Expert Presentation Delivered by:
Drs. Isakov and Zhdanov

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Abstract LBP500

Safety and Efficacy of Directly Acting Antivirals in 2432 HCV Patients with Advanced Fibrosis: an Interim Analysis of the Lombardia Regional Network for Viral Hepatitis

A.M. Aghemo¹, G. Cologni², F. Maggiolo², L. Pasulo², G. Rizzardini³, C. Magni³, T. Quirino⁴, L. Minoli⁵, G. Filice⁵, M. Zuin⁶, A. Colli⁷, M. Rumi⁸, M. Puoti⁹, S. Fagiuoli², M. Colombo¹ and Lombardia Regional Network for Viral Hepatitis Working Group

E-mail: alessio.aghemo@policlinico.mi.it

1. Fondazione IRCCS Ca’ Granda – Ospedale Maggiore, Milano, Milano
2. A.O. Papa Giovanni Xxiii-Bergamo, Bergamo
3. A.O. “Luigi Sacco” – Milano, Milano
4. A.O. Ospedale Di Circolo – Busto Arsizio, Busto Arsizio
5. Fondazione IRCCS Policlinico S. Matteo – Pavia, Pavia
6. A.O. “San Paolo” – Milano, Milano
7. A.O. Della Provincia Di Lecco, Lecco
8. Ospedale S. Giuseppe – Milano
Introduction

• Large real life data of chronic Hepatitis C (HCV) treatment are needed to assess the safety and efficacy of directly acting antivirals (DAAs) and to confirm results of Phase III trials.

• For this aim in May 2015 26 liver centers in the Lombardia Region in Northern Italy created the Regional Network for Viral Hepatitis.
Material and Methods

- Patients received the following regimens, dose and duration were dictated by EMA label: Genotype 1 patients received either a Sofosbuvir based regimen (SOF + Riba, SOF + Sim ± Riba, SOF + Dac ± Riba or SOF/LDV ± Riba) or Ritonavir boosted Paritaprevir/Ombitasvir/Dasabuvir ± Riba.

- Genotype 2 received SOF + RBV, Genotype 3 SOF + RBV, SOF + Dac ± Riba or PR + SOF.

- Genotype 4 received either a Sofosbuvir based regimen or Ritonavir boosted Paritaprevir/Ombitasvir/ + Riba.

- Sustained virological response was assessed at week 12 following treatment discontinuation.
Results

• Overall from December 2014 to December 2015, 2,432 patients received treatment. 81.8% of them had advanced fibrosis (14.8%) or compensated cirrhosis (67%), decompensated cirrhosis defined as Child Pugh B and C was present in (8%).

• HCV-1 and HCV-3 were the most prevalent genotypes being found in 1,534 (63%) and 419 patients (17%), respectively.

• 26 SAEs (1%) were recorded during treatment or follow-up, 15 in cirrhotics and 11 on the liver transplant (LT) waiting list or in the post-LT period. 6 of 26 SAEs (0.2%) were deemed related to therapy.
Results

• 2 patients died during treatment (0.08%), both patients had decompensated cirrhosis (MELD score 16 and 13).
• Death was liver related in 1, and was not attributed to therapy in both patients.
• At the time of analysis 1,534 patients have completed the treatment phase and 872 have been evaluated for SVR.
• By ITT analysis overall 90.4% (788/872) patients achieved an SVR.
• SVR rates were 92.9% in HCV-1 (498/536), 89.3% in HCV-2 (101/113), 81.1% in HCV-3 (116/143) and 88.9% in HCV-4 (71/80).
Conclusion

- In a large cohort of real-life HCV patients with advanced fibrosis/cirrhosis, DAA based treatment was safe and effective.
Abstract LBP510

Analysis of the Real-World Effectiveness of Direct Acting Antiviral Treatments for Hepatitis C in a Large Population

J. McCombs¹, J. McGinnis¹,², S. Fox¹,³, I. Tonnu-Mihara²
E-mail: justin.mcginnis@usc.edu

1. Schaeffer Center for Health Policy & Economics, University of Southern California, Los Angeles
2. Veterans Health Administration, United States Department of Veterans Affairs, Long Beach
3. Keck School of Medicine, University of Southern California, Los Angeles, United States
Methods

• Evaluation of the effectiveness of simeprevir/sofosbuvir, ledipasvir/sofosbuvir, and ombitasvir/paritaprevir/ritonavir/dasabuvir within the US Veterans Health Administration.

• Effectiveness rates were estimated across all three treatments, and multivariate logistic analysis was employed to explore the impact of treatment type, controlling for patient and disease characteristics.

Results

• The unadjusted rates of effectiveness were
  – 87.3% for simeprevir/sofosbuvir (n=3,068)
  – 93.2% for ledipasvir/sofosbuvir (n=5,524)
  – 93.4% for ombitasvir/paritaprevir/ritonavir/dasabuvir (n=1,012)

• Simeprevir/sofosbuvir yielded lower effectiveness rates than the other two study treatments (OR = 0.64 [0.49–0.85]).

• Patients with compensated and decompensated cirrhosis or HCC at the start of treatment were less likely to achieve SVR.

• Blacks and males were less likely to achieve SVR, while co-infection with HIV, hepatitis B, diabetes and obesity had no impact on treatment effectiveness.

• There was some limited evidence that patients younger than 60 years of age were less likely to respond.
Abstract SAT-158

Factors Impacting SVR12 For Patients With Advanced Cirrhosis Receiving Daclatasvir And Sofosbuvir With Ribavirin In The ALLY-1 Study

F. Poordad¹, R. Fontana², E. Schiff³, J.M. Vierling⁴, C. Landis⁵, Y. Zhao⁶, Y. Gandhi⁶, T. Garimella⁶, T. Eley⁶, S. Noviello⁶, E.S. Swenson⁷

E-mail: vierling@bcm.tmc.edu

1. Texas Liver Institute, University of Texas Health Science Center, San Antonio
2. University of Michigan Medical Center, Ann Arbor
3. Schiff Center for Liver Diseases, University of Miami Miller School of Medicine, Miami
4. Baylor College of Medicine, Houston
5. School of Medicine, University of Washington, Seattle
6. Research and Development, Bristol-Myers Squibb, Princeton
7. Research and Development, Bristol-Myers Squibb, Wallingford, United States
Background and Aims

- Despite therapeutic advances, HCV patients with decompensated cirrhosis remain difficult to treat.
- The phase 3 open-label ALLY-1 study assessed daclatasvir (DCV) + sofosbuvir (SOF) + ribavirin (RBV) in patients with advanced cirrhosis or posttransplant recurrence.
- In the advanced cirrhosis cohort, SVR12 rates were higher in patients with Child-Pugh class A or B (93%) compared with class C (56%).
- We investigated the relationship of RBV dosing, DCV concentration and viral kinetics to SVR12 in the advanced cirrhosis cohort of ALLY-1.

Methods

• Patients enrolled in the advanced cirrhosis cohort were treatment-naive or -experienced adults with chronic HCV infection (GT1–4).
• Patients received 12 weeks’ treatment with DCV 60 mg + SOF 400 mg once daily and RBV, initially 600 mg/day with potential adjustment up to 1,000 mg/day based on hemoglobin levels and creatinine clearance.
• This analysis includes treated patients with advanced cirrhosis of Child-Pugh class A (n = 12), B (n = 30), or C (n =14) who did not receive a liver transplant during the treatment period.
• RBV dose, RBV discontinuation, total/unbound plasma DCV concentration, and viral kinetics were analyzed by Child-Pugh class and SVR status.

Results

• Median daily RBV dose (adjusted for the full planned 12- week treatment for all patients) decreased slightly with worsening Child-Pugh class; Child-Pugh C patients received an average of 397 mg daily compared with 471 mg or 445 mg for Child-Pugh A or B, respectively.

• Among Child-Pugh C patients, the median daily RBV dose was 409 mg/day in SVR12 responders compared with 352 mg/day in non-responders; numerically lower Child-Pugh C patient dosing was not clinically meaningful.
Results

• Overall, 8 patients discontinued RBV due to adverse events; 6 achieved SVR12.

• DCV trough plasma and average concentrations (total and unbound) from a population pharmacokinetic model overlapped between SVR12 responders and non-responders and between patients with Child-Pugh A, B, and C.

• HCV RNA was undetectable at Week 4 in fewer patients with Child-Pugh C disease (33%) than in those with class A (67%) or B (61%) (Figure).
Results

Conclusions

- Differences in RBV dosing and DCV concentration do not fully account for the lower SVR12 rates in patients with Child-Pugh class C; however, it appears that Child-Pugh C patients have slower virologic response.

- A combination of disease-related and pharmacokinetic factors likely contributes to reduced SVR12 rates in patients with Child-Pugh C cirrhosis.

Abstract PS097

Antiviral Treatment In Patients With Advanced HCV Cirrhosis Using Sofosbuvir and Ledipasvir/ Daclatasvir With Or Without Ribavirin – 6 And 12 Month Outcomes Compared To Untreated Patients

M.C.M. Cheung¹, G.R. Foster¹, W.L. Irving², A.J. Walker³, B.E. Hudson⁴, S. Verma⁵, J. McLauchlan⁶, D.J. Mutimer⁷, A. Brown⁸, W. Gelson⁹, D. MacDonald¹⁰, K. Agarwal⁵ and HCV Research UK
E-mail: michelle.cheung@qmul.ac.uk

1. Blizard Institute, Barts and The London School of Medicine & Dentistry, Queen Mary University of London, London
2. NIHR Nottingham Digestive Diseases Biomedical Research Unit
3. Faculty of Medicine & Health Sciences, University of Nottingham, Nottingham
4. Hepatology Department, University Hospitals Bristol NHS Trust, Bristol
5. Institute of Liver Studies, King’s College London, London
6. MRC-University of Glasgow Centre for Virus Research, University of Glasgow, Glasgow
7. Centre for Liver Research, Queen Elizabeth Hospital, Birmingham
8. Department of Hepatology, St Mary’s Hospital, Imperial College London, London
10. UCL Institute of Liver and Digestive Health, Royal Free London NHS Foundation, London, United Kingdom
Background & Aims

- All-oral antivirals (sofosbuvir + NS5A inhibitor +/- ribavirin) used in England for patients with decompensated cirrhosis since April 2014 through the Expanded Access Programme (EAP)

- High sustained virological response was noted along with early improvement in liver function

- We have previously reported short term outcomes at 6 months – here we show outcomes at 15 months
HCV Research UK Database

EAP treated (1 April 14 - 11 Nov 14)  
N = 467

Untreated - enrolled with decompensated cirrhosis 6 months before EAP start  
N = 261

Extra-hepatic disease  
N = 14

Baseline liver transplant  
N = 44

 Decompensated cirrhosis  
N = 409

SVR12 achieved  
N = 329

Subsequently treated on EAP after 1 April 14  
N = 177
Results - Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Treated decompensated (N=409)</th>
<th>Untreated decompensated (N=261)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median, years</td>
<td>54</td>
<td>54</td>
</tr>
<tr>
<td>Prior HCV therapy, %</td>
<td>60</td>
<td>62</td>
</tr>
<tr>
<td>Genotype 1/ 3 HCV, %</td>
<td>49/ 42</td>
<td>49/ 35</td>
</tr>
<tr>
<td>Viral load, median, iu/mL</td>
<td>255,280</td>
<td>208,688</td>
</tr>
<tr>
<td>Bilirubin, median, µmol/L</td>
<td>28</td>
<td>26</td>
</tr>
<tr>
<td>Albumin, median, g/L</td>
<td>31</td>
<td>32</td>
</tr>
<tr>
<td>Platelet, median, x10^9/L</td>
<td>72</td>
<td>70</td>
</tr>
<tr>
<td>MELD, median</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Child Pugh B (%)</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>Child Pugh C (%)</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

Foster GR, Irving WL et al. J Hepatol 2016 Jan 29
Adverse Events in 329 Virological Responders
15 months (3 months Rx, 12 months post-Rx)

* p< 0.05

Survival - Improved in SVR patients over non-SVR

Which Patients Benefit from Viral Clearance?

Adverse event free survival at 15 months

- MELD <15
  - CPA: 61
  - CPB: 235
  - CPC: 30
- MELD >=15
  - N=71
  - CPA: 58

* p<0.05

MELD change - 6 & 15 months

0 - 6 months
(n=297)

- Mean score change -0.86

0 - 15 months
(n=77)

- Mean score change +0.44

p< 0.05

Patients without SVR, transplanted or died were excluded

Conclusions

- Antiviral therapy in patients with CP-B cirrhosis leads to prolonged improvement in the majority

- Only a minority of patients with CP-C cirrhosis derive long term benefit

- Early improvement does not necessarily translate into long term benefit
Abstract FRI-166

Long-term Follow-up Of Patients With Chronic HCV Infection Following Treatment With Direct Acting Antiviral Regimens: Maintenance Of SVR, Persistence Of Resistance Mutations and Clinical Outcomes

E.J. Lawitz¹, P. Ruane², C. Stedman³, G. Foster⁴, R.H. Hyland⁵, S. Coogan⁶, S. Moody⁷, H. Dvory-Sobol⁸, S.J. Knox⁵, D.M. Brainard⁵, A. Abergel⁹, K. Agarwal¹⁰, Z. Younes¹¹, C. Schwabe¹²
E-mail: lawitz@txliver.com

1. Texas Liver Institute, University of Texas Health Science Center, San Antonio, TX
2. Ruane Medical and Liver Health Institute, Los Angeles, CA, United States
3. Christchurch Hospital, Christchurch, New Zealand
4. Blizard Institute, Queen Mary University of London, London, United Kingdom
5. Clinical Research, Gilead Sciences, Inc.
6. Clinical Operations, Gilead Sciences Inc., Foster City, CA
7. Pharpoint Research, Inc., Durham, NC
8. Clinical Virology, Gilead Sciences, Inc., Foster City, CA, United States
9. Centre Hospitalier Universitaire de Clermont-Ferrand, Clermont-Ferrand, France
10. King’s College Hospital, London, United Kingdom
11. Gastro One, Germantown, TN, United States
12. Auckland Clinical Studies, Auckland, New Zealand
Objectives and Methods

• To determine long-term virologic and clinical outcomes in HCV patients treated with DAA regimens using registry study data

• Patients with chronic HCV treated in a Gilead-sponsored study were eligible for 1 of 2 ongoing 3-year registry studies
  – SVR Registry: patients who achieved a sustained virologic response 12 weeks after treatment end (SVR12) in parent study
  – Sequence Registry: patients with virologic failure in parent study

• Deep sequencing with 1% cutoff used

Outcomes

• SVR maintained in 99.7% (5414/5433) patients
  – 6 patients (0.1%) virologic evidence of late relapse
  – 12 patients (0.2%) virologic evidence of reinfection

• HCC was reported in 0.3% (16/5433) and 0.9% (5/536) of patients in the SVR and Sequence registries through Week 96 respectively.

Treatment-emergent NS5B RAVs at Baseline in Sequence Registry

Treatment-Emergent RAVs at Baseline in Sequence Registry

NS5B NI RAVs

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Patients With NS5B RAVs (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOF ± RBV ± PEG</td>
<td>11 (7/152)</td>
</tr>
<tr>
<td>LDV/SOF ± RBV</td>
<td>14 (3/21)</td>
</tr>
<tr>
<td>SOF/VEL ± RBV</td>
<td>0/24</td>
</tr>
</tbody>
</table>

Total number of patients is the number with baseline sequencing data available. NS5B nucleos(t)ide inhibitor (NI) RAVs were analyzed for patients who received regimens containing SOF. No patient had >1 NS5B RAV.

Treatment-emergent NS5A RAVs at Baseline in Sequence Registry

![Graph showing the percentage of patients with different NS5A RAVs based on treatment regimen.]

- **LDV ± VDV ± TGV ± PEG ± RBV**
  - Total: 148 patients
  - Patients with ≥7 RAVs: 9
  - Patients with 6 RAVs: 6
  - Patients with 5 RAVs: 2
  - Patients with 4 RAVs: 3
  - Patients with 3 RAVs: 2
  - Patients with 2 RAVs: 10

- **LDV/SOF ± RBV**
  - Total: 12 patients
  - Patients with ≥7 RAVs: 8
  - Patients with 6 RAVs: 1
  - Patients with 5 RAVs: 2
  - Patients with 4 RAVs: 2
  - Patients with 3 RAVs: 1

- **SOF/VEL ± RBV**
  - Total: 7 patients
  - Patients with ≥7 RAVs: 7
  - Patients with 6 RAVs: 0
  - Patients with 5 RAVs: 0
  - Patients with 4 RAVs: 0
  - Patients with 3 RAVs: 0
  - Patients with 2 RAVs: 0
  - Patients with 1 RAV: 0

Additional patients with NS5A RAVs at parent study BL that were observed at registry study BL, n:

- **LDV ± VDV ± TGV ± PEG ± RBV**
  - n=148

- **LDV/SOF ± RBV**
  - n=12

- **SOF/VEL ± RBV**
  - n=7

*Numbers inside bars are numbers of patients in each category. Total number of patients in each bar is the number with baseline sequencing data available. Graph includes patients with BL NS5A RAVs who developed new RAVs. NS5A RAVs were analyzed for patients who received an NS5A inhibitor-containing regimen.*

Outcomes

• Treatment-emergent RAVs in the parent study were present at baseline in the Sequence Registry
  – Fewer NS5A RAVs developed in patients who failed treatment with a SOF-containing regimen than one without SOF
Abstract PS007

European RAVs Database: Frequency And Characteristics Of RAVs In Treatment-naïve And DAA-experienced Patients

S. Susser¹, J. Dietz¹, J. Vermehren¹, K.-H. Peiffer¹, S. Passmann¹, D. Perner¹, C. Berkowski¹, P. Ferenci², M. Buti³, B. Müllhaupt⁴, B. Hunyadi⁵, H. Hinrichsen⁶, S. Mauss⁷, J. Petersen⁸, P. Buggisch⁸, A. Schober⁹, G. Felten¹⁰, D. Hüppe¹⁰, A. Zipf¹¹, G. Knecht¹², T. Lutz¹², T. Berg¹³, S. Zeuzem¹, C. Sarrazin¹

E-mail: julia.dietz@em.uni-frankfurt.de

1. Medizinische Klinik¹, Goethe-University Hospital, Frankfurt, Germany
2. Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria
3. Hospital Universitario Valle Hebron and Ciberehd, Barcelona, Spain
4. Swiss Hepato-Pancreato-Biliary Center and Department of Gastroenterology and Hepatology, University Hospital Zürich, Zürich, Switzerland
5. Somogy County Kaposi Mór Teaching Hospital, Kaposvár, Hungary
6. Practice of Gastroenterology, Kiel
7. Practice of Gastroenterology, Düsseldorf
8. Institute for Interdisciplinary Medicine IFI, Hamburg
9. Practice of Hepatology, Göttingen
10. Practice of Hepatology, Herne
11. Practice of Gastroenterology, Mannheim
12. Infektiologikum, Frankfurt
13. Department of Gastroenterology and Rheumatology, University Hospital Leipzig, Leipzig, Germany
Background and Aims

• Interferon-free combination therapies are the new standard for treatment of chronic hepatitis C virus (HCV) infection.
• The frequency of HCV RAVs (resistance associated variants) to direct antiviral agents (DAAs) varies between HCV genotypes, but pre-existing RAVs are often associated with virologic treatment failure.
• In this study frequencies of NS3, NS5A and NS5B RAVs were investigated in treatment-naïve and -experienced patients and consequences for DAA treatment options were evaluated.

Methods

- Serum samples of 3305 European HCV infected patients were collected and population-based sequencing of HCV NS3, NS5A and NS5B genes was performed.
- RAVs were considered as relevant if they were associated with treatment failure or were shown to confer a >2-fold changed drug susceptibility in comparison to the reference strain.
- RAVs were analysed in NS3 (positions 36, 43, 54, 55, 56, 80, 122, 155, 156, 158, 168, 170, 175), NS5A (24, 28, 30, 31, 58, 92, 93) and NS5B (159, 282, 321, 316, 368, 411, 414, 448, 553, 554, 556, 558, 559, 561).
Results

• Treatment-naïve and treatment-experienced patients infected with HCV genotype 1a (n = 1417), 1b (n = 1300), 1c-e (n = 5), 2 (n = 49), 3 (n = 389), 4 (n = 119), 5 (n = 7), 6 (n = 1), and 2k/1b (n = 18) were studied.

• Pre-existing RAVs could be observed in 38% of treatment-naïve patients.

• The proportion of selected RAVs in telaprevir, boceprevir and PEG/RBV pre-treated patients was 36%, 26%, and 34%, respectively.
Results

• After failure to SOF/RBV ± PEG no RAVs could be detected. In patients treated with SOF in combination with SMV, DCV, or LDV a much higher incidence of RAVs was observed (64%, 84%, and 60%) only exceeded by PTV/OMB/DSV failure patients who all selected RAVs (100%).

• Re-/ treatment without RAVs with currently approved regimens would be possible in 99% of the naïve patients and in 96% (TVR), 95% (BOC), 83% (SOF/RBV), 90% (SOF/PEG/RBV), 88% (SOF/SMV) 49% (SOF/DCV), 62% (SOF/LDV), 28% (PTV/OMB/DSV), and 98% (PEG/ RBV) of pre-treated patients.
## Results

<table>
<thead>
<tr>
<th>Treatment-naive</th>
<th>Tx status [n=]</th>
<th>total RAVs detected [n=]</th>
<th>special RAVs detected [n=]</th>
<th>(re-)Tx w/o RAVs possible in</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-treatment:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TVR</td>
<td>201</td>
<td>90 (45%)</td>
<td>72 (38%) NS3</td>
<td>96%</td>
</tr>
<tr>
<td>BOC</td>
<td>132</td>
<td>48 (36%)</td>
<td>34 (26%) NS3</td>
<td>95%</td>
</tr>
<tr>
<td>SOF/RBV</td>
<td>89</td>
<td>52 (58%)</td>
<td>0 (0%) NS5B</td>
<td>83%</td>
</tr>
<tr>
<td>SOF/PEG/RBV</td>
<td>39</td>
<td>18 (46%)</td>
<td>0 (0%) NS5B</td>
<td>90%</td>
</tr>
<tr>
<td>SOF/SMV</td>
<td>44</td>
<td>38 (86%)</td>
<td>28 (64%) NS3, NS5B</td>
<td>88%</td>
</tr>
<tr>
<td>SOF/DCV</td>
<td>43</td>
<td>38 (88%)</td>
<td>36 (84%) NS5A/B</td>
<td>49%</td>
</tr>
<tr>
<td>SOF/LDV</td>
<td>63</td>
<td>48 (76%)</td>
<td>38 (60%) NS5A/B</td>
<td>62%</td>
</tr>
<tr>
<td>PTV/OMB/DSV</td>
<td>18</td>
<td>18 (100%)</td>
<td>18 (100%) NS3, NS5A/B</td>
<td>28%</td>
</tr>
<tr>
<td>PEG/RBV</td>
<td>797</td>
<td>275 (34%)</td>
<td>275 (34%) NS3, NS5A/B</td>
<td>98%</td>
</tr>
</tbody>
</table>

### Table 1:

Tx-treatment; RAVs-resistance associated variants; w/o-without; TVR-telaprevir; BOC-boceprevir; SOF-sofosbuvir; RBV-ribavirin; PEG-pegylated interferon-alfa; SMV-simeprevir; DCV-daclatasvir; LDV-ledipasvir; PTV-paritaprevir; OMB-ombitasvir; DSV-dasabuvir

Conclusions

• For treatment naïve patients RAVs against NS3, NS5A or NonNuc NS5B inhibitors are observed with moderate frequency (5–57%) and RAVs-free treatment options are available for almost all patients.

• However, in patients with failure to multiple DAA combination regimens, RAVs were found in 36–100% of patients which may impose restrictions on effective retreatment options with currently approved DAA regimens.
Abstract PS102

Prevalence And Impact Of Baseline Resistance-associated Variants (RAVs) On The Efficacy Of Ledipasvir/Sofosbuvir Or Simeprevir/Sofosbuvir Against GT1 HCV Infection: HCV-TARGET Interim Analysis

G.P. Wang$^{1,2}$, J.D. Reeves$^3$, N. Terrault$^4$, J.K. Lim$^5$, G. Morelli$^1$, A. Kuo$^6$, J. Levitsky$^7$, K. Sherman$^8$, L.M. Frazier$^9$, A. Ramani$^{10}$, J. Peter$^1$, L. Akuskevich$^{11}$, M.W. Fried$^{11}$, D.R. Nelson$^1$

E-mail: gary.wang@medicine.ufl.edu

1. University of Florida
2. North Florida/South Georgia Veterans Health System, Gainesville
3. Monogram Biosciences, South San Francisco
4. University of California, San Francisco, San Francisco
5. Yale University School of Medicine, New Haven
6. University of California, San Diego, San Diego
7. Northwestern University Feinberg School of Medicine, Chicago
8. University of Cincinnati, Cincinnati
9. Liver Wellness Center, Little Rock
10. Mountainview Medical Center, Hudson
11. University of North Carolina, Chapel Hill, United States
Background and Aims

• This study aimed to evaluate the prevalence and impact of baseline (BL) resistance-associated variants (RAVs) on ledipasvir/sofosbuvir (LDV/SOF) ± ribavirin (RBV) or simeprevir/sofosbuvir (SMV/SOF) ± RBV regimens in patients with genotype (GT) 1 HCV infection in HCV-TARGET, a multi-centre, prospective, observational cohort study.

Methods

• A subset of patients enrolled in HCV-TARGET were consented to serum collection prior to initiating HCV therapy administered according to local standard of care.

• HCV resistance testing was performed on samples collected before May 12, 2015 using Monogram Biosciences assays (population sequence derived from Illumina MiSeq data with a 10% variant reporting threshold).

• LDV, SOF and SMV susceptibility was interpreted using Monogram’s rule-based algorithm.
Results

• BL resistance testing was performed for 486 patients treated with LDV/SOF (n = 209), LDV/SOF + RBV (n = 31), SMV/SOF (n = 186) or SMV/SOF + RBV (n = 60). Demographics included 63% male, 13% Black, 76% GT1a, 52% cirrhosis, 18% with liver transplant, and 55% with prior HCV therapy.

• The overall prevalence of SMV, LDV and SOF RAVs was 41% (196/480), 24% (116/484) and 2.7% (13/480), respectively.

• The prevalence of SMV, LDV and SOF RAVs in treatment-naïve (TN) patients (221/486) was 39%, 23%, and 3.2%, respectively, compared to 42%, 25%, and 2.3% in treatment-experienced (TE) patients (265/486).

• The prevalence of SMV, LDV and SOF RAVs in non-cirrhotic patients (233/486) was 37%, 24% and 2.2%, respectively, compared to 44%, 24% and 3.2% in cirrhotic patients (253/486).

Results

• To date (403/486 with SVR12 data), 91.3% (368/403) of patients achieved SVR12, and 8.7% (35/403) developed relapse, had no response or had virologic breakthrough.

• In the LDV/SOF ± RBV cohort (n = 168), 85% (17/20) with LDV or SOF RAVs achieved SVR12, whereas 95% (141/148) without LDV and SOF RAVs achieved SVR12.

• For the SMV/SOF ± RBV cohort (n = 227), 88% (85/97) with SMV RAVs and 90% (135/150) without SMV RAVs achieved SVR12. Multivariate analysis incorporating RAVs associated with SVR12 for the 486 patient cohort will be presented.
## Results

<table>
<thead>
<tr>
<th>Compound</th>
<th>AA positions associated with resistance analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMV</td>
<td>NS3: 36, 80, 122, 155, 168, 170</td>
</tr>
<tr>
<td>LDV</td>
<td>NS5A: 24, 28, 30, 31, 54, 58, 92, 93</td>
</tr>
<tr>
<td>SOF</td>
<td>NS5B: 142, 159, 282, 316</td>
</tr>
</tbody>
</table>

Conclusions

- SMV, LDV and SOF RAVs at BL for GT1 patients treated with LDV/SOF ± RBV or SMV/SOF ± RBV suggests that the prevalence was generally comparable between TN and TE patients, and between cirrhotic and non-cirrhotic patients.
Abstract SAT-273

Efficacy and Safety of Ombitasvir, Paritaprevir/Ritonavir, And Dasabuvir Without Ribavirin In Patients With HCV Genotype 1b With Or Without Compensated Cirrhosis: Pooled Analysis Across 5 Clinical Trials

T.M. Welzel¹, V. Isakov², R. Trinh³, A. Streinu-Cercel⁴, J.-F. Dufour⁵, R.T. Marinho⁶, C. Moreno⁷, L. Liu³, W. Xie³, F. Tatsch³, N. Shulman³, A. Craxi⁸

1. J.W. Goethe University, Frankfurt, Germany
2. Department of Gastroenterology and Hepatology, Institute of Nutrition, Moscow, Russia
3. AbbVie Inc., North Chicago, IL, United States
4. Carol Davila University of Medicine and Pharmacy, National Institute for Infectious Diseases “Prof. Dr. Matei Bals”, Bucharest Romania
5. Inselspital Bern, Bern, Switzerland
6. Hospital S. Maria, Medical School of Lisbon, Lisbon, Portugal
7. CUB Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium
Background and Aims

• In GT1b-infected patients with cirrhosis, OBV/PTV/r + DSV with RBV for 12 weeks achieved an SVR12 rate of 98.5%.
• Regimens with RBV are associated with higher rates of adverse events (AEs), primarily anemia, and a higher pill burden.
• This post hoc, pooled analysis from 5 Phase 3/3b trials investigated the efficacy and safety of the RBV-free, 12-week regimen of OBV/PTV/r + DSV among HCV GT1b-infected patients with or without compensated cirrhosis.

Methods

• Data from 5 phase 3/3b trials of OBV/PTV/r + DSV were included in this post-hoc analysis
  – GT1b-infected patients without cirrhosis: PEARL-II, PEARL-III, TOPAZ-II, and MALACHITE-I
  – GT1b-infected patients with compensated cirrhosis: TURQUOISE-III
• Included treatment-naïve and PEG/RBV-experienced patients
Results

• The pooled analysis included 60 patients with cirrhosis and 521 patients without cirrhosis.

• SVR12 with OBV/PTV/r + DSV for 12 weeks was 100% (60/60) and 99% (515/521) in patients with and without cirrhosis, respectively.
  – Two patients without cirrhosis experienced on-treatment virologic failure.
  – One patient had virologic relapse.

• Treatment was well tolerated, with no discontinuations of study drugs due to AEs, and there were low rates of serious AEs and grade 3/4 laboratory abnormalities.
Abstract LBP503

Effect Of Baseline Resistance-associated Variants On SVR With The 3D Regimen With And Without RBV In GT1a And GT1b-infected Patients

C. Sarrazin\textsuperscript{1}, M.S. Sulkowski\textsuperscript{2}, P. Krishnan\textsuperscript{3}, R. Tripathi\textsuperscript{3}, G. Schnell\textsuperscript{3}, Y. Xie\textsuperscript{3}, D.E. Cohen\textsuperscript{3}, R. Trinh\textsuperscript{3}, L. Rodrigues, Jr.\textsuperscript{3}, Y. Luo\textsuperscript{3}, N. S. Shulman\textsuperscript{3}, T. Pilot-Matias\textsuperscript{3}, C. Collins\textsuperscript{3}

E-mail: christopher.brown@abbvie.com

1. J.W. Goethe University Hospital, Frankfurt, Germany
2. Viral Hepatitis Center, Johns Hopkins University, Baltimore
3. AbbVie Inc., North Chicago, United States
Introduction

• The 3D regimen (ombitasvir/paritaprevir/ritonavir [paritaprevir identified by AbbVie and Enanta] and dasabuvir) ± RBV, targeting HCV NS5A, NS3 and NS5B, respectively, is highly effective and is approved in the US and EU for the treatment of HCV GT1 infection.

• Baseline resistance associated variants (RAVs) in NS3 or NS5A have been shown to impact response to other DAA regimens.

• We assessed the prevalence of RAVs and impact on 3D response using GT1a and GT1b baseline samples from Phase 3 studies.

Material and Methods

• Next generation sequencing was conducted using Illumina MiSeq on baseline samples from naïve (PEARL-IV), treatment-experienced (SAPPHIRE-II), or cirrhotic (TURQUOISE-II; 24 week treatment arm) GT1a patients who received 3D + RBV, and treatment-experienced (PEARL-II) or cirrhotic (TURQUOISE-III) GT1b patients who received 3D without RBV.

• Patients who discontinued treatment early for non-virologic reasons were excluded.

• The prevalence and impact of baseline RAVs on SVR rates were determined using detection thresholds of 1% and 15%.

• The impact of baseline RAVs conferring ≥5-fold resistance to components of the 3D regimen in NS3, NS5A, and NS5B on treatment outcome was determined by comparing SVR rates in patients with or without detectable RAVs.
Results

• SVR rates were 96% in patients with GT1a and 100% in patients with GT1b.

• Using the 15% detection threshold, one or more NS5A RAVs were present in 11% of treatment-experienced or cirrhotic GT1a patients; whereas NS5A RAVs were found in 19% of GT1b patients.

• Similar SVR rates were seen in GT1a patients with or without NS5A RAVs.
Results

- All GT1b patients with NS5A RAVs, including at position Y93, achieved SVR. NS3 RAVs were uncommon in both subtypes (≤2%).
- NS5B RAVs were more common in GT1b than GT1a.
- NS3 RAVs were not seen in any of the 14 virologic failures and an NS5B RAV was seen in 1 of 14 virologic failures.
- The presence of the GT1a NS3 Q80K polymorphism had no impact on SVR.
- Patients harboring RAVs across multiple viral targets were rare; all achieved SVR.

Conclusion

- For current HCV therapies that include an NS5A inhibitor, understanding the impact of baseline NS5A RAVs on treatment outcome is of particular importance.

- GT1a patients treated with the approved 3D regimen + RBV achieved similarly high SVR rates, regardless of the presence or absence of baseline RAVs.

- All GT1b patients treated with the 3D regimen without RBV achieved SVR.
Abstract PS004

The Real-world Israeli Experience Of Treating Chronic Hepatitis C, Genotype 1 Patients With Advanced Fibrosis With Paritaprevir/Ritonavir/Ombitasvir, Dasabuvir With Or Without Ribavirin: A Large Multi-center Cohort

E. Zuckerman¹, E. Ashkenasi¹, Y. Kovalev¹, E. Weitsman², R.T. Kaspa³, M. Brown³, M. Cohen³, T. Saadi⁴, Y. Baruch⁴, M. Carlebach⁵, R. Hazzan⁶, R. Safadi⁷, T. Goldberg⁷, R. Oren⁷, Y. Ashur⁸, M. Carmiel⁹, Y. Kitay¹⁰, R. Hadari¹⁰, S.A. Mouch¹¹, Y. Menachem¹², H. Kathcman¹², R. Bruk¹², O. Shibolet¹²
E-mail: eli_zuckerman@yahoo.com

1. Liver Unit, Carmel Medical Center, Haifa
2. Sheba Medical Center, Ramat Gan
3. Liver Institute, Rabin Medical Center, Petach Tikva
4. Liver Unit, Rambam Medical Center
5. Liver Unit, Bnai Zion Medical Center, Haifa
6. Liver Unit, Haemek Medical Center, Afula
7. Liver Unit, Hadassah Medical Center
8. Liver Clinic, CHS, Jerusalem
9. Liver Unit, Western Galilee Medical Center, Naharya
10. Liver Unit, Meir Medical Center, Kfar Saba
11. Liver Unit, Hillel Yaffe Medical Center, Hadera
12. Liver Unit, Tel Aviv Medical Center, Tel Aviv, Israel
Background and Aims

• The paritaprevir/ritonavir/ombitasvir, dasabuvir with or without ribavirin (3D ± R) regimen is approved in USA and Europe for chronic hepatitis C (CHC) patients with GT 1 and 4.

• Approved in January 2015 in Israel for GT1, CHC patients with advanced fibrosis only (F3 and F4).

### Treatment Durations

#### Posology and Method of Administration and Pharmacological Properties, Clinical Studies

#### Treatment Regimen and Duration by Patient Population (Treatment-Naïve or Interferon-Experienced)

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Treatment*</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1a, without cirrhosis</td>
<td>3DAA + ribavirin</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Genotype 1a, with cirrhosis</td>
<td>3DAA + ribavirin</td>
<td>24 weeks**</td>
</tr>
<tr>
<td>Genotype 1b, without cirrhosis</td>
<td>3DAA</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Genotype 1b, with cirrhosis</td>
<td>3DAA + ribavirin</td>
<td>12 weeks</td>
</tr>
</tbody>
</table>

*Note: Follow the genotype 1a dosing recommendations in patients with an unknown genotype 1 subtype or with mixed genotype 1 infection.

**3DAA administered with ribavirin for 12 weeks may be considered for some patients based on prior treatment history [see Clinical Studies (14.3)].

### Baseline Characteristics

#### Demographics and Baseline Characteristics of Patients Treated with AbbVie 3D ± RBV

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AbbVie 3D ± RBV (N = 661)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender, n (%)</td>
<td>290 (44)</td>
</tr>
<tr>
<td>Mean age, years (range)</td>
<td></td>
</tr>
<tr>
<td>&gt; 65 years, n (%)</td>
<td>60 (19–84)</td>
</tr>
<tr>
<td>≥ 75 years, n (%)</td>
<td>185 (28)</td>
</tr>
<tr>
<td></td>
<td>66 (10)</td>
</tr>
<tr>
<td>Mean viral load, 6log₁₀ (range)</td>
<td>1.98 (0.35–38)</td>
</tr>
<tr>
<td>Genotype 1 subtype, n (%)</td>
<td></td>
</tr>
<tr>
<td>1b</td>
<td>568 (86)</td>
</tr>
<tr>
<td>1a</td>
<td>85 (13)</td>
</tr>
<tr>
<td>1</td>
<td>8 (1)</td>
</tr>
<tr>
<td>Metavir fibrosis, n (%)</td>
<td></td>
</tr>
<tr>
<td>F0–1</td>
<td>12 (2)</td>
</tr>
<tr>
<td>F2</td>
<td>5 (&lt;1)</td>
</tr>
<tr>
<td>F3</td>
<td>234 (35)</td>
</tr>
<tr>
<td>F4</td>
<td>410 (62)</td>
</tr>
<tr>
<td>Previous treatment: Peg-IFN/RBV*, n (%)</td>
<td>410 (62)</td>
</tr>
<tr>
<td>Post liver transplantation, n</td>
<td>22</td>
</tr>
</tbody>
</table>

* 5 patients: PI treatment (TPV, BOC) < 4 weeks.
Cirrhotic Patient Characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristics of Cirrhotic Patients Treated with 3DAA ± RBV</th>
<th>All patients (n = 410)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT class A/B/C</td>
<td>404/6/0</td>
</tr>
<tr>
<td>MELD Score &gt; 10</td>
<td>42 (10)</td>
</tr>
<tr>
<td>Ascites</td>
<td>3 (&lt;1)</td>
</tr>
<tr>
<td>Esophageal varices, n (%)</td>
<td>114 (28)</td>
</tr>
<tr>
<td>Baseline platelets &lt; 90,000/mL, n (%)</td>
<td>113 (28)</td>
</tr>
<tr>
<td>Baseline albumin &lt; 3.5 g/dL, n (%)</td>
<td>102 (25)</td>
</tr>
</tbody>
</table>

CPT = Child-Pugh-Turcotte; MELD = Model for End-stage Liver Disease.

Efficacy

Virologic Response to Treatment of Genotype 1 Cirrhosis vs. No Cirrhosis

3DAA ± RBV

Patients with undetectable HCV RNA (%)

Week 2

Week 4

EOT

SVR12 (mITT*)

No cirrhosis

Cirrhosis

57% 60%

42/74 76/127

182/212 280/352

215/216 364/366

161/163 251/253

99.5% 99.4%

99% 99%

*Excludes patients who did not achieve SVR12 for reasons other than virologic failure.

Safety

- 8 patients developed hepatic decompensation

### Decompensated Patients: Predictors of Hepatic Decompensation?

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients, n (%) (N = 661)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 75 years</td>
<td>3 (37.5) vs 63 (9.6)</td>
<td>0.005</td>
</tr>
<tr>
<td>PLT&lt;sub&gt;1&lt;/sub&gt; &lt; 90X10&lt;sup&gt;3&lt;/sup&gt;/mL</td>
<td>4 (50) vs 106 (16)</td>
<td>0.03</td>
</tr>
<tr>
<td>Albumin &lt; 3.5 g/dL</td>
<td>4 (50) vs 123 (19)</td>
<td>0.048</td>
</tr>
<tr>
<td>CPT score ≥ 7</td>
<td>1 (12.5) vs 5 (0.7)</td>
<td>0.07</td>
</tr>
<tr>
<td>MELD score &gt;10</td>
<td>3 (37.5) vs 39 (6)</td>
<td>0.01</td>
</tr>
<tr>
<td>Previous decompensation</td>
<td>3 (37.5) vs 0 (0)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

* Calculated by Fisher’s Exact test

<sup>1</sup>PLT=platelets

C-EDGE Head-To-Head: Efficacy and Safety of Elbasvir and Grazoprevir Compared with SOF/PEG/RBV: A Phase 3 Randomized Controlled Trial


1Institute for Clinical and Experimental Medicine, Prague, Czech Republic; 2Budai Hepatólogiai Centrum, Budapest, Hungary; 3Wojewódzki Szpital Obserwacyjno-Zakaźny im Tadeusza Browicza, Bydgoszcz, Poland; 4Hospital Universitario Donostia, San Sebastián, Spain; 5Institutul Național de Boli Infecțioase “Prof. Dr. Matei Bals”, Bucharest, Romania; 6Centre of Infectious Diseases, Vilnius University Hospital Santariskiu Klinikos, Vilnius, Lithuania; 7Semmelweis Egyetem, Budapest, Hungary; 8UNN Universitetssykehuset Nord Norge, Tromsø, Norway; 9Hacettepe University Medical Faculty, Ankara, Turkey; 10Department of Infectious Diseases, Rigshospitalet, Copenhagen, Denmark; 11Merck & Co., Inc., Kenilworth, United States

E-mail: jan.sperl@ikem.cz
C-EDGE Head to Head

TRIAL DESIGN

- Randomized, multi-site, open-label study
- Treatment naïve and PR treatment experienced patients; approximately 25% with cirrhosis
- If patients were expected to need more than 12 weeks of treatment, they were not enrolled in this trial.
  - Based on the sofosbuvir European Summary of Product Characteristics, “consideration should be given to potentially extending the duration of therapy beyond 12 weeks and up to 24 weeks; especially for those subgroups who have one or more factors historically associated with lower response rates to interferon-based therapies (e.g. advanced fibrosis/cirrhosis, high baseline viral concentrations, black race, IL28B non CC genotype, prior null response to peg interferon alfa and ribavirin therapy)”.

SVR12 IN THE FULL ANALYSIS SET

SVR12 estimated adjusted difference
8.7% (95% CI: 3.6%, 15.3%)

EBR/GZR | SOF/PR
---|---
100.0% | 99.0%
100.0% | 90.4%
99.0% | 100.0%
90.5% | 60.0%
128 | 129
114 | 126
18 | 18
17 | 17
104 | 105
94 | 104
6 | 6
3 | 5

All genotypes
GT1a
GT1b
GT4

Virologic failure
0
11
0
0
0
9
0
2

LTFU/discontinued
1
1
0
0
1
1
0
0

Non-inferiority was demonstrated
- The lower bound of this confidence interval, 3.6%, was greater than -10%,

Superiority of EBR/GZR over SOF/PR was also demonstrated
- The lower bound of the confidence interval, 3.6%, was greater than 0.

SVR12: Subgroup Analysis

### Subgroup Analysis

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Difference</th>
<th>95% CI</th>
<th>Treatment difference (95% CI)</th>
<th>SOF/PR n/N</th>
<th>EBR/GZR n/N</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ALL PATIENTS</strong></td>
<td>8.7</td>
<td>3.6, 15.3</td>
<td></td>
<td>114/126</td>
<td>128/129</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤40</td>
<td>5.6</td>
<td>-4.2, 18.3</td>
<td></td>
<td>34/36</td>
<td>37/37</td>
</tr>
<tr>
<td>41-50</td>
<td>6.1</td>
<td>-5.5, 19.8</td>
<td></td>
<td>31/33</td>
<td>31/31</td>
</tr>
<tr>
<td>51-60</td>
<td>11.4</td>
<td>-0.8, 26.7</td>
<td></td>
<td>31/36</td>
<td>40/41</td>
</tr>
<tr>
<td>61-70</td>
<td>17.6</td>
<td>-0.4, 41.4</td>
<td></td>
<td>14/17</td>
<td>20/20</td>
</tr>
<tr>
<td>71-80</td>
<td>—</td>
<td>—</td>
<td></td>
<td>4/4</td>
<td>0/0</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>11.3</td>
<td>4.4, 21.6</td>
<td></td>
<td>55/62</td>
<td>55/55</td>
</tr>
<tr>
<td>Female</td>
<td>6.5</td>
<td>-0.5, 15.9</td>
<td></td>
<td>59/64</td>
<td>73/74</td>
</tr>
<tr>
<td><strong>IL28B</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>3.8</td>
<td>-9.5, 19.1</td>
<td></td>
<td>25/26</td>
<td>26/26</td>
</tr>
<tr>
<td>Non-CC</td>
<td>10.2</td>
<td>4.3, 18.1</td>
<td></td>
<td>87/98</td>
<td>99/100</td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
<td>-61.5, 70.6</td>
<td></td>
<td>2/2</td>
<td>3/3</td>
</tr>
<tr>
<td>Genotype</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1a</td>
<td>0</td>
<td>-18.0, 18.9</td>
<td></td>
<td>17/17</td>
<td>18/18</td>
</tr>
<tr>
<td>1b</td>
<td>8.7</td>
<td>3.2, 16.0</td>
<td></td>
<td>94/104</td>
<td>104/105</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>-10.9, 78.1</td>
<td></td>
<td>3/5</td>
<td>6/6</td>
</tr>
<tr>
<td>Cirrhotic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>5.7</td>
<td>0.8, 12.3</td>
<td></td>
<td>98/105</td>
<td>106/107</td>
</tr>
<tr>
<td>Yes</td>
<td>23.8</td>
<td>6.9, 45.4</td>
<td></td>
<td>16/21</td>
<td>22/22</td>
</tr>
<tr>
<td>Baseline HCV RNA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤800,000 IU/mL</td>
<td>0</td>
<td>-9.1, 8.0</td>
<td></td>
<td>45/45</td>
<td>39/39</td>
</tr>
<tr>
<td>&gt;800,000 IU/mL</td>
<td>13.7</td>
<td>6.6, 23.2</td>
<td></td>
<td>69/81</td>
<td>89/90</td>
</tr>
<tr>
<td>Prior treatment experience</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naïve</td>
<td>3.4</td>
<td>-1.6, 9.9</td>
<td></td>
<td>87/91</td>
<td>99/100</td>
</tr>
<tr>
<td>PR null response</td>
<td>50</td>
<td>18.2, 73.6</td>
<td></td>
<td>7/14</td>
<td>11/11</td>
</tr>
<tr>
<td>PR partial response</td>
<td>12.5</td>
<td>-31.0, 48.4</td>
<td></td>
<td>7/8</td>
<td>6/6</td>
</tr>
<tr>
<td>PR relapse</td>
<td>0</td>
<td>-25.0, 23.5</td>
<td></td>
<td>13/13</td>
<td>12/12</td>
</tr>
</tbody>
</table>