INTEGRATED EFFICACY ANALYSIS OF FOUR PHASE 3 STUDIES IN HCV GENOTYPE 1A-INFECTED PATIENTS TREATED WITH ABT--450/R/ OMBITASVIR AND DASABUVIR WITH OR WITHOUT RIBAVIRIN

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This presentation contains information on the investigational products ABT-450/r, ombitasvir (ABT-267), and dasabuvir (ABT-333).

Background

Interferon-free regimens with direct-acting antiviral agents (DAAs) show great promise due to their improved efficacy and tolerability

DAA combinations can vary in efficacy by:

- HCV subgenotype (eg, GT1a vs GT1b)
- Treatment experience (eg, naive vs null)
- Fibrosis stage (eg, early fibrosis vs cirrhosis)

It is important to examine historical negative predictors of treatment response from the interferon era to determine which factors may still be associated with treatment failure in the era of DAAs

The 3 DAA (3D) Regimen

The 3D regimen includes:

- **ABT-450** - a potent NS3/4A protease inhibitor identified by AbbVie and Enanta. Co-dosing of ABT-450 with ritonavir* (r; ABT-450/r) increases the peak, trough, and overall drug exposures of ABT-450[1]
- **Ombitasvir** (formerly ABT-267) - a potent NS5A inhibitor
- **Dasabuvir** (formerly ABT-333) - a non-nucleoside NS5B polymerase inhibitor

*Ritonavir does not have antiviral activity against HCV.

1. Menon RM, et al. HEP DART. Kohala Coast, HI, USA; December 6–10, 2009. Abstract 57.

The 3D Regimen: Pooled Analyses From Clinical Development

The multi-targeted 3 DAA regimen has been evaluated in >2700 HCV GT1-infected treatment-naïve and -experienced patients with and without cirrhosis across six Phase 3 trials

- In a pooled analysis of two Phase 3 trials in HCV GT1b-infected patients without cirrhosis:
  - SVR12 rate with 3D ± RBV: 99% (592/598) of GT1b-infected treatment-naive and treatment-experienced patients[1]
  - Thus, RBV did not increase SVR12 rates in GT1b-infected patients and is not required in the treatment of HCV GT1b

Pooled analysis of HCV GT1a-infected patients with or without cirrhosis from four Phase 3 trials is presented

1. Bernstein D et al. ICAAC. September 5–9, 2014, Washington, DC.

Pooled Studies With GT1a Patients: SAPPHIRE-I and -II[1-2]; PEARL-IV[3]; TURQUOISE-II[4]

n/N (%)	Patients Without Cirrhosis		Patients With Cirrhosis	Total
	3D + RBV N = 593	3D + PBO N = 202	3D + RBV N = 263	3D ± RBV N = 1058
Treatment-naïve	420 (71)	202 (100)	122 (46)	744 (70)
Treatment-experienced	173 (29)	0	141 (54)	314 (30)

263/1058 (25%) of treated patients with GT1a infected had cirrhosis

1. Feld JJ, et al. *N Engl J Med*. 2014;370:1594-1603.
2. Zeuzem S, et al. *N Engl J Med.* 2014;370:1604-1614.
3. Ferenci P, et al. *N Engl J Med*. 2014;370:1983-1992.
4. Poordad F, et al. *N Engl J Med*. 2014;370:1973-1982.

Patient Eligibility Criteria[1-4]

Key inclusion criteria

- Chronic HCV GT1 infection (SAPPHIRE-I, SAPPHIRE-II, and TURQUOISE-II); GT1a infection (PEARL-IV)
- 18 to 70 years of age, inclusive
- Plasma HCV RNA >10,000 IU/mL

Key exclusion criteria

- Positive screen for hepatitis B surface antigen
- Positive screen for anti-HIV antibody

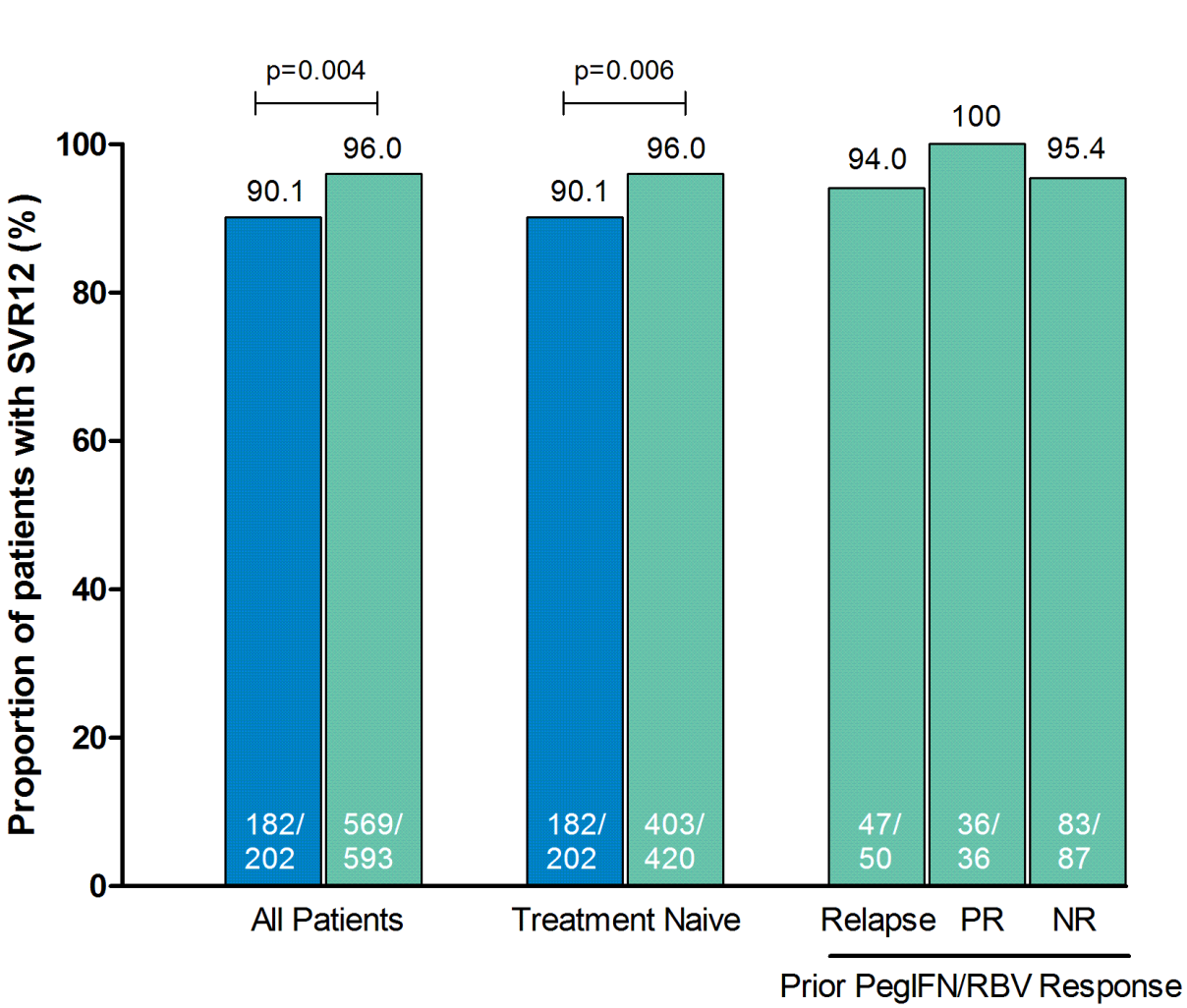
1. Feld JJ, et al. *N Engl J Med*. 2014;370:1594-1603.
2. Zeuzem S, et al. *N Engl J Med.* 2014;370:1604-1614.
3. Poordad F, et al. *N Engl J Med*. 2014;370:1973-1982.
4. Ferenci P, et al. *N Engl J Med*. 2014;370:1983-1992.

RESULTS IN HCV GENOTYPE 1A-INFECTED PATIENTS WITHOUT CIRRHOSIS

Baseline Characteristics of GT1a-Infected Patients Without Cirrhosis

	3D + PBO 12 Weeks N = 202	3D + RBV 12 Weeks N = 593
Male, n (%)	127 (62.9)	370 (62.4)
Race, n (%)		
White	168 (83.2)	531 (89.5)
Black	26 (12.9)	44 (7.8)
Hispanic/Latino, n (%)	18 (8.9)	46 (7.8)
Median age, years (range)	54 (21–70)	53 (18–70)
Median BMI, kg/m^2 (range)	25.9 (18.3–38.3)	26.1 (18.0–38.4)
Prior pegIFN/RBV experience, n (%)	0	173 (29.2)
IL28B genotype, n (%)		
CC	62 (30.7)	163 (27.5)
Non-CC	140 (69.3)	430 (72.5)

Rates of SVR12 in GT1a-Infected Patients



94-100% SVR12 in treatment-experienced patients without cirrhosis treated with 3D + RBV

SVR12 rates were higher in treatment-naïve patients treated with 3D + RBV compared to 3D

p values from Fisher's exact test
All 3D-treated patients were treatment-naïve at baseline

Analysis of Predictors of Interest on SVR12 in GT1a-Infected Patients Without Cirrhosis

Logistic regression with pre-planned covariates:

Viral factors

- Baseline HCV RNA level (continuous)

Host factors

- Age (continuous),
- Sex (Male vs Female)
- Race (Black vs non-Black)
- Region (North America vs non-North America)
- Baseline BMI (continuous)
- IL28B genotype (TT vs non-TT)
- Prior pegIFN/RBV treatment response (null vs not),
- Treatment regimen (3D + RBV vs 3D)
- History of diabetes (Yes vs No),
- History of depression/bipolar disorder (Yes vs No)
- History of IDU (Yes vs No)

Logistic Regression For Predictors of Not Achieving SVR12 in GT1a-Infected Patients Without Cirrhosis

Variable	*p* value
Baseline BMI	0.005
Treatment regimen (3D + RBV vs 3D)	0.007

Patients from both treatment groups (3D and 3D + RBV) were pooled

- 2/12 variables assessed were statistically significantly associated with lower SVR12 rates
- The odds ratio for baseline BMI was 0.90, 95% CI (0.84, 0.97)

In addition to the significant factors, the logistic regression also adjusted for age, sex, race, IL28B, ethnicity, region, BMI, HCV RNA, prior pegIFN/RBV treatment response (null vs not), history of IDU, diabetes, and depression/bipolar disorder

Adverse Events in Patients Without Cirrhosis: 3D Compared With 3D + RBV

Event, n (%)	3D + PBO 12 Weeks N = 202	3D + RBV 12 Weeks N = 593	Difference, %
Any AE	167 (82.7)	534 (90.1)	7.4
Any severe AE	3 (1.5)	18 (3.0)	1.5
Any serious AE	1 (0.5)	14 (2.4)	1.9
Any AE leading to treatment discontinuation	2 (1.0)	3 (0.5)	—0.5
Any AE leading to RBV dose modification	1 (0.5)	40 (6.7)	6.2

Discontinuations due to AEs occurred with similar rates in the 2 groups

For patients with RBV dose modification, SVR12 achieved by:

- 41/42 (97.6%) with 3D + RBV

Summary: GT1a Patients Without Cirrhosis

12 weeks of 3D +RBV achieved SVR12 in 96% of both treatment-naïve and treatment-experienced patients

RBV increased SVR12 rates by 6% (96.0% vs 90.1%) in treatment-naïve patients

- All treatment-experienced patients received RBV

High BMI was associated with a slight reduction in SVR12

Adverse events, which were mostly mild, were more common with RBV

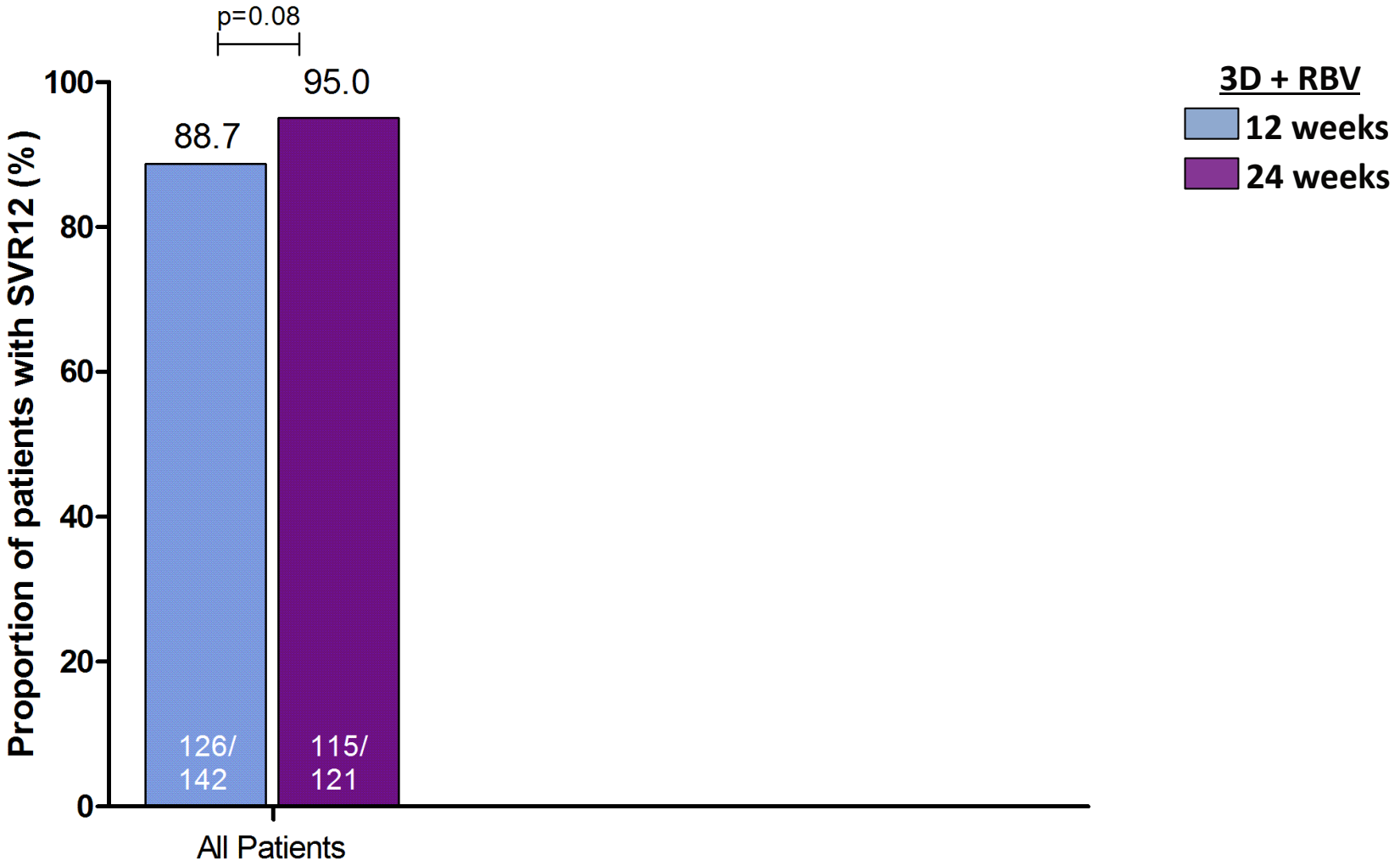
RBV dose was reduced infrequently (6.7%); SVR12 rates were 97.6% in patients who did

RESULTS IN HCV GENOTYPE 1A-INFECTED PATIENTS WITH CIRRHOSIS

Baseline Characteristics of GT1a-Infected Patients With Cirrhosis

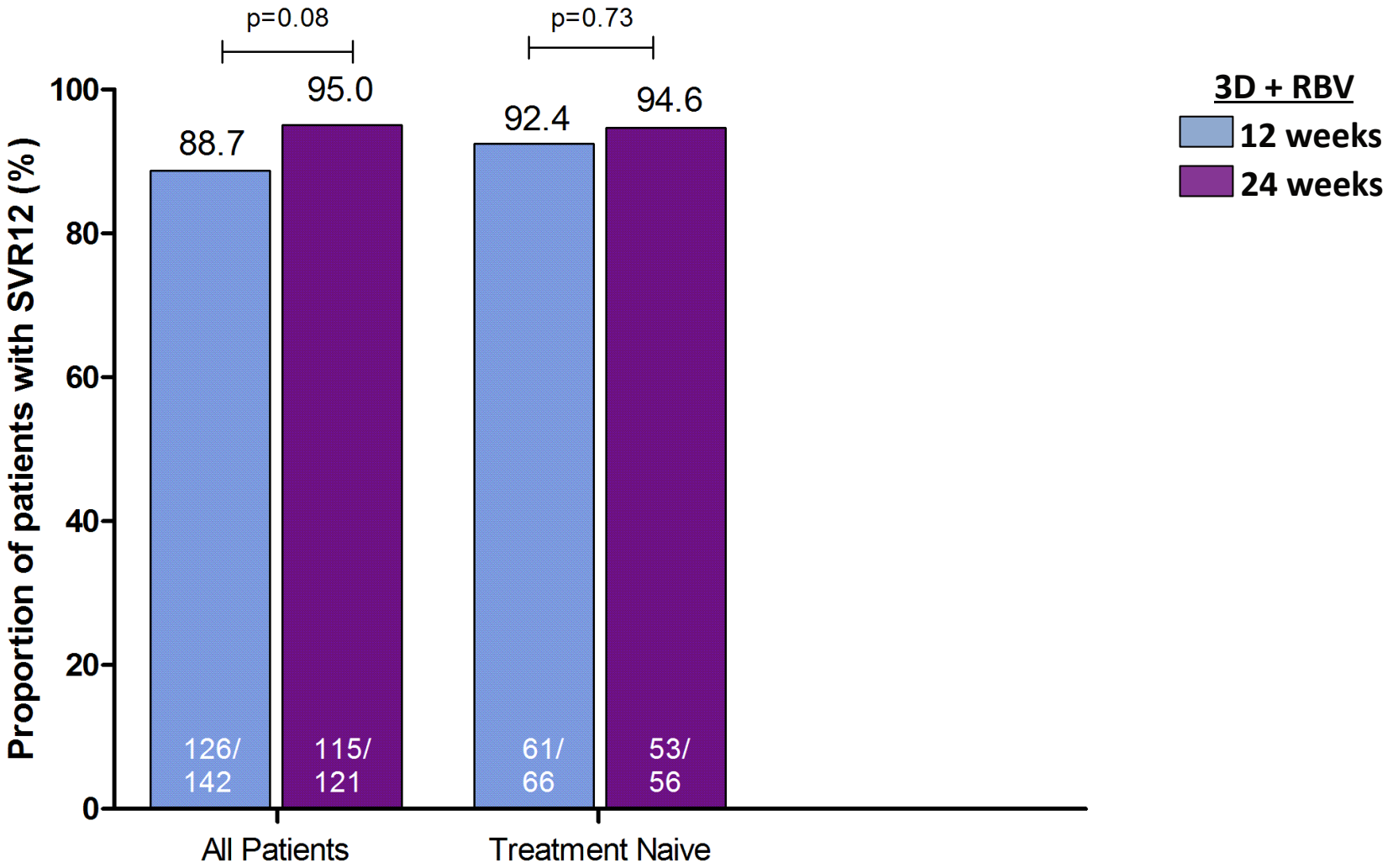
	3D + RBV 12 Weeks N = 142	3D + RBV 24 Weeks N = 121
Male, n (%)	104 (73.2)	89 (73.6)
Race, n (%)		
White	138 (97.2)	113 (93.4)
Black	4 (2.8)	6 (5.0)
Hispanic/Latino, n (%)	17 (12.0)	14 (11.6)
Median age, years (range)	56 (25–71)	57 (21–71)
Median BMI, kg/m^2 (range)	28.1 (19.4–39.3)	27.4 (20.0–38.0)
Prior pegIFN/RBV experience, n (%)	76 (53.5)	65 (53.7)
IL28B genotype, n (%)		
CC	26 (18.3)	25 (20.7)
Non-CC	116 (81.7)	96 (79.3)

High SVR12 Rates with 3D + RBV in All GT1a-Infected Patients With Cirrhosis



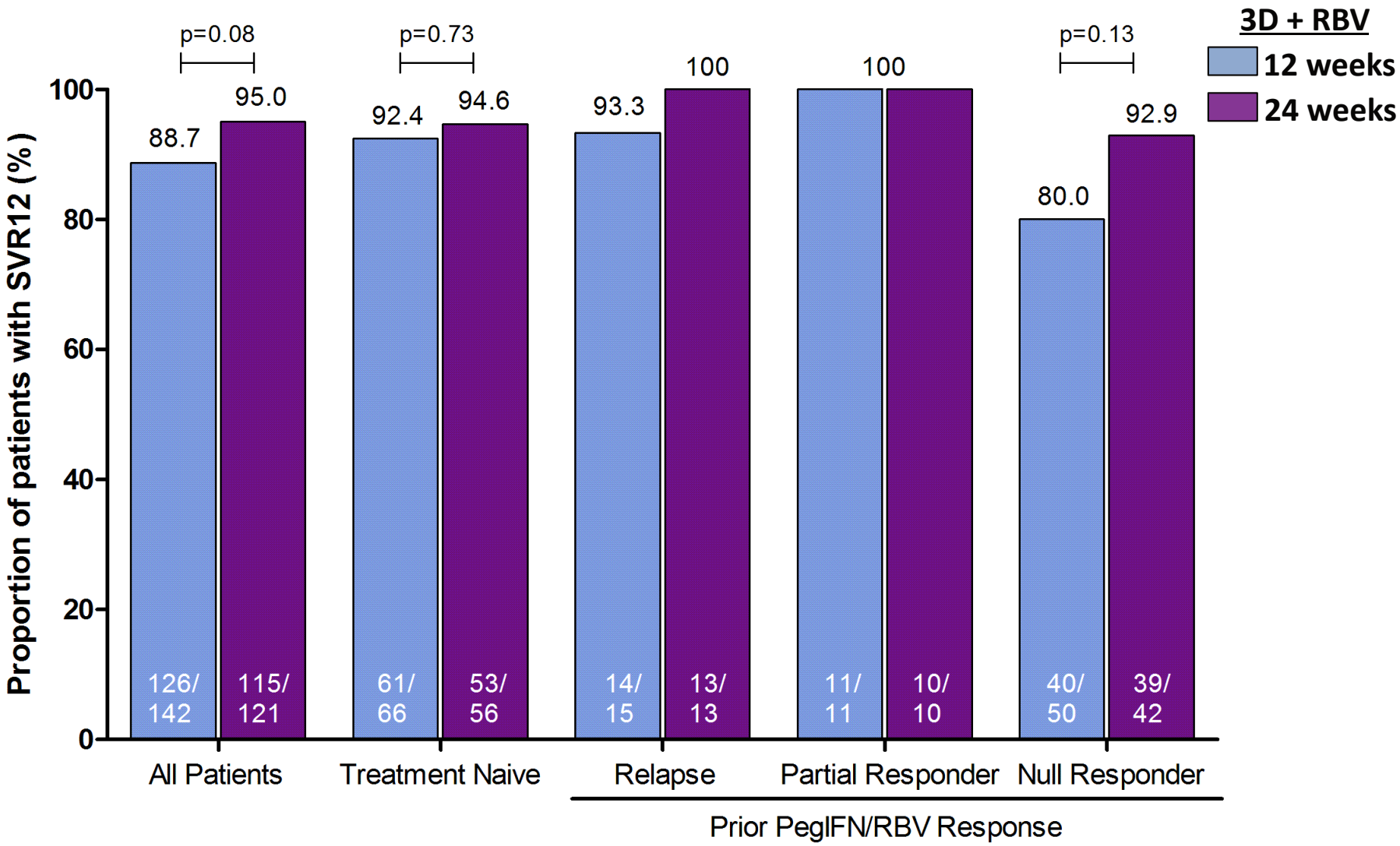
p values from Fisher's exact test

High SVR12 Rates with 3D + RBV in GT1a Treatment-Naïve Patients With Cirrhosis



p values from Fisher's exact test

High SVR12 Rates with 3D + RBV in GT1a Treatment-Naïve and -Experienced Patients With Cirrhosis



p values from Fisher's exact test

Analysis of Predictors of Interest on SVR12 in GT1a-Infected Patients With Cirrhosis

Logistic regression with pre-planned covariates:

Viral factors

- HCV RNA level (continuous)

Host factors

- Age (continuous)
- Sex (Male vs Female)
- Ethnicity
- BMI (continuous)
- IL28B genotype (TT vs non-TT),
- History of diabetes (Yes vs No)
- History of depression/bipolar disorder (Yes vs No)
- History of IDU (Yes vs No)
- Prior pegIFN/RBV treatment experience (Null vs not)

Disease factors (all continuous)

- Serum albumin, platelet count, serum AFP[1]

1. Sterling RK, et al. *Am J Gastroenterol.* 2012;107(1):64-74.

Logistic Regression For Predictors of Not Achieving SVR12 in GT1a-Infected Patients With Cirrhosis

Variable	*p* value
IL28B TT genotype	0.008
Prior null response	0.009
Region (North American vs EU)	0.045
History of IDU	0.047

Patients from both treatment groups (12 weeks and 24 weeks) were pooled

- 4/17 variables assessed were statistically significantly associated with lower SVR12 rates
- Trends were seen for treatment duration (p=0.094) and baseline HCV RNA (p = 0.091)

In addition to the significant factors, the logistic regression also adjusted for age, sex, race, ethnicity, region, BMI, albumin, platelets, AFP, Child-Pugh score, diabetes, and depression/bipolar disorder

Overview of Adverse Events: Patients With Cirrhosis 3D + RBV 12 Weeks vs 24 Weeks

Event, n (%)	3D + RBV 12 Weeks N = 142	3D + RBV 24 Weeks N = 121	Difference, %
Any AE	130 (91.5)	111 (91.7)	0.2
Any severe AE	13 (9.2)	11 (9.1)	—0.1
Any serious AE	10 (7.0)	5 (4.1)	—2.9
Any AE leading to treatment discontinuation	4 (2.8)	4 (3.3)	0.5
Any AE leading to RBV dose modification	10 (7.0)	9 (7.4)	0.4

All patients who required RBV dose reduction achieved SVR12

Discontinuations due to AEs occurred with similar rates in the 2 groups

Summary: GT1a Patients With Cirrhosis

SVR12 rates >90% were achieved with 3D + RBV in all patients treated

Lower SVR12 rates were associated with IL28B TT genotype, prior null response, North American region, and history of IDU

RBV dose reduction has no impact on SVR rates

Conclusions

GT1a-infected patients without cirrhosis benefit from inclusion of RBV with SVR12 rates of 96% after 12 weeks of therapy

GT1a- infected patients with cirrhosis had SVR12 rates >90% after treatment with 3D + RBV

RBV dose reduction had no impact on SVR rates in cirrhotic and non-cirrhotic patients

Although the overall virologic failure rates were low, further exploration of potential prognostic factors is planned for those patients with cirrhosis who experienced post-treatment relapse

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