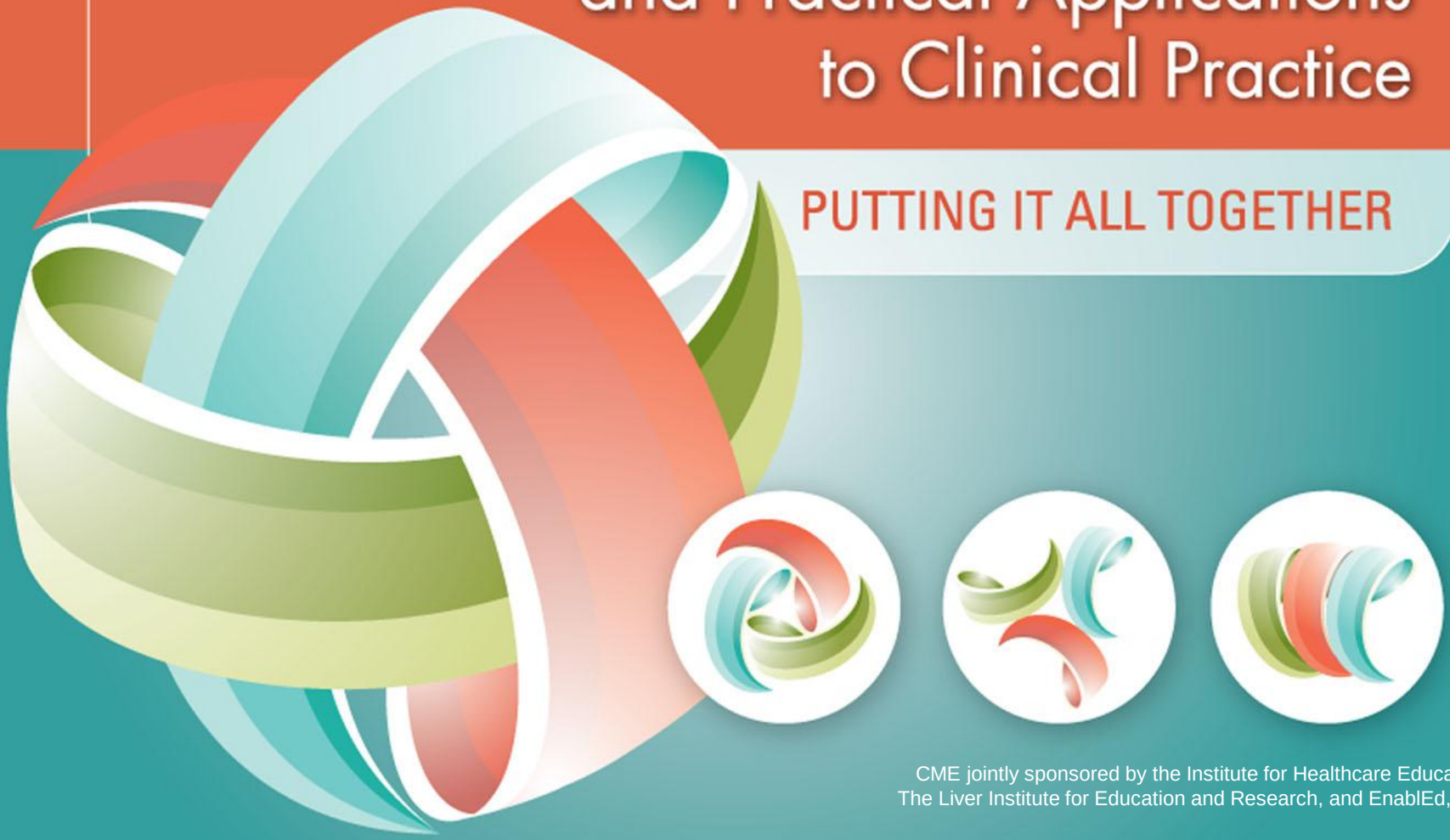
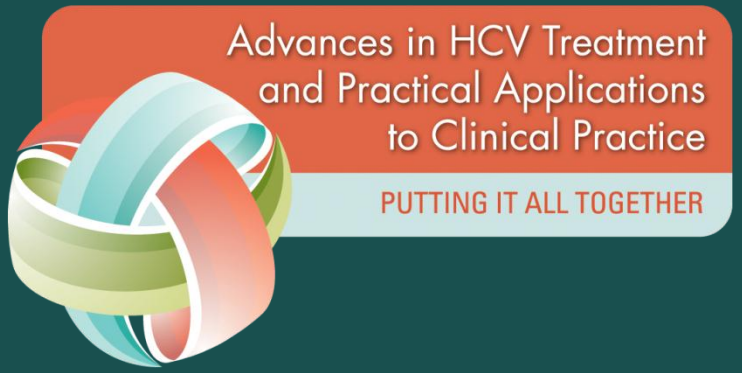
Advances in HCV Treatment and Practical Applications to Clinical Practice

PUTTING IT ALL TOGETHER



CME jointly sponsored by the Institute for Healthcare Education, The Liver Institute for Education and Research, and EnablEd, LLC



Case:
The Approach to the Patient with Cirrhosis

Patient with Cirrhosis

- 56-year-old man with genotype 1b HCV infection for at least 10 years
- Liver biopsy 9 years ago: Stage 1 fibrosis
- Lost to follow-up until recently; now back because of media attention to HCV
- Medical history: Diabetes for 6 years; elevated cholesterol
- Medications: Atorvastatin 20 mg/day, metformin 500 mg/day
- Physical examination: Mild hepatomegaly, no palpable spleen, no cutaneous signs of cirrhosis

Patient with Cirrhosis

- Laboratory data
  - Total bilirubin 0.8 mg/dL
  - ALT 67 IU/L, AST 82 IU/L
  - Albumin 3.7 g/dL
  - Total protein 7.2 g/dL
  - White blood cells 5,500/μL
  - Hemoglobin 14.5 g/L; A1C 6.7%
  - Platelets 98,000/μL
  - α-Fetoprotein 2.3 ng/mL

ALT = alanine aminotransferase; AST = aspartate aminotransferase.

Patient with Cirrhosis

- Imaging data
  - Magnetic resonance imaging (MRI): 1.6-cm enhancing lesion with early washout suspicious for hepatocellular carcinoma in Segment 5; enlarged caudate lobe; spleen 15 cm
  - Esophagogastroduodenoscopy: no varices

Patient with Cirrhosis

- What is the role of each of the following?
  - Biopsy of lesion in Segment 5
  - Biopsy of unaffected portion of liver
  - Ablation
  - Resection
  - Transplant evaluation
  - Antiviral therapy

Patient with Cirrhosis

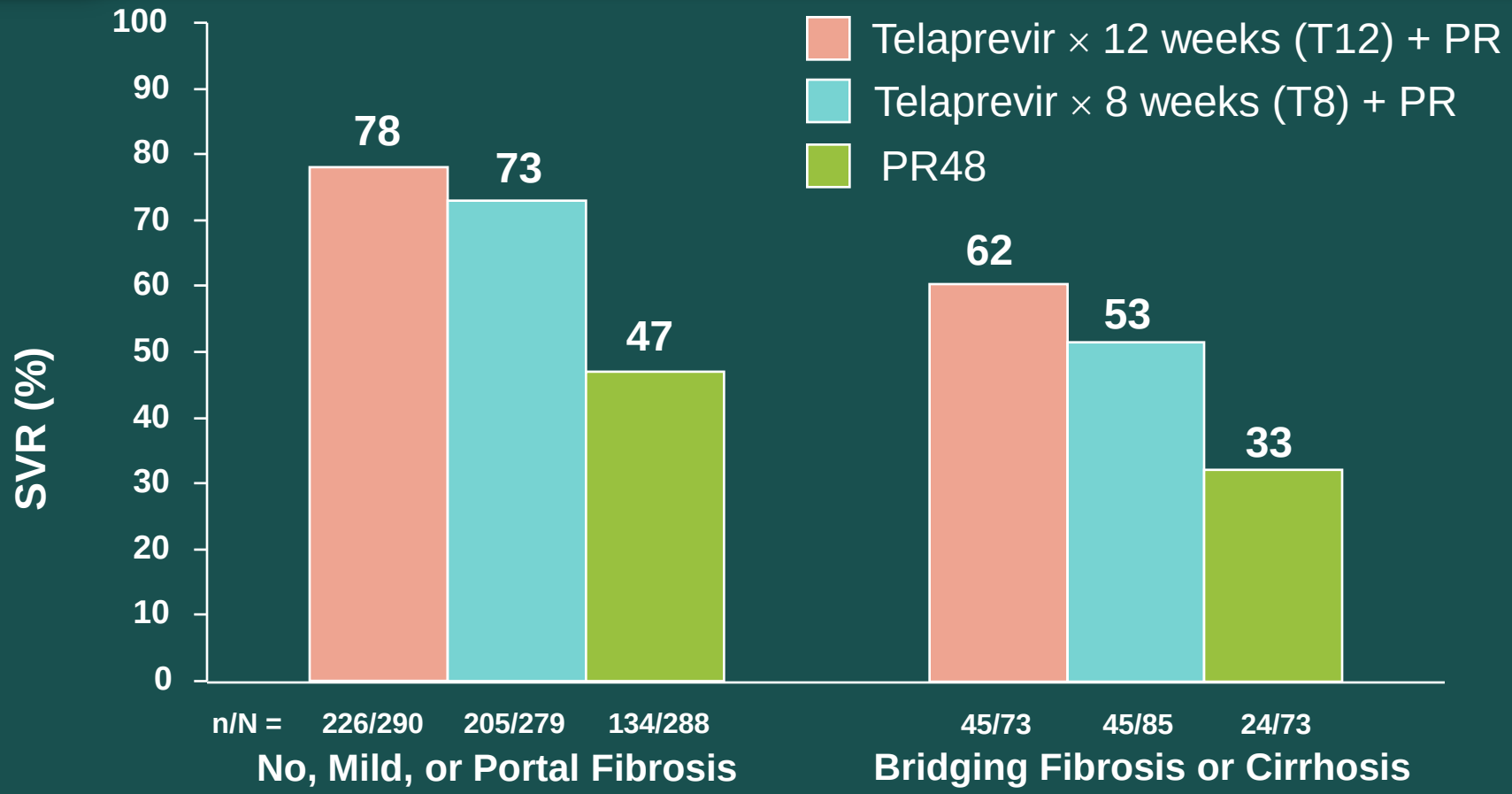
- Patient undergoes radiofrequency ablation of the Segment 5 lesion after initial evaluation by the transplant team
- Cardiac stress test: Unremarkable
- What would you do now?
  - Would you begin antiviral therapy?
    - If so, are any medication adjustments needed?
  - When would you repeat CT or MRI?

CT = computed tomography.

Patient with Cirrhosis

- 2 weeks later, treatment begins
  - Telaprevir, pegylated interferon (PEG-IFN) α-2a 180 μg/week, and ribavirin 1,200 mg/day
- Week 4
  - HCV RNA undetectable on PCR
  - Hemoglobin 9.4 g/dL
- Week 8
  - Hemoglobin 8.9 g/dL
  - Reports fatigue, exertional dyspnea
- How long would you treat this patient?
- How would you manage the hemoglobin?

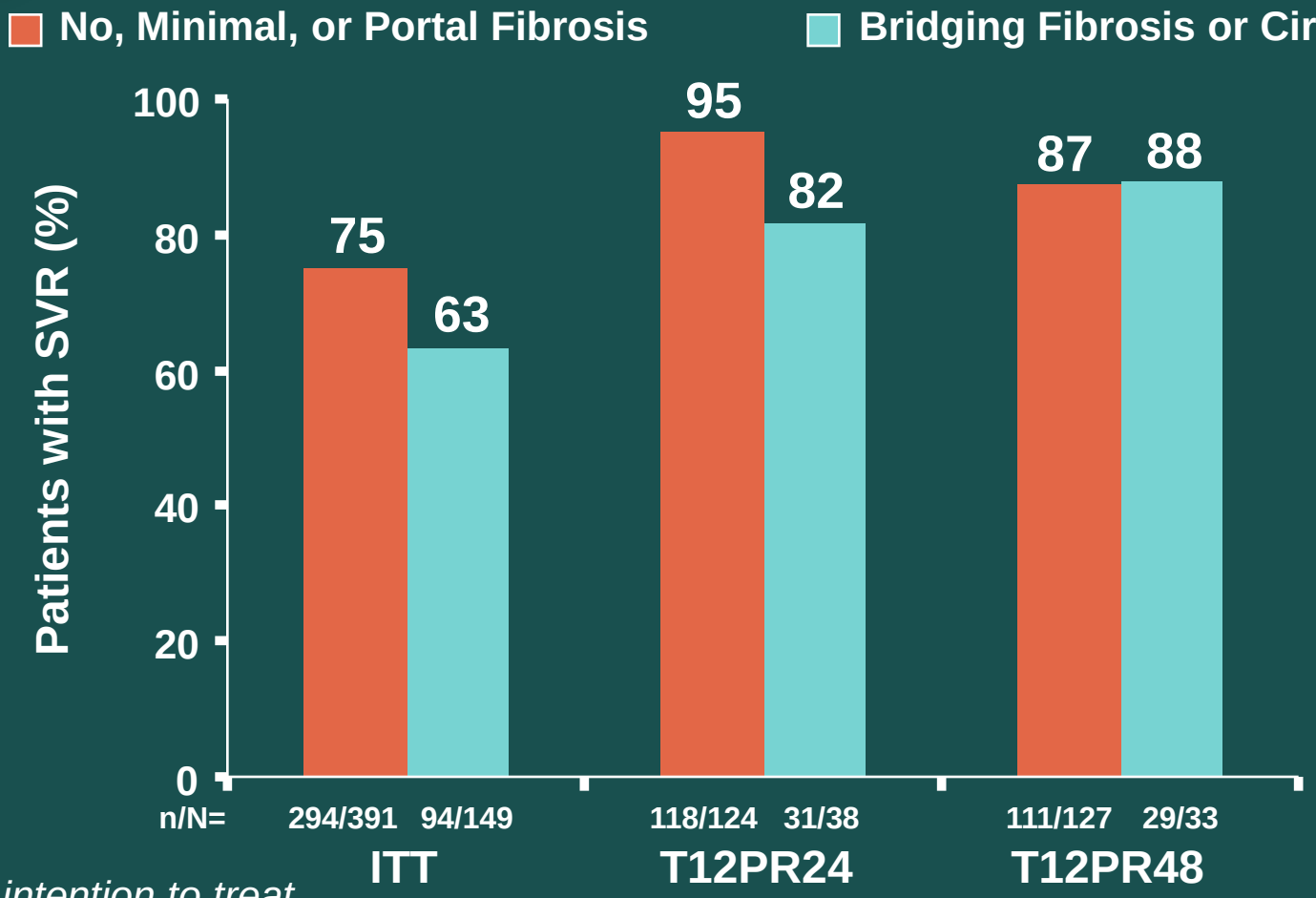
ADVANCE: Rates of Sustained Virologic Response (SVR) by Fibrosis Stage



PR(48) = PEG-IFN with ribavirin (for 48 weeks).

Jacobson IM, et al. N Engl J Med 2011;364(25):2405-16.

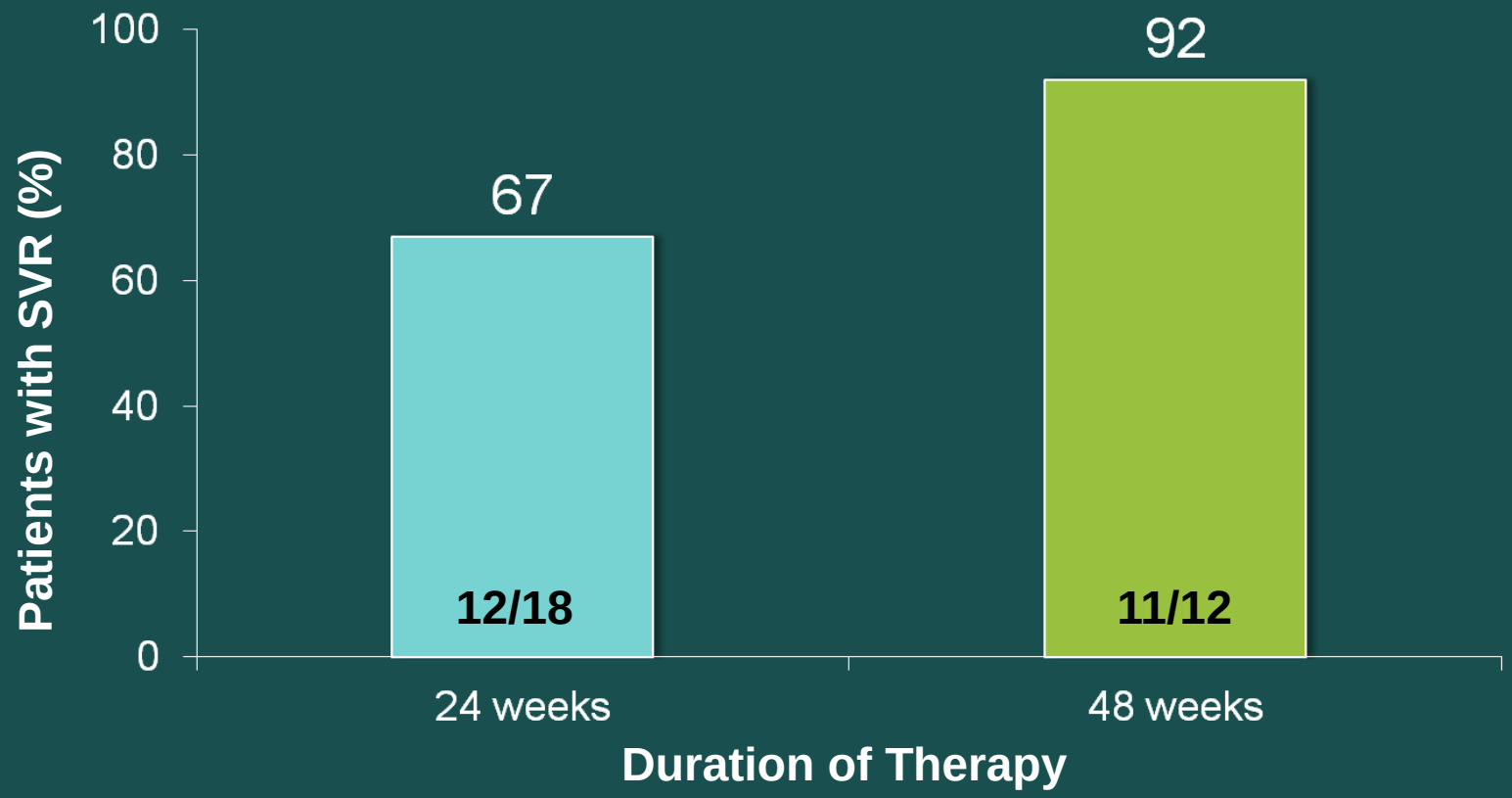
ILLUMINATE: High Overall SVR Rates in Patients with Bridging Fibrosis or Cirrhosis



ITT = intention to treat.

Sherman KE, et al. N Engl J Med 2011;365(11):1014-24.

Effect of Shortening Therapy in Cirrhotics with eRVR: ILLUMINATE



eRVR = extended rapid virologic response.

Telaprevir prescribing information.

SVR and Resistance-Associated Variants (RAVs) in Patients Treated with Telaprevir: Effects of Fibrosis

- Comparison of SVR rates with T12PR in pooled ADVANCE and ILLUMINATE patients versus PR (ADVANCE)
- Grade F0–2 fibrosis versus F3–4
- RAVs assessed in SVR failures

- Prevalence of RAVs similar in patients with F0–2 vs. F3–4 fibrosis who failed SVR
  - Low-level RAVs 38% in F0–2, 43% in F3–4
  - High-level RAVs 38% in F0–2, 44% in F3–4
  - Median time to loss of RAVs: 10 months

Fibrosis stage	Treatment	eRVR, n (%)	EOT, n (%)	SVR, n (%)	Relapse, n (%)*	VF, n (%)
F0–F2	T12PR (n=681)	444 (65)	602 (88)	520 (76)	38 (6)	39 (6)
	PR (n=288)	25 (9)	189 (66)	134 (47)	50 (26)	84 (29)
F3–F4	T12PR (n=222)	121 (55)	181 (82)	139 (63)	26 (14)	27 (12)
	PR (n=73)	4 (5)	40 (55)	24 (33)	14 (35)	31 (42)

Telaprevir associated with comparable improvements in SVR (+29%–30%) vs. PR for all fibrosis stages, but patients with more severe disease had lower SVR and higher relapse rates versus those with no/less severe fibrosis.

**Denominator is number of patients with HCV RNA undetectable at end of treatment (EOT). VF = virologic failure.*

Di Bisceglie A, et al. Can J Gastroenterol. 2012;26(Suppl A):A025.

Telaprevir Safety Data: Cirrhosis vs. No Cirrhosis

Treatment-Naïve

	T12 PR(ADVANCE, ILLUMINATE)		PR (ADVANCE)	
	Cirrhosis N=82	No cirrhosis N=821	Cirrhosis N=21	No cirrhosis N=340
Anemia				
Grade 3	55 (67%)	377 (46%)	5 (24%)	85 (25%)
Grade 4	2 (2%)	11 (1%)	0 (0%)	0 (0%)
Neutropenia				
Grade 3	8 (10%)	72 (9%)	4 (19%)	39 (11%)
Grade 4	2 (2%)	11 (1%)	0 (0%)	10 (3%)
Thombocytopenia				
Grade 3	10 (12%)	12 (2%)	0 (0%)	1 (<1%)
Grade 4	1 (1%)	0 (0%)	1 (5%)	0 (0%)

Kauffman RS, et al. HepDART December 2011.

Telaprevir Safety Data: Cirrhosis vs. No Cirrhosis

Treatment-Naïve

	T12PR (ADVANCE, ILLUMINATE)		PR (ADVANCE)	
	Cirrhosis N=82	No cirrhosis N=821	Cirrhosis N=21	No cirrhosis N=340
Stop TVR or placebo for AE	21 (26%)	152 (19%)	1 (5%)	15 (4%)
SAE	8 (10%)	38 (5%)	1 (5%)	6 (2%)
Transfusion	3 (4%)	21 (3%)	0 (0%)	1 (<1%)
Severe rash	4 (5%)	34 (4%)	0 (0%)	2 (1%)
Anorectal symptoms	29 (35%)	266 (32%)	2 (10%)	24 (7%)

(S)AE = (serious) adverse event; TVR = telaprevir.

Kauffman RS, et al. HepDART December 2011.

Telaprevir Safety Data: Cirrhosis vs. No Cirrhosis

Treatment-Experienced (REALIZE)

	T12PR		PR	
	Cirrhosis N=139	No cirrhosis N=391	Cirrhosis N=30	No cirrhosis N=102
Anemia				
Grade 3	90 (65%)	210 (54%)	10 (33%)	29 (28%)
Grade 4	3 (2%)	6 (2%)	0 (0%)	0 (0%)
Neutropenia				
Grade 3	20 (14%)	39 (10%)	2 (7%)	13 (13%)
Grade 4	5 (4%)	4 (1%)	1 (3%)	3 (3%)
Thombocytopenia				
Grade 3	15 (11%)	6 (2%)	1 (3%)	3 (3%)
Grade 4	1 (1%)	1 (<1%)	0 (0%)	0 (0%)

Kauffman RS, et al. HepDART December 2011.

Telaprevir Safety Data: Cirrhosis vs. No Cirrhosis

Treatment-Experienced (REALIZE)

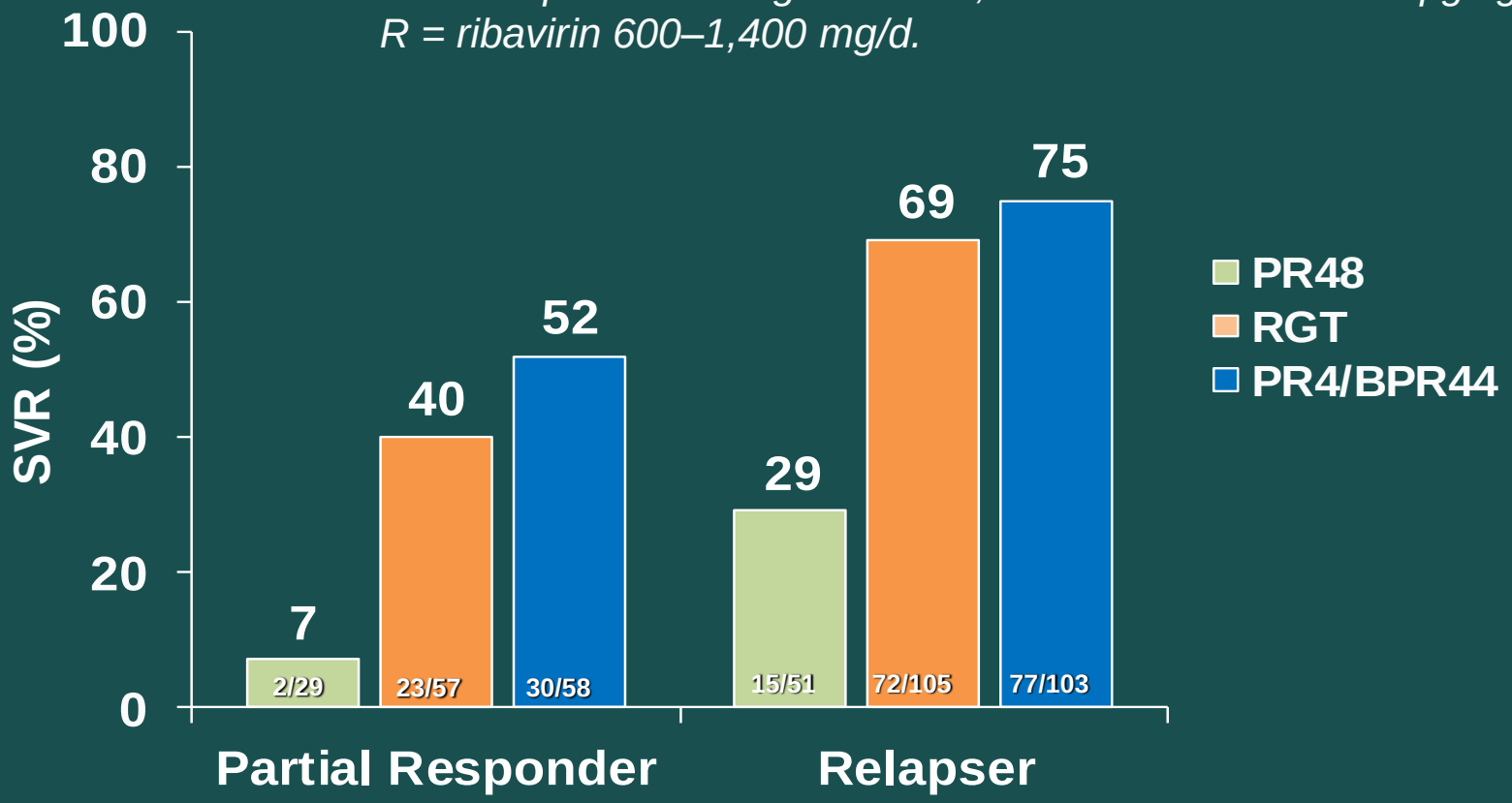
	T12PR		PR	
	Cirrhosis N=139	No cirrhosis N=391	Cirrhosis N=30	No cirrhosis N=102
Stop TVR or placebo for AE	21 (15%)	46 (12%)	0 (0%)	4 (4%)
SAE	15 (11%)	20 (5%)	1 (3%)	3 (3%)
Transfusion	12 (9%)	9 (2%)	1 (3%)	0 (0%)
Severe rash	7 (5%)	10 (3%)	0 (0%)	0 (0%)
Anorectal sx	31 (22%)	95 (24%)	0 (0%)	8 (8%)

sx = symptoms.

Kauffman RS, et al. HepDART December 2011.

RESPOND-2: SVR in Prior Relapsers or Partial Responders Treated with Boceprevir

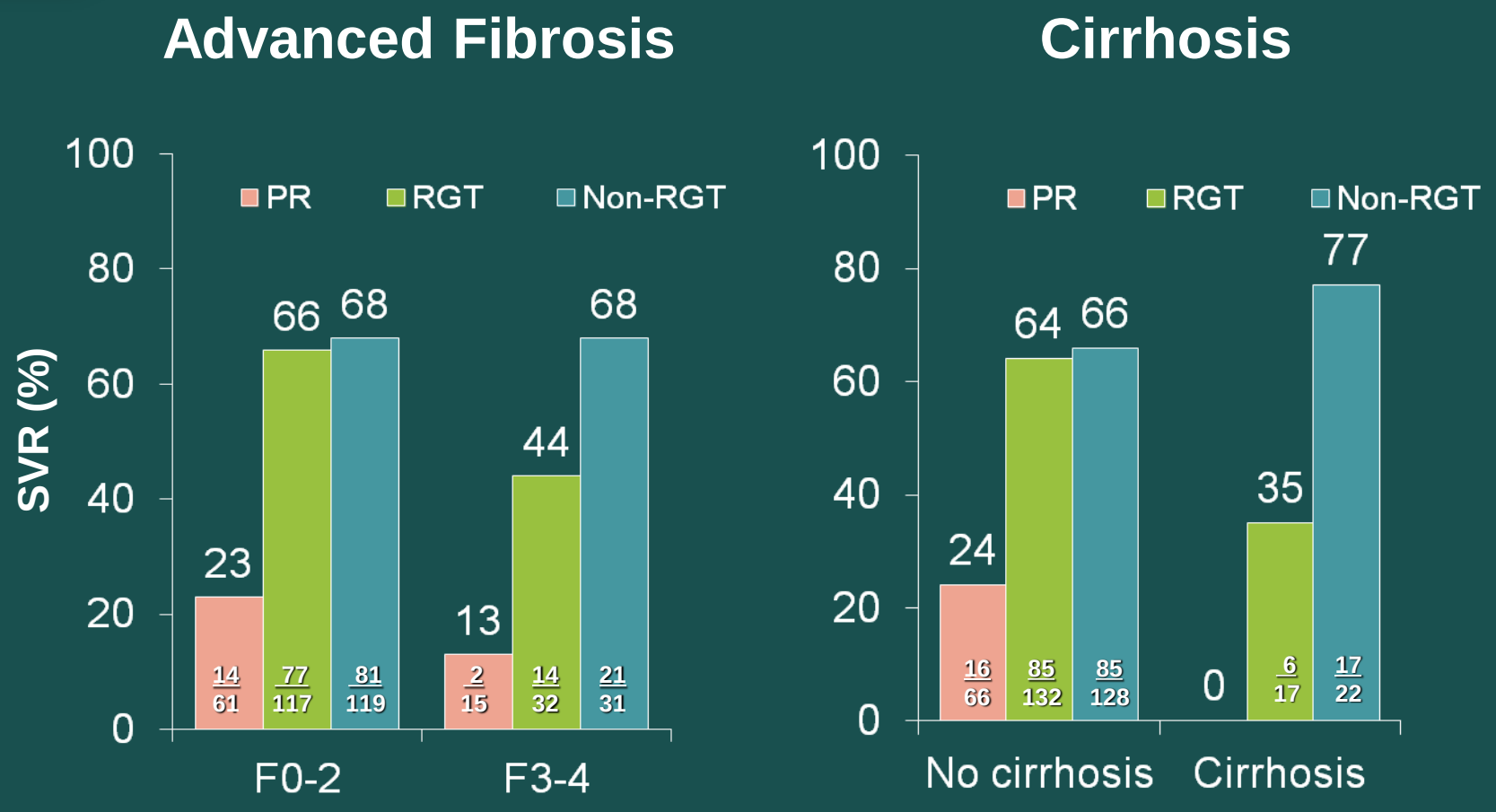
B = boceprevir 800 mg 3 times/d; P = PEG-IFN α-2b 1.5 µg/kg/wk; R = ribavirin 600–1,400 mg/d.



Cirrhotics drove the differences between RGT and 48 wks

Bacon BR, et al. N Engl J Med 2011;364:1207-17.

Advanced Fibrosis and Cirrhosis in RESPOND-2: Impact on SVR



Bacon BR, et al. N Engl J Med 2011;364:1207-17

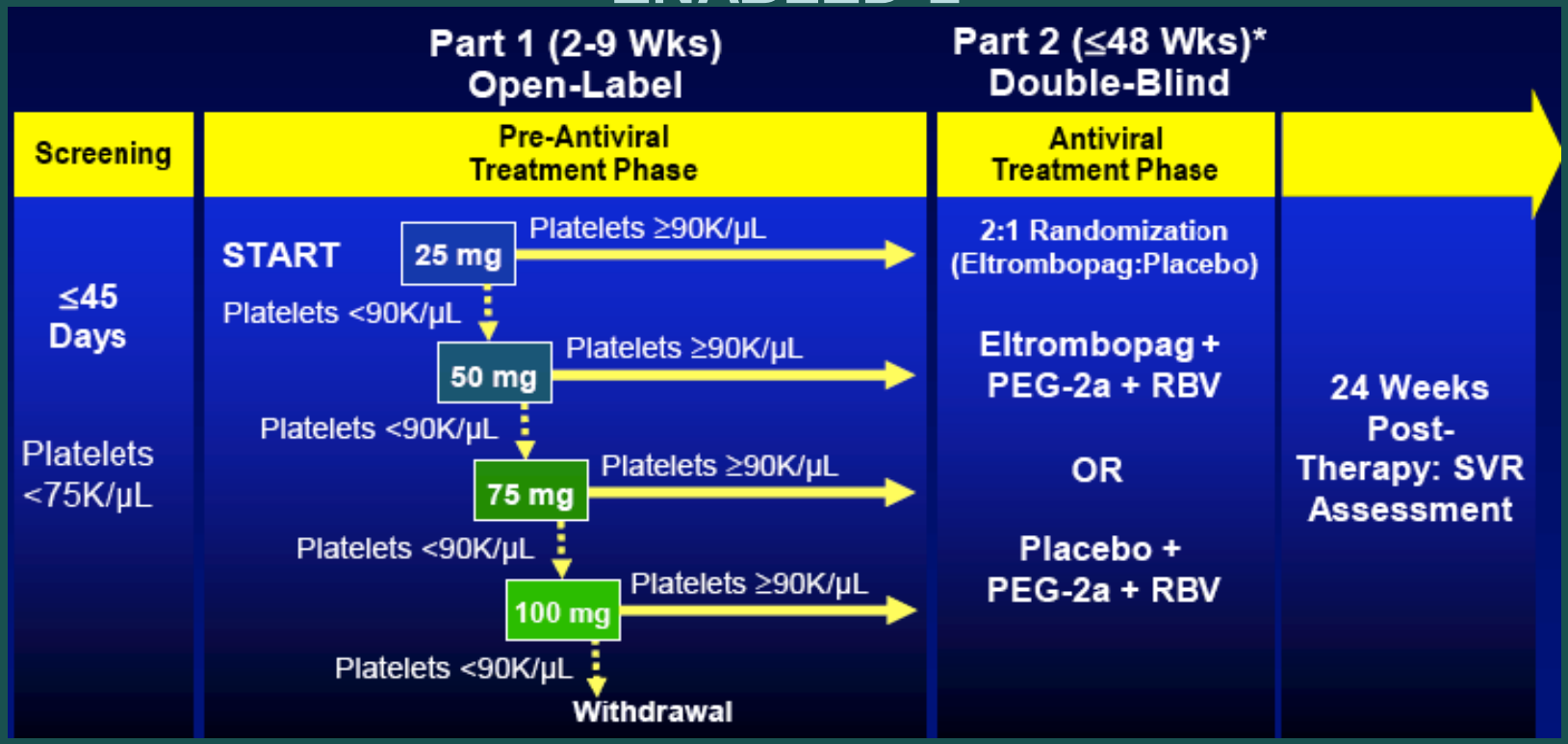
ANRS CO20-CUPIC: 16 Week Interim Analysis of TVR or BOC Plus PR in Cirrhotic Non-Responders

Child Pugh A – PR relapsers or partial responders	TVR n=296	BOC n=159
Median PI duration (days)	84	140
Serious adverse events (SAE)	144 (48.6)	61 (38.4%)
Discontinuation	77 (26%)	38 (23.9%)
Discontinuation due to SAE	43 (14.5%)	12 (7.4%)
Death	6 (2%)	2 (1.3%)
Anemia Grade 2 (8.0–<10.0g/dL)	58 (19.6%)	36 (22.6%)
Anemia Grade 3-4 (<8.0g/dL)	30 (10.1%)	16 (10.1%)
EPO use	168 (56.8%)	105 (66%)
Blood transfusion	45 (15.2%)	17 (10.7%)
Thrombopenia Grade 3–4(<50000/mm^3)	39 (13.2%)	11 (6.9%)
Thrombopoietin use	5 (1.7%)	3 (1.9%)
Rash Grade 3	20 (6.8%)	0 (0%)
SCAR	2 (0.7%)	0 (0%)
Grade 3–4 infection	26 (8.8%)	4 (2.5%)

Hézode C, et al. EASL 2012, Barcelona, #8

ENABLED Studies: Raising Platelet Counts to Allow Antiviral Therapy

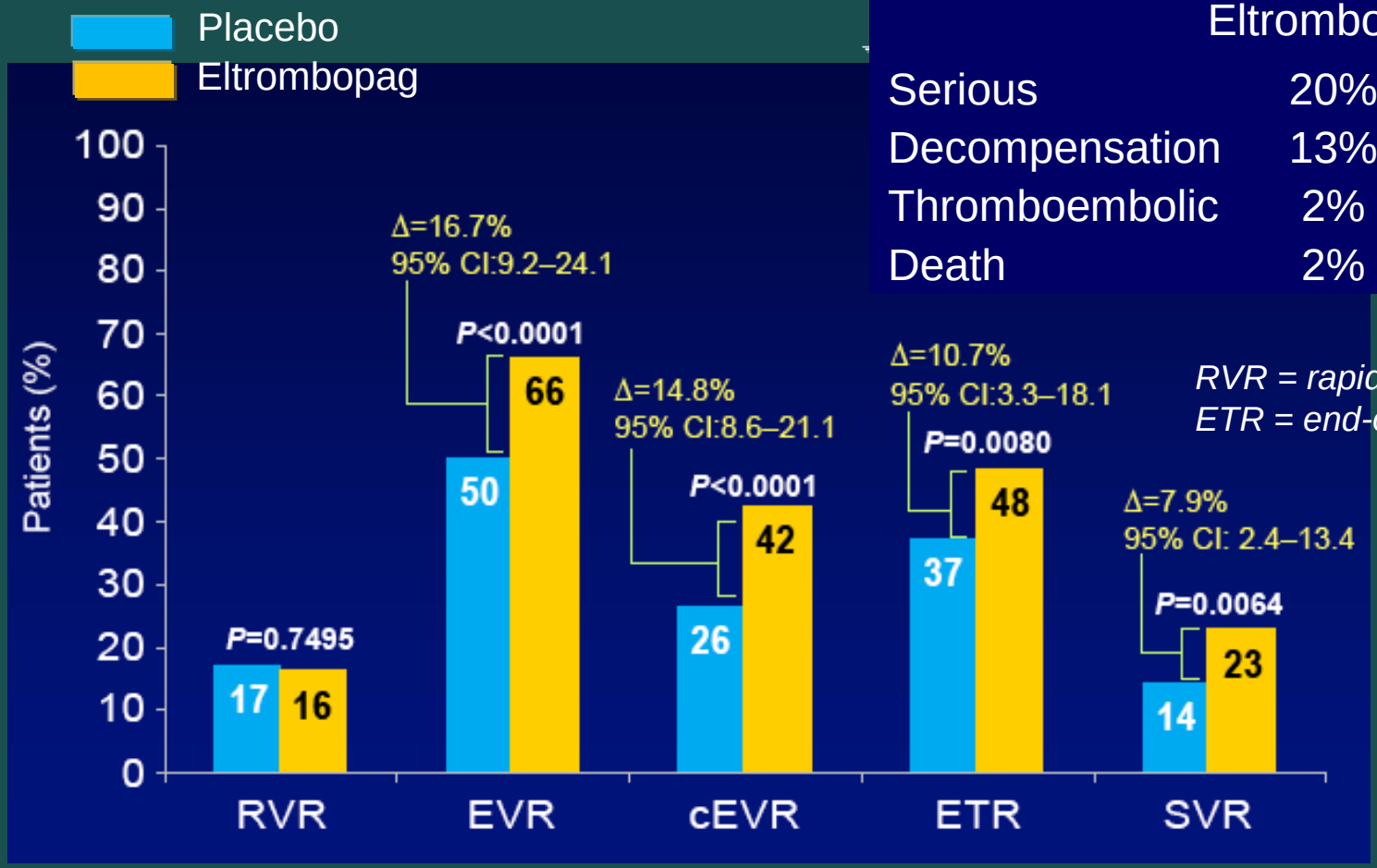
ENABLED-1



- Eltrombopag: oral nonpeptide thrombopoietin receptor agonist
- 6% of patients had Child-Pugh score of 7-9

Afdhal NH, et al. AASLD 2011 Abstract LB-3.

ENABLED-1: Virologic Responses in Intent-to-Treat Analysis



Adverse Events

	Eltrombopag	Placebo
Serious	20%	15%
Decompensation	13%	8%
Thromboembolic	2%	2%
Death	2%	3%

RVR = rapid virologic response
ETR = end-of-treatment response

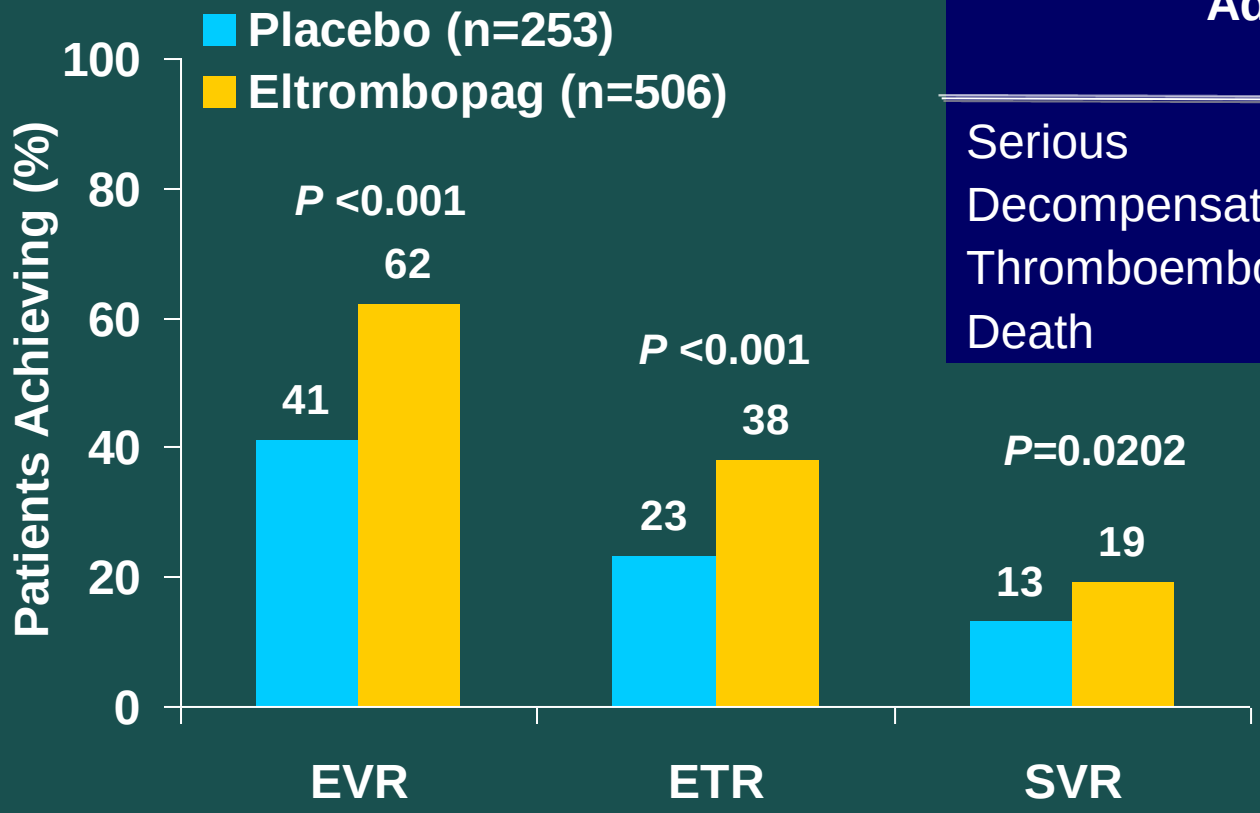
Afdhal NH, et al. AASLD 2011 Abstract LB-3.

ENABLED-2: Phase III Trial of Eltrombopag to Increase Platelets

- Part 1: Patients with HCV and platelets <75,000/μL received eltrombopag 25 mg, increased to 50, 75, or 100 mg daily until platelets reached ≥100,000/μL
- Part 2: Patients eligible for PEG-IFN α-2b (1.5 μg/kg/week) and ribavirin (weight-based) were randomized 2:1 to receive eltrombopag or placebo.
  - Treatment continued for 24 or 48 weeks according to genotype
- Primary endpoint: SVR

Dusheiko G, et al. EASL 2012 Abstract 60.

ENABLED-2: Phase III Trial of Eltrombopag to Increase Platelets



Adverse Events	Eltrombopag	Placebo
Serious	20%	15%
Decompensation	15%	8%
Thromboembolic	4%	<1%
Death	4%	2%

Dusheiko G, et al. EASL 2012 Abstract 60.

Should Patients with Cirrhosis Receive Response-Guided Therapy?

- Labels for both telaprevir and boceprevir advise or mandate 48 weeks of therapy (T12PR48 or PR4BPR44) for treatment-naïve and treatment-experienced patients with cirrhosis
- Only possible exception is cirrhotic relapsers treated with telaprevir
  - No explicit guidance given in US label for patients with cirrhosis

Telaprevir package insert; Boceprevir package insert.

Cirrhosis: Conclusions

- PI therapy associated with markedly improved SVR rates in patients with cirrhosis, but rates still lower than in noncirrhotic patients
- Those with compensated cirrhosis are strong candidates for PI-based therapy, if no contraindications to PEG-IFN/ribavirin therapy exist
- RGT is not applicable to cirrhotic patients, for either PI
- Higher rates of anemia in cirrhotic patients
- If SVR attained, patients still must undergo regular surveillance for hepatocellular carcinoma
- Need more data on DAA combination and quadruple-drug regimens in patients with cirrhosis

DAA = direct-acting antiviral agents; PI = protease inhibitor.