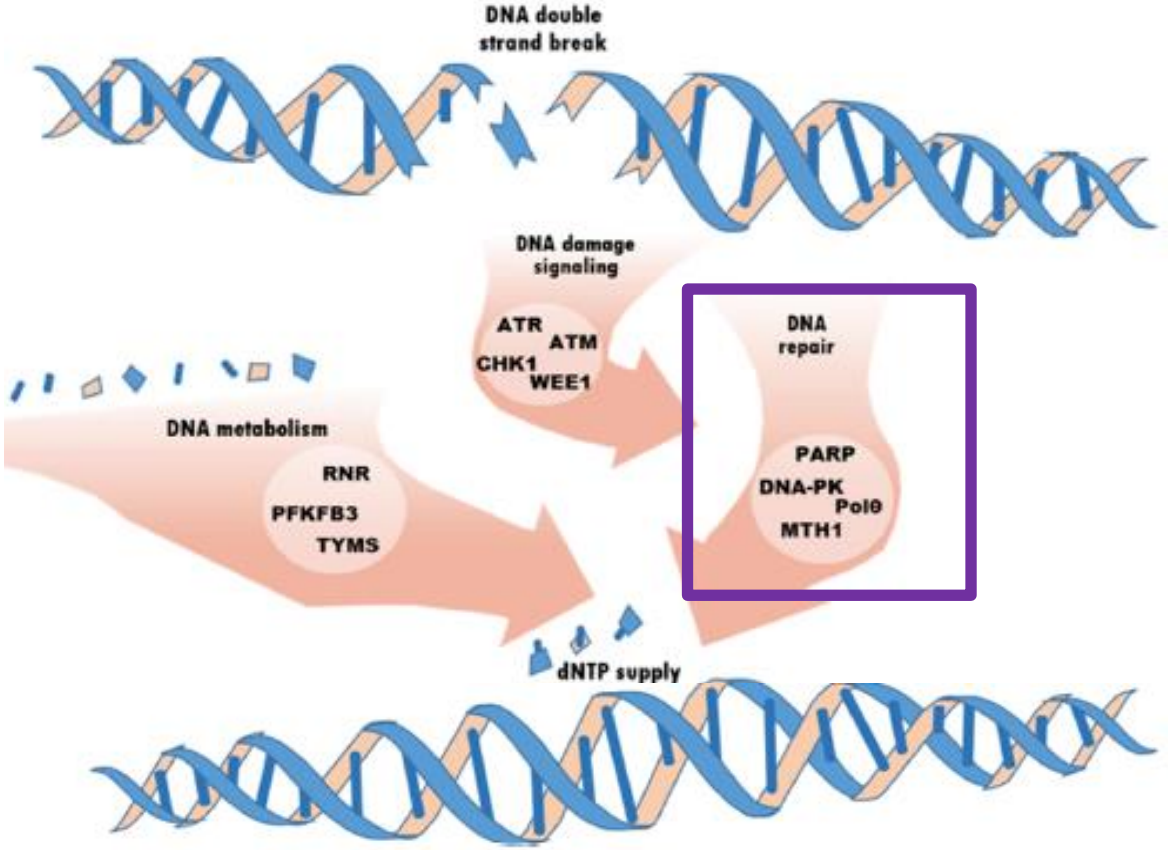

*Yap T et al. ASCO Educational Book 2019*

# Mecanismos de resistencia a iPARP


- Sobreexpresion ABCB1


- Estabilizan el replicación fork – anulan el efecto trapping
- Inicio del NHEJ → perdida de 53BP1
- Pérdida de fenotipo HRD

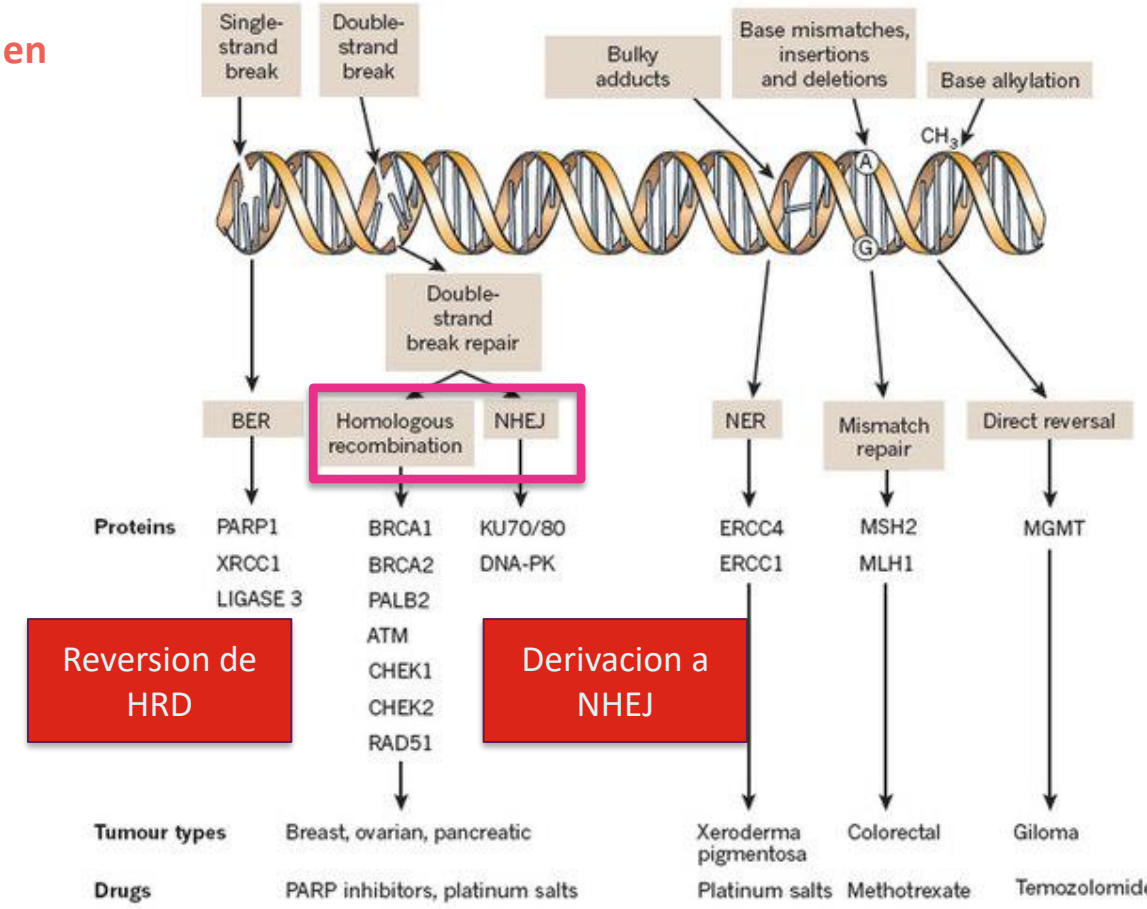

- Modifican checkpoint intrafase S
- Amplificación CCNE1
- Perdida de SLFN11




*Yap T et al. ASCO Educational Book 2019*

## Tipos de daño en DNA

## Mecanismos de reparación




*Lord CJ, Ashworth A. Nature 2012*

The Journal of Clinical Investigation

RESEARCH ARTICLE

# RING domain–deficient BRCA1 promotes PARP inhibitor and platinum resistance

Cancer Research

Therapeutics, Targets, and Chemical Biology

## The BRCA1-Δ11q Alternative Splice Isoform Bypasses Germline Mutations and Promotes Therapeutic Resistance to PARP Inhibition and Cisplatin

Yifan Wang[1], Andrea J. Bernhardy[1], Cristina Cruz[2,3], John J. Krais[1], Joseph Nacson[1],



The Journal of Clinical Investigation

RESEARCH ARTICLE

# *BRCA1*$^{185delAG}$ tumors may acquire therapy resistance through expression of RING-less BRCA1

Rinske Drost,[1] Kiranjit K. Dhillon,[2] Hanneke van der Gulden,[1] Ingrid van der Heijden,[1] Inger Brandsma,[3] Cristina Cruz,[4,5]

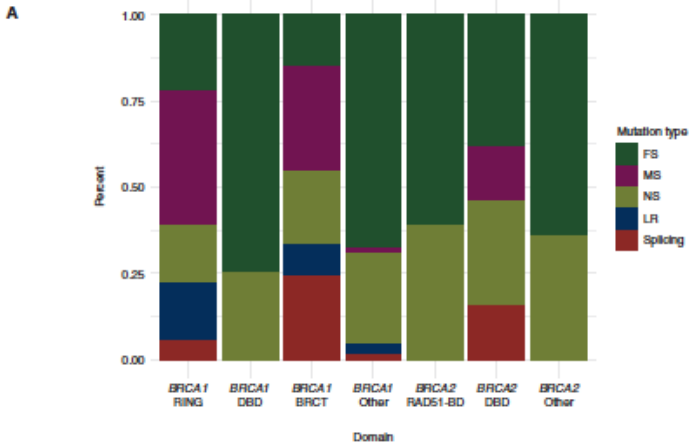
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

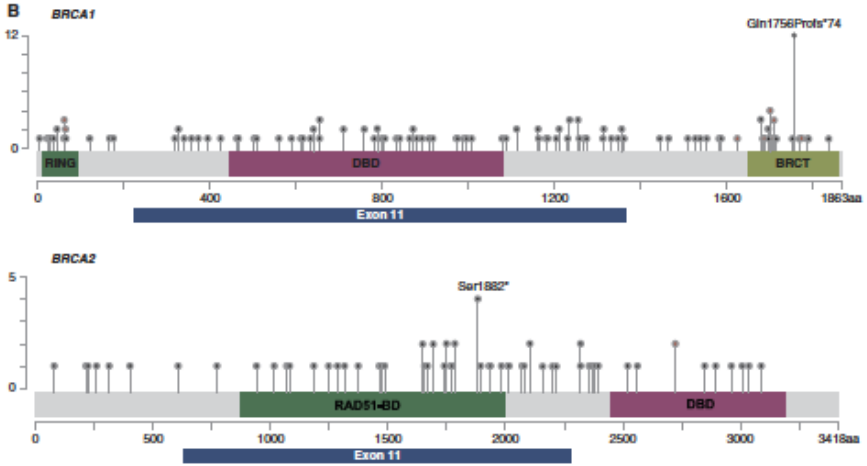
ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

# Association of location of *BRCA1* and *BRCA2* mutations with benefit from olaparib and bevacizumab maintenance in high-grade ovarian cancer: phase III PAOLA-1/ENGOT-ov25 trial subgroup exploratory analysis

S. I. Labidi-Galy[1,2*†], M. Rodrigues[3,4,5†], J. L. Sandoval[1,2], J. E. Kurtz[5,6], F. Heitz[7,8,9], A. M. Mosconi[10,11], I. Romero[12,13], U. Denison[14,15], S. Nagao[16,17], I. Vergote[18,19], G. Parma[20,21], T. J. Nøttrup[22,23], E. Rouleau[24], G. Garnier[25,26], A. El-Balat[9,27,28], C. Zamagni[29], C. Martín-Lorente[13,30], E. Pujade-Lauraine[5,6], A. Fiévet[24] & I. L. Ray-Coquard[5,6,31,32]



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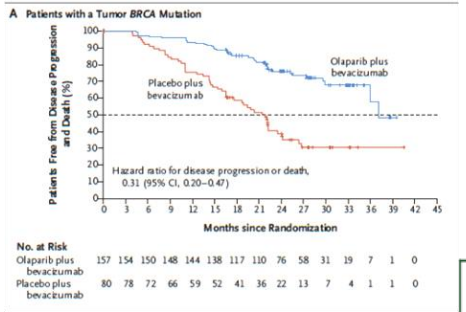


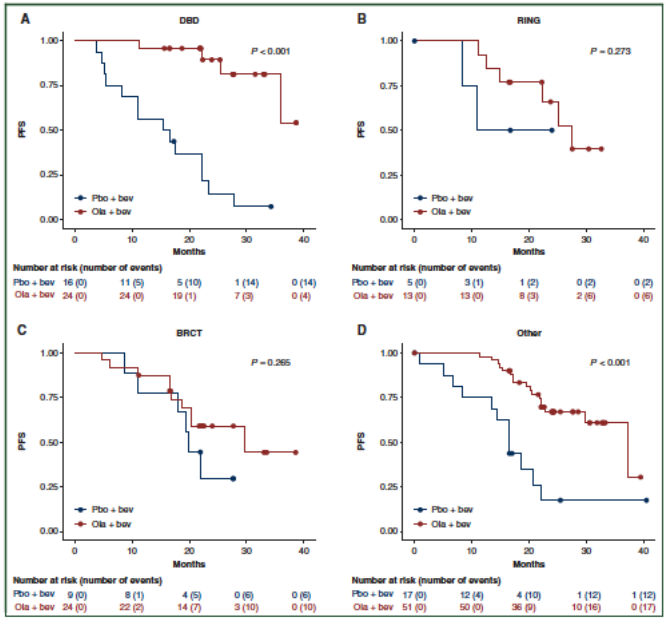


Figure 2. PFS according to the location of mutations in *BRCA1*. (A) DBD. (B) RING. (C) BRCT. (D) Other locations.
Bev, bevacizumab; BRCT, C-terminal domain of *BRCA1*; DBD, DNA-binding domain; Ola, olaparib; Pbo, placebo; PFS, progression-free survival; RING, Really Interesting New Gene.

No parece que el tipo de mutacion sean predictor de no actividad de ola-beva

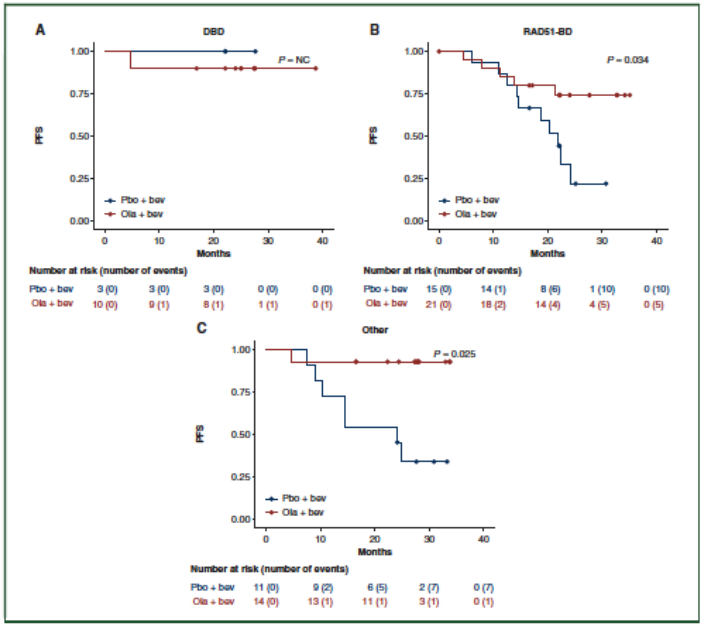


Figure 3. PFS according to the location of mutations in *BRCA2*. (A). DBD. (B) RAD51-BD. (C) Other locations.
Bev, bevacizumab; DBD, DNA-binding domain; NC, not calculated; Ola, olaparib; Pbo, placebo; PFS, progression-free survival; RAD51-BD, RAD51-binding domain.

BRCA1

BRCA2

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ORIGINAL ARTICLE

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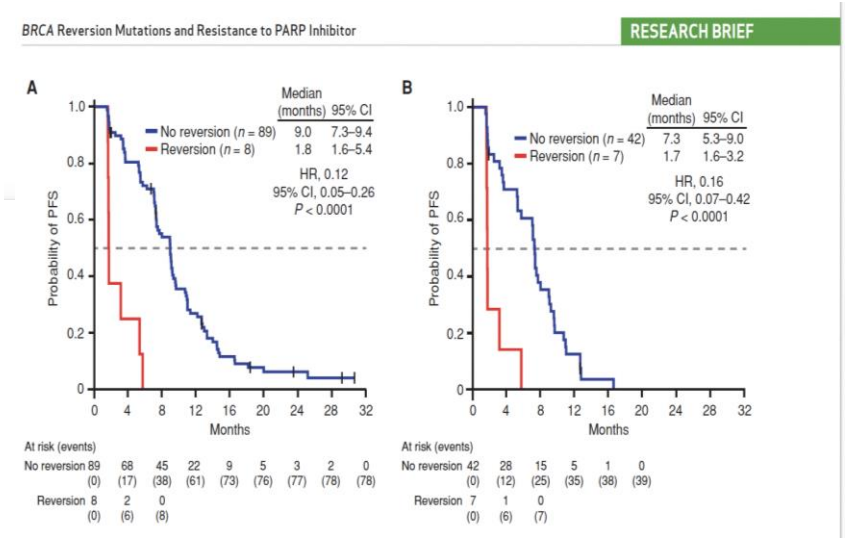
**Table 2. PFS according to the location of mutations in *BRCA1* and *BRCA2***

| | Region (AA) | Median PFS, placebo (95% CI) | Median PFS, olaparib (95% CI) | 24-month PFS, placebo (95% CI) | 24-month PFS, olaparib (95% CI) | Placebo events (cases) | Olaparib events (cases) | HR (95% CI) | *P* |
|---|---|---|---|---|---|---|---|---|---|
| Gene | | | | | | | | | |
| *BRCA1* (*n* = 159) | | 17.6 | 36 | 0.2 (0.11-0.39) | 0.7 (0.61-0.79) | 34 (47) | 37 (112) | 0.26 (0.16-0.41) | <0.001 |
| *BRCA2* (*n* = 74) | | 22.2 | NR | 0.5 (0.34-0.73) | 0.84 (0.73-0.96) | 17 (29) | 7 (45) | 0.22 (0.09-0.54) | 0.001 |
| Functional domain of *BRCA1* | | | | | | | | | |
| RING (*n* = 18) | 8-96 | 11 | 27.4 | 0.5 (0.19-1) | 0.66 (0.43-1) | 2 (5) | 6 (13) | 0.38 (0.07-2.13) | 0.273 |
| DBD (*n* = 40) | 452-1092 | 16 | NR | 0.15 (0.04-0.51) | 0.89 (0.76-1) | 14 (16) | 4 (24) | 0.08 (0.02-0.28) | <0.001 |
| BRCT (*n* = 33) | 1646-1736 | 19.9 | 29.6 | 0.3 (0.1-0.88) | 0.59 (0.42-0.84) | 6 (9) | 10 (24) | 0.55 (0.2-1.56) | 0.265 |
| Other (*n* = 68) | 1760-1855 | 16.6 | 37.2 | 0.18 (0.05-0.59) | 0.67 (0.55-0.82) | 12 (17) | 17 (51) | 0.24 (0.11-0.51) | <0.001 |
| Functional domain of *BRCA2* | | | | | | | | | |
| RAD51-BD (*n* = 36) | 900-2000 | 21.7 | NR | 0.33 (0.15-0.75) | 0.74 (0.57-0.97) | 10 (15) | 5 (21) | 0.31 (0.11-0.92) | 0.034 |
| DBD (*n* = 13) | 2459-3190 | NR | NR | 1 (1-1) | 0.9 (0.73-1) | 0 (3) | 1 (10) | NC | NC |
| Other (*n* = 25) | | 24 | NR | 0.55 (0.32-0.94) | 0.93 (0.8-1) | 7 (11) | 1 (14) | 0.09 (0.01-0.75) | 0.025 |
| Exon 11 mutation | | | | | | | | | |
| Yes (*n* = 123) | | 17.6 | 37.2 | 0.34 (0.14-0.43) | 0.78 (0.68-0.89) | 34 (47) | 18 (76) | 0.2 (0.11-0.36) | <0.001 |
| No (*n* = 110) | | 19.9 | NR | 0.45 (0.3-0.68) | 0.7 (0.6-0.81) | 17 (29) | 26 (81) | 0.41 (0.22-0.75) | 0.004 |

AA, amino acid; BRCT, C-terminal domain of *BRCA1*; CI, confidence interval; DBD, DNA-binding domain; HR, hazard ratio; NC, not calculated; NR, not reached; PFS, progression-free survival; RAD51-BD, RAD51-binding domain; RING, Really Interesting New Gene.


Pacientes BRCA mutadas del estudio ARIEL2 (fase II) tratadas con rucaparib, se les recogio muestra de tumor y ctDNA pre-tto y post-tto




**En la muestra de ctDNA pretto:**
**18% de las platino-refractarias**
**13% de las platino-resistentes**
**2% de las platino-sensibles**

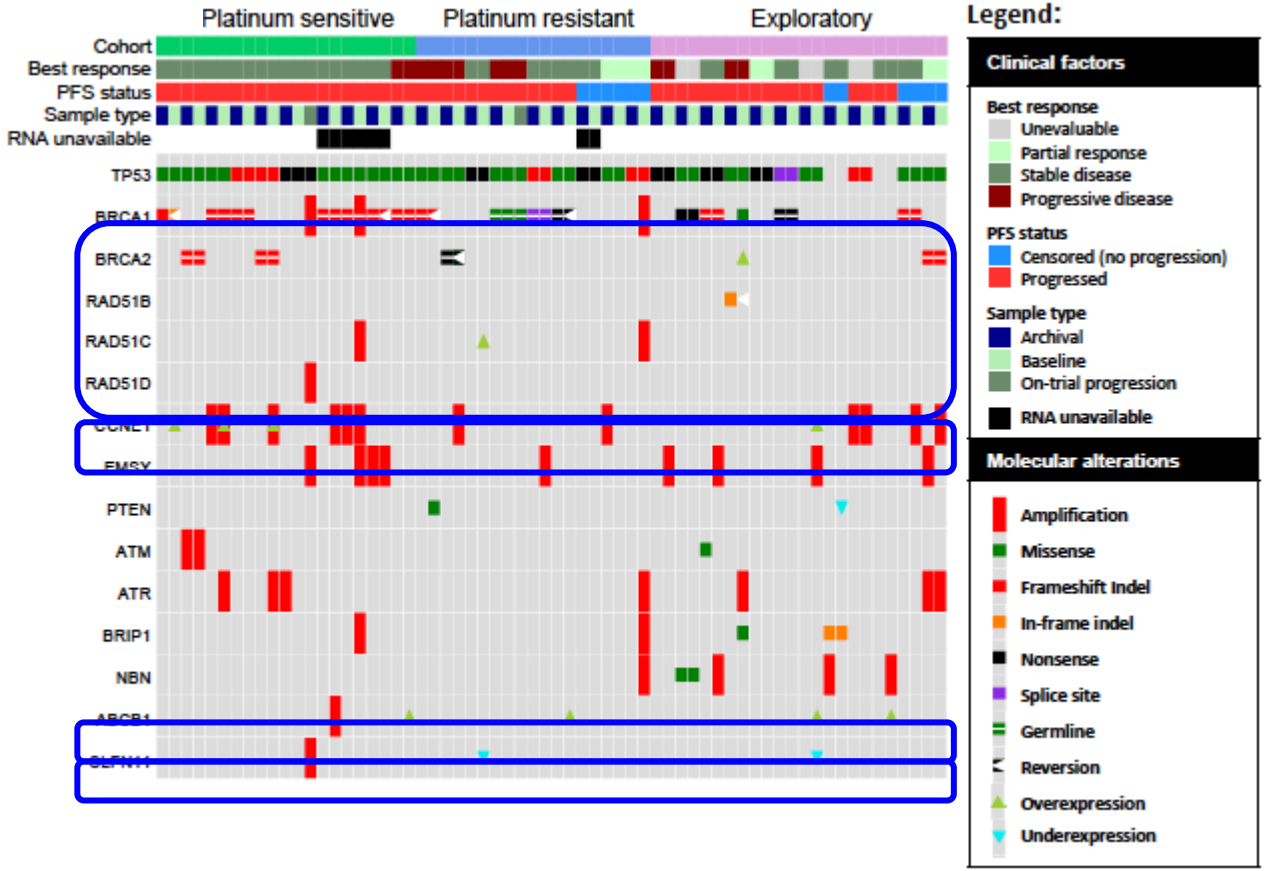
**Tenian reversion de la mutación BRCA**

Las pacientes con reversion tenían una PFS mucho más corta a rucaparib que las que no habían revertido BRCA antes de iniciar rucaparib

**EVOLVE: A Multicenter Open-Label Single-Arm Clinical and Translational Phase II Trial of Cediranib Plus Olaparib for Ovarian Cancer after PARP Inhibition Progression**

Stephanie Lheureux, Ana Oaknin, Swati Garg, et al.

*Clin Cancer Res* Published OnlineFirst May 22, 2020.

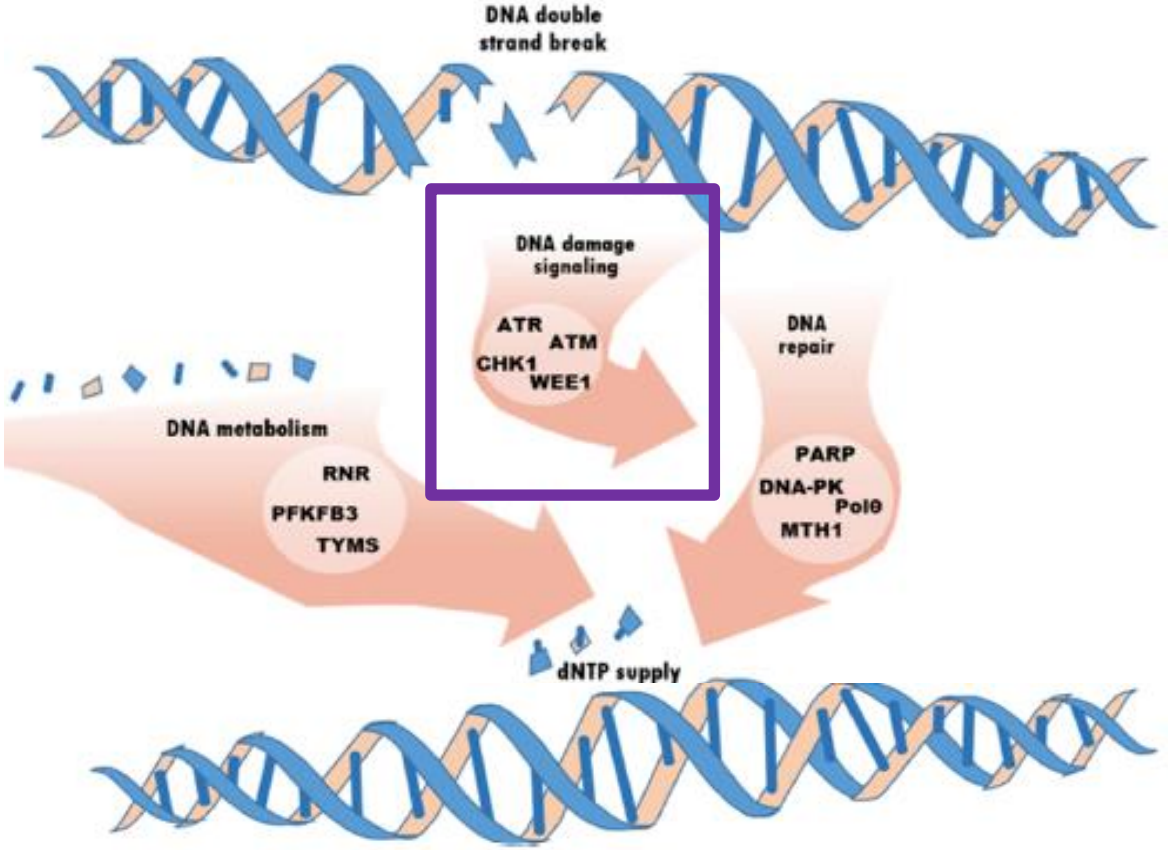


# EVOLVE trial

Olaparib + Cediranib
treatment

**Array**

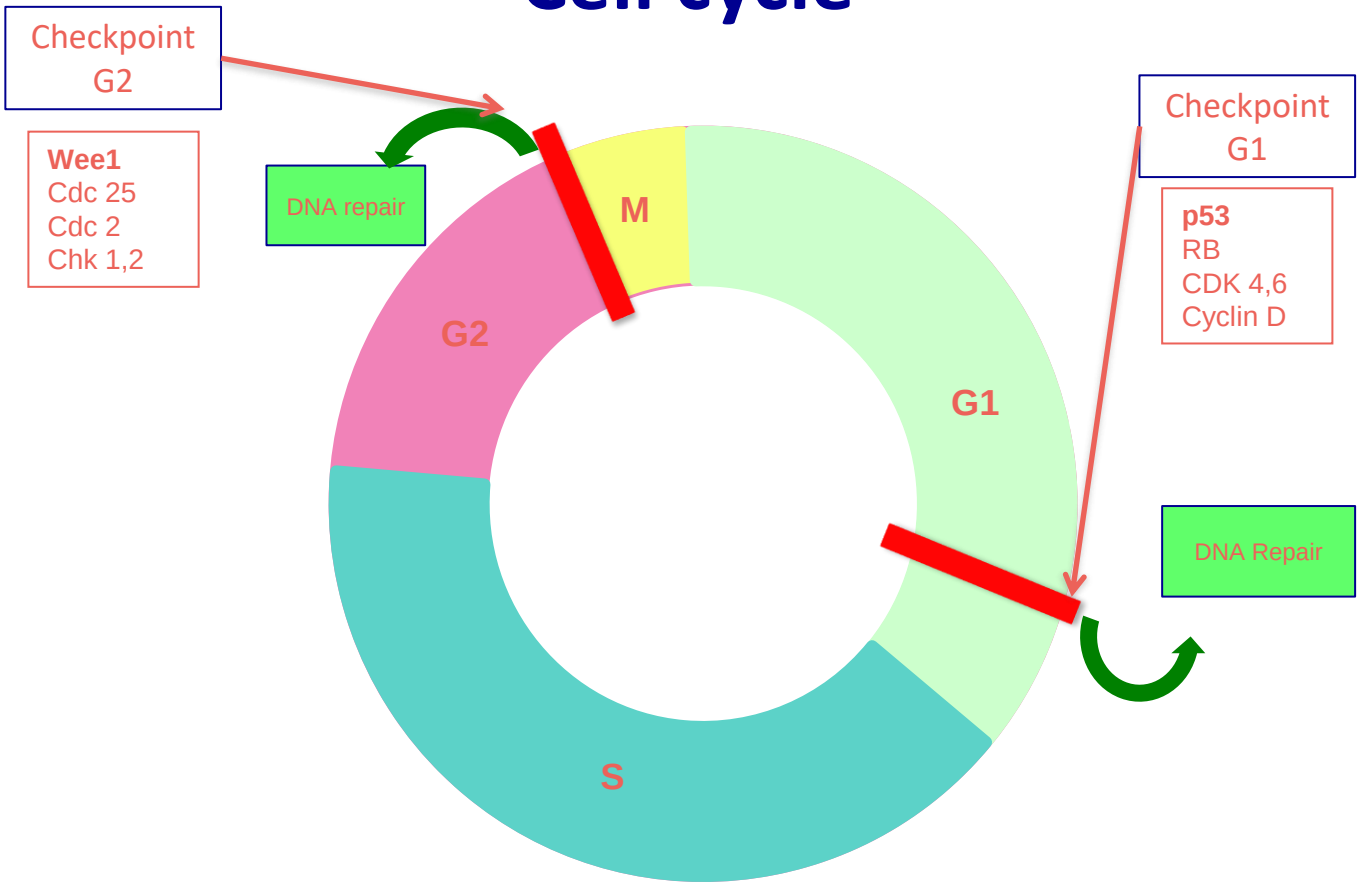
**Array**
**BRCA and RAD51c mutations reversion 19%**
**CCNE1 amplification 16%**
**ABCB1 upregulation 15%**
**SLFN11 downregulation 11%**



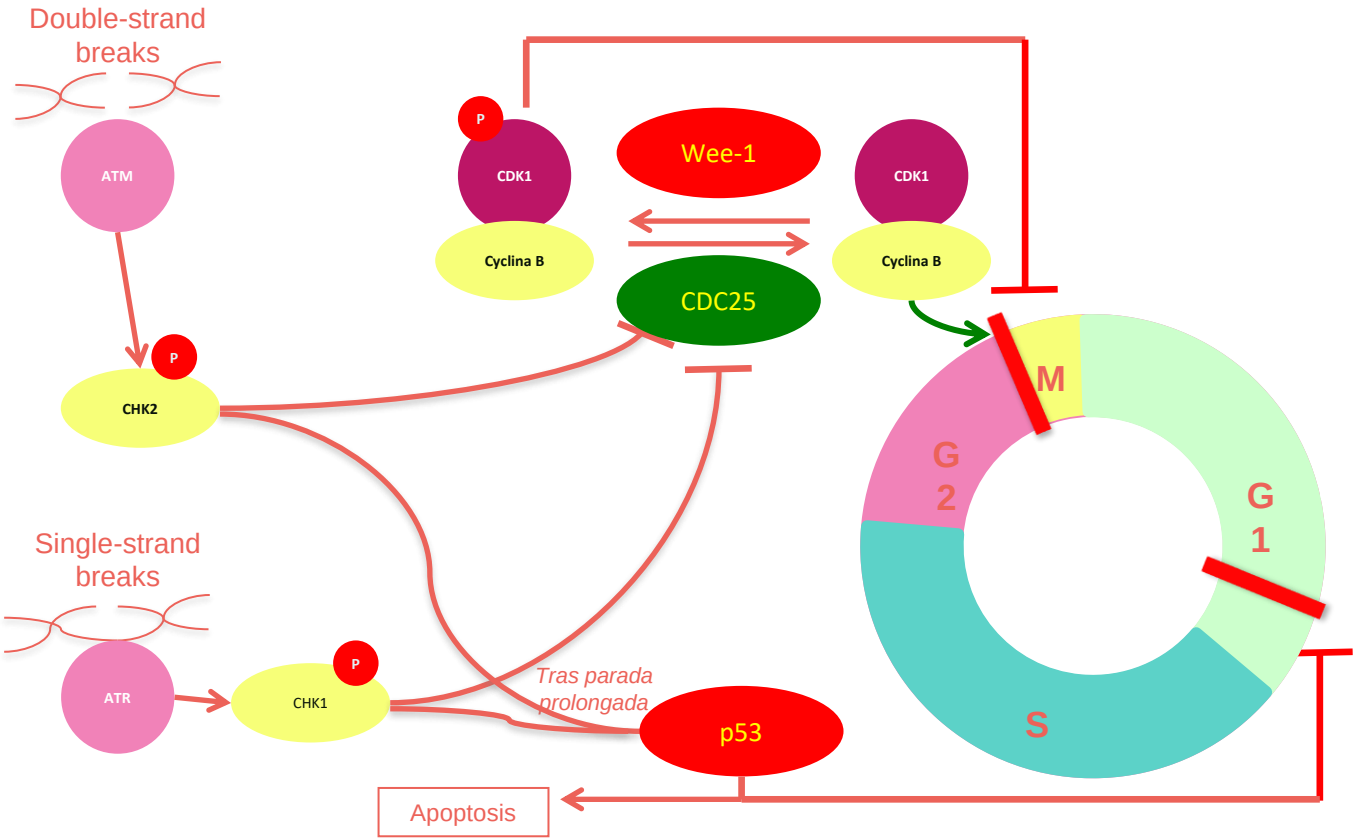

*Yap T et al. ASCO Educational Book 2019*

# DNA damage signalling

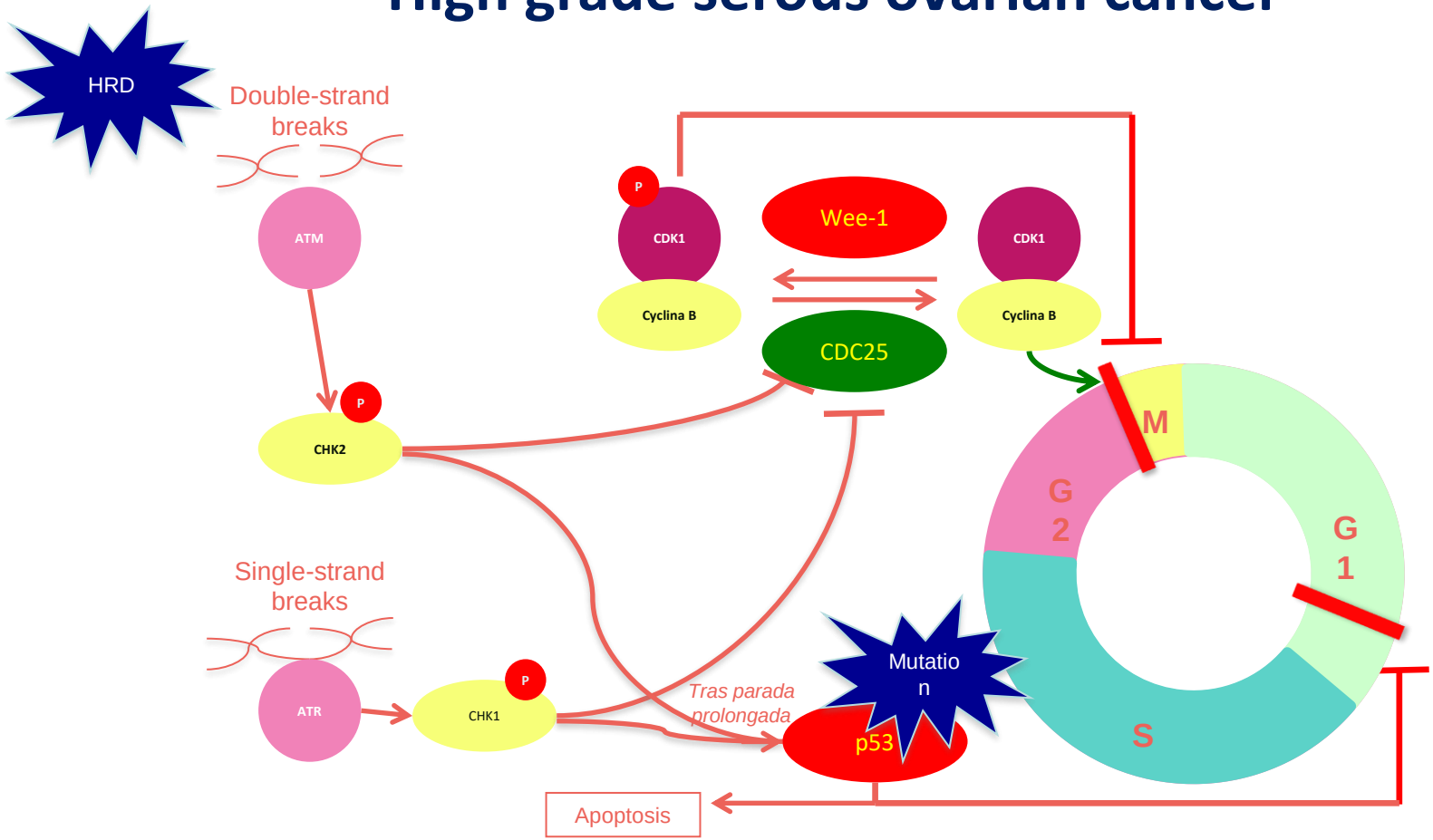
# Cell cycle


Checkpoint
G2
Wee1
Cdc 25
Cdc 2
Chk 1,2
DNA repair
M
G2
G1
S
Checkpoint
G1
p53
RB
CDK 4,6
Cyclin D
DNA Repair

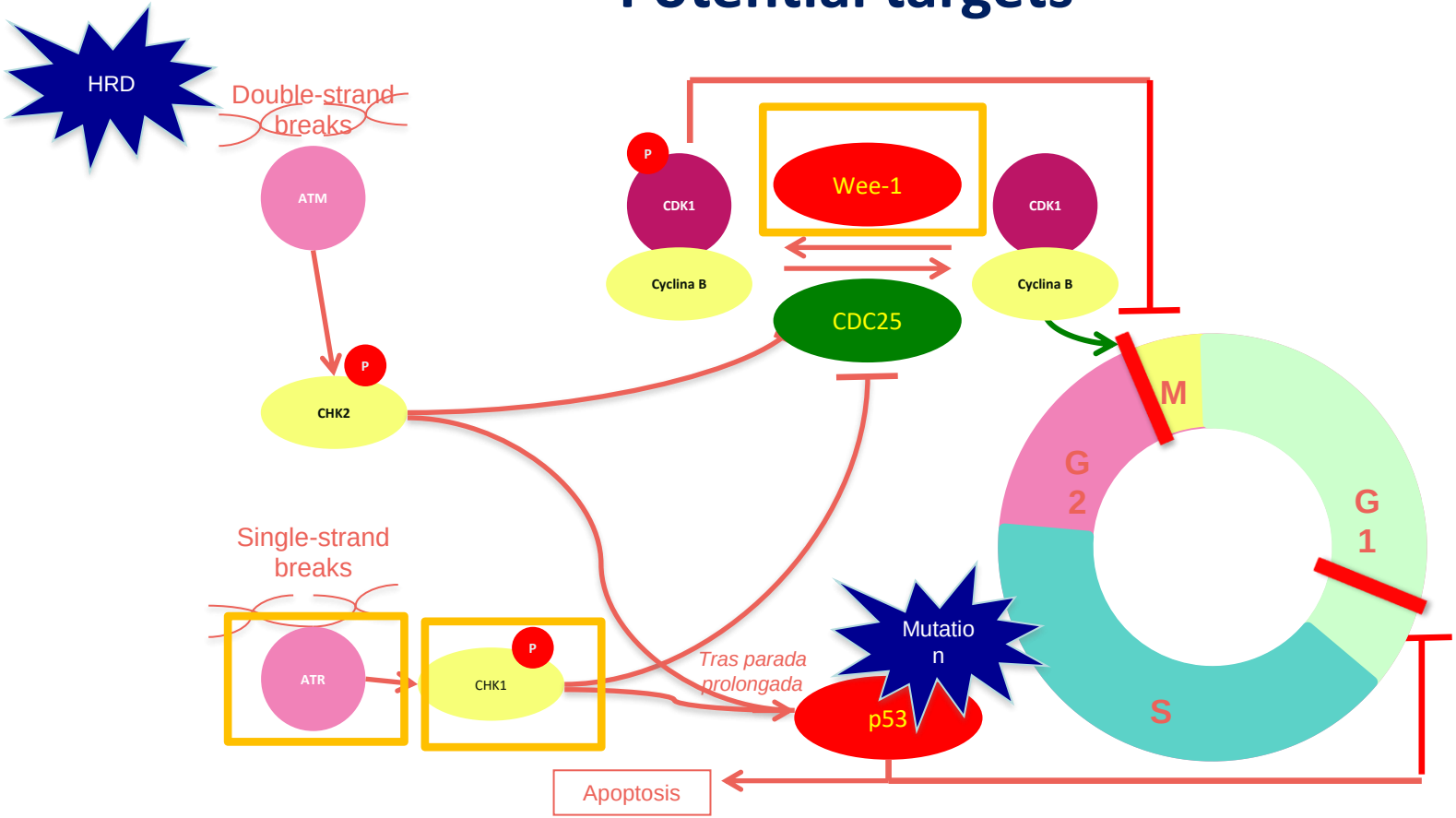
# Cell cycle and DNA repair system

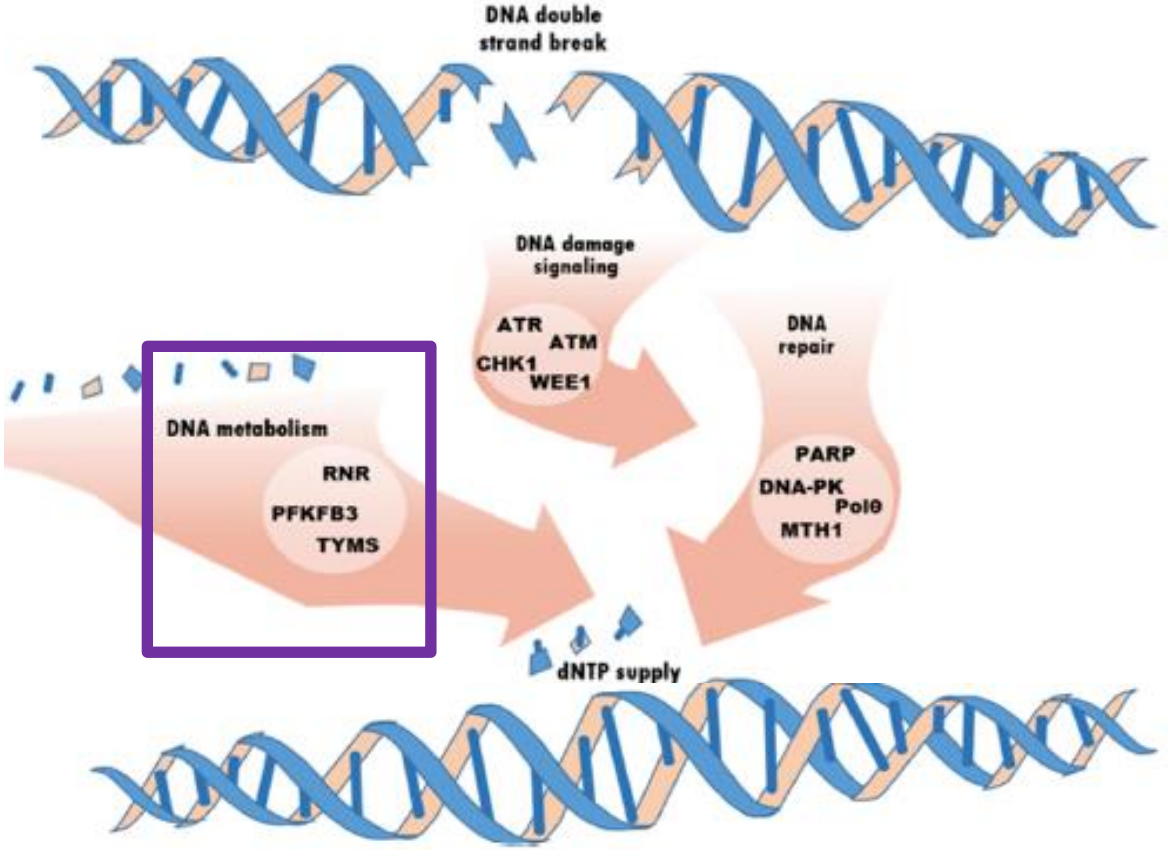


# High grade serous ovarian cancer



# Potential targets






*Yap T et al. ASCO Educational Book 2019*

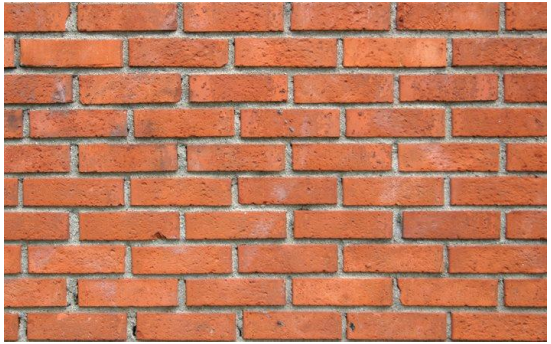
# dNTP
# deoxyriboNucleosideTriPhosphate

**dNTP**

**Nitrogenous Base (A, T, G, C)**

Deoxyribose sugar

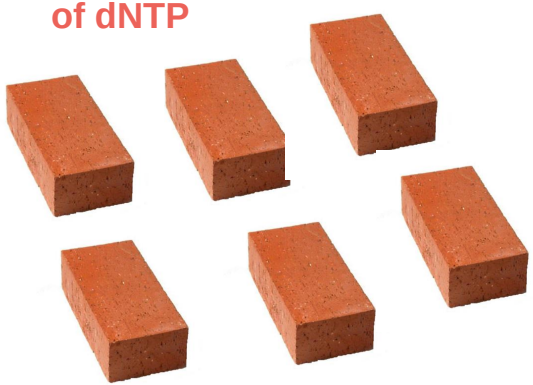
**dNTP**

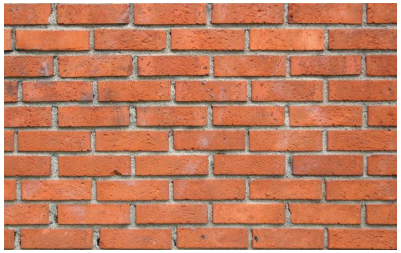


**DNA**

# dNTP pool

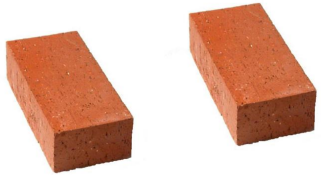
**Increased pool of dNTP**

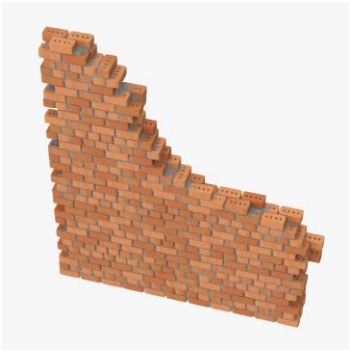




**DNA**

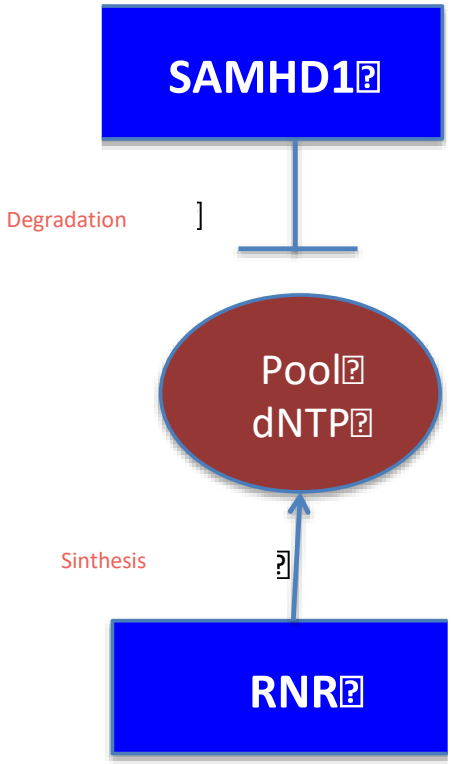
**Decreased pool of dNTP**





**DNA**

# dNTP pool balance




*RNR: Ribonucleotide Reductase*
*SAMHD1: Sterile Alpha Motive and HD domain protein 1*

# EVOLVE trial

Olaparib + Cediranib treatment

**Array**

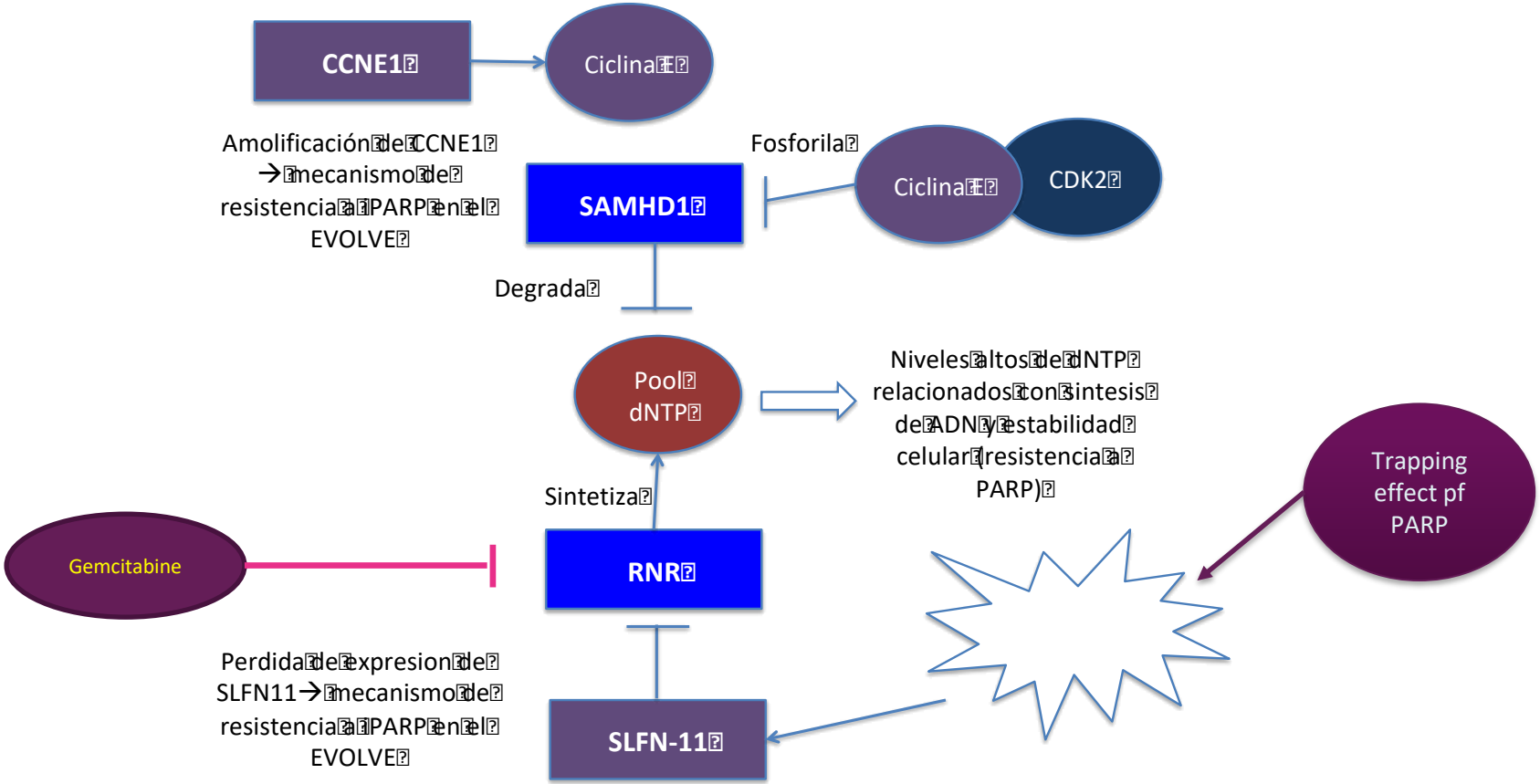
**Array**

BRCA and RAD51c mutations reversion 19%

**CCNE1 amplification 16%**

ABCB1 upregulation 15%

**SLFN11 downregulation 11%**

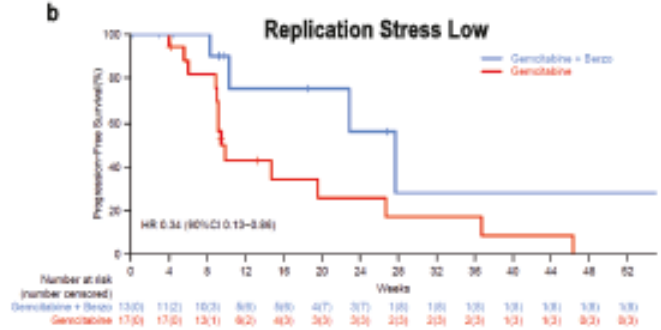

CCNE1
Ciclina E
Amolificación de CCNE1 → mecanismo de resistencia a PARP en el EVOLVE
Fosforila
SAMHD1
Ciclina E
CDK2
Degrada
Pool dNTP
Niveles altos de dNTP relacionados con síntesis de ADN y estabilidad celular (resistencia a PARP)
Sintetiza
Gemcitabine
RNR
Trapping effect pf PARP
Perdida de expresion de SLFN11 → mecanismo de resistencia a PARP en el EVOLVE
SLFN-11

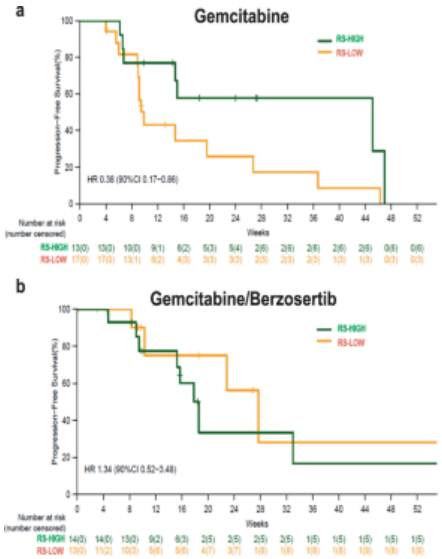
ARTICLE

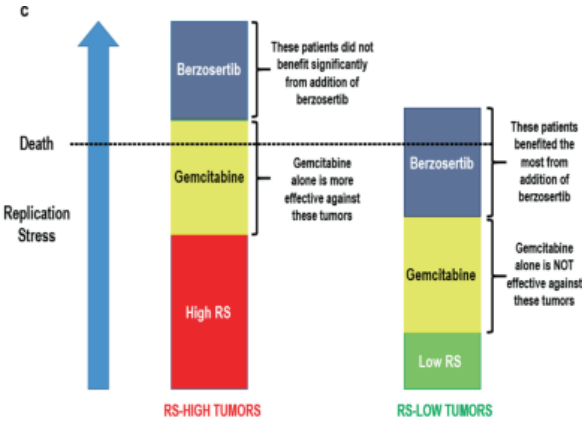
https://doi.org/10.1038/s41467-021-25904-w OPEN

# A Replication stress biomarker is associated with response to gemcitabine versus combined gemcitabine and ATR inhibitor therapy in ovarian cancer

Panagiotis A. Konstantinopoulos[1✉], Alexandre André B. A. da Costa[2,10], Doga Gulhan[3,10],



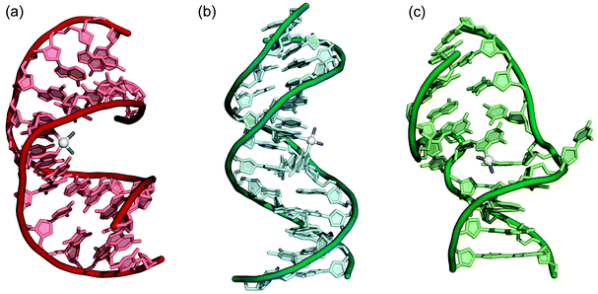



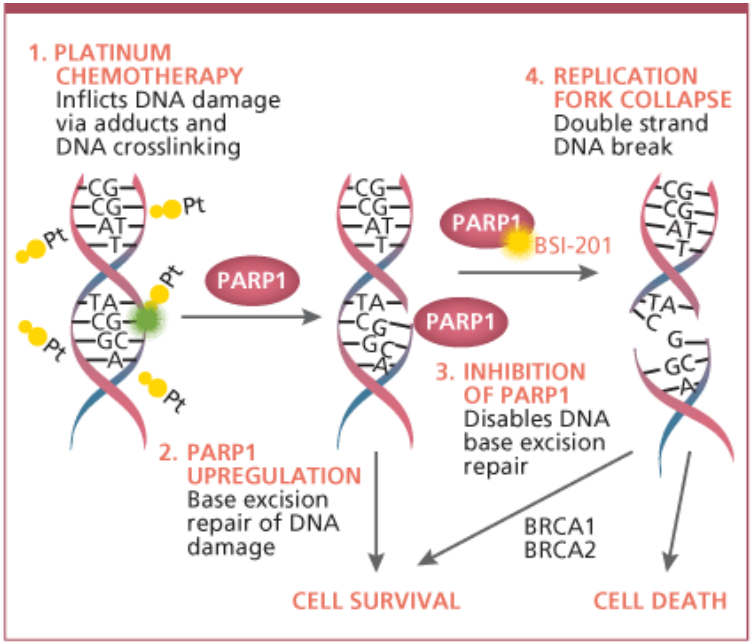
¿Existe una resistencia cruzada PARPi-platino?

# Carboplatin + PARPi

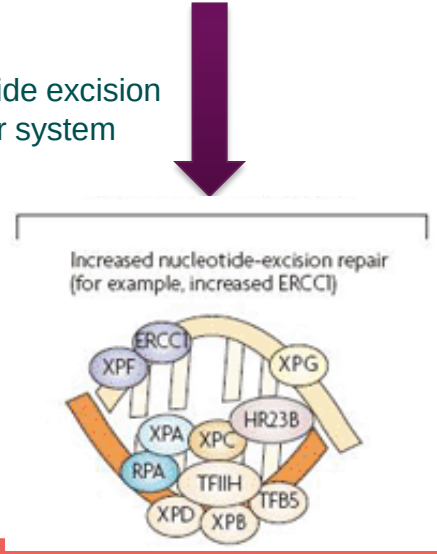
**Platinum DNA damage**




BER and Homologous recombination repair systems

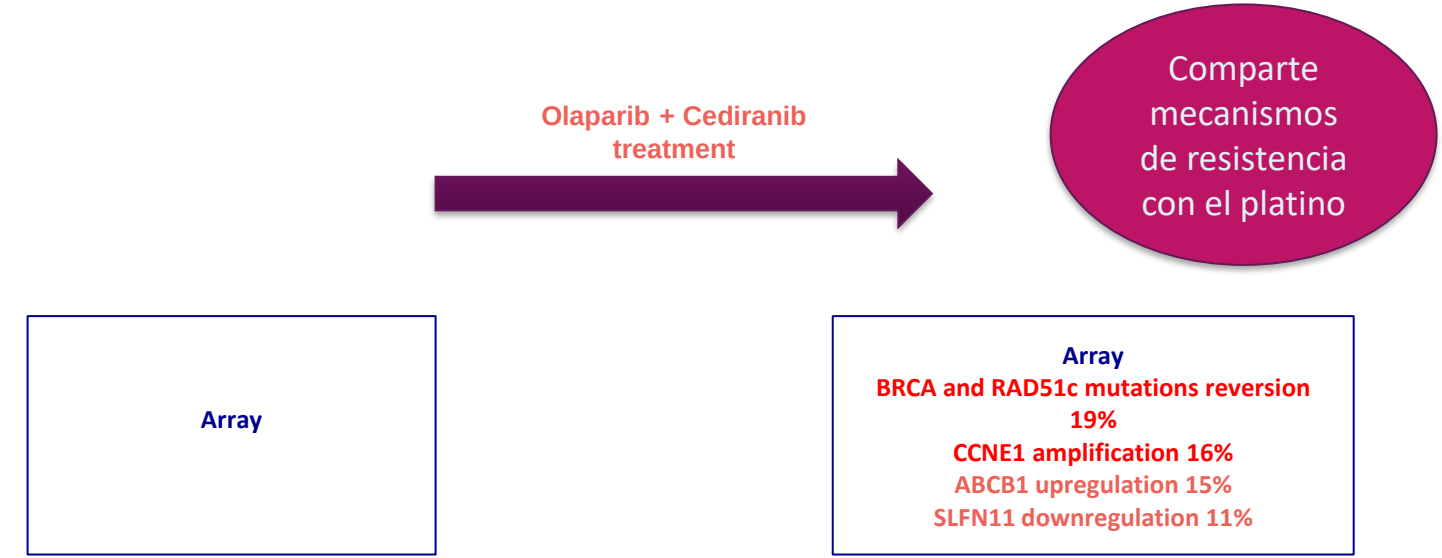



Nucleoside excision repair system




*Kelland LI Nat Rev Cancer 2007*
*Reedijk J Platinum Metals Rev 2008*
*O`Shaughnessy J et al. JCO 2009 (abstract 3)*

# EVOLVE trial



## ¿Existe una resistencia cruzada PARPi-platino?

| PARPi mechanism of resistance (EVOLVE) | Is a cross-resistant mechanism with Platinum? |
|---|---|
| HRD phenotype<br>- BRCA mutation reversion<br>- RAD51c reversion mutations | <br>Yes<br>yes |
| Multidrug resistance:<br>- ABCB upregulation | <br>No? |
| Cell-cycle regultaion:<br>- CCNE1 upregulation<br>- SLFN11 downregulation | <br>Yes<br>? |

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

# Efficacy of subsequent chemotherapy for patients with *BRCA1/2*-mutated recurrent epithelial ovarian cancer progressing on olaparib versus placebo maintenance: *post-hoc* analyses of the SOLO2/ENGOT Ov-21 trial

J. S. Frenel[1*], J. W. Kim[2], N. Aryal[3], R. Asher[3], D. Berton[1], L. Vidal[4], P. Pautier[5], J. A. Ledermann[6], R. T. Penson[7], A. M. Oza[8], J. Korach[9], T. Huzarski[10], S. Pignata[11], N. Colombo[12], T. W. Park-Simon[13], K. Tamura[14], G. S. Sonke[15], A. E. Freimund[16], C. K. Lee[3] & E. Pujade-Lauraine[17]

**Table 1.** Characteristics of patients who received chemotherapy as subsequent therapy regimen, with comparison between olaparib- and placebo-treated patients

| Characteristics | Overall population ($N = 147$) | | | Platinum-based cohort ($N = 96$) | | | Non-platinum-based cohort ($N = 51$) | | | SOLO2 population ($N = 295$) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Olaparib $n = 78$ | Placebo $n = 69$ | *P* value | Olaparib $n = 54$ | Placebo $n = 42$ | *P* value | Olaparib $n = 24$ | Placebo $n = 27$ | *P* value | Olaparib $n = 196$ | Placebo $n = 99$ |
| **Mean (SD) age, years** | 57 (40-83) | 56 (39-75) | 0.41 | 57 (40-83) | 57 (40-75) | 0.58 | 56 (45-68) | 55 (39-70) | 0.65 | 56 (51-63) | 56 (49-63) |
| **ECOG, *n* (%)** | | | | | | | | | | | |
| Normal activity | 62 (81) | 54 (78) | 0.61 | 46 (87) | 31 (74) | 0.11 | 16 (67) | 23 (85) | 0.12 | 162 (84) | 77 (78) |
| Restricted activity | 15 (19) | 15 (22) | | 7 (13) | 11 (26) | | 8 (33) | 4 (15) | | 32 (16) | 22 (22) |
| Missing | 1 | | | 1 | | | | | | 2 | 0 |
| **Primary tumor location, *n* (%)** | | | | | | | | | | | |
| Ovary | 65 (83) | 59 (86) | 0.86 | 45 (83) | 36 (86) | 0.67 | 20 (83) | 23 (85) | 0.55 | 164 (84) | 86 (87) |
| Fallopian | 5 (6) | 3 (4) | | 5 (9) | 2 (5) | | 0 (0) | 1 (4) | | 13 (7) | 4 (4) |
| Other | 8 (10) | 7 (10) | | 4 (7) | 4 (10) | | 4 (17) | 3 (11) | | 19(9) | 9 (9) |
| **Histology, *n* (%)** | | | | | | | | | | | |
| Serous | 75 (96) | 63 (91) | 0.37 | 53 (98) | 38 (90) | 0.22 | 22 (92) | 25 (93) | 0.90 | 183 (93) | 86 (87) |
| Endometrioid | 3 (4) | 5 (7) | | 1 (2) | 3 (7) | | 2 (8) | 2 (7) | | 9 (5) | 8 (8) |
| Others | 0 (0) | 1 (1) | | 0 (0) | 1 (2) | | 0 (0) | 0 (0) | | 4 (2) | 5 (5) |
| **Myriad *BRCA* status, *n* (%)** | | | | | | | | | | | |
| *BRCA1* | 53 (71) | 43 (63) | 0.43 | 36 (69) | 24 (59) | 0.28 | 17 (74) | 19 (70) | 0.78 | 132 (69) | 61 (64) |
| *BRCA2* | 22 (29) | 25 (37) | | 16 (31) | 17 (41) | | 6 (26) | 8 (30) | | 58 (31) | 35 (36) |
| Missing | 3 | 1 | | 2 | 1 | | 1 | 126 | | 6 | 3 |
| **Previous platinum-free interval, *n* (%)** | | | | | | | | | | | |
| 6-12 months | 40 (51) | 33 (48) | 0.68 | 28 (52) | 20 (48) | 0.68 | 12 (50) | 14 (52) | 0.89 | 79 (40) | 40 (40) |
| >12 months | 38 (49) | 36 (52) | | 26 (48) | 22 (52) | | 12(50) | 13 (48) | | 117 (60) | 59 (60) |
| **Previous platinum-based regimen, *n* (%)** | | | | | | | | | | | |
| 2 | 41 (53) | 37 (54) | 0.15 | 30 (56) | 23 (55) | 0.49 | 11 (46) | 14 (52) | 0.25 | 110 (56) | 62 (63) |
| 3 | 28 (36) | 17 (25) | | 18 (33) | 11 (26) | | 10 (42) | 6 (22) | | 60 (31) | 20 (20) |
| >3 | 9 (12) | 15 (22) | | 6 (11) | 8 (19) | | 3 (13) | 7 (26) | | 25 (13) | 17 (17) |
| **Disease status at inclusion in the SOLO2 trial, *n* (%)** | | | | | | | | | | | |
| Partial response | 60 (77) | 41 (59) | **0.02** | 40 (74) | 23 (55) | **0.05** | 20 (83) | 18 (67) | 0.17 | 91 (46) | 47 (47) |
| Complete response | 18 (23) | 28 (41) | | 14 (26) | 19 (45) | | 4 (17) | 9 (33) | | 105 (54) | 52 (53) |
| **Prior use of bevacizumab, *n* (%)** | | | | | | | | | | | |
| Yes | 14 (18) | 18 (26) | 0.23 | 12 (22) | 14 (33) | 0.22 | 2 (8) | 4 (15) | 0.47 | 33 (17) | 20 (20) |
| No | 64 (82) | 51 (74) | | 42 (88) | 28 (77) | | 22 (92) | 23 (85) | | 163 (83) | 79 (80) |

Bold values are statistically significant.
ECOG, Eastern Cooperative Oncology Group; SD, standard deviation.

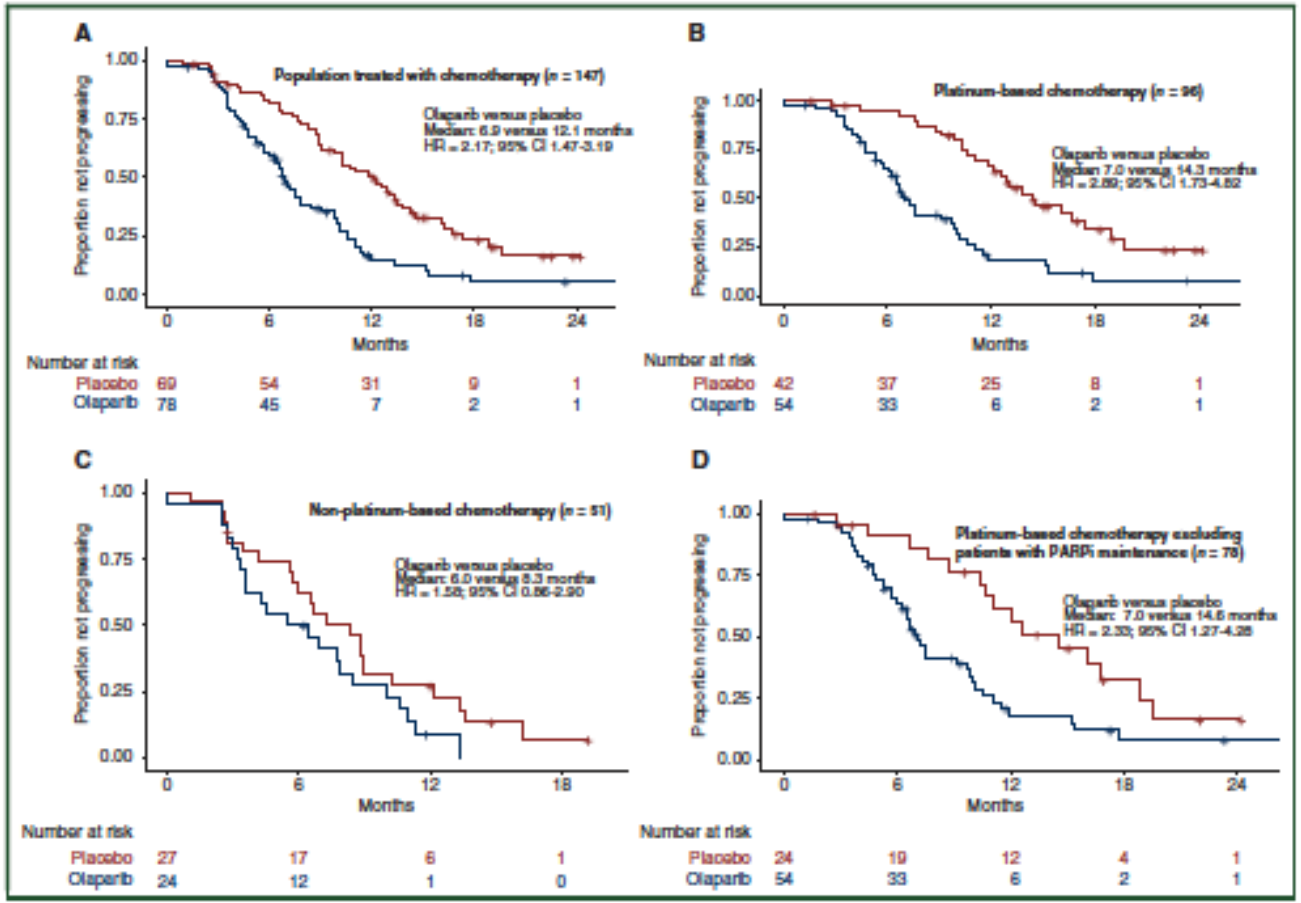



**Figure 2. Time to second progression according to subsequent therapy type.** CI, confidence interval; HR, hazard ratio; PARPi, poly (ADP-ribose) polymerase inhibitor.

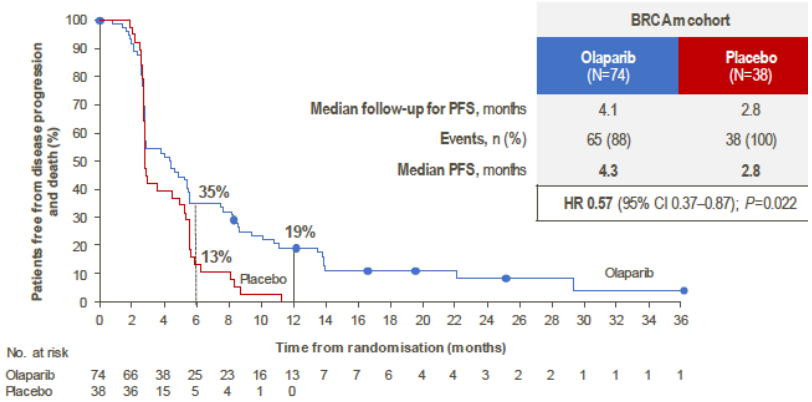
# Maintenance olaparib rechallenge in patients with ovarian carcinoma previously treated with a PARP inhibitor: Phase IIIb OReO/ENGOT Ov-38 trial

# Resistencia cruzada Platino-iPARP en BRCAwt?

Eric Pujade-Lauraine,[1] Frédéric Selle,[2] Giovanni Scambia,[3] Bernard Asselain,[4] Frederik Marmé,[5] Kristina Lindemann,[6] Nicoletta Colombo,[7] Radoslaw Madry,[8] Rosalind Glasspool,[9] Coraline Dubot,[10] Ana Oaknin,[11] Claudio Zamagni,[12] Florian Heitz,[13] Laurence Gladieff,[14] Maria Jesús Rubio-Pérez,[15] Paolo Scollo,[16] Christopher Blakeley,[17] Bob Shaw,[17] Isabelle Ray-Coquard,[18] Andrés Redondo[19]

## A statistically significant PFS benefit was observed with olaparib in the BRCAm cohort

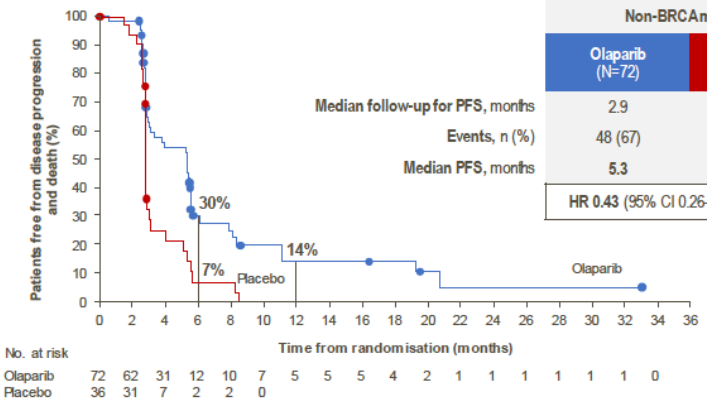
A proportion of patients derived clinically relevant long-term benefit




| BRCAm cohort | Olaparib (N=74) | Placebo (N=38) |
|---|---|---|
| Median follow-up for PFS, months | 4.1 | 2.8 |
| Events, n (%) | 65 (88) | 38 (100) |
| Median PFS, months | 4.3 | 2.8 |
| **HR 0.57** (95% CI 0.37–0.87); *P*=0.022 | | |

## A statistically significant PFS benefit was observed with olaparib in the non-BRCAm cohort

A proportion of patients derived clinically relevant long-term benefit




| Non-BRCAm cohort | Olaparib (N=72) | Placebo (N=36) |
|---|---|---|
| Median follow-up for PFS, months | 2.9 | 2.8 |
| Events, n (%) | 48 (67) | 30 (83) |
| Median PFS, months | 5.3 | 2.8 |
| **HR 0.43** (95% CI 0.26–0.71); *P*=0.0023 | | |

## ¿Qué podemos hacer tras progresión platinosensible a PARPi?

| ¿Evitar reintroducción de platinos? | ¿Reintroducir platino? |
|---|---|
| Trabectedina-DLP | Reintroducir platino y luego reintroducir iPARP (OREO) |
| Nuevas drogas?:<br>- Mirvetuximab<br>- Otros | Reintroducir platino y asociar Bevacizumab (Carbo-Caelyx-Bev o Carbo-Gem-Beva) |
| Si oligometastatica: citorreduccion secundaria y mantener mismo iPARP??? | Citorreducción secundaria → platino + una de las dos anteriores |