MAMAS Y TEJIDOS BLANDOS

➢ Fertilidad y Cáncer de mama

INVESTIGADORES: Katia Roque, Sophia Lozano, Zaida Morante, Silvia Neciosup, Henry Gómez.

REVISTA: Carcinos 2020; 10(2): 57-64

ABSTRACTO: El cáncer de mama es el tipo de cáncer más frecuente diagnosticado a nivel mundial en la población femenina y representa la principal causa de mortalidad relacionada a cáncer. En los últimos años la sobrevida de esta enfermedad se ha incrementado, especialmente en mujeres jóvenes. Precisamente, es en esta población, que se encuentra en edad fértil y con deseo genésico no satisfecho en donde el tema del embarazo y la preservación de la fertilidad toma un rol importante. Esta revisión se centra en la seguridad del embarazo y los tratamientos de fertilidad disponibles para las pacientes con cáncer de mama.

➢ Tumor-Specific Major Histocompatibility-II Expression Predicts Benefit to Anti-PD-1/L1 Therapy in Patients With HER2-Negative Primary Breast Cancer

INVESTIGADORES: Paula I Gonzalez-Ericsson, Julia D Wulfkhule, Rosa I Gallagher, Xiaopeng Sun, Margaret L Axelrod, Quanhu Sheng, Na Luo, Henry Gomez, Violeta Sanchez, Melinda Sanders, Lajos Pusztai, Emanuel Petricoin, Kim R M Blenman, Justin M Balko, I-SPY2 Trial Team (listed in Collaborators).

REVISTA: Clin Cancer Res 2021 Jul 27. doi: 10.1158/1078-0432.CCR-21-0607.

ABSTRACTO: Purpose: Immunotherapies targeting PD-1/L1 enhance pathologic complete response (pCR) rates when added to standard neoadjuvant chemotherapy (NAC) regimens in early-stage triple-negative, and possibly high-risk estrogen receptor-positive breast cancer. However, immunotherapy has been associated with significant toxicity, and most patients treated with NAC do not require immunotherapy to achieve pCR. Biomarkers discerning patients benefitting from the addition of immunotherapy from those who would achieve pCR to NAC alone are clearly needed. In this study, we tested the ability of MHC-II expression on tumor cells, to predict immunotherapy-specific benefit in the neoadjuvant breast cancer setting. Patients and methods: This was a retrospective tissue-based analysis of 3 cohorts of patients with breast cancer: (i) primary nonimmunotherapy-treated breast cancers (n = 381), (ii) triple-negative breast cancers (TNBC) treated with durvalumab and standard NAC (n = 48), and (iii) HER2-negative patients treated with standard NAC (n = 87) or NAC and pembrolizumab (n = 66). Results: HLA-DR positivity on ≥5% of tumor cells, defined a priori, was observed in 10% and 15% of primary non-immunotherapy-treated hormone receptor-positive and triple-negative breast cancers, respectively. Quantitative assessment of MHC-II on tumor cells was predictive of durvalumab + NAC and pembrolizumab + NAC (ROC AUC, 0.71; P = 0.01 and AUC, 0.73; P = 0.001, respectively), but not NAC alone (AUC, 0.5; P = 0.99). Conclusions: Tumor-specific MHC-II has a strong candidacy as a specific biomarker of anti-PD-1/L1 immunotherapy benefit when added to standard NAC in HER2-negative breast

cancer. Combined with previous studies in melanoma, MHC-II has the potential to be a pan-cancer biomarker. Validation is warranted in existing and future phase II/III clinical trials in this setting.

- **Genetic epidemiology of BRCA1- and BRCA2-associated cancer across Latin America**

INVESTIGADORES: Josef S Herzog, Yanin Chavarri-Guerra, Danielle Castillo, Julio Abugattas, Cynthia Villarreal-Garza, Sharon Sand, Jessica Clague-Dehart, Rosa M Alvarez-Gómez, Talia Wegman-Ostrosky, Alejandro Mohar, Pamela Mora, Azucena Del Toro-Valero, Adrian Daneri-Navarro, Yenni Rodriguez, Marcia Cruz-Correa, Patricia Ashton-Prolla, Bárbara Alemar, Rosa Mejia, Lenny Gallardo, Robin Shaw, Kai Yang, Aleck Cervantes, Kevin Tsang, Bita Nehoray, Hugo Barrera Saldana, Susan Neuhausen, Jeffrey N Weitzel.

REVISTA: NPJ Breast Cancer 2021 Aug 19;7(1):107. doi: 10.1038/s41523-021-00317-6.

ABSTRACTO: The prevalence and contribution of BRCA1/2 (BRCA) pathogenic variants (PVs) to the cancer burden in Latin America are not well understood. This study aims to address this disparity. BRCA analyses were performed on prospectively enrolled Latin American Clinical Cancer Genomics Community Research Network participants via a combination of methods: a Hispanic Mutation Panel (HISPANEL) on MassARRAY; semiconductor sequencing; and copy number variant (CNV) detection. BRCA PV probability was calculated using BRCAPRO. Among 1,627 participants (95.2% with cancer), we detected 236 (14.5%) BRCA PVs; 160 BRCA1 (31% CNVs); 76 BRCA2 PV frequency varied by country: 26% Brazil, 9% Colombia, 13% Peru, and 17% Mexico. Recurrent PVs (seen ≥3 times), some region-specific, represented 42.8% (101/236) of PVs. There was no ClinVar entry for 14% (17/125) of unique PVs, and 57% (111/196) of unique VUS. The area under the ROC curve for BRCAPRO was 0.76. In summary, we implemented a low-cost BRCA testing strategy and documented a significant burden of non-ClinVar reported BRCA PVs among Latin Americans. There are recurrent, population-specific PVs and CNVs, and we note that the BRCAPRO mutation probability model performs adequately. This study helps address the gap in our understanding of BRCA-associated cancer in Latin America.

- **Copy Number Aberration Analysis to Predict Response to Neoadjuvant Anti-HER2 Therapy: Results from the NeoALTTO Phase III Clinical Trial**

INVESTIGADORES: David Venet, Mattia Rediti, Marion Maetens, Debora Fumagalli, David N Brown, Samira Majjaj, Roberto Salgado, Lajos Pusztai, Nadia Harbeck, Sarra El-Abed, Yingbo Wang, Cristina Saura, Henry Gomez, Vladimir Fedorovich Semiglazov, Evandro de Azambuja, Jens Huober, Paolo Nuciforo, Serena Di Cosimo, Martine Piccart, Sherene Loi, Françoise Rothé, Christos Sotiriou.

REVISTA: Clin Cancer Res 2021 Jul 28. doi: 10.1158/1078-0432.CCR-21-1317.

ABSTRACTO: Purpose: The heterogeneity of response to anti-HER2 agents represents a major challenge in patients with HER2-positive breast cancer. To better understand the sensitivity and resistance to trastuzumab and lapatinib, we investigated the role of copy number aberrations (CNA) in predicting pathologic complete response (pCR) and survival outcomes in the NeoALTTO trial. Experimental design: The neoadjuvant phase III NeoALTTO trial enrolled 455 patients with HER2-positive early-stage breast cancer. DNA samples from 269 patients were assessed for genome-

wide copy number profiling. Recurrent CNAs were found with GISTIC2.0. Results: CNA estimates were obtained for 184 patients included in NeoALTTO. Among those, matched transcriptome and whole-exome data were available for 154 and 181 patients, respectively. A significant association between gene copy number and pCR was demonstrated for ERBB2 amplification. Nevertheless, ERBB2 amplification ceased to be predictive once ERBB2 expression level was considered. GISTIC2.0 analysis revealed 159 recurrent CNA regions. Lower copy number levels of the 6q23-24 locus predicted absence of pCR in the whole cohort and in the estrogen receptor-positive subgroup. 6q23-24 deletion was significantly more frequent in TP53 wild-type (WT) compared with TP53-mutated, resulting in copy number levels significantly associated with lack of pCR only in the TP53 WT subgroup. Interestingly, a gene-ontology analysis highlighted several immune processes correlated to 6q23-24 copy number. Conclusions: Our analysis identified ERBB2 copy number as well as 6q23-24 CNAs as predictors of response to anti-HER2-based treatment. ERBB2 expression outperformed ERBB2 amplification. The complexity of the 6q23-24 region warrants further investigation.

- **Practice-Changing Use of the 21-Gene Test for the Management of Patients With Early-Stage Breast Cancer in Latin America**

INVESTIGADORES: Henry L Gomez, Juan E Bargallo-Rocha, Roberto J Billinghurst, Aníbal R Núñez De Pierro, Federico A Coló, Lisandro L B Gil, Carola Allemand, Ignacio L McLean, Mauricio Lema-Medina, Fernando Herazo-Maya, Francisco J Terrier, Raquel G Cwilich, Mauricio Leon, Silvia G Falcon, Roberto E Castaño, Sergio C Oliveira, Debbie M Jakubowski, Calvin Chao.

REVISTA: JCO Glob Oncol 2021 Aug;7:1364-1373. doi: 10.1200/GO.21.00008.

ABSTRACTO: Purpose: We present a physician survey of the impact of 21-gene Breast Recurrence Score test results on treatment decisions in clinical practice in Latin America.Methods: This prospective survey enrolled consecutive patients at 14 sites in Argentina, Colombia, Mexico, and Peru who had routine 21-gene testing. Physician surveys captured patient and tumor characteristics and treatment decisions before and after 21-gene test results. The survey spanned the period before and after Trial Assigning Individualized Options for Treatment (TAILORx) results reported (June 2018). Overall net percent change in adjuvant chemotherapy recommendations was estimated, and asymptotic 95% CIs with continuity correction were calculated. The proportion with a change between pretest treatment recommendation and actual treatment received was calculated overall and by Recurrence Score groups per TAILORx. Results: Between March 2015 and December 2019, the survey was completed for 647 patients; 20% were node-positive. The mean patient age was 54 years (24-85 years); 55% were postmenopausal; 17%, 63%, and 20% had grade 1, 2, and 3 tumors, respectively; and 30% had tumors > 2 cm. Recurrence Score (RS) results were as follows: 20% RS 0-10, 56% RS 11-25, and 24% RS 26-100. Overall, chemotherapy recommendations fell by a relative proportion of 39% (95% CI, 33.4 to 44.3) after 21-gene testing (33% decrease in node-negative and 55% decrease in node-positive). Among node-negative patients, the relative decrease in chemotherapy recommendations was 28% (95% CI, 18.9 to 39.5) before TAILORx and 36% (95% CI, 28.4 to 43.7) after. Conclusion: To our knowledge, this large survey of 21-gene test practice patterns was the first conducted in Latin America and showed the relevance of 21-gene testing in low-

and medium-resource countries to minimize chemotherapy overuse and underuse in breast cancer. The results showed substantial reductions in chemotherapy use overall-especially after TAILORx reported-indicating the practice-changing potential of that study.

- **PIK3CA mutation in non-metastatic triple-negative breast cancer as a potential biomarker of early relapse: A case report**

INVESTIGADORES: Guillermo Arturo Valencia, Patricia Rioja, Zaida Morante, Jhajaira M Araujo, Heberth Daniel Vallejos, Henry Guerra, Henry L Gomez.

REVISTA: World J Clin Oncol 2021 Aug 24;12(8):702-711. doi: 10.5306/wjco.v12.i8.702.

ABSTRACTO: Background: Currently, the detection of PIK3CA mutations is of special interest in personalized medicine because it is frequently found in triple-negative breast cancer (TNBC). The PI3KCA mutation is an independent negative prognostic factor for survival in metastatic breast cancer, and its prognostic value in liquid biopsy as a biomarker of treatment and early relapse is under investigation, both for metastatic disease and neoadjuvant scenario with curative intent. Case summary: A 54-year-old female patient with TNBC clinical stage IIIA, who, after receiving neoadjuvant chemotherapy (based on anthracyclines and taxanes), surgery, radiotherapy, and adjuvant capecitabine, was detected with a PI3KCA mutation in tissue and peripheral blood (ctDNA in liquid biopsy). After 10 mo, the patient had disease relapse of left cervical node disease. Conclusion: The detection of PIK3CA mutation in TNBC after neoadjuvant treatment might be associated with early relapse or rapid disease progression.

- **Concurrent Detection of Circulating Tumor Cells and Circulating Tumor DNA in Triple-negative Breast Cancer**

INVESTIGADORES: Henry L Gómez, Carlos A. Castaneda, Miluska Castillo, James Reuben, Hui Gao, Nancy Suarez, Luis A. Bernabe, Jose M. Cotrina, Jorge Dunstan, Marco Velarde, Julio Abugattas, Henry Guerra.

REVISTA: Asian Pac J Cancer Care, 6 (4), 373-377. DOI:10.31557/APJCC.2021.6.4.373

ABSTRACTO: Objective: Circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA) provide tumor information in breast cancer. Our objective was to characterize CTCs, and contrasted them with ctDNA PIK3CA mutation in 24 triple negative breast cancer (TNBC). Methods: CTCs genes were characterized by AdnaTest protocol and ctDNA by digital PCR. Results: We found CTCs genes in 37.5% and ctDNA PIK3CA mutations in 29.16%. Three cases with CTCs genes had concurrent ctDNA PIK3CA mutations. MUC1 or GA733-2 were found in 4 cases, and 3 of them had concurrent ctDNA PIK3CA. CTCs ALDH1/TWIST1 were found in 2 cases, AKT2 in one and PI3Kα in another, and none had concurrent ctDNA PIK3CA mutations. There was no correlation between CTCs and ctDNA detection. All 3 cases with CTC & cDNA concurrent finding underwent death during follow up. Conclusion: Infrequent concurrent detection of CTC and ctDNA

presence suggests that both represent independent processes in TNBC patients, and could identify worst prognosis cases.

- **Alpha-smooth Muscle Actin Expression in the Stroma Predicts Resistance to Trastuzumab in Patients with Early-stage HER2-positive Breast Cancer**

INVESTIGADORES: Ioannis A Vathiotis, Myrto K Moutafi, Prajan Divakar, Thazin Nwe Aung, Tao Qing, Aileen Fernandez, Vesal Yaghoobi, Sarra El-Abed, Yingbo Wang, Sebastien Guillaume, Paolo Nuciforo, Jens Huober, Serena Di Cosimo, Sung-Bae Kim, Nadia Harbeck, Henry Gomez, Saba Shafi, Konstantinos N Syrigos, George Fountzilas, Christos Sotiriou, Lajos Pusztai, Sarah Warren, David L Rimm.

REVISTA: Clin Cancer Res 2021 Aug 31. doi: 10.1158/1078-0432.CCR-21-2103.

ABSTRACTO: Purpose: The companion diagnostic test for trastuzumab has not changed much in the last 25 years. We used high-plex digital spatial profiling to identify biomarkers besides HER2 that can help predict response to trastuzumab in HER2-positive breast cancer. Experimental design: Fifty-eight protein targets were measured in three different molecularly defined compartments by the NanoString GeoMx Digital Spatial Profiler (DSP) in a tissue microarray containing 151 patients with breast cancer that received adjuvant trastuzumab as part of the Hellenic Cooperative Oncology Group 10/05 clinical trial. Promising candidate biomarkers were orthogonally validated with quantitative immunofluorescence (QIF). RNA-sequencing data from the Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimisation Study (NeoALTTO) were accessed to provide independent cohort validation. Disease-free survival (DFS) was the main outcome assessed. Statistical analyses were performed using a two-sided test (α = 0.05) and multiple testing correction (Benjamini-Hochberg method, FDR < 0.1). Results: By DSP, high expression of alpha-smooth muscle actin (α-SMA), both in the leukocyte and stromal compartments, was associated with shorter DFS in univariate analysis (P = 0.002 and P = 0.023, respectively). High α-SMA expression in the stroma was validated by QIF after controlling for estrogen receptor and progesterone receptor status [HR, 3.12; 95% confidence interval (CI), 1.12-8.68; P = 0.029] showing recurrence on trastuzumab in the same cohort. In the NeoALTTO cohort, elevated levels of ACTA2 were predictive for shorter DFS in the multivariate analysis (HR, 3.21; 95% CI, 1.14-9.05; P = 0.027). Conclusions: This work identifies α-SMA as a novel, easy-to-implement biomarker of resistance to trastuzumab that may be valuable in settings where trastuzumab is combined with other therapies.

- **A biomarker study in Peruvian males with breast cancer**

INVESTIGADORES: Carlos A Castaneda, Miluska Castillo, Luis A Bernabe, Joselyn Sanchez, Ebert Torres, Nancy Suarez, Katherine Tello, Hugo Fuentes, Jorge Dunstan, Miguel De La Cruz, Jose Manuel Cotrina, Julio Abugattas, Henry Guerra, Henry L Gomez.

REVISTA: World J Clin Oncol 2021 Oct 24;12(10):926-934. doi: 10.5306/wjco.v12.i10.926.

ABSTRACTO: Background: Breast cancer (BC) frequency in males is extremely low and tumor features vary from its female counterpart. Breast cancer clinical and pathological features differ by race in women. Tumor infiltrating lymphocyte (TIL) levels, mismatch repair (MMR) protein loss, androgen receptor (AR) expression, and PIK3CA gene mutations are predictive biomarkers of response to biological therapy in female BC. There is limited information about clinical and pathological features as well as predictive biomarkers in males of non-Caucasian races with BC. Aim: To investigate clinicopathological features and biomarkers of BC tumors in males and their prognostic value in Peruvian population. Methods: This study looked at a single-institution series of 54 Peruvian males with invasive BC who were diagnosed from Jan 2004 to June 2018. Standard pathological features, TIL levels, MMR proteins, AR immunohistochemistry staining, and PIK3CA gene mutations were prospectively evaluated in cases with available paraffin material. Percentage of AR and estrogen receptor (ER) positive cells was additionally calculated by software after slide scanning. Statistical analyses included association tests, intraclass correlation test and Kaplan Meier overall survival curves. Results: The median age was 63 years and most cases were ER-positive (85.7%), HER2 negative (87.2%), Luminal-A phenotype (60%) and clinical stage II (41.5%) among our male breast tumors. Median TIL was 10% and higher levels tended to be associated with Luminal-B phenotype and higher grade. AR-positive was found in 85.3% and was correlated with ER (intraclass index of 0.835, $P < 0.001$). Loss of MMR proteins was found in 15.4% and PIK3CA mutation (H1047R) in 14.3% (belonged to the Luminal-A phenotype). Loss of MMR proteins was associated with AR-negative ($P = 0.018$) but not with ER ($P = 0.43$) or TIL ($P = 0.84$). Early stages ($P < 0.001$) and lower grade ($P = 0.006$) were associated with longer overall survival. ER status, phenotype, AR status, TIL level, MMR protein loss nor PIK3CA mutation was not associated with survival ($P > 0.05$). Conclusion: Male BC is usually ER and AR positive, and Luminal-A. MMR loss and PIK3CA mutations are infrequent. Stage and grade predicted overall survival in our South American country population.

➢ SELNET clinical practice guidelines for soft tissue sarcoma and GIST

INVESTIGADORES: J Y Blay, N Hindi, J Bollard, S Aguiar Jr, M Angel, B Araya, R Badilla, D Bernabeu, F Campos, C H S Caro-Sánchez, B Carvajal, A Carvajal Montoya, S Casavilca-Zambrano, V Castro-Oliden, M Chacón, M Clara, P Collini, R Correa Genoroso, F D Costa, M Cuellar, A P Dei Tos, H R Dominguez Malagon, D Donati, A Dufresne, M Eriksson, M Farias-Loza, P Fernandez, A M Frezza, T Frisoni, D Y Garcia-Ortega, H Gelderblom, F Gouin, M C Gómez-Mateo, A Gronchi, J Haro, L Huanca, N Jimenez, M Karanian, B Kasper, B B Lopes David, A Lopez-Pousa, G Lutter, H Martinez-Said, J Martinez-Tlahuel, C A Mello, J M Morales Pérez, S Moura David, A G Nascimento, E J Ortiz-Cruz, E Palmerini, S Patel, Y Pfluger, S Provenzano, A Righi, A Rodriguez, R Salas, T T G Santos, K Scotlandi, T Soule, S Stacchiotti, C Valverde, F Waisberg, E Zamora Estrada, J Martin-Broto.

REVISTA: Review Cancer Treat Rev 2021 Nov 14;102:102312. doi: 10.1016/j.ctrv.2021.102312.

ABSTRACTO: Soft tissue sarcoma (STS) is a heterogeneous group of neoplasms, encompassing > 80 different histologic subtypes. Approximately three quarter of sarcoma arise from soft-tissue, about 15% are gastrointestinal stromal

tumours (GISTs) and bone sarcoma represent the remaining 10%. The current guidelines will focus on soft-tissue and GIST, excluding Kaposi sarcoma and non-pleomorphic rhabdomyosarcoma.

- **The tale of TILs in breast cancer: A report from The International Immuno-Oncology Biomarker Working Group**

INVESTIGADORES: Khalid El Bairi, Harry R Haynes, Elizabeth Blackley, Susan Fineberg, Jeffrey Shear, Sophia Turner, Juliana Ribeiro de Freitas, Daniel Sur, Luis Claudio Amendola, Masoumeh Gharib, Amine Kallala, Indu Arun, Farid Azmoudeh-Ardalan, Luciana Fujimoto, Luz F Sua, Shi-Wei Liu, Huang-Chun Lien, Pawan Kirtani, Marcelo Balancin, Hicham El Attar, Prerna Guleria, Wenxian Yang, Emad Shash, I-Chun Chen, Veronica Bautista, Jose Fernando Do Prado Moura, Bernardo L Rapoport, Carlos Castaneda, Eunice Spengler, Gabriela Acosta-Haab, Isabel Frahm, Joselyn Sanchez, Miluska Castillo, Najat Bouchmaa, Reena R Md Zin, Ruohong Shui, Timothy Onyuma, Wentao Yang, Zaheed Husain, Karen Willard-Gallo, An Coosemans, Edith A Perez, Elena Provenzano, Paula Gonzalez Ericsson, Eduardo Richardet, Ravi Mehrotra, Sandra Sarancone, Anna Ehinger, David L Rimm, John M S Bartlett, Giuseppe Viale, Carsten Denkert, Akira I Hida, Christos Sotiriou, Sibylle Loibl, Stephen M Hewitt, Sunil Badve, William Fraser Symmans, Rim S Kim, Giancarlo Pruneri, Shom Goel, Prudence A Francis, Gloria Inurrigarro, Rin Yamaguchi, Hernan Garcia-Rivello, Hugo Horlings, Said Afqir, Roberto Salgado, Sylvia Adams, Marleen Kok, Maria Vittoria Dieci, Stefan Michiels, Sandra Demaria, Sherene Loi, International Immuno-Oncology Biomarker Working Group.

REVISTA: Review NPJ Breast Cancer 2021 Dec 1;7(1):150. doi: 10.1038/s41523-021-00346-1.

ABSTRACTO: The advent of immune-checkpoint inhibitors (ICI) in modern oncology has significantly improved survival in several cancer settings. A subgroup of women with breast cancer (BC) has immunogenic infiltration of lymphocytes with expression of programmed death-ligand 1 (PD-L1). These patients may potentially benefit from ICI targeting the programmed death 1 (PD-1)/PD-L1 signaling axis. The use of tumor-infiltrating lymphocytes (TILs) as predictive and prognostic biomarkers has been under intense examination. Emerging data suggest that TILs are associated with response to both cytotoxic treatments and immunotherapy, particularly for patients with triple-negative BC. In this review from The International Immuno-Oncology Biomarker Working Group, we discuss (a) the biological understanding of TILs, (b) their analytical and clinical validity and efforts toward the clinical utility in BC, and (c) the current status of PD-L1 and TIL testing across different continents, including experiences from low-to-middle-income countries, incorporating also the view of a patient advocate. This information will help set the stage for future approaches to optimize the understanding and clinical utilization of TIL analysis in patients with BC.