INSTITUTE
OF ONCOLOGY
LJUBLJANA

Združenje za
senologijo Slovenije
Slovenian Senologic
Society

WHAT'S NEW IN THE MANAGEMENT OF *BRCA* POSITIVE OVARIAN AND BREAST CANCER PATIENTS – 2ND CONFERENCE

Grand Hotel Union Ljubljana, Slovenia
- Thursday, 19th of October 2017 -

SPEAKERS:

Judith Balmaña, Vall D'Hebron Institute of Oncology, Barcelona, Spain

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Roche

Ljubljana, 19th October 2017

PROGRAM:

15:30 – 16:00 *Participants gathering*

16:00 – 16:10 INTRODUCTION, **Mateja Krajc**

16:10 – 16:50 Cancer genetic counselling and testing in view of new treatment options/establishing new clinical pathways (Spanish experiences)

PARP inhibitors in breast cancer. a look back and a look forward (OlympiAD trial), **Judith Balmaña**

16:50 – 17:40 Cancer genetic counselling and testing in view of new treatment options/establishing new clinical pathways (Belgian experiences)

Tumor testing – where is its position in clinical pathways, **Kathleen Claes**

17:40 – 18:00 DISCUSSION

18:00 – 18:15 *Coffee Break*

18:15 – 19:15 HEREDITARY BREAST AND OVARIAN CANCER – SLOVENIAN EXPERIENCES

- HBOC – germline/ somatic genetic testing – laboratory experiences (latest updates), **Srdjan Novaković**
- Cancer genetic counselling – new clinical pathways in view of treatment options, **Ana Blatnik, Mateja Krajc and Ksenija Strojnik**
- Slovenian experiences with olaparib in ovarian cancer treatment, **Erik Škof and Maja Ravnik**
- PARP inhibitors in breast cancer – current and future perspectives in Slovenia, **Simona Borštnar**
- Surgical treatment of *BRCA* positive breast cancer patients – current practice and Slovenian results, **Janez Žgajnar**

19: 15 – 19:30 DISCUSSION

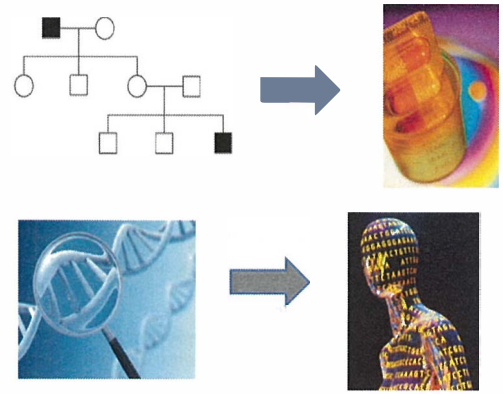
19:30 - *Dinner*

Vall d'Hebron Hospital

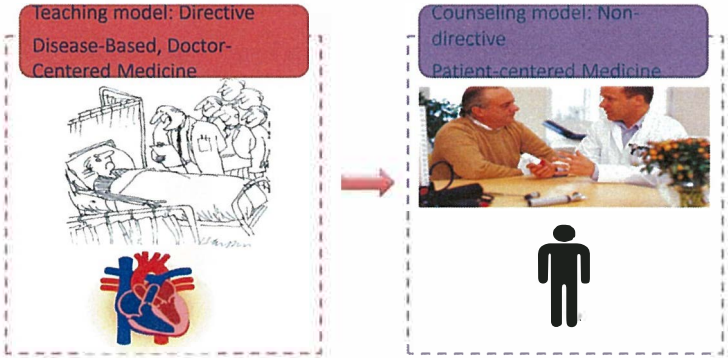
VHIO VALL D'HEBRON Institute of Oncology

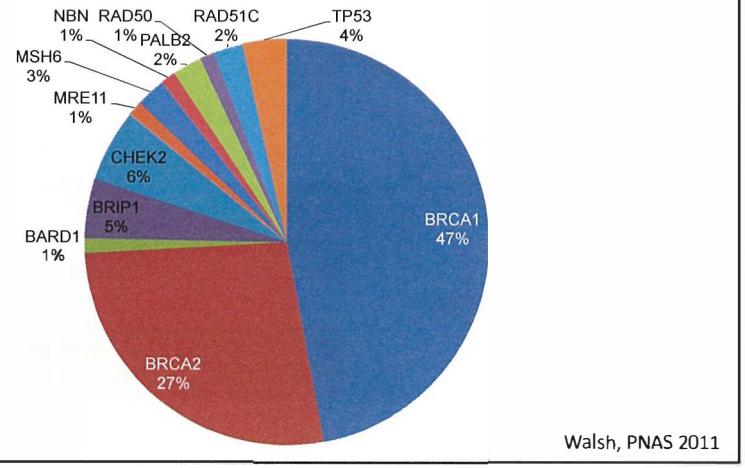
Cancer genetic counseling and testing in view of new treatment options/establishing new clinical pathways

Judith Balmaña
Clinical cancer genetics
Medical Oncology Department
Hospital Vall d'Hebron



New paradigms



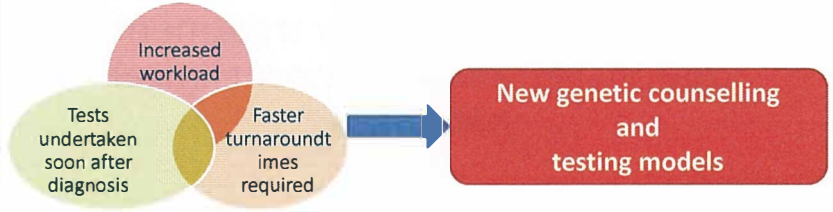


Walsh, PNAS 2011

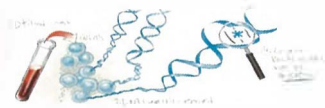
BRCA-targeted approved therapies

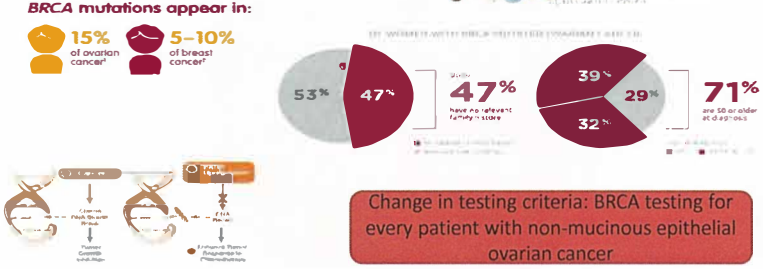
- Olaparib (Lynparza™, AstraZeneca)
  - EMA (Dec2014): Monotherapy maintenance treatment of platinum-sensitive relapsed **BRCA-mutated (germline and/or somatic)** high-grade serous ovarian cancer patients
  - FDA (Dec2014): Monotherapy for **germline BRCA1/2 mutated** advanced ovarian cancer patients who have been treated with minimum three prior lines of chemotherapy. Aug 2017: FDA approved olaparib as maintenance treatment of patients with recurrent epithelial ovarian cancer who are in a response to platinum-based chemotherapy.
- Rucaparib (Rubraca™, Clovis Oncology)
  - FDA (Dec2016) : Monotherapy for patients with advanced ovarian cancer and deleterious **BRCA mutation (germline and/or somatic)** who have been treated minimum two chemotherapies.
- Niraparib (Zejula™, Tesaro)
  - FDA (Mar2017) : Monotherapy for maintenance treatment of patients with recurrent epithelial ovarian cancer, whose tumours have a response to platinum-based chemotherapy.

Treatment implications



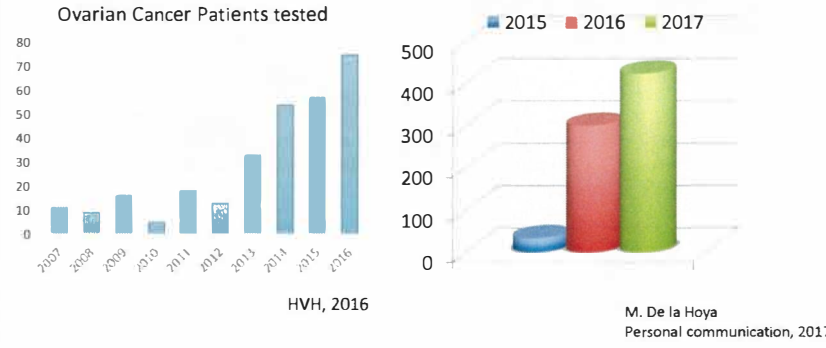
BRCA1/2 testing





Change in testing criteria: BRCA testing for every patient with non-mucinous epithelial ovarian cancer

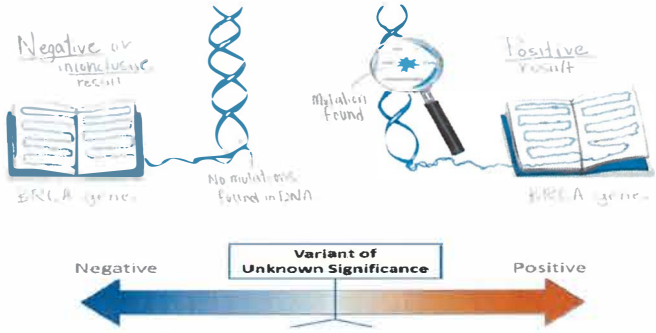
Zhang et al. Gynecologic Oncology (2011)



HVH, 2016

M. De la Hoya
Personal communication, 2017

BRCA1/2 testing results



Treatment implication → New Genetic Counselling models

The 'DNA-direct' model (The Netherlands)

Telephone pretest GC | BRCA testing | Face-to-face postest GC

Processing time is reduced. Similar psychological outcomes, but patients were not randomised

Telephone-based counselling model (USA)

Telephone pretest GC | BRCA testing | Telephone postest GC

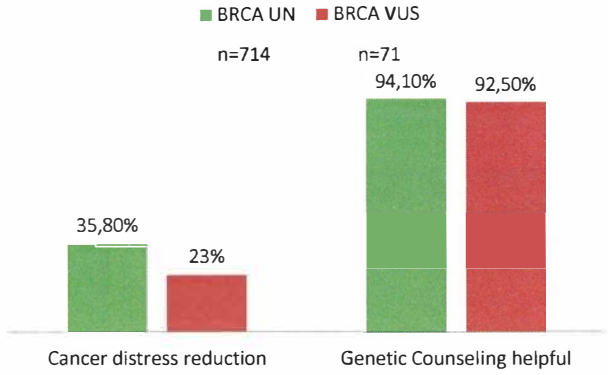
Lower uptake. Not recommended for newly diagnosed or metastatic cancer patients.

Royal Marsden testing model (UK)

Approved clinicial explain BRCA testing | BRCA testing | Clinician gives results and refer to genetics if positive

[illegible] undertake online training

VUS and cancer distress



Curver et al. Clin Genet. 2013

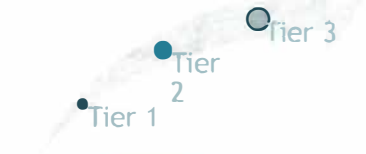
Clinical validity for cancer risk assessment *BRIP1*, *RAD51C*, *RAD51D*

GENES	CASES	CONTROLS	MEAN AGE	RELATIVE RISK (95% CI)
BRIP1	**0.9% 0.6%**	**0.09%**	**63.8y (93%>50y)**	**Seg. 3.4 (2-5) 5.8% at 80y cc. 11.2 (3-34)**
BARD1	0.12%	0.06% (p=.39)	55.5 y (53-60)	-
PALB2	0.28%	0.09% (p=.08)	56 y (49-65)	-
NBN	0.28%	0.23% (p=.61)	NA	-
RAD51C	**0.41%**	**0.07%**	**70% >50y**	**5.2 (1.1-24) 5% at 70y**
RAD51D	**0.35%**	**0.04%**	**92% >50y**	**12 (1.5-90) 12% at 70y**

Gene	Mammography (clinical breast examination and/or breast MRI	RRSO	Colonoscopy	Pancreatic screening
ATM	Annual starting at 40*	Family history[‡]	Family history[#]	Clinical trial
CHEK2 (truncating)	Annual starting at 40*‡	Family history[‡]	Discussat 40 years	NA
NBN	Annual starting at 40*	Family history[‡]	Family history[#]	NA
PALB2	Annual starting at 30	Family history[‡]	Family history[#]	Clinical trial
BRIP1/RAD51C/ RAD51D	Family history[§]	50–55 years[¶]	Family history[#]	NA

Tung, Nature Reviews

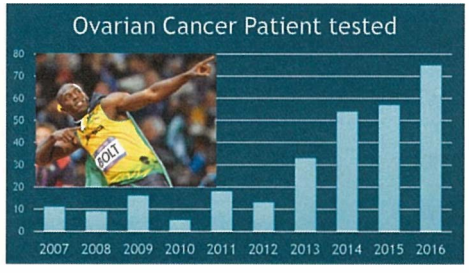
NGS → Change in genetic counseling model



Key themes (tier 1 elements) in the tiered-binned model

1. Testing can identify varying risks (high, moderate, and uncertain) for a wide spectrum of cancers.
2a. Implications of results vary depending on the gene and result.
2b. Finding a mutation may or may not change your current medical care.
3. The evidence and support for medical recommendations varies by gene and result (e.g., in some cases there are evidence-based recommendations, others consensus guidelines, others no clear consensus or guidelines).
4a. Some genes are associated with risks for cancer in childhood, while others only confer risks in adulthood. Some genes are associated with disorders other than cancer.
4b. For some genes, there is currently insufficient information to recommend testing for relatives.
5. There is the potential for various uncertainties (e.g., uncertain results, uncertain risks, and uncertainty regarding medical management options).
6. Given a range of testing options and variable risks, benefits, and utilities, patients should be aware that testing is a choice.
7. Risk estimates and cancer spectrum may be revised over time. Ongoing communication with the cancer genetics team will be beneficial, particularly in the setting of uncertain results or recommendations.

Challenges of panel testing

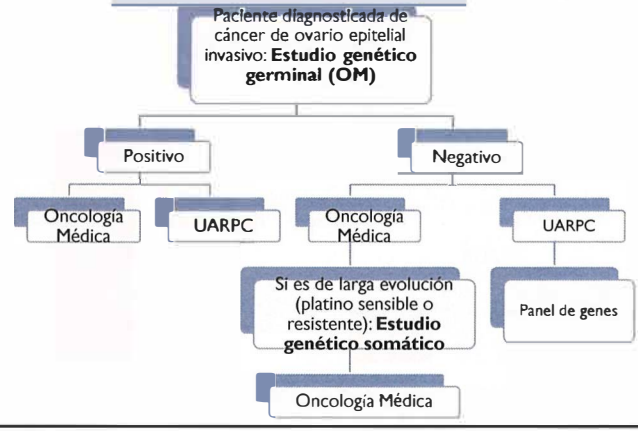


HVH data

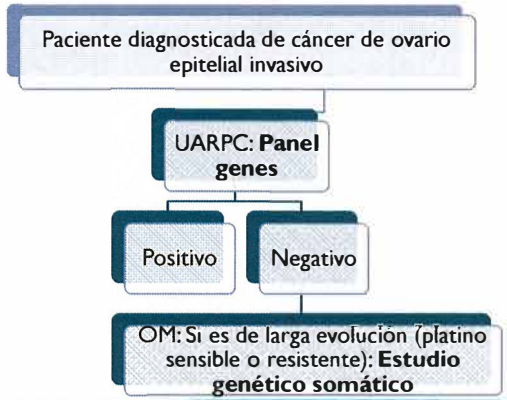
51% and 30% of breast cancer patients at average risk and with a VUS or no-BRCA mutation underwent bilateral mastectomy

Kurian, JCO 2017

BRCA germline testing first for urgent therapeutics



Gene panel testing first



PARP inhibitors in breast cancer - a look back and a look forward

Multidisciplinary units

Phase II/III studies with PARPi & biomarker analysis in breast cancer

1. Phase II: ABRAZO - talazoparib, mBC, gBRCA
   Cohort 1: platinum-treated (ORR 21%)
   Cohort 2: platinum-naïve, but heavily pre-treated (ORR 37%)
2. Phase III: OlympiaAD – olaparib, mBC, gBRCA
3. Phase III: BRAVO – niraparib, mBC, gBRCA
4. Phase III: EMBRACA – talazoparib , mBC, gBRCA

Background

- Cancers arising in women with deleterious germline mutations in breast cancer susceptibility genes 1 or 2 (*BRCA1* and *BRCA2*) are deficient in DNA double-strand break repair and repair of stalled replication forks[1-3]
  - These cells depend on poly (ADP-ribose) polymerase (PARP) for DNA repair
- PARP inhibitors
  - Inhibit PARP catalytic activity[4]
  - Trap PARP at sites of DNA damage[4]
  - Prevent DNA damage repair, resulting in cell death in *BRCA1/2*-mutated cancer cells

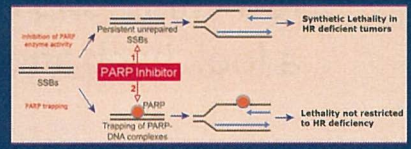
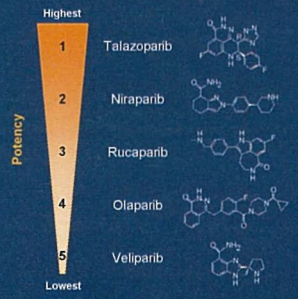


Figure adapted from Murai J et al. *Cancer Res*. 2012;72:5588-5599, with permission from AACR.

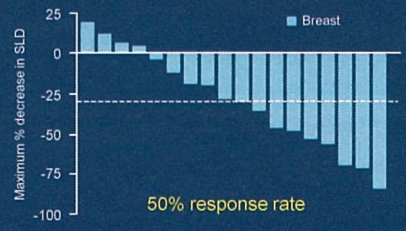
1. Ashworth A. *J Clin Oncol*. 2008;26:3785-3790; 2. Jalve M, Curtin NJ. *Ther Adv Med Oncol*. 2011;3:257-267; 3. Helleday T. *Mol Oncol*. 2011;5:387-393; 4. Lord CJ, Ashworth A. *Science*. 2017;355:1152-1158.

Background – Talazoparib

Talazoparib is a highly potent inhibitor of PARP[1]



Phase 1 trial – 18 breast cancer patients with *BRCA1/2* germline mutations[2]



Graph shows percentage change in target lesion for patients undergoing treatment with talazoparib who have gBRCA breast cancer. Positive values indicate tumor growth, negative values indicate tumor reduction, and the dashed line represents the definition of partial response from RECIST guidelines. Patients from parts 1 and 2 of the trial are included.
Abbreviation: SLD, sum of longest diameter.

1. Lord CJ, Ashworth A. *Science*. 2017;355:1152-1158; 2. de Bono J et al. *Cancer Discov*. 2017 Feb 27. doi: 10.1158/2159-8290.CD-16-1250.

Phase 2 Clinical Trial – Key Eligibility Criteria

- Patients with advanced breast cancer who carry a deleterious or suspected deleterious germline *BRCA1/2* mutation (by central laboratory or a local report approved by the sponsor)
  - Cohort 1: PR or CR to last platinum-containing regimen for metastatic disease with disease progression > 8 weeks following the last dose of platinum
  - Cohort 2: 3 or more prior cytotoxic regimens for metastatic disease; no prior platinum for metastatic disease
- Measurable disease by RECIST v1.1
- ECOG performance status 0 or 1
- Adequate organ and bone marrow function
- CNS metastases permitted, provided stable following local therapy
- HER2+ breast cancer permitted, provided the patient's disease is refractory to HER2-targeted therapy
- Washout from prior therapy (systemic therapy, RT, surgery): 14 days

Abbreviations: CNS, central nervous system; CR, complete response; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1; RT, radiation therapy.

Study Design

Objectives

- Primary endpoint: confirmed ORR by central independent radiology facility (IRF) using RECIST v1.1
- Secondary endpoints:
  - DOR, CBR lasting ≥ 24 weeks, PFS, OS
  - Safety

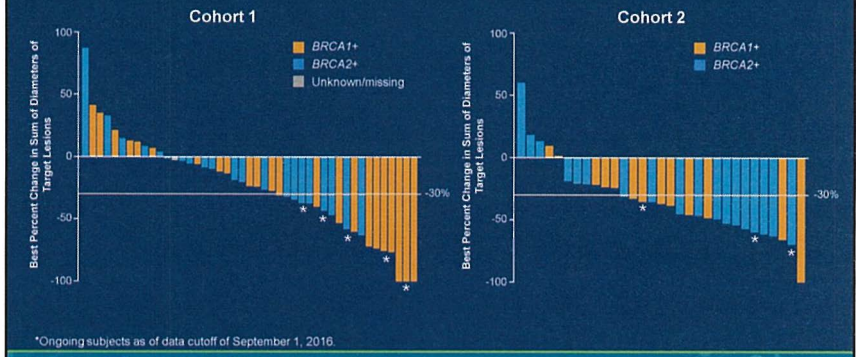
Abbreviations: CBR, clinical benefit rate; DOR, duration of response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

Select Baseline Characteristics
ITT Population

	Cohort 1 Prior Platinum (n = 49)	Cohort 2 3L+, No Prior Platinum (n = 35)	Total (N = 84)
Age, median (range), years	50 (31-74)	52 (33-75)	50 (31-75)
ECOG = 0, No. (%)	34 (69)	15 (43)	49 (58)
History of CNS metastasis, No. (%)	8 (16)	1 (3)	9 (11)
Visceral disease, No. (%)	38 (78)	23 (66)	61 (73)
Hormone receptor status, No. (%)			
HER2+	1 (2)	5 (14)	6 (7)
Triple-negative	29 (59)	6 (17)	35 (42)
ER+ or PR+	20 (41)	29 (83)	49 (58)
BRCA status, No. (%)			
BRCA1+	26 (53)	15 (43)	41 (49)
BRCA2+	22 (45)	20 (57)	42 (50)
Unknown	1 (2)	0	1 (1)

Abbreviations: ER+, estrogen receptor positive; ITT, intent-to-treat; PR+, progesterone receptor positive.

Maximal Percent Change in Sum of Diameters of Target Lesions by *BRCA* Mutation Status



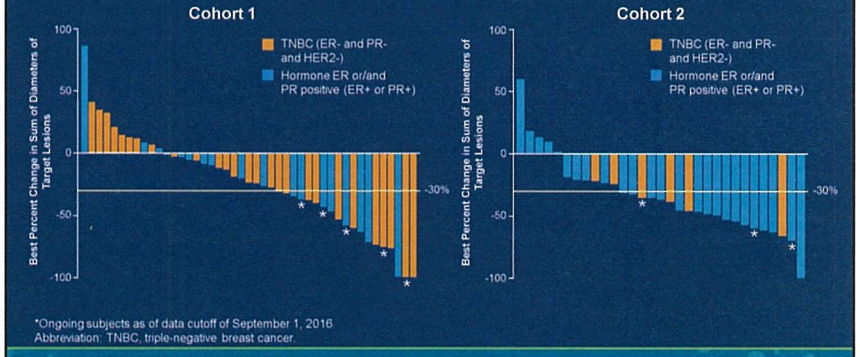
*Ongoing subjects as of data cutoff of September 1, 2016.

Primary Efficacy Endpoint – ORR by Independent Radiologist Facility

	Cohort 1 Prior Platinum (n = 48)	Cohort 2 3L+, No Prior Platinum (n = 35)	Total (N = 83)
Objective response rate, % (95% CI)	**21 (10-35)**	**37 (22-55)**	28 (18-39)
Best overall response, % (No.)			
Complete response	4 (2)	0	2 (2)
Partial response	17 (8)	37 (13)	25 (21)
Stable disease	38 (18)	51 (18)	43 (36)
Progressive disease	38 (18)	11 (4)	27 (22)
Not evaluable	4 (2)	0	2 (2)

Objective response using RECIST v1.1. Confirmation of CR and PR required.
Data cutoff for primary endpoint was September 1, 2016.
Abbreviation: CI, confidence interval.

Maximal Percent Change in Sum of Diameters of Target Lesions by Hormone Receptor Status

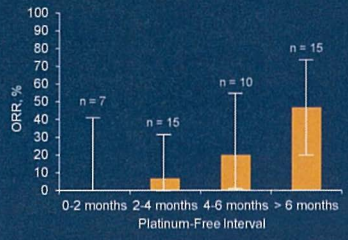


*Ongoing subjects as of data cutoff of September 1, 2016.
Abbreviation: TNBC, triple-negative breast cancer.

Platinum-Free Interval

ITT Population in Cohort 1 (Patients Who Received Prior Platinum, n = 48)

- Median time from last platinum dose to progression was 4.0 months (range, 0.03-49.15)



Safety – Nonhematologic

All TEAEs in ≥ 20% of patients and G3+ TEAEs in ≥ 5% of patients

	Cohort 1 Prior Platinum (n = 48)			Cohort 2 3L+, No Prior Platinum (n = 35)		
	All Grade	Grade 3	Grade 4	All Grade	Grade 3	Grade 4
Number of patients ≥ 1 TEAE, No. (%)	47 (97.9)	13 (27.1)	2 (4.2)	34 (97.1)	11 (31.4)	3 (8.6)
Fatigue	29 (60.4)	3 (6.3)	0	8 (22.9)	0	0
Nausea	20 (41.7)	2 (4.2)	0	15 (42.9)	0	0
Diarrhea	17 (35.4)	1 (2.1)	0	10 (28.6)	0	0
Decreased appetite	11 (22.9)	1 (2.1)	0	9 (25.7)	0	0
Dyspnea	11 (22.9)	1 (2.1)	1 (2.1)	9 (25.7)	2 (5.7)	0
Alopecia (grade 1)	11 (22.9)	0	0	7 (20.0)	0	0
Back pain	11 (22.9)	0	0	7 (20.0)	0	0
Vomiting	10 (20.8)	0	0	7 (20.0)	0	0
Pleural effusion	4 (8.3)	3 (6.3)	0	4 (11.4)	2 (5.7)	0

No grade 5 TEAEs were observed.

Safety – Hematologic

All TEAEs in ≥ 15% of patients and G3+ TEAEs in ≥ 5% of patients

	Cohort 1 Prior Platinum (n = 48)			Cohort 2 3L+, No Prior Platinum (n = 35)		
	All Grade	Grade 3	Grade 4	All Grade	Grade 3	Grade 4
Number of patients ≥ 1 TEAE, No. (%)	31 (64.6)	23 (47.9)	2 (4.2)	23 (65.7)	15 (42.9)	2 (5.7)
Anemia	24 (50.0)	16 (33.3)	0	19 (54.3)	13 (37.1)	0
Thrombocytopenia	18 (37.5)	8 (16.7)	2 (4.2)	9 (25.7)	4 (11.4)	2 (5.7)
Neutropenia	10 (20.8)	6 (12.5)	0	12 (34.3)	6 (17.1)	0
Leukopenia	7 (14.6)	1 (2.1)	0	6 (17.1)	2 (5.7)	0

No grade 5 TEAEs were observed.

OlympiAD study design

- HER2-negative metastatic BC
  - ER+ and/or PR+ or TNBC
- Deleterious or suspected deleterious g*BRCA*m
- Prior anthracycline and taxane
- ≤2 prior chemotherapy lines in metastatic setting
- HR+ disease progressed on ≥1 endocrine therapy, or not suitable
- If prior platinum use
  - No evidence of progression during treatment in the advanced setting
  - ≥12 months since (neo)adjuvant treatment

Olaparib 300 mg tablets bd

2:1 randomization

Chemotherapy treatment of physician's choice (TPC)
- Capecitabine
- Eribulin
- Vinorelbine

Treat until progression

Primary endpoint:
- Progression-free survival (RECIST 1.1, BICR)

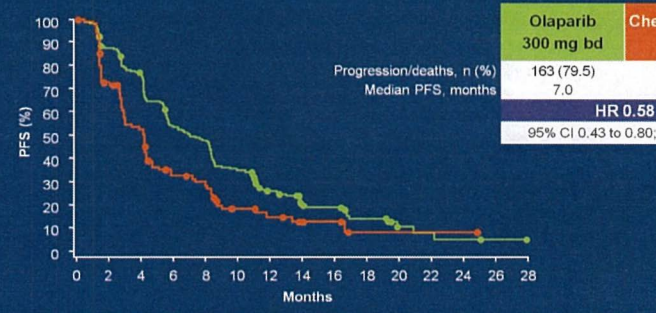
Secondary endpoints:
- Time to second progression or death
- Overall survival
- Objective response rate
- Safety and tolerability
- Global HRQoL (EORTC-QLQ-C30)

BICR, blinded independent central review; ER, estrogen receptor; HRQoL, health-related quality of life; PR, progesterone receptor; RECIST, response evaluation criteria in solid tumors; TNBC, triple negative breast cancer

Patient characteristics

	Olaparib 300 mg bd (N=205)	Chemotherapy TPC (N=97)
Age, years (median, range)	44 (22–76)	45 (24–68)
Male, n (%)	5 (2)	2 (2)
White race, n (%)	134 (65)	63 (65)
BRCA mutation status, n (%)		
BRCA1	117 (57)	51 (53)
BRCA2	84 (41)	46 (47)
Both	4 (2)	0
Hormonal receptor status, n (%)		
ER+ and/or PR+	103 (50)	49 (51)
TNBC	102 (50)	48 (49)
Prior chemotherapy for metastasis, n (%)	146 (71)	69 (71)
Prior platinum treatment, n (%)	60 (29)	26 (27)

Primary endpoint: progression-free survival by BICR



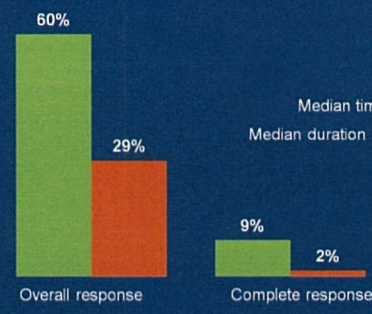
	Olaparib 300 mg bd	Chemotherapy TPC
Progression/deaths, n (%)	163 (79.5)	71 (73.2)
Median PFS, months	7.0	4.2
HR 0.58		
95% CI 0.43 to 0.80; *P*=0.0009		

Patient characteristics

n (%)	Olaparib 300 mg bd (N=205)	Chemotherapy TPC (N=97)
De novo metastatic breast cancer	26 (13)	12 (12)
Measurable disease	167 (82)	66 (68)
≥2 sites	159 (78)	72 (74)
Bone metastases only	16 (8)	6 (6)
Prior lines of chemotherapy for metastases		
0	68 (33)	31 (32)
1	80 (39)	42 (43)
2	57 (28)	24 (25)
Chemotherapy TPC*		
Capecitabine	NA	41 (45)
Eribulin		34 (37)
Vinorelbine		16 (18)

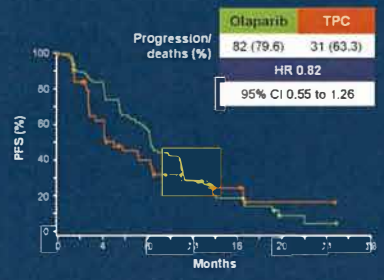
*6 patients did not receive study treatment

Objective response by BICR

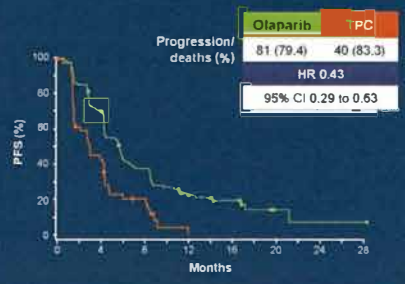


	Olaparib 300 mg bd	Chemotherapy TPC
n	167	66
Median time to response, days	47	45
Median duration of response, months	6.2 (4.6–7.2)	7.1 (2.8–12.2)

Subgroup analyses: PFS by BICR



ER+ and/or PR+



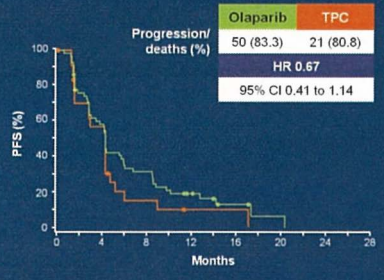
TNBC

Safety summary: adverse events and exposure

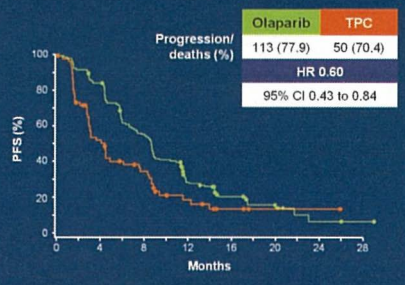
n (%)	Olaparib 300 mg bd (N=205)	Chemotherapy TPC (N=91*)
Grade 1–2	124 (60.5)	42 (46.2)
Grade ≥3	75 (36.6)	46 (50.5)
Death	1 (0.5)	1 (1.1)
AEs leading to drug discontinuations	10 (4.9)	7 (7.7)
AEs leading to dose reductions	52 (25.4)	28 (30.8)
AEs leading to dose interruptions/delay	72 (35.1)	25 (27.5)
Median duration of treatment, months	8.2 (0.5–28.7)	3.4 (0.7–23.0)

*6 patients did not receive study treatment and are not evaluable for safety

Subgroup analyses: PFS by BICR

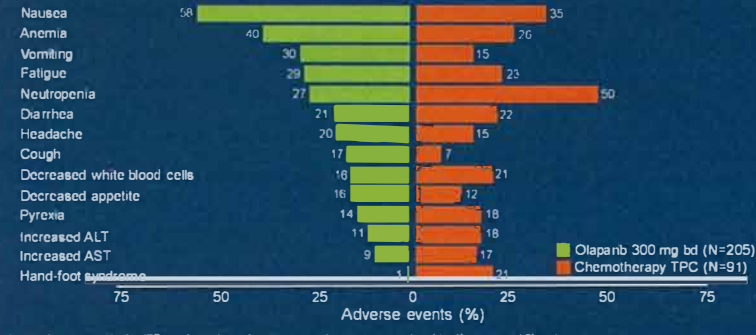


Prior platinum



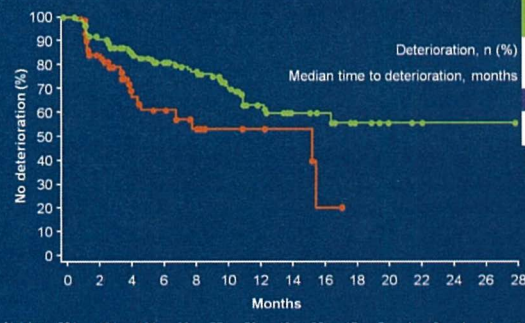
No prior platinum

Adverse events (any grade) in ≥15% of patients



Irrespective of causality. MedDRA preferred terms for adverse events have been combined for 1) anemia and 2) neutropenia
ALT, alanine aminotransferase; AST, aspartate aminotransferase

Time to deterioration of global HRQoL



	Olaparib 300 mg bd	Chemotherapy TPC
Deterioration, n (%)	49 (24)	25 (27)
Median time to deterioration, months	NC	15.3
HR 0.44		
95% CI 0.25 to 0.77		
P=0.0043		

Deterioration is defined as ≥10 point decrease from baseline

Thank you

jbalmana@vhio.net

Conclusions

- Olaparib tablet monotherapy provided a statistically significant and clinically meaningful PFS benefit versus standard-of-care chemotherapy for patients with HER2-negative metastatic breast cancer and a g*BRCA*m
- Olaparib was generally well tolerated with <5% discontinuing treatment for toxicity and a lower rate of Grade ≥3 AEs compared with chemotherapy
- OlympiAD is the first Phase III study in metastatic breast cancer patients demonstrating benefit for a PARP inhibitor over an active comparator

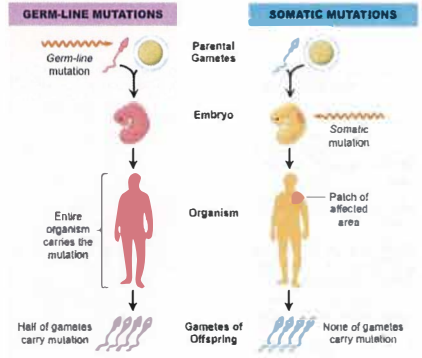
Cancer genetic counselling and testing in view of treatment options/establishing new clinical pathways (Belgian experiences)

Tumor testing – where is its position in clinical pathways

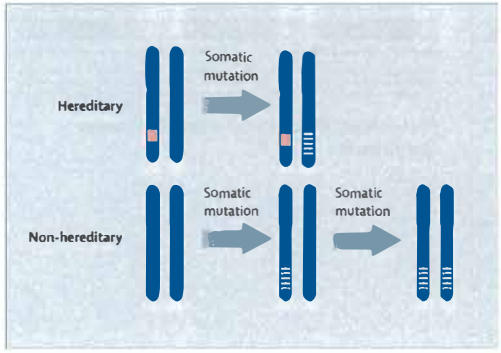
CRIG

UZ

Germline versus somatic mutations



2 hit hypothesis



BRCA1/2 germline mutations lead to increased ovarian cancer risk

BRCA1/2 somatic mutations are restricted to the neoplastic cells and may drive ovarian tumorigenesis in individuals without a germline mutation

Belgium: reimbursement since December 1st 2015

Hoofdstuk IV, nieuwe § xxx0000

a) De specialiteit LYNPARZA komt voor vergoeding in aanmerking indien ze wordt toegediend als monotherapie voor de onderhoudsbehandeling van volwassen patiënten met een BRCA-gemuteerd platinagevoelig recidief hooggradig sereus epitheliaal ovarium, tuba- of primair peritoneaal carcinoom, die nog nooit behandeld zijn met olaparib of een andere PARP-inhibitor in een voorafgaande lijn.

De patiënte moet minstens 2 voorafgaande lijnen platina bevattende chemotherapie gekregen hebben en een volledige of partiële respons vertonen (volgens RECIST criteria) op de laatst gekregen platina bevattende chemotherapie en dat tot het einde van de chemotherapie.

Het interval tussen de voorlaatste lijn platina bevattende chemotherapie en ziekteprogressie bedroeg minstens 6 maanden.

De patiënte mag niet meer dan 8 weken voor de aanvang van de behandeling met LYNPARZA haar laatste lijn platina bevattende chemotherapie hebben voltooid.

Een BRCA mutatie (kiembaan en/of somatisch)

Belgian Journal of Medical Oncology: May 2015
Consensus paper with Belgian geneticists & oncologists

Therapy-orienting testing of BRCA1 and BRCA2 germline mutations in women with ovarian cancer

Key messages for clinical practice

1. As positive test results do not only have implications for the patient but also for relatives, all patients should receive adequate pre- and post-test genetic counselling.
2. Women with high-grade serous epithelial ovarian cancer and in good general condition (i.e. eligible for systemic treatment with low toxicity) should be eligible at any age for therapy-orienting germline *BRCA1/2* testing.
3. The request for germline *BRCA1/2* testing should be made as soon as possible in the course of first-line treatment.
4. For patients for whom the *BRCA1/2* test results will have therapeutic implications, the turnaround time could be shortened if pre-test genetic counselling visits are organised in a collaborative effort between adequately trained clinical geneticists, and gynaecological and medical oncologists. The input of well-trained genetic counsellors, who would deal with counselling of all aspects of hereditary forms of breast/ovarian cancer, may be required in the future.
5. Offering testing for germline *BRCA1/2* mutations to all patients with high-grade serous epithelial ovarian cancer who are eligible for systemic treatment with low toxicity will lead to a limited increase in the number of requests for germline *BRCA1/2* testing in the coming years in Belgium.

http://www.beshg.be/download/guidelines/Guidelines_HBOC_2012.pdf

BeSHG guidelines for HBOC testing

- Woman with breast cancer + one or more of the following :
  - diagnosed ≤ 35 yrs
  - diagnosed < 50 yrs and one relative with bilateral, or ovarian, or breast < 50, or male breast cancer
  - bilateral breast cancer and both diagnosed < 50 yrs
  - ovarian cancer, any age
  - triple negative breast cancer < 50 yrs
  - three individuals with breast cancer, one is a first degree relative (FDR) ofthe other two (excluding male transmitters) and one diagnosed < 50 years
  - individual of ethnicity associated with higher frequency of specific mutations (eg, Ashkenazi Jewish): eligible for founder mutation testing
  - other family situations (eg multiple pancreatic cancer) 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
- Woman with high grade serous or papillary epithelial ovarian cancer at any age (excludes borderline, low grade and mucinous ovarian cancer)
- Male with breast cancer
- Individual with pancreatic cancer at any age with ≥ 2 FDR excluding male transmitters with breast where one diagnosed
- Family history
  - 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

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2018
BRCA-Related Breast and/or Ovarian Cancer Syndrome

NCCN Guidelines Index
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Discussion

BRCA1/2 TESTING CRITERIA[a,b]

Meeting one or more of these criteria warrants further personalized risk assessment, genetic counseling, and often genetic testing and management.
Testing of an individual without a cancer diagnosis should only be considered when an appropriate affected family member is unavailable for testing.

- Individual from a family with a known deleterious *BRCA1/BRCA2* gene mutation
- Personal history of breast cancer[b] + one or more of the following:
  - Diagnosed ≤45 y
  - Diagnosed ≤50 y with:
    - An additional breast cancer primary[c]
    - ≥1 close blood relative[d] with breast cancer at any age
    - ≥1 close relative with pancreatic cancer
    - ≥1 relative with prostate cancer (Gleason score ≥7 or metastatic)
    - An unknown or limited family history[e]
  - Diagnosed ≤60 y with:
    - Triple negative breast cancer
  - Diagnosed at any age with:
    - ≥2 close blood relatives with breast cancer, pancreatic cancer, or prostate cancer (Gleason score ≥7 or metastatic) at any age
    - ≥1 close blood relative[d] with breast cancer diagnosed ≤50 y
    - ≥1 close blood relative[d] with ovarian[e] carcinoma
    - A close male blood relative[d] with breast cancer
    - For an individual of ethnicity associated with higher mutation frequency (eg, Ashkenazi Jewish) no additional family history may be required[f]
- Personal history of ovarian[e] carcinoma
- Personal history of male breast cancer
- Personal history of prostate cancer (Gleason score ≥7 or metastatic) at any age with ≥1 close blood relative[d] with ovarian carcinoma at any age or breast cancer ≤50 y or two relatives with breast, pancreatic, or prostate cancer (Gleason score ≥7 or metastatic) at any age
- Personal history of metastatic prostate cancer (radiographic evidence of or biopsy-proven disease)
- Personal history of pancreatic cancer at any age with ≥1 close blood relative[d] with ovarian carcinoma at any age or breast cancer ≤50 y or two relatives with breast, pancreatic cancer, or prostate cancer (Gleason score ≥7 or metastatic) at any age
- Personal history of pancreatic cancer and Ashkenazi Jewish ancestry
- *BRCA1/2* pathogenic mutation detected by tumor profiling on any tumor type in the absence of germline mutation analysis
- Family history only (significant limitations of interpreting test results for an unaffected individual should be discussed):
  - First- or second-degree blood[d] relative meeting any of the above criteria
  - Third-degree blood[d] relative who has breast cancer[b] and/or ovarian[e] carcinoma and who has ≥2 close blood relatives[d] with breast cancer (at least one with breast cancer ≤50 y) and/or ovarian[e] carcinoma

BRCA testing criteria met → See Follow-up (BRCA-2)

If BRCA testing criteria not met, consider testing for other hereditary syndromes → If criteria for other hereditary syndromes not met, then cancer screening as per NCCN Screening Guidelines

[a] For further details regarding the nuances of genetic counseling and testing, see BR/OV-A
[b] For the purposes of these guidelines, invasive and ductal carcinoma in situ breast cancers should be included.
[c] Two breast cancer primaries includes bilateral (contralateral) disease or two or more clearly separate ipsilateral primary tumors either synchronously or asynchronously.
[d] Close blood relatives include first-, second-, and third-degree relatives on same side of family. (See BR/OV-B)
[e] ... fallopian tube and primary peritoneal cancers. BRCA-related ovarian cancers are associated with epithelial non-mucinous histology. Lynch syndrome can be associated with both nonmucinous and mucinous epithelial tumors. Be attentive for clinical evidence of Lynch syndrome (see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal). Specific types of non-epithelial ovarian cancers and tumors can also be associated with other rare syndromes. Examples include an association between sex-cord tumors with annular tubules and Peutz-Jeghers syndrome or Sertoli-Leydig tumors and DICER1-related disorders.
[f] Testing for Ashkenazi Jewish founder-specific mutation(s) should be performed first. Comprehensive genetic testing may be considered if ancestry also includes non-Ashkenazi Jewish relatives or if other BRCA-related criteria are met. Founder mutations exist in other populations.

Box 1. Criteria for Further Genetic Evaluation for Hereditary Breast and Ovarian Cancer

- Women affected with one or more of the following have an increased likelihood of having an inherited predisposition to breast and ovarian, tubal, or peritoneal cancer and should receive genetic counseling and be offered genetic testing:
  - Epithelial ovarian, tubal, or peritoneal cancer
  - Breast cancer at age 45 years or less
  - Breast cancer and have a close relative[†] with breast cancer at age 50 years or less or close relative[†] with epithelial ovarian, tubal, or peritoneal cancer at any age
  - Breast cancer at age 50 years or less with a limited or unknown family history[‡]
  - Breast cancer and have two or more close relatives[†] with breast cancer at any age
  - Breast cancer and have two or more close relatives[†] with pancreatic cancer or aggressive prostate cancer (Gleason score equal to or greater than 7)
  - Two breast cancer primaries, with the first diagnosed before age 50 years
  - Triple-negative breast cancer at age 60 years or less
  - Breast cancer and Ashkenazi Jewish ancestry at any age
  - Pancreatic cancer and have two or more close relatives[†] with breast cancer; ovarian, tubal, or peritoneal cancer; pancreatic cancer; or aggressive prostate cancer (Gleason score equal to or greater than 7)
- Women unaffected with cancer, but with one or more of the following have an increased likelihood of having an inherited predisposition to breast and ovarian, tubal, or peritoneal cancer and should receive genetic counseling and be offered genetic testing:
  - A first-degree or several close relatives[†] that meet one or more of the aforementioned criteria
  - A close relative[†] carrying a known *BRCA1* or *BRCA2* mutation[§]
  - A close relative[†] with male breast cancer

The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

Society of Gynecologic Oncology

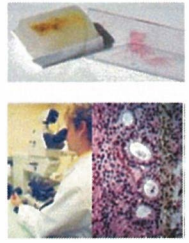
ACOG PRACTICE BULLETIN

Clinical Management Guidelines for Obstetrician–Gynecologists

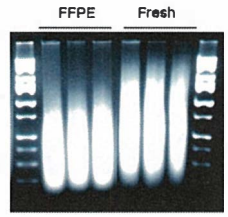
NUMBER 182, SEPTEMBER 2017 (Replaces Practice Bulletin Number 103, April 2009)

Hereditary Breast and Ovarian Cancer Syndrome

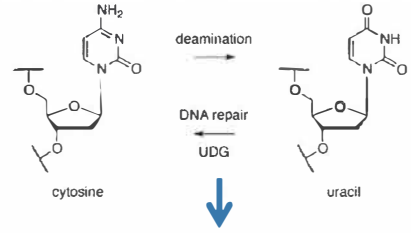
tBRCA testing - workflow



FFPE: caveats



Fragmentation of DNA



artificial C:G > T:A SNVs

1

>20% tumor cells

Time between resection and fixation: <1h

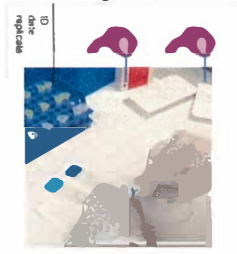
Fixation time: 6-72h
10% formaline

2

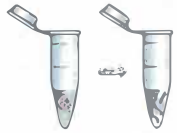
4-6 slides
10 µM

3

tumor region: 5x5 mm

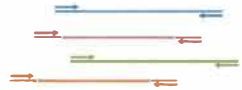


4



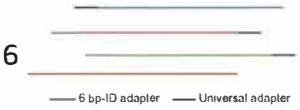
DNA

5



Multiplex PCR

6

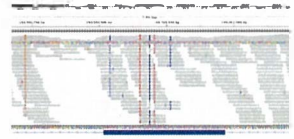


Library preparation

7

sequencing

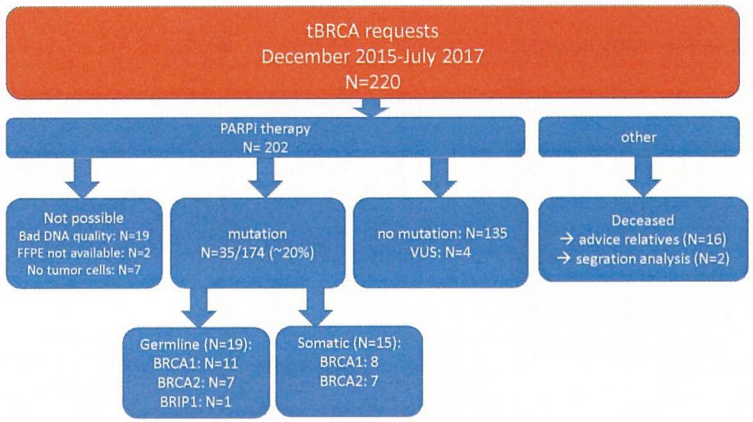
8



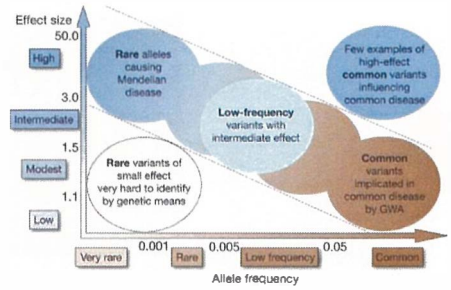
data analysis

9

report

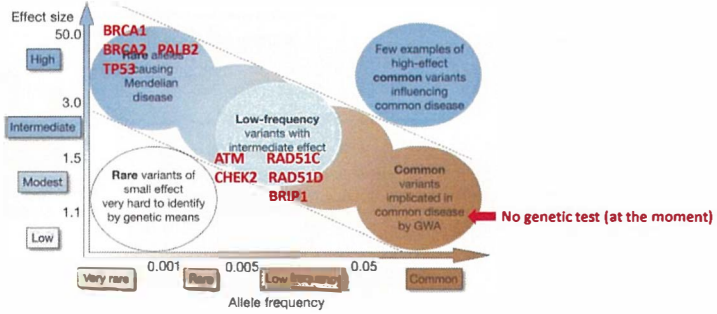


Missing heritability in complex diseases



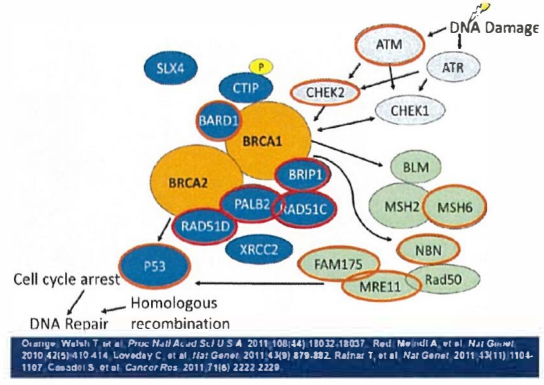
Maniolo et al. Nature. 2009 Oct 8;461(7265):747-53

Genetic architecture of HBOC



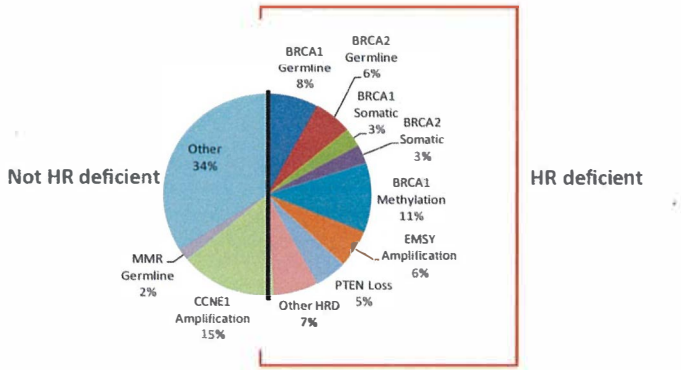
Maniolo et al. Nature. 2009 Oct 8;461(7265):747-53

There is more to repair than BRCA1/2



Orange: Walsh T, et al. Proc Natl Acad Sci U S A. 2011;108(44):18032-18037. Red: Neveling K, et al. Nat Genet. 2010;42(5):410-414. Loveday C, et al. Nat Genet. 2011;43(9):879-882. Reinar T, et al. Nat Genet. 2011;43(11):1104-1107. Casadei S, et al. Cancer Res. 2011;71(6):2222-2229.

Homologous recombination deficiency



Cancer Genome Atlas

Potential for PARP inhibitors

Variant classification

Purpose	Type of variant (source of DNA)	Classification recommendations
Cancer risk assessment of a person + relatives; PGD/PND	Germline (blood)	5-tier IARC/ACMG (1)
Clinical actionability: diagnosis, prognosis, treatment	Somatic (tumor)	5-tier (2, 3, 4) vs. 4-tier (5)

Variant classification – genetics: 5 classes

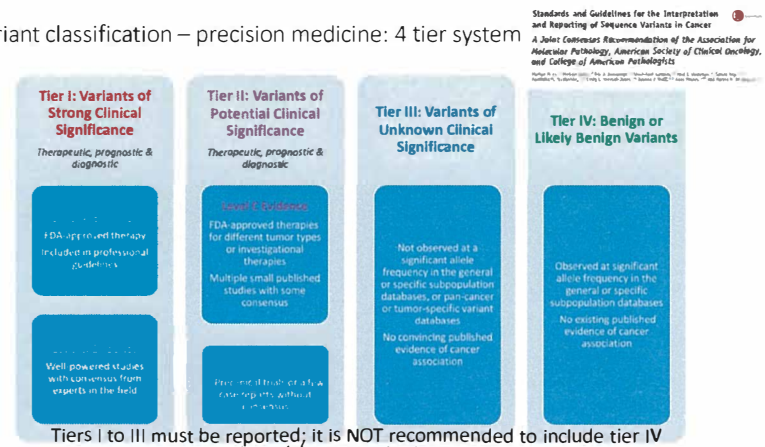
- >0.99 • **Class 5**
  - Predicted to be pathogenic , this result therefore confirms the diagnosis
- 0.95-0.99 • **Class 4**
  - Likely pathogenic, consistent with the diagnosis

Predictive testing
Prenatal testing
PGD

- 0.05-0.949 • **Class 3**
  - Uncertain pathogenicity, does not confirm or exclude diagnosis
  - Unsure about the pathogenicity and offer further work before offering further diagnostic or carrier testing.
- 0.001-0.049 • **Class 2**
  - Unlikely to be pathogenic, diagnosis not confirmed molecularly.
  - No evidence suggesting pathogenicity but not at a high enough frequency to say it's not pathogenic?
- <0.001 • **Class 1**
  - Not pathogenic.
  - "Commom" polymorphism.
  - No evidence suggesting pathogenicity and at "high" frequency.

Classes 3, 4, 5 are reported

Variant classification – precision medicine: 4 tier system



Tiers I to III must be reported; it is NOT recommended to include tier IV variants/alterations in the report

Variant classification – precision medicine: 5 tier system

Classification methods for somatic cancer variants

Classification*	SVC method [21••]	PHIAL method [22••]	BWH/DFCI method
Class 1	Clinically actionable for therapeutic, prognostic, or diagnostic purposes for same tumor type	Validated therapeutic, prognostic, or diagnostic implications for same tumor type	Validated therapeutic, prognostic, or diagnostic implications for same tumor type
Class 2	Clinically actionable for therapeutic, prognostic, or diagnostic purposes for a different tumor type	Limited evidence of therapeutic, prognostic, or diagnostic implications for same tumor type	Validated therapeutic implications for a different tumor type, or limited evidence of prognostic or diagnostic implications for same tumor type
Class 3	Other variants in this gene in this primary tumor are established as actionable for same tumor type	Clinical evidence of therapeutic response from another tumor type	Preclinical or inferential therapeutic, prognostic, or diagnostic implications
Class 4	Other variants in this gene in this primary tumor are established as actionable for a different tumor type	Preclinical association to therapeutic response	Novel or unstudied in cancer
Class 5	(A) Gene is not actionable for any tumor type (B) Established as benign	Inferential association to therapeutic response	Established as benign

BWH/DFCI = Brigham Women's Institute/Dana Farber Cancer Institute.
* PHIAL method classifications referred to as Levels A–E, while other methods refer to as Tiers.

Hoskinson et al, Current Opinion in Genetics and Development, 2017

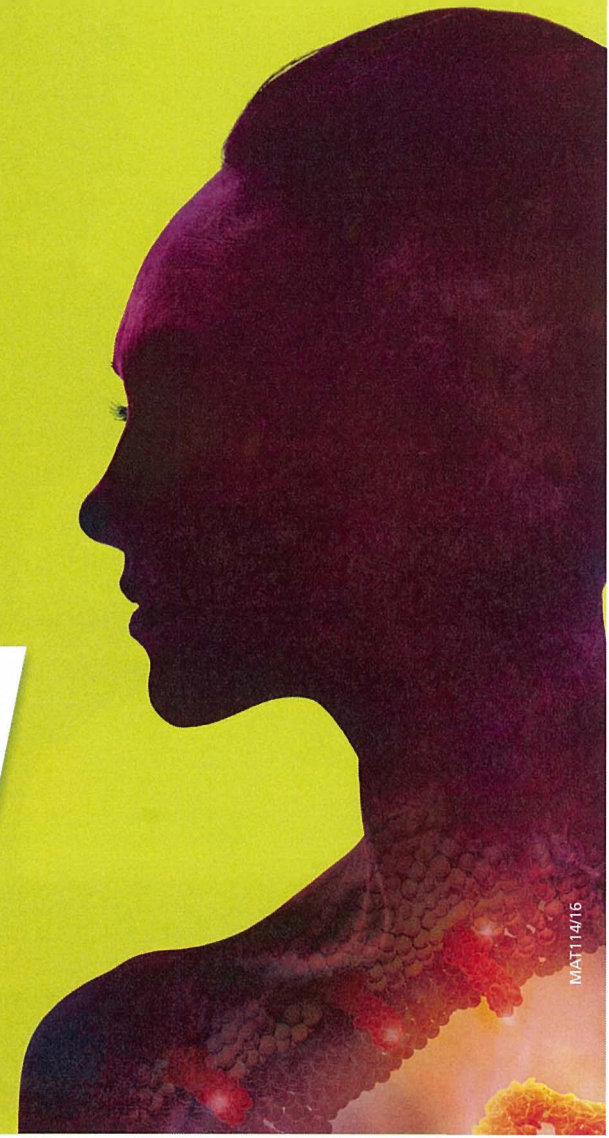
Tumor first? Germline first?

- Discusson advantages and disadvantages

Illustrative examples

AstraZeneca

KORAK NAPREJ **pri zdravljenju** onkoloških bolnikov.



AstraZeneca UK Limited, Podružnica v Sloveniji, Verovškova 55, 1000 Ljubljana, t. 01/51 35 600.

Datum priprave informacije: avgust 2016

ONKOLOŠKI INŠTITUT LJUBLJANA | INSTITUTE OF ONCOLOGY LJUBLJANA

HBOC – germline/ somatic genetic testing – laboratory experiences (latest updates)

Srdjan Novaković

ONKOLOŠKI INŠTITUT LJUBLJANA | INSTITUTE OF ONCOLOGY LJUBLJANA

Hereditary breast and ovarian cancer - HBOC

- Five to ten percent of all breast/ovarian cancers (HBOC) are inherited, primarily due to mutations in *BRCA1* or *BRCA2* genes.
- The rest of HBOC hereditary cancers are a result of mutations in other genes such as *TP53, STK11, PTEN, CDH1, MSH2, MLH1, MSH6, PMS2, EPCAM, CHEK2, PALB2, ATM, RAD51c, BLM, BRIP1, RAD51D, NBN, NF1, BARD1, MRE11A, XRCC2, ABRAXAS, CYP1A1, CYP17, GSTP* or others.

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BRCA1 and *BRCA2*

Since the identification and cloning of *BRCA1/2* genes, according to ClinVar data base, more than 5000 different pathogenic or likely pathogenic mutations have been discovered, most of them in only one or few families.

Risks of Breast, Ovarian, and Contralateral Breast Cancer for *BRCA1* and *BRCA2* Mutation Carriers

BRCA 1/2 testing criteria

NCCN Guidelines Version 2.2017
BRCA-Related Breast and/or Ovarian Cancer Syndrome

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Discussion

BRCA1/2 TESTING CRITERIA[a,b]

Meeting one or more of these criteria warrants further personalized risk assessment, genetic counseling, and often genetic testing and management. Testing of an individual without a cancer diagnosis should only be considered when an appropriate affected family member is unavailable for testing.

- Individual from a family with a known deleterious *BRCA1/BRCA2* gene mutation
- Personal history of breast cancer[c] + one or more of the following:
  - Diagnosed ≤45 y
  - Diagnosed ≤50 y with:
    - An additional breast cancer primary[d]
    - ≥1 close blood relative[e] with breast cancer at any age
    - ≥1 close blood relative with pancreatic cancer
    - ≥1 relative with prostate cancer (Gleason score ≥7)
    - An unknown or limited family history[f]
  - Diagnosed ≤60 y with:
    - Triple negative breast cancer
  - Diagnosed at any age with:
    - ≥2 close blood relatives with breast cancer, pancreatic cancer, or prostate cancer (Gleason score ≥7) at any age
    - ≥1 close blood relative[e] with breast cancer diagnosed ≤50 y
    - ≥1 close blood relative[e] with ovarian[g] carcinoma
    - A close male blood relative[e] with breast cancer
    - For an individual of ethnicity associated with higher mutation frequency (eg, Ashkenazi Jewish) no additional family history may be required[h]
- Personal history of ovarian[g] carcinoma
- Personal history of male breast cancer
- Personal history of prostate cancer (Gleason score ≥7) at any age with ≥1 close blood relative[e] with ovarian carcinoma at any age or breast cancer ≤50 y or two relatives with breast, pancreatic, or prostate cancer (Gleason score ≥7) at any age
- Personal history of pancreatic cancer at any age with ≥1 close blood relative[e] with ovarian carcinoma at any age or breast cancer ≤50 y or two relatives with breast, pancreatic cancer, or prostate cancer (Gleason score ≥7) at any age
- Personal history of pancreatic cancer and Ashkenazi Jewish ancestry
- *BRCA1/2* mutation detected by tumor profiling in the absence of germline mutation analysis
- Family history only (significant limitations of interpreting test results for an unaffected individual should be considered):
  - First-, or second-degree blood[i] relative meeting any of the above criteria
  - Third-degree blood[i] relative who has breast cancer[j] and/or ovarian[g] carcinoma and who has ≥2 close blood relatives[e] with breast cancer (at least one with breast cancer ≤50 y) and/or ovarian[g] carcinoma

BRCA testing criteria met → See Follow-up (BRCA-2)

If BRCA testing criteria not met, consider testing for other hereditary syndromes → If criteria for other hereditary syndromes not met, then cancer screening as per NCCN Screening Guidelines

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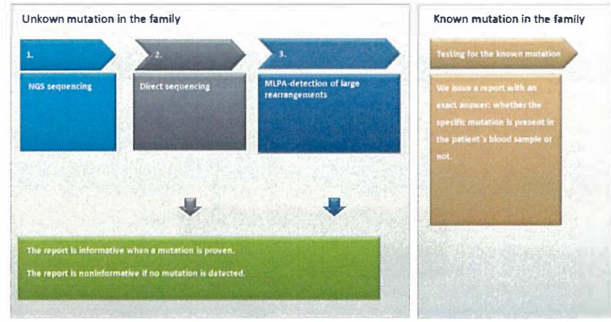
BRCA1 and *BRCA2* screening strategy



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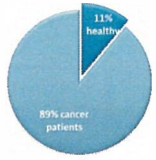
Results of *BRCA1/2* mutation screening 1999 - december 2016

3071 tested individuals from 2095 Slovene breast and/or ovarian cancer families

Ratio of healthy and diseased probands among the first tested family members



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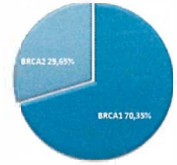
Results of *BRCA1/2* mutation screening 1999 – december 2016

- 452 *BRCA1/2* positive families
  - *BRCA1* – 318
  - *BRCA2* – 134



- Mutation detection rate: 21.6% (452/2095)

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BRCA 1/2 mutation spectrum 1999 - december 2016

94 different deleterious mutations:

43 in *BRCA1*
- missense mutations affecting the 5'RING domain
- nonsense mutations
- frame-shift mutations
- deletions of whole exons
- splice site mutations

51 in *BRCA2*
- splice site mutations
- nonsense mutations
- frame-shift mutations

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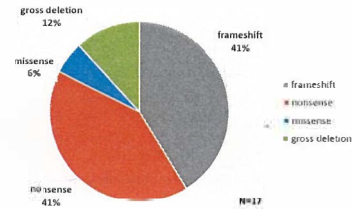
Novel mutations - pathogenic variants in *BRCA1* and *BRCA2*

In the period from 1999 to 2016

gene	cHGVS	pHGVS
BRCA1	c.121dupC	p.(His41Profs*25)
	c.181T>A	p.(Cys61Ser)
	c.457_458delAG	p.(Ser153Cysfs*5)
	c.1193C>A	p.(Ser398*)
	c.4356delA	p.(Ala1453Glnfs*3)
	c.5377A>T	p.(Lys1793*)
	deletion of exons 4-9	
	deletion of exons 4-7	
BRCA2	c.775A>T	p.(Arg259*)
	c.5101C>T	p.(Gln1701*)
	c.5291C>G	p.(Ser1764*)
	c.5433_5436delGGAA	p.(Glu1811Aspfs*3)
	c.6100delinsTA	p.(Arg2034*)
	c.6421_6424dupGGTT	p.(Ser2142Trpfs*6)
	c.6491_6494delAGTT	p.(Gln2164Argfs*3)
	c.7303C>T	p.(Gln2435*)
	c.8808delG	p.(Asn2937Metfs*39)

Novel BRCA1 and BRCA2 mutations



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BRCA 1/2 mutation spectrum 1999 - december 2016

- The most common mutation found in the *BRCA1* gene was missense mutation c.181T > G (p.Cys61Gly). It was detected in 82 families.
- The most common mutation in the *BRCA2* gene was a splice site mutation c.7806-2A > G. It was detected in 33 families.

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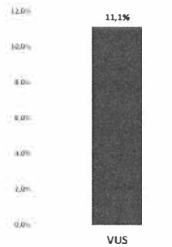
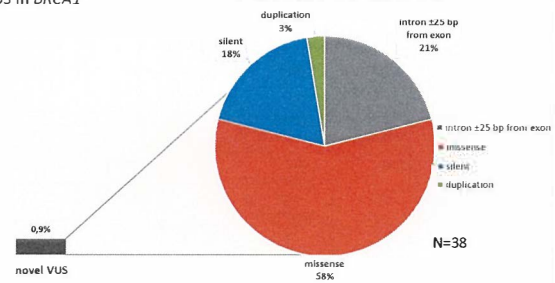
BRCA1 and *BRCA2* - variants of uncertain significance (VUS)

% patients harbouring VUS in *BRCA1* and *BRCA2*



novel *BRCA1* and *BRCA2* VUS



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NGS - genes tested in breast and ovarian cancer patients in 2015 - 2016

NGS panel 2015:
ATM, BRCA1, BRCA2, CDH1, CHEK2, EPCAM, MLH1, MSH2, MSH6, PALB2, PMS2, PTEN, STK11, TP53

NGS panel 2016:
ATM, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, MLH1, MSH2, MSH6, NF1, NBN, PALB2, PMS2, PTEN, RAD51C, RAD51D, STK11, TP53

Number of patients with different mutations detected with NGS in 2015 - 2016

BRCA1	BRCA2	TP53	STK11	PTEN	CDH1	MSH2	MLH1	MSH6	PMS2	EPCAM	CHEK2	PALB2	ATM	BRIP	NF1	NBN	RAD51C	RAD51D
116	16	1		2	6	1	1		2		14	11	11	1		3	4	1

*in a single patient mutations in both *BRCA2* and in *ATM* were detected simultaneously

Reported incidental findings

SMARCA	FH	BLM	FLCN	XPA	SLX	MUTYH
1	3	2	1	1	1	5

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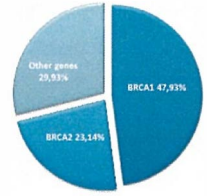
Distribution of mutations detected with NGS in breast and ovarian cancer patients in 2015 - 2016

Mutation detection rate in 2015 - 2016: 28,70%



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BRCA1/2 mutations in ovarian cancer patients in the period 2012-2016

Most ovarian cancer patients have been tested for germline *BRCA* mutations
Only lately have we begun to offer testing of somatic *BRCA* mutations

Patients carrying germline or somatic BRCA mutation have been associated with a better prognosis as well as better response to platinum-based therapy and PARP inhibitors

Altogether 302 tested ovarian cancer patients
Mutations detected in 31,79% of cases

GENE	No. of patients with mutation	%	No. Of different mutations
BRCA1	76	79,17%	28
BRCA2	20	20,83%	16
BRCA1/2	96	100%	44

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Conclusion

Even though the testing focus in HBOC families is on detection of BRCA mutations, other highly penetrant, but less frequently mutated genes, have been recommended for testing

Genetic testing of *BRCA* genes provides the key to:

- Accurate cancer risk assessment
- Effective genetic counseling
- Appropriate medical follow-up
- Appropriate treatment
  - DNA quality from FFPE tissue is a major obstacle
  - Improve analysis and interpretation by:
    - Running in duplicate
    - being careful with assay design and minimum coverage
  - Additional steps (e.g. Uracil-DNA Glycosylase (UDG) treatment) can help minimise deamination artefacts

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Onkološki inštitut Ljubljana

Institute of Oncology Ljubljana

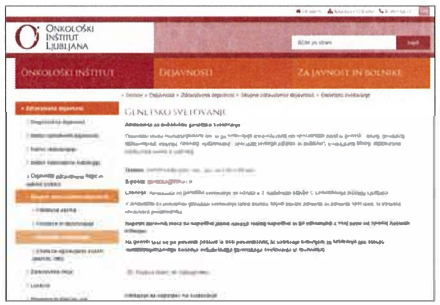
S. NOVAKOVIĆ

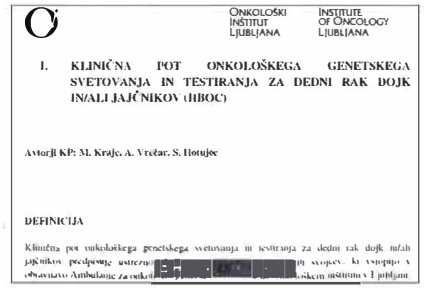
Cancer genetic counselling – new clinical pathways in view of treatment options

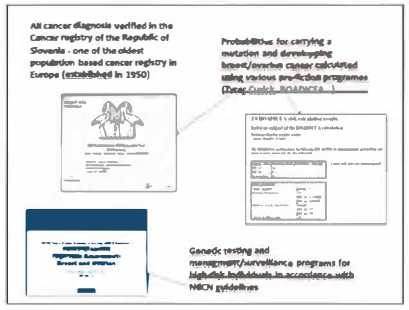
Ana Blatnik, Mateja Krajc, Ksenija Strojnik

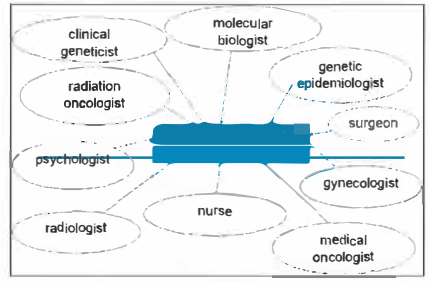
HBOC at the Institute of Oncology

- 1999 - genetic testing for *BRCA* genes available - in collaboration with Vrije Universiteit Brussel
- 2008 - all tests performed at the Institute of Oncology Ljubljana, state insurance covers the costs of counseling and testing when indicated
- 2010 –management of individuals at high risk for breast/ovarian cancer at our institution
- 2011 – clinical pathways established
- 2014/2015 – genetic testing performed using an NGS based approach (multi-gene panel)
- **2014 – priority assessment for therapeutical purposes introduced**









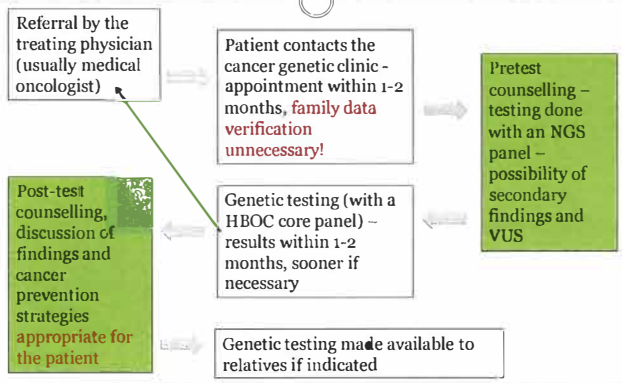
Increase in the number of counselling sessions

1999-2017:
- ~500 BRCA positive families
- ~additional 2-3 family members tested from each family
- loose testing criteria, yet a high mutation detection rate!

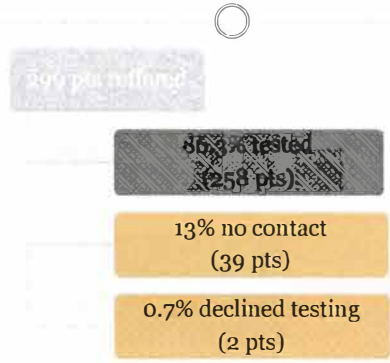
Olaparib as a game changer!

- PARP inhibitor olaparib approved for *BRCA* mutation carriers as maintenance therapy in recurrent platinum sensitive OC
- in October 2014 we started offering *BRCA* tests to all ovarian cancer, fallopian tube and primary peritoneal serous carcinoma patients with high grade serous histology
- need for fast-tracking - how to manage the additional workload?

Simplifying the clinical pathway

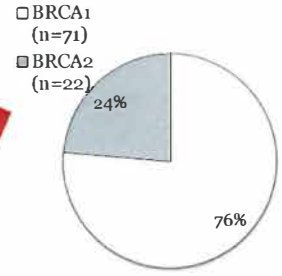


Attendance rate



BRCA mutation detection rate

Mutation status	No of pts (258)	%
None identified	150	58.1%
BRCA 1/2	**93**	**36.0%**
other*	15	5.8%



*other genes from Illumina TruSight Cancer sequencing panel

Other findings

Mutation identified	No of pts (258)	%
None	150	58.1%
BRCA1/2	93	36.0%
other*	**15**	**5.8%**

*Other gene mutations identified from the panel	No of pts (n=15)
ATM	4
RAD51C	3
RAD51D	1
MUTYH	2
CHECK2	1
MSH2	1
PALB2	1
CDH1	1
STK11	1

Mutation detection rate depending on family history

Positive family history:
165 pts (64%)

- BRCA 1/2 mutation detection rate: **44.8%** (74/165 pts)

Negative family history:
93 pts (36%)

- BRCA 1/2 mutation detection rate: **18.3%** (17/93 pts)

Mutation rate in patients tested when diagnosed with ovarian cancer

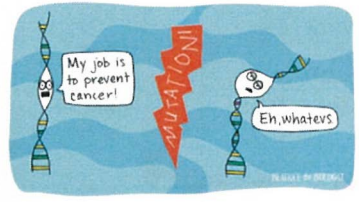
BRCA 1/2 mutation detection rate in 134 pts tested at the time of OC diagnosis

Excluding patients with recurrent OC or a long disease-free interval

33.6%
(45/134 pts)

Conclusions

- Testing all high-grade serous OC yielded an unusually **high mutation detection rate** – a higher prevalence of mutation carriers in the Slovene population or a selection bias?
- Panel testing (VUS, secondary findings, mutations in OC genes with no therapeutic implications)
- Adopting a modified strategy of germline testing with patients attending a cancer genetics clinic feasible for OC, but with breast cancer...
- Tumor tissue genetic testing – **pros** and **cons** (detecting somatic mutations vs more limited panels)?
- Testing for defective homologous repair?



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UKC MARIBOR Univerzitetni klinični center Maribor

Slovenian experiences with olaparib in ovarian cancer treatment

Maja Ravnik, Erik Škof

What's new in the management of BRCA positive ovarian and breast cancer patients- 2nd conference

19th of October 2017

Ovarian cancer: Slovenija

- Incidence – 177*
- Median age – 60 years
- Stage of disease:
  - 75% advanced (FIGO IIIC/IV)
- Histology
  - „High-grade" serous (75%),
- Frequent relapses (80%)
- 5 y OS in SLO 43%*

* Cancer in Slovenia 2013

Ovarian cancer: Slovenija

- Study 19
  - showed **7** months PFS* benefit of maintenance therapy with olaparib in patients with relapsed BRCA+ ovarian cancer[1].
  - Olaparib prolonged overal survival for 4,7 months compared to placebo [2] (the difference was not statistically significant).
- EMA approval of olaparib for relapsed BRCA+ ovarian cancer on 16/12/2014
- Since **5th of february 2016** olaparib therapy is reimbursed by ZZZS (Health Insurance Institute of Slovenia) for patients with relapsed BRCA+ ovarian cancer in Slovenia

PFS* – progression-free survival

1. Ledermann J et al, Lancet Oncol 2014
2. Ledermann J et al. Lancet Oncol 2016

Ovarian cancer: Slovenija

- Since september 2014:
  - All patients with HGS* cancer of ovaries, fallopian tubes or PPSC are offered to perform BRCA genetic testing **at diagnosis**
  - The aim of BRCA genetic testing is:
    - **treatment with olaparib**
    - prevention of breast and ovarian cancer
  - Active search for BRCA+ patients
    - confidential data
    - multidisciplinary genetic consilium

HGS* - High-grade serous

Slovenian guidelines for treatment of ovarian cancer 2014/15

Olaparib experience in Slovenija

- Systemic therapy is applied in two Institutions:
  - Institute of Oncology Ljubljana
  - University Medical centre Maribor
- No clinical trial with olaparib in Slovenia
- First 2 pts received olaparib through „Early-access programme" in November 2015.
- Label for olaparib is the same as in Study 19.

Ovarian cancer: Slovenija

- Current recommendations:
  - The „need for speed" of gBRCA testing results:
    - Medical oncologist → recommends genetic counseling
    - Geneticist → pretest counseling+ blood sample
    - Molecular lab. → blood testing results
    - Geneticist → posttest counseling
    - Medical oncologist → therapy with olaparib

    <3 months
  - Waiting list for genetic counseling
    - „Highest-priority" patients with relapsed HGS** ovarian cancer
    - „High-priority" patients with HGS at diagnosis
- Near future – upfront tBRCA* testing ?
  - Faster results
  - Complete results – tBRCA = sBRCA+gBRCA
  - No need for genetic counselling in majority (pts. and relatives)

tBRCA*: BRCA mutation in tumor
HGS** - high-grade serous

Olaparib experience in Slovenija

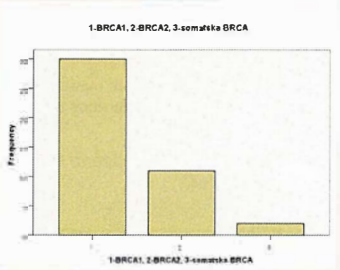
- Overall 48 pts recieved therapy with olaparib
  - At the moment: 25 pts on treatment
  - Duration of th: range 1-23 months (median 5 months)
  - AE – mild nausea, fatigue, anemia (G1)
  - 12 pts. had progression of the disease
  - 4 pts SAE – G3 anemia
    - 2pts continue th with reduced dose (50% dose)
  - 2 pts declined th. without evidence of AE

Olaparib experience in Slovenija
(data from Institute of Oncology Ljubljana)

- Median age - 60 years
  - BRCA 1 – 56 years
  - BRCA 2 – 63 years
- BRCA 1 – 70%

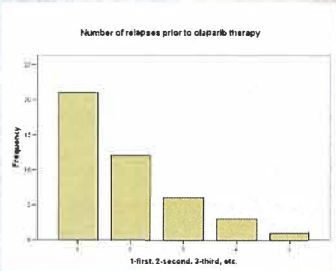
1-BRCA1, 2-BRCA2, 3-somatska BRCA

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	30	69.8	69.8	69.8
	2	11	25.6	25.6	95.3
	3	2	4.7	4.7	100.0
	Total	43	100.0	100.0	



Olaparib experience in Slovenija

(data from Institute of Oncology Ljubljana)



1-prvi, 2-drugi, 3-tretji

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	21	48,8	48,8	48,8
	2	12	27,9	27,9	76,7
	3	6	14,0	14,0	90,7
	4	3	7,0	7,0	97,7
	6	1	2,3	2,3	100,0
	Total	43	100,0	100,0	

Olaparib experience in Slovenija

(data from Institute of Oncology Ljubljana)

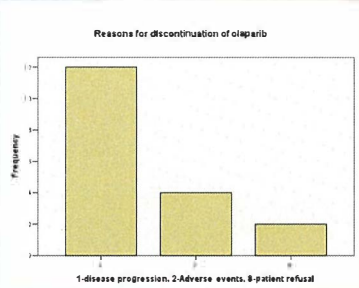
- Adverse events of olaparib:
  - Nausea
    - – usually first month (metoclopramid p.p.)
  - Fatigue
    - - in majority first month (? KT)
  - Anemia
    - - in majority G1 (no transfusion needed)
    - - G3 (Hb <80g/l) – 4 patients
      - 2 patients continue with dose reduction (50%) – G1 anemia – still on therapy
      - 1 patient with dose reduction (50%) had disease progression – end of therapy
      - 1 patient despite dose reduction (50%) persistent G3 anemia – end of therapy due to SAE

1-nausea, 2-fatigue, 3 anemia,... 12-nausea and fatigue,..

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	0	4	9,3	9,3	9,3
	1	6	14,0	14,0	23,3
	2	3	7,0	7,0	30,2
	12	20	46,5	46,5	76,7
	13	1	2,3	2,3	79,1
	123	9	20,9	20,9	100,0
	Total	43	100,0	100,0	

Olaparib experience in Slovenija

(data from Institute of Oncology Ljubljana)



1-progres, 2-AE, 8-odklon

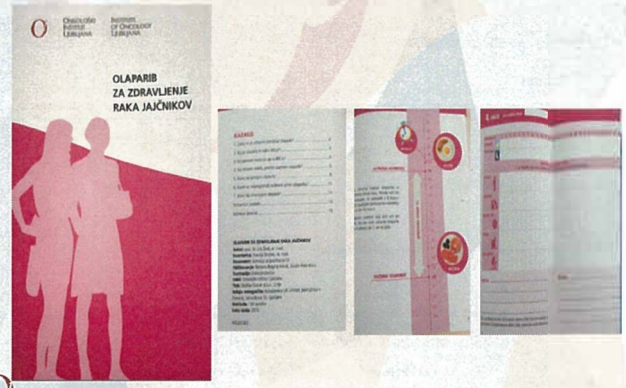
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	12	66,7	66,7	66,7
	2	4	22,2	22,2	88,9
	8	2	11,1	11,1	100,0
	Total	18	100,0	100,0	

17/21 patients with 1. relapse are still on therapy

SAE – G3 anemia (despite dose reduction)

Genetic counseling – information for patients

Olaparib – information for patients



Thank you !

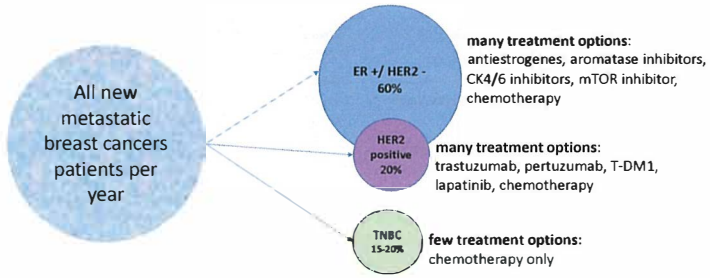
PARP inhibitors in breast cancer – current and future perspectives in Slovenia

Simona Borštnar
Division of Medical Oncology
Institute of oncology Ljubljana

Questions

- ❑ What is the proportion of metastatic breast cancer patients suitable for treatment with PARP inhibitors?
- ❑ What is current approach in the treatment of BRCA mutation carriers?
- ❑ When PARP inhibitors will be available for the treatment of patients with breast cancer in Slovenia?
- ❑ Are we ready to use PARP inhibitors in breast cancer?

Clinical Breast Cancer Subsets Defined by IHC in metastatic disease



Overall survival of patients with metastatic breast cancer (2008–2013)

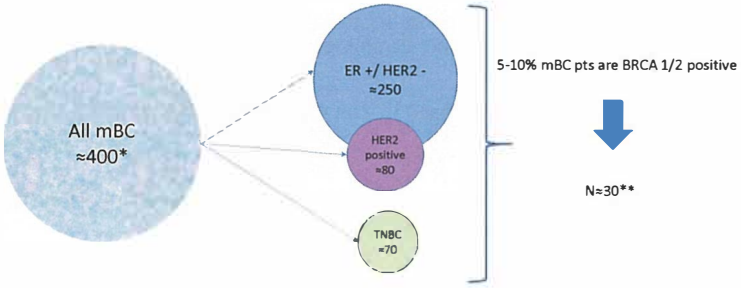
Breast cancer subtype	2008	2009	2010	2011	2012	2013
HR+/HER2– (n = 9908)	**43.7** (40.2–46.6)	**42.0** (38.9–44.6)	**40.9** (38.0–43.4)	**42.0** (3926–45.04)	**44.5** (41.8–47.3)	**40.3** (37.8–NR)
HER2 +++ (n = 2861)	**38.67** (33.6–44.6)	**42.3** (38.3–50.8)	**40.1** (35.2–45.6)	**42.38** (36.5–49.8)	**51.1** (46.5–NR)	Median NR
HR-/HER2– (n = 2317)	**15.1** (12.7–16.4)	**15.1** (13.0–17.4)	**14.7** (13.2–17.0)	**14.0** (11.4–15.9)	**13.9** (11.4–15.9)	**14.1** (12.5–15.5)

new therapies are needed

HR, hormone receptor; NR = not reached.

Delaloge S, *et al.* ASCO 2017 (Abstract 1078).

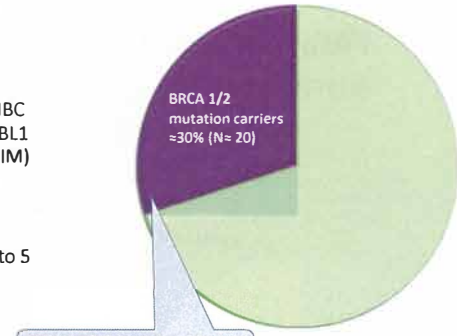
Estimated number of metastatic breast cancer (mBC) patients according to different subtypes in Slovenia



* Estimated number of new mBC per year: primary metastatic (N ≈90) and secondary metastatic (N ≈300-320)
** estimated number of BRCA positive mBC per year

Characteristics of TNBC

- Most TNBC are invasive ductal, minority represent medullary, metaplastic or adenoid cystic carcinoma.
- By gene expression profiling TNBC are classified in two basal-like (BL1 and BL2), immunomodulatory (IM) and luminal androgen receptor (LAR) subtype.
- Distant metastatic recurrences tend to occur within the first 2 to 5 years after diagnosis, late recurrences are rare.



Narod SA. Nat Rev Clin Oncol 2010

Current treatment in BRCA positive breast cancer patients

- Traditionally, BRCA carriers have received conventional systemic chemotherapy based on their baseline tumor characteristics.
- Tumors arising in patients with BRCA mutations were shown to be particularly sensitive to platinum compounds or inhibitors of PARPs.
- BRCA1-mutation carriers seem to benefit from anthracycline–taxane-containing regimens as much as sporadic triple-negative breast cancers do.

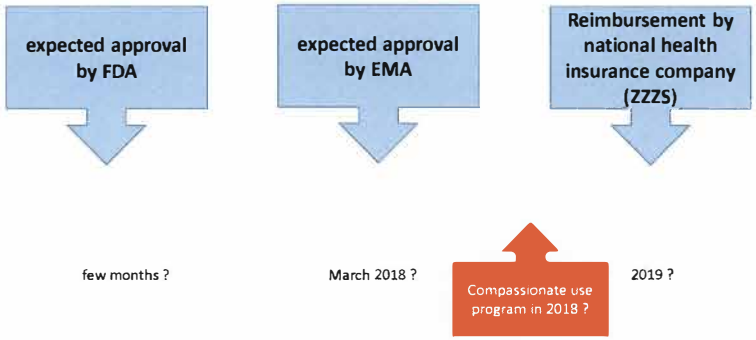
Sikov WM et al. JCO 2015; Rugo HS et al. NEJM 2016; von Minckwitz G et al. Lancet Onc. 2014

Clinical studies with PARPs in BRCA1/2 positive advanced breast cancer

Study name	PHASE	INVESTIGATIONAL ARM	COMPARATOR ARM	PRIMARY ENDPOINT
OlympiAD	3	olaparib	Physician choice ChT	PFS COMPLETED
BROCADE	2	veliparib+ temozolamide or carbo/pacli	Placebo+ Carbo/pacli	PFS
NCT02163694	3	veliparib+ carbo/pacli	placebo+ carbo/pacli	PFS
EMBRACA	3	tazaloparib	Physician choice ChT	PFS
ABRAZO	2	tazalopatib	Single arm study	ORR
BRAVO	3	niraparib	Physician choice ChT	PFS
NCT00664781	2	Rucaparib+ cisplatin	Cisplatin	ORR, safety

Livraghi L and Garber JE. MC Medicine 2015: 13:188

When PARP inhibitors will be available for the treatment of patients with breast cancer in Slovenia?



Are we ready to use PARP inhibitors for breast cancer in Slovenia?

Genetic testing is available to all breast cancer patients who meet the criteria:

- a family member with BRCA mutation
- diagnosis of BC under the age of 45
- diagnosis of TNBC under the age of 60
- diagnosis of two separate breast cancers (one of which was diagnosed under the age of 50)
- diagnosis of breast cancer and ovarian cancer in same person
- diagnosis of ovarian cancer
- man with breast cancer
- one or more close blood relatives with breast cancer that was diagnosed under the age of 50

It is very likely that we will have information about the BRCA mutation in majority of patients at the time of relapse.

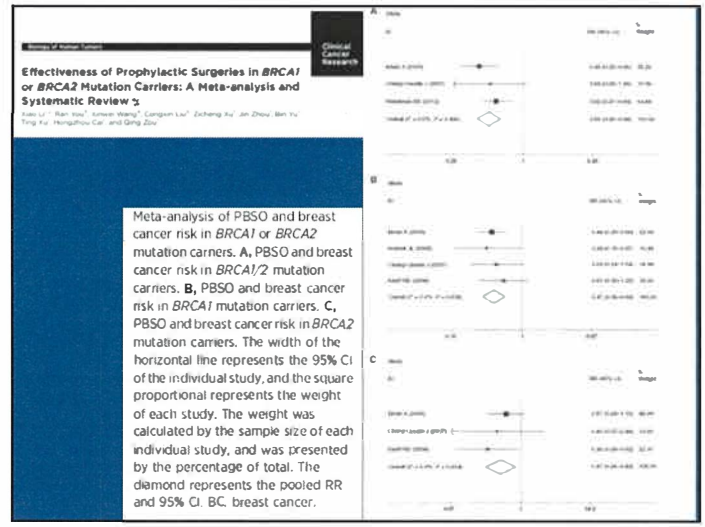
Surgical treatment of BRCA positive breast
cancer patients – current practice and Slovenian results

Janez Zgajnar
Institute of Oncology Ljubljana

All data presented are unpublished

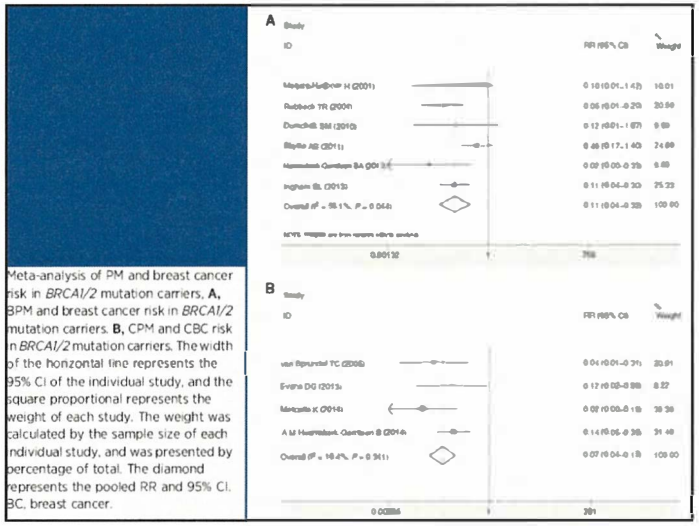
Strategies in BRCA1/2 mutation carriers

- Intensive follow up
- Chemoprevention – (tamoxifen)
- Prophylactic surgery
  - Oophorectomy
  - Mastectomy

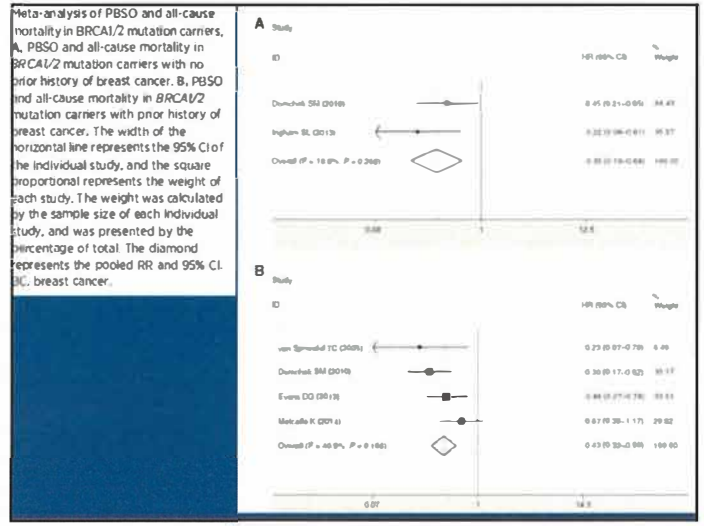


Effectiveness of Prophylactic Surgeries in *BRCA1* or *BRCA2* Mutation Carriers: A Meta-analysis and Systematic Review

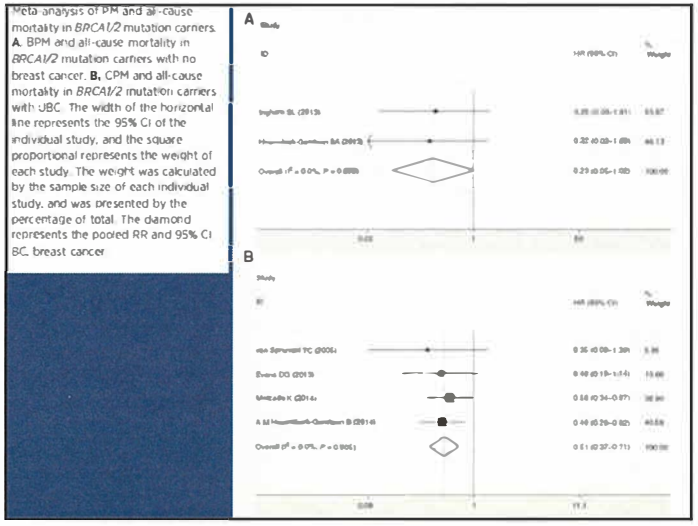
Meta-analysis of PBSO and breast cancer risk in *BRCA1* or *BRCA2* mutation carriers. **A,** PBSO and breast cancer risk in *BRCA1/2* mutation carriers. **B,** PBSO and breast cancer risk in *BRCA1* mutation carriers. **C,** PBSO and breast cancer risk in *BRCA2* mutation carriers. The width of the horizontal line represents the 95% CI of the individual study, and the square proportional represents the weight of each study. The weight was calculated by the sample size of each individual study, and was presented by the percentage of total. The diamond represents the pooled RR and 95% CI. BC, breast cancer.



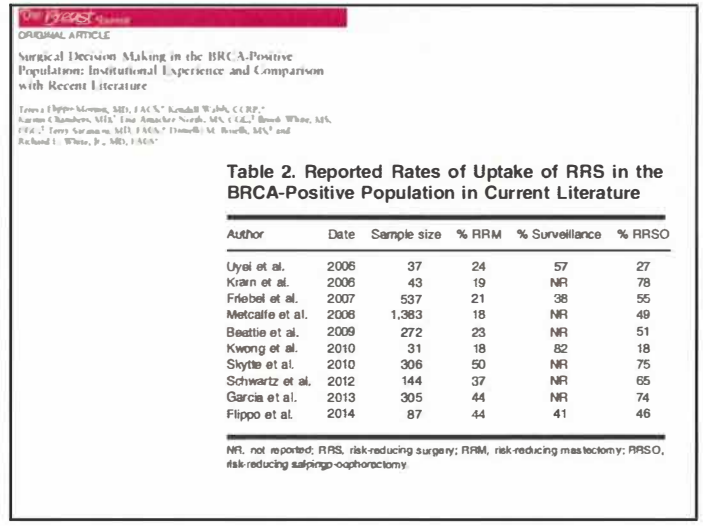
Meta-analysis of PM and breast cancer risk in *BRCA1/2* mutation carriers. **A,** BPM and breast cancer risk in *BRCA1/2* mutation carriers. **B,** CPM and CBC risk in *BRCA1/2* mutation carriers. The width of the horizontal line represents the 95% CI of the individual study, and the square proportional represents the weight of each study. The weight was calculated by the sample size of each individual study, and was presented by percentage of total. The diamond represents the pooled RR and 95% CI. BC, breast cancer.



Meta-analysis of PBSO and all-cause mortality in BRCA1/2 mutation carriers. A, PBSO and all-cause mortality in *BRCA1/2* mutation carriers with no prior history of breast cancer. B, PBSO and all-cause mortality in *BRCA1/2* mutation carriers with prior history of breast cancer. The width of the horizontal line represents the 95% CI of the individual study, and the square proportional represents the weight of each study. The weight was calculated by the sample size of each individual study, and was presented by the percentage of total. The diamond represents the pooled RR and 95% CI. BC, breast cancer.



Meta-analysis of PM and all-cause mortality in *BRCA1/2* mutation carriers. **A**. BPM and all-cause mortality in *BRCA1/2* mutation carriers with no breast cancer. **B,** CPM and all-cause mortality in *BRCA1/2* mutation carriers with UBC. The width of the horizontal line represents the 95% CI of the individual study, and the square proportional represents the weight of each study. The weight was calculated by the sample size of each individual study, and was presented by the percentage of total. The diamond represents the pooled RR and 95% CI BC, breast cancer



ORIGINAL ARTICLE

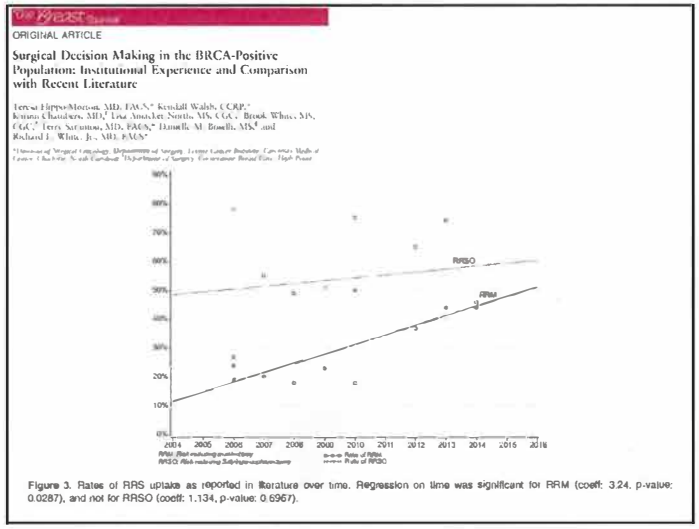
Surgical Decision Making in the BRCA-Positive Population: Institutional Experience and Comparison with Recent Literature

Terry Flippo-Morton, MD, FACS,* Kendall Walsh, CCRP,* Karen Chambers, MD,† Lisa Amacker North, MS, CGC,‡ Brock White, MS, CGC,‡ Terry Sarmiento, MD, FACS,* Donnell M. Booth, MS,§ and Richard L. White, Jr., MD, FACS*

Table 2. Reported Rates of Uptake of RRS in the BRCA-Positive Population in Current Literature

Author	Date	Sample size	% RRM	% Surveillance	% RRSO
Uyei et al.	2006	37	24	57	27
Kram et al.	2006	43	19	NR	78
Friebel et al.	2007	537	21	38	55
Metcalfe et al.	2008	1,383	18	NR	49
Beattie et al.	2009	272	23	NR	51
Kwong et al.	2010	31	18	82	18
Skytte et al.	2010	306	50	NR	75
Schwartz et al.	2012	144	37	NR	65
Garcia et al.	2013	305	44	NR	74
Flippo et al.	2014	87	44	41	46

NR, not reported; RRS, risk-reducing surgery; RRM, risk-reducing mastectomy; RRSO, risk-reducing salpingo-oophorectomy.



ORIGINAL ARTICLE

Surgical Decision Making in the BRCA-Positive Population: Institutional Experience and Comparison with Recent Literature

Teresa Hippo-Morton, MD, FACS,* Kendall Walsh, CCRP,* Kristine Chambers, MD,† Lisa Amacker-Norris, MS, CGA,‡ Brook White, MS, CGC,‡ Terri Sarantou, MD, FACS,* Danielle M. Brasfield, MS,§ and Richard L. White, Jr., MD, FACS*

Figure 3. Rates of RRS uptake as reported in literature over time. Regression on time was significant for RRM (coeff: 3.24, p-value: 0.0287), and not for RRSO (coeff: 1.134, p-value: 0.6967).

RESULTS OF THE INSTITUTE OF ONCOLOGY LJUBLJANA

- Evaluate the uptake of the risk reducing surgery in BRCA 1 and BRCA 2 mutation carriers in Slovenia
- Analyze the breast reconstruction rate in patients with risk reducing mastectomy
- Comparisson of two periods
  - Until end of 2015
  - Year 2016

PATIENTS INCLUDED
until end of 2015

- FEMALE,
  BRCA 1 AND BRCA 2
  MUTATION POSITIVE
- DATA AVAILABLE
- NO CANCER HISTORY (n= 174)
  OR
- BREAST CANCER AT ANY TIME (n=232)
- PATIENTS WITH OTHER CANCER TYPES WERE EXCLUDED

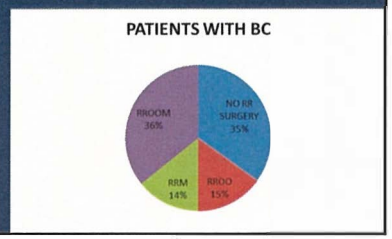
PATIENTS INCLUDED
until end of 2015

- FEMALE,
  BRCA 1 AND BRCA 2
  MUTATION POSITIVE
- DATA AVAILABLE
- NO CANCER HISTORY (n= 174)
  OR
- BREAST CANCER AT ANY TIME (n=232)
- PATIENTS WITH OTHER CANCER TYPES WERE EXCLUDED

PATIENTS WITH BREAST CANCER	N	%
	232	100
NO RR SURGERY	81	35
RROO	35	15
RRM	33	14
RROOM	83	36

~ 65 % RISK REDUCING SURGERY

RRM 116/232 – 50%

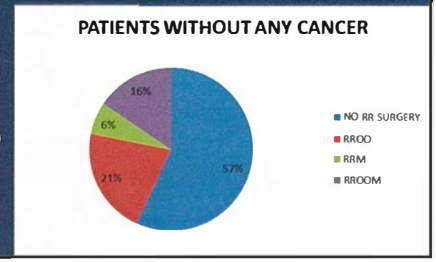


PATIENTS WITHOUT ANY CANCER	N	%
	174	100
NO RR SURGERY	99	57
RROO	37	21
RRM	11	6
RROOM	27	16

~ 40 % RISK REDUCING SURGERY

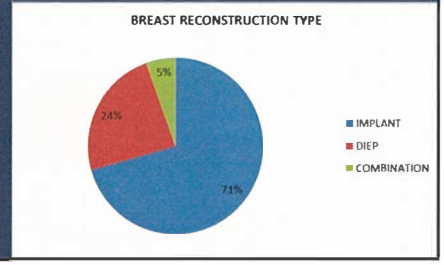
RRM 38/174 – 22%

22/38 – 2013-15



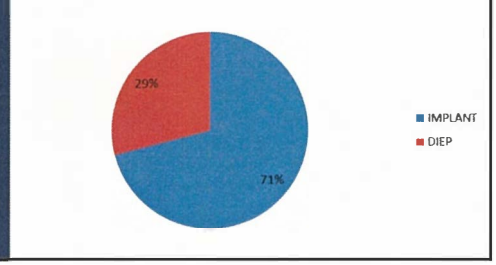
PATIENTS WITH BREAST CANCER	N	%
	116	100
NO RECONSTRUCTION	24	21
IMPLANT	65	56
DIEP	22	19
COMBINATION	5	4

~ 80 % BREAST RECONSTRUCTION RATE



PATIENTS WITHOUT ANY CANCER	N	%
	38	100
NO RECONSTRUCTION	7	18
IMPLANT	22	58
DIEP	9	24

~ 80 % BREAST RECONSTRUCTION RATE



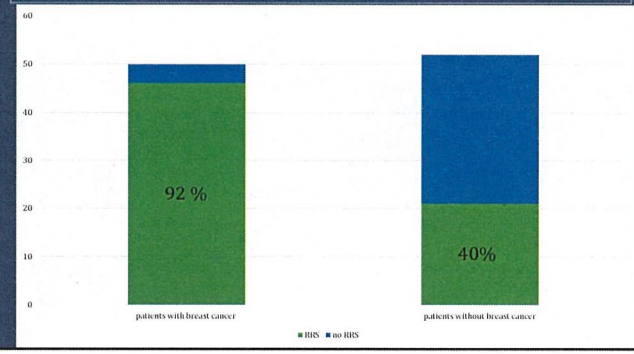
PATIENTS INCLUDED
year 2016

- 102 patients
- NO CANCER HISTORY (n= 52)
  OR
- BREAST CANCER AT ANY TIME (n=50)

- EXCLUDED 97 carriers
  - 26 male patients
  - 39 ovarian cancer patients
  - 7 Bilateral BC patients
  - 22 missing data!
  - 4 others

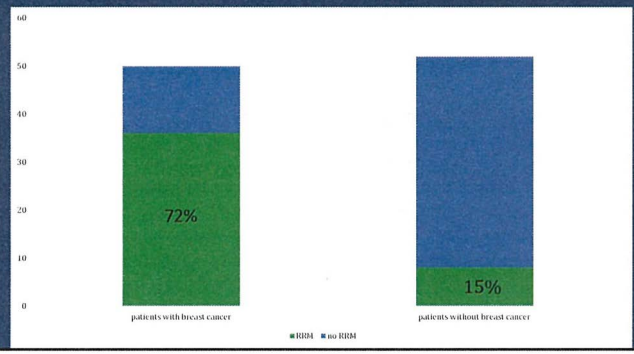
Risk reducing surgery of any type

	patients with breast cancer	patients without breast cancer
RRS	46	21
no RRS	4	31



RRM

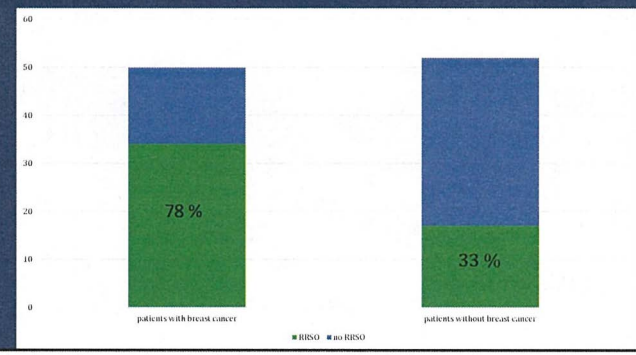
	patients with breast cancer	patients without breast cancer
RRM	36	8
no RRM	14	44



RROO

	patients with breast cancer	patients without breast cancer
RRSO	34	17
no RRSO	16	35

← 22/35 age > 40



Breast Reconstruction rate

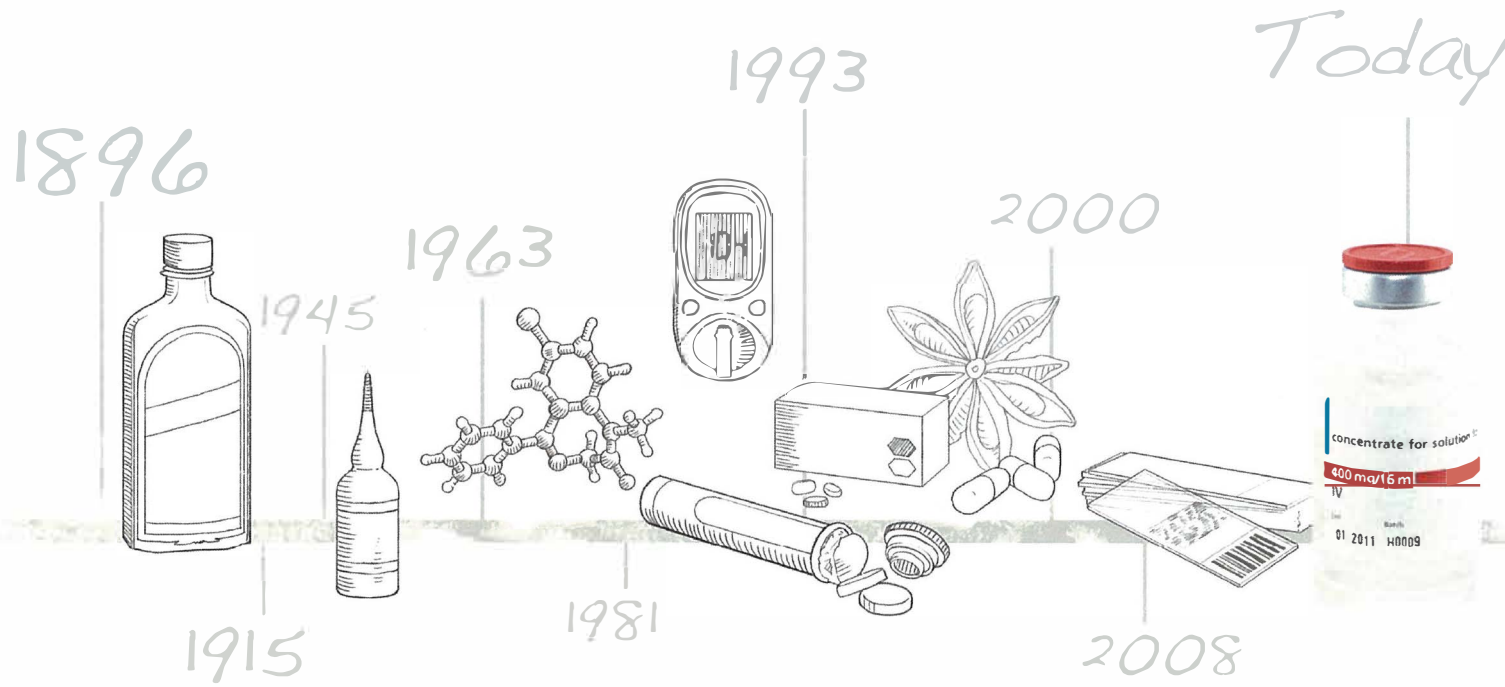
- Patients with BC
  - 33/36 92%
- Patients without BC
  - 8/52 15%

comparison

		until 2015		2016
any RRS	with BC	65%	with BC	92%
	without BC	40%	without BC	40%
RRM	with BC	50%	with BC	72%
	without BC	22%	without BC	15%
RROO	with BC	51%	with BC	78%
	without BC	37%	without BC	33%

conclusion

- Patients with a history of BC have a higher uptake of risk reducing surgeries compared to patients without cancer
- The overall risk reducing surgery uptake is becoming higher
- Patients at hereditary risk performing PM have a higher rate of immediate breast reconstruction compared to patients with sporadic BC



Za boljše življenje.
Že vse od 1896.

Tradicija napredka znanosti in medicine. Včeraj, danes in jutri.

Roche