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

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A randomised phase III trial of carboplatin compared to docetaxel in BRCA1/2 mutated and pre-specified triple negative breast cancer subgroups: the TNT Trial - Supplementary Appendix

1. Trial governance and site information

TNT Trial Oversight Committees

Trial Management Group	Andrew Tutt, Alan Ashworth, Peter Barrett-Lee, Judith Bliss, Hannah Baber, Liz Bradford, Joseph Cope, Philip Debruyne, Helena Earl, Paul Ellis, Lisa Fox, Cheryl Gillett, Catherine Harper-Wynne, Mark Harries, Lindsay Johnson, Sarah Kernaghan, Lucy Kilburn, Alison Jones, Robert Leonard, Nicola Macfarlane, David Miles, Susan O'Reilly, Peter Parker, Max Parmar, Marylyn Pilkington, Sarah Pinder, Nazneen Rahman, Jorge Reis-Filho, Rebecca Roylance, Ashley Shaw, Ian Smith, Rose Thompson, Christy Toms, Andrew Wardley, Mark Verrill
Biological Sub-Committee	Andrew Tutt, Alan Ashworth, Judith Bliss, Robert Brown, Peter Campbell, Maggie Cheang, Ian Ellis, Lisa Fox, Cheryl Gillett, Anita Grigoriadis, Bryan Hennessy, Sarah Kernaghan, Lucy Kilburn, Peter Parker, Charles Perou, Sarah Pinder, Nazneen Rahman, Jorge Reis-Filho, Rebecca Roylance, Adam Shaw, Christy Toms, Malcolm Ward
Response Evaluation Committee	Jyoti Parikh, Hema Verma, Zaid Viney, Vicky Goh
Independent Data Monitoring Committee	Christopher J Poole, Jacques Bonnetterre, John Robertson, Walter Gregory, PierFranco Conte
ICR-CTSU Breast Systemic Therapies Trial Steering Committee	Richard Gray, Richard Sainsbury, Dion Morton, Gordon Rustin, David Dodwell

The trial was co-sponsored by The Institute of Cancer Research and Kings College London, approved by the East London and The City Main Research Ethics Committee and registered on appropriate trial data bases (ISRCTN97330959, NCT00532727, CRUK/07/012). The study was conducted according to the principles of GCP. The Institute of Cancer Research Clinical Trials & Statistics Unit (ICR-CTSU), London had responsibility for all aspects of trial management and statistical analysis. The Trial Management Group oversaw day-to-day trial conduct with strategic oversight provided by an Independent Trial Steering Committee.

Funding was provided by Cancer Research UK (Cancer Research UK grant number CRUK/07/012) and Breast Cancer Now (and their legacy charity Breakthrough Breast Cancer). Cancer Research UK and Breast Cancer Now had no role in trial design, data collection, data analysis, data interpretation, or writing of the report.

Funding was provided from Myriad Genetics, Inc., to cover costs of nucleic extraction from tumour blocks appropriate for Next Generation Sequencing. Myriad Genetics, Inc. validated germline *BRCA1* and *BRCA2* sequencing and generated tumour *BRCA1* and *BRCA2* sequence analysis but were not involved in analysis of interaction with outcome data. Myriad Genetics, Inc. were involved in reviewing the manuscript prior to submission. Prosigna reagent kits were provided by NanoString Technologies, Inc. NanoString Technologies, Inc. reviewed the manuscript prior to submission.

The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Full list of centres and Investigators

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Wishaw General Hospital, Wishaw	Jonathan Hicks
West Suffolk Hospital	Cathryn Woodward
Yeovil District Hospital	Geoffrey Sparrow

2. Eligibility criteria

Inclusion criteria

Either:

- Histologically confirmed ER-, PgR-, HER2- primary invasive breast cancer. Allred/quick score ≤ 3 or H score ≤ 10 or ER and PgR negative, if other cut-offs used (e.g., 1%, 5% or 10%). HER2 negative defined as immunohistochemistry scoring 0 or 1+ for HER2, or 2+ and non-amplified for HER2 gene by FISH or CISH.

or:

- PgR unknown but ER- and HER2-, and otherwise eligible.

or:

- Confirmed *BRCA1* or *BRCA2* mutation carrier, with any ER, PgR and HER2 status

plus:

- Measurable confirmed metastatic or recurrent locally advanced disease unsuitable for local therapy but suitable for taxane chemotherapy.
- Patients with stable, treated brain metastases will be eligible providing informed consent can be given and that other sites of measurable disease are present
- Patients with bone metastases currently receiving bisphosphonates for palliation will be eligible providing other sites of measurable disease are present
- ECOG Performance Status 0, 1 or 2
- Adequate haematology, biochemical indices (FBC, U & Es)
- LFTs = Normal bilirubin, AST and/or ALT $\leq 3 \times$ ULN if Alk Phos $> 5 \times$ ULN (or an isolated elevation AST/ALT of $\leq 5 \times$ ULN)
- Adequate renal function – Glomerular Filtration Rate (GFR) of > 25 mls per minute
- Written informed consent, able to comply with treatment and follow-up

Exclusion criteria

- Original primary tumour or subsequent relapse known to be positive for any of ER, PR, or HER2 receptors (defined above) unless patient is a known *BRCA1* or *BRCA2* mutation carrier
- Patients unfit for chemotherapy or those with neuropathy $>$ grade 1 (sensory or motor)
- Known allergy to platinum compounds or to mannitol
- Known sensitivity to taxanes
- Patients with inoperable locally advanced disease suitable for local radiotherapy or an anthracycline containing regimen.
- Previous chemotherapy for metastatic disease other than an anthracycline as in inclusion criteria above.
- Previous exposure to a taxane in adjuvant chemotherapy within 12 months of trial entry
- Previous treatment with a taxane for recurrent locally advanced disease which was not completely excised.
- Previous treatment with a platinum chemotherapy drug
- LFTs = Abnormal bilirubin ($>$ ULN) and/or AST and/or ALT $> 3 \times$ ULN with Alk Phos $> 5 \times$ ULN, or an isolated elevation AST/ALT of $> 5 \times$ ULN.
- Patients with a life expectancy of less than 3 months
- Previous malignancies other than adequately treated in situ carcinoma of the uterine cervix or basal or squamous cell carcinoma of the skin, unless there has been a disease-free interval of at least 10 years
- Previous or synchronous second breast cancer (unless also confirmed ER-, PgR-/unknown and HER2-)
- Patients with bone limited disease

- Other serious uncontrolled medical conditions or concurrent medical illness likely to compromise life expectancy and/or the completion of trial therapy
- Pregnant, lactating or potentially childbearing women not using adequate contraception.

3. Supplementary Methods

3.1. Randomisation and masking

ICR-CTSUs allocated patients to carboplatin or docetaxel (1:1 ratio) utilising a computerised minimisation algorithm with a random element. Balancing factors were centre, previous adjuvant taxane chemotherapy, presence of liver or lung metastasis, performance status (0/1 vs 2) and recurrent locally advanced vs metastatic carcinoma.

3.2. Treatment

Both chemotherapy treatments were open label, prescribed according to local practice and dispensed from hospital stock. Clinical, haematological and biochemical assessments and toxicity reporting followed each cycle. Prophylactic antibiotics and G-CSF could be given with carboplatin according to local protocol or for the persistence of neutropenic fever. At the trial's inception prophylactic G-CSF was optional for patients treated with docetaxel, becoming mandatory following an IDMC recommended protocol amendment (May 2011). Pre-treatment with dexamethasone (8mg po bd for at least two days) 24 hours prior to docetaxel infusion was also recommended. Anti-emetics were given as per local policy for the allocated treatment.

3.3. Statistical methods

Crossover treatment was evaluated in the patient population who received such treatment following a progression.

Relative dose intensity was defined as observed dose intensity divided by protocol planned dose intensity at each cycle. This was calculated for each cycle and averaged across cycles received for each patient.

The "as treated" population defined for safety analyses included all patients who received any trial treatment, comparing worst adverse event grade reported during trial treatment (Fisher's exact tests, $p < 0.01$ allowing adjustment for multiple testing). All pre-specified toxicities and any MedDRA coded event satisfying pre-defined criteria ($\geq 10\%$ incidence, $p < 0.01$ or $> 1\%$ incidence difference between treatment groups) are presented. Emerging safety and efficacy data were reviewed regularly in confidence by an Independent Data Monitoring Committee.

Where stated that models were adjusted for known prognostic factors, the following terms were included in the model: previous adjuvant taxane chemotherapy (yes/no); presence of liver or lung metastasis (yes/no); performance status (0-1/2); carcinoma type (recurrent locally advanced/metastatic); age group ($< 40/40-50/50-60/60+$); presence of visceral disease (yes/no) and time since diagnosis to randomisation (< 1 year/1-3 years/3-5 years/ > 5 years).

4. Translational analysis

4.1. Needle micro-dissection

Tumour sections were cut, placed on UV treated glass slides and dried at 36°C prior to micro-dissection. Using digital images, tumour cellularity was semi-quantitatively assessed for each sample, demonstrating that the surface area of tumour enriched region varied from ~ 4 to 400mm^2 in this study. The number of sections cut for each tumour sample was dependent on its tumour cellularity. On average 5 sections of $10\mu\text{m}$ thickness were used for RNA and DNA dual extraction.

H&E stained sections were scanned using the Nanozoomer 2.0 HT scanner (Hamamatsu, Japan) resulting in digital images with a spatial resolution of $0.45\mu\text{m}/\text{pixel}$. In addition, sections were examined under the stereomicroscope and tumour regions were micro-dissected from the surrounding non-tumour tissue components by using a sterile needle or scalpel, and immediately placed in a pre-labelled 2ml Eppendorf tube with $500\mu\text{l}$ of heptane. In this procedure, malignant tissue was not identified through staining, instead a single H&E section with marked regions of interest were used as guides.

4.2. DNA/RNA extraction

We used the TCGA protocol¹ in which the QIAamp DNA FFPE Tissue Kit (Qiagen, Cat# 56404) was used for DNA purification, and the High Pure miRNA Isolation Kit (Roche, Cat# 05080576001) extracted total RNA. Both procedures were performed according to their manufacturer's protocols. An initial preparation procedure step was performed, including a Heptane based deparaffinization and de-cross-linking specific to FFPE-derived tissues. Quality of extracted DNA was assessed with the Qubit dsDNA BR Assay Kit (Life Technologies, Cat# Q32850), while Bioanalyzer 6000 RNA Nano Kit (Agilent Technology, Cat# 5067-1511) was used to estimate RNA concentration and integrity.

4.3. Tumour BRCA1 and BRCA2 mutation analysis (Myriad)

Genomic DNA from blood white cell preparations and tumour DNA extracted as described in 4.2 was subjected to Illumina next-generation sequencing. Sequence reads generated on the HiSeq2500 were trimmed at both the start and end to remove low quality bases that could generate spurious variant calls as described previously². Sequence trimming was largely performed according to the BWA program's trimming algorithm^{3,4}. For more detail see <http://solexaqa.sourceforge.net/>. Phred value 20 was used as a threshold for trimming at the start of sequences and 30 for trimming at the end. These thresholds were derived empirically. A higher threshold was used at the end of sequences as it was expected that the sequence quality would deteriorate towards the end of a read. Variant and LR classification methods were the same for both germline and somatic mutations. Classification was performed as per previously specified criteria⁵.

For each read an in-house implementation of the Burrow Wheeler Transform algorithm³ was executed which performed a search of all exons in the Myriad database to determine the matching exon for each read.

To call variants each read was aligned with the expected wildtype sequence of the exon. This alignment was a pairwise alignment performed by JAligner (<http://jaligner.sourceforge.net/>). Any differences represent variants. Variant calls from all reads for a sample were compiled in order to calculate the frequencies of all identified variants. Variant and LR classification methods were the same for both germline and somatic mutations. Classification was performed as per previously specified criteria⁵.

4.3.1 Large rearrangement detection

For large rearrangement detection the number of reads N that mapped back to each base was normalized (N_{norm}) using the total number of mapped back reads across all genes and SNP locations. A median normalized read count value N_{med} in a large set of samples was determined for each base. Centered normalized read counts, defined as $N_{cent} = N_{norm} / N_{med}$, were reviewed to detect large rearrangements encompassing one or more exons. The CV of centered normalized read counts for the exon 11 (largest exon) of both *BRCA1* and *BRCA2* was determined. If CV was below 0.09, all detected rearrangements were called. If the CV was between 0.09-0.12, only rearrangement encompassing two or more exons were called. If the value exceeded 0.12 the sample was rejected as not being able to call.

4.4. BRCA1 Next Generation Sequencing Promoter Methylation Assay (Myriad and Imperial College of London)

BRCA1 methylation analysis was performed by bisulfite sequencing, using a 2-step amplicon based approach. DNA was isolated from source material and approximately 100ng (50 – 300 ng) was subjected to bisulfite conversion. Conversion was accomplished using the EpiTect Bisulfite kit according to the manufacturer's instructions (EpiTect Plus Bisulfite conversion handbook September 2010). PCR primers specific for bisulfite converted DNA were designed to the promoter region in exon 1A of the 5' untranslated region of the *BRCA1* gene, 5'-TGAGAGGTTGTTGTTTAG-3' and 5'-CTAAAAAACCCACACCTATC-3'. Converted DNA and *BRCA1* primers were combined, annealed at 60°C and amplified (step1. 96°C 2:30, step2. 96°C 0:30, step3. 62°C 0:30, step4. 72°C 1:00, go to step 2 34X, step5. 72°C 5:00). Following amplification 2ul of PCR product was used as template in a secondary reaction using Fluidigm access array index primers (1-96); template and primers were annealed at 60°C and amplified (step1. 96°C 2:00, step2. 96°C 0:30, step3. 60°C 0:30, step4. 72°C 1:00, go to step 2 32X, step5. 72°C 5:00). Following the secondary PCR, amplified product was size fractionated using a Pippin Prep (Sage Science) to isolate product between 250bp and 300bp in length. The purified reaction product was sequenced using a MiSeq sequencer (Illumina).

Each read was aligned to the *BRCA1* promoter amplicon using JAligner which generated a pairwise alignment. The called base at each of the ten CpG sites is then inspected. To be considered a valid read, the read must have had either a "C" or "T" nucleotide at all ten CpG sites. If it did not, then the read was excluded. For valid reads, the number of CpG site bases with a "C" nucleotide was counted. This represented the number of CpG sites that were methylated. Reads that had either zero or one methylated CpG sites were considered to be not methylated.

Reads that had either nine or ten methylated CpG sites were considered to be methylated. All other reads were ignored because their methylation status was ambiguous. A methylation score (%) for the sample was then computed as the proportion of methylated reads relative to the total number of reads that were either methylated or not methylated.

4.4.1. Quality control

Imperial College London obtained bisulfite-sequencing data for 342 DNA samples (including primary, positive lymph node and recurrent tissues). The sequence data corresponded to a 143bp amplicon covering the *BRCA1* promoter (chr17:41277339-41277481 [hg19]) and contained 11 CG dinucleotides where DNA methylation could potentially occur (Figure S8). Cytosines occurring in a non-CG context are rarely (if ever) methylated in somatic tissues, and therefore read as thymine following bisulfite conversion and amplification. Conversion of cytosines to thymine at non-CpG sites therefore served as an important control for successful bisulphite conversion of samples, as incomplete conversion would give false positive results.

For each sample, each nucleotide position of the 143bp amplicon was broken down into the percentage of reads that call each of the four nucleotide options; the sum of percentages at each nucleotide position for each sample would therefore always be 100%. Due to an Illumina sequencing artefact that affected the first base of the amplicon, we ignored nucleotide 1 in all analyses. The net effect was a 142x1368 data matrix.

Before analysing the bisulfite-sequencing data it was important to identify potential sources of error, which could later impact the quality and outcomes of the data analysis. To this end, we used three quality control tests that identify 12 samples (3.5%) for removal.

i) Samples with missing sequence data

The aim here was to identify samples for exclusion based on missing sequence data. Although most data points within the data matrix were expressed as a percentage, there were 17 nucleotides affecting 3 samples that were denoted 'Insufficient'. This resulted in no base being called at these positions in affected samples and thus excluded from analysis of *BRCA1* methylation status.

ii) Imperfect base-calling when compared to the *in silico* converted reference DNA sequence

The aim here was to identify samples for exclusion that showed mismatches in the sequence between what was observed and what was expected. Because sodium bisulfite treatment rapidly converts unmethylated cytosine to thymine, but effectively leaves methylated cytosines unchanged, it was important to gauge sequencing accuracy by comparing the sequencing data obtained to an *in silico* converted reference sequence. Moreover, because DNA methylation is heterogeneous – particularly in cancer phenotypes – it was important to remove Cs in CG dinucleotides from the *in silico* converted reference sequence to avoid confusing partially methylated bases being incorrectly called.

After removing the 11 Cs in CG dinucleotides, we compared sequences pertaining to a 131bp amplicon, and identified 6 samples showing at least one mismatch (3 of these samples were already identified for removal in the previous analysis).

iii) Failed bisulfite conversion

The aim of this test was to identify samples that showed incomplete or low bisulfite conversion efficiency, as failing to do so could have potentially inflated the estimate of DNA methylation across affected CG nucleotides. To estimate bisulfite conversion efficiency, we examined the percentage of reads that call C's at non-CG dinucleotides, which in somatic tissues is extremely rare (unmethylated cytosine reads as thymine following bisulfite conversion). Since A's and G's should not be called at positions where C occurs in the reference sequence, we could use their percentages to crudely estimate sequencing error. Bisulfite conversion at each of the 21 non-CG dinucleotides was calculated as: $1 - \max(0, \%C - \{\%A + \%G\})$. We then took the mean percentage over the 21 non-CG dinucleotides to index bisulfite conversion efficiency. Samples showing <95% were deemed to exhibit low bisulfite conversion efficiency; 11 samples met this criterion and were removed from subsequent analysis; 5 of these samples were identified in the two previous analyses.

Summary

Together, these three tests identified 12 samples (3.5%) from the cohort of 342 samples that were excluded from subsequent analysis.

4.5 Definition of *BRCA1* mRNA-Low

We defined *BRCA1* mRNA-Low status by quantifying the expression of *BRCA1* mRNA using total-RNA sequencing data from primary tumour specimens (described in detail below). The cut-point to define *BRCA1* mRNA-Low status was determined using Cutoff Finder software⁶, applying an expectation–maximization algorithm to create a fixed mixture model of two Gaussian distributions fitted to the histogram of *BRCA1* mRNA expression data generated from total RNA-sequencing (as described in detail below). An optimal cut-off is determined as the value where the probability density functions of the mixing distribution coincide.

4.6 Total RNA-sequencing (University of North Carolina at Chapel Hill)

300-1000ng of RNA, extracted from needle micro-dissected archived primary tumour as described above, was used as the input for the Illumina TruSeq Total RNA Sample Preparation Kit with Ribo-Zero Gold (RS-122-2301 or RS-122-2302). Libraries were prepared according to manufacturer's instructions. In general we submitted libraries with concentrations greater than 5 ng/ul but samples with concentrations as low as 3 ng/ul were submitted for sequencing for samples when there was limited quantity of RNA. Libraries were sequenced two per lane on an Illumina HiSeq2000 machine with a 48x7x48 sequence configuration. All samples were processed as described in The Cancer Genome Atlas¹. Bases and QC assessment of sequencing were generated by CASAVA 1.8. QC-passed reads were aligned to the NCBI build 37 (hg19) human reference genome using MapSplice⁷ v12_07, and the profile was assessed by Picard Tools v1.64 (<http://picard.sourceforge.net/>). The aligned reads were translated to transcriptome reference of UCSC hg19 GAF2.1 KnownGenes using UBU v1.0 (<https://github.com/mozack/ubu>). The abundance of transcripts was then estimated using an Expectation-Maximization algorithm implemented in the software package RSEM⁸ v1.1.13. Quality control of RNA-seq data was performed as described in Zhao et al.⁹ RSEM data was upper quartile normalized and log2 transformed.

4.7 Basal-like subtype by Prosigna™ (Institute of Cancer Research, Royal Marsden Hospital and NanoString®)

55ng-120ng of primary tumour RNA was extracted from needle micro-dissected archived primary tumour as described above, and was subjected to PAM50 gene expression profiling using the commercial Prosigna™ kit. NanoString® platform nCounter analysis was performed at the Institute of Cancer Research and Royal Marsden Hospital and gene expression profiles were sent to NanoString where the Prosigna™ algorithm was used to define intrinsic subtype (Basal-like, HER2-enriched, Luminal A and Luminal B). A research use only version of PAM50 proliferation score was calculated according to the published PAM50 classifier at Institute of Cancer Research¹⁰.

4.8 Central determination of “Triple Negative status” and “Core Basal” subtype defined by Immunohistochemical based (IHC) panel (King's College London)

Representative areas of the available primary tumours, lymph node metastasis and local recurrences were marked on H&E stained sections. Tissue microarrays were constructed, using the Beecher Manual Tissue Microarrayer Model MTA-1 (Sun Prairie, WI, USA) with 0.6mm stylets. Tissue microarrays were made in triplicate mainly from the periphery of the carcinoma and also other representative areas.

Expression of ER, PgR and HER2 was assessed on formalin-fixed paraffin-embedded (FFPE) 3-µm-thick whole tissue sections stained using automated VENTANA (Roche) platform with UltraView universal DAB Detection kit. IHC was performed using anti-Estrogen Receptor (ER) (SP1) Rabbit Monoclonal Ventana 790-4324/4325 antibody with CC1 tissue pre-treatment for 64min at 95°C, anti-Progesterone Receptor (PR) (1E2) Rabbit Monoclonal Ventana 790-2223/4296 Ab with CC1 tissue pre-treatment for 32min at 95°C and anti-HER-2/neu (4B5) Rabbit Monoclonal Ventana 790-2991 (05278368001) antibody with CC1 tissue pre-treatment for 36 minutes at 95°C.

Expression of CK5 and EGFR were assessed on 3-µm-thick tissue microarray sections, also using Ventana. Ck5 (XM26) Mouse monoclonal Novocastra NCL-CK5 antibody was diluted 1:50 with CC1 tissue pre-treatment for 64min at 95°C and EGFR(EGFR.25) Mouse monoclonal Novocastra NCL-L-EGFR-384 antibody was diluted 1:25 with CC1 tissue pre-treatment for 64min at 95°C.

Scoring of tissue sections was carried out by two observers (SEP and CG) using standard methods. HER2 was scored as 0 when no staining observed, or membrane staining in <10% of tumour cells, +1 when a faint/barely perceptible membrane staining detected in >10% of tumour cells; the cells are only stained in part of the membrane, +2 when a weak to moderate complete membrane staining observed in >10% of tumour cells, +3

when a strong complete membrane staining is observed in >10% of the tumour cells. The score 0 and +1 are giving negative result, score +2 borderline needing ISH validation and +3 as HER2 strong positive.

ER and PgR were scored using Allred system with score given for proportion of stained cells from 0 to 5 (0= no staining, 1= <1% nuclear staining, 2= 10% nuclear staining, 3= 11–33% nuclear staining, 4= 34–66% nuclear staining and 5= 67–100% nuclear staining) and score for intensity from 0 to 3 (0 - No staining, 1 - Weak staining, 2 - Moderate staining, 3 - Strong staining). The score above 2 was a positive. CK5 was scored as percent positive tumour cells, with no staining (0%) considered negative and any staining (1-100%) considered positive. EGFR membrane was scored using the HER2 system, with a score of 0 to 1+ considered negative and 2+ to 3+ positive. Core Basal subtype is defined as (ER-, PgR-, HER2-) and (CK5/6+ and/or EGFR+). Those negative for all markers are referred to as 5NP¹³.

4.9 Homologous recombination deficiency (HRD) Assay (Myriad)

DNA (200 ng) was provided by ICR to Myriad. A custom enrichment panel was developed which targeted 54,091 single nucleotide polymorphisms (SNPs) distributed across the complete human genome. The panel also included an additional 685 probes targeting the complete coding region of *BRCA1* and *BRCA2*. Agilent SureSelect target enrichment was followed by sequencing on Illumina HiSeq2500. Variant and large rearrangement detection was performed on sequence from *BRCA1* and *BRCA2*. Mutations identified were only included in the analysis if classified as deleterious or suspected deleterious based on previously described criteria¹⁴.

Sequence covering SNP positions was used to generate allelic imbalance profiles. A hidden Markov model (HMM) was used to define regions and breakpoints with these profiles. Allele specific copy number (ASCN) for each of the regions was determined using an algorithm similar to that described by Popova et al¹⁵. TAI (number of regions of allelic imbalance that extend to one of the subtelomeres but do not cross the centromere) and LST (number of break points between regions longer than 10 Mb after filtering out regions shorter than 3 Mb) scores were calculated using the allelic imbalance profiles, while LOH (Number of subchromosomal LOH regions longer than 15 Mb) was calculated using ASCN. Homologous recombination deficiency (HRD) score was defined as sum of TAI, LST, and LOH scores¹⁶.

A training set completely independent of the TNT study cases was assembled using four publicly available or previously published cohorts (497 breast and 561 ovarian cases) that included 78 breast and 190 ovarian cancers lacking a functional copy of either *BRCA1* or *BRCA2* (i.e. *BRCA1/2* deficient) based on mutation and methylation data. Assay methods and sample acquisition for these studies have been previously published^{2,16-19}. Specifically, tumors selected as *BRCA1/2* deficient had either (i) one deleterious mutation in *BRCA1* or *BRCA2*, with LOH in the wild-type copy (ii) two deleterious mutations in the same gene, or (iii) promoter methylation of *BRCA1* with LOH in the wild-type copy. This cohort was used to define a threshold for the HRD score intended to reflect HR deficient versus HR non-deficient status. The threshold selected was the 5th percentile of HRD scores in tumors lacking a functional copy of *BRCA1* or *BRCA2* with a HRD score of 42 defining the cut-point.

Dichotomized HRD score: is defined as high for HRD score ≥ 42 , and low for HRD score < 42 .

HRD status: is defined using the combination of the dichotomized HRD score and *BRCA1/2* mutation calls from the HRD assay. A tumour is classified as HR Deficient if it has either high HRD score or *BRCA1/2* mutations; else it is classified as HR Non-deficient, with the exception that a tumour with a failed HRD score and no *BRCA1/2* mutation is classified as undetermined. Samples failing both the HRD score and mutation call are also classified as undetermined.

4.10 Statistical analysis of the translational biomarker subgroups

For each biomarker, patients with unknown biomarker status were excluded from analysis. Analysis by PAM50 subgroups excluded patients with *BRCA1* or *BRCA2* germline mutations who were entered into the trial with ER or HER2 positive disease. Patients without confirmation of triple negative disease by central review were excluded from the analysis by IHC classification. All tumour based biomarkers presented in this manuscript were based on data from archived treatment naïve primary tumour samples only.

Primary analysis was performed on dichotomised/categorised data for each of the biomarkers. Response rates within subgroups were compared between treatment groups using 2-sided Fishers' exact tests. A logistic regression model was also fitted including terms for treatment, biomarker and an interaction between treatment and biomarker to determine the significance of an interaction.

5. Additional results

5.1. Centrally confirmed triple negative disease

Sensitivity analysis was conducted restricting analysis to the 205 patients (100 carboplatin, 105 docetaxel) who had centrally confirmed triple negative disease. Response rates were 31/100 (31.0%) carboplatin vs. 37/105 (35.2%) docetaxel, absolute difference (C-D) = -4.2% (95%CI: -17.1 to 8.7) exact p=0.56). This did not change the conclusions of the main comparison in all patients.

6 Supplementary tables and figures

Table S1. Pre-planned biomarker subgroup analyses

Biomarker	Groups	Hypothesis
Germline <i>BRCA1/2</i> mutation	<i>BRCA1/2</i> mutation +; <i>BRCA1/2</i> mutation -	<i>BRCA1/2</i> + patients will benefit from carboplatin over docetaxel
Tumour <i>BRCA1/2</i> mutation	<i>BRCA1/2</i> mutation +; <i>BRCA1/2</i> mutation -	<i>BRCA1/2</i> + patients will benefit from carboplatin over docetaxel
<i>BRCA1</i> Methylation	Methylated (>10% methylated); Non-methylated (≤10% methylated)	Methylated patients will benefit from carboplatin over docetaxel
<i>BRCA1</i> mRNA-low	Low ($\log_2(\text{BRCA1}) < 8.4$); <i>BRCA1</i> mRNA not-low ($\log_2(\text{BRCA1}) \geq 8.4$)	<i>BRCA1</i> mRNA low patients will benefit from carboplatin over docetaxel
Basal like PAM50	Basal like; Non-basal	Basal like tumours will benefit from carboplatin over docetaxel
Core basal IHC	Core basal; Non-core basal (5NP)	Core basal tumours will benefit from carboplatin over docetaxel
Dichotomised HRD score	HRD high (≥42) HRD Low (<42)	HRD high patients will benefit from carboplatin over docetaxel
HR deficiency	HR Deficient (HRD high OR <i>BRCA1/2</i> mutation) HR Non-deficient (HRD low & no known <i>BRCA1/2</i> mutation)	HR deficient patients will benefit from carboplatin over docetaxel

Table S2. Baseline characteristics

	Carboplatin		Docetaxel	
	N=188		N=188	
Patient status as per local assessment, n (%)				
TN, no known mutation*	167	88.8%	171	91.0%
Known BRCA1	4	2.1%	1	0.5%
Known BRCA2	6	3.2%	2	1.1%
TN & known BRCA1/2	7	3.7%	9	4.8%
Not TN and no known mutation*	4	2.1%	5	2.7%
Age in years, median (IQR)	55.7 (47.6-62.9)		54.9 (47.9-63.5)	
Ethnicity, n(%)				
White	159	84.6%	169	89.9%
Asian/Asian British/Other Asian	8	4.3%	3	1.6%
Black/Black British/Other Black	13	6.9%	10	5.3%
Mixed	0	0.0%	1	0.5%
Not stated/Missing	8	4.3%	5	2.7%
Stage, n(%)				
Locally advanced	17	9.0%	20	10.6%
Metastatic	171	91.0%	168	89.4%
ECOG performance status, n (%)				
0 or 1	174	92.6%	176	93.6%
2	14	7.4%	12	6.4%
Taxane chemotherapy use in the adjuvant setting, n (%)				
Yes	65	34.6%	61	32.4%
No	123	65.4%	127	67.6%
Liver or parenchymal lung metastases, n(%)				
Yes	98	52.1%	100	53.2%
No	90	47.9%	88	46.8%
Time since diagnosis to initial relapse (years), n (%)				
0-1	30	16.0%	38	20.2%
1-3	100	53.2%	89	47.3%
3-5	41	21.8%	33	17.6%
>5	16	8.5%	25	13.3%
Unknown	1	0.5%	3	1.6%
Visceral disease present at baseline, n (%)				
Yes	136	72.3%	136	72.3%
No	52	27.7%	52	27.7%
Germline BRCA mutation status – local/central review**, n (%)				
No mutation	128	68.1%	145	77.1%
BRCA1 mutation	16	8.5%	15	8.0%
BRCA2 mutation	9	4.8%	3	1.6%
Unknown	35	18.6%	25	13.3%
Tumour BRCA mutation status, n (%)				
No mutation	90	47.9%	90	47.9%
BRCA1 mutation	16	8.5%	11	5.9%
BRCA2 mutation	1	0.5%	3	1.6%
BRCA1 & BRCA2 mutation	1	0.5%	0	0.0%
Unknown	80	42.6%	84	44.7%
BRCA1 Methylation, n (%)				
Methylated	14	7.4%	19	10.1%

Non-methylated	93	49.5%	86	45.7%
Unknown	81	43.1%	83	44.1%
BRCA1 mRNA-low, n (%)				
mRNA-low	14	7.4%	17	9.0%
Non-mRNA-low	82	43.6%	78	41.5%
Unknown	92	48.9%	93	49.5%
Prosigna PAM50, n (%)				
Basal-like	83	44.1%	87	46.3%
HER2 Enriched	9	4.8%	13	6.9%
Luminal A	8	4.3%	5	2.7%
Luminal B	1	0.5%	0	0.0%
Tested but not triple negative	5	2.7%	4	2.1%
Unknown	82	43.6%	79	42.0%
Core basal (IHC) , n (%)				
Basal	67	35.6%	65	34.6%
5NP	26	13.8%	31	16.5%
Tested but not triple negative	11	5.9%	6	3.2%
Unknown	84	44.7%	86	45.7%
Definitive surgery for primary disease, n (%)				
Yes	166	88.3%	163	86.7%
WLE	84	44.7%	87	46.3%
Mastectomy*	81	43.1%	76	40.4%
Missing	1	0.5%	0	0.0%
No	18	9.6%	22	11.7%
Locally advanced inoperable disease at diagnosis	0	0.0%	1	0.5%
Metastatic at diagnosis	17	9.0%	20	10.6%
Other	1	0.5%	0	0.0%
Unknown	0	0.0%	1	0.5%
Missing	4	2.1%	3	1.6%
Axillary surgery performed, n (%)				
Yes	166	88.3%	158	84.0%
Level 2/3 dissection	98	52.1%	82	43.6%
Level 1/sampling	15	8.0%	31	16.5%
SLNB	34	18.1%	29	15.4%
Level 2/3 dissection and Level 1/sampling	4	2.1%	5	2.7%
Level 2/3 dissection and SLNB	6	3.2%	2	1.1%
Level 1/sampling and SLNB	6	3.2%	8	4.3%
Missing	3	1.6%	1	0.5%
No	20	10.6%	24	12.8%
Missing	2	1.1%	6	3.2%
Number of lymph nodes involved, n (%)				
0	75	39.9%	71	37.8%
1-3N+	53	28.2%	51	27.1%
≥4N+	39	20.7%	42	22.3%
Unknown	21	11.2%	24	12.8%
Side of tumour, n (%)				
Left	108	57.4%	111	59.0%
Right	78	41.5%	74	39.4%
Missing	2	1.1%	3	1.6%
Vascular invasion, n (%)				
Yes	80	42.6%	69	36.7%
No	76	40.4%	83	44.1%
Not reported	28	14.9%	30	16.0%
Missing	4	2.1%	6	3.2%

Tumour grade, n (%)				
G1	0	0·0%	2	1·1%
G2	28	14·9%	29	15·4%
G3	151	80·3%	150	79·8%
Not known	6	3·2%	4	2·1%
Missing	3	1·6%	3	1·6%
Multifocal disease, n (%)				
Yes	34	18·1%	22	11·7%
No	146	77·7%	155	82·4%
Missing	8	4·3%	11	5·9%
Pathological invasive tumour size (cm), n (%)				
<2	42	22·3%	40	21·3%
2-5	100	53·2%	108	57·4%
>5	26	13·8%	17	9·0%
Missing	20	10·6%	23	12·2%
Histological type, n (%)				
Ductal/NST	167	88·8%	170	90·4%
Lobular	4	2·1%	5	2·7%
Mixed ductal and lobular	3	1·6%	4	2·1%
Metaplastic	5	2·7%	4	2·1%
Mixed ductal/NST and special type	1	0·5%	0	0·0%
Special type	1	0·5%	0	0·0%
Missing/unknown	7	3·7%	5	2·7%
Adjuvant chemotherapy, n (%)				
Yes	147	78·2%	136	72·3%
FEC	57	30·3%	46	24·5%
FEC-T	37	19·7%	38	20·2%
E-CMF	20	10·6%	15	8·0%
AC/EC	9	4·8%	8	4·3%
AC-P/EC-P	7	3·7%	8	4·3%
AC-T/EC-T	3	1·6%	6	3·2%
E-X	2	1·1%	2	1·1%
PG-EC	2	1·1%	0	0·0%
EC-PG	1	0·5%	1	0·5%
P-EC	0	0·0%	1	0·5%
Other	9	4·8%	11	5·9%
No	41	21·8%	50	26·6%
Missing	0	0·0%	2	1·1%
Anthracycline chemotherapy for metastatic/locally advanced disease, n (%)				
Yes	16	8·5%	20	10·6%
No	172	91·5%	166	88·3%
Missing	0	0·0%	2	1·1%

*This group will include patients who were tested and no mutation was identified as well as those who were never tested. Information about testing was only collected if a mutation had been identified prior to trial entry.

**No discordant results were identified between the local and central assessment of BRCA status. 29 patients had a known BRCA mutation at trial entry; central testing identified an additional 14 patients with germline BRCA mutations.

Table S3. Breakdown of subtypes against *BRCA1/2* mutation, *BRCA1* methylation and *BRCA1* mRNA-Low status

	<i>PAM50</i>						Basal by IHC			
	Basal Like	<i>HER2</i> <i>Enriched</i>	Luminal A	Luminal B	Not TNBC	Unknown	Core basal	5NP	Not TNBC	Unknown
Germline BRCA1										
Mutation	14 (45.2 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	3 (9.7 %)	14 (45.2 %)	16 (51.6 %)	2 (6.5 %)	1 (3.2 %)	12 (38.7 %)
Wildtype	135 (47.4 %)	20 (7.0 %)	11 (3.9 %)	1 (0.4 %)	6 (2.1 %)	112 (39.3 %)	100 (35.1 %)	49 (17.2 %)	14 (4.9%)	122 (42.8 %)
Unknown	21 (35.0 %)	2 (3.3 %)	2 (3.3 %)	0 (0.0 %)	0 (0.0 %)	35 (58.3 %)	16 (26.7 %)	6 (10.0 %)	2 (3.3 %)	36 (60.0 %)
Germline BRCA2										
Mutation	0 (0.0 %)	1 (8.3 %)	0 (0.0 %)	0 (0.0 %)	2 (16.7 %)	9 (75.0 %)	0 (0.0 %)	1 (8.3 %)	2 (16.7 %)	9 (75.0 %)
Wildtype	149 (49.0 %)	19 (6.3 %)	11 (3.6 %)	1 (0.3 %)	7 (2.3 %)	117 (38.5 %)	116 (38.2 %)	50 (16.4 %)	13 (4.3 %)	125 (41.1 %)
Unknown	21 (35.0 %)	2 (3.3 %)	2 (3.3 %)	0 (0.0 %)	0 (0.0 %)	35 (58.3 %)	16 (26.7 %)	6 (10.0 %)	2 (3.3 %)	36 (60.0 %)
Tumor <i>BRCA1/2</i>										
<i>BRCA1</i> Mutation	21 (77.8%)	0 (0.0%)	1 (3.7%)	0 (0.0%)	3 (11.1%)	2 (7.4%)	23 (85.2%)	2 (7.4%)	1 (3.7%)	1 (3.7%)
<i>BRCA2</i> Mutation	2 (50.0%)	1 (25.0%)	0 (0.0%)	0 (0.0%)	1 (25.0%)	0 (0.0%)	2 (50.0%)	1 (25.0%)	1 (25.0%)	0 (0.0%)
<i>BRCA1</i> and <i>BRCA2</i> mutation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)
Wildtype	143 (79.4%)	18 (10.0%)	12 (6.7%)	1 (0.6%)	4 (2.2%)	2 (1.1%)	100 (55.6%)	51 (28.3%)	13 (7.2%)	16 (8.9%)
Unknown	4 (2.4%)	3 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	157 (95.7%)	7 (4.3%)	3 (1.8%)	1 (0.6%)	153 (93.3%)
<i>BRCA1</i> methylation										
Yes	28 (84.8 %)	2 (6.1 %)	1 (3.0 %)	0 (0.0 %)	2 (6.1 %)	0 (0.0 %)	22 (66.7 %)	6 (18.2%)	2 (6.1 %)	3 (9.1 %)
No	136 (76.0 %)	19 (10.6 %)	12 (6.7%)	1 (0.6 %)	7 (3.9 %)	4 (2.2 %)	103 (57.5 %)	47 (26.3 %)	15 (8.4 %)	14 (7.8 %)
Unknown	6 (3.7 %)	1 (0.6 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	157 (95.7 %)	7 (4.3 %)	4 (2.4 %)	0 (0.0 %)	153 (93.3 %)
<i>BRCA1</i> mRNA - Low										
Yes	22 (71.0 %)	1 (3.2 %)	6 (19.4 %)	0 (0.0 %)	2 (6.5 %)	0 (0.0 %)	16 (51.6 %)	7 (22.6 %)	3 (9.7 %)	5 (16.1 %)
No	129 (80.6 %)	17 (10.6 %)	4 (2.5 %)	1 (0.6 %)	7 (4.4 %)	2 (1.3 %)	98 (61.3 %)	40 (25.0 %)	10 (6.3 %)	12 (7.5 %)
Unknown	19 (10.3 %)	4 (2.2 %)	3 (1.6 %)	0 (0.0 %)	0 (0.0 %)	159 (85.9 %)	18 (9.7 %)	10 (5.4 %)	4 (2.2 %)	153 (82.7 %)

Figure S1. Crossover response rate

Absolute differences between treatment groups within biomarker subgroups are presented; p-values for the differences are calculated using a 2-sided Fisher's exact test. P-values for interactions are based on a logistic regression model of response with terms for biomarker status, treatment group and interaction.

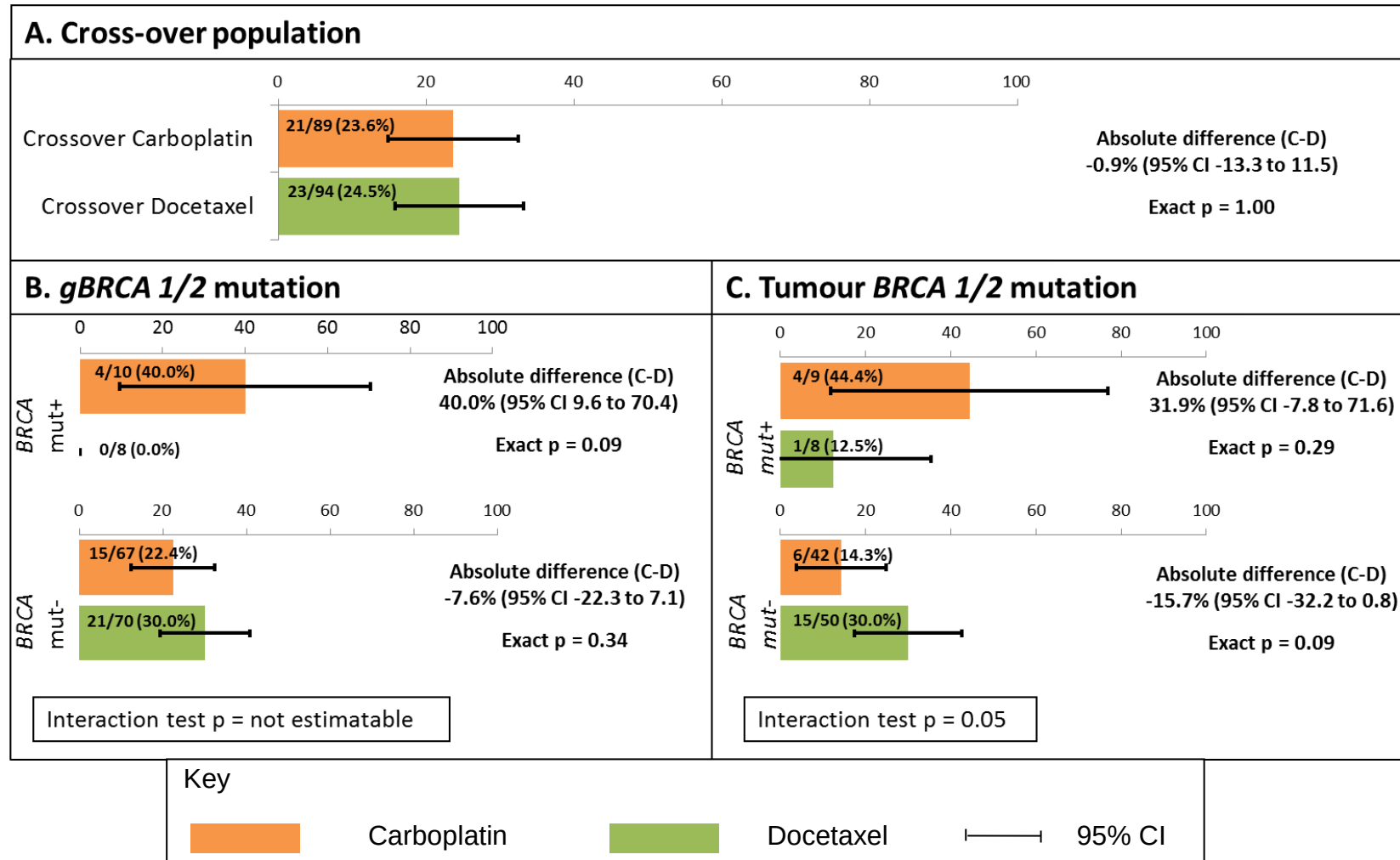


Figure S2. Kaplan Meier graph for overall survival by randomised treatment

Data presented is the difference in OS restricted mean (95% CI). A negative value indicates a better response to docetaxel, positive values indicate better response to carboplatin. P-values are calculated using a 2-sided t-test comparing the mean survival between treatments (within biomarker groups as appropriate). C=Carboplatin; D=Docetaxel.

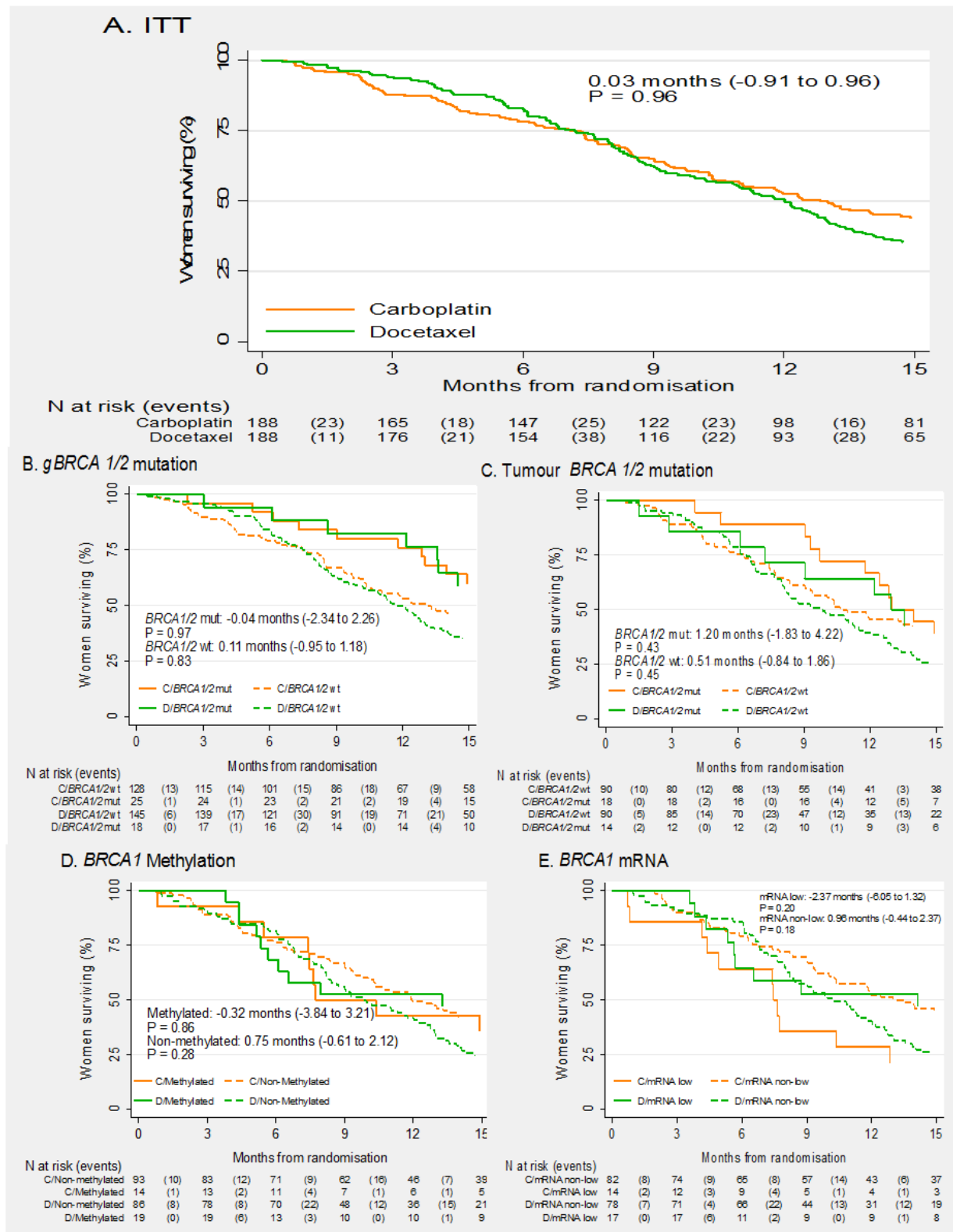


Table S4. Crossover of germline and tumour *BRCA* 1/2 mutation status

		Germline <i>BRCA</i>			Total
		Positive	Negative	Unknown	
Tumour <i>BRCA</i>	Positive	21	8	3	32
	Negative	1	156	23	180
	Unknown	21	109	34	164
Total		43	273	60	376

Relationship between germline and tumour *BRCA* status in all 376 patients entered into the trial.

Figure S3. Distribution of *BRCA1* mRNA expression

A. *BRCA1* mRNA expression from RNAseq on 191 archival primary tumour samples expressed on the Log₂ scale; A fixed mixture model of two Gaussian (normal) distributions fitted to the *BRCA1* mRNA expression data and bimodality analysis of the frequency distribution informed the selected cut point of 8.4 for mRNA-low status (vertical interrupted line).

B. Relationship of *BRCA1* methylation and *BRCA1* mRNA expression expressed on the Log₂ scale in the 184 patients archival primary tumour samples where both biomarkers available on the same sample. Red: Distribution of *BRCA1* mRNA expression within group of tumours defined as *BRCA1* methylated. Blue: Distribution of *BRCA1* mRNA expression within group of tumours defined as *BRCA1* non-methylated. A Kolmogorov-Smirnov (two-sided) test was used to compare the two distributions.

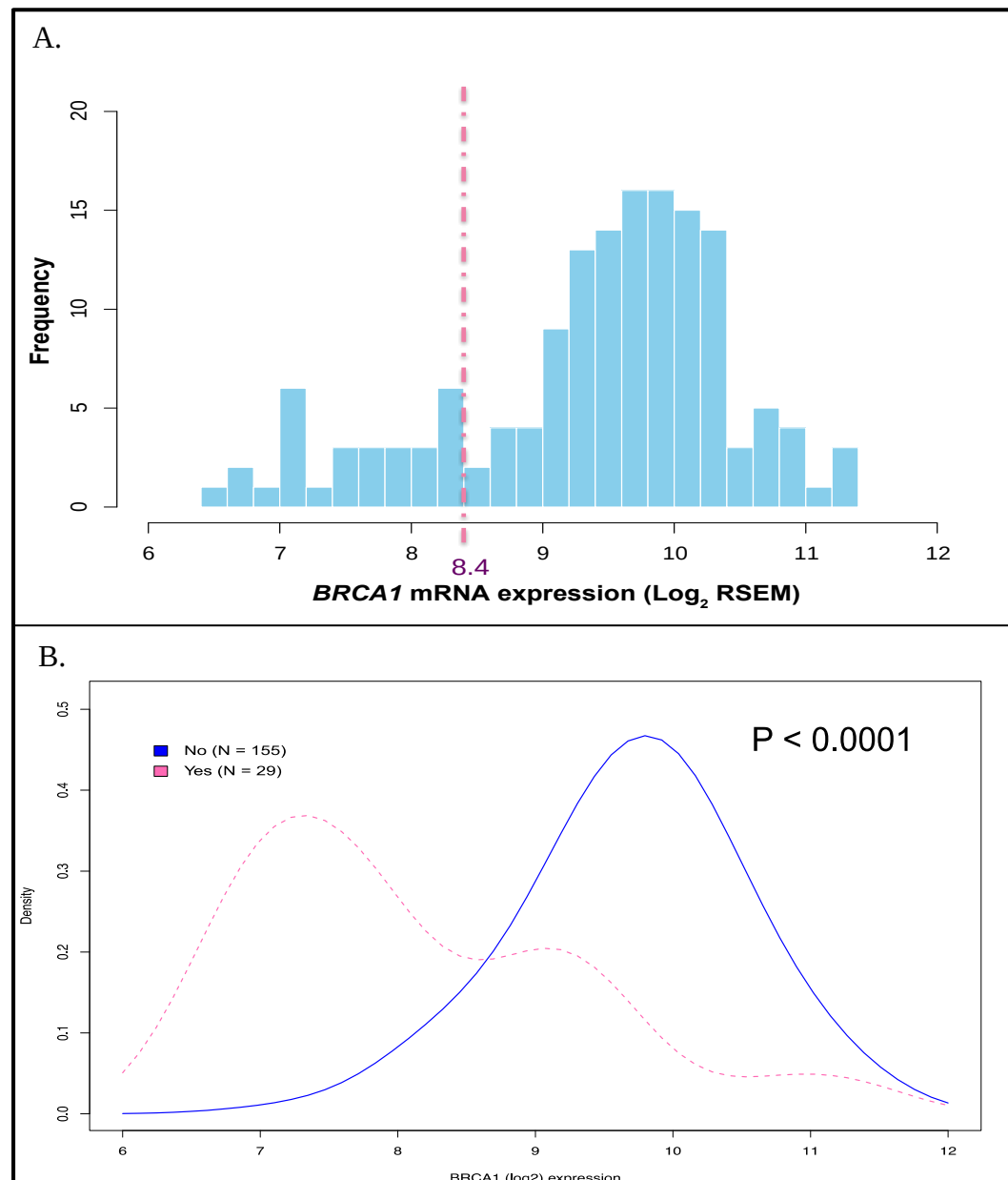


Table S5. Table relating *BRCA1* methylation and *BRCA1* mRNA-low status

	Methylated	Non-methylated	Total
BRCA1 mRNA-low	19	12	31
BRCA1 mRNA-non-low	10	143	153
Total	29	155	184

Relationship between *BRCA1* methylation and *BRCA1* mRNA-low status in the 184 patients with archival primary tumour samples where both biomarkers available on the same sample.

Figure S4. HRD score by *BRCA1/2* mutation and *BRCA1* methylation status

HRD scores presented by treatment group indicating (A) *gBRCA1/2* mutation status Blue *BRCA1or2* mutated, Black *BRCA1or2* wild-type, Grey *BRCA1or2* unknown and (B) *gBRCA1/2* mutation status as A and *BRCA1* methylation status Red. Red lines in the plot represent the median and interquartile range of HRD score for each group. N=195 patients with HRD scores available.

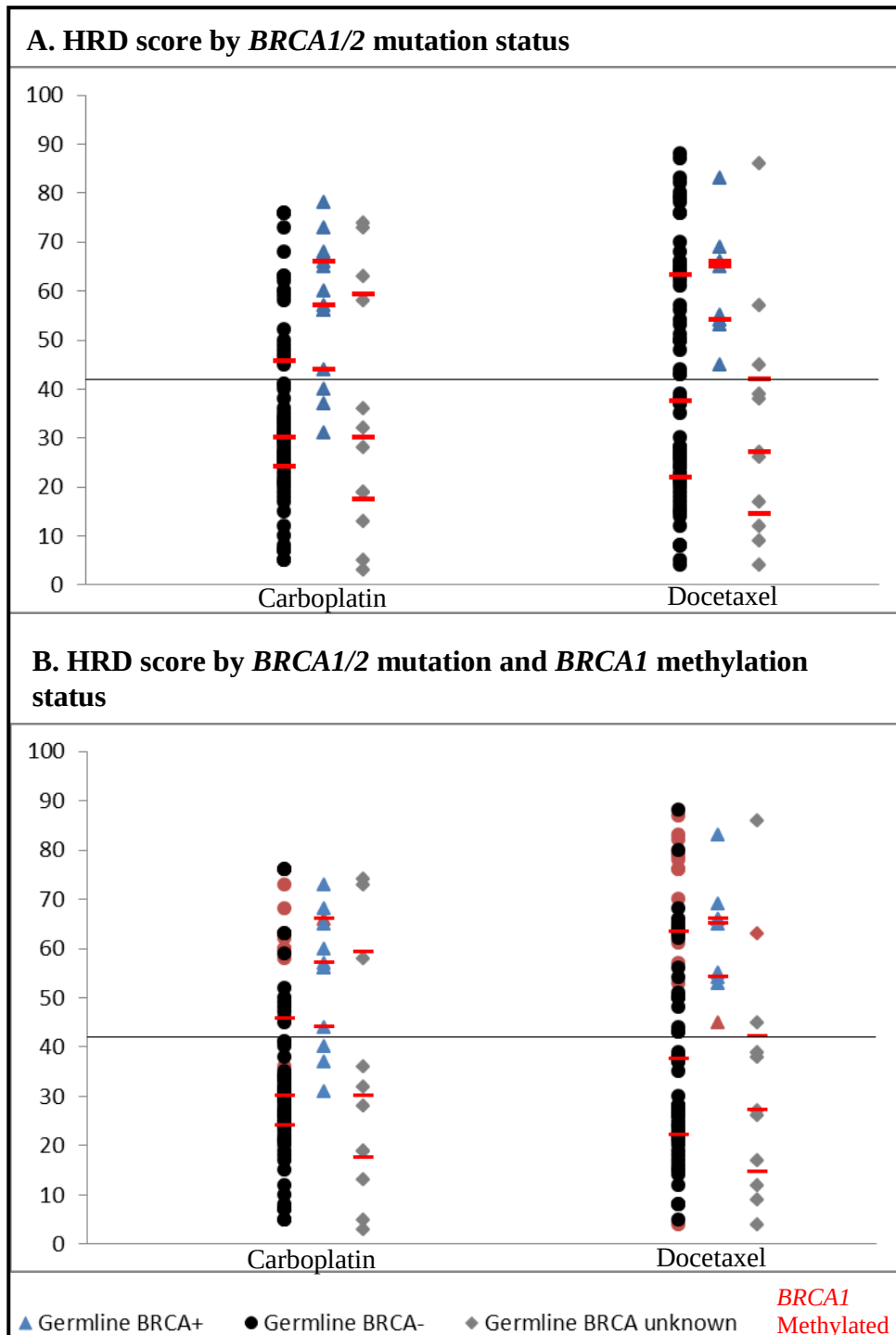
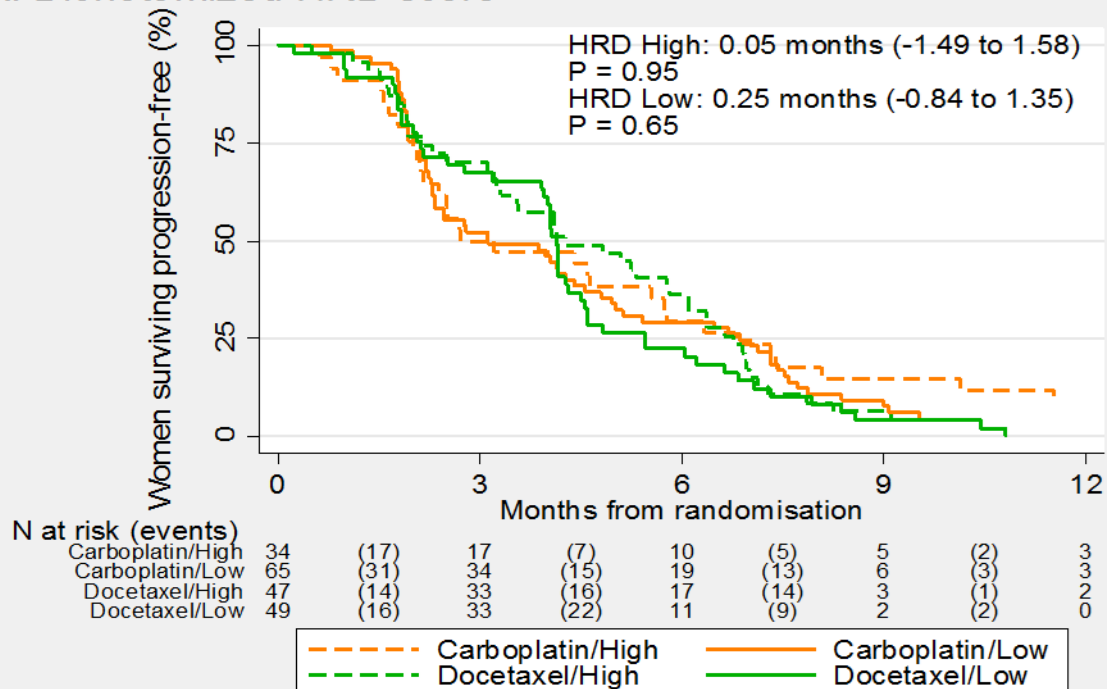


Figure S5. PFS by dichotomised HRD score and HR deficient status

Data presented shows the difference in PFS restricted mean (95% CI) within each subgroup. A positive value shows a better response to carboplatin. P-values are calculated using a 2-sided t-test comparing the mean survival between treatments within HRD subgroups.

A. Dichotomized HRD score



B. HR Deficiency status

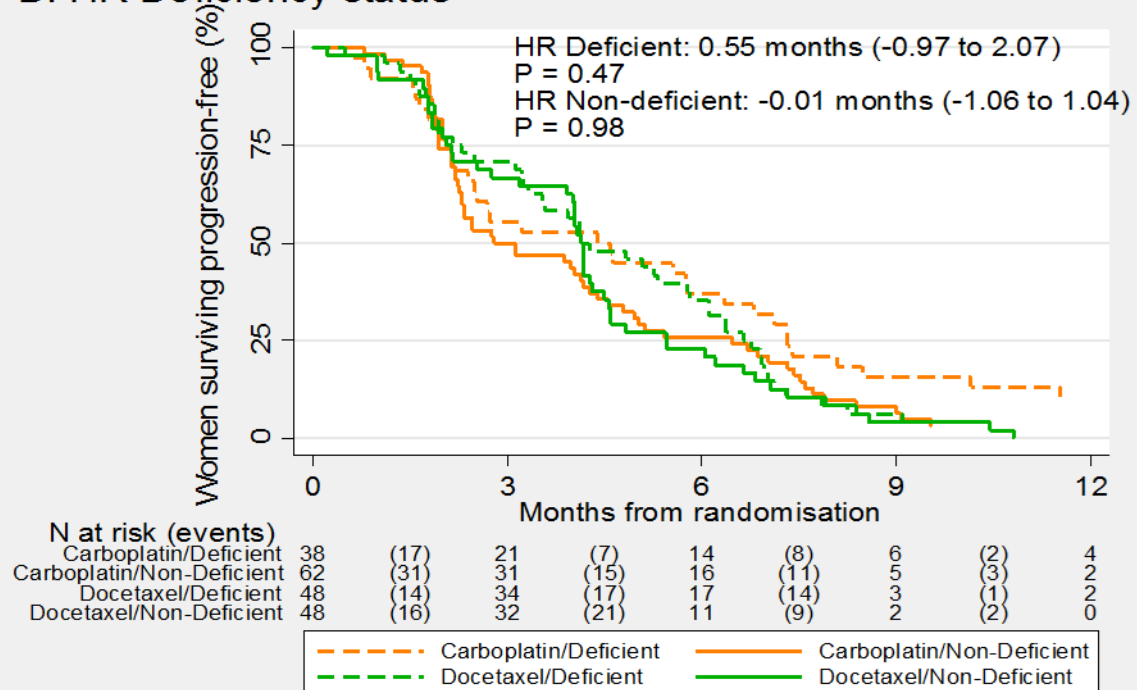


Figure S6. Crossover response rate graphs

Absolute differences between treatment groups within PAM50 basal subgroups are presented; p-values for the differences are calculated using a 2-sided Fisher's exact test. P-value for the interaction is based on a logistic regression model of response with terms for basal status, treatment group and interaction.

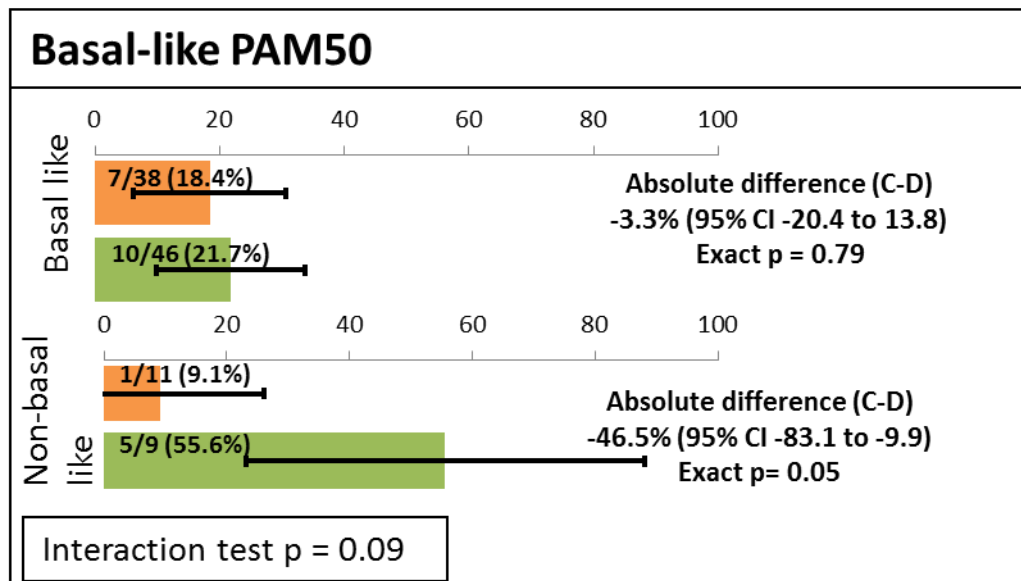


Figure S7. Kaplan Meier graph for overall survival by randomised treatment

Data presented is the difference in PFS restricted mean (95% CI). A negative value indicates a better response to docetaxel, positive values indicate better response to carboplatin. P-values are calculated using a 2-sided t-test comparing the mean survival between treatments (within biomarker groups as appropriate). C=Carboplatin; D=Docetaxel.

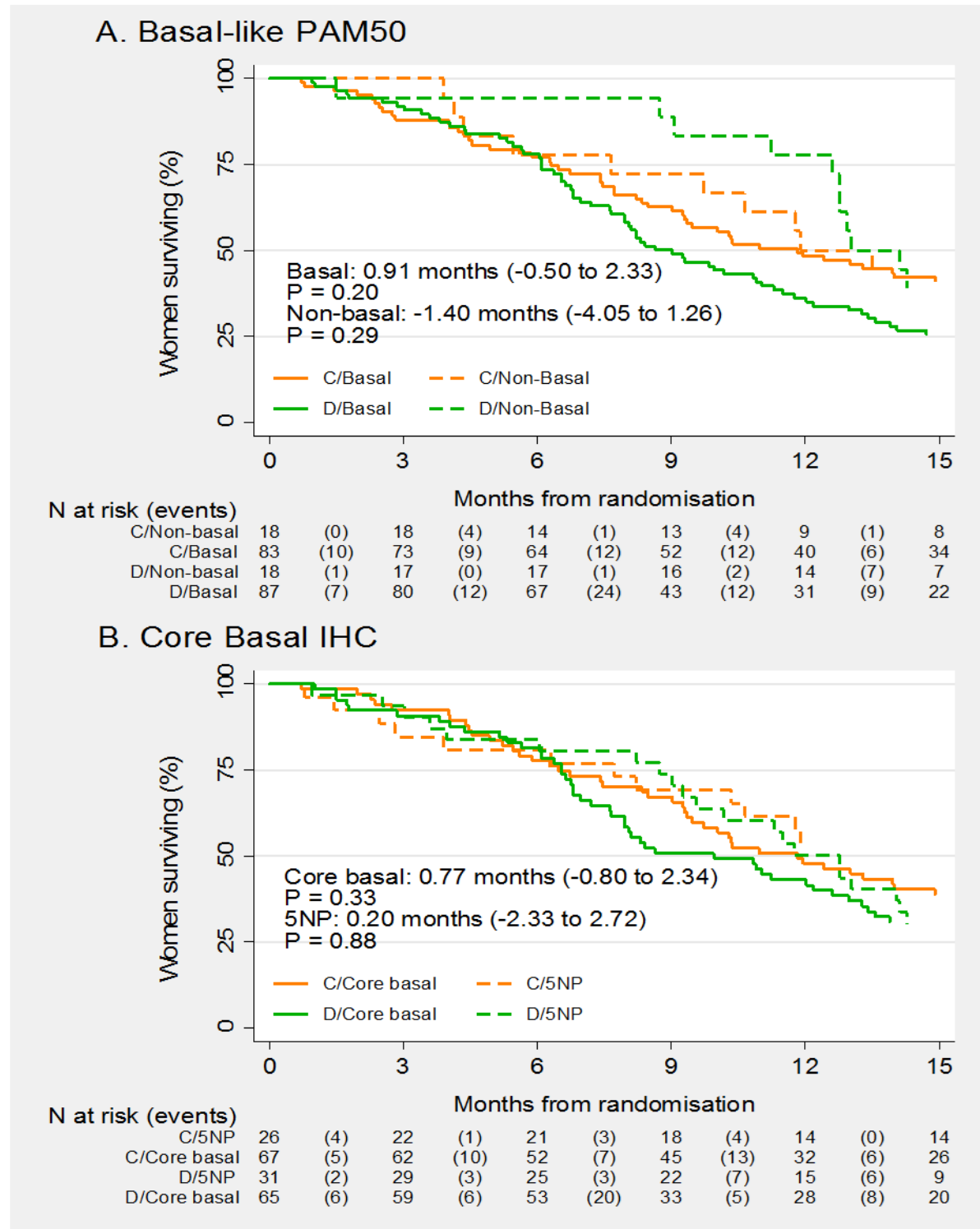


Table S6. Results of logistic regression testing the significance of basal-like subtype determined by PAM50 adjusting for gBRCA mutation status

	Without gBRCA1/2 mutation		With gBRCA1/2 mutation	
	Odds ratio	P value	Odds ratio	p-value
Arm	1·08	0·83	1·07	0·85
<i>gBRCA1/2</i> mutation	NA	NA	2·14	0·17
PAM50	9·75	0·001	10·52	0·001
PAM50*Arm[†]	0·05	0·002	0·05	0·002

[†]Interaction between PAM50 basal status and treatment arm

N= 181 patients with known *gBRCA* status and known PAM50 status.

Table S7. Adverse events reported by randomised treatment (any grade and grade 3+ only) meeting one of the following criteria: difference in overall proportion between treatments is >1%; overall proportion in either treatment group>10%; statistically significant difference (p<0.01) between the two treatments according to 2-sided Fisher's exact

Toxicity	Carboplatin Any grade	Carboplatin Grade 3/4	Docetaxel Any grade	Docetaxel Grade 3/4	p-value*
Abdominal pain	10 (5%)	3 (2%)	7 (4%)	2 (1%)	0.62
Abdominal pain upper	2 (1%)	1 (1%)	4 (2%)	0 (0%)	0.45
Agitation	3 (2%)	0 (0%)	1 (1%)	0 (0%)	0.62
Alanine aminotransferase	5 (3%)	0 (0%)	0 (0%)	0 (0%)	0.06
Alanine aminotransferase increased	12 (7%)	0 (0%)	7 (4%)	1 (1%)	0.35
Alopecia	65 (35%)	0 (0%)	162 (89%)	1 (1%)	<0.0001
Anaemia	53 (29%)	8 (4%)	20 (11%)	1 (1%)	<0.0001
Anaphylactic reaction	0 (0%)	0 (0%)	2 (1%)	2 (1%)	0.25
Anxiety	3 (2%)	0 (0%)	1 (1%)	0 (0%)	0.62
Arthralgia	8 (4%)	2 (1%)	38 (21%)	3 (2%)	<0.0001
Aspartate aminotransferase increased	8 (4%)	0 (0%)	3 (2%)	1 (1%)	0.22
Asthenia	3 (2%)	0 (0%)	0 (0%)	0 (0%)	0.25
Back pain	15 (8%)	0 (0%)	20 (11%)	4 (2%)	0.38
Blister	2 (1%)	0 (0%)	0 (0%)	0 (0%)	0.50
Blood albumin decreased	2 (1%)	0 (0%)	0 (0%)	0 (0%)	0.50
Blood alkaline phosphatase	14 (8%)	2 (1%)	6 (3%)	2 (1%)	0.11
Blood alkaline phosphatase abnormal	3 (2%)	1 (1%)	0 (0%)	0 (0%)	0.25
Blood alkaline phosphatase decreased	3 (2%)	0 (0%)	0 (0%)	0 (0%)	0.25
Blood alkaline phosphatase increased	27 (15%)	1 (1%)	22 (12%)	0 (0%)	0.54
Blood bilirubin increased	0 (0%)	0 (0%)	4 (2%)	2 (1%)	0.06
Blood creatinine decreased	0 (0%)	0 (0%)	2 (1%)	1 (1%)	0.25
Blood creatinine increased	3 (2%)	0 (0%)	1 (1%)	0 (0%)	0.62
Bone pain	3 (2%)	1 (1%)	6 (3%)	0 (0%)	0.34
Breast pain	7 (4%)	0 (0%)	2 (1%)	0 (0%)	0.17
Cancer pain	2 (1%)	1 (1%)	0 (0%)	0 (0%)	0.50
Candidiasis	2 (1%)	0 (0%)	6 (3%)	0 (0%)	0.17
Cellulitis	2 (1%)	0 (0%)	4 (2%)	0 (0%)	0.45
Chest discomfort	2 (1%)	0 (0%)	0 (0%)	0 (0%)	0.50
Colitis	0 (0%)	0 (0%)	2 (1%)	1 (1%)	0.25
Conjunctivitis	0 (0%)	0 (0%)	2 (1%)	0 (0%)	0.25
Constipation	113 (61%)	1 (1%)	107 (59%)	2 (1%)	0.67
Contusion	4 (2%)	0 (0%)	0 (0%)	0 (0%)	0.12
Cough	15 (8%)	0 (0%)	18 (10%)	0 (0%)	0.59
Decreased appetite	83 (45%)	3 (2%)	100 (55%)	5 (3%)	0.08
Deep vein thrombosis	0 (0%)	0 (0%)	5 (3%)	4 (2%)	0.03
Diarrhoea	63 (34%)	5 (3%)	117 (64%)	12 (7%)	<0.0001
Dizziness	14 (8%)	0 (0%)	7 (4%)	0 (0%)	0.18
Dry skin	3 (2%)	0 (0%)	8 (4%)	0 (0%)	0.14
Dysgeusia	16 (9%)	0 (0%)	28 (15%)	0 (0%)	0.05
Dyspepsia	11 (6%)	0 (0%)	19 (10%)	1 (1%)	0.13
Dysphagia	4 (2%)	0 (0%)	1 (1%)	0 (0%)	0.37
Dyspnoea	43 (23%)	11 (6%)	25 (14%)	6 (3%)	0.02
Epistaxis	3 (2%)	0 (0%)	6 (3%)	0 (0%)	0.34

Extravasation	0 (0%)	0 (0%)	6 (3%)	1 (1%)	0.01
Eye infection	0 (0%)	0 (0%)	3 (2%)	0 (0%)	0.12
Eye pain	0 (0%)	0 (0%)	7 (4%)	0 (0%)	0.01
Fatigue	174 (95%)	29 (16%)	172 (95%)	29 (16%)	1.00
Febrile neutropenia	31 (17%)	4 (2%)	63 (35%)	37 (20%)	0.0001
Flushing	1 (1%)	0 (0%)	4 (2%)	0 (0%)	0.21
Foreign body sensation in eyes	2 (1%)	0 (0%)	0 (0%)	0 (0%)	0.50
Fungal infection	0 (0%)	0 (0%)	2 (1%)	0 (0%)	0.25
Gamma- glutamyltransferase abnormal	3 (2%)	0 (0%)	0 (0%)	0 (0%)	0.25
Gastritis	0 (0%)	0 (0%)	2 (1%)	1 (1%)	0.25
Haemoglobin	22 (12%)	1 (1%)	8 (4%)	0 (0%)	0.01
Haemoglobin abnormal	44 (24%)	8 (4%)	14 (8%)	0 (0%)	<0.0001
Haemoglobin decreased	95 (52%)	5 (3%)	60 (33%)	0 (0%)	0.0003
Headache	21 (11%)	1 (1%)	14 (8%)	4 (2%)	0.29
Hot flush	2 (1%)	0 (0%)	7 (4%)	0 (0%)	0.10
Hyperglycaemia	3 (2%)	0 (0%)	0 (0%)	0 (0%)	0.25
Hypersensitivity	37 (20%)	0 (0%)	60 (33%)	1 (1%)	0.01
Infection	27 (15%)	0 (0%)	32 (18%)	6 (3%)	0.48
Infusion site infection	8 (4%)	4 (2%)	3 (2%)	1 (1%)	0.22
Infusion site reaction	0 (0%)	0 (0%)	3 (2%)	0 (0%)	0.12
Insomnia	9 (5%)	0 (0%)	13 (7%)	1 (1%)	0.39
Joint swelling	1 (1%)	0 (0%)	3 (2%)	0 (0%)	0.37
Lacrimation increased	2 (1%)	0 (0%)	24 (13%)	1 (1%)	<0.0001
Leukopenia	20 (11%)	3 (2%)	3 (2%)	1 (1%)	0.0003
Local swelling	3 (2%)	0 (0%)	0 (0%)	0 (0%)	0.25
Localised infection	1 (1%)	0 (0%)	4 (2%)	0 (0%)	0.21
Lower respiratory tract infection	6 (3%)	0 (0%)	17 (9%)	7 (4%)	0.02
Lymphoedema	4 (2%)	0 (0%)	9 (5%)	1 (1%)	0.17
Mucosal inflammation	69 (38%)	0 (0%)	117 (64%)	6 (3%)	<0.0001
Muscle spasms	6 (3%)	0 (0%)	3 (2%)	0 (0%)	0.50
Muscular weakness	3 (2%)	1 (1%)	9 (5%)	3 (2%)	0.09
Musculoskeletal chest pain	13 (7%)	1 (1%)	2 (1%)	0 (0%)	0.01
Musculoskeletal pain	7 (4%)	1 (1%)	2 (1%)	0 (0%)	0.17
Myalgia	5 (3%)	0 (0%)	41 (23%)	3 (2%)	<0.0001
Nail bed tenderness	0 (0%)	0 (0%)	2 (1%)	0 (0%)	0.25
Nail discolouration	0 (0%)	0 (0%)	5 (3%)	0 (0%)	0.03
Nail disorder	0 (0%)	0 (0%)	31 (17%)	0 (0%)	<0.0001
Nail dystrophy	0 (0%)	0 (0%)	2 (1%)	0 (0%)	0.25
Nail toxicity	0 (0%)	0 (0%)	2 (1%)	0 (0%)	0.25
Nausea	144 (78%)	10 (5%)	116 (64%)	8 (4%)	0.003
Neck pain	8 (4%)	1 (1%)	1 (1%)	0 (0%)	0.04
Neuropathy peripheral	61 (33%)	1 (1%)	129 (71%)	10 (5%)	<0.0001
Neutropenia	34 (18%)	15 (8%)	6 (3%)	3 (2%)	<0.0001
Neutropenic sepsis	3 (2%)	2 (1%)	1 (1%)	1 (1%)	0.62
Neutrophil count	10 (5%)	1 (1%)	1 (1%)	1 (1%)	0.01
Neutrophil count abnormal	18 (10%)	4 (2%)	1 (1%)	0 (0%)	0.0001
Neutrophil count decreased	15 (8%)	2 (1%)	1 (1%)	0 (0%)	0.0004
Oedema	1 (1%)	0 (0%)	4 (2%)	1 (1%)	0.21
Oedema peripheral	5 (3%)	0 (0%)	18 (10%)	0 (0%)	0.005
Onycholysis	0 (0%)	0 (0%)	2 (1%)	0 (0%)	0.25
Oral candidiasis	4 (2%)	0 (0%)	12 (7%)	0 (0%)	0.04

Oral pain	1 (1%)	0 (0%)	3 (2%)	0 (0%)	0.37
Oropharyngeal pain	3 (2%)	0 (0%)	5 (3%)	2 (1%)	0.50
Pain in extremity	11 (6%)	2 (1%)	14 (8%)	3 (2%)	0.54
Palmar-plantar erythrodysesthesia syndrome	2 (1%)	0 (0%)	8 (4%)	1 (1%)	0.06
Paraesthesia	1 (1%)	0 (0%)	7 (4%)	0 (0%)	0.04
Pharyngitis	1 (1%)	0 (0%)	4 (2%)	0 (0%)	0.21
Phlebitis	1 (1%)	0 (0%)	3 (2%)	0 (0%)	0.37
Photosensitivity reaction	0 (0%)	0 (0%)	2 (1%)	0 (0%)	0.25
Platelet count decreased	61 (33%)	13 (7%)	1 (1%)	0 (0%)	<0.0001
Platelet count increased	0 (0%)	0 (0%)	4 (2%)	0 (0%)	0.06
Platelet disorder	28 (15%)	9 (5%)	0 (0%)	0 (0%)	<0.0001
Pneumonia	0 (0%)	0 (0%)	2 (1%)	2 (1%)	0.25
Pulmonary embolism	3 (2%)	2 (1%)	1 (1%)	1 (1%)	0.62
Pyrexia	5 (3%)	1 (1%)	15 (8%)	6 (3%)	0.02
Rash	43 (23%)	0 (0%)	87 (48%)	3 (2%)	<0.0001
Skin infection	2 (1%)	0 (0%)	0 (0%)	0 (0%)	0.50
Thrombocytopenia	33 (18%)	11 (6%)	0 (0%)	0 (0%)	<0.0001
Tinnitus	7 (4%)	1 (1%)	1 (1%)	0 (0%)	0.07
Tongue coated	0 (0%)	0 (0%)	2 (1%)	0 (0%)	0.25
Toothache	1 (1%)	0 (0%)	4 (2%)	1 (1%)	0.21
Urinary tract infection	11 (6%)	0 (0%)	4 (2%)	0 (0%)	0.11
Vision blurred	0 (0%)	0 (0%)	2 (1%)	0 (0%)	0.25
Vomiting	86 (47%)	10 (5%)	63 (35%)	4 (2%)	0.02
Vulvovaginal candidiasis	0 (0%)	0 (0%)	3 (2%)	0 (0%)	0.12
Weight increased	0 (0%)	0 (0%)	2 (1%)	0 (0%)	0.25
White blood cell count	37 (20%)	3 (2%)	6 (3%)	1 (1%)	<0.0001
White blood cell count decreased	73 (40%)	4 (2%)	9 (5%)	0 (0%)	<0.0001
White blood cell count increased	0 (0%)	0 (0%)	2 (1%)	0 (0%)	0.25
White blood cell disorder	29 (16%)	7 (4%)	2 (1%)	0 (0%)	<0.0001

*p-value calculated from 2-sided Fisher's exact test

Carboplatin n=184 patients who started carboplatin treatment

Docetaxel n=182 patients who started docetaxel treatment

Table S8. Adverse events reported by crossover treatment (any grade and grade 3+ only) meeting one of the following criteria: difference in overall proportion between treatments is >1%; overall proportion in either treatment group>10%; statistically significant difference (p<0.01) between the two treatments according to 2-sided Fisher's exact

Toxicity	Cross-over Carboplatin Any grade	Cross-over Carboplatin Grade 3/4	Cross-over Docetaxel Any grade	Cross-over Docetaxel Grade 3/4	p-value*
Abdominal discomfort	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1.00
Abdominal distension	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1.00
Abdominal pain	6 (7%)	0 (0%)	3 (3%)	0 (0%)	0.32
Abdominal tenderness	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0.49
Ageusia	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0.49
Alanine aminotransferase	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0.49
Alanine aminotransferase increased	6 (7%)	1 (1%)	4 (4%)	1 (1%)	0.53
Alopecia	62 (70%)	0 (0%)	82 (87%)	0 (0%)	0.004
Anaemia	20 (22%)	1 (1%)	20 (21%)	2 (2%)	0.86
Anosmia	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0.49
Anxiety	3 (3%)	1 (1%)	1 (1%)	0 (0%)	0.36
Aphasia	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1.00
Arthralgia	9 (10%)	1 (1%)	19 (20%)	1 (1%)	0.07
Arthritis	1 (1%)	1 (1%)	0 (0%)	0 (0%)	0.49
Aspartate aminotransferase	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0.49
Aspartate aminotransferase increased	5 (6%)	1 (1%)	2 (2%)	0 (0%)	0.27
Ataxia	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0.49
Atrioventricular block second degree	1 (1%)	1 (1%)	0 (0%)	0 (0%)	0.49
Axillary pain	0 (0%)	0 (0%)	4 (4%)	0 (0%)	0.12
Back pain	14 (16%)	0 (0%)	9 (10%)	2 (2%)	0.27
Bacterial infection	0 (0%)	0 (0%)	1 (1%)	1 (1%)	1.00
Blood albumin abnormal	1 (1%)	0 (0%)	2 (2%)	0 (0%)	1.00
Blood alkaline phosphatase	5 (6%)	2 (2%)	4 (4%)	1 (1%)	0.74
Blood alkaline phosphatase abnormal	3 (3%)	2 (2%)	2 (2%)	0 (0%)	0.68
Blood alkaline phosphatase increased	16 (18%)	1 (1%)	13 (14%)	2 (2%)	0.54
Blood creatinine	4 (4%)	0 (0%)	0 (0%)	0 (0%)	0.05
Blood creatinine increased	1 (1%)	0 (0%)	2 (2%)	0 (0%)	1.00
Blood magnesium	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1.00
Blood magnesium decreased	0 (0%)	0 (0%)	2 (2%)	0 (0%)	0.50
Blood potassium decreased	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1.00
Body temperature	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1.00
Bone pain	4 (4%)	0 (0%)	2 (2%)	0 (0%)	0.43
Breast pain	1 (1%)	0 (0%)	2 (2%)	0 (0%)	1.00
Breast swelling	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0.49
Chest pain	5 (6%)	1 (1%)	3 (3%)	0 (0%)	0.49
Clumsiness	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0.49
Confusional state	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0.49
Conjunctivitis	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1.00
Constipation	48 (54%)	1 (1%)	50 (53%)	1 (1%)	1.00
Contusion	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1.00

Convulsion	2 (2%)	1 (1%)	0 (0%)	0 (0%)	0.24
Cough	5 (6%)	1 (1%)	11 (12%)	1 (1%)	0.19
Cystitis	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0.49
Deafness	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0.49
Decreased appetite	41 (46%)	2 (2%)	59 (63%)	1 (1%)	0.03
Deep vein thrombosis	1 (1%)	1 (1%)	0 (0%)	0 (0%)	0.49
Depression	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1.00
Diarrhoea	28 (31%)	0 (0%)	39 (41%)	0 (0%)	0.17
Disturbance in attention	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0.49
Dry eye	0 (0%)	0 (0%)	2 (2%)	0 (0%)	0.50
Dry mouth	2 (2%)	0 (0%)	1 (1%)	0 (0%)	0.61
Dry skin	4 (4%)	0 (0%)	3 (3%)	0 (0%)	0.71
Dysgeusia	6 (7%)	0 (0%)	12 (13%)	0 (0%)	0.22
Dyspepsia	8 (9%)	0 (0%)	5 (5%)	0 (0%)	0.40
Dysphagia	0 (0%)	0 (0%)	2 (2%)	0 (0%)	0.50
Dysphonia	0 (0%)	0 (0%)	3 (3%)	0 (0%)	0.25
Dyspnoea	10 (11%)	1 (1%)	17 (18%)	2 (2%)	0.22
Dyspnoea exertional	1 (1%)	0 (0%)	4 (4%)	0 (0%)	0.37
Ear congestion	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0.49
Ear infection	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0.49
Ear pain	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1.00
Epistaxis	0 (0%)	0 (0%)	2 (2%)	0 (0%)	0.50
Eructation	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0.49
Extravasation	0 (0%)	0 (0%)	2 (2%)	0 (0%)	0.50
Eye disorder	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1.00
Eye pain	2 (2%)	0 (0%)	1 (1%)	0 (0%)	0.61
Facial pain	1 (1%)	1 (1%)	0 (0%)	0 (0%)	0.49
Fatigue	83 (93%)	11 (12%)	90 (96%)	19 (20%)	0.53
Febrile neutropenia	20 (22%)	4 (4%)	30 (32%)	18 (19%)	0.18
Flatulence	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0.49
Fluid retention	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1.00
Flushing	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0.49
Foreign body sensation in eyes	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1.00
Furuncle	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0.49
Gait disturbance	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0.49
Gamma-glutamyltransferase	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1.00
Gamma-glutamyltransferase increased	0 (0%)	0 (0%)	2 (2%)	1 (1%)	0.50
Gastroenteritis	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1.00
Gastrointestinal pain	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1.00
Gastrooesophageal reflux disease	0 (0%)	0 (0%)	2 (2%)	0 (0%)	0.50
Glossodynia	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0.49
Groin pain	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1.00
Haematochezia	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1.00
Haematology test abnormal	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0.49
Haemoglobin	11 (12%)	0 (0%)	6 (6%)	0 (0%)	0.21
Haemoglobin abnormal	17 (19%)	2 (2%)	12 (13%)	1 (1%)	0.31
Haemoglobin decreased	48 (54%)	5 (6%)	44 (47%)	0 (0%)	0.38
Haemoptysis	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1.00
Haemorrhoids	1 (1%)	0 (0%)	2 (2%)	0 (0%)	1.00
Headache	7 (8%)	2 (2%)	5 (5%)	0 (0%)	0.56
Hearing impaired	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1.00
Hepatomegaly	0 (0%)	0 (0%)	1 (1%)	1 (1%)	1.00

Herpes zoster	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0.49
Hot flush	1 (1%)	0 (0%)	2 (2%)	0 (0%)	1.00
Hyperglycaemia	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1.00
Hypersensitivity	24 (27%)	1 (1%)	22 (23%)	0 (0%)	0.61
Hypoaesthesia	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1.00
Hypoalbuminaemia	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1.00
Hypocalcaemia	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0.49
Hypokalaemia	1 (1%)	1 (1%)	0 (0%)	0 (0%)	0.49
Hypomagnesaemia	2 (2%)	1 (1%)	1 (1%)	0 (0%)	0.61
Hyponatraemia	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0.49
Hypotension	0 (0%)	0 (0%)	2 (2%)	0 (0%)	0.50
Infection	18 (20%)	1 (1%)	15 (16%)	4 (4%)	0.56
Influenza	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1.00
Influenza like illness	2 (2%)	0 (0%)	0 (0%)	0 (0%)	0.24
Infusion site haematoma	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1.00
Infusion site infection	1 (1%)	0 (0%)	2 (2%)	1 (1%)	1.00
Infusion site pain	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1.00
Infusion site reaction	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1.00
Injection site extravasation	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1.00
Injection site reaction	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1.00
Insomnia	7 (8%)	1 (1%)	5 (5%)	0 (0%)	0.56
Intestinal perforation	0 (0%)	0 (0%)	1 (1%)	1 (1%)	1.00
Irritable bowel syndrome	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0.49
Joint swelling	0 (0%)	0 (0%)	4 (4%)	0 (0%)	0.12
Lacrimation increased	4 (4%)	0 (0%)	6 (6%)	0 (0%)	0.75
Lethargy	0 (0%)	0 (0%)	1 (1%)	1 (1%)	1.00
Leukopenia	6 (7%)	1 (1%)	4 (4%)	0 (0%)	0.53
Local swelling	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1.00
Localised infection	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1.00
Lower respiratory tract infection	4 (4%)	0 (0%)	10 (11%)	3 (3%)	0.16
Lung infection	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1.00
Lymphadenopathy	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0.49
Lymphoedema	5 (6%)	1 (1%)	8 (9%)	1 (1%)	0.57
Lymphopenia	2 (2%)	1 (1%)	1 (1%)	0 (0%)	0.61
Malaise	1 (1%)	1 (1%)	0 (0%)	0 (0%)	0.49
Migraine	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0.49
Mood altered	0 (0%)	0 (0%)	2 (2%)	0 (0%)	0.50
Mucosal inflammation	31 (35%)	0 (0%)	65 (69%)	3 (3%)	<0.001
Muscular weakness	2 (2%)	1 (1%)	0 (0%)	0 (0%)	0.24
Musculoskeletal chest pain	1 (1%)	0 (0%)	3 (3%)	0 (0%)	0.62
Musculoskeletal stiffness	0 (0%)	0 (0%)	2 (2%)	0 (0%)	0.50
Myalgia	3 (3%)	0 (0%)	20 (21%)	2 (2%)	0.0002
Nail bed infection	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1.00
Nail discolouration	1 (1%)	0 (0%)	2 (2%)	0 (0%)	1.00
Nail disorder	6 (7%)	0 (0%)	10 (11%)	1 (1%)	0.44
Nail dystrophy	0 (0%)	0 (0%)	2 (2%)	0 (0%)	0.50
Nail infection	1 (1%)	1 (1%)	0 (0%)	0 (0%)	0.49
Nausea	58 (65%)	3 (3%)	62 (66%)	2 (2%)	1.00
Neck pain	1 (1%)	0 (0%)	4 (4%)	0 (0%)	0.37
Neuropathy peripheral	50 (56%)	3 (3%)	58 (62%)	10 (11%)	0.46
Neurotoxicity	0 (0%)	0 (0%)	1 (1%)	1 (1%)	1.00
Neutropenia	15 (17%)	4 (4%)	5 (5%)	3 (3%)	0.02
Neutropenic sepsis	0 (0%)	0 (0%)	4 (4%)	3 (3%)	0.12
Neutrophil count	9 (10%)	2 (2%)	1 (1%)	1 (1%)	0.01
Neutrophil count	6 (7%)	2 (2%)	0 (0%)	0 (0%)	0.01

abnormal					
Neutrophil count decreased	15 (17%)	8 (9%)	0 (0%)	0 (0%)	<0.001
Night sweats	2 (2%)	0 (0%)	1 (1%)	0 (0%)	0.61
Ocular hyperaemia	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0.49
Oedema	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1.00
Oedema peripheral	3 (3%)	0 (0%)	8 (9%)	0 (0%)	0.21
Oesophagitis	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1.00
Onychalgia	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1.00
Onychoclasia	0 (0%)	0 (0%)	2 (2%)	0 (0%)	0.50
Onycholysis	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1.00
Onychomadesis	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0.49
Open wound	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1.00
Oral candidiasis	1 (1%)	0 (0%)	2 (2%)	0 (0%)	1.00
Oropharyngeal pain	2 (2%)	0 (0%)	4 (4%)	0 (0%)	0.68
Orthostatic hypotension	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1.00
Ototoxicity	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0.49
Pain	2 (2%)	0 (0%)	7 (7%)	1 (1%)	0.17
Pain in extremity	7 (8%)	2 (2%)	12 (13%)	4 (4%)	0.34
Pain of skin	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1.00
Palmar-plantar erythrodysesthesia syndrome	0 (0%)	0 (0%)	6 (6%)	1 (1%)	0.03
Palpitations	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1.00
Pancytopenia	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0.49
Paraesthesia	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1.00
Paraesthesia oral	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0.49
Paronychia	1 (1%)	0 (0%)	2 (2%)	0 (0%)	1.00
Pelvic pain	1 (1%)	1 (1%)	0 (0%)	0 (0%)	0.49
Petechiae	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0.49
Pharyngitis	4 (4%)	0 (0%)	1 (1%)	0 (0%)	0.20
Phlebitis	1 (1%)	0 (0%)	2 (2%)	0 (0%)	1.00
Photophobia	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0.49
Platelet count decreased	34 (38%)	13 (15%)	0 (0%)	0 (0%)	<0.0001
Platelet count increased	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1.00
Platelet disorder	9 (10%)	4 (4%)	2 (2%)	0 (0%)	0.03
Pleural effusion	1 (1%)	0 (0%)	2 (2%)	0 (0%)	1.00
Postoperative wound infection	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0.49
Pulmonary embolism	4 (4%)	1 (1%)	1 (1%)	1 (1%)	0.20
Pyrexia	1 (1%)	0 (0%)	9 (10%)	2 (2%)	0.02
Radiculopathy	0 (0%)	0 (0%)	1 (1%)	1 (1%)	1.00
Rash	24 (27%)	0 (0%)	43 (46%)	1 (1%)	0.01
Respiratory tract infection	1 (1%)	0 (0%)	2 (2%)	0 (0%)	1.00
Rhinitis	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1.00
Salivary hypersecretion	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0.49
Sepsis	0 (0%)	0 (0%)	1 (1%)	1 (1%)	1.00
Sinusitis	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0.49
Skin infection	1 (1%)	1 (1%)	0 (0%)	0 (0%)	0.49
Social avoidant behaviour	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1.00
Swelling	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1.00
Tearfulness	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1.00
Thrombocytopenia	9 (10%)	3 (3%)	0 (0%)	0 (0%)	0.001
Thrombophlebitis	0 (0%)	0 (0%)	2 (2%)	0 (0%)	0.50
Tinnitus	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1.00
Tooth abscess	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1.00

Toothache	1 (1%)	1 (1%)	0 (0%)	0 (0%)	0.49
Tremor	2 (2%)	2 (2%)	0 (0%)	0 (0%)	0.24
Upper respiratory tract infection	2 (2%)	0 (0%)	1 (1%)	0 (0%)	0.61
Vertigo	0 (0%)	0 (0%)	1 (1%)	1 (1%)	1.00
Vision blurred	2 (2%)	0 (0%)	0 (0%)	0 (0%)	0.24
Visual impairment	2 (2%)	0 (0%)	1 (1%)	0 (0%)	0.61
Vomiting	34 (38%)	1 (1%)	35 (37%)	0 (0%)	1.00
Vulvovaginal pain	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1.00
Vulvovaginal pruritus	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1.00
Weight increased	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0.49
White blood cell count	14 (16%)	1 (1%)	1 (1%)	0 (0%)	0.0002
White blood cell count decreased	42 (47%)	2 (2%)	8 (9%)	0 (0%)	<0.0001
White blood cell disorder	12 (13%)	3 (3%)	2 (2%)	0 (0%)	0.004
Wound infection	0 (0%)	0 (0%)	2 (2%)	0 (0%)	0.50

*p-value calculated from 2-sided Fisher's exact test

Carboplatin n=89 patients who started crossover carboplatin treatment

Docetaxel n=94 patients who started crossover docetaxel treatment

Table S9. Grade 3 or 4 Toxicity by germline *BRCA1/2* mutation status

Hematological				
	Docetaxel		Carboplatin	
	No mutation	gBRCA1/2	No mutation	gBRCA1/2
Grade 3/4	33 (23·2%)	4 (23·5%)	38 (30·2%)	9 (36·0%)
No Grade 3/4	109 (76·8%)	13 (76·5%)	88 (69·8%)	16 (64·0%)
Total	142 (100·0%)	17 (100·0%)	126 (100·0%)	25 (100·0%)
	exact p=1·00		exact p=0·64	
Non-hematological				
	Docetaxel		Carboplatin	
	No mutation	gBRCA1/2	No mutation	gBRCA1/2
Grade 3/4	68 (47·9%)	9 (52·9%)	39 (31·0%)	12 (48·0%)
No Grade 3/4	74 (52·1%)	8 (47·1%)	87 (69·1%)	13 (52·0%)
Total	142 (100·0%)	17 (100·0%)	126 (100·0%)	25 (100·0%)
	exact p=0·80		exact p=0·110	

P-values are calculated from 2-sided Fisher's exact test.

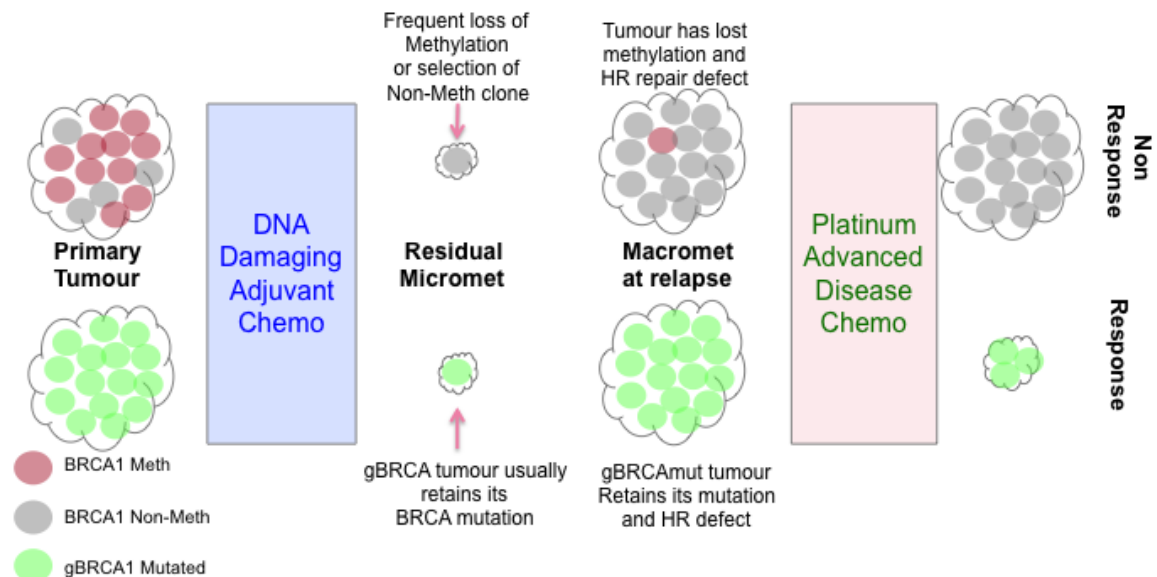
Docetaxel n = 159 patients with known BRCA mutation status who started randomised docetaxel treatment

Carboplatin n = 151 patients with known BRCA mutation status who started randomised carboplatin treatment

Figure S8. 143bp target sequence at *BRCA1* promoter. CG dinucleotides, which are potential targets for DNA methylation, are underlined.

5'
TGAGAGGCTGCTGCTTAGCGGTAGCCCCTTGGTTTCCGTTGGCAACCGGAAAAGCGCGGGAA
TTACAGATAAATTAAACTGCGACTGCGCGGCGTGAGCTCGCTGAGACTTCCTGGACCGG
GGACAGGCTGTGGGGTTTCTCAG 3'

Figure S9. Hypothetical model to explain genetic and epigenetic BRCAness biomarker breast cancer treatment response interactions



In this trial *BRCA1/2* mutation is determined in germline whereas *BRCA1* methylation status is determined in archival treatment naïve primary tumour.

Germline *BRCA1* or *BRCA2* mutated tumours have by definition universal mutation in one allele and near universal loss of the remaining wild-type alleles whereas those with *BRCA1* methylation have some unmethylated sub-clones. Both *BRCA1/2* mutation and *BRCA1* methylation cause a high Myriad HRD Score in breast and ovarian cancer (Timms et al).

When a selective pressure of DNA damaging adjuvant chemotherapy is applied the methylated tumour some clones will survive by demethylation and these as well as any unmethylated clones may be more likely to survive as micrometastases at the end of treatment. Although reversion mutations in *BRCA1* and *BRCA2* are described this loss of HR deficiency is predicted to happen less frequently (“Hard BRCAness”) than loss of the HR deficiency associated with methylation (“Soft BRCAness”).

When the micrometastases proliferate and emerge clinically as advanced TNBC a previously methylated primary tumour is now, as a metastasis, no longer significantly methylated. It cannot however reverse its Myriad HRD “genomic scar” which is permanently fixed in the genome. While the gBRCA mutated tumour retains its mutation and HR deficiency and has a high response rate to carboplatin the originally *BRCA1* methylated tumour has lost any previous HR deficiency and differential carboplatin sensitivity. The Myriad HRD high status, by being present as a result of both “hard” genetic and “soft” epigenetic BRCAness has high negative predictive value but poor positive predictive value and unlike *BRCA1/2* mutation has no interaction with treatment effect in a prior adjuvant therapy exposed advanced breast cancer setting.

Timms KM, Abkevich V, Hughes E, Neff C, Reid J, Morris B, et al. Association of *BRCA1/2* defects with genomic scores predictive of DNA damage repair deficiency among breast cancer subtypes. *Breast Cancer Res* 2014;16:475.

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