Risk Factors and Natural History of Hepatocellular carcinoma (HCC): Observations following successful sofosbuvir-based treatment in HCV patients with cirrhosis

Poster # 4116-A

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Conclusions

- Patients with cirrhosis who achieved SVR remain at risk of HCC despite successful treatment
- Low albumin level, low platelet count, and F4 on LS are predictive of an increased risk of de novo HCC development in cirrhotic subjects with SVR post-DAA
- Majority of HCC cases developed greater than 2 years after treatment completion and therefore require close monitoring for an extended period following SVR

References:

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Introduction

- Hepatitis C virus (HCV) infection is a major risk factor for hepatocellular carcinoma (HCC)[1]
- The annual rate of progression to cirrhosis in chronic HCV infected patients with advanced fibrosis is ~10%. Approximately 1 to 4% of people per year with established cirrhosis will develop to hepatocellular carcinoma[2,3,4]
- Direct acting antivirals treatment for 8 to 12 weeks are the cornerstone of Hepatitis C therapy and are highly effective at clearing infection in more than 90% of patients[5]
- People living with HCV who have achieved sustained virologic response (SVR) after treatment remain at high risk of HCC[6]
- Limited data exist that clearly assess the potential predictors of HCC in people who have a history of HCV and residual advanced fibrosis and achieved successful eradication of HCV
- Therefore, there is a need to identify predictors of HCC development after SVR, to optimize the efficiency of HCC screening
- Prospective data collection was conducted through a Gilead-sponsored registry (#NCT02292706) that tracked individuals with HCV cirrhosis. These individuals had successfully achieved SVR using a sofosbuvir-based DAA regimen, and the data collection extended for up to 5 years[1]
- 14,848 individuals underwent treatment with IFN-free, DAA regimens, with 14,428 patients (97%) from the registry included in the analysis. 3,549 patients (25%) had compensated cirrhosis, while 607 patients (4%) had decompensated cirrhosis. Out of the 4,156 patients with liver cirrhosis, 1,557 patients reached 240-weeks of follow-up
- The vast majority; 99%, received SOF-based regimens, and 91% achieved SVR at 12 weeks

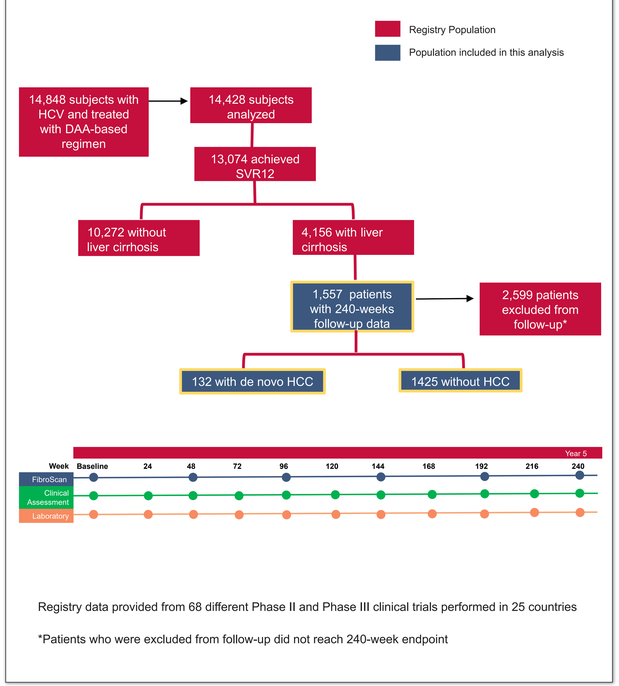
Objective

- Determine risk factors of HCC and characterize the natural history of HCC development in patients with cirrhosis who have achieved SVR with sofosbuvir-based direct-acting antiviral therapy (DAA)
- Calculate the incidence of HCC in patients with cirrhosis successfully treated with sofosbuvir-based regimen

Study Design

- This was a prospective, observational, registry-based study that evaluated risk factors for patients with HCV cirrhosis who had previously achieved SVR with a sofosbuvir-based DAA regimen for up to 5 years
- Key inclusion criteria for this analysis included:
  - Received an all-oral SOF-based regimen
  - Have achieved SVR-12, SVR was defined as HCV RNA < LLOQ approximately 12 weeks following last dose of treatment
  - Have liver cirrhosis, as defined in the treatment protocol and have not had a liver transplant after receiving a SOF-containing regimen
- Key exclusion criteria for this analysis included:
  - Individuals planning to initiate a new course of HCV therapy, including approved products and any investigational agents, during the course of this Registry
  - History of clinically-significant illness or any other major medical disorder that may interfere with the follow-up, assessments, or compliance with the protocol

Figure 1. Study Population & Assessments



Registry data provided from 68 different Phase II and Phase III clinical trials performed in 25 countries

*Patients who were excluded from follow-up did not reach 240-week endpoint

Methods

- Data were collected prospectively from a Gilead-sponsored registry which enrolled and followed people with HCV cirrhosis who had achieved SVR with a sofosbuvir-based DAA regimen for up to 5 years
- Primary outcomes included the development of HCC after successful treatment with DAA while followed in the registry
- Risk factors associated with the development of HCC were evaluated
- Baseline characteristics at time of entry into the registry after achieving SVR included: demographics, HCV genotype, prior HCV treatment experience, hemoglobin A1c, liver chemistries, Child-Pugh Turcotte score, enhanced liver fibrosis score (ELF) score (F0-F2 <9.8; F3 9.8-11.3; F4 >11.3) and liver stiffness (LS) by transient elastography (TE) (F0-F2 <9.5; F3 9.6-12.5; and F4 >12.5 kPa)
- Univariate and multivariate analyses were performed to determine risk factors for development of HCC and death by Cox regression analysis.
- A Kaplan-Meier plot was utilized to analyze time to HCC diagnosis in baseline CPT A vs CPT B+C Patients

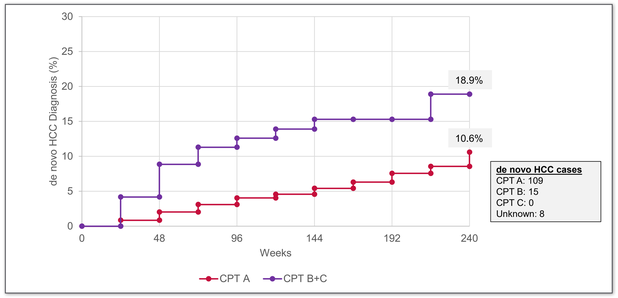
Results

Baseline Demographics and Disease Characteristics

		de novo HCC (n=132)	No HCC (n=1425)	Overall (n=1557)
Demographics and Baseline Characteristics	Mean age, y (range)	61 (46-81)	59 (26-86)	59 (26-86)
	Male, n (%)	97 (73.5%)	965 (67.7%)	1062 (68.2%)
	White, n (%)	119 (90.2%)	1232 (86.5%)	1351 (86.8%)
	Mean BMI, kg/m^2 (SD)	28.9 (4.83)	29.7 (6.13)	29.6 (6.03)
	Median MELD score (Q1, Q3)	8 (7, 10)	7 (6,9)	7 (6, 9)
	Median ELF score (Q1, Q3)	10.7 (9.9, 11.6)	9.8 (9.1, 10.7)	9.9 (9.2, 10.8)
	Median FIB4 score (Q1, Q3)	3.9 (2.3, 6.0)	2.4 (1.5, 4.0)	2.4 (1.6, 4.2)
	CPT score, n (%)			
	5	89 (67.4%)	1147 (80.5%)	1236 (79.4%)
	6	20 (15.2%)	106 (7.4%)	126 (8.1%)
	7	12 (9.1%)	60 (4.2%)	72 (4.6%)
	8	2 (1.5%)	22 (1.5%)	24 (1.5%)
	9	1 (0.8%)	8 (0.6%)	9 (0.6%)
	Median LS, kPa (Q1, Q3)	20.4 (12.6, 34.3)	13.9 (9.2, 21.3)	14.3 (9.5, 21.8)
	Mean platelet count, x10^3/µL (SD)	118.0 (59.87)	148.3 (68.68)	145.8 (68.48)
	Mean AFP level, ng/mL (SD)	74.8 (774.58)	10.5 (122.83)	16.0 (254.81)

- 90% of the individuals entered the registry >6 months post-end of treatment (EOT)
  - Mean time from EOT and entry into the registry was 57.3 wks for patients who developped HCC vs 59.4 wks for those without HCC
- Out of 1557 individuals in the registry, 132 (11.2%) developed de novo HCC

Time to HCC Diagnosis in CPT A vs CPT B+C Individuals



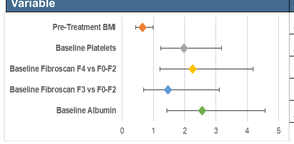
- Increased risk of de novo HCC with CPT B+C
- 12% of participants developed de novo HCC within the first 6 months after entering registry
- 52% of participants who developed de novo HCC were diagnosed greater than 2 years after entering the registry

Factors Associated with de novo HCC and Deaths

Univariate Analysis Cox Regression Model (n=132)			
Variable	**Comparison**	**Hazard Ratio (95% CI)**	**P-value**
Age	≥ 65 vs < 65 years	0.959 (0.621; 1.482)	0.8507
Sex	Male vs Female	1.388 (0.943; 2.043)	0.0963
Race	Black vs White	0.406 (0.166; 0.993)	0.0482
Pre-treatment BMI	≥ 30 vs < 30kg/m^2	0.917 (0.640; 1.314)	0.6362
CPT	CPT A vs CPT B+C	0.461 (0.269; 0.791)	0.0049
HCV Genotype	G3 vs Any Other	0.999 (0.665; 1.502)	0.9966
Prior treatment experience	Experienced vs Naïve	1.323 (0.878; 1.992)	0.1805
Baseline ALT	≤ 1.5 vs > 1.5XULN	1.457 (0.464; 4.572)	0.5193
Baseline HbA$_1$c	≥ 5.7 vs < 5.7%	0.809 (0.560; 1.170)	0.2604
Baseline Albumin	≤ 3.5 vs >3.5 g/dL	2.955 (1.750; 4.989)	<0.0001
Baseline LS by TE	F4 vs F0-F2	3.261 (1.819; 5.846)	<0.0001
	F3 vs F0-F2	1.674 (0.797; 3.518)	0.1739
Baseline Platelets	≤ 150 vs >150X10^3/uL	2.766 (1.828; 4.184)	<0.0001

Factors Associated with de novo HCC

Multivariate Analysis Cox Regression Model (n=132)			
Variable	**Comparison**	**Hazard Ratio (95% CI)**	**P-value**
Pre-Treatment BMI	≥ 30 vs < 30kg/m^2	0.652 (0.431; 0.989)	0.0441
Baseline Platelets	≤ 150 vs >150X10^3/uL	2.561 (1.433; 4.578)	0.0015
Baseline Fibroscan F4 vs F0-F2	F4 vs F0-F2	2.255 (1.215; 4.183)	0.0099
Baseline Fibroscan F3 vs F0-F2	F3 vs F0-F2	1.469 (0.696; 3.103)	0.3130
Baseline Albumin	≤ 3.5 vs >3.5 g/dL	1.976 (1.231; 3.173)	0.0048



Factors Associated with Deaths

Deaths in Patients with de-novo HCC (n=20)			
Variable	**Comparison**	**Hazard Ratio (95% CI)**	**P-value**
Baseline CPT	CPT A vs CPT B+C	0.183 (0.069; 0.488)	0.0007

- 20 patients (15.2%) with HCC died during the registry: 13 patients had CPT A at baseline and 6 had CTP B+C (n=1 was missing data)
- Median survival time (based on days in study at time of death) is 1079 days for CPT A, and 779 days for CTP B+C

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