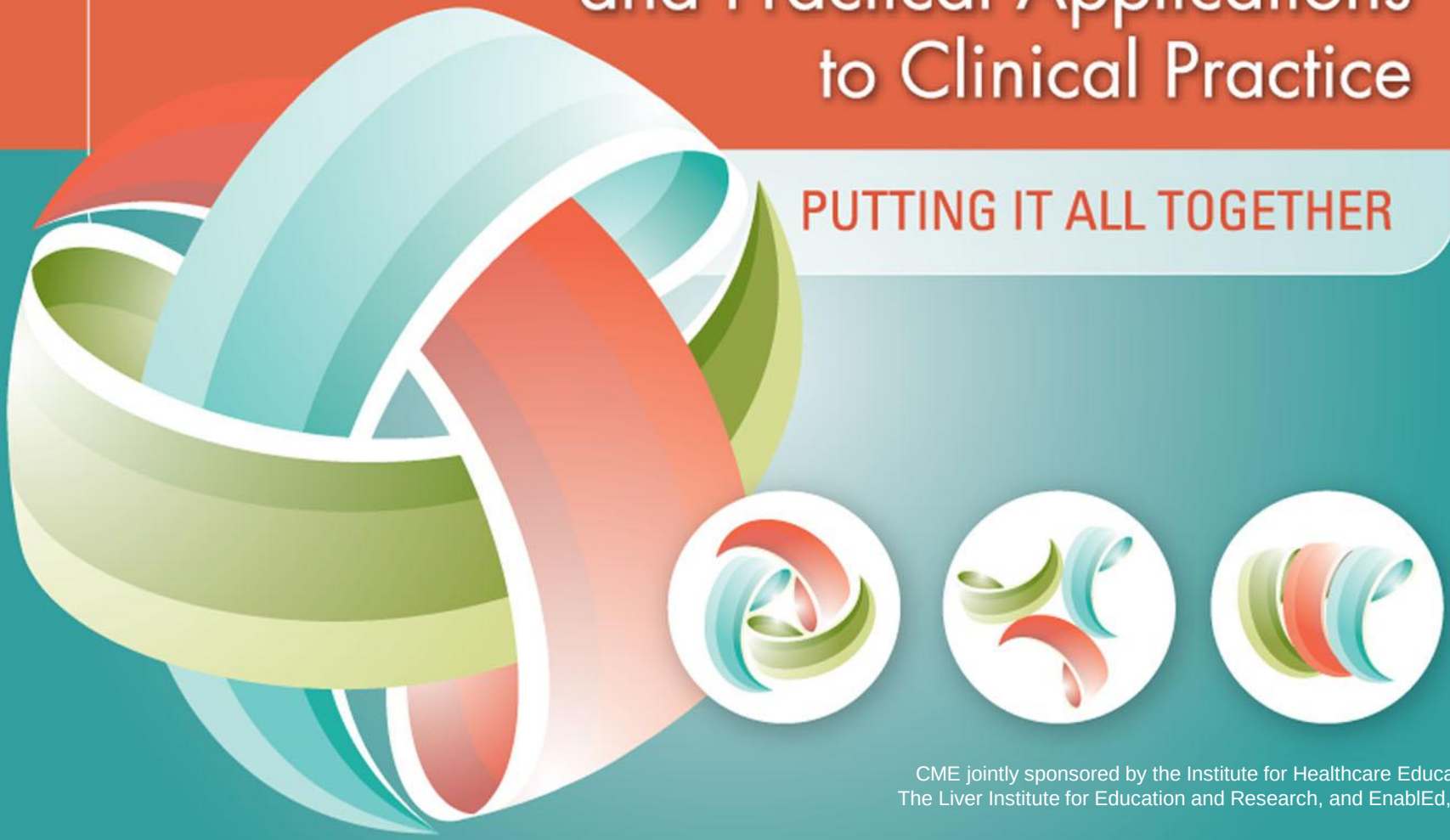
Advances in HCV Treatment and Practical Applications to Clinical Practice

PUTTING IT ALL TOGETHER



CME jointly sponsored by the Institute for Healthcare Education,
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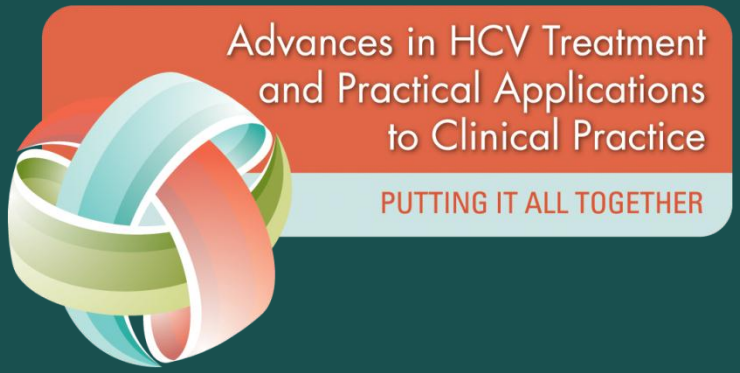


Case:
Approach to the Null Responder

Approach to the Null Responder

- 65-year-old man with chronic HCV, genotype 1b, biopsy-proven cirrhosis
- Treated 3 years ago with PEG-IFN α-2a and ribavirin
  - Baseline HCV RNA 3 million IU/mL
  - Week 12 HCV RNA 140,000 IU/mL (1.3-log decrease) despite good compliance
  - Nadir hemoglobin 10.2 g/dL, no major AEs
  - Treatment stopped for futility

PEG-IFN = pegylated interferon; AEs adverse events.

Approach to the Null Responder

- History
  - Former smoker; 1 pack/day until 5 years ago
  - Alcohol: 2 glasses wine/night until 5 years ago
    - Now 3 glasses/week
  - Mild COPD, no functional impairment
  - Hypertension
  - Hypercholesterolemia
- Medications
  - Hydrochlorothiazide 50 mg/day
  - Rosuvastatin 20 mg/day

COPD = chronic obstructive pulmonary disease.

Approach to the Null Responder

- Physical examination
  - Hepatomegaly; edge 3 cm below costal margin
  - Palpable spleen tip
  - Palmar erythema
  - Few spider angiomas
  - No ascites
  - No jaundice

Approach to the Null Responder

- Laboratory data
  - White blood cells 4,500/μL; hemoglobin 13.9 g/dL; platelets 85,000/μL
  - Total bilirubin 0.8 mg/dL
  - ALT 58 IU/L; AST 87 IU/L
  - Albumin 3.4 g/dL, globulins 3.8 g/dL
  - α-Fetoprotein 22.9 ng/mL
  - MRI: nodular liver, enlarged caudate lobe, no focal lesions, spleen 16 cm
  - Esophagogastroduodenoscopy: Grade 1 varices

ALT = alanine aminotransferase; AST = aspartate aminotransferase.

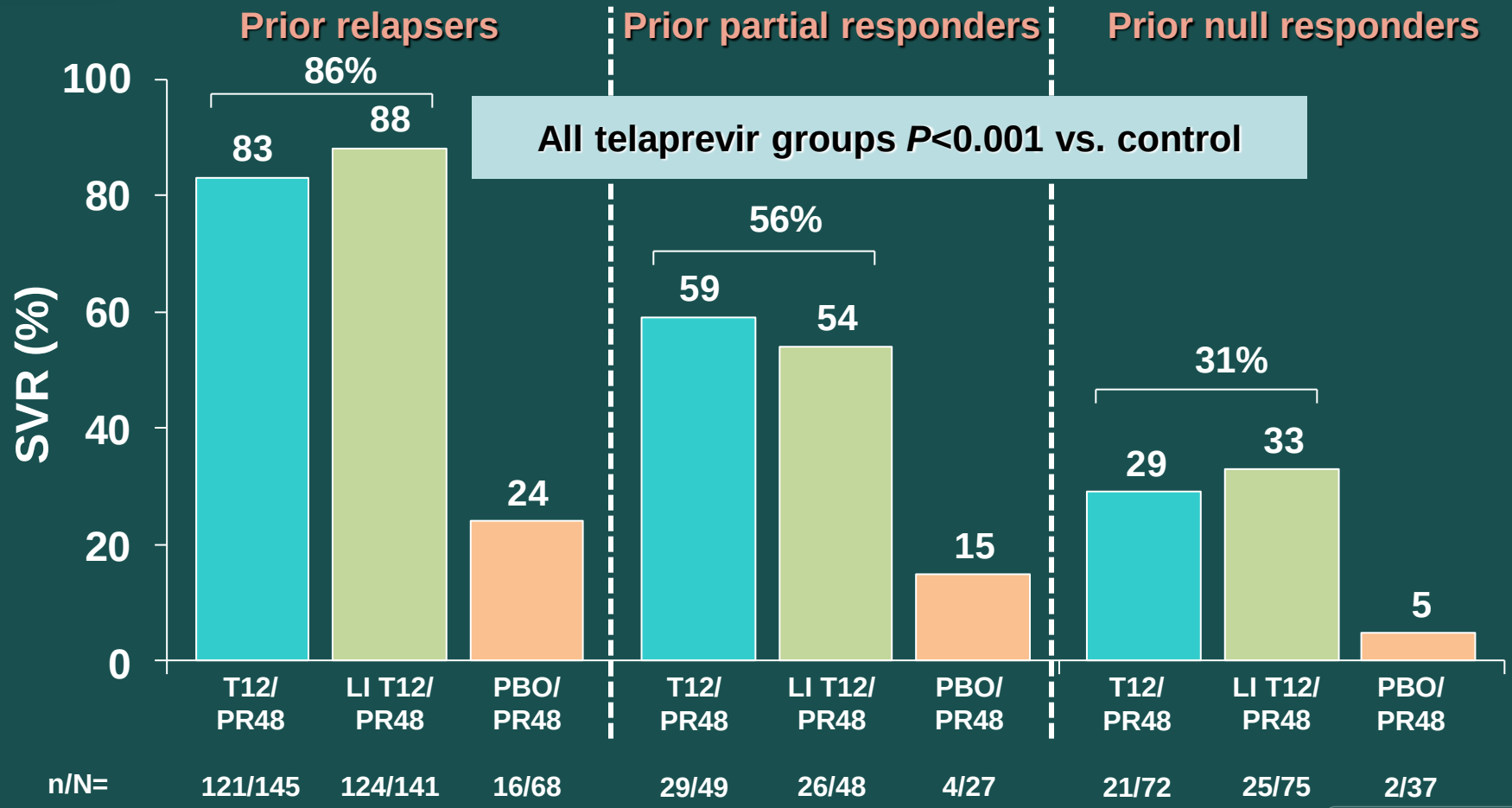
Approach to the Null Responder

- How would you manage this patient?
- What are his chances of SVR with therapy with either protease inhibitor (PI)?
- Do the patient's other comorbid conditions and medications need to be taken into consideration?

- Would you treat this patient at the present time?

SVR = sustained virologic response.

REALIZE: SVR with Telaprevir in Prior Relapsers, Prior Partial Responders, and Prior Null Responders



T12 = telaprevir x 12 wks; PR48 = PEG-IFN/ ribavirin x 48 wks; LI = lead-in; PBO = placebo

Zeuzem S, et al. N Engl J Med 2011;364:2417-27

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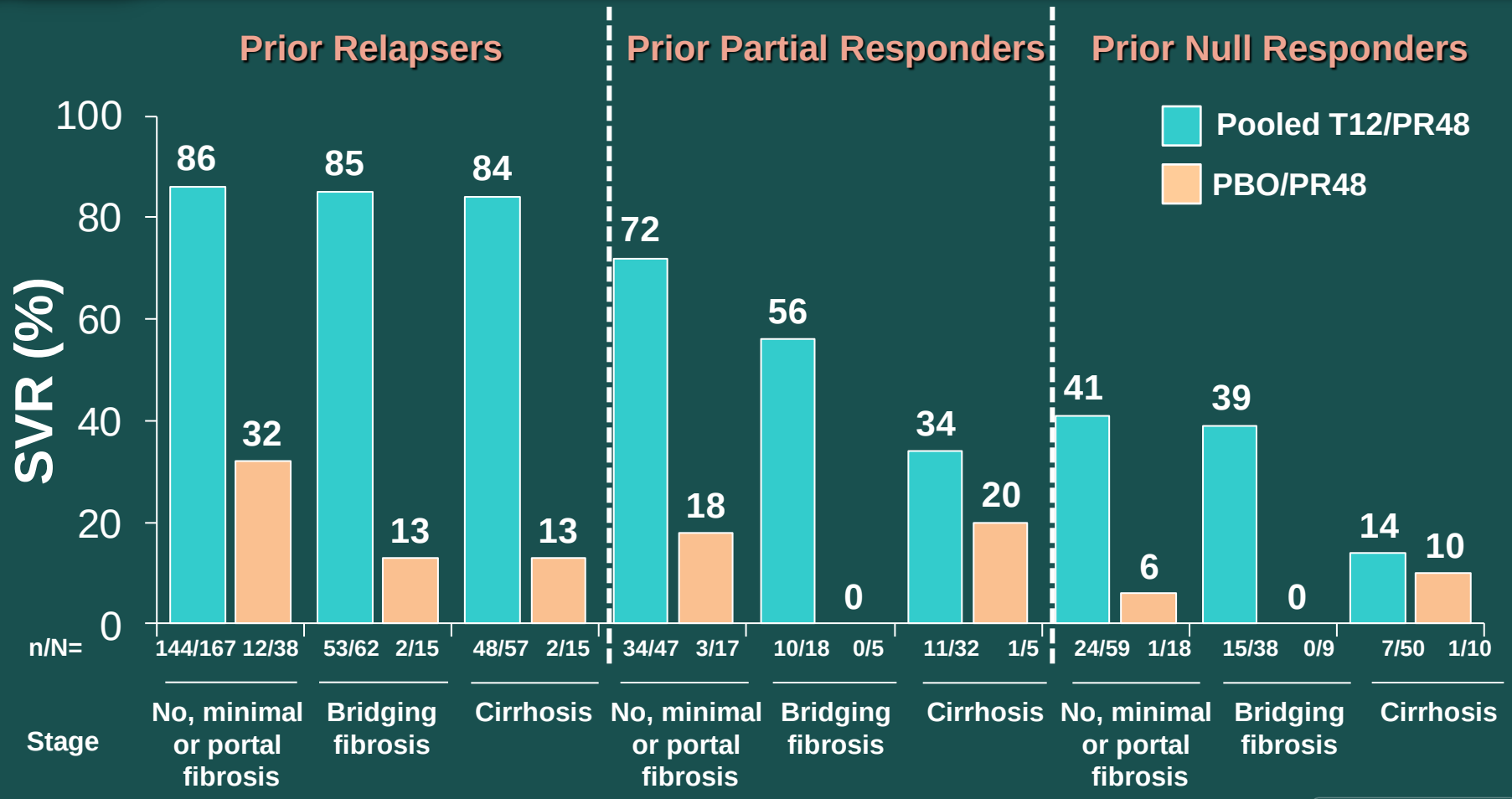
REALIZE: SVR by Baseline Fibrosis Stage and Prior Response

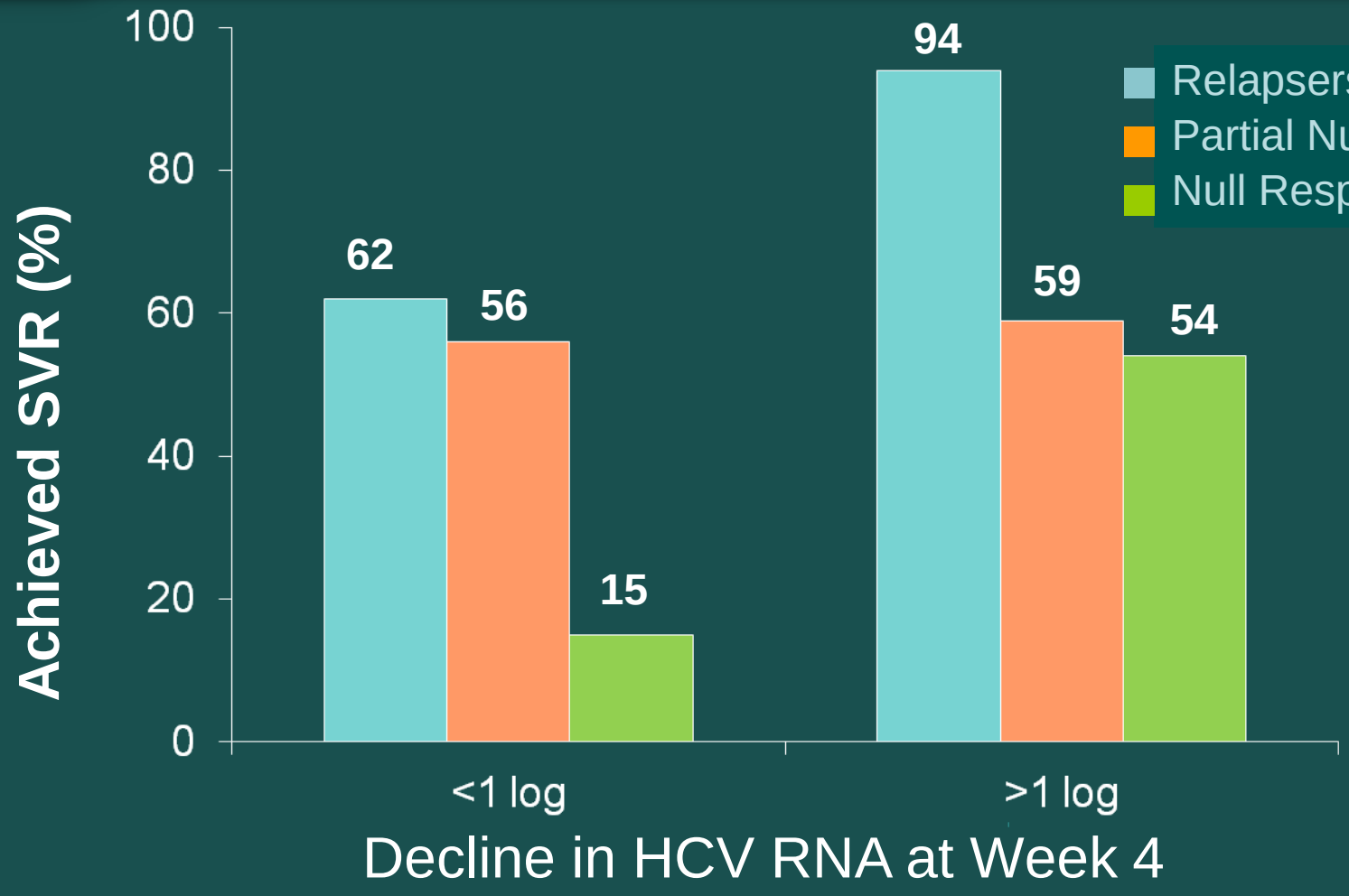


Zeuzem S, et al. EASL 2011, Abstract 5.

Approach to the Null Responder

- If you were going to treat with telaprevir, would you consider a 4-week lead-in period of PEG-IFN and ribavirin before starting the PI?

SVR by Response at Week 4 in the Lead-In Arm of REALIZE



Foster G et al, EASL 2011 Abstract 6.

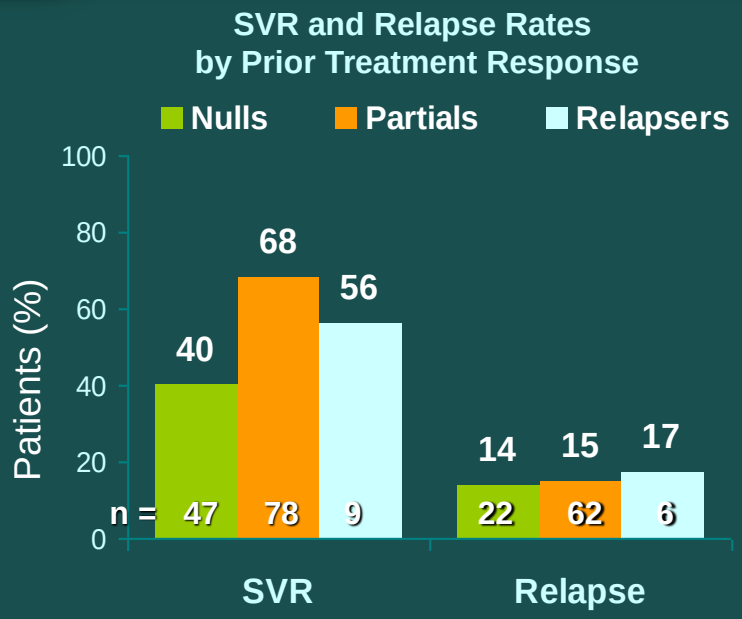
PROVIDE: Efficacy of Boceprevir in Prior Null Responders to PR

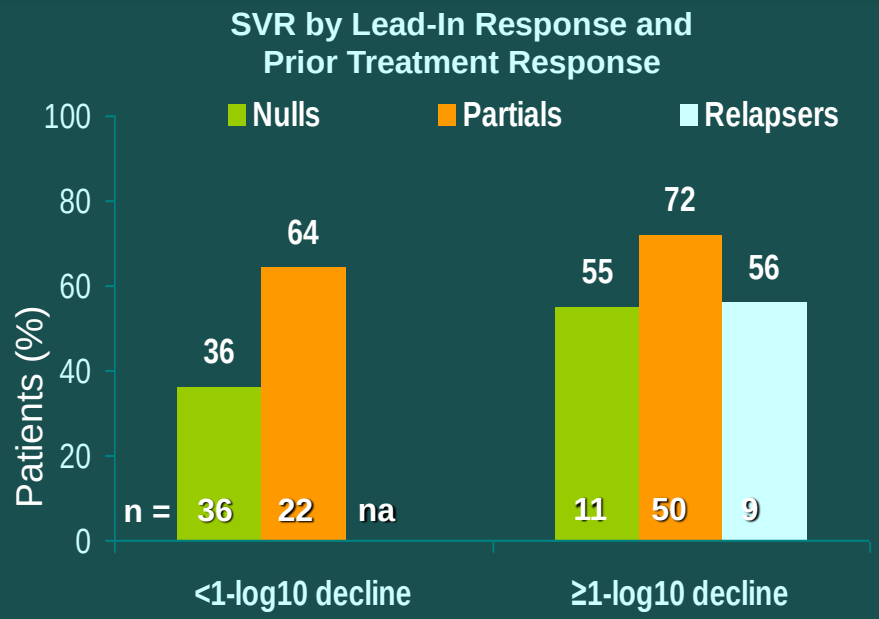
- SVR data for null responders treated with BOC are lacking because they were excluded from RESPOND-2 (Phase III study)
- PROVIDE study: Treatment of non-SVR patients from SPRINT-2 and RESPOND-2 with open-label PR/BOC
  - Prior null responders
    - n=37 from SPRINT-2, n=11 from RESPOND-2
    - 8% had F3/4 fibrosis
    - 65% had genotype 1a, 35% had 1b
- If >2 week window since treatment, then 4-week lead-in used

BOC = boceprevir.

Jacobson IM, et al. HepDART 2011.

PROVIDE: SVR Rates with BOC/PR After Prior PR Treatment Failure





- Retreatment with BOC/PR in PR arms of Phase II/III BOC studies without SVR
- N=168 (10% cirrhosis, 61% G1a) received BOC 800 mg three times/day, PEG-IFN 1.5 μg/kg/wk, and ribavirin 600–1,400 mg/kg/day (2 divided doses) for up to 44 weeks
- 7% discontinued due to adverse events

Bronowicki JP, et al. EASL 2012 Barcelona, #11

Bronowicki JP, et al. EASL 2012 Abstract 204.

Potential Arguments for a Lead-in PEG-IFN + Ribavirin Dosing Period

- Can stop therapy and avoid side effects in face of likely futility
- Avoid likelihood of resistance
- Maintain patient's eligibility for trials of new direct-acting antivirals when few PI failure studies are available
- Assess hematologic response to PEG-IFN/ribavirin therapy, make needed dose adjustments before starting PI

Kwo PY, et al. Lancet 2010;376(9742):705-16.

Pros and Cons for Treatment of Null Responders with TVR or BOC

- Pros
  - SVR rates suboptimal, but only option to offer at present
  - With less advanced fibrosis, SVR rates more substantial (40%, even F3)
  - Patients highly motivated; many have proven they can tolerate therapy
  - Resistant variants that emerge with failure appear to wane over time
- Cons
  - SVR rates are lower than those attainable with regimens being studied
  - SVR rates poor with cirrhosis
  - With failure comes high likelihood of resistant variants; some may persist
  - First dose of PI disqualifies patient from trials until PI-failure trials begin

TVR = telaprevir.

Zeuzem S, et al. EASL 2011, Abstract 5; Zeuzem S, et al. N Engl J Med 2011;364:2417-27; Jacobson IM, et al. HepDART 2011; Sullivan J, et al. EASL 2011, Berlin, Oral 8; Vierling JM, et al. EASL 2010. Abstract 2016.