Disclosures
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  - **Genentech, Merck, Vertex, Janssen, Bristol-Myers Squibb, AbbVie, Gilead,**
- **Consultant:**
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- HCV-TARGET: Co-Principal Investigator

THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

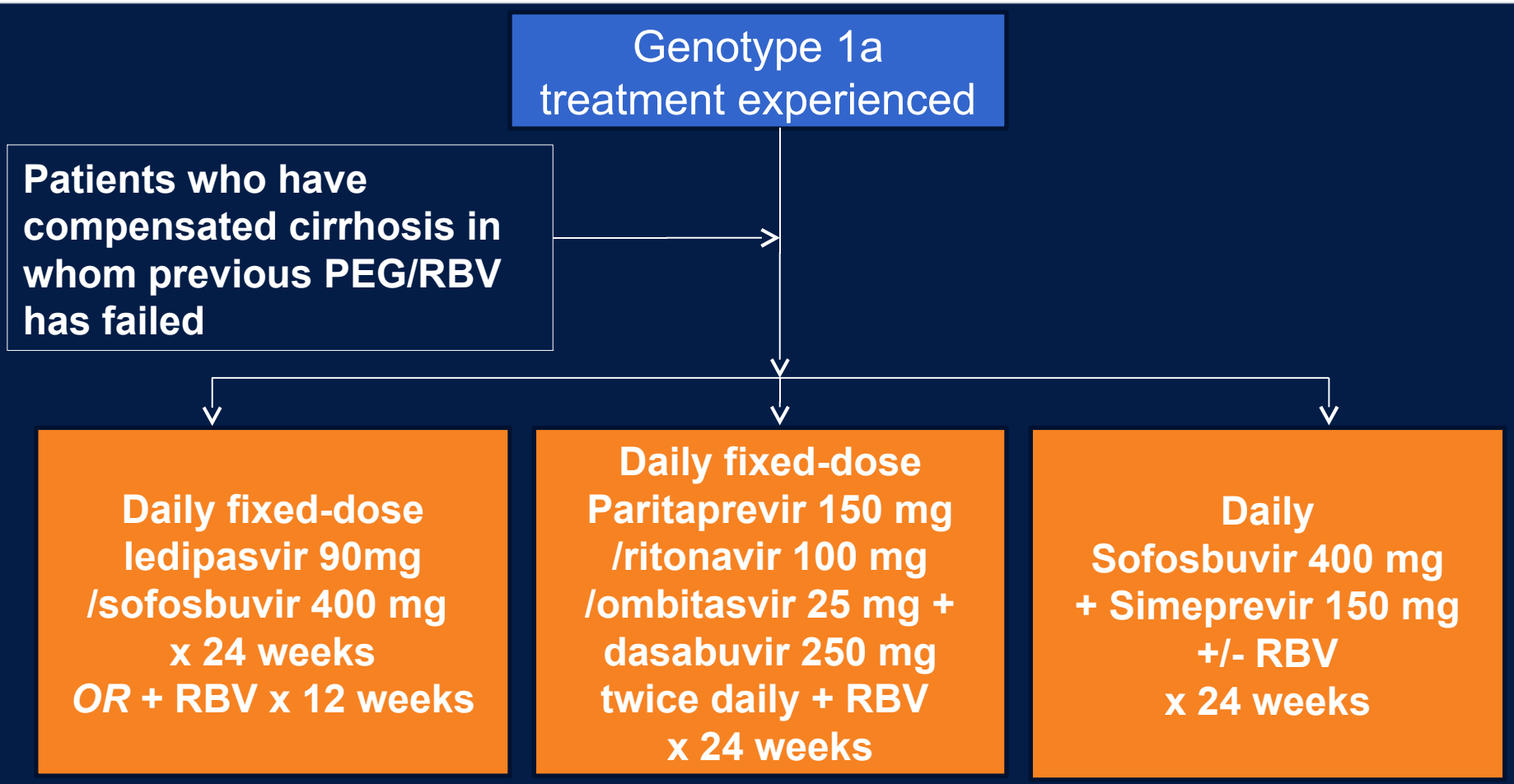
Case: Woman with HCV Genotype 1 Infection and Prior Treatment

- 51-year-old woman with HCV genotype 1a infection
  - No comorbid medical conditions
  - Works full-time and has 2 children (ages 14 and 16)
- Infected as a young child following blood transfusion
  - Liver biopsy in 2001 with portal fibrosis
  - Fibroscan 2014: 14.6 kPS
  - *IL28B* CT
  - HCV RNA = 8.7 million IU/mL

Case: Woman with HCV Genotype 1 Infection and Prior Treatment (cont'd)

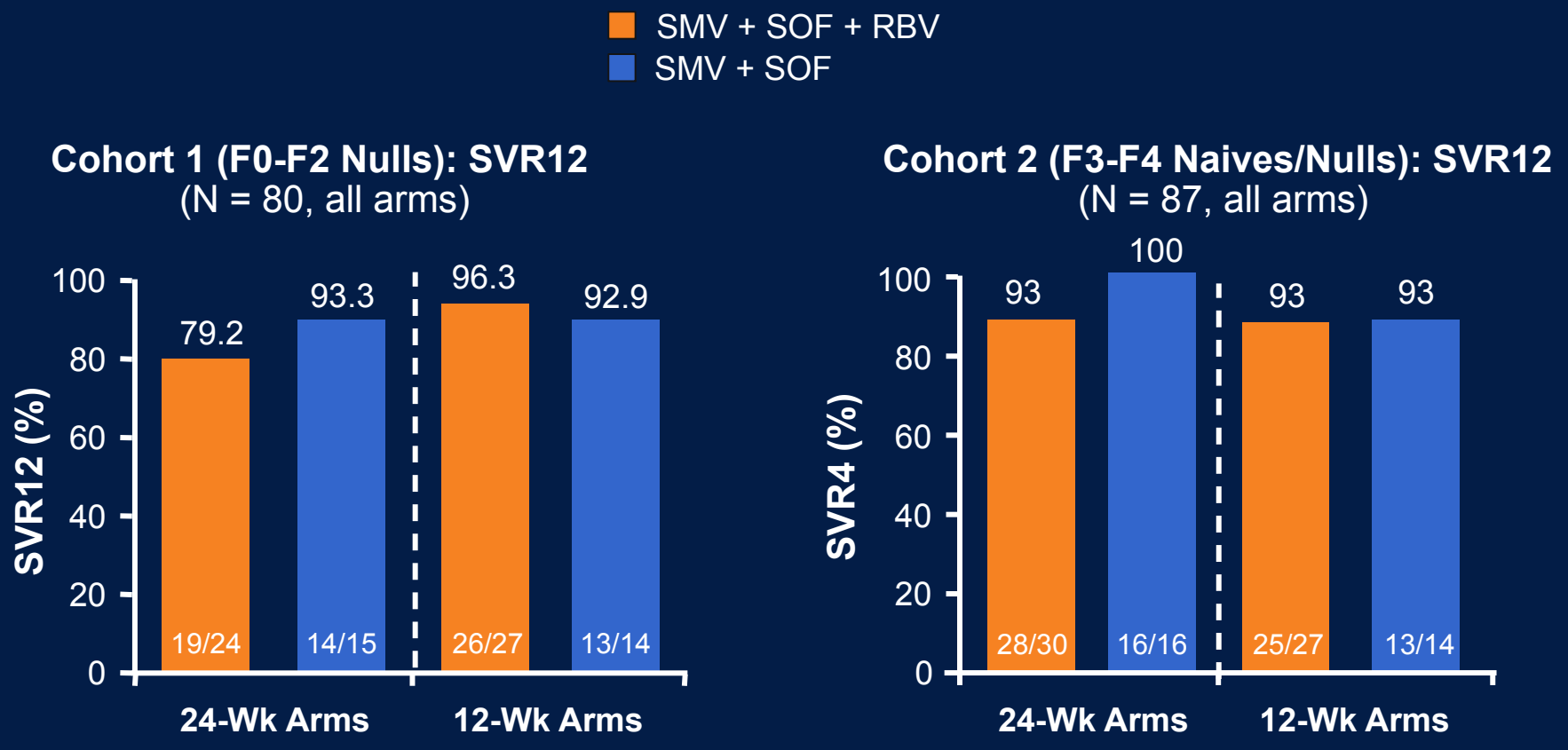
- She was treated in 2007 with PEG-IFN/RBV x 12 weeks –Partial response
- She returned for care after seeing an advertisement on TV
- She wants to be cured

AASLD/IDSA Recommendations for HCV Genotype 1a for Patients in Whom Previous Treatment Has Failed



AASLD/IDSA/IAS–USA. Recommendations for testing, managing, and treating hepatitis C. www.hcvguidelines.org. Accessed 01/05/15.

Combination of Sofosbuvir and Simeprevir: COSMOS



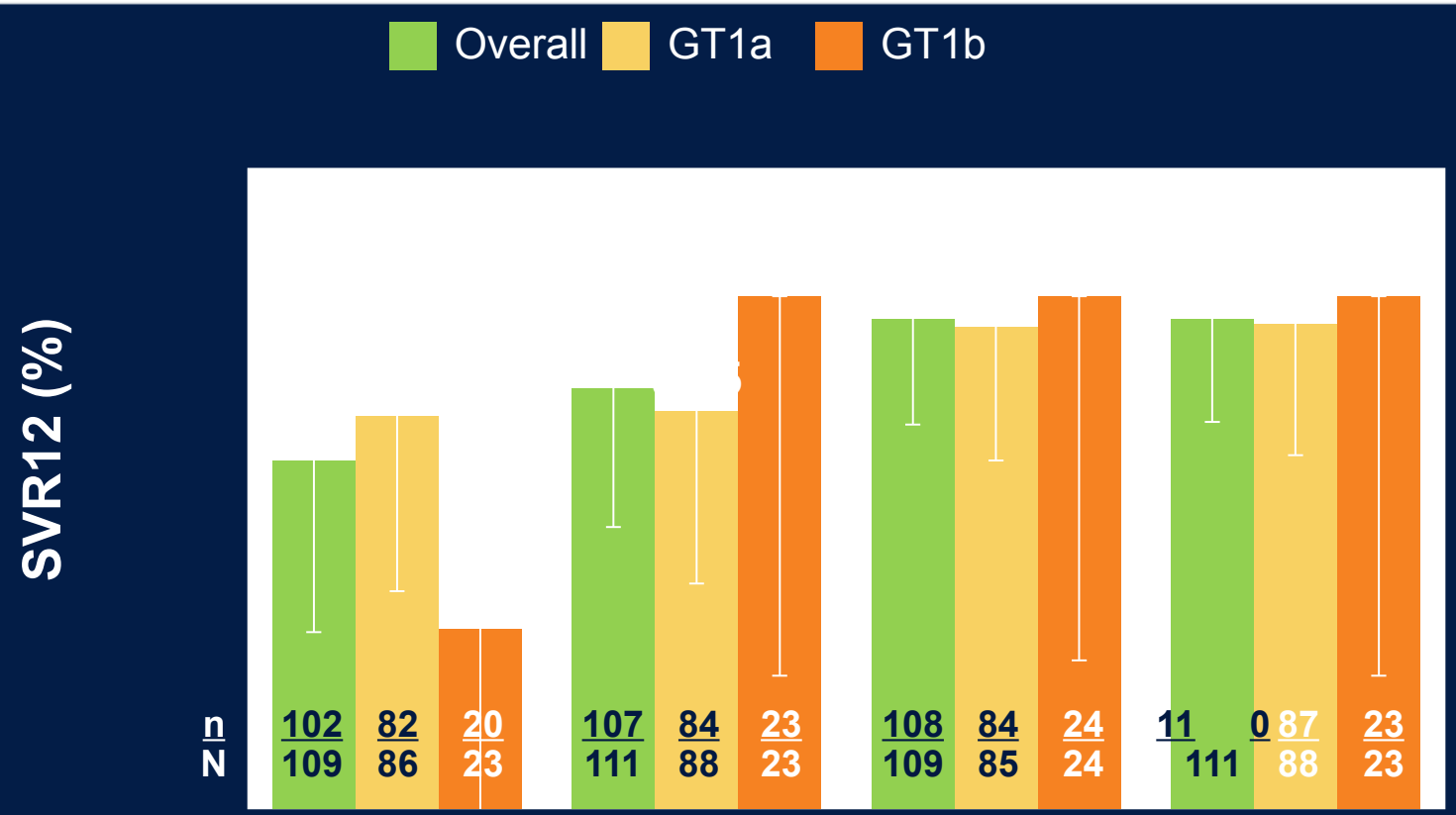
Relapse in 3 pts in Cohort 1, and 3 pts in Cohort 2.
SVR in Q80K+ = 86%-100%

Lawitz E, et al. *Lancet*. 2014; pii: S0140-6736(14)61036-9. doi: 10.1016/S0140-6736(14)61036-9. [Epub ahead of print]

Sofosbuvir (NUC) + Ledipasvir (NS5A) in G1
Insights on Treatment Duration and Role of Ribavirin in Treatment Experienced Patients: ION-2

Afdhal N, et al. *N Engl J Med*. 2014;370:1483-1493.

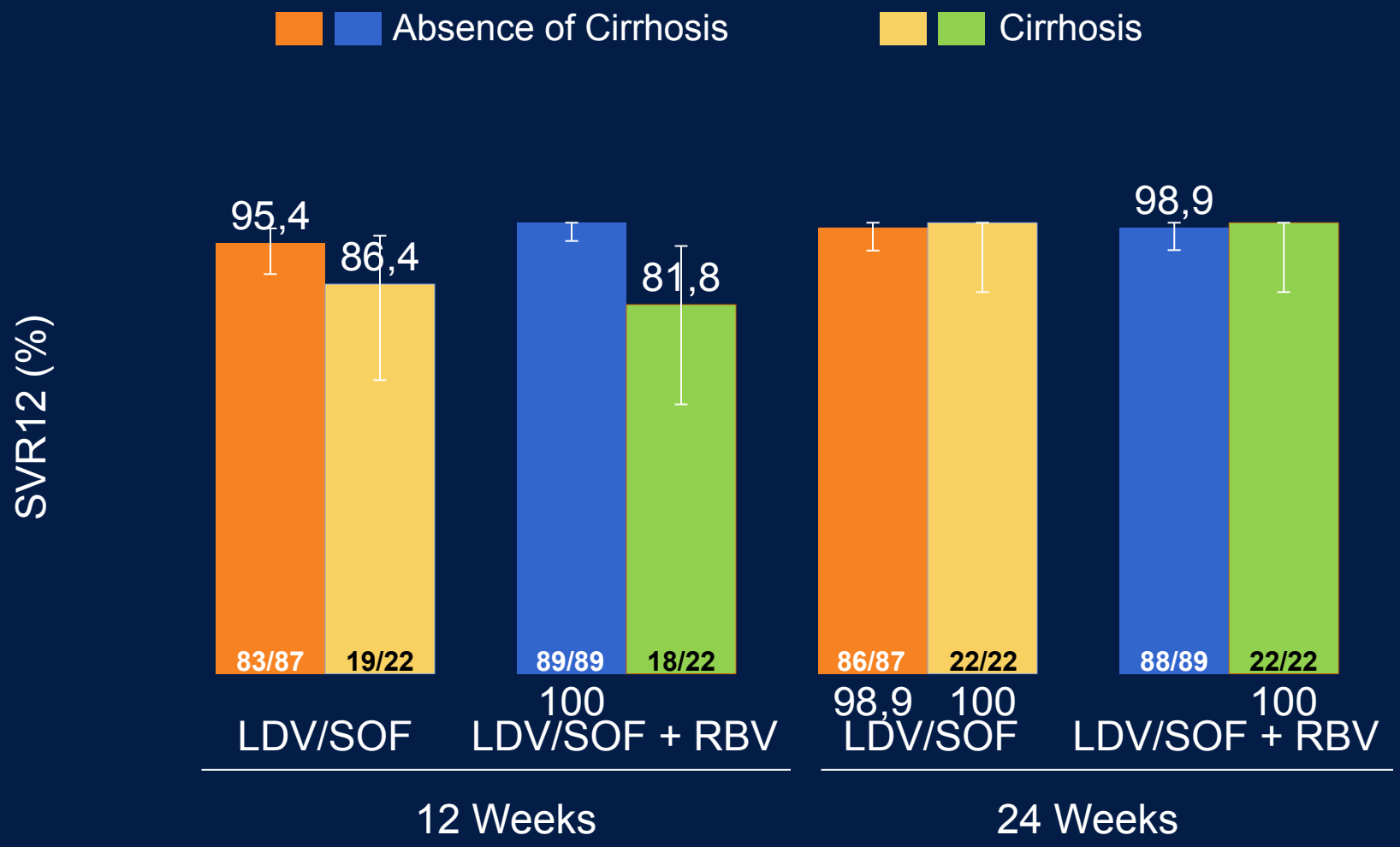
ION-2: SOF/LDV ± RBV in G1 Treatment-experienced Patients



- SOF = 400 mg/day; LDV = 90 mg/day; RBV = 1000 or 1200 mg/day.
- * One patient achieved SVR12, but was not subgenotyped.
- Error bars: 95% CI.

Afdhal N, et al. *N Engl J Med*. 2014;370:1483-1493.

ION-2: SVR12 – Absence of Cirrhosis vs. Cirrhosis



Error bars represent 95% confidence intervals

Afdhal N, et al. *N Engl J Med*. 2014;370:1483-1493.

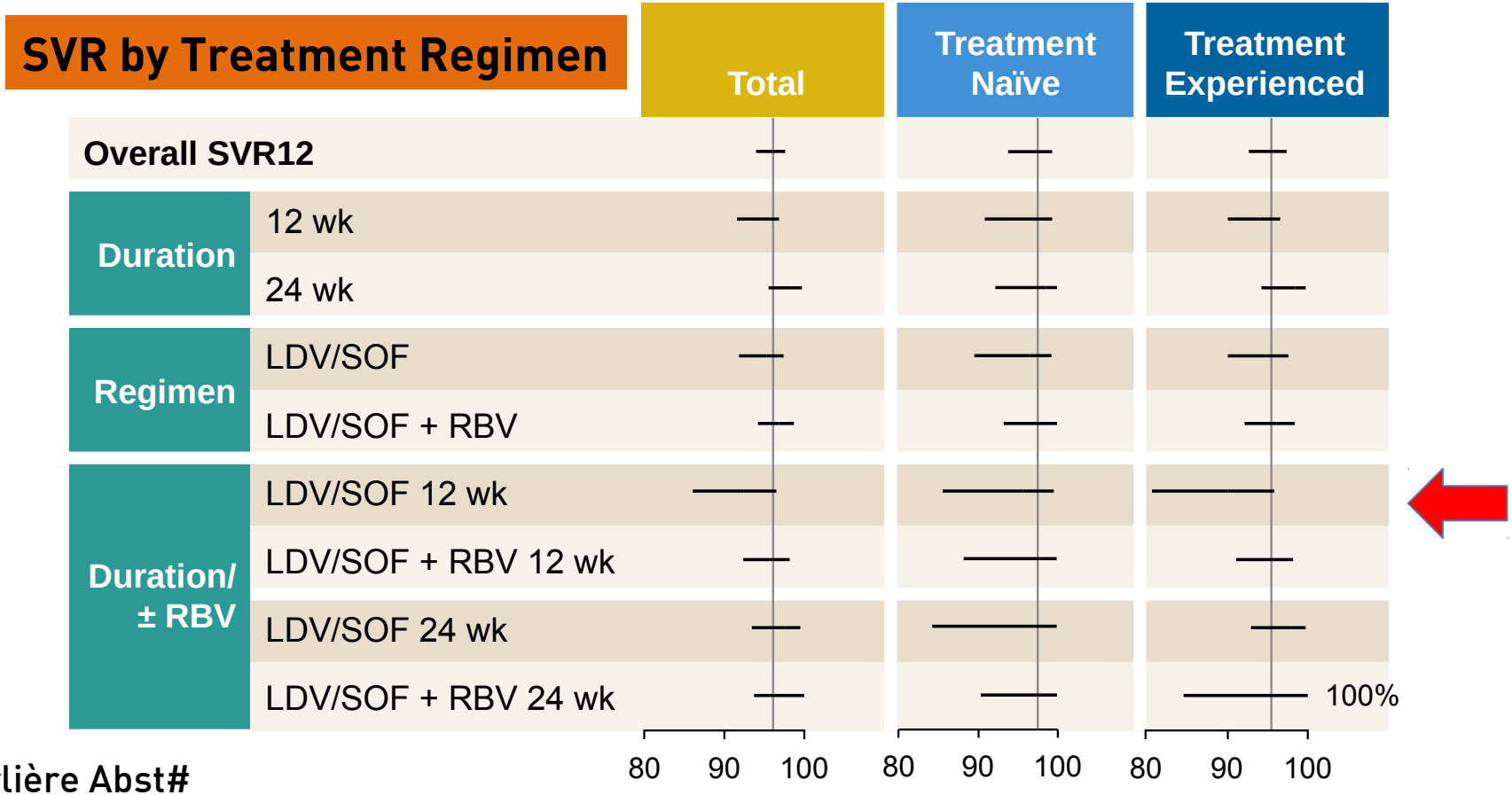
SIRIUS: Ledipasvir/Sofosbuvir is Safe and Efficacious in Cirrhotic Patients who have Previously Failed Protease Inhibitor Triple Therapy

- Randomized, placebo controlled study
- Prior failures to triple therapy with protease inhibitors
  - Compensated cirrhosis = 100%
    - Platelets < 100K = 18%
    - Serum albumin < 3.5 g = 13%
- All patients completed treatment except 1 discontinuation due to sepsis
- Improved biochemical and synthetic parameters noted

Bourlière M, et al. Presented at AASLD: The Liver Meeting. November 7-11, 2014. Boston, Massachusetts. LB-6.

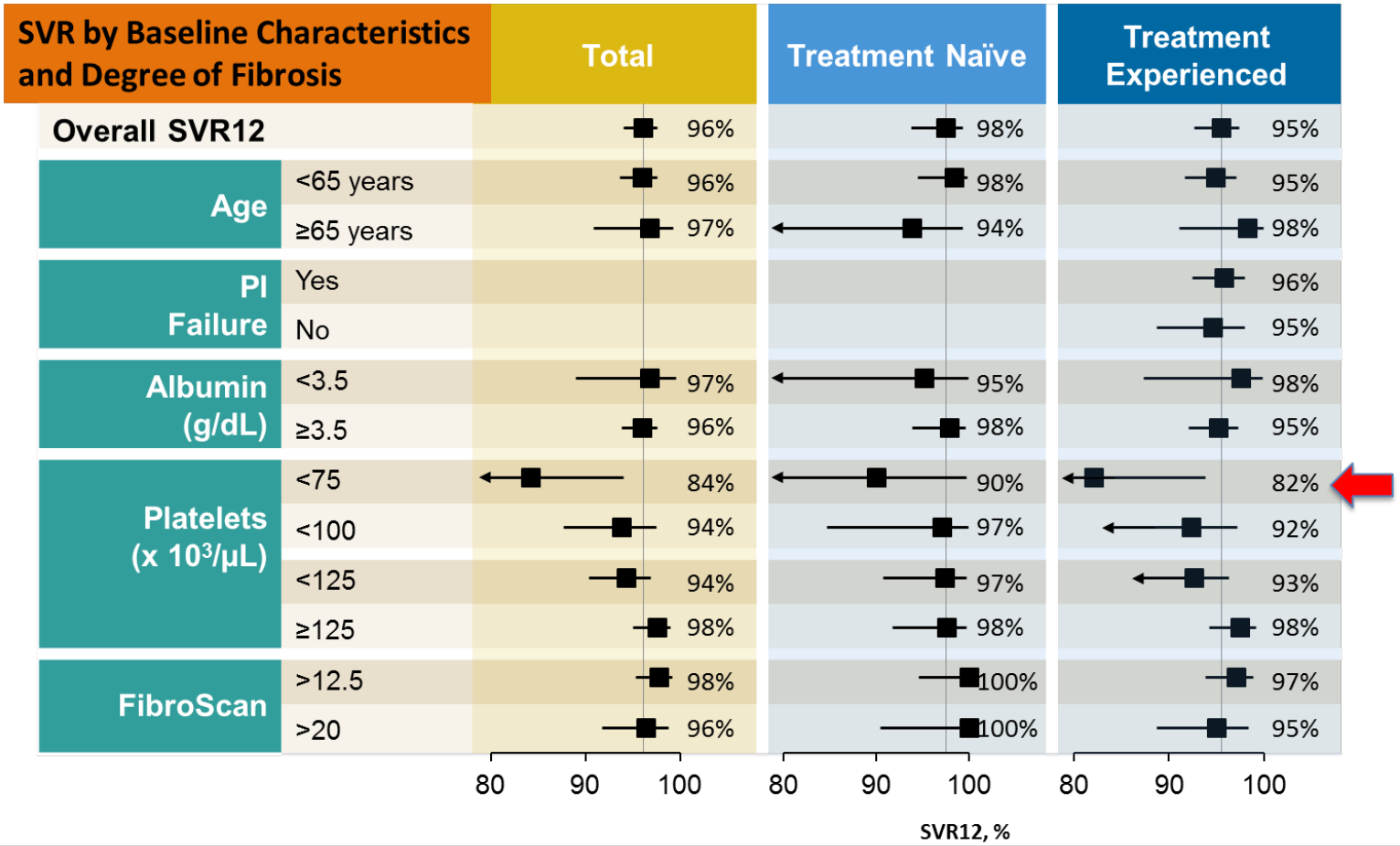
Safety and Efficacy Analysis of >500 Patients with Compensated Cirrhosis Treated with Ledipasvir/Sofosbuvir +/- RBV

- **Pooled data from phase 2/3 trials (n= 513 pts w/compensated cirrhosis)**
  - **Treatment naïve = 31%, Treatment Exp. = 69% (PI Failure = 68%)**
  - **Mean platelets 146K (37-489) (Platelets < 100K = 29%)**
  - **Mean albumin 3.9 (2.8-5.1)**



M. Bourlière Abst#

Safety and Efficacy Analysis of >500 Patients with Compensated Cirrhosis Treated with Ledipasvir/Sofosbuvir +/- RBV

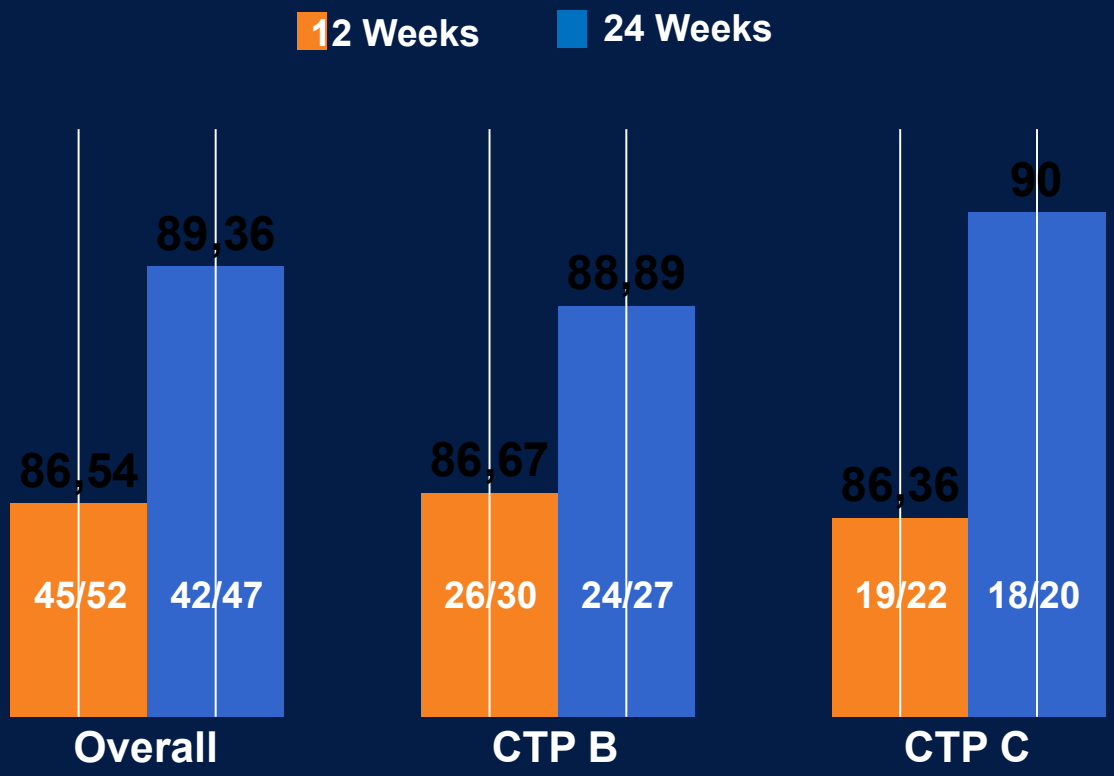


- Regimen was safe in compensated cirrhosis:
  - Few treatment discontinuations due to AE (<1%)
  - Ribavirin was frequent reason for dose reduction and lab abnormalities

M. Bourlière Abst# 82

Ledipasvir/Sofosbuvir + RBV in Patients with Decompensated Cirrhosis: Preliminary Results of a Prospective, Multicenter Study

- Randomized to SOF + LDV + RBV (600 mg w/ escalation) for 12 or 24 weeks
- Patients with G1 or 4 and decompensated cirrhosis
  - Most patients with MELD > 10 (MELD= 16-20 in 10-46%)
  - Median Albumin= 2.6- 3.0 g/L; Median platelets = 71-88 K

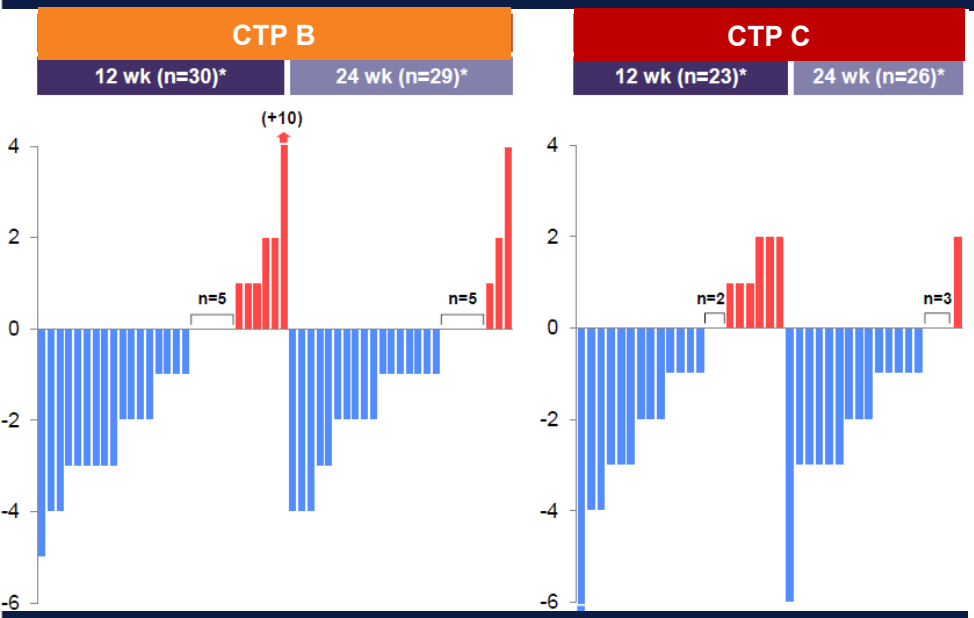


Flamm SL, et al. Presented at AASLD: The Liver Meeting. November 7-11, 2014. Boston, Massachusetts. Abstract 239.

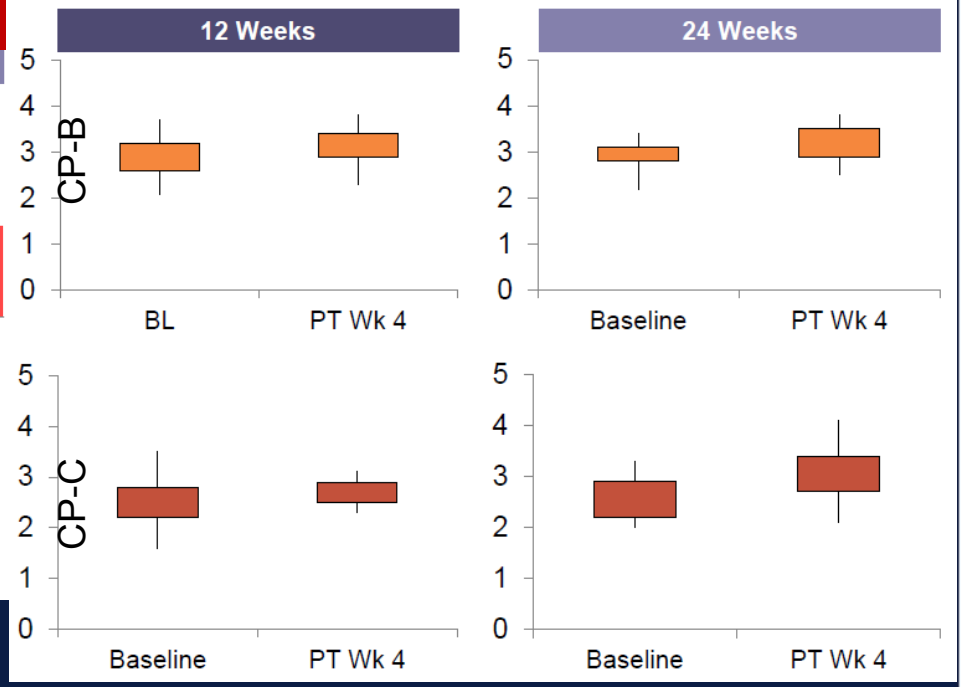
Ledipasvir/Sofosbuvir + RBV in Patients with Decompensated Cirrhosis: Preliminary Results of a Prospective, Multicenter Study

- Safety: Only 3 early discontinuation due to AE
- SAE = 10%-42% (only 4 considered treatment-related)
- 5 deaths: Septic shock (4), renal failure/cardiac arrest

Most patients had a decrease in MELD

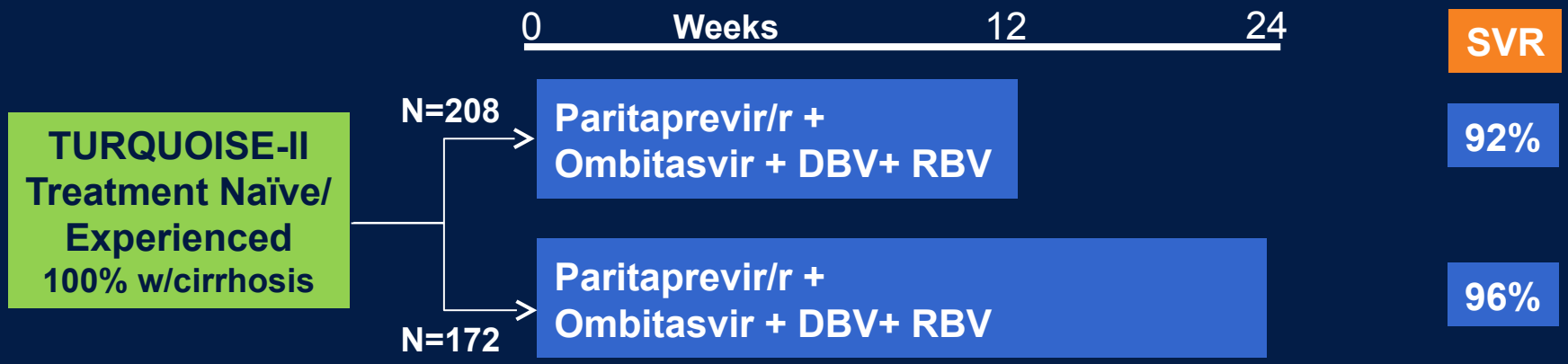


Albumin increased during post-treatment follow-up



Flamm SL, et al. Presented at AASLD: The Liver Meeting. November 7-11, 2014. Boston, Massachusetts. Abstract 239.

Paritaprevir/r (PI) + Ombitasvir (NS5A) + Dasabuvir (NNI) + RBV in Patients with Cirrhosis: TURQUOISE-II

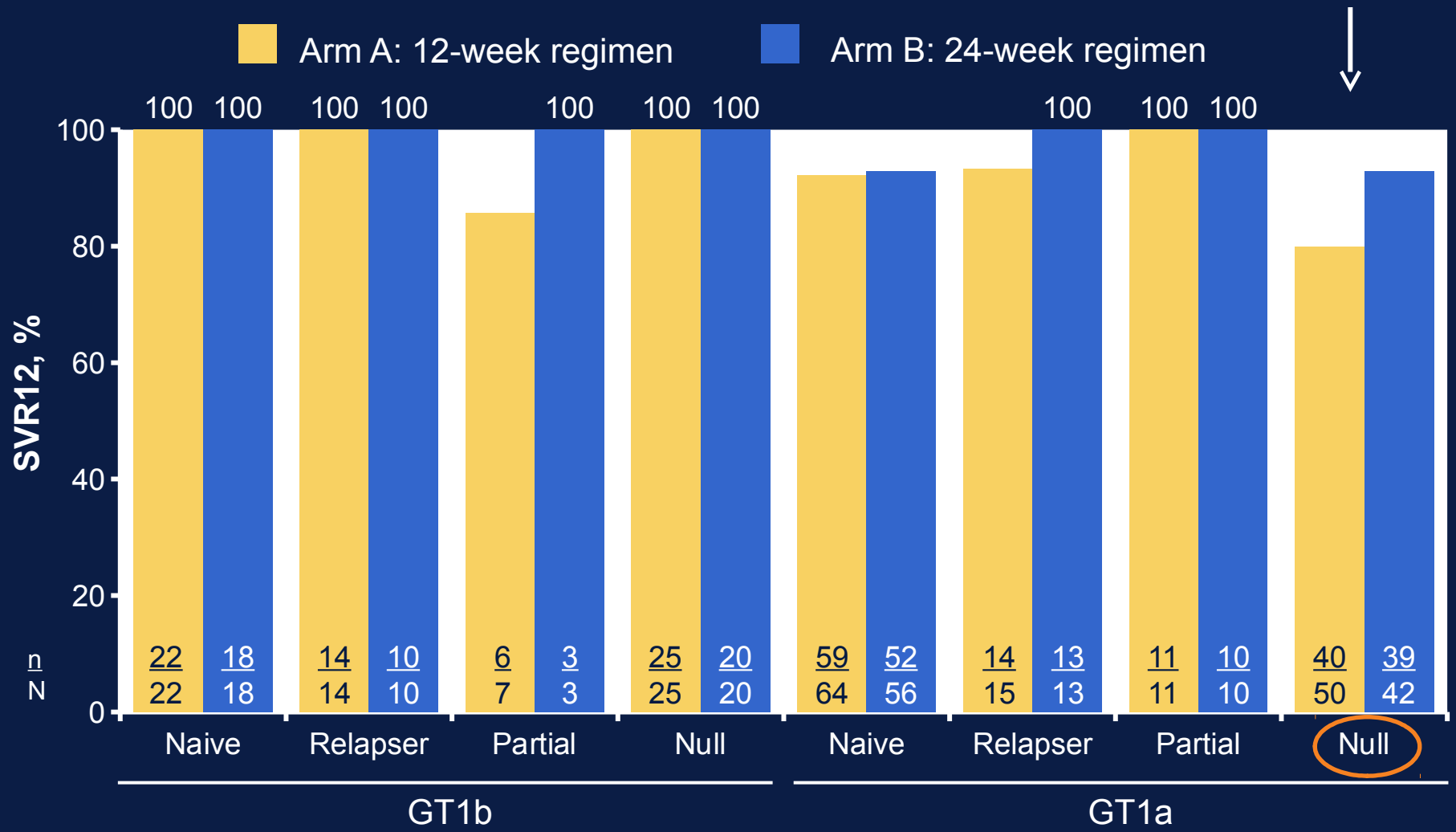


- Included only compensated cirrhosis
- Relapse/viral breakthrough in 6% (12 weeks) and 2% (24 weeks)

DBV: Dasabuvir

Poordad F, et al. *N Engl J Med*. 2014;370:1973-1982.

Which Population Drove the Difference Between 12 and 24 Weeks in TURQUOISE-II?



Implication: HCV G1a null responders should receive 24 weeks of therapy

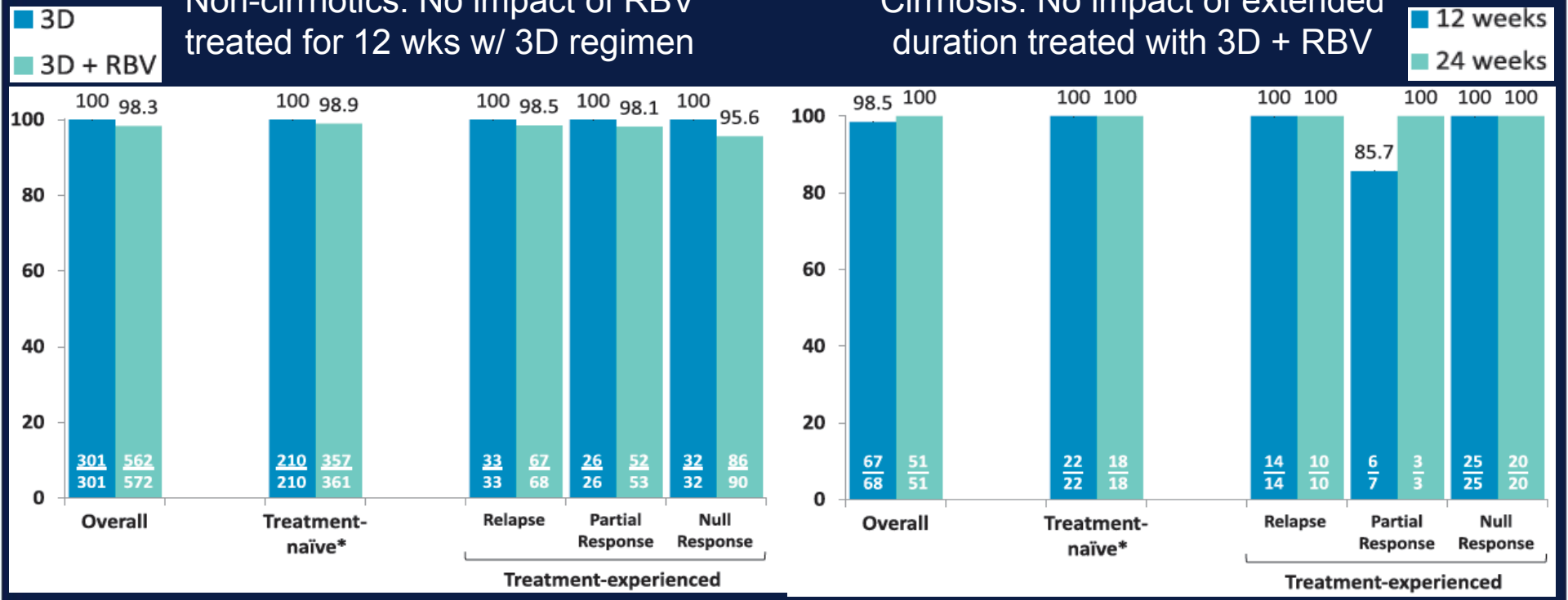
Poordad F, et al. *N Engl J Med*. 2014;370:1973-1982.

SVR12 Rate of 98.6% in 992 HCV Genotype 1b Patients Treated with Paritaprevir/r/Ombitasvir + Dasabuvir With or Without Ribavirin

- Pooled analysis of phase 3 trials restricted to patients with G1b (naïve and experienced)
- Non-cirrhotics treated with 12 wks of 3D or 3D + RBV
- Cirrhotics treated with 12 or 24 weeks of 3D + RBV

Non-cirrhotics: No impact of RBV treated for 12 wks w/ 3D regimen

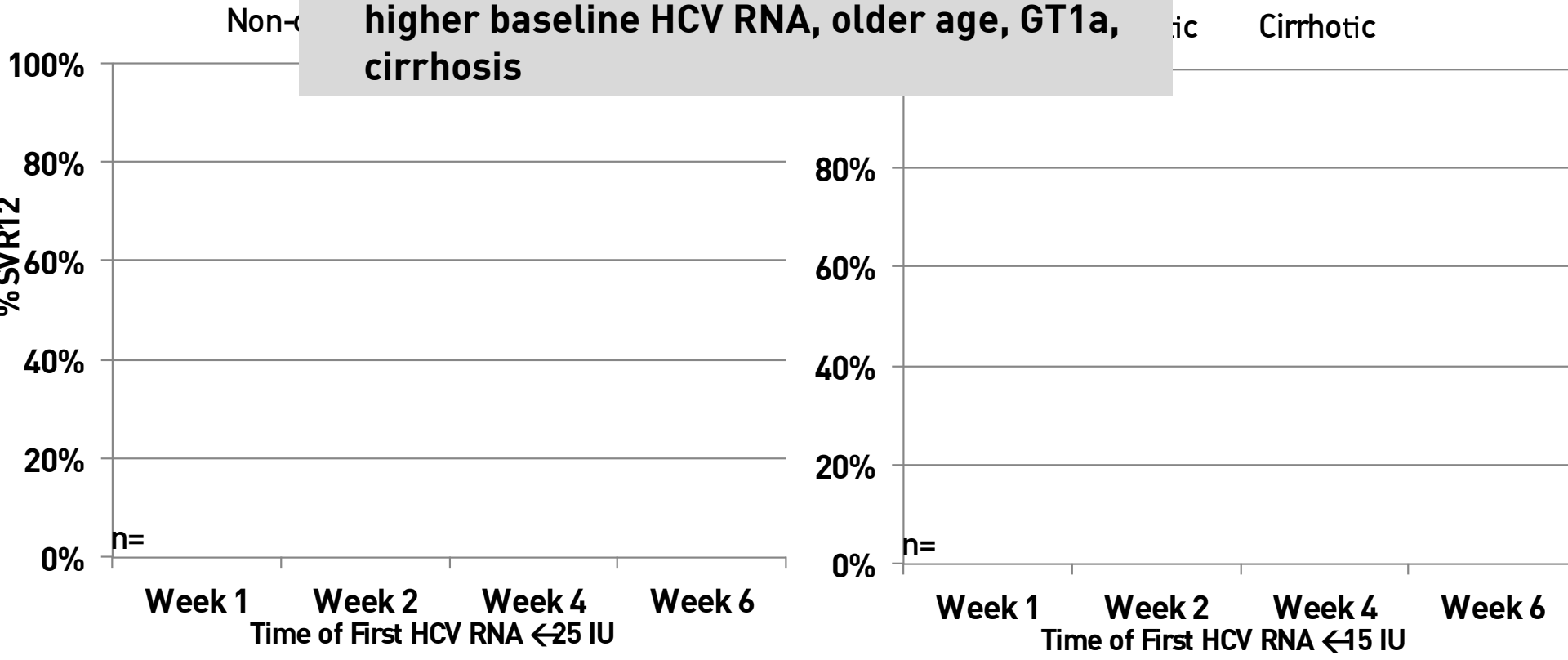
Cirrhosis: No impact of extended duration treated with 3D + RBV



Colombo M, et al. Presented at AASLD: The Liver Meeting. November 7-11, 2014. Boston, Massachusetts. Abstract 1931.

Time to Viral Suppression is Not Related to Achievement of SVR12 IN GT1 Treated with ABT-450/r/Ombitasvir + Dasabuvir With or Without Ribavirin

- Pooled analysis of 6 phase 3 trials
- Aim: To evaluate the predictive value of time of first occurrence of HCV RNA BLOQ and SVR12
- Longer time to suppression assoc. with higher baseline HCV RNA, older age, GT1a, cirrhosis



Sulkowski, 1950

All-oral Treatment of HCV Infection: Genotype 1

DAA	Additional Regimen Components	Considerations
Sofosbuvir 400 mg daily (SOF)	Ledipasvir, 90 mg daily in fixed dose, single tablet with sofosbuvir (LDV/SOF)	▪ Naïve to previous therapy dosed 12 weeks ▪ Naïve, non-cirrhotic, HCV RNA <6 million IU/mL consider dosing for 8 weeks ▪ Previous treatment failure (non-cirrhotic) dosed 12 weeks ▪ Previous treatment failure (cirrhosis) dosed 24 weeks
Simeprevir 150 mg daily (SMV)	Sofosbuvir, 400 mg daily (SOF)	▪ Naïve to previous therapy (non-cirrhotic) dosed 12 weeks ▪ Previous treatment failure (non-cirrhotic) dosed 12 weeks ▪ Compensated cirrhosis dosed 24 weeks
Ombitasvir, paritaprevir, ritonavir 12.5/75/50 mg daily	Dasabuvir 250 mg twice daily	▪ G1a, without cirrhosis: Add RBV, dosed 12 weeks ▪ G1a, with cirrhosis: Add RBV, dosed 24 weeks ▪ G1b, without cirrhosis: Dosed 12 weeks ▪ G1b, with cirrhosis: Add RBV, dosed 12 weeks

Ledipasvir and sofosbuvir [package insert]. Gilead Sciences, Inc. October 2014.
Simeprevir [package insert]. Titusville, NJ: Janssen Products; November 2014.
Ombitasvir, paritaprevir, and ritonavir; dasabuvir [package insert]. AbbVie Inc., December 2014.