Lay Language Summary

DNADX-PARSIFAL

In advanced hormone receptor-positive and HER2-negative (HR+/HER2-) breast cancer following endocrine therapy and CDK4/6 inhibition: a correlative analysis from the PARSIFAL phase II randomized trial

Context

The study of the genetic material of a tumor by means of sequencing its DNA is crucial for the development of targeted therapies and personalized cancer treatments. Traditionally, obtaining tumor DNA for sequencing required an invasive surgical procedure to collect a tumor sample, known as a solid tumor biopsy.

Tumors release fragments of DNA into the bloodstream as they evolve and their cells die. These fragments, known as "circulating tumor DNA" (ctDNA), serve as a valuable tool for identifying genetic alterations in tumors. Liquid biopsy, involving a simple blood sample collection, represents a non-invasive procedure to obtain this ctDNA, overcoming difficulties associated with invasive solid tumor biopsies. This can be especially relevant for patients with metastatic cancer, since obtaining solid tumor biopsies from metastatic sites is challenging.

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About DNADX-PARSIFAL and the patients

DNADX is a novel machine learning-based tool that uses non-invasive liquid biopsy to classify patients into 4 different subtypes based on genetic signatures present in their ctDNA. These signatures provide relevant clinical information similar to what is typically obtained from a standard invasive solid tumor biopsy. Additionally, these signatures are associated with the treatment response and the survival of patients with metastatic breast cancer.

The PARSIFAL trial was the first clinical trial that directly explored the optimal hormone therapy agent (fulvestrant vs letrozole) to be used in combination with palbociclib as a first-line treatment for patients with hormone receptor-positive (HR+), human-epidermal growth factor receptor 2- negative (HER2-) advanced breast cancer. Involving a total of 486 patients, the trial found nonsignificant differences between fulvestrant-palbociclib or letrozole-palbociclib in terms of therapeutic efficacy or side effects.

This new exploratory and retrospective study seeks to further evaluate DNADX's efficacy in predicting the prognosis (chance of recovery or recurrence) of patients from the PARSIFAL trial, as well as to identify the subgroup of patients who might benefit more from either of the two hormone treatments.

In this study, baseline liquid biopsies from 122 patients (25.1% of the total 486 participants in the PARSIFAL trial) were used to obtain ctDNA, which was subsequently analyzed using DNADX technology. These patients had similar characteristics and outcomes than the whole PARSIFAL population. Those samples with a ctDNA tumor fraction (TF) $\geqslant$ 3% (a parameter that indicates the presence of a tumor) were classified into the 4 different ctDNA-based subtypes (Clusters-1, -2, -3, and -4). In patients with a ctDNA TF = 0, DNADX predicted a lower risk of disease progression and a lower risk of death compared to patients classified in the clusters (TF $\geqslant$ 3%). Additionally, a significant benefit of fulvestrant treatment over letrozole was observed in patients within Cluster-1 and Cluster-4 in contrast to the other subtypes.

Conclusions

In summary, the analysis of ctDNA in baseline blood samples using the DNADX signature could successfully predict patients' outcomes in advanced HR+/HER2- breast cancer patients receiving palbociclib in combination with hormone therapy, potentially identifying the optimal hormone treatment for each patient.

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.

About REVEAL GENOMICS®

REVEAL GENOMICS, S.L. is a biotechnology start-up seeking to change the way biomarkers are used in oncology. It is focused on developing innovative diagnostic tools to define the best therapeutic options for patients with cancer. The company uses pioneering techniques, sophisticated computer applications, and machine learning to reveal new cancer research data.
REVEAL GENOMICS, S.L. is a spin-off company of Hospital Clínic of Barcelona, IDIBAPS, the University of Barcelona (U.B.), and the Vall d'Hebron Institute of Oncology (VHIO).