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MEETING SUMMARY
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IMPACT OF HEPATITIS C SUSTAINED VIRAL RESPONSE ON THE RISK OF DE NOVO AND RECURRENT HEPATOCELLULAR CARCINOMA

DISCLAIMER

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Please note:

The views expressed within this presentation are the personal opinion of the author. They do not necessarily represent the views of the author's academic institution or the rest of the HCC CONNECT group

CHRONIC HCV INFECTION MAY LEAD TO LIVER DISEASE AND LIVER CANCER

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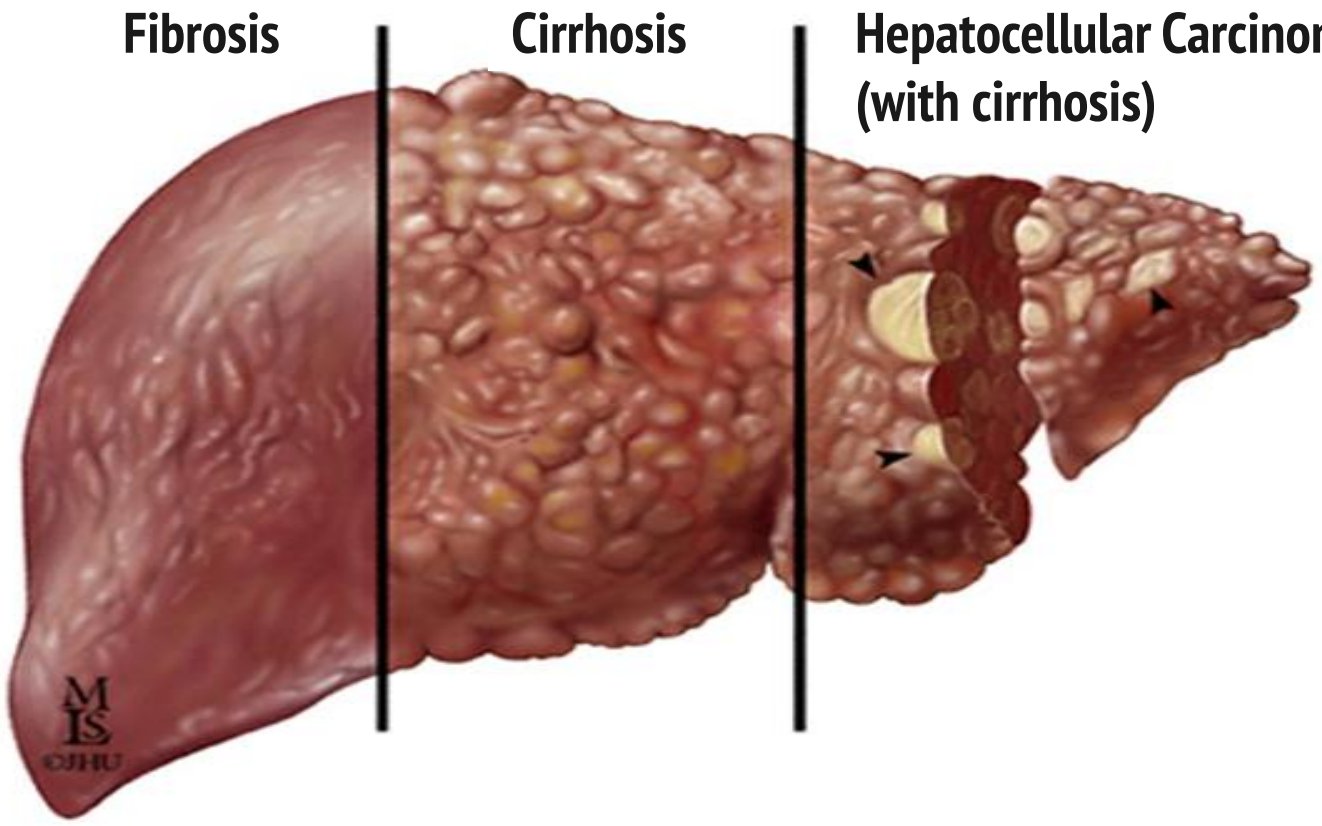
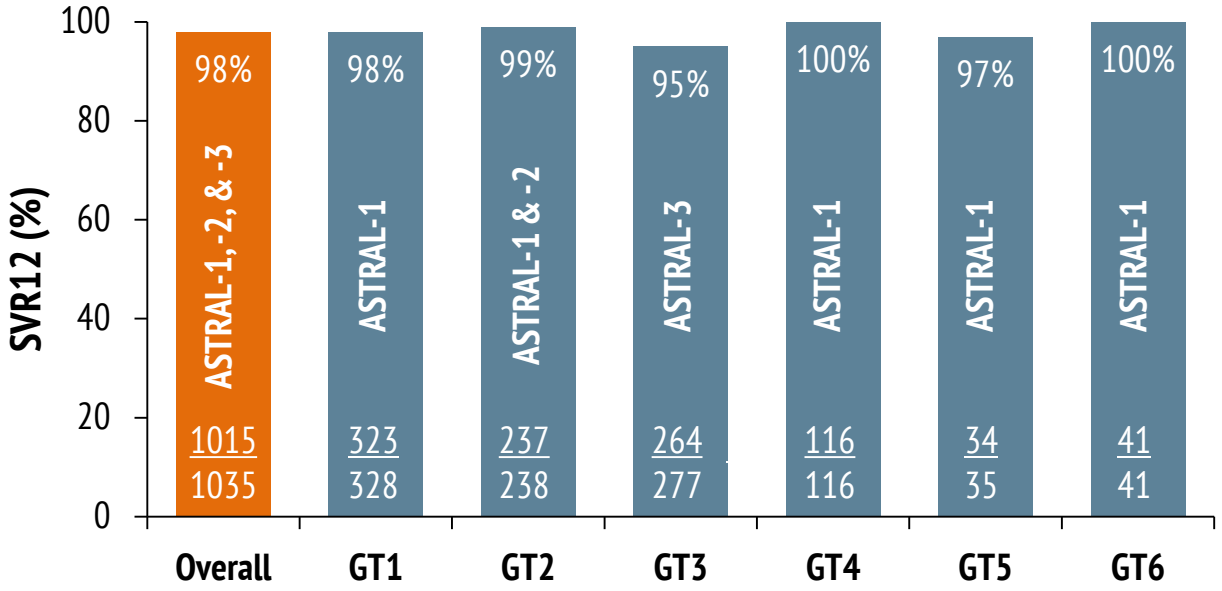


~75% of patients infected with HCV will develop a chronic infection

Liang TJ, et al. *Ann Intern Med.* 2000;132:296-305.
HCV, hepatitis C

EFFICACY OF SOFOSBUVIR AND VELPATASVIR FOR 12 WEEKS IN TN/TE PATIENTS WITH AND WITHOUT COMPENSATED CIRRHOSIS

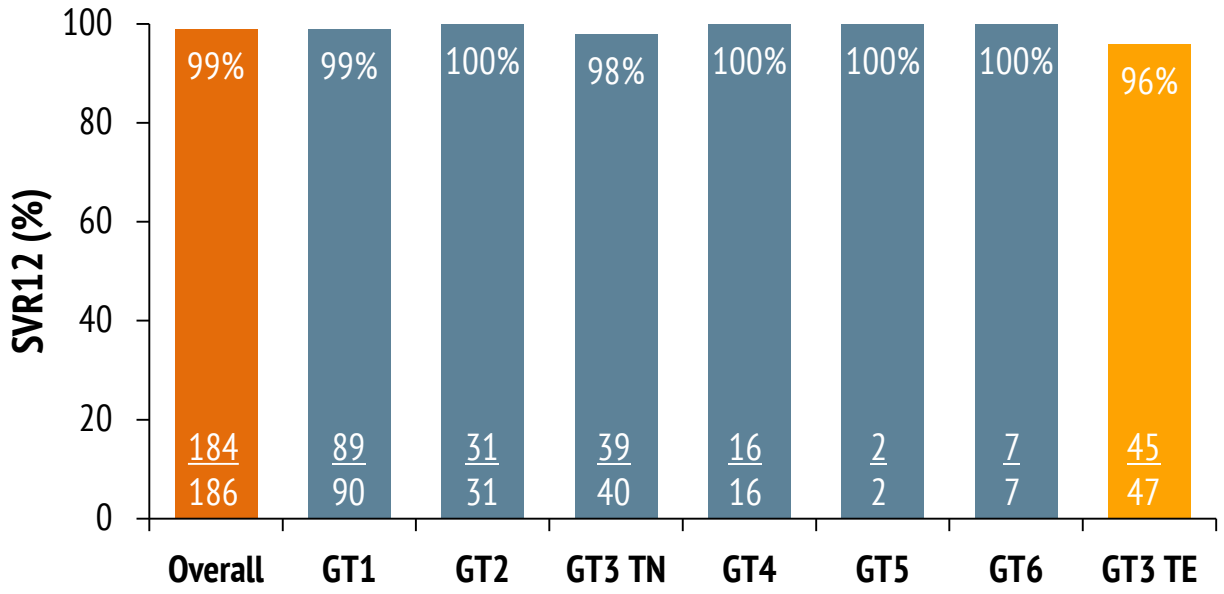


- **ASTRAL-1:** Double-blind, placebo-controlled study in GT 1, 2, 4, 5, or 6 subjects (N=740). GT 1, 2, 4, or 6 subjects were randomized 5:1 to receive sofosbuvir + velpatasvir or placebo for 12 weeks; GT 5 subjects received sofosbuvir + velpatasvir for 12 weeks. Overall SVR was 99% (n=618/624).
- **ASTRAL-2:** Open-label study in GT 2 subjects (N=266). Subjects received sofosbuvir + velpatasvir or sofosbuvir + ribavirin for 12 weeks.
- **ASTRAL-3:** Open-label study in GT 3 subjects (N=552). Subjects received EPCLUSA for 12 weeks or sofosbuvir + ribavirin for 24 weeks. SVR12 for sofosbuvir + velpatasvir ranged from 89% (treatment-experienced with compensated cirrhosis) to 98% (treatment-naïve without cirrhosis).

These studies did not include subjects with decompensated cirrhosis (Child-Pugh B or C).

EPCLUSA US full Prescribing Information. Gilead Sciences, Inc. Foster City, CA. November 2017
GT, genotype; SVR, sustained virologic response; TE, treatment experienced; TN, treatment naïve

EFFICACY OF GLECAPREVIR AND PIBRENTASVIR FOR 12 OR 16 WEEKS IN PATIENTS WITH COMPENSATED CIRRHOSIS

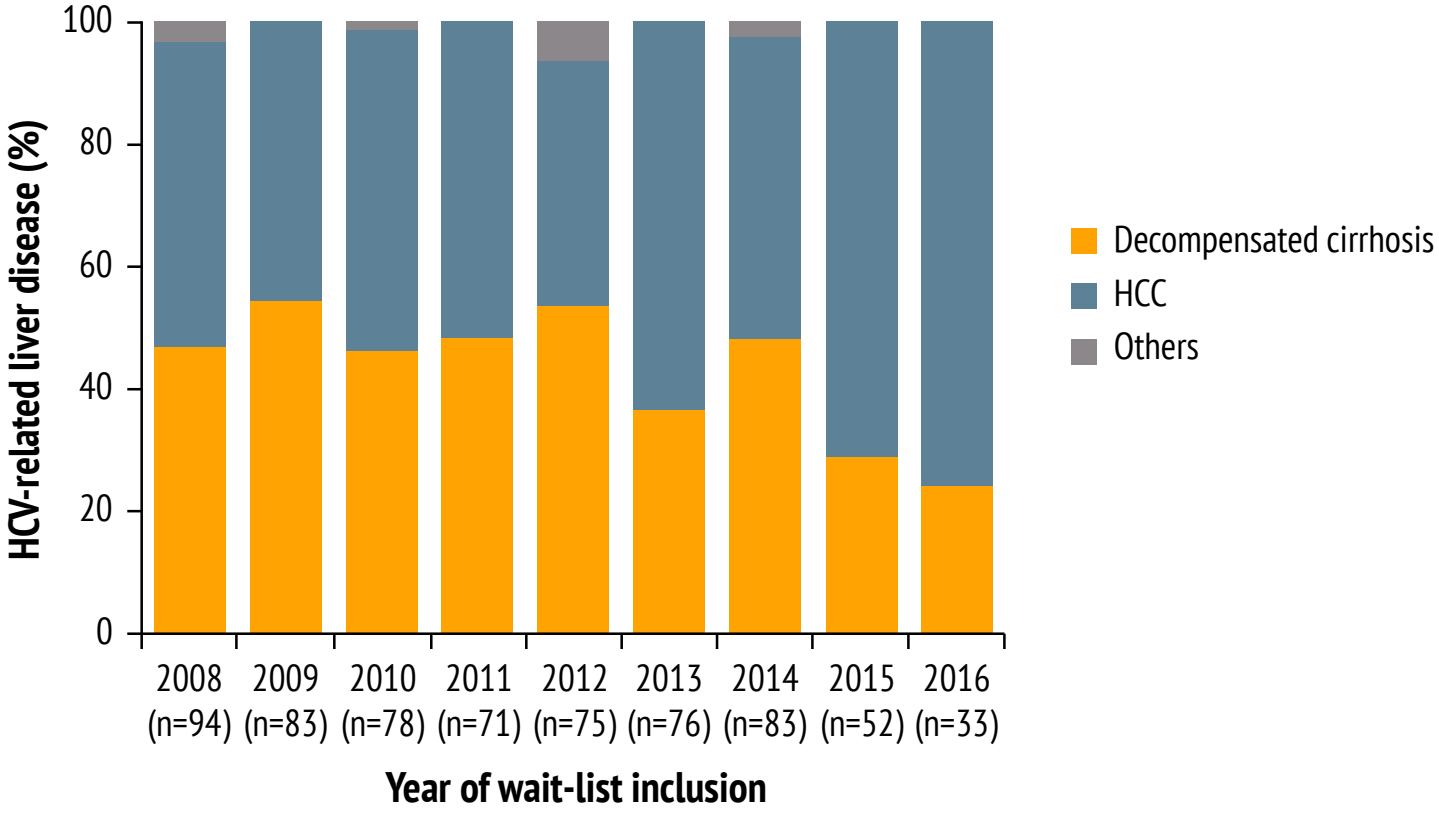


- GT1, 2, 4-6 TN/TE and GT3 TN patients received glecaprevir and pibrentasvir for 12 weeks
- GT3 TE patients received glecaprevir and pibrentasvir for 16 weeks

Wyles D, et al. *Hepatology*. 2018;67:514–523. Forns X, et al. *Lancet Infect Dis*. 2017;17:1062-1068

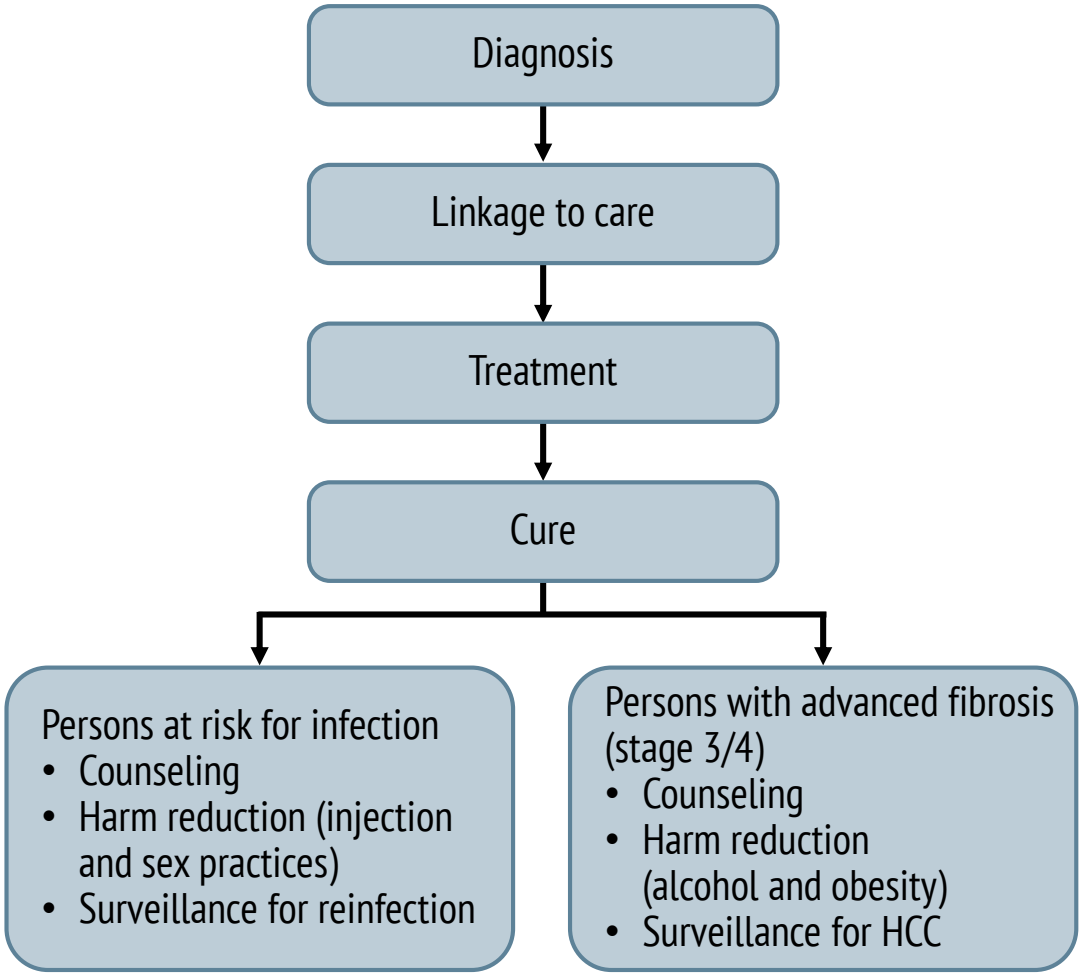
GT, genotype; SVR, sustained virologic response; TE, treatment experienced with interferon or pegylated interferon ± ribavirin, or sofosbuvir + ribavirin ± pegylated interferon; TN, treatment naïve. Data pooled from SURVEYOR-II and EXPEDITION-1.

PATIENTS WITH HCV WAITLISTED FOR LIVER TRANSPLANT WITH DECOMPENSATED CIRRHOSIS OR HEPATOCELLULAR CARCINOMA



Crespo et al. *J Hepatol.* 2018;69:11-17.
HCC, hepatocellular carcinoma; HCV, hepatitis C

EXTENDED HEPATITIS C CARE CONTINUUM



Falade-Nwulia O, et al. *J Hepatol.* 2017;66:267-269.
HCC, hepatocellular carcinoma

INCIDENCE AND PREDICTORS OF DE NOVO HEPATOCELLULAR CARCINOMA FOLLOWING ACHIEVEMENT OF SUSTAINED VIROLOGIC RESPONSE WITH DIRECT ACTING ANTIVIRALS: RESULTS FROM THE GILEAD SVR AND CIRRHOSIS REGISTRIES

Reddy K, et al. Abst #635

AIM

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To evaluate the **incidence and predictors of *de novo* HCC following SVR** in a well characterized cohort of over 6700 patients enrolled in Gilead registries.

Reddy K, et al. AASLD 2018. Abstract #635
HCC, hepatocellular carcinoma; SVR, sustained virologic response

METHODS

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- **Pooled analysis** to assess the incidence and predictors of *de novo* HCC among patients enrolled in the **Gilead SVR and Cirrhosis registries**
- Patients with SVR who had received a sofosbuvir-based regimen could be enrolled < 60 weeks of completing a study or 2 years of achieving SVR following treatment in clinical practice
- **Assessments** every 24 weeks for up to 3 or 5 years (in patients with cirrhosis)
  - Laboratory, clinical, and radiographic assessments for clinical outcomes, including HCC

Reddy K, et al. AASLD 2018. Abstract #635
HCC, hepatocellular carcinoma; SVR, sustained virologic response

RESULTS

- **6757 patients** who received interferon-free DAA regimens were included in this interim analysis
- Prior **treatment history**
  - Ledipasvir / sofosbuvir ± ribavirin: 36% (n = 2455)
  - Sofosbuvir / velpatasvir ± ribavirin,: 26% (n = 1772)
  - Sofosbuvir + ribavirin: 19% (n = 1275)
  - Sofosbuvir / velpatasvir / voxilaprevir: 13% (n = 892)
  - Other regimens: 5% (n = 364)
- **Patient characteristics**
  - 63% male
  - 85% white
  - Median age 57 years
  - 28% compensated cirrhosis (n = 1877)
  - 4% decompensated cirrhosis (n = 292)

Reddy K, et al. AASLD 2018. Abstract #635
DAA, direct-acting antiviral; SVR, sustained virologic response

RESULTS

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- 81 patients (1.2%) developed de novo **HCC** or suspected HCC from SVR12
  - Median observation time of 135 weeks (range 0.3–288)
- Median **time to HCC onset** from SVR12: 68 weeks (range 3-181)
  - 14 (17%) cases occurred < 24 weeks of achieving SVR12
- **Exposure-adjusted incidence rates** of HCC from SVR12
  - 0.07 per 100 PY (8 cases) in patients without cirrhosis
  - 1.13 per 100 PY (46 cases) in patients with compensated cirrhosis
  - 4.35 per 100PY (27 cases) in patients with decompensated cirrhosis
- **Factors associated with development of HCC** (per multivariate analysis):
  - Decompensated cirrhosis (HR 9.6, p = 0.0004)
  - Compensated cirrhosis (HR 6.1, p < 0.0001)
  - Pretreatment albumin ⩽ 3.5g/ dL (HR 2.8, p = 0.0014)
  - Genotype 3 infection (HR 2.7, p = 0.0007)
  - Pretreatment platelets ⩽ 150 x 10^3/uL (HR 2.2, p = 0.019)
  - Male gender (HR 2.2, p = 0.012)
  - Age ⩾ 60 years (HR 2.1, p = 0.004)

Reddy K, et al. AASLD 2018. Abstract #635
HCC, hepatocellular carcinoma; HR, hazard ratio; PY, person-years

CONCLUSION

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- In this analysis of a large cohort of patients successfully treated with DAAs and followed long term (median 135 weeks), the **incidence rate of *de novo* HCC was low**
- Patients with **decompensated cirrhosis** who were traditionally excluded from interferon therapy were at the **highest risk** of *de novo* HCC
- Cirrhosis, genotype 3 infection, older age, lower pretreatment albumin and platelet count were **independently associated** with the development of HCC

Reddy K, et al. AASLD 2018. Abstract #635
HCC, hepatocellular carcinoma

NO DIFFERENCE BETWEEN DIRECT-ACTING ANTIVIRALS FOR HEPATITIS C IN HEPATOCELLULAR CARCINOMA RISK

Mun E, et al. Abst #654

AIMS

- To **compare different DAA regimens** with respect to **risk of *de novo* HCC** following antiviral therapy
- **Rationale:**
  - If some DAAs truly increased HCC risk, there would be differences between different DAA regimens in the risk of HCC after antiviral treatment
  - If no differences between DAA regimens in the risk of HCC are found, it would strongly suggest that DAAs do not have direct carcinogenic effects, as it would be extremely unlikely that different DAAs, belonging to different classes, would have identical carcinogenic effects

Mun E, et al. AASLD 2018. Abstract #654.
DAA, direct-acting antiviral; HCC, hepatocellular carcinoma

METHODS

- **33,137 patients** were identified to have initiated HCV antiviral treatment in the **VA healthcare system** between 12/06/2013 and 12/31/2015 with one of four DAA-only regimens (± ribavirin) :
  - Ledipasvir/ Sofosbuvir (n=19,282)
  - Paritaprevir/ Ritonavir/Ombitasvir/Dasabuvir (ProD) (n=6,289)
  - Sofosbuvir (n=4,356)
  - Sofosbuvir+Simeprevir (n=3,210)
- Patients were **retrospectively followed** until 6/15/2017 to identify incident (*de novo*) cases of HCC
- Propensity score-adjusted Cox proportional hazards regression was used to compare different DAA regimens with respect to HCC risk

Mun E, et al. AASLD 2018. Abstract #654.
DAA, direct-acting antiviral; HCV, hepatitis C; VA, Veterans Affair

RESULTS

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- Mean follow-up: 1.52 years
- **741 new cases of HCC** were diagnosed after antiviral treatment
  - Incidence = 1.47 per 100 PY
- Patients treated with sofosbuvir + simeprevir had the highest HCC incidence (2.47 per 100 PY), followed by sofosbuvir (1.91), ledipasvir/sofosbuvir (1.26), and PrOD (0.95)
- There were great differences between DAA-treated patients in prevalence of cirrhosis, markers of advanced fibrosis, thrombocytopenia, and other HCC risk factors
- **After adjustment for baseline characteristics** associated with HCC, there were **no significant differences in HCC risk** between the four DAA regimens

Mun E, et al. AASLD 2018. Abstract #654.
DAA, direct-acting antiviral; HCC; hepatocellular carcinoma; PY, patient years; PrOD, Paritaprevir/Ritonavir/Ombitasvir/Dasabuvir

CONCLUSION

- There are **no significant differences between DAA regimens** belonging to different classes **in HCC risk** after antiviral treatment
- This suggests that **DAAs do not have direct carcinogenic effects** as it would be unlikely that different DAAs would have identical carcinogenic effects

Mun E, et al. AASLD 2018. Abstract #654.
DAA, direct-acting antiviral; HCC; hepatocellular carcinoma

DIRECT-ACTING ANTIVIRAL THERAPY SIGNIFICANTLY REDUCES EARLY HCC RECURRENCE: A MULTICENTER U.S. COHORT STUDY

Singal A, et al. Abst #92

HCC, hepatocellular carcinoma

AIM

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To compare **HCC recurrence patterns** among DAA-treated and untreated patients who achieved HCC complete response (CR)

Singal A, et al. AASLD 2018. Abstract #92
DAA, direct-acting antiviral; HCC, hepatocellular carcinoma

METHODS

- North-American **multicenter retrospective cohort study** of patients with **HCV-related HCC who achieved CR** after resection, ablation, transarterial chemo/radioembolization or radiation therapy from 1/2013 to 12/2016
  - Patients who received DAA prior to CR or achieved CR via transplant or systemic therapy were excluded
- Cox regression was used to examine the association between DAA therapy and time-to-recurrence from CR
  - DAA therapy was analyzed as a time-varying exposure
  - Patients were censored at death, transplant or last follow-up

Singal A, et al. AASLD 2018. Abstract #92
CR, complete response; DAA, direct-acting antiviral; HCC, hepatocellular carcinoma; HCV, hepatitis C

RESULTS

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- **866 HCV-HCC patients** from 31 health systems were included
  - 355 patients (41%) received DAA therapy
  - 511 patients (59%) were untreated
- **DAA treated patients versus untreated patients**
  - Were older (62.5 vs 61.4 years, p=0.03)
  - More likely had BCLC 0/A HCC (87% vs 77%, p=0.001)
  - More likely received resection or ablation (58% vs 43%, p<0.001)
  - A similar proportion presented within Milan Criteria (85% vs 83%, p=0.60)
- Median **time from HCC treatment to CR**: 1.6 months
- Median **time from CR to DAA initiation**: 4.9 months

Singal A, et al. AASLD 2018. Abstract #92
BCLC, Barcelona Clinic Liver Cancer; CR, complete response; DAA, direct-acting antiviral; HCC, hepatocellular carcinoma; HCV, hepatitis C

RESULTS

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- Recurrence presented as a new intrahepatic lesion in 86 (58.1%) and 169 (57.1%) patients in DAA treated patients versus untreated patients
- **DAA therapy was associated with significantly reduced HCC recurrence risk** (HR 0.41, 95% CI 0.32–0.52)
  - Adjusting for study site, age, sex, Child-Pugh class, AFP level, initial tumor burden and HCC therapy leading to CR
  - Results were similar when considering early recurrence only (HR 0.42 95% CI 0.30–0.60)
- Most recurrences were **within Milan Criteria**, in both DAA-treated and untreated patients (91.0% vs 90.6%, p=0.84)
- More DAA treated than untreated patients received **potentially curative therapy** (transplant, resection or ablation) for HCC recurrence (34.2% vs 25.7%, p=0.06)
  - Similar proportions achieved CR/PR to treatment of recurrence (49.6% vs 51.0%, p=0.80)

Singal A, et al. AASLD 2018. Abstract #92
AFP, alpha fetoprotein; CI, confidence interval; CR, complete response; DAA, direct-acting antiviral; HCC, hepatocellular carcinoma; HR, hazard ratio; PR, partial response

CONCLUSION

In the largest cohort study to date, **DAA therapy was associated with significantly reduced HCC recurrence**, including early recurrence, **after CR**.

HCC **recurrence patterns**, including tumor burden and treatment response, were **similar** in DAA treated and untreated patients.

Singal A, et al. AASLD 2018. Abstract #92
CR, complete response; DAA, direct-acting antiviral; HCC, hepatocellular carcinoma

DIRECT ANTIVIRAL AGENTS AFTER SUCCESSFULLY TREATED EARLY HEPATOCELLULAR CARCINOMA IMPROVES SURVIVAL IN CIRRHOTIC PATIENTS WITH CHRONIC HEPATITIS C

Cabibbo G, et al. Abst #95

AIM

To assess if **SVR by DAAs** is effective in **reducing overall mortality and preventing HCC recurrence** in patients with HCV cirrhosis and previously treated HCC

Cabibbo G, et al. AASLD 2018. Abstract #95
DAA, direct-acting antiviral; HCC, hepatocellular carcinoma; HCV, hepatitis C; SVR, sustained virologic response

METHODS

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- **221 consecutive HCV patients** with a first diagnosis of BCLC 0/A HCC achieving radiological CR after curative resection or ablation and subsequently treated with DAAs were prospectively enrolled
- Patients were monitored by **web-based RESIST-HCV network**
  - Clinical, virologic and radiologic data were collected before DAAs start and during follow-up
- **Endpoints**
  - Primary: OS from start of DAAs (Kaplan-Meier)
  - Secondary: TTR (Kaplan-Meier)
  - Predictors of OS (Cox regression multivariate analysis)

Cabibbo G, et al. AASLD 2018. Abstract #95
BCLC, Barcelona Clinic Liver Cancer; CR, complete response; DAA, direct-acting antiviral; HCC, hepatocellular carcinoma; HCV, hepatitis C; OS, overall survival; TTR, time to HCC recurrence

RESULTS

- **Patient characteristics**
  - 86% Child-Pugh class A
  - 76% BCLC A

- Median **time-lag** between HCC radiological CR and DAA start: 1.7 months (range 0.5–5.5)
- Median **duration of follow-up** after DAA start: 17 months (range 1–34)

- 188 patients achieved **SVR (85%)**, by ITT analyses
- **52 HCC recurrences** were observed
  - 83% nodular pattern
  - 17% infiltrative pattern

Cabibbo G, et al. AASLD 2018. Abstract #95
BCLC, Barcelona Clinic Liver Cancer; CR, complete response; DAA, direct-acting antiviral; HCC, hepatocellular carcinoma; ITT, intention-to-treat

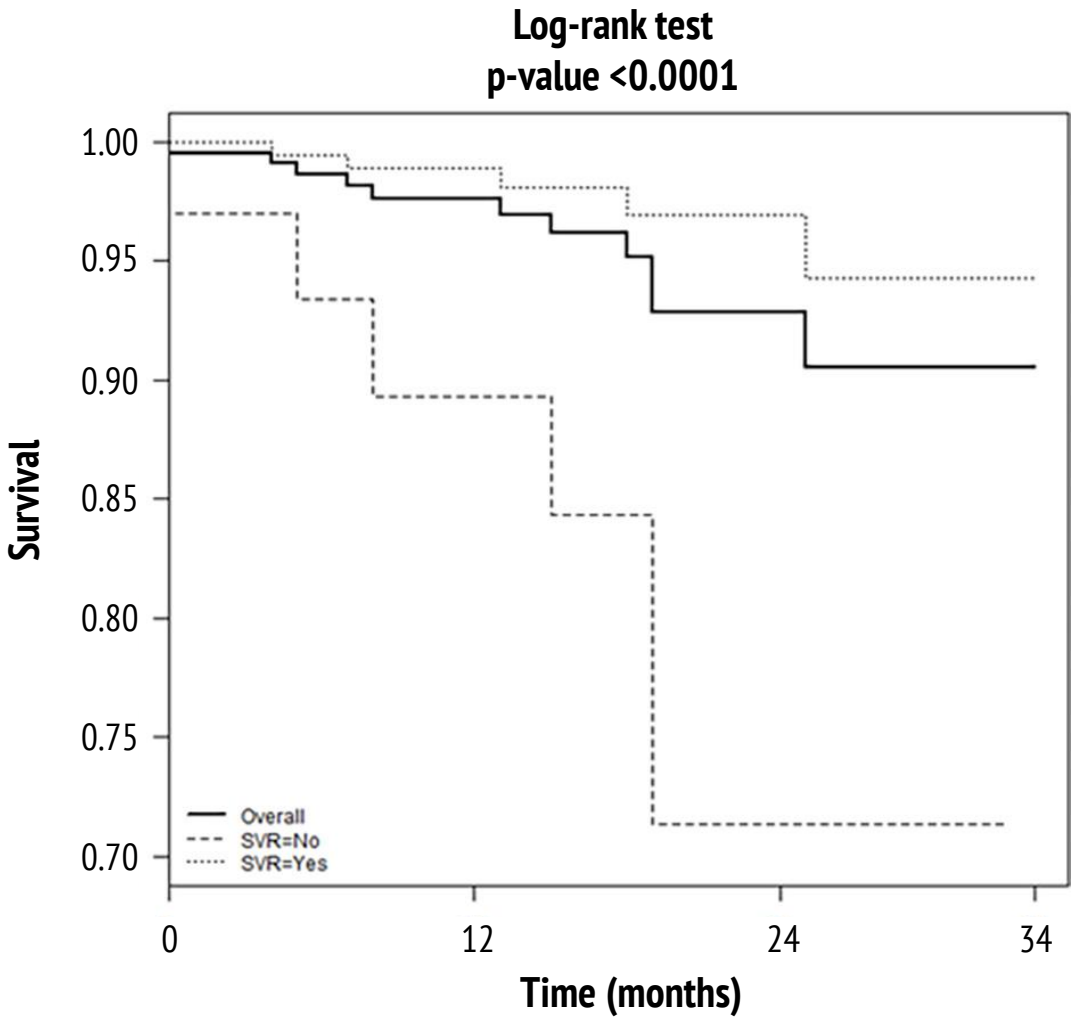
RESULTS

- 11 patients died (5%)
- Actuarial **OS** rates
  - 97.6% at 1 years
  - 92.9% at 2 years
- Actuarial **HCC recurrence rates**
  - 7.6% at 6 months
  - 18% at 1 year
  - 34.5% at 2 years
- The **SVR** group had significantly **longer OS** ($p < 0.0001$) **and TTR** ($p = 0.008$) than the no-SVR group
- **Independent predictors of OS**
  - SVR (HR = 0.17; 95% CI 0.05–0.58)
  - Albumin level (HR = 0.30; 95% CI 0.10–0.92)
- **Independent predictors of TTR**
  - SVR (HR = 0.48; 95% CI = 0.25–0.91)

Cabibbo G, et al. AASLD 2018. Abstract #95

CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio; OS, overall survival; SVR, sustained virologic response; TTR, time to HCC recurrence

RESULTS



Cabibbo G, et al. AASLD 2018. Abstract #95
SVR, sustained virologic response

CONCLUSION

This study demonstrated for the first time by multivariate analysis that in patients with HCV cirrhosis and successfully treated early HCC, **SVR achieved by DAAs improves OS and reduces the risk of HCC recurrence**

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