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STRONG ASSOCIATION BETWEEN PATHOLOGICAL RESPONSE TO NEOADJUVANT CHEMOTHERAPY, TILS AND MODELED CA125 KELIM IN OVARIAN CARCINOMAS: CHIVA TRIAL, GINECO

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Introduction/Background* As stated by ESGO-ESMO, there is a need for indicators of chemotherapy efficacy in ovarian carcinoma patients treated in first-line setting (Colombo et al, IGCS, 2020). The pathological chemotherapy response score (CRS) and the modeled CA-125 KELIM during neo-adjuvant chemotherapy were reported as potential markers. Moreover, changes in tumor infiltrating lymphocytes (TILs) after neo-adjuvant chemotherapy were reported as a prognostic factor (Leary et al, Cancer Immunol Immunother, 2021). We studied the relationships between changes in TILs, the pathological response (pR) and KELIM in patients treated with neo-adjuvant chemotherapy +/- interval debulking surgery (IDS) from CHIVA phase II trial.

Methodology The patients were enrolled in the randomized phase II trial CHIVA (NCT01583322, neo-adjuvant carboplatin-paclitaxel +/- nintedanib, +/- IDS, n=188 patients). KELIM were previously calculated (You et al CCR 2020). The 30 patients with the highest KELIM (very chemosensitive) or the lowest KELIM (poorly chemosensitive) were selected. HE-stained sections from available tissue blocks at baseline and after chemotherapy were analyzed for stromal TILs (sTILs, surface of the tumor stroma occupied by lymphocytes) and intra-epithelial TILs (ieTILs, brisk or non-brisk). The pathological response (pR) was assessed on the most tumoral available tissue block obtained after chemotherapy (good response if extensive fibrous changes with no or isolated tumor cells, or <2 mm cell clusters). Descriptive statistics assessed the relationships between KELIM, TIL changes, and pR.

Result(s)* No relationships between KELIM and TILs infiltrates on baseline tumor samples were found. However, strong associations were found between KELIM and TIL infiltrates after neo-adjuvant chemotherapy for sTILs (median KELIM for sTILs 0-5% vs >5%: 0.28 versus 1.32, P < 0.001) and for ieTILs (median KELIM for ieTILs non-brisk versus brisk: 0.31 versus 1.31, P = 0.04). Similarly, an association was found between KELIM and the quality of pR (median KELIM for patients with poor vs good pR: 0.31 versus 1.32, P = 0.05).

Conclusion* High consistency was found between the modeled CA125 KELIM calculated during the first 100 days of neo-adjuvant chemotherapy and the pathological response, consistent with their values as indicators of the tumor chemosensitivity in first-line setting. Moreover, TILs changes were strongly associated with chemosensitivity, opening hypotheses about the mechanisms of chemosensitivity, and immunotherapy opportunity.

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DEVELOPMENT AND VALIDATION OF A MACHINE-LEARNING-DERIVED RNAseq PROGNOSTIC SIGNATURE IN ENDOMETRIAL CANCER

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Introduction/Background* Because of inter-tumor heterogeneity of endometrial carcinoma (EC), prognostication remains challenging. We aimed to develop a RNAseq signature to stratify EC patient prognosis beyond molecular subtyping.

Methodology A prognostic signature was identified using a LASSO-penalized Cox regression model on TCGA (N=543 patients). A polyA-RNAseq-based method was developed for validation of the signature in a cohort of stage I-IV EC patients treated in two Paris Hospitals between 2010 and 2017. Model performances were evaluated using time-dependent ROC curves (prediction of disease-specific-survival (DSS)). The additional value of the RNAseq signature was evaluated using uni/multivariable Cox models (hazard ratio (HR) with [95% confidence interval]) and Kaplan-Meier analysis.

Result(s)* Among 209 patients included in the validation cohort (median follow-up 55 months IQR [41-69]), 61 (30%), 10 (5%), 52 (25%), and 82 (40%), had mismatch repair-deficient, POLE-mutated, TP53-mutated tumors, and tumors with no specific molecular profile, respectively. The 38-genes signature accurately predicted DSS (AUC=80%). Using a composite classifier accounting for the RNAseq signature and the TP53-mutated group, three groups were identified: good prognosis tumors based on RNAseq signature and without TP53 mutation, characterized by excellent outcome (N=103 patients, 5-years DSS rates of 99%) (reference), poor prognosis tumors based on RNAseq signature and without TP53 mutation (N=49 patients, 5-years DSS rates of 81%; HR: 5.86 [1.16; 29.7]), and TP53-mutated tumors whatever the RNAseq signature (N=52 patients, 5-years DSS rates of 52%; HR: 11.14 [2.40; 51.7]) (HR adjusted on FIGO stage). In 81 (38%) patients with adverse features (2020 ESGO/ESTRO/ESP

guidelines: non-endometrioid histology or stage III-IVA or TP53-mutated tumors), TP53-mutated molecular group was not significantly associated with poor prognosis ($p=0.18$). The composite classifier identified three classes within this subgroup: RNAseq-good prognosis ($N=24$), non-TP53/RNAseq-poor prognosis ($N=16$), and TP53-mutated tumors ($N=41$), with 5-years DSS rates of 100%, 59%, and 71%, respectively ($p=0.015$). Transcriptome analyses suggested the underlying involvement of immune deprivation and wound healing processes in tumors with poor prognosis.

Conclusion* We demonstrate that RNAseq characterization can refine prognostication in EC beyond molecular subgroups and main prognostic features, and warrants validation for potential RNAseq-based adjuvant therapeutic strategies in EC.

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CLINICAL IMPACT OF MESOTHELIN EXPRESSION IN OVARIAN CANCER: A TISSUE MICROARRAY STUDY ON 113 PATIENTS

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Introduction/Background* Mesothelin (MSLN) is a CA125 binding protein that mediates cell adhesion. This interaction was suggested to play a role in the peritoneal metastasis development. In preclinical models, MSLN overexpression activates the PI3K/Akt, NFκB, and MAPK/ERK pathways, to promote cell proliferation, migration and metastasis. For these reasons, MSLN represents an attractive molecule for targeted ovarian cancer (OC) therapies.

Methodology Paraffin-embedded tumor tissue samples from 113 primary OC patients were selected from TOC biobank (www.toc-network.de) and assessed for the immunohistochemical expression of MSLN on Tissue Microarray. For 51 included HGSOc patients, also paired recurrent samples were available and selected for MSLN evaluation.

All patients were treated at Charité Medical University Berlin, Germany, through primary cytoreduction followed by platinum-based chemotherapy. MSLN expression profiles were correlated with patients' clinic-pathological and survival data. MSLN expression was also compared between paired primary and recurrent HGSOc samples.

Result(s)* 164 samples were assessed for MSLN expression (113 primary OC and 51 recurrent OC).

Among the primary OC cohort, results showed that MSLN (+) samples were 85% of cases (96/113), whereas MSLN was negative in the remaining 15% of cases (17/113). MSLN expression did not differ among different OC histological subtypes (serous, clear cells and endometrioid), but MSLN(+) samples were diagnosed more frequent in the group of advanced FIGO stage (65/96 vs 31/96, $p=0.022$) and in platinum sensitive patients (85/96 vs 11/96, $p=0.001$).

Survival analysis showed that MSLN(+) was associated with a significant survival advantage at 5yOS ($p=0.022$) in HGSOc patients. No survival impact (5yPFS and/or 5yOS) of MSLN expression could be detected for other OC histologies.

Pairwise analysis on paired primary and recurrent HGSOc, also revealed that MSLN(+) tumors were more frequent

among primary rather than recurrent HGSOc (46/51 vs 38/51, $p=0.012$); Furthermore, Spearman test showed a significant correlation among primary and recurrent samples in terms of MSLN expression decrease at recurrence ($p=0.003$).

Conclusion* Overexpression of MSLN was observed in FIGO advanced stage and in platinum sensitive primary OC patients. MSLN expression was equally distributed among different OC histologies, but in HGSOc conferred survival advantage. Moreover, its expression significantly decreased from primary to recurrent OC.

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CONTRIBUTION OF NETOSIS IN ADVANCED STAGES OF HIGH-GRADE SEROUS OVARIAN CANCER: DIAGNOSTIC IMPLICATIONS

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Introduction/Background* NETosis has recently been described as a new form of neutrophils' immune response, by which they release extracellular networks (NETs) of DNA, histones and proteins. In the tumor environment, NETs participate in immunothrombosis, tumor progression, metastasis, and evasion of the immune system. Recent studies show that NETosis is involved in the initial metastasis of high-grade serous ovarian cancer (HGSOc), although its contribution in advanced stages or as a diagnostic biomarker is unknown, which is the objective of this study.

Methodology We analyzed paired plasma and ascites fluid samples from women with HGSOc ($n=28$) and controls ($n=16$). As NETosis markers, we quantified cell-free circulating DNA (cfDNA, Quant-iT PicoGreen dsDNA kit), nucleosomes (Cell Death Detection ELISA^{PLUS} kit), calprotectin (Human Calprotectin ELISA kit) and myeloperoxidase (MPO) (Human MPO ELISA kit) and we evaluated their differences with the SPSS program (v.21).

Result(s)* Patients with HGSOc presented a higher concentration of cfDNA in plasma (median 1785,9 ng/mL; Q1-Q3, 1618,5-2181,6) compared to the controls (1526,7; 1452,0-1610,9) ($p<0,001$). In addition, we observed an increase in the 4 NETosis markers evaluated in patients' ascites: cfDNA [(2128,9; 1477,8-2814,5) vs. (1148,1; 990,8-1235,3), $p<0,001$], nucleosomes [(2,58 AU; 1,27-3,16) vs. (0,09; 0,003-0,55), $p<0,001$], calprotectin [(2606,8 ng/mL; 1028,3-5021,7) vs. (353,5; 195,5-722,3), $p<0,001$] and MPO [(73,3 ng/mL; 48,8-141,4) vs. (25,3; 22,6-29,4); $p<0,001$] (figure 1).

The levels of the 4 markers were positively correlated with each other in both biofluids ($p<0.032$) and with the levels of neutrophils in plasma ($p<0.001$). We also observed that cfDNA in plasma was able to distinguish patients from controls (AUC=0.842). Furthermore, the levels of cfDNA,