A Continuing Medical Education Internet Symposium

The 46th Annual Meeting of the European Association for the Study of the Liver (EASL)

Advances in Chronic Hepatitis C Management and Treatment

Jointly sponsored by the Postgraduate Institute for Medicine and ViralEd, LLC.
Updates on Current Status of HCV Therapy

K. Rajender Reddy, MD
Professor of Medicine, Professor of Medicine in Surgery, Director of Hepatology and Medical Director of Liver Transplantation
University of Pennsylvania
Philadelphia, Pennsylvania
HCV in Europe: Impact of Treatment on Future HCV-related Morbidity and Mortality

• Data from France, Belgium, Germany, Italy, Spain and UK in 2010
• 33% of patients were HCV-RNA negative (ranging 31% in Italy to 42% in France), 20% after successful treatment
• 49% were aware of their infection
• Cirrhosis 15% (31% decompensation)
• HCC 5%

Deuffic-Burban S, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 122.
HCV in Europe: Impact of Treatment on Future HCV-related Morbidity and Mortality

- Current treatment paradigm will reduce HCV mortality by 13% until 2025
- Cirrhosis incidence will also be reduced by 21% until 2025
- If all naïve patients and 70% of NR are treated with PI, HCV mortality would be reduced by an additional 15%

Deuffic-Burban S, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 122.
Extension for Community Health Outcomes (ECHO): Objectives

• Train primary care clinicians in rural areas and prisons to treat hepatitis C in rural New Mexico

• Show that such care is as safe and effective as in a university clinic

• Show that Project ECHO improves access to hepatitis C care for minorities

ECHO: Method

- Use Technology (telemedicine and internet) to leverage scarce healthcare resources
- Disease Management Model focused on improving outcomes by reducing variation in processes of care and sharing “best practices”
- Case based learning: Co-management of patients with UNMHSC specialists
- HIPAA compliant centralized database to monitor outcomes

ECHO: Participants

- Study sites
  - Intervention (ECHO)
    - Community-based clinics: 16
    - New Mexico Department of Corrections: 5
  - Control: University of New Mexico Liver Clinic

- Subjects meeting inclusion/exclusion criteria
  - Community cases seen by primary care physicians
  - Consecutive University patients
• 407 hepatitis C patients met inclusion and exclusion criteria
  – Age: 43.0 ± 10.0 years
  – Men: 63.3%
  – Minority: 65.2%
  – Genotype 1: 57.0%
  – \( \log_{10} \) viral load: 5.89 ± 0.95
### ECHO: Treatment Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ECHO</th>
<th>UNMH</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minority</td>
<td>68%</td>
<td>49%</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>SVR (Cure) Genotype 1/4</td>
<td>50%</td>
<td>46%</td>
<td>NS</td>
</tr>
<tr>
<td>SVR (Cure) Genotype 2/3</td>
<td>70%</td>
<td>71%</td>
<td>NS</td>
</tr>
</tbody>
</table>

ECHO: Conclusions

• Rural primary care clinicians deliver hepatitis C care through Project ECHO that is as safe and effective as that given in a university clinic

• Project ECHO improves access to hepatitis C care for New Mexico minorities

ITPA Gene Variant Protects Against Anemia and Improves Viral Clearance by PEG-IFN/RBV

- Multicenter, retrospective cross-sectional study of chronic HCV treated with PegIFN/RBV from 4 centers in Japan (N=474)
- 3 SNPs within or adjacent to ITPA gene were genotyped (rs6051702, rs7270101, rs1127354)
- A functional SNP, rs1127354 was strongly associated with a protection against anemia
  - Only 1/129 (0.8%) patients with variant A developed severe anemia

Sakamoto N, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 469.
ITPA Gene Variant Protects Against Anemia and Improves Viral Clearance by PegIFN/RBV

• In patients who were treated with 24-week PegIFN/RBV regimen
  – Excluding HCV genotype 1b and high viral load

• Patients with ITPA minor variant A achieved higher SVR than those with major variant CC

Sakamoto N, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 469.
ITPA Gene Variant and Response to Therapy: Genotype 1b

- Retrospective analysis of chronic HCV genotype 1b treated with PegIFN/RBV in Japan (N=355)
- SNP of the ITPA gene (rs1127354) and IL28B gene (rs8099917) were genotyped
- Frequency of ITPA minor allele A was 0.16
- Incidence of anemia was less in the patients with AA/CA than CC genotype:

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Week 4</th>
<th>Through Week 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA/CA</td>
<td>0%</td>
<td>39%</td>
</tr>
<tr>
<td>CC</td>
<td>42%</td>
<td>75%</td>
</tr>
</tbody>
</table>

Kurosaki M, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011: Abst. 441.
AA/CA genotypes were associated with lower incidence of relapse and higher rate of SVR in a subset of Japanese patients with the favorable IL28B genotype

Kurosaki M, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011: Abst. 441.
Effect of Fluvastatin in HCV Treated with PegIFN/RBV

• Double-blinded, placebo-controlled, RCT at single center in Romania

• Chronic HCV patients randomized to fluvastatin 20 mg QD or placebo (total of 72 weeks) in additional to 48-week PegIFN/RBV (N=209)
**Potential Enhancement of Virological Response by Fluvastatin in HCV Treated with PEG-IFN/RBV**

**Viral responses in all patients**

<table>
<thead>
<tr>
<th></th>
<th>Fluvastatin</th>
<th>Placebo</th>
<th>( P ) value</th>
<th>( \Delta )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EVR (n=144)</strong></td>
<td>76.0%</td>
<td>61.9%</td>
<td>0.041</td>
<td>+15.1%</td>
</tr>
<tr>
<td><strong>SVR (n=118)</strong></td>
<td>63.5%</td>
<td>49.5%</td>
<td>0.05</td>
<td>+14.0%</td>
</tr>
</tbody>
</table>

**Viral responses in patient without metabolic syndrome (50/209)**

<table>
<thead>
<tr>
<th></th>
<th>Fluvastatin</th>
<th>Placebo</th>
<th>( P ) value</th>
<th>( \Delta )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EVR</strong></td>
<td>85.4%</td>
<td>71.4%</td>
<td>0.034</td>
<td>+14.0%</td>
</tr>
<tr>
<td><strong>SVR</strong></td>
<td>74.4%</td>
<td>58.4%</td>
<td>0.049</td>
<td>+16.0%</td>
</tr>
</tbody>
</table>

Georgescu EF, et al. 46th EASL; Berlin, Germany; March 30-April 3; Abst. 10.
SVR among HCV G1 Patients with Elevated LDL Treated with Intensified PEG-IFN Regimen

- Retrospective analysis from PROGRESS study
- Evaluated HCV genotype 1, VL $\geq 400,000$ IU/mL and BW $\geq 85$ kg (N=537)
- Randomized (1:1:2:2) to 48 wks of 180 µg PEG-IFN $\alpha$-2a plus RBV either at a dose of 1200 or 1400/1600 mg/day, or 12 wks of 360 µg PEG-IFN $\alpha$-2a followed by an additional 36 wks of 180 µg plus RBV either at a dose of 1200 or 1400/1600 mg/day
- LDL cut-point =100 mg/dL

Harrison SA, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 238.
Intensified dosing of PEG-IFNα-2a increases SVR rates among patients with elevated LDL

<table>
<thead>
<tr>
<th>Parameter</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;40 vs. &gt;40 years</td>
<td>2.30 (1.51-3.49)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HCV RNA &lt;800,000 vs. &gt;800,000 IU/mL</td>
<td>2.05 (1.22-3.44)</td>
<td>0.0063</td>
</tr>
<tr>
<td>Genotype 1b vs. 1a</td>
<td>1.99 (1.32-2.99)</td>
<td>0.0010</td>
</tr>
<tr>
<td>Steatosis score &lt;5% vs. &gt;5%</td>
<td>1.82 (1.18-2.81)</td>
<td>0.0070</td>
</tr>
<tr>
<td>RBV (pts with LDL &lt;100 mg/dL) 1600/1400 vs. 1200 mg</td>
<td>0.66 (0.39-1.13)</td>
<td>0.1273</td>
</tr>
<tr>
<td>RBV (pts with LDL &gt;100 mg/dL) 1600/1400 vs. 1200 mg</td>
<td>1.33 (0.79-2.23)</td>
<td>0.2816</td>
</tr>
<tr>
<td>PegIFN α-2a (pts with LDL &lt;100 mg/dL) 360/180 vs. 180 µg</td>
<td>0.70 (0.40-1.24)</td>
<td>0.2214</td>
</tr>
<tr>
<td>PegIFN α-2a (pts with LDL &gt;100 mg/dL) 360/180 vs. 180 µg</td>
<td>2.16 (1.25-3.73)</td>
<td>0.0060</td>
</tr>
</tbody>
</table>
SVR rates are higher among HCV G1 patients with elevated LDL levels when treated with intensified PEG-IFN regimen.

Harrison SA, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 431.
Infections during PEG-IFN/RBV Use Associated with Magnitude of Decline in Lymphocyte Count

• While on Rx, 36% had infections (of any grade) and 19% had moderate to life-threatening infections

Infections during PEG-IFN/RBV Use Associated with Magnitude of Decline in Lymphocyte Count

- Multivariate analysis: predictors for moderate to life threatening infections

<table>
<thead>
<tr>
<th>Factors</th>
<th>Odds ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PegIFN α-2b vs. α-2a</td>
<td>0.84</td>
<td>0.37</td>
</tr>
<tr>
<td>Gender (female vs. male)</td>
<td>1.61</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>METAVIR score (F0/1/2 vs. F3/4)</td>
<td>1.17</td>
<td>0.22</td>
</tr>
<tr>
<td>Baseline HCV-RNA</td>
<td>1.00</td>
<td>0.32</td>
</tr>
<tr>
<td>Age</td>
<td>0.99</td>
<td>0.10</td>
</tr>
<tr>
<td>Minimum on-Rx neutrophils</td>
<td>1.00</td>
<td>0.98</td>
</tr>
<tr>
<td>Minimum on-Rx lymphocytes</td>
<td>0.48</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Minimum on-Rx hemoglobin</td>
<td>0.96</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Infections during PEG-IFN/RBV Use Associated with Magnitude of Decline in Lymphocyte Count
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Advances in Chronic Hepatitis C Management and Treatment

Jointly sponsored by the Postgraduate Institute for Medicine and ViralEd, LLC.
Boceprevir Studies

Fred Poordad, MD
Chief, Hepatology
Cedars-Sinai Medical Center
Associate Professor of Medicine
David Geffen School of Medicine at UCLA
Los Angeles, California
Study to compare safety/efficacy of two treatment strategies with boceprevir added to peginterferon/ribavirin (PR) versus PR alone in treatment naïve HCV genotype 1 patients

Control
48 P/R
N = 363

PR lead-in

Week 4

PR + Placebo

Week 28

Follow-up

Week 48

Tw 8-24 HCV-RNA Undetectable

Week 72

Follow-up

BOC
RGT
N = 368

PR lead-in

PR + Boceprevir

PR + Placebo

Follow-up

BOC/PR48
N = 366

PR lead-in

PR + Boceprevir

Follow-up

SPRINT-2: Study Design

Poordad F, et al. 61st AASLD; Boston, MA; October 29 – November 2, 2010; Abst. LB-4.
RESPOND-2: Study Design

Study to assess safety/efficacy of BOC plus PegIFN (P) and RBV (R) in re-treatment of previous non-responders (NRs) and relapsers to P/R therapy

- **Control**
  - 48 P/R
  - N = 80
  - Week 4: PR lead-in
  - Week 28: PR + Placebo
  - Week 48: Follow-up
  - Week 72: Follow-up

- **BOC RGT**
  - N = 162
  - Week 4: PR lead-in
  - Week 12: Futility
  - Week 28: PR + Boceprevir
  - TW 8-24 HCV-RNA Undetectable
  - TW 8-24 HCV-RNA Detectable
  - Week 48: PR + Placebo
  - Follow-up
  - Week 72: Follow-up

- **BOC/PR48**
  - N = 161
  - Week 4: PR lead-in
  - Week 28: PR + Boceprevir
  - Follow-up
  - Week 72: Follow-up

Bacon B, et al. 61st AASLD; Boston, MA; October 29 – November 2, 2010; Abst. 216.
**SPRINT-2 and RESPOND-2: Evaluation of Predictive Value of PegIFN/RBV 4-week Lead-in Therapy**

### Relationships Between Week 4 Lead-in and SVR

<table>
<thead>
<tr>
<th></th>
<th>Poorly responsive to interferon</th>
<th>Responsive to interferon</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;1.0 log₁₀ viral load decline at treatment Week 4</td>
<td>≥1.0 log₁₀ viral load decline at treatment Week 4</td>
</tr>
<tr>
<td><strong>SPRINT-2</strong></td>
<td>3/83 (4%) 27/97 (29%) 36/95 (36%) 0/12 (0%) 15/46 (33%) 15/44 (34%)</td>
<td>133/260 (51%) 203/252 (81%) 200/254 (79%)</td>
</tr>
<tr>
<td><strong>RESPOND-2</strong></td>
<td>17/67 (25%) 80/110 (73%) 90/114 (79%)</td>
<td></td>
</tr>
</tbody>
</table>

Vierling JM, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011: Abst. 481.
**SPRINT-2: SVR Based on Early Interferon Response**

- In SPRINT-2, the degree of real-time interferon responsiveness at week 4 correlated with SVR.

Vierling JM, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011: Abst. 481.
RESPOND-2: SVR Based on Early Interferon Response

- For those in BOC/PR48 and BOC/RGT arms with a $<1.0 \log_{10}$ week 4 HCV-RNA decline, 33%-34% attained SVR compared with no patients attaining SVR in the P/R control arm.
- For the 6% of patients who attained undetectable HCV-RNA at week 4 in any of the treatment arms, >90% achieved SVR.

Vierling JM, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011: Abst. 481.
SPRINT-2 Sub-Group Analysis SVR for RGT, BOC/PR48 vs. Control

SPRINT-2: SVR in Early Responders (Undetectable HCV-RNA at Treatment Week 8), Overall Population

- SVR in the overall population of early responders was 88% and 90% in BOC RGT and BOC/PR48.
SPRINT-2: SVR in Early Responders (Undetectable HCV-RNA at Treatment Week 8), Overall Population and by Key Baseline Characteristics

- SVR in subgroups was similar in both the BOC RGT and BOC/PR48 arms with the exception of advanced fibrosis (F3/F4, <15 patients per group)

Manns MP, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011: Abst. 448.
Results

RESPOND-2: SVR in Early Responders (Undetectable HCV-RNA at Treatment Week 8) by Baseline Characteristics

- 46% of patients had undetectable HCV RNA at week 8 (early responders) and 86% achieved SVR with a total treatment duration of 36 weeks

Manns MP, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011: Abst. 448.
SPRINT-2
SVR and Relapse Rate by Fibrosis Score

SPRINT-2 and RESPOND-2: BOC + PegIFN/RBV in HCV GT 1 with Advanced Fibrosis/Cirrhosis

<table>
<thead>
<tr>
<th>Fibrosis Score</th>
<th>SVR (PR48)</th>
<th>Relapse F0/1/2 (BOC)</th>
<th>Relapse F3/4 (BOC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F0/1/2</td>
<td>38%</td>
<td>67%</td>
<td>67%</td>
</tr>
<tr>
<td>F3/4</td>
<td>38%</td>
<td>41%</td>
<td>52%</td>
</tr>
<tr>
<td></td>
<td>22%</td>
<td>9%</td>
<td>9%</td>
</tr>
</tbody>
</table>

N=328 N=319 N=24 N=34 N=42 N=158 N=233 N=231 N=12 N=17 N=25

Bruno S, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 7.
SPRINT-2: SVR in Early (Week 8 HCV-RNA-negative) and Late (Week 8 HCV-RNA-positive) Responders by Fibrosis Score

Bruno S, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 7.
RESPOND-2SVR: SVR in Early (Week 8 HCV-RNA-negative) and Late (Week 8 HCV-RNA-positive) Responders by Fibrosis Score

Bruno S, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 7.
SPRINT-2 and RESPOND-2: Adverse Events

Most Common Treatment-Related AEs (incidence ≥ 20% in any arm) and Other Events of Interest

<table>
<thead>
<tr>
<th>AE</th>
<th>P/R N=547</th>
<th>BOC/P R N=1548</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>57</td>
<td>57</td>
</tr>
<tr>
<td>Headache</td>
<td>43</td>
<td>44</td>
</tr>
<tr>
<td>Nausea</td>
<td>40</td>
<td>45</td>
</tr>
<tr>
<td>Insomnia</td>
<td>31</td>
<td>32</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>31</td>
<td>31</td>
</tr>
<tr>
<td>Anemia</td>
<td>29</td>
<td>49</td>
</tr>
<tr>
<td>Chills</td>
<td>29</td>
<td>33</td>
</tr>
<tr>
<td>Rash/skin eruption</td>
<td>27</td>
<td>30</td>
</tr>
<tr>
<td>Alopecia</td>
<td>25</td>
<td>26</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>25</td>
<td>22</td>
</tr>
<tr>
<td>Myalgia</td>
<td>24</td>
<td>23</td>
</tr>
<tr>
<td>Pruritus</td>
<td>23</td>
<td>21</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>23</td>
<td>25</td>
</tr>
<tr>
<td>Irritability</td>
<td>22</td>
<td>23</td>
</tr>
<tr>
<td>Depression</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18</td>
<td>23</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>18</td>
<td>23</td>
</tr>
<tr>
<td>Dysguesia</td>
<td>15</td>
<td>37</td>
</tr>
<tr>
<td>Other events of interest</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>Anorectal discomfort</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Hemorrhoids</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.60 to 5.09 x ULN (WHO grade 2)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>5.10 to 10.0 x ULN (WHO grade 3)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>&gt;10.0 x ULN (WHO grade 4)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Manns MP, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 449.
Anemia Associated with Increased SVR

Adverse Event of Anemia (Hb <10 g/dL) and Nadir Hemoglobin by Modified WHO Grade During the Treatment Phase

<table>
<thead>
<tr>
<th>Anemia</th>
<th>Previously Untreated (SPRINT-2)</th>
<th>Previous Treatment Failures (RESPOND-2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PR48 N=358</td>
<td>BOC/PR N=728</td>
</tr>
<tr>
<td>Anemia</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Hb &lt;10 g/dl</td>
<td>109 (30)</td>
<td>366 (50)</td>
</tr>
<tr>
<td>HB &lt;8.5</td>
<td>15 (4)</td>
<td>53 (7)</td>
</tr>
<tr>
<td>By WHO grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>WHO Grade</td>
<td>n (%)</td>
</tr>
<tr>
<td>&gt;11</td>
<td>0</td>
<td>161 (45)</td>
</tr>
<tr>
<td>9.5 to &lt;11.0</td>
<td>1</td>
<td>130 (36)</td>
</tr>
<tr>
<td>8.0 to &lt;9.5</td>
<td>2</td>
<td>61 (17)</td>
</tr>
<tr>
<td>6.5 to &lt;8.0</td>
<td>3</td>
<td>6 (2)</td>
</tr>
<tr>
<td>&lt;6.5</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

- Anemia (Hb <10 g/dL) occurred more often in the BOC (49-50%) arms than the control arms (25-30%)

Sulkowski M, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 476.
• In both studies, Hb levels returned to baseline post-therapy in the control (PR48) and experimental (BOC/PR) arms

• The pattern of mean Hb concentration over time was similar in the BOC/PR arms and the PR48 control arms

The x-axis numbers are not to scale.

Sulkowski M, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 476.
Results

Anemia on treatment was identified as a significant factor for attaining SVR ($P<0.001$)

Sulkowski M, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 476.
SVR rate in patients managed with R dose reductions alone were comparable to those in patients managed with EPO, with or without R dose reduction.

Sulkowski M, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 476.
Distribution of IL-28B Polymorphisms

SPRINT-2 and RESPOND-2: Assessment of Effect of IL28B Polymorphism on Virologic Response

- IL28B polymorphisms assessed with DNA Sanger Sequencing
  - rs12979860/rs12980275/rs8103143
- Patients analyzed were consented prospectively and received at least one dose of BOC or placebo (63%)

Poordad F, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 12.
Early Interferon Response (Lead-In) Further Defines Likelihood of Success for Non-CC Patients

SPRINT-2 and RESPOND-2 combined

Poordad F, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 12.
Assessment of Virologic Response in HCV GT 1 Previous Non-responders and Relapsers to BOC + PegIFN/RBV

<table>
<thead>
<tr>
<th>Arm 1</th>
<th>Arm 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo + PEG2a/R</td>
<td>BOC + PEG2a/R</td>
</tr>
<tr>
<td>Follow-up 24 wks</td>
<td>Follow-up 24 wks</td>
</tr>
</tbody>
</table>

**Weeks**

<table>
<thead>
<tr>
<th>8</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>72</th>
</tr>
</thead>
</table>

**Stopping Rule:**
Patients with detectable HCV-RNA at week 12 were discontinued from treatment for futility. Peginterferon alfa-2a (PEG2a) administered subcutaneously at 180 μg once weekly, plus ribavirin (R) using weight-based dosing of 1000-1200 mg/day in a divided daily dose. BOC administered 800 mg TID

Flamm S, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 1366.
Results

Sustained Virologic Response (SVR) and Relapse Rates for Randomized Patients Who Received at Least One Dose of Any Study Drug

• Significantly more patients achieved SVR in the BOC treatment arm than in the PEG2a/R arm

Flamm S, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 1366.
Results

Sustained Virologic Response (SVR) by Early Response to Treatment (ie, Undetectable HCV RNA By Treatment Week 8)

- Early response (undetectable HCV RNA at week 8) was associated with high SVR

Flamm S, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 1366.
A Continuing Medical Education Internet Symposium

The 46th Annual Meeting of the European Association for the Study of the Liver (EASL)

Advances in Chronic Hepatitis C Management and Treatment

Jointly sponsored by the Postgraduate Institute for Medicine and ViralEd, LLC.
Telaprevir Studies

Mark Sulkowski, MD
Associate Professor of Medicine and Medical Director,
Viral Hepatitis Center,
Johns Hopkins University School of Medicine
Baltimore, Maryland
**ADVANCE Study Design: Telaprevir + PegIFN/RBV in G1 Treatment-naïve Patients**

- **Treatment duration for telaprevir arms:**
  - Patients with eRVR (undetectable HCV-RNA at Week 4 and Week 12): receive 24 weeks of therapy
  - Patients without eRVR continue on PegIFN and RBV for a total of 48 weeks

G=genotype; CHC=chronic hepatitis C; TVR=telaprevir; eRVR=extended rapid virological response; f/u=follow-up

Higher RVR and SVR Rates with Telaprevir + PegIFN/RBV Versus PegIFN/RBV Alone

ADVANCE

RVR=rapid virological response

Patients eligible to receive 24 wks of total treatment

P<0.0001

SVR= sustained virological response

SVR Rates in All Treatment Groups

Δ 4.5%
(2-sided 95% CI = –2.1% to +11.1%)

Patients With SVR (%)

ADVANCE: Influence of Patient and Virus Factors on SVR with Telaprevir + PegIFN/RBV

Patients Achieving SVR (%)

- Genotype 1b: 79%
- Genotype 1a: 71%
- Race < 800,000: 78%
- Race ≥ 800,000: 74%
- Fibrosis F0-2: 78%
- Fibrosis F3-F4: 62%

Marcellin P, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011. Abst. 451;
ADVANCE/ILLUMINATE: Viral Response According to Race/ethnicity

Dusheiko GM, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 415.
ADVANCE: SVR According to IL28B Genotype – Telaprevir

Jacobson IM, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 1369.

SVR (%)

- CC: 90, T12PR: 87, T8PR: 64, PR: 25
- CT: 71, T12PR: 58, T8PR: 25, PR: 23
- TT: 73, T12PR: 59, T8PR: 23, PR: 23

Jacobson IM, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 1369.
Patients who achieved sustained viral response according to anemia and by Ribavirin dose reduction due to an AE.

Jacobson IM, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 1369.
REALIZE Study: TVR + PR in G1 Non-responders and Relapsers to PR – Phase III

Randomisation (2:2:1, stratified by viral load and type of prior response)
CHC = chronic hepatitis C; G1 = genotype 1; NR = Null responders (<2 log10 drop at week 12 of prior therapy); PR = partial responders (≥2 log10 drop at week 12 but never HCV RNA negative by week 24); REL = relapsers
* Peg-IFN alfa-2a 180 µg, RBV 1000/1200 mg/d

Zeuzem S, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 5.
REALIZE: SVR in Prior Relapsers, Prior Partial Responders and Prior Null Responders

<table>
<thead>
<tr>
<th></th>
<th>Prior Relapsers</th>
<th>Prior Partial Responders</th>
<th>Prior Null Responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>T12/PR48</td>
<td>83 *</td>
<td>59 *</td>
<td>29</td>
</tr>
<tr>
<td>LI T12/PR48</td>
<td>88 *</td>
<td>54 *</td>
<td>33</td>
</tr>
<tr>
<td>Pbo/PR48</td>
<td>24</td>
<td>15</td>
<td>5</td>
</tr>
</tbody>
</table>

n/N = 121/145 124/141 16/68 29/49 26/48 4/27 21/72 25/75 2/37

*P<0.001 vs. Pbo/PR48

Zeuzem S, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 5.
REALIZE: SVR by Baseline Fibrosis Stage and Prior Response

Zeuzem S, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 5.
REALIZE: SVR by Prior Response Category and Week 4 Response to PegIFN/RBV Lead-in

<1 log_{10} HCV RNA Reduction at Week 4

≥1 log_{10} HCV RNA Reduction at Week 4

Overall

Proportion of patients

SVR rate

Patients (%)

90 90
59 58
62 60
60 41
15 41
56 54
10 59
40 54
59 30
40 30
56 30
15 30

Prior relapers
Prior partial responders
Prior null responders

Zeuzem S, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 5.
SVR Rates by IL28B Genotype and Prior Response

Zeuzem S, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 5.
Loss of Resistance by NS3 Position

Analysis includes only patients with follow-up data and resistant variant(s) (probability starts at 100%)

Hash marks indicate censored observations

Zeuzem S, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 5.
Absolute Unbound Concentration of R-methadone Was Not Affected by TVR Co-administration

Methadone alone

R-methadone Concentration

Bound

Unbound

Methadone + TVR

No change in concentration
(but free fraction =26%)

Unbound (= effective) concentration is not affected

Zeuzem S, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 5.
Novel Therapies and Strategies

Nezam H. Afdhal, MD
Associate Professor of Medicine,
Harvard School of Medicine
Chief of Hepatology, Director of Liver Center,
Beth Israel Deaconess Medical Center
Boston, Massachusetts
PROTON: PSI-7977 + PegIFN/RBV (Phase IIb)

HCV GT1

Week 0  12  24  48  72

N=50
PSI-7977 200 mg QD Peg-IFN + RBV  Peg-IFN + RBV  Non-RVR Peg-IFN + RBV  SVR

N=50
PSI-7977 400 mg QD Peg-IFN + RBV  Peg-IFN + RBV  Non-RVR Peg-IFN + RBV  SVR

N=25
Peg-IFN + RBV

SVR Follow-Up

HCV GT2/GT3

Week 0  12

N=25
PSI-7977 400 mg QD Peg-IFN + RBV  SVR12  SVR24

2. Lalezari J, et al. ibid; Abst. 61.
### PROTON: HCV GT 2/GT 3 Results

<table>
<thead>
<tr>
<th></th>
<th>Week 2</th>
<th>Week 4 RVR</th>
<th>Week 12 cEVR/EOT</th>
<th>SVR12</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (evaluable)</td>
<td>24</td>
<td>24</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>HCV RNA &lt;LOD</td>
<td>21</td>
<td>24</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>% Response</td>
<td>88%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>% Response (ITT)</td>
<td>84%</td>
<td>96%</td>
<td>96%</td>
<td>96%</td>
</tr>
</tbody>
</table>

PROTON: HCV GT 1 Results


Proportion of Subjects with HCV RNA < LOD

- PSI-7977 400 mg + PEG/RBV
- PSI*7977 200 mg + PEG/RBV
- Placebo + PEG/RBV

Time (Weeks)

Nuclear: PSI-7977 and PSI-938

- 40 HCV GT 1, treatment-naïve subjects
  - 8 active and 2 placebo per cohort
- HCV RNA >50,000 IU/mL, no evidence of cirrhosis

<table>
<thead>
<tr>
<th>Cohort 1</th>
<th>Cohort 2</th>
<th>Cohort 3</th>
<th>Cohort 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 0</td>
<td>Day 7</td>
<td>Day 14</td>
<td></td>
</tr>
<tr>
<td>PSI-938 300 mg QD</td>
<td>PSI-938 300 mg QD</td>
<td>PSI-7977 400 mg QD</td>
<td>PSI-7977 + PSI-938</td>
</tr>
<tr>
<td>PSI-7977 + PSI-938</td>
<td>PSI-7977 + PSI-938</td>
<td>PSI-7977 + PSI-938</td>
<td>PSI-7977 + PSI-938</td>
</tr>
</tbody>
</table>

Lawitz E, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011. Abst. 1370.
### Median (Q1,Q3) HCV RNA Change from Baseline and Number of Subjects with HCV RNA <15 IU/mL (LOD) by Cohort

<table>
<thead>
<tr>
<th>Arm</th>
<th>Day 7</th>
<th>Day 14</th>
<th>Total &lt; 15 IU/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSI-938</td>
<td>-4.5 (-4.3,-4.7)</td>
<td>-5.2 (-4.8,-5.8)</td>
<td>4/8 (50%)</td>
</tr>
<tr>
<td>PSI-938/PSI-7977 + PSI-938</td>
<td>-4.6 (-4.2,-5.0)</td>
<td>-5.2 (-4.8,-5.5)</td>
<td>8/8 (100%)</td>
</tr>
<tr>
<td>PSI-7977/PSI-938 + PSI-7977</td>
<td>-4.7 (-4.3,-4.8)</td>
<td>-5.0 (-4.6,-5.4)</td>
<td>7/8 (88%)</td>
</tr>
<tr>
<td>PSI-7977 + PSI-938</td>
<td>-4.4 (-4.2,-4.8)</td>
<td>-5.0 (-4.7,-5.3)</td>
<td>7/8 (88%)</td>
</tr>
</tbody>
</table>

Lawitz E, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011. Abst. 1370.
ZENITH: VX-222 + TVR ± PR or RBV

<table>
<thead>
<tr>
<th>ARM</th>
<th>VX-222 100 mg BID + TRV 1125 mg BID</th>
<th>VX-222 400 mg BID + TVR 1125 mg BID + PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>HCV RNA undetectable at Week 2 &amp; Week 8: Stop Treatment</td>
<td>HCV RNA undetectable at Week 2 &amp; Week 8: Stop Treatment</td>
</tr>
<tr>
<td>B</td>
<td>HCV RNA detectable at Week or Week 8: Receive PR to Week 36</td>
<td>HCV RNA detectable at Week or Week 8: Receive PR to Week 24</td>
</tr>
</tbody>
</table>

VX-222 100 mg BID + TRV 1125 mg BID
VX-222 400 mg BID + TVR 1125 mg BID
VX-222 100 mg BID + TRV 1125 mg BID + PR
VX-222 400 mg BID + TVR 1125 mg BID + PR

### ZENITH: Results

<table>
<thead>
<tr>
<th></th>
<th>n%</th>
<th>A (N=18)</th>
<th>B (N=29)</th>
<th>C (N=29)</th>
<th>D (N-30)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Week 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV RNA Undetectable†</td>
<td>4 (22)</td>
<td>7 (24)</td>
<td>11 (38)</td>
<td>17 (57)</td>
<td></td>
</tr>
<tr>
<td>RCV RNA &lt;LLOQ‡</td>
<td>12 (67)</td>
<td>19 (66)</td>
<td>27 (93)</td>
<td>26 (87)</td>
<td></td>
</tr>
<tr>
<td><strong>Week 4 (RVR)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV RNA Undetectable†</td>
<td>3 (17)</td>
<td>17 (59)</td>
<td>25 (86)</td>
<td>26 (87)</td>
<td></td>
</tr>
<tr>
<td>RCV RNA &lt;LLOQ‡</td>
<td>4 (22)</td>
<td>25 (86)</td>
<td>28 (97)</td>
<td>29 (97)</td>
<td></td>
</tr>
<tr>
<td><strong>Weeks 2 and 8</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV RNA Undetectable†</td>
<td>0</td>
<td>4 (14)</td>
<td>11 (38)</td>
<td>15 (50)</td>
<td></td>
</tr>
<tr>
<td>RCV RNA &lt;LLOQ‡</td>
<td>0</td>
<td>11 (38)</td>
<td>25 (86)</td>
<td>24 (80)</td>
<td></td>
</tr>
<tr>
<td><strong>Week 12</strong> (cEVR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV RNA Undetectable†</td>
<td>0</td>
<td>7 (24)</td>
<td>24 (83)</td>
<td>27 (90)</td>
<td></td>
</tr>
<tr>
<td>RCV RNA &lt;LLOQ‡</td>
<td>0</td>
<td>7 (24)</td>
<td>24 (83)</td>
<td>27 (90)</td>
<td></td>
</tr>
<tr>
<td><strong>Viral breakthrough</strong></td>
<td><strong>Total</strong></td>
<td>3 (17)</td>
<td>9 (31)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

† HCV RNA was evaluated using the TaqMan assay version 2.0 (LLOQ 25 IU/mL)
‡ HCV RNA <LLOQ: HCV RNA below limit of quantification (25 (IU/mL), detectable or undetectable

ASPIRE: TMC435 + PegIFN/RBV

Study of TMC435 in patients with HCV GT1 who have previously failed PegIFN/RBV

<table>
<thead>
<tr>
<th>Interim analysis</th>
<th>Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12</td>
</tr>
<tr>
<td>TCM 435 + PegIFN/RBV</td>
<td>PegIFN/RBV</td>
</tr>
<tr>
<td>TCM 435 + PegIFN/RBV</td>
<td>PegIFN/RBV</td>
</tr>
<tr>
<td>TMC435 + PegIFN/RBV</td>
<td>PegIFN/RBV</td>
</tr>
<tr>
<td>TMC435 + PegIFN/RBV</td>
<td>PegIFN/RBV</td>
</tr>
<tr>
<td>TMC435 + PegIFN/RBV</td>
<td>PegIFN/RBV</td>
</tr>
<tr>
<td>PegIFN/RBV + TMC-matched placebo</td>
<td>PegIFN/RBV</td>
</tr>
</tbody>
</table>


TMC435 100 mg QD
TMC435 150 mg QD
ASPIRE: Observed Virologic Responses at Week 24

Tegobuvir (GS-9190) + GS-9256 ± PegIFN/RBV or RBV


<table>
<thead>
<tr>
<th>Weeks</th>
<th>Assigned Study Treatment</th>
<th>SOC Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>GS-9256 + TGV (n=16)*</td>
<td>pegIFN+RBV</td>
</tr>
<tr>
<td>1</td>
<td>GS-9256 + TGV + RBV (n=15)*</td>
<td>pegIFN+RBV</td>
</tr>
<tr>
<td>2-3</td>
<td>GS-9256 + TGV + PegIFN/RBV (n=15)</td>
<td>pegIFN+RBV</td>
</tr>
<tr>
<td>4</td>
<td>pegIFN+RBV</td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>pegIFN+RBV</td>
<td></td>
</tr>
<tr>
<td>72</td>
<td>pegIFN+RBV</td>
<td></td>
</tr>
</tbody>
</table>

* Early initiation of PegIFN/RBV SOC if poor response/breakthrough

TGV + GS-9256 ± PegIFN/RBV or RBV: Results

**Median HCV RNA Change from Baseline**

- TGV + GS-9256 (n=15): -4.1
- TGV + GS-9256 + RBV (n=13): -5.1
- TGV + GS-9256 + PEG/RBV (n=14): -5.7

**HCV RNA <25 IU/mL**

- Week 4: (1/15)
- Week 12: (5/13)
- Week 24: (14/14)

**Virologic Response over Time**

- Week 4:
  - TGV + GS-9256: 100%
  - TGV + GS-9256 + RBV: 100%
  - TGV + GS-9256 + PEG/RBV: 100%
- Week 12 (SOC):
  - TGV + GS-9256: 100%
  - TGV + GS-9256 + RBV: 80%
  - TGV + GS-9256 + PEG/RBV: 100%
- Week 24 (SOC):
  - TGV + GS-9256: 100%
  - TGV + GS-9256 + RBV: 67%
  - TGV + GS-9256 + PEG/RBV: 92%

Tegobuvir (GS-9190) for HCV GT 1

24-48 weeks treatment with TGV + PegIFN/RBV vs. 48 weeks PegIFN/RBV alone for HCV GT 1

Antiviral Efficacy

% with HCV RNA <25 IU/mL

<table>
<thead>
<tr>
<th>Week</th>
<th>PegIFN/RBV (Wk 48)</th>
<th>PegIFN/RBV + TGV (Wk 48)</th>
<th>PegIFN/RBV + TGV RGT (Wk 24 &amp; 48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wk 4</td>
<td>20</td>
<td>53</td>
<td>58</td>
</tr>
<tr>
<td>Wk 12</td>
<td>58</td>
<td>76</td>
<td>81</td>
</tr>
<tr>
<td>Wk 24</td>
<td>72</td>
<td>75</td>
<td>69</td>
</tr>
<tr>
<td>Wk 48</td>
<td>66</td>
<td>65</td>
<td>61</td>
</tr>
<tr>
<td>SVR</td>
<td>56</td>
<td>56</td>
<td>56</td>
</tr>
</tbody>
</table>

Alisporovir (DEB025) + PegIFN/RBV in HCV GT 1, Treatment-naïve Patients

- Four arms (N=288)
  - DEB025 + PegIFN/RBV (48wks)
  - DEB025 + PegIFN/RBV (24wks)
  - DEB025 + PegIFN/RBV RGT by RVR (24 vs. 48 wks)
  - PegIFN/RBV

- Hyperbilirubinemia in 4.2% of DEB025 pts, reversible, no ALT elevations
- Jaundice in 10%
- Bilirubin elevation mixed attributed to transporter effect

SILENC-2: BI201335 with PegIFN/RBV in G1 Nonresponders

Nonresponders (N=290) with 2:1:1 randomization

*BI120335 240 mg qd/PR PR
*BI201335 240 mg qd/PR PR
*BI201335 240 mg bid qd/PR PR

**eRVR 24 vs 48 wks

240 mg LI 240 mg LI 240 mg BID/LI

SVR (%) 24 Weeks

Overall Nulls Partials
240 mg LI 240 mg 240 mg

Adverse Events higher in arm 3 and jaundice and rash most common

*3-day PR lead-in
**eRVR 24 vs 48 wks

Sulkowski M, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011. Abst. 66
Meracitabine (RG7128) RGT Combined with PEG IFN/RBV in HCV GT 1/4, Treatment-naive

- **Study arms (all MCB 1000 mg BID):**
  - RGT:
    - MCB/PR 24 wks if eRVR
    - MCB/PR 24 wks then PR 24 wks if no eRVR (n=81)
  - PegIFN/RBV 48 weeks (n=85)

- **No significant AE or resistance issues**

RVR, eRVR, TW24

<table>
<thead>
<tr>
<th></th>
<th>RVR</th>
<th>eRVR</th>
<th>TW24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm A</td>
<td>63</td>
<td>60</td>
<td>91</td>
</tr>
<tr>
<td>Arm B</td>
<td>14</td>
<td>13</td>
<td>62</td>
</tr>
</tbody>
</table>

**SVR12 in Arm A patients with eRVR**

<table>
<thead>
<tr>
<th>SVR</th>
<th>Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>76% (37/49)</td>
<td>24% (12/49)</td>
</tr>
</tbody>
</table>

BMS-790052 (NS5A inhibitor) + BMS-650032 (PI) ± PR in null responders: phase IIa study

Randomisation
Null response defined as <2 log10 decline in HCV RNA following 12 weeks of treatment with PR

# BMS-790052 + BMS-650032 ± PR in null responders: results

<table>
<thead>
<tr>
<th>n (%)</th>
<th>Dual therapy (N=11)</th>
<th>Quadruple therapy (N=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV RNA &lt;10 IU/mL at week 4</td>
<td>7 (63.6%)</td>
<td>6 (60%)</td>
</tr>
<tr>
<td>SVR24</td>
<td>4 (36.4%)</td>
<td>10 (100%)</td>
</tr>
<tr>
<td>Viral breakthrough</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Relapse</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

- 19/21 had *IL28B* genotypes CT or TT
- Safety:
  - Diarrhoea was the most common AE (71.4%) (mainly mild-moderate)
  - 6 patients experienced ALT >3x ULN, all had total bilirubin <2x ULN
  - 6 patients (all receiving PR) experienced Grade 3/4 neutropenia
  - No SAEs/discontinuations due to AEs
  - All genotype 1B patients had SVR

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