Can a blood test be used instead of a tissue sample to select people with advanced breast cancer who would benefit from targeted treatment?

Results of the UK plasma based Molecular profiling of Advanced breast cancer to inform Therapeutic CHoices (plasmaMATCH) Trial:

A multiple parallel cohort, open-label, multi-centre phase IIa clinical trial aiming to provide proof of principle efficacy for designated targeted therapies in patients with advanced breast cancer where the targetable mutation is identified through ctDNA screening.

We have provided you with this information because you kindly took part in a clinical trial called **plasmaMATCH** as part of your treatment for breast cancer. We would like to thank you for taking part and share how your participation has helped to improve treatment for future patients.

Who carried out the trial?

The plasmaMATCH trial was funded by Cancer Research UK, AstraZeneca UK and Puma Biotechnology with support received from Guardant Health, BioRad, Breast Cancer Now and Asociacion Espanola Contra el Cancer (Spanish Association Against Cancer). The Chief Investigator is Professor Nicholas Turner of The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research. plasmaMATCH is coordinated by the Clinical Trials and Statistics Unit at The Institute of Cancer Research (ICR-CTSU).

What was the aim of the trial?

Breast cancer is the most common cancer in UK women with approximately 50,000 cases diagnosed each year. Despite advances in the management of advanced breast cancer it remains a cancer of substantial unmet need. The plasmaMATCH trial aimed to find out whether a screening blood test could be used instead of removing a small sample of the cancer called a 'biopsy' to select patients with advanced breast cancer who would be more likely to benefit from targeted treatment.

Why was the research needed?

Cells within the body contain genetic information stored in the form of **DNA**. Changes in DNA are known as **mutations**. Cancer cells contain mutations which alter their function and make them behave differently to normal cells. There are many different types of breast cancer, all of which are defined by the mutations present within the cancer cells. The most common way that these mutations are found is by looking at a sample of the cancer collected via a biopsy. The mutations present in cancer cells often change after a patient receives treatment such as chemotherapy, radiotherapy or targeted biological therapies, or when the cancer spreads to another part of the body.

When cells die they can release pieces of their DNA into the blood stream. The DNA from cancer cells is found in the blood of 90% of patients with advanced breast cancer. The DNA from cancer cells found in the blood is called '**circulating tumour DNA'** or **ctDNA**.

Treatments that target specific mutations within the cancer cells are known as **targeted therapy** and have led to improvements in the treatment of breast cancer. It is not always possible to perform further biopsies in patients with advanced breast cancer because the cancer may be in parts of the body where it is difficult to do a biopsy. Therefore, the choice of targeted therapy for advanced breast cancer is often based on the mutations identified in the original breast cancer biopsy and this may differ to the mutations present in advanced breast cancer.

The **Screening Component** of the plasmaMATCH trial, aimed to assess whether analysing the blood for mutations in ctDNA could provide an alternative approach to a biopsy for identifying the mutations present in advanced breast cancer.

The **Treatment Component** of the plasmaMATCH trial aimed to assess whether patients with advanced breast cancer who have a mutation identified through ctDNA screening benefit from a treatment targeting that specific mutation.

Who participated in the trial and what treatment did they receive?

In the **Screening Component** of the plasmaMATCH trial, **1103 women** with advanced breast cancer took part from **18 hospitals** across the UK (from 2016 to 2020).

In the **Treatment Component** of the plasmaMATCH trial, **217 women received trial treatment** according to mutations found in ctDNA in their blood sample. There were **five treatment groups** as shown in the table below:

Group	Mutation Type	Trial Treatment
A	**ESR1 mutation** a type of mutation in the oestrogen receptor (ER)	**84** participants received **fulvestrant** more frequently than normally given
B	**HER2 mutation** a mutation in the gene called HER2	**21** participants received either: **neratinib and fulvestrant** (if the cancer was sensitive to oestrogen) or **neratinib alone** (if the cancer was not sensitive to oestrogen)
C	**AKT1 mutation** a mutation in the gene called AKT1	**18** participants with received **capivasertib (a new drug) and fulvestrant** (if the cancer was sensitive to oestrogen)
D	**AKT-activating mutation** a mutation in one of the genes that causes activation of a process called the AKT pathway	**19** participants with received **capivasertib (a new drug)**
E	**Triple Negative Breast Cancer (TNBC)** a type of breast cancer in which there is a mutation in the gene called HER2 and the cancer cells are not sensitive to oestrogen or progesterone	**75** participants received **olaparib and ceralasertib (a new drug)**

What happened during the trial?

During the trial, blood samples were collected from participants for ctDNA screening to look for specific mutations in ctDNA. Data was collected on the results of ctDNA screening and the medical history of the participants. For participants who joined a treatment group data was collected on any treatment received, assessments performed to monitor their progress and any side effects experienced. Further blood and tissue samples were also collected from these participants. This involved regular assessments performed by health care professionals.

What were the results of the trial?

Researchers at the Institute of Cancer Research have analysed the data and tested the blood and biopsy samples collected during the trial.

Screening Component Results

The researchers compared the results from the two different ctDNA testing techniques used within the trial. They also compared the mutations found in the biopsies from advanced breast cancer with the mutations found in ctDNA in the blood samples.

Researchers found that:

- The two different ctDNA testing techniques identified the same mutations for 96% - 99% of samples, depending on the gene.
- The mutations found in ctDNA were the same as those found in the biopsy sample for between 93% - 95% of samples, depending on ctDNA testing technique used.
- When the biopsy and ctDNA samples were taken at the same time (within 2 months), the same mutations were found in 98% - 100% of samples.

Based on these findings, the researchers concluded that ctDNA screening is a highly accurate, rapid and less invasive method of identifying the mutations present in the advanced breast cancer to help decide which targeted treatment option is best for the patient.

Treatment Component Results

The researchers analysed how the trial treatment was working for the participants and how certain sub-groups of cancer responded to trial treatment in each of the treatment groups.

Researchers found that the cancer responded to treatment in:

- 6 out of 74 participants (8%) in group A
- 5 out of 20 participants (25%) in group B
- 4 out of 18 participants (22%) in group C
- 2 out of 19 participants (11%) in group D
- 12 out of 70 participants (17%) in group E

Based on the results from the treatment groups the researchers concluded that:

- **Group A** showed that receiving fulvestrant more frequently than normally given **may not** be a useful treatment for people with ESR1 mutations in advanced breast cancer.
- **Group B** showed that neratinib alone or given in combination with fulvestrant is a **potentially beneficial treatment** for people with a HER2 mutation in advanced breast cancer and needs to be further investigated.
- **Group C** showed that capivasertib and fulvestrant given in combination is a **potentially beneficial treatment** for people with AKT1 mutations in ER positive advanced breast cancer and needs to be further investigated.
- **Group D** showed that capivasertib **may not** be a useful treatment for people with mutations in the AKT pathway in advanced breast cancer.
- **Group E** showed that olaparib and ceralasertib in combination **may not** be a useful treatment for people with TNBC, however further research is needed to investigate whether olaparib, or olaparib and ceralasertib given in combination, may be of potential benefit to those with specific mutations.

What do our researchers say about the plasmaMATCH trial results?

Professor Nicholas Turner, Professor of Molecular Oncology at the ICR and Consultant Medical Oncologist at the RMH and plasmaMATCH Chief Investigator said:

"The choice of targeted treatment we give to patients is usually based on the mutations found in the original breast tumour. But the cancer can have different mutations after it has moved to other parts of the body.

We have now confirmed that liquid biopsies can quickly give us a bigger picture of what mutations are present within multiple tumours throughout the body, getting the results back to patients accurately and faster than we could before.

This is a huge step in terms of making decisions in the clinic – particularly for those women with advanced breast cancer who could quickly be put on new targeted treatments matched to their cancer if it evolves to become drug resistant."

Professor Judith Bliss, Professor of Clinical Trials at the ICR and Director of the Cancer Research UK funded ICR-CTSU and plasmaMATCH Methodology Lead said:

"We designed this study to look at several targeted treatments within a single trial platform. This setup has enabled us to study these multiple rare mutations effectively and quickly, reporting the results of the trial within only three years since the study started. These kinds of efficient clinical trial designs are key in cutting down the time it takes for new targeted treatments to reach patients."

Katrina Randle, plasmaMATCH Participant Representative said:
"It is a real privilege and honour to be able to contribute to this study and work alongside such dedicated researchers and clinicians that work tirelessly in seeking better outcomes and treatments for cancer patients.

I find it really exciting to see that this study has proven a reduction in timescales to translate study outcomes into targeted treatments for use in routine patient care is achievable.

Having a less invasive test available that can contribute to treatment decisions and more personalise treatment for patients is a very big step forward in improving cancer care.

For me, knowing the treatment you are receiving is more personalised to your tumour means it is going to have a greater impact on changing the course of the disease and improving overall outcomes for patients is hugely important. The impact on the longer-term mental wellbeing of cancer patients as a result of this cannot be underestimated.

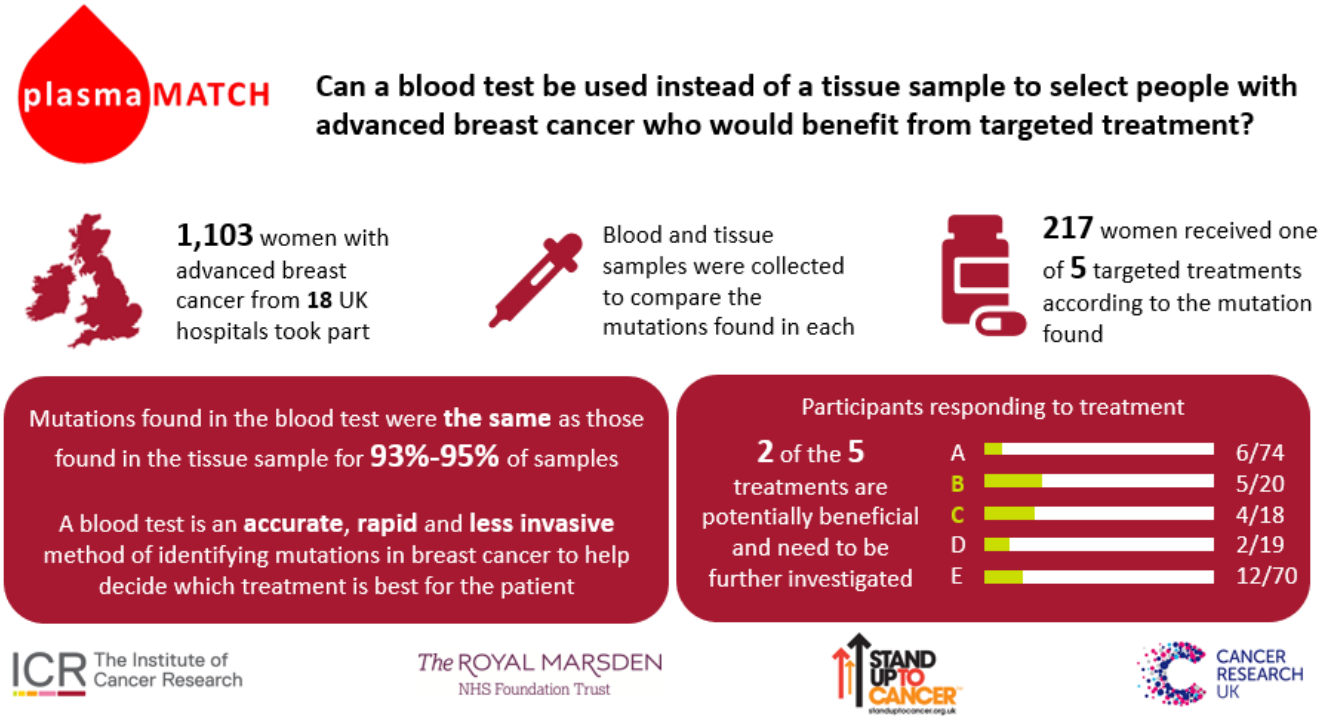
On behalf of all future patients, I would like to express my thanks and gratitude to all those patients that have taken part in this study. Without your involvement ad participation, improvements in cancer patient care and treatments available would not be possible."

Where can you learn more about this study?

You can read more about the plasmaMATCH trial in the medical journals Lancet Oncology and Clinical Cancer Research as well as the Cancer Research UK Cancer Help website where you can also search for further information on the trial treatments used within plasmaMATCH:

- The Lancet Oncology journal publication: https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(20)30444-7/fulltext (full results for the screening component and treatment groups A – D)
- Clinical Cancer Research journal publication: https://aacrjournals.org/clincancerres/article/29/23/4751/730229/Olaparib-and-Ceralasertib-AZD6738-in-Patients-with (full results for treatment group E)
- Cancer Research UK Cancer Help website: https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-using-a-blood-test-to-find-certain-gene-changes-and-decide-treatment-for-advanced-breast#undefined

The plasmaMATCH trial "at a glance"



Would you like to help influence cancer research in the future?

We are recruiting trial participants to become patient advocates to help us to develop and deliver our research. You can find out more about our work at the Institute of Cancer Research Clinical Trials and Statistics Unit on our website: https://www.icr.ac.uk/our-research/centres-and-collaborations/centres-at-the-icr/clinical-trials-and-statistics-unit

If you would like to help us, then please contact us via email on ppi-icrctsu@icr.ac.uk and we will send you further details.