REPORT
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CANCER

LIQUID BIOPSIES FOR IDENTIFICATION OF RESISTANCE MECHANISMS TO PARP INHIBITORS OF IN CANCERS ASSOCIATED WITH BRCA1/2

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1. Summary

Background

Breast cancer is one of the most frequently diagnosed cancers and the leading cause of cancer-related death among women in industrialized countries. Some breast cancers are caused by inherited mutations in DNA repair genes, namely BRCA1 and BRCA2, which causes DNA repair deficiency. Targeted treatments against another DNA repair protein named PARP, have been developed for these patients, but they sometimes do not work.

Main objective

We have developed blood tests that help predict response to PARP inhibitors in patients with BRCA1/2 associated cancers. In parallel, we performed an economic evaluation of selecting patients for PARPi treatment based on a novel protein-based test developed by VHIO, compared to current selection criteria.

Sub-aims

Subproject 1:

1.1 To identify mechanisms of resistance to PARPi by sequencing of circulating tumor DNA and to study the association with PARPi response.

1.2 To establish the status of homologous recombination deficiency (HRD) using protein-based biomarkers including RAD51 nuclear foci in circulating tumor cells and in tumor samples, and to study the association with PARPi response.

Subproject 2:

2.1 To perform a cost-effectiveness analysis of selecting for PARPi treatment based on the RAD51 score compared with current selection criteria.

2.2 To perform a budget-impact analysis.

Study design

Subproject 1:

We have analyzed longitudinal blood and tumor samples from patients with BRCA1/2-associated metastatic breast cancer treated with a PARPi in the clinic (N=34).Targeted capture DNA sequencing was performed with an especial focus to identify BRCA1/2 reversion mutations in matched pretreatment and progression blood samples. To

establish the status of protein-based biomarkers of DNA repair deficiency in CTCs we optimized the RAD51 test that had been developed for paraffin-embedded tumor samples.

Subproject 2:
An economic decision analytic model populated with data from the literature was developed to assess the efficiency of treating patients with PARPi based on the RAD51 test compared with current selection criteria (all-comers with BRCA1/2) or based on genomic scars (another patient stratification biomarker frequently tested in clinical trials). A budget impact was obtained assuming the incidence figures for breast cancer from the Health Department of the Catalan Government with a time horizon of 3 years. To assess the robustness of the results, deterministic and probabilistic sensitivity analyses (PSAs) were conducted.

2. Results

Subproject 1

ctDNA sequencing identified reversion mutations in 4% of the patients before PARPi treatment and in 31% of the post-treatment samples. Other genetic mechanisms of resistance, including alterations in 53BP1, were identified in 4% and 8% of the pre-and post-treatment samples, respectively. The presence of mutations in the pretreatment samples was associated with the lack of response to PARP inhibitors. Also, we were able to optimize the protocol to quantify RAD51 in circulating tumor cells. In 11/24 (46%) samples we were able to detect CTCs and in 6/24 (25%) we were able to evaluate RAD51.

Subproject 2

The most efficient scenario with respect to the all-comers scenario is the RAD51 scenario, which is dominant (more effectiveness at lower cost). Both the tBRCA scenario and the genomic HRD scenario save costs compared to the all-comers scenario, although reducing effectiveness (that is, they are possible alternatives in cases of disinvestment).The economic benefit of adopting the RAD51 test in the routine clinical practice is a consequence of an average saving of approximately 1,500 euros per patient, while increasing the average probability of complete pathological response

to treatment, compared to the all-comers strategy (and compared to the other screening tests).

3. Relevance and future implications

Doctors can now assess the need to perform a sequencing test (commercial or local) on liquid biopsy to determine the presence of BRCA1/2 reversion mutations associated with resistance to PARP inhibitors, which will help them to decide whether this is the most suitable treatment. In parallel, the RAD51 test can be attempted on circulating tumor cells to assess the status of functional HRD at VHIO.

In the economic analysis, the strategy based on RAD51 is dominant: higher health results at a lower cost (the results of the 3-year budget impact show savings of more than 3.5m euros for the Catalan public health service). Furthermore, its lower cost (tBRCA and genomic HRD tests are notably more expensive) and ease of use would facilitate its inclusion in the service portfolio of healthcare centers with few available resources.

4. Generated bibliography

Publications

1. Harvey-Jones E, Raghunandan M, Robbez-Masson L, Magraner-Pardo L, Alaguthurai T, Yablonovitch A, Yen J, Xiao H, Brough R, Frankum J, Song F, Yeung J, Savy T, Gulati A, Alexander J, Kemp H, Starling C, Konde A, Marlow R, Cheang M, Proszek P, Hubank M, Cai M, Trendell J, Lu R, Liccardo R, Ravindran N, Llop-Guevara A, Rodriguez O, Balmana J, Lukashchuk N, Dorschner M, Drusbosky L, Roxanis I, Serra V, Haider S, Pettitt SJ, Lord CJ, Tutt ANJ. Longitudinal profiling identifies co-occurring BRCA1/2 reversions, TP53BP1, RIF1 and PAXIP1 mutations in PARP inhibitor resistant advanced breast cancer. Ann Oncol. 2024 Jan 18:S0923-7534(24)00010-3. doi: 10.1016/j.annonc.2024.01.003. Epub ahead of print. PMID: 38244928. IF (2023)=50.5

2. Pimentel I, Forné C, Llop-Guevara A, …, Serra V, Rué M, Balmaña J. Cost-effectiveness of RAD51 test to identify untreated triple-negative breast cancer patients

sensitive to platinum-based neoadjuvant chemotherapy: analysis of the GeparSixto randomized clinical trial. *Manuscript in preparation.*

3. Domènech H, Simonetti S, Llop-Guevara A, Viaplana C, García-Durán C, Romero P, Joval L, Pawlikowska P, Rodríguez A, Pedretti F, Herencia-Ropero A, Guzmán M, Rodríguez O, Oliveira M, Pimentel I, Harrington E.A, Aguilar S, Vivancos A, Oaknin A, Nuciforo P, Dienstmann R, Farace F, Saura C, Prat A, Balmaña J, Serra V. Optimization and validation of a functional HRD assay as a diagnostic test for anticancer therapies. *Manuscript in preparation.*

Communications in scientific conferences (posters):

1. Carles Forné, Isabel Pimentel, Judith Balmaña, Montse Rué, Misericòrdia Carles-Lavila, María José Pérez-Lacasta, Alba Llop-Guevara, Violeta Serra. Evaluación económica del RAD51 como nuevo marcador para identificar deficiencia de recombinación homóloga en cáncer de mama triple negativo metastásico: Estudio RAD51predict. Oral Communication, XLII Jornadas AES (Asociación de Economía de la Salud), July 5-7 2023, Girona, Catalonia (Spain).

2. Isabel Pimentel, Carles Forné, Alba Llop-Guevara, Misericòrdia Carles-Lavila, Violeta Serra, Montserrat Rué, Judith Balmaña. Cost-effectiveness analysis of RAD51 functional biomarker for platinum sensitivity in the GeparSixto trial. Poster presentation, 2023 San Antonio Breast Cancer Symposium® (SABCS), December 5-9 2023, San Antonio, Texas (USA).

3. Heura Domènech, Patrycja Pawlikowska, Flaminia Pedretti, Andrea Herencia-Ropero, Sara Arce-Gallego, Françoise Farace, Alba Llop-Guevara, Judith Balmaña, Violeta Serra. Development of a circulating tumor cell-based test to identify cancer patient candidates for PARP inhibitor therapy. Poster presentation, 2022 European Association for Cancer Research Congress® (EACR), June 20-23 2022, Sevilla, Andalusia (Spain).

Communications in scientific conferences (talks):

Violeta Serra:

-Functional HRD to Identify PARP Inhibitor Sensitive Tumors. AACR Annual Meeting 2023, Orlando, USA. 17/04/2023

-Advances using Functional HRD to Identify PARP Inhibitor Sensitive Tumors. Washington University in St. Louis' Center for Reproductive Health Sciences seminar series, Online 28/10/2022
-Advances using Functional HRD to Identify PARP Inhibitor Sensitive Tumours. EMBO Workshop The DNA damage response, immunity and aging, Singapore. 10/10/2022
-Modern translational correlatives for synthetic lethality. ESMO Congress 2022, Paris. 09/09/2022
-Response and resistance to PARP inhibitors in breast cancer. BACR Response and Resistance in Cancer Therapy. British Association of Cancer Research, Online. 06/09/2021

Alba Llop:
-RAD51 as a functional biomarker of homologous recombination deficiency (HRD) in tumors. Cancer Research Malaysia (Kuala Lumpur). 22/08/2022
-RAD51 as a functional biomarker of HR deficiency. HBOC-VUS workshop (Leiden, Holland). 28-30/06/2022
-Presentation of the project to high-school students at Institut Narcís Oller (Valls). #100tífiques program organized by BIST and FCRI. 11/02/2022

Heura Domènech:
-Presentation of the project in internal scientific meetings at VHIO (Benchstorming seminars) 03/05/2022
-Presentation of the project in a PhD meeting (PhD Day 2023) organized by student committees from VHIR and VHIO. 23/11/2023

Related doctoral thesis:
This project is part of two PhD theses being carried out by the PhD student Heura Domenech and by the oncologist Isabel Pimentel. Heura Domenech was awarded a Severo Ochoa PhD fellowship.