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[3 – DISTINGUISHED ABSTRACT] RADIATION SEGMENTECTOMY FOR EARLY-STAGE HEPATOCELLULAR CARCINOMA IN PATIENTS WITH NON-ALCOHOLIC STEATOHEPATITIS VERSUS CHRONIC VIRAL HEPATITIS

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Abstract Category: Locoregional Therapy

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Background/Aim: Hepatocellular carcinoma (HCC) most often arises in patients with cirrhosis. Hepatitis C virus (HCV) and non-alcoholic steatohepatitis (NASH) are two of the most common causes of liver disease in Western populations. Studies have raised question if the underlying liver disease may play a role in treatment response. In advanced-stage HCC, NASH-induced HCC has been reported to be less responsive to immunotherapy compared to viral-induced HCC. This study aimed to determine if the outcomes of radiation segmentectomy for treatment-naïve HCC within Milan criteria differ in patients with NASH vs HCV.

Methods: This is a retrospective analysis of consecutive patients with liver disease related to NASH or HCV who received radiation segmentectomy as initial treatment for HCC from January 2017 through June 2022. Eligibility criteria included solitary tumor ≤ 8 cm or up to 3 HCC ≤ 3 cm, ECOG 0-1, and absence of macrovascular invasion or extrahepatic disease. Imaging best response was assessed at 3- and 6-month follow-up per Modified Response Evaluation Criteria in Solid Tumors. Target tumor and overall progression, time-to-progression (TTP), and overall survival (OS) were assessed. All outcomes were censored for liver transplantation (LT). Complete pathologic response (CPN) was determined as absence of viable target tumor after LT.

Results: Of 142 patients included (NASH: 61; HCV: 81), most had underlying cirrhosis (NASH: 87%; HCV: 86%), were male (NASH: 72%; HCV: 74%) and had tumors < 3 cm (median size NASH: 2.3 cm; HCV: 2.5 cm). Patients with NASH had higher BMI (p<0.001) and worse ALBI scores (p=0.003). Patients with HCV had a higher frequency of ALBI grade 1 liver function (p=0.008), younger age (p<0.001), higher AFP levels (p=0.034), and 73% had achieved sustained virologic response. Median dose (NASH: 508 Gy; HCV: 452 Gy) and specific activity (NASH: 700 Bq; HCV: 698 Bq) were similar between cohorts. Objective response was 100% and 97% in the NASH and HCV cohorts, respectively. Mean non-censored follow-up was 26.5 months (95% CI 22.6-30.3) in NASH and 33.2 months (95%CI, 29.5-37.1) in HCV patients, while mean censored follow-up was 15.6 months (95% CI 12.4-18.8) in NASH and 20.5 months (95%CI 16.9-24.0) in HCV patients. Target tumor progression occurred in 1 (2%) NASH and 8 (10%) HCV patients. Target tumor TTP was not met for either cohort. Overall progression occurred in 23 (38%) NASH and 39 (48%) HCV patients. Overall TTP was 17.4 months (95%CI 13.5-22.2) in NASH and 13.5 months (95%CI 0.4-26.6) in HCV patients (p=0.86). LT was performed in 27 (44%) NASH and 33 (41%) HCV patients, with a CPN rate of 64% and 54%, respectively. OS was not met in the NASH cohort and 53.9 months (95%CI 32.1-75.7) in the HCV cohort (p=0.15).

Conclusion: Although NASH and HCV are associated with different mechanisms of liver injury, patients with treatment naïve tumors within Milan criteria treated with radiation segmentectomy achieve comparable outcomes.

[7 – DISTINGUISHED ABSTRACT] IMPACT OF VIRAL ETIOLOGY IN THE PHASE 3 HIMALAYA STUDY OF TREMELIMUMAB (T) PLUS DURVALUMAB (D) IN UNRESECTABLE HEPATOCELLULAR CARCINOMA (uHCC)

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Abstract Category: Systemic Therapy (trials)

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Background/Aim: In HIMALAYA (NCT03298451), a single, high priming dose of T plus D (STRIDE) significantly improved overall survival (OS) vs sorafenib (S), and D was noninferior to S in uHCC (Abou-Alfa et al. *NEJM Evid* 2022;1(8)). Viral etiology is associated with hepatic impairment in HCC development and may influence immunotherapy activity. Thus, we analyzed the impact of viral etiology on clinical outcomes.

Methods: This exploratory analysis assessed STRIDE, D and S in patients (pts) with hepatitis B virus (HBV; presence of HBsAg and/or anti-HBcAb with detectable HBV DNA), hepatitis C virus (HCV) or nonviral/other (NV) etiology. OS hazard ratios (HRs) were calculated using a Cox proportional hazards model. As subsets were not sized for formal comparisons, no multiplicity adjustments were made. A post hoc multivariate analysis was used to identify chance imbalances in key prognostic factors that may bias estimated treatment effects.

Results: Baseline demographic and disease characteristics were similar across treatment arms in the HBV and NV subsets. However, in the HCV group, multivariate analysis identified imbalances in two prognostic variables: extrahepatic spread (EHS; more frequent for STRIDE than S) and albumin-bilirubin (ALBI; score ≥2 more frequent for STRIDE and D than S). OS and progression-free survival were improved with STRIDE vs S in the HBV and NV groups, but not in the HCV group (Table). Using a stratified Cox proportional hazards model to account for imbalances in EHS and ALBI in the HCV subset, OS HRs favored STRIDE vs S. OS HRs continued to favor STRIDE when adjusting for EHS and ALBI in the other groups. Results for D vs S showed similar trends to those for STRIDE vs S (Table).

Conclusions: In HIMALAYA, OS favored STRIDE vs S (HR <1) for all etiologies when subsets were adjusted for prognostic factor imbalances in the HCV cohort; similar trends were observed with D vs S across subsets. These results confirm the benefits of STRIDE and D in pts with uHCC, irrespective of underlying etiology.

Table.

		OS HR vs S; 95% CI	OS Cox-stratified[a] HR vs S; 95% CI	Objective response, %	Disease control rate, %	Median time to response, months	Median duration of response, months
HBV	**STRIDE** n=122	0.64; 0.48–0.86	0.64; 0.47–0.86	21.3	59.0	1.9	25.7
	D n=119	0.78; 0.58–1.04	0.78; 0.58–1.04	14.3	49.6	1.9	9.5
	S n=119			5.0	48.7	2.8	17.0
HCV	**STRIDE** n=110	1.06; 0.76–1.49	0.89; 0.63–1.25	35.5	65.5	3.6	13.5
	D n=107	1.05; 0.75–1.48	0.93; 0.66–1.31	22.4	57.9	2.0	12.9
	S n=104			9.6	70.2	7.3	15.7
NV	**STRIDE** n=161	0.74; 0.57–0.95	0.77; 0.59–1.00[b]	18.0	57.1	2.1	13.2
	D n=163	0.82; 0.64–1.05	0.80; 0.62–1.03	19.0	56.4	3.7	13.8
	S n=166			6.0	63.3	3.7	6.0

[a]Adjusted for EHS and ALBI. [b]n=160; one pt with missing ALBI score excluded.

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[13 – DISTINGUISHED ABSTRACT] MOLECULAR PROFILING OF HEPATOCELLULAR CARCINOMA PREDICTS OUTCOMES POST LIVER TRANSPLANT

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Abstract Categories: Surgical Therapy including Transplant Surgery; Translational, Pre-Clinical

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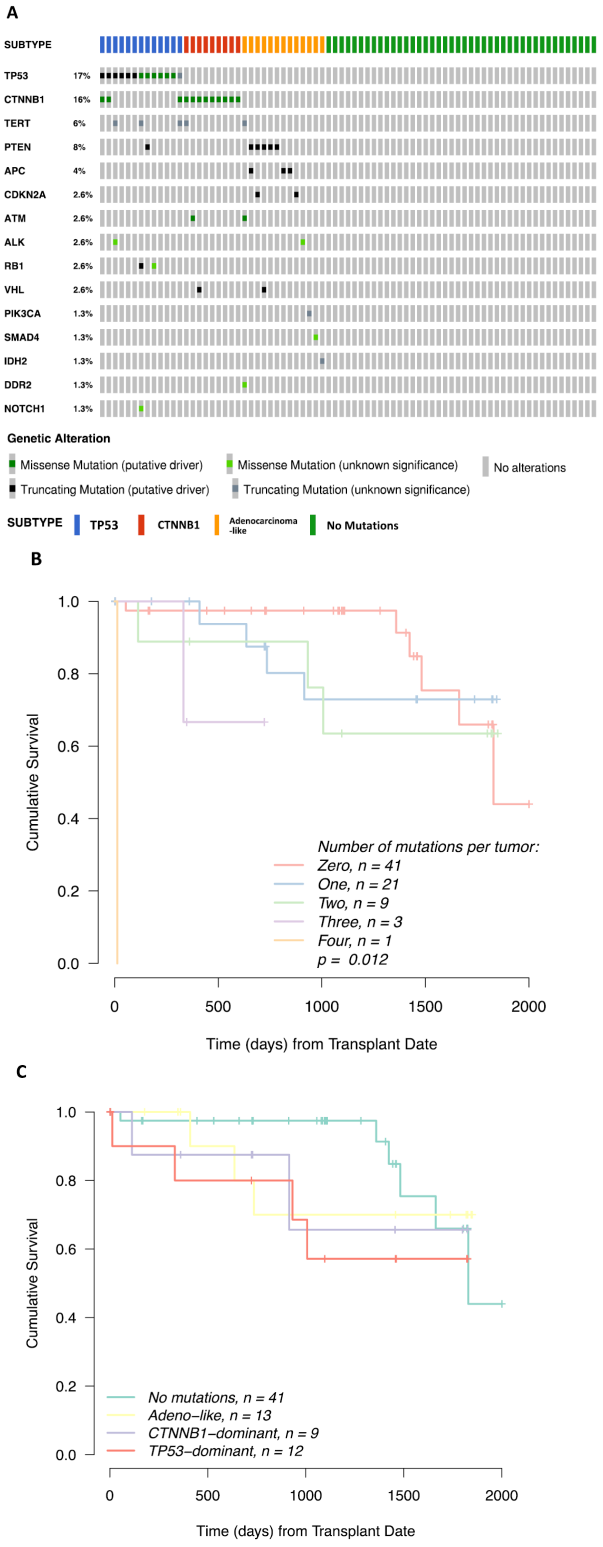
Background/Aim: Hepatocellular carcinoma (HCC) is a potentially lethal malignancy with rising incidence and mortality rates in the United States and globally. Though best outcomes are achieved by liver transplantation (LT), current selection criteria based on tumor size and number may not reflect tumor biology, can restrict patient access and do not guide adjunct therapy. There is a need for translation of advances in tumor molecular biology to better inform HCC care.

Methods: We performed targeted next-generation sequencing (NGS) of 50 genes in 77 HCC specimens from 77 patients. Formalin-fixed paraffin-embedded tumor specimens were obtained from liver explants following LTs performed between January 2016 and December 2022 at a single center. Median post-operative follow-up was 1095 days. NGS read alignment and annotation adhered to guidelines from the National Cancer Institute Genomic Data Commons. Analyses were performed in R.

Results: Somatic mutations were detected in 15 genes in 35 (45% of 77) specimens. The most frequently altered driver genes included TP53 (17%), CTNNB1 (16%), PTEN (8%), APC (4%), and the TERT promoter region (6%; Figure 1). Mutual exclusivity was not observed. Non-supervised k-means clustering by genetic alterations identified four subtypes: TP53-dominant (n=13, 17%), CTNNB1-dominant (n=9, 12%), Adenocarcinoma-like (n=13, 17%), and no observed driver gene mutations (n=42, 55%). Adenocarcinoma-like cases were histologically consistent with HCC but only bore alterations in genes more frequently associated with luminal tumors, including PTEN, APC, PIK3CA, SMAD4, and IDH2. Adenocarcinoma-like cases were qualitatively distinct clinically, with lower age, BMI, and Model for End-Stage Liver Disease score at transplant, as well as being more common in non-Caucasians, females, and HCV-positive patients. CTNNB1-dominant trended towards HBV positivity and alcohol use, while TP53-dominant subtypes were larger tumors seen in older patients. At the univariate level, better outcomes were seen with carriers of PTEN, APC and VHL alterations, whereas poorer outcomes were seen with TERT and TP53 mutations as well as higher numbers of driver gene mutations overall (Figure 1B). In a multivariable Cox proportional hazards model, CTNNB1- and TP53-dominant subtypes were significantly associated with worse outcomes than No Mutation and Adenocarcinoma-like subtypes (Figure 1C), as was lympho-vascular invasion.

Conclusions: Molecular profiling of HCC is associated with both clinical variables and outcomes. This may potentially inform pre-LT patient selection and post-LT surveillance. For example, worse outcomes seen with higher HCC mutational burden may suggest a role for immunotherapy pre-LT in these patients. More so, an adenocarcinoma-like subtype identified here with HCC histology yet clinical and molecular features resembling cholangiocarcinoma may also benefit from tailored systemic therapy. Future work will characterize patients' HCC molecular profiles pre-LT to direct appropriate candidates to clinical trials.

Figure 1: A. Oncoprint summarizing HCC sequencing and subtype clustering. B, C. Post-LT patient survival stratified by number of mutations (B) or HCC subtype (C).



[1]
LIVER STEREOTACTIC BODY RADIOTHERAPY (SBRT) WITH SUPER-PARAMAGNETIC IRON OXIDE NANOPARTICLES (SPION) USED AS MRI-CONTRAST AGENT ON MR-LINAC: PRELIMINARY RESULTS OF PROSPECTIVE STUDY

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Abstract Category: Locoregional Therapy

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Background:

Ferumoxytol® (Feraheme, AMAG Pharmaceuticals, Waltham, MA) is a SPION agent that is increasingly utilized off-label as MRI contrast agent. In addition to its excellent safety profile in patients with impaired kidney function, this agent has the advantage of providing a functional assessment of the liver based upon its uptake within hepatic Kupffer cells proportionate to vascular perfusion, resulting in strong T2 and T2* relaxation effects and enhanced contrast of malignant tumors, which lack Kupffer cells. The latter characteristic is especially important in patients with advanced cirrhosis, and those who have undergone prior liver-directed therapies, in whom the functional liver reserve may be overestimated by conventional imaging techniques. The purpose of this study was to assess visibility of liver tumors and functional hepatic parenchyma utilizing SPION-enhanced 1.5T MRI during per-fraction adaptive SBRT planning on the Elekta Unity MR-Linac (Elekta; Sweden) in patients with pre-existing liver conditions. A second goal of this study was to determine radiomodulating properties of human monocytes and macrophages loaded with SPIONs *in vitro*.

Methods: Patients underwent MRI simulation after Ferumoxytol® injection for visualization of hepatic parenchyma. SPION-enhanced MR image set of tumor and functional hepatic parenchyma during per-fraction MR-guided liver SBRT was acquired for online treatment plan adaptation. Functional liver volumes (FLV) obtained from SPION-MRI were compared to anatomical liver volumes, as were dosimetric parameters when radiation dose constraints were adapted exclusively to FLV. Hepatic function, toxicity, and radiographic response were documented every 3 months following SBRT.

For the *in vitro* study human monocyte and macrophages cell line in cultures were loaded with clinically relevant concentration of Ferumoxytol for 2 and 24 h and irradiated at SBRT dose range. Cells were cultured for additional 24 and 48 h prior to assessing their phenotypic activation, viability, proliferation and cytokine expression.

Results: With median follow-up of 6.5 months, 16 patients with primary (12) and metastatic (4) liver malignancies completed SPION-enhanced MRI simulations and received MRI guided SBRT to a median dose 46.5 Gy in 1–5 fractions on Elekta Unity 1.5T MR-Linac. All patients in this study had pre-existing liver conditions including Child-Pugh B hepatic cirrhosis (7), prior liver resections (4), prior TACE (3), HAI (1) or combinations of the above (5). An automated contouring algorithm was generated for delineation and guided avoidance of residual best functional hepatic parenchyma identified on SPION-MRI during liver SBRT planning. Prolonged SPION-contrast retention within functional hepatic parenchyma allowed daily per-fraction treatment plan adaptation with superior MR visualization of tumors throughout the entire treatment course. Functional volume loss was observed in all patients (mean, 586.5 cc or 46.3%, $p< 0.0001$). While tumors received ablative irradiation, the mean dose to residual FLV was below tolerance in all patients at 136.80 cGy difference with mean dose to the total liver volume on MRI ($p=0.03$). One patient completed liver transplant at 3 months after completion of SBRT as a bridge to transplant. No incidence of RILD or Child-Pugh class migration was observed at 4+ months post SBRT. Treatment toxicity was limited to Grade ≤2 fatigue.

Results of the *in vitro* study demonstrate that SPION affected both human monocytes and macrophages. Specifically SPION decreased radiation-induced apoptosis and prevented radiation-induced inhibition of human monocyte proliferative activity. Furthermore, Ferumoxytol protected monocytes from radiation-induced modulation of phenotype. For example in macrophages, Ferumoxytol counteracted the ability of radiation to up-regulate cell polarization to $CD11b^{+}CD14^{+}$ phenotype, and prevented radiation-induced down-regulation of expression of HLA-DR and CD86. Finally, Ferumoxytol uptake by human monocytes down-regulated expression of pro-inflammatory chemokines. In macrophages, Ferumoxytol reversed the effect of radiation on the expression of IL-1RA, IL-8, IP-10 and TNF-α, and up-regulates expression of MCP-1 and MIP-1α. The effect is radiation dose-dependent and depends on the duration of Feraheme uptake.

Conclusion: This is the first report detailing the use of the SPION contrast agent Ferumoxytol® for enhanced visualization of liver tumors and assessment of residual functional hepatic parenchymal volume during per-fraction adaptive planning of liver SBRT on 1.5T Elekta Unity MR-Linac. We report low toxicity and excellent local control leading to satisfactory outcomes in patients with pre-existing liver conditions. Ferumoxytol increases resistance of human monocytes to radiation-induced cell death *in vitro* and supports anti-inflammatory phenotype of human macrophages under radiation.

[6]
PATIENT-REPORTED SYMPTOMS AND INTEREST IN ELECTRONIC SYMPTOM MONITORING AMONG PATIENTS WITH HEPATOCELLULAR CARCINOMA RECENTLY TREATED WITH LOCOREGIONAL THERAPIES

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Abstract Category: Locoregional Therapy

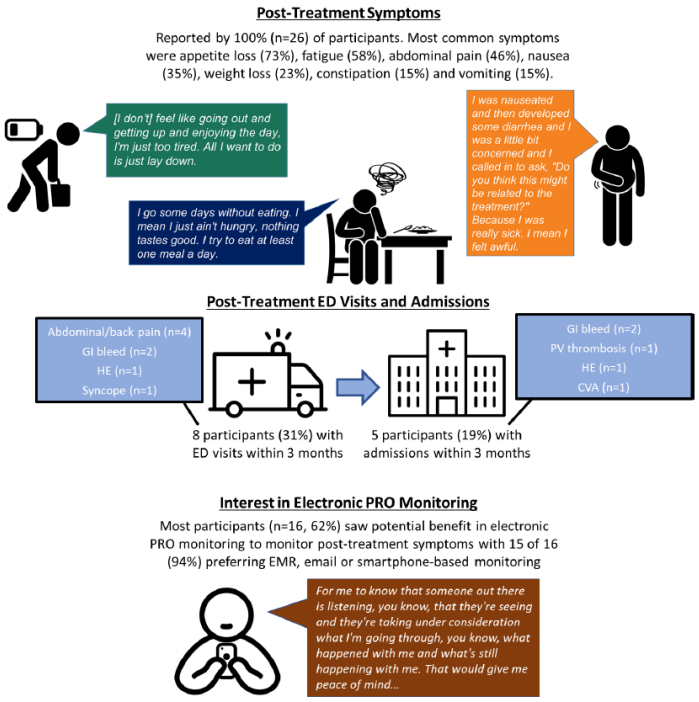
Background/Aims: Understanding and monitoring post-treatment symptoms among patients with hepatocellular carcinoma (HCC) who received locoregional therapies (LRT) could improve treatment decisions and post-treatment outcomes. Recent evidence, including the multicenter PRO-TECT Trial, demonstrated that electronic patient reported outcome (ePRO) monitoring significantly improves patients' health-related quality of life, decreases healthcare utilization and improves overall survival in patients with metastatic cancer. The effect of monitoring ePROs has not yet been assessed in patients with HCC. We conducted a qualitative study using semi-structured individual interviews with adult patients who had recently undergone LRT for HCC to (1) identify common and distressing post-treatment symptoms and (2) gauge patient interest in an ePRO symptom monitoring system.interviews with adult patients who had recently undergone LRT for HCC to (1) identify common and distressing post-treatment symptoms and (2) gauge patient interest in an ePRO symptom monitoring system.

Methods: This was a single-center qualitative study that included 26 adult patients who received transarterial chemoembolization (TACE), transarterial radioembolization (TARE), thermal ablation, or stereotactic body radiation therapy (SBRT) for treatment-naïve HCC. Trained qualitative interviewers performed semi-structured post-treatment telephone interviews to assess patients' symptoms and interest in ePRO monitoring. Interviews were performed a median of 26 days (IQR 21-33) after treatment. Interviews were audio recorded and transcribed. Qualitative content analysis was conducted to identify emerging themes and sub-themes.

Results: The study included 26 participants with HCC who received TACE (n=10, 38%), TARE (n=6, 24%), SBRT (n=6, 24%) or thermal ablation (n=4, 15%). Participants had a median age of 67 years (range 40-86), were predominantly male (n=20, 77%), white (n=20, 77%) and with CP-A cirrhosis (n=22, 84%). Half (n=13) of the participants had very early or early stage (BCLC-0/A) HCC. Eight participants (31%) had advanced stage (BCLC-C) HCC due to an ECOG performance status of 1 or 2. A total of 16 (62%) participants described no symptoms prior to HCC diagnosis. Conversely, all participants (n=26, 100%) reported at least one post-treatment physical symptom. The most common symptoms were appetite loss (n=19, 73%), fatigue (n=15, 58%), abdominal pain (n=12, 46%), and nausea (n=9, 35%). Other potentially actionable symptoms included vomiting, diarrhea, dizziness, urinary retention/frequency and feelings of fear, anger, depression, and loneliness. Eight participants (31%) had an emergency department (ED) visit within 3 months post-treatment and five participants (19%) required inpatient hospitalizations in the 3 months after treatment. The sample size precluded definitive between-treatment comparisons. However, post-treatment symptoms, and particularly GI-related side effects, were particularly common after intraarterial therapies. SBRT was well tolerated by most participants but placement of fiducials was often described as unexpected and uncomfortable. The most common post-ablation symptoms were bleeding or discomfort at the laparoscope or probe insertion site. Most participants (n=16, 62%) stated they saw potential benefit in post-treatment ePRO symptom monitoring and, among these, 15 (94%) preferred remote electronic surveys using email, patient electronic chart communication or text/FaceTime on a smartphone. Participant recommendations for frequency of ePRO symptom monitoring ranged from weekly, biweekly, or monthly using remote electronic surveys.

Conclusions: This qualitative study of patients with HCC who had recently received LRTs identified many different physical and psychological symptoms, including some that led to ED visits. Most patients expressed interest in an ePRO monitoring system that could be used by the HCC care team to monitor and proactively address post-treatment symptoms. Given the demonstrable clinical benefits in patients with metastatic cancers, ePRO monitoring warrants investigation in patients who have received LRT for HCC.

Figure 1: Post treatment symptoms, health care utilization and interest in electronic PRO monitoring among patients with HCC who have received locoregional therapies.



[12]
A PROSPECTIVE, MULTICENTER, OPEN-LABEL, CLINICAL TRIAL DESIGN TO EVALUATE THE SAFETY AND EFFICACY OF Y90 RESIN MICROSPHERES FOR TREATMENT OF UNRESECTABLE HEPATOCELLULAR CARCINOMA (HCC): DURATION OF OBJECTIVE RESPONSE WITH ARTERIAL YTTRIUM-90 (DOORWAY^{90})

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Abstract Category: Locoregional Therapy

Disclosure statements:

AM: Research grant from Sirtex Medical, Boston Scientific/BTG, Siemens Healthineers, ABK Biomedical. Consultant: Sirtex Medical, ABK Biomedical

SG: Former employee of Sirtex Medical

SB: No disclosures

RS, DJ: Current employees of Sirtex Medical

SK: Research grant from Sirtex Medical, Boston Scientific, ABK Biomedical. Consultant: Boston Scientific, Terumo Medical

DOORwaY^{90} is sponsored by Sirtex Medical, Woburn, MA. NCT04736121.

Background: HCC is often diagnosed when potentially curative resection or transplantation is not feasible. Selective internal radiation therapy (SIRT) with Y90 resin microspheres (SIR-Spheres®) is an established locoregional treatment option for unresectable HCC with regulatory approval outside the USA. SIRT has the potential to deliver a lethal dose of radiation to hepatic tumors, while sparing surrounding healthy liver tissue. SIRT has been successfully used to bridge patients to transplantation or downstage HCC to within transplantation criteria or resection.

DOORwaY^{90} is a pivotal, prospective, multicenter, open-label single arm study designed to evaluate the safety and effectiveness of Y90 resin microspheres as first-line treatment in patients with unresectable or unablatable HCC. DOORwaY^{90} is unique because it will be the first US registration trial to utilize and delineate personalized dosimetry treatment planning and to define actionable post-treatment dosimetric verification for endpoint assessment.

Methods: For each patient, an eligibility review committee will review diagnostic imaging and confirm final eligibility and treatment planning. Key eligibility criteria include unresectable/unablatable HCC (LI-RAD 4/5 or by histology); Barcelona Clinic Liver Cancer (BCLC) stage A, B1, B2, or C with maximal single tumor diameter ≤8 cm and maximal sum of all tumor diameters of ≤12 cm; at least one tumor ≥1 cm (long axis) per RECIST; no macrovascular invasion; no extrahepatic disease; Child-Pugh score A5 or A6; and ECOG≤1. Personalized dosimetry, using the partition method, which is based on anatomic and physiologic imaging, will determine the prescribed Y90 activity. For efficacy, the target mean dose to tumor is ≥150 Gy. For safety, >33% total liver volume must be disease free and spared of SIRT. Target mean dose to lungs is <30 Gy for single treatment and <50 Gy cumulative dose for repeat treatment. Infusion of Y90 resin microspheres is from subsegmental to lobar approach based on investigator preference. Post-treatment dosimetry is confirmed using Y90 SPECT/CT or Y90 PET/CT with SurePlan™ LiverY90 dosimetry software. SIRT retreatment can be performed within 4 weeks if post-treatment dosimetry indicates mean dose to tumor(s) was <75 Gy. Imaging and lab assessments occur at 2-, 4-, 6-, 9-, and 12-months follow-up and safety data are captured up to 24 months follow-up.

Co-primary endpoints are 1) overall response rate (ORR) by localized mRECIST criteria through 9 months and 2) duration of response, defined as the interval from partial or complete response to disease progression as defined by localized mRECIST criteria. Secondary endpoints include grade ≥3 toxicity (CTCAE v5.0) at 2 and 6 months, QoL (FACT-Hep and EQ-5D-5L) and incidence of liver resection and transplantation post-SIRT.

Results/Conclusions: Target recruitment is up to 100 patients. The study is conducted in accordance with the Declaration of Helsinki and approved by ethics committee. At the time of submission, DOORwaY[90] is open to enrollment. The use of personalized dosimetry can potentially inform effective treatment approaches, supporting continued investigation.

Clinical Trial Registry Number: NCT04736121.

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[2]
IPILIMUMAB PLUS NIVOLUMAB COMBINATION THERAPY IN ADVANCED HEPATOCELLULAR CARCINOMA AFTER PRIOR PD-(L)1 BLOCKADE

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Abstract Category: Systemic Therapy (non-trials)

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Background/Aim: Combination PD-(L)1/CTLA-4 inhibitor therapy is approved in patients with hepatocellular carcinoma (HCC) in the first line setting or after prior treatment with sorafenib. Whether this treatment has efficacy after prior anti-PD-(L)1 therapy is not known. We evaluated responses to ipilimumab (IPI, anti-CTLA-4) plus nivolumab (NIVO, anti-PD-1) in patients with HCC previously treated with anti-PD-(L)1 therapy.

Methods: We performed a multicenter retrospective review of patients with advanced stage HCC treated with IPI+NIVO after prior anti-PD-(L)1 therapy. Patients with prior treatment with anti-CTLA4 therapy were excluded.

Results: 31 patients met inclusion criteria, of whom 48.4% received bevacizumab plus atezolizumab and 32.3% received prior anti-PD-1 (nivolumab or pembrolizumab). The median number of prior lines of systemic therapy was two (range 1-8). The ORR with IPI+NIVO was 22.6% (1 CR, (3.2%), 6 PR (19.4%)), 8 SD (25.8%), 15 PD (48.4%), and 1 NE (3.2%). Among patients who had an objective response to IPI+NIVO, none had an objective response to prior PD-(L)1 inhibition. Response rates were similar across major clinical and etiological subsets of HCC. Responses with IPI+NIVO were associated with improved PFS and OS: median PFS for PD/SD/NE 2.4 months (95% CI: 2.0-NR) vs. PR/CR not reached (NR) (95% CI: 7.5-NR), p = 0.004, and OS for PD/SD/NE 5.9 months (95% CI: 3.1-NR) vs. PR/CR NR (95% CI: NR-NR), p = 0.02. Immune related adverse events (irAEs) were reported in 13 patients (41.9%), and six patients experienced grade 3-4 irAEs (19.4%). One patient experienced a fatal irAE (autoimmune hepatitis). Five patients discontinued IPI+NIVO due to irAEs.

Conclusions: IPI+NIVO has clinical efficacy in patients with HCC previously treated with anti-PD-(L)1 therapy, suggesting that prior PD-(L)1-based treatment should not preclude the use of IPI+NIVO. Prospective studies are needed to define the optimal sequence of therapies in HCC.

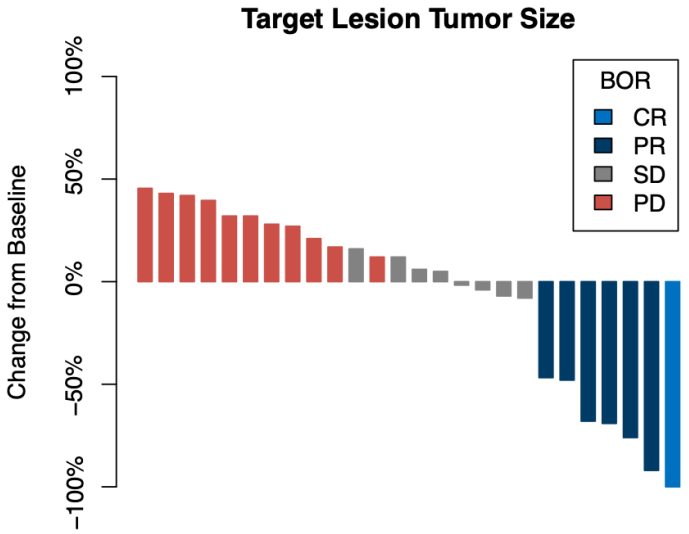

Table 1. Best Overall Response to Ipilimumab plus Nivolumab

PD	15 (48.4%)
SD	8 (25.8%)
PR	6 (19.4%)
CR	1 (3.2%)
NE	1 (3.2%)

[8]
ADVERSE EVENT PROFILES AND TIME TO ONSET AND RESOLUTION WITH TREMELIMUMAB PLUS DURVALUMAB IN PATIENTS WITH UNRESECTABLE HEPATOCELLULAR CARCINOMA IN THE PHASE 3 HIMALAYA TRIAL

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Abstract Category: Systemic Therapy (trials)

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Background/Aim: In the Phase 3 HIMALAYA study (NCT03298451) of unresectable hepatocellular carcinoma (uHCC), a single, high priming dose of tremelimumab (T) plus durvalumab (D) in the STRIDE regimen significantly improved overall survival (OS) versus sorafenib (S), and D monotherapy was noninferior to S. Incidences of treatment-related adverse events (TRAEs) of Grade 3 or 4 and those leading to treatment discontinuation were generally lower for STRIDE and D, than for S (Abou-Alfa et al. *NEJM Evid* 2022;1(8)). To further assess the safety of STRIDE and D, we analyzed the adverse event (AE) profiles in the STRIDE, D and S arms, including time to onset (TTO) and time to resolution (TTR; if available) for TRAEs and immune-mediated (im)AEs, and TRAEs leading to discontinuation.

Methods: Safety was assessed in patients (pts) who received at least one dose of STRIDE (T 300 mg plus D 1500 mg [one dose] plus D 1500 mg once every 4 weeks [Q4W]; N=388), D (1500 mg Q4W; N=388) or S (400 mg twice daily; N=374). AEs were captured for individual pts in MedDRA preferred terms. Treatment causality was assessed by the investigator. TTO and TTR were analyzed descriptively.

Results: Duration of exposure to D was 327.2 and 312.7 total treatment years for the STRIDE and D arms, respectively. Duration of exposure to S was 234.9 total treatment years. The median (interquartile range) number of treatment cycles of D received was 6.0 (2.0–16.0) for STRIDE and 5.0 (3.0–14.5) for D. TRAEs occurred in 294 (75.8%) pts on STRIDE, 202 (52.1%) pts on D and 317 (84.8%) pts on S. TRAEs that occurred in ≥10% of pts in the STRIDE or D treatment arms were rash, pruritis, diarrhea and hypothyroidism (Table). TRAEs leading to discontinuation occurred in 32 (8.2%) pts on STRIDE, 16 (4.1%) pts on D and 41 (11.0%) pts on S. TRAEs leading to discontinuation that occurred in >1 pt in the STRIDE or D treatment arms included pneumonitis (STRIDE, 2 [0.5%]), colitis (STRIDE, 2 [0.5%]), diarrhea (STRIDE, 2 [0.5%]), hepatitis (STRIDE, 4 [1.0%]), immune-mediated hepatitis (STRIDE, 3 [0.8%]), rash (STRIDE, 2 [0.5%]), alanine aminotransferase increased (STRIDE, 2 [0.5%]; D, 2 [0.5%]), and aspartate aminotransferase increase (STRIDE, 2 [0.5%]). TRAEs leading to death occurred in 9 (2.3%) pts on STRIDE, 0 pts on D and 3 (0.8%) pts on S. imAEs of any grade occurred in 139 (35.8%) pts on STRIDE, 64 (16.5%) pts on D and 30 (8.0%) pts on S. imAEs of any grade requiring high-dose steroids (≥40 mg prednisone or equivalent per day) occurred in 78 (20.1%) pts on STRIDE, 37 (9.5%) pts on D and 7 (1.9%) pts on S. imAEs of any grade leading to discontinuation occurred in 22 (5.7%) pts on STRIDE, 10 (2.6%) pts on D and 6 (1.6%) pts on S. imAEs of any grade that occurred in ≥5% of pts in any treatment arm were hepatic events, diarrhea/colitis and hypothyroid events (Table).

Conclusions: The AE profiles of STRIDE and D in HIMALAYA were consistent with known safety profiles. STRIDE and D were tolerable, with manageable AEs per treatment guidelines and low rates of discontinuation due to TRAEs. Median TTO of common AEs was generally less than 90 days with STRIDE or D; TTR varied by the type of AE. OS and safety data from HIMALAYA support STRIDE and D as new treatment options for pts with uHCC.

Table. Frequency and median (range) TTO/TTR (days) for common TRAEs/imAEs.

TRAE	STRIDE (N=388)	D (N=388)	S (N=374)
Rash, n (%)	76 (19.6)	29 (7.5)	46 (12.3)
TTO;	16.0 (1–989);	48.0 (1–419);	15.5 (5–503);
TTR	38.0 (2–1027)	29.0 (2–408)	36.5 (2–577)
Pruritis, n (%)	66 (17.0)	28 (7.2)	21 (5.6)
TTO;	29.0 (1–733);	43.5 (1–732);	17.0 (2–432);
TTR	45.0 (3–739)	37.0 (3–496)	18.0 (6–270)
Diarrhea, n (%)	64 (16.5)	23 (5.9)	145 (38.8)
TTO;	23.0 (1–344);	78.0 (2–542);	29.0 (1–927);
TTR	21.0 (1–246)	6.5 (1–56)	27.0 (1–654)
Hypothyroidism n (%)	42 (10.8)	15 (3.9)	8 (2.1)
TTO;	85.0 (26–1197);	175.0 (62–951);	63.5 (1–195);
TTR	140.0 (15–460)	31.0 (31–31)	28.0 (28–28)
imAE			
Hypothyroid events, n (%)	42 (10.8)	19 (4.9)	11 (2.9)
TTO;	85.0 (26–763);	165.0 (1–951);	55.0 (1–755);
TTR	195.5 (15–460)	NC	207.0 (55–359)
Hepatic events, n (%)	29 (7.5)	26 (6.7)	1 (0.3)
TTO;	29.0 (13–313);	29.0 (15–258);	167.0 (167–167);
TTR	71.5 (8–382)	44.0 (13–154)	141.0 (141–141)
Diarrhea/colitis, n (%)	23 (5.9)	3 (0.8)	1 (0.3)
TTO;	18.0 (2–327);	63.0 (11–215);	8.0 (8–8);
TTR	31.5 (7–99)	NC (NC–NC)	127.0 (127–127)

NC, not calculable.

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[14]
TEGAVIVINT: A FIRST-IN-CLASS TRANSDUCIN β-LIKE PROTEIN 1 (TBL1) INHIBITOR TARGETING WNT/BETA-CATENIN SIGNALING IN PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA HAVING BETA-CATENIN ACTIVATING MUTATIONS

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Abstract Category: Systemic Therapy (trials)

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Background: Hepatocellular cancer (HCC) is the 3rd leading cause of death worldwide with approximately 40% of patients possessing a beta-catenin pathway activating mutation. Despite recent progress in combination with VEGF inhibition, resistance to immune checkpoint inhibitors (ICI) still occurs in the majority of HCC patients. Recent studies suggest that activated beta-catenin regulates both tumor metabolism and immune microenvironment in CTNNB1-mutated HCCs. These data suggest that targeted inhibitors of Wnt/beta-catenin signaling may be useful in the treatment of HCC.

Transducin β-like protein 1 (TBL1) has been demonstrated to be necessary for beta-catenin oncogenic activity. During Wnt-signaling, TBL1 binds to beta-catenin, inhibiting its degradation, and forms an active transcriptional complex that binds to promoters to activate downstream cancer-related genes such c-MYC, Cyclin D1 and others. Mutations and translocations of TBL1 have also been observed in multiple types of cancers. High expression of TBL1 is associated with poor prognosis and unfavorable characteristics in HCC. Tegavivint is a first-in-class small molecule inhibitor of TBL1, a novel downstream Wntsignaling pathway target. Tegavivint binds to TBL1 in the beta-catenin pocket, disrupting the formation of the activation complex necessary for oncogenic activity.

Tegavivint also enables the degradation of free nuclear beta-catenin. Increased expression of beta-catenin and TBL1 are associated with metastasis and poor prognosis in a broad range of cancers. Importantly, tegavivint's targeting of TBL1 does not affect membrane-bound and cytoplasmic beta-catenin pools necessary for normal cellular function, avoiding toxicities commonly associated with other inhibitors of the Wnt pathway. The safety, pharmacodynamics, pharmacokinetics, and clinical activity of tegavivint was demonstrated through a proof-of-concept study in desmoid patients with activating beta-catenin mutations and is currently being studies through Investigator Initiated Trials (IITs) in AML, pediatric solid tumors, NSCLC, and lymphoma.

Materials and Methods: Tegavivint was studied preclinically in a genetically engineered C57BL/6J mouse model of β-Catenin^{exon3} mutant HCC and the H22 syngeneic HCC model. Both models were used to evaluate tegavivint activity relative to vehicle controls. In addition to measuring tumor volume and number, immunohistochemistry was used to characterize the immune microenvironment and the expression of TBL1 and canonical Wnt target genes. Based on activity observed in these models, the FDA has allowed a phase 1/2 exploratory study of the TBL1 inhibitor, tegavivint (BC2059), in patients with advanced hepatocellular carcinoma.

Results: This is a phase 1/2, open-label study of tegavivint in patients with advanced hepatocellular carcinoma to characterize safety, pharmacokinetics, pharmacodynamics, and preliminary antitumor activity. This study will be conducted in 2 parts. First, tegavivint will be administered as a single agent in a dose escalation/optimization and subsequent expansion cohort at the recommended phase 2 dose in advanced hepatocellular carcinoma (HCC) patients who have progressed after at least one prior line of systemic therapy. Dose escalation will follow a standard 3+3 design to determine the tegavivint maximum tolerated dose (MTD). Upon completion of the dose escalation review of all available safety, efficacy, PK and PD data the Safety Review Committee will recommend two dose levels for dose selection optimization. The dose selection optimization will expand the two dose levels to at least 10 patients before declaring the recommended phase 2 dose (RP2D). The RP2D will be explored in the monotherapy dose expansion in advanced HCC patients with mutations in either *CTNNB1* or *AXIN1* genes. If sufficient clinical benefit is observed, the combination of tegavivint with pembrolizumab in patients with mutations in either *CTNNB1* or *AXIN1* genes and previously treated with a PD-1/PD-L1 inhibitor will be explored in the second part of the study.

Primary objectives are to assess safety, dose limiting toxicities (DLTs), MTD or maximum administered dose (MAD), and RP2D of tegavivint alone and in combination with pembrolizumab. Secondary objectives include evaluating preliminary efficacy of tegavivint first alone, and then in combination with pembrolizumab by Response Evaluation Criteria in Solid Tumors (RECIST v1.1); and characterize pharmacokinetics and pharmacodynamics of tegavivint alone and in combination with pembrolizumab.

Tegavivint will be administered intravenously on day 1, 8, 15, and 22 of a 28-day cycle in the single agent dose escalation and expansion. In the combination dose escalation and expansion, tegavivint will be administered on day 1, 8, and 15 of a 21-day cycle with pembrolizumab 200 mg via a 30-minute IV infusion on day 1 of the 21-day cycle.

Conclusions: Nearly 40% of HCC patients harbor beta-catenin pathway activating mutations and recent evidence demonstrate that elevated nuclear beta-catenin levels correlate with poor responses to standard of care in these patients. Tegavivint is a first-in-class inhibitor of TBL-1, a necessary co-activator for nuclear beta-catenin's oncogenic activity. This Phase 1/2 clinical study was declared safe to proceed by the FDA and will study tegavivint in advanced HCC patients with activating beta-catenin mutations. Completion of this study will provide valuable data on the therapeutic potential for inhibiting nuclear beta-catenin activity through targeting TBL1 in HCC.

[11]
COMBINATION OF FATTY ACID SYNTHASE INHIBITOR WITH TYROSINE KINASE INHIBITORS SHOWS SYNERGISTIC EFFICACY IN HCC PRECLINICAL MODELS, A NOVEL POTENTIAL APPROACH FOR CLINICAL DEVELOPMENT

Marie O'Farrell[1], Haichuan Wang[2,3], Eduardo B. Martins[1], Wen-Wei Tsai[1], George Kemble[1], Xin Chen[2,4]

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Abstract Category: Translational, Pre-Clinical

Background: Hepatocellular carcinoma (HCC) is the most common form of liver cancer, and the third highest cause of cancer mortality globally. HCC is a heterogeneous disease both at the molecular level and etiology. Immune therapy combinations have shown recent promise in treatment of HCC, but response rates are relatively low (approximately 30% with the new standard of care of atezolizumab and bevacizumab). There is a major need for new treatment strategies coupled with enrichment for HCC patient subsets most likely to respond. Fatty acid synthase (FASN) is the rate-limiting enzyme in the de novo lipogenesis (DNL) pathway and is upregulated in HCC. Tumors upregulate DNL to produce lipids required for membrane production, metabolism, intracellular signalling, and to prevent ferroptosis. Genetic and pharmacology studies in mouse HCC models have shown that FASN is required for neoplastic progression induced by overexpression of AKT, c-MET or MYC, or loss of PTEN. Denifanstat (TVB-2640) is a first in class FASN inhibitor in Ph2b development for nonalcoholic steatohepatitis (NASH). In NASH clinical trials, denifanstat decreases DNL, liver fat and biomarkers of inflammation and fibrosis. Denifanstat may also have application in treatment of HCC. The recommended Ph2 dose in oncology has been established in a Ph1 cancer study.

Objective: To test the efficacy of FASN inhibitors in combination with kinase inhibitors in mouse models of defined molecular subsets of HCC. The focus was on HCC models driven by oncogenes likely to be FASN-dependent based on prior genetic studies.

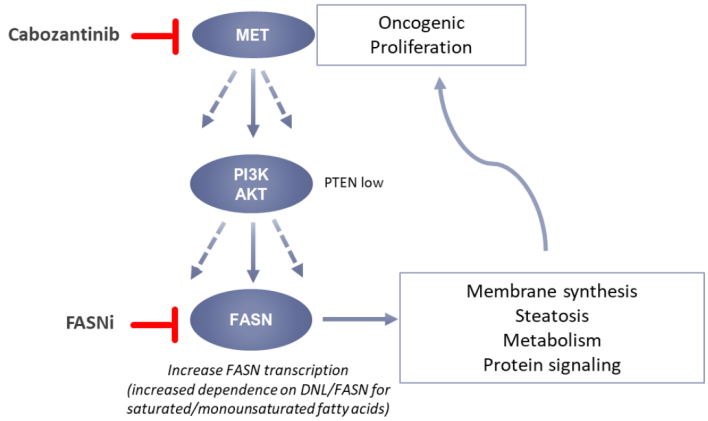
Methods: Mouse models of HCC were generated by hydrodynamic tail injection with plasmids expressing oncogenes including px330-Cas9-sgPTEN, pT3-EF1α-c-Met (human c-MET), pT3-EF1α-ΔN90-β-catenin (N-terminal Myc tag) or pT3EF1α-c-Myc. Mice were treated orally with the FASN inhibitor TVB-3664 and/or kinase inhibitors cabozantinib (inhibits MET and VEGFR) or sorafenib (inhibits RAF, VEGFR), and/or subcutaneous anti-PDL-1. TVB-3664 is a FASN inhibitor related to TVB-2640 but with superior mouse pharmacokinetics. Tumor size was measured

by liver weight. Gene and protein expression were assessed by RNA-Seq or western blot. Tumor features were analyzed by IHC or Oil-Red O staining.

Results: Analysis of the Cancer Genome Atlas indicated that human HCC patients with high MET/low PTEN constitute 34% of human HCC (n=120). This subset showed a poorer survival versus other subgroups (37 versus 69 to 83 months). A mouse model of MET high/PTEN low (sgPTEN/c- MET) HCC was established. Three-week treatment with TVB-3664, cabozantinib or both was initiated when moderate tumor burden was established. Single agent treatment with TVB-3664 (10 mg/kg) or cabozantinib (60mg/kg) slowed tumor growth but did not regress tumors. The combination decreased tumor size below pre-treatment levels indicating tumor regression. Severe hyperlipidemia in the sgPTEN/c- MET tumor-bearing mice was also ameliorated by combination treatment, and TVB-3664 single agent or combination significantly reduced lipid accumulation in tumor nodules measured by Oil-Red O. Combination treatment significantly decreased the PTEN negative areas and Ki-67 positive areas. RNA-Seq and protein phosphorylation analysis of tumors showed that FASN inhibition primarily modulated metabolism, cabozantinib primarily inhibited cancer-related pathways while the combination also decreased p-AKT Thr308 and cell cycle–related proteins (CCND1, PCNA, and p-Rb). Additional HCC models showed that efficacy of the combination was also seen in a MYC HCC model for TVB-3664 with cabozantinib or sorafenib. However, FASN inhibition did not enhance efficacy in combination with cabozantinib in a Wnt-driven high MET model (β-cateninΔ90/c-MET), or with anti-PD-L1 treatment in the sgPTEN/c-MET HCC, although the immunogenicity of the latter model was not established in this study.

Conclusion: This preclinical series of studies indicates that specific subsets of HCC are FASN-dependent including HCC driven by high MET/low PTEN, or MYC. Combination therapy of a FASN inhibitor plus kinase inhibitors showed tumor regression in these models. Analysis of human clinical databases for gene signatures corresponding to FASN sensitivity is the next step to translate these findings to patient selection for clinical trial design. The incidence of NASH-related HCC is increasing consistent with world-wide NASH epidemic. FASN inhibition may provide an approach to treat both NASH and HCC.

Model for additive effect in FASN-dependent HCC



ORAL ABSTRACT PRESENTATION SCHEDULE

FEBRUARY 24, 2023

3:30–3:45 PM

Radiation Segmentectomy for Early-Stage Hepatocellular Carcinoma in Patients with Non-Alcoholic Steatohepatitis versus Chronic Viral Hepatitis
Locoregional Therapy

Cynthia De la Garza Ramos, MD
Interventional Radiology Resident
Mayo Clinic Florida
Jacksonville, FL

3:45–4:00 PM

Impact of viral etiology in the Phase 3 HIMALAYA study of tremelimumab (T) plus durvalumab (D) in unresectable hepatocellular carcinoma (uHCC)
Systemic Therapy (trials)

Mark Yarchoan, MD
Johns Hopkins Sidney Kimmel Comprehensive Cancer Center
Baltimore, MD

4:00–4:15 PM

Molecular Profiling of Hepatocellular Carcinoma Predicts Outcomes Post Liver Transplant
Surgical Therapy including Transplant Surgery

Ashton Connor MD, PhD, FRCSC
Abdominal Transplant and Hepatobiliary
J.C. Walter Jr. Transplant Center
Assistant Professor of Surgery
Houston Methodist Academic Institute
Assistant Clinical Member
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