

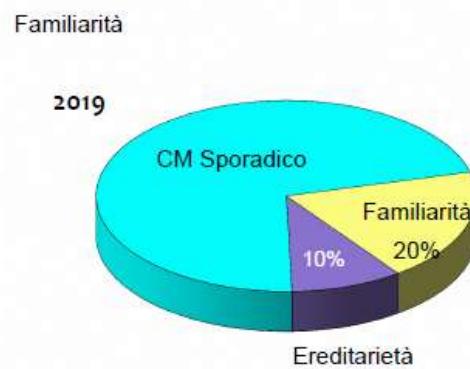
Rucaparib nelle pazienti con carcinoma mammario metastatico gBRCA wild type e HRD

Dott.ssa Elena Maccaroni, MD, PhD

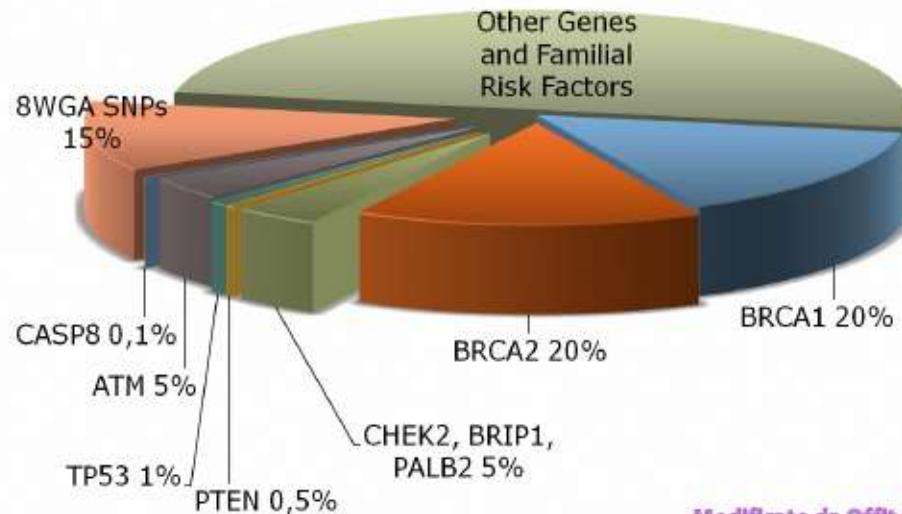
**Clinica Oncologica
AOU Ospedali Riuniti di Ancona**



Tumori eredo-familiari della mammella



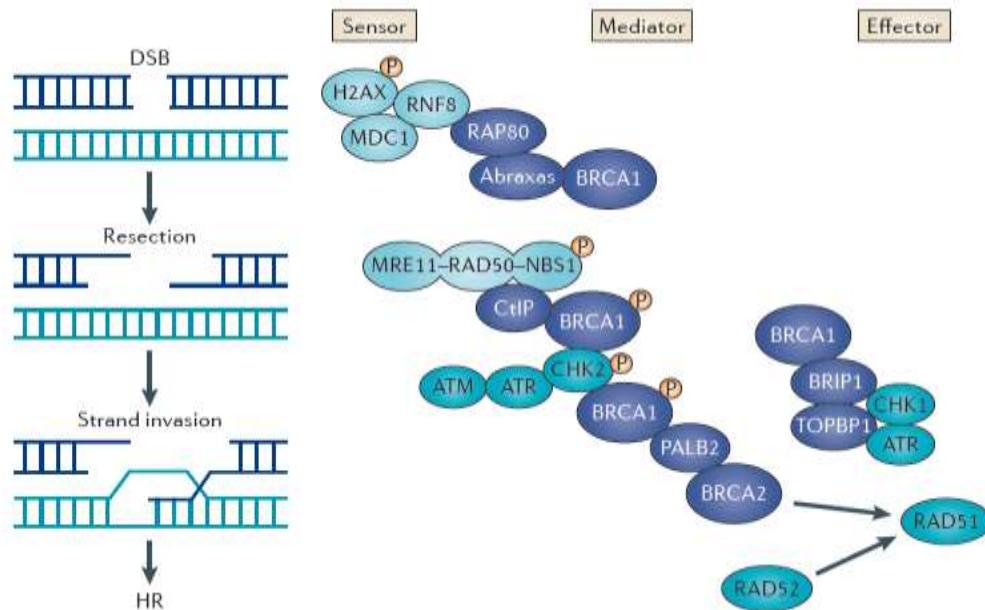
Geni predisponenti al CM



Modificato da Offit 2010

What is the function of BRCA 1 and BRCA 2 ?

- Tumor suppressor genes involved in DNA repair
- Autosomally transmitted (chromosomes 17 and 13)
- When mutated: higher incidence of hereditary breast and ovarian cancer (HBOC syndrome)

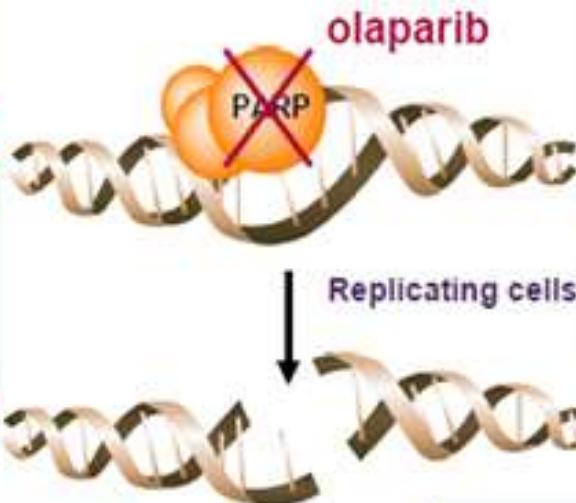


**HOMOLOGOUS
RECOMBINATION**

PARP-inibitori e letalità sintetica

10,000's DNA SSBs occur each day in cells

During replication unrepaired SSBs bound by PARP result in fork collapse and DNA DSBS



Olaparib traps PARP on the DNA single strand break preventing repair and effectively generating a protein-DNA adduct

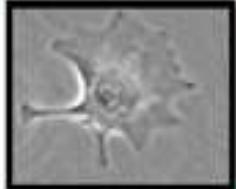
Combination with DNA damaging therapies (chemotherapy and IR)

Normal cell

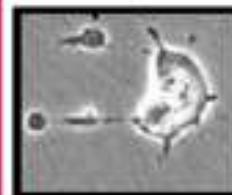
Cancer cell with HRD

Repair by Homologous Recombination

Survival



Tumour-specific killing by single agent
olaparib
(Synthetic Lethality)

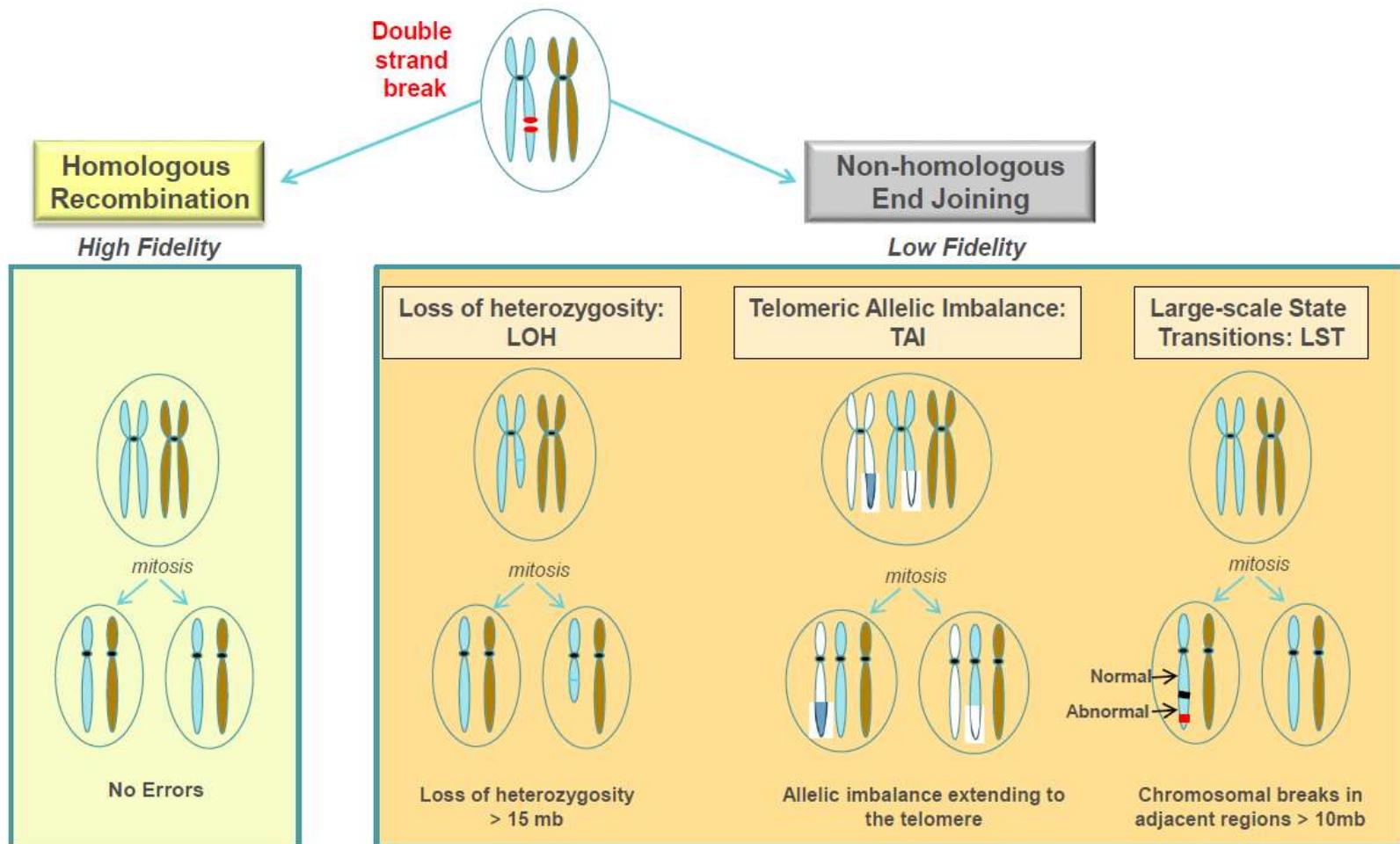


No effective repair (No HRR pathway)

Cell death

BRCA, HRD and LOH

Homologous recombination deficiency (HRD) –Dysregulation in the HR pathway (due to genetic mutations or alterations) leading to cellular genomic instability and an inability to efficiently repair damaged DNA. HRD positive cells may be more susceptible to the effects of DNA damaging agents, such as platinum agents or PARP inhibitors



BRCA, HRD and LOH

HRD can be tested using three main strategies

Germline mutation screening of HRD related genes

Somatic mutation screening of HRD related genes

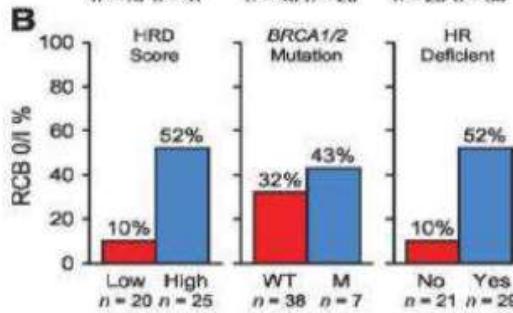
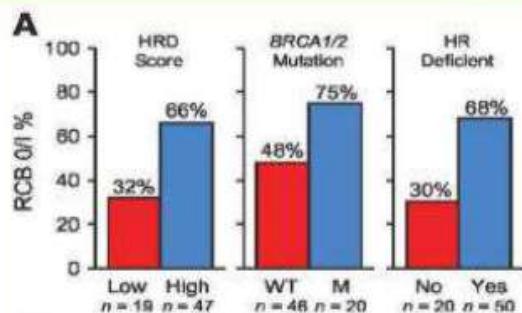
Evaluation of “genomic scar” (genomic instability secondary to HRD) in BRCAwt patients

- A high LOH (> 14-16%), suggests the presence HRD (ARIEL 2 – Rucaparib PSR)
- LOH can also be evaluated together with telomeric allelic imbalance and large-scale transitions to generate an HRD score (MyChoices HRD test, Myriad Genetics) >42 – benefit from maintenance niraparib in the NOVA trial.

Loss-of-function mutations involving other HR pathway genes

- hypermethylation of the BRCA1 promoter - EMSY amplification - ATM, ATR, BARD1, BRIP1, MRE11A, PALB2, RAD50, RAD51D, RAD54, NBS1, CHEK1, and CHEK2, components of the Fanconi anemia repair pathway

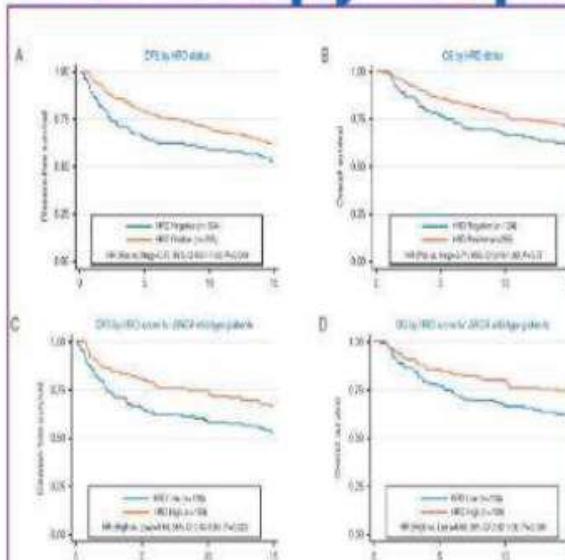
Homologous recombination deficiency in TNBC and chemotherapy response



Homologous Recombination Deficiency (HRD) Score Predicts Response to Platinum-Containing Neoadjuvant Chemotherapy in Patients with Triple-Negative Breast Cancer

Martinez-Losa¹, Kieran M¹, Immpink², Jia Li³, Sankar Marimuthu⁴, Gordon B. Mills⁵, Kristin C. Jensen⁶, Zohar Sandler⁷, William R. Berry⁸, Eric P. Winer⁹, Nadine H. Turner¹⁰, Steven J. Salomone¹¹, Pauline D. Ryan¹², April Givens-Cohen¹³, Alexander Gitter¹⁴, Zafra Sangher¹⁵, Olana Linn¹⁶, Chris Loeffl¹⁷, Victor Alvarez¹⁸, Joshua T. Jones¹⁹, Jerry S. Larsen²⁰, Anne-Marie Hartman²¹, Judy E. Barlow²², James M. Ford²³, Daniel P. Salomone²⁴, and Andrew E. Hickman²⁵

High HRD score associated with increased pathological response to neoadjuvant platinum-based therapy (single arm studies)



ANNALS
ONCOLOGY

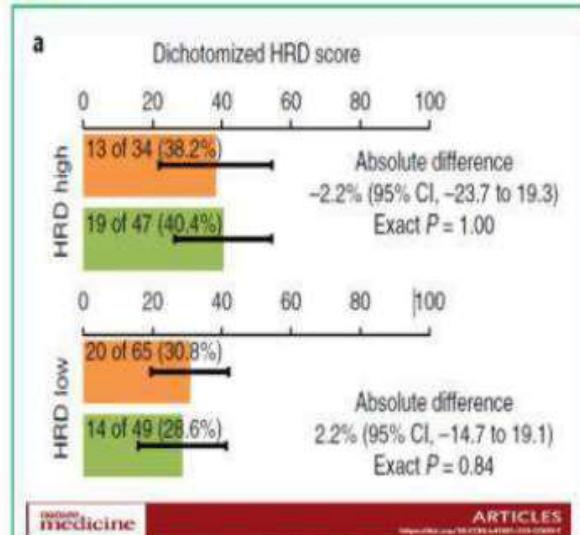
ORIGINAL ARTICLE

ESMO
European Society
for Medical Oncology

Impact of homologous recombination deficiency biomarkers on outcomes in patients with triple-negative breast cancer treated with adjuvant doxorubicin and cyclophosphamide (SWOG S9313)

P. Chansky¹, W.C. Bryant², A.E. Gotwin³, D. Petrelli⁴, K. Johnson⁵, D. Williams⁶, J.M. Jimmie⁷, A.R. Herman⁸, H.J. Weinstock⁹, H.M. Lindem¹⁰, C. Isopathy¹¹, J.A. Hornick¹², B.G. Hayes¹³

High HRD score associated with better DFS and OS in the presence of adjuvant AC



EMERGING
medicine

ARTICLES

Carboplatin in *BRCA1/2*-mutated and triple-negative breast cancer BRCAness subgroups: the TNT Trial

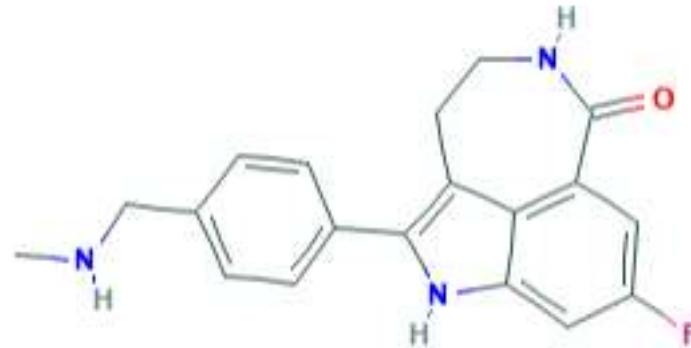
Andrew Salt^{1,2*}, Holly Sawyer³, Maggie Chou Li⁴, Shuang Karmegowda⁵, Lucy Kilmer⁶, Patricia Gourley⁷, Ann Smith⁸, Jerome Abramoff⁹, Sophie Bower¹⁰, Peter Boenigk-Lyon¹¹, Robert Broder¹², Stephen Chan¹³, Mitchell Dowsett¹⁴, James N Flanagan¹⁵, Lisa Fox¹⁶, Anita Grignani¹⁷, Alexander Grdinic¹⁸, Catherine Harper-Werner¹⁹, Matthew Q. Hatten²⁰, Katherine A. Headley²¹, Ruth Jackson²², Peter Jackson²³, Charles M. Pettay²⁴, Rebecca Rastan²⁵, Vassilis Skord²⁶, Adam Stann²⁷, Ian E. Smith²⁸, Kirsten M. Thomas²⁹, Andrew M. Wardley³⁰, Gregory Wilson³¹, Cheryl Gillett³², Jerry S. Larsen³³, Alan Schwartz³⁴, Suzanne Rahman^{35,36}, Mark Harris³⁷, Paul Ellis³⁸, Sarah E. Plender^{39,40} and Judith M. Blinn⁴¹

Metastatic TNBC – primary tumor high HRD score not associated with preferential benefit from carboplatin compared to docetaxel.

BRCA mutation status associated with benefit from carboplatin.

PARP-inhibitors under investigation in breast cancer

- **Olaparib**
- **Talazoparib**
- **Veliparib**
- **Niraparib**
- **Rucaparib**



Rucaparib structure

Rucaparib is an orally bioavailable tricyclic indole and inhibitor of poly(ADP-ribose) polymerases (PARPs) 1 (PARP1), 2 (PARP2) and 3 (PARP3), with potential chemo/radiosensitizing and antineoplastic activities. Upon administration, rucaparib selectively binds to PARP1, 2 and 3 and inhibits PARP-mediated DNA repair. This enhances the accumulation of DNA strand breaks, promotes genomic instability and induces cell cycle arrest and apoptosis. This may enhance the cytotoxicity of DNA-damaging agents and reverse tumor cell resistance to chemotherapy and radiation therapy

Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial

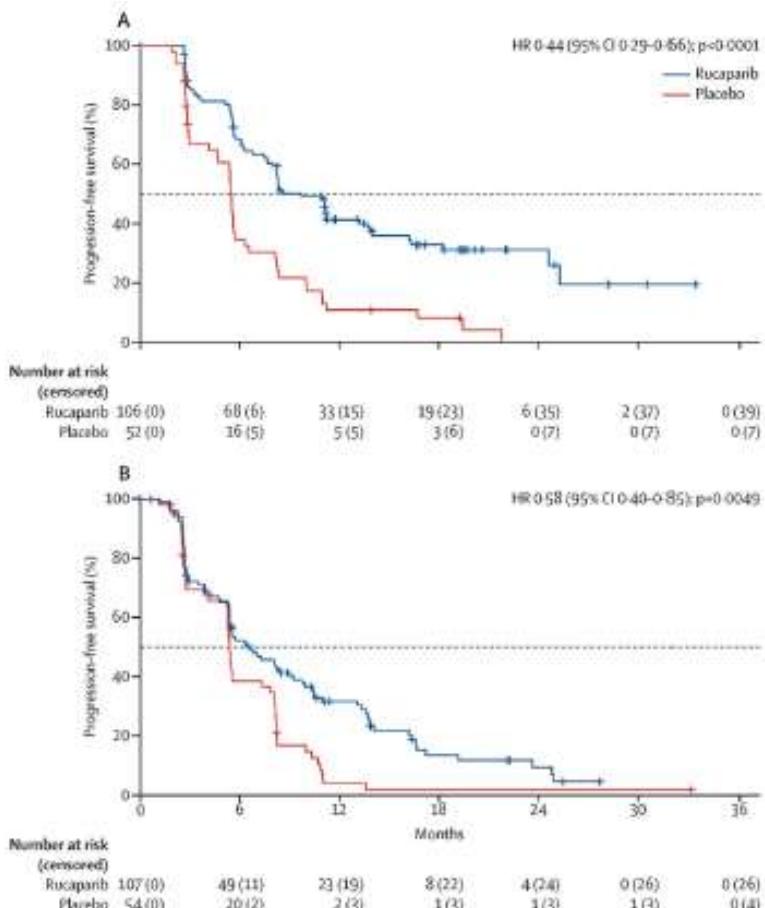
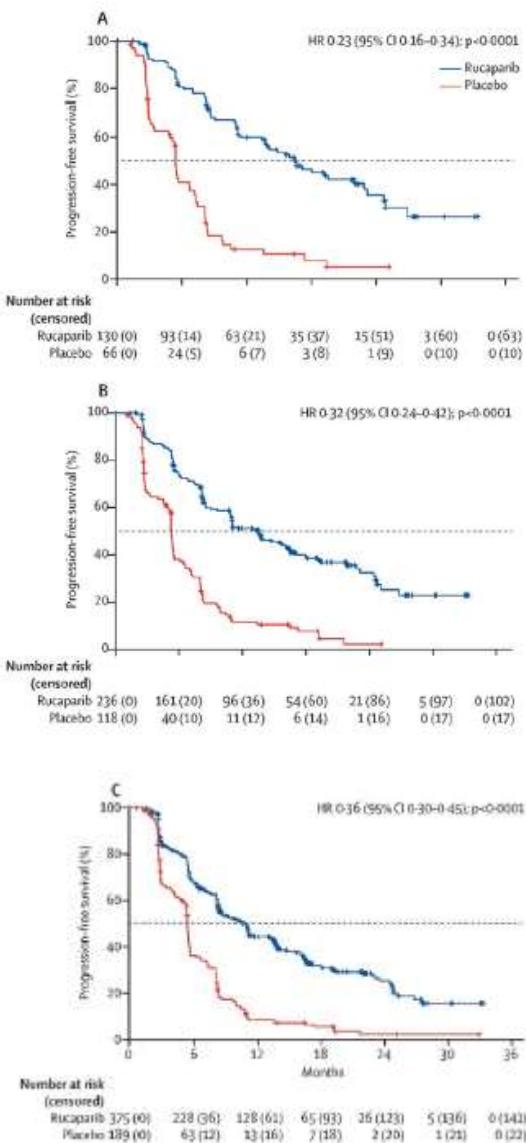


Figure 5.
Progression-free survival in patients with a BRCA wild-type carcinoma
Kaplan-Meier estimates of progression-free survival as assessed by the investigator for patients with a BRCA wild-type carcinoma with high (A) and low (B) loss of heterozygosity. HR=hazard ratio.

Phase III trials with PARP-Inhibitors in BRCAmut breast cancer pts

Table 1. PARP Inhibitors in Phase III Trials

Drug	Trial Identifier	Setting	Design	Population	Status
Olaparib	OlympiAD ²⁰ NCT02000622	Advanced/Metastatic	Olaparib vs PCT	Advanced/Metastatic gBRCA, ≤2 prior lines	Resulted
	OlympiA NCT02032823	Adjuvant	Olaparib vs placebo	Early-stage gBRCA, post completion SOC adjuvant therapy	Recruiting
Veliparib	BROCADE 3 NCT02163694	Advanced/Metastatic	C + P + veliparib vs C + P + placebo	Metastatic gBRCA, 0–2 lines of prior therapy	Recruiting
	BrighTNess ²⁹ NCT02032277	Neoadjuvant	C + P + veliparib → AC vs C + P + placebo → AC vs Placebo + placebo + P → AC	Neoadjuvant TNBC	Resulted
Talazoparib	EMBRACA ²³ NCT01945775	Advanced/Metastatic	Talazoparib vs PCT	Advanced/Metastatic gBRCA, ≤3 prior lines	Resulted
Niraparib	BRAVO NCT01905592	Advanced/Metastatic	Niraparib vs PCT	Advanced/Metastatic gBRCA, ≤2 prior lines	Not recruiting

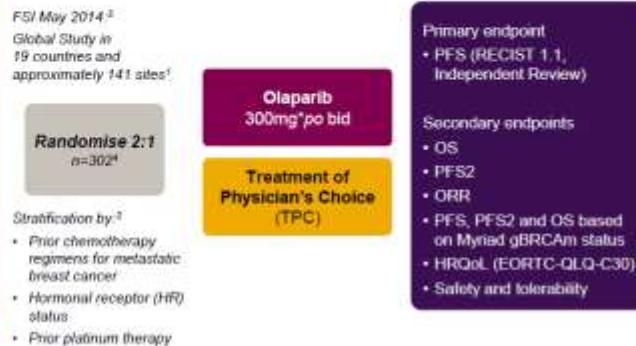
Abbreviations: AC, doxorubicin + cyclophosphamide; C, carboplatin; gBRCA, germline BRCA; P, paclitaxel; PCT, physician's choice chemotherapy; SOC, standard of care; TNBC, triple-negative breast cancer.

Olaparib e Talazoparib in metastatic BRCAmut breast cancer pts

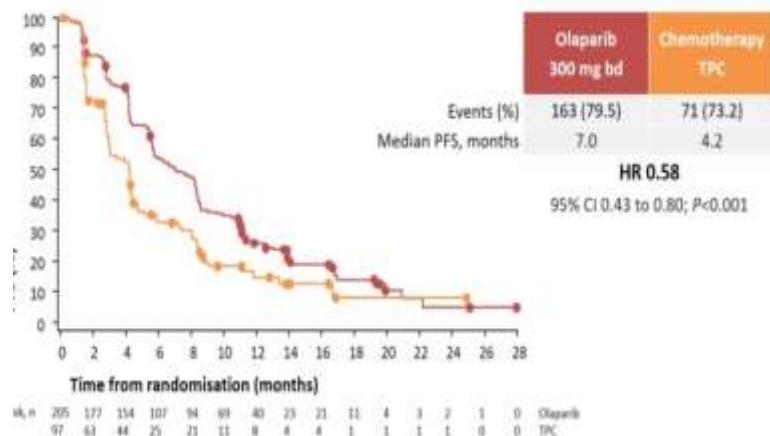
OlympiAD: Phase III study of olaparib vs. TPC in gBRCAm HER2- mBC¹

Study design

- gBRCAm mBC
- TNBC or HER2-negative, ER/PR positive
- ≤2 prior chemotherapy lines for mBC
- Previous treatment with anthracycline and taxane in either the (neo)adjuvant or metastatic setting
- Hormone receptor positive (HR+) disease progressed on ≥1 endocrine therapy, or not suitable
- If patients have received platinum therapy there should be:
 - No evidence of progression during treatment in the advanced setting
 - At least 12 months since (neo)adjuvant treatment and randomisation
- ECOG PS 0-1
- At least one lesion that can be assessed by RECIST v1.1

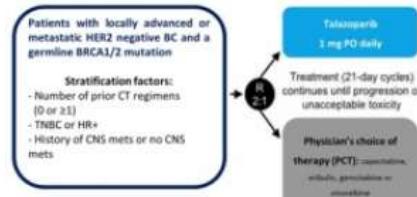


Primary endpoint: PFS by blinded independent review



Data adapted from Velasco et al. J Clin Oncol. 2017; 35(15):333-339.

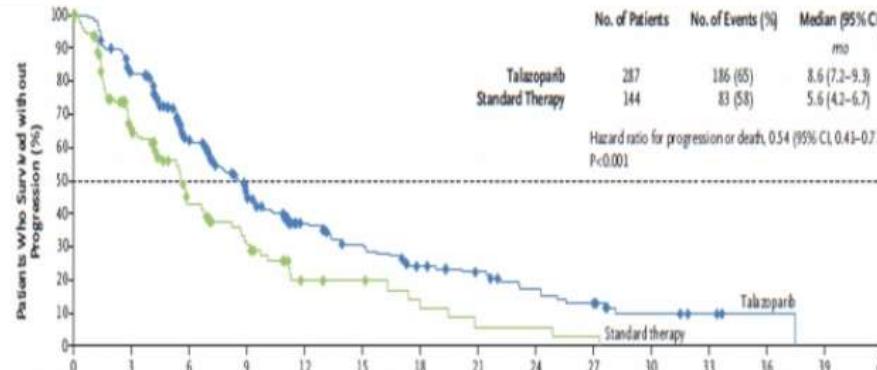
EMBRACA trial: Talazoparib vs TPC in MBC with gBRCAmut



ORR 62.6% (T) vs 27.2% (CT)
Median duration of response: 5.4 (T) and 3.1 (CT) months

	No. of Patients	No. of Events (%)	Median (95% CI)
Talazoparib	287	186 (65)	8.6 (7.2–9.3)
Standard Therapy	144	83 (58)	5.6 (4.2–6.7)

Hazard ratio for progression or death, 0.54 (95% CI 0.41–0.71)
P<0.001



Rucaparib: phase I trials

ClinicalTrials.gov Search Results 09/26/2019

	Title	Status	Study Results	Conditions	Interventions
1	A Study of Rucaparib Administered With Radiation in Patients With Triple Negative Breast Cancer With an Incomplete Response Following Chemotherapy	Recruiting	No Results Available	•Breast Cancer	•Drug: Rucaparib •Radiation: Radiotherapy
2	Window of Opportunity Trial, PARP Inhibitor Rucaparib Affect on PD-L1 Expression in Triple Negative Breast Tumors	Recruiting	No Results Available	•Breast Cancer	•Drug: Rucaparib
3	A Combination Study of Rucaparib and Atezolizumab in Participants With Advanced Gynecologic Cancers and Triple-Negative Breast Cancer	Active, not recruiting	No Results Available	•Gynecologic Neoplasms	•Drug: Atezolizumab •Drug: Rucaparib
4	A Study Evaluating the Safety, Pharmacokinetics and Efficacy of Ipatasertib Administered in Combination With Rucaparib in Participants With Advanced Breast, Ovarian Cancer, and Prostate Cancer	Recruiting	No Results Available	•Breast Cancer •Prostate Cancer •Ovarian Cancer	•Drug: Part 1, Dose Level 1 and Dose Level 2a: Ipatasertib •Drug: Part 1, Dose level 2b and dose level 3: Rucaparib •Drug: Part 1, Dose Level 1 and Dose Level 2b: Rucaparib •Drug: Part 1, Dose Level 2a and Dose Level 3: Rucaparib
5	A Study to Evaluate Rucaparib in Combination With Other Anticancer Agents in Patients With a Solid Tumor (SEASTAR)	Recruiting	No Results Available	•Ovarian Cancer •Triple-negative Breast Cancer •Urothelial Carcinoma •Solid Tumor	•Drug: Rucaparib •Drug: Lucitanib •Drug: Sacituzumab govitecan
6	Open-Label Safety and Tolerability Study of INCB057643 in Subjects With Advanced Malignancies	Terminated	No Results Available	•Solid Tumors	•Drug: INCB057643 •Drug: Gemcitabine •Drug: Paclitaxel •Drug: Rucaparib •Drug: Abiraterone •Drug: Ruxolitinib •Drug: Azacitidine

Rucaparib: phase II trials

ClinicalTrials.gov Search Results 09/26/2019

	Title	Status	Study Results	Conditions	Interventions
1	A Study to Assess the Efficacy of Rucaparib in Metastatic Breast Cancer Patients With a BRCAneSS Genomic Signature	Active, not recruiting	No Results Available	•Metastatic Breast Cancer	•Drug: rucaparib
2	PARP Inhibition for Triple Negative Breast Cancer (ER-/PR-/HER2-)With BRCA1/2 Mutations	Active, not recruiting	No Results Available	•Breast Cancer	•Drug: Cisplatin •Drug: Rucaparib
3	Rucaparib(CO-338;Formerly Called AG-014699 or PF-0136738) in Treating Patients With Locally Advanced or Metastatic Breast Cancer or Advanced Ovarian Cancer	Completed	No Results Available	•brca1 Mutation Carrier •brca2 Mutation Carrier •Breast Cancer •Ovarian Cancer	•Drug: rucaparib (CO-338; formerly AG-014699 or PF-0136738) •Genetic: protein expression analysis •Genetic: western blotting •Other: immunohistochemistry staining method •Other: liquid chromatography •Other: mass spectrometry •Other: pharmacological study
4	A Study to Evaluate Rucaparib in Combination With Other Anticancer Agents in Patients With a Solid Tumor (SEASTAR)	Recruiting	No Results Available	•Ovarian Cancer •Triple-negative Breast Cancer •Urothelial Carcinoma •Solid Tumor	•Drug: Rucaparib •Drug: Lucitanib •Drug: Sacituzumab govitecan
5	Open-Label Safety and Tolerability Study of INCB057643 in Subjects With Advanced Malignancies	Terminated	No Results Available	•Solid Tumors	•Drug: INCB057643 •Drug: Gemcitabine •Drug: Paclitaxel •Drug: Rucaparib •Drug: Abiraterone •Drug: Ruxolitinib •Drug: Azacitidine

Advanced Breast cancer

An open-label, phase II study of rucaparib, a PARP inhibitor, in HER2- metastatic breast cancer patients with high genomic loss of heterozygosity

A. Patsouris¹, O. Tredan², L.Campion¹, A. Gonçalves³, M. Arnedos⁴, MP. Sablin⁵, P. Jezequel¹, M. Jimenez⁶, V. Pezzella⁶, I. Bieche⁵, C. Callens⁵, A. Loehr⁷, D. Nenciu¹, C. Vicier³, F. André⁴

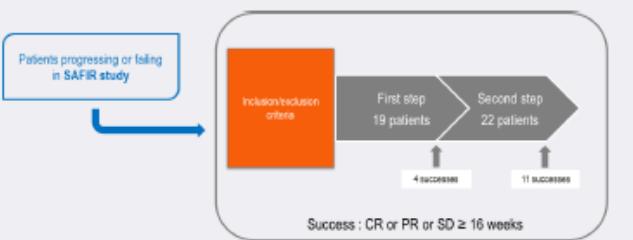
¹Institut de Cancérologie de l'Ouest, Angers/Nantes – France • ²Centre Léon Bérard, Lyon – France • ³Institut Paoli-Calmettes, Marseille – France • ⁴Gustave Roussy Cancer Campus, Villejuif – France • ⁵Institut Curie, Paris/Saint-Cloud – France • ⁶UNICANCER, Paris – France • ⁷CLOVIS ONCOLOGY, San-Francisco – USA

RUBY STUDY

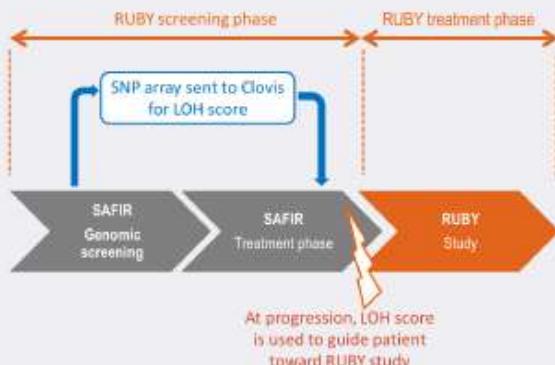
This single arm, open-label, multicenter phase II study (NCT02505048) is evaluating the efficacy and safety of rucaparib in patients (pts) with HER2- metastatic breast cancer associated with a high tumor genomic LOH and/ or somatic *BRCA* mutation (excluding germline mutation).

Study methods and design

- The primary endpoint is clinical benefit rate (CBR), defined by complete (CR) and partial response (PR) and stable disease (SD) ≥ 16 weeks. If CBR is significant, the objective response rate will be assessed according to a hierachic procedure.
- Secondary endpoints:
 - Progression Free Survival
 - Overall Survival
 - Safety
 - To evaluate the predictive value of high genomic LOH
 - To evaluate the prognostic value of high genomic LOH
- Targeted enrollment is 41 pts using a Simon two-stage design.



Study assessments and procedures



- The RUBY screening phase is covered by the SAFIR patient informed consent form.
- LOH is determined by Clovis Oncology on Affymetrix (CytoScan HD or OncoScan) array available from the SAFIR protocol.
- For patients to be eligible for RUBY, a prespecified cutoff of $\geq 18\%$ was used to define high genomic LOH based on platinum-based chemotherapy outcome data for both primary breast tumors in The Cancer Genome Atlas (TCGA) and metastatic breast tumors in the SAFIRO1 (NCT01414933) and SAFIRO2 (NCT02299999) studies (André et al, Lancet Oncol 2014).
- If LOH high, or somatic *BRCA* mutation, and baseline assessments fulfill inclusion criteria, patient can be included in RUBY.

**Primary end-point: clinical benefit rate
(CR+PR-SD) ≥ 16 Weeks**

Eligibility

INCLUSION CRITERIA:

- Women age ≥ 18 years
- Histologically proven breast cancer, Her2 negative
- WHO Performance Status 0/1
- At least one line of chemotherapy in the metastatic setting
- High genomic LOH as defined by the Clovis genomic signature or inactivating *BRCA1/2* somatic mutation (without known germline *BRCA* mutation)
- Measurable target lesion (RECIST criteria v1.1)

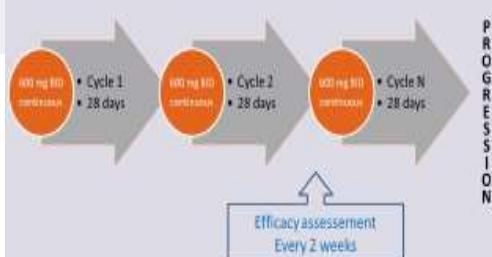
EXCLUSION CRITERIA:

- BRCA1* or *BRCA2* germline known mutation
- Life expectancy < 3 months
- Patients previously treated with a PARP inhibitor
- Toxicities of grade ≥ 2 from any previous anti-cancer therapy, with the exception of alopecia
- Altered haematopoietic, liver and renal function

Study progress

- Study initiated in August 2016
- To date
 - 582 SNP array data have been screened by Clovis Oncology
 - 19 pts have been enrolled in the 1st step and 7 pts in the 2nd step, with enrollment ongoing

TREATMENT SCHEME



Patients receive oral rucaparib 600mg BID continuously in 28-day cycles until disease progression.

RUBY: A phase II study testing rucaparib in germline (g) BRCA wild-type patients presenting metastatic breast cancer (mBC) with homologous recombination deficiency (HRD).

[Anne Patsouris](#), [Olivier Tredan](#), [Daniel Nenciu](#), [Alicia Tran-Dien](#), [Loic Campion](#), [Anthony Goncalves](#), [Monica Arnedos](#), [Marie-Paule Sablin](#), [Wilfried Gouraud](#), [Marta Jimenez](#), [Nathalie Droin](#), [Ivan Bieche](#), [Celine Callens](#), [Andrea Loehr](#), [Cecile Vicier](#), [Fabrice Andre](#)

Background: PARP-inhibitors improve PFS in mBC patients (pts) harboring a gBRCA mutation (mut). However, unlike ovarian cancer, there is no evidence until now that this class of agents has efficacy in gBRCA wild-type (WT) pts. In RUBY, we evaluated rucaparib in gBRCA WT mBC pts, and whose tumor present with HRD as assessed by genome-wide Loss of Heterozygosity (LOH) score. **Methods:** 713 gBRCA WT women with HER2- mBC, initiating a first metastatic chemo, were screened for high ($\geq 18\%$) genomic tumor LOH generated from a SNP array on metastatic sample. Eligible pts with a high LOH score or somatic (s)BRCA mut and ≥ 1 prior chemo regimen were proposed to enter RUBY and receive oral rucaparib 600 mg BID continuously in 28-day cycles until disease progression. The primary endpoint was clinical benefit rate (CBR), defined by complete (CR) and partial response (PR) or stable disease (SD) ≥ 16 weeks. We used a Simon's two-stage design ($p_0=20\%$; $p_1=40\%$), responses in $\geq 4/17$ pts were expected to move to second step, and $\geq 11/37$ pts to be considered of clinical interest ($\alpha=10\%$ and power of 90%). Whole genome sequencing (WGS) was performed retrospectively to further assess potential biomarkers of PARP inhibitor response.

Results: Tumors from 221 (31%) pts were LOH high. 41 pts were enrolled, including 4 pts with sBRCA mut. Median prior metastatic chemo lines was 2 (1-5), 17 pts had TNBC at diagnosis. As of 14 Jan 2019, 16 pts were alive, 5 are still on treatment. The median number of cycles was 2 (1 -20), and 37/40 patients were evaluable for CBR. 5 pts (13.5%) demonstrated clinical benefit (1 CR [LOH high], 3 PR [2 LOH high, 1 sBRCA2] and 1 SD>31 weeks [sBRCA1]). 19 pts had grade 3-4 toxicities. 3 pts discontinued due to toxicity. 4/5 responders pts had their tumor profiled by WGS: preliminary analyses showed that 4 pts presented high large scale state transitions, and 3 presented a somatic biallelic loss of function in HR-related genes. The fifth responder harbored a mut on gPALB2 and sBRCA2 at inclusion. **Conclusions:** In this study, rucaparib demonstrates antitumor activity in a subset of gBRCA WT mBC pts whose tumor has high LOH. Final analyses of WGS will provide insights about HRD signatures and drivers alterations associated with response.

Early Breast cancer

Abstract

1082

Cisplatin with or without rucaparib after preoperative chemotherapy in patients with triple-negative breast cancer (TNBC): Final efficacy results of Hoosier Cancer Research Network BRE09-146

Kathy D. Miller¹, Yan Tong¹, David R. Jones¹, Tom Walsh², Michael A. Danso³, Cynthia X. Ma⁴, Paula Silverman⁵, Mary-Claire King², Sunil S. Badve¹, and Susan M. Perkins¹



Indiana University Melvin and Bren Simon Cancer Center¹; University of Washington²; Virginia Oncology Associates/US Oncology³; Siteman Cancer Center, Washington University⁴; University Hospitals Ireland Cancer Center, Case Comprehensive Cancer Center⁵



BACKGROUND

Some pts with TNBC and/or BRCA mutations may be sensitive to DNA-damaging chemotherapy and/or PARP inhibition.^{1,2} Patients with TNBC who have substantial residual disease after neoadjuvant therapy have a high risk of recurrence but no standard systemic therapy has proven benefit.³ The post-neoadjuvant setting provides an excellent opportunity to study new therapies.

OBJECTIVES

Primary Objective - 2 year DFS
Secondary Objectives: safety, 1 year DFS, 3 year OS
Correlative Objectives= genomic predictors of outcome and toxicity

KEY ELIGIBILITY CRITERIA

Triple negative invasive breast cancer, stage I-III at diagnosis

- Local assessment of ER/PR/HER2 accepted for study entry
- Patients with ER+ and/or PR+ allowed ONLY if they are known carriers of a deleterious mutation in BRCA1 or BRCA2.

Completed neoadjuvant chemotherapy

- No prior cisplatin. Prior carboplatin allowed.
- Substantial residual disease at definitive resection
- Milner-Payne class 0-2⁴
- Residual Disease Burden (RCB) classification II or III⁵
- Residual lymph node (NL-N3) involvement
- Residual 2 cm invasive disease in the breast
- Radiation therapy completed if indicated.

Treatment Plan

Cisplatin 75 mg/m² D1 every 21 days

Rucaparib (combined therapy)

- Safety cohort 1 - 16 mg IV D1,2,3 cycle 1, escalate to 24 mg C2-4
- Safety cohort 2 - 24 mg IV D1,2,3 cycle 1, escalate to 30 mg C2-4
- RP2 - 24 mg IV D1,2,3 cycle 1, escalate to 30 mg C2-4

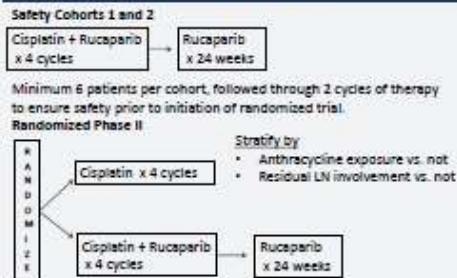
Rucaparib monotherapy

- 30 mg IV or 100 mg po weekly x 24 weeks

CLINICAL TRIALS.GOV IDENTIFIER

NCT01074970

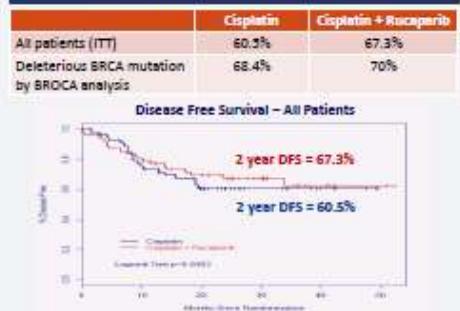
STUDY SCHEMA



TOXICITY (% patients)

NC-CTC Grade	Cisplatin			Cisplatin + Rucaparib		
	2	3	4	2	3	4
Neutropenia	25	17	0	21	25	2
Anemia	8	0	0	11	0	0
Platelets	3	0	0	0	3	0
Nausea	20	0	0	25	5	0
Anorexia	5	0	0	11	0	0
Fatigue	22	5	2	17	10	0
Tinnitus	25	2	0	19	2	0
Renal	2	0	0	3	0	0
Neuropathy	0	0	0	2	2	0

2 YEAR DISEASE FREE SURVIVAL



Exploratory analysis

2 year DFS	Cisplatin	Cisplatin + Rucaparib
Prior anthracycline	38.6%	73.3% (p=0.03)
Both treatment arms combined	2 year DFS in patients with mutation by BROCA = 63.7%	2 year DFS in patients without mutation by BROCA = 66.6%

CONCLUSION

The addition of low dose rucaparib did not impact the toxicity of cisplatin or improve 2-yr DFS.

- The dose of rucaparib used in this study was substantially less than the recommended monotherapy dose (600 mg orally twice daily) and may not have been sufficient to adequately inhibit PARP activity.

SUPPORT

Rucaparib provided and clinical trial supported by Pfizer and Clovis Oncology.
Correlative analyses (ongoing) supported by Susan G Komen for the Cure and the Breast Cancer Research Fund.

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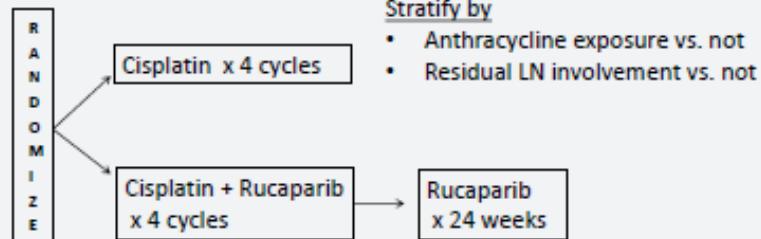
STUDY SCHEMA

Safety Cohorts 1 and 2



Minimum 6 patients per cohort, followed through 2 cycles of therapy to ensure safety prior to initiation of randomized trial.

Randomized Phase II



PATIENT CHARACTERISTICS

	Cisplatin (n = 65)	Cisplatin + Rucaparib (n = 63)
Median age	48 (27-69)	47 (21-75)
African American	20%	17.5%
Known germline BRCA1 or 2 mutation at entry	BRCA 1 – 1 BRCA 2 - 2	BRCA 1 – 1 BRCA 2 - 2
Deleterious BRCA mutation by BROCA analysis*	21.5%	12.7%
Neoadjuvant Chemo		
Anthracycline	66%	48%
Taxane	92%	89%
Carboplatin	0	9.5%
Radiation Therapy	88%	86%
Median residual tumor	1.9 cm (0-9)	1.9 cm (0-11.5)
Median residual LN+	1 (0-15)	1 (0-38)
Median Residual Cancer Burden	2.6 (0-5.0) (n=53)	2.7 (0-5.3) (n=59)

2 YEAR DISEASE FREE SURVIVAL

	Cisplatin	Cisplatin + Rucaparib
All patients (ITT)	60.5%	67.3%
Deleterious BRCA mutation by BROCA analysis	68.4%	70%



Exploratory analysis

2 year DFS	Cisplatin	Cisplatin + Rucaparib
Prior anthracycline	58.6%	73.3% (p=0.03)

Both treatment arms combined

2 year DFS in patients with mutation by BROCA = 63.7%

2 year DFS in patients without mutation by BROCA = 68.8%

CONCLUSION

The addition of low dose rucaparib did not impact the toxicity of cisplatin or improve 2-yr DFS.

- The dose of rucaparib used in this study was substantially less than the recommended monotherapy dose (600 mg orally twice daily) and may not have been sufficient to adequately inhibit PARP activity.

Conclusioni

Rucaparib è un PARP-inibitore che ha dimostrato efficacia nelle pazienti affette da carcinoma ovarico anche in assenza di mutazione BRCA ma con LOH

LOH utile marker per valutare HRD, indipendentemente dal meccanismo implicato (somatico vs germinale)

Nelle pazienti con carcinoma mammario avanzato g BRCA – WT dati ancora molto preliminari

In corso studi di fase I e fase II nelle pazienti con carcinoma mammario HRD