PRESS RELEASE

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NATURE MEDICINE

A NEW ANTIBODY-DRUG CONJUGATE SHOWS PROMISING RESULTS IN METASTATIC BREAST CANCER

In ICARUS-BREAST 01 study, more than half of the patients with metastatic breast cancer saw their disease reduce or disappear completely thanks to the treatment. In some cases, this response has now lasted for more than two years. Dr Barbara Pistilli, Head of the Breast Cancer Group at Gustave Roussy and Guillaume Montagnac, Inserm researcher, Head of Tumor Cell Dynamics unit, coordinated the study, the results of which have just been published in *Nature Medicine*. They highlight the efficacy of patritumab deruxtecan (HER3-DXd), an antibody HER3-directed-drug conjugate (ADC), in patients with hormone receptor-positive metastatic breast cancer who had already received multiple treatments, including hormone therapy, chemotherapy, and targeted therapies. The study also offers early insights into why some patients respond better to this targeted therapy than others. This research was conducted within the UNLOCK program at the IHU Prism, in collaboration with Daiichi Sankyo.

Breast cancer remains the most common malignant tumour among women, with 2.3 million new cases and 685,000 deaths worldwide in 2020[1]. These figures underline the urgent need to develop new treatments in this indication.

Antibody-drug conjugates (ADCs) are an emerging class of therapeutics that combine an antibody, designed to recognise and bind to cancer cells, with a cytotoxic agent, often a chemotherapy drug. The antibody delivers its toxic payload directly into the cancer cell while sparing as much healthy tissue as possible.

ADCs have already shown highly encouraging clinical results in a number of solid and haematological tumours. However, despite their promise, their efficacy remains variable across patients. To date, the biological mechanisms underlying this variability, especially the causes of resistance, are still poorly understood. Identifying predictive biomarkers of response is a key challenge in optimising the personalised use of these therapies.

Published in *Nature Medicine*, ICARUS-BREAST 01 is a phase II trial sponsored by Gustave Roussy. It evaluated the efficacy and safety of patritumab deruxtecan (HER3-DXd) in

[1]Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA: A Cancer Journal for Clinicians 2024;74(1):12–49

99 patients with HR+/HER2- metastatic breast cancer whose disease had progressed following treatment with a CDK4/6 inhibitor and one line of chemotherapy. The trial also included an exploratory component aimed at identifying biomarkers predictive of response or resistance to this innovative therapy.

Promising Clinical Results

Patritumab deruxtecan is an ADC designed to target the HER3 protein, which is expressed in a high proportion of hormone receptor-positive breast cancer cells. This protein is known to play a role in resistance mechanisms to certain standard treatments, including hormone therapy and some targeted therapies.

From May 2021 to June 2023, ninety-nine women received patritumab deruxtecan by infusion every three weeks, until disease progression or the onset of a serious toxicity. The study met its primary endpoint: 53.5%of patients experienced a significant reduction in tumour size with patritumab deruxtecan, and around 63% of patients derived clinical benefit from the treatment (tumour shrinkage or disease stabilisation lasting at least six months). Notably, two patients experienced complete disappearance of visible signs of disease, a response that has now lasted more than two years.

The median follow-up period was 15.3 months. Median progression-free survival was 9.2 months, and the average duration of response was 9.3 months. The most common adverse events were fatigue (83%), nausea (75%) and diarrhoea (53%). The safety profile was consistent with that previously reported.

The Role of the UNLOCK Programme

The exploratory research component of ICARUS-BREAST 01 shed light on why some patients respond better than others do to patritumab deruxtecan, by identifying biomarkers linked to resistance mechanisms. This research, conducted within Gustave Roussy's UNLOCK programme at the IHU Prism, was based on exploratory analysis of tumour samples taken before and after treatment, as well as imaging and genetic data.

These exploratory analyses suggest that the response to the drug may be linked to how HER3 is distributed within the tumour and to the absence of certain mutations, such as ESR1. Another finding indicates that disease control may last longer in patients whose tumours express higher levels of HER3.

Samples collected during treatment revealed that the drug's efficacy appears to depend on its ability to penetrate the tumour, and on the activation of a specific immune response marked by an interferon signature, proteins naturally produced by the body that play a key role in stimulating the immune system.

"In this study, HER3-DXd demonstrated promising efficacy and good tolerability in patients with advanced hormone receptor-positive breast cancer who had exhausted standard treatment options," says Dr Pistilli. She adds, *"ICARUS-BREAST 01 also highlights interesting biological insights that could ultimately help us better identify patients who are most likely to benefit from this approach. These initial results now need to be confirmed by larger trials, some of which are already under way internationally and will soon open in France. Another study, ICARUS-BREAST 02, is currently ongoing with HER3-DXd. It aims to evaluate the*

efficacy of this ADC in combination with Olaparib following progression on a previous ADC, trastuzumab deruxtecan (T-DXd).”

Source

Nature Medicine
Patritumab deruxtecan in HR+HER2− advanced breast cancer: a phase 2 trial
https://www.nature.com/articles/s41591-025-03885-3
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About Gustave Roussy

Ranked first in France, first in Europe and fourth in the world, Gustave Roussy is a centre of global expertise entirely dedicated to patients living with cancer. The Institute is a founding pillar of the Paris-Saclay Cancer Cluster. Source of therapeutic innovations and diagnostic breakthroughs, the Institute welcomes nearly 50,000 patients each year, including 3,500 children and adolescents, and develops an integrated approach combining research, care and teaching. An expert in rare cancers and complex tumours, Gustave Roussy treats all cancers at all stages of life. It offers its patients personalised care that combines innovation and humanity, taking into account both care and the physical, psychological and social quality of life. With 4,100 employees at two sites, Villejuif and Chevilly-Larue, Gustave Roussy brings together the expertise essential for high-level cancer research; 32% of treated patients are included in clinical studies. To find out more about Gustave Roussy and follow the Institute’s news: www.gustaveroussy.fr/en, X, Facebook, LinkedIn, Instagram and Bluesky.

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