SCIENTIFIC BITES®

Cancer research
e-learning platform

State of the art in Hereditary Ovarian Cancer

Begoña Graña Suárez MD Ph.D

Medical Oncology Department
University Hospital A Coruña
July 2021

by SOLTI

Disclosures

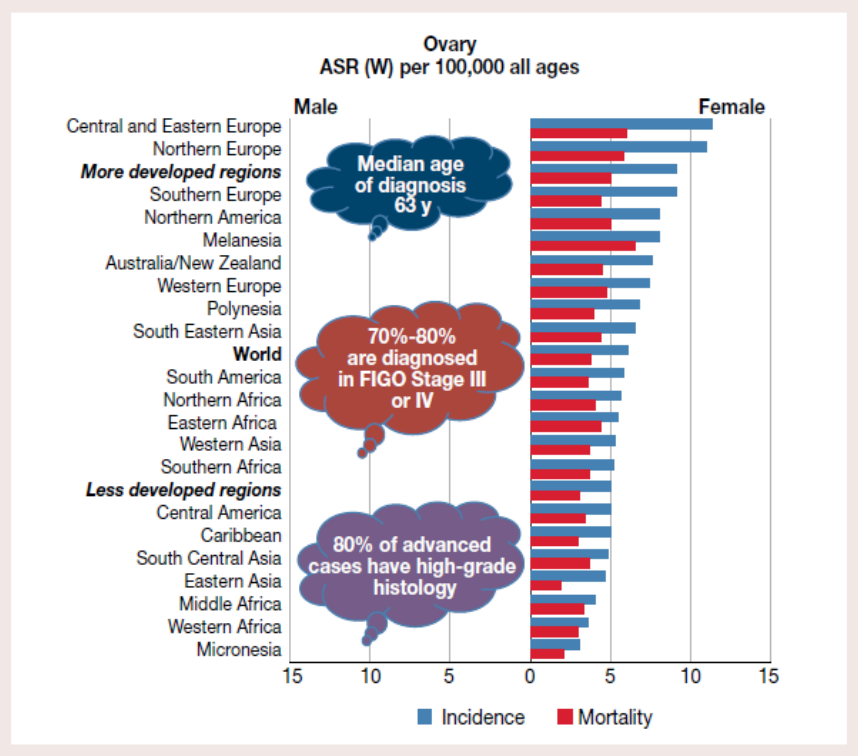
- Clinical trial participation as PI: AMGEN, ERYTECH, SANOFI, GILEAD, BMS, INCYTE
- Registration and attending scientific meetings: CELGENE, AMGEN, SANOFI, MERCK, ROCHE, SERVIER, EISAI, PIERRE FABRE

Index: state of the art in Hereditary Ovarian Cancer

1. Epidemiology and classification of ovarian cancer
2. Gene testing and genetic counselling in ovarian cancer
3. Management of hereditary ovarian cancer síndromes:BRCA1/2, PALB2, RAD51C/D, Lynch syndrome
4. Treatment: PARP inhibitors
5. Conclusions

1. Epidemiology and classification of ovarian cancer

1. Epidemiology and classification of ovarian cancer



Among gynaecological cancers, ovarian cancer (OC) is the second most common in the developed world, but the most common cause of gynaecological cancer death (fifth highest in women)

Gynaecological Tumours
Essentials for Clinicians

ISBN: 978-88-941795-1-4

2. Gene testing and genetic counselling in ovarian cancer

2. Gene testing and genetic counselling in ovarian cancer

Reasons for considering germinal gene testing in ovarian cancer:

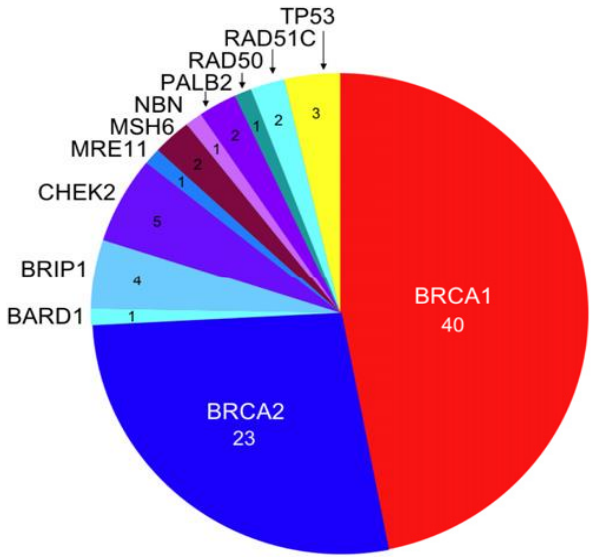
Cancer risk estimation and genetic counselling

Prevention

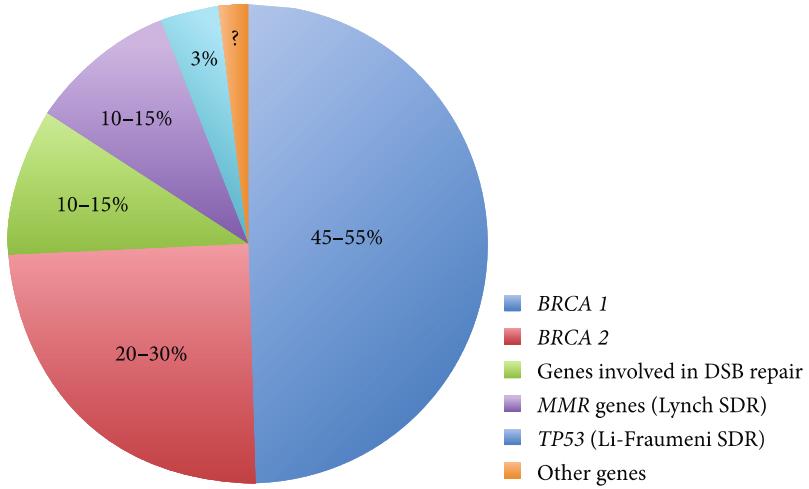
Treatment biomarker

2. Genetic testing in ovarian cancer

Susceptibility genes and their prevalence in hereditary ovarian syndromes

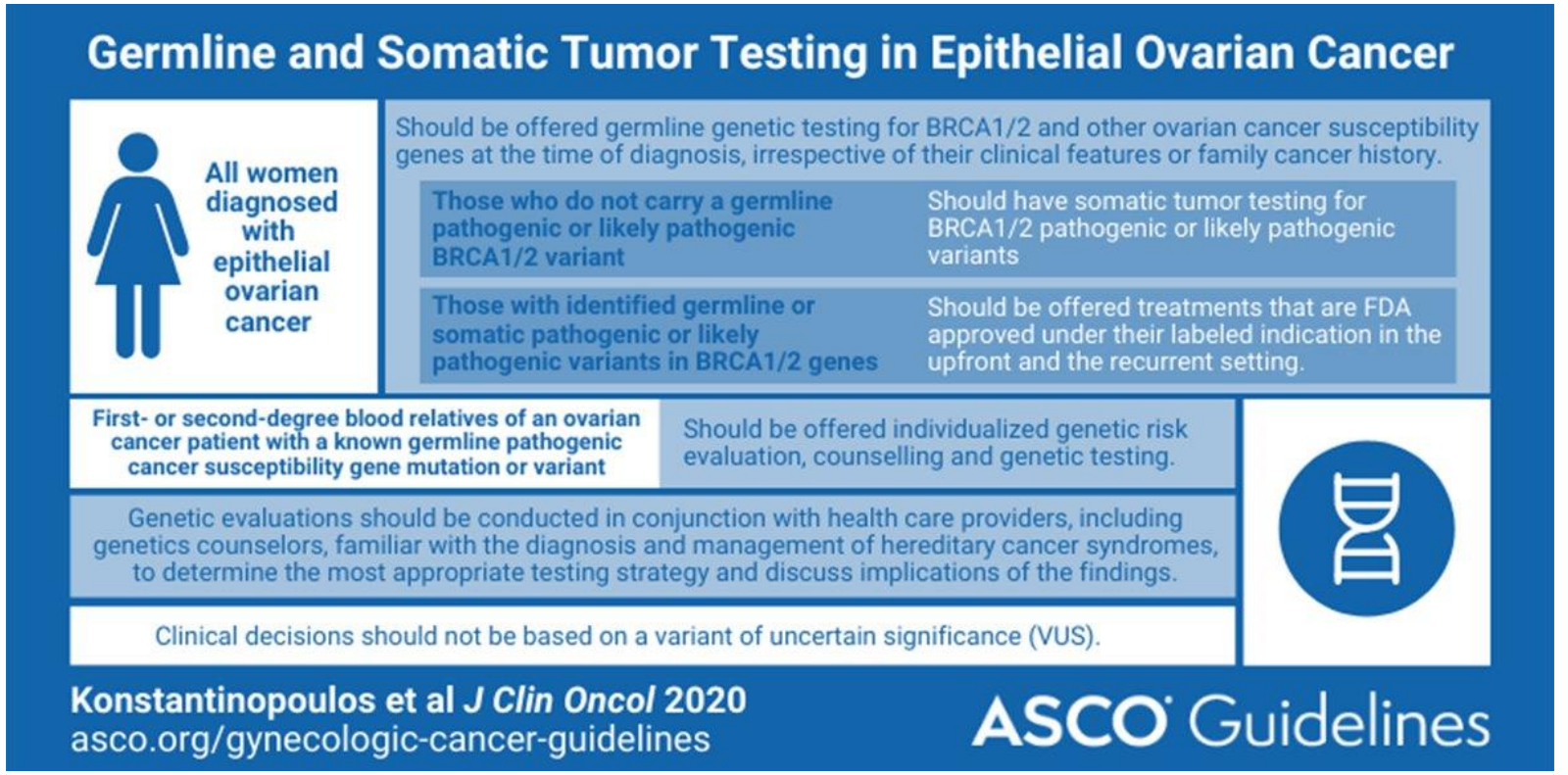


Walsh *et al.* PNAS 2011.
Germline mutations in 85/360 unselected women with ovarian, fallopian tube or peritoneal cancer.

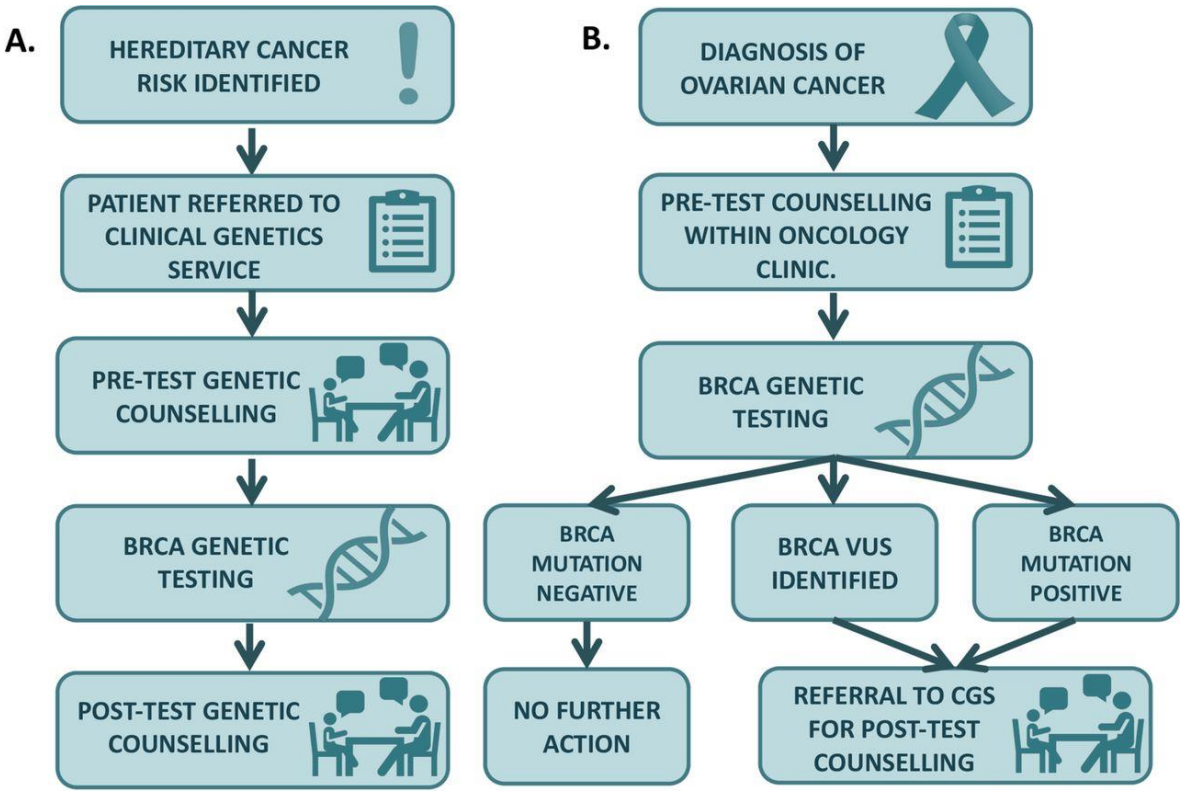


Fostira F, *et al.* Annals of Translational Medicine, Vol 8, No 24 December 2020.

2. Genetic testing in ovarian cancer



2. Mainstreamed genetic testing in ovarian cancer



McLeavy L, et al. Mainstreamed genetic testing in ovarian cancer: patient experience of the testing process. Int J Gynecol Cancer. 2020 Feb;30(2):221-226.

3. Management of hereditary ovarian cancer síndromes:BRCA1/2, PALB2, RAD51C/D, Lynch syndrome

3. Risks of Breast (BC), Ovarian (OC), and Contralateral BC for BRCA1/2 Mutation Carriers

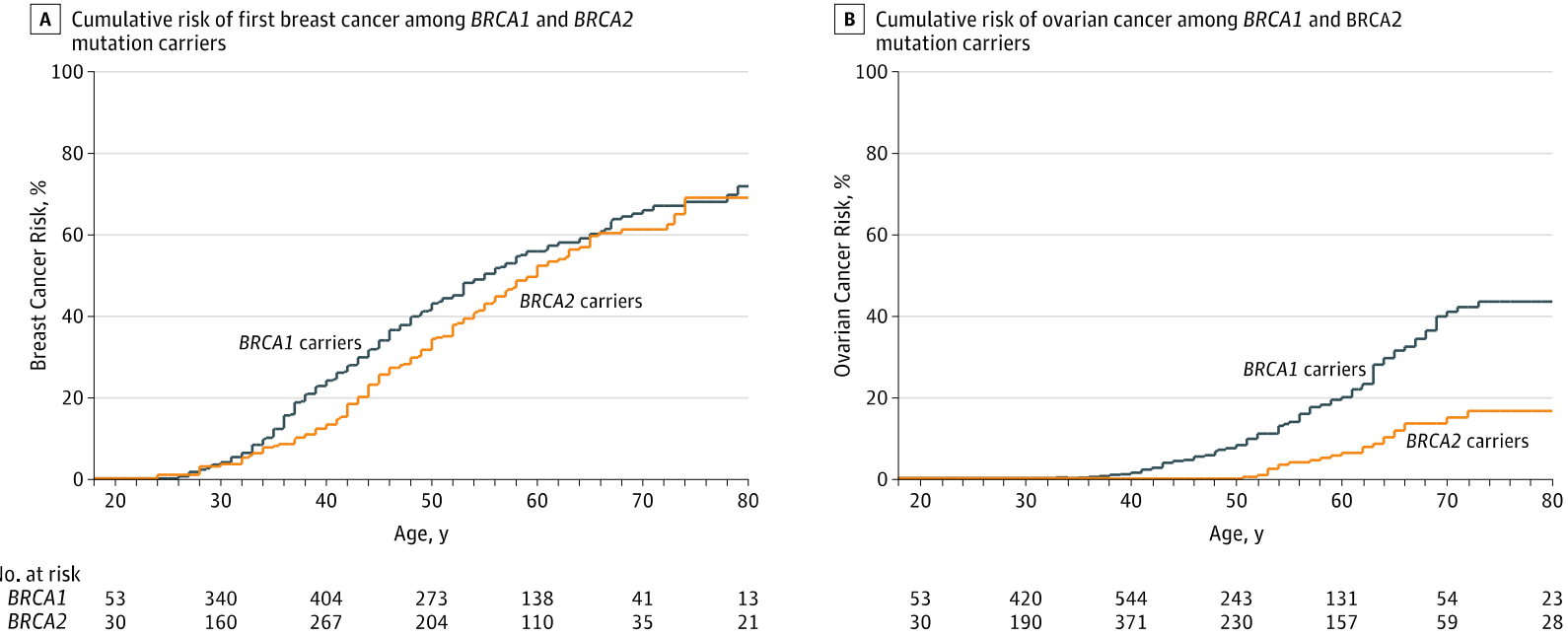
Prospective cohort
Recruited in 1997-2011

6,036 *BRCA1+* 3,820 *BRCA2+*

5,046 unaffected

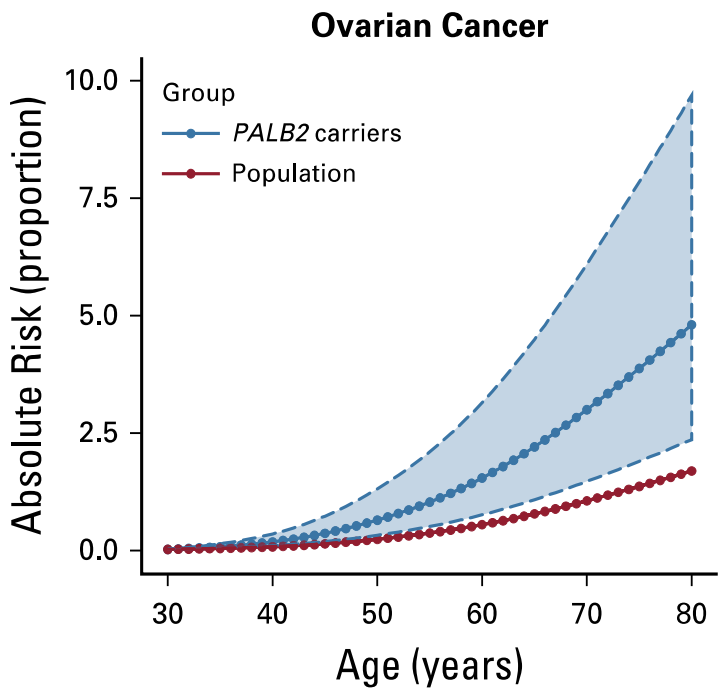
4,810 with breast and/or ovarian cancer or both

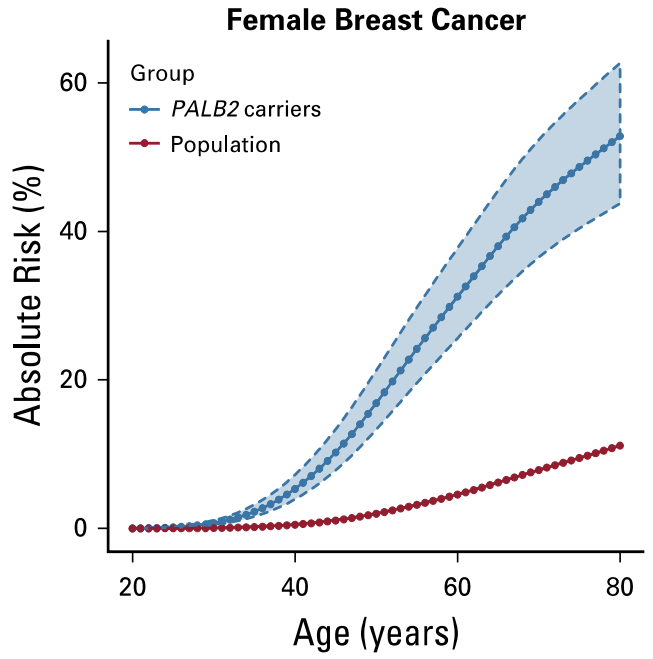
Figure 2. Estimated Cumulative Risks of Breast and Ovarian Cancer in Mutation Carriers



Kuchenbaecker KB, et al. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. JAMA. 2017 Jun 20;317(23):2402-2416.

3. Absolute Risks of Breast, Ovarian Cancer for PALB2 pathogenic variants





Yang X, et al. Cancer Risks Associated With Germline PALB2 Pathogenic Variants: An International Study of 524 Families. J Clin Oncol. 2020 Mar 1;38(7):674-685.

3. Absolute Risks of Breast, Ovarian Cancer for RAD51C and RAD51D pathogenic variants

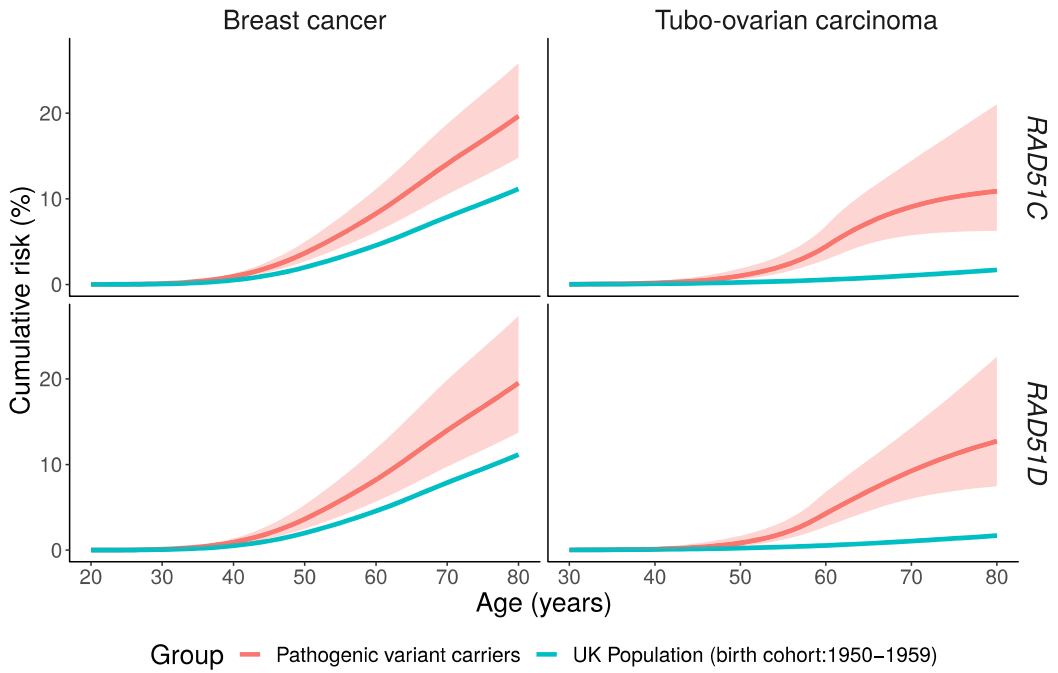


Figure 1. Estimated age-specific tubo-ovarian carcinoma and breast cancer cumulative risks in RAD51C and RAD51D pathogenic variant carriers. The shaded areas cor- respond to the 95% confidence intervals.

RAD51C - 154 families
23 study centers in 10 countries

RAD51D - 65 families
15 study centers in 9 countries

Yang X, et al. Ovarian and Breast Cancer Risks Associated With Pathogenic Variants in RAD51C and RAD51D. J Natl Cancer Inst. 2020 Dec 14;112(12):1242-1250.

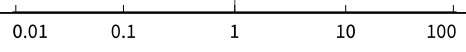
Risk-reducing bilateral salpingo-oophorectomy in women with BRCA1 or BRCA2 mutations (Review)

Cochrane Library

Cochrane Database of Systematic Reviews 2018, Issue 8. Art. No.: CD012464.
DOI: 10.1002/14651858.CD012464.pub2.

Analysis 1.1. Comparison 1 Risk-reducing salpingo-oophorectomy (RRSO) versus no RRSO in BRCA1 or BRCA2 mutation carriers, Outcome 1 Overall survival.

Study or subgroup	Control N	Risk-reducing surgery N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Random, 95% CI	Weight	Hazard Ratio IV, Random, 95% CI
1.1.1 BRCA1 or BRCA2						
Domchek 2006	0	0	-1.4 (0.561)		23.49%	0.24[0.08,0.72]
Domchek 2010	0	0	-0.8 (0.389)		48.8%	0.45[0.21,0.96]
Ingham 2013	0	0	-1.5 (0.516)		27.71%	0.22[0.08,0.6]
Subtotal (95% CI)					**100%**	**0.32[0.19,0.54]**
Heterogeneity: $Tau^2=0$; $Chi^2=1.56$, df=2(P=0.46); $I^2=0\%$						
Test for overall effect: Z=4.21(P<0.0001)						

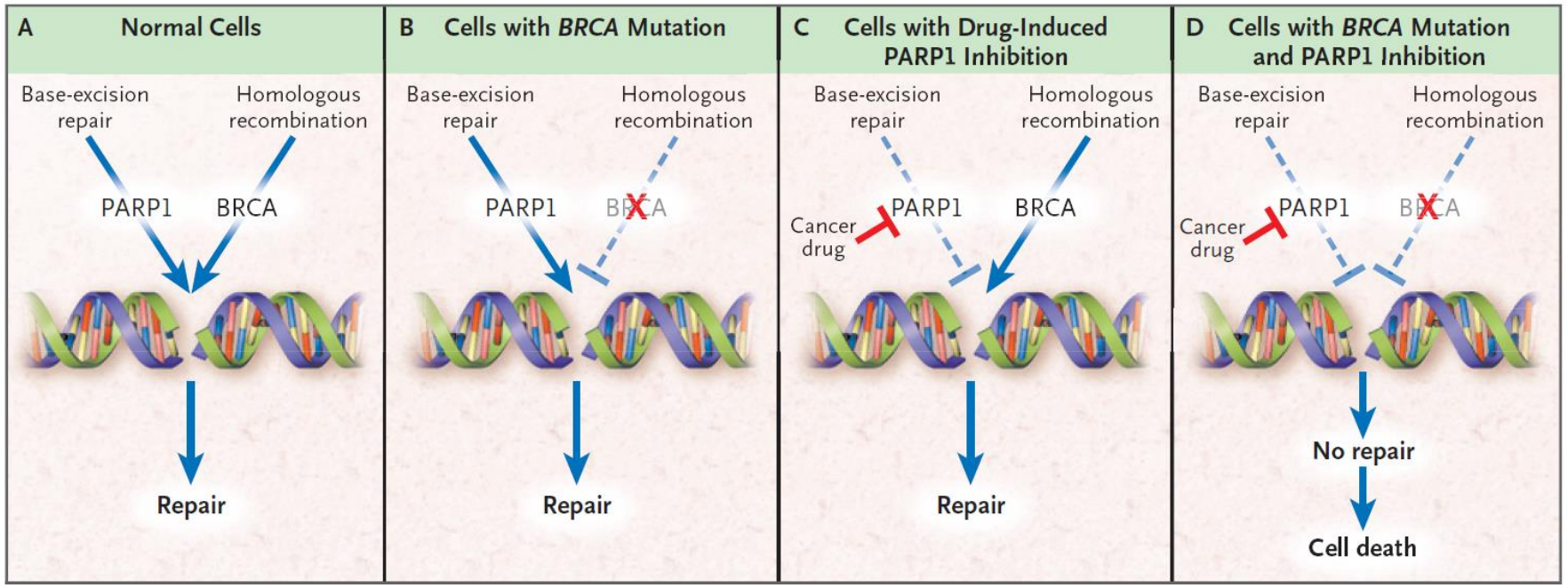


Favours RRSO — Favours control

4. Treatment: PARP inhibitors

4. PARP Inhibitors and Homologous Recombination repair of DNA damage

Synthetic lethality



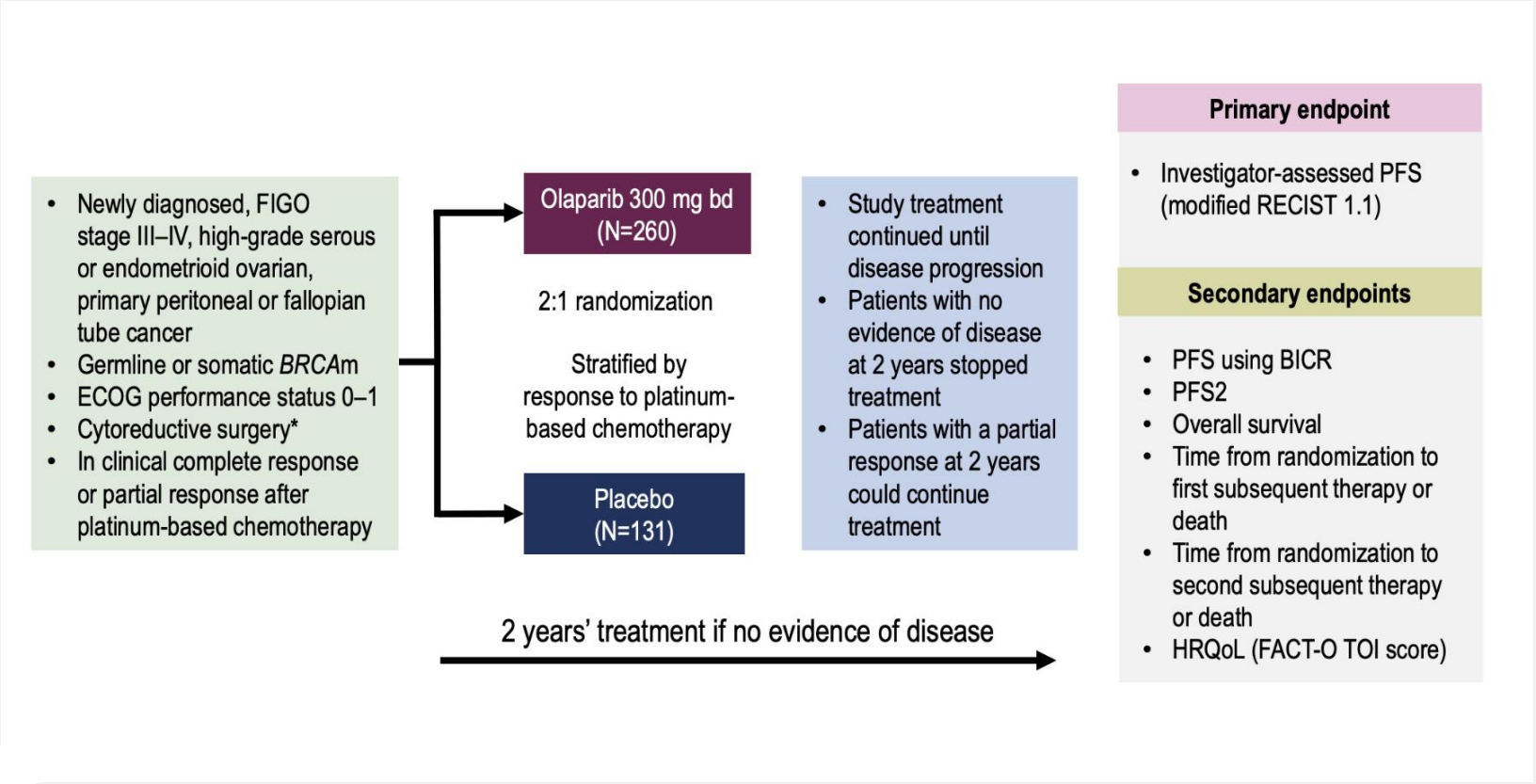
Iglehart JD, Silver DP. Synthetic lethality--a new direction in cancer-drug development. N Engl J Med. 2009 Jul 9;361(2):189-91. doi: 10.1056/NEJMe0903044. Epub 2009 Jun 24. PMID: 19553640.

4. Clinical Development of PARP inhibitors in ovarian cancer

Monotherapy **BRCAmut** ≥ ≥ 2 lines	Maintenance 1st line	Maintenance > 1st line
Study 42 (O)	SOLO-1 (O) **BRCAmut**	SOLO-2 (O) **BRCAmut**
Study 10& Ariel-2 (R)	PAOLA (O+bevacizumab)	Study-19 (O)
QUADRA (N)	PRIMA (N)	NOVA (N)
		ARIEL-3 (R)

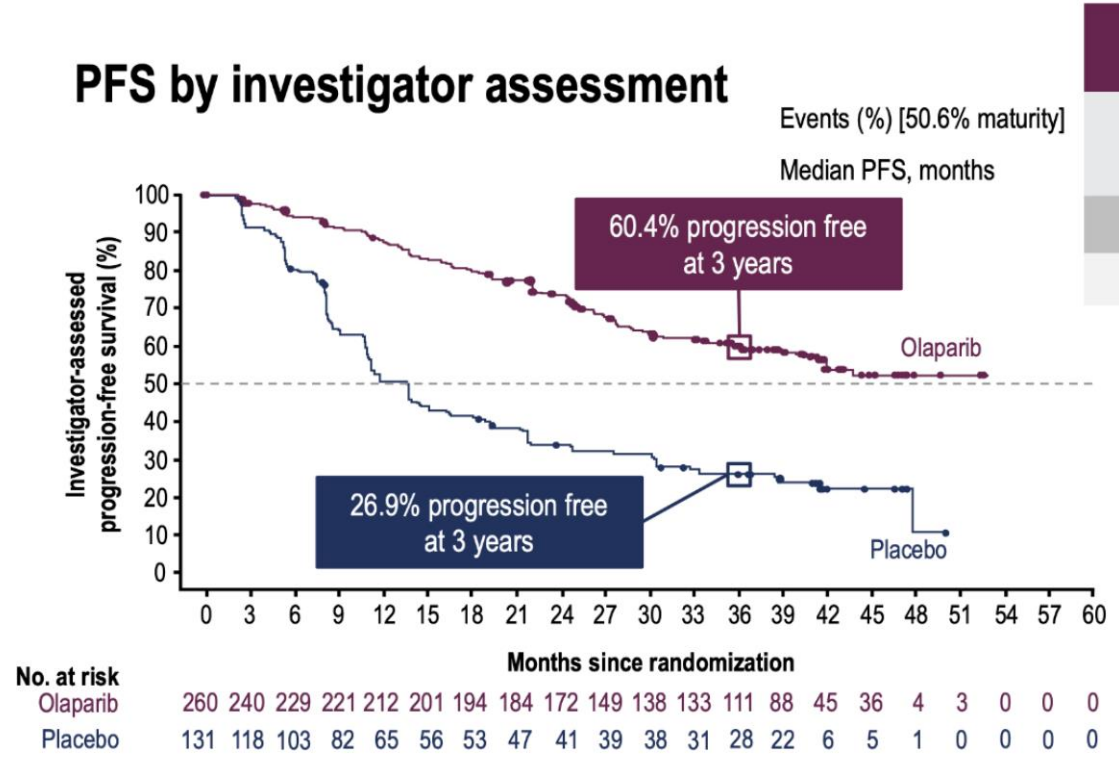
O: olaparib; **N**: niraparib; **R**: rucaparib

4. SOLO-1: maintenance 1st line platinum sensitive ovarian cancer BRCAmut



Moore K, et al. Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N Engl J Med. 2018 Dec 27;379(26):2495-2505.

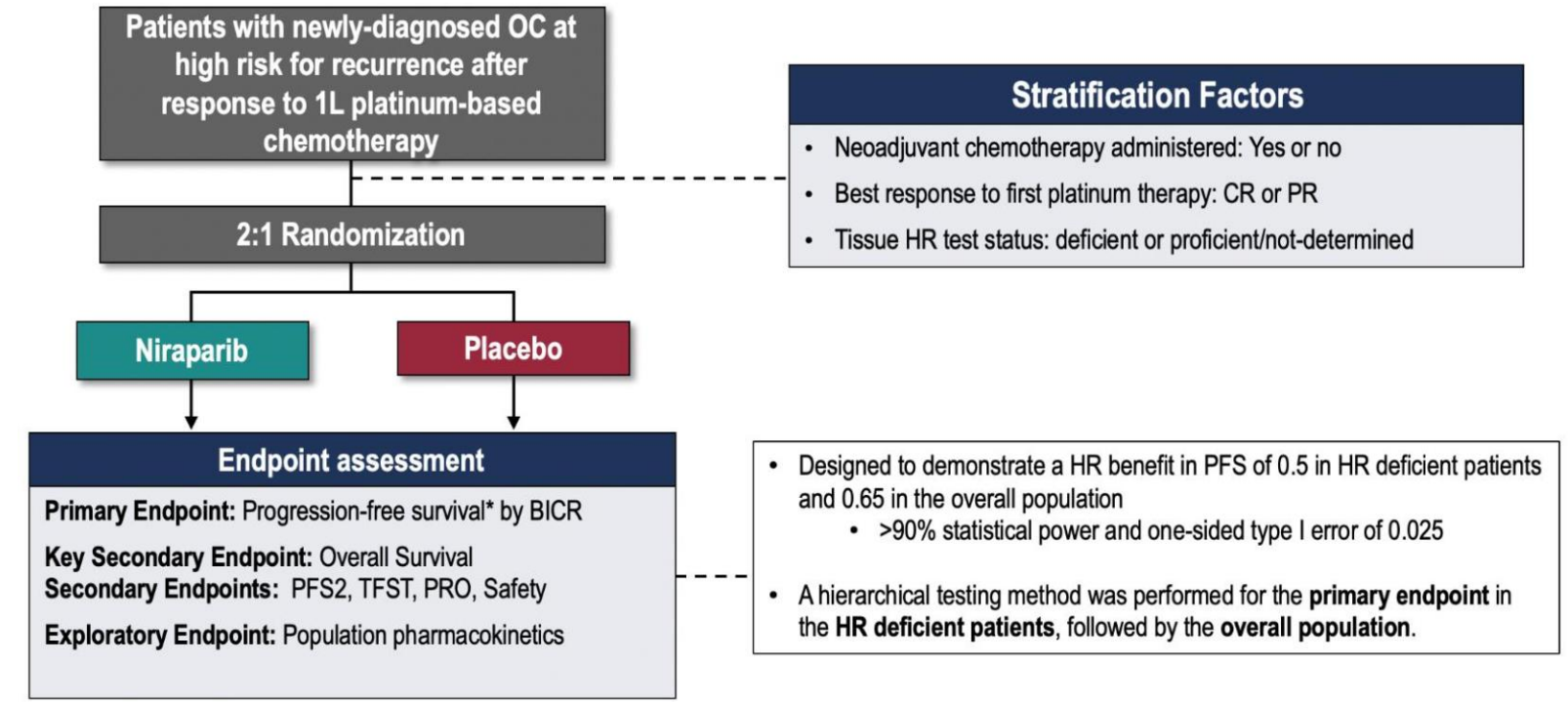
4. SOLO-1 maintenance 1st line platinum sensitive ovarian cancer BRCAmut



	Olaparib (N=260)	Placebo (N=131)
Events (%) [50.6% maturity]	102 (39.2)	96 (73.3)
Median PFS, months	NR	13.8
HR 0.30		
95% CI 0.23, 0.41; *P*<0.0001		

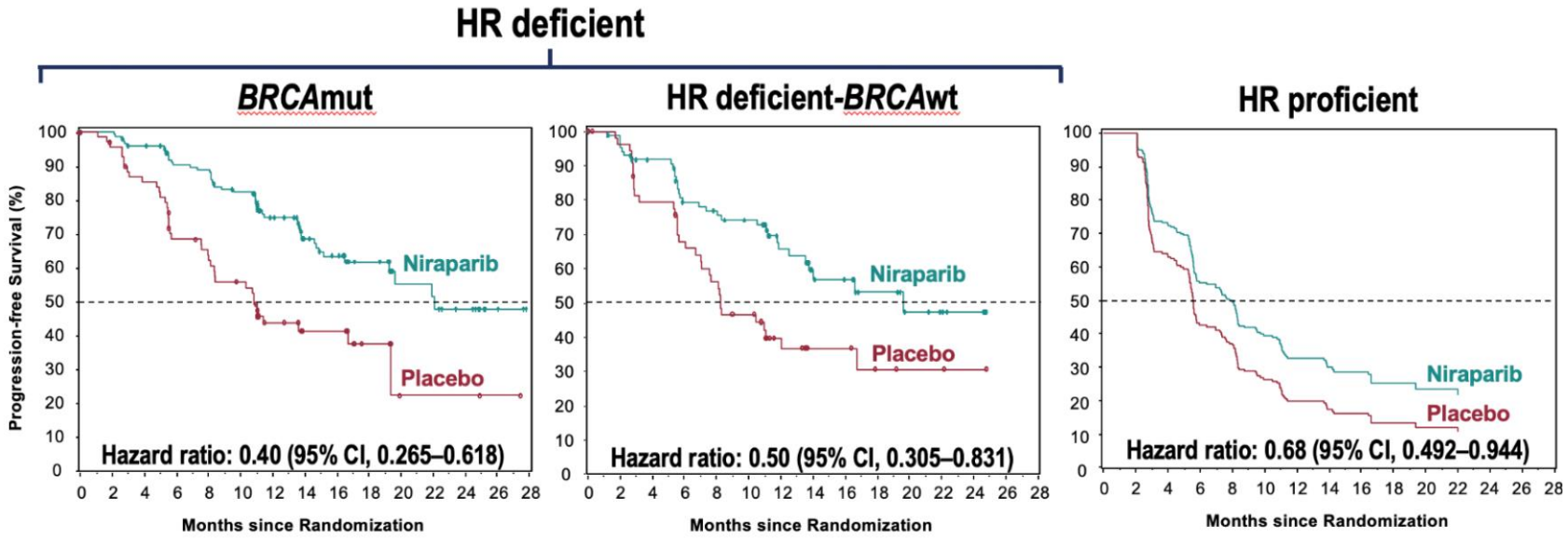
Moore K, et al. Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N Engl J Med. 2018 Dec 27;379(26):2495-2505.

4. PRIMA maintenance 1st line niraparib (high risk OC platinum sensitive)



González-Martín A, et al. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N Engl J Med. 2019 Dec 19;381(25):2391-2402.

4. PRIMA PFS benefit in biomarker subgroup



- Niraparib provided similar clinical Benefit in the HR deficient subgroups (BRCAmut and BRCAwt)
- A continuum of niraparib benefit was observed across biomarker subgroups: HR deficient BRCAmut > HR deficient BRCAwt > HR proficient

González-Martín A, et al. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N Engl J Med. 2019 Dec 19;381(25):2391-2402.

FDA/EMA approvals of PARPi

Tumor type	Treatment	Selection biomarker	Line	PARPi	PFS	HR	Reference
Ovarian Cancer	Monotherapy	gBRCA mut s/gBRCA mut	≥ 3-4L	olaparib rucaparib	9.4 (in pt-sensitive) 11.1 (in pt-sensitive)		Domcheck et al, Gynecol Oncol 2016 Oza et al, Gynecol Oncol 2017
	Maintenance	pt-sensitive pt-sensitive	Relapsed	olaparib niraparib rucaparib	8.4 vs. 4.8 months 21.0 vs 5.5 (gBRCA); 12.9 vs 3.8 (HRD+); 9.3 vs 3.9 (HRD-) 10.8 vs. 5.4 months	0.35 0.27; 0.38; 0.45 0.36	Lederman et al, Lancet Oncol 2014 & 2016 Mirza et al NEJM 2016 Coleman et al, Lancet 2017
	Maintenance	pt-response, s/gBRCA mut pt-response, s/gBRCA mut and/or HRD+ pt-response, all comers	1L	olaparib olaparib + beva niraparib	36 vs. 13.8 months 37.2 vs. 17.7 months 21.9 vs. 10.4 months	0.30 0.33 (0.43 in HRD+/BRCA-) 0.62 (0.43 in HRD+)	Moore et al, NEJM 2018 Ray-Coquard et al, NEJM 2019 González-Martín et al, NEJM 2019
Breast Cancer	Monotherapy	gBRCA mut gBRCA mut	≥ 3L	olaparib talazoparib	7.0 vs. 4.2 months 8.6 vs. 5.6 months	0.58 0.54	Robson et al, NEJM 2017 Litton et al, NEJM 2018
Pancreatic Cancer	Maintenance	gBRCA mut	1L	olaparib	7.4 vs. 3.8 months	0.53	Golan et al, NEJM 2019
Prostate Cancer	Monotherapy	tHRR gene mut/tBRCA mut s/gBRCA mut	Hormone-resistant	olaparib rucaparib	7.4 vs 3.6 months 8.1	0.34 (single arm)	de Bono et al, NEJM 2020 Abida et al, JCO 2020

5. Take home messages

5. Conclusions/Take home messages

State of the art in Hereditary Ovarian Cancer

5. Conclusions/Take home messages I/II

- Approximately 10-15 % of epithelial ovarian cancers are due to inherited mutations.
- All women diagnosed with epithelial ovarian cancer should be offered genetic testing.
- *BRCA1*, *BRCA2*, and the mismatch repair genes account for the majority of hereditary ovarian
- cancer, usually in high grade serous ovarian cancer , with clinical implications of several other genes being evaluated.
- Ovarian screening has not been proven to improve outcome, so risk reduction salpingoophorectomy with careful pathological examination of the specimen is recommended for carriers of deleterious variants in high risk ovarian cancer genes.
- Mutation carriers should be counselled regarding screening , risk-reducing surgery, and implications for children and future childbearing.
-
- Although panel testing for multiple genes may have advantages, caution must be exercised as the clinical implications of mutations in many genes available for testing remain unclear, and there is the potential to identify an increased risk of other unrelated conditions or variants
- of uncertain significance.

5. Conclusions/Take home messages II/II

- Mutation carriers may benefit from treatment with PARP inhibitors
- Olaparib is the first licensed PARP inhibitor directed at a genotypically defined predictive marker (BRCA mutation) in ovarian cancer.
- Significant improvement in PFS with maintenance therapy using **olaparib (BRCAmut)** or **niraparib (all)** in patients **newly diagnosed** with platinum-sensitive high-grade serous ovarian, fallopian or peritoneum carcinoma.
- **Olaparib, niraparib and rucaparib** are approved as maintenance treatment for **all** patients with recurring platinum-sensitive high-grade serous ovarian, fallopian or peritoneum carcinoma, responding to platinum-based therapy.
- 15% of BRCAmut patients on olaparib with remain on I-Parp treatment for > 5 years.
- PARP inhibitors are well-tolerated oral medications- low drop-out rate due to side effects.
- Studies combining PARP inhibitors with anti-angiogenic drugs or immune checkpoint inhibitors are in progress.

SCIENTIFIC BITES®

Cancer research
e-learning platform

Thank you

by SOLTI