Informe de Actividades 2023 y Planificación futura de la Cátedra UAM-Fundación Instituto Roche de Medicina Personalizada de Precisión

Cátedra de
Medicina Personalizada de Precisión

UAM Universidad Autónoma de Madrid

Fundación InstitutoRoche

Diciembre de 2023

Apartados

Generación de Conocimiento

1. Publicación del artículo científico "Usefulness and real-world outcomes of next generation sequencing testing in patients with cancer: an observational study on the impact of selection based on clinical judgement"

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Usefulness and real-world outcomes of next generation sequencing testing in patients with cancer: an observational study on the impact of selection based on clinical judgement

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Summary

Background Next Generation Sequencing (NGS) panels are increasingly used in advanced patients with cancer to guide therapy. There is, however, controversy about when should these panels be used, and about their impact on the clinical course.

Methods In an observational study of 139 patients with cancer having an NGS test [from January 1st, 2017 to December 30th, 2020, in two hospitals (Hospital Universitario de La Princesa and Hospital Universitario Quironsalud Madrid) from Spain], we evaluated whether the clinical course (progression-free survival, PFS) was influenced by drug-based criteria [druggable alterations, receiving a recommended drug, having a favourable ESCAT category (ESMO Scale for Clinical Actionability of molecular Targets)] or clinical judgement criteria.

Findings In 111 of 139 cases that were successfully profiled, PFS was not significantly influenced by either having druggable alterations [median PFS for patients with druggable alterations was 170 (95% C.I.: 139–200) days compared to 299 (95% C.I.: 114–483) for those without; $p = 0.37$], receiving a proposed matching agent [median PFS for patients receiving a genomics-informed drug was 195 days (95% C.I.: 144–245), compared with 156 days for those that did not (95% C.I.: 85–226); $p = 0.50$], or having favourable ESCAT categories [median PFS for patients with ESCAT I-III was 183 days (95% C.I.: 104–261), compared with 180 (95% C.I.:144–215) for patients with ESCAT IV-X; $p = 0.87$]. In contrast, NGS testing performed within clinical judgement showed a significantly improved PFS [median PFS for patients that were profiled under the recommended scenarios was 319 days (95% C.I.: 0–658), compared to 123 days (95% C.I.: 89–156) in the non-recommended categories; $p = 0.0020$].

Interpretation According to our data, real-world outcomes after NGS testing provide evidence of the benefit of clinical judgement in patients with either advanced cancers that routinely need multiple genetic markers, patients with advanced rare cancers, or patients that are screened for molecular clinical trials. By contrast, NGS does not seem to be valuable when performed in cases with a poor PS, rapidly progressing cancer, short expected lifetime, or cases with no standard therapeutic options.

Funding RC, NR-L and MQF are recipients of the PMP22/00032 grant, funded by the ISCIII and co-funded by the European Regional Development Fund (ERDF). The study also received funds from the CRIS Contra el Cancer Foundation.

Keywords: NGS panels; NGS testing; Precision medicine; Precision oncology; Targeted therapies; Real world outcomes; ESCAT; Clinical judgement

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Las figuras clave de la publicación son las siguientes:

En la primera se muestra que cuando se solicita una NGS en la categoría de "no útil", la supervivencia es peor que la de los casos que hemos definido como "útiles", confirmando por tanto nuestra hipótesis

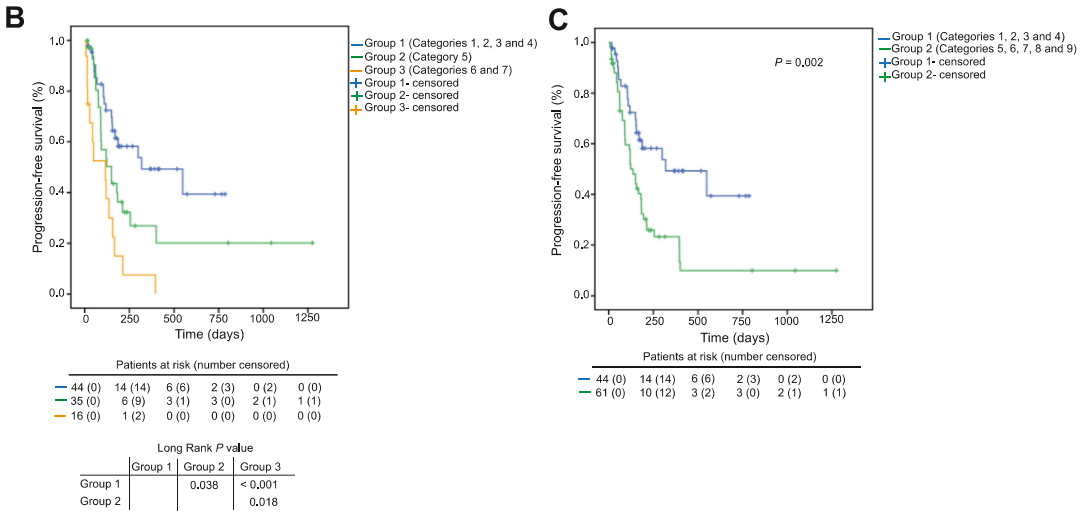
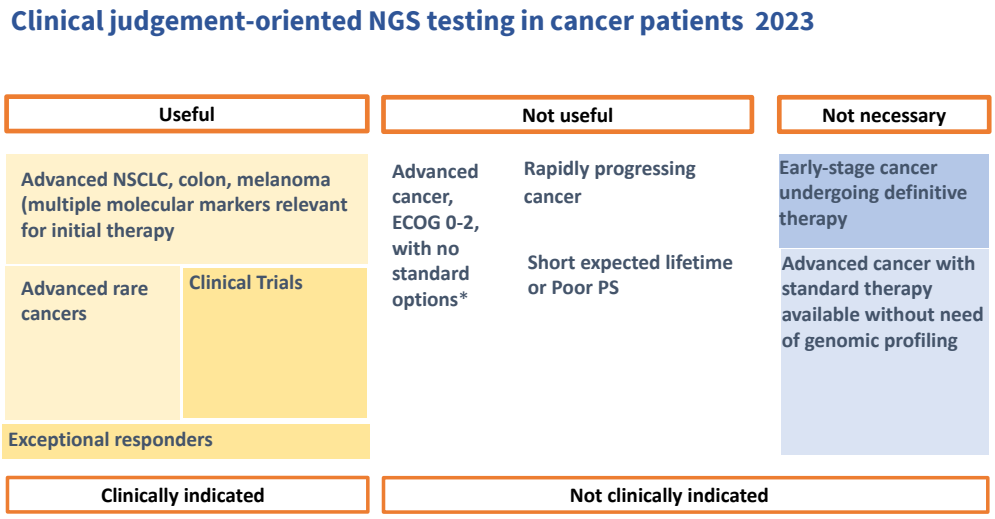


Fig. 4: **Impact of genomic profiling test on PFS** (B) Kaplan-Meier PFS curve of advanced patients with cancer with NGS testing indication (categories 1–4) versus patients in the "not useful" categories (6 and 7) or the new "not useful" category 5. (C) Kaplan-Meier PFS curve of advanced patients with cancer with NGS testing categorised as "useful" (categories 1–4) versus "not useful" or "not indicated" (categories 5–9).

En la segunda gráfica presentamos nuestra gráfica actualizada para 2023 de los categorías "útil", "no útil" y "no necesaria"



2. Publicación del artículo "Tertiary lymphoid structures and B lymphocytes: a promising therapeutic strategy to fight cancer"

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Tertiary lymphoid structures and B lymphocytes: a promising therapeutic strategy to fight cancer

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Tertiary lymphoid structures (TLSs) are clusters of lymphoid cells with an organization that resembles that of secondary lymphoid organs. Both structures share common developmental characteristics, although TLSs usually appear in chronically inflamed non-lymphoid tissues, such as tumors. TLSs contain diverse types of immune cells, with varying degrees of spatial organization that represent different stages of maturation. These structures support both humoral and cellular immune responses, thus the correlation between the existence of TLS and clinical outcomes in cancer patients has been extensively studied. The finding that TLSs are associated with better prognosis in some types of cancer has led to the design of therapeutic strategies based on promoting the formation of these structures. Agents such as chemokines, cytokines, antibodies and cancer vaccines have been used in combination with traditional antitumor treatments to enhance TLS generation, with good results. The induction of TLS formation therefore represents a novel and promising avenue for the treatment of a number of tumor types.

KEYWORDS

tertiary lymphoid structures, B cells, adaptive anti-tumor response, TLS modulation, immunotherapy

En la figura siguiente se resumen las propuestas terapéuticas de este artículo de revisión

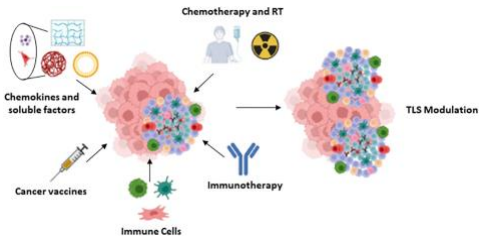

FIGURE 4
TLS modulation: Summary of the different approaches proposed for the modulation of the TLS.

3. Publicacion del artículo "A Comprehensive Analysis of Immune Response in Patients with Non-Muscle-Invasive Bladder Cancer"

Cancers (Basel) (IF: 6.13; **Q1**)

cancers

MDPI

Article

A Comprehensive Analysis of Immune Response in Patients with Non-Muscle-Invasive Bladder Cancer

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Simple Summary: A comprehensive characterization of cell subpopulations involved in the immune response against bladder cancer has not been performed so far. In addition, due to the high prevalence, recurrence and progression capacity of non-muscle-invasive bladder cancer (NMIBC), the identification of novel biomarkers of tumor progression and response to therapy is of utmost importance. The detailed analysis of the immune landscape in these patients is highly relevant to anticipating tumor behavior and optimizing diagnosis methods and tumor management. We present here the results of the first detailed characterization of immune cell populations in the normal bladder, tumor samples and peripheral blood from patients with NMIBC. We have found specific immune cell subsets differentially expressed in these samples and identified potential markers of tumor progression and patient outcome in peripheral blood. These findings provide relevant information about the host immune response against bladder cancer and set the basis for novel non-invasive procedures for patient stratification and monitoring.

Abstract: Background. Bladder carcinoma has elevated morbimortality due to its high recurrence and progression in localized disease. A better understanding of the role of the tumor microenvironment in carcinogenesis and response to treatment is needed. Methods. Peripheral blood and samples of urothelial bladder cancer and adjacent healthy urothelial tissue were collected from 41 patients and stratified in low- and high-grade urothelial bladder cancer, excluding muscular infiltration or carcinoma in situ. Mononuclear cells were isolated and labeled for flow cytometry analysis with antibodies aimed at identifying specific subpopulations within T lymphocytes, myeloid cells and NK cells. Results. In peripheral blood and tumor samples, we detected different percentages of CD4+ and CD8+ lymphocytes, monocyte and myeloid-derived suppressor cells, as well as differential expression of activation- and exhaustion-related markers. Conversely, only a significant increase in bladder total monocytes was found when comparing bladder and tumor samples. Interestingly, we identified specific markers differentially expressed in the peripheral blood of patients with different outcomes. Conclusion. The analysis of host immune response in patients with NMIBC may help to identify specific markers that allow optimizing therapy and patient follow-up. Further investigation is needed to establish a strong predictive model.

Keywords: bladder cancer; immunotherapy; immune response; T-cells; tumor microenvironment; biomarkers

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Citation: Celada Luis, G.; Albers Acosta, E.; de la Fuente, H.; Velasco Balanza, C.; Arroyo Correas, M.; Romero-Laorden, N.; Alfranca, A.; Olivier Gómez, C. A Comprehensive Analysis of Immune Response in Patients with Non-Muscle-Invasive Bladder Cancer. *Cancers* **2023**, *15*, 1364. https://doi.org/10.3390/cancers15051364

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4. Publicación del artículo científico "PROREPAIR-B: A Prospective Cohort Study of the Impact of Germline DNA Repair Mutations on the Outcomes of Patients with Metastatic Castration-Resistant Prostate Cancer"

Journal of Clinical Oncology (IF: 6.13; **Q1**)

original report

PROREPAIR-B: A Prospective Cohort Study of the Impact of Germline DNA Repair Mutations on the Outcomes of Patients With Metastatic Castration-Resistant Prostate Cancer

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abstract

PURPOSE Germline mutations in DNA damage repair (DDR) genes are identified in a significant proportion of patients with metastatic prostate cancer, but the clinical implications of these genes remain unclear. This prospective multicenter cohort study evaluated the prevalence and effect of germline DDR (gDDR) mutations on metastatic castration-resistance prostate cancer (mCRPC) outcomes.

PATIENTS AND METHODS Unselected patients were enrolled at diagnosis of mCRPC and were screened for gDDR mutations in 107 genes. The primary aim was to assess the impact of ATM/BRCA1/BRCA2/PALB2 germline mutations on cause-specific survival (CSS) from diagnosis of mCRPC. Secondary aims included the association of gDDR subgroups with response outcomes for mCRPC treatments. Combined progression-free survival from the first systemic therapy (PFS) until progression on the second systemic therapy (PFS2) was also explored.

RESULTS We identified 68 carriers (16.2%) of 419 eligible patients, including 14 with BRCA2, eight with ATM, four with BRCA1, and none with PALB2 mutations. The study did not reach its primary end point, because the difference in CSS between ATM/BRCA1/BRCA2/PALB2 carriers and noncarriers was not statistically significant (23.3 v 33.2 months; P = .264). CSS was halved in germline BRCA2 (gBRCA2) carriers (17.4 v 33.2 months; P = .027), and gBRCA2 mutations were identified as an independent prognostic factor for CCS (hazard ratio [HR], 2.11; P = .033). Significant interactions between gBRCA2 status and treatment type (androgen signaling inhibitor v taxane therapy) were observed (CSS adjusted P = .014; PFS2 adjusted P = .005). CSS (24.0 v 17.0 months) and PFS2 (18.9 v 8.6 months) were greater in gBRCA2 carriers treated in first line with abiraterone or enzalutamide compared with taxanes. Clinical outcomes did not differ by treatment type in noncarriers.

CONCLUSION gBRCA2 mutations have a deleterious impact on mCRPC outcomes that may be affected by the first line of treatment used. Determination of gBRCA2 status may be of assistance for the selection of the initial treatment in mCRPC. Nonetheless, confirmatory studies are required before these results can support a change in clinical practice.

J Clin Oncol 37:490-503.

ASSOCIATED CONTENT
Appendix
Data Supplements
Author affiliations and support information (if applicable) appear at the end of this article.
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A complete list of the PROREPAIR-B investigators is provided in the Appendix.

INTRODUCTION

Inherited mutations in several genes involved in DNA damage repair (DDR) have been reported to predispose men to prostate cancer[1-4]; these include mutations in BRCA2, the genetic event that confers the greatest risk of the disease.[5] Recent next-generation sequencing studies have revealed that germline deleterious mutations in DDR genes are present in 8% to 12% of patients with metastatic prostate cancer.[6-8] In a retrospective multi-institutional pooled analysis by Pritchard et al,[7] the most frequently mutated genes were BRCA2 (5.3%), CHEK2 (2%), ATM (1.6%), and BRCA1 (0.9%). Mutations in the other 16 genes analyzed accounted for less than 0.5% of cases. A prevalence of 12% is significantly higher than that reported in localized prostate cancer (5%) or in the general population (3%),[7,9] which suggests an association with aggressive disease. In fact, germline mutations in BRCA2 seem to be an independent poor prognostic factor for localized disease associated with shorter metastasis-free survival and cause-specific

5. Publicación del artículo "Prospective Assessment of Bone Metabolism Biomarkers and Survival in Metastatic Castration-resistant Prostate Cancer Patients Treated with Radium-223: The PRORADIUM Study"

European Urology Oncology (IF: 2.51; **Q1**)

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Prospective Assessment of Bone Metabolism Biomarkers and Survival in Metastatic Castration-resistant Prostate Cancer Patients Treated with Radium-223: The PRORADIUM Study

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Abstract

Background: Radium-223 is an active therapy option for bone metastatic castration-resistant prostate cancer (mCRPC). The lack of adequate biomarkers for patient selection and response assessment are major drawbacks for its use.

Objective: To assess the prognostic value of bone metabolism biomarkers (BMBs) in ra-223–treated mCRPC patients.

Design, setting, and participants: A prospective cohort study of mCRPC patients treated with Ra-223 (PRORADIUM study; NCT02925702) was conducted.

Outcome measurements and statistical analysis: The main objective of the study was to evaluate the association between high (≥median) baseline values in at least three bone formation (bone alkaline phosphatase [BAP] and C-terminal type-I collagen propeptide)

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6. Publicación del artículo "Impact of concurrent tumour events on the prostate cancer outcomes of germline BRCA2 mutation carriers"

European Journal of cancer (IF: 9.16; **Q1**)

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Original Research

Impact of concurrent tumour events on the prostate cancer outcomes of germline *BRCA2* mutation carriers

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7. Publicación del artículo "p27^{Kip1} V109G as a biomarker for CDK4/6 inhibitors indication in hormone receptor–positive breast"

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p27^{Kip1} V109G as a biomarker for CDK4/6 inhibitors indication in hormone receptor–positive breast cancer

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‡These authors contributed equally to this work.

Abstract

CDK4/6 inhibitors benefit a minority of patients who receive them in the breast cancer adjuvant setting. p27^{Kip1} is a protein that inhibits CDK/Cyclin complexes. We hypothesized that single-nucleotide polymorphisms that impaired p27^{Kip1} function could render patients refractory to endocrine therapy but responsive to CDK4/6 inhibitors, narrowing the patient subpopulation that requires CDK4/6 inhibitors. We found that the p27^{Kip1} V109G single-nucleotide polymorphism is homozygous in approximately 15% of hormone-positive breast cancer patients. Polymorphic patients experience rapid failure in response to endocrine monotherapy compared with wild-type or heterozygous patients in the first-line metastatic setting (progression-free survival: 92 vs 485 days, $P < .001$); when CDK4/6 inhibitors are added, the differences disappear (progression-free survival: 658 vs 761 days, $P = .92$). As opposed to wild-type p27^{Kip1}, p27^{Kip1} V109G is unable to suppress the kinase activity of CDK4 in the presence of endocrine inhibitors; however, palbociclib blocks CDK4 kinase activity regardless of the p27^{Kip1} status. p27^{Kip1} genotyping could constitute a tool for treatment selection.

La figura que muestra el efecto de los inhibidores de CDK sobre la resistencia endocrina es esta:

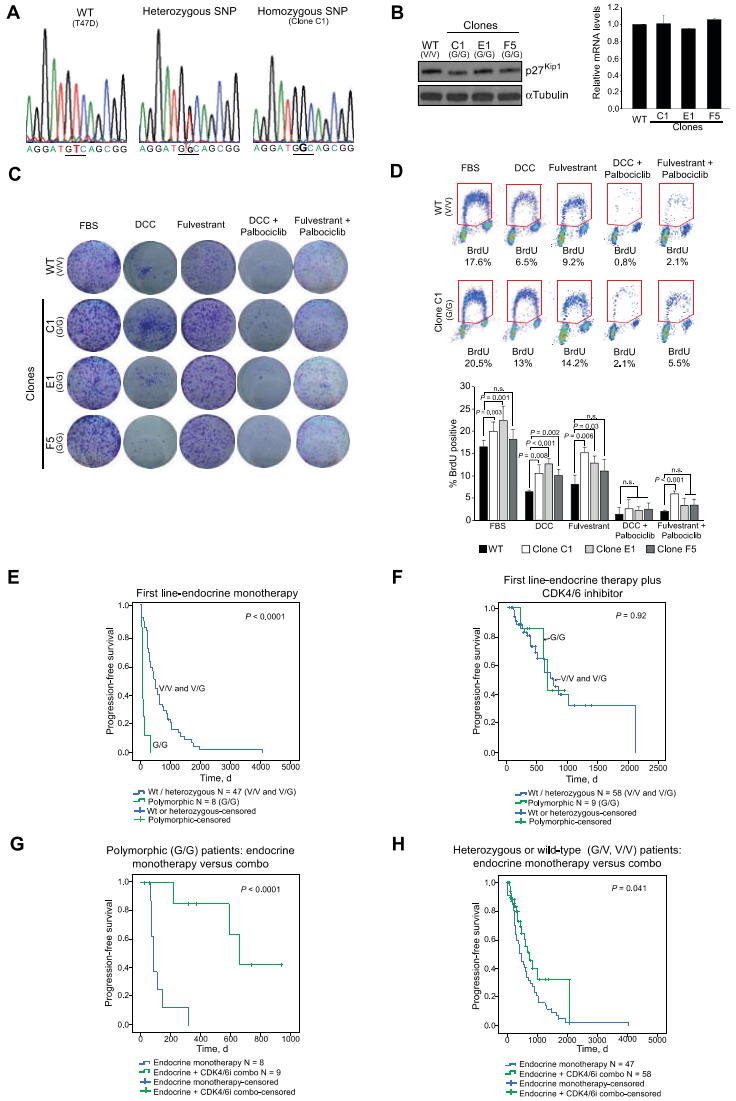

Figure 1. p27^{Kip1} V109G single-nucleotide polymorphism (SNP) impairs endocrine sensitivity, but it is rescued with CDK4/6 inhibitors in preclinical models and patients. **A**) Electropherogram showing the 3 possible sequences in position 329 of P27^{Kip1}, generated from the parental T47-D cells: T/T (**left**, wild type [WT]), T/G (**middle**, heterozygous), and G/G (**right**, homozygous for the polymorphism, clone C1). The results obtained with the heterozygous variants are not shown because they behaved like the wild type. **B**) P27^{Kip1} protein (**left**) and mRNA (**right**) levels in wild-type T47-D cells and 3 polymorphic T47-D clones. **C**) Representative colony assays and relative plating efficiency chart comparing the survival of wild-type and polymorphic T47-D clones in DCC (Dextran-Coated Charcoal) medium (tissue culture medium deprived from estrogens), in FBS (Fetal Bovine Serum) medium (full medium) plus 0.5 nM fulvestrant, or the same conditions plus 25 nM palbociclib. **D**) Representative BRDU-uptake charts of wild-type T47-D cells (**upper panels**) and polymorphic variants (Clone C1, **lower panels**), in full medium, DCC medium, fulvestrant, DCC plus palbociclib or fulvestrant plus palbociclib, showing the relative resistance to cell cycle arrest in response to hormonal deprivation but sensitivity to palbociclib combos in the polymorphic clone. The accompanying chart shows the comparison between the BRDU fraction among the different conditions in all clones. **E**) Kaplan-Meier progression-free survival (PFS) curves for patients treated with endocrine monotherapy in the first-line setting, according to their P27^{Kip1} genotype. **F**) Kaplan-Meier PFS curves for patients treated with CDK4/6 inhibitor plus endocrine therapy according to their P27^{Kip1} genotype. **G**) Kaplan-Meier PFS curves for polymorphic and wild-type or heterozygous patients **H**) comparing the PFS when receiving endocrine monotherapy or combination with CDK4/6 inhibitors. **Error bars**: standard error. The log-rank test performed for comparing the PFS curves shown in **E-H** PFS functions were computed using the Kaplan-Meier estimator. Cell cycle assays (D) were compared with 2-sided unpaired t tests and considered statistically significant when $P < .05$. All P values are 2-sided.

8. Publicación del artículo científico "Expert consensus of the Spanish Society of Pathology and the Spanish Society of Medical Oncology on the determination of biomarkers in pancreatic and biliary tract cancer"

Clinical and Translational Oncology (IF: 3.4; Q3)

Clinical and Translational Oncology
https://doi.org/10.1007/s12094-023-03329-9

BRIEF RESEARCH ARTICLE

Distribution of PD-L1, TROP2 and HER2-"lowness" in early triple-negative breast cancer: an opportunity for treatment de-escalation

Maria Jose Bueno[1] · Silvana Mouron[1] · Eduardo Caleiras[2] · Mario Martínez[3] · Luis Manso[4] · Ramón Colomer[5] · Miguel Quintela-Fandino[1]

Received: 21 July 2023 / Accepted: 25 September 2023

Abstract

Background HER2, TROP2 and PD-L1 are novel targets in triple-negative breast cancer (TNBC). The combined expression status of these targets, and whether they can define prognostic subgroups, is currently undefined.

Methods Immunohistochemistry was used to determine HER2, TROP2 and PD-L1 levels in 459 TNBC cases, that received in the adjuvant/neoadjuvant setting active surveillance, CMF, anthracycline-, anthracycline plus taxane-, or carboplatin-containing regimes.

Results HER2-low patients with PD-L1 > 1 CPS (double-positive, herein "DP") had a mean PFS of 4768 days (95% CI: 4267–5268) versus 3522 days (95% CI: 3184–3861) for non-DP patients ($P = 0.002$). Regarding the received adjuvant treatment, DP patients (versus non-DP) receiving anthracyclines plus taxanes exhibited a mean PFS time of 4726 (95% CI: 4022–5430) versus 3302 (95% CI: 2818–3785) days ($P = 0.039$). Finally, 100% of DP patients that received a carboplatin-based regimen were long-term disease-free.

Conclusions Early HER2-low, PD-L1-positive TNBC patients have a very good prognosis, particularly if treated with anthracycline/taxane- or carboplatin-containing regimes.

Keywords Triple-negative breast cancer · PD-L1 · TROP2 · HER2-low · Carboplatin

Introduction

Traditionally, triple-negative breast cancer (TNBC) has been viewed as a disease lacking druggable targets [1]. Recently, the positive effects of immunotherapies in the early [2, 3] and advanced [4–6] disease settings challenge this view. Similarly, the efficacy of the antibody–drug conjugates (ADCs) sacituzumab govitecan against TROP-2 and trastuzumab deruxtecan against HER2 have improved clinical outcomes in the general TNBC subpopulation [7] and in the HER2-low (positive, non-amplified) TNBC subpopulation [8], respectively. Whether these targets expression/co-expression and/or their levels of expression determine different TNBC sub-types, or drive its clinical history regardless of the use of those drugs is currently unknown; however, these datasets of the drug development focus on three novel targets (PD-L1, TROP2 and HER2) in this disease.

In the past, we have approached the complexity of TNBC with complex taxonomic techniques mixing genomics and phosphoproteomics to find prognostic [9]

Maria Jose Bueno and Silvana Mouron have contributed equally to this manuscript.

✉ Miguel Quintela-Fandino
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2 Histopathology Unit, CNIO Spanish National Cancer Research Center, Madrid, Spain

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5 Medical Oncology Department, Hospital Universitario de La Princesa, Madrid, Spain

Published online: 18 October 2023

9. Publicacion del artículo "RANK is a poor prognosis marker and a therapeutic target in ER-negative postmenopausal breast cancer"

EMBO Mol Med (IF: 12.14; **Q1**)

Report

TRANSPARENT PROCESS OPEN ACCESS

EMBO Molecular Medicine

RANK is a poor prognosis marker and a therapeutic target in ER-negative postmenopausal breast cancer

Marina Ciscar[1,2,†], Eva M Trinidad[2,†], Gema Perez-Chacon[1], Mansour Alsaleem[3,‡], Maria Jmenez[1], Maria JJmenez-Santos[4], Hector Perez-Montoyo[2], Adrian Sanz-Moreno[2], Andrea Vethencourt[2,5], Michael Toss[3], Anna Petit[6], Maria T Soler-Monso[6], Victor Lopez[1], Jorge Gomez-Miragaya[2], Clara Gomez-Aleza[2], Lacey E Dobrolecki[7], Michael T Lewis[7], Alejandra Bruna[8,§], Silvana Mouron[9], Miguel Quintela-Fandino[9], Fatima Al-Shahrour[4], Antonio Martinez-Aranda[2,5], Angels Sierra[2,–], Andrew R Green[3], Emad Rakha[3] & Eva Gonzalez-Suarez[1,2,*]

Abstract

Despite strong preclinical data, the therapeutic benefit of the RANKL inhibitor, denosumab, in breast cancer patients, beyond the bone, is unclear. Aiming to select patients who may benefit from denosumab, we hereby analyzed RANK and RANKL protein expression in more than 2,000 breast tumors (777 estrogen receptor-negative, ER$^-$) from four independent cohorts. RANK protein expression was more frequent in ER$^-$ tumors, where it associated with poor outcome and poor response to chemotherapy. In ER$^-$ breast cancer patient-derived orthoxenografts (PDXs), RANKL inhibition reduced tumor cell proliferation and stemness, regulated tumor immunity and metabolism, and improved response to chemotherapy. Intriguingly, tumor RANK protein expression associated with poor prognosis in postmenopausal breast cancer patients, activation of NFKB signaling, and modulation of immune and metabolic pathways, suggesting that RANK signaling increases after menopause. Our results demonstrate that RANK protein expression is an independent biomarker of poor prognosis in postmenopausal and ER$^-$ breast cancer patients and support the therapeutic benefit of RANK pathway inhibitors, such as denosumab, in breast cancer patients with RANK$^+$ ER$^-$ tumors after menopause.

Keywords breast cancer patient-derived xenografts; ER negative breast cancer; menopause; pharmacological RANKL inhibitors; RANK-RANKL
Subject Categories Biomarkers; Cancer
DOI 10.15252/emmm.202216715 | Received 8 August 2022 | Revised 24 January 2023 | Accepted 8 February 2023 | Published online 7 March 2023
EMBO Mol Med (2023) 15: e16715

Introduction

Despite recent advances in treatment, breast cancer (BC) is the main cause of mortality by cancer in women, highlighting the unmet need of identifying new prognosis markers and personalized treatments. BC shows a high pathological and biological heterogeneity in histology, genetics, and sensitivity to therapies. The expression of estrogen and progesterone receptor (ER, PR), human epidermal growth factor receptor 2 (HER2) and KI67 are determinant for BC prognosis

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10. Publicacion del articulo "miR-203 drives breast cancer cell differentiation"

Breast Cancer Res (IF: 6.47; **Q1**)

Martínez-Illescas *et al. Breast Cancer Research* (2023) 25:91
https://doi.org/10.1186/s13058-023-01690-9

Breast Cancer Research

RESEARCH **Open Access**

miR-203 drives breast cancer cell differentiation

Nuria G. Martínez-Illescas[1,2,3], Silvia Leal[4], Patricia González[5], Osvaldo Graña-Castro[6,7], Juan José Muñoz-Oliveira[8], Alfonso Cortés-Peña[8], María Gómez-Gil[5], Zaira Vega[5], Verónica Neva[5], Andrea Romero[5], Miguel Quintela-Fandino[9], Eva Ciruelos[2,10], Consuelo Sanz[2,10], Sofía Aragón[2,10], Leisy Sotolongo[2,10], Sara Jiménez[2,10], Eduardo Caleiras[5], Francisca Mulero[4], Cristina Sánchez[1,2*], Marcos Malumbres[3,11,12*] and María Salazar-Roa[1,2,3*]

Abstract

A hallmark of many malignant tumors is dedifferentiated (immature) cells bearing slight or no resemblance to the normal cells from which the cancer originated. Tumor dedifferentiated cells exhibit a higher capacity to survive to chemo and radiotherapies and have the ability to incite tumor relapse. Inducing cancer cell differentiation would abolish their self-renewal and invasive capacity and could be combined with the current standard of care, especially in poorly differentiated and aggressive tumors (with worst prognosis). However, differentiation therapy is still in its early stages and the intrinsic complexity of solid tumor heterogeneity demands innovative approaches in order to be efficiently translated into the clinic. We demonstrate here that microRNA 203, a potent driver of differentiation in pluripotent stem cells (ESCs and iPSCs), promotes the differentiation of mammary gland tumor cells. Combining mouse in vivo approaches and both mouse and human-derived tridimensional organoid cultures, we report that miR-203 influences the self-renewal capacity, plasticity and differentiation potential of breast cancer cells and prevents tumor cell growth in vivo. Our work sheds light on differentiation-based antitumor therapies and offers miR-203 as a promising tool for directly confronting the tumor-maintaining and regeneration capability of cancer cells.

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[12]ICREA, Passeig Lluís Companys 23, Barcelona, Spain

11. Publicacion del articulo "T regulatory lymphocytes specific for SARS-CoV-2 display increased functional plasticity"

Clin Immunol (IF: 3.97; **Q3**)

Clinical Immunology 256 (2023) 109806

Contents lists available at ScienceDirect

Clinical Immunology

journal homepage: www.elsevier.com/locate/yclim

T regulatory lymphocytes specific for SARS-CoV-2 display increased functional plasticity

Laura Esparcia-Pinedo [a], Ángel Lancho-Sánchez [a], Ilya Tsukalov [b], María I. Pacheco [c], Pedro Martínez-Fleta [a], Belén Pérez-Miés [e], José Palacios-Calvo [e], Francisco Sánchez-Madrid [a,b,d], Enrique Martín-Gayo [b,f], Arantzazu Alfranca [a,b,d,*]

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ARTICLE INFO

Keywords:
COVID-19
SARS-CoV-2
Vaccines
Treg
Chemokine receptors

ABSTRACT

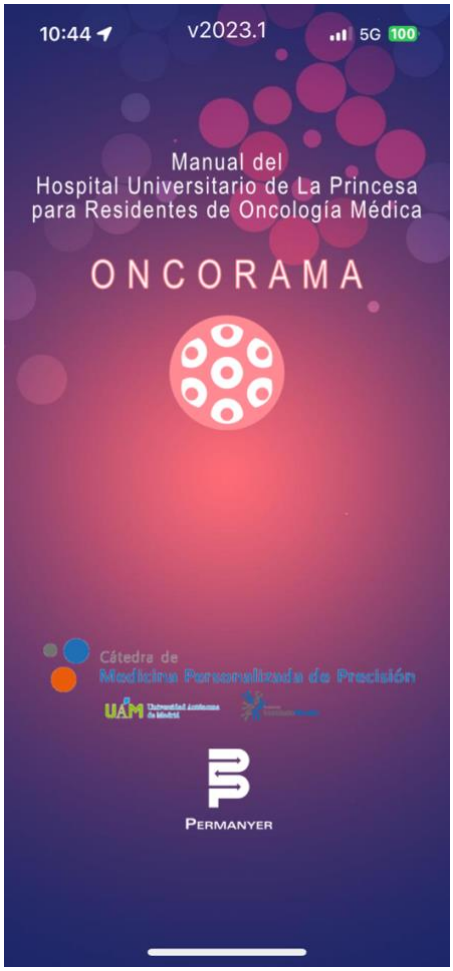
The study of phenotypic and functional characteristics of immune cells involved in host response to SARS-CoV-2 is relevant for understanding COVID-19 pathogenesis and individual differences in disease progression. We have analyzed chemokine receptor expression in SARS-CoV-2-specific CD4+ T lymphocytes from vaccinated donors, and have found an increase of CCR9+ and CCR6+ cells. CCR9+ specific CD4+ cells are enriched in T regulatory (Treg) lymphocytes. These cells specifically show heterogeneous regulatory activity, associated with different profiles of CCR9/CCR6 expression, individual differences in IL-10 and IL-17 production, and variable FoxP3 and Notch4 expression. A higher heterogeneity in FoxP3 is selectively observed in convalescent individuals within vaccinated population. Accordingly, SARS-CoV-2-specific CD4+ lymphocytes from COVID-19 patients are also enriched in CCR9+ and CCR6+ cells. CCR6+ specific Treg lymphocytes are mainly increased in critically ill individuals, indicating a preferential role for these cells in lung injury pathogenesis. We provide experimental evidence for a SARS-CoV-2-specific Treg population with increased plasticity, which may contribute to the differential pathogenic response against SARS-CoV-2 among individuals, and underlie the development of autoimmune conditions following SARS-CoV-2 infection.

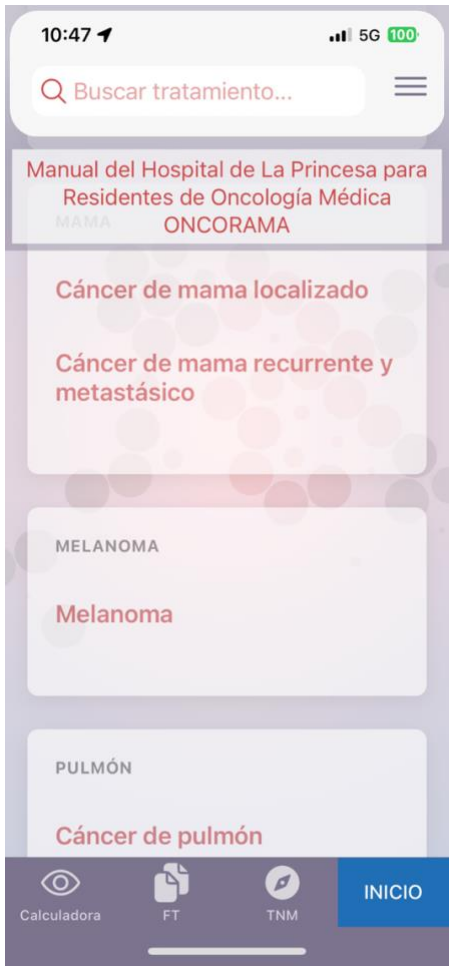
Difusión del Conocimiento

1. Disponibilidad en abierto de la App de la Cátedra de Medicina Personalizada de Precisión titulada Manual del Hospital la Princesa para Residentes de Oncología Médica (ONCORAMA)"

Esta App está disponible para Android y Apple iOS desde junio de 2023.

La versión actual es la 2023.1



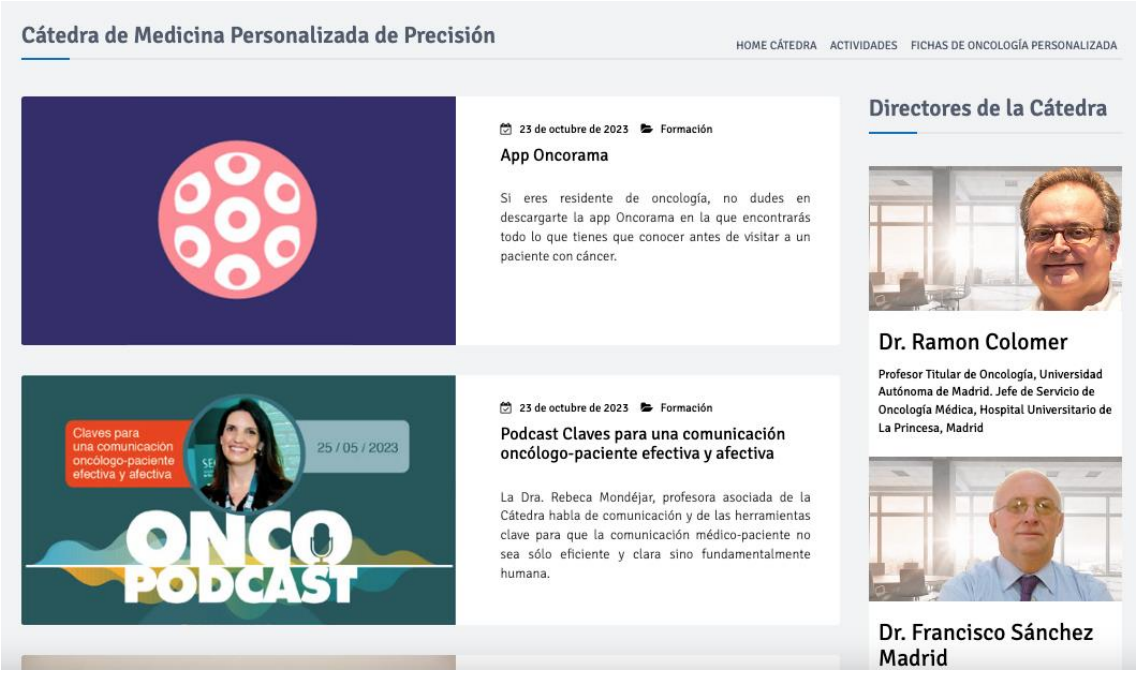


2. Podcast "Claves para una comunicación oncólogo-paciente efectiva y afectiva"

La Dra. Rebeca Mondéjar, profesora asociada de la Cátedra habla de comunicación y de las herramientas clave para que la comunicación médico-paciente no sea sólo eficiente y clara sino fundamentalmente humana.
En este capítulo, la periodista Mamen Mendizábal entrevista a la Dra. Rebeca Mondéjar, oncóloga médica, Cátedra de Medicina Personalizada de Precisión del Hospital Universitario La Princesa de Madrid, para hablar de comunicación y de las herramientas clave para que la comunicación médico-paciente no sea sólo eficiente y clara sino fundamentalmente humana. Durante la conversación, se habla de la relación oncólogo-paciente, de las claves para una buena comunicación, de las barreras y de los condicionantes, y de las destrezas y habilidades necesarias para conseguir una comunicación efectiva y afectiva.

Link al podcast: https://seom.org/component/muscol/M/332-claves-para-una-comunicacion-oncologo-paciente-efectiva-y-afectiva

3. Manteniniento y actualización de la *website* de la Cátedra de Medicina de Precisión, de modo que sirva de plataforma de difusión de sus actividades



La dirección es la siguiente: https://www.institutoroche.es/catedra

4. Seminario para Parlamentarios “Medicina Personalizada de Precisión: ¿Medicina del futuro o Medicina del presente?” . Sala Campoamor, Carrera de San Jeronimo

Seminario para parlamentarios:
“Medicina Personalizada de Precisión: ¿Medicina del futuro o Medicina del presente?”

Fecha: miércoles 22 de febrero de 2023
Lugar: Congreso de los Diputados

Hora	Contenido
16:00h	**Inauguración** **Dña. Rosa Romero** *Presidenta de la Comisión de Sanidad y Consumo del Congreso de los Diputados.* **D. Ramón Colomer** *Director de la Cátedra de Medicina Personalizada de Precisión UAM- Fundación Instituto Roche.* **D. Federico Plaza** *Vicepresidente de la Fundación Instituto Roche.*

Formación

1. Convocatoria y concesión de la Beca SEOM 2023 a la mejor Tesis Doctoral sobre Medicina personalizada de Precisión (9 de octubre de 2023)

La doctora Milana Arantza Bergamino Sirvén, oncóloga médica del Instituto Catalán de Oncología (ICO) de Badalona, es la ganadora del Premio a la Tesis Doctoral, *Unravelling the molecular complexities of early-stage oestrogen receptor positive breast cancer to identify biomarkers of resistance to endocrinetherapy*, del Programa de Becas, Proyectos y Premios SEOM 2023 financiada por la Cátedra de Medicina Personalizada de Precisión de la Universidad Autónoma de Madrid - Fundación Instituto Roche.

2. Lectura de Tesis Doctoral Jacobo Rogado

Predictores de respuesta tratamiento con anticuerpos monoclonales frente al receptor de muerte programada (anti-PD-1) en paciente diagnosticados de cáncer de pulmón, Jacobo Rogado Revuelta, Madrid, 06/03/2023, Sobresaliente *cum laude*

3. Lectura Tesis Doctoral Anabel Ballesteros

Evolucion temporal del tratamiento neoadyuvante del cancer mama.
Ana Isabel Ballesteros García, Madrid, 20/12/22 Sobresaliente *cum laude*

4. Convocatoria de dos Plazas de Profesor Asociado en la Facultad de Medicina de la UAM, 2023

Código de concurso: 22/23-526
Centro: Facultad de Medicina (Hospital Universitario La Princesa)
Departamento: Medicina
Área de Conocimiento: Medicina (Oncología Médica)
Nº de plazas: 2
Procedencia de la plaza: Cátedra UAM-Fundación Instituto Roche Medicina personalizada de precisión
Categoría: Profesor Asociado en Ciencias de la Salud
Dedicación: a tiempo parcial (3 horas)
Actividades a realizar: Docencia teórico y práctica en Oncología Médica-Medicina Personalizada de Precisión
Vigencia del contrato: Hasta 31 de agosto de2024.

Investigación

1. Inicio del Proyecto de Investigación titulado "Integrating longitudinal patient-generated data and multi-omic profiling for comprehensive precision oncology in womens' cancers" (Expediente No: PMP22/00032), dentro de la Convocatoria de Proyectos de Investigación de Medicina Personalizada del Instituto de Salud Carlos III.

Este proyecto de investigación explora distintos aspectos de la Medicina Personalizada de Precisión de una manera integrada. La financiación concedida para el período 2023-2025 ha sido de 2.439.992,50 €. En este proyecto multicéntrico participan las siguientes instituciones:

20/2/23 10:33 Las 'gemelas digitales' de mujeres con cáncer permitirán hacer una asignación "mucho más exacta" de los tratamientos | Salud y bienestar | EL...

EL PAÍS

LA SALUD VA POR BARRIOS · NUTRIR CON CIENCIA · ENFÓRMATE · NOSOTRAS RESPONDEMOS · SALUD MENTAL · ÚLTIMAS NOTICIAS

CÁNCER >

Las 'gemelas digitales' de mujeres con cáncer permitirán hacer una asignación "mucho más exacta" de los tratamientos

Un proyecto español analiza datos sobre los hábitos de vida, la alimentación y las emociones de las pacientes para averiguar la trayectoria que seguirá la enfermedad en cada caso

Miguel Ángel Quintela, de pie a la derecha, posa con otros nueve investigadores del proyecto en la sede del CNIO en Madrid. LUIS SEVILLANO

Tabla de reclutamiento hasta Noviembre de 2023

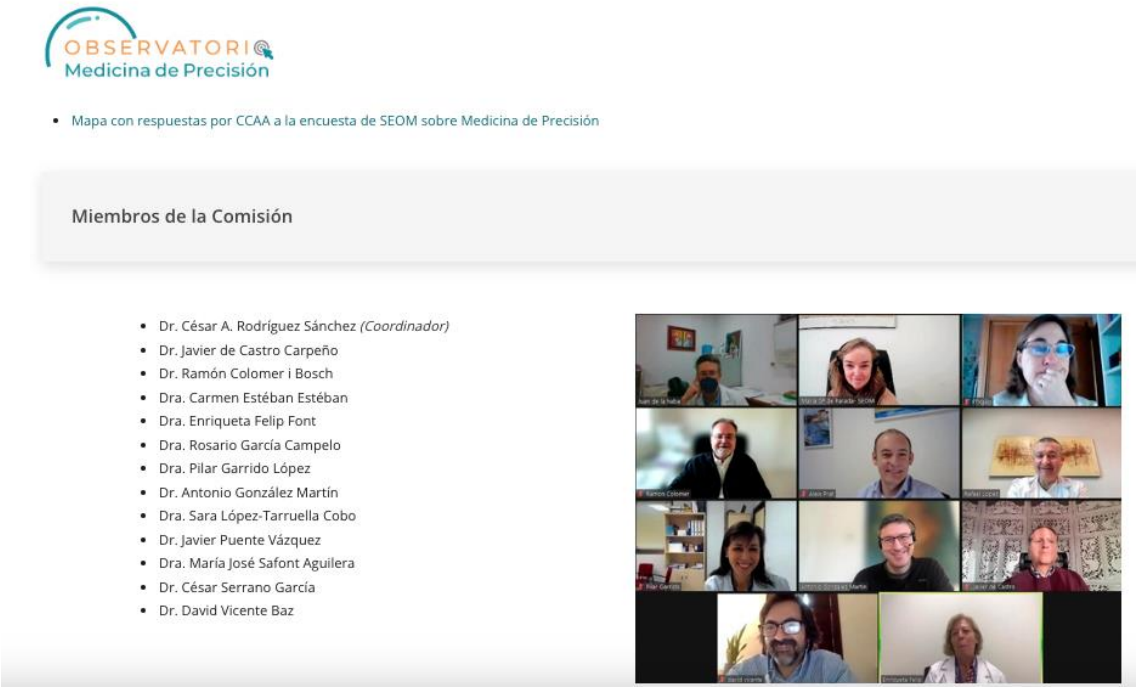
CENTRO / SITE		ACTIVAS EN ESTUDIO			DISCONTINUADAS DEL ESTUDIO		
		C. Mama	C. Pulmón	C. Colon	C. Mama	C. Pulmón	C. Colon
1	Hospital Universitario de Fuenlabrada	1	1	1	2		
2	Instituto de Investigación Sanitaria Hospital de La Princesa	2	3	1		1	
3	Hospital Clínico Universitario de Valencia	2					
4	ICO Hospitalet Bellvitge	7		1			
5	Hospital Universitario Son Espases	2	1				
6	Hospital Universitario de Navarra	3	1	2			
7	Hospital Universitario Virgen de la Macarena		7				
8	Hospital San Pedro de Alcántara	2					
9	Complexo Hospitalario Universitario de A Coruña	4					
TOTAL		23	13	5	2	1	0
		41			3		

2. Otros proyectos de investigación de los miembros de la Cátedra

- Estudios en poblaciones minoritarias de cáncer:
    - Pacientes con cáncer de mama hormono-positivo y amplificación de FGFR1/2 con fallo a inhibidores de CDK4/6 y aromatasa (rogaratinib). Dr M Quintela
    - Paciente con cáncer de mama triple-negativo y sobre-activación de CDK4/6 y ERK (binimetinib+palbociclib). Dr M Quintela
- Creación de un grupo emergente de investigación en biomarcadores de respuesta inmune en cáncer de próstata en el Hospital La Princesa y otros centros asociados. Dra N Romero-Laorden
- Caracterización clínica y molecular del cáncer de próstata avanzado en el Hospital Universitario de la Princesa. Secuenciación de 100 casos de CPRC de forma retrospectiva (PROYECTO CAPPRICE). Dra N Romero-Laorden
- Inmunoterapia de Precisión
    - Caracterizacion evolutiva del fenotipo inmune en cancer de prostata metastasico. Dra N Romero-Laorden
    - Biomarcadores de respuesta inmune en pacientes con cancer de prostata resistente a la castracion (CPRC). Dra N Romero-Laorden
    - Evaluación del papel de CCL21 en la respuesta al tratamiento con anticuerpos anti-PD-1 en cáncer de pulmón no microcítico (FIS22/01542). Dra A Alfranca
    - Treg-less: Targeting CCR7-mediated homeostasis of Tregs to Break the Immune Tolerance in Solid tumors (PLEC2022-009312). Dra A Alfranca
- Plataformas ISCIII de apoyo a la I+D+I en Biomedicina y Ciencias de la Salud **(**PT23/00060**)**, financiado por el ISCIII y con cofinanciación de fondos FEDER; Dr R Colomer (IP: Dr Francisco Abad)

Otras Actividades Relevantes en 2023

1. Participación en el Grupo de Trabajo de Medicina de Precisión de la Sociedad Española de Oncología Médica (SEOM)



2. Coordinación de la Comisión de Becas y Premios de la Sociedad Española de Oncología Médica (SEOM)

Comisión SEOM de Becas

Las funciones básicas consisten en diseñar la convocatoria de becas (número, cuantía, categorías etc.) y fallar las becas basándose en las puntuaciones de los evaluadores externos.

Esta Comisión está compuesta por los siguientes doctores:

Dr. Ramón Colomer (Coordinador)
Hospital Universitario de la Princesa. Madrid

Dra. Sonia Pernas Simón
Institut Catala d'Oncologia (ICO) L'Hospitalet, Barcelona

Dra. Ana Collazo Lorduy
Hospital Universitario Puerta de Hierro Majadahonda. Madrid

Dr. Javier Puente Vázquez
Hospital Universitario Clínico San Carlos, Madrid

Dra. Susana de la Cruz Sánchez
Hospital Universitario de Navarra, Pamplona

Dr. César A. Rodríguez Sánchez
Complejo Asistencial Universitario de Salamanca

Dra. Tania Fleitas Kanonnikoff
Hospital Clínico Universitario de Valencia

Dr. César Serrano García
Hospital Universitario Vall D'Hebron. Barcelona

Dr. Javier Pascual López
Hospital Universitario Virgen de la Victoria de Málaga

3. Funcionamiento la Unidad Funcional de Dermatooncología de Precisión en el Hospital de la Princesa de Madrid

Esta UF está formada por miembros de los Servicios de Dermatología, Oncología Médica, con la participación de radiología, Anatomía Patológica, entre otros.

Funciona desde septiembre de 2022, coordinada por los Dres Pedro Rodríguez Jiménez y Berta Hernández Marín.

PLAN DE ACTIVIDADES PARA EL AÑO 2024

1. Actualización 2024 del Módulo de Medicina Personalizada de Precisión del Máster de Oncología Médica de la Sociedad Española de Oncología Médica (SEOM) y la Universitat de Girona.
2. Elaboración de la publicación " Biomarkers in breast cancer 2024: An updated consensus statement by the Spanish Society of Medical Oncology and the Spanish Society of Pathology"
3. Elaboración de la publicación "Clinical characteristics and treatment patterns of metastatic colorectal cancer patients: A real world data study using natural language processing and machine learning"
4. Elaboración de una publicación científica de “Posicionamiento de expertos sobre la integración de la Inmunoterapia Oncológica en la Medicina Personalizada de Precisión”
5. Edición 2024 de las Fichas de Oncología Personalizada Publicación de las *slide decks* de los Consensos de Biomarcadores realizados por la SEOM y la SEAP
6. Lectura de Tesis Doctoral Análisis de supervivencia del cáncer colorrectal metastásico. Estudio retrospectivo de la vida real. Patricia Toquero Díez Matricula 11/2020, UAM
7. Tercera edición del Premio a la mejor Tesis Doctoral de Medicina Personalizada de Precisión
8. Planificación de un Curso de Medicina Personalizada de Precisión en colaboración con el Centro Nacional de Investigaciones Oncológicas