SABC Abstract 3662. PS1-13-06

# Personalised Therapy in Triple Negative breast cancer (TNBC), evaluating predictive performance of Bayesian AI Digital Twins.

N. Somaiah[1,2] , R. Kow[1,2] , S. Anbalagan[1,2] , I. Roxanis[1] , R. Chauhan[1] , S. Kannambath[1] , L. Gothard[1,2] , S. Nimalasena[2] , J. Noble[2] , A. Johns[3] , E. Misirlioglu[3] , B. Plummer[3] , A. Biankin[4] , I. Babina[3] , M. Griffiths[3] , U. S. Asghar[3,5]

[1]The Institute of Cancer Research, London, UK. [2]The Royal Marsden NHS Foundation, London, UK. [3] Concr Limited, Regent House, 316a Beulah Hill, London, UK. [4]Wolfson Wohl Cancer Research Centre, School of Cancer Sciences, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, UK.
[5] Guys and St Thomas NHS Foundation Trust, Medical Oncology, London, UK.

## Background:

Despite multiple therapeutic strategies, approximately 40% of women with stage 2-3 Triple Negative breast (TNBC) cancer will die. Biomarkers are sparse and treatment related toxicities can be significant, especially when drugs fail. FarrSight®-Twin is a predictive tool which integrates multi-modal data, specifically clinical, pathological and genomic data and predicts probability of treatment response and overall survival for individual cancer patients.

## Objective:

Evaluate the clinical application of FarrSight®-Twin for predicting therapeutic response to neoadjuvant chemotherapy in TNBC.

## Aims:

1. In TNBC, assess the ability of FarrSight®-Twin to prospectively identify patients unlikely to achieve a pathological complete response (pCR).
2. Report the first set of accuracy metrics for predicting treatment response to anthracycline, taxane and platinum chemotherapy.

## Methods:

VISION is an observational, retrospective clinical study (n=200 RMH, UK) which analysed the performance of the predictive algorithm FarrSight®-Twin (2024-2025). Study population included stage 2-3 TNBC, treated with neoadjuvant chemotherapy+/- immunotherapy (IO). Participants were recruited into Arm A (pCR) or Arm B if they had residual disease (non-pCR) [Figure 1]. Digital or virtual twins of individuals were created using their clinical data, cancer stage and tumour molecular data (WES (n=66), RNA seq n= (43), WES + RNAseq (n=42)) from an FFPE diagnostic biopsy. Treatment response and overall survival were predicted for individuals using a leave one out approach. Performance and accuracy were assessed by comparing predictions against real outcomes [Figure 2].

## Results:

In this first pre-planned analysis, 34 women were recruited into Arm A and 60 into Arm B with a median age of 51 (24-77yrs). 87% stage 2 (n=82) and 13% stage 3 (n=12) [Table 1]. Neoadjuvant treatments administered were anthracycline-taxane (33%), anthracycline-taxane-platinum (34%) or anthracycline-taxane-platinum-IO (21%) or "Other". pCR was used to assess treatment response. pCR rates were highest for anthracycline-taxane-platinum-IO (50%). Similar pCR rates were reported for anthracycline-taxane (35%) and anthracycline-taxane-platinum regimens (31%). "Other" regimens consisting of de-escalated regimens following on treat toxicities and these women had pCR rates of 27% [Figure 3]. The overall negative predictive value for FarrSight®-Twin i.e. likelihood that an individual will not have a pCR following neoadjuvant chemotherapy was 74% [Table 2]. Treatment predictions were robust for predicting lack of response/sub-optimal (NPV) response to neoadjuvant anthracyclines (NPV=89%), taxanes (NPV=83%), and platinum treatments (NPV=79%).

## Conclusion:

FarrSight®-Twin integrates molecular data from routine diagnostic FFPE breast cancer samples with limited clinical information, making it both scalable and suitable for incorporation into standard care pathways. In stage II-III TNBC, it accurately predicts an individual patient's probability of non-response or suboptimal response (i.e., non-pCR) to neoadjuvant chemotherapy, an outcome observed in 50-70% of this population. Next generation predictive tools (genomic + AI) such as digital twin technology can help build more effective personalised treatment plans for cancer patients.

**Acknowledgements:** This work was funded by Innovate UK [grant number 10083274] for Precision Medicine.
**Contact details:** Dr Navita Somaiah: navita.somaiah@icr.ac.uk ; Dr Uzma Saddia Asghar: uzma.asghar3@nhs.net.

### VISION study design



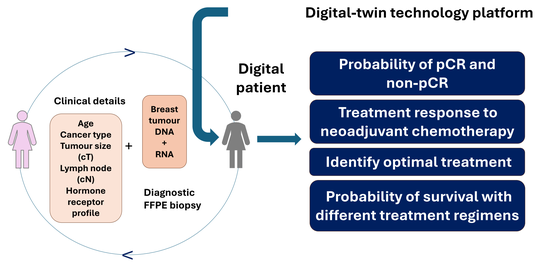

**Figure 1: VISION clinical trial design for retrospective stage**
An observational, retrospective study validating FarrSight®-Twin algorithm for patient prognostication and treatment stratification of neoadjuvant chemotherapy in the stage 2 -3 TNBC population; NCT06409221. Available clinical and molecular data for 34 individuals in Arm A and 60 individuals in Arm B was evaluated in the first interim analyses. This part of the study was conducted at The Royal Marsden NHS Foundation Trust.

| Patient characteristics n=94 | Arm A (n) | Arm B (n) | Total (n) | % |
|---|---|---|---|---|
| Female | 34 | 60 | 94 | 100% |
| Age (Years) at diagnosis | 47 (24-73 yrs) | 53 (28-77 yrs) | 51 (24-77 yrs) | |
| Age ≤ 40 (Years) | 8 | 4 | 12 | 13% |
| Ethnicity | | | | |
| White | 28 | 50 | 78 | 83% |
| Black | 2 | 4 | 6 | 6% |
| Asian | 3 | 3 | 6 | 6% |
| Chinese | 1 | 0 | 1 | 1% |
| Arab | 0 | 0 | 0 | 0% |
| Mixed | 0 | 1 | 1 | 1% |
| Missing data | 0 | 2 | 2 | 2% |
| Bilateral Breast Cancer | | | | |
| Yes | 3 | 0 | 3 | 3% |
| No | 31 | 60 | 91 | 97% |
| Laterality | | | | |
| Left | 18 | 32 | 50 | 53% |
| Right | 16 | 28 | 44 | 47% |
| Disease Stage at Diagnosis | | | | |
| Stage 2A | 24 | 33 | 57 | 60% |
| Stage 2B | 7 | 18 | 25 | 27% |
| Stage 3A | 3 | 9 | 12 | 13% |
| Tumour staging at diagnosis (largest tumour) | | | | |
| cT1 | 3 | 33 | 36 | 38% |
| cT2 | 26 | 17 | 43 | 46% |
| cT3 | 5 | 10 | 15 | 16% |
| cT4 | 0 | 0 | 0 | 0% |
| Nodal staging at diagnosis | | | | |
| N0 | 22 | 32 | 54 | 57% |
| N1 | 10 | 28 | 38 | 40% |
| N2 | 2 | 0 | 2 | 2% |
| N3 | 0 | 0 | 0 | 0% |
| Presentation | | | | |
| First | 34 | 57 | 91 | 97% |
| Recurrent | 0 | 3 | 3 | 3% |
| Hormone receptor status | | | | |
| ER 0 – 2 negative | 32 | 57 | 89 | 95% |
| ER 3 | 2 | 3 | 5 | 5% |
| PR 0 – 2 | 33 | 58 | 91 | 97% |
| PR 3 | 1 | 2 | 3 | 3% |
| HER2 status | | | | |
| HER2 0 | 21 | 50 | 71 | 76% |
| HER 2 1+ | 9 | 7 | 16 | 17% |
| HER2 2+ ISH negative | 4 | 3 | 7 | 7% |

**Table 1: Patient characteristics (n=94)**

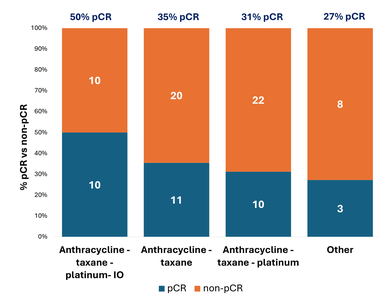
### Figure 2: Outputs of FarrSight®-Twin predictions

FarrSight®-Twin creates a digital patient linked to an actual TNBC patient and can predict best standard of care, probability of response by RECIST and overall survival according to the different neoadjuvant chemotherapy regimes.




### Figure 3: Actual responses to different neoadjuvant chemotherapy regimens in the VISION study.

pCR rate was 50% for chemotherapy – immunotherapy (n=20), 35% for anthracyclines- taxane (n=31), 31% for anthracycline-taxane-platinum (n=32) and 27% for "other" regimens (n=11). "Other" represents de-escalated regimens such as anthracycline sparing or a taxane-platinum regimen. De-escalation resulted due to drug toxicities, needing to omit specific drugs. In the VISION study, epirubicin was the anthracycline, paclitaxel/nab-paclitaxel was the taxane, carboplatin was the platinum and pembrolizumab was the administered immunotherapy.




| FarrSight®-Twin predictions for probability of pCR to different neoadjuvant chemotherapy | Nos | AUC | Accuracy TP + TN / TP+TN+FP+FN | Positive predictive value TP / TP + FP | Negative predictive value TN / TN+FN |
|---|---|---|---|---|---|
| Clinical data + Pathological data + Mutation (DNA) | 66 | 0.77 | 71% | 60% | **74%** |

**Table 2: Accuracy metrics for predicting pCR in TNBC.**
FarrSight®-Twin correctly predicted 74% of the time the individuals which were not going to have a pCR following neoadjuvant chemotherapy +/ -immunotherapy i.e. the negative predictive value. Limited clinical data (age, tumour type, clinical tumour size (cT), clinical nodal status (cN)) and molecular data from an FFPE diagnostic biopsy was needed as input. Whole exome sequencing and RNA seq was performed on the diagnostic biopsies. The first set of accuracy metrics have been reported using data from only 66 women with TNBC. The AUC was 0.77, 71% for prediction accuracy and 60% for positive predictive value.

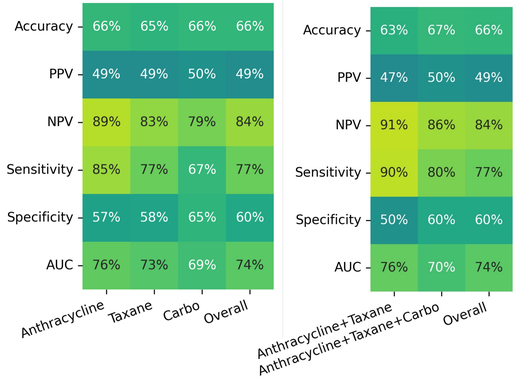



**Figure 4: FarrSight®-Twin accuracy metrics for predicting treatment response to neoadjuvant chemotherapy, specifically anthracyclines, taxanes and carboplatin.**
Heatmaps illustrating the different accuracy metrics assess for predicting therapeutic response to different chemotherapy drug classes in the neoadjuvant setting. Six accuracy metrics were reported: Accuracy = overall accuracy, PPV= Positive predictive value, NPV = negative predictive value, Sensitivity, Specificity and AUC (Area Under the Curve). FarrSight®-Twin was reliably able to identify those individuals who would not benefit/have sub-optimal benefit, if treated with an anthracycline 89% of the time, a taxane 83% of the time and carboplatin 79% of the time. Accuracy metrics for lack of response and AUC improved for regimens. These 1st set of accuracy metrics are based upon data from only 66 women with TNBC with molecular and clinical data, recruited into the VISION study.