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Heterozygote Germline Mutations in Homologous Recombination Core Genes Can Predict for Pathologic Complete Response in Early Triple Negative Breast Cancer

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Abstract

Background: BSMO 2014-01 is a published prospective phase 2 study investigating neoadjuvant weekly paclitaxel and carboplatin, followed by epirubicin and cyclophosphamide in 63 patients with triple-negative breast cancer. Pathological complete response (pCR) was 54%. A secondary endpoint was to correlate pCR rate to the presence of germline pathogenic variants in DNA damage response (DDR) genes and in core genes involved in Homologous Recombination (HR).

Methods: Peripheral blood from 60 TNBC patients was collected for germline DNA analysis. Whole Exome Sequencing was performed; we considered only rare variants (minor allelic frequency < 0.01) in 276 DDR genes of which 88 HR and 21 HR core genes. The correlation between pCR rate and mutations in DDR or HR genes was analyzed using the Fisher's exact test. The same was done for the correlation between DDR gene mutations and the presence of hematologic toxicities.

Results: Thirty-five out of 60 patients (58.3%) carried a protein disrupting germline mutation in a DDR gene. Twenty-four of these 35 patients (68.6%) had a pCR, compared to 40% without a DDR mutation (p=0.026). In 14/15patients (93.3%) with a HR core gene mutation a pCR was obtained, while a pCR was present in 44.4% without a HR core gene mutation (p=0.0007**).** HR core gene mutations were detected in BRCA1 (5), BRCA2 (4), RAD52 (4), RAD50 (1), BARD1 (1) and EME1 (1).

Conclusions: This is the first study to demonstrate that germline pathogenic variants in genes involved in HR core genes predict for pCR after platinum-containing neoadjuvant chemotherapy.

Keywords: Breast Cancer; DNA damage

Introduction

Most TNBC are highly proliferative cancers that lack the expression of estrogen and progesterone receptors as well as amplification of the Her2 oncogene. [1]. Preoperative chemotherapy is the standard of care in TNBC because of the prognostic significance of the pathologic response on long-term outcome and the opportunity to tailor subsequent adjuvant therapy to the quality of the response obtained [3-5]. Several studies have indicated that patients with TNBC benefit from the addition of platinum to the neoadjuvant chemotherapy, however impact on survival is still uncertain [6-9]. Given the fact that platinum adds to the toxicity of the regimen, an important question

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is whether all TNBC do benefit to the same degree. Applying the HRDetect mutational-signature-based algorithm, fifty to sixty percent of TNBC harbour a HR repair deficiency explained by BRCA1/2 germline/somatic mutations or other genomic (germline and somatic) instabilities, which provides specific therapeutic opportunities for the use of DNA double-strand break-inducing agents, including platinum salts, anthracyclines, alkylating agents and poly-ADP-ribose polymerase (PARP) inhibitors [10]. Up to date,it is still debated whether patients with a homologous recombination deficient TNBC, more broadly defined than only BRCA1/2 mutations, benefit more than other TNBC patients from the addition of platinum. Some studies using an HRD-score, based on loss of heterozygosity, telomeric allelic imbalance and large-scale state transitions, support that this might be the case or at least that these patients respond better to neoadjuvant platinum combinations [11,12]. This hypothesis has not been investigated using germline mutation analysis of genes involved in DDR. By performing whole exome sequencing and investigating in more details the genes involved in the DDR machinery, we tried to identify genomic germline biomarkers allowing a better selection of the patients, who will benefit from therapies with DNA damaging agents such as platinum, in order to avoid useless toxicity.

Patient and Methods

Patient population

Between June 2015 and May 2016, 65 TNBC patients were included in a previously published phase II neoadjuvant BSMO 2014-01 study [13]. The prospective, multicenter phase II trial explored the efficacy of neoadjuvant dose-dense weekly paclitaxel and carboplatin, followed by biweekly epirubicin and cyclophosphamide. The primary objective was to determine the pCR rate. One of the preplanned secondary objectives was to examine the correlation between pCR and germline carrier status of mutations in DDR or HR genes. Patients older than 18 years and with operable stage II and III were included after signing an informed consent. Two patients were excluded from the analysis because they were not assessable for the primary endpoint (one received doxorubicin instead of epirubicin and one refused surgery). As reported in the publication of the clinical results, 20 extra patients were recruited and treated with the same regimen with the purpose to have 60 samples to do whole exome sequencing. Eleven patients (patient ID 0202; 0909; 0912; 1305; 1901; 1902; 2001; 2002; 2602; 2904; 3001) from the first publication did not consent for translational research and 8 consecutive patients(patient ID: 0107; 0913; 0205; 0206; 2104; 2105; 2610; 3004) from the extra pool agreed to participate to the genomic analysis. Triple negativity was defined as estrogen and progesterone receptor expression in less than 10% of tumor cells and no Her2 amplification as defined by Her2 IHC 0-1 or FISH ratio less than two (ASCO/CAP guideline recommendations for HER2 testing) [14].

Study procedures

All patients were treated for 12 weeks with weekly paclitaxel (wP) 80mg/m² concurrent with weekly carboplatin (Cp) at an area under the curve (AUC) dose of 2, followed by epirubicin 90mg/m² and cyclophosphamide 600mg/m² (EC) biweekly for four cycles with myeloid growth factor support on day 2. Response assessment was planned at 2 time points of the neoadjuvant systemic therapy. The extent of surgery and subsequent irradiation was performed according to the local guidelines of the participating centers and no further adjuvant chemotherapy was foreseen in the study, although this was at the discretion of the investigator. Subsequently, patients were prospectively followed for recurrence and survival status.

Pathological evaluation

Histopathologic evaluation of response after neoadjuvant chemotherapy was done in accordance to the Pinder tumour response system [15]. Pathologic response was determined locally without central pathologic review. All surgical pathology reports were centrally reviewed. pCR rate was defined as no remaining invasive cancer in the breast and resected axillary lymph nodes (ypT0/isypN0).

Germline BRCA1/2 testing

Germline testing for BRCA1/2 was performed in the individual institutions utilizing available validated gene panel tests, according national guidelines. Patients with a germline BRCA1/2 mutation or other breast cancer predisposition genes were counselled as per institutional guidelines and considering the gene risk profile and familial cancer phenotype.

Whole exome sequencing

Blood samples (EDTA) were obtained at diagnosis, before any treatment from 60 TNBC patients participating in the fore mentioned clinical study. DNA was extracted and sent to BGI (www.bgi.com) for genome sequencing. Whole exome sequencing (WES) was performed using the SureSelect Human All Exon V6 kit from Agilent for target enrichment. Paired-end sequencing was performed on an Illumina instrument. The lists of genomic variants (compared to the reference genome hg19) obtained for each patient were provided as Variant Call Format (VCF) files. Further filtering was performed to retain only variants strongly affecting protein structure (nonsense, frameshift and splice-site variants) and variants with a minor allele frequency (MAF) <0.01. To exclude false positives, variants occurring in 10% (or more) of the samples were also discarded. To categorize genes as participating in the DDR or HR pathway, we refer to a recent publication by Knijnenburg et al [16]. The publication qualifies 276 genes as belonging to the DDR pathway, of which 88 belongs to the HR pathway and 21 to

the HR core pathway. Data available in Table 6 All reported variants were manually reviewed and validated making use of the Integrative Genomic Viewer (IGV) from the Broad Institute [17]. All patients signed an informed consent allowing germline exome sequencing and the study was approved by the institutional ethics committee.

Statistical methods

The correlation between pCR rate and germline defects in genes involved in DDR or specifically in HR, was examined using the Fisher's exact test. All reported *P* values are from one sided tests for pCR correlation and two sided tests for correlation with hematologic toxicity. All analyses were performed using SPSS Statistics version 27.

Results

Patient characteristics

The demographics and clinicopathologic data of the sixty evaluable patients are shown in Table 1. Most of the patients were between 40 and 60 years old, with a median age of 55 (33-76yrs; SD: 11.7). Ninety percent of the patients had stage IIA or IIB disease, with a majority of T2 tumours and clinically node negative disease. Ninety seven percent of the patients were diagnosed with an invasive ductal carcinoma and in a large majority grade 3. One patient had a lobular carcinoma and one a mixed ductal and lobular carcinoma. Mastectomy was performed in 17 patients, breast conserving surgery in 43 and axillary dissection in 36 patients.

Table 1: Patient Characteristics (n=60)

Variable	.	Statistics N (%)
ClinicalCharacteristics		
Age yrs	Median	55 yrs
	Range	(33-76 yrs)
Histology	Invasiveductal carcinoma	58 (97%)
	Invasiveductal/lobular carcinoma	1 (1.5%)
	Lobular carcinoma	1 (1.5%)
Clinical stage	IIA	31 (51.7%)
	IIB	23(38.4%)
	IIIA	5 (8.4%)
	IIIC	1 (1.5%)
Tumourgrade	2	9 (15%)
	3	48 (80%)
	unknown	3 (5%)
ER and PR expression	0% and 0%	48 (80%)
	<10% and/or < 10%	12 (20%)
Breast surgery	Mastectomy	17 (28%)
	Breast conservingsurgery	43 (72%)
Axillarysurgery	Axillarydissection	36 (60%)
	Sentinel node sampling	23 (38.5%)
	Unknown	1 (1.5%)
Primaryendpoints		
ypT0/isypN0	Yes	32 (53%)
	No	28(47%)
ypT0/isypN0 in BRCAm patients	Yes	8 (89%)
	No	1 (11%)
Secondaryendpoints		
gBRCA1/2 mutation	Positive	9 (15%)
	Negative	51 (85%)
DDR gene mutation	Yes	35 (58%)
	No	25 (42%)
HR gene mutation	yes	19 (31.5%)
	No	41 (68.5%)
HRcore mutation	Yes	15 (25%)
	No	45 (75%)
ypT0/isypN0 in BRCAm patients		8 (89%)
ypT0/isypN0 in BRCAwt patients		26 (51%)
ypT0/isypN0 in DDRm patients		24 (68.5%)
ypT0/isypN0 in DDRwt patients		10 (40%)
ypT0/isypN0 in HRm patients		16 (84%)
ypT0/isypN0 in HRwt patients		18 (44%)
ypT0/isypN0 in HRcorem patients		14 (93%)
ypT0/isypN0 in HRcorewt patients		20 (44%)

Germline gene testing

Routine diagnostic germline gene panel testing was performed in an initial step and revealed a deleterious BRCA1/2 mutation in nine patients (15%). Subsequent whole exome sequencing (see Table 2 for an overview of the relevant data) could detect a germline DDR gene mutation in 35 (58%) of the 60 TNBC patients. In 19 of these 35 patients (31.5%) the mutated DDR gene was a HR gene. More specifically, fifteen of these 19 patients had a mutation in a HR core gene, including the nine patients with a BRCA1 or BRCA2 mutation and six patients with a deleterious mutation in the RAD50, RAD52, BARD1 or EME1 genes. One patient had a mutation

in two different HR core genes (RAD50 and RAD52). Four patients had a mutation in non-core HR genes: RECQL5, RECQL4 and EME2. Sixteen patients had germline DDR mutations not involving the HR machinery (eg in CHEK2). All pathogenic BRCA1 and BRCA2 mutations found during routine testing were also detected in the subsequent WES. No additional BRCA1/2 mutations were identified. Each of the nine BRCA1 or BRCA2 mutations was found only once, whereas two different RAD52 mutations were found each in two patients.

Table 2: List of the pathogenic variants identified in DDR genes of 60 TNBC patients

Patient ID	Gene 1 Gene2 Gene 3	Variant 1, Variant 2 and variant3	Gene Family*
101	none	none	none
102	RAD50	NM_005732.3:p.Ser451fs/ c.1353_1356delTAAG	HRcore
	RAD52	NM_001297419.1:p.Ser346*/ c.1037C>A	HRcore
103	BRCA2	NM_000059.3:p.Thr772fs/ c.2313_2314dupAA	HRcore
	NEIL1	NM_001256552.1:c.692+2T>C	DDR
104	none	none	none
105	BRCA2	NM_000059.3:p.Ala938fs/ c.2808_2811delACAA	HRcore
106	none	none	none
107	RECQL5	NM_004259.6:c.1812+2T>C	HR
201	none	none	none
204	BRCA1	NM_007300.3:p.Gln563*/ c.1687C>T	HRcore
205	BRCA1	NM_007300.3:p.Gln94*/ c.280C>T	HRcore
206	none	none	none
301	RAD52	NM_001297419.1:p.Tyr415*/ c.1245T>G	HRcore
302	ENDOV	NM_173627.4:c.364-2A>G	DDR
701	BRCA1	NM_007300.3:p.Val1734fs/ c.5200delG	HRcore
801	none	none	none
802	RECQL4	NM_004260.3:p.Gln864*/ c.2590C>T	HR
803	POLN	NM_181808.3:p.Lys132fs/ c.395delA	DDR
804	ERCC2	NM_000400.3:p.Arg450fs/ c.1347_1377+7del	DDR
805	none	none	none
901	RAD52	NM_001297419.1:p.Tyr415*/ c.1245T>G	HRcore
902	none	none	none
903	none	none	none
904	EXO5	NM_022774.1:p.Arg344fs/ c.1029_1030insG	DDR
	FANCL	NM_001114636.1:p.Thr372fs/ c.1111_1114dupATTA	DDR
905	none	none	none
906	none	none	none
907	CHEK2	NM_001005735.1:p.Thr410fs/ c.1229delC	DDR
910	none	none	none
911	RAD1	NM_002853.3:p.Arg109*/ c.325C>T	DDR
913	RAD52	NM_001297419.1:p.Ser346*/ c.1037C>A	HRcore
1201	MSH6	NM_000179.2:p.Lys1101fs/ c.3285_3300dup	DDR
1302	APLF	NM_173545.2:p.Arg510fs/ c.1528delA	DDR
1303	none	none	none
1307	none	none	none
1402	none	none	none
1501	FAAP100	NM_025161.5:p.Ala816fs/ c.2446_2462del	DDR
1901	none	none	none
1902	none	none	none
1903	BARD1	NM_000465.3:p.Arg406*/ c.1216C>T	HRcore
	PNKP	NM_007254.3:c.1029+2T>C	DDR
1905	none	none	none
1906	EME2	NM_001257370.1:p.Gln322*/ c.964C>T	HR
	ENDOV	NM_173627.4:c.364-2A>G	DDR
2101	APEX1	NM_001244249.1:p.Leu292fs/ c.872dupT	DDR
2102	none	none	none
2103	EXO5	NM_022774.1:p.Arg344fs/ c.1029_1030insG	DDR
2105	none	none	none
2401	BRCA1	NM_007300.3:p.Glu787fs/ c.2359dupG	HRcore
2402	EME1	NM_001166131.1:p.Arg504*/ c.1510C>T	HRcore
2601	ENDOV	NM_173627.4:c.364-2A>G	DDR
2603	none	none	none
2604	none	none	none
2605	BRCA2	NM_000059.3:p.Val464fs/ c.1389_1390delAG	HRcore
	EME2	NM_001257370.1:p.Gly55fs/ c.164delG	HR
	ALKBH3	NM_139178.3:p.Arg70*/ c.208C>T	DDR
2606	none	none	none
2607	NEIL1	NM_001256552.1:c.692+2T>C	DDR
	ENDOV	NM_173627.4:c.364-2A>G	DDR
2610	APLF	NM_173545.2:p.Arg510fs/ c.1528delA	DDR
2701	none	none	none

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2702	none	none	none
2703	BRCA2	NM_000059.3:p.Asn1784fs/ c.5351dupA	HRcore
2901	none	none	none
2902	EXO5	NM_022774.1:p.Arg344fs/ c.1029_1030insG	DDR
3001	none	none	none
3002	BRCA1	NM_007300.3:p.Arg1203*/ c.3607C>T	HRcore
3003	none	none	none
3004	EXO5	NM_022774.1:p.Arg344fs/ c.1029_1030insG	DDR

• (*) In this colomn, a gene assigned to the family "DDR" is a DDR gene not belonging to the subgroup of HR genes. Also, a gene assigned to the family "HR" is a HR gene not belonging to the subgroup of HR core genes.

Correlation between germline defects and pathologic complete response:

Association of DDR versus HR gene mutation and response to platinum-based chemotherapy

A pathologic complete remission was obtained in 68.5% of the DDR mutated patients compared to 40% in the non-DDR mutated population (p=0.026). When we restricted our analyses to the patients with a mutation in the HR genes, the pCR rates increased to 84% in comparison to 44% to the patients lacking a HR gene mutation (p = 0.003). When further considering only the HR core genes, a pCR was observed in 93% (14/15) of the patients and in 44% (20/45) of the patients without a HR core gene mutation (p = 0.0007). The only patient not presenting a pCR in this subgroup carried a BRCA1 mutation. For the patients with a DDR gene mutation not included in the HR core gene panel, the pCR dropped to 50% (10/20), which was much closer to what we found in patients without a DDR mutation (40%) as shown in Table 3 and Table 4.

This table provides in the first column, the number of TNBC patients for which a germline mutation was found respectively in a DDR gene, in a DDR minus HR core gene, without a DDR germline mutation, in a HR gene, a HR core gene or the BRCA 1/2 genes. In the five subsequent columns the number of patients presenting the characteristics specific for each of five different clinical parameters are indicated. Statistical correlations between mutation carriership and each of the five clinical parameters were investigated using Fisher's Exact tests.

Association of DDR versus HR gene mutation and hematologic toxicities.

DDR neither HR germline gene mutations did clearly predict for hematologic toxicities, such as febrile neutropenia G3 and G4 (p=0.78; p=1), neutropenia G3 and G4 (p=0.05; p=1), anemia G3 (p=1; p=0.76), trombopenia G3 and G4 (p = 0.73; p=0.26) as shown in Table 3 and Table 5. Since neutropenia G3 and G4 appeared to occur somewhat less frequently in patients without a DDR mutation (13/25) than in patients with such mutation (27/35; p=0.055, which is at limit of significance), we further compared patients without a DDR mutation to patients with a DDR mutation that did not benefit well from the therapy (excluding the patients with a HR core gene mutation). Patients with such a mutation suffered clearly more from neutropenia G3 and G4 (13/25) than patients without a DDR mutation (13/25; P=0.027, see Table 3).

Triple-negative breast cancer is generally more sensitive to neoadjuvant platinum-based chemotherapy than other subtypes of breast cancer [18]. Several reports indicated an increased effectiveness of preoperative platinum based systemic treatment in BRCA1/2 mutant and non-BRCA mutant HRD-positive breast cancer [11, 12, 18, 19]. In these studies, BRCA1/2 sequencing with or without an HRD-scoring was used [where the HRD score is the sum of three metrics of chromosomal level aberration: LOH (loss of heterozygosity), TAI (telomeric allelic imbalance) and LST (large-scale state transitions)]. It is so far unclear whether BRCA1/2 mutations or HRD as defined by an HRD score select for patients that benefit more from the addition of platinum. There are also no publications that examined the correlation of broad germline analysis of DDR or HR genes with response to neoadjuvant chemotherapy. In the current study we investigated to what extent a dose-dense platinum containing regimen was more efficacious in triple-negative breast cancer patients with or without a germline defect in the DNA repair machinery as defined from the sequencing of a panel of 276 DDR genes. Finding a predictive biomarker is essential as the inclusion of platinum significantly adds to the toxicity of the chemotherapy. On the other hand, striving for the highest efficacy is important as obtaining a pCR has crucial prognostic significance in terms of the risk of relapse and survival [4, 5]. We used whole-exome sequencing to maximize the discriminative power between cancer patients that have no DNA repair defect and those that do. Therefore, in this study the cohort without a germline DNA damage repair defect is less likely to be diluted by non-identified repair defects. For the design of the virtual DDR gene panel, we relied on a recent publication by Knijnenburg et al [16]. The proportion of TNBC patients with a germline HR defect as defined in our study is 31.5 %, (25% if considering only HR core genes). The proportion of patients with any DDR germline defect was 58%. This means that a large fraction of TNBC patients have a proven or probable genetic etiologic factor. We did find a high pCR rate in the overall population (53%) consistent with other studies. A higher pCR rate was observed in patients with a DDR gene germline defect (68.5%). This increased pCR rate was driven by the

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Table 3: Correlation between germline defects in DDR genes of 60 TNBC patients and 5 clinical parameters

Patients with a DDR mutation	**pCR**	**Febrile NP G3/G4**	**NP G3/G4**	**Anemia G3**	**Trombopenia G3/G4**
Yes 35	Yes 24	Yes 10	Yes 27	Yes 10	Yes 5
	No 11	No 25	No 8	No 25	No 30
No 25	Yes 10	Yes 8	Yes 13	Yes 7	Yes 5
	No 15	No 17	No 12	No 18	No 20
P (one sided)	0.026	0.717	0.04	0.598	0.826
P (two sided)	0.036	0.783	0.055	1	0.728
Patients with a DDR mutation but not a HR core mutation 20	Yes 10	Yes 5	Yes 17	Yes 4	Yes 1
	No 10	No 15	No 3	No 16	No 19
Patients without a DDR mutation	Yes 10	Yes 8	Yes 13	Yes 7	Yes 5
25	No 15	No 17	No 12	No 18	No 20
P (one sided)	0.356	0.8	0.02	0.833	0.978
P (two sided)	0.557	0.745	0.027	0.729	0.204
Patients with a HR mutation	**pCR**	**Febrile NP G3/G4**	**NP G3/G4**	**Anemia G3**	**Trombopenia G3/G4**
Yes 19	Yes 16	Yes 6	Yes 13	Yes 6	Yes 5
	No 3	No 13	No 6	No 13	No 14
No 41	Yes 18	Yes 12	Yes 27	Yes 11	Yes 5
	No 23	No 29	No 14	No 30	No 36
P (one sided)	0.003	0.542	0.544	0.465	0.16
P (two sided)	0.005	1	1	0.763	0.263
Patients with a HR core mutation	**pCR**	**Febrile NP G3G4**	**NP G3/G4**	**Anemia G3**	**Trombopenia G3/G4**
Yes 15	Yes 14	Yes 5	Yes 10	Yes 6	Yes 4
	No 1	No 10	No 5	No 9	No 11
No 45	Yes 20	Yes 13	Yes 30	Yes 11	Yes 6
	No 25	No 32	No 15	No 34	No 39
P (one sided)	7E-04	0.491	0.63	0.202	0.207
P (two sided)	8E-04	0.754	1	0.324	0.25
Patients with a BRCA mutation	**pCR**	**Febrile NP G3/G4**	**NP G3/G4**	**Anemia G3**	**Trombopenia G3/G4**
Yes 9	Yes 8	Yes 4	Yes 7	Yes 5	Yes 4
	No 1	No 5	No 2	No 4	No 5
No 51	Yes 26	Yes 14	Yes 31	Yes 12	Yes 6
	No 25	No 37	No 20	No 39	No 45
P (one sided)	0.035	0.257	0.281	0.063	0.034
P (two sided)	0.064	0.431	0.464	0.101	0.034

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Table 4: List of pathogenic variants in DDR genes of 60 TNBC patients and pathologic response.

Patient ID	Variant 1	Gene family*	Variant 2	Gene family*	Variant 3	Gene family*	Pathologic response
101	none		none		none		PR
102	RAD50 frameshift	HRcore	RAD52 Stop gain	HRcore	none		CR
103	BRCA2 frameshift	HRcore	NEIL1 splice	DDR	none		CR
104	none		none		none		CR
105	BRCA2 frameshift	HRcore	none		none		CR
106	none	none	none		none		No response
107	RECQL5 splice	HR	none		none		CR
201	none	none	none		none		No response
204	BRCA1 stop gain	HRcore	none		none		CR
205	BRCA1 stop gain	HRcore	none		none		CR
206	none	none	none		none		CR
301	none	none	none		none		CR
302	none	none	none		none		CR
701	BRCA1 frameshift	HRcore	none		none		CR
801	none	none	none		none		PR
802	RECQL4 stop gain	HR	none		none		CR
803	POLN frameshift	DDR	none		none		No response
804	ERCC2 frameshift	DDR	none		none		CR
805	none	none	none		none		CR
901	RAD52 stop gain	HRcore	none		none		CR
902	none	none	none		none		CR
903	none	none	none		none		No response
904	EXO5 frameshift	DDR	FANCL	DDR	none		CR
905	none	none	none		none		PR
906	none	none	none		none		PR
907	CHECK2 frameshift	DDR	none		none		PR
910	none	none	none		none		CR
911	RAD1 stop gain	DDR	none		none		PR
913	RAD52 stop gain	HRcore	none		none		CR
1201	MSH6 frameshift	DDR	none		none		CR
1302	APLF frameshift	DDR	none		none		CR
1303	none	none	none		none		PR
1307	none	none	none		none		PR
1402	none	none	none		none		PR
1501	FAAP100 frameshift	DDR	none		none		No response

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1903	BARD1 stop gain	HRcore	PNKP splice	DDR			CR
1905	none	none	none		none		PR
1906	EME2 stop gain	HR	ENDOV splice	DDR	none		PR
2101	APEX1 frameshift	DDR	none		none		PR
2102	none	none	none		none		CR
2103	EXO5 frameshift	DDR	none		none		No response
2104	RECQL5 splice	HR	none		none		PR
2105	none	none	none		none		CR
2401	BRCA1 frameshift	HRcore	none		none		CR
2402	EME1 stop gain	HRcore	none		none		CR
2601	ENDOV splice	DDR	none		none		CR
2603	none	none	none		none		No response
2604	none	none	none		none		PR
2605	BRCA2 frameshift	HRcore	EME2 frameshift	HR	ALKBH3 stop gain	DDR	CR
2606	none	none	none		none		PR
2607	NIEL1 DDR	none	ENDOV splice	DDR			No response
2610	APFL frameshift	DDR					PR
2701	none	none					CR
2702	none	none					PR
2703	BRCA2 frameshift	HRcore					CR
2901	none	none					CR
2902	EXO5 frameshift	DDR					CR
3002	BRCA1 stop gain	HRcore					PR
3003	none	none					CR
3004	EXO5 frameshift	DDR					CR

• (*) In these columns, a gene assigned to the family "DDR" is a DDR gene not belonging to the subgroup of HR genes. Also, a gene assigned to the family "HR" is a HR gene not belonging to the subgroup of HR core genes.

patients with HR gene mutations (pCR rate of 84%), and more specifically by the patients with HR core gene defects (pCR rate of 93%). The pCR rate observed in the patients without a HR core gene defect was 44,4% and within the range of pCR rates found when platinum is not included in the neoadjuvant chemotherapy [20]. DDR defects other than HRD have also been proposed to sensitize for DNA damaging chemotherapy including cisplatinum. Our study does not support this as the pCR rates observed in patients without a germline DDR mutation and patients with a DDR gene mutation not including a HR core gene mutation are in the same range: 10/25 (40%) versus 20/45 (44.4%) respectively. Therefore, a logical proposal would be to restrict the addition of platinum to TNBC patients having a germline HR core gene mutation. It is clear that the current prospective phase 2 study does not prove that platinum is needed to achieve this result, and it could be that these tumours are simply more chemo-responsive cancers. However, our results are in line with other studies that show a high pCR rate in patients with BRCAness, which was defined in different manners

Table 5: List of pathogenic variants and hematologic toxicities.

Patient ID	Variant 1 Variant2 Variant 3	Gene family*	Febrile neutropenia G3/G4	Neutro penia G3/G4	Anemia G3	Trombopenia G3/G4
101	none	none	1	1	0	1
102	RAD50	HRcore	0	1	0	0
103	BRCA2	HRcore	1	1	0	0
104	none	none	0	0	0	0
105	BRCA2	HRcore	0	1	1	0
106	none	none	1	1	0	1
107	RECQL5	HR	0	1	0	1
201	none	none	1	0	1	1
204	BRCA1	HRcore	1	0	0	1
205	BRCA1	HRcore	0	1	0	0
206	none	none	1	1	1	1
301	RAD52	HRcore	0	0	0	0
302	ENDOV	DDR	0	1	1	0
701	BRCA1	HRcore	1	0	1	1
801	none	none	0	1	0	0
802	RECQL4	HR	0	1	0	0
803	POLN	DDR	0	1	0	0
804	ERCC2	DDR	0	1	0	0
805	none	none	1	0	0	0
901	RAD52	HRcore	0	1	0	0
902	none	none	0	1	0	0
903	none	none	0	1	0	0
904	EXO5	DDRDDR	1	1	0	0
905	none	none	0	0	1	0
906	none	none	0	0	0	0
907	CHEK2	DDR	0	0	0	0
910	none	none	0	1	1	0
911	RAD1	DDR	0	1	0	0
913	RAD52	HRcore	1	0	1	0
1201	MSH6	DDR	1	0	1	0
1302	APLF	DDR	0	1	0	0
1303	none	none	0	1	0	0
1307	none	none	1	1	0	0
1402	none	none	0	1	0	0
1501	FAAP100	DDR	0	1	1	0
1903	BARD1	HRcore	0	1	0	0

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1905	none	none	1	0	1	0
1906	EME2	HR	1	1	0	0
2101	APEX1	DDR	1	1	0	0
2102	none	none	1	0	1	1
2103	EXO5	DDR	0	1	1	0
2104	RECQL5	HR	0	0	0	0
2105	none	none	0	0	0	0
2401	BRCA1 frameshift	HRcore	0	1	1	0
2402	EME1	HRcore	0	0	0	0
2601	ENDOV	DDR	0	1	0	0
2603	none	none	0	1	0	0
2604	none	none	0	0	0	0
2605	BRCA2	HRcore	1	1	1	1
2606	none	none	0	0	0	0
2607	NIEL1	DDR	0	1	0	0
2610	APFL	DDR	0	1	0	0
2701	none	none	0	0	0	0
2702	none	none	0	0	0	0
2703	BRCA2	HRcore	0	1	1	0
2901	none	none	0	1	0	0
2902	EXO5	DDR	0	1	0	0
3002	BRCA1	HRcore	0	1	0	1
3003	none	none	0	1	1	0
3004	EXO5	DDR	1	1	0	0

(*)In this colomn, a gene assigned to the family “DDR” is a DDR gene not belonging to the subgroup of HR genes. Also, a gene assigned to the family “HR” is a HR gene not belonging to the subgroup of HR core genes.

[11, 12]. The GEPARsixto trial showed a significant benefit only in HRD triple negative breast cancers, although the authors did not consider these data as definitive because of the cohort size and there was no cyclophophamide included [12]. Comprehensive gene sequencing of the germline as in this study might enrich the specific HRD population and the discriminative power of the studies. A recent meta-analysis of Chai Y et al found a significant higher efficacy of platinum-based regimens in BRCA-mutated TNBC compared to BRCA wild type patients (p =0.002) and the same was true for the HRD-positive versus HRD-negative tumors with a p < 0.001 [21]. Another meta-analysis comparing platinum-based versus platinum-free neoadjuvant chemotherapy in TNBC patients showed no significant increase in pCR rate with the addition of platinum in the BRCA-mutated patients. In this last study, the authors underlined that the number of included BRCA patients was too small to correctly evaluate the effect of platinum compounds in mutated versus non-mutated patients [22].These studies have less than optimal discriminative power as the non-BRCA1/2 mutant cohorts also include patients with other HRD defects. Also the predictive value of HRD remains controversial as in the TNT phase 3 clinical trial there was no correlation between carboplatin response and a high score in a Myriad HRD assay [23]. Moreover only a HRD score threshold of 42 had the potential to identify patients who might benefit from platinum based preoperative systemic therapy and the HRD status is more suitable for variation between the groups.

The ongoing PEARL phase 3 trial comparing anthracyclines followed by a taxane with anthracyclines followed by taxane plus carboplatin as neoadjuvant treatment in TNBC patients, stratified by BRCA 1/2 mutation status will be published in 2023, but this study will have the same limitation of incomplete HRD specification.

Table 6: List of 276 DDR genes, 88 HR genes and 21 HR core genes to be sequenced.

DDR (DNA damage repair)	HR (Homologous Recombination, pathway membership	HR (Homologous Recombination, core pathway membership
APLF	LIG1	MRE11A
APTX	MRE11A	NBN
ASCC3	NBN	RAD50
DNTT	PARG	TP53BP1
LIG1	PARP1	XRCC2
LIG3	PARPBP	XRCC3
LIG4	RAD50	BARD1
MRE11A	TP53BP1	BLM
NBN	XRCC2	BRCA1
NHEJ1	XRCC3	BRCA2
PARG	EXO1	BRIP1
PARP1	PCNA	EME1
PARP3	POLD1	GEN1
PARPBP	POLD2	MUS81
PNKP	POLD3	PALB2
POLB	POLD4	RAD51
POLL	RFC1	RAD52
POLM	RFC2	RBBP8
PRKDC	RFC3	SHFM1
RAD50	RFC4	SLX1A
RNF168	RFC5	TOP3A
RNF8	RPA1	
TP53BP1	RPA2	
XRCC1	RPA3	
XRCC2	RPA4	
XRCC3	BARD1	
XRCC4	BLM	
XRCC5	BRCA1	
XRCC6	BRCA2	
UBE2A	BRIP1	
EXO1	DMC1	
HMGB1	DNA2	
MLH1	EID3	
MLH3	EME1	
MSH2	EME2	
MSH3	ERCC1	
MSH6	FANCM	
PCNA	FEN1	
PMS1	GEN1	
PMS2	H2AFX	
POLD1	HELQ	
POLD2	HFM1	
POLD3	INO80	
POLD4	KAT5	
RFC1	MUS81	
RFC2	NFATC2IP	
RFC3	NSMCE1	
RFC4	NSMCE2	
RFC5	NSMCE3	
RPA1	NSMCE4A	
RPA2	PALB2	
RPA3	PARP2	
RPA4	PAXIP1	
ALKBH1	POLH	
ALKBH2	POLQ	
ALKBH3	PPP4C	
APEX1	PPP4R1	
APEX2	PPP4R2	
APITD1	PPP4R4	
ATM	RAD51	
ATR	RAD51B	
ATRIP	RAD51C	
ATRX	RAD51D	
BARD1	RAD52	
BLM	RAD54B	
BRCA1	RAD54L	
BRCA2	RBBP8	
BRE	RDM1	
BRIP1	RECQL	
CCNH	RECQL4	
CDK7	RECQL5	
CETN2	RMI1	
CHAF1A	RMI2	
CHEK1	RTEL1	
CHEK2	SHFM1	
CLK2	SLX1A	
CUL3	SLX1B	
CUL4A	SLX4	
CUL5	SMARCAD1	
DCLRE1A	SMC5	
DCLRE1B	SMC6	
DCLRE1C	SPO11	
DDB1	SWSAP1	
DDB2	TOP3A	
DMC1	TOP3B	
DNA2	UIMC1	
DUT	WRN	
EID3	ZSWIM7	

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EME1		
EME2		
ERCC1		
ERCC2		
ERCC3		
ERCC4		
ERCC5		
ERCC6		
ERCC8		
FAAP100		
FAAP24		
FAAP20		
FAM175A		
FAN1		
FANCA		
FANCB		
FANCC		
FANCD2		
FANCE		
FANCF		
FANCG		
FANCI		
FANCL		
FANCM		
FEN1		
GADD45A		
GADD45G		
GEN1		
GTF2H1		
GTF2H2		
GTF2H3		
GTF2H4		
GTF2H5		
H2AFX		
HELQ		
HES1		
HFM1		
HLTF		
HMGB2		
HUS1		
INO80		
KAT5		
MAD2L2		
MBD4		
MDC1		
MGMT		

MMS19		
MNAT1		
MPG		
MPLKIP		
MRPL40		
MUS81		
MUTYH		
NABP2		
NEIL1		
NEIL2		
NEIL3		
NFATC2IP		
NSMCE1		
NSMCE2		
NSMCE3		
NSMCE4A		
NTHL1		
NUDT1		
NUDT15		
NUDT18		
RRM1		
RRM2		
OGG1		
PALB2		
PARP2		
PARP4		
PAXIP1		
PER1		
POLA1		
POLE		
POLE2		
POLE3		
POLE4		
POLG		
POLH		
POLI		
POLK		
POLN		
POLQ		
PPP4C		
PPP4R1		
PPP4R2		
PPPR4		
PRPF19		
RAD1		
RAD17		

RAD18		
RAD23A		
RAD23B		
RAD51		
RAD51B		
RAD51C		
RAD51D		
RAD52		
RAD54B		
RAD54L		
RAD9A		
RBBP8		
RBX1		
RDM1		
RECQL		
RECQL4		
RECQL5		
REV1		
REV3L		
RIF1		
RMI1		
RMI2		
RNMT		
RRM2B		
RTEL1		
SETMAR		
SHFM1		
SHPRH		
SLX1A		
SLX1B		
SLX4		
SMARCAD1		
SMC5		
SMC6		
SMUG1		
SPO11		
STRA13		
SWSAP1		
TCEA1		
TCEB1		
TCEB2		
TCEB3		
TDG		
TDP1		
TELO2		
TOP3A		
TOP3B		
TOPBP1		

TP53		
TREX1		
TREX2		
TYMS		
UBE2B		
UBE2N		
UBE2T		
UBE2V2		
UIMC1		
UNG		
USP1		
UVSSA		
WDR48		
WRN		
XAB2		
XPA		
XPC		
ZSWIM7		
PTEN		
TDP2		
ENDOV		
SPRTN		
RNF4		
SMARCA4		
IDH1		
SOX4		
WEE1		
RAD9B		
AEN		
PLK3		
EXO5		
CDC5L		
BCAS2		
PLRG1		
YWHAB		
YWHAG		
YWHAE		
CDC25A		
CDC25B		
CDC25C		
BABAM1		
BRCC3		
TTK		
SMARCC1		
SWI5		
MORF4L1		
RNF169		
HERC2		

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Conclusion

The present study using a comprehensive germline DDR gene mutation analysis is hypothesis generating, and suggest that platinum addition in the neoadjuvant treatment of TNBC could be restricted to patients with a germline HR core gene mutation. However prospective phase 3 trials should include broad HR gene characterization beyond BRCA1/2 to confirm our finding. This study also indicated that a high proportion of TNBC has a possible genetic etiology. Finally, in accordance with these data, additional studies should be performed to investigate whether a clear correlation between germline mutation carriership in a HR core gene and a response to therapies targeting cells with double strand DNA break repair deficiency can also be found in other cancer types, such as prostate cancer.

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Compliance with ethical standards

Conflict of interest

All authors declare to have no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

References

1. Boyle P. Triple-negative breast cancer: epidemiological considerations and recommendations. Ann Oncol 23 (2012): 7-12
2. Burnstein HJ, Curigliano G, Loibl S, et al. Estimating the benefit of therapy for early-stage breast cancer: the St. Gallen International Consensus Guidelines for the primary therapy of early-stage breast cancer. Ann Oncol 30 (2019): 1541-1557
3. Cardoso F, Kyriakides S, Ohno S, et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 30 (2019): 1194-1220.
4. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and longterm clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 384 (2014): 1664-1672
5. Huang M, O'Shaughnessy J, Zhao J, et al. Association of pathological complete response with long-term survival outcomes in triple-negative breast cancer: a meta-analysis. Cancer Res 80 (2020): 5427-5434
6. Loibl S, o'Shaughnessy J, Untch M, et al. Addition of the PARP inhibitor veliparib plus carboplatin or carboplatin alone to standard neoadjuvant chemotherapy in triple-negative breast cancer (BrighTNess): a randomized, phase 3 trial. Lancet Oncol 19 (2018): 497-509
7. Sikov WM, Berry DA, Perou CM, et al. Impact of the addition of carboplatin and/or bevacizumab to neoadjuvant once-per-week paclitaxel followed by dose-dense doxorubicin and cyclophosphamide on pathologic complete response rates in stage II to III triple negative breast cancer. CALGB 40603 (Alliance). J Clin Oncol 33 (2015): 13-21
8. von Minckwitz G, Schneeweiss A, Loibl S, et al. Neoadjuvant carboplatin in patients with triple negative and Her2-positive early breast cancer (GeparSixto; GBG 66): A randomized phase 2 trial. Lancet Oncol 15 (2014): 747-756
9. Sharma P, Lopez-Tarruella S, Garcia-Saenz JA, et al. Pathological response and survival in triple-negative breast cancer following neoadjuvant carboplatin plus docetaxel. Clin Cancer Res 24 (2018): 5820-5829.
10. Staaf J, Glodzik D, Bosch A, et al. Whole-genome sequencing of triple-negative breast cancers in a population-based clinical study. Nature Medicine 25 (2019): 1526-1533.
11. Telli ML, Timms KM, Reid J, et al. Homologous recombination deficiency (HRD) score predicts response to platinum-containing neoadjuvant chemotherapy in patients with triple-negative breast cancer. Clin Cancer Res 22 (2016): 3764-3773.
12. Loibl S, Weber KE, Timms KM, et al. Survival analysis of carboplatin added to an anthracycline/taxane-based neoadjuvant chemotherapy and HRD score as predictor of response-final results GeparSixto. Ann Oncol 29 (2018): 2341-2347.
13. Fontaine C, Renard V, Van den Bulk H, et al. Weekly carboplatin plus neoadjuvant anthracycline-taxane-based regimen in early triple-negative breast cancer: a prospective phase II trial by the Breast Cancer Task Force

of the Belgian Society of Medical Oncology (BSMO). Breast Cancer ResTreat 3 (2019): 607-615.

14. Tchrakian N, Flanagan L, Harford J, et al. New ASCO/CAP guideline recommendations for Her2 testing increase the proportion of reflex in situ hybridization tests and of her2 positive breast cancers. Virchows 468 (2016): 207-211.

15. Pinder SE, Provenzano E, Earl H, et al. Laboratory handling and histology reporting of breast specimensfrom patients who received neoadjuvant chemotherapy. Histopathology 50 (2007): 409-417.

16. Knijnenburg TA, Wang L, Zimmerman MT, et al. Genomic and molecular landscape of DNA damage repair deficiency across the cancer genome atlas. Cell Rep 23 (2018): 239-254.

17. Peck B, Bland P, Mavrommati I, et al. 3D functional genomics screens identify CREBBP as a targetable driver in aggressive triple-negative breast cancer. Cancer Res 81 (2021): 847-859.

18. Von Minckwitz G, Fontanella C, et al. Selecting the neoadjuvant treatment by molecular subtype: How to maximize the benefit? The Breast 22 (2013): S149-S151.

19. Telli ML, Hellyer J, Audeh W, et al. Homologous recombination deficiency (HRD) status predicts response to standard neoadjuvant chemotherapy in patients with triple negative or BRCA 1/2 mutation-associated breast cancer. Breast Canc Res Treat 168 (2018): 625-630

20. Liedtke C, Mazouni C, Hess K, et al. Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. J Clin Oncol 26 (2008): 1275-1281.

21. Chai Y, Chen Y, Zhang D, et al. Homlogous recombination deficiency (HRD) and BRCA 1/2 gene mutation for predicting the effect of platinum-based neoadjuvant chemotherapy of early-stage triple-negative breast cancer (TNBC) : a systematic review and meta-analysis. J Pers Med 12 (2022): 1-13.

22. Poggio F, Bruzzone M, Ceppi M, et al. Platinum-based neoadjuvant chemotherapy in triple-negative breast cancer: a systemic review and meta-analysis. Ann Oncol 29 (2018): 1479-1508

23. Tutt A, Tovey H, Cheang M, et al. Carboplatin in BRCA 1/2-mutated and triple-negative breast cancer BRCAness subgroups: The TNT Trial. Nat Med 24 (2018): 628-637.

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