PARP Inhibitors for the Treatment of Ovarian Cancer: Rationale and Clinical Outcomes



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Comprehensive Cancer Center

Outline

- Histopathogenetic classification of ovarian cancers
- DNA damage repair in ovarian cancers
- Biologic rationale for PARP inhibitors
- Clinical trials with PARP inhibitors
- Future directions

Annual Estimated US Cancer Deaths

Women
275,370



26%	Lung & bronchus
14%	Breast
9%	Colon & rectum
7%	Pancreas
6%	Ovary
4%	Leukemia
3%	Non-Hodgkin lymphoma
3%	Uterine corpus
2%	Liver & intrahepatic bile duct
2%	Brain/other nervous system
24%	All other sites

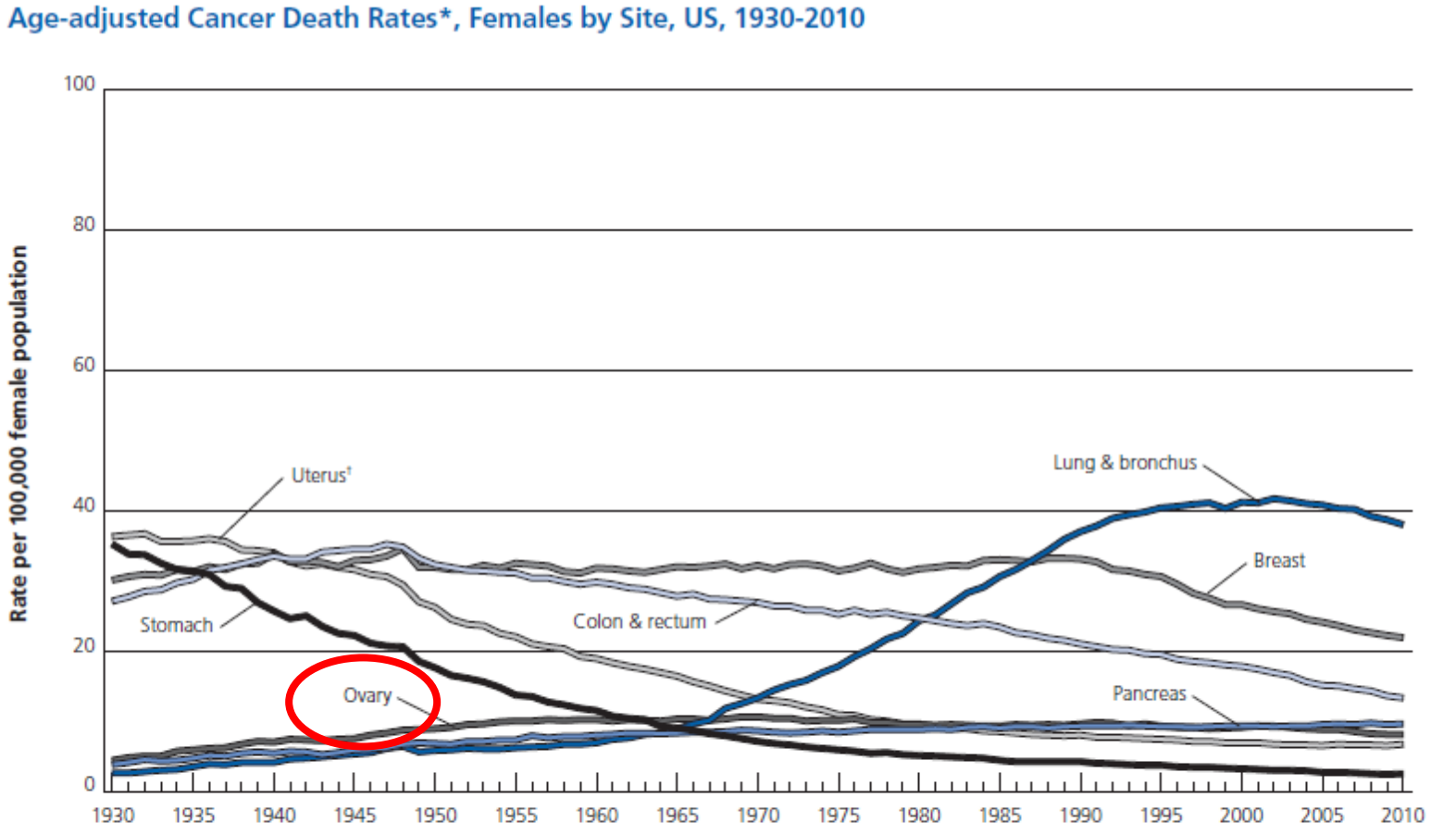
↔ 5 year survival is ~50%

Treatment:
Surgery + Chemotherapy

Platinum and Taxane Chemotherapy

American Cancer Society

Ovarian Cancer



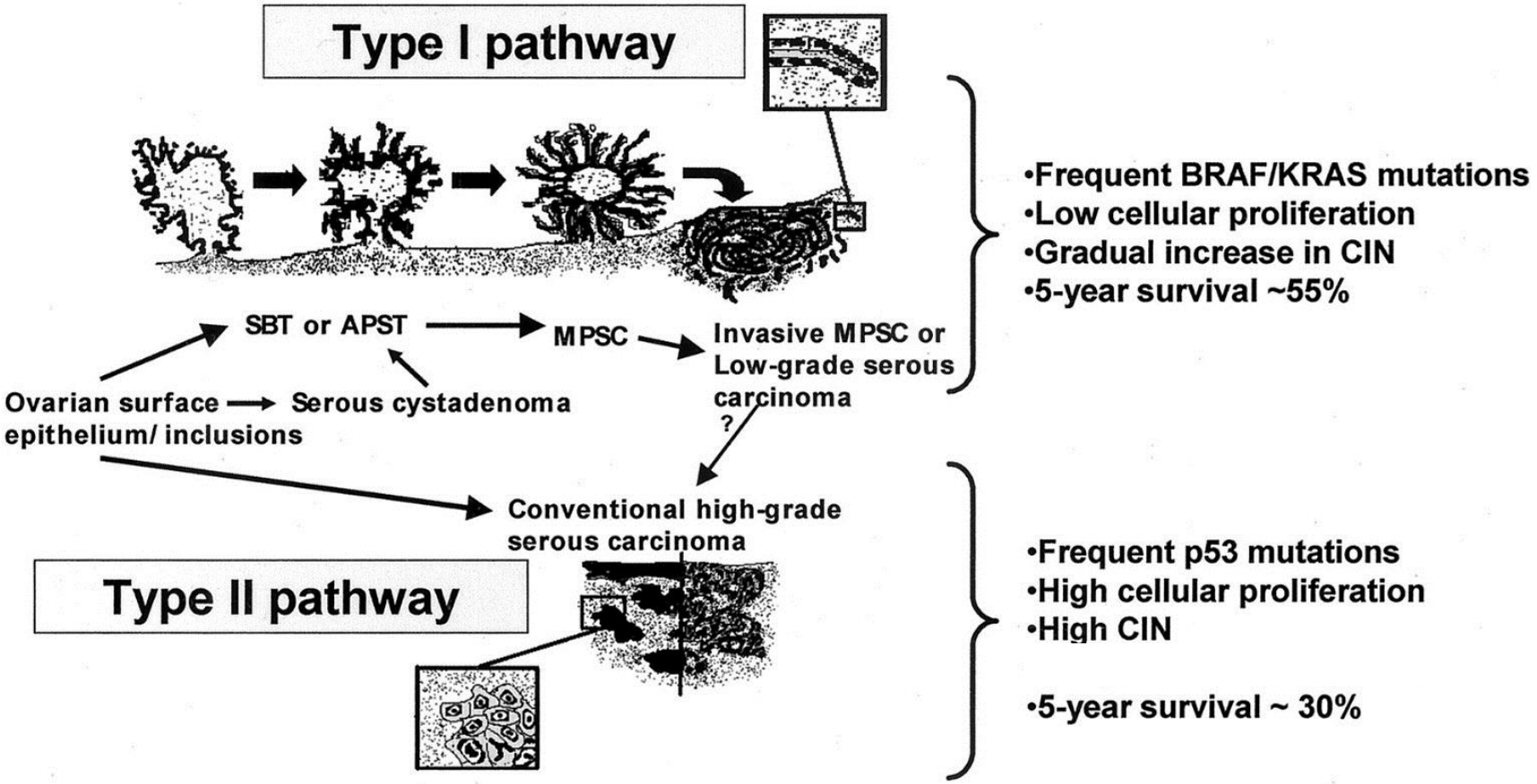
*Per 100,000, age adjusted to the 2000 US standard population. †Uterus refers to uterine cervix and uterine corpus combined.

Note: Due to changes in ICD coding, numerator information has changed over time. Rates for cancer of the lung and bronchus, colon and rectum, and ovary are affected by these coding changes.

Source: US Mortality Volumes 1930 to 1959 and US Mortality Data 1960 to 2010, National Center for Health Statistics, Centers for Disease Control and Prevention.

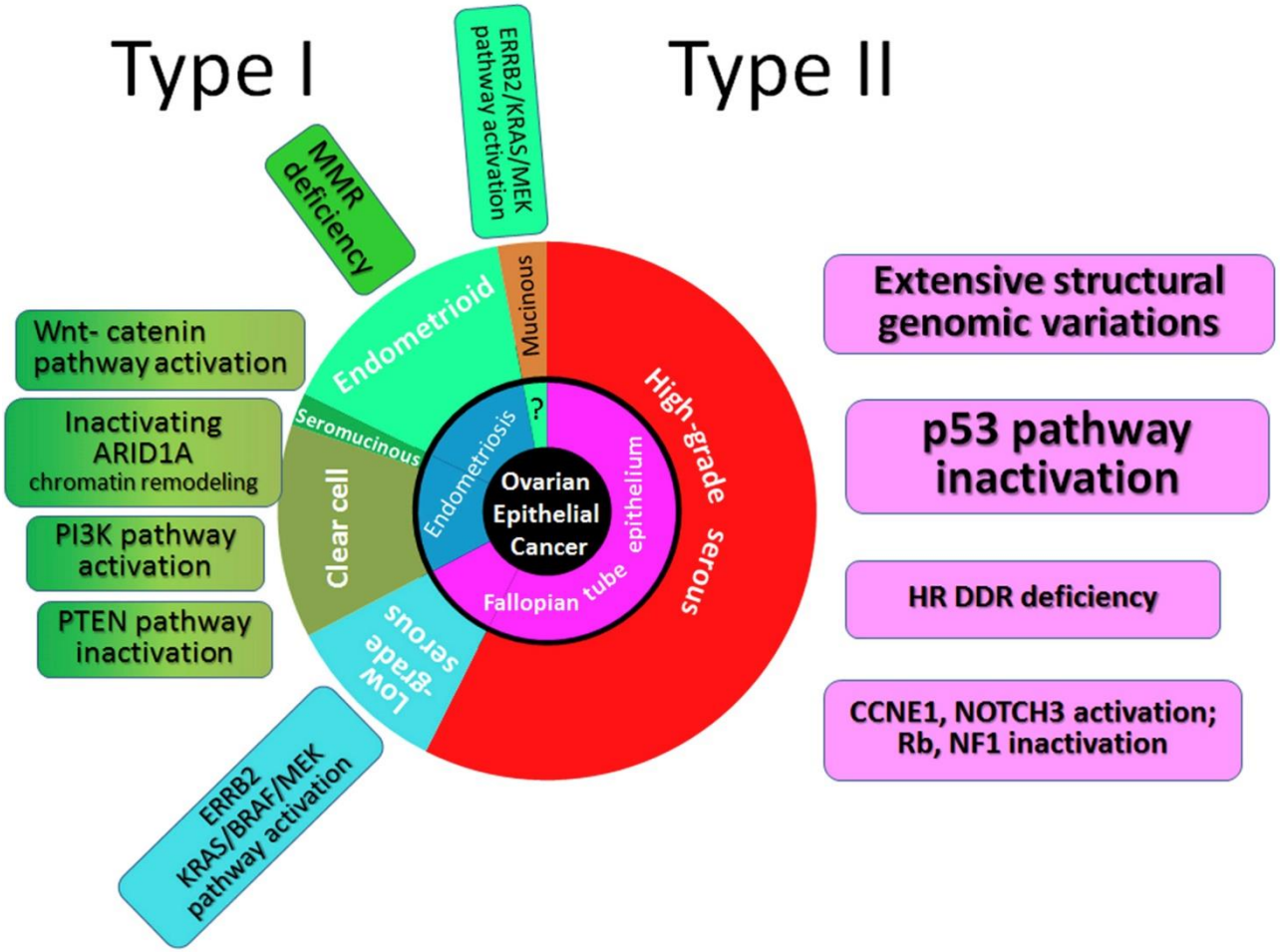
©2014, American Cancer Society, Inc., Surveillance Research

Dualistic Model of Ovarian Cancers



Kurman and Shih, The American Journal of Pathology 2004 164, 1511-1518

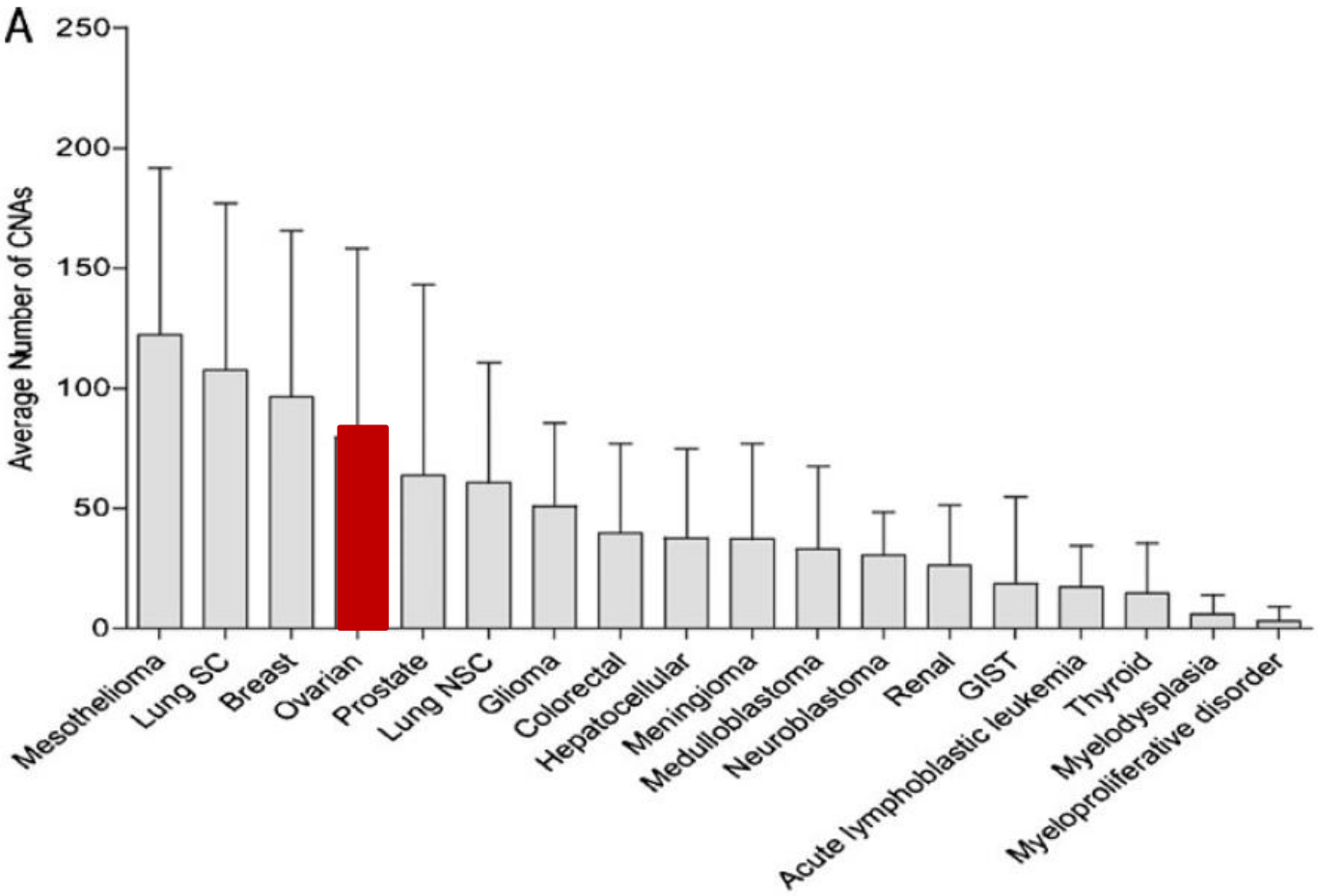
Mutational Profile of Ovarian Cancers



The American Journal of Pathology 2016 186, 733-747

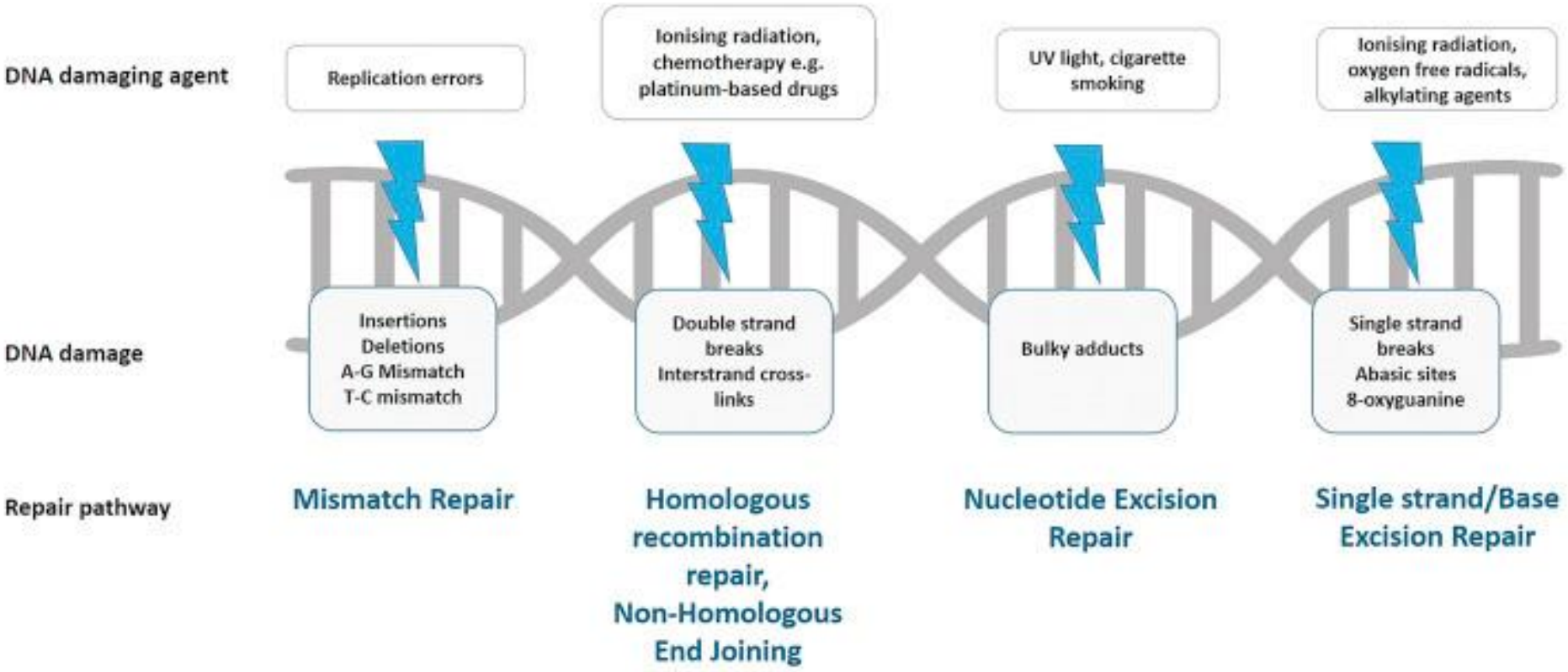
Genomic Instability in Ovarian Cancer

Fig. 4 Pan-cancer trends in genome instability. **a** Average number of copy number alterations for cell lines from each cancer type. *Error bars* represent standard deviation.



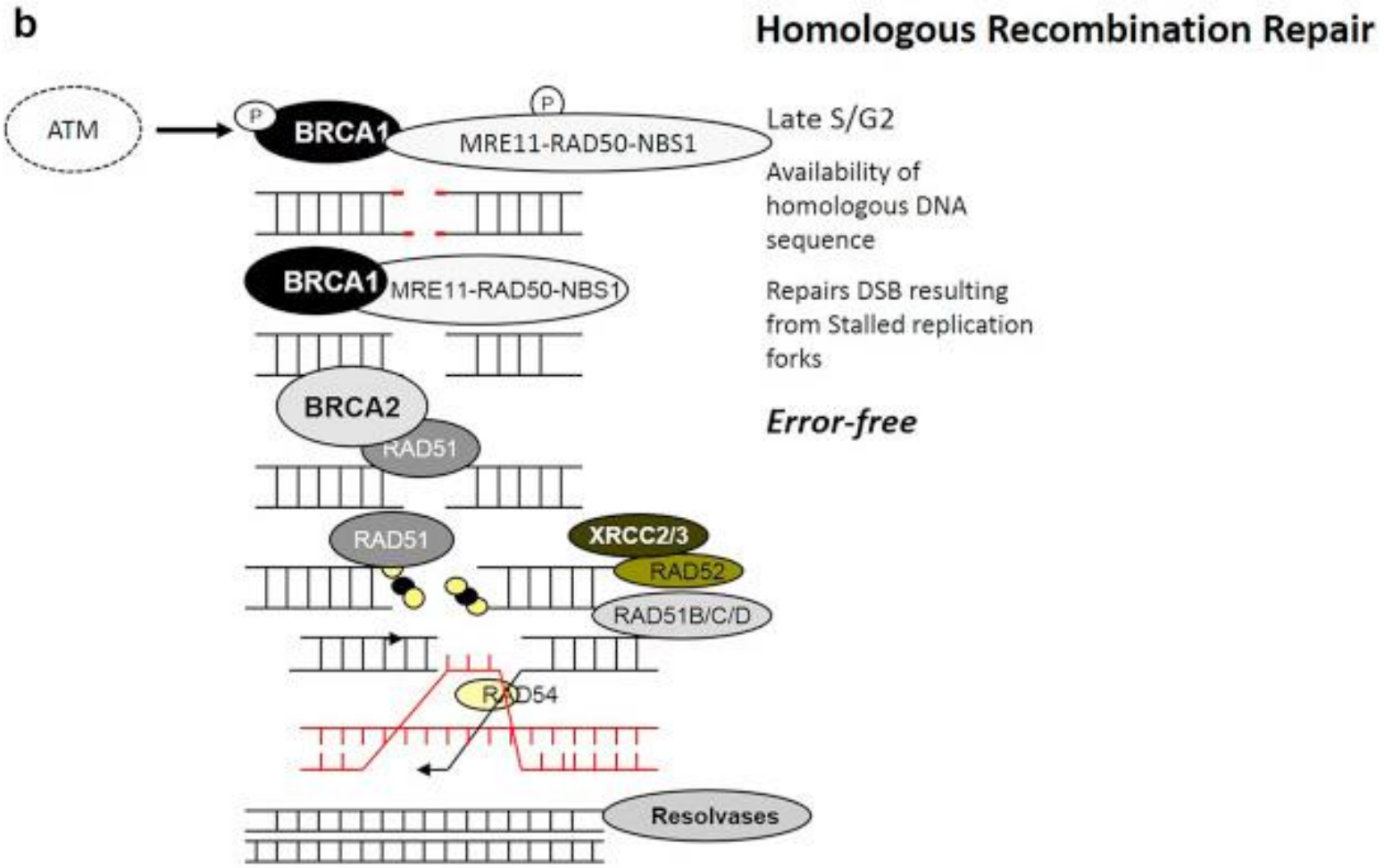
Cancer Metastasis Rev (2013) 32:341–352

DNA Damage Repair Pathways



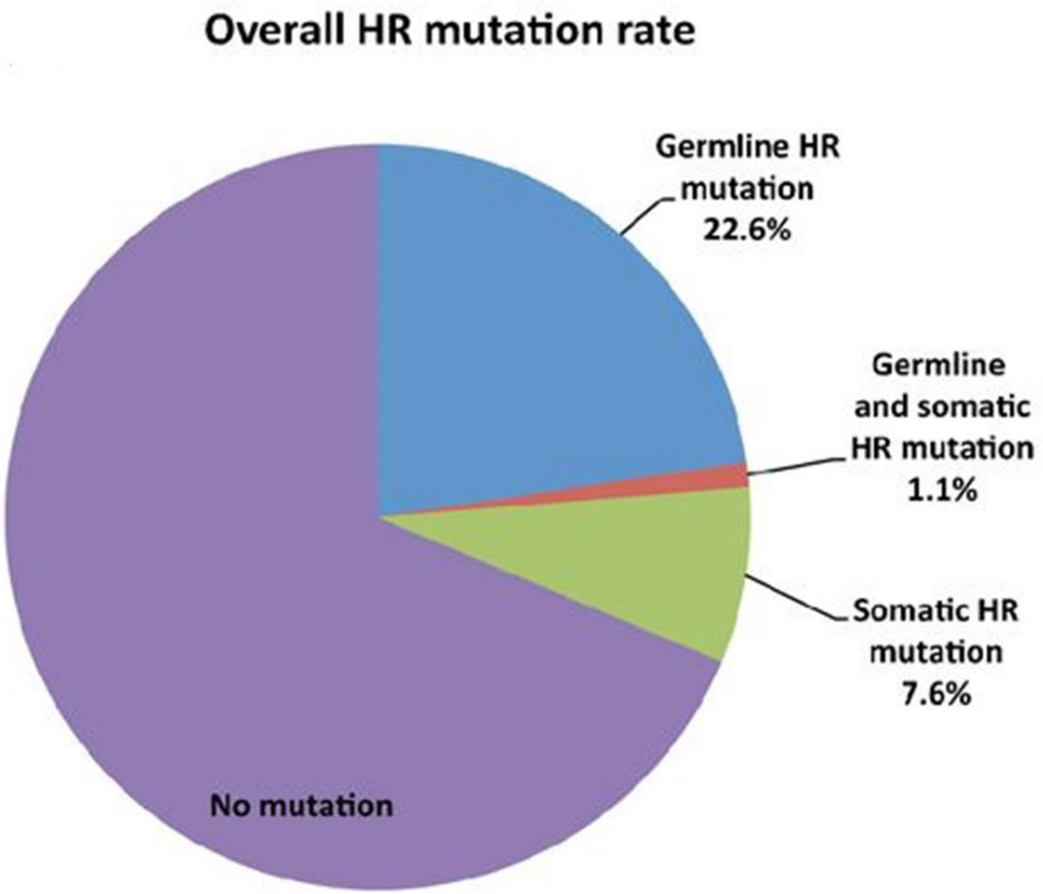
Ledermann et al, Eur J Cancer 60:49-58 (2016)

DNA Damage Repair



Ledermann et al, Eur J Cancer 60:49-58 (2016)

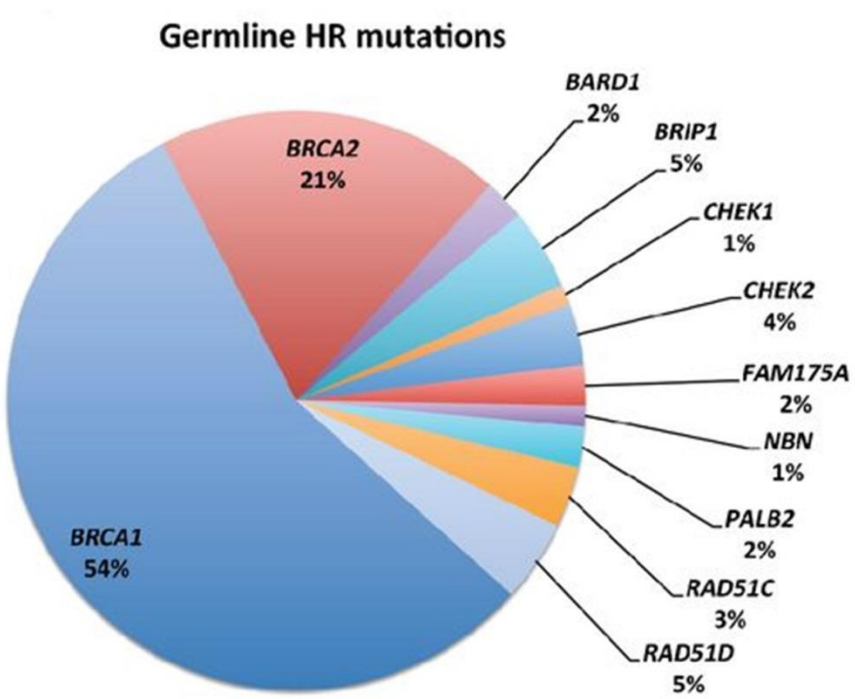
Mutation Frequency in Ovarian Cancer

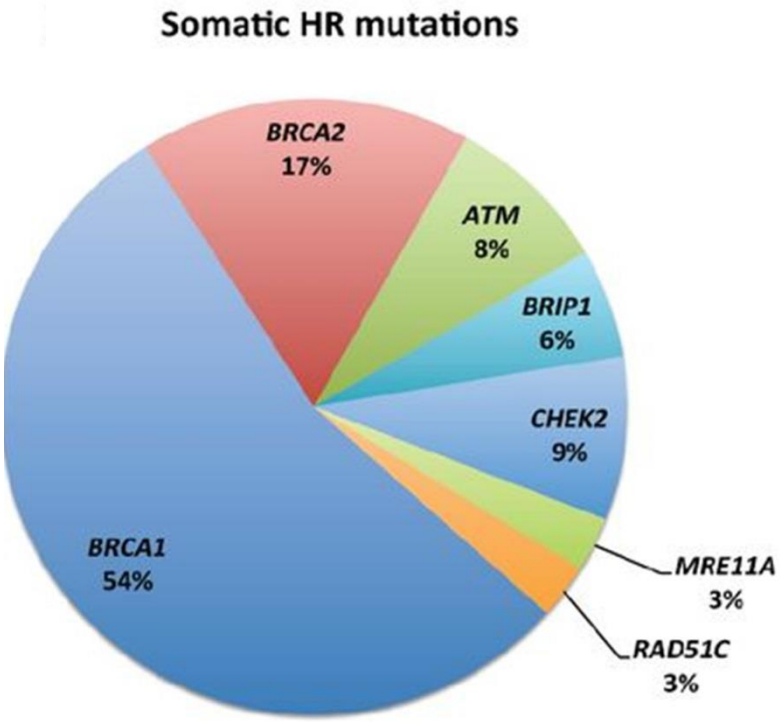


Histology	N (of 390)
High-grade[b] serous	249
Low-grade[c] serous	9
Poorly differentiated NOS	48
Clear cell	19
High-grade[b] endometrioid	20
Low-grade[c] endometrioid	6
Carcinosarcoma	12
Other[d]	4

Pennington et al. Clin Cancer Res 2014;20:764-775

Specific Mutations Identified





Pennington et al. Clin Cancer Res 2014;20:764-775

Society of Gynecologic Oncology Position Statement: Genetic Testing for Ovarian Cancer

October 2014

Women diagnosed with epithelial ovarian, fallopian tube, and peritoneal cancers should receive genetic counseling and be offered genetic testing.

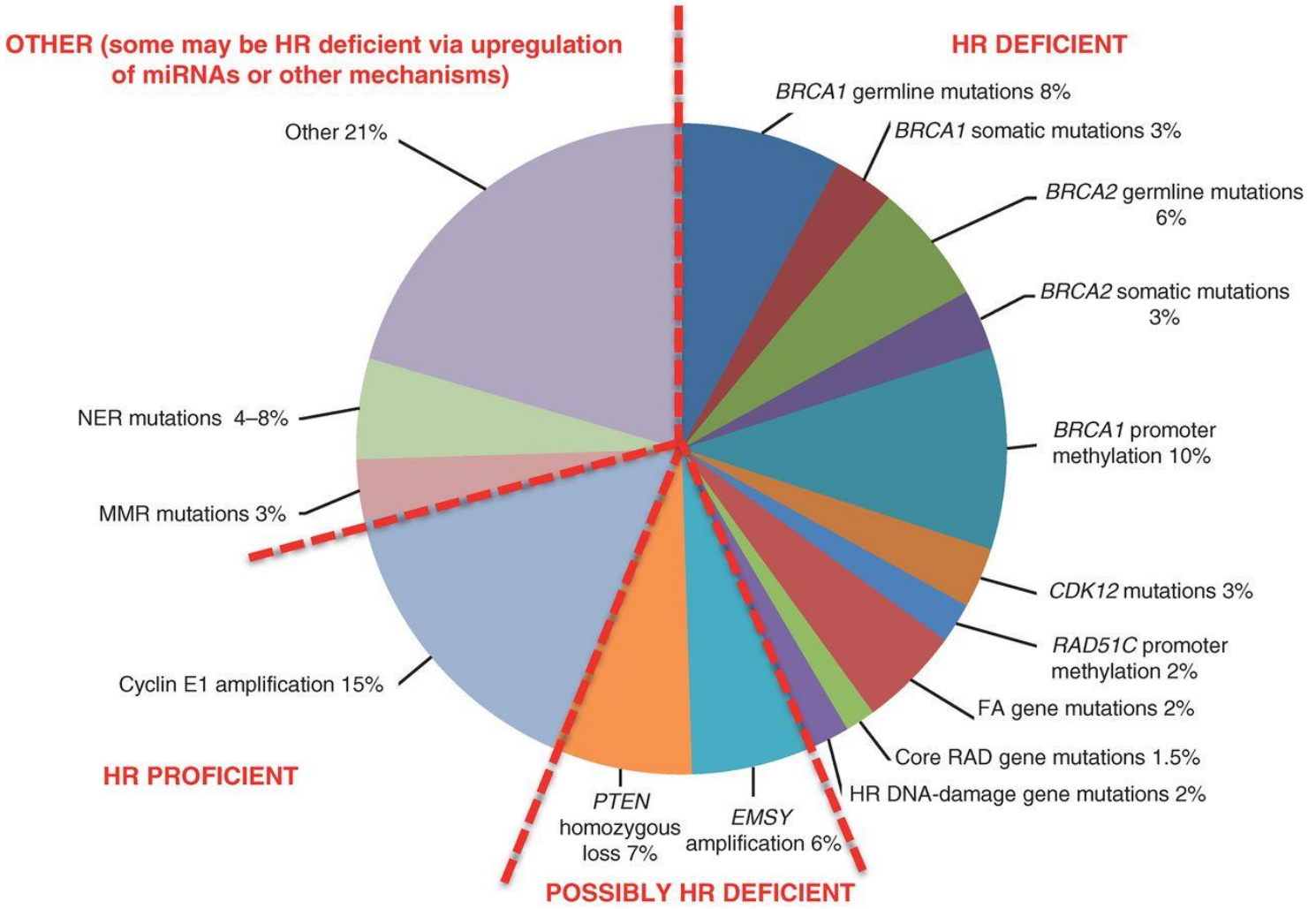
Multi-gene Panels

High-Risk Genes	Moderate-Risk Genes	Newer Genes
• BRCA1, BRCA2, CDH1, EPCAM, MLH1, MSH2, MSH6, PMS2, PTEN, STK11, TP53 • Well studied • Significantly increased risk of developing breast and/or ovarian cancer (often at least 4-fold) • Can increase risk for other cancers • Guidelines for screening and prevention established	• ATM, CHEK2, PALB2 • Well studied • Moderately increased risk of developing breast and/or ovarian cancer (generally 2-3 fold) • Can increase risk for other cancers • Guidelines for screening and prevention not yet established	• BARD1, BRIP1, FANCC, NBN, RAD51C, RAD51D, XRCC2 • Not as well studied, data based on a small number of patients or patients within a specific ethnicity • Precise lifetime risks not yet determined • May increase risk for other cancers • Guidelines for screening and prevention not yet established

Table 1: Composition of Breast/Ovarian Cancer Panel

Ambry Genetics

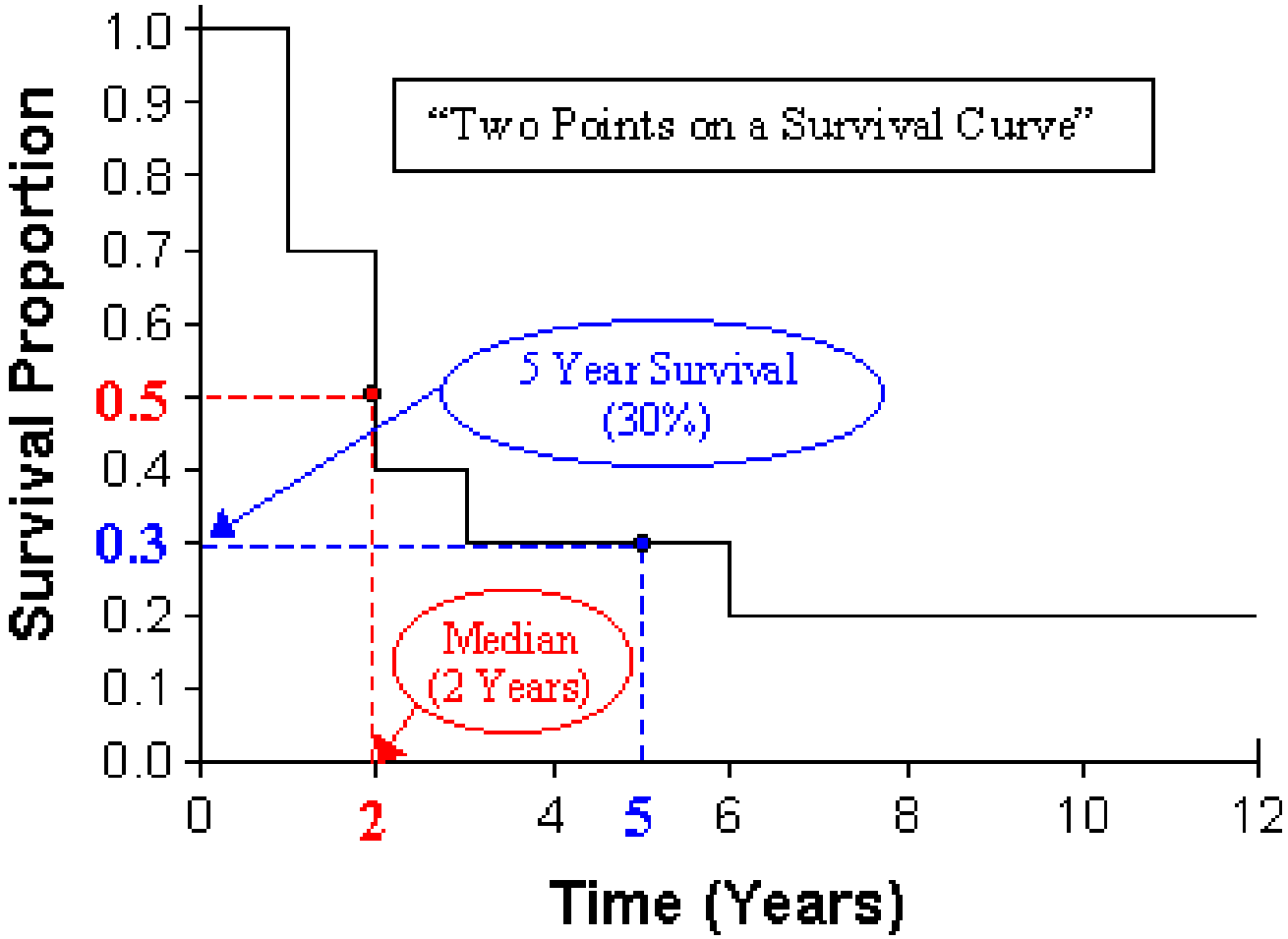
HR Defects in High Grade Serous Ovarian Cancer



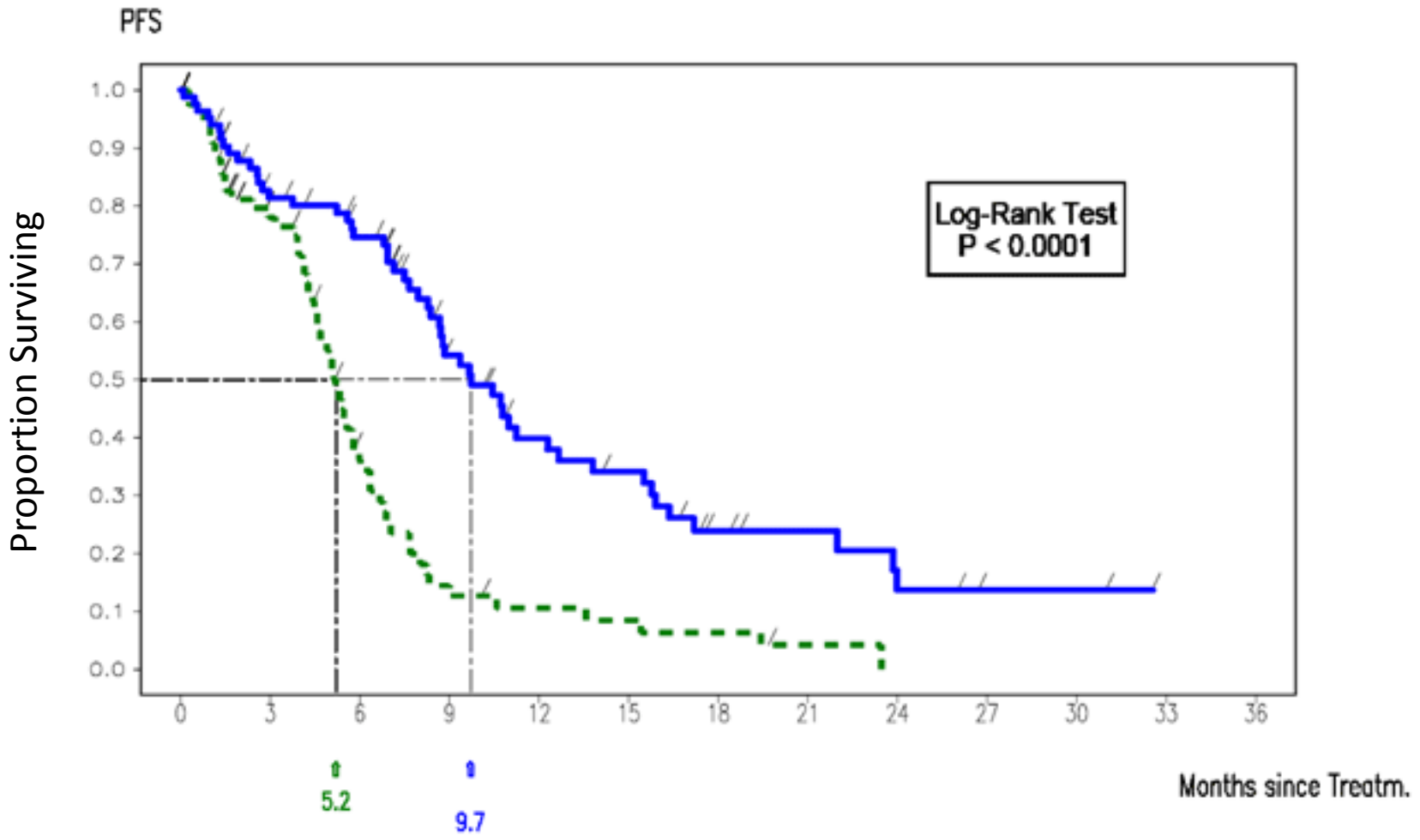
"BRCA-ness" Phenotype

Konstantinopoulos et al. Cancer Discov 2015;5:1137-1154

Kaplan Meier Survival Curves

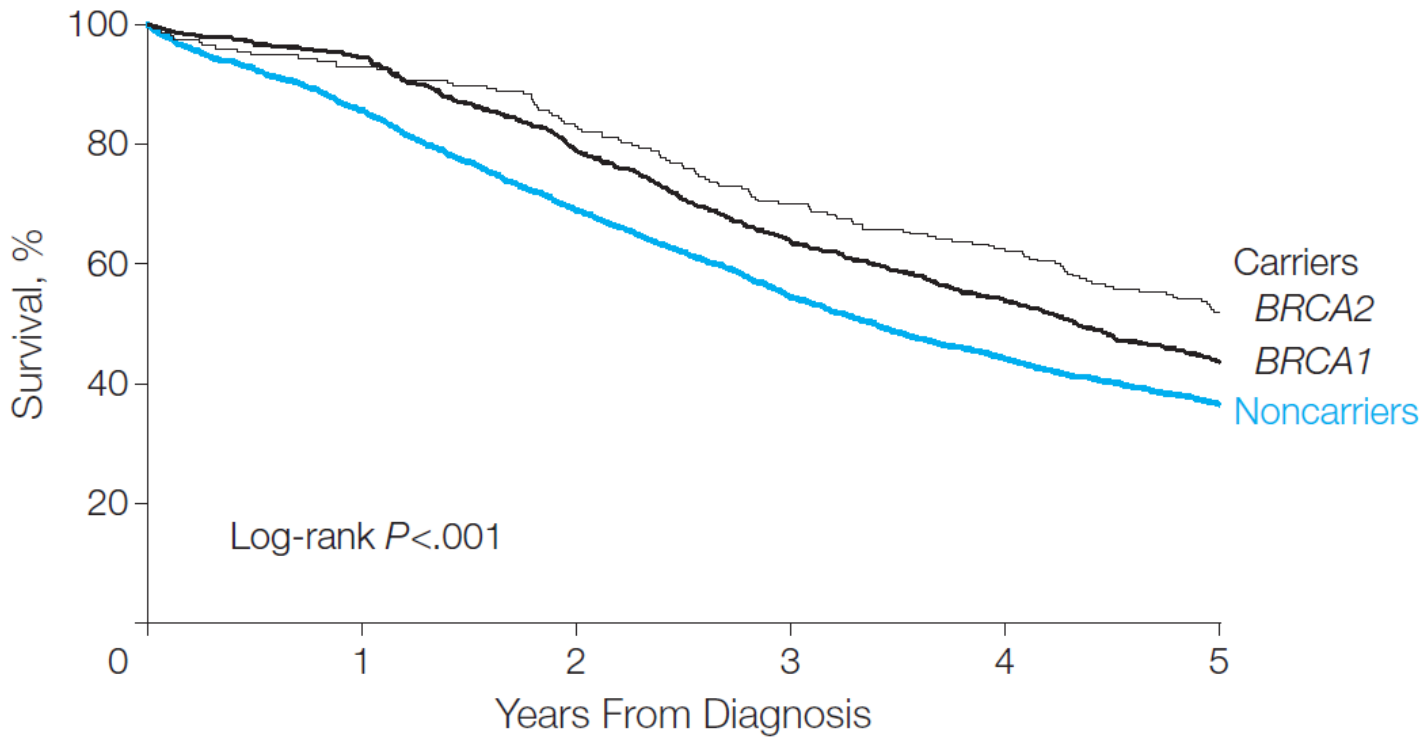


Kaplan Meier Survival Curves



Survival with Germline BRCA Mutation

Figure. Kaplan-Meier Estimates of Cumulative Survival According to *BRCA1/2* Status

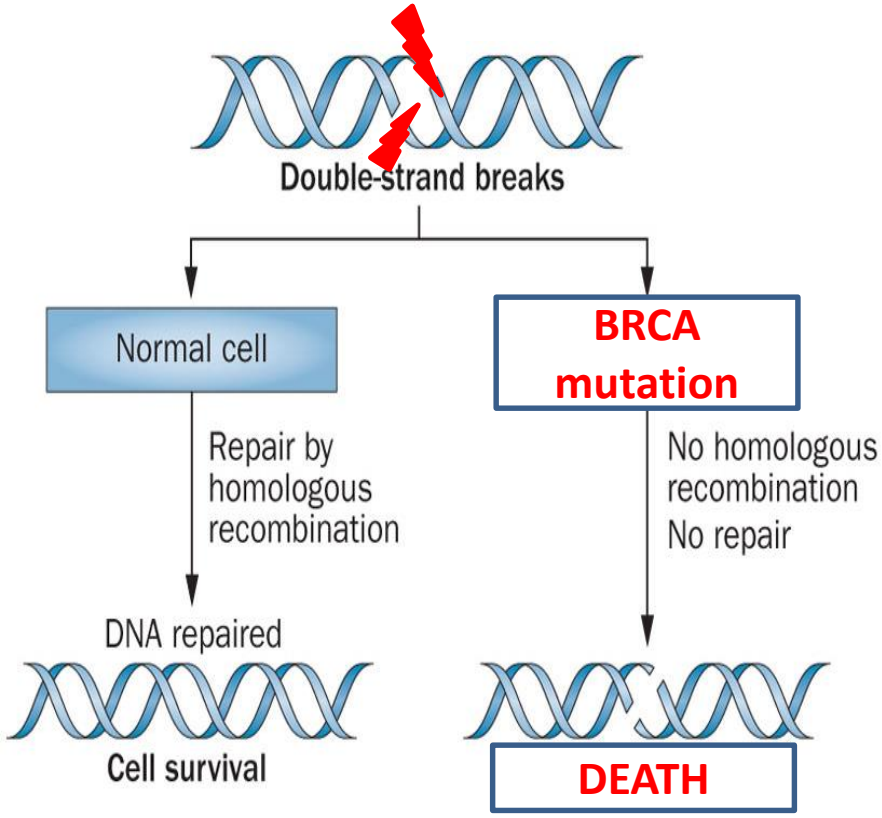


Bolton et al *JAMA. 2012;307(4):382-390*

Why the improved response to chemotherapy?

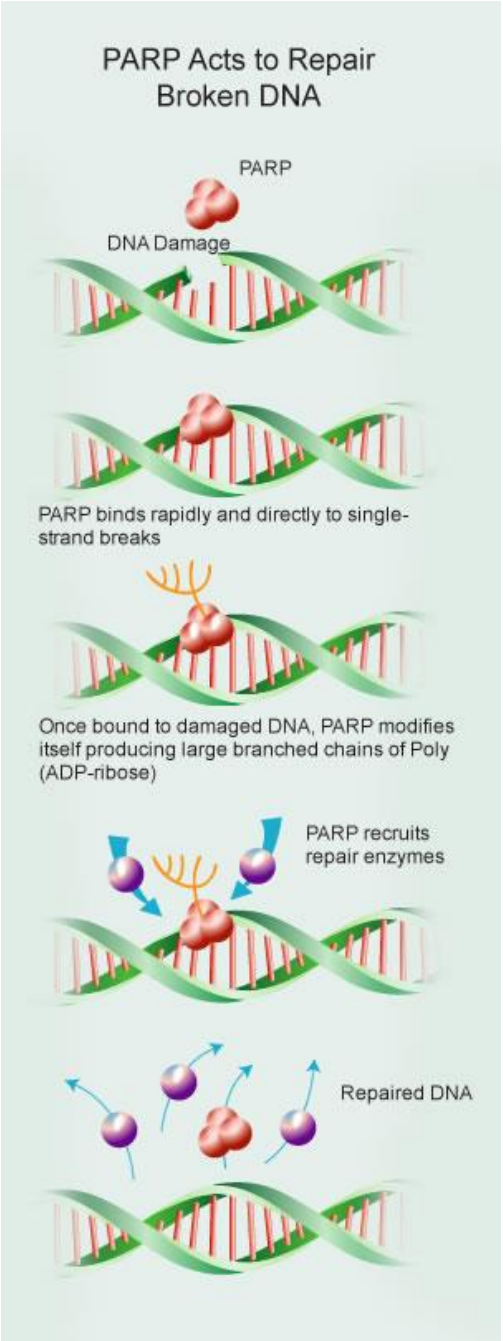
Cisplatin targets DNA

- Inter- and intra-strand cross-linking
- leading to dsDNA breaks

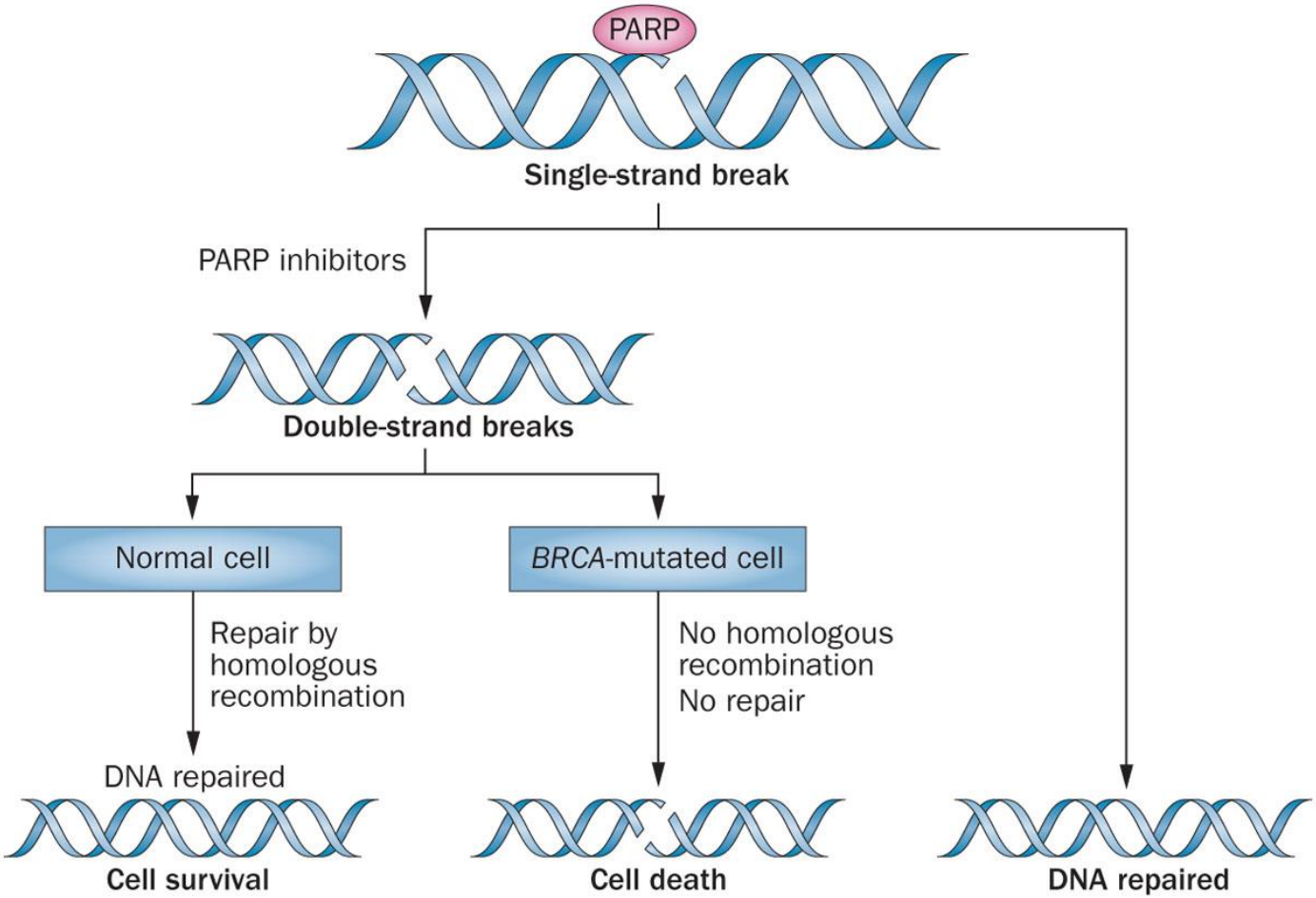


PARP (poly ADP ribose polymerase) Inhibitors

- Olaparib
- Rucaparib
- Niraparib
- Talazoparib
- Veliparib



Synthetic Lethality



Banerjee et al, Nat Rev Clin Oncol 2010; 7:508-519

Clinical Trials

- Platinum-sensitive = more than 6 months
- Platinum-resistant = less than 6 months
- Maintenance therapy

- Trial endpoints
  - Progression free survival (PFS)
  - Overall survival (OS)

Clinical Trials with PARP Inhibitors

- Platinum-sensitive vs.
  Platinum-resistant vs.
  maintenance therapy
- BRCA mutation status
- Without or with chemotherapy
- Without or with other targeted therapies

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

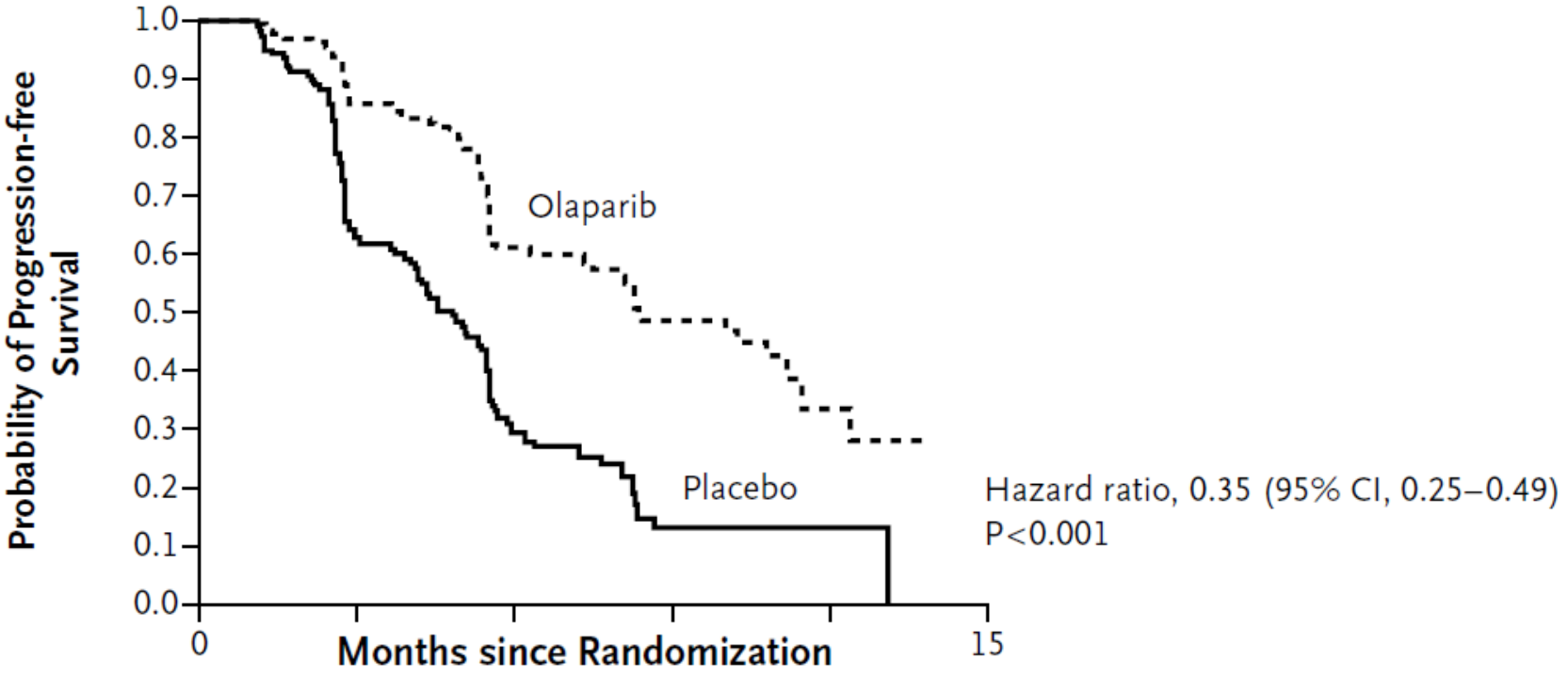
Olaparib Maintenance Therapy in Platinum-Sensitive Relapsed Ovarian Cancer

Study 19

Ledermann et al, NEJM 2012, 366:15

- Phase II randomized, placebo-controlled trial
- Olaparib 400 mg bid versus placebo
- N=265
- Platinum sensitive
- ≥2 platinum therapies with partial or complete response to most recent treatment

Study 19



<u>All patients</u>

PFS: 8.4 vs 4.8m

p<0.0001

<u>BRCA mutation (N=136)</u>

PFS: 11.2 vs 4.3m

p<0.0001

No difference in OS

PARP Inhibitor Side-Effects

Common:

- Fatigue (48%), nausea (68%), anemia (17%)
- Diarrhea (23%), altered taste (14%), headache (18%), “cold-like” symptoms (12%)

Rare, serious:

- Pneumonitis (<1%)
- Myelodysplastic syndrome/AML (<1%)

Olaparib Plus Chemotherapy

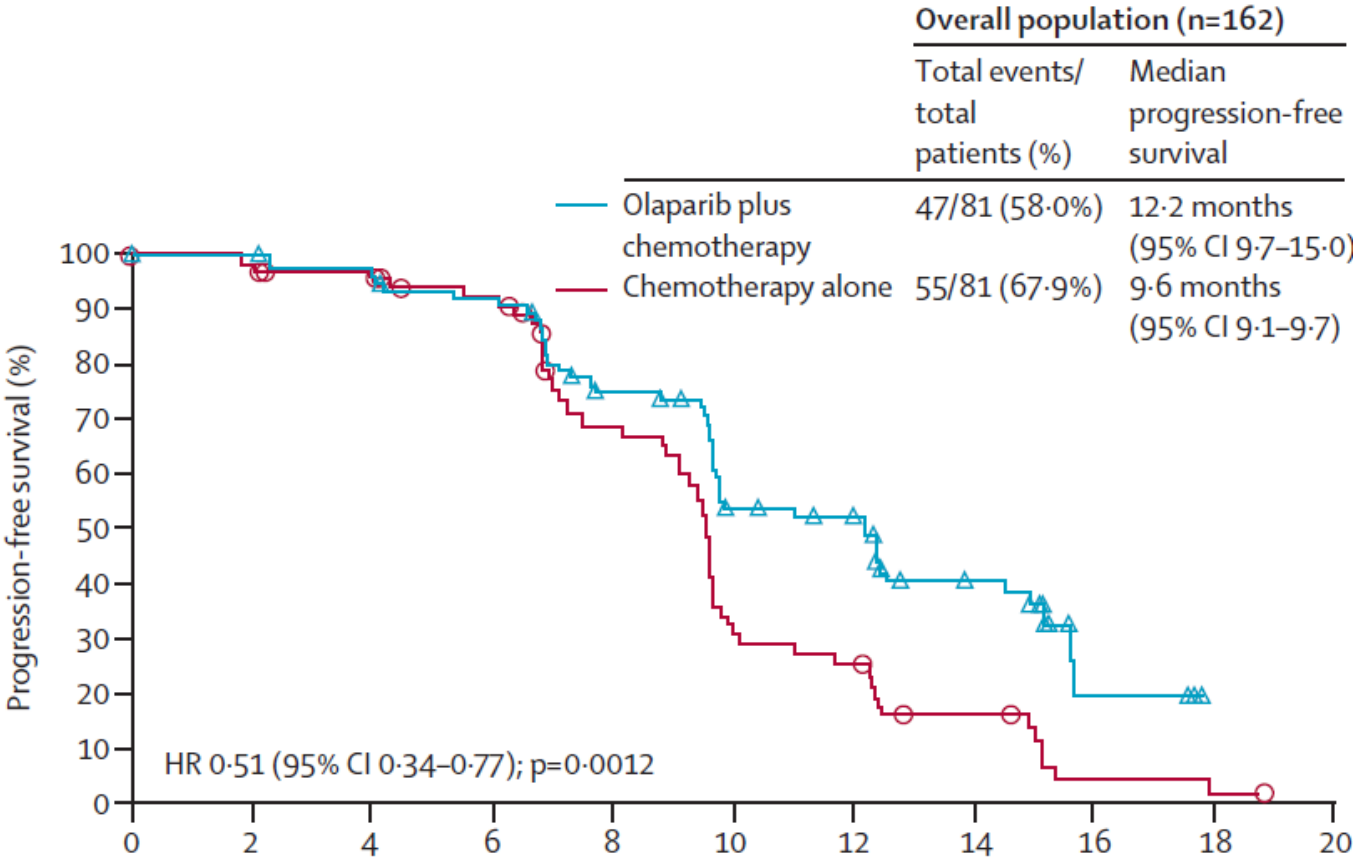
Olaparib combined with chemotherapy for recurrent platinum-sensitive ovarian cancer: a randomised phase 2 trial

Amit M Oza, David Cibula, Ana Oaknin Benzaquen, Christopher Poole, Ron H J Mathijssen, Gabe S Sonke , Nicoletta Colombo, Jiří Špaček, Peter Vuylsteke, Holger Hirte, Sven Mahner, Marie Plante, Barbara Schmalfeldt, Helen Mackay, Jacqui Rowbottom, Elizabeth S Lowe, Brian Dougherty, J Carl Barrett, Michael Friedlander

Lancet Oncol 2015; 16: 87–97

- Platinum sensitive, recurrent high grade serous ovarian cancer
- Up to 3 prior chemotherapy regimens
- Carboplatin (AUC4) + Taxol + Olaparib and Olaparib maintenance vs. Carboplatin (AUC6) + Taxol

Olaparib + Carboplatin/Taxol



<u>All patients</u>

PFS: 12.2 vs 9.6m

p=0.0012

<u>BRCA mutation (N=41)</u>

PFS: NR vs 9.7m

p=0.0015

No difference in OS

Toxicities

	Combination phase				Maintenance phase			
	All grades		Grade ≥3		All grades		Grade ≥3	
	Olaparib plus chemotherapy (n=81)	Chemotherapy alone (n=75)	Olaparib plus chemotherapy (n=81)	Chemotherapy alone (n=75)	Olaparib (n=66)	No treatment (n=55)	Olaparib (n=66)	No treatment (n=55)
Patients with any adverse event	81 (100%)	73 (97%)	53 (65%)	43 (57%)	64 (97%)	41 (75%)	19 (29%)	9 (16%)
Haematological adverse events								
Neutropenia*†	40 (49%)	29 (39%)	35 (43%)	26 (35%)	7 (11%)	4 (7%)	3 (5%)	0
Anaemia*	21 (26%)	16 (21%)	7 (9%)	5 (7%)	8 (12%)	5 (9%)	5 (8%)	1 (2%)
Thrombocytopenia*	18 (22%)	13 (17%)	5 (6%)	6 (8%)	5 (8%)	1 (2%)	0	0

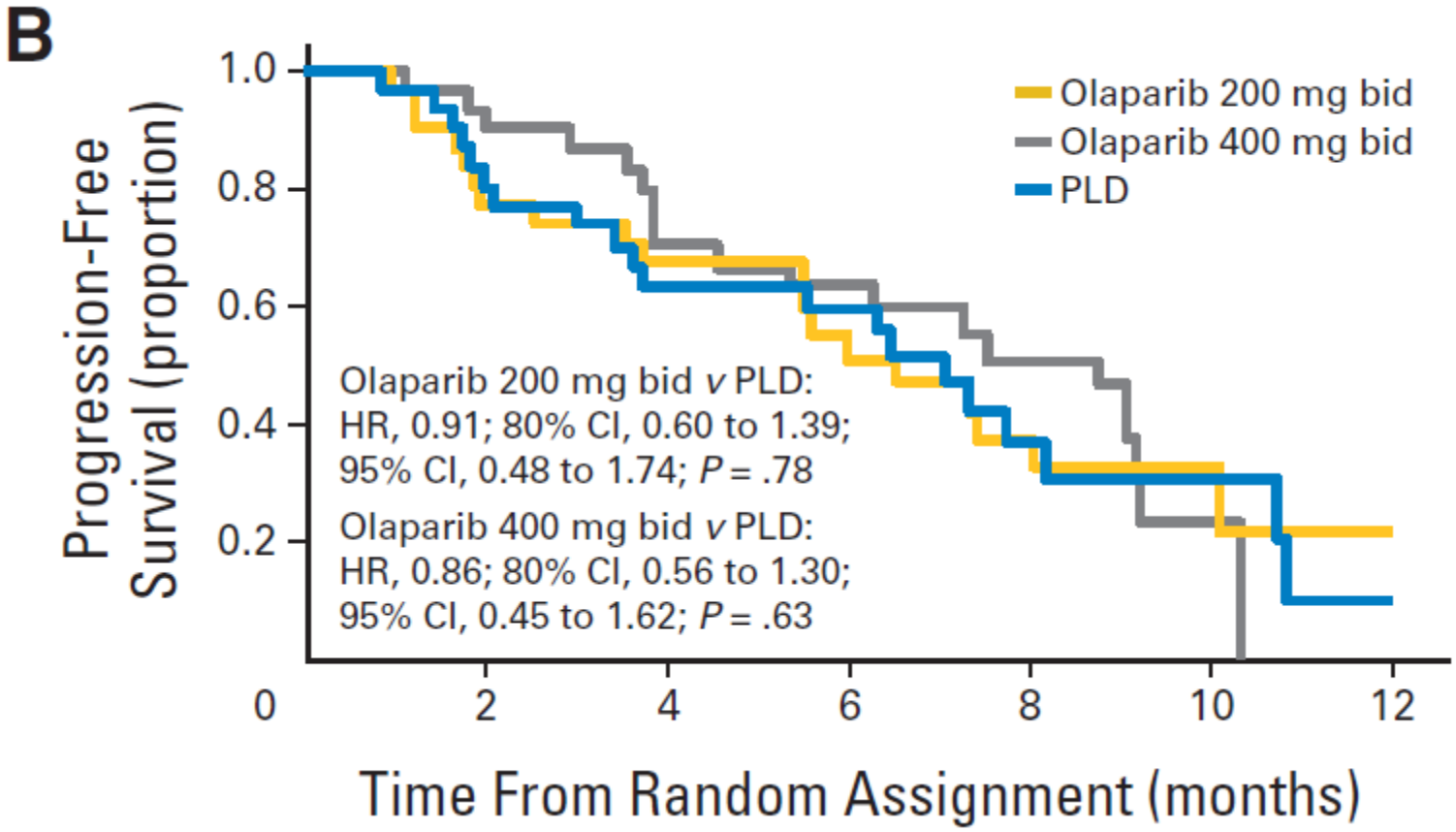
Dose-limiting hematologic toxicities when PARP inhibitors combined with chemotherapy

Phase II, Open-Label, Randomized, Multicenter Study Comparing the Efficacy and Safety of Olaparib, a Poly (ADP-Ribose) Polymerase Inhibitor, and Pegylated Liposomal Doxorubicin in Patients With *BRCA1* or *BRCA2* Mutations and Recurrent Ovarian Cancer

Stan B. Kaye, Jan Lubinski, Ursula Matulonis, Joo Ern Ang, Charlie Gourley, Beth Y. Karlan, Amit Amnon, Katherine M. Bell-McGuinn, Lee-May Chen, Michael Friedlander, Tamar Safra, Ignace Vergote, Mark Wickens, Elizabeth S. Lowe, James Carmichael, and Bella Kaufman

JCO 2012; 30:372

- Germline BRCA mutation patients
- *Recurrence within 12 months*
- Primary outcome PFS
- N=97



- Doxil vs 400mg olaparib vs 200mg olaparib
- PFS 6.5 vs 8.8 vs 7.1 months

Olaparib Monotherapy in Patients With Advanced Cancer and a Germline *BRCA1/2* Mutation

Bella Kaufman, Ronnie Shapira-Frommer, Rita K. Schmutzler, M. William Audeh, Michael Friedlander, Judith Balmaña, Gillian Mitchell, Georgeta Fried, Salomon M. Stemmer, Ayala Hubert, Ora Rosengarten, Mariana Steiner, Niklas Loman, Karin Bowen, Anitra Fielding, and Susan M. Domchek

JCO 2015; 33:244

- Phase II, germline BRCA1/2 mutation
  - ovarian cancer resistant to prior platinum therapy
  - breast cancer with ≥ three chemotherapy regimens for metastatic disease
  - pancreatic cancer with prior gemcitabine treatment
  - prostate cancer with progression on hormonal and one systemic therapy
- Primary end-point: tumor response rate

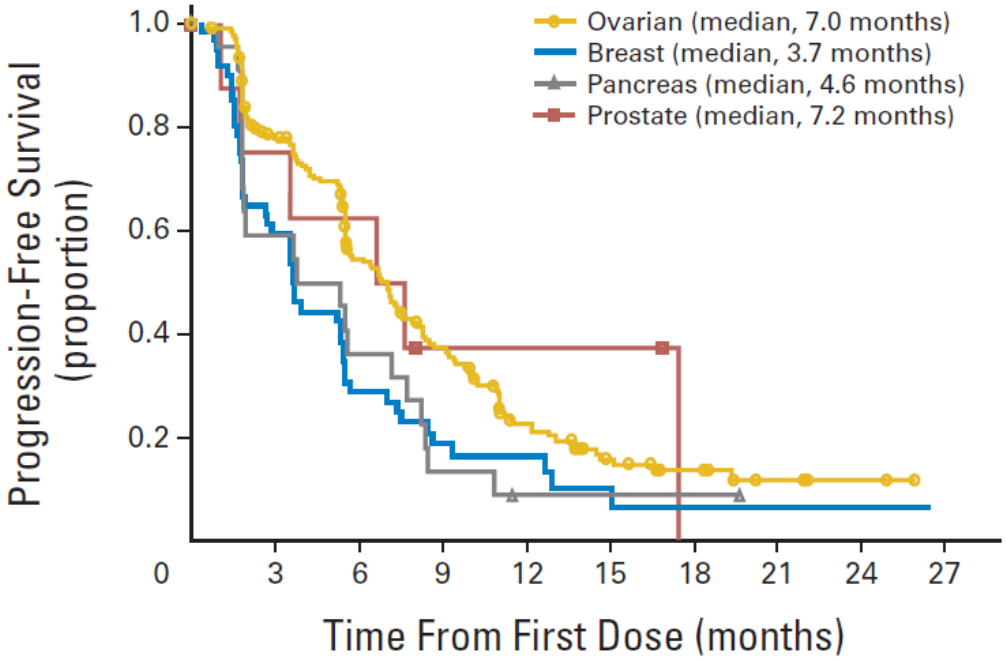
- 193 ovarian cancer patients, mean 4.3 prior therapies

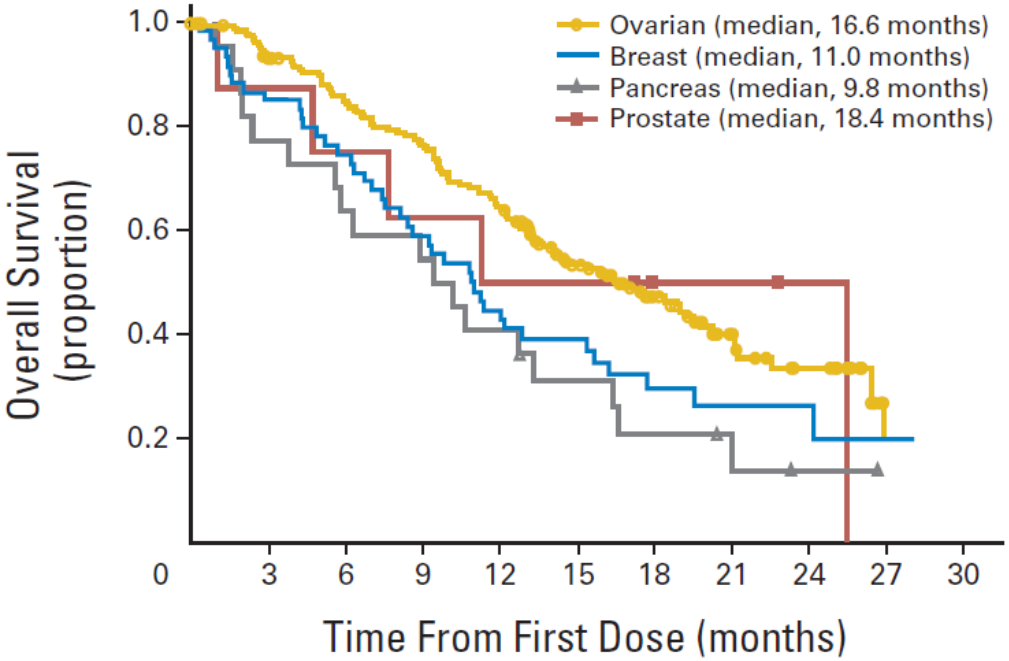
Response Rates

Table 2. Tumor Response Rates (full analysis set)

Response	Ovarian (n = 193)		Breast (n = 62)		Pancreas (n = 23)		Prostate (n = 8)		Other (n = 12)		Total (N = 298)	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Tumor response rate	60	31.1	8	12.9	5	21.7	4	50.0	1	8.3	78	26.2
95% CI	24.6 to 38.1		5.7 to 23.9		7.5 to 43.7		15.7 to 84.3		0.02 to 38.5		21.3 to 31.6	
CR*	6	3	0	0	1	4	0	0	0	0	7	2
PR*	54	28	8	13	4	17	4	50	1	8	71	24
Stable disease ≥ 8 weeks	78	40	29	47	8	35	2	25	7	58	124	42
95% CI	33.4 to 47.7		34.0 to 59.9		16.4 to 57.3		3.2 to 65.1		27.7 to 84.8		36.0 to 47.4	
Stable disease	64	33	22	36	5	22	2	25	6	50	99	33
Unconfirmed PR	12	6	7	11	3	13	0	0	1	8	23	8
PD†	41	21	23	37	9	39	2	25	3	25	78	26
95% CI	15.7 to 27.7		25.2 to 50.3		19.7 to 61.5		3.2 to 65.1		5.5 to 57.2		21.3 to 31.6	
RECIST progression	33	17	16	26	6	26	1	13	3	25	59	20
Early death‡	8	4	7	11	3	13	1	13	0	0	19	6

JCO 2015; 33:244





JCO 2015; 33:244

Phase III Trials - Ongoing

Table 2 Ongoing phase III studies of PARP inhibitors for ovarian cancer treatment

Trial and NCI trial number	Study arms	Trial population	Primary endpoint
Newly diagnosed ovarian cancer			
SOLO1 (NCT01844986)	Olaparib versus placebo post-platinum-based chemotherapy	BRCAm only, HGSOC, or endometrioid stage III and IV only	PFS
GOG-3005 (NCT02470585)	Carboplatin and paclitaxel versus carboplatin, paclitaxel, and veliparib versus carboplatin, paclitaxel, and veliparib followed by veliparib maintenance therapy	Advanced HGSOC, both BRCAm and BRCAwt	PFS
PAOLA1 (NCT02477644)	Platinum/taxane/bev, bev maintenance versus platinum/taxane/bev, bev/olaparib maintenance	Newly diagnosed high-grade ovarian cancer	PFS

Curr Oncol Rep 2016; 18:29

Phase III Trials - Ongoing

Recurrent ovarian cancer			
NOVA (NCT01847274)	Niraparib versus placebo post platinum-based chemotherapy	Platinum-sensitive, HGSOC, BRCA-stratified	PFS
SOLO2 (NCT01874353)	Olaparib versus placebo post platinum-based chemotherapy	Platinum-sensitive BRCAm only, HGSOC, or endometrioid	PFS
ARIEL3 (NCT01968213)	Rucaparib versus placebo post-platinum-based chemotherapy	Platinum-sensitive recurrence, HGSOC or endometrioid BRCA-stratified	PFS
SOLO3 (NCT02282020)	Olaparib versus MD choice non-platinum chemotherapy	Platinum-sensitive BRCAm HGSOC	PFS
NRG-GY004 (NCT02446600)	Olaparib versus olaparib/cediranib versus platinum doublet	Platinum-sensitive recurrent high-grade ovarian cancer BRCA-stratified	PFS
NRG-GY005 (NCT02502266)	Olaparib/cediranib versus single-agent chemotherapy	Platinum resistant recurrent high-grade ovarian cancer	PFS (ph 2) OS (ph 3)

Curr Oncol Rep 2016; 18:29

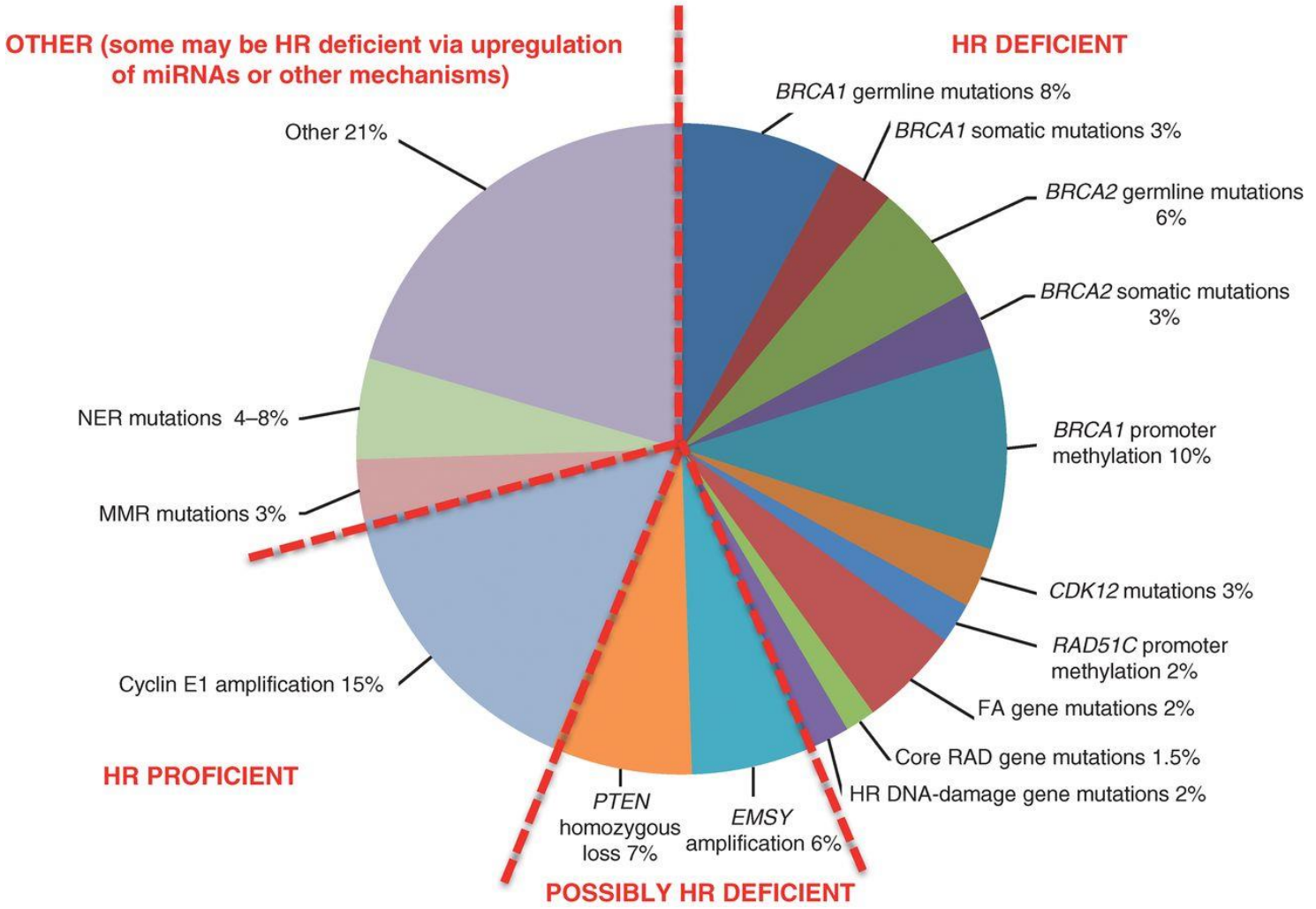
European PARP Inhibitor Approval

Monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed *BRCA*-mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.

FDA Approval

- Olaparib (Lynparza)
- December 19, 2014 – accelerated approval
- BRACAnalysis CDx – companion diagnostic
- Germline BRCA mutation positive and 3 prior lines of chemotherapy

HR Defects in High Grade Serous Ovarian Cancer



"BRCA-ness" Phenotype

Konstantinopoulos et al. Cancer Discov 2015;5:1137-1154

Identifying “BRCA-ness”

- How can we identify patients who will demonstrate an enhanced response to PARP inhibitor therapy?

Genomic Scarring

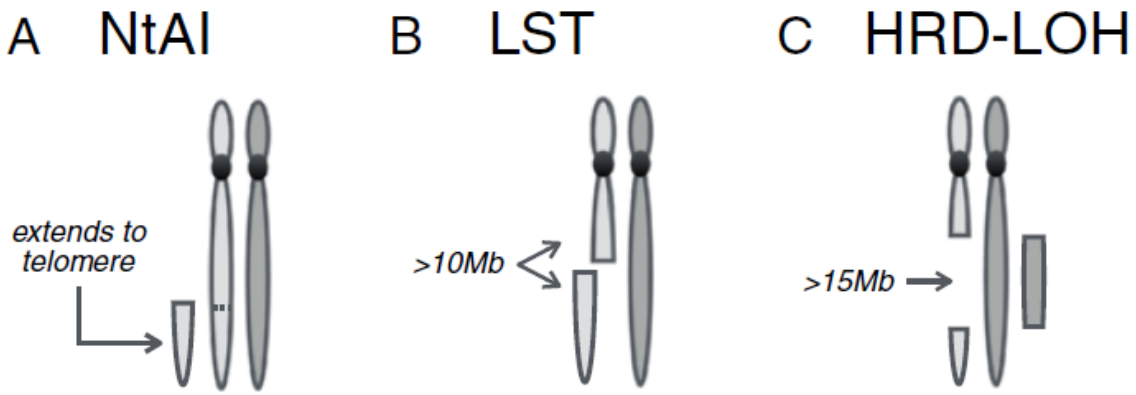
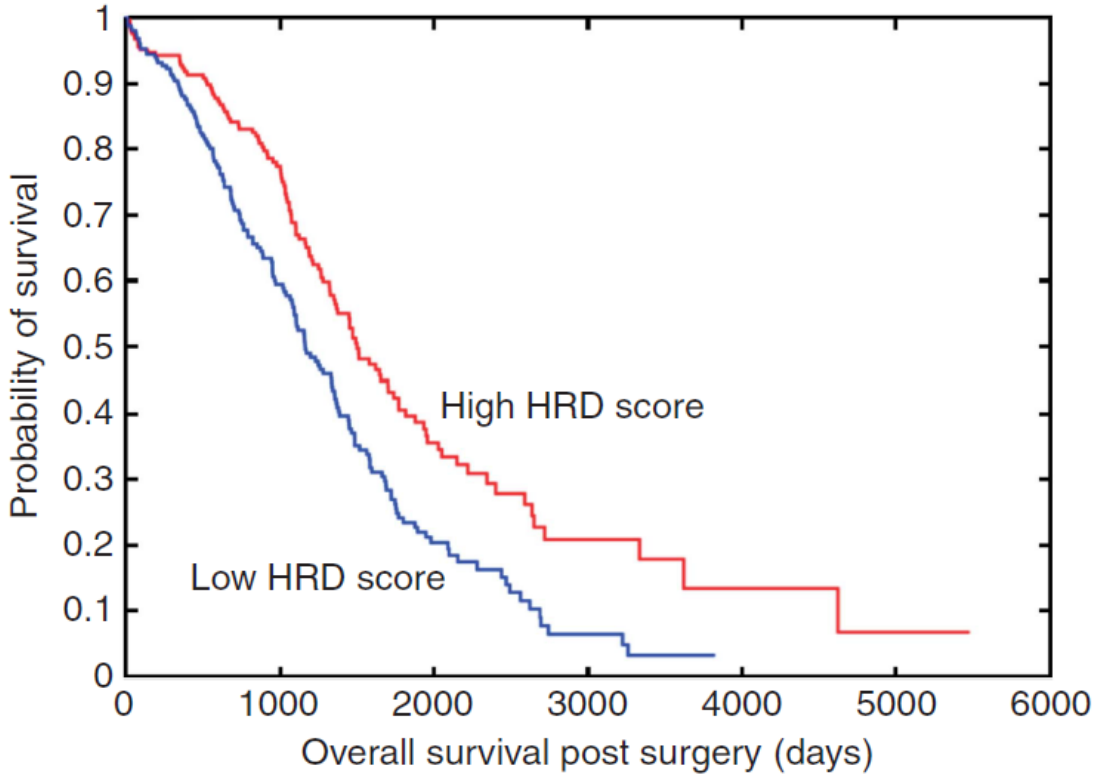


Figure 1 Overview of the type of genomic scars measured by each HR signature. Dark and light grey are used to indicate paternal and maternal chromosomes. **A**: Number of telomeric allelic imbalances (NtAI) counts the number of subtelomeric regions with allelic imbalance, that start beyond the centromere and extend to the telomere. **B**: Large-scale state transitions (LST) counts the number of chromosomal breaks between adjacent regions of at least 10 Mb. **C**: Homologous recombination deficiency score (HRD-LOH) measures the number of regions with LOH which are larger than 15 Mb, but shorter than the whole chromosome.

HRD Score

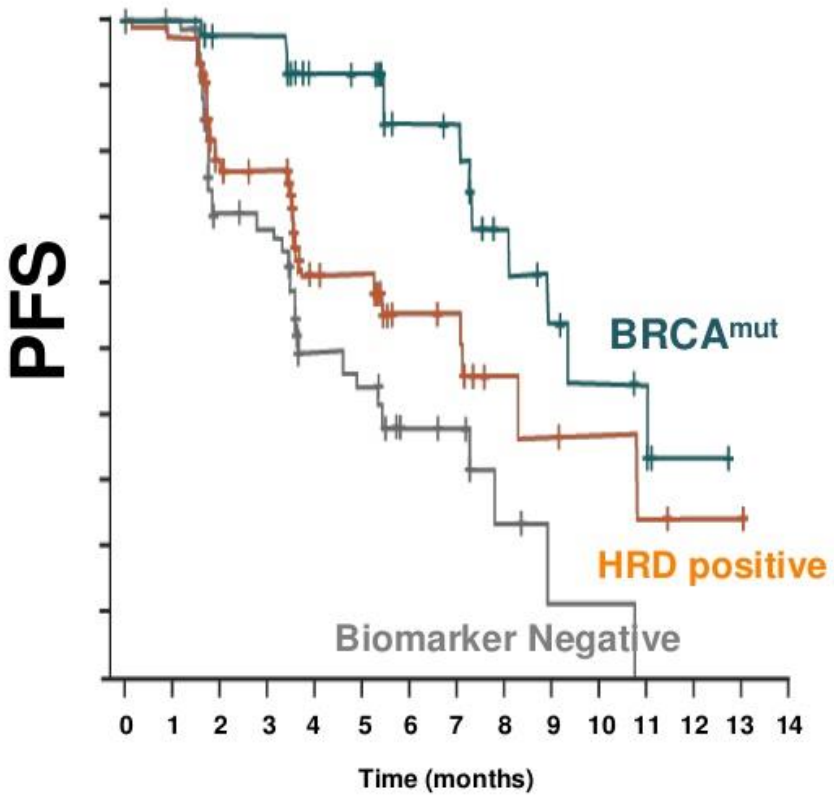
Patterns of genomic loss of heterozygosity predict homologous recombination repair defects in epithelial ovarian cancer



Abkevich et al, BJC, 2012; 107:1776

HRD score predicts PARPi response
ARIEL2 Rucaparib

PFS by HRD biomarker status

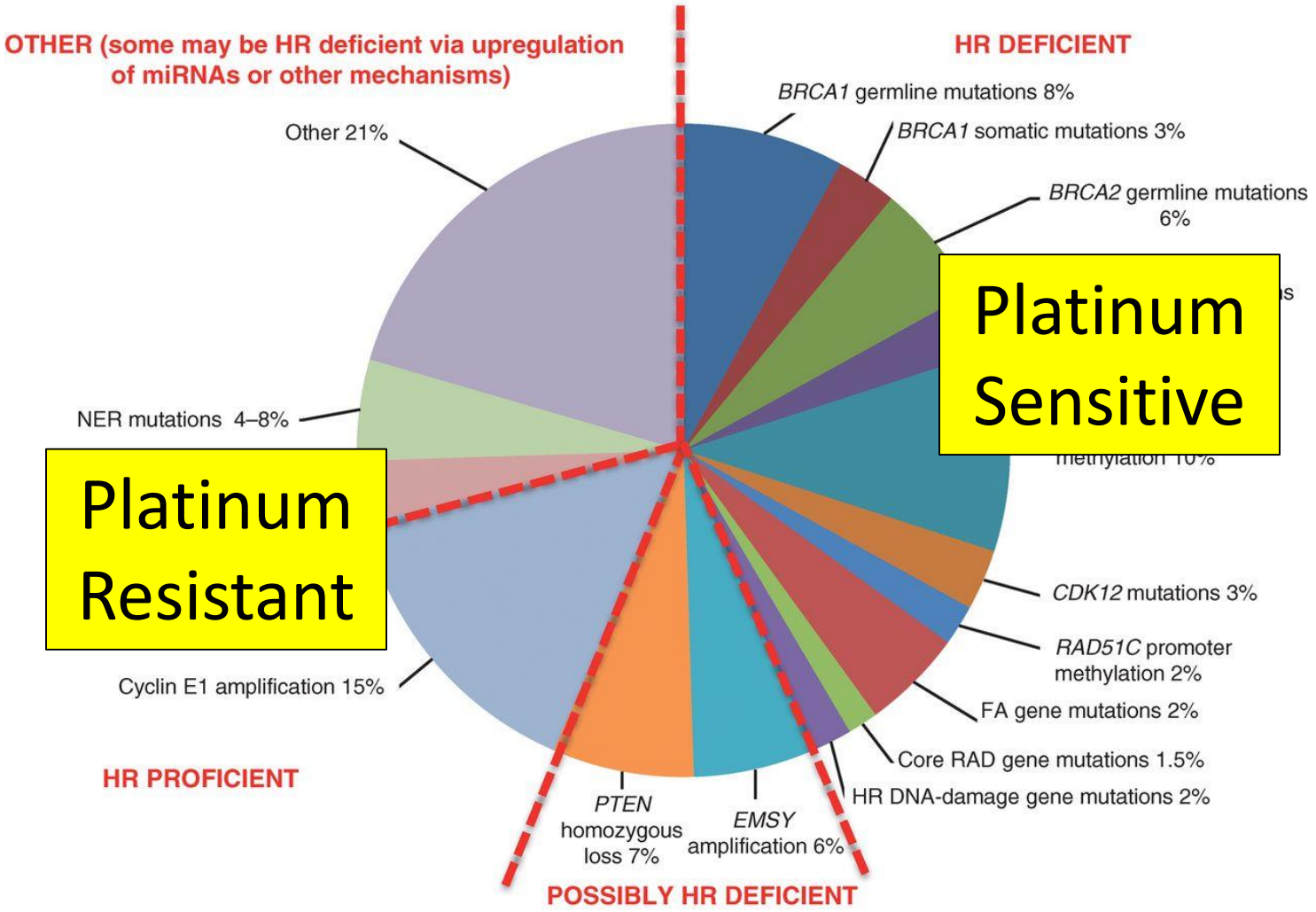


HRD Subgroup	Median PFS, mo (90% CI)
BRCA^{mut}	9.4 (7.3, Not Reached)
HRD positive	7.1 (3.7, 10.8)
Biomarker Negative	3.7 (3.5, 5.5)

Subgroup Comparison	Hazard Ratio (90% CI)
BRCA^{mut} vs Biomarker Negative	0.47 (0.35, 0.64)
HRD vs Biomarker Negative	0.61 (0.41, 0.92)

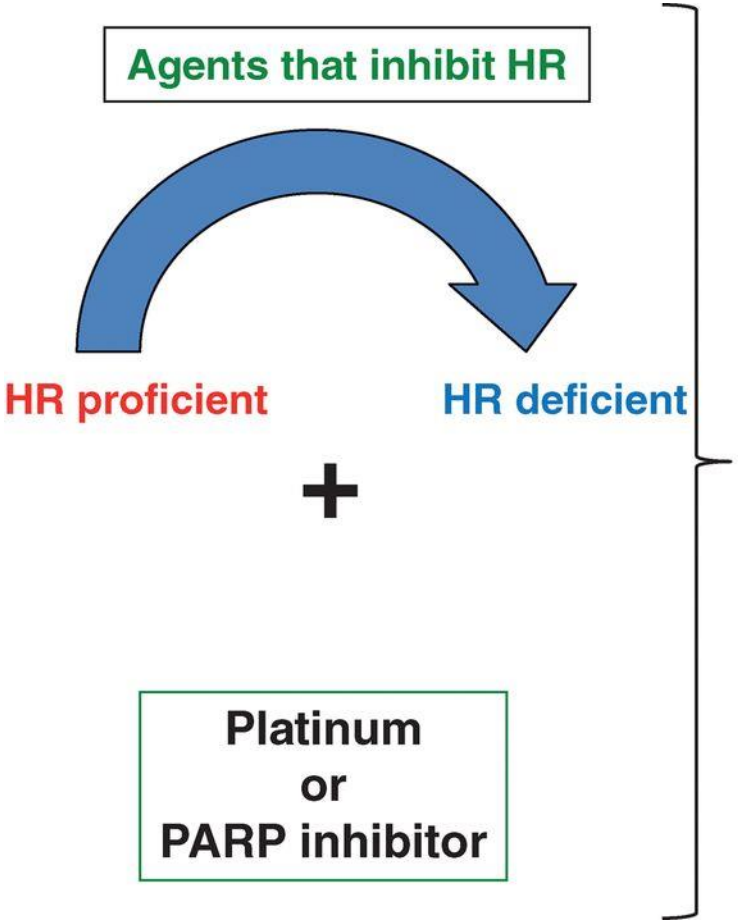
McNeish and colleagues
ARIEL2

HR Defects in High Grade Serous Ovarian Cancer



Konstantinopoulos et al. Cancer Discov 2015;5:1137-1154

Can We Make Tumors HR Deficient?



Combinations	Possible mechanism of HR suppression	Status
PARPi/CDK1 inhibitors	Inhibition of phosphorylation of BRCA1	Phase I clinical trial (Veliparib+dinaciclib)
PARPi/PI3K pathway inhibitors	Increased activation of ETS1 and suppression of BRCA1/2 expression	Phase I clinical trials (Olaparib + BKM120) (Olaparib + AZD5363)
PARPi/VEGFR3 inhibitors	Downregulation of BRCA1/2 gene expression	Randomized phase II trial (Olaparib+Cediranib)
PARPi/HSP90 inhibitors	BRCA1 and other HR pathway genes are HSP90 client proteins	Preclinical
PARPi/HDAC inhibitors	Downregulation of HR pathway genes	Preclinical
PARPi/CDK12 inhibitors	Downregulation of HR pathway genes	Phase I clinical trial (Veliparib+dinaciclib)

Panagiotis A. Konstantinopoulos et al. Cancer Discov 2015;5:1137-1154

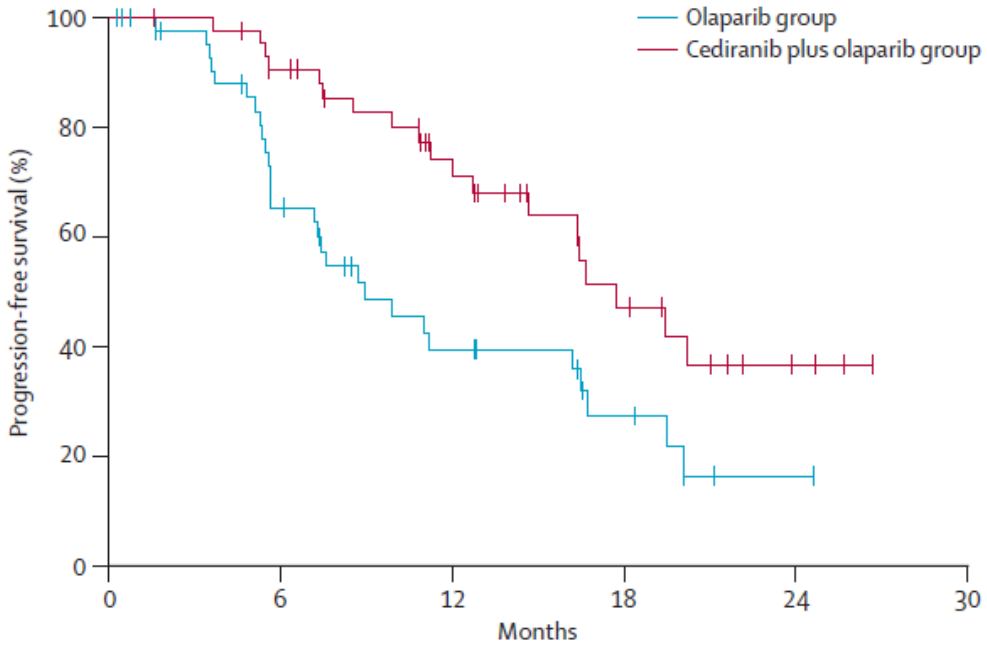
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AACR American Association for Cancer Research
CANCER DISCOVERY

Combination cediranib and olaparib versus olaparib alone for women with recurrent platinum-sensitive ovarian cancer: a randomised phase 2 study

Lancet Oncol 2014; 15: 1207–14

Joyce F Liu, William T Barry, Michael Birrer, Jung-Min Lee, Ronald J Buckanovich, Gini F Fleming, BJ Rimel, Mary K Buss, Sreenivasa Nattam, Jean Hurteau, Weixiu Luo, Philippa Quy, Christin Whalen, Lisa Obermayer, Hang Lee, Eric P Winer, Elise C Kohn, S Percy Ivy, Ursula A Matulonis



PFS: 17.7m vs 9.0m
P=0.005

Grade 3 and 4:
Fatigue, diarrhea, hypertension

BRCA mut and BRCA wt

When to Use PARP Inhibitors?

- What patients? What clinical setting?

  We are still answering this question!
- Many phase III trials in progress
- Side-effect profile versus cytotoxic chemotherapy
- FDA-approved patients only
- Cost? $13,000 per month

The big question with ovarian cancers:
How can we improve OVERALL SURVIVAL?

PARP Inhibitors for the Treatment of Ovarian Cancer: Rationale and Clinical Outcomes



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Comprehensive Cancer Center