effective clinical therapy for patients with metastatic colorectal cancer (mCRC), particularly for those with KRAS, NRAS, BRAF and PI3KCA wild-type cancer. However, only a fraction of patients receives clinical benefit from therapy with anti-EGFR antibodies. The HER2 gene amplification has been implicated as one of the mechanisms for primary and acquired resistance to anti-EGFR therapies in mCRC. However, little is known about the role of HER2 in cancer resistance to anti-EGFR antibodies.

Material and methods We transfected stably colon cancer cells, sensitive to anti-EGFR antibodies (LIM1215 and SW48), with HER2 plasmid. We characterised the transfected cells in terms of molecular profile and sensitivity to several drugs through cell proliferation assays and western blot analysis. Furthermore, HER2 amplified cells were engrafted into nude mice and treated to find the best therapeutic treatment.

Results and discussions We observed a strong upregulation on the HER family receptors EGFR, HER3, and HER4 in cells with HER2 amplification, but also an over-exression of intracellular transducers such as Akt, MAPK, and MEK proteins compared to parental cells. Furthermore, we treated LIM1215-HER2 and SW48-HER2 cells with several combinations of antibodies and small molecules directed to HER receptor family, such as anti-EGFR receptor antibodies of first, second and third generation (cetuximab, SYM004 and MM151); trastuzumab, pertuzumab and lapatinib directed against HER2 receptor; and duligotuzumab as anti-HER3 receptor. We observed a strongest growth inhibition effect after treatment with trastuzumab in combination with lapatinib compared to other treatments. Moreover, we incubated the HER2 amplified cells with drugs directed to the downstream domains of the DNA polymerase encoded by POLE gene. A PILOT STUDY in vivo xenografts CRC models.

Conclusion These results suggest that the treatment with refametinib and pictilisib could be a strategy for patients with HER2 amplification that do not receive clinical benefit from anti-EGFR therapies.

Introduction Tumours characterised by high-mutation rate and neoepitope load, which are hypothesised to be responsible for their high immunogenicity, are known to respond to the immune checkpoint inhibitor therapy. Microsatellite instability (MSI) in patients with colorectal cancer (CRC) is a biomarker for the high mutation rate is these patients. Besides MSI, there exists a subset of CRC patients with stable microsatellites (MSS) and germline or somatic mutations in functional domains of the DNA polymerase encoded by POLE gene who can benefit from the immune checkpoint therapy. The aim of this retrospective pilot study was to detect POLE mutations and identify patients with MSS CRC who could benefit from the immune checkpoint inhibitor therapy. Because the detection of POLE mutations requires sensitive methods, we used single tube nested PCR to improve the sensitivity of the method.

Material and methods In this pilot study, 34 patients with the diagnosis of CRC aged 52 or less out of 270 CRC patient cohort have been enrolled. The lymphocyte infiltration and MSI were determined. PCR primers were designed for exons 9, 11 and 13 of the POLE gene, one pair of external primers as well as one pair of internal primers for each exon. The amplicons were sequenced according to the Sanger method using internal primers. The sequences were aligned with the reference sequence (ENST0000032057.9).

Results and discussions The average age of our patients was 43.9 years. The nested PCR was optimised by touch down approach with two different annealing temperatures for external and internal primers. In our pilot study, we were not able to find any of the previously described pathogenic mutations. In one case of colorectal adenocarcinoma with mucinous elements (48y), a silent substitution c.893C>T resulting in p. L283L was detected with forward and reverse primers. This substitution is not described in dSNP. Using MutationTaster, we have found a possible effect of this substitution on RNA splicing, which still has to be confirmed on the RNA level.

Conclusion Mutations in POLE gene in CRC and endometrial cancer are associated with hypermutated tumours and are promising predictive biomarkers in immune checkpoint inhibitor therapy. It is important to develop sensitive methods that enable the detection of somatic mutations in routine clinical setting. Supported by Biomedical Centre Martin (ITMS 26220220187) and APVV-16-0066.

PO-521 EXPRESSION OF OESTROGEN RECEPTOR BETA AS A PREDICTIVE MARKER OF PLATINUM AND TAXANE-BASED CHEMOTHERAPY IN OVARIAN CANCER PATIENTS

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Introduction Predictive markers of platinum-based chemotherapy efficacy in patients with ovarian cancer have been widely discussed in recent years. Oestrogen receptors (ER) are involved in regulation of proliferative factors responsible for tumour growth, so they could predict the effectiveness of anticancer
chemotherapy. 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 41.1%. 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 lover 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-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 chemotherapies are 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, EGF, 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 have identified several potential candidates that may hold therapeutic potential for targeted treatment of these tumours.

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’ plasma 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 (Ion Torrent). Bioinformatics analysis was performed using the tools bowtie2 and cufflinks for genome alignment, annotation and quantification. Analysis was...