Expert Perspectives:
Best of HCV from EASL 2015

David Bernstein, MD
Mitchell Shiffman, MD

Endorsed by:

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Grazoprevir (GZR; MK-5172) + Elbasvir (EBR; MK-8742)

Future Treatment Option
New Fixed Dose Combination: GZR/EBR

- HCV NS3/4A inhibitor
  - 100 mg once daily, oral

- HCV NS5A inhibitor
  - 50 mg once daily, oral

Grazoprevir
(MK-5172)

Elbasvir
(MK-8742)

- Broad *in vitro* activity against most HCV genotypes
- Retains *in vitro* activity against many clinically relevant RAVs

Abstract G07

The Phase 3 C-EDGE Treatment-Naïve Study of a 12-Week Oral Regimen of Grazoprevir (GZR; MK-5172)/Elbasvir (EBR; MK-8742) in Patients With Chronic HCV GT 1, 4 or 6 Infection

S. Zeuzem et al
SVR 12: Full Analysis Set

Zeuzem et al., Abstract #G07, EASL 2015
Abstract O001

C-SALVAGE: Grazoprevir (GZR; MK-5172), Elbasvir (EBR; MK-8742) and Ribavirin (RBV) for Chronic HCV-Genotype 1 Infection After Failure of Direct Acting Antiviral (DAA) Therapy

X. Forns et al
GZR + EBR + RBV x 12 Weeks: SVR12 By Subgroup

<table>
<thead>
<tr>
<th>All Subjects</th>
<th>N = 79</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>SVR12</td>
<td>76</td>
<td>(96.2%)</td>
</tr>
<tr>
<td>Relapse</td>
<td>3</td>
<td>(3.8%)</td>
</tr>
<tr>
<td><strong>By Prior PI Therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boceprevir</td>
<td>27/28</td>
<td>(96%)</td>
</tr>
<tr>
<td>Telaprevir</td>
<td>41/43</td>
<td>(95%)</td>
</tr>
<tr>
<td>Simeprevir</td>
<td>8/8</td>
<td>(100%)</td>
</tr>
<tr>
<td><strong>By Prior Failure Category</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On treatment failure</td>
<td>38/40</td>
<td>(95%)</td>
</tr>
<tr>
<td>Relapse</td>
<td>25/26</td>
<td>(96%)</td>
</tr>
<tr>
<td>Intolerance</td>
<td>13/13</td>
<td>(100%)</td>
</tr>
<tr>
<td><strong>By Time Since Therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1.1 year</td>
<td>22/24</td>
<td>(92%)</td>
</tr>
<tr>
<td>≥1.1 year</td>
<td>46/46</td>
<td>(100%)</td>
</tr>
<tr>
<td><strong>By Presence of NS3 RAVs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>43/43</td>
<td>(100%)</td>
</tr>
<tr>
<td>Present</td>
<td>31/34</td>
<td>(91%)</td>
</tr>
<tr>
<td><strong>By Genotype</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G1a</td>
<td>28/30</td>
<td>(93%)</td>
</tr>
<tr>
<td>G1b</td>
<td>48/49</td>
<td>(98%)</td>
</tr>
<tr>
<td><strong>By Cirrhosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>32/34</td>
<td>(94%)</td>
</tr>
<tr>
<td>No</td>
<td>44/45</td>
<td>(98%)</td>
</tr>
<tr>
<td><strong>By Viral Load</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤800,000 IU/mL</td>
<td>27/29</td>
<td>(93%)</td>
</tr>
<tr>
<td>&gt;800,000 IU/mL</td>
<td>49/50</td>
<td>(98%)</td>
</tr>
</tbody>
</table>

- Highly efficacious in patients who failed first generation protease inhibitor/PEG/RBV treatment

Forns et al., Abstract #O001, EASL 2015
Advanced Chronic Kidney Disease
Review of New Data
Abstract L-01

Safety of Ombitasvir/Paritaprevir/Ritonavir Plus Dasabuvir for Treating HCV GT 1 Infection in Patients With Severe Renal Impairment or End-Stage Renal Disease: The RUBY-1 Study

P. Pockros et al
Background/Objectives

• 12 weeks of OBV/PTV/r + DSV
  – GT 1 treatment-naïve
    • Included RBV for GT 1a
    • No RBV for GT 1b
  – CKD stage 4/5, including 60% on hemodialysis
  – Excluded cirrhotics

Pockros, et al. Abstract #LP-01, EASL 2015
Summary

- Regimen has been well tolerated, including those on hemodialysis, with or without RBV
- Hemoglobin reductions were managed with monitoring and RBV dose interruption (8/13) and erythropoietin use (4/13)
- No virologic failures to date and all 10 subjects who reached PTW4

Pockros, et al. Abstract #LP-01, EASL 2015
Abstract LP-02

C-SURFER: Grazoprevir Plus Elbasvir in Treatment-naïve and Treatment-experienced Patients With HCV GT 1 Infection and Chronic Kidney Disease

D. Roth et al
Background/Objectives

- <1% of GZR and EBR is renally excreted
- This study evaluated GZR+EBR in HCV-infected patients with CrCl<30 mL/min, including patients on hemodialysis
  - GT 1 treatment-naïve or treatment-experienced
  - CKD stage 4/5
  - Included compensated cirrhotics

Roth, et al. Abstract #LP-02, EASL 2015
SVR12: GZR/EBR for 12 Weeks in GT1 Patients With Chronic Kidney Disease

• GZR/EBR was generally safe and well tolerated.

Noncirrhotic, interferon-intolerant patient with HCV GT1b infection relapsed at FW12.

Lost to follow-up (n = 2), n = 1 each for death, noncompliance, withdrawal by subject, and withdrawal by physician (owing to violent behavior).

aNoncirrhotic, interferon-intolerant patient with HCV GT1b infection relapsed at FW12.
bLost to follow-up (n = 2), n = 1 each for death, noncompliance, withdrawal by subject, and withdrawal by physician (owing to violent behavior).
How Do We Currently Manage HCV-infected Patients With CKD Stage 4/5?

Are We Concerned With Using RBV For GT 1a Patients?
GT 3 Update
Abstract L-05

Sofosbuvir Plus Peg-IFN/RBV for 12 Weeks vs Sofosbuvir/RBV for 16 or 24 Weeks in Genotype 3 HCV-Infected Patients and Treatment-experienced Cirrhotic Patients With Genotype 2 HCV: The BOSON Study

G. Foster et al
Study Design

- Multicenter study, open-label, randomized (1:1:1) study at 80 sites in UK, Australia, USA, Canada, and New Zealand
- GT 2 patients: treatment experienced (TE) with cirrhosis
- GT 3 patients: TE or treatment naïve (TN), with or without cirrhosis
- Stratification
  - Cirrhosis
  - HCV Genotype
  - Prior HCV treatment
- Platelets ≥60,000 cells/mm³

Foster et al., Abstract #L-05, EASL 2015
Overall SVR12 (GT 2 and GT 3 Combined)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SVR12 (%)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOF + RBV 16 Weeks</td>
<td>141/196</td>
<td>p=0.0013</td>
</tr>
<tr>
<td>SOF + RBV 24 Weeks</td>
<td>170/199</td>
<td>p=0.023</td>
</tr>
<tr>
<td>SOF + PEG/RBV 12 Weeks</td>
<td>183/197</td>
<td></td>
</tr>
</tbody>
</table>

Error bars represent 95% confidence intervals.

Foster et al., Abstract #L-05, EASL 2015
SVR12: GT 2 vs GT 3

Error bars represent 95% confidence intervals.

Foster et al., Abstract #L-05, EASL 2015
SVR12 in GT 3 by Treatment History and Cirrhosis Status

<table>
<thead>
<tr>
<th></th>
<th>Treatment History</th>
<th>Cirrhosis Status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment Naïve</td>
<td>Treatment Expei</td>
</tr>
<tr>
<td>SOF + RBV 16 weeks</td>
<td>83</td>
<td>12</td>
</tr>
<tr>
<td>SOF + RBV 24 weeks</td>
<td>90</td>
<td>18</td>
</tr>
<tr>
<td>SOF + PEG/RBV 12 weeks</td>
<td>96</td>
<td>21</td>
</tr>
</tbody>
</table>

Foster et al., Abstract #L-05, EASL 2015

International Coalition of Hepatology Education Providers
Abstract LP-05

Daclatasvir Plus Sofosbuvir With or Without Ribavirin in Patients With HCV Genotype 3 Infection: Interim Analysis of a French Multicenter Compassionate Use Program

C. Hezode et al
SVR4: DCV/SOF + RBV in GT 3 Patients (12 vs 24 Weeks)

EASL Recommendation: GT 3 cirrhotics should receive SOF/DCV + RBV for 24 weeks

Hezode et al., Abstract #LP-05, EASL 2015
Is SOF + PEG/RBV for 12 Weeks Standard of Care for GT 3?
Can We Shorten Treatment Duration of SMV/SOF?
SVR12: SMV/SOF in GT 1 Non-cirrhotics (8 vs 12 Weeks)

Kwo et al., Abstract #LP-14, EASL 2015
Can We Shorten Treatment Durations to <12 Weeks By Combining Potent DAAs from Different Classes?
Abstract O006

C-SWIFT: Grazoprevir/Elbasvir + Sofosbuvir in Cirrhotic and Noncirrhotic Treatment-naive Patients With Hepatitis C Virus GT 1 Infection, for Durations of 4, 6 or 8 Weeks and GT 3 Infection for Durations of 8 or 12 Weeks

F. Poordad et al
SVR12 in GT 1 Treatment-naïve Patients

<table>
<thead>
<tr>
<th></th>
<th>4 weeks</th>
<th>6 weeks</th>
<th>6 weeks</th>
<th>8 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breakthrough</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Relapse</td>
<td>20</td>
<td>4</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Excluded*</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>3†</td>
</tr>
</tbody>
</table>

*Excluded patients who discontinued due to reasons other than virologic failure
† One of the 3 patients who discontinued had HCV G2 at discontinuation

Poordad et al., Abstract #0006, EASL 2015
SVR12 in GT 3 Treatment-naïve Patients

HCV RNA <15 IU/mL (%, 95% CI)

- Non-cirrhotic
  - 8 weeks: 93% (14/15)
  - 12 weeks: 100% (14/14)
  - 12 weeks: 91% (10/11)

- Cirrhotic
  - 8 weeks: 100% (14/14)

mITT analysis excluded patients who discontinued early due to reasons other than virologic failure

Poordad et al., Abstract O006, EASL 2015
Advanced Cirrhosis/Post-OLT
Regimens With New Data

• SOLAR 2: SOF/LDV/RBV (G02; Manns, et al)
  - 12 vs 24 week treatment
  - GT 1 CPT B&C
  - SVR12: 88% (57/65) (12 wk arm) vs 89% (54/61) (24 wk arm)

• UK EAP: SOF + LDV or DCV + RBV (O002; Foster, et al)
  - 12 week treatment
  - GT 1 and GT 3 CP-B and C patients (Mean MELD=11.9)
  - Virologically effective with >40% showing improvement in liver function
  - For patients <65 years if albumin is >35 g/L, improvement in liver function is more likely than harm
Regimens With New Data

• **ALLY 1: DCV/SOF/RBV** (L-08; Poordad, et al)
  - 12 week treatment
  - Any genotype enrolled but predominantly GT 1
  - Advanced cirrhosis (CPT A, B and C patients) and post-OLT
  - SVR12: CPT A=92% (11/12), CPT B=94% (30/32), CPT C=56% (9/16) and post-OLT=94% (50/53)

• **C-SALT: GZR/EBR** (O008; Jacobson, et al)
  - 12 week treatment
  - GT 1 CPT B patients (Mean MELD=9.9)
  - SVR12: 90% (27/30)
Advantages vs Disadvantages of Treating Advanced Cirrhosis vs Post-OLT
This activity is supported by educational grants from AbbVie, Bristol-Myers Squibb, Gilead Sciences, and Merck.