Carcinoma mammario nelle donne giovani: Oltre i geni BRCA1 e BRCA2

Laura Cortesi

AUSL-IRCCS Reggio Emilia

Università degli Studi di Modena e Reggio Emilia

Selection of Germline Genetic Testing Panels in Patients With Cancer: ASCO Guideline for high penetrance hereditary syndromes

GENES	TUMORAL SPECTRUM	BC MANAGEMENT	BC RISK
BRCA1/2	Breast, ovary, prostate, pancreas	Annual mammography and breast MRI with contrast screening starting at age 30 Discuss the option of RRM	>60%
PALB2	Breast, ovary, pancreas	Annual mammography and breast MRI with contrast from age 30 Discuss the option of a risk-reduction strategy	41-60%
PTEN (Cowden)	Multiple benign and malignant manifestations, including breast, renal, and endometrial cancer, Mucocutaneous hamartomas and other dermatological lesions, melanoma, macrocephaly, benign thyroid disease, gastrointestinal polyps	Annual mammography and breast MRI with contrast screening starting at age 35 or 10 before the earliest known breast cancer in the family. Discuss the option of a risk-reduction strategy	40-60%
CDH1 (Diffuse Gastric Cancer)	Breast cancer, lobular phenotype, and gastric cancer	Annual mammography and consider breast MRI with contrast starting at age 30 Discuss the option of a risk-reduction strategy	41-60%
STK11 (Peutz-Jeghers)	Breast, pancreatic, and rare gynecological cancers Mucocutaneous pigmentation and hamartomatous gastrointestinal polyps	Annual mammography and breast MRI with contrast starting at age 30 Discuss the option of a risk-reduction strategy	32-54%
TP53 (Li Fraumeni)	Sarcomas, adrenal carcinomas, brain tumors, leukemias, BC, and other cancers	Annual breast MRI with contrast and mammography Discuss the option of a risk-reduction strategy	>60%

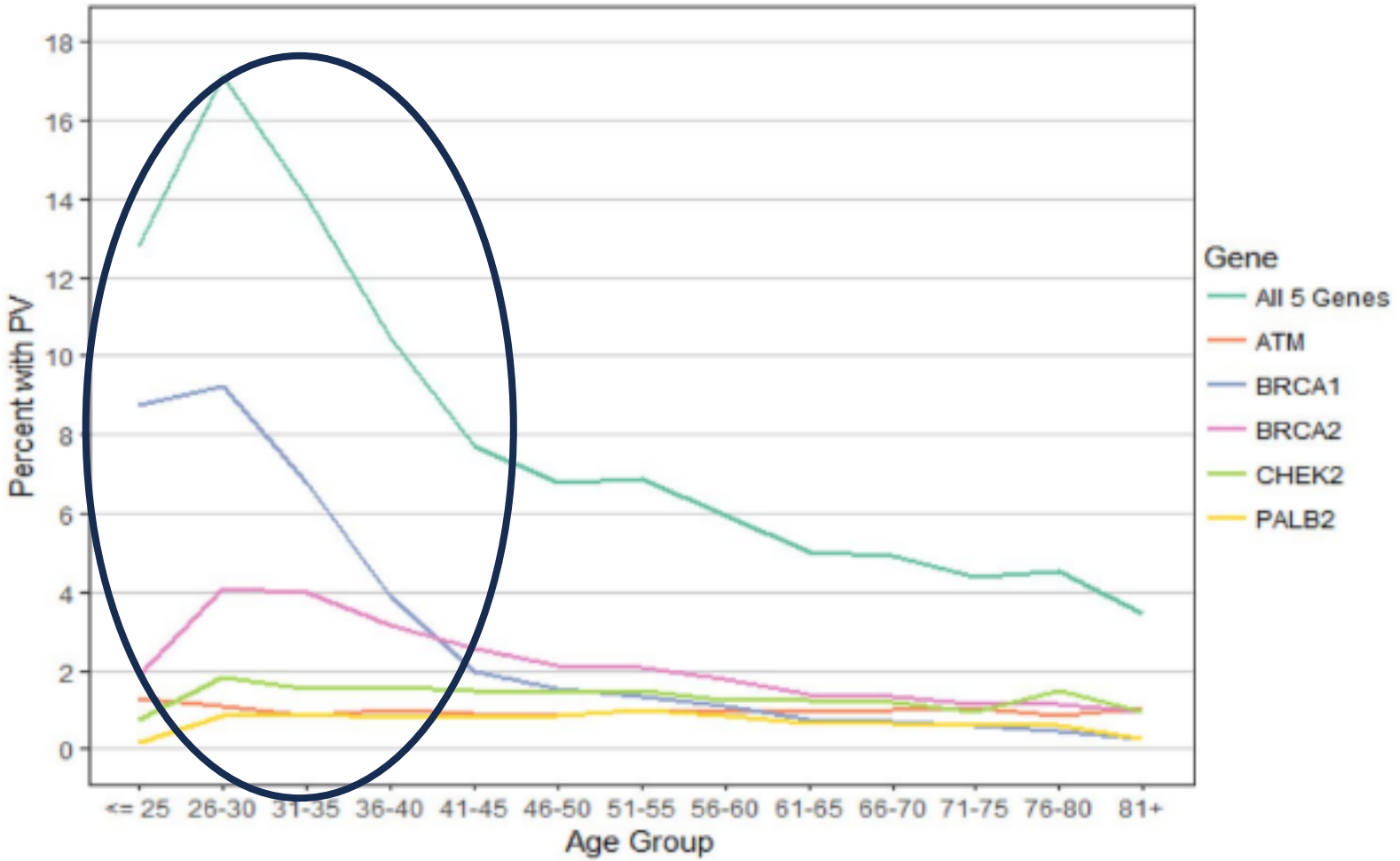
Tung N et al., JCO 2024 Fabi A et al, Crit Rev Oncol and Haematol, 2024

Selection of Germline Genetic Testing Panels in Patients With Cancer: ASCO Guideline for moderate penetrance hereditary syndromes

GENES	TUMORAL SPECTRUM	BC MANAGEMENT	BC RISK
ATM	Breast,ovarian, pancreatic, and prostate cancers	Annual mammography from age 40 and consider breast MRI with contrast starting at age 30–35	20-30%
CHEK2	Breast cancer, possibly other cancers	Annual mammography from age 40 and consider breast MRI with contrast starting at age 30–35	20–40 %
BARD1	Breast cancer	Annual mammography and consider breast MRI with contrast starting at age 40	17-30%
NF1	Nervous system tumors (especially malignant peripheral nerve sheath tumors), gastrointestinal stromal tumors and breast cancer	Annual mammography starting at age 30 and consider breast MRI with contrast from ages 30–50	20-40%
RAD51C/D	Breast and ovarian cancer	Annual mammography and consider breast MRI with contrast starting at age 40	17-30%

Tung N et al., JCO 2024; Fabi A et al, Crit Rev Oncol and Haematol, 2024

The association between age at breast cancer diagnosis and prevalence of pathogenic variants



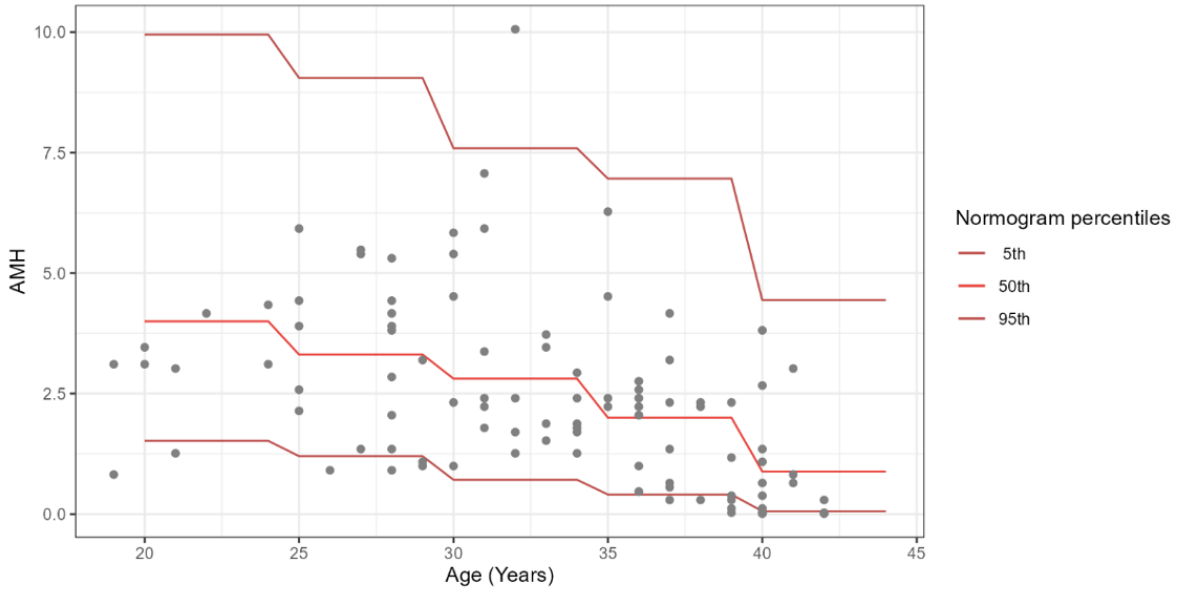
Daly MB et al, BRCT 2023

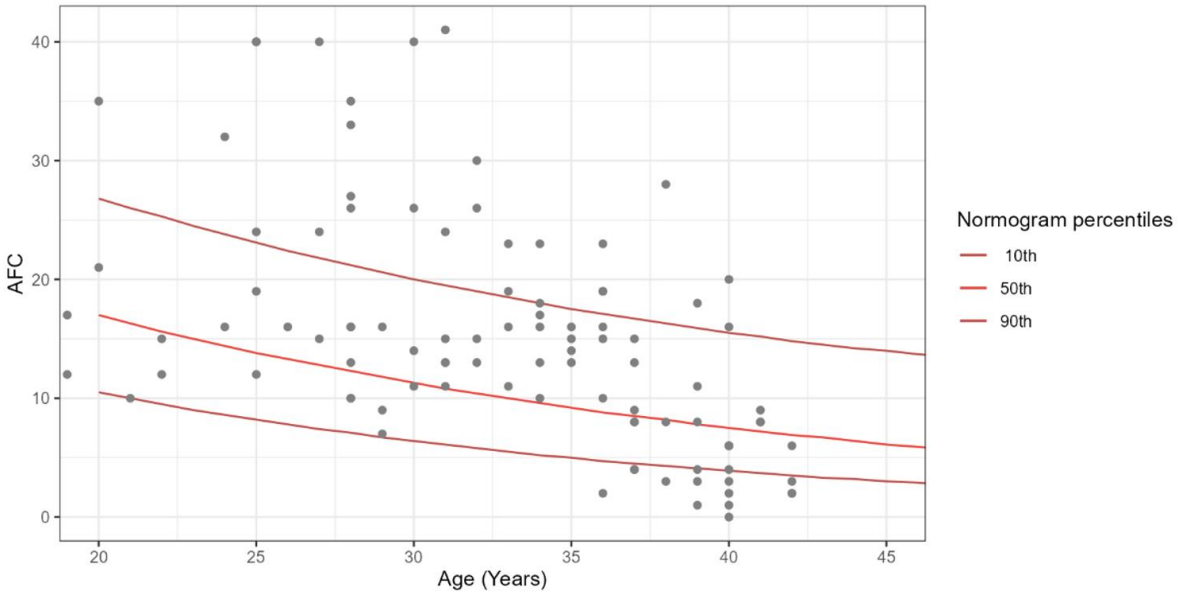
Author	Year	Selection criteria	No. of pts tested	*BRCA1/2* status	*TP53* (likely) pathogenic variant prevalence (%)
Lalloo F et al [37]	2006	BC ≤ 30 years	100	18% *BRCA1/2* mutated	4% (4/100)

Blondeaux E et al., CTR 2023

OVARIAN RESERVE ACCORDING TO AMH AND AFC IN YOUNG HBOC WOMEN

32 BRCA1, 45 BRCA2, 1 TP53, 1 RAD50, 1 CHECK2, 1RAD51D, 2 PALB2 and 2 ATM gene





Overall in HBOC, AMH significantly decrease starting at 25 years old.
The lower values are mostly due to BRCA1-mutation carriers.

Overall in HBOC, AFC is significantly higher due to the higher sensitivity of current ultrasound.
Despite this, AFC significantly decrease in HBOC starting at 35 years old.

Sighinolfi G et al., Comm medicine 2025

	N	N (%)	No gPV	All gPV	P-values No gPV vs gPV	BRCA 1/2	PALB2	RAD51C/D	MUTYH	ATM	OTHER gPV	P-value among gPV
		400	310 (88)	90 (22)		41 (10)	21 (5)	8 (2)	7 (2)	4 (1)	9 (2)	
Age at diagnosis (median)	400	51 (25-91)	52 (25-91)	50 (32-80)	0.9	46 (32-69)	**58 (34-80)**	**46 (39-62)**	**52 (39-77)**	**53 (49-56)**	**49 (36-63)**	0.9
Familiarity	400											
BC		102 (25)	74 (24)	28 (31)	0.9	14 (34)	8 (34)	3 (37)	0	1 (25)	2 (22)	0.9
OC		2 (1)	0	2 (2)	0.9	0	0	2 (26)	0	0	0	-
None		296 (74)	236 (76)	60 (67)	0.9	27 (66)	13 (62)	3 (37)	7 (100)	3 (75)	7 (78)	0.9
P-values			0.001	0.001		0.001	0.001	0.001		0.001	0.001	
Histotype	400											
IDC		380 (95)	292 (95)	88 (98)	0.9	41 (100)	21 (100)	8 (100)	6 (86)	4 (100)	8 (89)	0.5
Other		19 (4)	17 (4)	2 (2)	0.8	0	0	0	1 (14)	0	1 (11)	0.5
Missing		1 (1)	1 (1)	0								
P-values			0.001	0.001								
Grading	400											
G1		2 (1)	2 (1)	0	0.9	0	0	0	0	0	0	-
G2		58 (14)	48 (15)	10 (11)	0.9	5 (12)	2 (10)	0	1 (14)	1 (25)	1 (11)	0.3
G3		335 (84)	257 (83)	78 (87)	0.9	35 (85)	19 (90)	8 (100)	6 (86)	3 (75)	7 (78)	0.7
Missing		5 (1)	3 (1)	2 (2)		1 (3)	0	0	0	0	1 (11)	
P-values			0.001	0.001		0.001	0.001		0.1	0.4	0.5	
Ki67	400											
<20%		43 (11)	34 (11)	9 (10)	0.9	2 (5)	**1 (5)**	**5 (63)**	**0**	**0**	**1 (11)**	**0.05**
≥20%		336 (84)	260 (84)	76 (85)	0.9	37 (90)	**18 (85)**	**3 (37)**	**7 (100)**	**4 (100)**	**7 (78)**	**0.4**
Missing		21 (5)	16 (5)	5 (5)		2 (5)	**2 (10)**	**0**	**0**	**0**	**1 (11)**	
P-values			0.001	0.001		0.001	0.001	0.6			0.5	
Pathological stage	400											
Stage I/ II		314 (79)	243 (78)	71 (79)	0.6	36 (88)	**18 (85)**	**6 (75)**	**2 (28)**	**3 (75)**	**6 (67)**	**0.3**
Stage III		58 (15)	45 (15)	13 (15)	0.9	4 (10)	**1 (5)**	**2 (25)**	**4 (58)**	**1 (25)**	**1 (11)**	**0.05**
Stage IV		13 (3)	9 (3)	4 (4)	0.9	0	**1 (5)**	**0**	**1 (14)**	**0**	**2 (22)**	**0.1**
Missing		15 (4)	13 (4)	2 (2)		1 (2)	**1 (5)**	**0**	**0**	**0**	**0**	
P-values			0.01	0.01		0.001	0.001	0.3	0.7	0.5	0.7	

TNBC and gPV:

Aged > BRCA1/2

Low Ki67 RAD51

High stage MUTYH

Cortesi L., Under review

Spectrum and characteristics of germline PALB2 pathogenic variants in 1556 early-onset breast cancer patients in China

Table 1 (continued)

Variable n (%)	All cases (n = 1556)	Non-*PALB2* (n = 1544)	*PALB2* carriers		*p*
			(n = 12)	Prevalence %	
Morphology					0.080
IDS	1235 (83.3)	1226 (83.3)	9 (75.0)	0.73	
IMPC	47 (3.2)	45 (3.1)	2 (16.7)	4.26	
Others	201(13.6)	200 (13.6)	1 (8.3)	2.17	
Unknown	73	73	0		

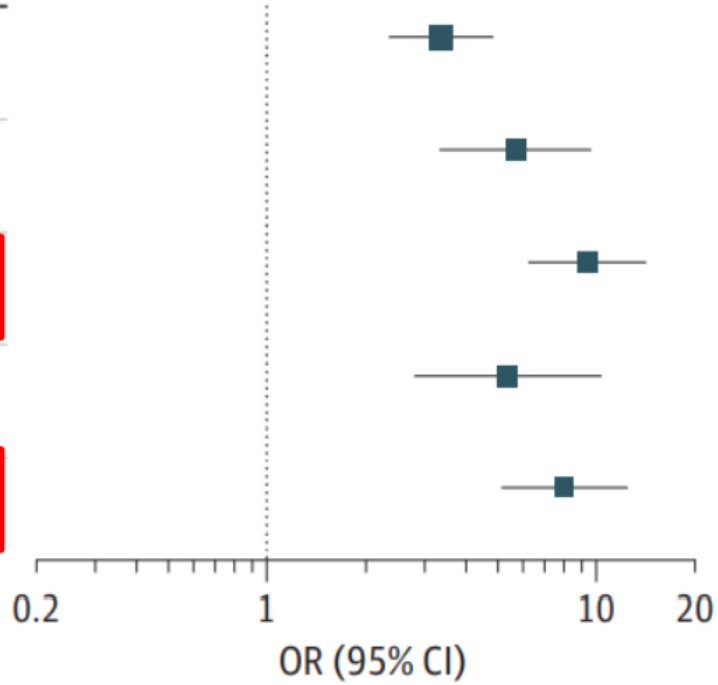
BC breast cancer; *FH* family history; *OC* ovarian cancer; *HER2* human epidermal growth factor receptor-2; *ER* estrogen receptor; *PR* progesterone receptor; *HR* hormone receptor; *TNBC* triple-negative breast cancer; *IDC* invasive ductal carcinoma; *PMC* pure mucinous carcinoma; *IMPC* invasive micropapillary carcinoma (pure or mix with invasive ductal carcinoma)

Jing Li et al., Journal of Cancer Research and Clinical Oncology (2024) 150:322

PALB2-associated breast cancer pathology

A *PALB2*

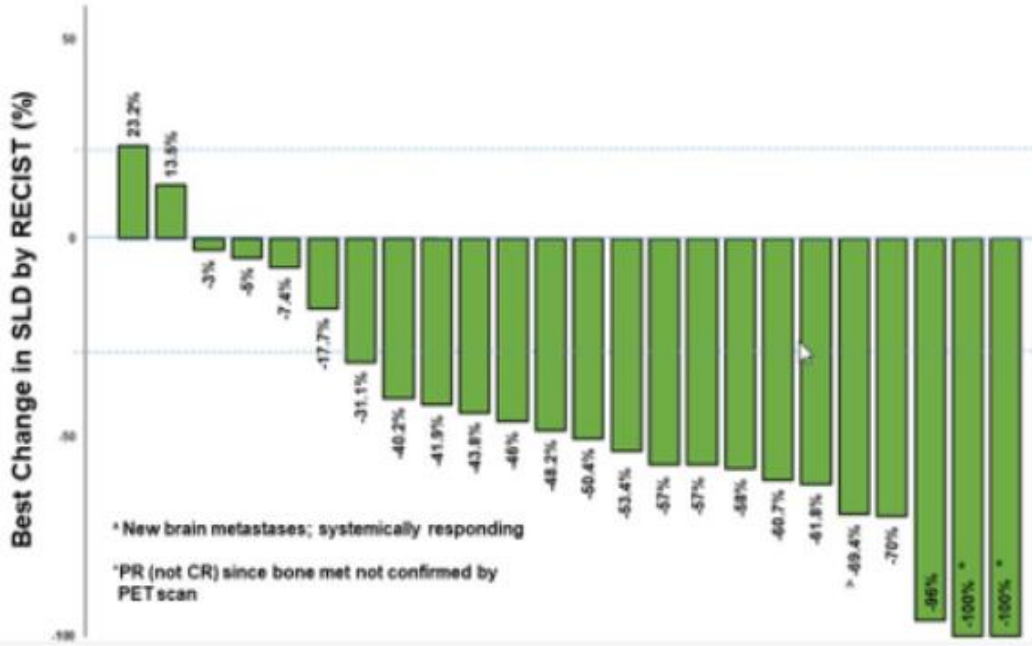
	OR (95% CI)
HR positive, ERBB2 negative low grade	3.39 (2.35-4.89)
HR positive, ERBB2 positive	5.70 (3.35-9.70)
HR positive, ERBB2 negative high grade	9.43 (6.24-14.25)
HR negative, ERBB2 positive	5.41 (2.81-10.44)
Triple negative	8.05 (5.17-12.53)



Responses for g*PALB2*

g*PALB2* N=24	
Best Response	**Responses (rate, %)**
Complete Response (CR)	1 (4%)
Partial Response (PR)	17 (71%)
Stable Disease (SD)	5 (21%)
Progressive Disease (PD)	1 (4%)
ORR = 75% (18/24, 80%-CI: 60%-86%)	
CBR (18 wks) = 83% (20/24, 90%-CI: 66%-94%)	

Datacut May 3, 2024



Tumor subtype	Responses
TNBC	2/2
ER+/HER2-neg	13/19
HER2+	3/3

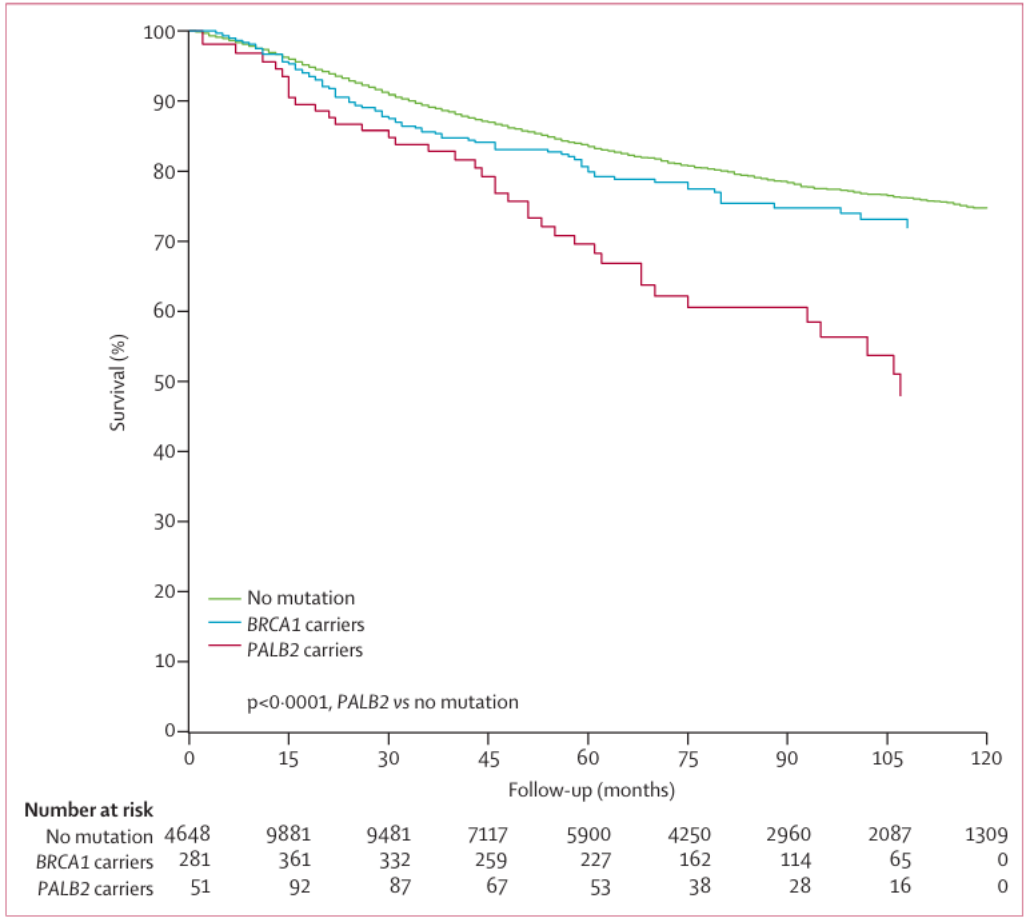


Figure 1: **10-year crude survival after diagnosis of breast cancer in patients with a *PALB2* mutation, a *BRCA1* mutation, and in women with neither mutation**

Clinical outcomes in women with breast cancer and a PALB2 mutation: a prospective cohort analysis

*Cezary Cybulski, *Wojciech Kluźniak, *Tomasz Huzarski, *Dominika Wokołorczyk, Aniruddh Kashyap, Anna Jakubowska, Marek Szwiec, Tomasz Byrski, Tadeusz Dębniak, Bohdan Górski, Victoria Sopik, Mohammad R Akbari, Ping Sun, Jacek Gronwald, Steven A Narod, Jan Lubiński, and the Polish Hereditary Breast Cancer Consortium†*

Lancet Oncology, 2015

116 Polish BC were found to be carrying PALB2 founder gPV

Study design: an observational retrospective European registry of PALB2 BC

- Evidence of gPALB2m BC Stage I-IV BC
- At least 300 pts registered with PALB2m compared to 300 not carriers
- Outcome of pts

N°	Center	PI
1	**University Modena Hospital (IT)**	**Laura Cortesi**
2	University Parma Hospital (IT)	Benedetta Pellegrino
3	IRST Meldola (IT)	Ugo de Giorgi
4	University of Groningen (NL)	Geertruda de Bock
5	Institute Julie Bordet Bruxelles (BE)	Diogo Martins Branco
6	University Hospital Leuven (BE)	Kevin Punie
7	Maria Sklodowska-Curie Oncology Warsaw (PL)	Katarzyna Pogoda
8	Medical College of Rzeszow University (PL)	Aleksander Myzska
9	Karolinska University Hospital Stockolm (SW)	Svetlana Bajalica Lagercrantz
10	Institute of Hereditary Pathology Lviv (UKR)	Hayane Akopyan
11	Health Medical Novi Sad (SRB)	Lazar Popovic
12	East Tallin Central Hospital (EE)	Elen Vettus
13	Institute of Oncology Ljubljana (SL)	Mateja Krajc
14	Campus Miguel de Unamuno Salamanca (ES)	Alonso Atanasio Pandiella
15	Gynecology Oncology University Hamburg (DE)	Volkmar Muller

Primary End-Points

Incidence, Mortality rates

Modalities of Dx and Imaging Characteristics

Surgery (mono or bilateral)

Clinical path characteristics

(in situ vs. invasive, Multifocal vs multicentric)

RAD51 assay in control BC for sPALB2 mutations search

Prognosis and outcome

(DFS, DDFS, OS)

Secondary End-points

Age at dx (<60y vs >=60y)

Mutations (C4 and C5)

HR,HER2 status

Type of treatment

Exposure to CT (yes/not)

Exposure to HT (yes/not)

Exposure to PARPi (yes/not)

FH

Second primary BC

Other second tumors

Comparison between RAD51 assay and academic HRD test

The PALBreast study:start on 3/11/2023

2023-2024

PRELIMINARY DATA

	PALB2		CONTROL		*P VALUE*
	NUM 91	**% 100**	**NUM 69**	**%100**	
STAGE					
I	46	50,5	23	33,4	0.1
II	32	35,2	28	40,6	0.6
III	9	9,9	11	15,9	0.09
IV	2	2,2	4	5,8	0.1
NA	2	2,2	3	4,3	
P VALUE	0.001		0.001		
HISTOTYPE					
IDC	66	72,5	51	73,9	0.8
ILC	16	17,6	3	4,3	0.8
OTHER	5	5,5	12	17,5	0.7
NA	4	4,4	3	4,3	
P VALUE	0.001		0.001		
GRADING					
G1	2	2,2	5	7,2	0.5
G2	29	31,9	27	39,2	0.8
G3	54	59,3	30	43,5	0.8
NA	6	6,6	7	10,1	0.8
P VALUE	0.07		0.4		
PHENOTYPE					
HR+/HER2-	**29**	**31,9**	**27**	**39,1**	**0.08**
HR+/HER2+-	**12**	**13,2**	**9**	**13,0**	**0.5**
HR-/HER2+	**25**	**27.4**	**2**	**2.9**	**0.005**
HR-/HER2-	**22**	**24,2**	**31**	**44,9**	**0.002**
NA	**3**	**3,3**	**6**	**8,7**	
P VALUE	**0.02**		**0.001**		
MIB-1					
≤30%	58	63,7	39	56,5	0.3
>30%	30	33	25	36,3	0.2
NA	3	3,3	5	7,2	0.1
P VALUE	0.01		0.2		

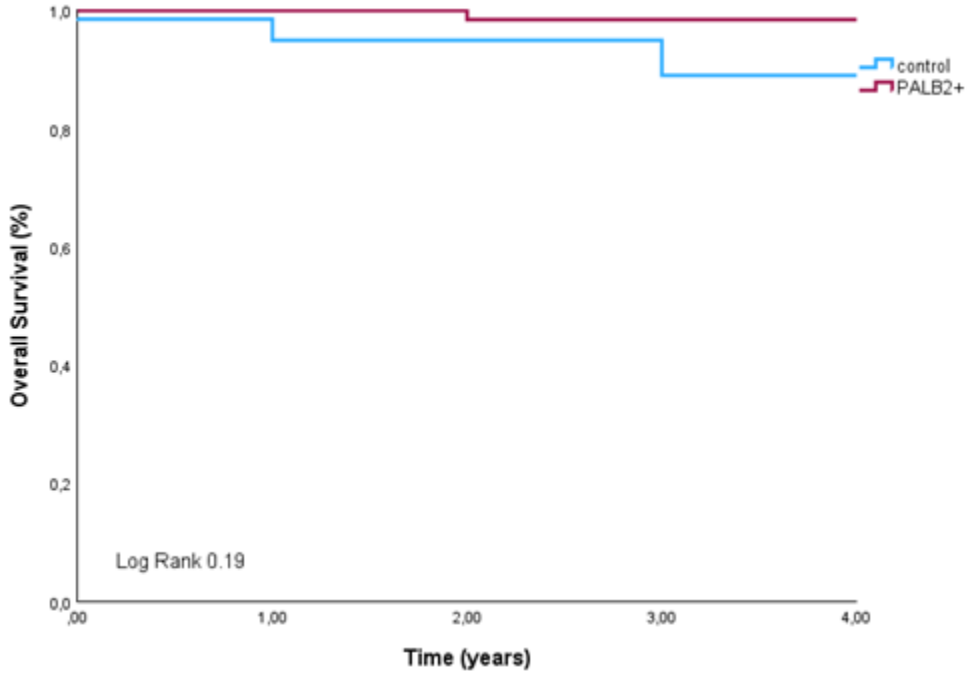
Among the 32 PALB2 pts who received neoadjuvant CT, only 7 had a pCR (21.9%), while 9 of the 43 pts in the control group who received neoadjuvant tp (20.9%) had a pCR.

All patients who achieved a complete pathological response had a triple-negative phenotype and a Ki67 > 30%.

	PALB2		CONTROL		P VALUE
	NUM 91	% 100	NUM 69	% 100	
TREATMENT					
UPFRONT SURGERY	**54**	**59,3**	**32**	**46,4**	**0.4**
POST NACT SURGERY	**32**	**35,2**	**31**	**44,9**	**0.9**
NO SURGERY	**2**	**2,2**	**5**	**7,2**	**0.9**
NA	**3**	**3,3**	**1**	**1,5**	**0.9**
P VALUE	**0.06**		**0.9**		
TYPE OF SURGERY ON T					
QUADRANTECTOMY	**51**	**56**	**40**	**57,9**	**0.8**
UNILATERAL MASTECTOMY	**27**	**29,7**	**21**	**30,5**	**0.8**
BILATERAL MASTECTOMY	**11**	**12,1**	**2**	**2,9**	**0.07**
NA	**2**	**2,2**	**6**	**8,7**	**0.8**
P VALUE	**0.02**		**0.04**		
TYPE OF SURGERY ON N					
BLS	53	58,2	41	59,4	0.5
DCA	36	39,6	21	30,5	0.4
NA	2	2,2	7	10,1	0.3
P VALUE	0.1		0.04		
TYPE OF NACT					
EC - CBDA+TXL	11	34,4	8	25,8	0.8
EC-TXL	14	43,7	14	45,2	1
CDBA +TXL+PEM - EC+PEM	1	3,1	4	12,9	0.8
FEC - TXL	2	6,3	1	3,2	0.8
CMF	1	3,1	0	0	0.8
TXL+TRASTUZUMAB	1	3,1	4	12,9	0.8
CDK4/6i+ IA	2	6,6	0	0	0.8
P VALUE	0.01		0.01		
ADIUVANT					
YES	61	67	43	62,3	0.8
NO	27	29,7	23	33,4	0.8
NA	3	3,3	3	4,3	1
P VALUE	0.002		0.04		
TYPE OF ADJ THERAPY					
AC+TXL	31	50,8	22	51,2	0.8
FEC+TXL	16	26,2	6	13,9	0.1
AC+CMF	2	3,3	0	0	0.8
CMF	2	3,3	0	0	0.8
CAPECITABINE	5	8,2	9	20,9	0.8
PEMBROLIZUMAB	1	1,6	3	7	0.8
TXL+TRASTUZUMAB	2	3,3	3	7	0.8
CDK4/6i+ IA	2	3,3	0	0	0.8
P VALUE	0.01		0.001		

PRELIMINARY DATA

OS



PALB2

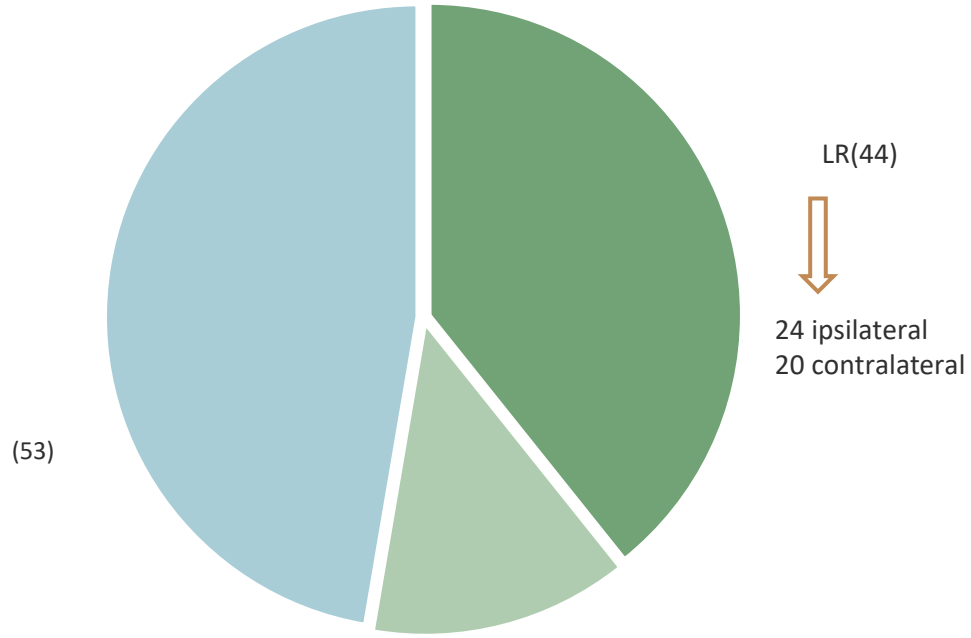
CG

MEDIAN FOLLOW-UP IN MONTHS 43,5 (2-235)

OS PALB2=98% vs. CG=89%

PRELIMINARY DATA

PALB2 POPULATION:LR OR SECOND TUMOR

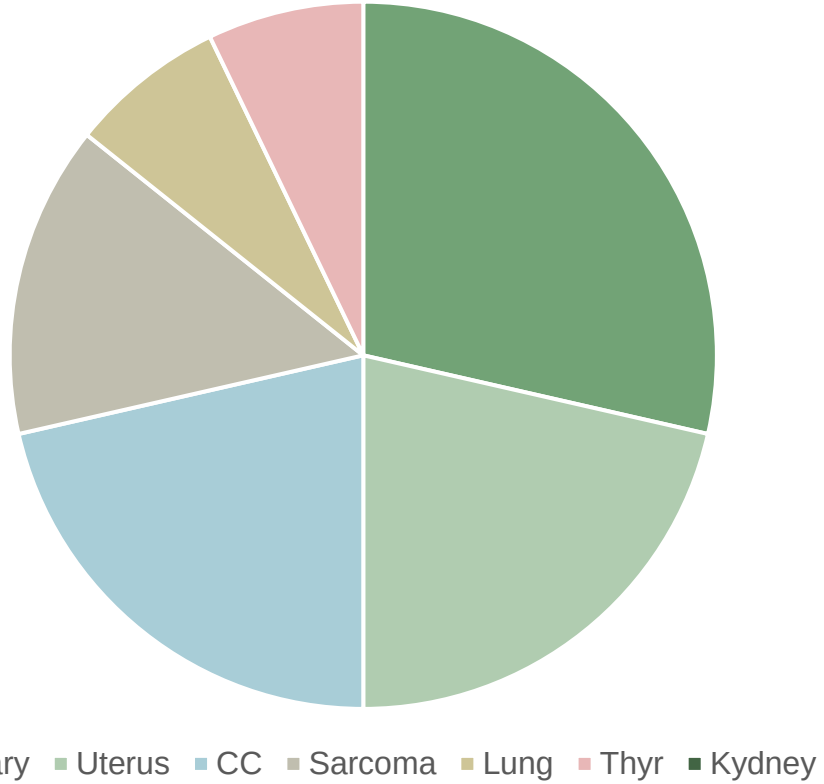


(53)

LR(44)

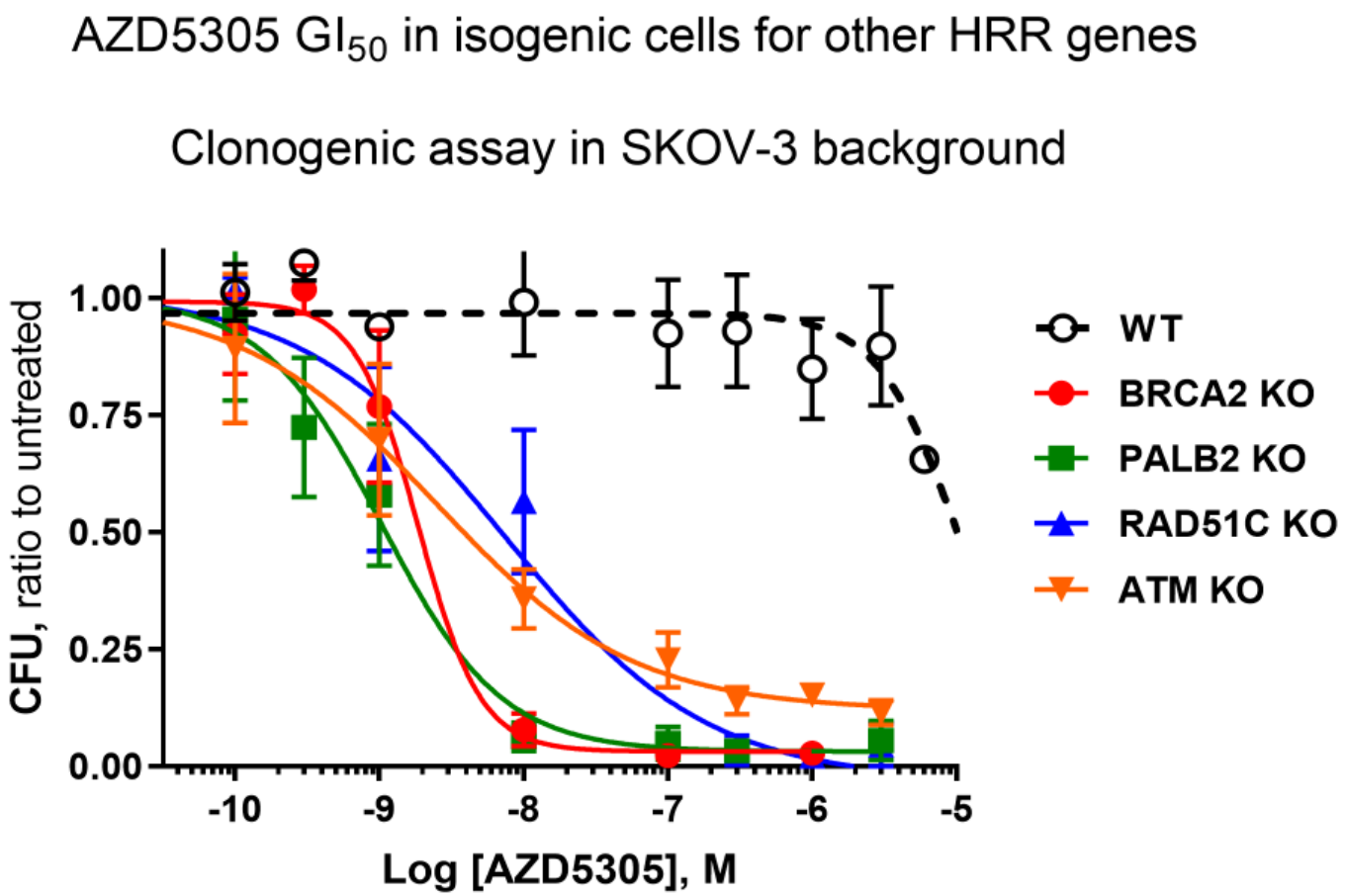
24 ipsilateral
20 contralateral

Other C(15)



AZD5305 potently inhibits proliferation in cancer cell lines "beyond BRCAm"

AZD5305 GI_{50} in isogenic cells for other HRR genes



Cell line:	AZD5305 GI50 (nM)
WT	30,000
BRCA2 KO	2
PALB2 KO	1
RAD51C KO	7
ATM KO	5

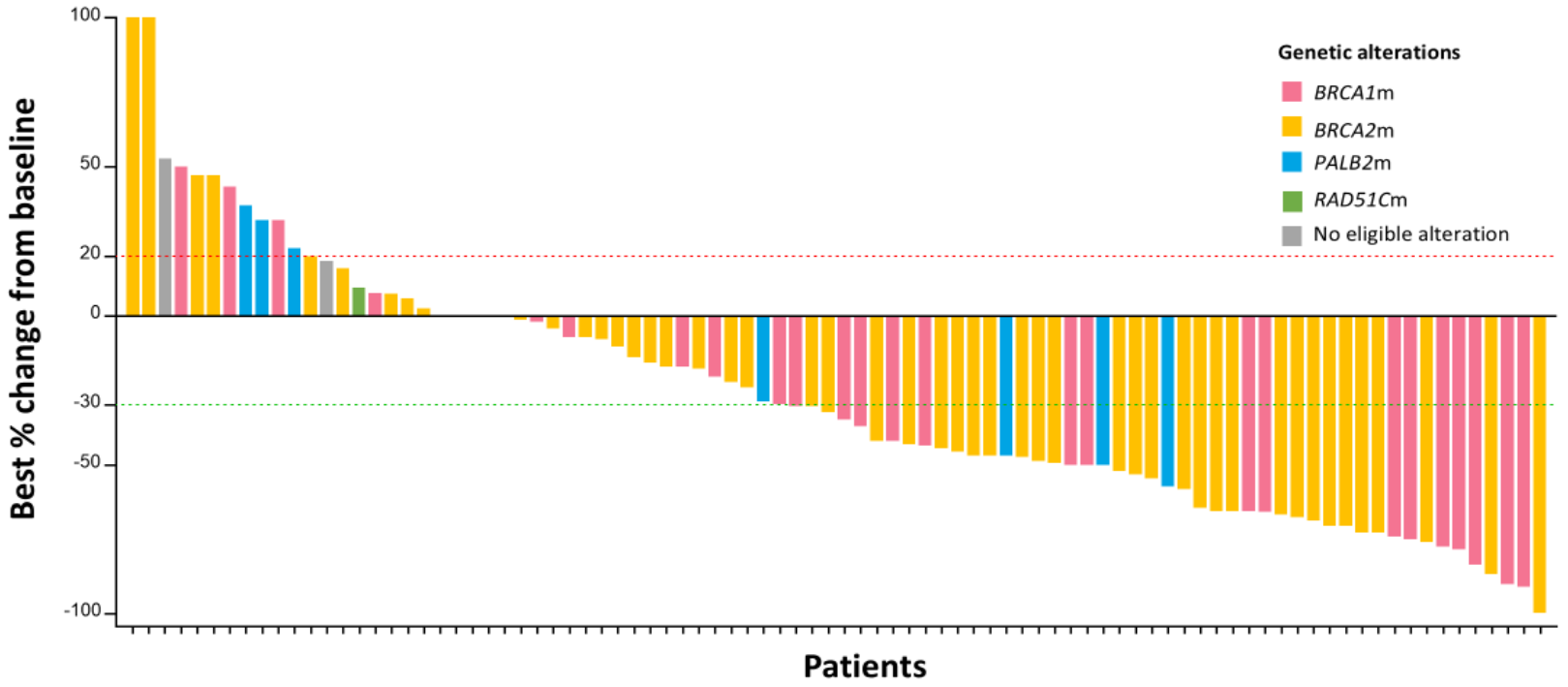
Mean of 4 independent experiments

AZD5305 treatments lead to low nM GI_{50} in the HRD cells; double-digit mM in the wt isogenics.
AZD5305 has also minimal effects in non-cancer cells (MCF10-A)

1. Illuzzi G et al., Clin Cancer Res. 2022 28:4724-4736 2. Zheng J et al., Front Pharmacol. 2023 13:979873 3. Dellavedova G et al., Cancer Res Commun. 2023 3:489-500

Tumour response was also observed across mutation types

Key eligibility criteria: No limit on prior chemotherapy lines and BRCA1/2m, PALB2m, or RADC51C/Dm



Response based on RECIST version 1.1 (response and progression defined as -30% and +20% change from baseline, respectively).
*Interim analysis set: defined as all dosed patients who had measurable disease at baseline and who received first dose of saruparib at least 17 weeks prior to data cutoff (2 June 2023). †Patient had *BRCA2*m by local test but unconfirmed by central assessment. ‡Imputed value for best percent change from baseline in target lesion size; patient died due to progression prior to first RECIST scan. §Patient had *CHEK2*m but no other eligible mutation.
*BRCA1/2*m, breast cancer gene 1/2 mutation; HER2–, human epidermal growth factor receptor 2 negative; *PALB2*m, partner and localizer of *BRCA2* mutation; QD, once daily; *RAD51C/D*m, RAD51 recombinase homolog C/D mutation; RECIST, Response Evaluation Criteria in Solid Tumors

1. Yap TM, et al. Presented at AACR 2022. 8–13 April. New Orleans, Louisiana. Abstract #CT007

A randomized phase III study of first-line saruparib (AZD5305) plus camizestrant vs CDK4/6i plus physician's choice endocrine therapy or plus camizestrant in patients with *BRCA1*/*BRCA2*/*PALB2* mutations and HR+/HER2– advanced breast cancer (EvoPAR-Breast01)

Pedram Razavi,*[1] Judith Balmaña,[2] Stephen J. Luen,[3] Mario Campone,[4] Laura Cortesi,[5] Norikazu Masuda,[6] Kyong Hwa Park,[7] Qingyuan Zhang,[8] Emily Nizialek,[9] Cathy Qi,[10] Karen Cui,[9] Sibylle Loibl,[11] Mark Robson,[1] Filipa Lynce[12]

*Presenting author

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]Vall d'Hebron Instituto de Oncología (VHIO), Barcelona, Spain; [3]Peter MacCallum Cancer Centre, Melbourne, Australia; [4]Institut de Cancérologie de l'Ouest (ICO), Angers, France; [5]University of Modena and Reggio Emilia, Modena, Italy; [6]Kyoto University, Kyoto, Japan; [7]Korea University Anam Hospital, Seoul, Republic of Korea; [8]Harbin Medical University Cancer Hospital, Harbin, China; [9]AstraZeneca, Gaithersburg, MD, USA; [10]AstraZeneca, Macclesfield, UK; [11]GBG Forschungs GmbH, Neu-Isenburg and Centre for Haematology and Oncology, Neu-Isenburg

San Antonio Breast Cancer Symposium® – December 10–13, 2024
Poster number: P2-10-17

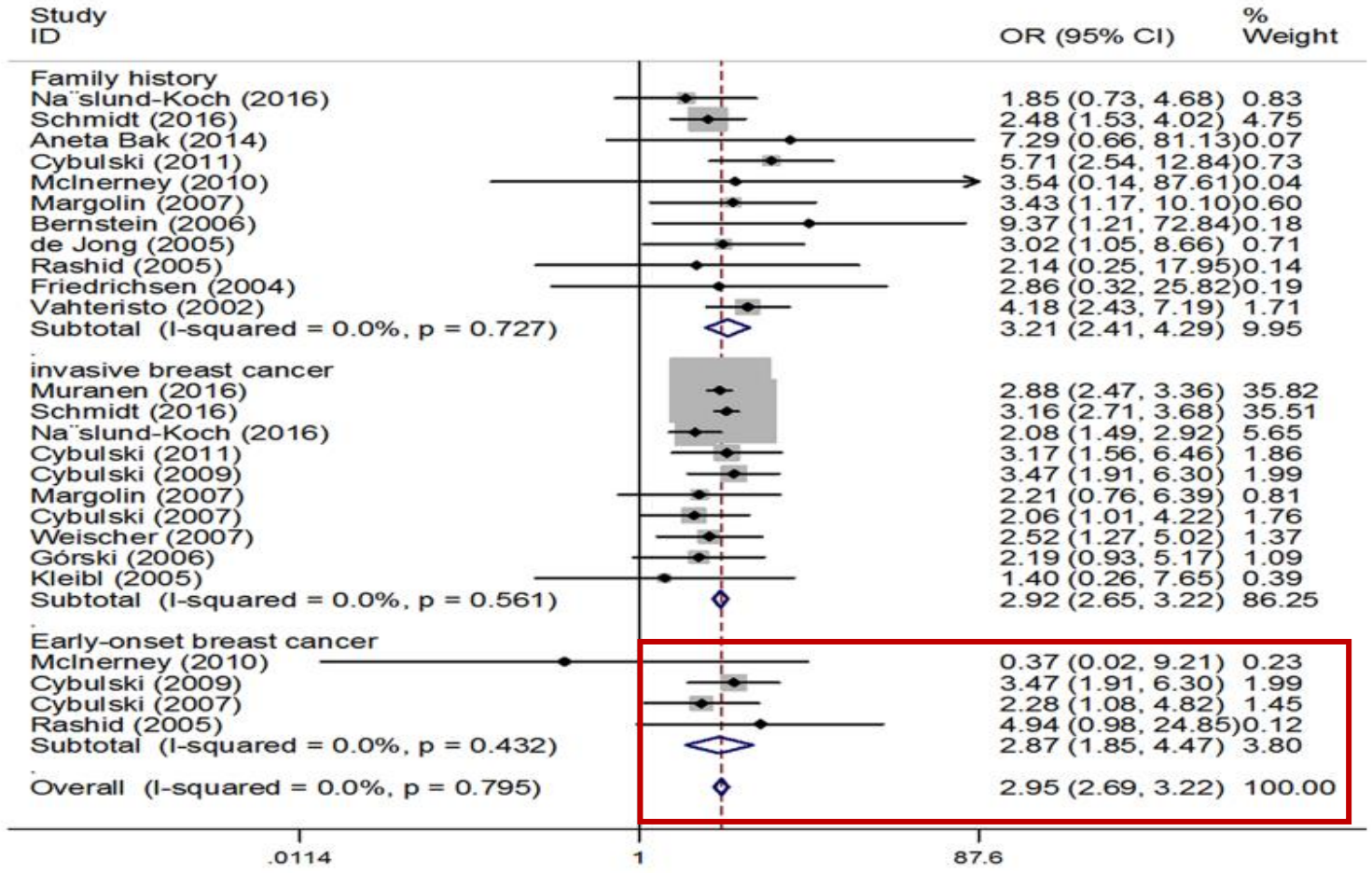
Table 1 Characteristics of women diagnosed with breast cancer at 36–40 years of age in the South Swedish Health Care Region between January 1, 2000 and December 31, 2019

	All women diagnosed with BC	Women tested previously[a]	Women tested in this study	*P*[b]
Number of patients, *n*	816	403	176	
Age at BC diagnosis, years, median (IQR)	39.1 (37.8–39.1)	38.7 (37.3–38.7)	39.9 (38.5–39.9)	<0.001
Year of BC diagnosis, *n* (%)				<0.001
2000–2009	331 (40.6)	115 (28.5)	83 (47.2)	
2010–2017	381 (46.7)	204 (50.6)	83 (47.2)	
2018–2019	104 (12.7)	84 (20.8)	10 (5.7)	
Time between BC diagnosis and genetic testing, years, median (IQR)	2.2 (0.5–2.2)	0.9 (0.3–0.9)[c]	12.4 (8.9–12.4)	<0.001
Vital status, *n* (%)				
Alive	644 (78.9)	336 (84.2)	176 (100.0)	N/A
Dead	150 (18.4)	60 (15.0)	N/A	
Emigrated	9 (1.1)	5 (1.3)	N/A	
Moved to other healthcare region	10 (1.2)	2 (0.5)	N/A	
Unknown identity	3 (0.4)	N/A	N/A	
PV carriers, *n* (%)				
No PV	477 (83.0)	318 (78.9)	159 (90.3)	N/A[d]
ATM	8 (1.4)	2 (0.5)	6 (3.4)	
ATM + *CHEK2*	1 (0.2)	1 (0.2)	0 (0.0)	
BARD1	1 (0.2)	0 (0.0)	1 (0.6)	
BRCA1	34 (5.9)	31 (7.7)	3 (1.7)	
BRCA2	26 (4.5)	26 (6.5)	0 (0.0)	
CHEK2	16 (2.8)	11 (2.7)	5 (2.8)	
PALB2	3 (0.5)	1 (0.2)	2 (1.1)	
TP53	4 (0.7)	4 (1.0)	N/A	
Other	3 (0.5)	3 (0.7)	N/A	
Unknown PV	2 (0.3)	2 (0.5)	N/A	
Unknown result	4 (0.7)	0 (0.0)	N/A	
Missing/not tested (*n*)	237			

Augustinsson A et al., BCRT 2024

Association Between CHEK2*1100delC and Breast Cancer: A Systematic Review and Meta-Analysis

Fig. 4 Forest Plot on Association of *CHEK2* 1100delC Heterozygosity with Family, Invasive and Early-onset Breast Cancer Risk. *CI* confidence interval, *OR* odds ratio



Liang M et al., Mol Diagn & Ther 2018

Characteristics and Prognosis of pI157T CHEK2 PV

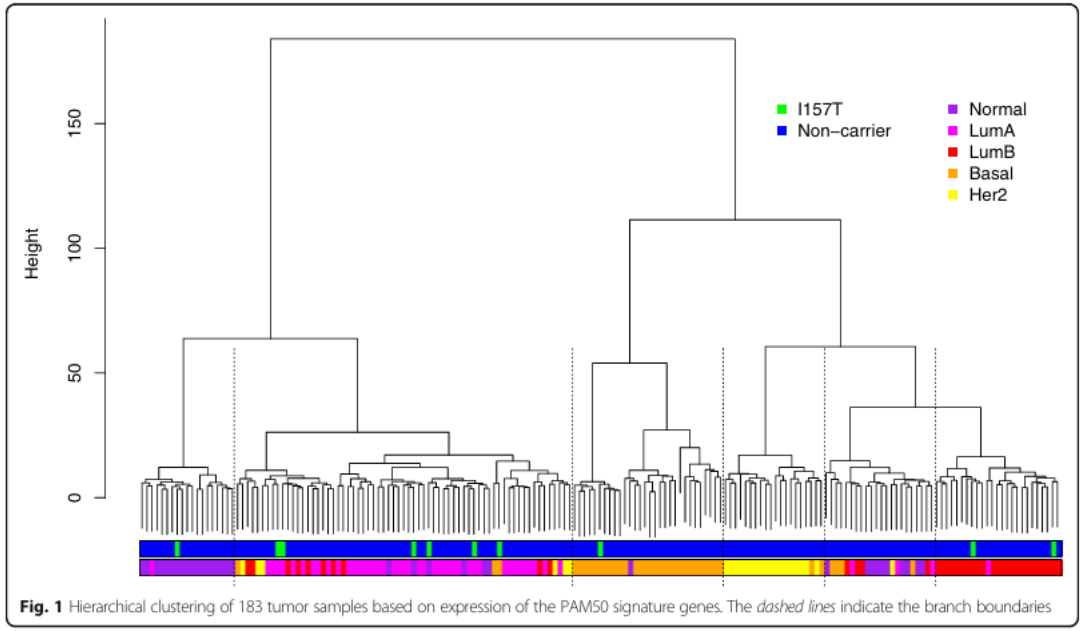


Fig. 1 Hierarchical clustering of 183 tumor samples based on expression of the PAM50 signature genes. The *dashed lines* indicate the branch boundaries

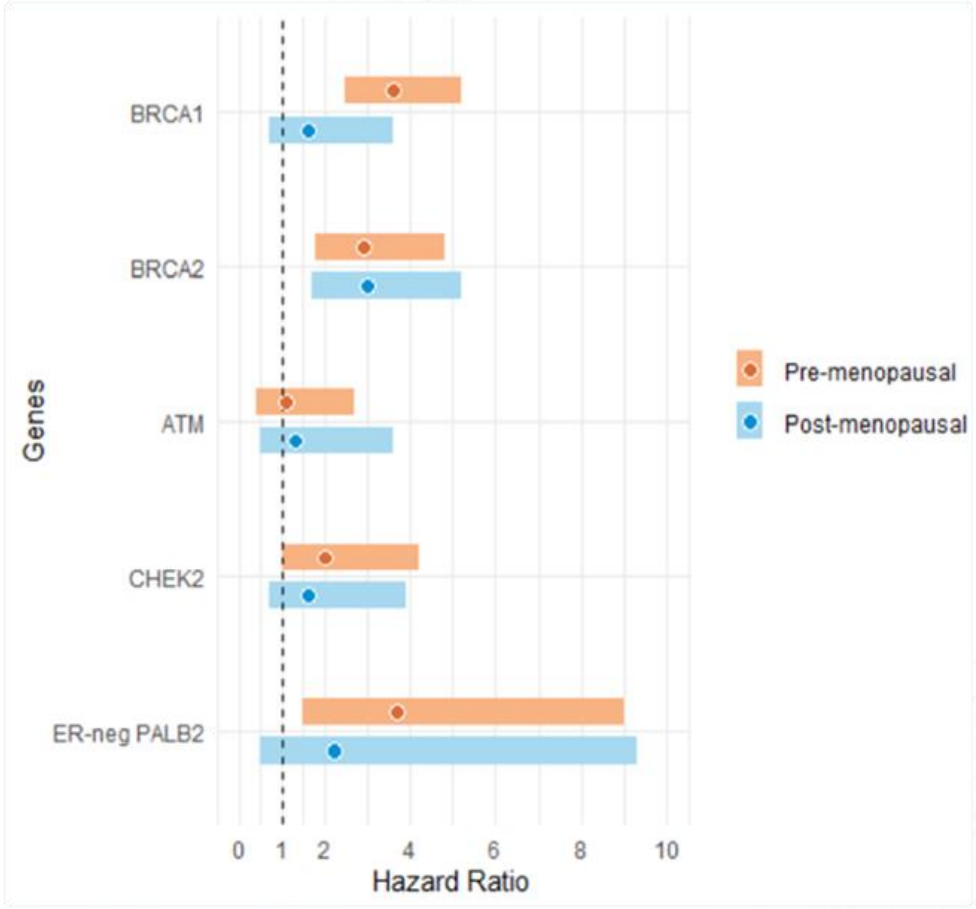
P.I157T was not associated with increased risk of early death, breast cancer-associated death or distant metastasis relapse, and there was a significant difference in prognosis associated with the two CHEK2 mutations, p.I157T and c.1100delC. Furthermore, p.I157T was associated with lobular histological type and clinico-pathological markers of good prognosis, such as ER and PR expression, low TP53 expression and low grade. Gene expression analysis suggested luminal A to be the most common subtype for p.I157T carriers.

Table 3 Risk of death or disease recurrence associated with *CHEK2*:p.I157T

(a) All breast cancer patients	Univariate analysis			Adjusted analysis		
	I157T/nc	I157T/1100delC	1100delc/nc	I157T/nc	I157T/1100delC	1100delC/nc
Early death	0.85 [0.68 - 1.07]	0.74 [0.50 - 1.09]	1.28 [1.00 - 1.64]	0.80 [0.60 - 1.07]	0.51 [0.29 - 0.90]	1.32 [0.94 - 1.86]
	0.16	*0.12*	*0.054*	*0.13*	*0.0190*	*0.11*
Breast cancer-specific death	0.85 [0.60 - 1.20]	0.64 [0.37 - 1.12]	1.44 [1.04 - 2.00]	0.93 [0.62 - 1.40]	0.46 [0.21 - 1.03]	1.25 [0.78 - 2.00]
	0.36	*0.12*	*0.030*	*0.73*	*0.058*	*0.36*
Distant metastasis relapse	1.04 [0.79 - 1.37]	0.66 [0.38 - 1.14]	1.38 [0.90 - 2.11]	1.05 [0.75 - 1.47]	0.62 [0.31 - 1.23]	1.37 [0.83 - 2.26]
	0.79	*0.13*	*0.14*	*0.76*	*0.17*	*0.22*
Locoregional relapse	1.43 [0.92 - 2.23]	0.81 [0.58 - 1.13]	2.07 [1.16 - 3.69]	1.62 [0.99 - 2.66]	0.91 [0.33 - 2.52]	1.26 [0.59 - 2.70]
	0.11	*0.21*	*0.014*	*0.056*	*0.85*	*0.55*
Second breast cancer	1.54 [0.85 - 2.78]	0.69 [0.47 - 1.03]	2.88 [1.68 - 4.98]	2.03 [1.05 - 3.92]	0.69 [0.42 - 1.13]	3.62 [1.82 - 7.21]
	0.15	*0.070*	*0.00015*	*0.035*	*0.14*	*0.00026*
(b) Patients with ER+ breast cancer	Univariate analysis			Adjusted analysis		
	I157T/nc	I157T/1100delC	1100delc/nc	I157T/nc	I157T/1100delC	1100delC/nc
Early death	0.81 [0.61 - 1.07]	0.62 [0.39 - 0.99]	1.32 [0.98 - 1.78]	0.77 [0.55 - 1.07]	0.46 [0.25 - 0.85]	1.52 [1.06 - 2.17]
	0.14	*0.044*	*0.067*	*0.12*	*0.013*	*0.022*
Breast cancer-specific death	0.80 [0.51 - 1.23]	0.47 [0.23 - 0.96]	1.46 [0.96 - 2.22]	0.80 [0.49 - 1.32]	0.33 [0.13 - 0.84]	1.50 [0.92 - 2.45]
	0.30	*0.038*	*0.074*	*0.39*	*0.019*	*0.10*
Distant metastasis relapse	1.00 [0.71 - 1.40]	0.55 [0.29 - 1.02]	1.58 [0.99 - 2.54]	1.03 [0.70 - 1.51]	0.56 [0.26 -1.19]	1.61 [0.94 - 2.77]
	0.98	*0.057*	*0.056*	*0.88*	*0.13*	*0.083*
Locoregional relapse	1.46 [0.86 - 2.47]	0.77 [0.52 - 1.14]	2.33 [1.19 - 4.57]	1.58 [0.90 - 2.79]	0.93 [0.29 - 2.98]	1.08 [0.44 - 2.66]
	0.16	*0.19*	*0.014*	*0.11*	*0.90*	*0.87*
Second breast cancer	1.33 [0.64 - 2.75]	0.58 [0.37 - 0.92]	4.09 [2.31 - 7.26]	1.81 [0.82 - 3.96]	0.61 [0.36 - 1.04]	4.39 [2.17 - 8.87]
	0.44	*0.019*	*1.4E-06*	*0.14*	*0.067*	*3.8E-05*
(c) Patients with lobular breast cancer	Univariate analysis					
	I157T/nc					
Early death	0.67 [0.39 - 1.15]					
	0.14					
Breast cancer-specific death	0.91 [0.46 - 1.80]					
	0.79					
Distant metastasis relapse	0.87 [0.48 - 1.57]					
	0.64					
Locoregional relapse	2.45 [0.95 - 6.34]					
	0.065					
Second breast cancer	1.92 [0.57 - 6.49]					
	0.29					

Muranen et al., BCR 2016

Contralateral Breast Cancer Risk by **Menopausal Status** at First Breast Ca Diagnosis



Adjusted Hazard Ratios

	10-year Cumulative Incidence of CBC*	
	Pre-menopausal	**Post-menopausal**
Non-carriers	5.8%	3.7%
BRCA1	33%	11%
BRCA2	27%	9.5%
ATM	2.9%	4.6%
CHEK2	13%	4.3%

*: Unadjusted analysis

Yadav S, JCO 2023

TABLE 2 Contralateral breast cancer risk (hazard ratio) by treatment for first primary breast cancer and *CHEK2* c.1100delC status. Stratified by time since first primary breast cancer diagnosis.

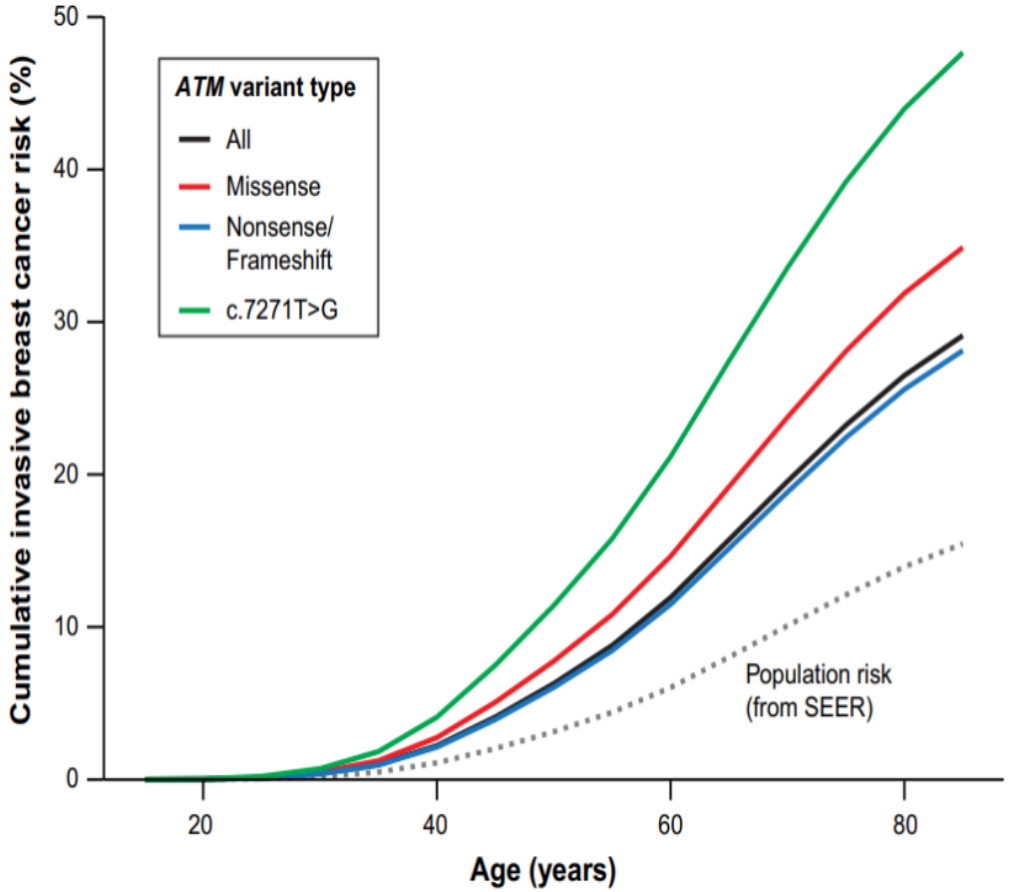
	Total follow-up time			**<5-year follow-up**			**>5 years follow-up**		
No of patients	82,701			73,354			62,688		
No of CBC events	1816			656			1160		
	HR (95% CI)	*p*-value	*p*-int	HR (95% CI)	*p*-value	*p*-int	HR (95% CI)	*p*-value	*p*-int
CHEK2 c.1100delC status	2.37 (1.82–3.08)	<0.001		3.08 (2.12–4.48)	<0.001		1.93 (1.33–2.80)	<0.001	
Radiotherapy			0.31			0.30			0.77
No radiotherapy	Ref			Ref			Ref		
Radiotherapy	1.07 (0.94–1.21)	0.33		0.98 (0.81–1.19)	0.84		1.12 (0.96–1.31)	0.16	
Systemic therapy			0.46			0.70			0.39
No systemic therapy	Ref			Ref			Ref		
CT, no ET	0.77 (0.62–0.96)	0.02		0.58 (0.41–0.83)	0.003		0.90 (0.70–1.15)	0.39	
ET, no CT	0.70 (0.58–0.83)	<0.001		0.62 (0.46–0.84)	0.002		0.73 (0.59–0.91)	0.005	
Both CT and ET	0.65 (0.55–0.78)	<0.001		0.50 (0.37–0.68)	<0.001		0.75 (0.62–0.93)	0.007	

Note: Adjusted for age at diagnosis, ER status, tumor size, nodal status and grade of first primary breast cancer.

Abbreviations: CBC, contralateral breast cancer; CT, chemotherapy; ER, estrogen receptor; ET, endocrine therapy; *p*-int, *p*-value for the comparison of a model including an interaction term between *CHEK2* c.1100delC status and a specific treatment (radiation or systemic treatment) with a model without any interaction term.

Morra A et al., Cancer Med 2023

ATM PV site-specific variability in cancer risk



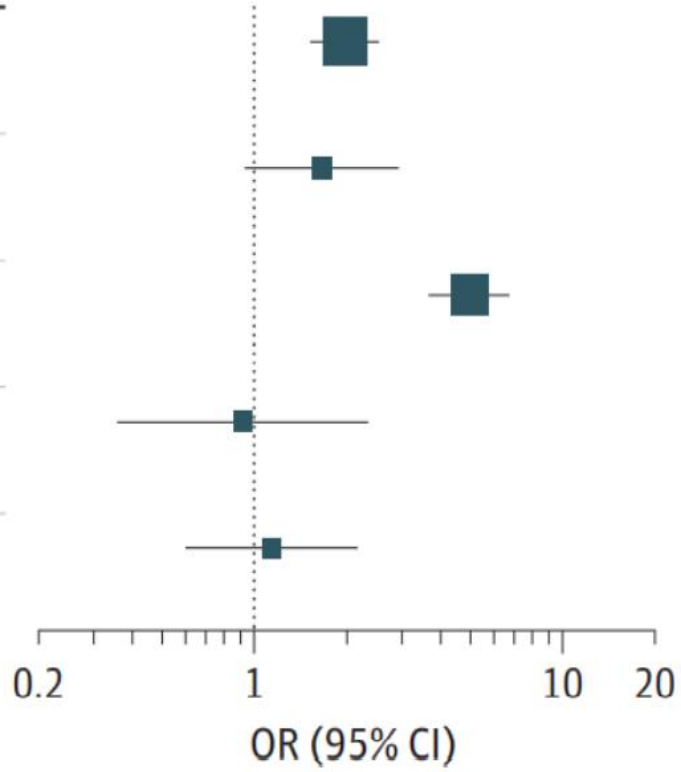
- Missense variant c.7271T>G carries risks comparable to high penetrance genes (50-60%)
- Genotype ⇔ phenotype correlations can impact management discussions

Hall et al., *Cancer Prev Res* 2021, PMID: 33509806; Goldgar et al., *Breast Cancer Research* 2016, PMID: 21787400

ATM-associated breast cancer pathology

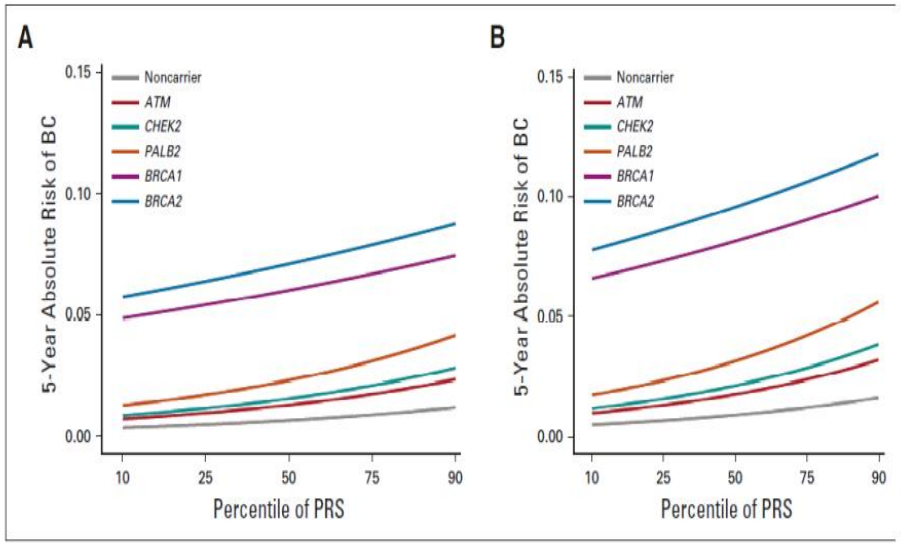
C *ATM*

	OR (95% CI)
HR positive, ERBB2 negative low grade	1.97 (1.52-2.55)
HR positive, ERBB2 positive	1.66 (0.93-2.95)
HR positive, ERBB2 negative high grade	4.99 (3.68-6.76)
HR negative, ERBB2 positive	0.92 (0.36-2.35)
Triple negative	1.14 (0.60-2.17)

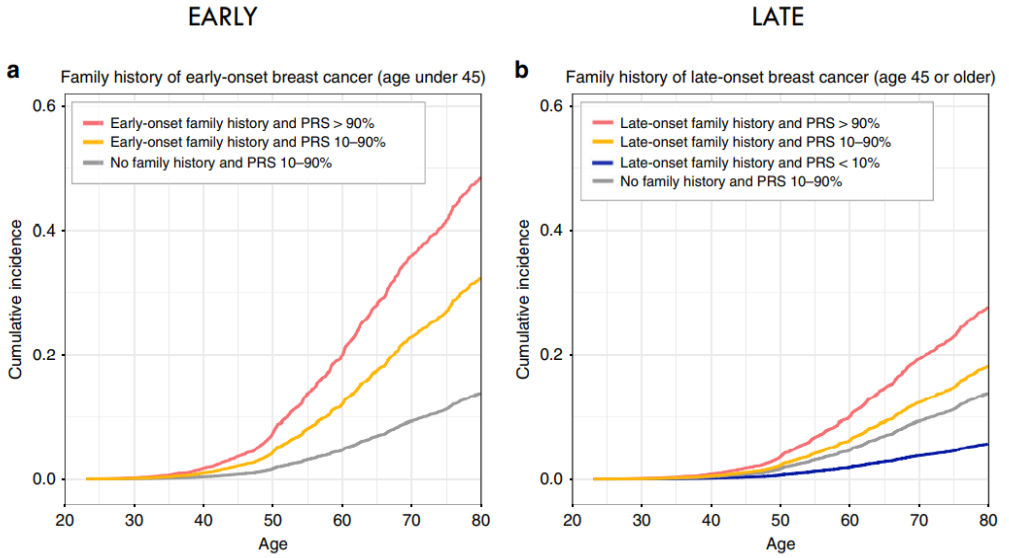


Mavaddat et al., Breast Cancer Association Consortium, *JAMA Oncology* 2022, PMID: 35084436

The impact of Poligenic Risk Score in mutation carriers



Gao et al, J Clin Oncol 2021



The PRS refines the risk assessment of women with FDR diagnosed with BC, particularly among women with positive family history of early-onset BC

RAD51C & *RAD51D:* age-specific breast cancer RR

Cancer and models considered	Age, y	RR (95% CI)	P*
RAD51C			
Breast cancer			
Age-constant model	20–79	1.99 (1.39 to 2.85)	1.55×10^{-4}
Age-specific model, separate parameters	20–29	1.19 (0.09 to 16.12)	
for each decade of age	30–39	3.25 (1.60 to 6.62)	
	40–49	2.50 (1.41 to 4.45)	
	50–59	0.96 (0.34 to 2.71)	
	60–69	1.54 (0.45 to 5.36)	
	70–79	2.57 (0.61 to 10.81)	
Age-specific model, separate parameters	20–49	2.42 (1.61 to 3.63)	
for two age groups: 20–50 and 50–80 y	50–79	1.36 (0.70 to 2.63)	
RAD51D			
Breast cancer			
Age-constant model	20–79	1.83 (1.24 to 2.72)	0.0002
Age-specific model, separate parameters	20–39	2.25 (1.25 to 4.04)	—
for each decade of age except for 20–39	40–49	1.46 (0.69 to 3.09)	—
y age group	50–59	1.56 (0.69 to 3.51)	—
	60–69	1.63 (0.54 to 4.98)	—
	70–79	4.19 (1.51 to 11.62)	—
Age-specific model, separate parameters	20–49	1.84 (1.12 to 3.02)	—
for two age groups: 20–50 and 50–80 y	50–79	1.83 (1.02 to 3.26)	—

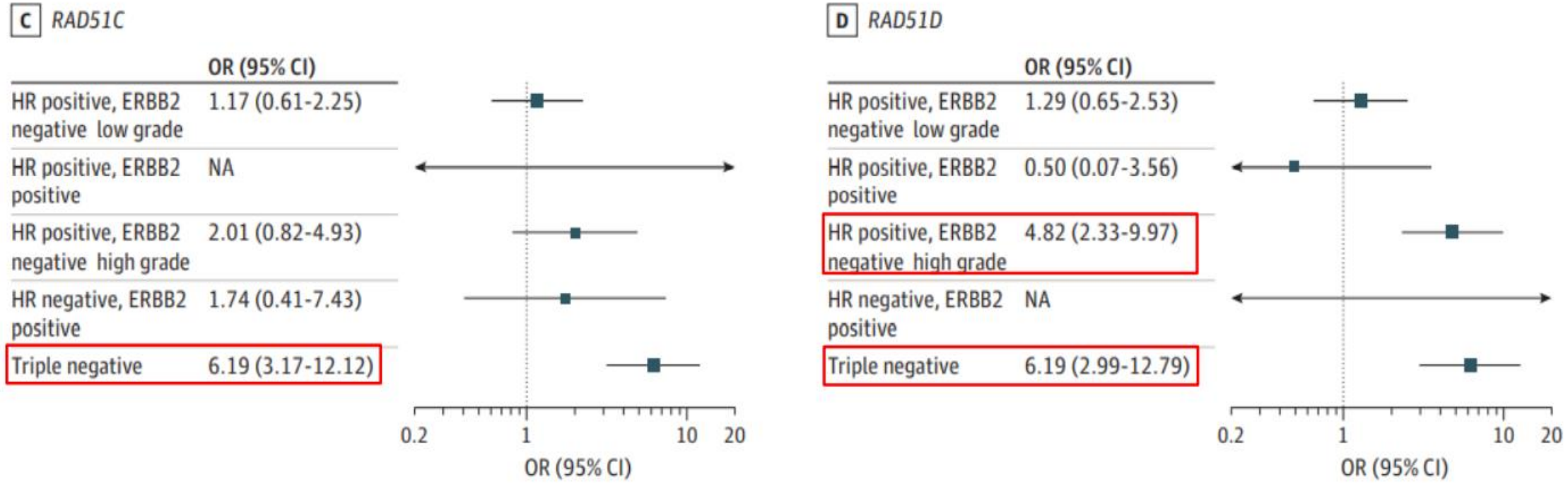
Table 3. Estimated age-specific cancer incidences and cumulative cancer risks for *RAD51C* and *RAD51D* pathogenic variant carriers

	RAD51C pathogenic variant carriers		*RAD51D* pathogenic variant carriers	
Age, y	BC	TOC	BC	TOC
Estimated incidences per 1000 person-years (95% CI)*				
30	0.4 (0.2 to 0.5)	0.05 (0.01 to 0.2)	0.3 (0.2 to 0.5)	0.03 (0.007 to 0.1)
40	2 (1 to 3)	0.3 (0.2 to 0.8)	2 (1 to 2)	0.3 (0.1 to 0.7)
50	5 (3 to 6)	2 (1 to 3)	4 (3 to 6)	2 (1 to 3)
60	6 (4 to 9)	7 (4 to 11)	6 (4 to 9)	6 (4 to 8)
70	7 (5 to 10)	3 (1 to 8)	7 (4 to 10)	5 (2 to 9)
79	8 (5 to 11)	1 (0.2 to 8)	7 (5 to 11)	3 (0.9 to 12)
Estimated cumulative risks, % (95% CI)*				
30	0.1 (0.08 to 0.2)	0.02 (0.02 to 0.02)	0.1 (0.07 to 0.2)	0.02 (0.02 to 0.02)
40	1 (0.7 to 1)	0.2 (0.08 to 0.4)	0.9 (0.6 to 1)	0.1 (0.06 to 0.3)
50	4 (3 to 6)	1 (0.6 to 2)	4 (2 to 5)	0.8 (0.5 to 2)
60	9 (6 to 12)	4 (3 to 7)	8 (6 to 12)	4 (3 to 7)
70	15 (11 to 21)	9 (6 to 14)	14 (10 to 20)	9 (6 to 14)
80	21 (15 to 29)	11 (6 to 21)	20 (14 to 28)	13 (7 to 23)

- 125 *RAD51C* families, 60 *RAD51D* families
- LTR BC ~20% for either mutation
- *RAD51C*: RR BC higher <50 v. >50
- *RAD51D*: RR BC higher ages 20-39 and 70-79

Yang et al., *JNCI* 2020, PMID 32107557

RAD51C- and RAD51D-associated breast cancer pathology



Associations with TNBC (RAD51C/D) and high-grade HR+ BC (RAD51D)

Mavaddat et al., Breast Cancer Association Consortium, *JAMA Oncology* 2022, PMID: 35084436

TP53 and Early-Onset BC

Table 2 *TP53* testing in early-onset breast cancer patients

Study	Proband	Number of patients	Family History	*BRCA* status	*TP53* mutation (%)
Lallo et al. [14]	Breast cancer <30	82	Unselected	Negative	4.9
Walsh et al. [15]	Breast cancer <35	21	≥ 4 relatives with breast/ovarian cancer, one breast cancer < 35 who did not meet Li-Fraumeni syndrome criteria	Negative	0
Bouregard et al. [16]	Breast cancer <33	45	Negative	Negative	6.7
Tinet et al. [12]	Breast cancer <36	128	Negative	Negative	3.9
Ruijis et al. [17]	Breast cancer <30	12	Negative	Negative	8.3
Ginsburg et al. [18]	Breast cancer <30	95	Unselected	Negative	0
Gonzalez et al. [19]	Breast cancer <30	14	Negative	Negative	7.1
Mouchawar et al. [20]	Breast cancer <30	52	Unselected	Unknown	3.8

This table summarizes the results of *TP53* testing in breast cancer patients in eight studies published in the past 10 years [12, 14–20]

Mc Cuaig JM et al., Fam Can 2012

TP53 Breast Cancer Characteristics

Author	Year	*TP53* carriers with BC N	HER2 positive tumors N	Other findings
Wilson JRF et al [56]	2010	12*	10* (83%)	–
Melhem-Bertrandt A et al [57]	2012	30	20 (67%)	–
Masciari S et al [58]	2012	32*	20 (63%)	–
Bakhuizen JJ et al [33]	2019	8	5 (63%)	–
Packwood K et al [59]	2019	36	20 (56%)	–
Le A et al [60]	2020	38*	22 (58%)	–
Alyami H et al [61]	2021	21*	10 (53%)	2 cases of malignant phyllodes tumor
Kuba MG et al [62]	2021	17	9 (53%)	2 cases of HER2 negative BC by IHC (1 +) but positive by FISH.
Rippinger N et al [63]	2021	32	11 (34%)	10 cases (31.3%) of luminal B-like BC
Breast Cancer Association Consortium, Mavaddat N et al [34]	2022	51	NR (46%)	OR for HER2 + BC 7.14 (95%CI 3.34–15.28)
Sandoval RL et al [64]	2022	87	32 (41%)	43 cases (55%) of luminal-like BC

Blondeaux E et al., Cancer Treat Review 2023

❑ The High Risk Rare Genes

PTEN

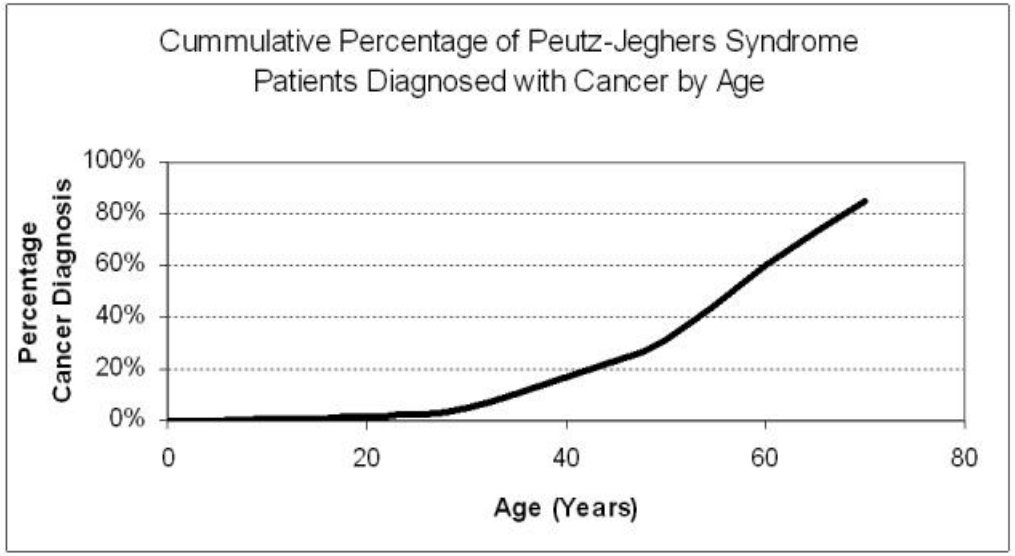
- PTEN Hamartoma Tumor syndrome (PHTS) encompasses a clinical spectrum of heritable disorders including Cowden syndrome (CS), Bannayan–Riley–Ruvalcaba syndrome, and Proteus and Proteus-like syndrome
- **Breast cancer risk estimates (67–85 %) for women with germline PTEN mutations** are similar to those quoted for patients with germline mutations in the BRCA1/2 genes
- **MRI surveillance or Prophylactic IRRM or CLRRM should be discussed**

CDH1

- **Bilateral LBC with or without family history of LBC, with age at onset < 50 years; and (B) unilateral LBC with family history of LBC, with age at onset < 45 years.**
- Following the above-mentioned clinical criteria, a CDH1 germline mutation could be identified in 3% of the screened population
- **MRI or Prophylactic IRRM or CLRRM should be discussed**
- Diffuse HGC should be screened – Prophylactic Total Gastrectomy needs to be discussed

Peutz-Jeghers Syndrome

- Pancreatic Cancer
- Liver
- Lung
- Breast
- Ovary
- Uterine Cancer
- Testis
- Others



The management of Peutz-Jeghers Syndrome: EHTG guidelines

The following breast surveillance is recommended in female PJS patients: Raising awareness at age 18 years e.g., by starting breast self-examination; Clinical breast exam every 6–12 months starting at age of 25 years; Annual breast contrast MRI screening (or breast ultrasound if MRI contraindication or unavailability) at age 25–30 years; Annual mammogram with consideration of tomosynthesis and ultrasound for dense breast and annual breast contrast MRI at age 30–50 years; Annual mammogram with consideration of annual breast contrast MRI for dense breast pattern at age 50–75 years; Management should be considered on an individual basis from age > 75 years.

Level of evidence: low

Strength of recommendation: moderate

The optimal breast surveillance strategy in female PJS patients remains debated and the benefits of surveillance remain to be established. Therefore, it is recommended that surveillance is conducted at centers of expertise in the framework of a study or registry.

Level of evidence: low

Strength of recommendation: strong

As evidence for its benefit is lacking, prophylactic mastectomy is currently not recommended for female PJS patients. Risk reducing mastectomy should be discussed in a multidisciplinary setting also taking into account family history and other clinical factors.

Level of evidence: low

Strength of recommendation: moderate

Wagner A et al., J Clin Med 2021

TAKE HOME MESSAGES

- 16% early onset BC carries gPV in BRCA1/2, PALB2, ATM,CHEK2 and TP53 genes
- Fertility preservation issues
- Similar outocome and response to PARPi in gPALB2 carriers
- Saruparib will be approved also in gPALB2 carriers
- CHEK2 1100delC is associated to EOBC
- ATM c7271T>G gPV increases the BC risk as well as a high penetrance gene
- RAD51D is associated to very young BC patients (20-39 years)
- TP53 gPV develop more frequently HER2+ BC
- Risk for second BC in gPALB2 TNBC a CHEK2 BC arisen in premenopausal age
- Perform a MGP test in case of very young BC patients