chimotherapy. The aim of the study was to determine the predictive value of ER-beta expression in a cohort of ovarian cancer patients treated with platinum and taxanes. The level of ER-beta expression was correlated with progression-free survival and also with a number of disease relapses during 40 months of monitoring.

**Material and methods** The quantitative immunofluorescence flow cytometry analysis was performed to detect ER-beta in 34 serous ovarian cancer surgical specimens. All the patients were treated with the first line platinum and taxane-based regimen. The primary anti-ER-beta (ab14C8) and the secondary antibodies (DyLight650, ab98729) were used for the analysis. The level of ER-beta expression was calculated by Kolmogorov-Smirnov statistical test as the ratio (%) of specifically fluorescent cells to the number of cells incubated only with secondary antibodies. Association of ER-beta expression levels with progression-free survival was analysed using the Kaplan-Meier method and log-rank tests.

**Results and discussions** ER-beta were revealed in all tumour specimens tested and the median value of the expression level was 41.5%. Patients were dichotomized in groups with low and high level of ER-beta expression, below- and above-median value respectively. Significant differences were shown between these groups. First, median of progression-free survival was larger in the high-level expression group as compared to the low-level expression group – 25.5 vs 8 months. Second, the disease rate during 40 months of monitoring was lower in the high-level expression group as compared the low-level expression group – 6 vs 15 respectively.

**Conclusion** A quantitative index of the ER-beta level expression in tumour tissue predicts the efficacy of the first line platinum and taxane-based chemotherapy in ovarian cancer patients. Progression-free survival was about 3.0 times longer and the number of the disease relapses during 40 months of monitoring was 1.5 times less in patients with high level of ER-beta expression. The study was supported in part by RSF 17-75-10212.

**PO-523**

**UNVEILING THE MICRORNA SIGNATURE OF GASTRIC CANCER EXOSOMES: LONGITUDINAL AND CROSS-SECTIONAL PERSPECTIVES**

**Introduction** There is no consensus regarding follow-up of Gastric Cancer (GC) patients. The available imaging tools and serological markers are poorly sensitive to monitor treatment response, minimal residual disease and tumour regrowth in a time-effective manner. We hypothesised that exosomes isolated from GC patients could contain specific small RNAs, useful to monitor tumour dynamics, likely to change during the therapy, anticipating disease relapse.

**Material and methods** We designed a prospective study of the small RNA profile of exosomes isolated from plasma of four GC patients collected at three timepoints: before, soon- and late-after surgery. Exosomes were isolated and characterised by ultracentrifugation and nanoparticle tracking analysis. Exosome and tumour RNA was extracted and profiled using small-RNA sequencing technology. Analysis was performed using the tools bowtie2 and cufflinks for genome alignment, annotation and quantification. Analysis was

**PO-522**

**GLOBAL PROTEOME AND PHOSPHOPROTEIN PROFILING OF MENINGIOMAS REVEALS NOVEL POTENTIAL THERAPEUTIC TARGETS AND BIOMARKERS**

**Introduction** Meningiomas are the most common primary intracranial brain tumour arising from meningeal tissue. Despite the majority of them displaying benign features, they can cause mild to severe morbidity. The current main therapeutic approach is complete tumour resection commonly with adjunct radiation therapy. However, tumour location can hamper complete resection and chemotherapy is ineffective. In this study we aim to elucidate the pathogenic signature of these tumours and identify novel molecular targets by deciphering the global proteome and phosphoprotein profile of different grades of meningiomas.

**Material and methods** Tumour lysates were collected from grade I, II and III frozen meningioma specimens and three normal healthy human meninges. Phosphoprotein purification was performed using QiaGen® PhosphoProtein Purification Kit. Proteins were separated by SDS-PAGE followed by in-gel tryptic digestion. Extracted peptides were purified and analysed by electrospray ionisation LC-MS/MS. Raw mass spectrometry files were analysed using MaxQuant®. Expression data were validated by Western blot and immunohistochemistry. In silico functional annotation of expression data was completed using Perseus 1.5.0.31 software suite, Ingenuity Pathway Analysis (IPA®) and DAVID 6.8.

**Results and discussions** We have quantified 3888 proteins and 3074 phosphoproteins across all grades of meningioma and normal meninges. Comparative analysis identified 181 proteins and 338 phosphoproteins to be commonly significantly upregulated (log2 fold-change ≥1.5; p<0.05) among all grades vs normal meninges, and further identified differential expression profiles between meningioma grades. Expression data was validated on samples analysed by MS and on an additional cohort of meningiomas for upregulated proteins including SET, EGFR, SRSF1, CKAP4 and HK2; and phosphoproteins including AKT1, AKT2 and RB1. Gene Ontology revealed commonly upregulated proteins to be enriched in terms including RNA helicase activity, whilst phosphoproteins were enriched in the phosphoprotein associated terms of signal complex assembly, Rho guanyl-nucleotide exchange factor activity and EGFR signalling.

**Conclusion** In summary, we performed a comprehensive quantitative proteomic analysis from meningioma tissue of all WHO grades compared to healthy meninges and identified several potential candidates that may hold therapeutic potential for targeted treatment of these tumours.
focused on microRNAs (miRs), the most abundant class of small RNAs in these samples. Informed consent was given by all patients.

**Results and discussions** On average, we detected 233 miRs in tumours and 175 in exosomes that were classified as present/absent and interrogated across samples. Cross-sectional analysis: same timepoint across patients. Longitudinal analysis: tumour and exosomes from the same patient. Cross-sectional analysis identified 49 miRs shared by all tumours, 33 by all exosomes collected before surgery, 83 by all exosomes collected after surgery. To pinpoint miRs useful to monitor tumour dynamics in each patient, three criteria were defined: 1) miRs present both in tumours and exosomes before surgery, and; 2) miRs present in tumours and absent in exosomes soon after surgery. We found 133 miRs in patients A, 50 in B, 34 in C and 11 in D. Combining the cross-sectional and longitudinal analysis, we found two miRs fulfilling the above criteria that were shared by three out of four patients. These two miRs were still detected in Patient D exosomes soon after surgery, likely reflecting non-curative surgery. Validation of these data is currently ongoing in a larger series of patients. **Conclusion** Overall, this study pinpointed two miRs that may prove useful to monitor tumour dynamics and response to treatment in GC. The longitudinal analysis holds the promise of revealing a set of miRs with clinical utility for anticipating disease relapse, on a personalised manner.

**PO-524 MT4-MMP, EGFR AND RB EXPRESSIONS ARE PREDICTIVE BIOMARKERS OF RESPONSE TO ERLOTINIB-PALBOCICLIB COMBINATION IN TNBC**

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**Introduction** Triple negative breast cancer (TNBC) comprises heterogeneous agressive tumours. The standard treatment relies entirely on chemotherapy. While EGFR is expressed in 50\%-75\% of TNBC, clinical trials with erlotinib or cetuximab fail to show clinical benefit. Recently, we demonstrated that EGFR interacts with MT4-MMP, the membrane-type 4 matrix metalloprotease in TNBC. Here, we investigated the clinical significance of the MT4-MMP/EGFR axis in inactivation of protein of retinoblastoma (Rb) in human TNBC samples and patient-derived xenografts (PDX). We tested the efficacy of targeting this pathway in vivo in xenografts and PDX with a distinct expression profile of MT4-MMP, EGFR and Rb.

**Material and methods** Immunohistochemistry (IHC) analysis for MT4-MMP, EGFR, Rb and Ki67 expression were performed on human TNBC samples (n=78) and Patient-Derived Xenograft (PDX-TNBC) (n=38). Single and combined treatments with erlotinib and palbociclib were applied in vitro and in vivo. In vitro 2D and 3D proliferation assays were performed on TNBC cells naturally producing EGFR and transfected or not with MT4-MMP cDNA. For the in vivo study, xenografts and PDX were engrafted with Rag1/- mice and nude mice, respectively. Mice bearing tumours producing or not MT4-MMP, EGFR and Rb were treated with vehicle, erlotinib (50 mg/kg/day), palbociclib (75 mg/kg/day) or the combination.

**Results and discussions** By IHC analysis we reveal that Rb is maintained functional in 68\% of human samples and 59\% of PDX-TNBC. Co-expression of MT4-MMP, EGFR and Rb is obtained in 49\% of human samples and 43\% in PDX-TNBC. In a 2D culture model, response to erlotinib and palbociclib is enhanced in cells expressing both MT4-MMP and EGFR. In 3D culture, their combination is synergistic for the inhibition of proliferation of MT4-MMP and EGFR expressing cells. In vivo, tumours expressing MT4-MMP and EGFR show a better response to erlotinib and palbociclib than tumours negative for MT4-MMP with a striking effect of the combination on MT4-MMP tumours. Moreover, PDX-TNBC expressing only EGFR and Rb show no response to erlotinib, a partial response to palbociclib and a strong response to the combination. Importantly, co-expression of EGFR and MT4-MMP strongly sensitises Rb positive PDX-TNBC to both erlotinib and palbociclib with a striking effect of the combination, whereas PDX-TNBC with Rb loss didn’t respond to any single or combination therapy.

**Conclusion** Our data highlight MT4-MMP, EGFR and Rb as predictive biomarkers for response to erlotinib-palbociclib combination.

**PO-525 MOLECULAR SIGNATURES OF CIRCULATING MICRONRNAS AS EARLY BREAST CANCER BIOMARKERS**

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**Introduction** Breast cancer is the leading cause of cancer death among women. The number of human diagnosed with breast cancer has been increased specially in middle and low countries. Early detection is a key to reduce cancer deaths. Biological fluids such as blood hold good opportunities to identify new non-invasive biomarkers. One the new and the promising classes of circulating cancer biomarkers is the microRNAs (miRNAs). These molecules are tissue-specific, are remarkably stable in several biological samples and have others intrinsic characteristics that make attractive as biomarkers. Thus to identify molecular signatures of circulating miRNAs that can be correlated with molecular subtypes of breast cancer in early stages can be an useful in clinical practice. We applied a new screening technology to determine the expression profile of circulating RNAs and to correlate molecular subtypes of early stage breast cancer and compare with healthy women.

**Material and methods** Fifty-four patients with early-stage breast cancer paired with twenty-seven women without breast cancer risk (controls). Total RNA was obtained from serum of cases and controls and the expression profile of differentially expressed serum miRNAs was obtained using the nCounter panel from NanoString Technology. Statistical analyses were performed in program R. The interaction networks miRNAs-genes predicted were constructed in the Cytoscape program and the functional enrichment analysis was applied to identify