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**0-01 PEROXIREDOXIN 2 DRIVES NASH PROGRESSION TOWARDS HEPATOCELLULAR CARCINOMA BY PERTURBING HEPATIC LIPID METABOLISM**

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**Disclosure of Interest:**

compounds may provide a valuable approach to prevent NASH-associated HCC.

**Conclusion:**

growing prevalence of NAFLD/NASH-driven HCC worldwide, the development of PRDX2-targeting therapeutic target for NASH and HCC prevention. Given the changes in lifestyles and the increasing loss-of-function studies in Huh7.5.1 hepatoma cells, we show that PRDX2 is directly involved in carcinogenesis by regulating oxidative stress and protecting cancer cells from apoptosis.

**Results:**

Moreover, we observed that Prdx2 KO markedly improved liver function. Mechanistic data unraveled that PRDX2 is overexpressed upon chronic liver injury and drives steatosis by impairing AMP-

**Method:**

To discover novel therapeutics for advanced liver disease and HCC prevention, we developed a simple and robust human liver cell-based system modeling a clinical prognostic liver signature (PLS) predicting long-term liver disease progression toward HCC in all major etiologies. Integrating functional analyses using the PLS cell-based system and computational analyses of global transcriptomes of fibrogenic/cirrhotic patient liver tissues we identified driver candidates for chronic liver disease progression towards HCC. Driver candidates were validated in NASH-HCC animal models and detailed mechanistic studies.

**Introduction:**

chronic liver diseases (CLD) and hepatocellular carcinoma (HCC) are major global health challenges with limited treatment options. The major etiologies are viral hepatitis induced by hepatitis C and B viruses (HCV, HBV), alcoholic liver disease (ALD), and nonalcoholic fatty liver disease (NAFLD) with its more severe form, the nonalcoholic steatohepatitis (NASH). CLD can progress from fibrosis, cirrhosis to HCC, a leading cause of cancer-related death worldwide and the major cause of death among cirrhotic patients. Given the changes in lifestyle with increasing incidence of obesity and diabetes, NASH will evolve as the major cause of HCC in the future. Despite tremendous efforts, pharmacological treatment options for NASH as well as chemopreventive strategies to prevent HCC are lacking. Therefore, discovery of novel therapeutic targets and clinically relevant markers of liver disease progression are urgently needed.

**Conclusion:**

that PRDX2 is directly involved in carcinogenesis by regulating oxidative stress and protecting cancer cells from apoptosis.

**Disclosure of Interest:**

0-02 CABOZANTINIB ENHANCES ANTI-PD1 EFFICACY AND ELICITS A NEUTROPHIL-BASED IMMUNE RESPONSE IN MURINE MODELS: IMPLICATIONS FOR HUMAN HCC

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**Disclosure of Interest:**

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**Background & Aims:**

Immune checkpoint inhibitors combined with anti-angiogenic agents produces benefits in the treatment of advanced hepatocellular carcinoma (HCC). We investigated the efficacy and immunomodulatory activity of cabozantinib alone and combined with anti-PD1 in experimental models of HCC, and explored the potential target population that might benefit from this combination.

**Approach & Results:**

C57BL/6J mice bearing subcutaneous Hep-G2 or Hep3B-S4 tumours received cabozantinib, anti-PD1, their combination or placebo. Tumour and blood samples were analysed by flow cytometry, immunohistochemistry, transcriptome and cytokine profiling. Cabozantinib-related effects were evaluated in a colorectal cancer PDX model. Transcriptomic data from three human HCC cohorts (Cohort 1: n=167; Cohort 2: n=57; TCGA, n=319) were used to cluster patients according to neutrophil features, and assess their impact on survival. The combination of cabozantinib and anti-PD1 showed increased anti-tumour efficacy compared to monotherapy and placebo (P<0.05).

**Conclusion:**

Cabozantinib alone significantly increased neutrophil infiltration and reduced CD8+-PD1+ T cell proportions in the tumour, while the combination with anti-PD1 further stimulated both effects and significantly decreased T regulatory cell infiltration (all P<0.05). In blood, cabozantinib and especially combination increased the proportions of overall T cells (P<0.01) and memory/effector T cells (P<0.05), while lowering the neutrophil-to-lymphocyte ratio (P<0.001 for combination).

**Conclusion:**

improving inflammatory HCC treatment observed with the treatment combination was linked to less proliferative phenotypes, and well-differentiated HCC with better prognosis. Neutrophil recruitment in both humans and mice was linked to CXOR2 ligands and CXCL12 (P<0.05).

**Introduction:**

The natural history of hepatocellular adenomas (HCA) remains to be better described especially in non-resected patients. We aim to identify the predictive factors of HCA evolution after estrogen withdrawal.

**Methods:**

We retrospectively included patients with a histological diagnosis of HCA on a biopsy or a surgical resection between 2000 and 2019 in 3 french centers. Clinical, radiological and pathological data were collected in order to identify predictive factors of radiological evolution of HCA in number and in size (using RECIST criteria) and of bleeding and malignant transformation. HCA were classified as HNF1A inactivated, inflammatory and CTNNB1 mutated HCA. We built a score based on variables modulating estrogen levels: body mass index, duration of estrogen-based contraception and alcohol intake. An external cohort from a 4th center was used to validate this score.

**Results:**

184 patients were included with 161 women (87.6%), 88.6% with an estrogen-based contraception during a median of 12 years, all have estrogen withdrawal after the diagnosis. 49.8% of patients had at least one inflammatory HCA, 31.1% at least on HNF1A inactivated HCA and 8% at least one CTNNB1 mutated HCA. 21 symptomatic bleedings (p = 0.012) and 12 transformation in HCC (6.5%, half in men) were identified. HCA > 5 cm in imaging was associated with symptomatic bleeding (p = 0.003). Male (p = 0.005) and HNF1A inactivated HCA (p = 0.0031) were associated with malignant transformation. An age < 37 years old (median age of the population) was associated with bleeding with a hazard ratio (p = 0.004) whereas those of > 37 years old were at risk of HCC occurrence (p = 0.024). 119 patients with residual HCA were followed-up for a median of 4.5 years. Radiological regression was observed in 31%, stabilization in 47% and progression in 22% of the cases. Weight loss was associated with regression (p = 0.0004) and weight gain with progression (p = 0.0021).

A high estrogen exposure score predicted radiological regression (OR 2.45, 95%CI [1.347-5.53]; p = 0.009) with a linear relation between the rate of estrogen exposure and the probability of regression. This result was confirmed in an external cohort of 72 female patients (p = 0.0032).
**IMMUNE PROFILING OF HEPATOCELLULAR CARCINOMA USING DEEP-LEARNING ON HISTOLOGICAL SLIDES**

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**Introduction:** Patients with hepatocellular carcinoma (HCC) display overexpression of particular immune gene signatures are likely to be more sensitive to immunotherapy approaches, however the use of such signatures in clinical settings remains challenging as they require expertise in molecular biology and bioinformatics. Digital histological slides contain a massive amount of information related to tumor biology and immune microenvironment, and we thus aimed to develop models able to perform immune profiling of HCC using deep-learning on Whole-Slide Histological Images (WSIs).

**Methods:** We performed attention-guided instance learning using CLAM models. CLAM was used with the aim to identify tumors with activation of 6 immune gene signatures previously shown to predict sensitivity to immunotherapy in patients with advanced HCC: “6-Gene Interferon Gamma”, “Gajewski 13-Gene Inflammatory”, “Interferon Gamma Biology”, “Ribas 10-Gene Interferon Gamma” and “T-cell Exhaustion”. For each signature, 10-fold Monte Carlo cross-validation CLAM models were trained on 349 hematoxylin-and-eosin-stained HCC WSIs. Ground-truth labels of WSIs were obtained by unsupervised clustering of RNA sequencing data. The trained best-fold models were further validated on an external validation dataset comprising 139 HCCs developed in patients from Henôl Mondor University Hospital (Créteil, France) (WSIs stained with different protocols and digitized with a different format). Ground-truth labels were determined using gene expression data obtained by the NanoString nCounter Immuno-Oncology 360 Panel. For all gene signatures, attention maps allowed pathological reviewing of areas with highly predictive value.

**Results:** Best-fold AUCs for the prediction of tumors with upregulation of the gene signatures in the discovery series were 0.744 (mean 0.604, sd 0.109), 0.868 (mean 0.717, sd 0.074), 0.844 (mean 0.688, sd 0.088), 0.827 (mean 0.737, sd 0.039), 0.866 (mean 0.708, sd 0.098) and 0.805 (mean 0.562, sd 0.134) for “6-Gene Interferon Gamma”, “Gajewski 13-Gene Inflammatory”, “Interferon Gamma Biology”, “Ribas 10-Gene Interferon Gamma” and “T-cell Exhaustion”, respectively. For each signature, we validated the best-fold models on our series of 139 WSIs from Henôl Mondor Hospital. The different models generalized well with AUC ranging from 0.745 to 0.912. Analysis of tissue areas with a highly predictive value showed enrichment in inflammatory cells, plasma cells, and neutrophils, while non-inflammatory areas more frequently displayed neoplastic cells.

**Conclusion:** Using deep-learning on digital histological slides, we have developed and validated models able to predict the activation of several immune gene signatures associated with response to immunotherapy in patients with advanced HCC. By the pathological reviewing of tissue areas classified as highly predictive, our approach also provides insights on the main morphological features that impact the model predictions. Our proof-of-concept study shows that our approach could represent a novel type of biomarker that will ease the translation of our biological knowledge of HCC into clinical practice. References 1 Sangro, Bruno, et al. “Association of inflammatory biomarkers with clinical outcomes in nivolumab-treated patients with advanced hepatocellular carcinoma.” Journal of hepatology. 73.6 (2020): 1460-1469. 2 Lu, Ming Y, et al. “Data-efficient and weakly supervised computational pathology on whole-slide images.” Nature Biomedical Engineering. (2021): 1-16.

**Disclosure of Interest:** No
**O-06** A NOVEL MICROENVIRONMENT-BASED CLASSIFICATION OF INTRAHEPATIC CHOLANGIOCARCINOMA

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**Introduction:** Intrahepatic cholangiocarcinoma (iCCA) represents an aggressive biliary malignancy associated with increasing incidence and dismal prognosis. The diversity of the tumor microenvironment (TME) has not been thoroughly assessed in previously described molecular classifications. We aimed to generate a novel iCCA classifier that integrates elements of the Stroma, Tumor and Immune Microenvironment (“STIM” classification).

**Methods:** We analyzed bulk gene expression data from publicly available datasets (n=464 resected iCCAs) using a training-validation approach. By applying virtual deconvolution to a training cohort of 122 iCCAs (GEO:G0000101000695), we devised a novel classification after selecting for the most relevant TME components from an unsupervised analysis. The novel classification was validated in 3 datasets (GSE33327, GSE69566, GSE9749, n=343) with gene expression, structural aberrations, methylation and clinical data available. We assessed actual immune and stromal presence in our Mount Sinai cohort (n=127, GSE33327) using hematoxylin eosin-stained slides, and performed immunostaining for CD8, FOXP3, and CD68 (n=57). Cancer associated fibroblast (CAF) subtypes and cell-cell interactions were identified using available single-cell RNA-sequencing data (GSE138709, GSE142784). Four different models were generated through hydrodynamic tail vein injection in C57BL/6 mice. Molecular and immune characterization of the murine tumors were performed by RNA-sequencing and flow cytometry, respectively.

**Results:** We identified 5 STIM clusters encompassing both inflamed and non-inflamed profiles. The Immune classical (~10%) and Inflammatory stroma (~25%) resembled hot tumors with high immune infiltration and higher presence of CD68+ cells (p<0.01). Despite its inflammatory phenotype, the Inflammatory stroma showed CD68+ cells exhaustion, and an abundant desmoplastic reaction associated with the myofibroblastic-CAP (mCAF) subtype and a TGFB program (p<0.001). Cell-cell interaction analysis identified a subset of the mCAFs as mediators of immune evasion through specific ligand-receptor interactions potentially disrupting the immune response (i.e. CCL3-IDE, CCL9-IDE). Comparative analysis between cycle pathways and poor survival (p<0.05). The last group (Desert-like, 20%) comprised samples associated with the myofibroblastic-CAF subtype and a TGFB program (p<0.001). Cell-cell interactions were identified using available single-cell RNA-sequencing data (GSE138709, GSE142784). Four different models were generated through hydrodynamic tail vein injection in C57BL/6 mice. Molecular and immune characterization of the murine tumors were performed by RNA-sequencing and flow cytometry, respectively.

**Conclusions:** We have generated a novel genomics-based classifier that integrates elements of the TME with tumor molecular features (Figure 1). This approach represents an improved patient stratification with increased granularity in defining the roles of immune- and non-immune-related factors influencing the iCCA phenotypes. Finally, cross-species analysis sheds light on murine models’ similarity to the human disease.

**Disclosure of Interest:** No

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**O-07** SINGLE-CELL RNA SEQUENCING UNRAVELS THE IMMUNOSUPPRESSIVE LANDSCAPE AND TUMOR HETEROGENEITY OF HBV-ASSOCIATED HEPATOCELLULAR CARCINOMA

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**Introduction:** The fundamental understanding of the immunocellular and molecular landscapes of hepatocellular carcinoma (HCC) remains elusive.

**Methods:** We performed single-cell RNA sequencing (scRNA-seq) on HBV-associated HCCs. The cellular composition, subclonal diversity, high-resolution multi-faceted landscapes of individual HCC cells and the immunosuppressive landscape were analyzed. Functional analyses were performed to validate the findings.

**Results:** From the scRNA-seq, we detected a statistically significant association between CD163 (M2 macrophage marker) and LAIR1 expression, which was further confirmed in both in-house and TCGA RNA-seq datasets. We observed frequent overlap of LAIR1 and CD163 immunofluorescence staining and detected a significant association between LAIR1 and CD163 expression in HCC. Besides, we established stable LAIR1 knockdown (shLAIR1) in macrophages using THP-1 cells. Co-culturing the shLAIR1 macrophages with CD68 T cells upregulated T cell activation, as exemplified by the increased proportion of CD44+CD62L- effector T cells. Of significance, using scRNA-seq, we identified a prominent co-inhibitory immune checkpoint signal via TIGIT-NECTIN2 axis in complementary T cells and antigen-presenting cells. Moreover, in both our in-house and TCGA RNA-seq cohorts as well as using IHC in our clinical specimens, we observed NECTIN2 was significantly upregulated in HCCs. We also detected a significant association between TIGIT and NECTIN2 expression in HCC but not in non-HCC, HBV-associated cirrhotic livers. This suggests that the TIGIT-NECTIN2 axis may likely be a tumor evasion strategy, instead of viral evasion one. Upon ligation to NECTIN2, TIGIT acts as an inhibitory receptor on T and NK cells. To investigate whether NECTIN2 expressed on HCC cells would lead to T cell exhaustion, we established Nectin2 knockout (KO) stable cells in mouse HCC cell line Hepa-1. Upon co-culturing mouse splenic T cells with Hepa-1 parental cells, anti-Nectin2 neutralizing antibody significantly restored both CD4+ and CD8+ T cell proliferation. Consistently, KO of Nectin2 in HCC cell lines also restored both CD4+ and CD8 T cell proliferation. To extend our observation in vivo, we performed hydrodynamic tail-vein injection to generate wildtype (WT) and Nectin2 KO mouse HCC. The Nectin2 KO HCC tumors were significantly smaller as compared to WT controls, accompanied with increased infiltration of T effector, CD4+, and CD8+ cells in HCC. Similar findings were also observed in our Nectin2 stable knockout orthotopic implantation model. In addition, the cell state transition of immune cells towards a more immunosuppressive and exhaustive status exemplified the overall cancer-promoting immunocellular landscape. Using global transcriptomic profiling, liver cancer stem cell markers, inferred copy number variation, and expression profile of receptor tyrosine kinase families, our findings collectively suggested the degree of inter-tumoral heterogeneity was more prominent than intra-tumoral one.

**Conclusion:** Taking advantage of the multi-dimensional capacity of scRNA-seq, we have revealed the novel cellular and immunosuppressive landscapes and demonstrated the important roles of LAIR1-expressing TAMs and TIGIT-NECTIN2 axis in shaping a cancer-promoting tumor microenvironment in HCC. Our overview of the immunosuppressive landscape and intercellular interactions provide useful mechanistic information for the design of efficacious immune-oncology treatments in HCC. Funding support: Hong Kong Research Grants Council Theme-based Research Scheme (T12-704116-R)

**Disclosure of Interest:** No
Oral Communications
Saturday, 4th September 2021

0-08
CYTOKINE GRADIENTS IN HUMAN HEPATOCELLULAR CARCINOMA MICROENVIRONMENT REGULATE INNATE LYMPHOCYTES
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Introduction: Hepatocellular carcinoma (HCC) represents a typical inflammation-associated cancer. Human innate lymphoid cells (ILCs) are a heterogeneous population of innate immune cells with diverse roles in infection, inflammation and homeostasis. ILCs have been suggested to control tumor surveillance [1], however, their role in cancer and anti-tumor immunity is not clearly defined. Here we studied how the tumor microenvironment and specifically the local cytokine milieu controls ILCs in HCC. Design We performed bulk RNA sequencing of HCC tissue as well as flow cytometry and single-cell RNA sequencing of 18,000 enriched ILCs from non-tumor liver, margin and tumor core derived from 48 HCC patients. Simultaneous measurement of protein and RNA expression at the single-cell level (Atelius) identified precise signatures of ILC subtypes. In-silico culturing of ILCs was used to validate findings from in-silico analysis. Analysis of RNA-sequencing data from large HCC cohorts allowed stratification and survival analysis based on transcriptomic signatures.

Results: RNA sequencing of tumor, non-tumor and margin identified tumor-dependent gradients of which were not only associated with poor survival but also control ILC plasticity. Single-cell RNA sequencing and flow cytometry of ILCs from HCC livers identified NK-like cells in the non-tumor tissue, losing their cytotoxic profile as they transitioned into tumor ILC1 and NK-like ILC3 cells. Tumor ILC composition was mediated by cytokine gradients that directed ILC plasticity towards activated tumor ILC2s. This was liver-specific and not seen in ILCs from PBMC. Patients with high ILC2/ILC1 ratio expressed IL-33 in the tumor that promoted ILC2 generation and was associated with better survival. Finally, a 22-gene signature derived from ILC2 correlated with patient outcome.


O-11 CACHEXIA IS PREVALENT IN PATIENTS WITH HEPATOCELLULAR CARCINOMA AND ASSOCIATED WITH WORSE PROGNOSIS
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Introduction: Cancer cachexia is a wasting syndrome associated with functional impairment and reduced survival that impacts up to 50% of patients with gastrointestinal cancers. However, data on the prevalence and clinical significance of cachexia in patients with hepatocellular carcinoma (HCC) is limited.

Methods: We performed a retrospective cohort study of patients diagnosed with HCC at two U.S. health systems between 2008 - 2018. Patient weights were recorded six months prior and at HCC diagnosis. We excluded patients lacking weight data at time of HCC diagnosis (+/- 1 month), as well as patients with detectable ascites on imaging 6 months prior to HCC diagnosis. Cachexia was defined as >5% weight loss (or >2% weight loss if BMI <20 kg/m2) and precachexia defined as >3% weight loss. Study end points included overall survival and progression-free survival.

Results: Of 604 patients with HCC, 201 (33.3%) had precachexia and 143 (23.7%) had cachexia at diagnosis, including 19.0%, 23.5%, 34.7%, and 34.0% of patients with BCLC stages A/B, C, and D, respectively. Notably, 43% of patients with cachexia had BCLC stage A/B tumors. BMI at HCC diagnosis was lower in patients with cachexia compared to those with precachexia or stable weight, (median BMI 25.4, 28.3, and 28.5, respectively). The proportion of patients with cachexia was significantly higher by sex (p=0.09), race/ethnicity (p=0.62) and age (p=0.42). In multivariable analyses, pre-treatment cachexia was associated with Child Pugh class B/C cirrhosis and tumor size >5 cm. Patients with cachexia were less likely to receive HCC treatment compared to those without cachexia (OR 0.39, 95% CI 0.19 – 0.50). Results were consistent in multivariable analyses after adjusting for age, sex, race/ethnicity (p<0.001) and usual care (p=0.38), Child Pugh tumor stage (OR 0.38, 95% CI 0.21 – 0.71). Patients with cachexia were less likely to receive HCC treatment (OR 0.38, 95% CI 0.21 – 0.71) and had worse survival than those with precachexia or stable weight (11.3 vs 20.4 vs 23.5 months, respectively, p<0.001). Survival differences between patients with cachexia, precachexia, and stable weight were consistent across BCLC stages (Figure 1) and Child Pugh classes, as well as by subgroups of sex, race/ethnicity, BMI category, and most definitive HCC treatment type. In multivariable analyses, after adjusting for age, sex, race, Child Pugh class, AFP, BCLC tumor stage and HCC treatment received, cachexia (HR 1.43, 95% CI 1.11 – 1.84) and precachexia (HR 1.30, 95% CI 1.02 – 1.65) were both independently associated with worse overall survival.

Conclusion: Cachexia is prevalent in patients with HCC and associated with worse survival and treatment outcomes. The presence of cancer-associated weight loss appears to be an early and independent predictor of worse outcomes in patients with HCC.

Disclosure of Interest: No

0-12 ERS: A SIMPLE, USER-FRIENDLY MODEL TO PREDICT EARLY RECURRENCE AFTER SURGICAL RESECTION FOR HEPATOCELLULAR CARCINOMA
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O-13 THE ASSOCIATION OF SUSTAINED VIROLOGIC RESPONSE ON DISCLOSURE OF INTEREST:

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enhanced MRI. All MR images were independently reviewed by two radiologists who were blinded to all clinical, biologic, pathological and follow-up information. A prognostic score encompassing all significant predictors for HCC-related death was constructed via Cox proportional hazards regression analysis with five-fold cross-validation. Model performances were estimated by the Harrell’s concordance index (C-index) and the calibration plot. OS were analyzed by using the Kaplan-Meier method and compared with the log-rank test.

Results: A total of 214 patients (mean age: 52.4 ± 11.6 years, 178 men [83.2%]) were evaluated, among whom 25 (12.0%) patients experienced death. The median follow-up period was 16.7 months (range: 3.1-65.8 months). At multivariate analysis, satellite nodule (hazard ratio [HR]=5.209), corona enhancement (HR=3.169), infiltrative appearance (HR=3.234), cirrhosis (HR=0.384) and serum AFP level > 400 ng/mL (HR=1.424) were independent predictors of death. Based on these features, the prognostic score (combining all significant parameters identified at multivariate analysis) achieved a C-index of 0.889 (95% confidence interval [CI]: 0.834-0.945) in predicting OS. The calibration curve showed good agreement for the risk evaluation by the prediction model and actual observations. With a cutoff of 8 scores, all patients were stratified into two subgroups with low (<8 scores; n=154) and high (>8 scores; n=60) risk of death, respectively. The corresponding median OS was undefined and 18.2 months, respectively (P < .001).

Conclusions: A prognostic score incorporating preoperative gadoxetic acid-enhanced MRI findings and serum AFP level can accurately predict survival of HCC patients after surgical resection.

Disclosure of Interest: No
Oral Communications

Sunday, 5th September 2021

General Session 3: Diagnosis, imaging and biomarkers

0-15 DETECTION OF EARLY-STAGE HCC BY ABBREVIATED MRI: MULTICENTER VALIDATION AGAINST SURGICAL PATHOLOGY


University of Texas Southwestern, University of Washington, University of Michigan, University of Maryland, Fred Hutch Cancer Research Center, University of Texas Southwestern, University of Texas Southwestern, University of Maryland, University of Maryland, University of Texas Southwestern, University of Texas Southwestern, University of Washington, University of Texas Southwestern, University of Michigan, University of Michigan, Fred Hutch Cancer Research Center, University of Texas Southwestern, University of Texas Southwestern, University of Texas Southwestern, University of Texas Southwestern, University of Texas Southwestern, University of Texas Southwestern, University of Texas Southwestern, University of Texas Southwestern, University of Texas Southwestern.

Introduction: Abbreviated Magnetic Resonance Imaging (AMRI) has been proposed as a surveillance tool for hepatocellular carcinoma (HCC) in patients with cirrhosis. A recent meta-analysis reported excellent diagnostic performance of AMRI (sensitivity and specificity ~90%), but studies relied on a composite reference standard of imaging (including diagnostic MRI, biopsy, or clinical follow-up), so the performance may have been overestimated. Our study’s aim was to evaluate early-stage detection of dynamic contrast enhanced AMRI (dynamic AMRI) in cirrhosis, against a rigorous independent reference standard of surgical pathology.

Methods: We conducted a multi-center retrospective case-control study at three academic liver transplantation centers in the United States on patients with cirrhosis who underwent liver resection or transplantation between 2009-2019 and had full dynamic contrast-enhanced liver MRI within 3 months of surgery. Patients were excluded if they had: biliary/oriental or systemic therapy prior to surgery; non-liver protocol MRI, hepatobiliary contrast MRI, tumor beyond Milan criteria on pathology (given the intent to evaluate early-stage detection), or HCC size less than 1 cm (given sub-threshold size for imaging diagnosis). Simulated dynamic AMRI exam was constructed from the pre-surgical full MRI by retaining only the localizing coronal T2-weighted and dynamic contrast enhanced T1-weighted sequences (pre-contrast, arterial, portal venous, and delayed phases), and omitting most non-contrast sequences. Two abdominal radiologists at each center independently reviewed AMRI images using 2018 Liver Imaging Reporting and Data System (LI-RADS) criteria, blinded to all clinical, pathological, and prior imaging data. Patients with liver observations categorized as LI-RADS 4, 5, or 0 were recorded as “positive” for HCC detection, and “negative” otherwise. Patients with pathologically-confirmed HCC were considered HCC+ (cases), and patients without HCC on pathology as HCC- (controls). Patients with pathologically-confirmed non-HCC mass (e.g. cholangiocarcinoma) were classified as HCC-. Early-stage status was pathologically confirmed by applying Milan criteria. Patient-level sensitivity and specificity for early-stage HCC detection were calculated in the HCC-positive and HCC-negative groups, respectively, for each reader as well as for the average reader. 95% confidence intervals were calculated for each point estimate.

Results: We enrolled 160 patients with early-stage HCC and 139 patients without HCC. The most common etiology of cirrhosis was hepatitis C among HCC+ (67.5%) and alcohol-related among controls (55.4%). Most HCC cases had Child-Pugh A cirrhosis (84.9%) and treated with resection (78.4%). Most HCC were unifocal (84.9%) and median diameter was 2.4 cm. Positivity and specificity of dynamic AMRI for early-stage HCC were 0.888 (95% CI: 0.841-0.931) and 0.892 (0.842-0.939), respectively (Table 1). There was variation in performance across readers, sites, and type of surgery (resection vs. transplantation). Notably, the sensitivity of AMRI was significantly higher for patients undergoing resection than those undergoing transplantation (95.7% vs. 62.1%).

Image:

Table 1: Detection Sensitivity and Specificity of Dynamic AMRI for Early-Stage HCC

<table>
<thead>
<tr>
<th>Site</th>
<th>Reader</th>
<th>Category</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site 1 Reader 1</td>
<td>0.904 (0.856, 0.937)</td>
<td>0.643 (0.577, 0.729)</td>
<td>0.628 (0.543, 0.744)</td>
<td>542 (60% transplant)</td>
<td></td>
</tr>
<tr>
<td>Site 2 Reader 1</td>
<td>0.592 (0.489, 1.000)</td>
<td>0.650 (0.700, 1.00)</td>
<td>0.600 (0.700, 1.00)</td>
<td>85 (23% transplant)</td>
<td></td>
</tr>
<tr>
<td>Site 3 Reader 1</td>
<td>0.708 (0.610, 0.873)</td>
<td>0.100 (0.067, 1.00)</td>
<td>0.909 (0.868, 1.00)</td>
<td>23 (4% transplant)</td>
<td></td>
</tr>
</tbody>
</table>

Average Reader

Total Sensitivity: 0.899 (0.842, 0.933)
Specificity: 0.959 (0.888, 0.998)
Positive Predictive Value: 90.3%
Negative Predictive Value: 99.7%

Conclusion: Using surgical pathology as the reference standard, dynamic AMRI had sensitivity and specificity of approximately 90% for detection of early-stage HCC in cirrhosis using the diagnostic LI-RADS algorithm. Our diagnostic performance estimates support use of AMRI as a potential surveillance tool in cirrhosis patients.

Disclosure of Interest: No

0-16 LIMITATIONS OF NON-INVASIVE RADIOLOGICAL CRITERIA FOR THE DIAGNOSIS OF ADVANCED HEPATOCELLULAR CARCINOMA

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Introduction: Advanced hepatocellular carcinoma (HCC) is commonly diagnosed using the non-invasive radiological criteria (NIR) defined by EASL or AASLD. In 2017, The National Institute for Clinical Excellence (NICE) mandated histological confirmation of disease to authorised use of sorafenib in the UK. This provided an opportunity to evaluate the safety of biopsy and also determine the sensitivity and positive predictive value of NICE in advanced HCC using histology as the gold standard reference.

Methods: This was a prospective multi-centre audit across 11 UK centres, in which patients potentially suitable for sorafenib were identified at multidisciplinary meetings. All clinical, radiological and histological data were reported locally according to standard of care and collected anonymously on a standardised case report form. The primary analysis cohort (FAC) was defined by the presence of Child-Pugh A class liver disease and performance status 0-2 as per NICE guidelines for sorafenib treatment.

Results: Eleven centres reported 418 cases of which 361 comprised the PAC. The median age was 68, 76% had chronic liver disease (alcohol 24%, HCV 20% and NASH/NAFLD 25%) and 66% were cirrhotic. Diagnostic imaging consisted of CT in 71%, MRI in 27% and 2% both. Of the 361 in the PAC, 164 were cirrhotic and satisfied NICE for HCC diagnosis (45.4%). Biopsy was deemed unsafe in 46 patients due to poor accessibility (20%), low platelets (13%), impaired clotting (9%) or ascites (2%) and 45 patients had previous histology. New biopsies were performed in the remaining 270 patients and confirmed HCC in 87.8%. Alternative histological diagnoses included cholangiocarcinoma (CC; 4.1%), combined HCC-CC (hCC-CC; 0.7%) and other (2.2%). Biopsy was non-diagnostic in 13 patients (4.6%). In cirrhotic patients, NICE criteria had a sensitivity of 85.4% (MRI vs CT, 69.9% and 64.6%) and positive predictive value of 91.4% (MRI vs CT, 93.9% and 90.3%) to detect HCC. Across the PAC cohort, only two adverse events (0.7%) consisting of mild post-biopsy bleeding were reported.

Conclusion: Our data demonstrate that the majority of patients with hepatocellular carcinoma do not present with diagnostic imaging and in those that do, up to 10% may have a non-HCC diagnosis. Biopsy is safe in patients with preserved liver function who are eligible for systemic therapy. Given these findings, we recommend that patients with suspected advanced HCC who are eligible for clinical trials or standard of care therapy should undergo histological confirmation of disease.

Disclosure of Interest: No

0-17 HEPATOCELLULAR CARCINOMA EARLY DETECTION USING MAGNETIC RESONANCE IMAGING IS COST-EFFECTIVE IN FRENCH HIGH-RISK PATIENTS WITH CIRRHOSIS

Pierre Nahon1, Kevin Zerca2, Richard Layese1, Marie Najean1, Carole Cagniot1, Laetitia Segar1, Nathalie Ganne-Carrié1, Gilles N’Korchilou1, Stanislas Pol3, Cendrine Chataff1, Sylvie Cleuret1, Fabrice Carrai1, Eteline Audunna1, Isabelle Durand-Zaleski4, for the ANRS C012 CirVir, ANRS C022 Hepather, GRETH/CHIRAL, and CRITIAL groups.

1APHP Avicenne; 2APHP URCeo; 3APHP Mondor; 4ANRS; 5APHP Cochin; 6APHP ST Louis; 7APHP ST Antoine

Introduction: Reinforced HCC surveillance programs using MRI could increase rates of cirrhotic patients eligible for curative procedures and subsequent survival. Such implementation might only be cost-effective in patients with a high annual HCC risk above 3%. The aim of this study was to assess the anticipated proportion of patients bearing an annual HCC risk ≥3% in France and to evaluate the cost-effectiveness of MRI for the detection of very early HCC<2cm in this population.

Methods: Patients with compensated cirrhosis included between 1998 and 2016 in 4 French prospective multicentre cohorts or trials dedicated to HCC surveillance were considered (ANRS CirVir, ANRS Hepather, APHP CRIRAL, APHP CIRHOC). HCC incidence and identification of risk factors were restricted to patients with non-viral causes of cirrhosis and/or cured HCV/controlled HBV
Infections using Cox models with construction of a scoring system to identify patients with an annual risk ≥3%. All analyzed features were considered as time-dependent covariates and took into account competing risks of death (Fine and Gray regression models). We used a previously published Markov model developed to predict the survival of a cohort of 10,000 patients aged 50 years, 65% male, with compensated cirrhosis. The economic evaluation estimated costs in life-years (LY) gained of MRI vs. US monitoring over a 20-year period. The incremental cost-effectiveness ratio (ICER) was calculated by dividing the incremental costs (i.e. difference in costs between two treatment options) by incremental LY. In the MRI group, we added the cost of two additional MRIs and specialist consultations each year. The costs of curative HCC treatments (radiofrequency ablation, resection, transplantation) were estimated from the French national hospital claims database.

Results: A total of 4973 patients were considered in the 4 cohorts, among whom 2513 had non-viral causes of cirrhosis (n=840, including 796 alcoholic) and/or cured HCV (n=1499) controlled HBV infections (n=184) and were included in the analyses. During a 37 months follow-up, 206 HCC were detected. The population was randomly divided into a training (n=1658) and validation (n=855) sets. The construction of a 16-points scoring system encompassing HCC predictors (male gender, older age, lower platelet count, higher bilirubin levels and higher GGT/AST levels) allowed the identification in both sets of 33.4% and 37.5% of patients with an annual HCC risk≥3% (C-index 75 and 76 respectively, Figures 1A and 1B). The medico-economic analysis revealed that for an annual incidence of 3% per year, 14% of all cancers detected by MRI were at very early stage, vs 63% in the MRI surveillance group. Patients in the MRI surveillance group gained 13.8 discounted LY, while those in the US surveillance group gained 13.4 discounted LY, yielding a difference of 0.4 discounted LY over the 20-year horizon. The total discounted costs per patient were 195,274€ and 99,464€ for MRI and US surveillance groups, respectively.

Image:

Disclosure of Interest: Yes - Advisory Board

Tuesday, 5th September 2021

A PHASE III STUDY OF ATEZOLIZUMAB (ATEZO) + BEVACIZUMAB (BEV) VS BEVACIZUMAB (BEV) IN PATIENTS (PTS) WITH UNRESECTABLE HEPATOCELLULAR CARCINOMA (HCC)

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Introduction: Atezo + bev has been approved in >70 countries for pts with unresectable HCC who have not received prior systemic therapy based on results from the IMbrave150 (NCT03434379) study (Finn RS, et al. N Engl J Med 2020). Overall survival (OS) benefit with atezo + bev vs sor was maintained with an additional 12 mo of follow-up since primary analysis (Finn RS, et al. ASCO GI 2021). We report an exploratory analysis of the possible impact of ALBI grade on outcomes by liver function at baseline.

Methods: Pts in this Phase III study were systemic treatment-naïve with unresectable HCC, ≥1 measurable untreated lesion (RECIST 1.1), Child-Pugh class A liver function and ECOG PS 0-1. Pts were randomised 2:1 to atezo 1000 mg q3w + bev 15 mg/kg q3w or sor 400 mg bid until unacceptable toxicity or loss of clinical benefit per investigator. Liver function in this analysis was assessed in both the intention-to-treat (ITT) and safety populations per modified (m)ALBI grade (Gr 1, 2, 3 at baseline). For ITT pts receiving atezo + bev, 191 (57%) had a mALBI grade (Gr) of 1, 22 (21%) were Gr 2a, 71 (21%) were Gr 2b and 0 were Gr 3 at baseline. For ITT pts receiving sor, 87 (53%) were Gr 1, 21 (13%) were Gr 2a, 25 (15%) were Gr 2b and 0 were Gr 3 at baseline. Strong OS benefit for atezo + bev vs sor was observed for mALBI Gr 1 pts (HR, 0.50 [95% CI: 0.35, 0.72]; see Table). In pts with mALBI Gr 2a or Gr 2b vs Gr 0, there appeared to be a trend that favours atezo + bev vs sor (Gr 2a: HR, 0.97 [95% CI: 0.59, 1.59]; Gr 2b: HR, 0.85 [95% CI: 0.54, 1.34]; Gr 2: HR, 0.82 [95% CI: 0.66, 1.02]; see Table). A similar pattern was observed for PFS (see Table). Median TTD was 10.5 mo (95% CI: 8.0; 11.1) in the atezo + bev arm vs 6.6 mo (95% CI: 6.2; 11.8) in the sor arm (unstratified HR, 0.82 [95% CI: 0.65, 1.04]).

Conclusion: Atezo + bev is the new standard of care for pts with previously untreated, unresectable HCC. Here we showed that in IMbrave150, pts with mALBI/ALBI grade 1 at baseline appeared to derive greater benefit from atezo + bev and that TTD of liver function was longer with the use of the atezo + bev combination vs sor in this exploratory analysis.

Disclosure of Interest: Yes - Honoraria

Saturday, 4th September 2021

CIRCULATING TUMOR CELL-BASED mRNA SCORING SYSTEM FOR PROGNOSTICATION OF HEPATOCELLULAR CARCINOMA - TRANSLATING HCC TISSUE-BASED mRNA PROFILING INTO A NON-INVASIVE SETTING

Yi-Te Lee1,2, Minghua Jin1, Jasmine J. Wang1, Benjamin Y. Tran1,2, Ryan Y. Zhang1, Dongping Qi1, Deng Zhang1, Pin-Jun Chen1, Saeed Sadeghi1, Richard S. Finn1, Sammy Saab1, Steven-Huy B. Han1, Ronald W. Butschi1, Renjun Pei1, Yuzhen Zhu1, Hsin-Rong Tseng1, Sungyang You4, Ju Dong Yang4,8,9, Vatche G. Agopian6,7,8,9

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O-18 IMBRAVE150: ALBUMIN-BILIRUBIN (ALBI) GRADE ANALYSES IN A PHASE III STUDY OF ATEZOLIZUMAB (ATEZO) + BEVACIZUMAB (BEV) VERSUS SOFARAFENIB (SOR) IN PATIENTS (PTS) WITH UNRESECTABLE HEPATOCELLULAR CARCINOMA (HCC)

Yes: Advisory Board

Abbbie, AstraZeneca, Bayer, BMS, Elixa, Gilead, Roche

13th ILCA ANNUAL CONFERENCE, 2019 - BOOK OF ABSTRACTS
Introduction: Numerous studies in hepatocellular carcinoma (HCC) have proposed tissue-based gene signatures for individualized prognostic assessments. Here, we develop a novel circulating tumor cell (CTC) based transcriptomic profiling assay to translate tissue-based mRNA signatures into a liquid biopsy setting for non-invasive HCC prognostication.

Methods: The HCC CTC miRNA Scoring System combines the NanoWear CTC Assay for enriching HCC CTCs and the NanoString nCounter platform for quantifying the HCC-CTC Risk Score (RS) panel in enriched HCC CTCs. The prognostic role of HCC-CTC RS was assessed in the Cancer Genome Atlas (TCGA) HCC cohort (n=362) and validated in an independent clinical CTC cohort (n=40).

Results: The HCC-CTC RS panel was developed through our integrated data analysis framework of 8 HCC tissue-based gene signatures, and identified the top 10 prognostic genes (E2R1, EH3AD1, AR, LUM, HSID17698, PMP141, TSKU, NEQAB2, LAD1, SL2C17A5) highly expressed in HCC with low expression in white blood cells. The panel accurately discriminated overall survival in TCGA-HCC cohort (hazard ratio [HR]: 2.01, 95% confidence interval [CI]: 1.39-2.91). Combined use of Scoring System and HCC-CTC RS panel successfully distinguished artificial blood samples spiked with an aggressive HCC cell type, SN1-387, from those spiked with PLC/PRF/5 cells (p=0.003). The prognostic value of HCC-CTC RS was validated in an independent CTC cohort (HR: 8.48, 95% CI: 1.89-38.93) by multivariable analysis.

Image:

Conclusions: Our studies demonstrate a novel interdisciplinary approach to translate tissue-based gene signatures into a liquid biopsy setting. This non-invasive approach will allow real-time disease profiling and dynamic prognostication of HCC.

Disclosure of Interest: No

O-20 IDENTIFICATION OF A PAN-GAMMA-Secretase inhibitor response signature for notch-driven Cholangiocarcinoma

Hitomi Takada, Yasuyuki Komiyama1, Ryoo Kato, Natsuko Nakakuki1, Shuya Matsuda, Masakazu Murakami, Yuichiro Suzuki, Akihisa Tatsumi, Yasuhiro Nakayama1, Taisuke Inoue1, Shinya Maekawa1, and Nobuyuki Enomoto1.

First Department of Internal Medicine, Faculty of Medicine

Introduction: Introduction: In the 3rd edition of the Cirrhosis Clinical Practice Guideline in Japan, sarcopenia / hypoalbuminemia / Child-Pugh grade B or C was described as a feature that should be additionally intervened. However, there are many unclear points between undernutrition and sarcopenia in hepatocellular carcinoma (HCC) cases. We investigated undernutrition and prognosis in patients with primary HCC.

Methods: This is a retrospective cohort study that focused sarcopenia diagnosed using Computed Tomography (CT) examination and prognosis in 708 patients with primary HCC. For muscle mass evaluation, the psoas muscle mass index (PMI) at the third lumbar vertebral (L3) was calculated, and body mass index, TNM stage, and PIVKA-â ¡ were independent. Multivariate analysis of prognostic factors showed the number of undernutrition-positive factors, body mass index, TNM stage, and PIVKA-â ¡ were independent. Prognosis stratification based on the number of positive factors was possible for each males and females. The male sarcopenia group had a shorter survival than the non-sarcopenia group (74 vs. 91 months, p = 0.027), while there was no difference in female survival with and without sarcopenia in females (p = 0.78).

Conclusion: Undernutrition is an independent factor affecting the prognosis of primary HCC patients, and sarcopenia might be an adequate biomarker representing the undernutrition in male HCC patients. On the other hand, sarcopenia might not be adequate in female HCC patients.

Disclosure of Interest: No

General Session 4: Therapy & Clinical Trials in 2021

O-21 NIVOLUMAB (nivo) in sorafenib (sor) naive and -experienced patients with advanced hepatocellular carcinoma (ahcc): 5-year follow-up from checkmate 040 cohorts 1 and 2

Jörg Trojan1, Tim Meyer2, Thomas Yaú3, Ignacio Melero4, Masatoshi Kudo5, Chitian Hui6, Iee-you Ki7, Akhila Chopra8, Samira Seleymani9, Jin Yao10, Jaclyn Neely11, Marina Tschaika12, Theodor H Welling III13, Bruno Sangro14, Anthony El-Khoueiry15

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Introduction: Introduction Patients (pts) with AHCC have a poor prognosis and high mortality. NIVO monotherapy has demonstrated clinical activity in pts with aORR based on the results from cohorts 1 and 2 of the CheckMate 040 study (NCT01688789). We report safety and efficacy data from the 5-year follow-up from this study.

Methods: Cohort 1 enrolled sorafenib-sor and sorafenib-experienced pts to receive NIVO monotherapy at escalating dose levels (0.1–10.0 mg/kg) Q2W. Cohort 2 enrolled sorafenib-sor and sorafenib-experienced pts to receive NIVO monotherapy at 3 mg/kg Q2W. Both cohorts enrolled pts regardless of HCC etiology and programmed death ligand 1 (PD-L1) expression status. We report data from sorafenib-sor and sorafenib-experienced pts treated with NIVO in this analysis of these dose-escalation-expansion cohorts. Tumor response was determined by blinded independent central review (BICR) and investigator assessment (IV) using RECIST v1.1. Other key endpoints included disease control rate (DCR), duration of response (DOR) per IV, overall survival (OS), and safety.

Results: Median (range) follow-up was 62.9 months (mo; 60–84) in sorafenib-sor pts (N = 85) and 62.8 mo (60–86) in sorafenib-experienced pts (N = 154), 140 (91%) of whom had progressed on sorafenib. In sorafenib-sor pts, the objective response rate (ORR; BICR) was 25%, and DOR (BICR) was 53%. Four percent of pts had complete response (CR); 16% had partial response (PR), 33% had stable disease (SD), and 40% had progressive disease (PD) as best response (BICR). Median (range) time to response (TTR) was 2.7 mo (1.3–5.5), and median DOR was 22.6 mo (4.2–56.8). In sorafenib-sor-experienced pts, the ORR and DOR were 14% and 56%, respectively. Three percent of pts had CR, 11% had PR, 44% had SD, and 38% had PD as best response (BICR). Median (range) TTR was 2.8 mo (1.2–7.0) and median DOR was 39.7 mo (3.2–79.8). In sorafenib-sor pts, the ORRs for uninfected, HIV-infected, and HBV-infected pts were 21%, 20%, and 13%, respectively. The ORRs were 27% and 13% for pts with tumor-cell PD-L1 expression > 1% and < 1%, respectively. In sorafenib-sor pts, the median OS (95% CI) was 26.6 mo (16.6–30.8). In sorafenib-sor-experienced pts, the median OS (95% CI) was 15.2 mo (13.0–18.2). The 3-year and 5-year OS rates (95% CI) were 27.6% (17.8–36.3) and 13.9% (8.9–23.3) for sorafenib-sor pts and 19.3% (13.9–26.7) and 12.1% (7.4–18.0) for sorafenib-experienced pts, respectively. Median OS rates (95% CI) in pts with best overall response (CR/PR) were 39.9 mo (26.0–not estimable [NE]) and not reached (28.1–NE) for sorafenib-sor and sorafenib-experienced pts, respectively. Grade 3–4 treatment-related adverse events (TRAEs) were observed in 33% of sorafenib-sor pts and in 21% of sorafenib-experienced pts. TRAEs leading to discontinuation occurred in 2.5% (grade 3–4) and 6.3% (any grade) of sorafenib-sor pts and 1.9% (grade 1–2) and 3.2% (any grade) of sorafenib-experienced pts. Biomarkers were also evaluated and will be presented.

Conclusion: With 5 years of follow-up, NIVO continues to demonstrate long-term survival and durable responses regardless of prior sor treatment. The safety profile was manageable and consistent with that previously reported.

Disclosure of Interest: Yes : Advisory Board
Oral Communications

Sunday, 5th September 2021

0-22

DATA FROM THE THIRD DOSE COHORT AND EXPANSION PHASE OF A PHASE 1 TRIAL OF ADP-A2AFP SPEAR T-CELLS FOR PATIENTS WITH HEPATOCELLULAR CARCINOMA AND OTHER CANCER TYPES EXPRESSING ALPHA-FETOPROTEIN

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Introduction: ADP-A2AFP specific peptide enhanced affinity receptor (SPEAR) autologous T-cells are genetically engineered to target alpha-fetoprotein (AFP)-expressing or -secreting tumors in the context of HLA-A*02:01. An ongoing Phase 1, first-in-human trial is evaluating the safety and anti-tumor activity of ADP-A2AFP SPEAR T-cells in patients (pts) with either advanced hepatocellular carcinoma (HCC) or other cancer types expressing AFP (NCT03132792). Here we describe data from the third dose cohort and ongoing expansion phase of this trial.

Methods: Eligible pts must be HLA-A*02:01+ or 02:64+ and have AFP expression by immunohistochemistry (IHC) at ≥1+ in >20% HCC cells or serum AFP ≥100 ng/ml, and ≤5% AFP expression by IHC in non-cancerous liver tissue. Leukapheresis is carried out in eligible patients to collect autologous T-cells for processing and manufacturing into ADP-A2AFP. Prior to ADP-A2AFP infusion, pts receive a lymphodepletion regimen including fludarabine 30 mg/m^2 once per day for 4 days and cyclophosphamide 600 mg/m^2 once per day for 3 days. A modified 3+3 design was applied: pts in Group 3 could receive 1.2–6.0x10^9 transduced T-cells, and pts in the expansion phase could receive 1.0–6.0x10^9 transduced cells.

Results: As of Mar 1, 2021, 10 pts (8 M, 2 F; age range between 32 and 75 years) with HCC were treated in Cohort 3 and expansion with a median dose of 5.3x10^9 transduced cells. Treatment was generally well tolerated. The adverse events (AEs) reported in 2 or more pts and considered related to T-cell infusion included leukopenia, neutropenia, lymphopenia, aspartate aminotransferase increased, alanine aminotransferase increased, pyrexia, and thrombocytopenia. Two pts reported a total of 3 treatment-related serious AEs including cyclophine release syndrome (grade 1), infection-related reaction grade 2, and neutropenia. The best overall responses in Cohort 3 per RECIST Version 1.1 included 1 complete response, 4 stable disease, 4 progressive disease, and 1 pt had no scan results at the time of data cut-off. In Cohort 3 with a complete response had 100% reduction in target lesion (TL) sum of lesion diameter (SLD) from Week 16 to Week 32. This was associated with a rapid and sustained decrease in serum AFP levels from 6531 ng/ml at baseline to 12 ng/ml at Week 24. Two pts have shown stable disease up to Week 24, and 3 pts have shown significant decreases (>75%) in serum AFP sustained through Week 4, one of which had a TL SLD decrease of 20% with resolution of one non-TL.

Conclusion: ADP-A2AFP SPEAR T-cells for patients with HCC has been well tolerated. There have been no clear reports of T-cell-related on-target or off-target toxicity, and no protocol-defined dose-limiting toxicities. There is promising early evidence of efficacy, and these data support continued investigation.

Disclosure of Interest: Yes – Consulting

Consultant/Advisor: Adaptimmune, AstraZeneca, Bayer, Bristol Myers Squibb, BTG, Eisai, Eli-Lilly, Incyte, Ipsen, Merck, Ono, Roche, Sirtex Medical Speaker: AstraZeneca, Bayer, Bristol Myers Squibb, Eisai, Eli-Lilly, Incyte, Ipsen, Roche, Sirtex Medical Research funding: Bristol Myers Squibb (Institution), Sirtex Medical (Institution)

0-23

TREATMENT-RELATED TOXICITY AND IMPROVED OUTCOMES WITH IMMUNE CHECKPOINT INHIBITORS IN PATIENTS WITH HEPATOCELLULAR CARCINOMA

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Background: The development of treatment-related adverse events (trAE) correlates favorably with clinical outcomes in multiple studies of patients receiving immune checkpoint inhibitors (ICI), however, this relationship is undefined in patients with hepatocellular carcinoma (HCC). This retrospective multi-center study aimed to examine whether trAEs are predictive of HCC outcomes. Patients and

Disclosure of Interest: We established an international consortium of 10 tertiary-care referral centers located in Europe (n=67), United States (n=248) and Asia (n=42) to test whether the development of clinically significant trAE (i.e. graded >2, trAE2) predicted for improved overall (OS), progression-free survival (PFS), and overall response rates (ORR) following ICI, and subsequently validated this association in a separate cohort of 406 HCC patients receiving ICI therapy as part of international clinical trials submitted to the US Food and Drug Administration (FDA) in support of marketing applications.

Results: In a multi-institutional cohort of 357 patients, 274 (77%) with Barcelona Clinic Liver Cancer (BCLC) stage C HCC mostly treated with ICI monotherapy (n=304, 85%), trAE2 were reported in 146 patients (41%). Development of trAE2 was associated with longer OS (23.3 versus 12.2 months) and PFS (8.6 months versus 3.7 months). After adjusting for viral aetiology, gender, presence of cirrhosis, Child-Pugh class, BCLC stage, and receipt of corticosteroid therapy, trAE2 were confirmed predictors of improved OS (HR 0.59; 95%CI:0.39-0.88) and PFS (HR 0.51; 95%CI: 0.35-0.74). TrAE2 were associated with higher ORR (27% versus 18%) from ICI. The association between trAE2 and patients’ OS (HR 0.49; 95%CI:0.39-0.67) was also observed in the FDA dataset. After a 6-weeks landmark selection, trAE2 were confirmed to be associated with improved PFS (HR 0.59; 95%CI:0.39-0.87); the additional analysis adjusted for tumour response and duration of treatment within the FDA cohort further confirmed the association with longer PFS (HR 0.67; 95%CI:0.47-0.94).

Conclusion: Development of trAE2 may correlate with response and survival in patients with HCC receiving ICI, a clinical setting where the lack of biomarkers still represents an unmet need. Prospective studies aimed at understanding the underlying immunologic foundations of such relationship are warranted to identify predictive biomarkers of toxicity and response.

Disclosure of Interest: Yes – Honoraria

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**Introduction:**

Multibipolar radiofrequency ablation (RFA) increase the ability to ablate hepatocellular carcinoma (HCC) up to 5 cm. The aim of this study is to compare multibipolar RFA to liver resection (LR) in patients with HCC within Milan criteria developed on advanced fibrosis or cirrhosis in order to identify the best candidate for each treatment.

**Methods:** We included retrospectively patients treated either by multibipolar percutaneous RFA or liver resection for a first diagnosis of HCC within Milan criteria developed on advanced fibrosis (F3) or cirrhosis (F4) in 9 centers between 2008 and 2018. Overall survival (OS), recurrence free survival (RFS) and adverse events were compared according to the type of treatments (RFA, laparoscopic or open LR) using a propensity score (double robust method). Patients were censored at the date of transplantation.

**Results:** 1060 patients were included (median age 64 years old, 82.7% of men) with 620 (58.5%) treated by RFA and 440 (41.5%) by LR (laparoscopic n=271; open n=169). HCC was unilobar in 83.8% of the cases, less than 3 cm in 30% of the case and developed on cirrhosis in 89% of the cases. Before treatment, patients treated by RFA were significantly older with more liver failure and portal hypertension and have more multimodular tumors of smaller size compared to patients treated by LR. After adjustment, OS (HR: 1.08; CI95%: 1.01-1.16; p=0.03) and RFS (HR: 1.11; CI95%: 1.02-1.20; p=0.02) were lower in patients treated by LR than RFA (95% survival for RFA and 67% for LR at 5 years) but without statistical difference in term of transplantation free survival (p=0.08). Morbidity (OR: 0.88; CI95%: 0.80-0.93; p=0.001) and mortality (OR: 0.96; CI95%: 0.93-0.99; p=0.03) were lower after RFA. For unique HCC < 3 cm, OS was identical between treatments (p=0.20) as well as RFS (p=0.06) and transplantation free survival (p=0.21). In patients with a unique HCC between 3 and 5 cm, OS was lower after RFA (p=0.01) with also a lower RFS (p=0.02). For multimodal HCC, OS (p=0.58) and RFS (p=0.70) was similar between RFA and LR with less morbidity after RFA (p=0.02), LR was more effective (longer OS, p=0.01, and longer RFS, p=0.01) for HCC localized in the left lobe whereas no significant difference was observed for HCC localized in the right lobe (OS p=0.63 and RFS p=0.39). Laparoscopic LR was associated with a longer OS (p=0.01) and a longer RFS (p=0.01) than RFA. In contrast, OS (p=0.70) and overall recurrence (p=0.001) were identical between RFA and open LR. In all the previous subgroup analysis, RFA was associated with less morbidity than LR. Based on these results, we proposed an algorithm adapted to patients and tumor features as well as the ability to do laparoscopic LR.

**Conclusion:** Multibipolar RFA and LR are two efficient treatments of early HCC developed on advanced fibrosis/cirrhosis. The treatment could be tailored according tumor size, tumor number, presence of portal hypertension/liver failure, tumor localization and the ability to perform laparoscopic resection.

**Disclosure of Interest:** Yes : Research/Education grant

JC Nault: Bayer research grant for INSER 1138

**0-25**

**REGOSAREFINB IN PATIENTS WITH UNRESECTABLE HEPATOCELLULAR CARCINOMA IN ROUTINE CLINICAL PRACTICE: UPDATED INTERIM ANALYSIS OF THE PROSPECTIVE OBSERVATIONAL REFINE TRIAL**

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**Introduction:** Regorafenib significantly improved overall survival (OS) versus placebo in patients with unresectable hepatocellular carcinoma (uHCC) who progressed on prior sorafenib in the phase 3 REFINE trial (Bruix J, 2017). A previous interim analysis of the first 500 patients enrolled in the observational REFINE study of regorafenib in uHCC in a real-world setting showed that REFINE had a more varied patient population compared with RESORCE (Lim HY, 2018). Here, we present an interim analysis of all patients enrolled in REFINE (N=1031).

**Methods:** This prospective, observational, multicenter study enrolled patients with uHCC for whom a decision to treat with regorafenib was made by the treating physician prior to enrollment according to the local health authority approved label. The primary objective was to assess the incidence of treatment-emergent adverse events (TEAEs) and dose modifications due to TEAEs (NCI-CTCAE v4.03). Secondary endpoints were OS, progression-free survival (PFS), time to progression, best overall tumor response, and duration of treatment. Tumor response and progression were investigator assessed according to local practices.

**Results:** Of the 1031 patients enrolled, 1008 were evaluable for analyses. Median age was 66 years (range: 21–94), 83% were male, and 55% were from Asia. At baseline, most patients were Barcelona Clinic Liver Cancer stage C (82%) and Child–Pugh A (62%); 83% had an Eastern Cooperative Oncology Group performance status of 0–1. Overall, 56% (54% in Japan) of patients had received 0±1±2 prior treatments, respectively; 96% had previously received sorafenib and 9% had previously received immunotherapy. At study entry, 59% of patients had metastases and 34% had vascular invasion. The median observation period was 6.8 months (range: <0.1–34.8), and 47% of patients initiated regorafenib at the approved dose (160 mg). Overall, 91% of patients experienced a TEAE and 44% experienced a TEAE leading to dose modification (Table). The most frequently reported TEAEs were hand–foot skin reaction (32%), diarrhea (29%), fatigue (19%), decreased appetite (16%), abdominal pain (11%), hypertension (11%), and asthenia (10%). Median OS was 12.9 months (95% confidence interval [CI] 11.4, 14.6) and median PFS was 3.8 months (95% CI 3.5, 4.1). Median duration of treatment was 3.7 months (95% CI 3.3, 4.1).

**Image:**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Regorafenib (mg)</th>
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<tr>
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<tr>
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<td>448 (144)</td>
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<td>367 (367)</td>
</tr>
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<td>9</td>
<td>310 (310)</td>
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</table>

**Conclusion:** The REFINE study is one of the largest observational studies of recently approved treatments in patients with uHCC. The results of this interim analysis, which included 1031 patients, are consistent with the preliminary data reported in the previous interim analysis and with the phase 3 REFINE trial. These data support the real-world efficacy and safety of regorafenib in a broad population of patients with uHCC.

**Disclosure of Interest:** Yes : Honoria
**O-26** SYSTEMATIC REVIEW AND META-ANALYSIS OF RCT (2002-2020): IS ETIOLOGY RELEVANT FOR IMMUNOTHERAPIES?

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**Background and Aims:** Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality with a rapidly changing landscape of treatments. In the past 20 years, numerous randomized controlled trials (RCT) have aimed at improving outcomes across disease stages. We aimed at analyzing the current evidence and identifying potential factors influencing response to therapies.

**Methods:** We conducted a systematic review of phase III RCTs across disease stages (2002-2020). Meta-analysis was designed to examine the relationship between etiology and outcome after systemic therapies with either tyrosine-kinase inhibitor/antiangiogenic or immune checkpoint inhibitors (ICI) therapy.

**Results:** Out of 10,100 studies identified, 76 were phase III RCT. Among them, a rigorous screening algorithm identified 49 with high-quality including a total of 22,113 patients undergoing adjuvant (n=7) and primary treatment for early (n=2), intermediate (n=7) and advanced stage disease (first-line, n=21; second-line, n=12). Nine of these trials were positive, six treatments have been adopted in guidelines [sorafenib (2 RCTs), lenvatinib, atezolizumab+bevacizumab, regorafenib, cabozantinib and ramucirumab] but two did not (adjuvant CIK cells and sorafenib-hepatic arterial infusion with FOLFOX). Meta-analysis of 8 trials including 3739 patients revealed ICI therapy to be significantly more effective in patients with viral hepatitis when compared with non-viral related HCC whereas no differences related to etiology were observed in patients treated with TKI/anti-VEGF.

**Conclusions:** Among 49 high-quality RCTs conducted in HCC during 2002-2020, nine resulted in positive results. A meta-analysis of systemic therapies suggest that immunotherapies are more effective in viral vs non-viral etiologies.

**Disclosure of Interest:** None Declared
P-01 TEMPORAL AND SPATIAL DYNAMICS OF HEPATIC STELLATE CELL ACTIVATION IN INTRAHEPATIC CHOLANGIOCARCINOMA

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Introduction: Cancer is increasingly being viewed as an ecosystem in which tumor cells coevolve and cooperate with host cells. In liver cancer, extensive biological changes have been reported in parenchymal hepatocytes (HCs) and non-parenchymal cells (NPCs) in the peritumoral microenvironment (pTME). However, it remains controversial how individual pTME populations contribute to liver tumorigenesis. We aim to develop an efficient in vitro model system to dissect the intricate relationship between liver tumor and its surroundings.

Methods: We used three-dimensional spheroid cocultures to study tumor-liver interaction in vitro. We then validated the results in a metastatic orthotopic allograft model established in immunocompetent mice.

Results: In this study, we established three-dimensional spheroid cocultures of primary mouse liver cells. We show that spheroids of HCs and NPCs can be readily generated in micropatterned multwell plates. When cocultured with liver tumor (T) spheroids derived from a PtenCreERT2, Ptenfl/fl, Tpo3fERT2, Rosa26-Green (PPTR) mouse model, NPC spheroids, but not HC spheroids, exhibited a potent suppression activity on tumor cell growth. However, tumor cells in NPC-T culture, while endur- ing growth suppression, showed a significant increase in dissemination compared to that in HC-T or T-alone culture. We then showed that hepatic stellate cells (HSCs) within the NPC population are a key contributor to this NPC-mediated tumor growth suppression and dissemination augmentation. When PPTR tumor cells were orthotypically transplanted into immunocompetent mice, we showed that tumor development induced widespread activation of HSCs in the pTME, and the accumulation of peritumoral HSCs at the tumor border is associated with retarded tumor growth and enhanced tumor dissemination. Lastly, we show that HSC-T interaction induced a significantly increased in CXL10 secretion and neutralizing CXL10 reduced tumor dissemination and relapse in vitro. In vivo validation is currently ongoing.

Image: 

Conclusions: This study reveals paradoxical roles of peritumoral HSCs in liver tumorigenesis beyond being simply pro- or anti-tumorigenic. Tumor development in mouse liver induces activation of peritumoral HSCs that effectively retard tumor growth but simultaneously induce tumor dissemination. Therefore, the therapeutic potential of targeting HSCs in liver cancer needs to be carefully evaluated.

Disclosure of Interest: Non

P-02 INTRA-TUMORAL EPIGENETIC HETEROGENEITY AND ABERRANT MOLECULAR CLOCKS IN HEPATOCELLULAR CARCINOMA

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Introduction: There is evidence of significant intratumoral genetic heterogeneity (ITH) in a subset of human hepatocellular carcinoma (HCC), but limited understanding of the epigenetic drivers of tumor evolution. We aimed at determining the extent and prognostic implications of epigenetic intra- tumoral heterogeneity in HCC, as well as how evolution affects tumor epigenetic age.

Methods: We quantify epigenetic intra-tumoral heterogeneity (ITH) with enhanced-reduced-representation bisulftite sequencing (eRRBS) on 47 multifocal tissue samples from 9 patients with treatment-naïve early stage HCC (~5 samples per patient) treated with surgical resection. We integrated these data with matching RNAseq, targeted DNA sequencing, tumor-infiltrating lymphocyte (TIL) and hepatitis-B virus (HBV) expression (Losic B et al. Nat Commun 2020). We used Horvath’s epigenetic clock (Horvath S. Genome Biol 2013) to estimate sample age and its relation with ITH. Promoter-aggregated site analysis provided coverage overlap at the gene level of 240 of the 353 genes from Horvath’s methylation clock.

Results: Patients were mostly male (70%), with median age 64 and mainly with HBV-related HCC (5/6). Median tumor size was 4.3 cm and 8/9 patients had single nodule HCC. There were 4/9 patients with significant eITH. Patient 4 had the highest ITH with one region having the highest relative number of differentially methylated promoters (n=1993, FDR < 0.05). These findings were confirmed even when using the promoter-specific methylation data. Although increased sampling rate (number of biopsies per tumor) increases power to detect eITH, we noticed that the most densely sampled patient (patient 9, biopsies = 6), had very few eITH. We identified site and promoter level eITH driven by tumor infiltrating lymphocytes, tissue type (normal vs HCC tumor), and HBV viral expression. As expected, the HCC vs normal DNA methylation differences accounted for most de-methylated loci (156,504 sites and 5,458 promoters, FDR < 0.05), followed by TIL-related sites and HBV-driven DNA methylation. Demethylated promoters and differentially expressed genes had low overlap for intra-tumor regional comparisons across 9 patients. In terms of Horvath’s clock, in most patients the predicted methylation ages across regional samples within tumor was higher than the predicted methylation age of the adjacent tissue. We observed a negative correlation between methylation clock age and TIL burden. We applied our methylation-age analysis to 366 single biopsy HCC samples from the TCGA. We validated advanced relative tumor methylation-age in 260/366 (71%) HCC patients. Patients with “old” methylation-aged tumors had significant better survival than those with “young” tumors (HR=0.667, p=0.037).

Conclusions: Our data reveal a novel, unique epigenetic ITH axis in HCC tumors that furthers our understanding of tumor evolution. Epigenetic analyses offer a unique ITH signal that may not be captured by gene expression information alone. Epigenetic tumor age correlates with patient outcomes.

Disclosure of Interest: No

P-03 AUTOIMMUNITY AND CANCER IMMUNOSURVEILLANCE IN THE BILARY TREE

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Introduction: Autoimmune cholangiopathy and primary biliary cholangitis (PBC) are both chronic cholangiopathies, i.e. diseases in which cholangiocytes are primarily damaged. Whereas PSC is a well-established inflammatory condition predisposing to CCA, CCA is close-to-never found in the autoimmune context of PBC. We hypothesized that PBC might favor immunosurveillance against CCA.

Methods: To assess whether or not PBC could protect from CCA onset, we adopted two models of cholangitis in mice and obtained CCA cell lines syngeneic in immunocompetent mice. PBC and control mice were challenged subcutaneously with CCA cells or with irrelevant cancer cells, and tumor growth was monitored. To assess the role of the lymphocyte subsets or cytokines in vivo, we performed their depletion or neutralization by injecting specific antibodies. Immune gene signature of murine tissue samples was analyzed by RNA-Seq and RT-qPCR. Enriched T cell clones are being investigated by single-cell T2DRNAseq. T cell activation was studied in lymphoid tissues by ex vivo restimulation and flow cytometry analysis.

Friday, 3rd September 2021

Top-Rated Poster Basic-Translational

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Top-Rated Poster Basic-Translational

Friday, 3rd September 2021

Results: In preclinical murine models of PSC or PBC challenged with syngeneic CCA, PSC did not affect tumor progression whereas PBC reduced the frequency of CCA development and delayed tumor growth kinetics. These PBC-related effects were accompanied by an increase of type-1 T helper (Th1) and cytotoxic (Tc1) lymphocytes in the liver, spleen, CCA tissues and tumor-draining lymph nodes. The protective effect of PBC was specific of CCA in the sense that it was not observed against other cancers including hepatocellular carcinoma. Depletion of CD4+ and CD8+ T cells as well as neutralisation of the Th1/Tc1 cytokine IFN-γ attenuated the anti-CCA effect of PBC. By contrast, IL-17 neutralisation did not abolish PBC-associated antitumor activity. Furthermore, preliminary data of single-cell TCR/RNA sequencing analyses indicate an enrichment of several clones of CD8+ T lymphocytes in both liver and tumor of PBC hosts.

Conclusion: Altogether, these results evidence a mechanistic overlapping between autoimmune and cancer immunosurveillance in the biliary tree. We believe that this project will not only improve our understanding of CCA immunosurveillance but also contribute to design novel immunotherapeutic as well as immunomodrphic strategies against this malignancy.

Disclosure of Interest: No

P-04 INFLAMED CLASS OF HCC: AN EXPANSION OF THE IMMUNE CLASS BASED UPON NEW MOLECULAR FEATURES

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Background: Oncogenic mechanisms contribute to shape inflamed/non-inflamed microenvironments which associated with immune response or immune evasion/resistance, respectively. We aimed to further refine the immune profiles of hepatocellular carcinoma (HCC) by assessing novel molecular features.

Method: We assessed the presence of immune infiltration, performed multiplex immuno-phenotyping for checkpoint molecules, TCR sequencing, RNA and white-exome sequencing in a new cohort of 240 HCCs balanced according to etiology.

Results: We further characterized the previously described Immune class of HCC (22% of the cohort, which presented higher immune infiltration (SO vs 32%, p = 0.05), higher expression of checkpoint molecules (CTLA-4: 58 vs 29%, p = 0.03; PD-L1: 31 vs 4%, p = 0.04) and more T cell repertoire when compared with the non-inflamed profiles. We identified an Immune-like class (15% of the cohort), that similarly presented high immune infiltration, interferon signaling, cytolytic activity and effector cytokine expression (Figure), but with more CTCN/BC1 mutations (64 vs 29%, p = 0.03) and Wnt-beta catenin activation (45 vs 3%, p < 0.001). In order to group all the immune–related subtypes (including active, exhausted and immune-like) in the newly defined inflamed class, we generated a 20-gene signature able to capture >90% of these tumors. In parallel, we characterized the non-inflamed Intermediate and Excluded classes. The Intermediate class was enriched in TP53 mutations (69 vs 29%, p = 0.03), higher broad chromosomal aberrations and deletions in subcytobands harboring immune-related genes (i.e. 4q21.1, 11XCL9, 11XCL10, 11XCL11). The Excluded class defined by Wnt-beta catenin activation was enriched in CTCN/BC1 mutations (93 vs restrict 27%, p < 0.001). These Excluded-CTCN/BC1 mutations induced very high activation of Wnt signaling and were significantly distinct from the immune CTCN/BC1 mutations that induced weak activation of this cascade.

Conclusions: In addition, tumors with inflamed-CTCN/BC1 mutations were associated to overexpression/demethylation of type I antigen presentation genes.

Disclosure of Interest: Yes: Honoraria
P-06 NEW THERAPEUTIC TARGETS IN CISPLATIN-RESISTANT HEPATOBLASTOMA

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Introduction: Hepatoblastoma (HB) is the most frequent liver tumor and is usually treated with cisplatin-based chemotherapy and subsequent tumor resection. Although current treatment lead to 80% survival at 5 years, some HB will develop resistance to chemotherapy. The molecular mechanisms underlying cisplatin resistance need to be addressed as well as the search for alternative therapeutic strategies.

Methods: We performed an integrated genomic analysis of 104 hepatoblastoma samples from 65 patients as well as 8 HB and 1 pediatric hepatocellular carcinoma (HCC) cell lines through whole-genome or whole-exome sequencing and RNAseq analysis. In addition, we screened the 9 cell lines to identify new therapeutic targets and the efficiency of one compound was compared to HB standard treatments in HepG2 xenografts.

Results: Mutational signature analysis revealed that HB cells can accumulate massive loads of cisplatin-induced mutations with a specific single base substitution signature SB5. In primary tumors, SB53 mutations were subclonal and only accumulated in specific sectors that were transcriptionally silenced. We performed an integrated genomic analysis of 104 hepatoblastoma samples from 65 patients as well as 8 HB and 1 pediatric hepatocellular carcinoma (HCC) cell lines through whole-genome or whole-exome sequencing and RNAseq analysis. In addition, we screened the 9 cell lines to identify new therapeutic targets and the efficiency of one compound was compared to HB standard treatments in HepG2 xenografts.

Conclusions: These data provide new insights into cisplatin resistance mechanisms in Hepatoblastoma and suggest alternative therapeutic strategies. Analysis of the evolution of mutational processes indicated that the deleterious SB53 mutations observed tumor resistant to cisplatin originated from progenitor cells that have proliferated under treatment. Drug screening in HB cell lines identified promising targets for cisplatin-resistant progenitor cells, validated in mouse xenograft experiments.

Disclosure of Interest: No

P-09 DEEP SEQUENCING OF HCC ENDOTHELIUM REVEALS AN ACTIVE ROLE IN IMMUNOSUPPRESSION AND HIGHLIGHTS THE ENDO NUCLEOTIDASE CD73 AS A POTENTIAL THERAPEUTIC TARGET.

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Introduction: Overcoming the immunosuppressive microenvironment in HCC is a major challenge. Better understanding of the cell specific contribution is required to help boost current immunotherapy. Endothelial cells are the gatekeeper for immune cell recruitment and we undertook RNA-seq analysis of immune-inflamed murine and human HCC endothelium to help define its contribution to the tumour microenvironment of HCC.

Methods: Endothelial cells were isolated from liver tissue using a validated method of Ulex-lectin binding. RNAseq was performed on endothelium from primary liver tumours and matched non-tumour endothelial cells. To explore the upregulation of CD73 from the sequencing data we undertook immunohistochemistry for CD73 in a cohort of human HCC, and the pattern of CD73 expression was compared to clinical outcomes. Immunofluorescence for CD73 was performed on isolated liver sinusoidal endothelial cells (LSEC).

Results: Analysis of 5 paired tumour and distal non-tumour samples taken from patients who underwent spleen-preserving surgery was performed. 45 genes were identified as being significantly differentially expressed between the tumour and non-tumour endothelium (adjusted p-value <0.05). 41 genes were upregulated in the tumour endothelium and 4 downregulated. Pathway analysis revealed 83 pathways that were down regulated (adjusted p-value <0.05) and these were further grouped into 7 key clusters. These clusters were all related to immune related pathways: leukocyte mediated immunity; leukocyte mediated toxicity; leukocyte proliferation; cell killing; exocytosis; cytokine. We focused on CD73 which has a well-established immunosuppressive function. Immunohistochemistry for CD73 on 100 HCC sections confirmed that the protein is present on vascular endothelium and in HCC tumours. The pattern of expression was different in compared to matched non-tumour control, with a per- membranous staining pattern and variable sinusoidal staining. We also confirmed cell membrane and intracellular expression of CD73 in cultured primary human LSEC using dual colour immunofluorescence.

Conclusion: Transcriptomic analysis of human HCC endothelium demonstrates a strong immunosuppressive signature. Interestingly the majority of differentially expressed genes were upregulated, suggesting that the endothelium plays an active role in immunosuppression and directly targeting...
these pathways could boost the efficacy of other immunotherapies. Validating these findings, CD73 expression was increased in cancer specimens. Furthermore, CD73 is expressed in isolated liver endothelium and, given its functional role in immunosuppression, endothelial CD73 may contribute to the immune HCC microenvironment and could be a promising target for immunotherapy.

**Disclosure of Interest:** No

### P-27 INCREASED HEPATIC PREGNANE X RECEPTOR PROTEIN EXPRESSION NEGATIVELY CORRELATES WITH TIGHT JUNCTION PROTEINS AND IS A TARGET FOR THERAPY IN PATIENTS WITH HEPATOCELLULAR CARCINOMA

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**Background & Aim:** The nuclear pregnane X receptor (PXR) is a master regulator of detoxification and plays a key role in xenobiotic metabolism through CYP3A4, thus protecting the body from toxic insults. In hepatocellular carcinoma (HCC), sorafenib resistance leads to failure of systemic therapy; thus leading to poor prognosis in HCC patients. Furthermore, deranged tight junction proteins in HCC leads to tumour dissemination and progression of HCC. This study aimed to identify the expression of PXR and tight junction proteins and their association with HCC pathogenesis.

**Methods:** Following institutional ethical committee approval, a total of 89 individuals (40 HCC cases and 49 normal healthy controls) were enrolled in the study. Baseline characteristics, biochemical parameters and alpha-fetoprotein (AFP) were analysed by Beckman Coulter autoanalyzer. Estimation of serum PXR and IL-1B were done by ELISA. Hepatic PXR and tight junction proteins expressions were analysed by western blotting and immunohistochemistry.

**Results:** We found significantly increased tumour marker AFP and coagulation profile tests PT/INR in HCC cases compared to healthy controls. Moreover, significantly increased serum PXR in HCC patients compared to normal healthy controls (4.27±0.53 Vs 1.14±0.08; p<0.0001), consistent with increased expression of PXR in HCC liver tissue. HCC patients showed a deranged hepatobiliary profile with increased inflammation as shown by a significant increase of IL-1 beta levels compared to healthy controls (83.94±31.49 Vs 16.71±5.34; p<0.0001). Furthermore, significantly decreased tight junction proteins ZO-1 and occludin in serum and liver tissue of HCC patients were observed compared to normal healthy controls.

**Conclusion:** Thus, our novel findings indicate that increased inflammation is associated with the upregulation of PXR and downregulation of tight junction proteins in HCC. Targeting PXR can be a useful biomarker approach to facilitate HCC treatment.

**Disclosure of Interest:** No

### P-53 A HUMANIZED CLAUDIN-1-SPECIFIC MONOCLONAL ANTIBODY FOR TREATMENT OF HEPATOCELLULAR CARCINOMA

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**Introduction:** Hepatocellular carcinoma (HCC) is the fastest rising and third leading cause of cancer death. While new therapeutic modalities have been recently approved, treatment response and survival in patients remain poor. Claudin-1 (CLDN1) is a cell membrane protein mediating cell-cell adhesion, fate and differentiation. Functionality of CLDN1 in solid tumors including HCC has been demonstrated by gain- and loss-of-function studies, yet its impact as a therapeutic target is unexplored.

**Methods:** Using humanized monoclonal antibodies (mAbs) targeting specifically the extracellular loop of human non-junctional CLDN1 and a large series of patient-derived cell-based and animal model systems we aimed to investigate the role of CLDN1 as a therapeutic target for treatment of HCC.

**Results:** Here we show that humanized monoclonal anti-CLDN1 mAbs robustly and significantly inhibit growth, migration and invasion of tumor cells in cell line-based models of HCC and patient-derived HCC spheroids. Moreover, the robust effect on tumor growth was confirmed in vivo in a large series of cell line derived xenograft (CDX) and patient-derived xenograft (PDX) mouse models. Functional studies in patient-derived and cell line-based tumor spheroids revealed that the mAbs perturbed the 3D tumor architecture. Furthermore, CLDN1 mAbs markedly and significantly suppressed epithelial-mesenchymal transition (EMT) and matrix metalloproteinase synthesis in tumor cells. Good treatment response in PDX models correlated with expression of genes that are associated with a fibrotic tumor environment, whereas presence of the angiogenic factor VEGFB predicted low treatment efficacy. Treatment with humanized anti-CLDN1 mAbs is considered to be safe, as administration in non-human primates and mouse models did not reveal any major toxicity even when high doses largely exceeding the therapeutic need were repeatedly applied.

**Conclusion:** These results provide robust pre-clinical proof-of-concept for humanized CLDN1-specific mAbs for treatment of HCC and pave the way for clinical development of CLDN1-targeting therapies using monoclonal antibodies. The unique and different mechanism of action provides opportunities to break the plateau of limited response and survival offered by currently approved therapies.

**Disclosure of Interest:** No
P-20 CHARACTERISTICS AND SURVIVAL OF HEPATOCELLULAR CARCINOMA IN NON-CIRRHOTIC LIVER: A SPANISH MULTICENTRE STUDY

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Introduction: Non-cirrhotic hepatocellular carcinoma (HCC) is an uncommon disease and limited data exist on its features, evolution and survival. An observational multicenter cohort study was designed to prospectively collect HCC patients without cirrhosis.

Methods: The sample included 106 non-cirrhotic patients (17 centers, May 2018-December 2020), with HCC diagnosed by histology. Exclusion of liver cirrhosis was performed by histological criteria in 89.6%, transient elastography in 4.7% and level 2 Mittal criteria in 5.7%. Statistical analysis: variables were described as percentages and median. Survival and relapse curves were estimated using the Kaplan-Meier method; the differences in the survival and relapse rates between the groups were compared using the log-rank test.

Results: Median age was 69.7 years. Eighty-six percent were male, 28.3% had other cancers, 57.5% had arterial hypertension and 20.8% had not underlying liver disease. Seventy-nine percent of patients without liver treatment had been treated with antiviral therapy. Fibrosis stage (91 patients) was stage 0-1 in 51.9%, stage 2 in 17%, stage 3 in 17% and unknown in 14.1%. Median transient elastography (53 cases) was 6.8 kPa. AFP was 0.46 and FIB-4 was 2.07. aMAP score had 19.2% in low-risk group, PAGE-B score and modified PAGE-B score in Caucasian patients with HBV hepatitis had no low-risk group. In 20.7% the diagnosis was made by follow-up ultrasonography, 53.8% was casual and 25.5% by symptoms. A single nodule was detected in 74.5%. The median size of main nodule was 54 (10-190) mm. The differentiation degree was: 32.1% well-differentiated, 52.8% moderately differentiated, 9.5% poorly differentiated, 0.9% undifferentiated and 4.7% other histologic variants. Median alpha-fetoprotein (AFP) was 5 (0.9–250000) ng/ml (33% >20 ng/ml). Typical hallmark for HCC at least in one of the dynamic imaging explorations was detected in 61.3%. Only 8.5% had vascular invasion and 2.8% had extraparenchymatous spread. Ninety-seven percent were 0-1 ECOG. Median follow-up was 17.4 months with 56.6% in remission and 19.6% of deaths (61.9% due to liver-related causes). The global 1- and 2-year survival rate was 89% and 74% respectively, and in patients treated with surgery was 96% and 86% respectively. AFP (>20 ng/ml / >20 ng/ml) was a predictor of survival and relapse (figure 1), which in relapse was independent of BCLC.

Conclusion: Most of the patients (79.2%) had underlying liver disease, mainly viral and NASH, with mild fibrosis in 68.9%. PAGE-B predicted all HCC in Caucasian HBV and aMAP 80.8% of the total. 3. Predominant stage was A (71.7%), although in 79.3% the diagnosis was causal or by symptoms. 4. The 2-year survival rate was 74%. AFP was a predictor of relapse independent of BCLC.

Disclosure of Interest: None Declared

P-21 PROGNOSIS OF PATIENTS WITH OTHER PRIMARY TUMORS ASSOCIATED TO HEPATOCELLULAR CARCINOMA

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Introduction: The clinical characteristics of patients with hepatocellular carcinoma (HCC) and other primary neoplasms (PN) remain poorly understood. It has been reported that the diagnosis of PN other than HCC does not affect survival in these patients. Our aim was to analyse the clinical characteristics and prognosis of patients with HCC and other PN.

Methods: This is a single center, retrospective cohort study with all HCC patients diagnosed between Jun 1st 2015 and Feb 28th 2021. We analyzed the baseline characteristics and evolutive events. Survival was censored at March 15th 2021, date of death or liver transplantation.

Results: Seven hundred and seventeen patients were consecutively registered, 86% were men, median age 67 years, most frequent etiology alcohol (40.6%) followed by HCV (26.4%). According to the BCLC stage at debut, the distribution of patients was BCLC 0 6.7%, A 44.6%, B 19.4%, C 21.5% and D 6.7%. Vascular invasion was present in 22% and extraparenchymal disease in 9%. Of the total of 271 patients with HCC, 111 had another PN and 18 had 2 or more PN. In most cases (55%) PN was cured at the moment of HCC diagnosis (group A), in 39% of cases HCC was diagnosed at the same time than PN or during the evolution of the other PN (group B). Finally in 6% of cases PN appeared during HCC follow-up (group C). The most frequent PN was lung cancer 18%, followed by colorectal cancer 16% and bladder cancer 15%. The prevalence of PN was similar in both sexes (p = 0.296). The presence of PN was associated with alcohol consumption (84.5% vs 15.5% (p = 0.000), smoking (74.7% vs 25.3% (p = 0.079), and absence of cirrhosis (15.5% vs 5.8% (p = 0.001). In contrast, viral etiology was associated with a lower risk of PN (18.6% vs 81.4% (p = 0.001). There were no differences in the proportion of HCC patients diagnosed within surveillance programs (p = 0.914), initial BCLC staging distribution (p = 0.082), nor survival (p = 0.865) between HCC patients with / without PN. In addition, there were no differences in survival within the PN patients among the three groups considered, 24 months in group A, 17 months in group B and 13 months in group C (p=0.914).

Conclusion: In our center, 18% of patients with HCC present other primary neoplasms. Those HCC patients without cirrhosis and those with alcohol related cirrhosis are at higher risk of presenting another primary neoplasms. Alcohol consumption and smoking are the associated risk factors. However, having another PN did not contribute significantly to poorer survival in HCC patients.

Disclosure of Interest: None Declared
P-29 DUAL FILTRATION SYSTEM FOR ISOLATION AND SINGLE CELL RNA SEQUENCING OF CIRCULATING TUMOR CELLS AND CLUSTERS IN HEPATOCELLULAR CARCINOMA: A PILOT STUDY

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Introduction: Hepatocellular carcinoma (HCC) is a major cause of cancer death worldwide. As tumor biopsy is not standard of care for diagnosis of median Child-Pugh score 8. Ethiology of cirrhosis was hepatitis C in 4 patients, non-alcoholic fatty liver disease in 2, alcohol in 1, and cryptogenic in 1. Barcelona Clinic Liver Cancer stage was C in 7/8 patients. We performed single cell RNA sequencing of 44 CT cells and 34 clusters from these patients. Uniform manifold approximation and projection demonstrated two distinct groups of CT cells/clusters (Fig. 1A). Group 1 had significantly higher expression than Group 2 of markers associated with epithelial phenotypes (CDH1, EPCAM, ASGR2, KRT8), epithelial-mesenchymal transition (CD44, VIM), and stemness (PROM1, POU5F1). There were no significant differences in candidate gene expression between CT cells vs. clusters (p > 0.05 for all). There was evidence of red blood cell contamination, but little evidence of white blood cell contamination in either batch. Five patients had >1 cell/ml white blood in Group 1 while the remainder had ≤ 1 cell/ml. Median overall survival was 39 days in patients with >1 Group1 cells/ml and 384 days in those with ≤ 1 cell/ml. Identification and sequencing of circulating tumor (CT) cells and clusters may allow for noninvasive molecular characterization of HCC.

Methods: We collected up to 10 ml of whole blood from patients with advanced-stage HCC and selected individual CT cells and clusters with a micropipette. Reverse transcription, polymerase chain reaction, and library preparation were performed using a SmartSeq2 protocol. Single cell RNA sequencing was performed on an Illumina MiSeq V3 platform, with 51-base paired-end sequencing and 150 cycles. Transcriptome alignment was conducted with STAR, imputation of missing data using Deepimpute, and downstream analysis by Seurat. Expression is reported as log(transcripts per million + 1).

Results: Of eight patients recruited, six had identifiable CT cells or clusters. Median age was 64 years, 7/8 were male, and 7/8 had cirrhosis with median Child-Pugh score 8. Ethiology of cirrhosis was hepatitis C in 4 patients, non-alcoholic fatty liver disease in 2, alcohol in 1, and cryptogenic in 1. Barcelona Clinic Liver Cancer stage was C in 7/8 patients. We performed single cell RNA sequencing of 44 CT cells and 34 clusters from these patients. Uniform manifold approximation and projection demonstrated two distinct groups of CT cells/clusters (Fig. 1A). Group 1 had significantly higher expression than Group 2 of markers associated with epithelial phenotypes (CDH1, EPCAM, ASGR2, KRT8), epithelial-mesenchymal transition (CD44, VIM), and stemness (PROM1, POU5F1, NTOR1, STAT3) (p < 0.05 for all) (Fig. 1B). This was despite no difference in expression of cell cycle markers (p > 0.05 for CCNB1 and CCND1). There were no significant differences in candidate gene expression between CT cells vs. clusters (p > 0.05 for all). There was evidence of red blood cell contamination, but little evidence of white blood cell contamination in either batch. Five patients had >1 cell/ml white blood in Group 1 while the remainder had ≤ 1 cell/ml. Median overall survival was 39 days in patients with >1 Group1 cells/ml and 384 days in those with ≤ 1 cells/ml (p = 0.04 by log rank test).

Image:

A. Uniform manifold approximation and projection plot

B. Expression of candidate genes

Conclusions: A dual filtration system allows for isolation and sequencing of CT cells and clusters in HCC and may identify cells expressing candidate genes known to be involved in cancer biology. Presence of CT cells/clusters expressing candidate genes is associated with poorer prognosis in advanced stage HCC.

Disclosure of Interest: No

P-34 SORAFENIB IN EXTENDED PATIENT POPULATIONS IN REAL-WORLD CLINICAL PRACTICE: BASELINE CHARACTERISTICS FROM OPTIMIS AND GIDEON

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Introduction: Sorafenib, lenvatinib, and atezolizumab + bevacizumab are first-line systemic treatments for advanced HCC. With multiple treatment options available, clinical characteristics of patients will inform selection of first-line systemic therapy. However, in a real-world clinical setting, certain patient populations may not be suitable for treatment with atezolizumab + bevacizumab. Patients with ECOG PS >1, Child–Pugh score B/C, moderate or severe ascites, a history of or active autoimmune disease or immune deficiency, or at high risk of bleeding events were excluded from the IMbrave150 trial (NCT03434376). Here, we evaluate eligibility criteria from IMbrave150 with baseline characteristics of patients with unselectable HCC enrolled in two international, prospective, non-interventional studies of sorafenib.

Methods: GIDEON (NCT009812175) was conducted between 2009 and 2012 and enrolled patients at the time a decision to treat with sorafenib was made by the patient’s physician. OPTIMIS (NCT01933945) enrolled patients between 2013 and 2017 who had their first TACE at study entry and subsequently received sorafenib (or not) after becoming TACE ineligible. Patients who received systemic anti-cancer therapy prior to first TACE were excluded. Baseline patient demographic and disease characteristics were collected prior to initiation of sorafenib treatment either at study start (GIDEON) or at last observation before start of sorafenib (OPTIMIS), including patient subgroups that were excluded from IMbrave150.

Results: For this analysis, 3202 patients from GIDEON and 373 from OPTIMIS of 1676 patients enrolled were eligible; most patients were male (82.2% and 81.5%, respectively) and the median age was 62 years in both studies. In GIDEON and OPTIMIS, respectively, 11.6% and 6.5% of patients had an ECOG PS >2, 8.8% and 22.3% were Child–Pugh class B, 2.3% and 1.9% were Child–Pugh class C, 5.7% and 3.2% had moderate or severe ascites at baseline, and 3.6% and 2.7% had a history of autoimmune disease or immune deficiency. Additionally, GIDEON and OPTIMIS enrolled patients at increased risk of bleeding, such as those with concomitant aspirin use (5.8% and 4.3%), or a history of bleeding (14.7% and 15.5%). Median OS for this pooled population of GIDEON and OPTIMIS was 10.8 months (95% CI 10.2, 11.4). In a pooled safety analysis of both studies, the most common treatment-emergent adverse events (TEAE) were diarrhea (29.2%), hand–foot skin reaction (24.2%), fatigue (16.2%), and decreased appetite (14.3%). Incidence of TEAEs and drug-related TEAEs were comparable between patients with Child–Pugh B liver function and the overall population.

Conclusions: Sorafenib has been evaluated in broad patient populations in large, real-world, non-interventional studies such as GIDEON and OPTIMIS. Despite differing timelines and study design, baseline characteristics were similar between patients enrolled in these studies. Median OS for this extended patient population, including patient subgroups who were excluded from IMbrave150, was similar to the phase 3 SHARP study (10.7 months). In addition, no new safety signals with sorafenib were identified. These data demonstrate the importance of patient characteristics to inform selection of first-line systemic therapy for HCC.

Disclosure of Interest: Yes - Research/Education grant

P-36 A PILOT STUDY OF THE COMBINATION OF IMMUNE CHECKPOINT INHIBITION WITH ABLATION IN SUBJECTS WITH HEPATOCELLULAR CARCINOMA; AN EVALUATION OF TRANS-ARTERIAL CHEMOEMBOLIZATION (TACE) AND RADIOFREQUENCY ABLATION (RFA)

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Introduction: Immune checkpoint inhibition has demonstrated compelling activity in hepatocellular carcinoma (HCC). Augmentation of the immune response by ablative procedures to improve efficacy of single immune checkpoint inhibitor has been previously demonstrated in HCC. However, the impact of ablation modality (TACE vs RFA) in combination with dual immune checkpoint inhibitors is

Disclosure of Interest: Yes - Research/Education grant

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with tremelimumab (anti-CTLA4) and durvalumab (anti-PD1) has not been previously described. The primary objective of this study was to establish the efficacy via 6-month progression-free survival (PFS) of combining tremelimumab and durvalumab in patients with advanced HCC either alone or with ablation. Secondary objectives were safety and feasibility of this combination treatment. An exploratory objective was overall survival (OS).

**Methods:** Eligible patients had advanced or unresectable HCC, were not candidates for curative-intent treatment and had either progressed on, refused, or been intolerant to sorafenib. Disease had to be technically amenable to TACE or RFA with at least two measurable lesions. Adequate organ function, Child-Pugh score of A/B if liver cirrhosis was present, Barcelona Clinic Liver Cancer (BCLC) stage B or C, and an ECOG performance status of 0 or 1 were required. Patients were treated with tremelimumab and durvalumab with or without tumor ablation (TACE or RFA). Tremelimumab and durvalumab were administered intravenously every 28 days for four cycles followed by durvalumab every 28 days until disease progression. Ablation was performed on day 36. Patients were imaged every 8 weeks and response was defined per RECIST v1.1 criteria. Interim PFS and OS will be presented and PFS and OS of TACE compared to RFA are evaluated here.

**Results:** A total of 30 patients with a median age of 64 (range 19-81) enrolled. 9 received immunotherapy alone and 21 were assigned to receive TACE or RFA. Seven patients underwent TACE and 7 underwent TACE. Thirty percent of patients had received prior sorafenib and locally advanced disease was present in fifty-seven percent of patients. Seventy-three percent of patients were BCLC stage C. 53% percent had hepatic C and 17% had hepatitis B. Eighty-six percent of patients who received BCLC stage C; 71% of patients that underwent TACE were BCLC stage C. Median OS and PFS in the group assigned to undergo ablation intention to treat in combination with immunotherapy vs immunotherapy alone was 13.6 m vs 19.2 m and 4.9 m vs 4.4 m in 44 respectively. In patients that underwent TACE compared to those that underwent RFA, the median PFS was 7.4 m vs 4.3 m, and median OS was 20.5 m vs 16.5 m. The most common grade 3-4 adverse events were hypothyroidism (43%), increased AST (43%), increased amylase (33%) and anemia (26%).

**Conclusion:** Combined checkpoint inhibition in combination with tumor ablation is a safe and effective treatment strategy for patients with advanced HCC, and the addition of ablative therapies may improve patient outcomes. Improvement in overall survival was noted in patients who underwent TACE over RFA. Results illustrate amplification of the immune response when ablation is combined with immunotherapy and may represent a therapeutic approach for patients with a contraindication to vascular endothelial growth factor (VEGF) inhibitor. Further studies are warranted to identify patient populations most likely to respond to these interventions.

**Disclosure of Interest:** No

**P-38 IMPACT OF METABOLIC SYNDROME AND NON-ALCOHOLIC FATTY LIVER DISEASE IN OUTCOMES AND TOLERANCE AFTER PERCUTANEOUS MULTIBIPOLAR RADIOFREQUENCY ABLATION FOR EARLY HEPATOCELLULAR CARCINOMA**

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**Introduction:** Long-term outcomes after percutaneous radiofrequency ablation (RFA) for hepatocellular carcinoma (HCC) in patients with non-alcoholic fatty liver disease (NAFLD) have been poorly studied. We aim to describe the outcomes after multipolar RFA in these patients compared to other etiologies and the prognostic impact of metabolic syndrome.

**Methods:** Patients who underwent multipolar RFA as first treatment for HCC within Milan criteria in 44 centers in France (2008-2018) were enrolled in a retrospective study. Patients with pure NAFLD-HCC were compared to those with alcoholic liver disease (ALD), hepatitis B (HBV) and hepatitis C virus (HCV). Oncologic outcomes after percutaneous RFA were assessed using Kaplan-Meier method and compared using log-rank test. The association of metabolic syndrome (MS) and NAFLD with adverse events was assessed using uni/multivariate analysis with the Cox model.

**Results:** Five hundred twenty patients were enrolled including 82% of male with a median age of 66 years. A total of 494 patients (85%) had cirrhosis, 421 patients (81%) had a unique nodule with a median size of 25 mm. Among the whole cohort, 390 patients (75%) had at least one of the component of MS including obesity in 155 patients (30%). Sixty-two patients (12.6%) had non-AFLD-HCC, 225 (45.5%) had ALD-HCC, 36 (7.3%) had HBV-HCC and 171 (34.6%) had HCV-HCC. Patients with pure NAFLD-HCC were significantly older (median age 72.6 years, p<0.0001), with higher BMI (median BMI 30.3 kg/m2, p=0.0001), more frequent diabetes mellitus (72.6%, p<0.0001), dyslipidemia (53.2%, p<0.0001), arterial hypertension (75.8%, p<0.0001) and ischemic heart disease (17.7%, p=0.017). In the whole series, median overall survival (OS) was 66.5 months with a 1-, 3- and 5-years OS of 94%, 74% and 56%, respectively. Patients with pure NAFLD-HCC achieved a median OS of 78 months (1-, 3- and 5-years OS of 90%, 71% and 59%, respectively). There were no differences in morbidity, tumor recurrence and OS in patients with pure NAFLD-HCC versus other etiologies. There was no prognostic impact of metabolic components on treatment-related adverse events. the number of sessions to achieve complete ablation and oncologic outcomes.

**Conclusion:** Percutaneous multipolar RFA is an efficient treatment resulting in a prolonged overall survival without increased morbidity in HCC patients with NAFLD or metabolic syndrome.

**Disclosure of Interest:** No

**P-41 EARLY IMMUNOLOGIC EXPOSURE IS NOT DETRIMENTAL TO RESPONSE TO IMMUNE CHECKPOINT INHIBITOR THERAPY FOR HEPATOCELLULAR CARCINOMA: EVIDENCE FROM AN OBSERVATIONAL STUDY.**

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**Introduction:** The impact of early immunologic exposure and its role on immune checkpoint inhibitor therapy for hepatocellular carcinoma (HCC) has not been thoroughly studied. We aim to describe the outcomes after multipolar RFA in these patients compared to other etiologies and the prognostic impact of metabolic syndrome.

**Methods:** Patients who underwent multipolar RFA as first treatment for HCC within Milan criteria in 44 centers in France (2008-2018) were enrolled in a retrospective study. Patients with pure NAFLD-HCC were compared to those with alcoholic liver disease (ALD), hepatitis B (HBV) and hepatitis C virus (HCV). Oncologic outcomes after percutaneous RFA were assessed using Kaplan-Meier method and compared using log-rank test. The association of metabolic syndrome (MS) and NAFLD with adverse events was assessed using uni/multivariate analysis with the Cox model.

**Results:** Five hundred twenty patients were enrolled including 82% of male with a median age of 66 years. A total of 494 patients (85%) had cirrhosis, 421 patients (81%) had a unique nodule with a median size of 25 mm. Among the whole cohort, 390 patients (75%) had at least one of the component of MS including obesity in 155 patients (30%). Sixty-two patients (12.6%) had non-AFLD-HCC, 225 (45.5%) had ALD-HCC, 36 (7.3%) had HBV-HCC and 171 (34.6%) had HCV-HCC. Patients with pure NAFLD-HCC were significantly older (median age 72.6 years, p<0.0001), with higher BMI (median BMI 30.3 kg/m2, p=0.0001), more frequent diabetes mellitus (72.6%, p<0.0001), dyslipidemia (53.2%, p<0.0001), arterial hypertension (75.8%, p<0.0001) and ischemic heart disease (17.7%, p=0.017). In the whole series, median overall survival (OS) was 66.5 months with a 1-, 3- and 5-years OS of 94%, 74% and 56%, respectively. Patients with pure NAFLD-HCC achieved a median OS of 78 months (1-, 3- and 5-years OS of 90%, 71% and 59%, respectively). There were no differences in morbidity, tumor recurrence and OS in patients with pure NAFLD-HCC versus other etiologies. There was no prognostic impact of metabolic components on treatment-related adverse events. the number of sessions to achieve complete ablation and oncologic outcomes.

**Conclusion:** Percutaneous multipolar RFA is an efficient treatment resulting in a prolonged overall survival without increased morbidity in HCC patients with NAFLD or metabolic syndrome.

**Disclosure of Interest:** No
ILCA 2020 VIRTUAL CONFERENCE - BOOK OF ABSTRACTS

Methods:
Efficacy of ICI is described in patients (pt) from 12 centres (250 USA, 91 Asia, 109 Europe), with median overall (OS), progression-free survival (PFS) and best response (RECIST 1.1) compared between pt with and without ATB exposure in the early immunotherapy period (EIOP) of 30 days before and after ICI initiation.

Results:
Most of our 450 pt were cirrhotic (232, 73.3%) due to viral hepatitis (271, 60.4%) with Barcelona Clinic Stage C (205, 72.4%), Child-Pugh class C (211, 33.5%) and AFP <400 IU/ml (206, 92.9%). OS was 15.4 months (95% CI 12.6-16.8) and PFS 4.4 months (95% CI 3.7-5.3). Most ICI was anti-PD-1 monotherapy (373, 84.9%) and given as 1st (198, 44.1%) or beyond 1st line (215, 55.9%). Best response to ICI was complete response in 26 pt (6%), partial response in 50 (11.7%), stable disease in 174 (40.7%) and progressive disease in 70 (15.6%). Hospital ATB was given to 170 pt (37.9%), prior to or early after (30 d) ICI initiation (EIOP) ATB use was independent of CI stage (p=0.76), ECOCOS performance status (p=0.50) and BCLC stage (p=0.63). mPFS in the EIOP+ group was significantly longer than the EIOP- group (6.1 vs 3.7 months, p=0.001). Observators were persisted at stratified by CP class (p=0.42) and ICI type (p=0.49). Overall objective response and disease control rates were similar between EIOP groups (ORR: 20.2% vs 16.1%, p=0.28; DCR: 63.1% vs 55.4%, p=0.11).

Conclusions: ATB in the 30 d before or after ICI initiation in HCC is does not impact clinical response to ICI. This is contrary to findings in other solid tumors. Evaluation of the immune-microbiologic determinants of response to ICI in HCC is a key research question.

Disclosure of Interest: Yes : Honoraria

P-42
A MULTICENTRE PHASE II CLINICAL TRIAL ON SERIAL COMBINATION OF YTTRIUM 90-RESIN MICROSFERES (Y90-RE) AND CHEMOTHERAPY FOR LOCALLY ADVANCED INTRA-HEPATIC CHOLANGIOCARCINOMA (ICC)
(p=0.007 and 0.02, respectively), as well as in the number of patients who stopped answering the AUDIT test. A trend for increased physical activity also between 2 and 3 years of follow-up was registered (p=0.08 and 0.09, respectively). The adherence to the Nurse-led LC Screening Program at six months, 1, 2, 3, and 4 years was 98%, 97%, 92%, 90%, and 80%, respectively.

**Conclusion:** The lifestyle changes habits in SVR patients after DAA such as a significant increase in alcohol consumption and increase in waist-hip ratio and BMI well-known risk factors for liver disease progression. Additionally, a very high adherence to a nurse-led liver cancer screening program could be a useful strategy to modulate lifestyle and reduce risk factors in these patients at risk of LC development.

**Disclosure of Interest:** Yes - Research/Education grant

Received congress inscriptions from Eisai
Molecular Pathogenesis, Cell Biology and Translational Research

**P-10 ACTIVATING MUCOSAL-ASSOCIATED IN Variant T CELLS (MAITs) IN vivo AS A NOVEL TARGET FOR lIVER CANCER IMMUNOTHERAPY**

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**Introduction:** Introduction: Mucosal-associated invariant T (MAIT) cells can represent the most abundant T cell subtype in the human liver. Due to the ample expression of IFN-γ and cytolytic effector molecules, MAIT cells could potentially play a pivotal role in anti-tumor immune responses. Recent studies have found marked MAIT cell-mediated anti-tumor function in vivo when activated by a combination of 5-OP-RU and Toll-like receptor 9 agonist CpG. MAIT-directed 5-OP-RU + CpG showed pronounced and consistent anti-tumor activity against primary liver cancer and liver metastasis and prolonged mouse survival. Importantly, such tumor inhibition was absent in MAIT-deficient MR1-/- mice. Additional pharmacological depletion studies showed that NK cells mediate the MAIT-induced tumor suppression.

**Results:** Using high-dimensional flow cytometry and spatially resolved analysis of multiplexed immunofluorescence microscopy images, we found impaired infiltration of MAIT cells into human HCC tumors compared to unaffected liver tissue. Thus, we sought out to experimentally increase MAIT cell infiltration into liver cancers using several murine models. Co-administration of 5-OP-RU and CpG induced a strong systemic in vivo expansion and activation of MAIT cells with high expression of activation makers like CD69, pronounced effector memory phenotype and liver tumor tissue from patients with NASH±HCC when compared to liver tissue from healthy subjects or subjects with pNaKtide when compared to non-treated animals (dose-related, p<0.01). Furthermore, Cav-1/Survivin proteins expression was higher in liver tumor tissue from rodents with NASH/HCC when compared to animals treated with pNaKtide (dose-related, p<0.01). In contrast, SMAC protein expression was lower in liver from rodents with NASH/HCC compared to liver tissue from healthy subjects (dose-related, p<0.01). Moreover, in humans the same pattern of significantly higher Cav-1 & Survivin expressions, and significantly lower SMAC protein expression, was observed in liver tumor tissue from patients with NASH/HCC when compared to healthy subjects (p<0.05). In vitro signal circuit exploration guided by RNA-seq revealed that Src- phosphorylation at the c1-NKA activates a PI3K/Akt dependent pathway, inhibition of this PI3K pathway promoted similar cellular responses observed in pNaKtide treatment and c1-knockdown cell lines have increased survivin expression.

**Conclusions:** Increasing evidence suggests that MAIT cells are important players in liver cancer immunology. MAITs undergo a phenotypic switch and massively expand in vivo upon 5-OP-RU + CpG treatment. These licensed and educated innate-like T cells can then mediate potent anti-tumor responses in murine models of liver cancer and represent an attractive novel target for cancer immunotherapy. Here, we provide a framework for how TCR-dependent pathogenic role of MAITs in HCC can be overcome using stimulatory agents.

**Disclosure of Interest:** No

**P-11 THE TUMOR SUPPRESSOR ROLE OF THE CD1-NA/K-ATPASE/SRC-P/ P3K SIGNALOME IN NASH RELATED HEPATOCELLULAR CARCINOMA: A TRANSLATIONAL STUDY.**


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**Methods:** Expression of Cav-1/SMAC/Survivin proteins was performed by confocal-microscopy on immunostained human HCC cell lines (HeP2 & SM24S), livers from a NASH-HCC rodent model, and livers from human patients. Liver tissue from human subjects included normal liver (n=10), NASH (n=20), NASH-HCC (n=11) and liver metastases (n=12). AUC, from pixels related to specific protein staining, was recorded for each animal/subject (n=8 images) to be evaluated among groups were accepted at p<0.05 using ANOVA/t-test.

**Results:** Blockage of Src-p at the c1-NKA promoted apoptosis in HCC cell lines in a dose-response manner; pNaKtide at IC50 drove the downregulation and upregulation of Survivin and SMAC expressions, respectively (p<0.05), while concomitantly decreased H3K9 histone acetylation in cell lines (p<0.01). Although digoxin exposure enhanced wild type cell lines’ proliferation, pNaKtide at IC50 showed pronounced and consistent anti-tumor activity against primary liver cancer and liver metastasis and prolonged mouse survival. Importantly, such tumor inhibition was absent in MAIT-deficient MR1-/- mice. CRSIPR/Cas9-mediated gene editing was used for targeted knockout of MR1 in tumor cells. A series of pharmacological depletion experiments was conducted to identify additional effector immune cells.

**Discussion of Interest:** No

**P-12 ENHANCER OF ZESTE HOMOLOG 2 MODULATES CANCER-ASSOCIATED AND METABOLIC PATHWAYS IN HEPATOCELLULAR CARCINOMA**

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**Introduction:** Treatment options for hepatocellular carcinoma (HCC) remain unsatisfactory despite recent improvements. Epignals that act on enzymes necessary for the maintenance and establishment of epigenetic modifications are currently being evaluated as cancer therapy.

**Image:**
The Erzh2 histone methyltransferase and catalytic subunit of Polycomb Repressive Complex 2 (PRC2) is hyperactive in both hepatocellular carcinoma (HCC) and fibrolamellar carcinoma (FLC). HCC is the most frequent pediatric liver tumor and 70-90% of HB harbor β-Catenin (CTNNB1) alteration. Apart from β-Catenin hit, only few recurrent driver alterations have been described in HB such as NF2 (5-10%) and TERT promoter mutations (2-5%). While rare genetic syndromes such as Familial Adenomatous Polyposis (APC alteration), Beckwith-Wiedemann syndrome (11p15.5 locus alteration) or Simpson-Golabi-Behmel (FG3C alteration) can predispose to hepatoblastoma, the etiology of HB is poorly understood.

Methods: Integrated genomic analysis of 126 pediatric liver tumors including whole-exome, whole-genome, RNAseq, RBB and MS-MLPA methylprobes analysis were performed. RNAseq of FG3C in situ hybridization was assessed in FFPE tumor and non-tumor slides.

Results: The 11p15.5 locus is a parental imprinted locus including IG2 oncogene, as well as H19 and CDKN1C tumor suppressor. This locus was the second most frequently altered locus in HB and HCC (84% and 89%, respectively) after CTNNB1 alteration. 11p15.5 locus alterations occurred mostly through copy-neutral loss of heterozygosity (cn-LOH, 51-56%) leading to a biallelic expression of IG2. Adding to LOH, we found IC1 hypermethylation (22% of HB and 33% of HCC, IC2 hypermethylation (5% of HB) and somatic mutations of CDKN1C in 4-6 HB patients. Importantly, in 10% of hepatoblastoma patients we identified a mosaic premalignant clonal expansion of cells with cn-LOH at 11p15.5 in non-tumor liver tissue. These patients were young (mean=8.4 months, P=0.045) and without clinical Beckwith-Wiedemann syndrome (BWS). Cell fraction carrying 11p15.5 locus alteration ranged from 6% to 58%. In non-tumoral liver samples of patients harboring a mosaic 11p15.5 alteration. Accordingly, RNAseq in situ hybridization revealed a massive overexpression of IG2 in both the tumor and adjacent non-tumor tissue.

Conclusion: These results give insight in HB natural history and identified that hepatoblastoma arise in ~10% of cases from a premalignant clonal expansions of “normal” hepatocytes with 11p15.5-LOH on both sides. These hepatoblastomas overexpress IG2 and can lead to HB formation after oncogenic CTNNB1 mutation.

Disclosure of Interest: No

P-14 MOLECULAR CHARACTERIZATION OF HCC IN MONGOLIA DELINATES UNIQUE GENOMIC FEATURES

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Background and Aims: Mongolia has the world’s highest incidence of hepatocellular carcinoma (HCC), with ~100 cases/105 inhabitants/year. Here, we aimed at performing a molecular characterization of H2C in Mongolia and compare it with Western HCC.

Methods: 192 paired fresh-frozen HCC/non-tumoral samples from patients undergoing resection were collected at the National Cancer Center in Ulaanbaatar, Mongolia. Whole exome sequencing (WES) and RNAseq were performed in 151 and 106 samples, respectively. WES and RNAseq and clinical data from an in-house Western cohort were used for comparison (n=187). Mutation calling and mutational signature analysis were evaluated. HB viral genotyping was assessed by direct sequencing.

Results: Mongolian patients, compared to Western, were younger (61 vs 66 years old), with lower male predominance (54% vs 80%), less advanced hepatic fibrosis (F3-F4, 38% vs 78%), higher rate of HBV/HCV co-infection (84% vs 7% of HB infected), and predominance of HBV genotype D (90% vs 43% of HB infected) at p < 0.001. Mongolian HCC presented unique molecular features including: a) Higher number of protein-coding mutations (121 vs 70 mut/tumor, p < 0.001), as

Introduction: Pediatric liver cancers include different tumor types: Hepatoblastoma (HB), Hepatocellular carcinoma (HCC) and fibrolamellar carcinoma (FLC). Hepatoblastoma is the most frequent pediatric liver tumor and 70-90% of HB harbor β-Catenin (CTNNB1) alteration. Apart from β-Catenin hit, only few recurrent driver alterations have been described in HB such as NF2, TERT promoter mutations (2-5%). While rare genetic syndromes such as Familial Adenomatous Polyposis (APC alteration), Beckwith-Wiedemann syndrome (11p15.5 locus alteration) or Simpson-Golabi-Behmel (FG3C alteration) can predispose to hepatoblastoma, the etiology of HB is poorly understood.

Methods: Integrated genomic analysis of 126 pediatric liver tumors including whole-exome, whole-genome, RNAseq, RBB and MS-MLPA methylprobes analysis were performed. RNAseq of FG3C in situ hybridization was assessed in FFPE tumor and non-tumor slides.

Results: The 11p15.5 locus is a parental imprinted locus including IG2 oncogene, as well as H19 and CDKN1C tumor suppressor. This locus was the second most frequently altered locus in HB and HCC (84% and 89%, respectively) after CTNNB1 alteration. 11p15.5 locus alterations occurred mostly through copy-neutral loss of heterozygosity (cn-LOH, 51-56%) leading to a biallelic expression of IG2. Adding to LOH, we found IC1 hypermethylation (22% of HB and 33% of HCC, IC2 hypermethylation (5%) of HB) and somatic mutations of CDKN1C in 4-6 HB patients. Importantly, in 10% of hepatoblastoma patients we identified a mosaic premalignant clonal expansion of cells with cn-LOH at 11p15.5 locus in non-tumor liver tissue. These patients were young (mean=8.4 months, P=0.045) and without clinical Beckwith-Wiedemann syndrome (BWS). Cell fraction carrying 11p15.5 locus alteration ranged from 6% to 58%. In non-tumoral liver samples of patients harboring a mosaic 11p15.5 alteration. Accordingly, RNAseq in situ hybridization revealed a massive overexpression of IG2 in both the tumor and adjacent non-tumor tissue.

Conclusion: These results give insight in HB natural history and identified that hepatoblastoma arise in ~10% of cases from a premalignant clonal expansions of “normal” hepatocytes with 11p15.5-LOH on both sides. These hepatoblastomas overexpress IG2 and can lead to HB formation after oncogenic CTNNB1 mutation.

Disclosure of Interest: No
P-15 EXOGENOUS ANTIOXIDANTS, N-ACETYLICYSTEINE AND GLUTATHIONE, ENHANCE CANCER INITIATION AND GROWTH IN HEPATOCELLULAR CARCINOMA

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Introduction: The controversy over the intake of antioxidants supplements in cancer patients persists for decades without efficient guideline. In tumor cells, increased metabolic activities are accompanied with increased antioxidants production to adapt to oxidative stress and maintain the malignancy. Here we investigated the effects of exogenous antioxidants on tumor initiation and growth, using hepatoacellular carcinoma (HCC) as a model.

Methods: We performed functional assays to investigate the effects of exogenous N-acetylcysteine (NAC) and glutathione (GSH) on tumor initiation and growth in multiple mouse models including diethylnitrosamine (DEN)-induced and CRISPR-Cas9-mediated Trp53KO/C-MycOE HCC models, and subcutaneous and orthotopic xenograft tumor models, as well as in HCC cell lines. We also evaluated the effect of antioxidants on Sorafenib treatment. RNA-sequencing was performed to identify the pathways affected by antioxidants. Immunobots targeting NAC and GSH metabolism were used to investigate the effects of the antioxidants.

Results: Exogenous NAC and GSH promoted colony formation, cell proliferation, sphere formation, and migratory and invasive abilities in human HCC cell lines. Both NAC and GSH enhanced tumor initiation in DEN-induced and CRISPR-Cas9 mediated TRP53KO/C-MYOCOE HCC models, and subcutaneous and orthotopic xenograft tumor models, as well as in HCC cell lines. We also evaluated the effect of antioxidants on Sorafenib treatment. RNA-sequencing was performed to identify the pathways affected by antioxidants. Immunobots targeting NAC and GSH metabolism were used to investigate the effects of the antioxidants.

Conclusions: HCC in Mongolia presents specific molecular traits characterized by a high mutational burden, a newly described mutational signature and two novel molecular classes. Further studies exploring environmental factors associated with these alterations are required.

Disclosure of Interest: No

P-16 DUAL MECHANISMS MEDIATED BY SPECIFIC TRANSCRIPTION FACTORS AND RALGAPA2 ACTIVATES RALA SIGNALING TO SUPPORT HCC DEVELOPMENT

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Introduction: Directly downstream of Ras, the Ras-like Ral small GTPases, RalA and RalB, function as proto-oncogenes and are capable of inducing malignant transformation in cancers. Cycling between the active GTP-bound and inactive GDP-bound forms, Ral can be activated by oncogenic Ras or through inactivation of its negative regulator, the Ral GTPase activating protein (RalGAP) complex. Although the functional loss of the RalGAP complex has been reported in several cancers, the involvement of RalGAP complex dysregulation in HCC is unclear. Besides, the mechanisms for Ral upregulation and relevance of RalGAP2-mediated Ral activation remain unclassified in cancers including HCC. In this study, we aimed to examine the clinical significance, functional implications, and underlying mechanisms of RalGAP2 dysregulation and Ral aberrant upregulation in promoting HCC progression.

Methods: By RNA-sequencing and qPCR, the mRNA expression levels of RalA and RalGAPA2 were detected in HCC samples followed by clinicopathological correlation analysis. RalA and RalGAPA2 knockdown/knockout and overexpression HCC cells were generated for functional characterization. The RalA activity and other associated signaling changes were assessed by Ral-specific activity assay and Western blot. Luciferase reporter assay and ChIP assay were performed to identify transcription factors that drive RalA expression. The specific Ral inhibitor, RBC8, when applied alone or in combination with sorafenib, was examined.

Results: Examination of our in-house and TCGA RNA-seq data revealed a specific and significant upregulation of RalA but not RalB in HCC. RalA showed a progressive stepwise increase along with tumor stages and this elevation was significantly correlated with more aggressive tumor behavior and poorer patient overall survival. Functionally, knockdown of RalA suppressed cell proliferation and migration. Also, RalA ablation attenuated cancer stemness properties as evidenced by the reduced tumor sphere formation ability and tumor initiating capacity. RalA knockdown was significantly associated with increased tumorsphere formation and increased tumor growth in vitro. Conversely, the overexpression of wildtype RalA or its dominant active form promoted the aforementioned phenotypic changes. RalA upregulation could be ascribed to the increased copy number of the RalA gene as well as its increased transcription by SP1 and ETS2, two transcription factors that could physically bind to the RalA promoter. On the other hand, increased RalA activity was achieved by RalGAPA2 downregulation, and this downregulation was also significantly associated with more aggressive tumor behavior and poorer prognosis in human HCCs. Functionally, increased RalA activity was observed in RalGAPA2 knockdown and knockout HCC models. Importantly, RalGAPA2 depletion promoted intrathoracic and extrathoracic metastasis in vivo. Ral inhibition by RBC8, a specific Ral inhibitor, was able to suppress colony formation, cell proliferation, and migration in a dose-dependent manner in multiple HCC cell lines. Interestingly, RalA activity was found to be inversely correlated with the sorafenib sensitivity in HCC cells. The combined treatment of RBC8 and sorafenib exerted a more prominent growth suppressive effect in HCC cells underlying enhanced inhibition of mTOR signaling.

Conclusions: Our results provide new biological insights on the dysregulation of RalA signaling through dual mechanisms to support the pro-oncogenic functions in HCC development. Targeting RalA might serve as a potential alternative therapeutic approach, alone or in combination with the currently available therapy.

Disclosure of Interest: No
Background: Modulation of adaptive immunity is postulated to underlie the efficacy of TACE. We evaluated the influence of TACE on T-cell function by assessing the phenotypic characteristics of lymphocyte populations from archival samples of patients who surgery with (T+) or without (T-) prior TACE treatment.

Methods: We profiled intra-tumoral (IT), peri-tumoral (PT) and non-tumoral background tissue (NT) to evaluate regulatory CD4+FoxP3+ (T-reg) and immune-exhausted CD8+PD1+ T-cells across T+ (n=68) and T- (n=63). We performed targeted transcriptomics and T-cell receptor sequencing in a restricted subset of samples (n=24) evaluated in relationship with the expression of actionable drivers of anti-cancer immunity including PD-L1, IDO-1, CTLA-4, Lag-3, Tim-3 and CD163.

Results: We analyzed samples from 119 patients resected (n=25, 21%) or transplanted (n=94, 79%) for Child Pugh A (65, 55%) and T stage II (n=73, 61%). HCC. T+ samples displayed lower IT CD4+ FoxP3+ (p=0.008), CD8+ (p=0.002) and CD8+PD1+ (p=0.001) and lower NT CD4+PD1+ (p=0.03) correlated with improved recurrence-free survival, with IT CD4+FoxP3+ density predicting for RFS benefit in multivariable analyses. In a subset of samples (12 T+, 12 T-), transcriptomic analysis revealed differential up-regulation of genes reflective of a pro-inflammatory response in T+. Compared to T-, T+ samples were significantly enriched for IF2 expression (p=0.01), an interferon-regulated transcription factor linked to immune-responsiveness in other malignancies. Expression PD-L1; IDO-1, CTLA-4, Lag-3, Tim-3 and CD163 was not different between T+ versus T- cell clonality by ImmunoSeq assay was not different in association with TACE pre-treatment.

Conclusions: Pre-treatment with TACE is associated by lower intra-tumoral density of immune-exhausted effector and regulatory T-cells, with significant up-regulation of pro-inflammatory pathways. This highlights the pleiotropic effects of TACE in modulating the tumour microenvironment and strengthens the rationale for developing immunotherapy alongside TACE to improve outcomes of HCC patients.

Disclosure of Interest: No

P-18 PORTAL VEIN THROMBOSIS IN HCC PATIENTS INFECTED WITH COVID-19

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Introduction: COVID-19 has become a global pandemic affecting people around the world and causing mortality in 0.5%–3% of infected individuals. Recent studies have shown that patients with SARS-CoV-2 (COVID-19) infection may have a hypercoagulable state which explains the increased incidence of thrombotic events in these patients without any known risk factors. It is attributed to the inflammatory state, endothelial dysfunction, platelet activation and blood stasis. The risk appears highest among critically ill inpatients. The prevalence of venous thromboembolism in COVID-19 patients has been reported to reach 80-35%, while autopsy rates raise it to nearly 60%. The most common thrombotic complication is pulmonary embolism. HCC is the 5th common cancer and the 3rd leading cause of cancer death worldwide. HCC is the first related cancer in Egypt in total population but the second cancer incidence in females after breast cancer. Portal vein thrombosis (PVT) is variably reported to occur in 0.6%-26% of patients with cirrhosis and in about 20%-44% of patients with hepatocellular carcinoma.

Patients and Methods: 100 HCC patients infected with COVID-19 presented to our multidisciplinary HCC unit in NUJ (National Liver Institute) from September 2020 till the end of March 2021 (group I). 100 HCC patients without COVID-19 infection in the same time interval their data were collected (group II). Clinical examination, radiological examination, performance status and laboratory evaluation of all patients in both groups were performed. COVID-19 was diagnosed by CD-RADS classification of CT chest examination and COVID-19 antibodies or polymerase chain reaction (PCR) for COVID-19 virus. All HCC patients in group I and group II diagnosed according to EASL and AASLD updated HCC guidelines for HCC management using abdominal ultrasonography, triphasic computed tomography (CT scan), dynamic magnetic resonance imaging (MRI) and liver biopsy if needed. Portal vein thrombosis was diagnosed in triphasic CT or dynamic MR and confirmed by color doppler ultrasonography.

Results: We analysed 200 HCC patients, 100 patients infected with COVID-19 virus (group I) and 100 patients not exposed to COVID-19 virus. PVT in HCC patients after COVID-19 infection was seen in a significantly higher rates than in HCC patients not infected with COVID-19. 63 patients (63%) in group I (patients 41% in group I p=0.05). Most PVT in group I (87% of patients) occurred within 45 days from COVID-19 infection diagnosis. Serum glutamic oxaloacetic transaminase and glutamyl transpeptidase transaminase were elevated significantly in group I than in group II (p<0.05). There was no significant difference as regards age, sex, AFP, INR, platelets number, Child-Pugh score and number of HCC lesions between patients exposed to COVID-19 infection and those not exposed to COVID-19 (p>0.05).

Conclusion: COVID-19 infection not only affects lung and the respiratory system causing chest infection and pulmonary thrombosis but also affects liver tissue causing elevation of the liver enzymes and increases the risk of PVT significantly in COVID-19 infected HCC patients compared to HCC patients not exposed to COVID-19 infection. Thromboprophylaxis using antiplatelets and anticoagulants in HCC patients infected with COVID-19 need to be studied thoroughly.

Disclosure of Interest: No

P-19 IDENTIFICATION OF IGF2 AS GENOMIC DRIVER AND ACTIONABLE THERAPEUTIC TARGET IN HEPATOMBLASTOMA

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Introduction: Hepatoblastoma (Hb) is the most common primary liver cancer in children with a median age of diagnosis of 1–2 years. The current therapeutic strategy, based on surgery and multi-agent chemotherapy, results in 5-year overall survival rates of 40%–50% and 70%–80% in stage I and II Hb, respectively. Although new targeted therapies are under investigation, no successful strategy has been established to target the disease. Here, we performed a comprehensive analysis aimed to identify driver mutations and actionable targets in Hb. To this end, we performed deep clinical exome and transcriptome sequencing in two consecutive Hb patients diagnosed at our institution, one with late-relapse disease and one with chemotherapy-resistant disease. In silico and clinical validation with additional sequenced patients and relevant public resources was performed. Finally, we performed preclinical experiments in a mouse model to test the efficacy of targeted therapies. Results: A comprehensive genomic and transcriptomic analysis of two consecutive Hb patients, one with late-relapse disease and one with chemotherapy-resistant disease, identified a novel in-frame frameshift IGF2 mutation (c.450_451delTA) that co-occurred with a frameshift in PTPRD (c.1555_1559del5). These alterations were confirmed by Sanger sequencing and functional analyses in a mouse xenograft model. In silico analysis predicted that IGF2 mutation results in a C-terminal truncation and gain of transcriptional activity. In vivo, IGF2 expression was increased in Hb tissues compared to normal liver, and knockdown of IGF2 in metastatic cells led to decreased cell proliferation and drug resistance in vitro. Furthermore, in vivo, the IGF2 knockdown significantly decreased tumor burden compared to controls in a mouse xenograft model. Conclusions: This study demonstrates the utility of comprehensive genomics and transcriptomics in identifying driver mutations and actionable targets in Hb. This approach could be applied to other childhood cancers to generate precision medicine strategies.
Background and Aims: Hepatoblastoma (HB), the most frequent pediatric liver cancer, has limited therapeutic options for patients whose tumors are refractory to standard perioperative platinum-based regimens, commonly cisplatin. Here, we aimed to identify actionable drivers in human HB and assess their response to molecular therapies in experimental models.

Method: Tumor and paired non-tumor (NT) tissues from 32 HB patients were analyzed at the transcriptomic, genomic and epigenomic level using RNAseq, SNP and methylation arrays. The main targetable driver in HB was identified by gene co-expression network analysis (GCN) and its overexpression was confirmed by qRT-PCR. The antitumor potential of inhibiting actionable drivers was assessed in vitro (cell lines and PDX-derived organoid model) and in vivo.

Results: RNAseq and GCN analysis identified IGFl as the top targetable deregulated pathway (hsa05206), and IGFl was overexpressed in 71% of samples (fold change > 4 in NT). Suppressor CTNNB1 was the most prevalent non-actionable mutation (~70%). IGFl-high tumors were enriched in proliferative and proliferative gene signatures and CTNNB1 mutations, while IGFl-low tumors were enriched in inflammatory signaling and TGF-B overexpression. IGFl-high tumors correlated with shorter recurrence-free survival after resection (median 34 vs not reached for IGFl-low; p = 0.02). Overall, we identified a mechanism of IGFl overexpression in 86% of IGFl-high tumors: a) overexpression of the IGFl fetal isoform due to promoter hypermethylation (50%), b) loss of heterozygosity (LOH) in the Inp15 chromosomal region containing IGFl (57%) and c) overexpression of MiR483 (55%), an enhancer of IGFl transcription. Xentuzumab, a monoclonal antibody against IGFl, significantly reduced proliferation and clonogenic capacity in IGFl-high HB cell lines, whereas in combination with cisplatin in an IGFl-high organoid model was able to increase cisplatin efficacy by 25-fold and promote apoptosis. In vivo, xentuzumab + cisplatin reduced viable tumor volume and extended time to sacrifice (1500 mm³) compared to cisplatin alone (p = 0.04).

Conclusion: IGFl overexpression associated with promoter hypermethylation, LOH and MiR483 overexpression is the main actionable alteration in human HB. In experimental models, IGFl inhibition with xentuzumab + cisplatin led to a remarkable antitumoral effect, thus providing the rationale for exploring this combination in early trials in patients with IGFl-high HB.

Disclosure of Interest: No

P-54 EMERGING ROLE OF CIRCULATING MiR-23B-3P AND TISSUE MiR-193A-3P AS POTENTIAL INNOVATIVE BIOMARKERS FOR HUMAN HEPATOCELLULAR CARCINOMA

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Introduction: Human hepatocellular carcinoma (HCC) is the most common liver cancer representing the third cause of cancer related death. The identification of molecular biomarkers for the early diagnosis of HCC and responsiveness to treatment still remains a challenge. MicroRNAs (miRs) are small non-coding RNAs involved in several physiological and pathological conditions. Because of their dysregulation during carcinogenesis and their release and stability in body fluids, miRs have emerged as valuable candidates with diagnostic potential in cancer, including HCC. miRNAs can be regulated by DNA methylation and the alteration of this epigenetic mark may also occur in cancer. In this study, we evaluated the potential clinical significance of circulating miR-23B-3p and miR-193A-3p as potential biomarkers for human HCC.

Methods: The expression levels of miR-193A-3p and miR-23B-3p were examined by stem-loop qPCR in primary HCC’s and their matched peritumoral (PT) counterparts in a cohort of HCC patients (n=67, n=59, respectively). The methylation-specific PCR was used to evaluate the DNA methylation as the possible epigenetic mechanism regulating the expression of these miRs.

Results: The expression levels of miR-193A-3p and miR-23B-3p resulted undetectable in the same plasma samples.

Conclusion: Our data provide evidences on the promising clinical relevance of tissue miR-193A-3p and circulating miR-23B-3p in the molecular characterization of HCC diagnosis and prognosis. Furthermore, our results outline new insights in the epigenetic regulation of these miRNAs.

Disclosure of Interest: No

P-22 GEOGRAPHIC, LINGUISTIC, AND CULTURAL FACTORS ARE ASSOCIATED WITH CLINICAL PRESENTATION, RECEIPT OF TREATMENT, AND SURVIVAL OF PATIENTS WITH HEPATOCELLULAR CARCINOMA

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Introduction: Seleniity, early detection and curative treatment of hepatocellular carcinoma (HCC) are the mainstays of interventions to improve survival for patients. Migrants face several challenges of receiving care including immigrant status, remoteness of residence and language barriers, which may be related to lower rates of screening and treatment for HCC. We reported the impact of country of origin, remoteness of residence, speaking non-English language on age at presentation, tumor stage and survival in migrants from Africa, Middle East, and Asian regions.

Methods: We conducted a retrospective cohort study of 1651 HCC patients (147 migrants) from January 1, 2007, to December 31, 2016. We used Wilcoxon rank-sum test to compare the median age at the time of diagnosis and chi-square test to test the association between demographic and socio-economic variables and receipt of curative treatment for HCC. Accelerated failure time regression was used to identify independent predictors of time to death and time ratios were reported.

Results: The median survival time after HCC diagnosis was 9.0 months (interquartile range 2.0–24.5). Metropolitan residence (P=0.02), non-English language (P=0.001), foreign country of origin (P<0.001), and hepatitis B virus etiology (P=0.001) were significantly associated with receiving surgical resection for HCC treatment. Patient survival was strongly predicted by underdiagnosed tumour at presentation time ratio (TR)=0.30, 95% credible interval (CI) 0.23–0.38, age >70 years (TR=0.42, 95%CI 0.34–0.53), living in remote areas (TR=0.67, 95%CI 0.65–0.82), and presence of ≥1 comorbidity (TR=0.69 95%CI 0.54–0.90). All the other covariates adjusted, including country of birth (TR=0.76, 95%CI 0.49–1.08) did not predict survival time.

Conclusion: Older age, comorbidities, advanced tumor stage at presentation, and poor survival suggest the significance of screening for viral hepatitis, conducting HCC surveillance in at-risk patients such as those with cirrhosis, and timely curative treatment to improving survival in these patients.

Disclosure of Interest: No

P-23 WHEN LIVER ELASTOMETRY ALLOWS A BETTER SELECTION OF CANDIDATES FOR HCC RESECTION.

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Introduction: Liver resection (LR) is a curative treatment for hepatocellular carcinoma (HCC) in selected patients. LR is an alternative to liver transplantation (LT), particularly in the current context of organ shortage, but the rate of recurrence remains high (almost 2/3 of patients recur at 5 years). Our objective was to propose a predictive score for recurrence, based on exclusively prognostic factors, in order to improve patient’s selection for LR.

Methods: Retrospective monocentric study including patients who underwent LR for HCC between January 2015 and December 2018 were included. Data were collected from our prospectively maintained Liver Resection database. We included patients initially transplantable according to the MELD score. Patients with a MELD score ≥22 were included. Follow-up included liver tests, AFP, and computed tomography or magnetic resonance imaging every 3–4 months. Recurrence
Introduction: Liver cancer is considered as one of the most widely spread neoplasms. Hepatocellular carcinoma (HCC) contains the vast majority of liver cancer cases. Various risk factors such as chronic liver damage, hepatitis B, hepatitis C, alcohol abuse, obesity and metabolic syndrome are highly related to this malignancy. Recently, immune check-point inhibition and combination with VEGF antagonism has shown promising anti-tumor efficacy but only one third of the patients can benefit. New prediction markers are urgently needed for patient allocation in clinical trials. Genetic heterogeneity of HCC has been depicted in a number of works but despite the effort of cataloguing HCC, mutational landscape does not support complete prognostic significance. Cancer cells are able to adapt their metabolism and survive in a hostile environment with less nutrient and oxygen concentration. Nevertheless, the metabolic feature of HCC cells is not fully understood. Therefore, our work is focused on studying the metabolic transcriptome in diverse HCC cohorts aiming at defining a clinically actionable metabolic classification of HCC. Furthermore, we aim at investigating prognostic significant of metabolic signatures in HCC.

Methods: Using The Cancer Genome Atlas (TCGA), the transcriptome of 371 primary liver cancers (HCC collection) were downloaded through the UCSC Xena browser. Liver metabolism pathways were selected using the Molecular signature database (MsigDB). We generated a pipeline of gene set adaptation to HCC transcriptome by means of gene-gene correlation matrix simplification and gene set scoring by Gene Set Variation Analysis (GSVA). Score matrix was created using Z score and a non-parametric test. We defined the pathways as consistent when there had size higher than 2 genes whose median correlation was higher than 0.2. In parallel, metabolic networks were built using Graph package. Node centrality was calculated for each gene, and top genes were determined for each metabolic function. TCGA patients were then divided according to the Z score and grouped based on the metabolic signature using unsupervised hierarchical clustering. Clustered heatmaps were performed using heatmap package. The package ggcourplot was used to infer correlated metabolic functions in HCC. TCGA metabolata source for each patient. Using the packages Survival and Summriner log Rank P test was performed. P value less than 0.05 was considered as significant. All analyses were performed using R studio.

Results: From a total of 59 metabolic gene sets, only 27 passed the pipeline threshold. Four large groups of metabolic functions could be found in TCGA-LIHC samples. Several hepatocyte intermediate metabolism pathways such as aminoacid, lipid, bile acid and drug-xenobiotic processing presented high pathway-pathway correlation. A high consistency was found for protein turnover-related pathways. Specific functions such as cholesterol-related or Endoplasmic-Reticulum associated degradation defined a separated cluster. Using the intermediate metabolism scores, the tumors could be divided into highly, medium and low metabolic, while using protein-turnover scores, tumors were divided into high or low protein turnover. In survival analyses, the intermediate metabolism showed a powerful prognostic significance with a dose-response pattern, with highly metabolic tumors having the longest overall survival. Protein turnover signature did not show an impact on patient survival.

Image: [Image]

Conclusions: Metabolism of HCC inferred by transcriptomic analysis has clinical prognostic significance

Disclosure of Interest: No

References:
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Introduction: Hepatocellular carcinoma (HCC) is the most frequent primary liver tumor and its heterogeneity makes it relevant to have useful prognostic factors for patient management. Recently, a prognostic index based on inflammatory parameters (ILIS) has been described, predictive of survival from the diagnosis of HCC.

Methods: The objective of the study is to validate the ILIS index in our cohort of patients, calculated from five baseline parameters: alpha-fetoprotein (AFP), alkaline phosphatase (AF), bilirubin (Bi), neutrophils (PMN), and albumin (ALB). The formula for calculating the described index is: 
\[ -0.057 \times \text{ALB (g/L)} + 0.978 \times \log (\text{Bi, } \mu \text{mol/L}) + 1.341 \times \log (\text{AF, IU/L}) + 0.086 \times \log (\text{AFP, } \mu \text{g/L}) + 0.301 \times \log (\text{PMN, } 10^3 \text{ cells/L}) + 0.695 \times \log \left(1 - 0.25^2 \times \text{ALB} \times \text{PMN} \right) \]

Results: Among 688 patients with HCC, we excluded 104 patients due to lack of any baseline parameter to calculate the ILIS. The ends of follow-up criteria have been established as the date of the last contact, end of follow-up, date of transplantation or death. The median follow-up was 11 months (95% CI: 0.00 - 25.75), 86% were men, median age 67 years, the most frequent etiology was alcohol (40.6%) followed by HCV (26.4%). The distribution of patients at debut was BCLC 0, 6.2%, A, 47.9%, B, 19.3%, C, 22.3% and D, 4.3%. 22% presented vascular invasion and 6% extrahepatic disease. Using the cut-off points described in the ILIS, 411 patients belonged to group 1, 139 to group 2 and 14 to group 3, with a median survival of 34, 10 and 3 months, respectively (p < 0.05). Within the BCLC A / A stages, the ILIS index divide patients into three groups with different survival rates. The difference in survival between different stages of BCLC as well as different stages of HKLC staging system. Performance and prognostic value of HKLC and BCLC staging systems were nearly the same (AUC = 0.667, 0.619 respectively). Out of 459 patients at BCLC stages B and C, 123 patients were already treated beyond BCLC treatment options but matching the HKLC recommendations. Their median survival time was 14.6 months which was not inferior to the 336 patients treated according to BCLC classification with median survival time of 12.3 months (p-value 0.001). Figure 1

Conclusion: In our study, the HKLC classification had a slightly better prognostic performance compared to the BCLC staging system and might provide a survival benefit to those expanding the treatment options for BCLC stages B and C.

Disclosure of Interest: No
The SARS-CoV-2 infection in cirrhotic patients has been associated with liver function deterioration and a 30-day COVID-19-associated mortality rate of 25% (Laxova et al. JHEP, 2021). However, there are no data about mortality in a large cohort of liver cancer patients with SARS-CoV-2 infection. The aim of this project was to evaluate the 30-day mortality of liver cancer patients with SARS-CoV-2 infection.

Method: CERO-19 is a retrospective, observational, multicenter and international project, evaluating clinical outcomes of SARS-CoV-2 in liver cancer. Variables related to type of liver cancer; BCLC or TMN 8th stage at SARS-CoV-2 diagnosis and others related to patient outcome were registered. The 30-day SARS-CoV-2-related mortality rates and hazard ratios (HR) were estimated considering non-related SARS-CoV-2 deaths as competing events. Hazard ratios were calculated considering non-related SARS-CoV-2 deaths as competing risks.

Results: This analysis evaluated 242 patients infected with SARS-CoV-2 from 38 centers (Europe, America, Asia, and Africa) from February to December 2020. From the 213 hepaticoportal carcinoma (HCC), 54 were de-novo diagnosis and 159 patients had prior history of HCC. The median age was 60 (IQR: 54.6 – 67) years and 29% received systemic treatment. Among the 29 intrahepatic cholangiocarcinoma (ICCA) only 6 were de-novo. Sixty-seven (27.7%) patients died: 42 deaths were SARS-CoV-2-related (71.4% were cirrhotic) and 25 non-SARS-CoV-2-related (92% were cirrhotic). The 30-day mortality rate of the whole cohort, and SARS-CoV-2-related death were 21.2% (95%CI: 15.7 – 26.7), and 17.4% (95%CI: 12.7 – 22.9), respectively. The 30-day mortality rate in patients with history of liver cancer were: 23.2% (95%CI: 16.2 – 30.2) with HCC and 42.9% (95%CI: 21.4 – 64.4) with ICCA. Table 1 describes the 30-day mortality due to SARS-CoV-2 infection according to BCLC, C, and D stage. From the 60 de-novo liver cancer diagnosis, 60% of the HCC were BCLC ≥ 3 stages and ≤ 1/6 of ICCA were stage N. The 30-day mortality rate in de-novo HCC was 8.3% (95% CI: 0.5 - 16.1).
Early detection of hepatocellular carcinoma (HCC) is main goal to many studies after treatment with Direct acting antivirals (DAAs) in cirrhotic patients due to HCV. Many risk factors were detected after interferon but after DAAs less studies. In Our Study to detect risk factors for HCC in cirrhotic patients & evaluate new score for HCC prediction after DAAs in chronic Hepatitis C.

Methods: We retrospectively evaluated 1350 patients treated with DAAs but 250 patients who had fibrosis in virology unit, National Liver Institute, Menoufia University after informed written consent. Pre-treatment laboratory data were collected after multivariate analysis to data we found risk factors for HCC with DAAs (High fibroscan, Diabetes mellitus, low paltates and older age) this data show in novel score to detect HCC (Age >60 equal points 2 or younger 1, Fibroscan > 16.5 kPa equal 2 or other equal 1, presence of DM equal 2 or other equal 1 and paltates <100 tu/ml equal 2) and calculated from (4-8 points).

Results: All patients who developed Hepatocellular carcinoma (HCC) was group (I) (55 patients; 0.41%) and who did not develop Hepatocellular carcinoma (HCC) group (II), Risk score was calculated from 250 patients who had liver stiffness by fibroscan in Kpa at base line assesment with AUC (0.91) and significant in table (1); after Demographic, clinical and laboratory data were compared between group developed HCC and not developed HCC, Multivariate models showed that Age (Age >60 years) (OR=8.9), (OR=4.1), presence of DM (OR = 8.91) OR= 12.25, (51), Fibroscan (OR =33.1) (OR =2.75), Platelets (OR =3.2) (OR 0.99 – 1.1).

Conclusion: 1. Novel risk score for HCC after DAAs with cut off level (6) with sensitivity (80%) and specificity (85%) can predict HCC with DAAs. 2. Higher fibroscan, older age, DM and lower paltates are risk factors for HCC after HCV eradication by DAAs.

Disclosure of Interest: No

P-58 DECIPHERING LIVER CANCER TISSUE ORGANIZATION BY 3D ELECTRON MICROSCOPY AND MACHINE LEARNING

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Introduction: Despite recent progress in the characterization of tumour components, the tri-dimensional (3D) organization of this pathological tissue and the parameters determining its internal architecture remain elusive.

Methods: We analysed the spatial organization of patient-derived xenograft tissues generated from hepatoblastoma, the most frequent childhood liver tumour, by serial block-face scanning electron microscopy using an integrated workflow combining 3D imaging, manual and machine learning-based semi-automatic segmentations, applied mathematics and informatics.

Results: By digitally reconstructing an entire hepatoblastoma sample with a blood capillary, a bile canaliculus-like structure, hundreds of tumour cells and their main organelles (e.g. cytoplasm, nucleus, mitochondria), we report unique 3D ultrastructural data about the organization of tumoral tissue. We found that the size of hepatoblastoma cells correlates with the size of their nucleus, cytoplasm and mitochondrial mass. We also discovered that the blood capillary controls the planar orientation and size of tumour cells in their 3D microenvironment. Finally, we found that a set of tumour cells polarized in the direction of a hot spot corresponding to a bile canaliculus-like structure.
Introduction: Gastrointestinal adverse events (GIAEs) are common in patients with advanced hepatocellular carcinoma (HCC) treated with sorafenib. Diarrhea is a prevalent event responsible for treatment interruptions and dosage modifications. The mechanisms and impact of diarrhea in sorafenib treated patients is not well understood. Absorption of nutrients depends on the integrity of the intestinal barrier. When this is compromised, the gut permeability increases, and this may prime development of gastrointestinal complications. We evaluate the role of baseline blood L-Glutamine (L-Gln) levels in the prediction of GIAE development early during treatment (eGIAE).

Methods: Blood L-Gln was measured in 135 patients with advanced HCC prior to starting sorafenib. The tumor response, survival time and adverse events of the two groups were compared, and the factors affecting the prognosis were analyzed.

Results: Fifteen per cent of patients developed eGIAE, being diarrhea the most frequent one. Patients displaying the lowest L-Gln levels presented a significant higher risk of eGIAE while those with the highest ones were protected from eGIAE (Figure 1a) and achieved a better survival (Figure 1b).

Conclusion: Our study shows for the first time the association of baseline blood L-Gln levels with eGIAE development in HCC patients during sorafenib treatment. Low L-Gln concentrations might reflect a potentially compromised intestinal barrier that becomes clinically relevant early after treatment start. Diarrhea is the most frequent of such events and their control may prime dose adjustments or even treatment interruption that may prevent the expected survival benefits of sorafenib.

Disclosure of Interest: No
P-37 A PHASE IB STUDY OF PEMBROLIZUMAB FOLLOWING TRANS-ARTERIAL CHEMOEMBOLIZATION (TACE) IN HEPATOCELLULAR CARCINOMA (HCC): PETAL.


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Background: The efficacy of TACE is secondary to its dual ischemic and cytotoxic effect, which promotes immunogenic tumour cell death. We hypothesized that TACE will prime adaptive immunity and enhance pembrolizumab efficacy (pembro; anti-PD-1). The aim of this phase Ib study was to evaluate safety, preliminary activity of combination therapy and explore mechanisms of efficacy.

Methods: Up to 32 patients (pts) with intermediate-stage HCC were planned to receive up to 2 rounds of TACE followed by pembrolizumab q3w 30-days post-TACE until disease progression or unacceptable toxicity for up to 1 year. Primary endpoint was safety with dose-limiting toxicities (DLT) emerging from the combination being evaluated over a 21-day window from commencement of pembro. Secondary endpoints included progression-free survival (PFS) and evaluation of tumour and host determinants of response in tissue, blood and stool samples.

Results: Of 11 eligible pts, 82% were males, 16% HCV-positive, 55% ECOG PS 0 with a median age of 68 years. Child-Pugh (CP) class was A in 10 pts and B7 in 1 pt. Median tumour size was 4 cm, and median number of tumour nodules was 2. Six pts received pembro after 1 TACE. 5 pts after 2. Pembrolizumab yielded a synergistic efficacy with TACE and no DLTs were reported. All-grade adverse events potentially related to treatment (tx) occurred in 90% of pts with most commonly skin rash (45%) and fatigue (45%). Median PFS was 9.7 months (95% CI 9.1-14.4) from TACE and 6.1 months (95% CI 3.8-8.3) from pembro initiation. Cause of withdrawal included disease progression (n=7), adverse events (n=1) worsening liver failure in the CP B7 pt, non-tx-related (n=1) and withdrawal due to Covid-19 pandemic (n=2). We document dynamic changes in peripheral T-cell subsets throughout treatment, with significantly higher proportions of MAIT cells post-pembro in responding patients. Serum metabolic profiling revealed that TACE plus pembro globally altered the lipid profile of patients, causing significant changes in phosphatidyolcholines, acylcarnitines and sphingomyelins. Treatment responders had higher levels of saturated and monounsaturated phosphatidylcholines, highlighting potential immune-metabolic mechanisms of efficacy.

Conclusions: The TACE plus pembro combination had a tolerable safety profile with no evidence of synergistic toxicity. Alongside emerging efficacy data, this encourages the clinical development of the combination in CP A pts.

Disclosure of Interest: No

P-37 THE NUMBER OF SMALL HEPATOCellular CARCINOMA NODULES IN PATIENTS LISTED FOR LIVER TRANSPLANTATION WITHIN THE ALPHA-FETOPROtein SCORE IS A PROGNOSTIC RISK FACTOR

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Introduction: In France, the current criteria for liver transplantation (LT) for hepatocellular carcinoma (HCC) require an alpha-fetoprotein (AFP) score ≤ 2. According to this score, patients with more than 3 HCC nodules are eligible for LT, as long as they are small (≤ 3 cm) and the AFP level is ≤ 100 ng/ml. This study shows that the number of small HCC nodules in patients within the AFP score before LT has a prognostic value.

Methods: We included 143 patients consecutively transplanted for HCC in our center, between 2013 and 2017, with an AFP score ≤ 2. The number and size of HCC nodules, and the AFP level were assessed at listing and at the last evaluation before LT. HCC histological features on native liver were assessed. We compared the overall survival (OS) and disease-free survival (DFS) post-LT of patients with ≤ 3 versus > 3 HCC nodules (current criteria) and, respectively, ≤ 5 versus > 5 HCC nodules.

Results: Among 196 patients listed for HCC, 36 (18.4%) were not transplanted due to drop-out. The median age of the 143 transplanted patients was 63.3 years. The two main causes of the underlying liver disease were alcohol (41.3%) and HCV infection (27.9%). The number of patients with more than 3 HCC nodules at listing and at the last imaging before LT was 16 (11%) and 17 (12%), respectively, 128 (89.5%) patients had at least one bridging treatment: transcatheter arterial chemoembolization n = 83, radiofrequency n = 16, surgical resection n = 22, other treatment n = 22, without any difference among the subgroups (≤ 3 versus > 3 HCC nodules). The median follow-up of the whole cohort was of 44 months. The 3-years OS of patients with ≤ 3 versus > 3 HCC nodules at listing were of 90.3% and 67.3%, respectively (p = 0.04). At last imaging before LT, 8 patients presented ≤ 5 HCC nodules, while still within the AFP score; they had a significantly lower OS than those with < 5 nodules: 5-years OS of 24.4% versus 78.1%, p = 0.01.

Conclusions: Although the current AFP score provides satisfactory outcomes post-LT for HCC, we highlight here the poorer outcomes of patients presenting five or more HCC nodules, despite bridging therapy. These results need to be confirmed by a larger validation cohort. In this case, a modification of the AFP score, by adding an upper threshold of five HCC nodules could be considered, to exclude progressive HCC after listing, as they show shorter survival rates.

Disclosure of Interest: No
E-Posters

P-44 COMPARATIVE LONG-TERM OUTCOMES OF LAPAROSCOPIC LIVER RESECTION AND RADIOFREQUENCY ABLATION FOR A SINGLE, SMALL HEPATOCELLULAR CARCINOMA LOCATED IN THE ANTEROLATERAL SEGMENTS OF THE LIVER
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Introduction: Laparoscopic liver resection (LLR) is considered the standard surgical approach for resecting small hepatocellular carcinomas (HCC) located in the anterolateral segments of the liver. However, few studies have compared LLR and radiofrequency ablation (RFA) in such cases.

Methods: We retrospectively compared the short- and long-term outcomes of 101 patients who underwent LLR and 264 patients who underwent RFA because of a newly diagnosed single, small (<4 cm) HCC located in the anterolateral segments of the liver. By applying 1:1 propensity score matching, we matched 61 patients in both groups.

Results: After matching, all demographic, tumor, and liver function variables were similar in both groups. There were no peri-treatment mortality in either group. The hospital stay was shorter in the LLR group than in the RFA group (5.1 vs. 8.9 days; p = 0.001), but the complication rate was not significantly different between the two groups (4.9 vs. 13.1%; p = 0.114). Although the 5-year overall survival rates were similar (83.6 vs. 84.5%; p = 0.913), the 5-year disease-free survival rate was greater in the LLR group (56.4% vs. 41.8%; p = 0.009). In patients with an B-fetoprotein level ≥100 ng/ml, the 5-year overall (100% vs. 80.0%; p = 0.025) and disease-free survival (76.6% vs. 45.5%; p = 0.006) rates were greater in the LLR group (Fig. 2).

Conclusion: For patients with a single, small HCC located in the anterolateral segments of the liver, LLR was associated with similar complication and overall survival rates, but better disease-free survival compared with RFA. LLR may be recommended for patients with higher B-fetoprotein levels.

Disclosure of Interest: No

P-46 EXPLORATORY NETWORK META-ANALYSES OF SELECTIVE INTERNAL RADIATION THERAPY VERSUS SORAFENIB, LENVATINIB, AND ATEZOLIZUMAB-BEVAZIZUMAB AS FIRST-LINE TREATMENT IN SUBGROUPS OF PATIENTS WITH HEPATOCELLULAR CARCINOMA
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Introduction: The IMbrave150 randomized controlled trial (RCT) of atezolizumab-bevacizumab (atezo-bev) versus sorafenib in the treatment of hepatocellular carcinoma (HCC) was the first to demonstrate superiority over sorafenib since the SHARP trial results were published in 2008. The subsequent regulatory and reimbursement decisions on atezo-bev have changed the first-line treatment landscape for patients with advanced HCC. In addition to systemic therapies and interventions with curative intent, locoregional therapies such as selective internal radiation therapy (SIRT) and transarterial chemoembolization (TACE) still have an important role to play in the HCC armamentarium. The objective was to establish the relative efficacy of SIRT with SIR-Spheres Y-90 resin microspheres, lenvatinib, and atezo-bev versus sorafenib in the first-line treatment of HCC based on a series of exploratory network meta-analyses (NMA)s conducted in subgroups of patients potentially eligible for SIRT.

Methods: A PROSPERO-registered systematic literature review was conducted to identify RCTs of first-line treatments for HCC. Studies were retrieved from PubMed, Embase, and the Cochrane Library, duplicates were removed, and titles and abstracts were screened independently by two reviewers. Data on overall survival (OS) were extracted from the included studies, focusing on three patient subgroups: one with no extrahepatic spread (EHS) or macrovascular invasion (MVI) at baseline, one in BCLC stage B at diagnosis, and one in Child-Pugh liver function class A. Centraal-based, fixed effect NMA s were then conducted using the genetic N package based on normal identity link models and with 50,000 burn-in iterations and 100,000 samplings. Convergence was checked using Gelman-Rubin-Brooks plots and results presented as mortality hazard ratios (HRs) relative to sorafenib, probability ranks, and surface under the cumulative ranking curve (SUCRA) plots.

Results: Four RCTs were identified, two RCTs comparing SIR-Spheres Y-90 resin microspheres with sorafenib (SARAH and SIREEVE), and one RCT each comparing lenvatinib and atezo-bev with sorafenib (REFLECT and IMbrave150, respectively; Figure). None of the analyses reported significant OS differences between the four treatments, with the small subgroup sizes contributing to a high degree of uncertainty (Table). Lenvatinib was excluded from the Child-Pugh A analysis as the most comparable subgroup (without EHS) also excluded all patients with MLM. Atezol-bev had the highest probability of being the most efficacious treatment in patients without EHS or MLM (71.8% probability), and in patients in Child-Pugh class A (72.6% probability), but the least efficacious treatment in patients diagnosed in BCLC stage B (51.1% probability). Across the three subgroup analyses, SIRT with SIR-Spheres Y-90 resin microspheres consistently had the highest likelihood of being the second most efficacious treatment option, while sorafenib was consistently ranked third.
Conclusions: The present analysis showed that there is a high level of uncertainty around the optimal first-line treatment in patients with HCC who would potentially be eligible for SIRT. This uncertainty was driven primarily by the small size of the subgroups and further research would be required to confirm the findings, but treatment probability rankings from a series of Bayesian NMAEs tentatively suggest that atelo-bev may not be the optimal treatment choice in specific subgroups of patients with HCC eligible for locoregional therapy with SIRT.

Disclosure of Interest: Yes - Consulting

VKB, IA, and FC are full-time employees of Sirtex Medical United Kingdom Ltd, and SS is a full-time employee and director of Sirtex Medical United Kingdom Ltd, the manufacturer of SIR-Spheres Y-90 resin microspheres. RFP is the director of Covalence Research Ltd, which received consultancy fees from Sirtex Medical United Kingdom Ltd to run the analyses and prepare the abstract.

P-47 PREVIOUS/CONCURRENCE RADIATION ENHANCED THE EFFICACY OF IMMUNOTHERAPY IN METASTATIC AND RECURRENT LIVER CANCER: A PILOT STUDY FROM THE REAL-WORLD DATA

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Introduction: Immune checkpoint inhibitor mono-therapy has emerged as a breakthrough therapy in the treatment of various cancer. However, programmed cell death (PD-1) inhibitors alone as secondary line treatment yield uncertain responses in liver cancer in different studies. Despite encouraging preclinical findings that radiation primes the immune system and produce a synergistic anti-tumor immunity for durable disease control, few clinical data is published so far. To investigate the efficacy and safety of the combination of radiation and PD-1 inhibitors in metastatic and recurrent liver cancer, we proposed this study.

Materials and Methods: Patients diagnosed with stage IV (American Joint Committee on Cancer Staging System 8th) or recurrent liver cancer, received radiation therapy followed by PD-1 inhibitors or concurrent radiation and PD-1 inhibitors were enrolled. Data regarding clinicopathologic characteristics, treatment protocols, response rates, toxicities, and survival were collected. Survival were calculated from the first delivery of immunotherapy using Kaplan-Meier method.

Results: From April 2017 to December 2020, 34 patients were eligible. Twenty-nine (85.3%) patients were male and 5 (14.7%) were female. The median age was 58 years old. Twenty-three patients (67.6%) had hepatocellular carcinoma. Totally, radiotherapy was delivered to 92 lesions (28 liver, 28 venous tumor emboli, 13 lymph nodes, 18 bone, 5 others) of these patients. The radiation dose ranged from 40Gy to 60Gy (2-5Gy per fraction). Seventeen patients, 15 patients, 5 patients, 1 patient and 1 patient received toripalmbibritunlimitolantramulzamibvolumulzamib and pembrolizumab, respectively. PD-1 inhibitors were administered very 3 weeks until progression or limiting toxicities. Thirty-one patients received targeted therapy during the utilization of immunotherapy and radiotherapy, including 17 patients with sorafenib, 10 patients with Lenvatinib, 3 patients with regorafenib and 1 patient with apatinib. After treatment, 3,18 and 11 patients achieved complete response, partial response and stable disease. The response rate and disease control rate were 61.8% and 94.1%, respectively. Grade 3 adverse events were observed in 11 patients (32.3%), including 6 patients with thrombocytopenia (2 with Grade 4, 4 with Grade 3), 2 patients with gastrointestinal events and 3 with others. No grade 5 adverse event was recorded. The median follow up time was 16.5 months. The median overall survival (OS) time and progression free survival (PFS) time were 15.4 months and 11.3 months. One-year OS and PFS were 62.9% and 46.5%, respectively. Two-year OS and PFS were 31.8% and 11.3%, respectively.

Conclusion: The combination of immunotherapy and radiotherapy was safe and tolerable. The application of radiation before or during PD-1 inhibitors delivery fostered the immune response and enhanced the efficacy of immunotherapy with prolonged PFS and OS in recurrent and metastatic liver cancer. A Phase II prospective trial is ongoing.

Disclosure of Interest: No

P-48 PROGRESSION PATTERNS AND CLINICAL OUTCOMES FOLLOWING IMMUNE CHECKPOINT INHIBITION FOR HEPATOCELLULAR CARCINOMA (HCC): A MULTI-INSTITUTIONAL OUTCOMES STUDY


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Introduction: Immune checkpoint inhibitors (ICIs) are revolutionising the treatment algorithm of patients with advanced hepatocellular carcinoma (HCC) and are currently available in clinical practice, either alone or in combinations across different treatment lines. Little is known about progression patterns and post-progression outcomes following IC in HCC. Different approaches are available after progressive disease (PD), including continuation of ICI, treatment switching to tyrosine kinase inhibitors (TKIs) and cessation of systemic therapy.

Methods: From an international consortium of 13 tertiary-care referral centres located in Europe, the United States and Asia, we screened 472 consecutive HCC patients treated with ICIs between...
Results: Of 472 patients, 268 had PD during observation, mostly following PD-1/PD-L1 monotherapy (67%). Of these 268 patients, 75% were BCLC-C and 72% were Child-Pugh A at ICI commencement. Median PPS was 5.5 months (95% CI: 4.5-7.7). At data cut-off, 100 patients (37%) did not receive any post-progression anti-cancer treatment. Patients who did not receive post-progression treatment were more likely to have ECOG PS 2 than those who did (10% vs. 0.6%; p = 0.0005) and more frequently had 1 or more treatment line prior to ICI-based therapy (71% vs. 56%; p = 0.0143). Continuation of ICI beyond first PD occurred in 54 patients (20%), mostly in the context of IHG (52%) or EHG (48%) and was associated with longer PPS (3.2 vs 4.8 months, HR 0.66 [95%CI:0.47-0.92]; p=0.0152). The presence of IHG (HR 1.44 [95%CI:1.03-2.03]; p=0.034) and nVI (HR 2.04 [95%CI:1.17-3.54]; p=0.012) at progression were significantly associated with shorter PPS, whereas NIH, NEH and EHG were not prognostic. Multivariate models adjusted for progression patterns and treatment line confirmed receipt of ICI beyond PD (HR 0.44 [95%CI:0.28-0.70]; p=0.001) and the receipt of any post-progression anticancer therapy excluding ICI (HR 0.24 [95%CI:0.16-0.35]; p<0.001) as independent predictors of longer PPS.

Image:

Conclusions: In our study 73% of patients received anti-cancer therapy after progression on ICI. Presence of nVI and IHG predict for poorer post-progression survival. Continuation of ICI beyond PD is frequent in routine practice and is associated with a prolonged PPS, independent of radiological pattern of disease progression and receipt of subsequent line anti-cancer therapy.

Disclosure of Interest: No

P-49

IDENTIFICATION OF REGORAFENIB PROGNOSTIC INDEX (REP INDEX) VIA RECURSIVE PARTITIONING ANALYSIS IN ADVANCED HEPATOCELLULAR CARCINOMA PATIENTS RECEIVING SYSTEMIC TREATMENT

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Introduction: The results of the pivotal RESORCE trial led to the approval of the second tyrosine kinase Regorafenib, as second line treatment in advanced HCC after Sorafenib failure. Data about prognostic factors in a second-line HCC setting are scarce.

Materials and Methods: We retrieved data about 260 patients affected by advanced HCC treated with regorafenib as second line treatment from three different Italian institutions and a recursive partitioning analysis was performed in order to build a score system.

Results: At the first-step univariate analysis for OS, AP resulted the most significant parameter in terms of OS, and was chosen as first node in our tree model. In the subpopulation of patients presenting AP ≥122 U/l (n=172) at the baseline, the most statistically significant split was by the PFS to Sorafenib treatment, between patients with a PFS ≥ 6 months (n=46) and patients with a PFS < 6 months (n=125). In the subpopulation of patients with AP ≥122 U/l and PFS to Sorafenib ≥8 months, the final split was determined between patients with HBV-related liver disease (n=24) and patients with no HBV-related liver disease (n=42). In the subpopulation of patients presenting AP >122 U/l (n=108) at the baseline, the most statistically significant split was by Aspartato-amino transferase (AST) value, between patients with AST ≤56 U/l (n=50) and patients with AST>56 U/l (n=58). We built the REP index which stratify the population in “low-risk”, “medium-risk” and “high-risk” patients. The difference in mOS between the three groups of risk was statistically significant, being 20.8 months (95% CI 10.0-46.3) in the “low-risk” group, 8.35 months (95% CI 7.3-143.9) in the “medium-risk” group and 5.5 months (95% CI 3.3-12.2) in the “high-risk” group.

The median PFS was 7.7 months (95% CI 3.7-19.3) and 2.5 months (95% CI 2.1-29.8) and 2.4 months (95% CI 1.6-8.1) for “low-risk”, “medium-risk” and “high-risk” group, respectively.
Conclusions: The REP index is an independent prognostic factor for OS and PFS in patients with advanced HCC treated with regorafenib.

Disclosure of Interest: No

P-50 IMPACT OF PREVIOUS SURGERY ON PROGNOSIS IN PATIENTS WITH CHOLANGIOCARCINOMA UNDER CHEMOTHERAPY

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Introduction: Biliary tract cancers (BTCs) have dramatic prognosis and the only curative strategy consists on surgery; unfortunately, recurrences are frequent. How a previous surgery impacts on survival outcomes of patients treated with chemotherapy is already unknown.

Materials and Methods: Pre-treatment demographic, clinical and laboratory data of 823 patients with advanced BTC from 15 Italian Institutions were retrieved. Survival outcomes of patients treated with chemotherapy is already unknown.

Results: Overall, patients with a previous R0 resection had an Overall Survival (OS) of 17.9 months (95% CI, 15.2-24.3) compared to 13.4 months (95% CI, 11.8-16.2) for patients who underwent surgery but had a non-R0 resection, and 11.0 months (95% CI, 9.4-13.4) for patients who did not undergo surgery. The multivariate analysis showed that patients who underwent a previous R0 resection had a longer OS compared to patients who had a R1/R2 resection or no surgery (HR = 0.75, 95% CI 0.61-0.92; p = 0.001). The REP index was an independent prognostic factor for OS and PFS.

Conclusions: Previous surgical resection is an independent favorable prognostic factor for OS and PFS.

Disclosure of Interest: No

P-51 FREE ANDROGEN INDEX LEVELS MAY INFLUENCE THE TRANS-ARTERIAL CHEMOEMBOLIZATION WITH DOXORUBICIN-ELUTING BEADS RESPONSE IN HEPATOCELLULAR CARCINOMA PATIENTS: PRELIMINARY RESULTS

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Introduction: Hepatocellular carcinoma (HCC) shows a male predominance. It has been demonstrated that testosterone avoid apoptosis and senescence in cells treated with doxorubicin. Bearing this mind, it can be hypothesized that testosterone can be related with a worse response to Trans-arterial Chemoembolization with Doxorubicin-Eluting Beads (DEB-TACE) in HCC. The aim of the present study is to analyze the effect of total testosterone levels and free androgenic index (FAI) in the DEB-TACE response in HCC patients.

Materials and Methods: 82 patients with advanced BTC from 15 Italian Institutions were retrieved. Survival outcomes of patients treated with chemotherapy is already unknown.

Results: Overall, patients with a previous R0 resection had an Overall Survival (OS) of 17.9 months (95% CI, 15.2-24.8), those with a previous R1/R2 resection had an OS of 13.1 months (95% CI, 7.7-16.9) and non-resected patients had an OS of 10.1 months (95% CI, 9.2-15.9) with p = 0.00038. No difference was found in terms of PFS to first-line chemotherapy (HR=2.6). 515 patients had intrahepatic cholangiocarcinoma (CCA): they showed an OS of 20.7 months (95% CI, 16.6-24.9) and a median OS of 10.2 months (95% CI, 7.8-12.0) in patients previously treated with a R0 resection, R1/R2 resection and no surgery, respectively. Finally, in the subgroup of patients receiving a second line therapy those with a previous R0 resection had a median OS of 22.5 months (95% CI, 16.6-49.9), 16.9 months (95% CI, 11.1-22.5) and 10.2 months (95% CI, 7.8-12.0) in patients previously treated with a R0 resection, R1/R2 resection and no surgery, respectively. 167 patients had intrahepatic cholangiocarcinoma (iCCA): they showed an OS of 14.0 months (95% CI, 11.1-16.6), 11.5 months (95% CI, 8.9-14.1) and 9.7 months (95% CI, 7.1-12.2) in patients previously treated with a R0 resection, R1/R2 resection and no surgery, respectively.

Conclusions: Previous surgery with curative intent is correlated to a better OS in the first-line setting for advanced BTC, chiefly in CCA.

Disclosure of Interest: No

**Table 1.** Baseline characteristics of the cohort

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**Abbreviations.** ECOG PS, eastern cooperative oncology group performance status; HBV, hepatitis B virus; BCLC stage, Barcelona clinic liver centre staging; Child-Pugh, Child-Turcotte-Pugh score; AFP, alpha fetoprotein; GPT, glutamic-pyruvic transaminase; Hb, Haemoglobin; NL R, Neutrophil-lymphocyte ratio; PNI, prognostic nutritional index; PFS, Progression Free Survival to Sorafenib.

**Table 2.** Baseline characteristics of the cohort

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Methods: Patients with HCC with any indication of DEB-TACE performance were included in the study. Total testosterone was measured by radio-immune assay and FAI was calculated by using the formula reported by Vermeulen et al. (1999). These determinations were performed the same day of the DEB-TACE. All chemoembolization were performed by a single radiologist and using the same kind of doxorubicin particles. Treatment response was measured after one month with a multiphase contrast-enhanced computed tomography (CT). Modified RECIST (mRECIST) criteria were used to evaluate the response to DEB-TACE in each patient. Parametric statistical tests were performed, using a threshold of p=0.05 for statistical significance.

Results: Forty-one DEB-TACE performed in 22 patients (3 women; mean age: 70.4 [SD=9.6]) were included in this analysis. A mean of 2 DEB-TACEs were performed per patient (rank: 1–5). The mean level of total testosterone prior to DEB-TACE was 4.7 ng/ml (SD=2.6) and the mean level of FAI was 26.2 (SD=13.8). Total response was achieved in 12 DEB-TACEs (29.3%) and partial response in 13 (31.7%). Stable disease was considered after 13 procedures (31.7%) and progression was found in 3 cases (7.3%). No significant differences were identified in total testosterone levels between the response groups (ANOVA; p=0.542). However, higher levels of FAI were identified in the progression group compared to the others (ANOVA; p=0.029). Bonferroni post-hoc test showed that the main difference was between progression and stable disease groups (45.6 vs. 20.6; p=0.025). Additionally, despite the few number of cases, a binary-logistic regression analysis showed that higher FAI levels were associated with a slight increase in the risk of progression after a DEB-TACE (OR=1.142; 95% CI. [1.008–1.293]; p=0.037).

Conclusion: Patients with higher levels of FAI prior to a DEB-TACE performance may be associated with a higher risk of progression at 1 month after the procedure.

Disclosure of Interest: No

P-60 EFFECTIVENESS AND SAFETY OF LENVATINIB IN PATIENTS WITH RECURRENT HEPATOCELLULAR CARCINOMA AFTER LIVER TRANSPLANTATION: RETROSPECTIVE ANALYSIS

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Introduction: Lenvatinib is the approved agent in patients with metastatic or recurrent hepatocellular carcinoma (HCC), but little is known about its clinical outcomes in patients with recurrence after liver transplantation (LT). We aimed to investigate the effectiveness and safety of lenvatinib in patients with recurrent HCC after LT.

Methods: This single center, retrospective study included 22 patients with recurrent HCC after LT who received lenvatinib in Asan Medical Center, Seoul, Korea, between November 2019 and March 2021. Lenvatinib was given 12mg/day for bodyweight ≥ 60 kg or 8 mg/day for bodyweight < 60 kg. Response and adverse events (AEs) were graded according to the RECIST v1.1 and NCI CTCAE v5.0.

Results: The median age was 58 years (range, 20-69 years) and 95.5% (n=21) were male. Most common etiology of HCC was hepatitis B (n=18, 81.8%), and all patients received immunosuppressants such as tacrolimus (n=21, 95.5%), everolimus (n=19, 86.4%), and mycophenolate mofetil (n=3, 13.6%). The median time to recurrence after LT was 6.6 months (95% CI: 4.2-9.1 months). Prior to systemic therapy, transarterial embolization (TACE) (n=12, 54.5%) was the most commonly used therapy for recurred HCC after LT. At the time of initiation of lenvatinib, 90.9% (n=20) were Child-Pugh A and 14 (63.6%) and 7 (31.8%) patients were classified as Albumin-Bilirubin (ALBI) grade 1 and 2, respectively. All patients were BCLC stage C. Lenvatinib was administered as the first- and second-line therapy in 19 (86.4%) and 3 (13.6%) patients, respectively. Objective response rate (ORR) was 15.0% (3 PR) and median time-to-response (TTR) was 1.7 months (95% CI: 1.5-2.2 months). With median follow-up duration of 5.2 months (range, 1.7-14.5 months), the median progression-free survival (PFS) was 6.6 months (95% CI: 3.6-9.5 months) and overall survival (OS) was 14.5 months (95% CI: not reached). The 6-month PFS and OS rates were 58.8% and 98.8%, respectively. Patients with ALBI grade 2 showed significantly poorer OS (11.1 months (95% CI: not reached)) compared to patients with ALBI grade 1 (14.5 months (95% CI: not reached)) (p=0.013). AEs were hypertension (n=8, 36.4%), thrombocytopenia (n=7, 31.8%), and fatigue (n=6, 27.3%). Most common grade 3-4 AEs were neutropenia (n=4, 18.2%) and hypertension (n=4, 18.2%).

Conclusion: Lenvatinib was effective and showed manageable toxicities in patients with recurrent HCC after LT. These outcomes are comparable to those in the pivotal REFLECT trial which patients with LT were excluded. The better baseline liver function (ALBI Grade 1) at lenvatinib was correlated with the better survival outcome.

Disclosure of Interest: No
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