subsets, points towards major differences in the immune mechanisms and pathogenesis between ICB-Hepatitis and AIH. Our results indicate T-cell-myeloid interactions as likely drivers of ICB-Hepatitis.

GS004

Prospective randomized controlled trial of biomarkers for early detection of hepatocellular carcinoma

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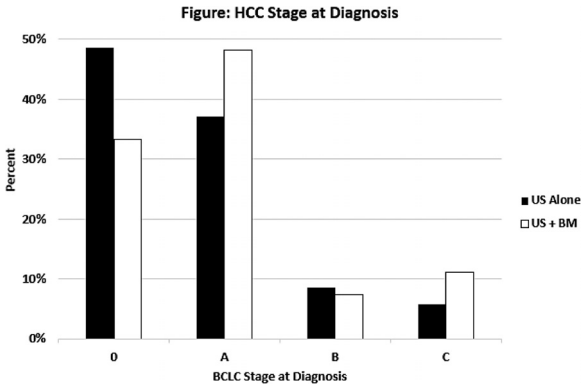
Background and aims: Surveillance for hepatocellular carcinoma (HCC) is key to early diagnosis and access to potentially curative therapy. Small studies have suggested that addition of serum biomarkers (BM) to 6-monthly ultrasound (US) surveillance may allow for earlier HCC diagnosis. Prospective validation of the utility of BMs is lacking.

Method: Adults with cirrhosis or high-risk HBV infection (REACH-B score >8) followed at the Toronto Centre for Liver Disease were randomized to HCC surveillance with US alone (Group A) or US + BM (Group B) with measurement of alpha-fetoprotein (AFP), lectin-reactive fraction of AFP (AFP-L3) and des-gamma-carboxy prothrombin (DCP). Elevated BM levels and/or findings on US triggered CT/MRI for confirmation of HCC diagnosis. The primary outcome was the proportion of HCCs diagnosed at a curable stage (BCLC 0/A) within Milan criteria. Cox regression was used to evaluate the association of the GALAD score (BM + age/sex) with HCC.

Results: 1, 208 patients were enrolled with median age 59 (18–88) years; 72% were male. HBV and HCV were the most common underlying liver diseases (64% and 21%, respectively) and 770 (64%) were cirrhotic. In Group A, after a median follow-up of 34 (1.2–70.4) months and 9.2 US per patient, 35 HCCs were diagnosed, 31 (87%) in cirrhotics, of which the BCLC was 0 for 17 (49%), A for 13 (37%), B for 3 (9%) and C for 2 (6%). In Group B, after a median follow-up of 19 (0.1–60.4) months and 7.9 US per patient, 27 HCCs were diagnosed, 24 (89%) in cirrhotics, of which BCLC was 0 for 9 (33%), A for 13 (48%), B for 2 (7%) and C for 3 (11%). In Group A, 30/35 (86%) HCCs were diagnosed at a curable stage (BCLC 0/A), compared to 22/27 (81%) in group B ($p = 0.63$) (Figure). In group A, 32 (91%) HCCs were identified first by the study US, while 3 (9%) were found incidentally by imaging done for other reasons with a negative prior study US giving an overall sensitivity for US of 27/35 (77%). In group B, 21 (78%) HCCs were evident on US and 9 (33%) were associated with elevated BM of which 6 (22%) were found by BM with a negative corresponding US. Of these 6, BCLC was 0 for 2, A for 3 and C for 1, confirming that curable HCCs may be identified by BM when US is negative. The GALAD score was associated with HCC risk (HR 1.86, $CI_{95\%}$ 1.48–2.32, $p < 0.001$). The previously identified threshold of >-0.63 was associated with increased HCC risk (HR 6.05, $CI_{95\%}$ 2.4–15.3, $p < 0.001$) and 3 of the 5 advanced (BCLC B/C) HCCs in the BM group would have had imaging triggered by GALAD >–0.63 at an earlier visit.



Conclusion: The probability of diagnosing HCC in a curable stage was similar with US and US + BM. However, some HCCs were diagnosed by elevated BM with a negative US and the GALAD score may have identified additional HCCs earlier. Further analyses will determine if certain patient populations may benefit from use of these BM in routine HCC surveillance.

GS005

Development and validation of the gender-equity model for liver allocation (GEMA) to prioritize liver transplant candidates

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Background and aims: The model for end stage liver disease (MELD) and its sodium-corrected variant (MELD-Na) have created gender disparities in accessing liver transplantation (LT). We derived and validated a new model that replaced creatinine with the Royal Free glomerular filtration rate (PMID: 27779785) within the MELD and MELD-Na formulas.

Method: The "Gender-Equity Model for liver Allocation" (GEMA) and its sodium-corrected variant (GEMA-Na) were trained and internally validated in adults listed for LT in the United Kingdom (2010–2020) using generalized additive multivariate Cox regression. The models were externally validated in an Australian cohort (1998–2020). The primary outcome was mortality or delisting due to clinical deterioration at 90 days. The Greenwood-Nam-D'Agostino test was used to test calibration.

Results: The study comprised 9, 320 patients: 5, 762 patients for model training, 1, 920 patients for internal validation, and 1, 638 patients for external validation. The prevalence of the primary outcome ranged from 5.3% to 6%. In the internal validation cohort, GEMA and GEMA-Na showed a Harrell's c-statistic = 0.752 and 0.766, respectively, for the primary outcome, which were significantly higher than those of the MELD score (0.712) and the MELD-Na score (0.742). Results were consistent in the external validation cohort. Among women, these differences were more pronounced (see Harrell's c-statistics in the table). GEMA and GEMA-Na were adequately calibrated and prioritized differently 43.9% and 41.8% of

LT patients, respectively. Patients prioritized by GEMA-Na were more often women, had higher prevalence of ascites and showed triple risk of the primary outcome compared to patients prioritized by MELD-Na. One in 15 deaths would be avoided by using GEMA instead of MELD, and 1 in 21 deaths would be avoided by using GEMA-Na instead of MELD-Na. Among women, 1 in 8 deaths would be avoided in either situation.

Conclusion: GEMA-Na predicts mortality or delisting due to clinical deterioration in patients awaiting LT more accurately than MELD-Na and its implementation may amend gender disparities.

COHORT	N	MELD	GEMA	MELD-Na	GEMA-Na
Training (overall)	5,762	0.753 (0.723–0.783)	0.780 (0.751–0.808) p <0.001	0.783 (0.755–0.810)	0.796 (0.769–0.823) p = 0.022
Training (women)	1,955	0.743 (0.690–0.795)	0.795 (0.748–0.842) p <0.001	0.784 (0.739–0.829)	0.821 (0.781–0.860) p < 0.001
Internal validation (overall)	1,920	0.712 (0.656–0.769)	0.752 (0.700–0.804) p = 0.001	0.742 (0.686–0.797)	0.766 (0.715–0.818) p = 0.006
Internal validation (women)	623	0.751 (0.658–0.844)	0.786 (0.698–0.874) p = 0.085	0.779 (0.688–0.871)	0.802 (0.716–0.888) p = 0.087
External validation (overall)	1,638	0.739 (0.682–0.796)	0.761 (0.703–0.819) p = 0.036	0.745 (0.690–0.800)	0.774 (0.720–0.827) p = 0.014
External validation (women)	432	0.736 (0.628–0.844)	0.789 (0.686–0.892) p = 0.004	0.714 (0.592–0.835)	0.796 (0.698–0.895) p = 0.009

GS006

Efficacy and safety of bulevirtide monotherapy given at 2 mg or 10 mg dose level once daily for treatment of chronic hepatitis delta: week 48 primary end point results from a phase 3 randomized, multicenter, parallel design study

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Background and aims: Bulevirtide (BLV) is a novel first-in-class entry inhibitor for the treatment of chronic HDV infection (CHD) that was conditionally approved in the EU in July 2020 based on Phase 2 data. In a pre-specified, alpha-controlled, interim 24 week analysis of a phase 3 study (MYR301; NCT03852719) it was demonstrated that monotherapy with BLV at 2 mg or 10 mg once daily had a significantly greater combined virologic/biochemical response compared with control with no active anti-HDV treatment and had a favorable safety profile. Here, we present findings for the Week 48 primary end point analysis of Study MYR301.

Method: 150 patients with CHD were randomized to 3 treatment groups and stratified based on the absence or presence of compensated cirrhosis: Arm A (control): no active anti-HDV treatment for 48 weeks followed by BLV 10 mg/d for 96 weeks (n = 51), and Arms B or C: immediate treatment with BLV at 2 mg/d (n = 49) or 10 mg/d (n = 50), respectively, each for 144 weeks, after which all arms enter treatment-free follow-up for additional 96 weeks. The primary end point of combined response was defined as undetectable HDV RNA or decrease by $\geq 2\log_{10}$ IU/ml from baseline and ALT normalization at Week 48; other end points included viral response (undetectable HDV RNA or decrease by $\geq 2\log_{10}$ IU/ml from baseline), ALT normalization, change in HDV RNA levels and change in liver stiffness measured by elastography.

Table. Efficacy and safety results at week 48.

n (%)	Arm A Control (N = 51)	Arm B BLV 2 mg (N = 49)	Arm C BLV 10 mg (N = 50)
Combined Response[1]: Responder at Week 48	1 (2.0%)	22 (44.9%)	24 (48.0%)
95% CI	(0.0%, 10.4%)	(30.7%, 59.8%)	(33.7%, 62.6%)
p-value[2]	-	<.0001	<.0001
Viral Response[3]: Responder at Week 48	2 (3.9%)	35 (71.4%)	39 (78.0%)
95% CI	(0.5%, 13.5%)	(56.7%, 83.4%)	(64.0%, 88.5%)
p-value[4]	-	<.0001	<.0001
Biochemical Response[5]: Responder at Week 48	6 (11.8%)	25 (51.0%)	28 (56.0%)
95% CI	(4.4%, 23.9%)	(36.3%, 65.6%)	(41.3%, 70.0%)
p-value[4]	-	<.0001	<.0001
Change from BL in HDV RNA levels (log-10 scale): LS means (95% CI)	-0.019 (-0.391, 0.352)	-2.551 (-2.933, -2.169)	-3.101 (-3.482, -2.719)
p-value	-	<.0001	<.0001
Change from BL in liver stiffness (Fibroscan, kPa): LS means (95% CI)	0.88 (-0.80, 2.56)	-3.08 (-4.70, -1.46)	-3.17 (-4.90, -1.44)
p-value	-	0.001	0.001
Adverse Events Number (%) of participants with any:			
AE	39 (77%)	40 (82%)	44 (88%)
AE with Grade 3-4	3 (6%)	5 (10%)	4 (8%)
AE Related to BLV	0	24 (49)	36 (72%)
SAE[6]	1 (2%)	2 (4%)	1 (2%)

AE: adverse event, BL: baseline, BLV: bulevirtide, CI: confidence interval; LS: least squares, SAE: serious adverse event.
Undetectable HDV RNA defined as below limit of detection (6 IU/mL). ALT normalization defined as: ≤31 U/L for females and ≤41 U/L for males (Russian sites); or ≤34 U/L for females and ≤49 U/L for males (all other sites). Confidence intervals were calculated using Clopper-Pearson (exact) for proportions.
[1] Undetectable HDV RNA or decrease by $\geq 2\log_{10}$ IU/ml from baseline and ALT normalization.
[2] Fisher's exact tests used for each comparison of Bulevirtide 2mg and 10mg vs. Control using a significance level of 0.04 at week 48.
[3] Undetectable HDV RNA or decrease by $\geq 2\log_{10}$ IU/ml from baseline.
[4] Fisher's exact tests used for each comparison of Bulevirtide 2mg and 10mg vs. Control using a significance level of 0.05.
[5] ALT normalization.
[6] No SAEs assessed as related to BLV treatment

Results: Baseline characteristics included: mean (SD) age 41.8 (8.4) years, 57.3% males, 82.7% White, 47.3% with compensated cirrhosis, 60% were on nucleos (t)ide analogues therapy; mean (SD) HDV RNA 5.05 (1.35) $\log_{10}$ IU/ml and mean (SD) ALT 110.9 (69.0) U/L. At Week 48, similar combined responses were seen in the two BLV arms which were significantly greater than in the control arm (Table). Viral and biochemical responses were also similar in the BLV arms and significantly greater than control (p < 0.0001). BLV was safe and well tolerated during the 48-week treatment period. Asymptomatic elevations in total serum bile salts and injection site reactions occurred at a greater frequency at the higher BLV dose level. There