2273P Influence of body mass index (BMI) on the response to chemotherapy in patients with HER2+ breast cancer: Role of the leptin axis

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Background: Obesity is associated with T-cell dysfunction and high PD-1 expression, resulting in paradoxical benefit from check-point inhibitor therapy. This effect is driven, in part, by leptin that exerts its action through binding to the leptin receptor (Ob-R), which is highly expressed in HER2+ BC. High tumor infiltrating lymphocytes (TILs) counts correlate with pathological response and long-term outcomes in BC, but the precise mechanism is not known. The aim of this study was to investigate the role of BMI in modulating TILs and pathological responses in early HER2+ BC patients who received neoadjuvant systemic treatment (NST).

Methods: Women with HER2+ BC receiving anti-HER2-based NST followed by surgical resection were included. Patient age, menopausal status, and height/weight (to calculate BMI) were recorded. Based on biopsy findings, tumors were categorized as HER2+/HR+ and HER2+/HR-. Ob-R expression was also measured and classified as over-expressed if there were >50% positive cells with weak or strong staining. TILs and PD-1 expression were determined centrally using pre-treatment biopsies. TILs were considered as continuous variables and binary, <30 vs ≥30%, and PD-1 as positive (>1%). Associations with pathological complete response (pCR) were assessed statistically.

Results: 27 of 85 HER2+ BC patients were overweight/obese (BMI ≥25kg/m^2). Patients with high BMI tended to have tumors with higher hormone receptor expression than lean patients (85 vs 64%; p=0.078). No differences were found in median Ki67 between the high or low BMI groups. A greater number of high BMI patients were menopausal (63 vs. 36%; p=0.038). Patients with high BMI had a significantly greater expression of Ob-R vs lean patients (78 vs 55%; p=0.045) and at the same time had a significantly higher expression of TILs (median 23 vs 16%; p=0.007). Despite having higher TIL counts, pCR were similar (63.0 vs 58.6%; p= 0.704). However, PD-1 expression was significantly higher in patients with high BMI (median 4 vs 1; p=0.012).

Conclusions: Our study shows for the first time how obesity, through the Ob-R/leptin axis, might activate TILs. However, this was not translated into higher CR; probably due to high PD-1 expression as exhaustion feature.

Editorial acknowledgement: Editorial assistance was provided by Content Ed Net (Madrid, Spain).

Legal entity responsible for the study: The authors.

Funding: Roche, ACS Foundation.

Disclosure: J. Pérez García: Financial Interests, Personal, Advisory Role: Lilly, Roche, Eisai, Daiichi Sankyo, AstraZeneca, Seattle Genetics, Gilead; Financial Interests, Personal, Other, Travel expenses: Roche. J. Cortés: Financial Interests, Personal, Advisory Role: Roche, Celgene, Cellestia, AstraZeneca, Seattle Genetics, Daiichi Sankyo, Erytech, Athenex, Polyphor, Lilly, Merck Sharp & Dohme, GSK, Leuko, Bioasis, Clovis Oncology, Boehringer Ingelheim, Ellipses, Hibercell, BioInvent, GEMoaB, Gilead, Menarini, Zymework; Financial Interests, Personal, Funding: Roche, Novartis, Celgene, Eisai, Pfizer, Samsung Bioepis, Lilly, Merck Sharp & Dohme, Daiichi Sankyo, AstraZeneca; Non-Financial Interests, Institutional, Research Funding: Roche, Ariad Pharmaceuticals, AstraZeneca, Baxalta GMBH/Servier Affaires, Bayer healthcare, Eisai, F. Hoffmann-La Roche, Guardant Health, Merck Sharp & Dohme, Pfizer, PIQUR Therapeutics, Puma C, Queen Mary University of London; Financial Interests, Personal, Stocks/Shares: MedSIR, Nektar Pharmaceuticals, Leuko (relative); Other, Personal, Other, Travel, accommodation, expenses: Roche, Novartis, Eisai, Pfizer, Daiichi Sankyo, AstraZeneca, Gilead; Financial Interests, Personal, Other, Patents: Pharmaceutical Combinations of A Pi3k Inhibitor and A Microtubule Destabilizing Agent. Javier Cortés Castán, Alejandro Piris Giménez, Violeta Serra Elizalde. WO 2014/199294 A. Issued. L. García Estevez: Financial Interests, Personal, Advisory Role: Roche, AstraZeneca, Daiichi Sankyo, Gilead. All other authors have declared no conflicts of interest.

https://doi.org/10.1016/j.annonc.2023.09.1301

2274P Deep learning-based prediction of pathologic complete response to neoadjuvant therapy in breast cancer using H&E images and RNA-Seq in the IMMUcan study

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Background: IMMUcan (SPECTA NCT02834884) is an European public-private effort to generate molecular and cellular profiling data of the human tumor microenvironment from up to 3000 cancer patients. Predicting pathologic complete response (pCR), which has been associated with better outcome after neoadjuvant treatment in breast cancer (BC), could help refining treatment strategies. Here, we aim to integrate multiple data layers using different Deep Learning (DL) approaches to predict pCR from baseline tumor samples in the context of the prospective IMMUcan Triple-Negative Breast Cancer (TNBC) and HER2-positive (HER2+) BC neoadjuvant cohorts.

Methods: At the cut-off date of June 29th, 2022, we identified a first cohort of 132 and 149 patients diagnosed with TNBC and HER2+ BC, respectively, for preliminary analyses. To predict pCR at the patient level, benchmark models using RNA-Seq, image DL were trained on Whole Slide Images (WSIs) and RNA-Seq data. The image models included two main components: a tiling algorithm pre-trained on TCGA WSI to extract a spatialized representation of the WSI and a classification part for the pCR prediction.

Results: Baseline RNA-Seq data were available for 109 and 115 patients with TNBC and HER2+ BC, respectively, pCR status was available for 130 TNBCs and 117 HER2+ BCs, while a baseline H&E-stained WSI was available for all patients. Among the models applied independently to each data type, the best performance was obtained using RNA-Seq in HER2+ BC (ROC AUC = 0.61, std = 0.04), and WSI in TNBC (ROC AUC = 0.63, std = 0.03).

Conclusions: These preliminary results show the potential of DL applied to WSI and RNA-Seq in predicting pCR for TNBC and HER2+ BC. Using DL models able to predict pCR provide the opportunity to better select patients and tailor neoadjuvant therapies in BC. Multimodal models combining RNASeq and WSI are currently being tested out by the team to improve performance.

Legal entity responsible for the study: EORTC.

Funding: IMI2 JU grant agreement 821558, supported by EU's Horizon 2020 and EFPIA.

Disclosure: C. Esposito, C. Maussion: Financial Interests, Personal, Full or part-time Employment: Owkin. M. Morfouace: Financial Interests, Personal, Full or part-time Employment: Merck Healthcare KGaA. L. Buisseret: Financial Interests, Institutional, Research Grant: AstraZeneca; Financial Interests, Personal, Financially Compensated Role: Association Jules Bordet; Financial Interests, Personal, Advisory Board: Domain Therapeutics, iTEOS Therapeutics; Financial Interests, Personal, Research Grant: Gilead. H.S. Hong: Financial Interests, Personal, Full or part-time Employment: Merck Healthcare KGaA. All other authors have declared no conflicts of interest.

https://doi.org/10.1016/j.annonc.2023.09.1302

2275P Circulating leptin and adiponectin levels in premenopausal women with and without breast cancer (BC) and a body mass index (BMI) ≥25 kg/m2

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Background: Obesity has a controversial effect on BC risk depending on the menopausal status. The mechanisms by which a high BMI protects against BC in premenopausal women are unknown. Adipose tissue produces two antagonistic hormones: leptin activates tumorigenesis in postmenopausal patients; by contrast, adiponectin has an anti-inflammatory effect. The aim of this study is to evaluate adiponectin and leptin levels according to the presence of not of BC in a group of premenopausal women with high BMI.

Methods: This prospective transversal study included premenopausal women with high BMI with recently diagnosed of early BC or without cancer. Age, weight, and height were recorded. Premenopausal status was confirmed by LH, FSH, and estradiol blood values. Fasting values of insulin, glucose, lipid profile, and vitamin D levels were also determined. Adiponectin and leptin levels were analyzed as continuous variable.

Adiponectin was also categorized as low, normal, and high considering age and weight. Patients with BC were classified in luminal, triple-negative, and HER2+ by IHC.

Results: Of the 86 women included in the study, 54 were BC-free and 32 with BC (luminal 23, triple-negative 5, and HER2+ 6). Women without cancer had significantly higher BMI (median 32.3 vs 26.8; $p<0.001$), leptin levels (median 27.3 vs 12.8; $p<0.001$), and insulin levels (median 10.8 vs 6.8; $p<0.003$) than BC patients. However, a significant correlation between high leptin and insulin levels was only observed in BC patients ($p<0.001$). Furthermore, a significant negative correlation was found between high leptin levels and low vitamin D levels in BC-free women ($p<0.004$). Conversely, there were no differences in adiponectin levels either as a continuous variable or in the categorization between BC and BC-free women.

Conclusions: This study analyzes, for the first time, the difference between leptin and adiponectin levels in premenopausal women with high BMI with or without BC. Although high leptin levels are associated with an increased risk of BC in postmenopausal women, this does not seem to occur in premenopausal women. Adiponectin levels are similar for both groups.

Editorial acknowledgement: Editorial assistance was provided by Content Ed Net (Madrid, Spain).

Legal entity responsible for the study: The authors.

Funding: Fundación Contigo.

Disclosure: J. Pérez García: Financial Interests, Personal, Advisory Role: Lilly, Roche, Eisai, Daiichi Sankyo, AstraZeneca, Seattle Genetics, Gilead; Financial Interests, Personal, Other, Travel expenses: Roche. J. Cortés: Financial Interests, Personal, Other, Consulting/Advisor: Roche, Celgene, Cellestia, AstraZeneca, Seattle Genetics, Daiichi Sankyo, Erytech, Athenex, Polyphor, Lilly, Merck Sharp & Dohme, GSK, Leuko, Bioasis, Clovis Oncology, Boehringer Ingelheim, Ellipses, Hibercell, BioInvent, GEMoaB, Gilead, Menarini, Zymework; Financial Interests, Personal, Funding: Roche, Novartis, Celgene, Eisai, Pfizer, Samsung Bioepis, Lilly, Merck Sharp & Dohme, Daiichi Sankyo, AstraZeneca; Financial Interests, Institutional, Research Funding: Roche, Ariad Pharmaceuticals, AstraZeneca, Baxalta GMBH/Servier Affaires, Bayer healthcare, Eisai, F. Hoffmann-La Roche, Guardant Health, Merck Sharp & Dohme, Pfizer, PIQUR Therapeutics, Puma C, Queen Mary University of London; Financial Interests, Personal, Stocks/Shares: MedSIR, Nektar Pharmaceuticals, Leuko (relative); Financial Interests, Personal, Other, Travel, accommodation, expenses: Roche, Novartis, Eisai, Pfizer, Daiichi Sankyo, AstraZeneca, Gilead; Financial Interests, Personal, Other, Patents: Pharmaceutical Combinations of A Pi3k Inhibitor and A Microtubule Destabilizing Agent. Javier Cortés Castán, Alejandro Piris Giménez, Violeta Serra Elizalde. WO 2014/199294 A. ISSUED Her2 as a predictor of response to dual HER2 blockade in the absence of. L. García Estevez: Financial Interests, Personal, Advisory Role: Roche, AstraZeneca, Daiichi Sankyo, Gilead. All other authors have declared no conflicts of interest.

https://doi.org/10.1016/j.annonc.2023.09.1303

2276P Regulation of major histocompatibility class-I gene methylation using DNA methyltransferase inhibitor and PD-L1 inhibitor in triple-negative breast cancer

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Background: There are many studies on gene methylation and immunotherapy in breast cancer, but there are few studies on the effect of DNA methyltransferase (DNMT) inhibitors and immunotherapy on major histocompatibility (MHC) class-I gene methylation in triple-negative breast cancer (TNBC).

Methods: The relationship between the expression of the MHC class-I gene and DNA methylation was analyzed using data from The Cancer Genome Atlas (TCGA). The expression of DNMTs and MHC class-I genes was analyzed in breast cancer tissue from TNBC patients and TNBC cell lines. DNA methylation analysis of the MHC class-I gene was performed with pyrosequencing in TNBC tissues and methylation specific PCR in TNBC cell lines. TNBC cell lines were treated with DNMT inhibitors Decitabine and Zebularine and PD-L1 inhibitor Atezolizumab, and then changes in the expression of DNMT, MHC-I gene, and methylation patterns of MHC class-I gene were analyzed.

Results: TCGA data analysis confirmed that there was an inverse correlation between DNA methylation and mRNA expression of the MHC class-I gene, but analysis in TNBC patients in this study did not show this correlation. After treating TNBC cell lines with DNMT inhibitors and PD-L1 inhibitor alone and in combination, the DNA methylation pattern of the HLA-B and HLA-C gene was suppressed, but there was no significant change in the DNA methylation of the HLA-A gene. The expression of the MHC class-I gene increased in BT-20 after Decitabine treatment, and only in BT-549 after Zebularine treatment. It increased in BT-549 after Atezolizumab treatment, and in MDA-MB231 after combination of Decitabine and Atezolizumab. After each drug treatment, the cell viability of TNBC cell lines was reduced due to the drug's own cancer treatment effect, which limited the analysis of the outcome of changes.

Conclusions: The treatment responses to DNMT inhibitors and PD-L1 inhibitor were different depending on the characteristics of TNBC and the types of drugs, suggesting that the treatment target needs to be applied differently. Further study is needed to determine specific treatment targets and appropriate drugs according to the characteristics of TNBC.

Legal entity responsible for the study: The author.

Funding: This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (No. 2020R1G1A1099646).

Disclosure: The author has declared no conflicts of interest.

https://doi.org/10.1016/j.annonc.2023.09.1304

2277P A colorimetric biosensor to track Trop-2 status of tumor cells for diagnosis of breast cancer

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Background: The emergence of antibody-drug conjugates (ADCs) targeting trophoblast cell-surface antigen-2 (Trop-2) has reshaped the therapeutic landscape of advanced breast cancer. Accurate profiling of the Trop-2 status of tumor cells can facilitate the identification of patients who will benefit from Trop-2-targeting therapy; however limited analytical method has hindered this process.

Methods: In this study, we have proposed a specific and sensitive biosensor for visual tracking of the Trop-2 status of breast cancer cells based on tetrahedral DNA nanostructure (TDN)-decorated Fe-based metal-organic framework nanoparticles (TDN-PCN-222 (Fe)).

Results: In the design, a dual-aptamer-assisted biomimetic capture strategy shows high capture efficiency while maintaining the viability and original phenotype of captured cells, ensuring the accurate profiling of the Trop-2 status. Meanwhile, by using the high intrinsic peroxidase activity and excellent targeting ability of Trop-2-specific aptamer-linked TDN-PCN-222 (Fe), specific detection of Trop-2-positive tumor cells can be achieved with a limit of detection (LOD) of 10 cells/mL, and the Trop-2 status of tumor cells can be visually tracked. Moreover, the proposed biosensor has been successfully used for tracking the Trop-2 status of tumor cells in breast cancer tissues, suggesting that our method has great promise for clinical applications.

Conclusions: a sensitive and specific colorimetric biosensor was proposed in this work for visually tracking the Trop-2 status of tumor cells. This sensor has been used for the visualized tracking of Trop-2 status of different cancer cell lines as well as breast cancer tumor cells. Therefore, the proposed sensor has considerable potential for visualized tracking of various drug targets on tumor cells from cancerous tissues or the circulating system, and this work may provide an unprecedented method with great promise for the companion diagnosis of Trop-2 ADCs.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

https://doi.org/10.1016/j.annonc.2023.09.1305

2278P Endothelial cell heterogeneity defined by single-cell spatial transcriptomic analysis of breast cancers

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Background: The heterogeneity of the tumor microenvironment is a major barrier for effective cancer therapies. Similar to the immune tumor microenvironment the stromal environment, composed of cancer-associated fibroblasts (CAFs), pericytes, adipocytes and endothelial cells, is also heterogeneous. Multiple studies showed that CAFs contain heterogenous cell populations with opposing pro and anti-tumoral function. The heterogeneity of endothelial cells (ECs) is less well described largely due to the relative low frequencies in tumor tissues compare to CAFs. We set out to study the heterogeneity of the tumor microenvironment using truly single-cell spatial transcriptomic by the 10x Genomics Xenium platform.

Methods: We analyzed 20 human breast tumors by Xenium single-cell analyzes using fluorescent in situ sequencing (FISSEQ). We used the available breast panel that contains 280 genes, with 8 probes for each gene. The analysis of the data was preformed using the Seurat pipeline in R (version 4.9.9.9039).

Results: We could readily identify blood vessel structures that surrounded PECAM1/VWF positive cells. After multiple clustering we identified five types of endothelial cells with divergent gene expression profiles. We defined the following clusters of ECs: 1) Proliferating ECs, 2) CXCL12+ ECs, 3) $POSTN^{Hi}/VWF^{Hi}$ ECs, 4) $TPD52^{Hi}$ ECs and $POSTN^{Low}/VWF^{Hi}$ ECs. The endothelial cells also showed spatial variations in