NOSTRA-Feasibility Study Results

What was the study called?
"**NOSTRA-Feasibility** - A prospective non-randomised, multi-centre feasibility study to assess if patients with residual cancer following dual-targeted neoadjuvant chemotherapy treatment for HER2-positive, ER-negative early breast cancer can be identified by multiple ultrasound-guided tumour bed core biopsies."

We will explain what this means below.

Who carried out the research?
We ran the study from the Cancer Research UK Clinical Trials Unit at the University of Birmingham. The Chief Investigator (lead doctor) was Professor Daniel Rea. The main funder was Roche (a drug company).

What public involvement there was in the study?
A patient advocate who had had breast cancer was part of our study management group. She was involved with the study design, meetings and patient documents. Another patient advocate attended the group overseeing the study.

We presented the study to a patient group in 2021, in the COVID-19 pandemic. We followed their advice to help make the study acceptable during that unusual time.

Where and when did the study take place?
18 UK hospitals' research teams recruited participants between 30-Sep-2019 and 28-Dec-2024.

Why was the research needed?

Many people with early breast cancer have chemotherapy/targeted therapy before surgery. Sometimes these initial treatments work so well that there are no cancer cells seen at surgery, known as a **pathological complete response (pCR)**. This means some people have surgery when there is no cancer left to remove.

The problem is, we cannot be sure how well the initial treatment worked until we look at the tissue after surgery.

What were the main questions studied?

1- Can biopsies (tissue samples) after initial treatment tell us if someone has a pCR **before** surgery?
2- Can we plan a study leaving out surgery, for people who appear to have a pCR?

We also included two sub-studies to see if blood tests and/or Magnetic Resonance Imaging (MRI) could help tell us how well the initial treatment worked.

Who participated in the study?
72 people with early-stage breast cancer took part.

What treatments/procedures did the participants receive?
All participants had:

1. Chemotherapy and targeted treatments.
2. Up to 8 tissue samples taken from the area where the cancer was (the extra, study procedure).
3. Surgery to remove either the area where the cancer was or the whole breast.
4. Further treatments after surgery, such as radiotherapy and hormone therapy.

What happened during the study?
61 people had all of the above treatments/procedures in the study.

We looked at their tissue samples from the biopsies and surgery.

Some participants also took part in sub-studies:

ctDNA Sub-study:
- 19 people had blood tests before and during initial treatment and after surgery.
- We tested them for circulating tumour DNA (ctDNA).
- ctDNA is genetic material shed from cancer, found in blood.

MRI Sub-study:
- 16 people had MRI scans taken before and after initial treatment.
- Two radiologists (imaging doctors) looked at the scans.
- We recorded response seen on the scans and compared it to response seen in the tissue.

What medical problems (adverse reactions) did the participants have?
We recorded problems caused by the biopsies:
- 18/61 (30%) participants had mild side effects, including haematoma (lump of clotted blood), pain, bruising and swelling.
- 1 had moderate pain.
- Noone had to go to hospital because of these problems.

We also collected Serious Adverse Events (SAEs):
- There were 5 SAEs. 4 were not related to the study.
- 1 participant had an infected seroma (pocket of fluid under the skin) after surgery.
- These problems got better.

What were the results of the study?

Main Study
When we looked at all the tissue samples, we found that some people had a **false negative** result. This means the biopsy results showed no cancer, but there *were* cancer cells present at surgery.

This was the case for:

- 17 people (28%) when we looked at both invasive cancer and Ductal Carcinoma in Situ (DCIS) cells
- 6 people (10%) when we looked at invasive cancer cells only

This was higher than we were hoping.

ctDNA Sub-study
One test showed:

1. In people with a pCR:
   - a drop in ctDNA during initial treatment
   - a drop in ctDNA after surgery

2. In people without a pCR:
   - an increase in ctDNA during initial treatment
   - a drop in ctDNA after surgery

This suggests that ctDNA blood tests could help us tell how well the initial treatment is working in future.

MRI Sub-study
We looked at 15 participants' scans:

- 7 showed a pCR:
  - All were correct
  - 1 had DCIS left at surgery, which we did not spot.

- 7 showed a partial response:
  - 4 were correct
  - 3 had a pCR, but we mistook swelling for cancer cells.

- 1 showed no response: correct.

We did not miss any invasive cancer on the scans, but it can be hard to tell post-treatment swelling from DCIS and cancer cells. This suggests that MRI could help us tell how well the initial treatment is working in future.

Conclusion
The biopsies in the study gave too many false negative results. They alone were not good enough to tell us if there would be cancer cells left in the tissue from surgery.

However, it may be possible in future to leave out surgery for people with early breast cancer using MRI and ctDNA testing **as well** as biopsies.

How has this study helped patients and researchers?
It has helped us to plan a future trial looking at leaving out surgery in some patients with early breast cancer.

We now know that it is not safe enough to use biopsies alone to tell us if all the cancer cells have gone after initial treatment. Participants taking part in the trial leaving out surgery will need to have clear biopsies, blood tests and MRI scans after initial treatment.

Where can I learn more about this study?
The CRUK website. https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-study-looking-at-ultrasound-guided-biopsies-for-breast-cancer-nostra