ABSTRACT BOOK 2020

O1

Development of a personalised human immunocompetent ex-vivo model for hepatocellular carcinoma.

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Experimental models of hepatocellular carcinoma (HCC) are mainly in animals and do not fully recapitulate the complex interactions between the immune system and tumour in humans, they also fail to capture inter-individual variability, 3D tissue architecture, cellular heterogeneity and tumour specific immune landscape. This has hindered understanding of disease pathogenesis, identification of novel immunotherapeutic treatment approaches and ability to predict efficacy and toxicity of new drugs. We aimed to develop ex-vivo human immunocompetent models of HCC using precision cut tumour slice (PCTS) technology from surgical waste for discard or explanted tissue to fulfil these limitations.

To date, we have collected resected tumour, background surrounding liver tissue and peripheral blood mononuclear cells from 8 HCC-patients. PCTS were cultured for 8 days in i) 95% O2, ii) atmospheric O2, iii) atmospheric O2 +microfluidic system (organ-on-a-chip, CNBio). Viability was assessed daily by measuring apoptotic vs non-apoptotic cell death (cytokeratin 18), lactate-dehydrogenase release, ATP content and histological analysis. Immunofluorescence was used to quantify proliferative capacity (Ki67). Metabolic capacity was examined by measuring adenylate energy charge using HPLC. Immunocompetency and checkpoint receptor expression was characterised using PCR microarray analysis.

Characteristic tissue architecture including tumour morphology, stroma and immune infiltration was maintained over the culture period, this was independently confirmed by clinical histopathologists. Tumour slices remained viable for up to 8 days in atmospheric O2, whereas surrounding tissue preferred high oxygen concentrations, suggesting the metabolic switch typical of cancer cells (Warburg effect). Finally, HCC slices displayed and maintained the classical immunological fingerprint that is associated with immune suppression and high expression of multiple inhibitory checkpoint receptors, including but not restricted to the programmed death-1 pathway.

We have successfully developed a human personalised ex-vivo pre-clinical model of HCC that retains the structural, metabolic and immunological signatures observed in-vivo.

O2

Unique molecular traits for NASH-related Hepatocellular Carcinoma

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Introduction: The molecular pathogenesis of hepatocellular carcinoma (HCC) related to non-alcoholic steatohepatitis (NASH) is still ill-defined. Here we seek to identify unique molecular traits that differentiate NASH-HCC from other HCC-etiologies.

Methods: Our cohort of 125 NASH and 110 NASH-HCC patients, all histologically confirmed, was analyzed by expression array (n=63 NASH-HCC; n=74 NASH), whole-exome sequencing (n=50), and targeted-exome sequencing (TES; n=50). Publicly available data from viral/alcohol-HCCs were used for comparative purposes. Tumors from 3 different NASH-HCC mouse models were analyzed by RNAseq/array and TES.

Results: NASH-HCC patients were predominantly male (82% vs 42%,p<0.001), and older (67 vs 54,p<0.01), compared to NASH non-HCC patients, more diabetic (72% vs 50%,p=0.004), higher hypertension (80% vs 52%,p<0.01) and cirrhosis (69% vs 29%,p<0.001). Analysis of signaling pathways in NASH-HCC showed upregulation of hallmarks of proliferation, PI3K-Akt-mTor and oxidative stress when compared to non-tumor adjacent tissue. NASH-HCC and viral/alcohol-HCC showed a similar distribution in terms of molecular classes. Mutational profiling identified TERT (54%), CTNNB1 (28%), TP53 (18%) and ACVR2A (10%) as the most prevalent mutations in NASH-HCC. Interestingly, ACVR2A mutations were more prevalent in NASH-HCC than in viral/alcohol-HCC (2.6%,p<0.05). Unsupervised clustering of mutational signatures showed that NASH-HCC is enriched in liver cancer signatures #16 (44%) and #5 (22%); and #3 (15%), which is novel in liver cancer. In contrast, viral/alcohol-HCCs did not show a cluster with #3. Tumor mutational burden (TMB) in NASH-HCC was 60 non-silent somatic mutations (53 in non-cirrhotic-NASH-HCC vs 70 in cirrhotic-NASH-HCC,p<0.001). High TMB was associated with immune infiltration. Comparing the transcriptome of NASH-HCC non-tumor adjacent livers and NASH livers, we found enrichment of poor-prognosis signatures and signatures of epithelial-mesenchymal transition, apoptosis, hypoxia and immunity (FDR<0.05). Analysis of NASH-HCC mouse models is ongoing.

Conclusions: NASH-HCC presents specific molecular traits: more ACVR2A mutations, and a unique mutational signature#3. Non-cirrhotic-NASH-HCC showed higher TMB and immune infiltrate.

O3

c-Rel is a novel tumour suppressor and early prognostic indicator of hepatocellular carcinoma development

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Background and Aims: The c-Rel subunit of the transcription factor NF-κB is widely considered to promote tumourigenesis. However, recently it has been described that c-Rel acts as a tumour suppressor in a murine model of B-cell lymphoma. We wish to discern whether c-Rel acts as a tumour suppressor in the development of hepatocellular carcinoma (HCC) and understand the cellular mechanisms underpinning it.

Method: Wild type (WT), global c-Rel knockout mice (Rel-/-) as well as epithelial specific c-Rel knockout mice (RelAlb), generated by crossing Alb-cre mice with Relfl/fl mice were used. The DEN model was used to induce HCC. Publicly available RNA-seq databases were interrogated for NF-κB expression, patient survival and mutational burden.

Results: Rel-/- mice develop more tumours than WT controls 30 weeks post DEN. The tumour suppressive role of c-Rel in the hepatocyte was confirmed in RelAlb mice that also exhibited a significant increase in tumour number and stage. Underpinning this was an increase in cell death as a result of genotoxic injury with both Rel-/- mice and RelAlb mice having increased liver damage following an acute dose of DEN.

Primary murine hepatocytes isolated from Rel-/- were more susceptible to DEN and ionising radiation-induced DNA damage. We show that c-Rel is a critical transcriptional regulator of the ATM-CHK2-p53 DNA damage response and propose that disruption of this pathway in Rel-/- mice drives genomic instability and tumourigenesis.

Examination of RNA-seq datasets highlights a previously unreported suppression of c-Rel in the tumours of patients with HCC. Survival curves that stratify patients based on NF-κB subunit expression, show that lower c-Rel expression is indicative of a poorer prognosis.

Conclusion: Our data provides the first evidence that c-Rel acts as a tumour suppressor in HCC and that c-Rel expression in early lesions may act as a biomarker to stratify patients with poorer prognosis.

O4

Tracking neutrophils within the hepatocellular carcinoma microenvironment – development of relevant orthotopic and ex-vivo 3D liver-HCC culture models

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Background and Aims: Immunotherapies have exciting potential in hepatocellular carcinoma (HCC). Despite this, clinical studies of checkpoint inhibitors in HCC are disappointing. Targeting multiple components of the immune microenvironment may improve response rates and our previous work supports neutrophils as candidate targets. To better understand the complex role of neutrophils in HCC our aims were to develop models with an immune-rich tumour microenvironment, in which to explore the importance of neutrophils for tumour growth.

Method: Murine liver hepatoma Hep 53.4 cells were injected into the left lateral lobe of wild type mice. A group of mice also underwent Ly6G antibody mediated neutrophil depletion prior to injection. Mice were harvested at 10 and 30 days and precision cut liver slices (PCLS) from cores of liver created. Slices were kept in a bespoke PCLS bioreactor. Isolated neutrophils were labelled and added to PCLS prior to multiphoton microscopy to visualise neutrophil uptake.

Results: Tumours engrafted in all mice injected and progressed up to 2cm in size (figure A). On microscopic examination we noted substantive collagen deposition and stromal formation (figure B, white lines). FACS sorting of dissociated tumours revealed infiltration by multiple immune cell types including neutrophils. Neutrophil depletion significantly reduced tumour growth. PCLS survived for 5 days and added neutrophils migrated through the full thickness of the liver tissue, but preferentially accumulated in peri-tumour regions (figure B, neutrophils in red).

Conclusion: We have developed a new orthotopic model of HCC in mice that has a rich immune infiltrate. Tumours can also be incorporated ex-vivo in a PCLS-HCC model, designed for drug discovery and mechanistic investigations. The Hep 53.4 model has the advantage of its speed of set up and the opportunity to interrogate effects of manipulation of specific immune cell types including neutrophils, which were confirmed as important drivers of HCC.

O5

LINE1 retrotransposons activate TGFβ signaling in hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) is the fourth most frequent cause of cancer-related deaths worldwide. Effective targeted therapies are limited to the the multikinase inhibitors, Sorafenib or Lenvatinib – delivering a median survival benefit of just a few weeks. Hence, there is an urgent need to develop novel therapeutic strategies for the disease. Recently, much effort has been directed towards molecular characterisation of HCC cases. We have previously demonstrated the activation and mutagenic consequences of long-interspersed repeat elements (LINE1s) in HCC1-2. We have gone on to analyse the TCGA-HCC RNAseq dataset in terms of LINE1 expression and correlated it with clinical features and HCC subclasses3-4, identifying LINE1 expression as a potential novel activator of the TGFβ-signaling pathway. 12 of the 18 members of the TGFβ-signaling superfamily had significant correlation with LINE1. Further, we carried out immunohistochemical staining of phosphorylated SMAD3 as a surrogate for TGFβ-signaling status and compared this with L1orf1p expression in an independent cohort from our own biobank. A positive correlation between pSMAD3 and L1orf1p was observed validating the above findings. The crosstalk between LINE1 and TGFβ was further verified using in vitro model systems - stable knockdown of LINE1 (L1-KD) expression in Huh7 cells and conditional-overexpression of L1orf1p in HepG2 cells. Downregulation of TGFβ signaling in Huh7-L1-KD cells compared to the non-targeted control cells was observed by RNAseq. PAI1promoter-luc reporter assay confirmed the downregulation of TGFβ signaling (~2-3 fold lower in Huh7-L1-KD compared to wildtype and non-target controls). Moreover, reduction in cell migration and cell invasive capacity was observed upon L1-KD in Huh7 cells. On the other hand, L1orf1p overexpression in HepG2 cells led to upregulation of TGFβ-signaling – increased Pai1 and vimentin expression. Overall, the data indicates a crosstalk between L1orf1p and TGFβ-signaling that may provide a novel therapeutic target or biomarker, worthy of further investigation.

O6

Preliminary experience of Selective Internal Radiation Therapy (SIRT) for HCC at a UK centre

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Aims:
To evaluate outcomes of patients with HCC treated with Selective Internal Radiation Therapy (SIRT) using TheraSphere® glass microspheres (BTG plc, UK).

Materials and Methods:
A retrospective review of all patients treated for HCC with SIRT using glass microspheres at a tertiary hepatobiliary referral centre in the UK. Information regarding demographics, procedural details, complications, mortality, lesion response and subsequent interventions was collected from the electronic patient record.

Results:
48 glass microsphere SIRT treatments were performed in 42 patients, with a median age of 71 years (range 39-84), between 4/12/2014 and 17/12/2019. 35/42 (83%) had uni-lobar disease and 7/42 (17%) had bi-lobar disease. 1/42 (2%), 33/42 (79%) and 8/42 (19%) had BCLC stage A, B and C disease respectively. Median follow-up period was 11 months (range 1-48). Mean size of the largest lesion was 7.3cm (range 3.3-19.1). Mortality at 30 days was zero. Post-operative complications requiring additional treatment or hospital stay occurred after 2/48 procedures (4%): 1 patient was re-admitted for management of pain and nausea; 1 patient had post-operative pneumonia. Disease control rates (complete response, partial response or stable disease according to mRECIST) at 3, 6 and 12 months were 31/39 (79%), 15/26 (58%) and 11/21 (52%) respectively. 20/42 (48%) patients remain free from progression after a median period of 12 months (range 1-48). 4 patients with unresectable solitary uni-lobar lesions >9cm in diameter were down-staged to enable resection and remain disease-free after a median follow-up of 46 months (range 39-48).

Summary:
We have shown promising response rates and tumour shrinkage with SIRT in our cohort. Four patients with inoperable disease have been down-staged to facilitate curative resection with durable outcomes. Analysis of patient subgroups (e.g. unilobar vs bilobar, multiple vs solitary lesions) and dosimetry is ongoing and expected to be completed by March 2020.

O7

The landscape of hepatocellular carcinoma in the UK in the past 20 years: the HCC-UK/NCRAS partnership

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Background: The HCC-UK/NCRAS partnership was created to facilitate a wide programme of research relating to hepatocellular carcinoma (HCC) using data available within the English National Cancer Registration and Analysis Service (NCRAS). NCRAS data includes tumour- and patient-specific variables, diagnosis and treatment information. These individual-level data are linked to multiple datasets including Hospital Episodes Statistics (HES).

Methods:
HCC cases between 1997 and 2017 were identified in NCRAS and corresponding population-based cancer registries in Wales, Northern Ireland and Scotland. Demographic characteristics were explored and European age-standardised incidence and mortality rates per 100,000 person years calculated. Linked HES codes were used to identify the presence and severity of cirrhosis.

Results: In the UK, there were 3468 new cases of HCC in 2016, up from 885 in 1997. The highest age-standardised incidence rates were in Scotland (7.7 per 100,000 in 2016, 95%CI 6.9-8.4, compared to 5.7, 95%CI 5.5-5.9, in the UK overall). In England, the mean age at diagnosis was 68.4 years and the male to female ratio was 3.4. Overall 25% of all HCC cases were from the most deprived population quintile. Whilst not included in the registry data, the presence and severity of cirrhosis can be derived from the linked HES dataset. These data identify 58% of HCC cases as having cirrhosis and, of these, 42% had decompensated cirrhosis. The majority of HCC patients did not receive specific anticancer treatment.

Conclusions: HCC incidence and mortality have tripled over the last 20 years; the most deprived individuals are most at risk. HCC is often associated with cirrhosis and more than one in five individuals diagnosed with HCC has advanced cirrhosis such that treatment options for HCC are severely limited. These trends highlight the urgent need to address prevention strategies for both liver disease generally and hepatocellular carcinoma specifically at the population level.

O8

DNA-PK as a predictive biomarker in hepatocellular carcinoma - a focus on liquid biopsy tools

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Introduction: DNA-Protein Kinase (DNA-PK) promotes DNA damage repair. Its elevated tumour tissue expression predicts shorter time to radiological progression following arterial chemoembolization (TACE)[1]. Circulating tumour cells (CTC) can be detected in 65% of patients with HCC using Imagestream fluorescent microscopy [2,3]. We explored DNA-PK liquid biopsy tools.

Materials and Methods: Tumour DNA-PK in biopsy tissues was quantified by immunohistochemistry (IHC) and Aperio Image analysis[1]. CTC detection was as previously described, with CTC characterised as biomarker negative or positive for DNA-PK or cytokeratin 3]. CtDNA DNA-PK copy number variation (CNV) was with digital droplet PCR (QX100 & Quantasoft) after plasma high centrifugation and DNA extraction (Qiagen ccfDNA kit). Post treatment, patients were classed as responders or progressors on 1st follow-up imaging using mRECIST criteria (>20% increase in size).

Results: High % nuclear DNA-PK+ in biopsies (n=56) confirmed elevation in tumour relative to paired non-tumour tissues (p=0.002). Tumour IHC elevation >median was associated with shorter time to progression (16.5 vs 5.6 months;p=0.102) and poorer survival (15.0 vs 33.4 months;p=0.014). 47/67 (70%) patient samples were CTC+ and >1CTC/4ml was associated with poorer survival (18.2 months vs 24.4 months;p=0.015). 22/67 (33%) had DNA-PK CTC+. % DNA-PK+ nuclei in tumour tissue correlated significantly with total CTC/ml (0.393; P=0.038), DNA-PK+ CTC/ml (0.453;p=0.016) and ddPCR DNA-PK CNV (0.493; P=0.027). Assessed by tissue IHC, 80% of progressors (versus 28% non-progressors) had elevated DNA-PK in diagnostic tissue (p=0.004 Chi-Square). 59% versus 22% had DNA-PK positive CTC (p=0.009). The ddPCR DNA-PK CNV assay lacked specificity and associations with response were not significant. In treated patients (4 surgical, 28 locoregional therapies, 4 medical), DNA-PK+ CTC were significantly associated with shorter TTP (6.9 vs 15.1 months, p=0.007), with a trend towards poorer survival (p=0.163).

Conclusion: DNA-PK is worthy of further exploration as a predictive/prognostic biomarker, with liquid biopsy tools showing promise.

O9

Suitability for second-line systemic therapy following sorafenib in patients with advanced hepatocellular carcinoma: a UK single-centre experience.

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Background: Until recently, standard second-line systemic therapy for patients with advanced hepatocellular carcinoma (aHCC) developing intolerance or disease progression on first-line sorafenib was unavailable outside of clinical trials. This study aimed to describe patient clinical status at discontinuation of sorafenib in a UK-based population, and evaluate suitability for further systemic therapies.

Methods: Sequential data on patients with aHCC who received sorafenib at The Christie NHS Foundation Trust (2008-2018) were analysed retrospectively. The primary end point was the percentage of patients with Child-Pugh class A (CPA) liver disease and ECOG-performance status (ECOG-PS) 0-1 at discontinuation of sorafenib.

Results: Sorafenib was received by 202 patients. Median age was 66 years (range 29-88), and 88% were male. Liver cirrhosis was documented in 75%; the most frequent aetiologies were alcohol misuse (43%), diabetes or steatohepatitis (37%), hepatitis C virus infection (HCV; 19%), HBV (8%), and haemochromatosis (5%). Prior curative therapy or loco-regional therapy had been received in 20% and 34% of patients respectively. On commencement of sorafenib, 94% of patients had CPA liver disease, and 97% were ECOG-PS 0-2. Median duration of sorafenib therapy was 3.2 months; reasons for discontinuation included toxicity (32%), radiological progression (32%) clinical progression (17%), death (8%), and patient/physician choice (7%). On discontinuation of sorafenib, 78 patients (39%) had CPA liver disease and 24 (12%) CPB7; 64 patients (32%) had ECOG-PS 0-1 and 43 (21%) ECOG-PS 2; 46 patients (23%) had both CPA and ECOG-PS 0-1, and a further 18 (9%) had CPA and ECOG-PS 2. Second-line therapy was received by 28 patients (14%), in a clinical trial in 25 patients.

Conclusion: Approximately a quarter of patients receiving sorafenib for aHCC were potentially suitable for further systemic therapies on treatment discontinuation using common CP and ECOG-PS criteria.

P1

Endothelial inducible T cell co-stimulator ligand (ICOSL) regulates adhesion molecule expression on liver endothelium: implications for senescence-mediated immune surveillance

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Clearance of precancerous cells from the liver is mediated via an inherent tumour suppressor mechanism known as oncogene-induced senescence (OIS), and is driven by the release of a proinflammatory cocktail or 'senescence-associated secretory phenotype' (SASP). OIS cell clearance from the liver is dependent on CD4+ T cells and we have previously shown that the SASP drives lymphocyte recruitment to primary human liver sinusoidal endothelial cells (LSEC) in vitro. However, it is not currently known how the SASP interacts with LSEC and which molecules/pathways mediate the CD4+ T cell-specific recruitment. We derived SASP from ER:RasG12V IMR90 cells (Ras) and challenged LSEC for 24 h. We then utilised RNAseq to explore gene regulation and gene set enrichment analysis was used to identify key pathways regulated. qPCR, immunocytochemical (ICC) staining, pharmacological inhibition and genetic manipulation of endothelial cells were all used to confirm findings from the RNAseq analysis. Next, we utilised flow-based adhesion assays to study target molecules in CD4+ T cell recruitment to LSEC under physiological flow conditions in vitro. Using RNAseq, we identified inducible T cell co-stimulator ligand (ICOSLG) as a key gene upregulated in LSEC in response to Ras stimulation and confirmed this via qPCR. We next elucidated a novel role for ICOSL in the specific recruitment of CD4+ T cell to LSEC. Using antibody blockade and siRNA knockdown of ICOSL expression in Ras-treated LSEC, we demonstrated significantly reduced transendothelial migration of CD4+ T cells under physiological shear stress. In corroboration with these findings, we also found ICOSL-dependent trafficking of intercellular adhesion molecule (ICAM)-1 to the cell surface under Ras stimulation. Here, we show that the SASP regulates endothelial activation and expression of co-stimulatory molecules, such as ICOSL, on primary human LSEC. This could be a unique pathway by which the SASP regulates the immune microenvironment of the liver.

P10

Healthcare resource use among patients with advanced hepatocellular carcinoma (aHCC) in the UK

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Background: Data on healthcare resources used to treat aHCC are limited. We conducted a clinician survey to assess healthcare resource use in patients with aHCC in the UK.

Methods: UK clinicians with aHCC expertise who had treated ≥10 patients with aHCC in the past 12 months were recruited. The online survey focused on healthcare resources used in secondary care by patients with aHCC for whom first-line sorafenib treatment had failed. Resource use was identified, including medical staff visits, hospitalisations and laboratory/radiological tests. Clinicians based their responses on their typical patient and reported the proportions of patients with stable disease (SD) or progressive disease (PD) requiring each resource.

Results: 28 clinicians responded, who had seen an average of 51 patients in the past 12 months. Each month, palliative care doctors visited 80% of patients with PD compared with 30% of those with SD. The proportions of patients with PD and SD, respectively, visited by other medical staff were: oncologists, 63% and 57%; clinical nurse specialists, 42% and 41%, general practitioners, 42% and 38%; palliative care nurses, 42% and 37%; gastroenterologists, 19% and 22%. Generally, the proportion of patients with PD hospitalised each month was greater than the proportion with SD hospitalised (general ward, 27% and 17%; accident and emergency, 26% and 20%; intensive care unit, 5% and 3%, respectively). Laboratory tests were performed for most patients (PD, 72%; SD, up to 80%); smaller proportions had radiological tests (PD, 43%; SD, up to 51%).

Conclusions: Patients with aHCC and PD have considerable monthly healthcare needs; patients with SD require less resources overall. Thus, treatments prolonging SD may have a positive impact on real-world clinical practice. This is the first study to provide robust evidence on resource use in aHCC in the UK and thus may be used to inform future economic models.

P11

A single liver transplant centre experience of an imaging based surveillance programme for HCC recurrence following liver transplantation

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Liver transplant (LT) is accepted as the treatment of choice for early HCC. However, despite stringent pre-operative selection criteria, post-LT HCC recurrence is reported in 11%-20% of recipients. This study aims to review a large LT centre's experience of undertaking imaging surveillance to identify recurrence in patients with HCC in the explanted liver.

Prospectively collected data of all patients undergoing a LT between 01/01/08 to 31/12/14 was retrospectively reviewed. Patients who had completed the five year surveillance programme were included. Data on clinical parameters, explant pathology and surveillance imaging were reviewed.

Of the 135 identified patients, 9 (6.7%) developed HCC recurrence. The most common recurrence sites were lung (56%) and bone (33%). 78% of recurrences were diagnosed incidentally in asymptomatic patients (mean time to recurrence 890 days).

The recurrence population demonstrated more unfavourable explant histology including higher grade (pT3 or higher 11% vs 1%), worse differentiation (poorly differentiated - 56% vs 22%), vascular invasion (44% vs 25%) and a higher number of viable lesions (3.4 vs 1.8 (mean)). Only 2 patients had surgical resection for their recurrence; 4 further patients received Sorafenib and/or radiotherapy. The mean post-recurrence survival was 549 days in treated vs 371 days in the non-treated cohort.

Additional incidental findings were seen in 27 patients (20%), including 2 synchronous primary lung malignancies. The most common benign incidental findings were graft lesions (18), lung nodules (10) and vascular abnormalities (5). Arterial hyper-enhancing graft lesions were identified in 16 patients, only 1 proved to be HCC recurrence and could be identified on both arterial and portal venous phase.

This data suggests routine imaging surveillance may identify a small number of asymptomatic recurrences where it is possible to offer potentially life-prolonging treatment. However, there is a large number of incidental findings requiring further investigation with the majority being benign.

P12

The HUNTER: Hepatocellular Carcinoma Expediter Network Registry

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Hepatocellular carcinoma (HCC) is the most predominant form of liver cancer and both its incidence and mortality continue to rise. Translational research for HCC has been hampered by the limited numbers of patients fit enough to treat, presenting to single centres, as well as the frequent lack of need for tissue diagnosis. Historical biobanks have been helpful, but without dedicated research staff support and adequately funded programmes of research, the quality of both tissues collection and storage, as well as the robustness of associated data, has been variable. There is an urgent need for active collaboration between centres caring for patients with HCC, with standardised protocols and high quality tissues and data collection from a contemporary cohort.

In association with the Italian (IACR) and Spanish (AECC) associations for research on cancer, Cancer Research UK have awarded an Accelerator grant entitled HUNTER: Hepatocellular carcinoma Expeditor Network, aiming to overcome these challenges. Part of the remit of the Newcastle HUNTER team was to create a patient registry, supporting the prospective recruitment of 1500 patients (1000 with HCC, 500 controls) over the next 4 years.

The HUNTER Registry has now been created (https://hunter-registry.ncl.ac.uk) by the Newcastle University Education Support Unit. This is a secure internet-based code-linked anonymised data collection system, accessible to HUNTER researchers, by individual user login. The dataset is a comprehensive one, supporting research on diagnosis, staging, treatment response, biomarker discovery and validation, as well as novel therapeutic strategies. The registry design will reduce errors and enhance high quality large-scale prospective data collection and sharing. The HUNTER Registry will be demonstrated at the HCC-UK meeting 2020. It is now in active use, with five collaborators already participating and eighteen prospective patients recruited by January 2020.

P13

Experience of HCC patient on an ongoing study with ADP-A2AFP SPEAR T-cells

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Background:

Adoptive T-cell therapy utilising genetically engineered, affinity-enhanced autologous SPEAR T-cells (AFPc332T-cells) directed towards HLA-A*02 is being evaluated in a first-in-human, Phase 1 trial in patients with hepatocellular carcinoma (HCC; NCT03132792). Patients must be HLA-A*02:01+ or 02:642+ and have AFP expression by immunohistochemistry (IHC) at ≥1+ in ≥20% HCC cells or serum AFP ≥400ng/ml, and ≤5% IHC AFP in non-cancerous liver tissue. Here we present the third and final patient recruited to the second cohort.

Case

This 42-year-old female was diagnosed with multifocal HCC in 2018. Prior therapy included left hepatectomy and trans-arterial embolisation. Subsequent sorafenib and lenvatinib were discontinued due to erythroderma and multifactorial bleeding diathesis, respectively. At baseline, the dominant liver lesion measured 14.5cm and serum AFP was 2718kIU/L. Autologous T-cells for manufacture of AFPc332T were obtained via leukapheresis. Lymphodepletion was performed with fludarabine 20mg/m² and cyclophosphamide 500mg/m² QDS for 3 days, followed by 1.14 x 10^9 transduced T-cells re-infused 7days later.

Findings

Within the first week following T-cell infusion, she experienced grade 1 lethargy, grade 3 neutropenia and transient grade 2 hyperkalaemia. Treatment was otherwise well-tolerated with no evidence of hepatic toxicity or cytokine release syndrome. No other treatment-related toxicity was reported during 12 weeks of follow-up. Blood ADP-A2AFP reached a peak 1.38 x 10^4 vector copies/µg DNA at 2 weeks post-infusion, persisted for 4 weeks but declined by week 8. Soluble serum AFP declined 25% at 2 weeks post-infusion and subsequently returned to baseline. Both pre and 6-week post-infusion biopsies demonstrated low levels of PD-L1 expression and CD3+ cell infiltration. CT/MR imaging at 8 weeks demonstrated stable disease by RECIST 1.1 criteria.

Conclusion

The cohort 2 regimen was well-tolerated with no dose limiting toxicity and this patient has had clinically stable disease for 3 months. Cohort 3 will evaluate a target dose of 5×10^9 transduced cells.

P2

L1 retrotransposable elements accumulates in Hepatitis C virus (HCV) infected liver cancer cells

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Background: Hepatocellular carcinoma (HCC) is the sixth most common type of cancer and third most frequent cause of cancer-related deaths worldwide(1). Chronic infection with hepatitis B or C virus (HBV or HCV) are amongst the common causes. The key drivers of HCC in chronic liver disease remain elusive. Recently, we demonstrated the activation and mutagenic consequences of long-interspersed repeat elements (L1s) in human HCC (2), when the epigenetic silencing of these elements is compromised. Since virus infection lead to global epigenetic changes, we hypothesise that L1s get activated during the process, mediating genomic instability.

Methods: An in vitro engineered-L1 retrotransposition assay was employed (3) in Huh7 cells in presence and absence of an HCV replicon (4). Protein expression was evaluated by western blotting and RT-qPCR was performed for transcriptional analysis. L1 transcript expression was evaluated in RNAseq dataset (GSE84346) of Chronic HCV Hepatitis (CHC) patients and controls using an in-house pipeline.

Results: We have observed approximately 4-fold increase in retrotransposition rate in Huh7 cells in presence of HCV compared to control cells. Upregulation of active retrotransposition could possibly be due to increased DNA damage exerted by HCV infection (validated by increased γH2AX levels in Huh7-HCV cells compared to control cells) or modulation of transcripts of other host factors like interferon stimulated genes known to negatively regulate both HCV and L1, or a combination of these factors. An increase in endogenous L1 protein level was also observed in Huh7-HCV cells compared to control cells. Moreover, L1 transcript expression was found to be significantly higher in CHC liver compared to controls ($p=0.001$), confirming an association of HCV infection with retrotransposon activation in HCV patients.

Conclusion: Together these data suggest that L1s are activated before oncogenic transformation in CHC patients, with HCV activated retrotransposition potentially mediating mutagenic consequences leading to HCC development.

P3

Direct acting antivirals reduce development of hepatocellular carcinoma in cirrhotic hepatitis C patients

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Introduction
Chronic untreated infection with hepatitis C is associated with an annual rate of hepatocellular carcinoma (HCC) development of 7.88%.[1] Sustained virological response with interferon-based treatment is associated with a reduced rate of HCC development.[2] Data on the effect of newer direct-acting antivirals (DAAs) on HCC occurrence and re-occurrence however is conflicting and limited by their novelty.[3,4] We examined data on HCC development from patients treated over 5 years on the expanded access programme – the longest of most studies to date.

Methods
A retrospective observational cohort study for 54 cirrhotic patients treated with DAAs under the compassionate care programme from NHS England at a tertiary London hospital. Demographic and outcome data was taken from electronic records.

Results
- Prior to treatment, three patients had HCC. One had been transplanted five years prior to therapy and two were treated spanning DAA therapy and transplanted at 3 and 7 months post starting DAAs. None had re-occurrence.
- The average annual rate of HCC occurrence was 4.62%, with peak rates at 1-12 and 25-36 months. 45% had risk factors other than hepatitis C including alcohol and fatty liver disease.
- Genotype 3 was associated with the highest risk of de novo HCC (27% of the genotype 3 cohort) and genotype 4 with the lowest (12.5%).
- The choice of DAA regimen did not affect development of de novo HCC.

Conclusions
Our data suggests DAAs reduce the development of HCC in cirrhotic patients compared with no treatment. These patients should continue to be monitored closely.
Genotype 3 is most associated with de novo HCC development after treatment, and also associated with higher mortality in the event of development. Genotype 1b appeared to have a lower relative risk of tumour development in this cohort, in contrast with accepted wisdom.[5]

P4

Baseline liver function and outcomes in the phase 3 REFLECT study in patients with unresectable hepatocellular carcinoma (uHCC) treated with lenvatinib (LEN) or sorafenib (SOR): Assessment of overall survival (OS), progression-free survival (PFS), objective response rate (ORR) and safety

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Child-Pugh score [CPS] and albumin-bilirubin grade [ALBI] are prognostic in uHCC patients receiving SOR but have not been assessed with LEN. Post hoc analysis of outcomes from REFLECT were stratified by baseline ALBI or CPS. OS and PFS were estimated by Kaplan–Meier method; ORR utilized mRECIST by independent review. Safety was assessed using NCI-CTCAE v4.0.

Median OS and ORR were improved in ALBI-1 or CPS-5 patients and was generally improved for LEN vs SOR. Rates of TEAEs grade ≥3 were lower in ALBI-1 or CPS-5 patients. LEN dose modifications occurred more often in patients with worse baseline liver function.
These data suggest ALBI (by OS, PFS and ORR) and CPS (by ORR) may be prognostic in uHCC patients. LEN also provided benefit vs SOR, regardless of baseline liver function. The benefit of LEN may be underestimated, as more ALBI-2 pts and fewer ALBI-1 pts received LEN vs SOR.

Clinical trial registration: NCT01761266

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P5

Evaluation of ALPPS and PVE in management of HCC

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I. Back ground:
Portal vein embolization (PVE) has been developed with the principle of inducing hypertrophy of the FLR (10–50 % after a period of 2–8 weeks). Tumor progression and insufficient hypertrophy of the FLR are the commonest causes that preclude definitive surgery in 10-30% of patients.
Recently, ALPPS has been proposed, with the goal of achieving a faster and magnified hypertrophy (74–87.2 % in 9–13 days) for patients with extensive colorectal liver metastases or hilar cholangiocarcinoma, however, introducing ALPPS for HCC on top of cirrhosis has been questioned, and not thoroughly investigated .

II- Methods:
A prospective observational study was conducted on patients who were admitted to the National Liver Institute from 2016 to 2018 with non-resectable liver tumors due to insufficient FLR. Hypertrophy of the future liver remnant, perioperative morbidity and mortality, overall survival, and other parameters were compared between patients who underwent ALPPS and patients who underwent PVE.

III- Results:

Nineteen patients, of which 17 patients had HCC, underwent 1st stage ALPPS. While, 26 patients, of which 20 patients had HCC, underwent PVE.
The mean of the percentage of hypertrophy at 2 weeks for ALPPS group was 41.62±39.7. The mean of hypertrophy post PVE at 2 weeks was 37±5.77 %.
Fourteen (73.6%) patients could be operated upon for definitive resection in the 2nd stage of ALPPS.
Fourteen (54%) patients underwent resection after PVE.
IV- Conclusion:
Despite the morbidity of ALPPS in cirrhotic patients, it still can be introduced with strict criteria. Although ALPPS produces more extensive hypertrophy than PVE and less likely progression of the tumor to the FLR, PVE has less overall morbidity and mortality.

P6

The role of soluble checkpoint receptor and intestinal permeability in Hepatocellular Carcinoma (HCC)

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Inhibitory checkpoint receptors, such as PD-1, have shown to be central to the impaired anti-tumour immunity observed in HCC patients and treatment with the anti-PD-1 antibody has achieved an objective response in approximately 20% of advanced HCC patients. However, the role of the soluble forms of checkpoint receptors in anti-HCC immunity is not well understood. Further to this, specific gut microbiome profiles have been associated with a favourable outcome to anti-PD1 therapy. How these microbes impart anti-tumour benefit is unknown, but it has been suggested that bacterial translocation from the gut may be modulating immunity. The aim of this study was to investigate whether soluble CRs, markers of bacterial translocation are involved in HCC.

Soluble (s)PD-1, sPD-L1, sPD-L2, sCTLA-4, sCD80 and D-Lactate (a marker of bacterial translocation) were quantified in baseline serum samples of 257 patients with advanced HCC who were subsequently treated with the anti-PD-1 antibody Nivolumab and in 11 healthy controls using Multiplex ELISA and colorimetric assays. Soluble checkpoint receptors and D-Lactate levels were compared between 65 HBV-HCC, 60 HCV-HCC, 132 uninfected-HCC and 11 healthy controls (Ctrl).

Baseline sPD-1, sPD-L1, sPD-L2, sCTLA-4, sCD80 expression was significantly higher in HCV-HCC patients compared to HBV-HCC, uninfected-HCC patients and Ctrl. However, no difference in D-Lactate levels was observed between HBV-HCC, HCV-HCC, uninfected-HCC patients and Ctrl. Additionally, HCV-HCC patients who did not respond to Nivolumab treatment had higher baseline levels of D-Lactate compared to HCV-HCC patients who did respond to treatment.

Our results suggest HCV-HCC patients express higher levels of soluble checkpoint receptors at baseline than HBV-HCC and uninfected-HCC patients, indicating an important role of soluble checkpoint receptors in HCV-HCC immunity. Our results also suggest that non-responder HCV-HCC patients have bacterial translocation although how this is associated with HCC pathogenesis is yet to be determined.

P7

A neutrophil metabolic switch in patients with hepatocellular carcinoma

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Hepatocellular carcinomas (HCC) develop on a background of chronic liver inflammation. Neutrophils are key mediators of the inflammatory-immune microenvironment, with emerging roles in cancer progression. In a murine HCC model, we showed neutrophil depletion had profound anti-tumour effects, while elevated circulating neutrophils in HCC patients independently predicted poorer survival. Pan-neutrophil depletion rendering patients susceptible to infection is not a viable therapeutic option. Here we aimed to define a functional cancer-specific neutrophil phenotype.
Patients with HCC (n=81), chronic liver disease (CLD) (n=25) and healthy volunteers (n=47) were studied (Newcastle, 2016-2019). Circulating neutrophil phenotype and apoptosis was evaluated by flow cytometry, including 10 surface markers, and mass spectrometry proteomics. Functional assays assessed respiratory burst, comparing basal and stimulated levels of reactive oxygen species (ROS), and metabolism (Seahorse Analyser).
Neutrophil surface markers (fold-change relative to healthy controls) were altered in HCC patients, with elevated CD62L expression (1.45±0.13, $p<0.01$), but decreased CD11b (0.75±0.04, $p<0.0001$) and CD10 levels (0.49±0.04, $p<0.0001$), alongside fewer apoptotic neutrophils (18.03%±1.38 vs 28.52%±3.05, $p<0.001$). Functionally, the respiratory burst capacity was altered compared to control patients, decreased following stimulation with fMLP and PAF (1557±108 vs 2046±223 healthy and 2327±282 CLD, $p<0.05$), but increased in response to PMA (155,210±10,430 vs 123,327±11,760 healthy, $p<0.05$). Proteomic analyses revealed increased levels of proteins involved in fatty acid oxidation and mitochondria oxidative phosphorylation in patients with HCC. Metabolic profiling concurred, showing elevated oxygen consumption and extracellular acidification, in keeping with a greater overall metabolic capacity. A downregulation in one of the fMLP receptors was also noted.
These data suggest neutrophils in HCC patients have a longer lifespan, acquiring phenotypic and functional changes with biological relevance – associated not only with their “pro-tumour” impact, but potentially also with the development of customized therapeutics to target these cells.

P8

Cost-effectiveness of lenvatinib in the treatment of hepatocellular carcinoma in the United Kingdom

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OBJECTIVES: Economic analysis was undertaken to assess the cost-effectiveness of LEN versus SOR in the treatment of adults with untreated a/u HCC, from a UK healthcare system perspective.

BACKGROUND: Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer in England. Lenvatinib (LEN) met the primary endpoint of non-inferiority in overall survival (OS) versus sorafenib (SOR) in the REFLECT trial, with a hazard ratio [HR] of 0.92 in favour of LEN (95% confidence interval [CI]: 0.79, 1.06), in patients with advanced or unresectable HCC (a/u HCC). However, baseline imbalances in the proportion of patients with AFP levels ≥ 200 ng/mL, and in HCV aetiology, may have favoured the SOR arm. After adjustment for baseline imbalances, the HR for OS was nominally superior in favour of LEN at 0.82 (95% CI: 0.70, 0.96).

METHODS: A partitioned survival model was used to extrapolate costs and quality-adjusted life-years (QALYs) over a lifetime time horizon. Survival curves for progression-free survival (PFS) and OS were based on multivariable parametric models adjusting for imbalances in baseline characteristics and other key prognostic variables. Using multivariable parametric survival models improves precision, avoiding conditional bias from covariate imbalance. Utility values were derived from EQ-5D-3L data collected in REFLECT, and costs were taken from published sources.

RESULTS: The model estimates a mean survival increase of 3.1 months with LEN, and incremental costs and QALYs of £8,541 and 0.18, respectively, resulting in an incremental cost-effectiveness ratio (ICER) of £48,494. A willingness to pay of £50,000 per QALY is assumed, which is an accepted UK threshold where end of life criteria apply.

CONCLUSIONS: Using list prices, LEN represents a cost-effective use of NHS resources. Results were robust to changes in key assumptions when sensitivity analyses were performed.

P9

A specialist HCC clinic improves time to treatment: The Oxford experience.

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Background:
Hepatocellular Carcinoma (HCC) typically occurs on a background of chronic liver disease. As a patient's liver function is pertinent to almost all decisions regarding cancer treatment there is a requirement for multi-specialist input, which can lead to slower decision-making pathways. In June 2018 we established a weekly dedicated HCC clinic attended jointly by a hepatologist and oncologist with the aim of streamlining management of HCC.

Methods:
Performance was evaluated through retrospective review of patient electronic records on time to treatment between January 2017 and December 2019. Data was collected on active treatment of patients with HCC undergoing either resection, loco-regional therapies, stereotactic ablative radiotherapy (SABR) or tyrosine kinase inhibitor (TKI) therapy.

Results:
Over the three-year period, 130 new patients presented with a diagnosis of HCC. Before the HCC clinic, a total of 35 treatments for HCC were administered to 32/70 (46%) patients. The mean time to treatment was 123 (SD +/-59.2) days from the first radiological evidence raising suspicion of a diagnosis or recurrence of HCC. After the HCC clinic, a total of 32 treatments were administered to 27/60 (45%) patients with a mean time to treatment of 83 (SD +/-47.8 p=0.004) days. Breakdown of time to treatment by treatment modality showed a reduction in mean time to treatment for resection, ablation, transarterial chemoembolisation and TKI by 54, 56, 34 & 52 days respectively. Only SABR was found to have a longer time to treatment (75 versus 101 days), explained by an outlier.

Conclusion:
The establishment of a multi-disciplinary HCC clinic lead to a significant reduction in time from first suspicion of an HCC diagnosis to treatment. That the effect was seen across treatment modalities is supportive of the role of a specialist HCC clinic in more streamlined decision making.

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