INTRODUCTION
Genomic instability (GIS) is a major tumorigenesis driving factor. Both - amplification of ERBB2 in breast cancer, and acute or cycling tumour hypoxia have been shown to result in increased GIS. Data concerning effects of chronic and mild hypoxia on GIS in cancer cells are conflicting and scarce. Therefore the aim of this study was to explore effects of chronic mild hypoxia (cmH) on GIS in HER2-positive breast cancer cell line SK-BR-3.

MATERIAL AND METHODS
State of GIS was characterised by proportion of micronuclei containing cells (immunostaining with anti-tubulin and DAPI), chromosomal breakpoints, copy number alterations (Illumina CytoSNP12 v2-1 Bead Chip), expression of genome stability related genes (qPCR); relative telomere length (RTL) (qPCR) after prolonged cultivation of SK-BR-3 (three passages) in hypoxia (2% O₂) or normoxia (control).

RESULTS AND DISCUSSIONS
Prolonged exposure to cmH resulted in significant 3.3-fold increase of micronuclei containing cells (hypoxia vs normoxia: 25.38 and 5.86 micronuclei per 1000 cells). Initial adaptation to cmH manifested as contraction of genome and decrease of chromosomal breakpoints (normoxia vs hypoxia: DNA index 2.06 and 1.90; breakpoint count: 4573 and 2678). Further cultivation in cmH resulted in additional reduction of DNA index (1.89) and increase in number of breakpoints (3037). CmH increased expression of ATM dependent DDR genes, significantly decreased expression of dsDNA-break reparation genes (H2AFX, BRCA1, FANCD2) and had no significant effect on aneuploidy-related gene expression. Initial exposure to cmH resulted in major increase of RTL (from 1.1 to 7.8), but further culture in hypoxia showed gradual decrease of RTL (down to 1.3). Low expression levels of telomerase (TERT) through all passages did not change significantly.

CONCLUSION
Initial adaptation to hypoxia was characterised by increased RTL, contraction of genome and decrease of genomic heterogeneity. Initial selection of hypoxia-fit SK-BR-3 subpopulations was followed by increased formation of chromosomal rearrangements. CmH in SK-BR-3 activated ATM-CHEK2 branch of DDR and decreased expression of genes involved in reparation of dsDNA breaks. Low expression levels of TERT through all passages did not change significantly and did not correlate with the RTL.

TUMOUR PROGRESSION
INVASION AND METASTASIS

INTRODUCTION
Triple-negative breast cancers (TNBCs) are characterised by increased tumour-infiltrating lymphocytes and the presence of complex compositions of structural and single nucleotide variations. We previously described HORMAD1, a Cancer/Testis (CT) antigen, as a novel driver of homologous recombination (HR) deficiency. Our ultimate aim was to identify biomarkers in HORMAD1 positive TNBCs that could be used to stratify patients for immunomodulatory and/or DNA damage response (DDR) targeted agents. In order to do this, we first defined the transcriptomics and genomics features of HORMAD1 positive TNBCs.

MATERIAL AND METHODS
HORMAD1 positive TNBCs were identified using either microarray or RNA-sequencing data. Gene set enrichment analysis was used to identify hyper- or hypo-activated pathways. Whole-exome sequencing (WES) from TCGA TNBCs was used to identify genes exclusively mutated in HORMAD1 positive TNBCs. Mutational signatures in tumours were delineated using whole-genome sequencing from ICGC TNBCs.

RESULTS AND DISCUSSIONS
In six independent TNBC cohorts (total n=719) HORMAD1 expression was bimodal. More than 50% of the TNBCs were identified as HORMAD1 positive and tended to display PAM50 basal-like, intClust 10, or a basal-like 1 TNBCypotype-4 subtype (P value<0.05). In HORMAD1 positive TNBCs, genes involved in DNA repair by HR or DNA mismatch repair displayed increased expression (Q value<0.05). WES from TCGA TNBCs (n=75) indicated that missense mutations in PIK3CA were found exclusively in HORMAD1 negative TNBCs (P value=0.002). Mutational signature 3 and rearrangement signature 5, previously associated with HR deficiency in BRCA1- and BRCA2-deficient tumours, were more prevalent in HORMAD1 positive ICGC TNBCs (n=72, Q value=0.049 and 0.028 respectively), as was an increase in substitution burden (P value=0.032). HORMAD1 positive TNBCs also displayed a transcriptomic signature reminiscent of activated CD4 +T cells (Q value<0.05). It is possible that the DNA damage caused by ectopic HORMAD1 expression, or its role as a CT antigen, or both, could drive an adaptive immune response, thus explaining this CD4 +T cell signature.

CONCLUSION
Taken together, the molecular profiles of HORMAD1 positive TNBCs indicate not only the underlying biology of this TNBC subset, but also opportunities for therapeutic exploitation, including agents that target the DDR and immune system.

INTRODUCTION
The extensive stromal deposition and remodelling of pancreatic ductal adenocarcinoma (PDAC) alters mechanical...
tumour-stroma integrations, promoting tumour development and metastatic spread. Few effective therapies mean that PDAC is predicted to be the second leading cause of cancer mortality by 2030. In highly metastatic mouse models of PDAC, we observed enhanced extracellular matrix (ECM) deposition and remodelling throughout disease progression. This was paralleled by an increased focal adhesion kinase (FAK) expression and activity, suggesting a role for FAK in the increased desmoplastic reaction that is typical of PDAC. Consequently, fine-tuned manipulation of the dense stroma by streamlined FAK inhibition (FAKi) presents a novel opportunity for PDAC management and improved response to chemotherapy.

**Material and methods** Intravital imaging of the FUCCI cell cycle reporter was used to dynamically monitor tumour cell response to combined FAKi and standard-of-care therapy with gemcitabine/Abraxane. This was overlaid with second harmonic generation (SHG) imaging of collagen fibres, to assess the efficacy of FAKi to disrupt the dense PDAC ECM. To complement our *in vitro* metastatic studies, we used sophisticated 3D *in vivo* models of invasion, anchorage-independent growth and shear-stress, in both primary and patient-derived PDAC cell lines.

**Results and discussions** We systematically demonstrated that using FAKi to modulate ECM prior to standard-of-care therapy enhanced treatment efficacy whilst also reducing metastatic spread *in vivo*. Further analysis revealed that FAKi sensitised cells to shear stress, impairing metastatic colonisation and the establishment of fibrotic niches in the liver. Stratified patient samples revealed a subset of patients likely to respond to FAK priming regimes, where fine-tuned ECM manipulation prior to chemotherapy may offer a novel opportunity in metastatic PDAC.

**Conclusion** This subtype-specific fine-tuned stromal manipulation may allow us to maximise gemcitabine/Abraxane therapy whilst reducing drug toxicity and potentially reducing metastatic spread in a preclinical setting.

**PO-230** CYSTEINE-RICH SECRETORY PROTEIN 3 REGULATES PROGRESSION FROM *IN SITU* TO INVASIVE PROSTATE CANCER

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**Introduction** One of the most challenging aspects of prostate cancer diagnosis is predicting whether cancer will remain indolent or progress to invasive, aggressive and potentially lethal disease. Current markers such as PSA are unreliable and tumours requiring treatment may remain undetected while others are overtreated. Cysteine-rich secretory protein 3 (CRISP3) is a member of a poorly defined family of proteins that is highly up-regulated in human prostate cancer.

**Material and methods** We sought to define the role of CRISP3 in the molecular pathology of prostate cancer through the generation of a Crisp3 knockout mouse line, which was crossed onto the Hi-MYC mouse model of prostatic adenocarcinoma. The pro-invasive actions of CRISP3 were also studied using human and mouse derived cell lines and purified recombinant CRISP3.

**Results and discussions** Here we show that CRISP3 induces migration and invasion of prostate cancer cells *in vitro*. Furthermore, and consistent with human expression data, CRISP3 was dramatically up-regulated with advanced disease in the Hi-MYC mouse model of prostatic adenocarcinoma and specifically associated with transformed and migratory cells both *in vivo* and *in vitro*. Importantly, Crisp3 deletion delayed the transition from prostatic intraepithelial neoplasia to carcinoma *in situ* and blocked the transition to the invasive disease. These effects are attributed to changes in the expression of EMT markers in response to CRISP3. We are currently validating potential CRISP3 binding partners identified by mass spectrometry.

**Conclusion** Collectively, these data define CRISP3 as pro-tumourigenic in the prostate through a role in promoting cancer invasion.

**PO-231** CTXIII EXPRESSION AROUND SINGLE TUMOUR CELLS OF INVASIVE BREAST CARCINOMA

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**Introduction** Studies of breast carcinoma indicated the presence of type I and III collagens localization at the invasion front of the tumour. Mesenchymal invasion accompanied by proteolysis, in particular collagens, and remodelling of tissue structures by matrix metalloproteases. Possible marker of this process is expression of Cross Linked C-telopeptide of Type III Collagen (CTX-III). The project is aimed to study frequency of CTX-III expression around different of single tumour cells subtypes of invasive breast carcinoma of no specific type.

**Material and methods** Fourteen patients with invasive breast carcinoma of no specific type (IC NST, all molecular subtypes, T1-3N0-3M0) were enrolled in study. CTX-III expression around different subtypes of single tumour cells were analysed in FFPE tumour samples using confocal microscope LSM780 (Carl Zeiss, Germany).

**Results and discussions** CTX-III expression around single tumour cells was observed at 21% of breast cancer patients. In positive cases only 5% of single tumour cells were express CTX-III and these cells have features of stemness, EMT or both.

**Conclusion** Only small part of single tumour cells showed signs of a mesenchymal type of invasion, and it didn’t depend on the state of stem and EMT.

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**PO-232** ACTIN-DEPENDENT EFFECT OF TUMOUR SUPPRESSOR PS3 ON HUMAN LUNG CANCER CELL MALIGNANT CHARACTERISTICS

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