Results and discussions Our data demonstrates that inhibition of MK2 increases the stability and expression of p53, indirectly by reducing the phosphorylation of its ligase MDM2. This suggests that MK2 plays a role in regulating p53, as inhibition of MK2 increased the levels of active p53 inside the nucleus. We also found that the combination of TMZ and MK2 inhibition did not induce G2/M arrest as expected, but G0/G1 arrest. This increase of cells in G0/G1 led to cellular senescence through the reactivation of the p53-p21 pathway. Moreover, we found that MK2 inhibition enhances the efficacy of TMZ by attenuating long-term clonal and 3D spheroid growth in p53 proficient cells, unlike previously described.

Conclusion The combination of MK2 inhibition alongside TMZ provides a new therapeutic strategy to enhance the effectiveness of current chemotherapy in p53 proficient tumours.

**PO-023**

**A MULTI-STEP FRAMEWORK TO ANALYSE HIGH-THROUGHPUT DRUG COMBINATION SCREENS**

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10.1136/esmoopen-2018-EACR25.558

Introduction Tailored, genotype-driven therapies are the future for treatment of heterogeneous cancers like breast cancer. However, despite their high therapeutic index, targeted agents often have limited success in single agent treatment setups due to variable clinical response rates and resistance. Thus, a framework to develop drug combinations for treatment of cancer is needed.

Material and methods Our group has an ongoing effort to systematically screen two-drug combinations in cancer type-specific and pan-cancer high-throughput drug combination screens. We have screened over 1000 combinations, including both broad-acting chemotherapeutics and targeted compounds. Cancer type-specific drug combination screens were conducted in breast and colorectal cancer cell lines, using a panel of 50 cell lines in each screen. Acquired data has been used to determine a strategy to extract the most promising drug combinations in each tissue.

Results and discussions We propose a multi-step analytical framework for the identification and prioritisation of synergistic combinations. Initial filtering is based on several parameters, including synergy (z-score), XMID and Emax. Robustness of drug response effects is assessed through rescreening of selected drug combinations. Further prioritisation of promising combinations in a tissue-specific setting is achieved through stratification of the combination drug response in cell line subgroups, including segregation based on commonly mutated genes and molecular subtypes (e.g. PAM50 subgrouping in breast cancer). Moreover, systematic exploration of genotype-drug synergy associations will be used to identify biomarkers of response for patient stratification.

Conclusion In conclusion, we have developed a multi-step framework to identify clinically relevant synergistic drug combinations complementing current cancer therapy options. This pipeline may facilitate future combination drug synergy predictions and validation.

**PO-024**

**PERIOPERATIVE BLOCKADE OF STRESS-INFLAMMATORY RESPONSES IMPROVES BIOMARKERS OF METASTASIS IN EXCISED TUMOURS AND BLOOD SAMPLES: PHASE II CLINICAL TRIALS IN COLORECTAL AND BREAST CANCER PATIENTS**

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10.1136/esmoopen-2018-EACR25.559
Introduction Excess release of catecholamines and prostaglandins has been shown to mediate pro-metastatic processes of stress and surgery, specifically during the critical perioperative period.

Material and methods Here, in two randomised placebo controlled clinical trials in colorectal (CRC, n=34) and in breast cancer patients (BC, n=38), we tested the combined 20 day perioperative use of the b-blocker, propranolol, and the COX2-inhibitor, etodolac, initiated 5 days before surgery. Tumour samples were collected during surgery, and were subjected to histological analyses, whole genome mRNA profiling, and transcriptional control pathways analyses. In BC patients, four blood samples were also collected perioperatively.

Results and discussions Drugs were well tolerated, with adverse effects equivalent to placebo. In blood samples, treatment reduced serum IL-6 and CRP levels even before surgery, improved markers of NK cytotoxicity, and enhanced induced production of IFNg and IL-12, without affecting anti-inflammatory soluble factors (cortisol and IL-10). In both studies, whole genome mRNA profiling of excised tumours showed decreased epithelial-to-mesenchymal transition (EMT); down-regulation of the transcriptional activity of CREB, NFkB, GATA family, and STAT3; reduced presence of tumor-associated monocyes; and increased presence of NK cells in CRC and B cells in BC tissue. The tumour proliferation marker Ki67 was tested in BC patients, and was significantly reduced by drug treatment. In CRC patients, three-year follow-up showed large but statistically insignificant improvement in disease free survival (DFS) in the treatment group (1/15 vs 5/19), further suggesting the safety of the paradigm.

Conclusion These findings suggest a critical impact to the short pre-operative period, clearly indicate the efficacy of this combined drug regimen, and suggest its metastatic-reducing impact, which should be tested in larger clinical trials. Such a stress-inflammatory-reducing approach can be exploited during the critical perioperative period, potentially improving long-term survival rates.

**PO-026** METFORMIN INHIBITS THE NGF-INDUCED INCREASE C-MYC AND VEGF LEVELS IN OVARIAN CANCER CELLS

**Introduction** Epithelial ovarian cancer (EOC) is a lethal malignance characterised by high levels of angiogenic and growth factors. Nerve Growth Factor (NGF) is overexpressed in EOC and promotes proliferation, survival and angiogenesis in EOC models. NGF stimulation of EOC explants increases proteins levels of c-MYC transcription factor and vascular endothelial growth factor (VEGF), both oncogenic proteins. Besides, the anti-diabetic drug metformin can regulates signalling pathways that can be activated by NGF: previous results have shown that metformin can prevent proliferative and pro-angiogenic effects of NGF in the EOC and endothelial cells, so that we wanted to deepen in the mechanism of metformin action. The aim of this study was to evaluate c-MYC and VEGF levels in A2780 cells stimulated with NGF and metformin.

**Material and methods** A2780 cells were stimulated with NGF (100 ng/mL; 2 or 24 hours) and/or metformin (10 mM; 48 hours). Then, supernatant were collected to measure VEGF through ELISA and cells were used to detect c-MYC protein levels by western blotting and immunocytochemistry.

**Results and discussions** NGF stimulation increased c-MYC protein levels in A2780 cells at 2 and 24 hours of (p<0.05) and also NGF increased levels of VEGF in culture medium from