MEDSIR
MEDICA SCIENTIA INNOVATION RESEARCH

Lay Language Summary

Exploratory study of the METALLICA trial

Impact of time to progression on CDK4/6 inhibitor therapy on progression-free survival (PFS) in HR+/HER2-/PIK3CA-mutated advanced breast cancer patients treated with alpelisib plus endocrine therapy: An exploratory analysis of the METALLICA trial

IMPORTANT:

- The document contains the summary of a clinical trial, and its sole purpose is to communicate the results of it to the general public.
- This document is not intended to promote recruitment or provide medical advice.
- The results reflected in this document may contradict those of other trials.
- It is not recommended to make decisions based on the information collected in this document; it should always be consulted with a medical professional beforehand.

ABOUT THIS SUMMARY

SPONSOR: MEDICA SCIENTIA INNOVATION RESEARCH S.L.

MEDICINE(S) STUDIED: Breast Cancer

DATES OF STUDY: 2020 August and 2022 March

TITLE OF THIS STUDY: Impact of time to progression on CDK4/6 inhibitor therapy on progression-free survival (PFS) in HR+/HER2-/PIK3CA-mutated advanced breast cancer patients treated with alpelisib plus endocrine therapy: An exploratory analysis of the METALLICA trial

DATE OF THIS REPORT: April 2024

PHARMACEUTIC PARTNERS: Novartis Pharmaceuticals

The content for this document was finalised by **MEDSIR** on the 2th of April of 2024. The information in this summary does not include additional information available after this date.

What was the purpose of this study?

Breast cancer (BC) is a disease in which breast cells grow up uncontrollably to produce masses called tumors. There are 5 stages of BC (0, I, II, III and IV) depending on the spread of BC cells upon diagnosis. In Stage III, BC cells spread into nearby tissues or lymph nodes around the breast (called "locally advanced") and, in Stage IV, BC cells spread to other parts further from the areas surrounding the breast (called "metastatic BC"). Advanced breast cancer (ABC) encompasses both Stage 3 and Stage 4 cancers.

Interestingly, breast cells can make changes in their activity because some substances bind protein molecules called "receptors", located on their surface. Estrogen and progesterone bind estrogen receptor (ER) and progesterone receptor (PR), respectively, to cause BC cell growth. Another receptor, the human epidermal growth factor receptor 2 (HER2), also has an important role, so blocking its activity by specific anticancer drugs could overcome BC. When BC cells have ER, PR, or both types of receptors, it is renamed as hormone receptor-positive (HR+) BC. In addition, BC can be HER2-negative (HER2-), which means that BC cells have low levels of HER2 or even absence of HER2.

Patients with HR+/HER2- ABC receive a standard treatment based on CDK4/6 inhibitors (CDK4/6i), to block the cell cycle of tumor cells, plus endocrine therapy (ET), to block the activity of sex hormones, which is ultimately necessary to avoid the development and growth of breast tumors. Between 30 and 40% of HR+/HER2- ABC patients have mutations in a gene called PIK3CA, which produces resistance to the standard therapy.

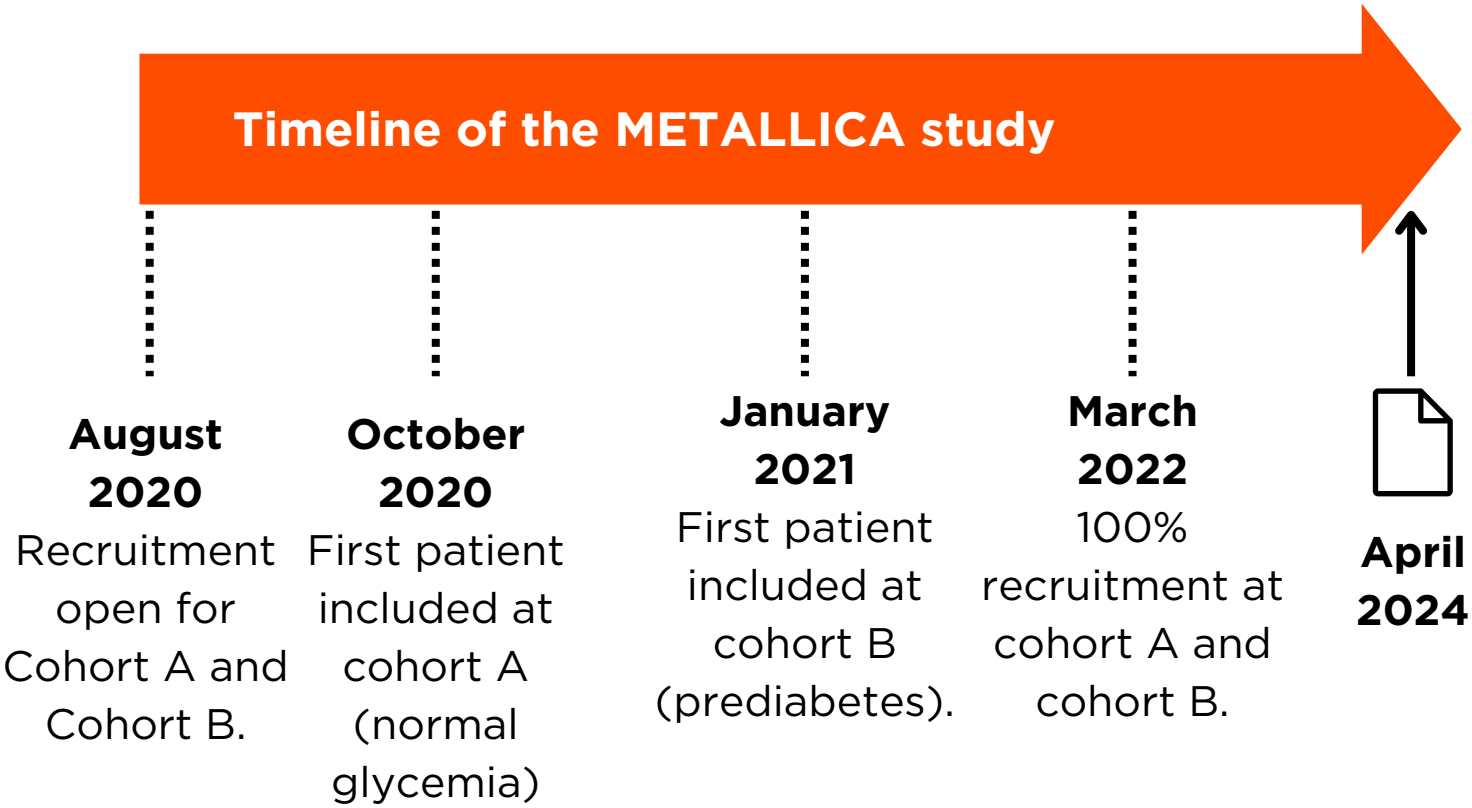
What did researchers want to find out?

Alpelisib was approved in combination with fulvestrant (a type of ET), to treat postmenopausal women and men with HR+/HER2-PIK3CA-mutated ABC whose disease has worsened. Although alpelisib has shown promising results in this type of patients, it produces some adverse effects such as hyperglycaemia (high blood sugar), and if it is severe enough, the treatment with alpelisib may be interrupted. Hyperglycemia is frequently managed with metformin, an agent used for prediabetic and diabetic patients to reduce the levels of blood sugar. METALLICA is a clinical trial that showed that the addition of metformin as a preventative treatment before treatment with alpelisib plus ET can reduced severe hyperglycaemia in HR+/HER2-/PIK3CA-mutated ABC patients with normal glycemia and prediabetes. The study found that only 2.1% of patients with normal glycemia and 15% of prediabetic patients experienced severe hyperglycaemia over the first 8 weeks of treatment.

Interestingly, an exploratory analysis of the EMERALD trial (performed in HR+/HER2- ABC patients) suggested that if BC starts growing again within a year after using CDK4/6i, it is a sign that it might not respond well to other hormone-based treatments afterwards. Here, we aimed to perform a similar exploratory analysis with the METALLICA patients.

When and where did the studies take place?

The METALLICA trial enrolled 68 adult patients with HR+/HER2-/PIK3CA-mutated ABC from Spanish hospitals between 30 August 2020 and 10 March 2022. Median age was 55.0 (range, 29-79) years old. 58 patients out of 68 had been treated with prior CDK4/6i for ABC and were included in this exploratory analysis. The goal of this exploratory analysis was to evaluated the progression free survival (PFS; the amount of time during and after treatment that the patient lived with the disease not getting any worse) and 1-year overall survival rate (1 year-OS; the percentage of patients that are alive after 12 months of treatment initiation) of patients recieving alpelisib, metformin and ET by analyzing the time the patients took to worsen on their prior CDK4/6i-based regimen <12 months vs. ⩾12 months for both rates.


Timeline of the METALLICA study
August 2020
Recruitment open for Cohort A and Cohort B.
October 2020
First patient included at cohort A (normal glycemia)
January 2021
First patient included at cohort B (prediabetes).
March 2022
100% recruitment at cohort A and cohort B.
April 2024

What were the results of the study?

The median time that patients were monitored after treatment was 7.8 months. Median PFS was 7.3 months for all patients that were previously treated with CDK4/6i. The patients that took ⩾12 months to worsen on previous CDK4/6i (35 out of 48), had a median PFS of 11.1 months and a 1-year OS of 96.7%, whereas the remaining 23 patients, whose disease got worse within one year on previous CDK4/6i had a shorter median PFS of 2.8 months and a smaller 1-year OS of 59.4%.

What were the main medical conclusions?

These results suggest that the longer it took for HR+/HER2-/PIK3CA-mutated ABC patients to worsen on their previous treatment of CDK4/6i-based therapy, the greater the associations with better efficacy outcomes after treatment with metformin, alpelisib, and ET.

What were the main social conclusions?

Profilactic metformin and alpelisib plus ET may be a promising therapy to get better efficacy outcomes in patients with HR+/HER2-/PIK3CA-mutated ABC if they took more than one year to worsen on CDK4/6i in the immediately prior treatment line.

Where I can find more information about the study?

Your doctor can help you understand more about this study and the results. Speak to your doctor about the treatment options available in your country. You should not make changes to your care based on the results of this or any single study. Keep taking your current treatment unless instructed by your doctor.

Thank you to the people who took part in the study

If you took part in this study, **MEDSIR**, as the Sponsor, extends its gratitude for your participation. This overview will outline the findings of the study. If you have any queries regarding the study or its outcomes, please reach out to the doctor or staff at your study location.

About MEDSIR

Founded in 2012, MEDSIR works closely with its partners to drive innovation in oncology research. Based in Spain and the United States, the company manages all aspects of clinical trials, from study design to publication, utilizing a global network of experts and integrated technology to streamline the process. The company offers proof-of-concept support and a strategic approach that helps research partners experience the best of both worlds from industry-based clinical research and investigator-driven trials. To promote independent cancer research worldwide, MEDSIR has a strategic alliance with Oncoclínicas, the leading oncology group in Brazil with the greatest research potential in South America.