TNT: A randomized phase III trial of carboplatin (C) compared with docetaxel (D) for patients with metastatic or recurrent locally advanced triple negative or BRCA1/2 breast cancer (CRUK/07/012)

Introduction
Subgroups within triple negative breast cancers (TNBCs) appear to share impaired DNA repair mechanisms with BRCA1/2 germline mutation +ve (gBRCA+); hypothesised to confer sensitivity to platinum. TNT tested this hypothesis for women with recurrent locally advanced (LABC) metastatic (MBC) gBRCA+ or TNBC.

Methods
Eligible patients (pts) had ER-, PgR-, HER2- BC or were known gBRCA+ (any ER/PgR/HER2). Pts were randomized to C (AUC 6 q3wk) or D (100mg/m² q3wk) for 6-8 cycles or until disease progression if sooner with crossover possible on progression. Ineligibility incl. 1) adjuvant taxane in ≤12mth 2) previous platinum 3) non-anthracyclines for MBC. Blood & archival tissue were requested for BRCA1/2 genotyping, central analysis of TN subtype & DNA repair deficiency biomarkers. Primary endpoint was ITT objective response rate (ORR) to cycle 6. Secondary endpoints incl. toxicity, PFS, OS & pre-planned subgroups (gBRCA+, HR deficiency (HRD), basal-like (IHC & PAM50). TNT aimed to detect a 15% improvement in ORR with C compared to D (α=0.05, power=90%).

Results
376 (188 C, 188 D) pts were recruited (74 UK centres, 08/08-03/14). Median age 55.3yr (IQR 48-63). 29 (8%) were known gBRCA+ (16 TNBC, 12 ER+ HER2-, 1 ER unk HER2-). 341 (91%) had MBC & 35 (9%) recurrent LABC. 34% had adjuvant taxane. Median relapse interval 2.1yr (IQR 1.4-3.4). Tumour (primary 309 pts, recurrent 102 pts), blood DNA (288 pts) was obtained.

ORRs were C 59/188 (31.4%, 95%CI 25-38) & D 67/188 (35.6%, 95%CI 29-42), abs. diff. -4.2% (95%CI -13.7-5.3) p=0.44. Median PFS C 3.1 (95%CI 2.5-4.2) vs D 4.5 (95%CI 4.1-5.2) mth; abs. diff. -0.4 (95%CI -1.1-0.3) p=0.29. Median OS C 12.4 (95%CI 10.4-15.3) vs D 12.3 (95%CI 10.5-13.6) mth; abs. diff. -0.2 (95%CI -1.1-0.8) p=0.31.

For 43 gBRCA+ pts (29 known & 14 research test), ORR of 68.0% with C (17/25, 95%CI 46.5-85.1) & 33.3% D (6/18, 95%CI 13.3-59.0) p=0.03. 273 gBRCA- pts, ORR=28.1% C (36/128, 95%CI 20.5-36.8) & 36.6% D (53/145, 95%CI 28.7-44.9) p=0.16. Interaction p=0.01.

195 pts had MYRIAD HRD scores. 81 high (≥42), ORR=38.2% with C (13/34, 95%CI 22.2-56.4) & 42.6% with D (20/47, 95%CI 28.3-57.8) p=0.82; 114 low (<42), ORR=29.2% C (19/65, 95%CI 18.6-41.8) & 34.7% D (17/49, 95%CI 21.7-49.6) p=0.55. Interaction p=0.91.

By central ER/PgR/HER2/CK5/EGFR IHC 116 pts were core basal-like, ORR=32.2% C (19/59, 95%CI 20.6-45.6) & 28.1% D (16/57, 95%CI 17.0-41.5) p=0.69 & 51 5-marker –ve non-basal (SNP), ORR=24.0% C (6/25, 95%CI 9.4-45.1) & 42.3% D (11/26, 95%CI 23.4-63.1) p=0.24. Interaction p=0.16.

By Prosigna PAM50 in pts entering as TN 174 had basal-like, ORR=32.6% C (28/86, 95%CI 22.8-43.5) & 35.2% D (31/88, 95%CI 25.3-46.1) p=0.75 & 36 pts non-basal subtypes, ORR=16.7% with C (3/18, 95%CI 3.6-41.4) & 73.7% with D (13/18, 95%CI 46.5-90.3) p<0.01. Interaction p=0.01.

Discussion
While TNT gives no evidence to support superior activity of C compared to D in unselected TNBC pts results for gBRCA+ pts support their greater sensitivity to C than D. Neither a dichotomised MYRIAD
HRD score nor 2 basal-like classifiers selected sensitivity to C. The sensitivity to D of a non-basal-like subgroup by Prosigna PAM50 warrants independent investigation.