Inibidores da PARP em Câncer de Mama

João Nunes - MD,PhD
Oncologia e Mastologia

- Dano no DNA de uma célula humana
    - Fenômeno fisiológico

- 1.000.000 lesões moleculares por dia

Lodish H, Berk A, Matsudaira P, Kaiser CA, Krieger M, Scott MP, Zipursky SL, Darnell J. (2004). Molecular Biology of the Cell, p963. WH Freeman: New York, NY. 5th ed.

Fontes de danos

Os danos no DNA podem ser divididos em dois tipos principais:

1. Danos endógenos

2. Danos exógenos

- Dano Endógeno Metabólico
  - espécies reativas de oxigênio,
  - espécies reativas de nitrogênio
  - espécies reativas de carbonila,
  - produtos de peroxidação lipídica
  - agentes alquilantes,

Deaminação por Espécies Reativas de Oxigênio

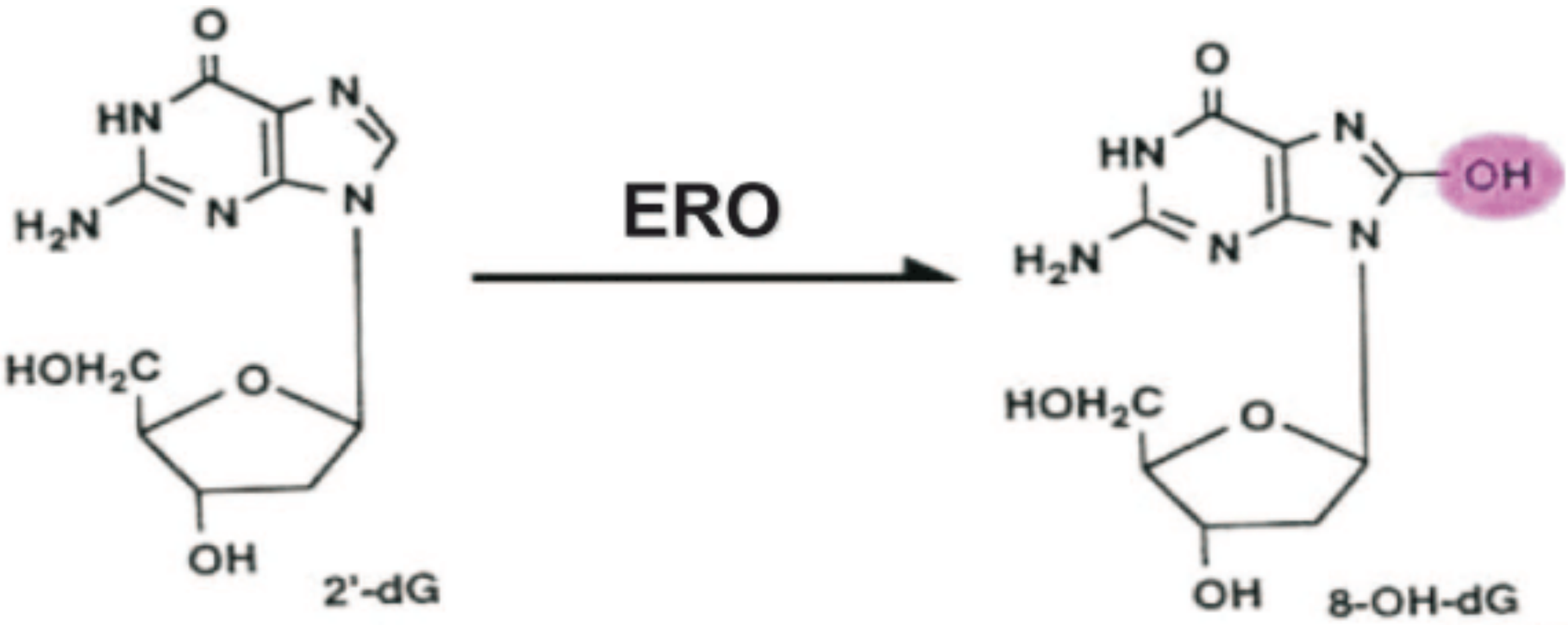
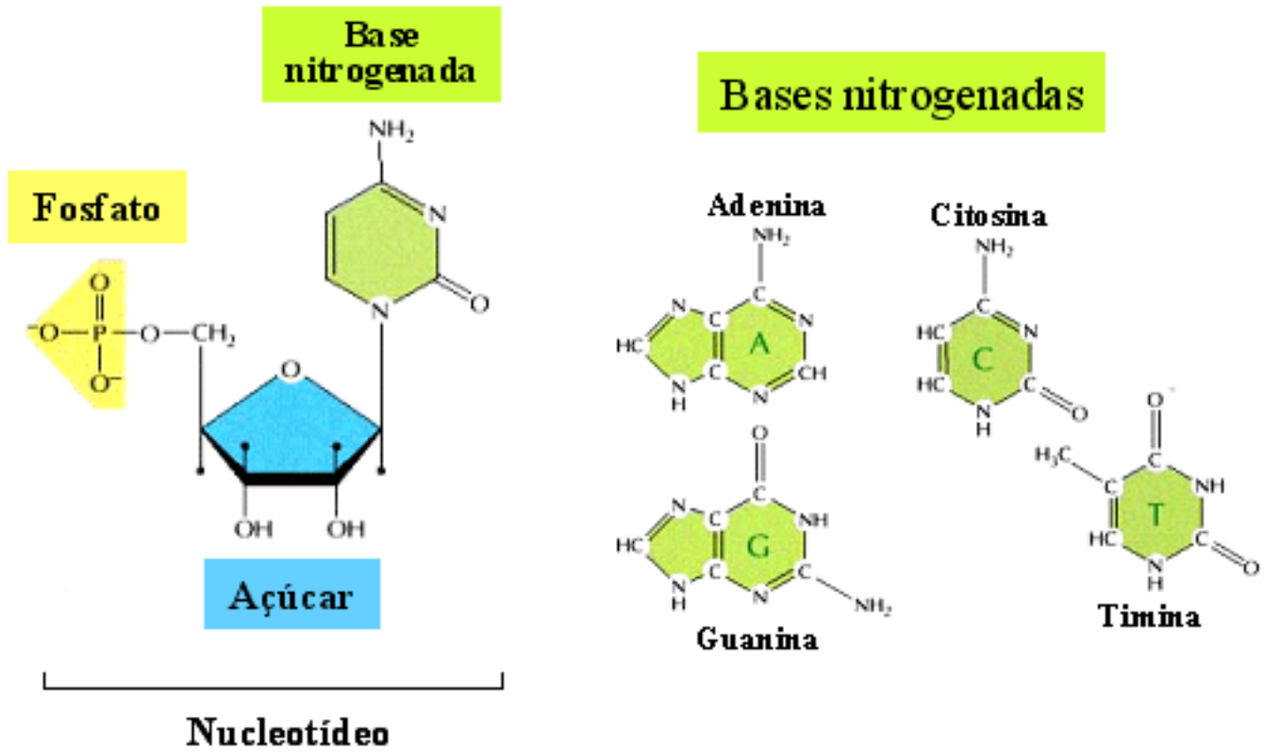
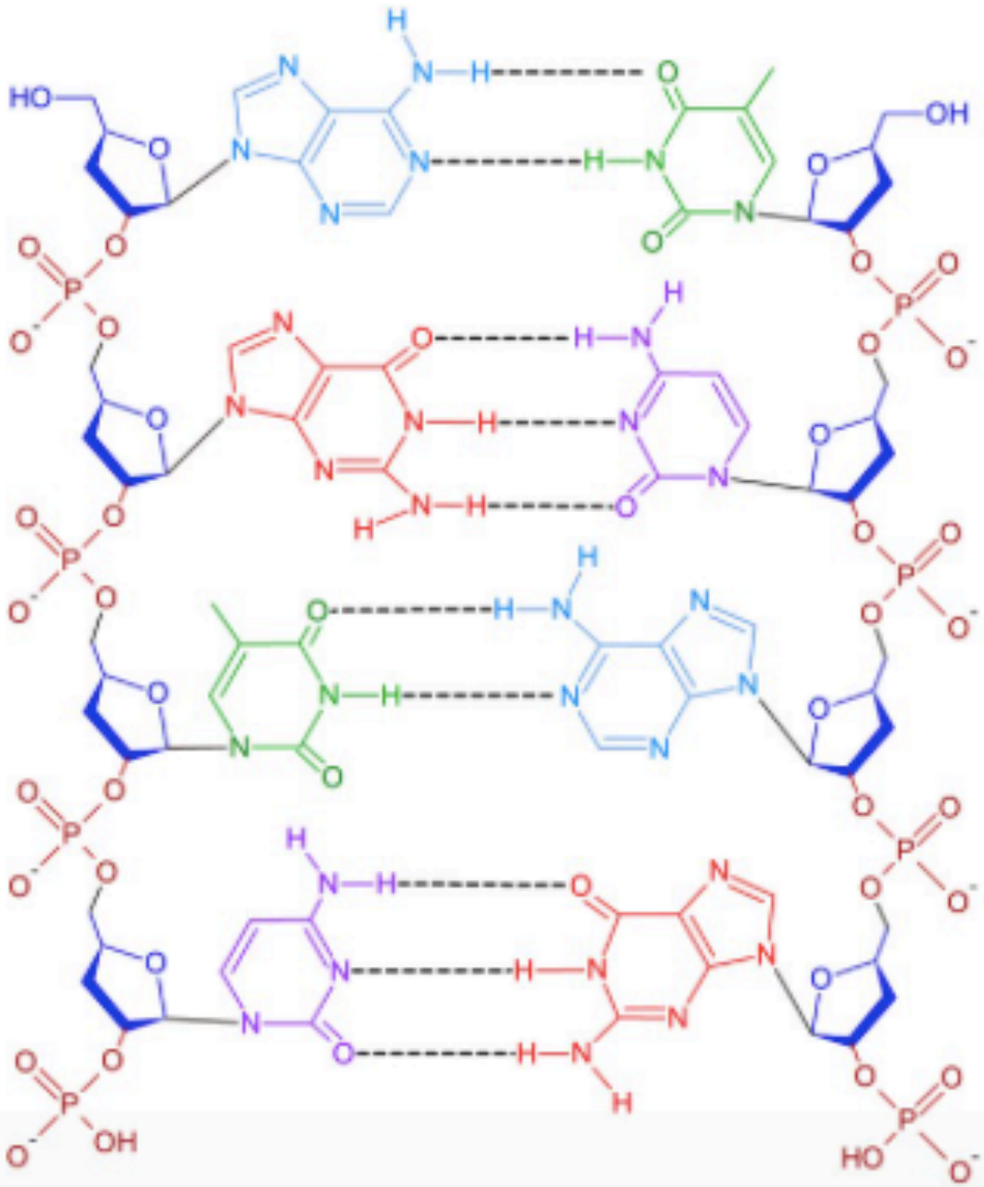
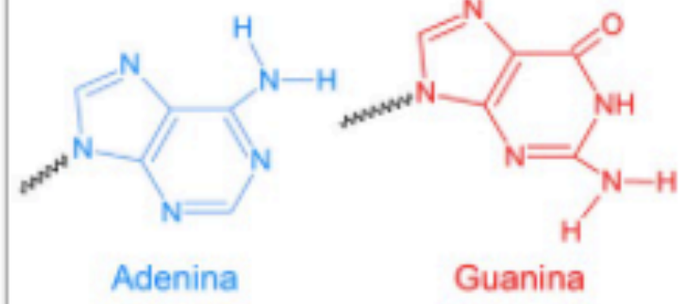


Figura 4 *- Formação de 8OHdG pelas espécies livres de oxigênio a partir da guanina (2'-dG).*

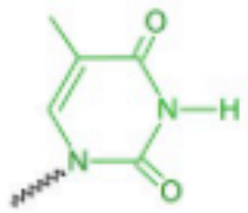

Base nitrogenada
Fosfato
Açúcar
Nucleotídeo
Bases nitrogenadas
Adenina
Citosina
Guanina
Timina



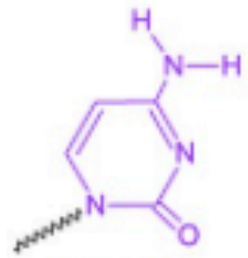


Adenina

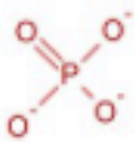
Guanina



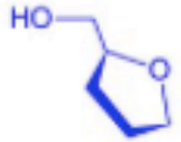
Timina



Citosina

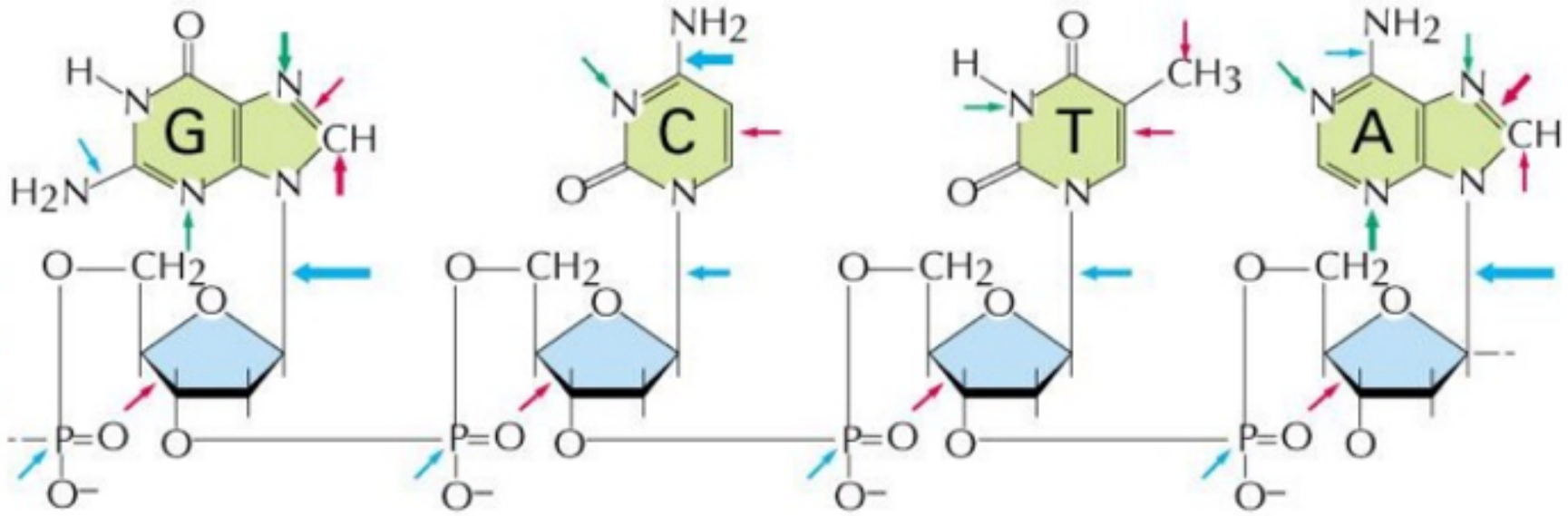


Fosfato



Desoxirribose

Alteração de bases:
Danos por oxidação
hidrólise
metilação



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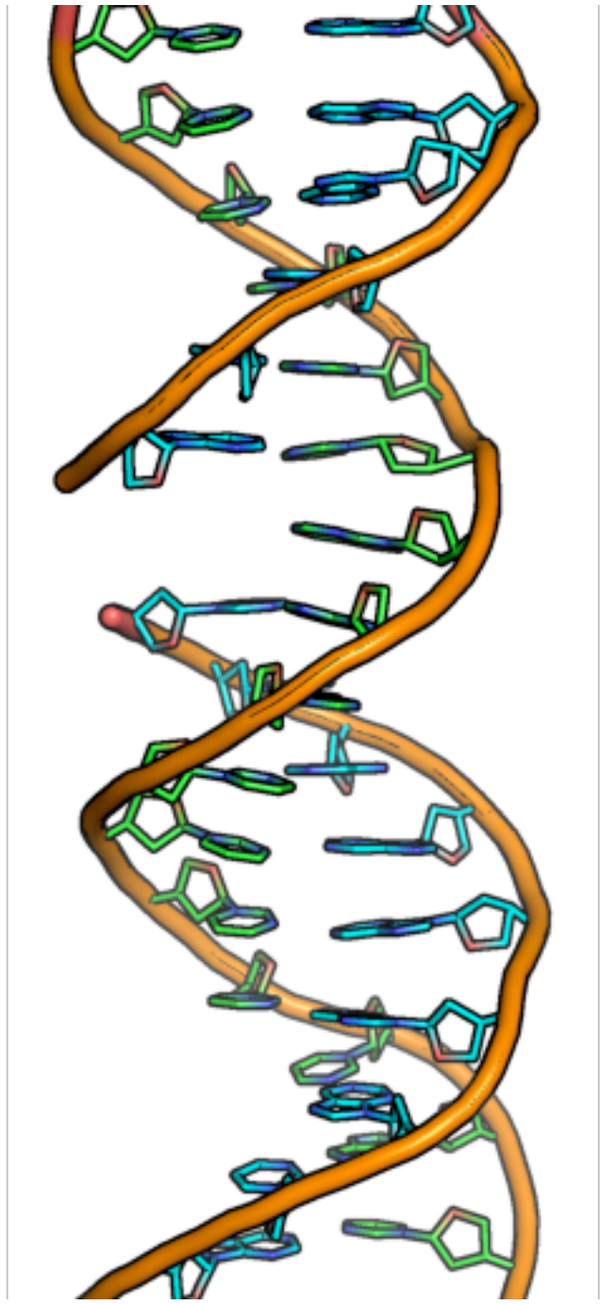

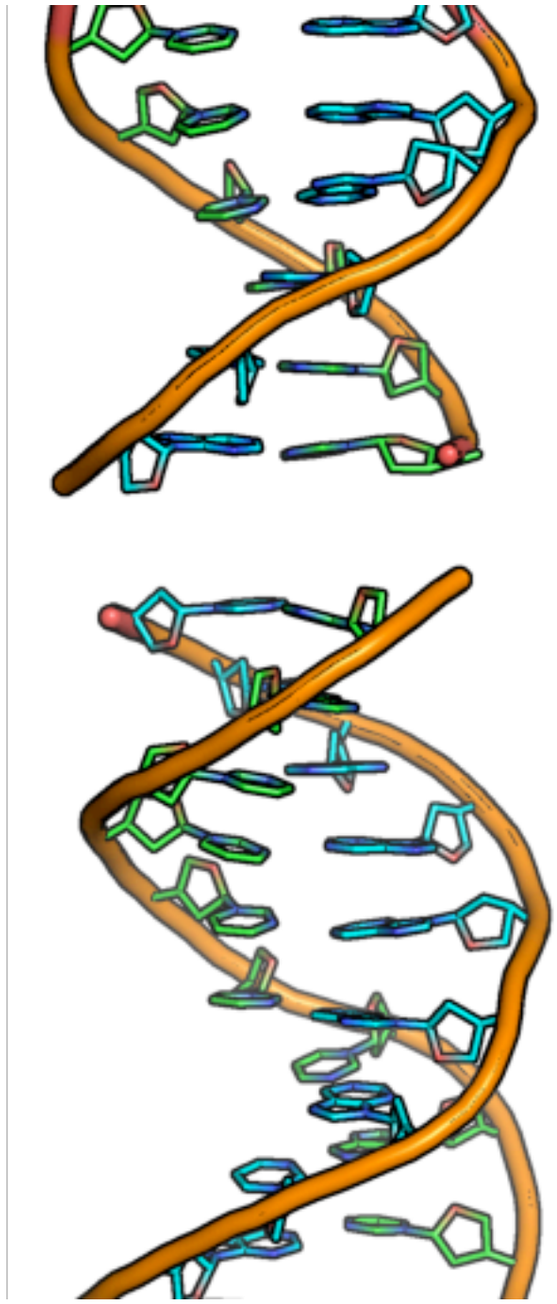

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- Dano é um fato comum, porém câncer é uma fato incomum... Por que?

Mecanimos de Reparo de DNA

Tomas Lindahl

Conhecido(a) por	Pesquisas sobre o câncer
Nascimento	28 de janeiro de 1938 (80 anos) Estocolmo
Nacionalidade	Sueco Britânico (naturalizado)
Alma mater	Instituto Karolinska, Universidade de Princeton, Universidade Rockefeller
Influenciados	**Lista** [Expandir]
Prêmios	Medalha Real (2007), Medalha Copley (2010), Nobel de Química (2015)
Instituições	London Research Institute
Campo(s)	Pesquisas sobre o câncer

Paul Modrich

Nascimento	13 de junho de 1946 (72 anos) Raton, Novo México
Nacionalidade	norte-americano
Alma mater	Instituto de Tecnologia de Massachusetts, Universidade Stanford
Prêmios	Prêmio Pfizer de Química de Enzimas (1983), Prêmio Charles S. Mott (1996), Nobel de Química (2015)
Campo(s)	Bioquímica, genética

Aziz Sancar

Nascimento	8 de setembro de 1946 (71 anos) Savur
Alma mater	Universidade de Istambul
Prêmios	Prêmio Presidencial Jovem Investigador (1984), Nobel de Química (2015)
Instituições	Universidade da Carolina do Norte em Chapel Hill

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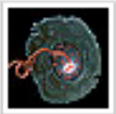
Updates

- New post in Green Science: I leave and heave a sigh and say goodbye
- New post in Saltwater Science: Thanks for the good times!
- New topic in Women in Science: Where to find Laura Hoopes' Women in Science future thoughts?
- New post in Saltwater Science: Microplastic in the

INTERMEDIATE

NUCLEIC ACID STRUCTURE AND FUNCTION | Lead Editor: Bob Moss



DNA Damage & Repair: Mechanisms for Maintaining DNA Integrity

By: Suzanne Clancy, Ph.D.

Citation: Clancy, S. (2008) DNA damage & repair: mechanisms for maintaining DNA integrity. *Nature Education* 1(1):103

DNA integrity is always under attack from environmental agents like skin cancer–causing UV rays. How do DNA repair mechanisms detect and repair damaged DNA, and what happens when they fail?

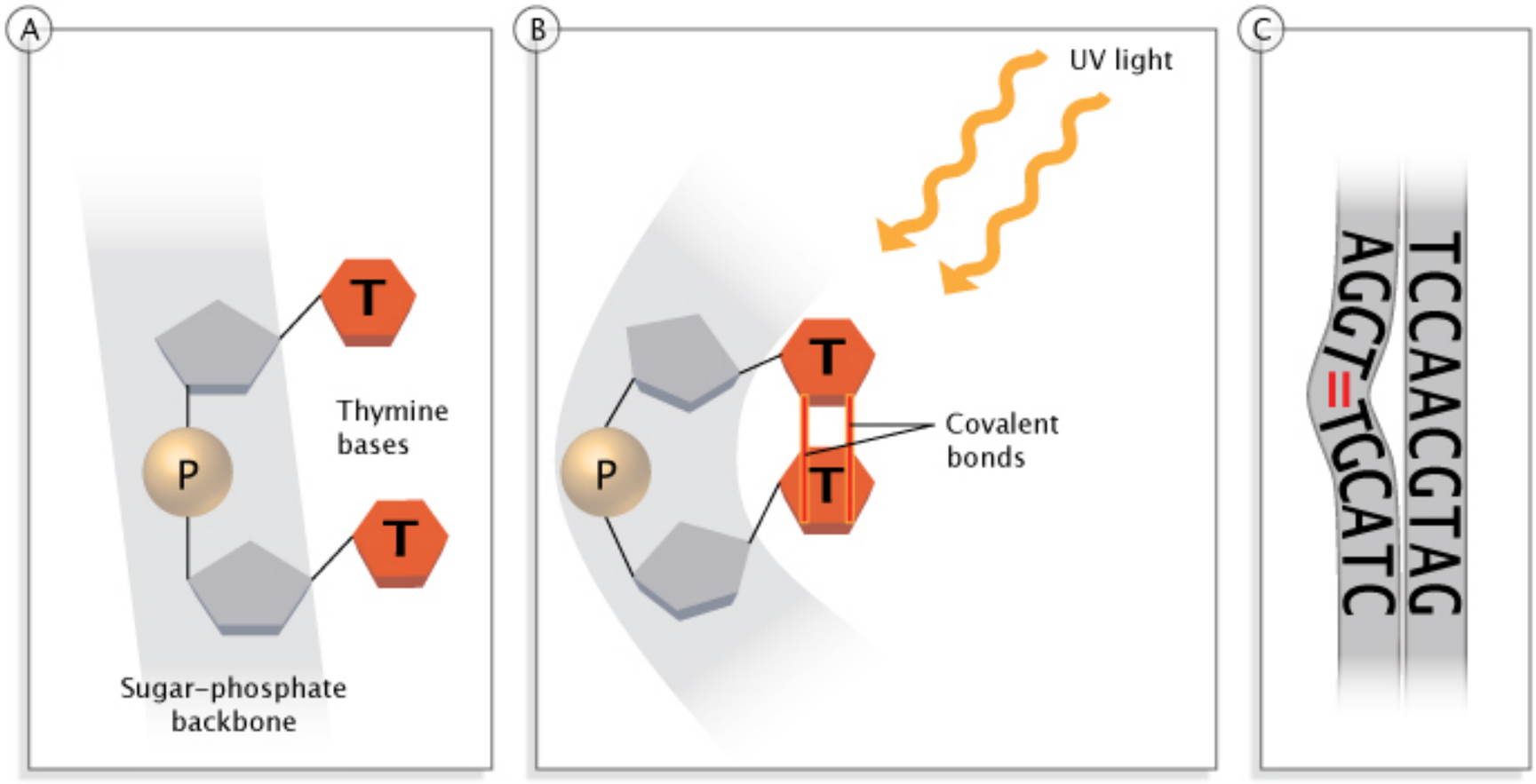
Aa Aa Aa

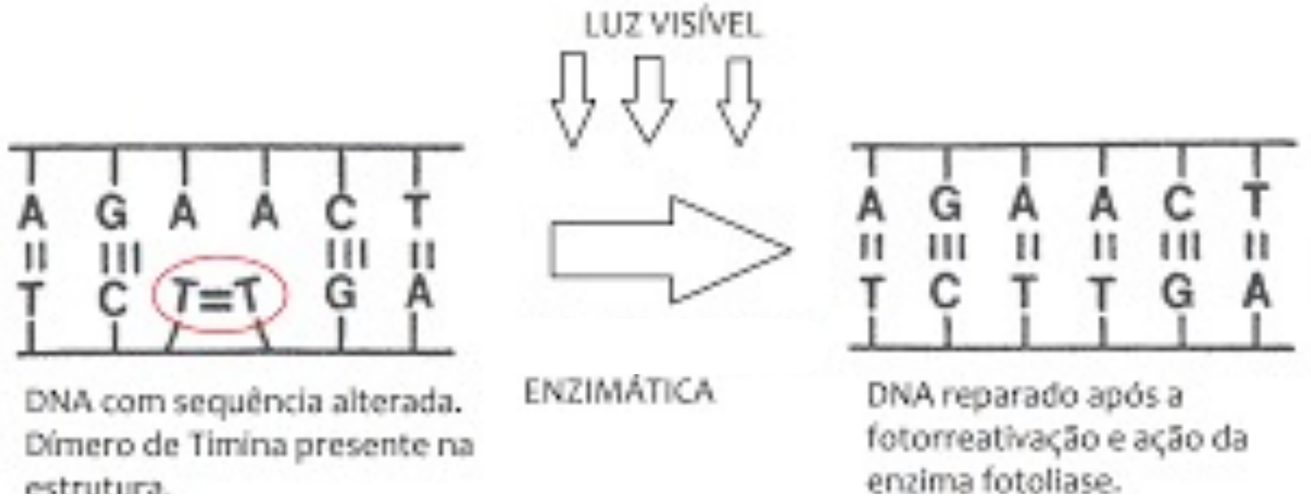
1a Forma de Reparo : reparo bioquímico

- Cells are known to eliminate types of damage to their DNA by ***chemically reversing*** it.

- These mechanisms do not require a template, since the types of damage they counteract can occur in ***only one of the four bases.***

- Such direct reversal mechanisms are specific to the type of damage incurred and do ***not involve breakage of the phosphodiester backbone.***





DNA com sequência alterada. Dímero de Timina presente na estrutura.

DNA reparado após a fotorreativação e ação da enzima fotoliase.

Single-strand damage

- When ***only one of the two strands of a double helix has a defect***, the other strand can be used as a template to guide the correction of the damaged strand.

- In order to repair damage to one of the two paired molecules of DNA, there exist a number of excision repair mechanisms that remove the damaged nucleotide and replace it with an **undamaged nucleotide complementary to that found in the undamaged DNA strand**

Watson JD, Baker TA, Bell SP, Gann A, Levine M, Losick R (2004). Molecular Biology of the Gene (5th ed.). Pearson Benjamin Cummings; CSHL Press. Ch. 9, 10. OCLC 936762772.

Single-strand damage

Three-step process which consists of:

. recognition of damage

. excision of damaged DNA both upstream and downstream of damage by endonucleases

. resynthesis of removed DNA region.

Reardon, J; Sancar, A (2006). "Purification and Characterization of Escherichia coli and Human Nucleotide Excision Repair Enzyme Systems". Methods in Enzymology. 408: 189–213. doi: 10.1016/S0076-6879(06)08012-8. PMID 16793370.

Single-strand damage

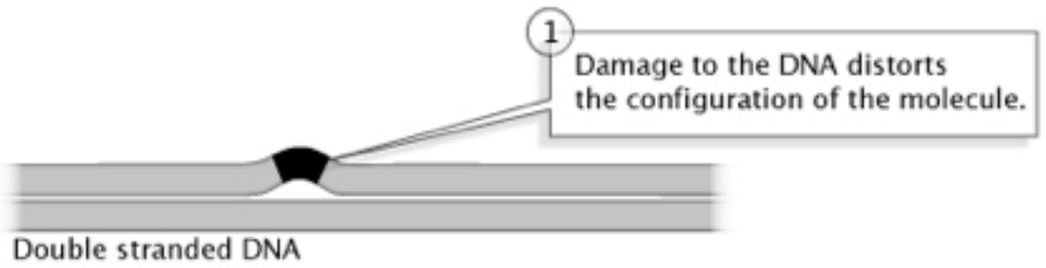
- ***Base excision repair (BER)*** repairs damage to a single nitrogenous base by deploying enzymes called glycosylases.

- Nucleotide excision repair (NER) repairs damaged DNA which commonly consists of bulky, helix-distorting damage.

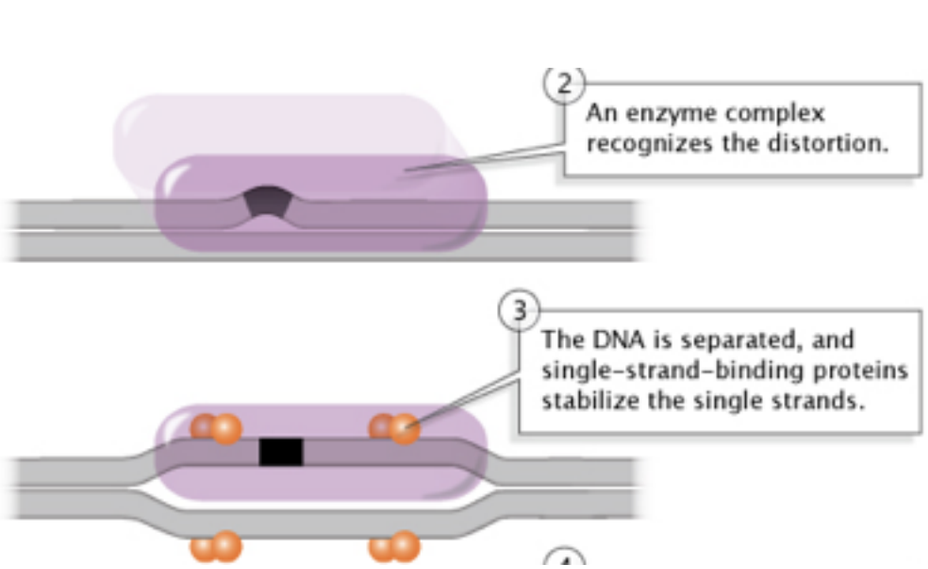
Damaged regions are removed in ***12–24*** nucleotide-long strands

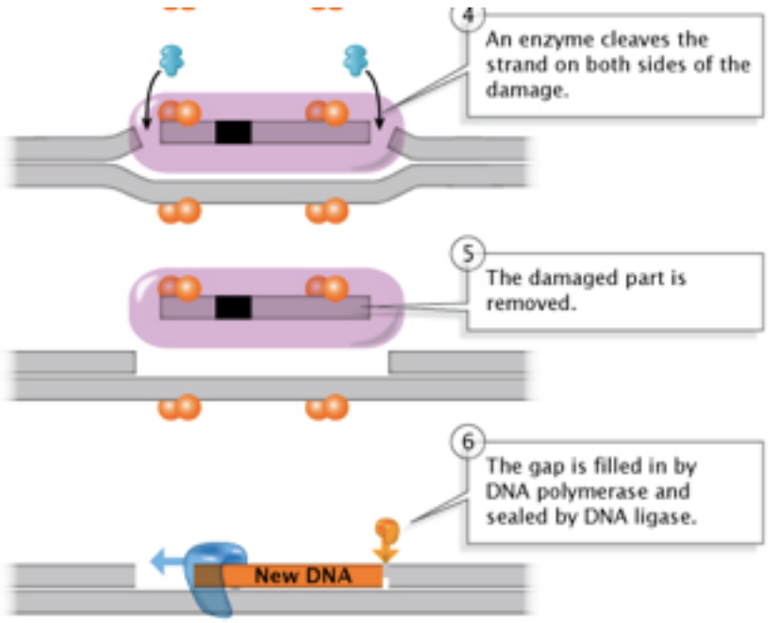
Willey, J; Sherwood, L; Woolverton, C (2014). Prescott's Microbiology. New York, New York: McGraw Hill. p. 381. ISBN 978-0-07-3402-40-6.

- **Damage to DNA alters the *spatial configuration* of the helix, and such alterations can be detected by the cell.**

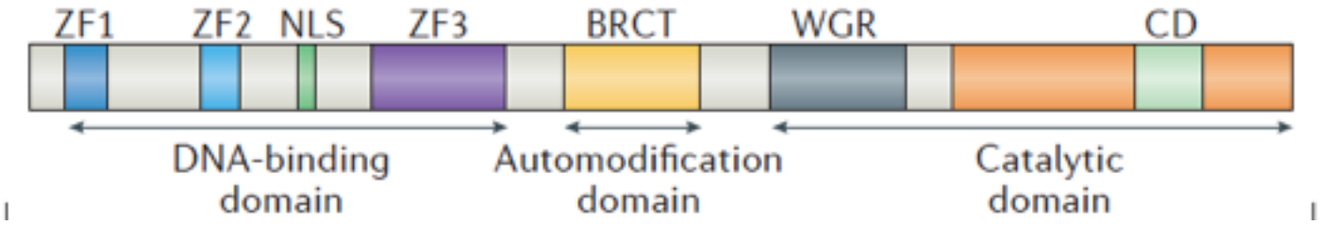


- **Once damage is localized, specific DNA repair *molecules bind at or near the site of damage*, inducing other molecules to bind and form a complex that enables the actual repair to take place.**





PARP 1q42.12



Biochemical activities of PARP1

- PARP1 was the first member of the PARP family to be identified, which now comprises 18 distinct members.

- The main role of PARP1 is to catalyse the ***polymerization of ADP-ribose units*** — derived from the ADP donor NAD+ — resulting in the attachment of either linear or branched PAR polymers to itself or other target proteins

NATURE REVIEWS | MOLECULAR CELL BIOLOGY ADVANCE ONLINE PUBLICATION

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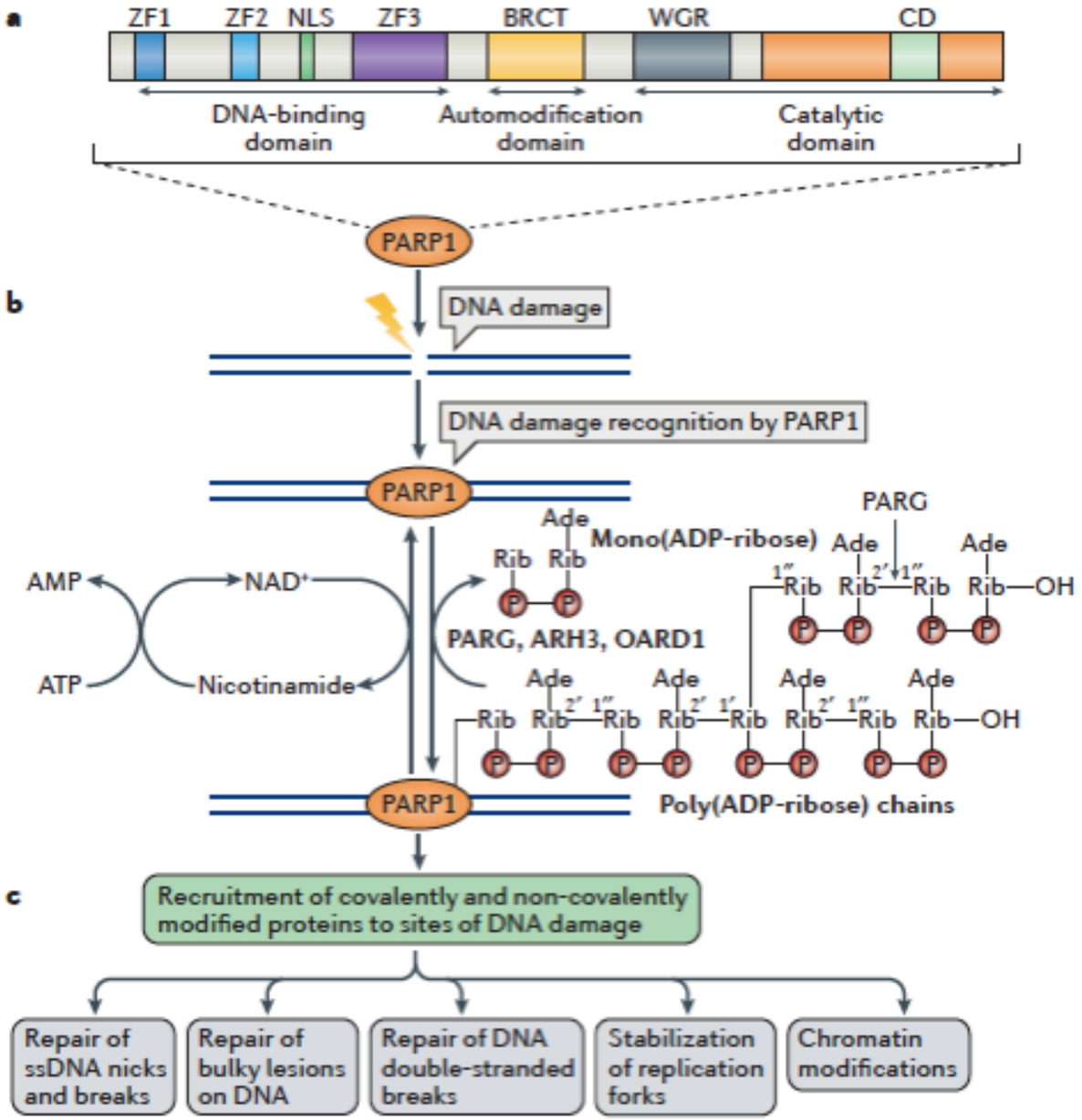
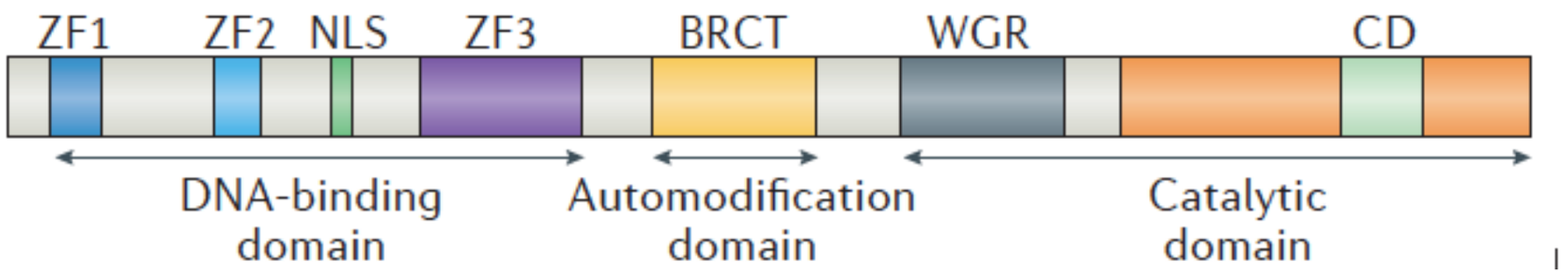
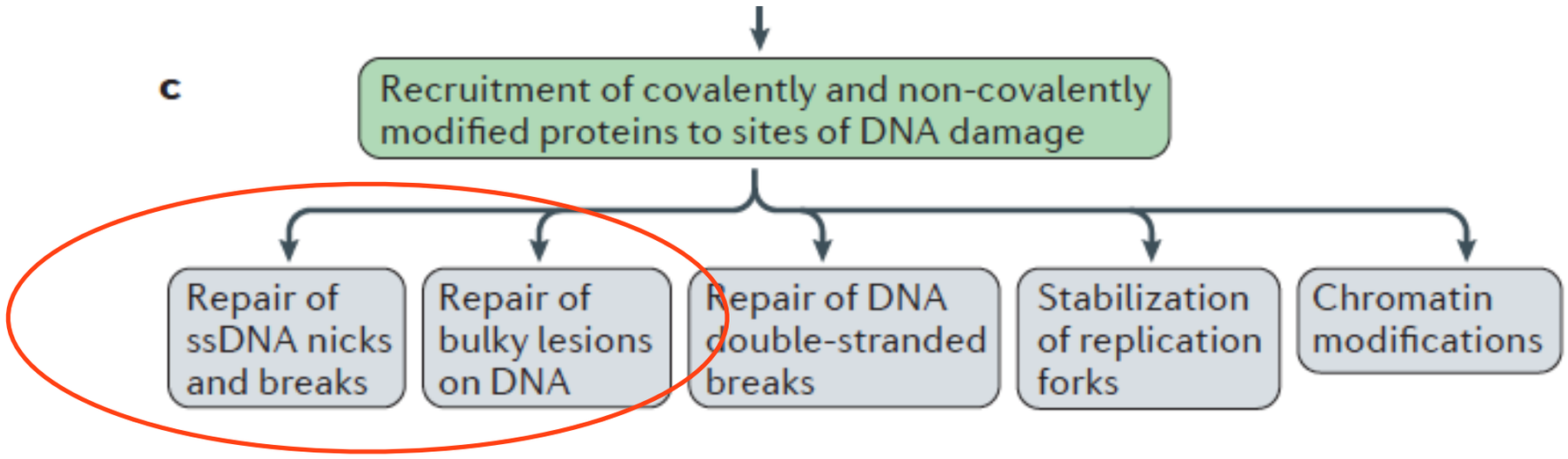
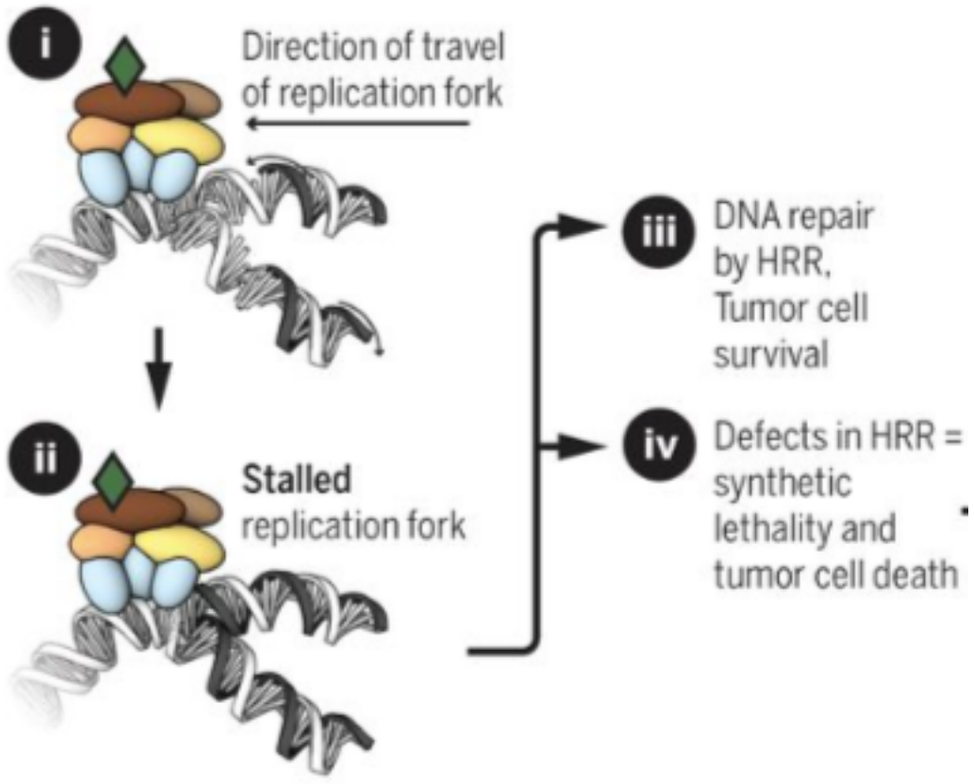

a
ZF1
ZF2
NLS
ZF3
BRCT
WGR
CD
DNA-binding domain
Automodification domain
Catalytic domain
PARP1
b
DNA damage
DNA damage recognition by PARP1
PARP1
AMP
ATP
NAD+
Nicotinamide
Ade
Rib
Mono(ADP-ribose)
PARG, ARH3, OARD1
PARG
OH
PARP1
Poly(ADP-ribose) chains
c
Recruitment of covalently and non-covalently modified proteins to sites of DNA damage
Repair of ssDNA nicks and breaks
Repair of bulky lesions on DNA
Repair of DNA double-stranded breaks
Stabilization of replication forks
Chromatin modifications





Até 200 bases !!!

DNA double-strand break repair



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Double-strand breaks, in which both strands in the double helix are severed, are particularly hazardous to the cell because they can lead to ***genome rearrangements.***

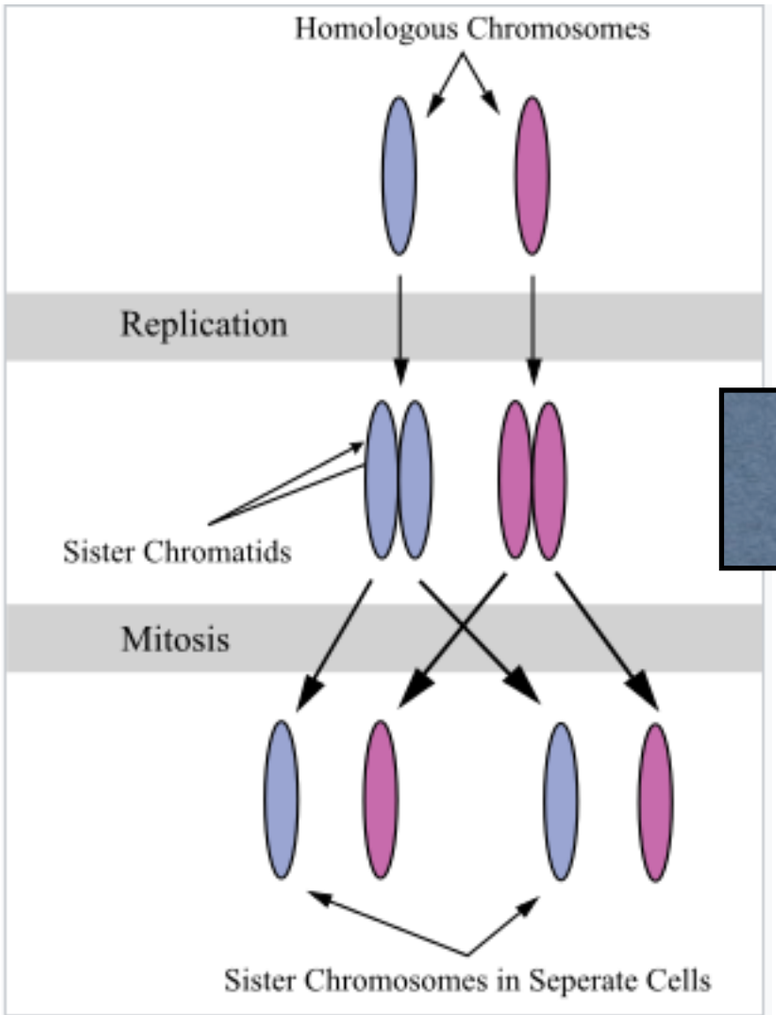
Bjorksten, J; Acharya, PVN; Ashman, S; Wetlaufer, DB (1971). "Gerogenic fractions in the tritiated rat". Journal of the American Geriatrics Society. 19 (7): 561–74. doi:10.1111/j. 1532-5415.1971.tb02577.x. PMID 5106728.

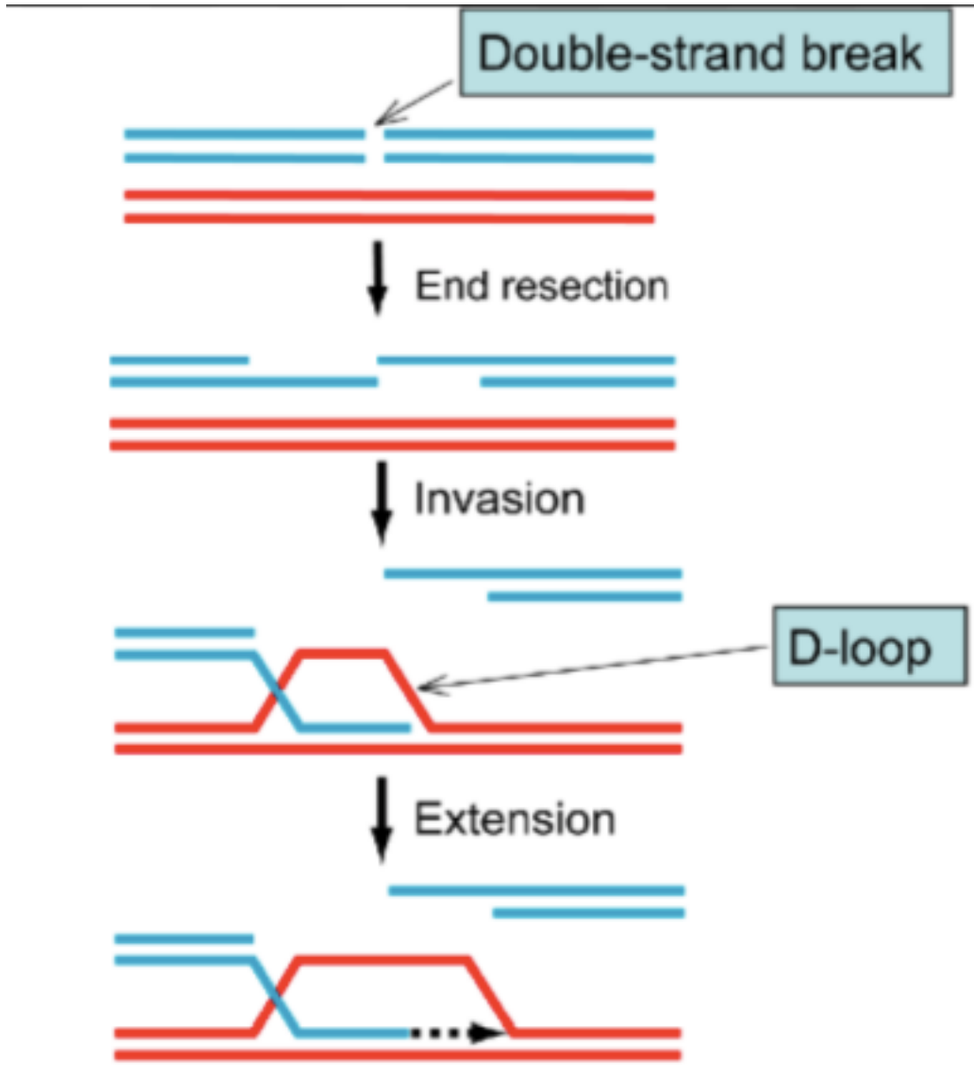
Three mechanisms exist to repair double-strand breaks (DSBs):

- non-homologous end joining (NHEJ),

- microhomology-mediated end joining (MMEJ),

- ***homologous recombination (HR)***





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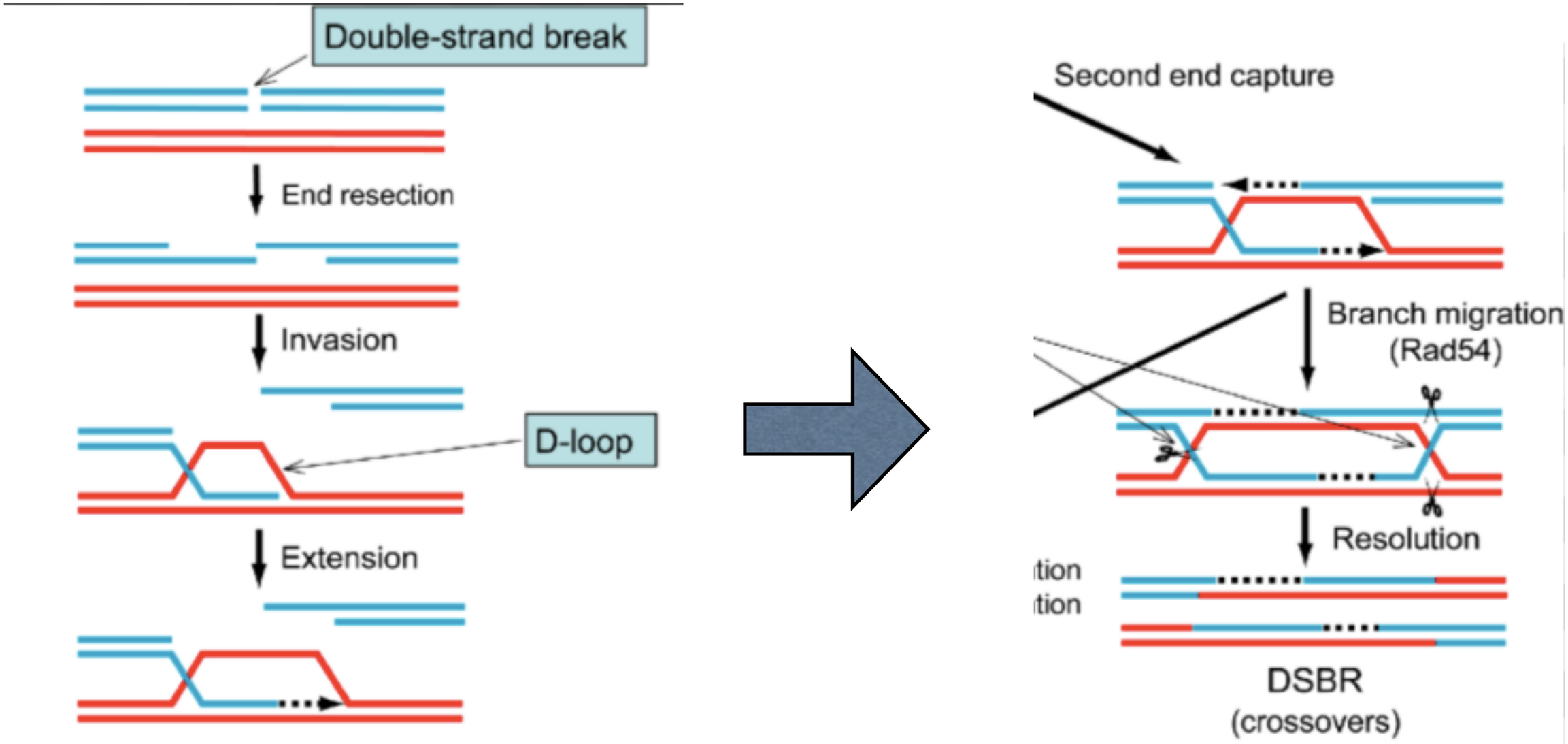
Double-strand break
End resection
Invasion
D-loop
Extension
Second end capture
Branch migration
(Rad54)
Resolution
tion
tion
DSBR
(crossovers)

Quem são os responsáveis por ativar o sistema de Recombinação Homóloga?

BRCAS

Functions of BRCA1 and BRCA2 in the biological response to DNA damage

Ashok R. Venkitaraman

University of Cambridge, CRC Department of Oncology and The Medical Research Council Cancer Cell Unit, Hutchison/MRC Research Centre, Hills Road, Cambridge CB2 2XZ, UK

(e-mail: arv22@cam.ac.uk)

Journal of Cell Science 114, 3591-3598 (2001) © The Company of Biologists Ltd

17q21.31

13q13.1

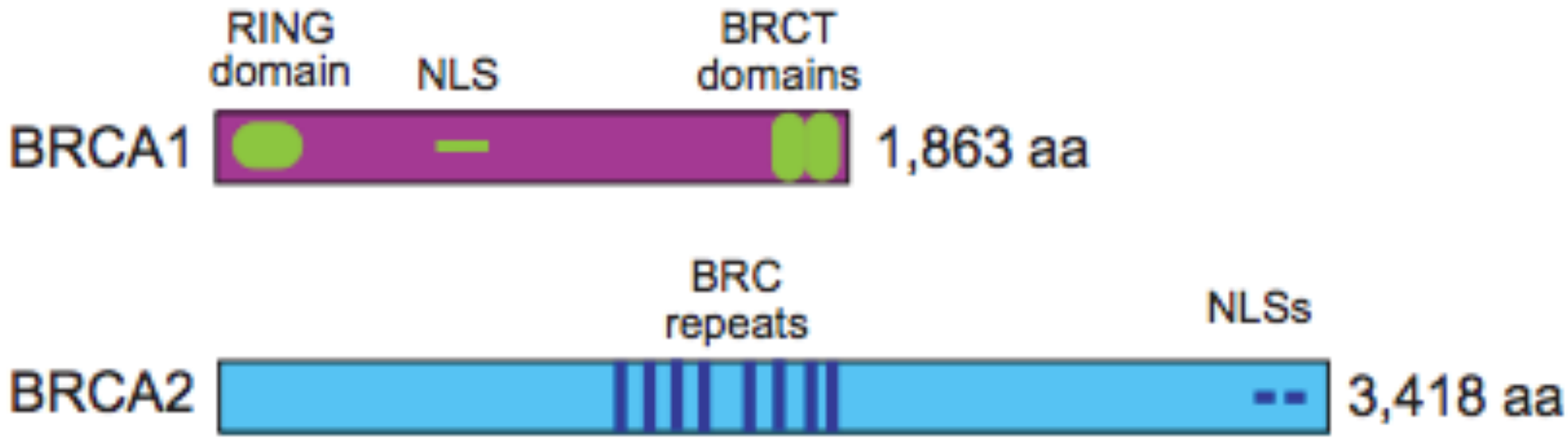

Fig. 1. Features of the BRCA proteins. The N-terminal RING domain, nuclear localisation signal (NLS) and C-terminal BRCT domains of BRCA1 are shown, as are the eight BRC repeat motifs in BRCA2. Modified from Venkitaraman, 2001 with the permission of Elsevier Science Ltd (Venkitaraman, 2001).

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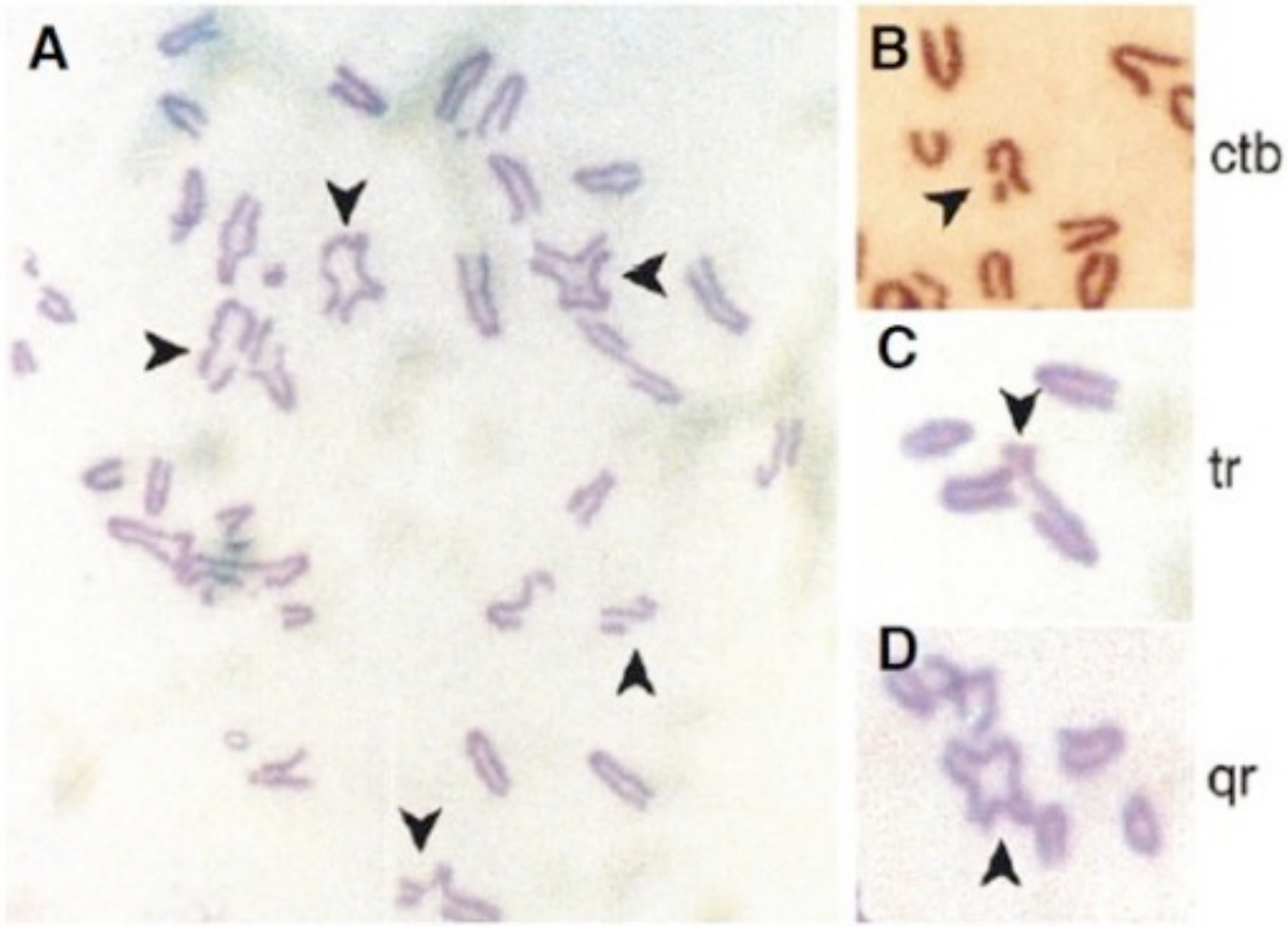
- There is now good evidence that BRCA2 is essential for DSB repair by homologous recombination.

- Cells that contain truncated Brca2 and Brca1 progressively accumulate aberrations in chromosome structure during passage in culture; these ***typically include tri-radial and quadri-radial chromosomes as well as chromosome breaks*** (Patel et al., 1998).



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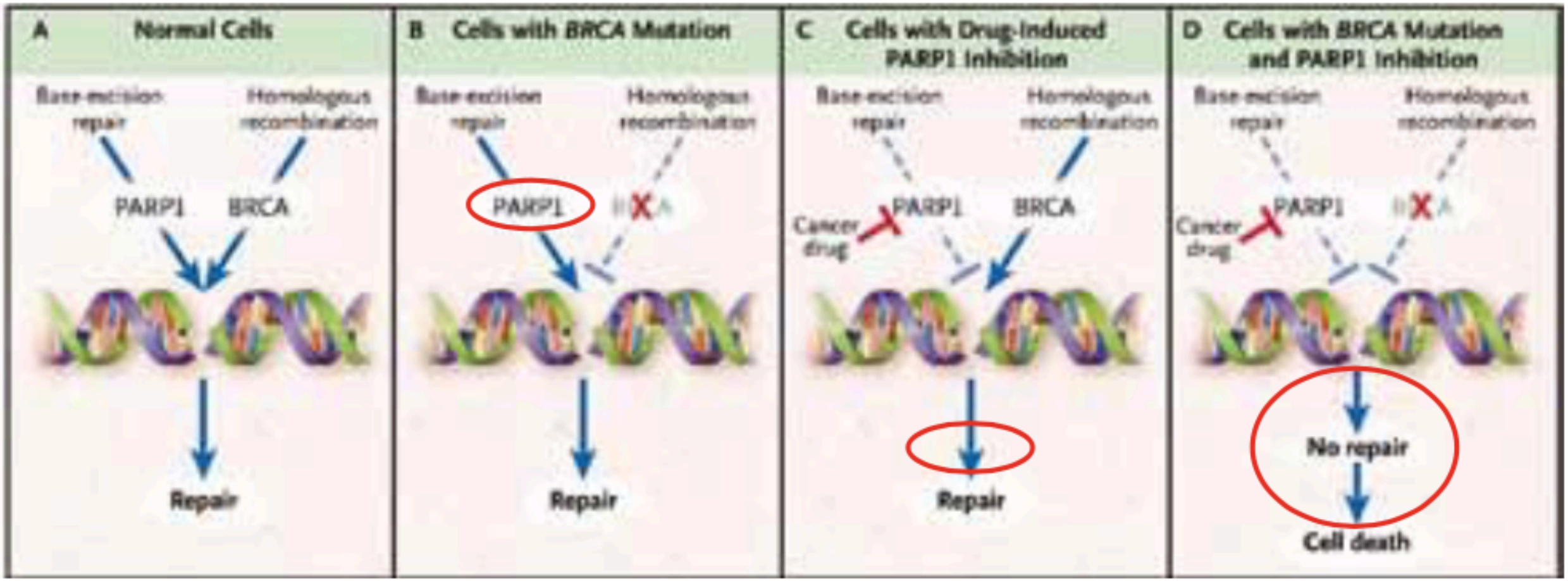
- **Janela de oportunidade na célula tumoral**

Healthy tissue BRCA cancer cells Healthy tissue BRCA cancer cells



Câncer de Ovário, BRCA e PARP

Niraparib — has shown efficacy as maintenance therapy in platinum-sensitive, relapsed disease, which appears independent of the presence of either *BRCA* mutation or homologous recombination deficiency (HRD). In the phase III ***NOVA*** study

Olaparib — has also been studied as maintenance therapy for those with platinum-sensitive relapsed disease in both women regardless of a *BRCA* mutation ***(Study 19)*** and specifically, in those with a *BRCA* mutation ***(SOLO2).***

Rucaparib — has shown efficacy both as maintenance therapy as well as monotherapy for recurrent, platinum-sensitive, high-grade ovarian carcinoma. Data for rucaparib as subsequent-line monotherapy for those with *BRCA*-mutated cancers are discussed elsewhereIn the phase III ***ARIEL3*** trial

- Inibidores da PARP em oncologia;
. Olaparib (AZD-2281, Lynparza®)
. Rucaparib (PF-01367338, Rubraca®)
. Niraparib (MK-4827, Zejula®)
. Talazoparib
. Veliparib

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Olaparib for Metastatic Breast Cancer in Patients with a Germline *BRCA* Mutation

Mark Robson, M.D., Seock-Ah Im, M.D., Ph.D., Elżbieta Senkus, M.D., Ph.D., Binghe Xu, M.D., Ph.D., Susan M. Domchek, M.D., Norikazu Masuda, M.D., Ph.D., Suzette Delaloge, M.D., Wei Li, M.D., Nadine Tung, M.D., Anne Armstrong, M.D., Ph.D., Wenting Wu, Ph.D., Carsten Goessl, M.D., Sarah Runswick, Ph.D., and Pierfranco Conte, M.D.

- Patients Eligible patients were at least 18 years of age and had ***HER2-negative*** metastatic breast cancer that was hormone-receptor positive (i.e., estrogen receptor positive, progesterone-receptor positive, or both) or was triple negative.

- Patients had a confirmed deleterious or suspected deleterious ***germline BRCA mutation***; the mutation was detected by central testing with BRACAnalysis (Myriad Genetics) in 297 patients and by local testing in 167 patients (with confirmation by central testing with BRACAnalysis in all but 5 of those patients).

- Patients had received ***no more than two previous chemotherapy regimens for metastatic disease***, and they had received neoadjuvant or adjuvant treatment or treatment for metastatic disease with an **anthracycline** (unless it was contraindicated) and a **taxane**.

- Patients with hormone-receptor–positive breast cancer had received at least **one endocrine therapy** (adjuvant therapy or therapy for metastatic disease) and had had disease progression during therapy, unless they had disease for which endocrine therapy was considered to be inappropriate.

- Previous neoadjuvant or adjuvant treatment with **platinum was allowed if at least 12 months** had elapsed since the last dose.

- Previous treatment with **platinum for metastatic disease** was allowed if there was **no evidence that disease progression** had occurred during treatment.

Trial Design and Treatments

- The OlympiAD trial was a randomized, controlled, open-label, multicenter, international, phase 3 trial.

- Randomization was stratified according to:
  .***previous use of chemotherapy*** for metastatic disease (yes vs. no)
  .***hormone-receptor status*** (hormone-receptor positive vs. triple negative), and
  .***previous use of platinum***-based therapy (yes vs. no);

Patients were randomly assigned, in a 2:1 ratio, to receive:

- **olaparib** tablets (300 mg twice daily) or

- **capecitabine** administered orally at a dose of 2500 mg per square meter of body-surface area daily (divided into two doses) for 14 days, repeated every 21 days

- **eribulin** mesylate administered intravenously at a dose of 1.4 mg per square meter on day 1 and day 8, repeated every 21 days;

- **vinorelbine** administered intravenously at a dose of 30 mg per square meter on day 1 and day 8, repeated every 21 days.

END POINTS AND ASSESSMENTS

The primary end point was ***progression-free survival***, which was defined as the time from randomization to objective radiologic disease progression (according to modified RECIST, version 1.1)

At the time of data cutoff for the primary end point (***after at least 230 events*** had occurred), additional data were collected for the following ***prespecified secondary end points:***

- safety outcomes, ***overall survival***, time from randomization to a second progression event or death after a first progression event (based on investigator assessment), objective response rate (based on blinded independent central review, according to modified RECIST, version 1.1), and scores for ***health-related quality of life.***

STATISTICAL ANALYSIS

We determined that a total of ***230 progression-free survival*** events would give the trial 90% power (at a two-sided significance level of 5%) to show a statistically significant difference in progression-free survival between the olaparib group and the standard-therapy group, with a corresponding ***hazard ratio for disease progression or death of 0.635.***

- The Kaplan–Meier method was used to generate time-to-event curves, from which medians were calculated.
- For the primary end point, a log-rank test (stratified according to hormone-receptor status and previous use of chemotherapy) was used to compare the Kaplan–Meier curves in the two treatment groups, and the P value derived from this comparison was reported.
- Hazard ratios and confidence intervals were estimated from the log-rank test statistics.
- ***Progression-free survival event rates at 12 months were calculated*** with the use of Kaplan–Meier curves.

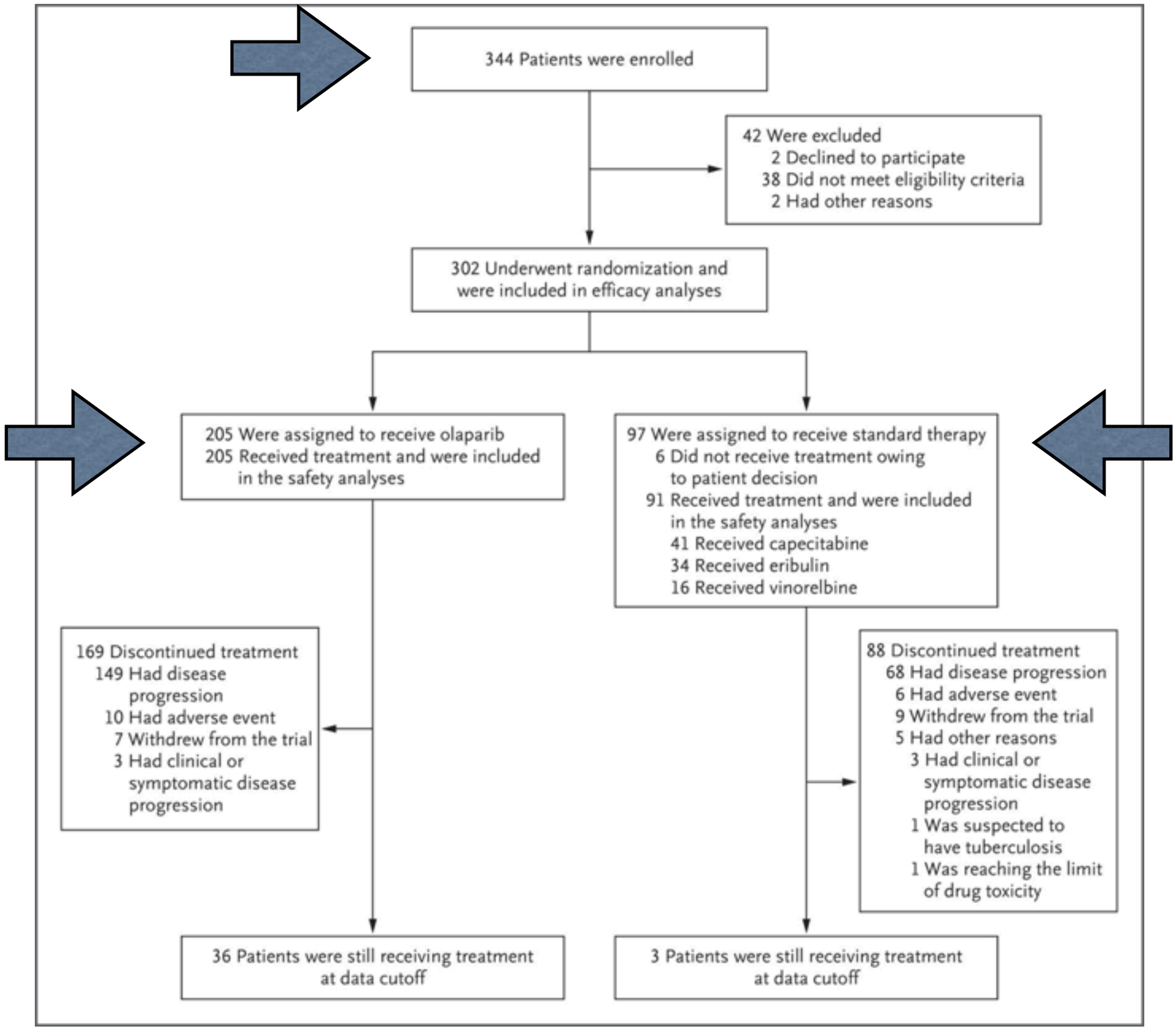


Table 1. Baseline Characteristics of the Patients.*

Characteristic	Olaparib Group (N = 205)	Standard-Therapy Group (N = 97)
Age — yr		
Median	44	45
Range	22–76	24–68
Male sex — no. (%)	5 (2.4)	2 (2.1)
Race or ethnic group — no. (%)†		
White	134 (65.4)	63 (64.9)
Asian	66 (32.2)	28 (28.9)
Other	5 (2.4)	6 (6.2)
ECOG performance status — no. (%)‡		
0	148 (72.2)	62 (63.9)
1	57 (27.8)	35 (36.1)
BRCA mutation type — no. (%)§		
BRCA1	117 (57.1)	51 (52.6)
BRCA2	84 (41.0)	46 (47.4)
BRCA1 and *BRCA2*	4 (2.0)	0

Hormone-receptor status — no. (%)¶		
Hormone-receptor positive	103 (50.2)	49 (50.5)
Triple negative	102 (49.8)	48 (49.5)
New metastatic breast cancer — no. (%)	26 (12.7)	12 (12.4)
Previous chemotherapy for metastatic breast cancer — no. (%)	146 (71.2)	69 (71.1)
Previous platinum-based therapy for breast cancer — no. (%)	60 (29.3)	26 (26.8)
≥2 Metastatic sites — no. (%)	159 (77.6)	72 (74.2)
Location of the metastasis — no. (%)		
Bone only	16 (7.8)	6 (6.2)
Other	189 (92.2)	91 (93.8)
Measurable disease — no. (%)	167 (81.5)	66 (68.0)

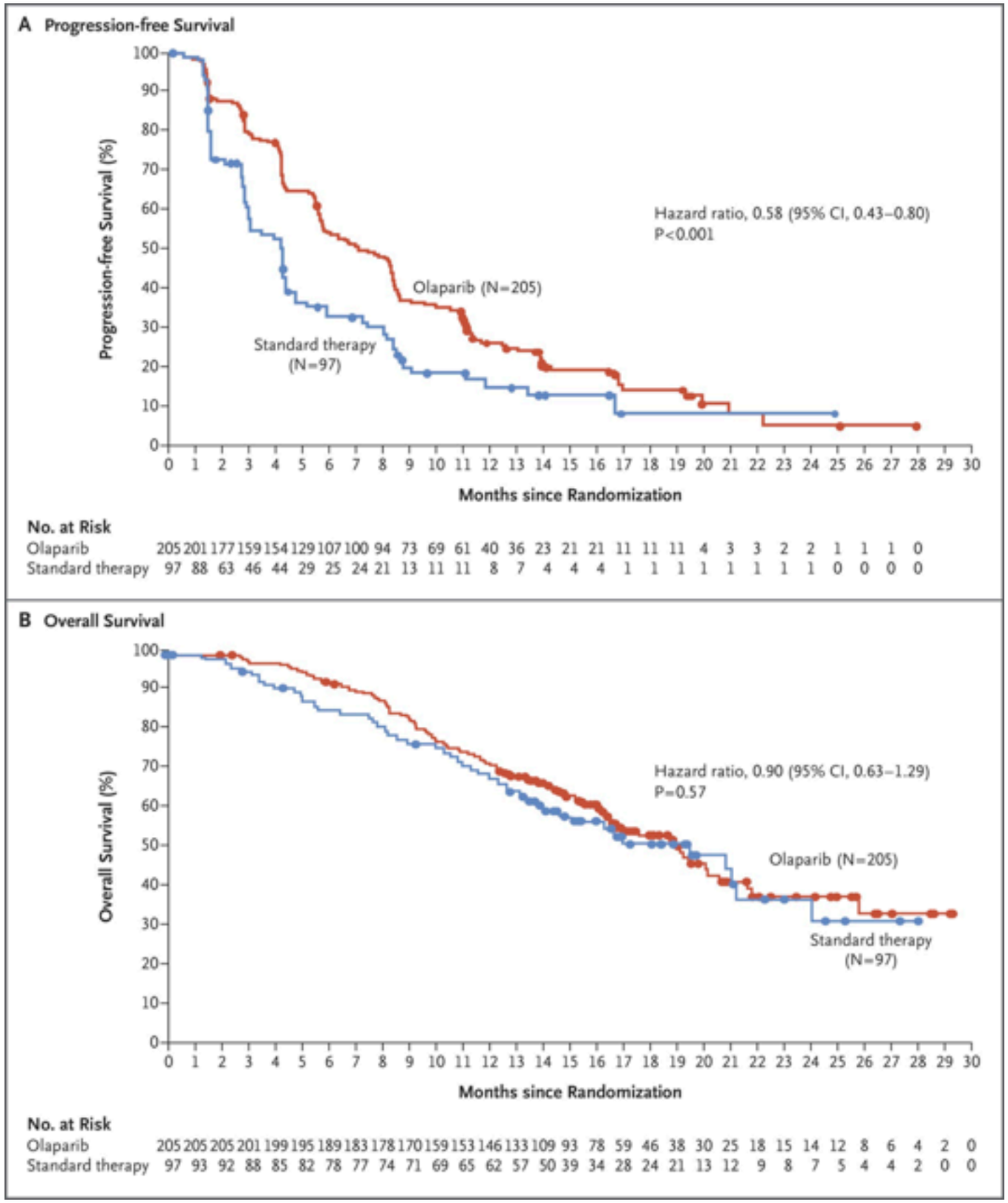
EFFICACY

Kaplan–Meier Estimates of Progression-free Survival and Overall Survival.

The primary end point was assessed ***after 234*** of the 302 patients (77.5%) had had disease progression (assessed by blinded independent central review) or had died

At the time of this analysis, median progression-free survival was significantly longer in the olaparib group than in the standard-therapy group (***7.0 months vs. 4.2 months***; hazard ratio for disease progression or death, 0.58; 95% confidence interval [CI], 0.43 to 0.80; P<0.001)

- At 12 months, ***25.9%*** of the patients in the olaparib group and ***15.0%*** of the patients in the standard-therapy group were free of progression or death.



Subgroup	Olaparib	Standard Therapy	Hazard Ratio (95% CI)
	no. of patients with events/total no. (%)		
All patients	163/205 (79.5)	71/97 (73.2)	0.58 (0.43–0.80)
Previous chemotherapy for metastatic breast cancer			
Yes	119/146 (81.5)	51/69 (73.9)	0.65 (0.47–0.91)
No	44/59 (74.6)	20/28 (71.4)	0.56 (0.34–0.98)
Hormone-receptor status			
Hormone-receptor positive	82/103 (79.6)	31/49 (63.3)	0.82 (0.55–1.26)
Triple negative	81/102 (79.4)	40/48 (83.3)	0.43 (0.29–0.63)
Previous platinum-based therapy for breast cancer			
Yes	50/60 (83.3)	21/26 (80.8)	0.67 (0.41–1.14)
No	113/145 (77.9)	50/71 (70.4)	0.60 (0.43–0.84)
Measurable disease			
Yes	139/165 (84.2)	56/72 (77.8)	0.58 (0.43–0.80)
No	24/40 (60.0)	15/25 (60.0)	0.57 (0.30–1.12)
Progressive disease at the time of randomization			
Yes	127/159 (79.9)	53/73 (72.6)	0.60 (0.43–0.83)
No	36/46 (78.3)	18/24 (75.0)	0.72 (0.41–1.30)
BRCA mutation type			
BRCA1	94/114 (82.5)	41/50 (82.0)	0.54 (0.37–0.79)
BRCA2	64/84 (76.2)	30/45 (66.7)	0.68 (0.45–1.07)
Age			
<65 yr	154/194 (79.4)	67/93 (72.0)	0.66 (0.49–0.88)
≥65 yr	9/11 (81.8)	4/4 (100.0)	Not calculated
Region			
Asia	46/59 (78.0)	21/28 (75.0)	0.57 (0.34–0.97)
Europe	77/97 (79.4)	34/35 (75.6)	0.71 (0.48–1.08)
North America and South America	40/49 (81.6)	16/24 (66.7)	0.39 (0.22–0.73)
Race			
White	109/134 (81.3)	47/63 (74.6)	0.67 (0.48–0.95)
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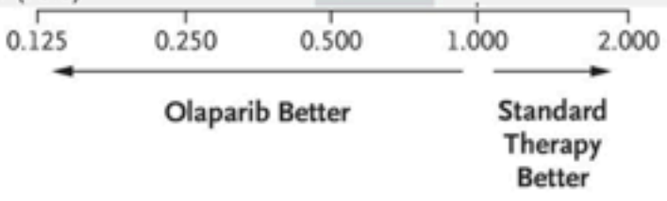

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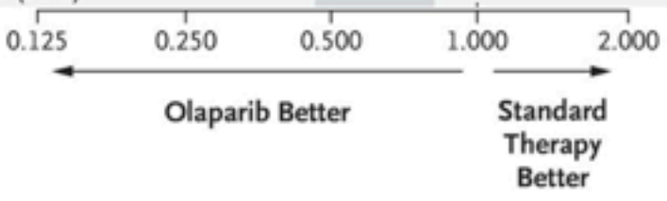

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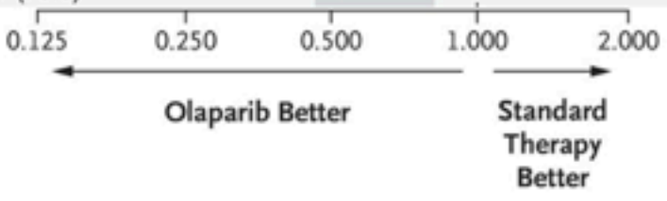

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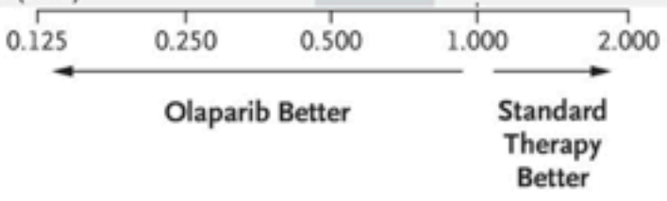

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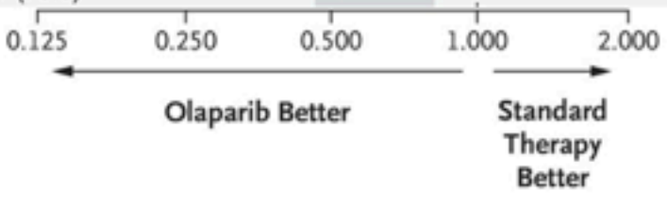

Table 2. Summary of Adverse Events.*

Variable	Olaparib Group (N=205)		Standard-Therapy Group (N=91)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number (percent)			
Adverse event				
Any	199 (97.1)	75 (36.6)	88 (96.7)	46 (50.5)
Anemia†	82 (40.0)	33 (16.1)	24 (26.4)	4 (4.4)
Neutropenia‡	56 (27.3)	19 (9.3)	45 (49.5)	24 (26.4)
Decreased white-cell count	33 (16.1)	7 (3.4)	19 (20.9)	9 (9.9)
Nausea	119 (58.0)	0	32 (35.2)	1 (1.1)
Vomiting	61 (29.8)	0	14 (15.4)	1 (1.1)
Diarrhea	42 (20.5)	1 (0.5)	20 (22.0)	0
Decreased appetite	33 (16.1)	0	11 (12.1)	0
Fatigue	59 (28.8)	6 (2.9)	21 (23.1)	1 (1.1)
Headache	41 (20.0)	2 (1.0)	14 (15.4)	2 (2.2)
Pyrexia	29 (14.1)	0	16 (17.6)	0
Cough	35 (17.1)	0	6 (6.6)	0
Increased alanine aminotransferase level	23 (11.2)	3 (1.5)	16 (17.6)	1 (1.1)
Increased aspartate aminotransferase level	19 (9.3)	5 (2.4)	15 (16.5)	0
Palmar–plantar erythrodysesthesia	1 (0.5)	0	19 (20.9)	2 (2.2)
Dose reduction owing to adverse event	52 (25.4)	NA	28 (30.8)	NA
Treatment interruption or delay owing to adverse event	72 (35.1)	NA	25 (27.5)	NA
Treatment discontinuation owing to adverse event	10 (4.9)	NA	7 (7.7)	NA

Discussion

Tutt A, Ellis P, Kilburn L, et al. **TNT**: A randomized phase III trial of carboplatin (C) compared with docetaxel (D) for patients with metastatic or recurrent locally advanced triple negative or BRCA1/2 breast cancer (CRUK/07/012). Presented at the 37th Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 9–13, 2014. abstract.

Since platinum agents were not included as treatment options in the control group, the trial cannot address the relative benefits of olaparib and platinum-based chemotherapy in patients with breast cancer and a germline *BRCA* mutation. It is worth noting, however, ***that the response rate of 59.9% and the median progression-free survival of 7.0 months that were observed with first-, second-, or third-line olaparib in this trial are similar to the response rate of 68.0%*** and the median progression-free survival of 6.8 months that were observed with first-line single-agent carboplatin in a similar population.

Future

Oncotarget
Open Access Impact Journal

Oncotarget. 2017 Oct 20; 8(50): 87638–87646.
Published online 2017 Sep 15. doi: 10.18632/oncotarget.20936

PMCID: PMC5675659
PMID: 29152107

Neoadjuvant olaparib targets hypoxia to improve radioresponse in a homologous recombination-proficient breast cancer model

Gerben R. Borst,[1,2,3] Ramya Kumareswaran,[1,2] Hatice Yücel,[1,2,3] Seyda Telli,[1,2] Trevor Do,[1,2] Trevor McKee,[1,2] Gaetano Zafarana,[1,2] Jos Jonkers,[4] Marcel Verheij,[3] Mark J. O'Connor,[5] Sven Rottenberg,[4,6] and Robert G. Bristow[1,2]

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Future

OXFORD JOURNALS
JNCI Journal of the National Cancer Institute

J Natl Cancer Inst. 2017 Jul; 109(7): djw306.
Published online 2017 Mar 9. doi: 10.1093/jnci/djw306

PMCID: PMC5408989
PMID: 28376176

J Natl Canc

Tumor Sequencing and Patient-Derived Xenografts in the Neoadjuvant Treatment of Breast Cancer

Matthew P. Goetz,✉ Krishna R. Kalari, Vera J. Suman, Ann M. Moyer, Jia Yu, Daniel W. Visscher, Travis J. Dockter, Peter T. Vedell, Jason P. Sinnwell, Xiaojia Tang, Kevin J. Thompson, Sarah A. McLaughlin, Alvaro Moreno-Aspitia, John A Copland, Donald W. Northfelt, Richard J. Gray, Katie Hunt, Amy Conners, Richard Weinshilboum, Liewei Wang, and Judy C. Boughey

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Future

MENU

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Review Article | Published: 07 October 2014

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Amir Sonnenblick, Evandro de Azambuja, Hatem A. Azim Jr & Martine Piccart

Nature Reviews Clinical Oncology **12**, 27–41 (2015) | Download Citation

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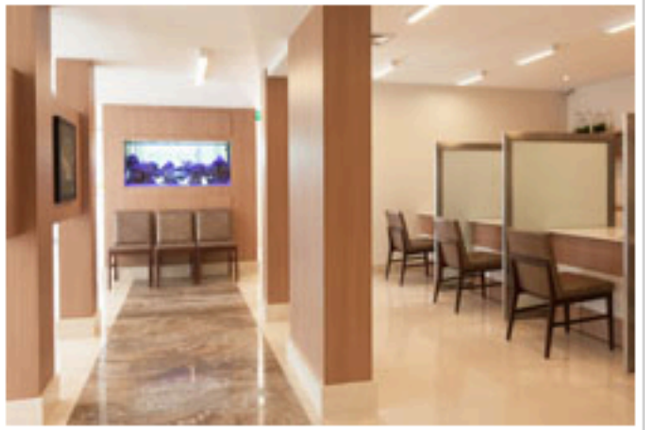
Phase I trial of olaparib in combination with cisplatin for the treatment of patients with advanced breast, ovarian and other solid tumors FREE

J. Balmaña ✉, N. M. Tung, S. J. Isakoff, B. Graña, P. D. Ryan, C. Saura, E. S. Lowe, P. Frewer, E. Winer, J. Baselga, ... Show more

Annals of Oncology, Volume 25, Issue 8, 1 August 2014, Pages 1656–1663,
https://doi.org/10.1093/annonc/mdu187
Published: 14 May 2014 **Article history** ▾

1. PARA QUE ESTE MEDICAMENTO É INDICADO?

LYNPARZA é indicado como monoterapia para o tratamento de manutenção (usado no intervalo entre dois tratamentos) de ***pacientes adultas com carcinoma de ovário seroso de alto grau*** (grau 2 ou maior) recidivado (recorrente), incluindo trompa de Falópio ou peritoneal primário, sensível à platina (que tenha respondido ao tratamento anterior com quimioterapia baseada em platina), com mutação (identificada através de teste específico) no gene de susceptibilidade ao câncer de mama (BRCA 1 e/ou 2; germinativa ou somática; patogênica e/ou suspeitamente patogênica) e que respondem (resposta parcial ou completa) à quimioterapia baseada em platina.




Sala de reunião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ANCHIETA