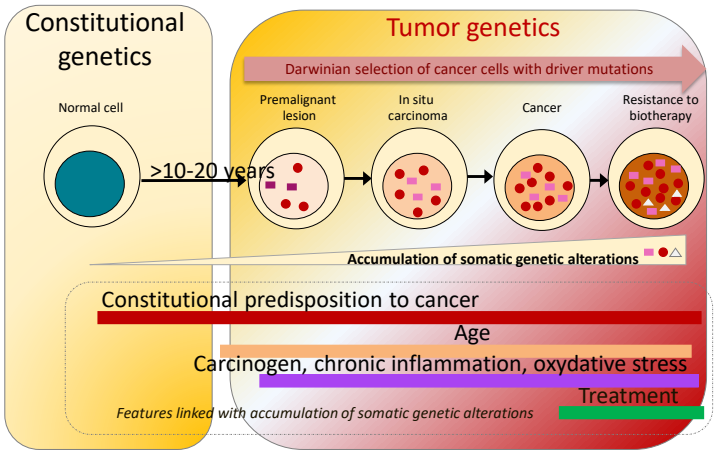
Inherited breast and ovarian cancer

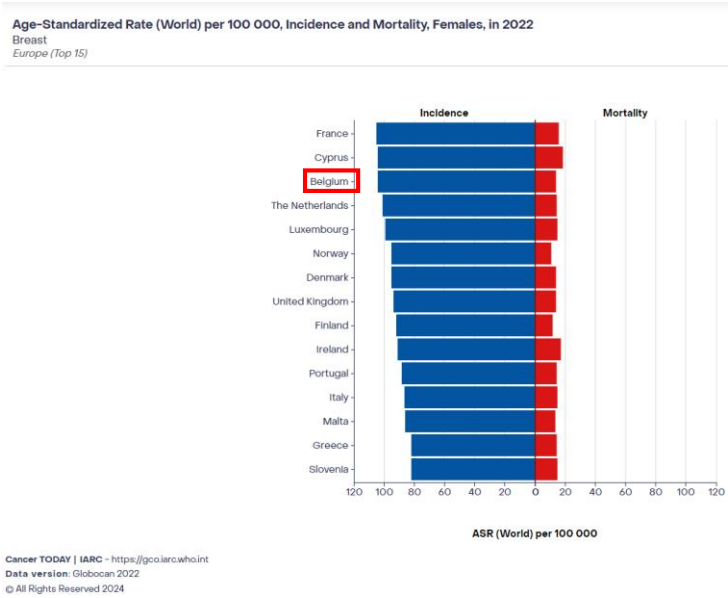
Pr François Duhoux
Medical Oncology and Clinical Genetics
9th February 2024

Accumulation of genetic alterations during carcinogenesis



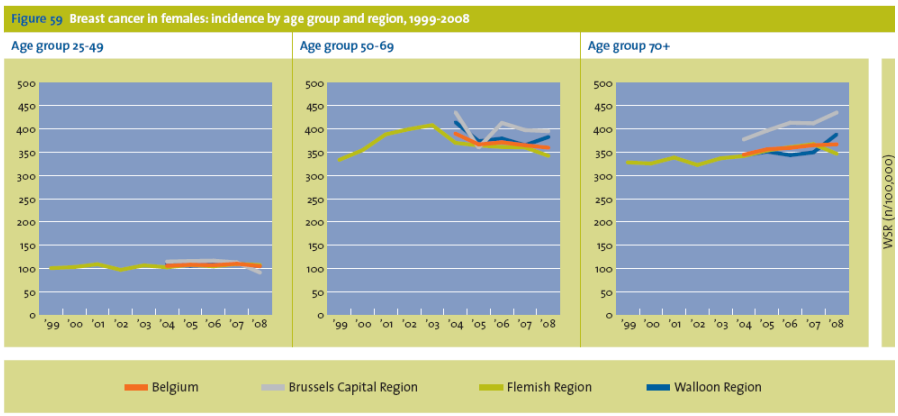
Stratton MR, et al. Nature 2009

Breast cancer



Incidence - Mortality
.be: 104.4 – 14.2
Lifetime risk : 12%

Breast cancer in Belgium according to age



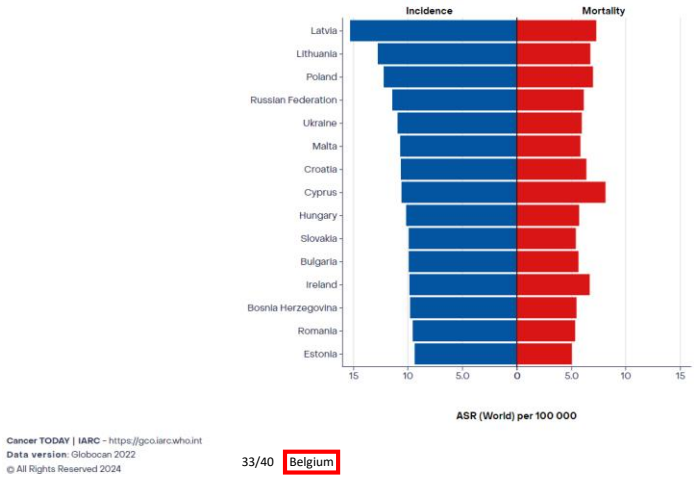
Breast cancer: risk factors

- Sex
  - 1 M / 100 F
- Age
  - the risk increases with age
  - but 15-20% before the age of 50
- Family history
- Personal history
- Environmental factors (geographic migration)
- Prolonged exposure to estrogens:
  - Early menarche
  - Late menopause
  - Late first pregnancy, few pregnancies
  - Lack of breast-feeding
- Other breast lesions (in situ carcinoma, atypical hyperplasia, radial scar, ...)
- Controversies: endocrine treatment for menopausal status, weight, alcohol, tobacco, …

Breast cancer – genetic risk

- 15% of healthy women have at least one 1st degree relative with breast cancer
  → risk x 2
- Breast cancer risk increases with the number of 1st degree relatives with breast cancer
  - 1: x 1.8
  - 2: x 2.9
  - 3: x 3.9
- *BRCA1* and *BRCA2* germline mutations are responsible for 20-25% of familial breast cancer cases, but < 5% of all breast cancers
- > 50% of the genetic predisposition to familial breast cancer remains unexplained

Ovarian cancer



Incidence - Mortality
.be: 6.9 – 3.7
Lifetime risk : 1.3%

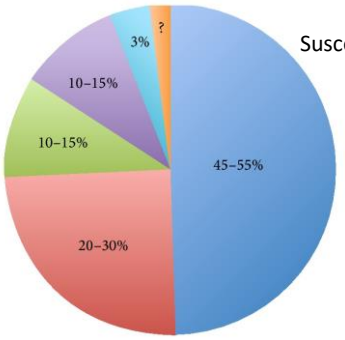
Ovarian cancer: risk factors

- Age
- Obesity
- Reproductive history
- Birth control
- Family history of breast, ovarian and colorectal cancer
- Personal history of breast cancer

Ovarian cancer genetics

23% of ovarian carcinomas have a hereditary predisposition

Germline *BRCA1* and *BRCA2* mutations account for 20-25% of high grade serous ovarian cancer



Susceptibility genes and their prevalence in hereditary ovarian syndromes

- *BRCA 1*
- *BRCA 2*
- Genes involved in DSB repair
- *MMR* genes (Lynch SDR)
- *TP53* (Li-Fraumeni SDR)
- Other genes

Pietragalla A et al, Int J Gyn Can 2020
Toss A et al, Biomed Res Int 2015

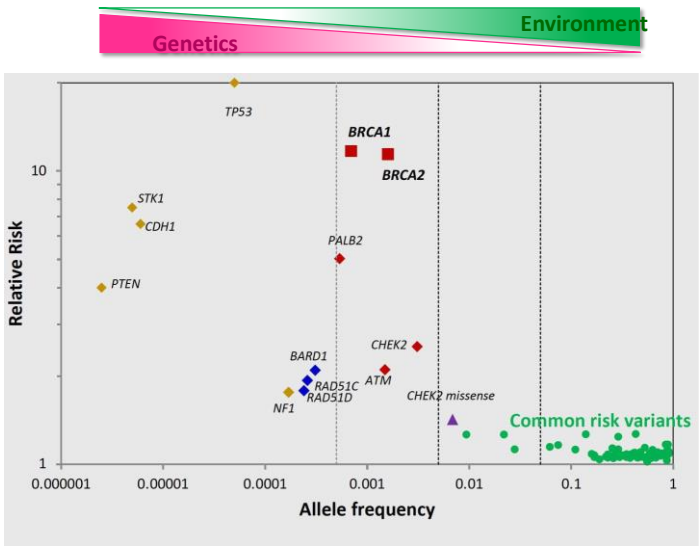
Breast and ovarian cancer : multidisciplinary team

- surgeon / gynaecologist
- medical oncologist
- radiation oncologist
- radiologist
- pathologist
- **geneticist**
- plastic surgeon

Definitions

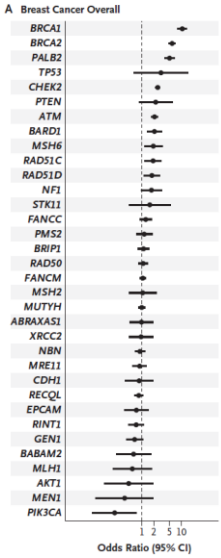
- Penetrance = the likelihood a given gene will result in disease
- High penetrance genes :
  - rare mutations
  - very high risk of disease
  - independently of other risk factors
- Low penetrance genes
  - frequent genetic variants
  - interact with exogenous factors to cause the diseases

Genetic variants by risk and frequency



Easton D | Membre du réseau Lid van het netwerk Huni | 12

Risk of breast cancer with protein-truncating variants in 34 genes



Breast Cancer Association Consortium, NEJM 2021

Guidelines for hereditary breast and/or ovarian cancer syndrome diagnostic testing criteria

COLLEGE GENETICS

New version : June 2023

I. Woman with breast cancer + one of the following:

- diagnosed ≤ 40yrs
- diagnosed < 50yrs and one relative with bilateral breast cancer, or breast cancer < 50yrs, or prostate cancer diagnosed < 60yrs
- a first or second degree relative with male breast cancer, ovarian cancer, pancreatic adenocarcinoma, or metastatic prostate cancer
- bilateral breast cancer if the first cancer was diagnosed < 50yrs
- triple negative breast cancer < 60yrs
- HER2 negative (hormone receptor-negative or hormone receptor-positive) breast cancer eligible for PARP-inhibitors: in high-risk (neo)adjuvant setting or metastatic setting
- ovarian cancer or pancreatic adenocarcinoma at any age
- ≥ 3 individuals with breast cancer and/or prostate cancer, one is a first degree relative of the other two (excluding male transmitters if father is not affected) and one diagnosed at an early age (< 60yrs)
- individual of ethnicity associated with a higher frequency of specific mutations (e.g., Ashkenazi Jewish): eligible for founder mutation testing
- other family situations with a priori chance of mutation >10% according to BRCAPRO or Evans criteria or Manchester score
- test more than one affected relative if criteria remain positive after excluding the negative case as a phenocopy

II. Women with high grade epithelial ovarian cancer at any age (excluding mucinous ovarian cancer)

III. Male with breast cancer

IV. Family history only

- first degree unaffected relative of any of the above on a case-by-case basis
- testing of unaffected family members should only be considered when no affected family member is available and then the unaffected family member with the highest probability of mutation should be tested

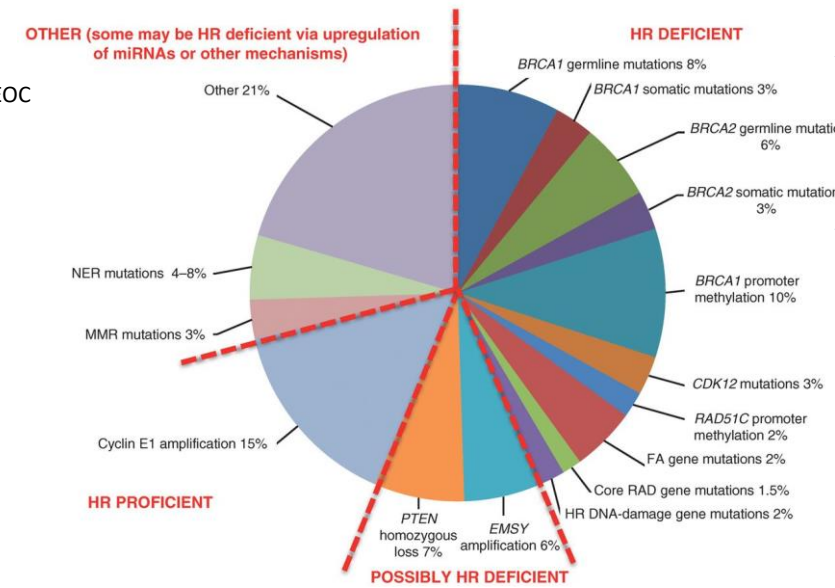
https://www.college-genetics.be/

BRCA1 and *BRCA2*

- Global prevalence of *BRCA1* or *BRCA2* mutations is estimated at 1/139 (Genome Medicine volume 12, Article number: 2 (2020))
- Responsible for the majority of « hereditary » breast cancer cases
- 30 - 50% of breast cancer patients carrying a mutation have no known or significant family history (Eur J Cancer, 43 (11) (2007 Jul), pp. 1713–1717)
- Specific *BRCA1* and *BRCA2* mutations are frequent in the Jewish Ashkenazi population (1/40 - 1/50)

BRCA1 and *BRCA2* : germline in breast cancer, germline or somatic in ovarian cancer

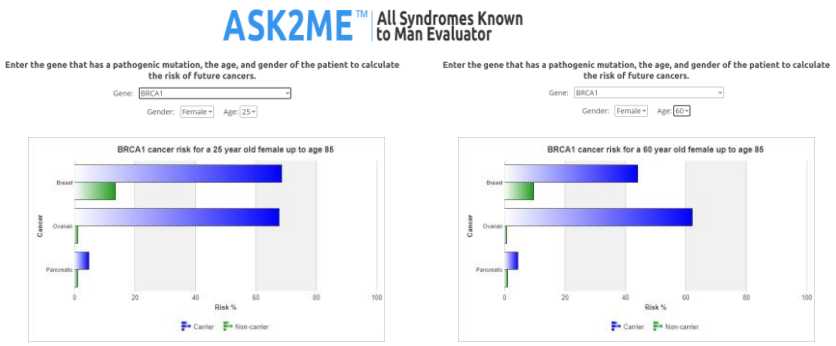
High grade serous EOC



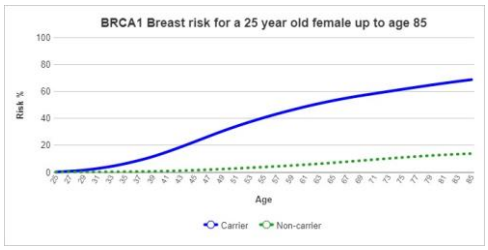
Konstantinopoulos et al, Cancer Discov 2015

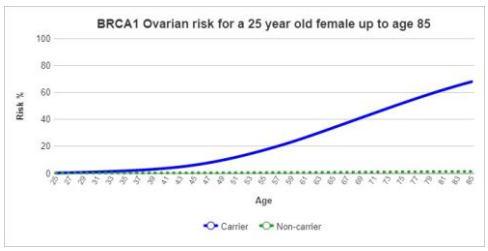
Roles of *BRCA1* and *BRCA2* in hereditary breast and ovarian cancer syndrome (HBOC)

- High penetrance but variable expression :
  - Cumulative risk of breast cancer : up to 70 % (at 80 y.o.)
  - Ovarian cancer : 40% (*BRCA1*) / 20% (*BRCA2*)



HBOC : the cumulative cancer risk varies with age → higher in younger women





BRCA1 and *BRCA2*

High penetrance : high risk of disease if mutation is found

But risk also depends on :

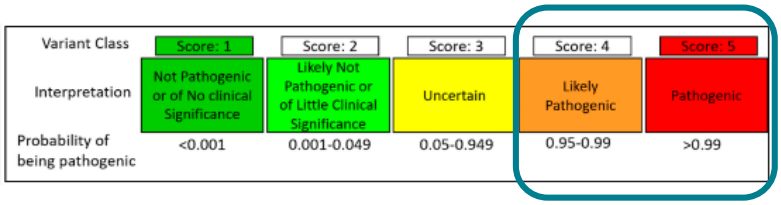
- Sex
  - 1 M / 100 F
- Age
  - the risk increases with age
  - but 15-20% before the age of 50
- Family history
- Personal history
- Environmental factors (geographic migration)
- Prolonged exposure to estrogens:
  - Early menarche
  - Late menopause
  - Late first pregnancy, few pregnancies
  - Lack of breast-feeding
- Other breast lesions (in situ carcinoma, atypical hyperplasia, radial scar, ...)
- Controversies: endocrine treatment for menopausal status, weight, alcohol, tobacco, …

BRCA1 and *BRCA2*

- Thousands of different sequence variants have been identified :
  - 1) mutations that are known or likely to be deleterious and disease-associated
  - 2) variants of unknown function
    = UV : unclassified variants
  - 3) genetic variants that are likely to be neutral and without clinical importance

BRCA1 and *BRCA2*: beware of VUSs

- VUS = variant of unknown significance



IARC classification for sequence variants identified by genetic testing

Jimenez-Sainz et al, Genes 2021 | Membre du réseau Lid van het netwerk Huni | 21

BRCA1 and *BRCA2*

BRCA1

Tumor	Risk	Comment
Breast cancer	60 – 80 % at 80 y	Higher risk for triple negative breast cancer
Contralateral breast cancer	Around 40% after 20 y	Risk table[1] can be used during counseling for a more accurate risk estimate
Male breast cancer	1%	
Ovarian cancer	Around 40% at 80 y	
Prostate cancer	Moderate increase	
Pancreatic cancer	Small but increased risk	Not in patient folder
Endometrial cancer	< 5%	Should not be reported in patient folder
Colorectal cancer	Slight increase (only < 50 y)	Should not be reported in patient folder

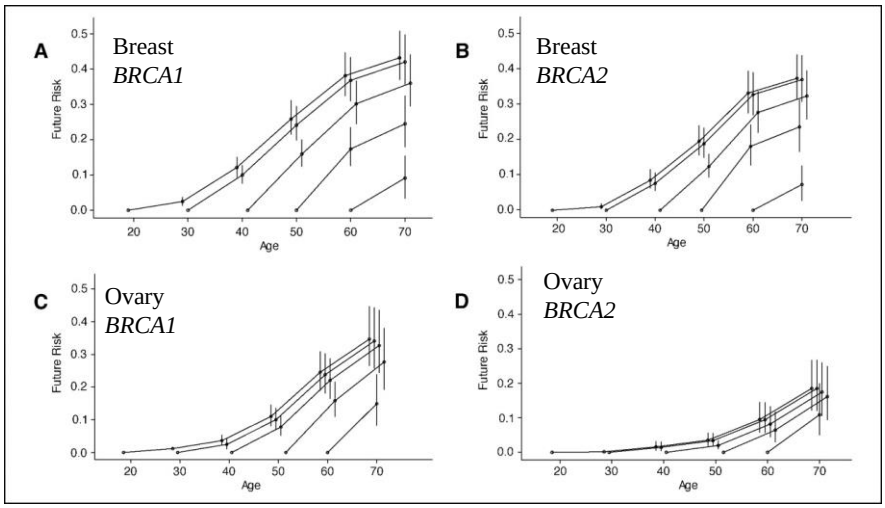
BRCA2

Tumor	Risk	Comment
Breast cancer	60 – 80 % at 80 y	
Contralateral breast cancer	Around 25% after 20 y	Risk table[1] can be used during counseling for a more accurate risk estimate
Male breast cancer	7%	
Ovarian cancer	Around 20% at 80 y	
Prostate cancer	15% before 65 y	
Pancreatic cancer	Small but increased risk	Not in patient folder

Belgian guidelines for Managing Hereditary Breast and Ovarian Cancer: 05/2023 Update

https://www.college-genetics.be/ | Membre du réseau Lid van het netwerk Huni | 22

Future risks of developing cancer for a female carrier at a range of ages in the next 10-year interval, 20-year interval, and so on



Chen, S. et al. J Clin Oncol; 24:863-871 2006

Annual Ovarian, Fallopian Tube and Peritoneal Cancer

Table 2. Annual Risks of Ovarian, Fallopian Tube, and Peritoneal Cancer in *BRCA1* and *BRCA2* Mutation Carriers With Intact Ovaries

	BRCA1				*BRCA2*			
Age Group (years)	No. of Patients	No. of Cancers	Person-Years	Annual Risk (per 100,000 per year)	No. of Patients	No. of Cancers	Person-Years	Annual Risk (per 100,000 per year)
30-34	413	2	865.6	231.1	47	0	90.4	0
35-39	566	6	2,223.1	269.9	92	0	388.7	0
40-49	1,009	43	3,958.6	1,086.2	276	1	1,174.3	85.2
50-59	549	34	2,029.9	1,675.0	207	5	853.2	586.1
60-69	216	9	975.3	922.8	98	3	475.2	631.3
70-74	128	4	659.1	606.9	59	1	363.2	275.3
Total	2,881	98	10,711.6	914.9	779	10	3,344.9	299.0

NOTE. Forty-six cancers diagnosed at prophylactic oophorectomy were excluded from this analysis.

Finch, A. et al. J Clin Oncol; 2014

Guidelines for the management of patients with *BRCA1* mutations

Tumor	Intervention	Recommendation
Breast cancer	Screening	Clinical examination every 6 months from 25* y AND • 25* – 35 y: Annual breast MRI • Consider baseline mammogram once at 30y to detect potential microcalcifications • 35 – 65 y: annual breast MRI and annual mammogram (+/- US when indicted by radiologist) alternating every 6 months • 65 – 75 y: Annual mammography (if quality is sufficient) • >75y: Consider mammogram every 2 y *Or 5 y younger than youngest diagnosis in the family if diagnosis <30y
	Risk reducing surgery	Bilateral mastectomy (comments: no standard follow-up with imaging after risk reducing mastectomy, nipple preservations is considered safe)
Ovarian cancer	Screening (not in folder)	Not recommended (comment: tailored program could be offered if patient refused risk reducing BSO ≥ 40 y)
	Risk reducing surgery	Strongly consider BSO < 40 y
Prostate cancer	Screening	Annual PSA and digital prostate exam from age 50 y (or 10y earlier than youngest diagnosis, whichever comes first)
Pancreatic cancer (not in folder)	Smoke cessation	Recommended
	Screening (preferentially in clinical trial)	**If ≥1 first degree relative with pancreatic cancer**: consider discussing pros and cons of screening according to CAPS guidelines (Goggins et al, Gut 2020)

Male breast cancer: **Routine screening not recommended**

PGD/PND for BRCA1? **PGT is offered in every center; PND is not offered by every genetic center**

Belgian guidelines for Managing Hereditary Breast and Ovarian Cancer: 05/2023 Update

https://www.college-genetics.be/ | Huni | 25

Guidelines for the management of patients with *BRCA2* mutations

Tumor	Intervention	Recommendation
Breast cancer	Screening	Clinical examination every 6 months from 25* y AND • 25* – 35 y: Annual breast MRI • Consider baseline mammogram once at 30y to detect potential microcalcifications • 35 – 65 y: annual breast MRI and annual mammogram (+/- US when indicted by radiologist) alternating every 6 months • 65 – 75 y: Annual mammography (if quality is sufficient) • >75y: Consider mammogram every 2 y *Or 5 y younger than youngest diagnosis in the family if diagnosis <30y
	Risk reducing surgery	Bilateral mastectomy (comments: no standard follow-up with imaging after risk reducing mastectomy, nipple preservations is considered safe)
Ovarian cancer	Screening (not in folder)	Not recommended (comment: tailored program could be offered if patient refused risk reducing BSO ≥ 50 y)
	Risk reducing surgery	Strongly consider BSO < 50 y
Prostate cancer	Screening	Annual PSA and digital prostate exam from age 40 y (or 10y earlier than youngest diagnosis, whichever comes first)
Pancreatic cancer (not in folder)	Smoke cessation	Recommended
	Screening (preferentially in clinical trial)	**If ≥1 first degree relative or ≥ 2 relatives of any degree with pancreatic cancer:** consider discussing pros and cons of screening according to CAPS guidelines (Goggins et al, Gut 2020)

Male breast cancer: Consider annual clinical exam by physician from age 40 y

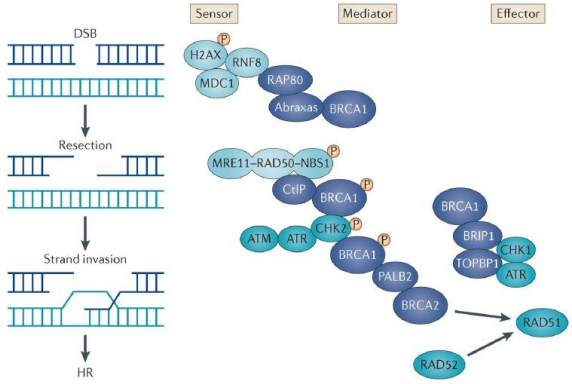
PGD/PND for BRCA2? **PGT is offered in every center; PND is not offered by every genetic center**

Belgian guidelines for Managing Hereditary Breast and Ovarian Cancer: 05/2023 Update

https://www.college-genetics.be/ | Huni | 26

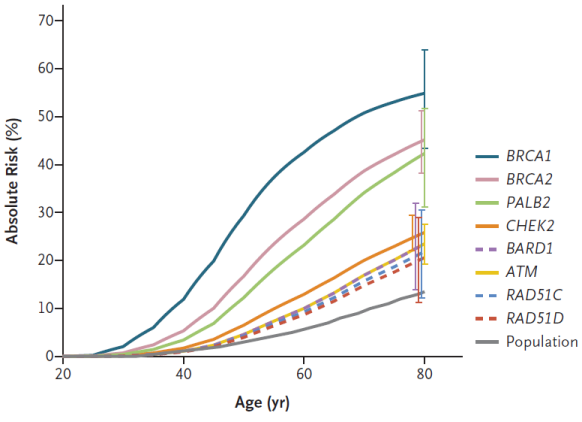
Other genes implicated in an increased risk of breast cancer

Molecular mechanisms of double-strand break DNA repair



Nat Rev Cancer.;12(1):68-78 | Membre du réseau Lid van het netwerk Huni

Estimated absolute risk of breast cancer associated with protein-truncating variants



Breast Cancer Association Consortium, NEJM 2021 | Membre du réseau Lid van het netwerk Huni

PALB2

- Breast (women) : cumulative risk 30-60%
  - importance of family history
  - increased risk of contralateral breast cancer
  - anticipation
- Ovary : cumulative risk 5-15%
- Breast (men) : 1%
- Pancreas: weak but increased

Tumor	Intervention	Recommendation
Breast cancer	Screening	Clinical examination every 6 months from 25* y AND • 25* – 35 y: Annual breast MRI • Consider baseline mammogram once at 30y to detect potential microcalcifications • 35 – 65 y: annual breast MRI and annual mammogram (+/- US when indicated by radiologist) alternating every 6 months • 65 – 75 y: Annual mammography (if quality is sufficient) • >75y: Consider mammogram every 2 y *Or 5 y younger than youngest diagnosis in the family if diagnosis <30y
	Risk reducing surgery	Bilateral mastectomy (comments: no standard follow-up with imaging after risk reducing mastectomy, nipple preservations is considered safe)
Ovarian cancer	Screening (not in folder)	Not recommended (comment: tailored program could be offered if patient refused risk reducing BSO ≥ 50 y)
	Risk reducing surgery	Strongly consider BSO at age of menopause (or earlier depending on family history
Pancreatic cancer (not in folder)	Smoke cessation	Recommended
	Screening (preferentially in clinical trial)	If ≥1 first degree relative with pancreatic cancer: consider discussing pros and cons of screening according to CAPS guidelines (Goggins et al, Gut 2020)

Male breast cancer: **Routine screening not recommended**

PGD/PND for PALB2? **PGT is offered in every center; PND is not offered by every genetic center**

Belgian guidelines for Managing Hereditary Breast and Ovarian Cancer: 05/2023 Update

https://www.college-genetics.be/

CHEK2

- Breast (women) : cumulative risk 20-45%
  - importance of family history
  - risk of contralateral cancer : 25% after 20 years
- Breast (men) : 0,5-1%
- Prostate : moderate increase

Tumor	Intervention	Recommendation
Breast cancer	Screening	Clinical examination every 6 months from 25 y AND 35 – 65 y: At least yearly breast MRI with 1-incidence mammogram +/- US if indicated by radiologist (or start 5 y before youngest diagnosis in family if diagnosis <40y) 65 – 75 y: Annual mammography (+/- ultrasound) >75y: Consider mammogram every 2 y (if patient is in good health)
	Risk reducing surgery	If strong family history or if diagnosed with breast cancer: consider risk reducing bilateral mastectomy
Prostate cancer	Screening	Annual PSA and digital prostate exam from age 50 y (or 10 y earlier than youngest diagnosis)

Female non-carriers with a 1st degree relative with breast cancer

Table 9: Recommendations for non-carrier with a first degree relatives (sister, daughter/mother) with breast cancer in CHEK2 families

Tumor	Intervention	Recommendation
Breast cancer	Screening	40 – 50 y: Annual mammogram 50 – 75 y: Mammogram every 2 years

Belgian guidelines for Managing Hereditary Breast and Ovarian Cancer: 05/2023 Update

https://www.college-genetics.be/

ATM

- Breast (women) : cumulative risk 30%
  - importance of family history
  - contralateral breast cancer?
- Breast (men) : 0,5-1%
- Prostate : moderate
- Pancreas : small

Tumor	Intervention	Recommendation
Breast cancer	Screening	Clinical examination every 6 months from 25 y AND 35 – 65y: At least yearly breast MRI with 1-incidence mammogram +/- US if indicated by radiologist (or start 5 y before youngest diagnosis in family if diagnosis <40y) 65 – 75y: Annual mammogram (+/- ultrasound) >75y: Consider mammogram every 2 y (if patient is in good health)
	Risk reducing surgery	Bilateral mastectomy can be considered based on patient preference
Prostate cancer	Screening	Annual PSA and digital prostate exam from age 50 y (or 10y earlier than youngest diagnosis)
Pancreatic cancer (not in folder)	Smoke cessation	Recommended
	Screening (preferentially in clinical trial)	**If ≥1 first degree relative with pancreatic cancer**: consider discussing pros and cons of screening according to CAPS guidelines (Goggins et al, Gut 2020)

- ***ATM* c.7271T>G (V2424G) is a high risk variant: BRCA breast screening according to literature**[1]

Female non-carriers with a 1st degree relative with breast cancer

Table 12: Recommendations for non-carrier with a first degree relatives (sister, daughter/mother) with breast cancer in ATM families

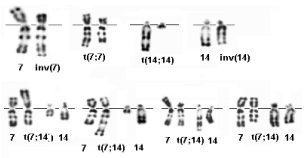
Tumor	Intervention	Recommendation
Breast cancer	Screening	40 – 50 y: Annual mammogram 50 – 75 y: Mammogram every 2 years

Belgian guidelines for Managing Hereditary Breast and Ovarian Cancer: 05/2023 Update

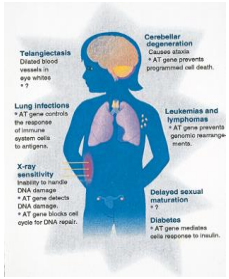
https://www.college-genetics.be/

ATM

- Risk of radiosensitivity in heterozygotes?
  - Not demonstrated : mammogram recommended by NCCN v1.2024, but caution advised by Belgian guidelines
- No evidence of deleterious effect of radiotherapy, but debated



- Beware of the risk of biallelic mutation in offspring:
- test the partner if child wish (risk 1/100)



Ataxia telangiectasia

- Congenital dysmorphic syndrome : small size, microcephaly, abnormal thumbs or forearms, face, neurological or retinian signs
- Predisposition to cancer (leukemia, lymphoma, carcinoma…)
- +/- medullary insufficiency
- +/- immune abnormalities

Int J Radiation Oncol Biol Phys, Vol. 105, No. 4, pp. 698e712, 2019

RAD51C and *RAD51D*

- Breast (women) : cumulative risk 20-45%
  - importance of family history
  - remaining risk in non-carriers
- Ovary: 5-10%

Tumor	Intervention	Recommendation
Breast cancer	Screening	Clinical examination every 6 months from 25 y AND • 35 – 65 y: At least yearly breast MRI with 1-incidence mammogram +/- US if indicated by radiologist (or start 5 y before youngest diagnosis in family if diagnosis <40y) • 65 – 75 y: Annual mammography (+/- US when indicted by radiologist) • >75y: Consider mammogram every 2 y (if patient is in good health)
	Risk reducing surgery	If strong family history or if diagnosed: consider risk reducing bilateral mastectomy
Ovarian cancer	Screening (not in folder)	Not recommended (comment: tailored program could be offered if patient refused risk reducing BSO ≥ 50 y)
	Risk reducing surgery	Consider BSO < 50 y

Comment: when a coincidental *RAD51C/RAD51D* mutation is found in absence of a family history of breast cancer (and an informative pedigree) it is reasonable to downgrade screening to annual mammogram starting at 40y, as breast cancer risk is estimated to be 20% for *RAD51C/RAD51D* women without family history

Female non-carriers with a 1st degree relative with breast cancer

Table 15: Recommendations for non-carrier with a first degree relatives (sister, daughter/mother) with breast cancer in RAD51/D families

Tumor	Intervention	Recommendation
Breast cancer	Screening	40 – 50 y: Annual mammogram 50 – 75 y: Mammogram every 2 years

Belgian guidelines for Managing Hereditary Breast and Ovarian Cancer: 05/2023 Update

https://www.college-genetics.be/

BARD1

- Breast (women) : cumulative risk 20-45%
  - importance of family history
  - remaining risk in non-carriers
  - higher risk for TNBC

Tumor	Intervention	Recommendation
Breast cancer	Screening	Clinical examination every 6 months from 25 y AND • 35 – 65 y: At least yearly breast MRI with 1-incidence mammogram +/- US if indicated by radiologist (or start 5 y before youngest diagnosis in family if diagnosis <40y) • 65 – 75 y: Annual mammography (+/- ultrasound when indicted by radiologist) • >75y: Consider mammogram every 2 y (if patient is in good health)
	Risk reducing surgery	If strong family history or if diagnosed: consider risk reducing bilateral mastectomy

Comment: when a coincidental *BARD1* mutation is found in absence of a family history of breast cancer (and an informative pedigree) it is reasonable to downgrade screening to annual mammogram starting at 40y, as breast cancer risk is estimated to be lower for *BARD1* women without family history

Female non-carriers with a 1st degree relative with breast cancer

Table 18: Recommendations for non-carrier with a first degree relatives (sister, daughter/mother) with breast cancer in BARD1 families

Tumor	Intervention	Recommendation
Breast cancer	Screening	40 – 50 y: Annual mammogram 50 – 75 y: Mammogram every 2 years

Belgian guidelines for Managing Hereditary Breast and Ovarian Cancer: 05/2023 Update

https://www.college-genetics.be/

BRIP1

- No increased risk of breast cancer
- Ovary: 5-10%

Tumor	Intervention	Recommendation
Ovarian cancer	Screening (not in folder)	Not recommended (comment: tailored program could be offered if patient refused risk reducing BSO ≥ 50 y)
	Risk reducing surgery	Consider BSO < 50 y

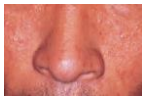
Belgian guidelines for Managing Hereditary Breast and Ovarian Cancer: 05/2023 Update

https://www.college-genetics.be/

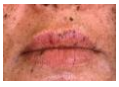
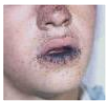
Rare syndromes

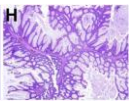
- *PTEN* – Cowden syndrome
  - Macrocephaly & autism
  - Hamartoma + trichilemmoma
  - Increased risk of breast cancer (60% at 70 y.o.) + thyroid carcinoma + endometrium + colon





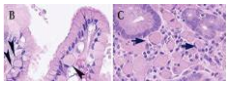
- *STK11* – Peutz-Jeghers syndrome
  - Hamartoma
  - Abnormal pigmentation of skin and mucosa
  - Increased risk of breast cancer (40-60% at 70 y.o.) + cervix and endometrium + digestive tract + pancreas + lung + sex cord tumors

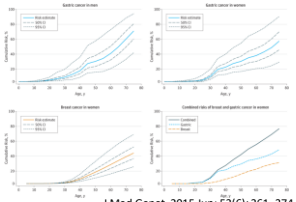





Rare syndromes

- *CDH1*
  - Lobular breast cancer (60% at 80 y.o., bilateral)
  - Diffuse gastric cancer
  - Cleft lip and palate





J Med Genet. 2015 Jun; 52(6): 361–374

- *TP53* – Li-Fraumeni syndrome
  - De novo mutations (7-20%), mosaicism → family history not always present
  - Breast cancer (HER2+) - 6% of women with breast cancer < 30 y.o; risk >60%
  - Sarcoma
  - Adrenocortical carcinoma
  - Leukemia
  - Brain tumor
  - Other cancers (lung, colon, pancreas, genito-urinary, skin, prostate, …)

AVOID RADIATION

Li-Fraumeni syndrome: heterozygous *TP53* mutation

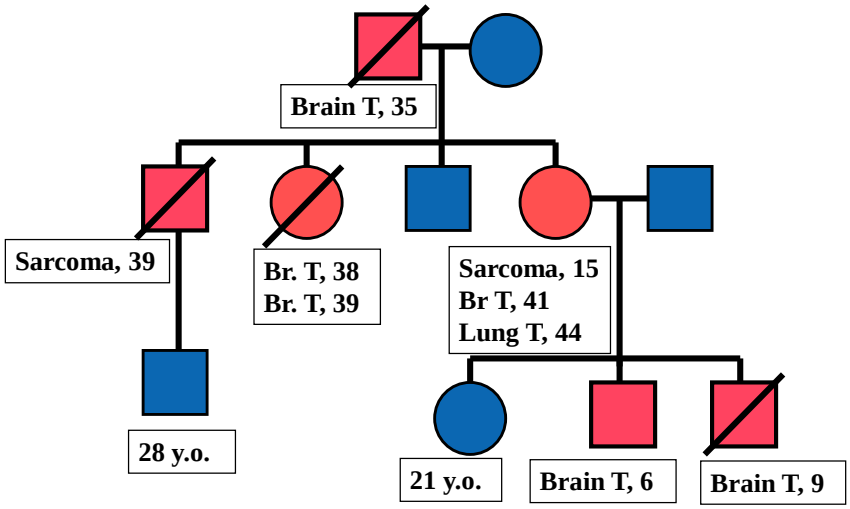


Table 1. 2009 Chompret Criteria for Germline *TP53* Mutation Screening

	Criterion
I.	Proband with tumor belonging to LFS tumor spectrum (eg, soft tissue sarcoma, osteosarcoma, brain tumor, premenopausal breast cancer, adrenocortical carcinoma, leukemia, lung bronchoalveolar cancer) before age 46 years AND at least one first- or second-degree relative with LFS tumor (except breast cancer if proband has breast cancer) before age 56 years or with multiple tumors; OR
II.	Proband with multiple tumors (except multiple breast tumors), two of which belong to LFS tumor spectrum and first of which occurred before age 46 years; OR
III.	Patient with adrenocortical carcinoma or choroid plexus tumor, irrespective of family history

Abbreviation: LFS, Li Fraumeni syndrome.

BUT : nowadays, included in panel testing!!!

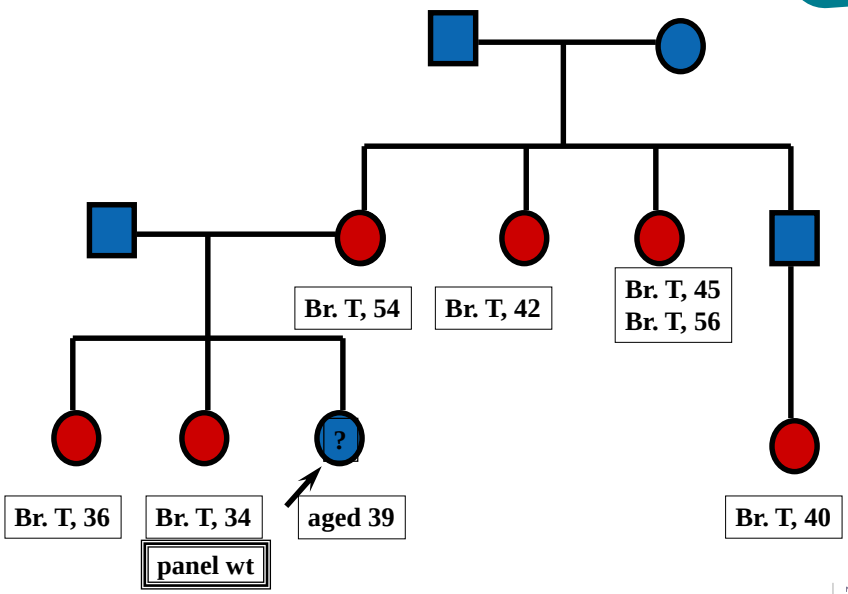
J Clin Oncol. 2009 Sep 10;27(26):e108-9

Other genetic predisposition factors to breast and/or ovarian cancer

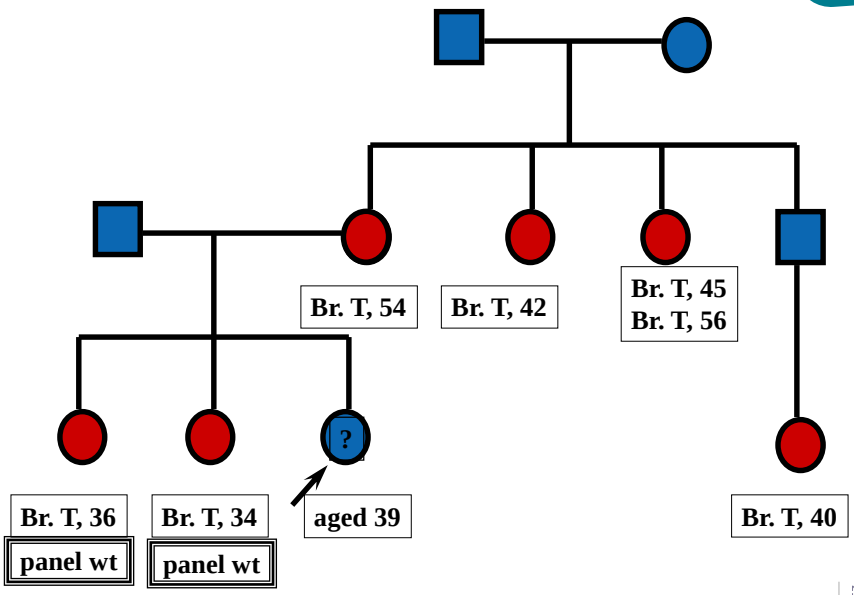
- Lynch syndrome
- …

→ Pr De Leener

What if no genetic alteration is found?

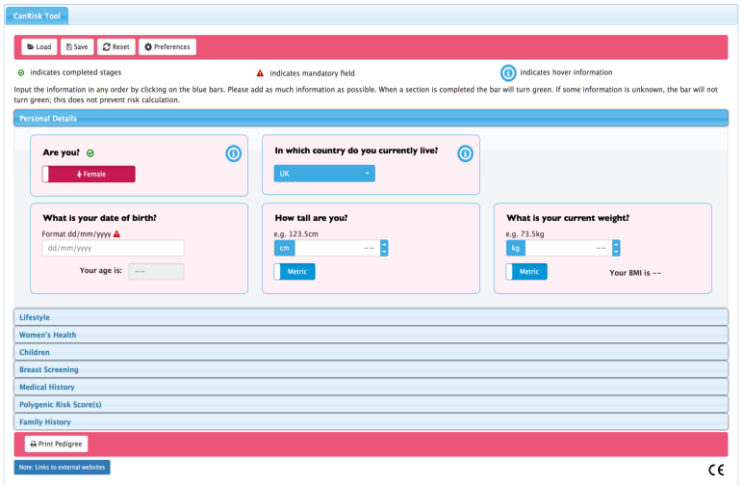


What if no genetic alteration is found?
→ exclude a phenocopy



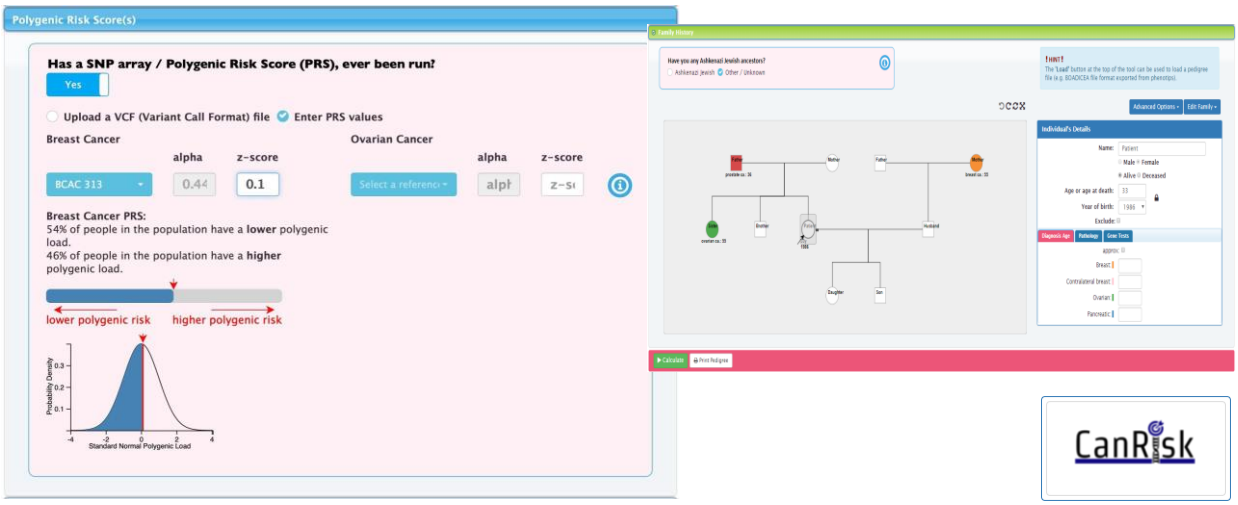
Multifactorial cancer risk prediction
If no genetic alteration is found --> importance of family history (and other risk factors!)

- Software for risk assessment
  - e.g. CanRisk



https://www.canrisk.org/ | Membre du réseau Lid van het netwerk Huni | 43

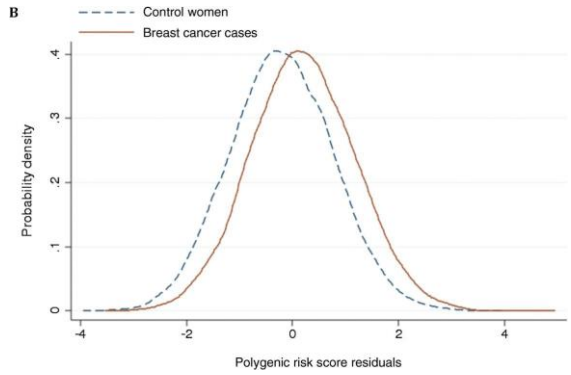
Polygenic risk scores and family history



Antonis C.Antoniou, ESMO Breast 2023 | Membre du réseau Lid van het netwerk Huni | 44

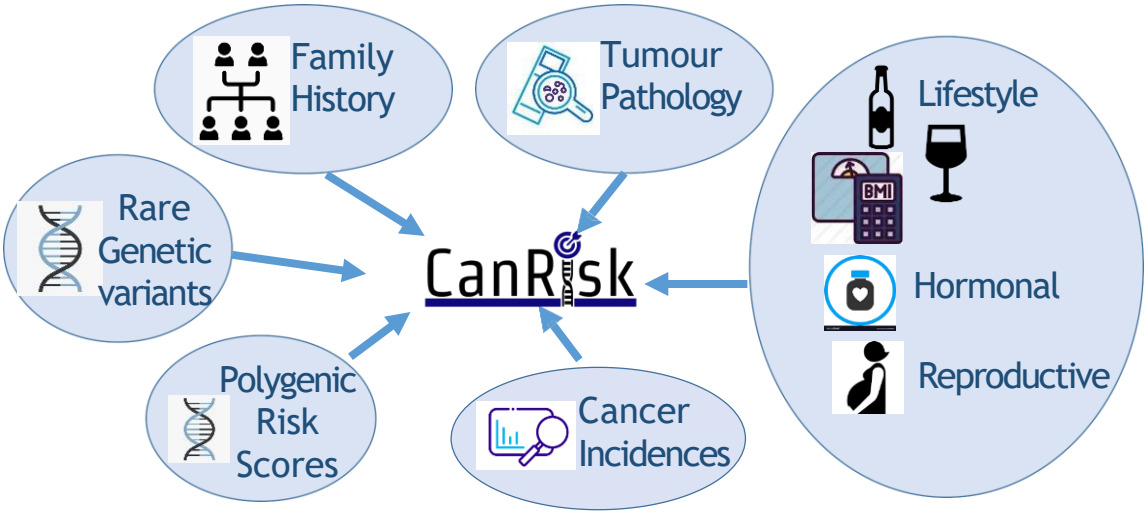
313 SNP Polygenic Risk Score – Breast Cancer

- Breast Cancer Association Consortium (BCAC)
- 94,094 breast cancer cases and 75,017 control women
- SNPs act multiplicatively on risk
- Validated in prospective cohorts
- Explains 20% of Familial Risk



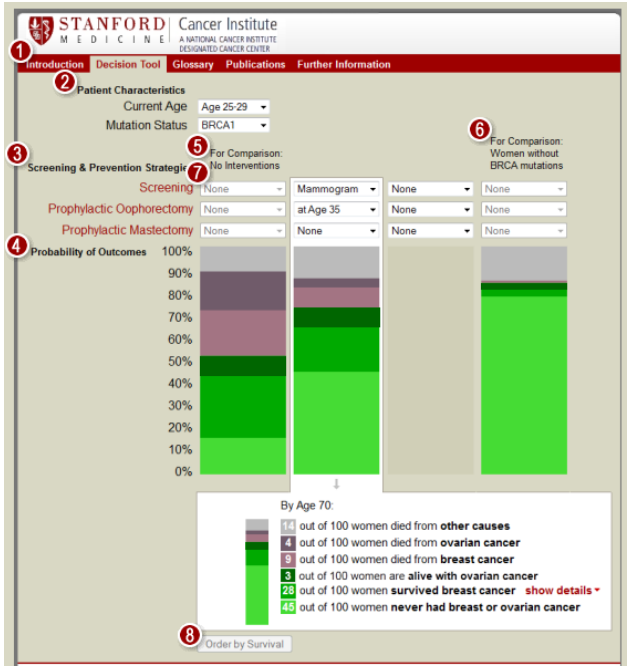
Mavaddat et al, AJHG 2019 | Membre du réseau Lid van het netwerk Huni | 45

Multifactorial cancer risk model



Membre du réseau Lid van het netwerk Huni | 46

BRCAtool



http://brcatool.stanford.edu/ | Membre du réseau Lid van het netwerk Huni | 47

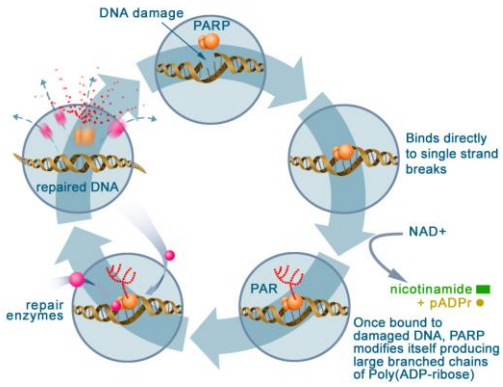
BRCA1 and *BRCA2*: how to interpret the results?

- Many mutations, different from one family to another
- A clearly deleterious mutation cannot be identified in all cases
- → 2-step process :
  - **Index case** (usually a family member treated for cancer at a young age)
  - then analyze the **relatives**, if appropriate (usually asymptomatic)
- If no mutation could be identified after the analysis of the index case, the test should be considered as non informative, because the presence of a deleterious mutation cannot be excluded, and no presymptomatic test can be offered to the relatives
- If a mutation is identified, a predisposition test can be offered to the relatives : if it is negative, it can be concluded that the relative has not inherited the familial predisposition factor
- Minors : no indication to test

Membre du réseau Lid van het netwerk Huni

PARP Inhibitors

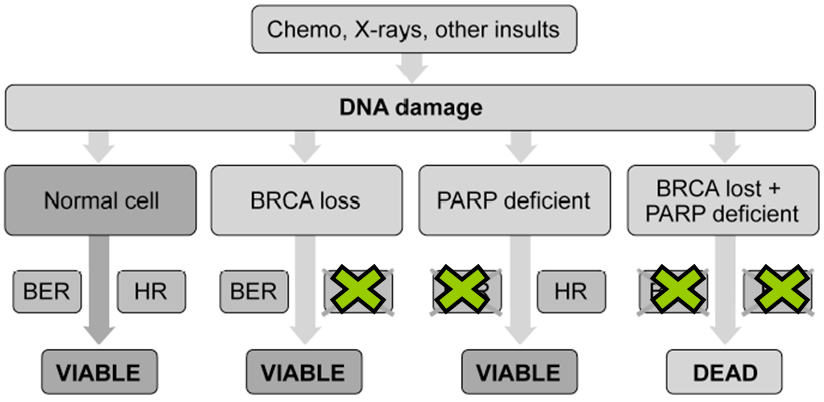
Poly (ADP-Ribose) Polymerase (PARP)



BRCA1 Dysfunction and PARP Inhibition

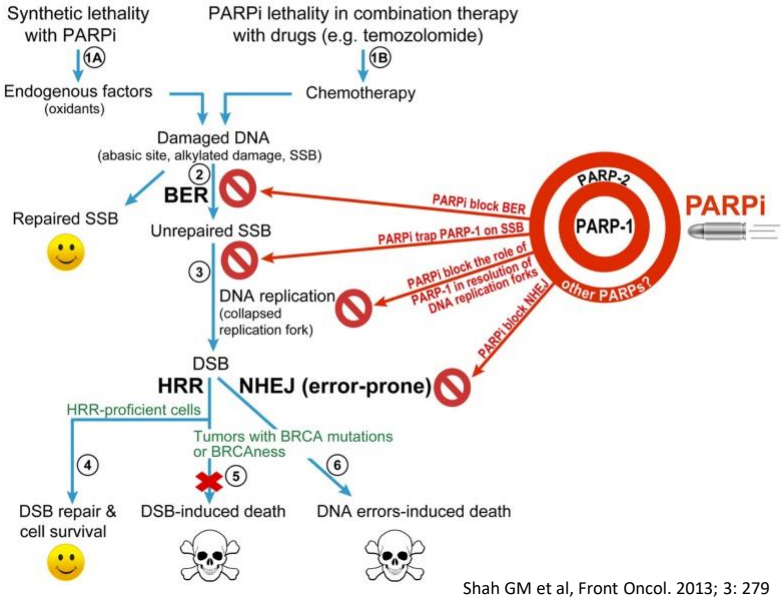
CONCEPT OF SYNTHETIC LETHALITY

Cell death by dual targeting of pathways that, in isolation, are not lethal



Adapted from Comen EA, et al. *Oncology.* 2010;24:55-62.

A Mechanisms of PARPi linked to BER/HRR nexus for tumors with BRCA mutations or BRCAness phenotype



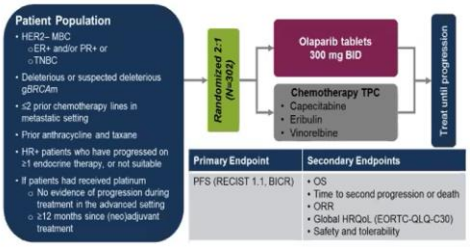
Shah GM et al, Front Oncol. 2013; 3: 279

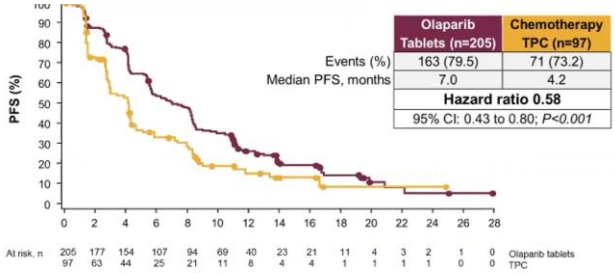
B Mechanisms of PARPi linked to other target pathways

Shah GM et al, Front Oncol. 2013; 3: 279

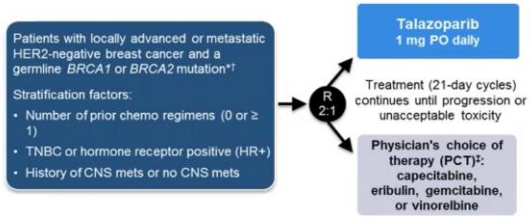
PARP inhibitors

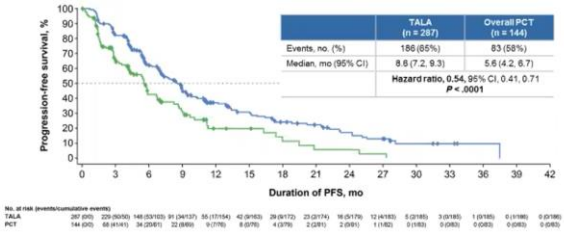
OLYMPIAD





EMBRACA





Litton J et al, NEJM 2018; Robson M et al, NEJM 2017 | Huni | 53

Olympia : trial schema

- Local genetic testing or on-study central screening (Myriad Genetics Inc.)
- Germline pathogenic or likely pathogenic *BRCA1/2* mutation
- HER2–negative (hormone receptor–positive or TNBC)
- Stage II-III Breast Cancer or lack of PathCR to NACT

Neoadjuvant Group
- *TNBC:* non-pCR
- *Hormone receptor–positive:* non-pCR and CPS+EG score ≥ 3

≥ 6 cycles Neoadjuvant Chemotherapy → Surgery → +/- Radiotherapy

Adjuvant Group
- *TNBC:* ≥ pT2 or ≥ pN1
- *Hormone receptor–positive:* ≥ 4 positive lymph nodes

Surgery → ≥ 6 cycles Adjuvant Chemotherapy → +/- Radiotherapy

1:1 Randomization N=1836

Olaparib 300 mg twice daily for 1 year

Placebo twice daily for 1 year

Primary End Point
- Invasive disease-free survival (IDFS) by STEEP system[1]

Secondary End Points
- Distant disease-free survival[1] (DDFS)
- Overall survival[1] (OS)
- BRCA1/2 associated cancers
- Symptom / Health related QoL
- Safety

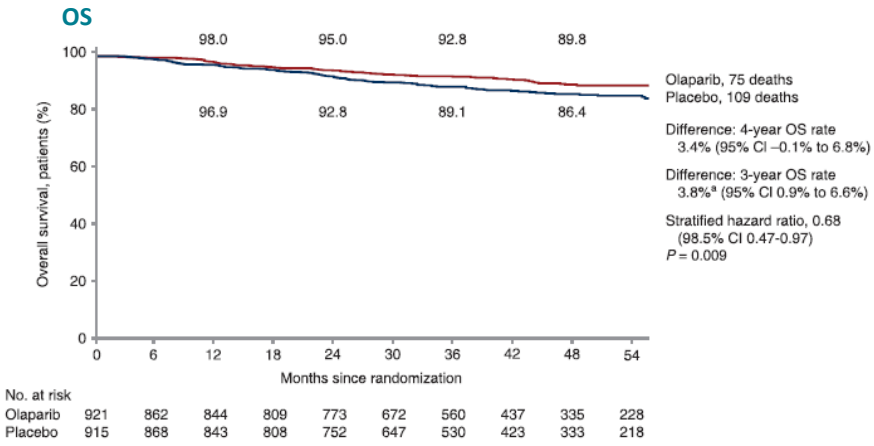
Stratification Factors
- Hormone receptor–positive vs. TNBC
- Neoadjuvant vs. adjuvant
- Prior platinum-based chemotherapy (yes vs. no)

Concurrent Adjuvant Therapy
- Endocrine therapy
- Bisphosphonates
- No 2nd Adjuvant Chemotherapy

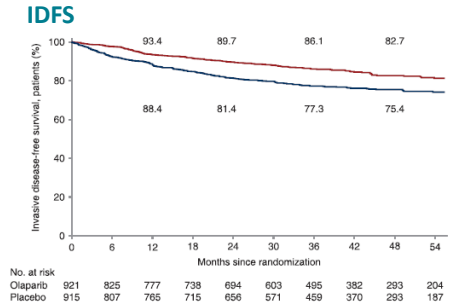
Hormone receptor +ve defined as ER and/or PgR positive (IHC staining ≥ 1%)
Triple Negative defined as ER and PgR negative (IHC staining < 1%)
[1]Hudis CA, J Clin Oncol 2007

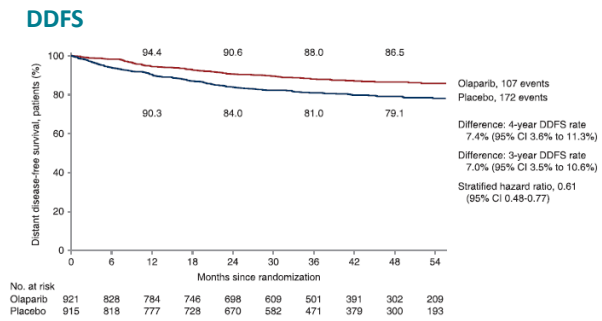
Tutt A et al, ASCO 2021 | Huni | 54

Olympia : pre-specified IA 2



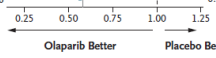
Olympia : pre-specified IA 2





Olympia : subgroup analyses

Subgroup	Olaparib	Placebo	3-Yr Invasive Disease–free Survival		Stratified Hazard Ratio for Invasive Disease or Death (95% CI)
			Olaparib	Placebo	
	no. of patients with an event/total no.		%		
All patients	106/921	178/915	85.9	77.1	0.58 (0.46–0.74)
Timing of previous chemotherapy					
Neoadjuvant	70/460	117/460	82.5	68.0	0.56 (0.41–0.75)
Adjuvant	36/461	61/455	89.3	85.4	0.60 (0.39–0.90)
Previous platinum-based chemotherapy					
Yes	34/247	43/239	82.0	77.0	0.77 (0.49–1.21)
No	72/674	135/676	87.3	77.1	0.52 (0.39–0.69)
Hormone-receptor status					
HR+ and HER2–	19/168	25/157	83.5	77.2	0.70 (0.38–1.27)
TNBC	87/751	153/758	86.1	76.9	0.56 (0.43–0.73)
Germline *BRCA* mutation					
BRCA1	70/558	126/558	85.0	73.4	0.52 (0.39–0.70)
BRCA2	22/230	38/209	88.6	78.0	0.52 (0.30–0.86)
BRCA1 and *BRCA2*	0/1	0/3	NC	NC	NC
Hormone-receptor status and timing of previous chemotherapy					
HR+ and HER2–, NACT	13/104	20/92	86.0	67.0	0.52 (0.25–1.04)
HR+ and HER2–, ACT	6/64	5/65	76.4	89.3	1.36 (0.41–4.71)
TNBC, NACT	57/354	97/368	81.4	67.7	0.57 (0.41–0.79)
TNBC, ACT	30/397	56/390	90.3	84.8	0.54 (0.34–0.83)
Previous platinum-based chemotherapy and timing of previous chemotherapy					
Yes, NACT	26/169	39/169	81.8	70.1	0.66 (0.40–1.07)
Yes, ACT	8/78	4/70	NC	NC	NC
No, NACT	44/291	78/291	83.1	66.8	0.51 (0.35–0.73)
No, ACT	28/383	57/385	90.4	84.2	0.51 (0.32–0.79)
CPS+EG score in patients with previous NACT					
Score of 2, 3, or 4	55/398	96/387	84.3	68.9	0.51 (0.37–0.71)
Score of 5 or 6	11/22	10/15	50.0	17.9	0.44 (0.19–1.06)
Primary database					
Breast International Group	95/810	160/806	86.0	76.7	0.58 (0.45–0.75)
NRG Oncology (United States)	11/111	18/109	85.0	80.6	0.57 (0.26–1.18)



Tutt et al, NEJM 2021 | Membre du réseau Lid van het netwerk Huni | 57

Olympia : adverse events

Adverse event, no. of patients (%)	Olaparib (n = 911)	Placebo (n = 904)
Any adverse event	836 (91.8)	758 (83.8)
Serious adverse event	79 (8.7)	78 (8.6)
Adverse event of special interest[b]	31 (3.4)	51 (5.6)
MDS/AML	2 (0.2)	3 (0.3)
Pneumonitis[c]	9 (1.0)	12 (1.3)
New primary malignancy[d]	21 (2.3)	36 (4.0)
Grade ≥3 adverse event	223 (24.5)	102 (11.3)
Grade 4 adverse event[e]	17 (1.9)	4 (0.4)
Adverse event leading to permanent discontinuation of treatment[f]	98 (10.8)	42 (4.6)
Adverse event leading to death[g]	1 (0.1)	2 (0.2)

Geyer CE et al, Ann Oncol 2022 | Membre du réseau Lid van het netwerk Huni | 58

Olympia : practical considerations

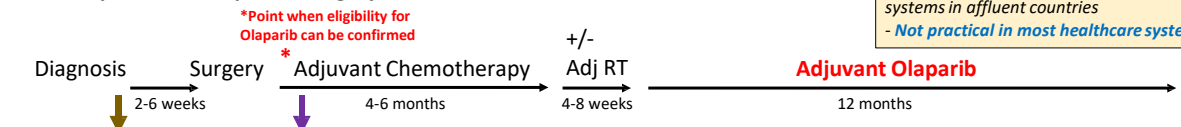
- Not to combine with adjuvant radiotherapy (not permitted in OlympiA - no safety data)
- Safe to combine with adjuvant endocrine therapy
- Start no earlier than 2 weeks and no later than 12 weeks from trial enrolment
  - from surgery, end of adjuvant chemotherapy or end of adjuvant radiotherapy if administered, whichever is latest

Identifying High Risk EBC Patients for Adjuvant Olaparib

Who and When to test for gBRCA mutations?

Everyone, as soon as possible
- *Possible in resource-rich healthcare systems in affluent countries*
- ***Not practical in most healthcare systems***

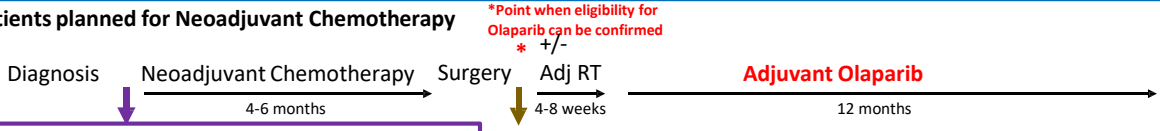
Patients planned for Upfront Surgery



Less practical to test before surgery
Unselected population
(not cost-effective)
Information too overwhelming for most newly diagnosed patients

Optimal to test after surgery, when eligibility for adjuvant olaparib is confirmed
Selected population (more cost-effective)
Months before adjuvant Olaparib is due to be started

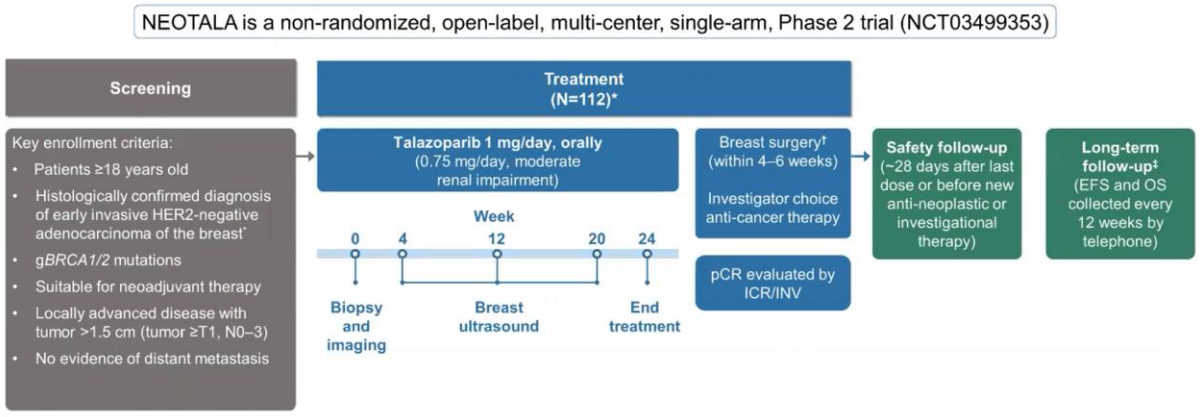
Patients planned for Neoadjuvant Chemotherapy



Optimal to test once decision made for neoadjuvant chemotherapy
A smaller selected high-risk population
Need to prioritize testing further?
- TNBC over HR+
- Fulfil conventional testing criteria *(age, family history, multiple cancers)*
- Higher stage patients *(less likely to achieve pCR)*

Suboptimal to test only after surgery
when eligibility for adjuvant olaparib is confirmed
Tight timelines to start adjuvant olaparib

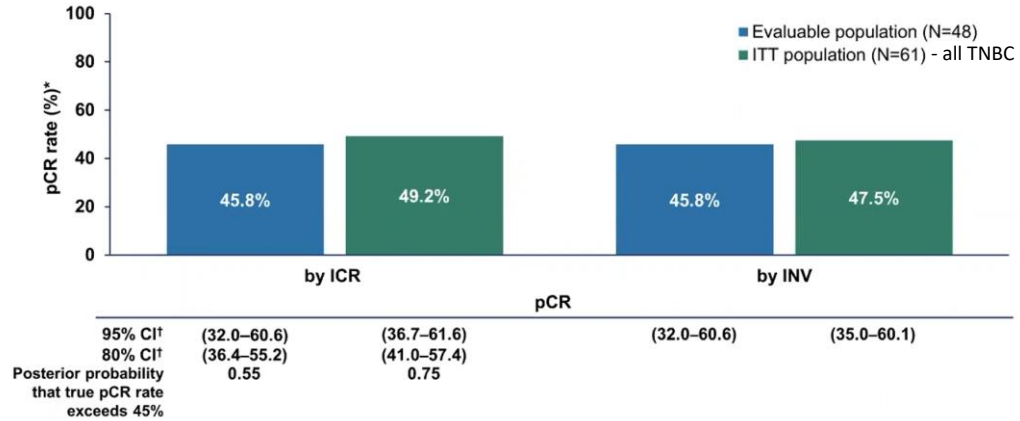
NeoTALA : trial schema



EFS=event-free survival; HR=hormone receptor; ICR=independent central review; INV=investigator; OS=overall survival.
*Study design was amended to include HR-positive, HER2-negative patients with BC and the patient numbers were reduced from 112 to 60 in order to address lower than expected enrollment.
†Breast/axillary tissue must be removed by either lumpectomy or mastectomy with clinically appropriate axillary surgery. Patients may not have had surgery due to progressive disease and initiation of new anti-cancer therapy.
‡Long-term follow-up planned to be at 3 years, starting from the date of surgery for EFS and after the first dose of drug for OS. However, Pfizer decided to make a strategic change in the development program for talazoparib in neoadjuvant BC and decided not to pursue further development in this setting. The study was closed after all patients completed safety follow-up and EFS/OS was not reached.

Litton JK et al, ASCO 2021 | Membre du réseau Lid van het netwerk Huni | 61

NeoTALA : pCR rate



*The denominator is N, the number of patients in the evaluable/ITT analysis set as per ICR/INV.
†The exact CI was calculated using the Blaker's method.

pCR rates comparable to those observed with combination anthracycline and taxane-based chemotherapy

Litton JK et al, ASCO 2021 | Membre du réseau Lid van het netwerk Huni | 62

Phase II study of maintenance olaparib in ovarian cancer: study 19

Patients

Platinum-sensitive high-grade serous ovarian cancer

≥2 previous platinum regimens

Maintained PR or CR following last platinum regimen

Olaparib 400mg bid, orally (n=136)

Randomized 1:1

Placebo (n=129)

Primary endpoint

PFS by RECIST

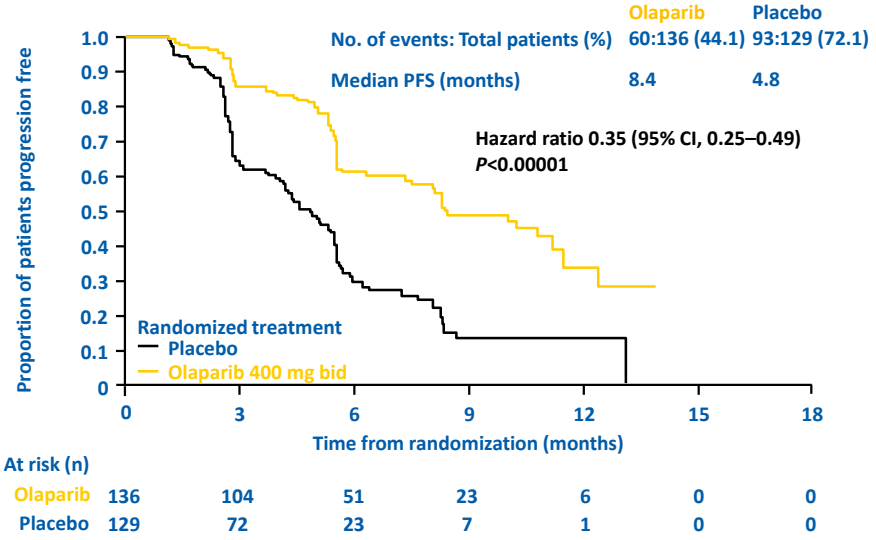
Secondary endpoints

TTP by CA-125 (GCIG criteria) or RECIST, OS, safety

82 sites in 16 countries

Ledermann et al. J Clin Oncol 2011;29 (suppl; abstr 5003); N Engl J Med. 2012 Apr 12;366(15):1382-92

Study 19: progression-free survival



Ledermann et al. J Clin Oncol 2011;29 (suppl; abstr 5003); N Engl J Med. 2012 Apr 12;366(15):1382-92

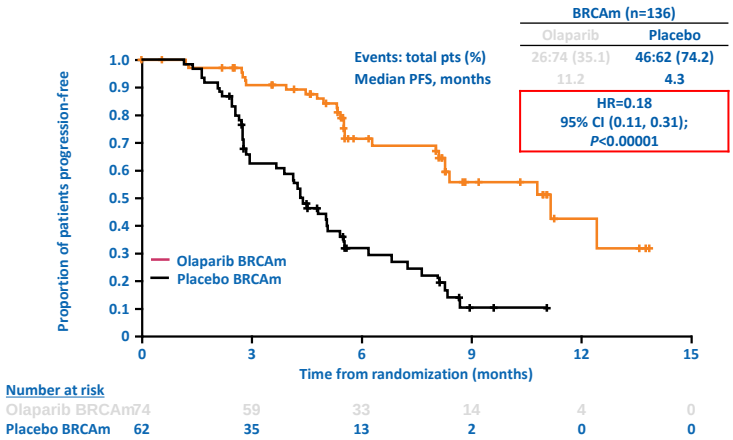
Study 19: common adverse events*

	Olaparib 400 mg bid (n=136)		Placebo (n=128)	
	Percentage of Patients			
Adverse event	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Any event	61	35	70	20
Nausea	66	2	35	0
Fatigue	42	7	34	3
Vomiting	29	2	13	1
Diarrhea	21	2	20	2
Headache	18	0	11	1
Decreased appetite	18	0	13	0
Abdominal pain	16	2	23	3
Anemia	12	5	4	1
Dyspepsia	16	0	9	0

*Adverse events graded according to maximum CTCAE version 3.0 grade, experienced by >15% of patients in either treatment group.

Ledermann et al. J Clin Oncol 2011;29 (suppl; abstr 5003); N Engl J Med. 2012 Apr 12;366(15):1382-92

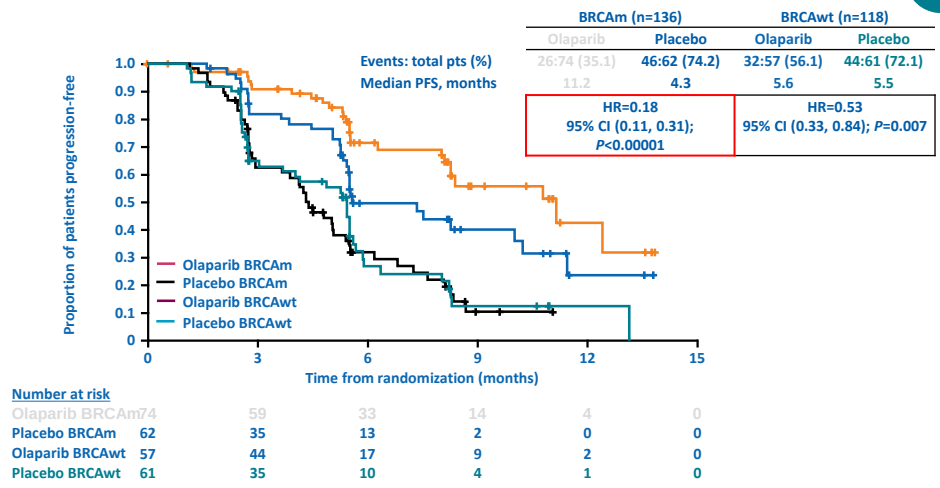
Study 19: PFS by BRCAm status



82% reduction in risk of disease progression or death with olaparib

Presented by: Jonathan Ledermann et al at ASCO 2013

Study 19: PFS by BRCAm status



BRCAwt, wild type (includes patients with no known BRCAm or a mutation of unknown significance)

Presented by: Jonathan Ledermann et al at ASCO 2013

General conclusions

- Breast cancer is frequent – ovarian cancer is rare
- Genetic predisposition is only partially explained by *BRCA1/2* mutations
  - +/- 10% of breast cancers are due to a genetic predisposition
  - < 5% are due to *BRCA1* or *BRCA2* germline mutations
  - Multiple different mutations exist
  - Only patients with a high probability of mutation should be tested
  - Other, rare genetic anomalies exist
- PARP inhibitors are now established treatment options for *BRCA*m breast and ovarian cancer patients
- Future breast and ovarian cancer treatments will take into account constitutional and somatic GENETIC alterations


INSTITUT
ROI ALBERT II
Cliniques universitaires
SAINT-LUC
UCLouvain
BRUXELLES
Thank you for
your attention