Abstract P214 Table 1 Predicted risk of ESLD in patients with PBC before and after OCA treatment[1]

Median (IQR)	Baseline (n=73)	DB Month 12 (n=68)	OLE Month 12 (n=58)	OLE Month 36 (n=48)	OLE Month 60 (n=24)
5-Year Risk (%)	1.9 (1.1, 3.5)	2.3 (1.1, 4.4)	1.4 (0.8, 3.3)*	1.3 (0.7, 2.1)*	1.6 (1.0, 2.7)*
10-Year Risk (%)	6.4 (3.8, 11.3)	7.5 (3.6, 14.0)	4.7 (2.7, 10.6)*	4.4 (2.5, 6.9)*	5.2 (3.3, 8.7)*
15-Year Risk (%)	11.5 (6.9, 19.9)	13.5 (6.6, 24.4)	8.5 (5.0, 18.8)*	8.0 (4.5, 12.5)*	9.4 (6.0, 15.7)*

[1] Patients received Placebo ± UDCA for 12 months during the double-blind phase, then OCA ± UDCA throughout the OLE.
*p<0.05. P-value for within group comparison using Wilcoxon Signed Rank test comparing Month 12 DB and Month 12, 36, or 60 OLE.
DB, double-blind; ESLD, end-stage liver disease; IQR, interquartile range, OCA, obeticholic acid; OLE, open label extension; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid.

aminotransferase (ALT), aspartate aminotransferase (AST) or alkaline phosphatase (ALP), and total bilirubin before and after 12 months of treatment to predict the risk of end-stage liver disease (ESLD), liver-related death or liver transplant. POISE, a randomised, double-blind (DB), placebo-controlled 12-month Phase 3 trial, investigated daily 5 mg to 10 mg obeticholic acid (OCA) for the treatment of PBC. After the DB phase, 97% of pts enrolled in an open label extension (OLE) wherein all pts received OCA. This analysis assessed the change in predicted risk of ESLD with the UK-PBC model in pts who had received placebo during the DB phase and transitioned to OCA during the OLE.

Methods POISE inclusion criteria: PBC diagnosis, ALP ≥1.67x upper limit of normal (ULN) and/or total bilirubin >ULN to <2x ULN, stable ursodeoxycholic acid (UDCA) dose or unable to tolerate UDCA. 73 pts were randomised to the placebo arm of the POISE trial, 66 of whom enrolled in the OLE. Baseline (BL), Month 12 of the DB phase, and OLE data through 60 months of OCA treatment were included in the UK-PBC algorithm to assess change in predicted risk of ESLD at 5, 10, and 15 years after 12 months of placebo and through the duration of OCA treatment in the same patient population.

Results At BL, the placebo group was median (interquartile range) 55 (14) years old, 93% female, 90% white, and 93% received daily UDCA at a median (interquartile range) dose of 15 (4) mg/kg. After 1 year of continued standard-of-care treatment, placebo pts demonstrated a slight increase in predicted risk of ESLD (table 1), due to worsening liver biochemistry. However, after 1 year of OCA treatment, predicted risk of ESLD at 5, 10, and 15 years was reduced to below BL levels. Furthermore, through the 60-month OLE the median risk of ESLD was sustained below BL levels.

Conclusions In POISE, the UK-PBC risk score predicted a trend for increased risk of ESLD in pts with PBC treated with placebo for 12 months in addition to standard of care. Addition of OCA led to sustained improvements in serum biochemistry and reductions in predicted risk of ESLD for up to 60 months of OCA treatment.

P215 UNIVERSAL TUMOUR ANTIGENS IN PRIMARY LIVER NEOPLASMS: CHOLANGIOCARCINOMA AND HEPATOCELLULAR CARCINOMA DIFFER

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Introduction The replicative immortality marker, Telomerase, and the apoptosis inhibitor, Survivin, have been described as universal tumour antigens (UTA) and are found in a wide range of malignant and pre-malignant neoplasms. The promoter variant rs9904341, encoding the -31C/G of Survivin promoter (pSurv) and the mutually exclusive C228T/C250T mutations in the Telomerase promoter (pTERT) increase transcription and are involved in tumour biology. We have characterised these UTA promoter sequences in primary liver Neoplasms (PLNs) using archived formalin fixed, paraffin embedded (FFPE) surgical resection specimens.

Methods All surgical resection samples from 2005 - 2018 were considered for study. Extrahepatic cholangiocarcinoma, non-primary liver tumours and needle biopsy samples were excluded. DNA was extracted of sufficient quality to amplify and analyse with Sanger sequencing from background liver & tumour tissues. Sequences were analysed using MacVector and statistical analysis was undertaken using SPSS (v24).

Results 111 cases were identified comprising 58 hepatocellular carcinoma (HCC); 36 cholangiocarcinoma (CCA); 7 mixed tumours (CCA-HCC); and 10 adenomas. DNA with a 260/280 ratio of >1.8 was successfully isolated from all tissue samples. Bidirectional sequences were obtained in nearly all cases (100% for pTERT and 98% for pSurv).

The pSurv was concordant between tumour and background liver in all sequences.

The mutated pTERT was found in 18/58 (31%) of HCCs, in 1/7 mixed tumours but was absent from adenomas (0/10) and all CCA (0/36, p<0.001). The mutant pTERT was restricted to tumour tissue and absent in background liver. In pooled analyses, mutated pTERT occurred in men (p = 0.001) and in tumours arising from fibrotic (p= 0.009) and cirrhotic (p=0.004) tissues. In HCC cases the presence of pTERT mutations correlate with clinical outcomes (mortality, p=0.043), and pathological features such as vascular invasion (p=0.031).

Conclusions Telomerase promoter mutations are not found in cholangiocarcinoma but occur frequently in tumours of hepatocellular origin. This driver mutation develops on a background of chronic inflammation with significant associations with tumours arising in fibrotic/cirrhotic liver tissues. Furthermore, un-pooled analysis has found that pTERT mutations correlate with aggressive tumour characteristics, albeit with small numbers in this surgically managed study cohort.

Our data suggests that UTA promoter sequences can differentiate between the two most common primary hepatic tumour types and demonstrate that useful sequencing information can be obtained from widely available FFPE tissue. Ongoing work includes assessment of telomerase and Survivin protein expression with immunohistochemistry and correlating this expression with promoter status.