

# Patient With HCV Infection and Advanced Liver Disease: Assessing the Impact on Treatment Decisions

---

# Educational Objectives

---

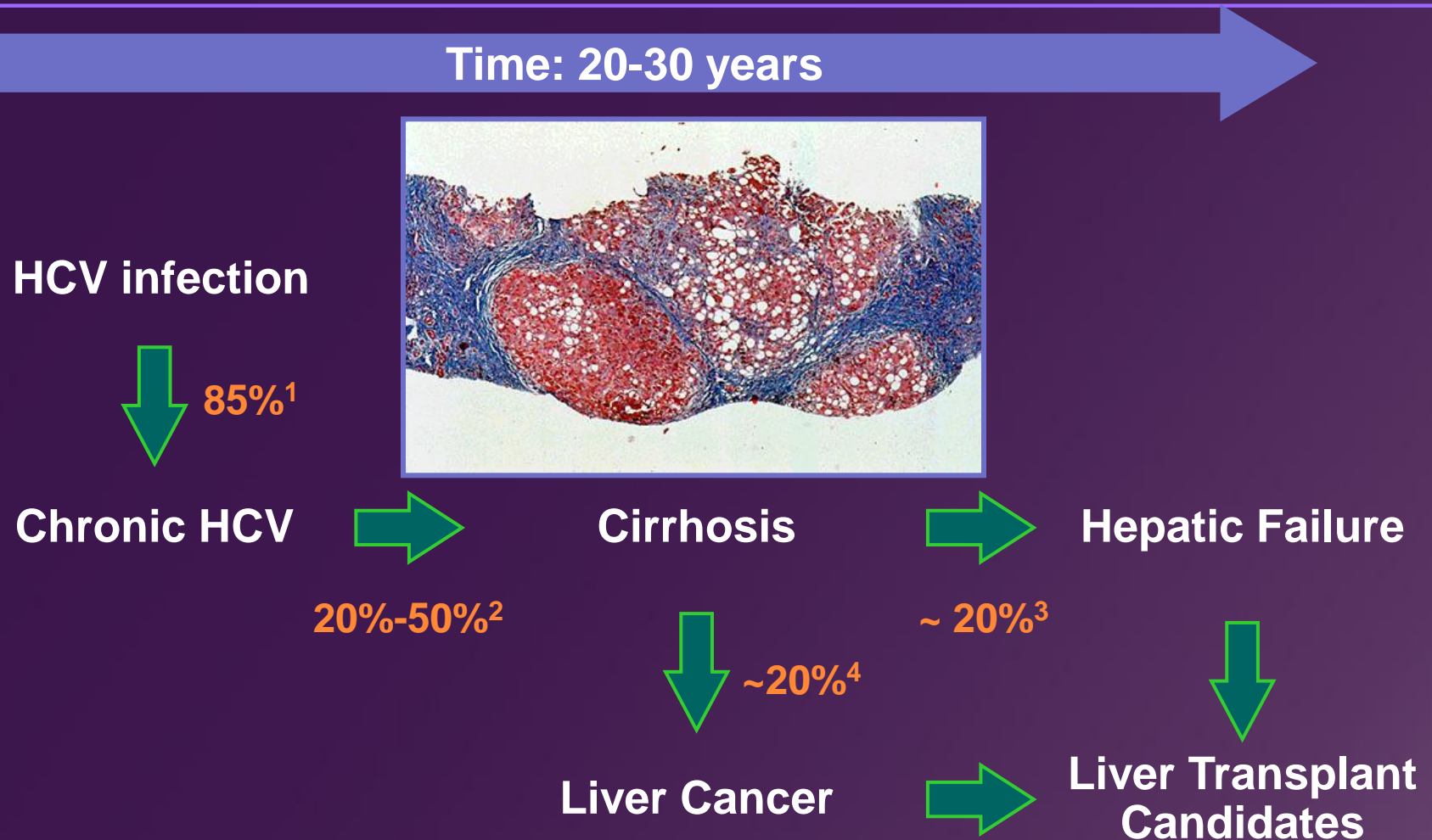
- ◆ Assess the impact of advanced liver disease on patient morbidity and mortality
- ◆ Evaluate benefits vs risks of HCV therapy on patient outcome
- ◆ Establish strategies to optimize treatment adherence and monitor patients for adverse events

# Projected Prevalence of Chronic HCV, Cirrhosis, and Complications Over 4 Decades

	<b>2000</b>	2010	2020	2030	<b>2040</b>
HCV infection	<b>2,940,678</b>	2,870,391	2,681,556	2,433,709	<b>2,177,089</b>
Cirrhosis	<b>472,103</b>	720,807	858,788	879,747	<b>828,134</b>
Decompensated cirrhosis	<b>65,294</b>	103,117	134,743	146,408	<b>142,732</b>
Hepatocellular carcinoma	<b>7,271</b>	11,185	13,183	13,390	<b>12,528</b>
Liver-related death	<b>13,000</b>	27,732	36,483	39,875	<b>39,064</b>

Davis GL et al. *Liver Transpl.* 2003;9:331-338. Projecting future complications of chronic hepatitis C in the United States. Davis GL, Albright JE, Cook SF, Rosenberg DM. *Liver Transpl.* 2003 Apr;9(4):331-8. Copyright 2003. Reproduced with permission of John Wiley & Sons, Inc.

# HCV: Disease Progression



1. NIH Consensus Development Conference Statement; March 24-26, 1997.
2. Davis GL et al. *Gastroenterol Clin North Am.* 1994;23:603-613.
3. Koretz RL et al. *Ann Intern Med.* 1993;119:110-115.
4. Takahashi M et al. *Am J Gastroenterol.* 1993;88:240-243.

# Natural History of Compensated HCV Cirrhosis: A 17-Year Cohort Study (N = 214)

Complication	Total %	Annual rate%
Death	35	4.0
HCC*	32	3.9
Ascites	23	2.9
Jaundice	17	2.0
GI Bleed	6	0.7
Encephalopathy	1	0.1

\*HCC was the main cause of death (44%) and the first complication to develop (27%).

# Natural History of HCV Cirrhosis

---

- ◆ Patients at risk for ESLD and HCC
  - Followed 61 months (n = 384)<sup>1</sup>
    - 18% developed decompensation
    - 7% developed HCC
    - 13% died of various causes
  - Followed 93 months (n = 254)<sup>2</sup>
    - 31% developed complications
    - 21% developed HCC
    - 16% died of liver-related diseases

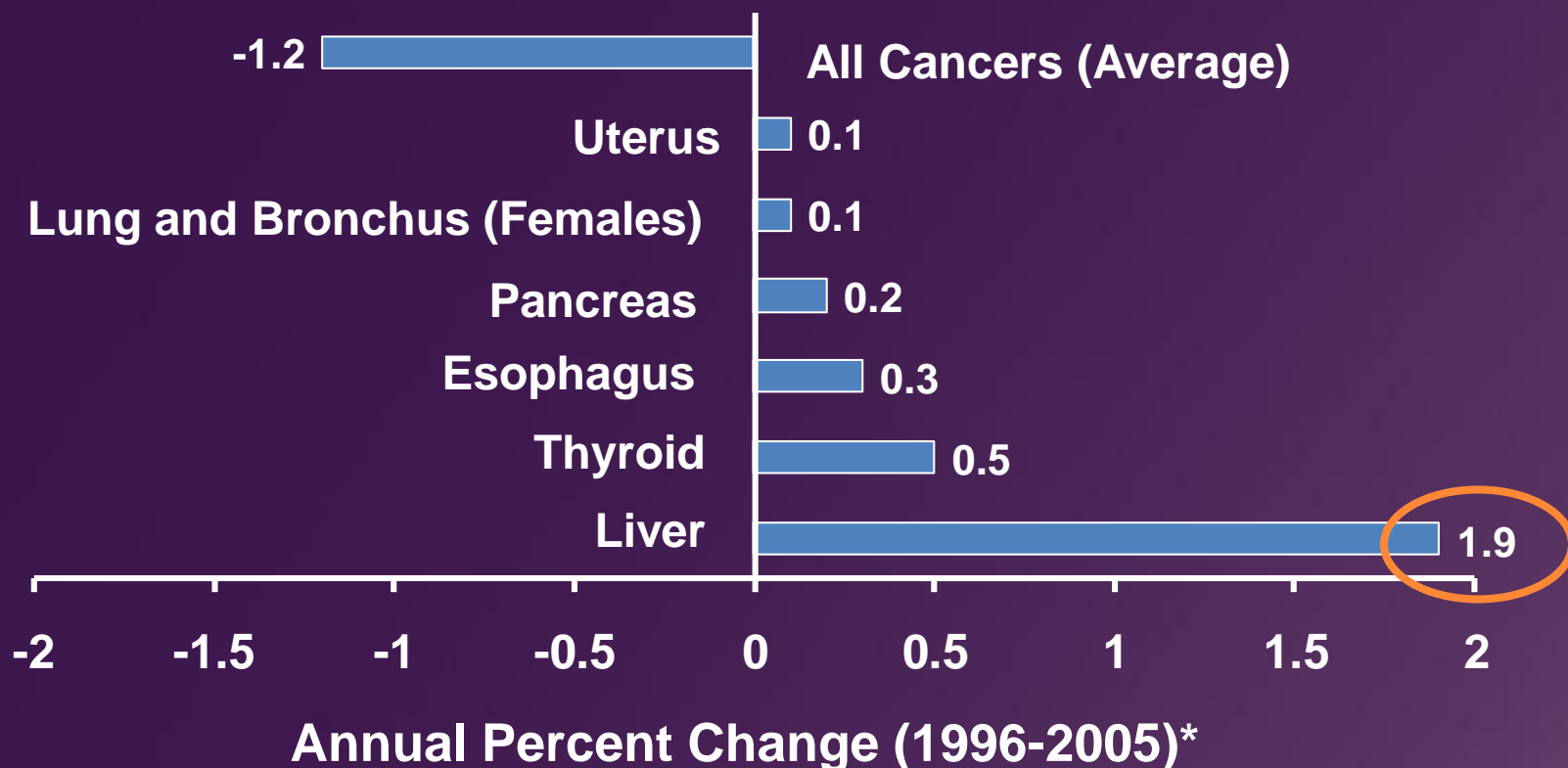
ESLD = end-stage-liver disease; HCC = hepatocellular carcinoma.

1. Fattovich G et al. *Gastroenterology*. 1997;112:463-472.

2. Benvegnù L et al. *Gut*. 2004;53:744-749.

# Liver Cancer Has the Fastest Growing Death Rate in the US

## Trends in US Cancer Mortality Rates



\*Represents the annual percent change over the time interval.

National Cancer Institute. SEER Cancer Statistics Review 1975-2005.

Available at: [http://seer.cancer.gov/csr/1975\\_2005](http://seer.cancer.gov/csr/1975_2005) Accessed February 5, 2009.

# HCV Patients With Decompensated Cirrhosis

---

## Magnitude of the problem

- ◆ Estimated that 375,000 Americans with HCV will develop cirrhosis by 2015
- ◆ Of these patients
  - 3.6% to 6.0%/y will experience decompensation
  - 1.4% to 3.3%/y will develop a hepatoma
  - 2.6% to 4.0%/y will die
- ◆ Decompensated cirrhosis with HCV
  - 5-year survival rate of only 50%
  - Typically listed for transplantation

# Patient CK: History

---

- ◆ 58-year old Caucasian man with chronic HCV
  - IVDU 35 years ago
  - DM and HTN
  - Referred to GE to consider treatment of HCV
- ◆ Evaluation
  - HCV: Genotype 1b, VL 1.8 million IU/mL
  - Alb 4.7 g/dL, T bili 0.6 mg/dL, INR 1.0, ALT 69 U/L
  - Hgb:13 g/dL, ANC: 1500/ $\mu$ L
  - Liver biopsy: grade 4, stage 4 (cirrhosis)
  - U/S shows echogenic liver with mild splenomegaly
  - EGD without varices, but mild portal gastropathy
- ◆ GE recommends treatment

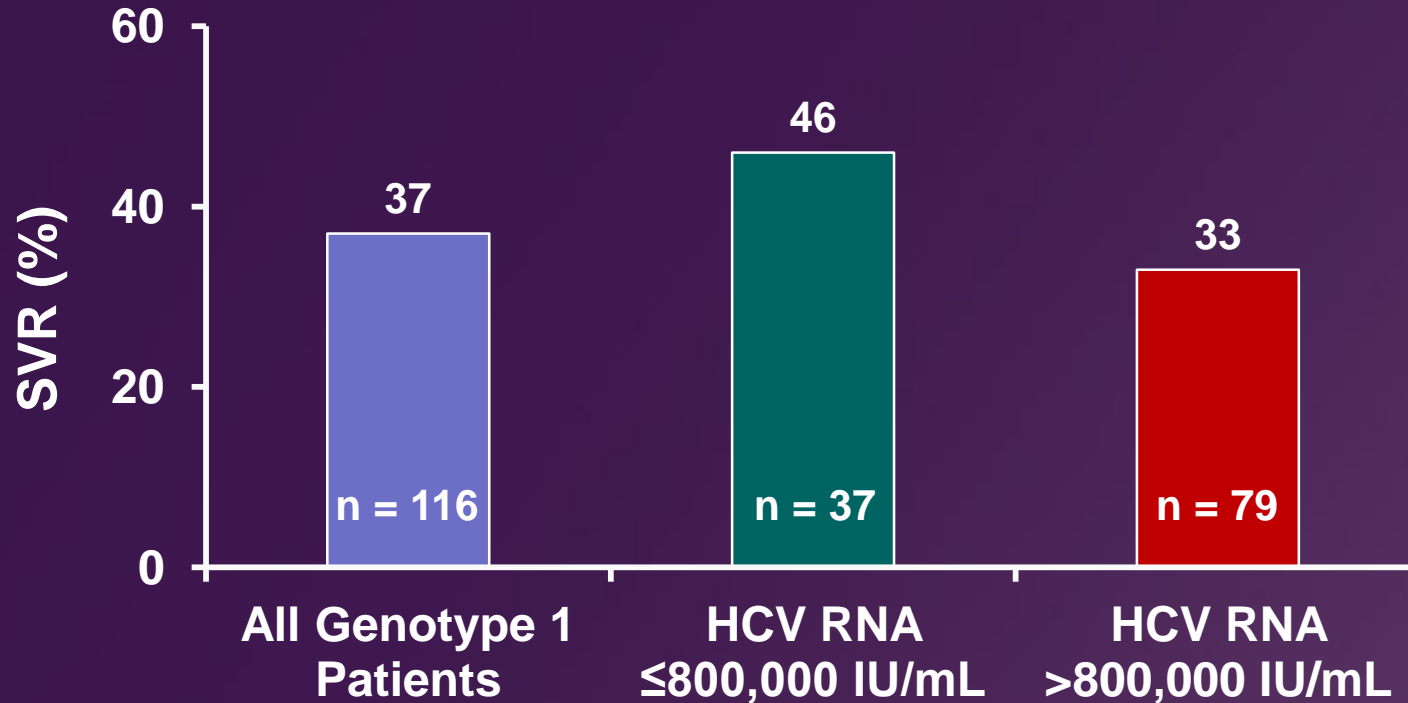
# Question 1

---

What is the likelihood that this patient will achieve an SVR?

- A. 5% to 10%
- B. 10% to 20%
- C. 20% to 30%
- D. 30% to 40%

# Peg-IFN $\alpha$ -2a + RBV in Patients With HCV Genotype 1 and Cirrhosis: SVR by Viral Load



Peg-IFN  $\alpha$ -2a 180  $\mu$ g/wk + RBV 1000-1200 mg/d for 48 weeks

# Peg-IFN $\alpha$ -2b + RBV in Patients With Cirrhosis: SVR by Viral Load and Genotype

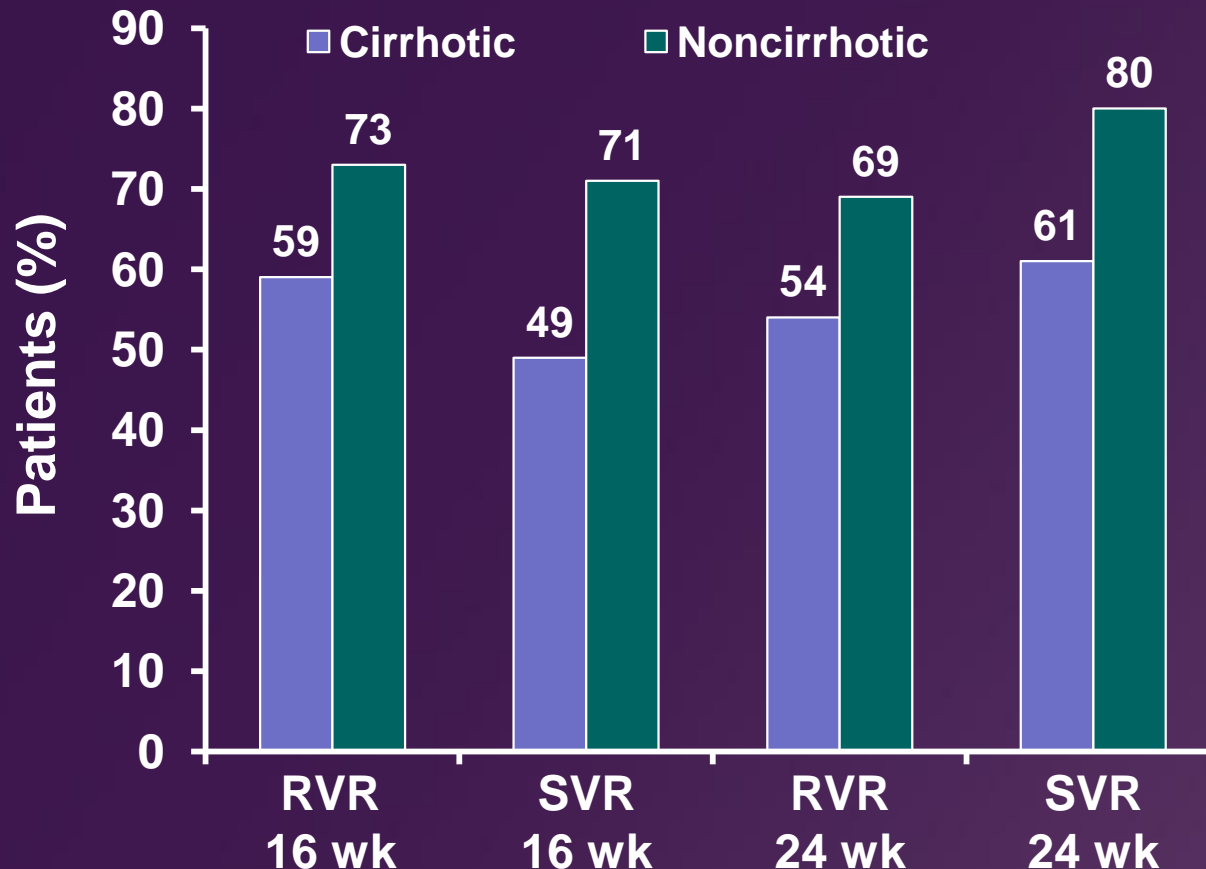
	Cirrhotics (n = 87)	Noncirrhotics (n = 278)
<b>Viral load</b>		
<1.5 x 10 <sup>6</sup>	22/37 (59.5%)	64/91 (70.3%)
≥1.5 x 10 <sup>6</sup>	18/50 ( 36.0%)	119/187 (63.6%)
<b>Genotype</b>		
1-4	9/44 (20.5%)	50/115 (43.5%)
2-3	31/43 (72.1%)*	133/163 (81.6%)*

\* $P < 0.01$  vs genotypes 1-4.

# Peg-IFN $\pm$ RBV in Compensated HCV Cirrhosis and Portal Hypertension

- ◆ 102 patients randomized 1:1 to peg-IFN  $\alpha$ -2b 1  $\mu$ g/kg/wk  $\pm$  RBV 800 mg/d up to 52 weeks
- ◆ SVR
  - 21.6% in combination therapy vs 9.8% in monotherapy ( $P = 0.06$ )
  - More frequent in G2 and G3 than G1 (66.6% vs 11.3%;  $P = 0.001$ )
- ◆ Predictors of SVR in G1: low baseline VL, HCV RNA negative at wk 4, adherence
- ◆ Fewer liver-disease–related complications with SVR (6.2% vs 38.3%;  $P = 0.03$ )

# ACCELERATE Trial: Peg-IFN $\alpha$ -2a + Ribavirin in HCV Genotype 2 or 3 Infection



- ◆ Patients with cirrhosis had lower response rates than those without cirrhosis
- ◆ SVR rates were higher in both groups with 24 weeks of treatment

# Chronic HCV Infection With Severe Fibrosis: Treatment With Peg-IFN $\alpha$ -2b + Ribavirin

	<u>Standard Treatment</u> Peg-IFN $\alpha$ -2b 1.5 $\mu$ g/kg/wk + Ribavirin 800 mg/d SVR (%)	<u>Low-Dose Treatment</u> Peg-IFN $\alpha$ -2b 0.75 $\mu$ g/kg/wk + Ribavirin 800 mg/d SVR (%)
All patients	44.5	37.2
Genotypes 1, 4, 5	25.0	16.9
Patients with cirrhosis	39.1	34.5
Patients with severe fibrosis (F3)	49.1	40.1

- ◆ Significantly less discontinuation/treatment reduction in the low-dose group

# Patient CK (cont)

---

- ◆ Started on therapy with peg-IFN  $\alpha$ -2a 180  $\mu$ g/wk and RBV 1000 mg/d
- ◆ Tolerated therapy well
- ◆ Hgb decreased to 9.2 g/dL by week 4 and erythropoietin was added
- ◆ Hgb increased to 11 g/dL by week 8 and remained stable
- ◆ ANC decreased to 600/ $\mu$ L by week 12 and stabilized
  - No growth factor support initiated
- ◆ HCV RNA negative at week 12

## Question 2

---

Can fibrosis or cirrhosis be reversed with successful antiviral therapy?

A. Yes

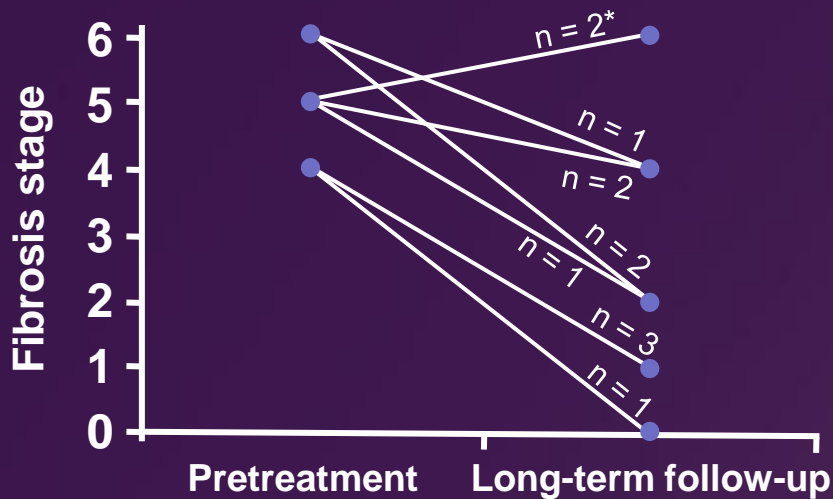
B. No

# Fibrosis Regression With Antiviral Therapy

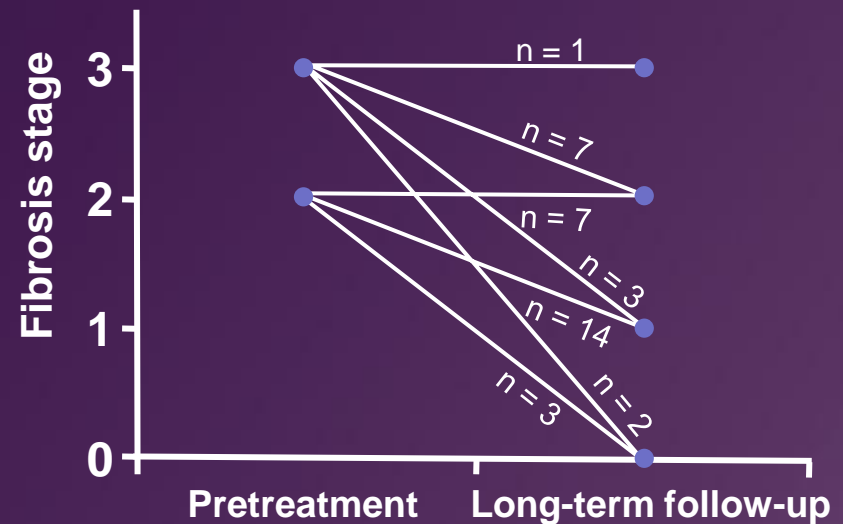
- ◆ 3010 treatment-naive patients with HCV
  - Significantly reduced fibrosis progression rates
  - Reversal of cirrhosis seen in 49% of patients with baseline cirrhosis
  - Factors associated with absence of significant fibrosis after treatment
    1. Baseline fibrosis stage
    2. SVR
    3. Age <40 years
    4. BMI <27 kg/m<sup>2</sup>
    5. No or minimal baseline activity
    6. VL <3.5 million copies/mL

# Fibrosis Regression in Patients With SVR

Patients with pretreatment Ishak fibrosis scores of 4 or greater



Patients with pretreatment Ishak fibrosis scores of 3 or less



N = 49

\*These patients developed HCC.

# Role of Maintenance Therapy in HCV Cirrhosis

---

## Question 3

---

Does maintenance therapy prevent development of ESLD complications or HCC?

A. Yes

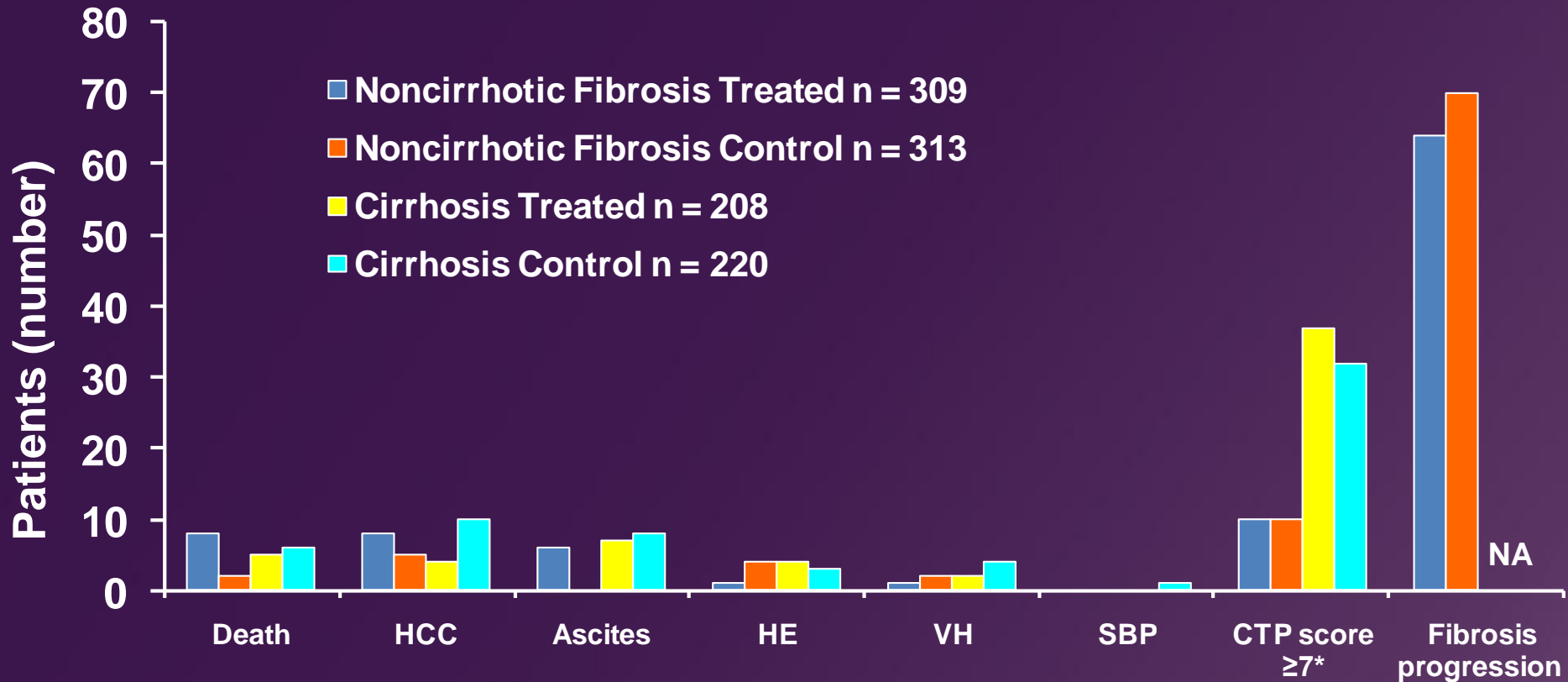
B. No

# HALT-C: Study Design and Results

- ◆ Randomized controlled trial of peg-IFN  $\alpha$ -2a 90  $\mu$ g/wk for 3.5 years vs no treatment in nonresponders to previous treatment with peg-IFN + RBV with advanced liver fibrosis (N = 1050)
  - Patients stratified according to fibrosis stage (noncirrhotic fibrosis and cirrhosis)
  - Primary end point: progression of liver disease

	Treatment Group	Control Group	P Value
Primary outcome	34.1%	33.8%	0.90
$\geq 1$ serious adverse event	38.6%	31.8%	0.07

# HALT-C: First Primary Outcome



\*On 2 consecutive visits.

HCC = hepatocellular carcinoma; HE = hepatic encephalopathy; VH = variceal hemorrhage; SBP = spontaneous bacterial peritonitis; CTP = Child-Turcotte-Pugh score; NA = not applicable.

# Decompensated Cirrhosis

---

# Treatment of Patients With HCV and Decompensated Cirrhosis: AASLD Guidelines

---

- ◆ Refer patients with clinically decompensated cirrhosis for consideration for transplantation
- ◆ Low-dose antiviral therapy may be initiated in patients with mild degrees of hepatic compromise, but only
  - By experienced clinicians
  - With vigilant monitoring for adverse events
  - In designated candidates for liver transplantation (preferably)
- ◆ Growth factors can be used for treatment-associated anemia and leukopenia
  - May limit need for antiviral dose reductions

## Question 4

---

Patients with cirrhosis treated with antiviral therapy who achieve SVR and subsequently undergo liver transplantation may not experience HCV recurrence.

A. True

B. False

# Trials of Antiviral Therapy in Patients With HCV-Related Cirrhosis With Signs of Decompensation

Author N % G1	Type of IFN	RBV	Decom- pensated (%)	Overall SVR n (%)	G1 and G4 SVR n (%)	G2 and G3 SVR n (%)
Crippin et al N = 15 73% G1	IFN $\alpha$ -2b	Yes/No	100	0	0	0
Thomas et al N = 20 67% G1	IFN $\alpha$ -2b	No	100	4 (20)	2 (10)	2 (100)
Forns et al N = 30 83% G1	IFN $\alpha$ -2b	Yes	43	6 (20)	3 (12)	3 (60)
Everson et al N = 124 70% G1	IFN $\alpha$ -2b	Yes	63	30 (24)	11 (13)	19 (50)
Iacobellis et al N = 66 65.2% G1	Peg-IFN $\alpha$ -2b	Yes	100	13 (19.7)	3 (7)	10 (43.5)

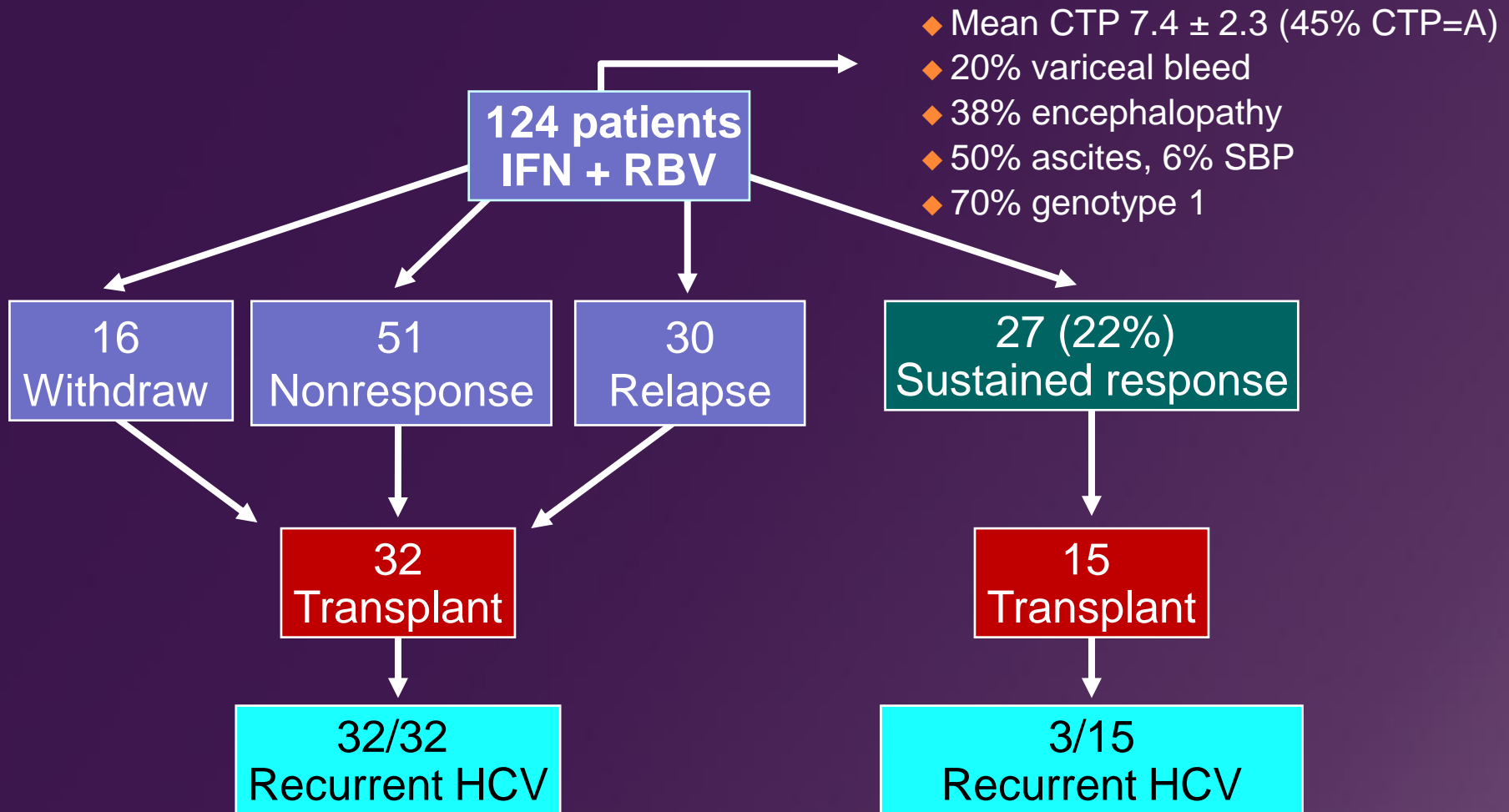
# Low Accelerating Dosage Regimen (LADR) Protocol

- ◆ Stepwise increase in doses to maximum tolerated
- ◆ 1.5 MU IFN\* TIW + RBV 600 mg QD
- ◆ Wk 2: increase IFN\* to 3 MU
- ◆ Wk 4: increase RBV by 200 mg weekly
- ◆ G-CSF/erythropoietin used to keep PMN > 800/ $\mu$ L, Hgb > 10 g/dL
- ◆ GOAL: IFN 3 MU TIW and RBV 1-1.2 g/d

\* Conventional IFN, not pegylated IFN.

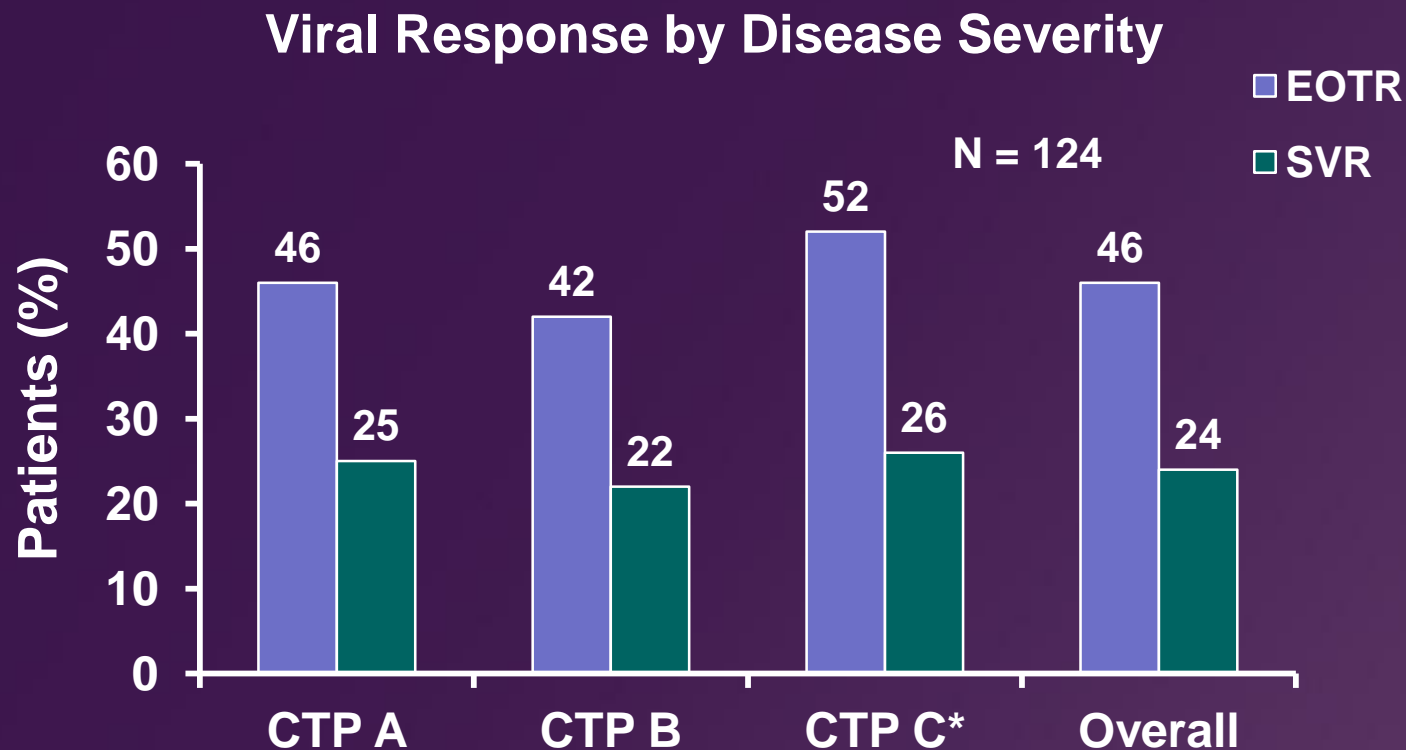
G-CSF = granulocyte colony-stimulating factor; PMN = polymorphonuclear.

# Antiviral Therapy in Patients With Decompensated Liver Disease



CTP = Child-Turcotte-Pugh score; SBP = spontaneous bacterial peritonitis.

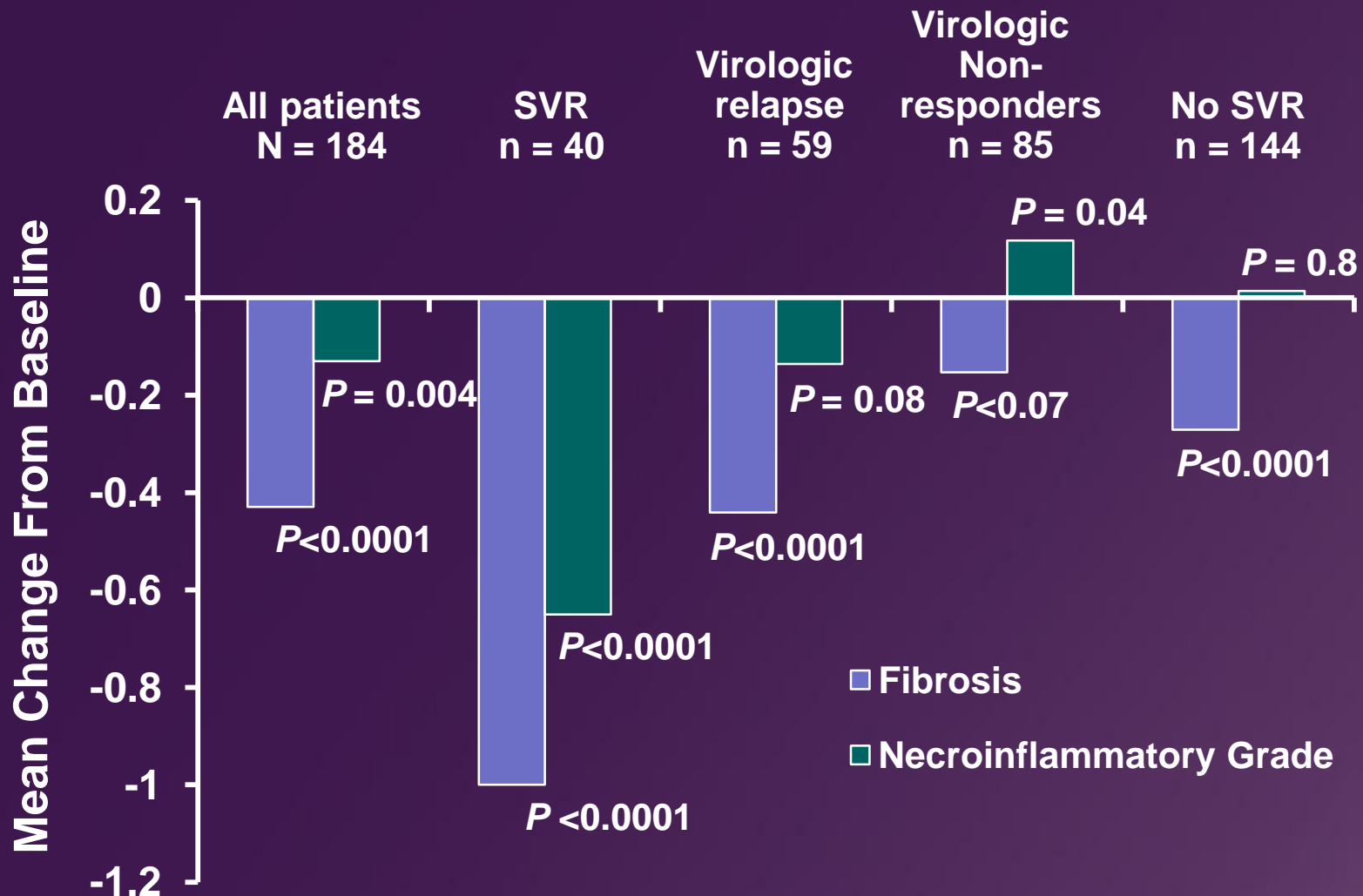
# LADR: Low Accelerating Dosage Regimen in Advanced HCV



- ◆ Predictors of SVR: non-1 genotype, CTP class A (genotype 1 only), and ability to tolerate full dose and duration of treatment ( $P < 0.0001$ )

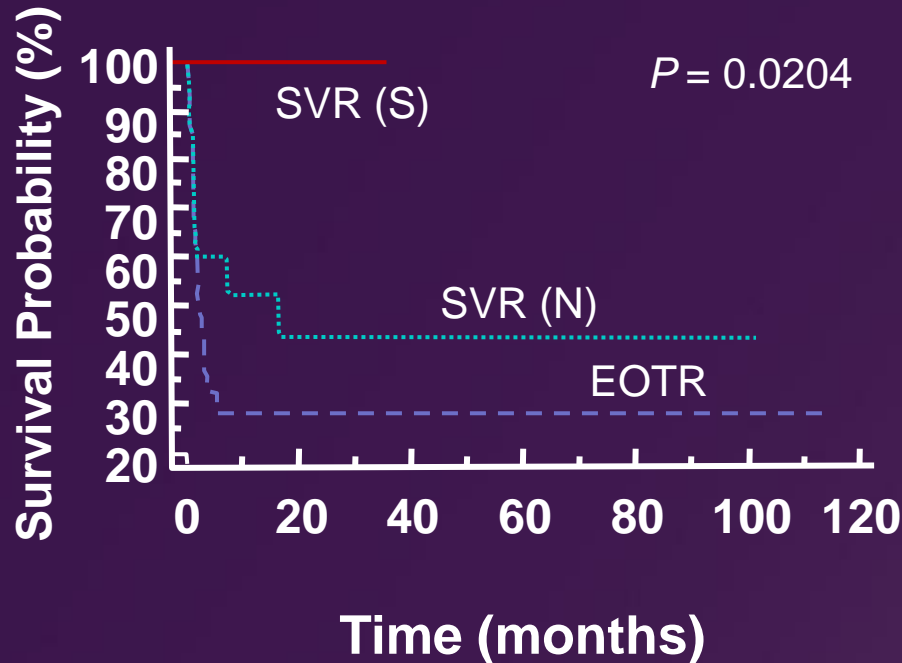
CTP = Child-Turcotte-Pugh; EOTR = end-of-treatment response; SVR = sustained virologic response.  
\*CTP C had a greater proportion of non-1 genotype.

# Peg-IFN $\alpha$ -2a Monotherapy in HCV With Advanced Fibrosis or Compensated Cirrhosis: Histologic Benefits

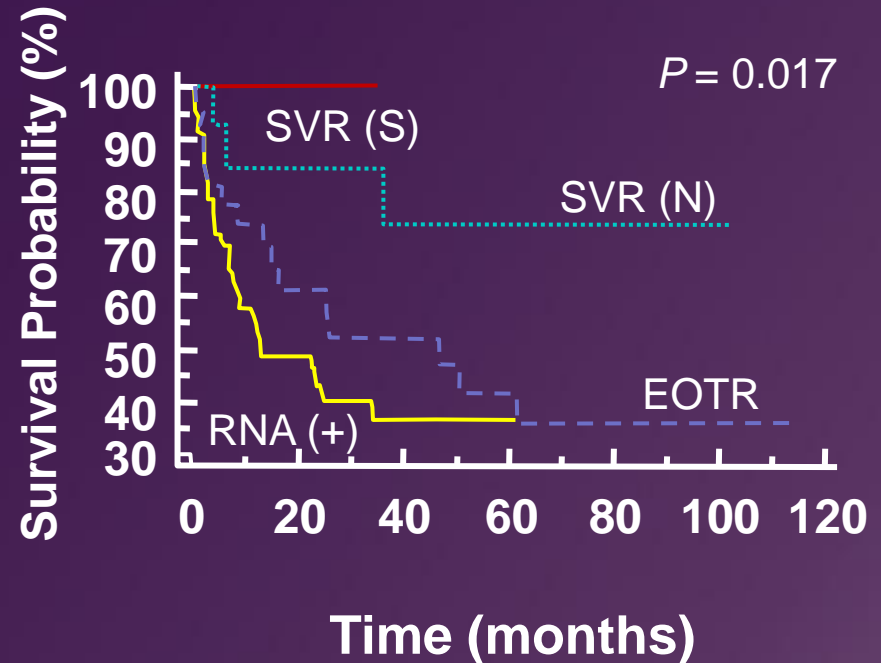


# Outcomes in Cirrhotic Patients Who Were Treated and Subsequently Received Liver Transplantation

## Virologic Recurrence-Free Survival



## Histologic Recurrence-Free Survival



EOTR = end-of-treatment response.

# Anti-HCV Therapy in Patients With Decompensated Cirrhosis

---

- ◆ Tolerability and safety of therapy in decompensated cirrhosis is related to severity of underlying liver disease
  - CTP A/B- better tolerated than CTP B+/C
  - Growth factors important in managing cytopenias
- ◆ Overall efficacy is reduced
  - Dose reductions and discontinuations frequent
  - Non-1 HCV genotype and early decline in HCV RNA levels are best predictors of response
- ◆ Reduced risk of recurrent HCV after transplantation
  - ~ 20% “success” among treated patients

# Suggested Guidelines for the Use of Interferon-Based Therapy in Patients With Cirrhosis

<b>International Liver Transplantation Society Expert Panel, 2003</b>		
<b>Consider Treatment</b>	<b>CTP score</b>	<b>MELD score</b>
Strongly consider	≤7	≤18
Possibly consider	8-11	18-25
No, avoid treatment	>11	>25

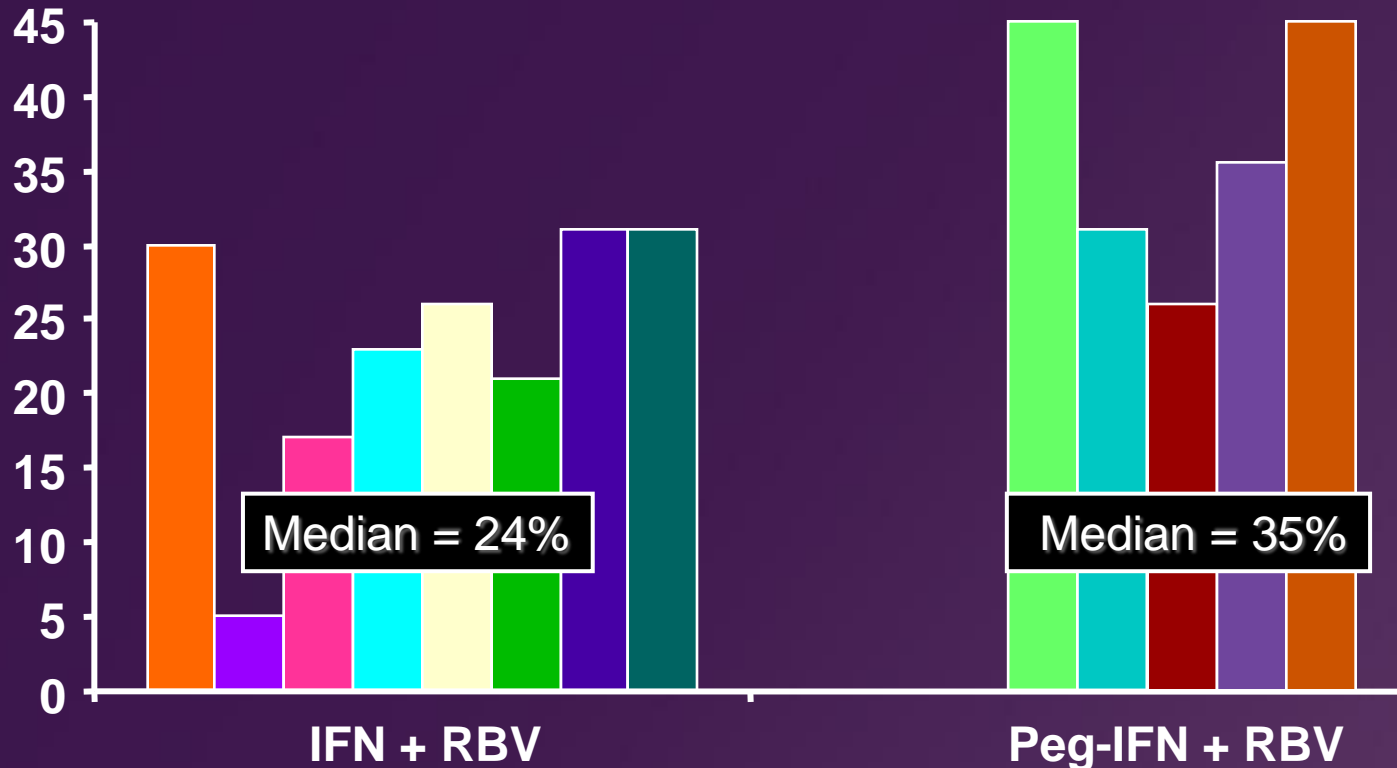
CTP = Child-Turcotte-Pugh; MELD = model for end-stage liver disease.

Iacobellis A et al. *World J Gastroenterol*. 2008;14:6467-6472. Reprinted with permission.

# Waiting Until After Transplantation to Treat HCV

---

# Sustained Virologic Response\* in LT Patients With Recurrent HCV



\*Includes only reports with  $\geq 20$  patients, treatment duration 48 wks.

1. Firpi RJ et al. *Liver Transpl.* 2002;8:1000-1006;
2. Shakil AO et al. *Hepatology.* 2002;36:1253-1258;
3. Lavezzo B et al. *J Hepatol.* 2002;37:247-252;
4. Narayanan Menon KV et al. *Liver Transpl.* 2002;8:623-629;
5. Bizollon T et al. *Gut.* 2003;52:283-287;
6. Samuel D et al. *Gastroenterology.* 2003;124:642-650;
7. Giostra E et al. *Transpl Int.* 2004;17:169-176;
8. Abdelmalek MF et al. *Liver Transpl.* 2004;10:199-207;
9. Dumortier J et al. *J Hepatol.* 2004;40:669-674;
10. Mukherjee S et al. *Transplant Proc.* 2003;35:3042-3044;
11. Rodriguez-Luna H et al. *Transplantation.* 2004;77:190-194;
12. Neumann U et al. *Transplantation.* 2006;82:43-47;
13. Oton E et al. *Am J Transplant.* 2006;6:2348-2355.

# Tolerability and Safety of Interferon-Based Therapy + Ribavirin After LT

---

- ◆ Dose reductions
  - IFN: 40%-60%
  - Ribavirin: 50%-90%
- ◆ Drug discontinuation
  - IFN: 10%-15%
  - Ribavirin: 20%-50% (more in early post-LT period)
- ◆ Risk of rejection
  - No difference in controlled trials, but in uncontrolled studies 0%-33%

# Treatment of Recurrent HCV Post LT: Current Status

---

- ◆ Combination therapy superior to monotherapy
  - Peg-IFN probably superior to non-peg IFN
  - Genotype most consistent factor associated with SVR
  - Dose reductions frequent
  - Growth factors essential
- ◆ Risk of rejection appears to be low
  - No differences between treated/untreated patients in controlled trials
  - Concurrent reductions in IMS with recurrence of HCV potentially confound uncontrolled trials

# Patient CK: Follow-up

---

- ◆ Completed 48 weeks of combination therapy without need for dose reduction
- ◆ Had end-of-treatment response and sustained virologic response