Embedding) analysis tools were used to identify and visualise the composition of the lymphoid and myeloid cell populations of the innate and adaptive immune compartments in the tissues.

Results and discussions We identified 220 immune cell subsets, including tumor-resident CD8+CD45RO+CD103+PD-1+, CD4+CD45RO+CD103+PD-1+ and CD4+CD45RO+1-COS+CD27+ T cell populations that were not found in tumor-associated lymph nodes, adjacent normal mucosa, and peripheral blood samples of CRC patients. In addition, we identified an overrepresentation of CD3+CD7+CD56+CD45RO+CD127- intermediate innate lymphoid cells in mismatch-repair deficient cancers and an enrichment of CD14+ myeloid populations in mismatch-repair proficient cancers. Unsupervised clustering of the samples based on the composite immune profile separated the aforementioned groups.

Conclusion High-dimensional immunophenotyping of colorectal cancers reveals tumor-specific immune signatures and charts the complexity of innate and adaptive immune cell populations in the tumour microenvironment. Furthermore, previously unappreciated immune cell subsets further differentiate the two main pathways of tumorigenesis in this cancer type. This work may support the delineation of alternative and tailored immunotherapeutic approaches to improve treatment in colorectal cancer.

PO-261 MULTIMODAL MASS SPECTROMETRY IMAGING TO UNDERSTAND DRUG DELIVERY, METABOLISM, RESPONSE AND AMP; RESISTANCE IN Pancreatic Ductal Adenocarcinoma.

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10.1136/esmoopen-2018-EACR25.776

Introduction The desmoplastic Tumour MicroEnvironment (TME) in Pancreatic Ductal Adenocarcinoma (PDa) plays a key role in drug delivery, metabolism and resistance; drug interventions in turn regulate tumour metabolism. Mass Spectrometry Imaging (MSI) techniques may provide information about regional tumour metabolic profile and drug delivery to enhance our understanding of TME heterogeneity and its impact on drug efficacy and resistance.

Material and methods Multimodal MSI acquisition of the tissue distribution of gemcitabine, the ATR inhibitor AZD6738, their metabolites and the endogenous metabolome was performed in a KPC GEMM mouse model of PDa.

Targeted analysis of the compounds and their metabolites were used to evaluate drug delivery. Small molecule quantitation including haem and metabolic markers such as ATP/ADP/AMP, were used together with H and E and staining for known molecular biomarkers including Pan-CK and αSMA to characterise tissue architecture.

Untargeted analyses including statistical identification of discriminative or colocalised metabolites were used to identify de novo endogenous metabolite biomarkers and cellular phenotypes driving tumour heterogeneity.

Results and discussions MSI revealed significant intratumoural heterogeneity of drug delivery and drug metabolism. Highest delivery of the parent compounds (AZD6738 and dFdC) were found to colocalise with haem in areas confirmed histologically to be necrotic and haemorrhagic. dFdC metabolism appeared related to TME metabolic heterogeneity. The active and inactive metabolites of gemcitabine (including dFdCTP and dFdU) demonstrated differential distribution, both from the parent compounds and each other in the tissue.

Unsupervised clustering based segmentation and colocalisation analysis of the MSI metabolomic data enabled identification and characterisation of these distinct tissue regions based on similarities in their metabolic profile.

Conclusion We have shown that MSI allows spatial resolution of drug delivery, metabolism and that MSI-based metabolomics analysis enables detection of greater tumour heterogeneity than visible by traditional pathology methods such as H and E. Combining this with biomarker information from Imaging Mass Cytometry (IMC) may enable identification of the cell types and phenotypes responsible for the differential metabolic effects observed with combination therapies. Innovative, information-rich technologies such as IMC and MSI may drive greater understanding of the impact of tumour heterogeneity on drug efficacy in vivo and ultimately in patients.

PO-262 REMODELLING OF THE TUMOUR MICROENVIRONMENT BY PEGVORHYALURONIDASE ALFA (PEGPH20): A NOVEL, FIRST-IN-CLASS BIOLOGIC THAT ENZYMATICALLY DEGRADATES TUMOUR HYALURONAN (HA) TO IMPROVE ANTI-TUMOUR EFFICACY

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Introduction Hyaluronan (HA) is a naturally occurring glycosaminoglycan that can accumulate in the tumour microenvironment (TME). In pancreatic and other cancers, high levels of HA are associated with poor clinical outcome. In mouse models, high levels of HA in the TME can increase interstitial fluid pressure and compress tumour vasculature, thereby impeding delivery of anti-cancer therapeutics. Here, a novel, first-in-class biologic that enzymatically degrades HA, PEGPH20, increased tumour vascular volume (VV) and improved anti-tumour efficacy when combined with chemotherapy or checkpoint inhibitor antibodies in multiple HA-accumulating tumour models.

Material and methods Various human and mouse cancer cell lines were transduced with hyaluronan synthase 3 (HAS3) to increase HA production, and implanted in the mammary fat pad (4T1/HAS3) or adjacent to the tubal peritoneum (all other cell lines). Tumour VV was measured by high resolution ultrasound coupled with micro-bubbles (A549/HAS3 and WT-CLS1/HAS3), or IHC (CT26/HAS3), following PEGPH20 treatment (0.0375 mg/kg or 1 mg/kg, IV, 2qw). For BxPC3/HAS3 studies, mice were dosed with vehicle or PEGPH20 (4.5 mg/kg, IV, 2qw)±nab paclitaxel (NAB, 10 mg/kg, IV, 2qw)±gemcitabine (GEM, 180 mg/kg, IP; 24 hour after PEGPH20 ±NAB, qw). For AsPC1/HAS3 studies, mice were dosed with vehicle or PEGPH20 (0.0375 mg/kg, IV, 2qw)±NAB (10 mg/kg, IV, qw)±GEM (180 mg/kg, IP; 24 hour after PEGPH20 ±NAB, qw). For checkpoint inhibitor studies (CT26/HAS3, 4T1/HAS3, Pan02/HAS3), mice were dosed
with PEGPH20 (0.0375 mg/kg, IV) 24 hour prior to anti-CTLA4 (clone 9D9, 4 mg/kg, IP) or anti-PD-L1 (clone 10F.9G2, 5 mg/kg, IP).

Results and discussions PEGPH20 administration resulted in degradation of HA in all tumour models tested, and resulted in increased VV in the 3 models tested. PEGPH20 +GEM + NAB led to enhanced tumour growth inhibition (TGI) compared to GEM+NAB in the BxPC3/HAS3 (104% v 70%, respectively, p<0.0001) and AsPC1/HAS3 (78% v 53%, respectively, p<0.0021) models. In CT26/HAS3, PEGPH20 +anti-CTLA4 resulted in enhanced TGI compared to anti-CTLA4 alone (p=0.002). PEGPH20 +anti-PD-L1 resulted in enhanced TGI compared to anti-PD-L1 alone 4 T1/HAS3 (93% v 18%, respectively, p<0.0001) and Pan02/ HAS3 (50% v 5%, respectively, p<0.01).

Conclusion These studies demonstrate that the use of PEGPH20 to enzymatically remodel the TME in HA-high tumours may represent a novel approach for enhancing the efficacy of cancer therapeutics. A Phase 3 study of GEM and NAB ±PEGPH20 in patients with prospectively selected HA-high PDA is ongoing (NCT02715804).