State of The Art Therapy for HCV

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Conflicts of Interest

• Speaker and consultancy fees received from
• AbbVie, BI, BMS, Gilead, Janssen, Roche, Merck, Novartis, Springbank, Achillion, Idenix
HCV – Effective Antivirals

• The drugs

• The patients
HCV – New Antivirals

• The drugs

• The patients
HCV Targets

Most DAAs currently in development target one of three viral proteins: NS3/4A, NS5A, and NS5B

- RAH = resistance-associated variants.
Genotype 1 without Interferon

• Two strategies emerging:-

• Sofosbuvir + anything

• Potent protease + 1 or 2 other drugs
Sofosbuvir based regimes

• You can add sofosbuvir to anything and HCV dies

• (Simeprevir, daclatasvir, Channel No 5)

(One of the above is wrong)
Real-world experience (TRIO Network): 8 or 12 week LDV/SOF in treatment-naive patients with non-cirrhotic, G1 HCV

**Patient disposition**
- TN, non-cirrhotic (n=895)
  - 8 wks LDV/SOF (n=263)
  - 12 wks LDV/SOF ± RBV (n=632)*

<table>
<thead>
<tr>
<th>Duration</th>
<th>SVR achieved (n)</th>
<th>SVR not achieved (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 wks</td>
<td>251</td>
<td>3</td>
</tr>
<tr>
<td>12 wks</td>
<td>604</td>
<td>6</td>
</tr>
</tbody>
</table>

*21 Patients were on 12 weeks of LDV/SOF+RBV

**SVR12 by duration**
- 8 weeks: 95% (251/263) Relapse 9, Death 0, LTFU 6, DC 3
- 12 weeks: 96% (604/632) Relapse 6, Death 2, LTFU 16, DC 4

**SVR12 by fibrosis**

<table>
<thead>
<tr>
<th>Fibrosis</th>
<th>F0</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 wks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**SVR12 rates by baseline viral load**

<table>
<thead>
<tr>
<th>Viral Load</th>
<th>&lt;6MM</th>
<th>6MM+</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 weeks</td>
<td>95%</td>
<td>95%</td>
</tr>
<tr>
<td>12 weeks</td>
<td>96%</td>
<td>95%</td>
</tr>
</tbody>
</table>

Curry M, et al. AASLD 2015, San Francisco. #1046
Real-world experience from the TRIO Network: Failure with all-oral DAA regimens

SVR rates inside vs outside FDA guidelines

<table>
<thead>
<tr>
<th></th>
<th>LDV/SOF ± RBV</th>
<th>VKP ± RBV</th>
<th>SMV + SOF ± RBV</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outside guidelines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outside guidelines</td>
<td>85% (115/135)</td>
<td>83% (5/6)</td>
<td>63% (5/8)</td>
<td>84% (125/149)</td>
</tr>
<tr>
<td>Inside guidelines</td>
<td>95% (1391/1462)</td>
<td>93% (38/41)</td>
<td>82% (27/33)</td>
<td>95% (1456/1536)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>94% (1506/1597)</td>
<td>91% (43/47)</td>
<td>78% (32/41)</td>
<td>94% (1581/1685)</td>
</tr>
</tbody>
</table>

Patients outside of guidelines: G1a on VKP without RBV, tx failure cirrhotic patients on 12 weeks of VKP ± RBV, LDV/SOF without RBV, or SMV + SOF ± RBV

Afdhal N, et al. AASLD 2015, San Francisco. #LB-17

Predictors of response

<table>
<thead>
<tr>
<th>Variable</th>
<th>Full population distribution, % (n)</th>
<th>Treatment failure distribution, % (n)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets &lt;100k/mL</td>
<td>11% (170) 89% (1320)</td>
<td>40% (19) 60% (29)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Platelets 100l+/mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>31% (504) 69% (1138)</td>
<td>70% (35) 30% (15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No cirrhosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outside FDA guidelines</td>
<td>10% (149) 90% (1536)</td>
<td>33% (17) 37% (34)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inside FDA guidelines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>58% (975) 42% (710)</td>
<td>76% (39) 24% (12)</td>
<td>0.008</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

• Real life regimens for G1 when applied according to guidelines have achieved SVR rates comparable to clinical trials
Treatment outcomes with 8-, 12- and 24-week regimens of SOF/LDV: Analysis of a multicenter prospective, observational study

- TARGET Registry: Pts treated according to local standards of care at academic (n=44) and community medical centers (n=17) in North America and Europe: N=2321 started Tx, virologic outcome known for 1074

<table>
<thead>
<tr>
<th>Regimen</th>
<th>SVR12, n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOF/LDV 8 wks</td>
<td>150/154 (97)</td>
</tr>
<tr>
<td>SOF/LDV 12 wks</td>
<td>607/627 (97)</td>
</tr>
<tr>
<td>SOF/LDV 24 wks</td>
<td>153/161 (95)</td>
</tr>
<tr>
<td>SOF/LDV 12 wks + RBV</td>
<td>86/89 (97)</td>
</tr>
<tr>
<td>SOF/LDV 24 wks + RBV</td>
<td>12/13 (92)</td>
</tr>
</tbody>
</table>

- SOF/LDV-containing 8 and 12-wk treatment regimens are generally safe, well tolerated, and highly effective across a broad spectrum of patients and clinical practices
- 8-week regimen underutilized
- Overall SVR rates high, although PPI use associated with higher rate of VF

Terrault N, et al. AASLD 2015, San Francisco. #94
An Integrated Safety and Efficacy Analysis of >500 Patients with Compensated Cirrhosis Treated with LDV/SOF±RBV

- 513 patients with HCV GT 1, compensated cirrhosis
- Pooled data from Phase 2 and 3 LDV/SOF ± RBV studies
  - LONESTAR, ELECTRON, ELECTRON-2, Japan phase 3 study, ION-1, ION-2, SIRIUS
- Primary efficacy endpoint: SVR12

Bourliere, AASLD, 2014, Oral #82
# Results: SVR12 by Treatment Regimen

Among TE cirrhotic patients, 12 weeks of LDV/SOF + RBV resulted in similar SVR rates to 24 weeks of LDV/SOF alone.

<table>
<thead>
<tr>
<th>Overall SVR12</th>
<th>Treatment Naïve</th>
<th>Treatment Experienced</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>98%</td>
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<th>Duration</th>
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<tr>
<th>Regimen</th>
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<tbody>
<tr>
<td>LDV/SOF</td>
<td>96%</td>
<td>95%</td>
</tr>
<tr>
<td>LDV/SOF + RBV</td>
<td>99%</td>
<td>96%</td>
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<table>
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<th>Duration/± RBV</th>
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<tr>
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</tr>
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<td>98%</td>
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Bourliere, AASLD, 2014, Oral #82
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<tr>
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<td>97%</td>
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<td>99%</td>
<td>96%</td>
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### Duration

<table>
<thead>
<tr>
<th>Duration ± RBV</th>
<th>Treatment Naïve</th>
<th>Treatment Experienced</th>
</tr>
</thead>
<tbody>
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</tr>
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<td>100%</td>
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**Among TE cirrhotic patients, 12 weeks of LDV/SOF + RBV resulted in similar SVR rates to 24 weeks of LDV/SOF alone.**

Bourliere, AASLD, 2014, Oral #82
Sofosbuvir + Ledipasvir

- A single tablet
- Cures most G1 in 8 weeks – side effect free
- Cures cirrhosis in 12 weeks
  (needs ribavirin, some side effects)
Genotype 1 without Interferon

• Two strategies emerging:-
  
  • Sofosbuvir + anything
  
  • Potent protease + 1 or 2 other drugs
SAPPHIRE-I: GT1 treatment-naive patients — SVR12 rates by HCV GT1 subtype

### Treatment-naive

<table>
<thead>
<tr>
<th>Subtype</th>
<th>SVR12 (%)</th>
<th>n</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>96.2</td>
<td>455</td>
<td>473</td>
</tr>
<tr>
<td>GT1a</td>
<td>95.3</td>
<td>307</td>
<td>322</td>
</tr>
<tr>
<td>GT1b</td>
<td>98.0</td>
<td>148</td>
<td>151</td>
</tr>
</tbody>
</table>

Error bars: 95% CI.
PEARL-III: SVR rates with 3D ± RBV in GT1b treatment-naive patients

- ABT-450/r/ABT-267 + ABT-333 + RBV: 99.5% (95% CI)
- ABT-450/r/ABT-267 + ABT-333: 99.0% (95% CI)

Error bars: 95% CI.

TURQUOISE-II and -III: patients with compensated cirrhosis – study design and SVR12

100% of cirrhotic GT1b patients treated with OBV/PTV/r + DSV achieved SVR12

AbbVie Regimes

• For naïve 1a patients (+/- cirrhosis):
  12 weeks ‘3D’ with ribavirin

• For naïve 1b patients (- cirrhosis)
  12 weeks ‘3D’ without ribavirin
  (?? add ribavirin for cirrhosis)

• For experienced patients with cirrhosis extend for 24 weeks in 1a non-responders
Genotype 1 HCV

• Sorted!

• At present NHSE funds patients with cirrhosis

• NICE recommend that ALL patients get treated
  (Final confirmation of NICE due soon)
Emerging Issues - Resistance

• Current story is that Resistance Associated Variants (RAVs) have no impact on SVR

• Is this really true?
SOF/LDV and NS5A RAVs

Pooled analysis (phase 2/3 trials*) of 513 cirrhotic patients with GT1 treated with LDV/SOF ± RBV for 12 or 24 weeks. SOF has a high barrier to resistance.

BL NS5A RAVs were detected in 18% of genotypable isolates.

9% of GT1a-infected patients and 17% of GT1b-infected patients had NS5A RAVs that conferred a >100-fold shift in EC₅₀.

SVR12 rates were lower in patients with BL RAVs and GT1a infection. However, the high barrier to resistance provided by SOF improves SVR12 rates.

- LONESTAR, ELECTRON, ELECTRON-2, 337-0113, ION-1, ION-2, and SIRIUS trials.
- Presence of RAVs was evaluated by deep sequencing with assay cut-offs of 1%.

RAVS

- They matter (sometimes)
- Is it worth hunting them down?
- Strategy A –
  - Ignore them and worry about them in the failures
- Strategy B –
  - Spend a fortune finding them first time round
Genotype 2

- 80% of Genotype 2 patients respond to 24 weeks of Peg+Riba

- (Patients who respond rapidly may have duration reduced to 12 weeks)
# Genotype 2

**Sofosbuvir + Ribavirin for 12 weeks**

<table>
<thead>
<tr>
<th>NAIVE</th>
<th>EXPERIENCED</th>
</tr>
</thead>
<tbody>
<tr>
<td>G2</td>
<td>G2</td>
</tr>
<tr>
<td></td>
<td>12 WEEKS</td>
</tr>
<tr>
<td>Non Cirrhosis</td>
<td>Cirrhosis</td>
</tr>
<tr>
<td>92%</td>
<td>94%</td>
</tr>
</tbody>
</table>

Jacobson NEJM 2013
Genotype 2

- Interferon works (and is cheap)
- Interferon is going to stay as first line for easy patients
- ‘Hard to cure patients’ may get tablet only therapy
Genotype 3
PegIFN + Ribavirin

Data are from an audit of 639 patients treated with PegIFN/RBV; Shoeb D, et al. Eur J Gastroenterol Hepatol 2011;23:747–753
Genotype 3
PegIFN + Ribavirin

Data are from an audit of 639 patients treated with PegIFN/RBV; Shoeb D, et al. *Eur J Gastroenterol Hepatol* 2011;23:747–753

![Bar chart showing patients achieving SVR by subgroup](chart.png)
Sofosbuvir struggles with G3
Sofosbuvir for G3 24 weeks therapy

Overall

Naïve, Noncirrhotic

Naïve, Cirrhotic

Experienced, Noncirrhotic

Experienced, Cirrhotic

Overall

Noncirrhotic

Cirrhotic

Valence NEJM 2014
Sofosbuvir for G3

- 12 weeks sofosbuvir is £35K
- 24 weeks sofosbuvir is £70K

- 24 weeks sofosbuvir is NEVER going to get NHSE support
Treating Genotype 3 BOSON

- 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
# BOSON study - Demographics

<table>
<thead>
<tr>
<th></th>
<th>SOF + RBV 16 weeks n=196</th>
<th>SOF + RBV 24 weeks n=199</th>
<th>SOF + PEG/RBV 12 weeks n=197</th>
<th>Total N=592</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean age, y (range)</strong></td>
<td>51 (20-69)</td>
<td>49 (23-71)</td>
<td>50 (19-73)</td>
<td>50 (19-73)</td>
</tr>
<tr>
<td><strong>Male, n (%)</strong></td>
<td>134 (68)</td>
<td>129 (65)</td>
<td>132 (67)</td>
<td>395 (67)</td>
</tr>
<tr>
<td><strong>Asian, n (%)</strong></td>
<td>28 (14)</td>
<td>26 (13)</td>
<td>25 (13)</td>
<td>79 (13)</td>
</tr>
<tr>
<td><strong>Mean BMI, kg/m² (range)</strong></td>
<td>28 (18-50)</td>
<td>28 (18-55)</td>
<td>28 (19-45)</td>
<td>28 (18-55)</td>
</tr>
<tr>
<td><strong>IL28B CC, n (%)</strong></td>
<td>75 (38)</td>
<td>73 (37)</td>
<td>78 (40)</td>
<td>226 (38)</td>
</tr>
<tr>
<td><strong>HCV genotype 3, n (%)</strong></td>
<td>181 (92)</td>
<td>182 (92)</td>
<td>181 (92)</td>
<td>544 (92)</td>
</tr>
<tr>
<td><strong>Mean baseline HCV RNA, log_{10} IU/mL (range)</strong></td>
<td>6.3 (4.0-7.6)</td>
<td>6.2 (3.3-7.6)</td>
<td>6.3 (3.7-7.5)</td>
<td>6.3 (3.3-7.6)</td>
</tr>
<tr>
<td><strong>Treatment experienced, n (%)</strong></td>
<td>105 (54)</td>
<td>105 (53)</td>
<td>103 (52)</td>
<td>313 (53)</td>
</tr>
<tr>
<td><strong>Cirrhosis, n (%)</strong></td>
<td>72 (37)</td>
<td>73 (37)</td>
<td>74 (38)</td>
<td>219 (37)</td>
</tr>
</tbody>
</table>
Results: SVR12 in GT 3

- **SOF + RBV 16 weeks**
- **SOF + RBV 24 weeks**
- **SOF + PEG/RBV 12 weeks**

<table>
<thead>
<tr>
<th>Treatment History</th>
<th>SVR12 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Cirrhosis</td>
<td>80/124</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>79/57</td>
</tr>
<tr>
<td>Naïve</td>
<td>77/70</td>
</tr>
<tr>
<td>Experienced</td>
<td>64/58</td>
</tr>
</tbody>
</table>

- No Cirrhosis
  - 99/124
  - 109/126
  - 117/123

- Cirrhosis
  - 29/57
  - 44/56
  - 51/58

- Naïve
  - 70/91
  - 83/94
  - 89/94

- Experienced
  - 58/90
  - 70/88
  - 79/87

• intervals.
SVR12 in GT 3 by Treatment History and Cirrhosis Status

Treatment Naïve

SOF + RBV 16 weeks

SOF + RBV 24 weeks

SOF + PEG/RBV 12 weeks

No Cirrhosis

Cirrhosis

Treatment Experienced

SVR12 (%)

0 20 40 60 80 100

58

65

68

12

18

21

41

54

44

49

17

26

30

70

72

71

21

22

23

54

52

36

34

35

83

90

96

57

82

91

76

82

94

47

77

86

35
Genotype 3

- The best way to cure ‘difficult’ Genotype 3 is with Interferon and sofosbuvir
G3 Without Interferon

<table>
<thead>
<tr>
<th></th>
<th>Treatment-naive</th>
<th>Treatment-experienced</th>
<th>Treatment-naive</th>
<th>Treatment-experienced</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SVR12, %(^a)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent Present</td>
<td>97</td>
<td>94</td>
<td>95</td>
<td>91</td>
</tr>
<tr>
<td>Present</td>
<td>58</td>
<td>69</td>
<td>73</td>
<td>63</td>
</tr>
<tr>
<td><strong>Cirrhosis(^b)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent Present</td>
<td>73/75</td>
<td>32/34</td>
<td>72/76</td>
<td>39/43</td>
</tr>
<tr>
<td>Present</td>
<td>11/19</td>
<td>9/13</td>
<td>16/22</td>
<td>5/8</td>
</tr>
<tr>
<td><strong>FibroTest(^c)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F0-F3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Absent Present</td>
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<td></td>
</tr>
<tr>
<td>Present</td>
<td></td>
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</tbody>
</table>

\(^a\) HCV RNA < LLOQ (25 IU/mL); error bars reflect 95% confidence intervals.

\(^b\) Cirrhosis determined by liver biopsy (METAVIR > F3), FibroScan (> 14.6 kPa), or FibroTest score ≥ 0.75 and aspartate aminotransferase to platelet ratio index > 2.

\(^c\) FibroTest assessments could have been performed up to Day 1 (baseline).
ALLY-3+ Phase 3 Study: All-oral treatment with DCV + SOF + RBV for 12 or 16 weeks in HCV G3-infected patients with advanced fibrosis or cirrhosis

Leroy V, et al. AASLD 2015, San Francisco. #LB-3

Demographics

<table>
<thead>
<tr>
<th></th>
<th>DCV + SOF + RBV 12 weeks, n=24</th>
<th>DCV + SOF + RBV 16 weeks, n=26</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range) yrs</td>
<td>53.0 (36–73)</td>
<td>56.0 (42–62)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>18 (75)</td>
<td>22 (85)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>23 (96)</td>
<td>26 (100)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (4)</td>
<td>0</td>
</tr>
<tr>
<td>IL28B non-CC, n (%)</td>
<td>13 (54)</td>
<td>15 (58)</td>
</tr>
<tr>
<td>HCV RNA, median (range) log&lt;sub&gt;10&lt;/sub&gt; IU/mL</td>
<td>6.70 (4.6–7.6)</td>
<td>6.91 (4.7–7.8)</td>
</tr>
<tr>
<td>HCV RNA category (IU/mL), n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 2 million</td>
<td>18 (75)</td>
<td>20 (77)</td>
</tr>
<tr>
<td>≥ 6 million</td>
<td>11 (46)</td>
<td>15 (58)</td>
</tr>
</tbody>
</table>

Demographics cont.

<table>
<thead>
<tr>
<th></th>
<th>DCV + SOF + RBV 12 weeks, n=24</th>
<th>DCV + SOF + RBV 16 weeks, n=26</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrosis stage, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Advanced fibrosis (F3)</td>
<td>6 (25)</td>
<td>8 (31)</td>
</tr>
<tr>
<td>Cirrhosis (F4)</td>
<td>18 (75)</td>
<td>18 (69)</td>
</tr>
<tr>
<td>Albumin, med (range) g/L</td>
<td>43.0 (33–47)</td>
<td>42.5 (34–48)</td>
</tr>
<tr>
<td>Platelets, median (range) × 10&lt;sup&gt;9&lt;/sup&gt; cells/L</td>
<td>161 (63–299)</td>
<td>155 (84–324)</td>
</tr>
<tr>
<td>Prior HCV Tx-experience, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naive</td>
<td>6 (25)</td>
<td>7 (27)</td>
</tr>
<tr>
<td>Experienced</td>
<td>18 (75)</td>
<td>19 (73)</td>
</tr>
<tr>
<td>IFN-based</td>
<td>15 (63)</td>
<td>16 (62)</td>
</tr>
<tr>
<td>SOF-based</td>
<td>3 (13)</td>
<td>3 (12)</td>
</tr>
</tbody>
</table>

1:1 randomization (N=50)

Stratified by fibrosis stage (F3 or F4)

24-week follow-up
ALLY-3+ Phase 3 Study: All-oral treatment with DCV + SOF + RBV for 12 or 16 weeks in HCV G3-infected patients with advanced fibrosis or cirrhosis

SVR12 by prior treatment

**Efficacious (90% SVR12) for G3 patients with advanced fibrosis or compensated cirrhosis, a population in urgent need of treatment**

- Comparable SVR12 for 12- (88%) and 16-weeks (92%)
- No on-treatment VFs; two relapses in each treatment arm

**100% SVR12 among patients with advanced fibrosis, 86% among patients with cirrhosis**

Leroy V, et al. AASLD 2015, San Francisco. #LB-3
Genotype 3

• For people without cirrhosis – most drugs work (Interferon is cheapest)

• For people with cirrhosis – interferon and sofosbuvir is best (and cheapest)

• For people who cannot take interferon sofosbuvir+ daclatasvir works well –

• ? 12 weeks ? Longer?
Phase 3 evaluation of SOF/VEL FDC for 12 weeks in naive and experienced G1, 2, 4, 5, 6 patients with and without cirrhosis:
ASTRAL-1 study

Virologic failure, n (%)

- On-treatment failure: 0
- Post-treatment relapse: 2 (<1)

Other reasons for classification as failure to achieve SVR 12, n (%)

- Lost to follow-up: 2 (<1)
- Withdrew consent: 1 (<1)
- Death: 1 (<1)

*HCV RNA <15 IU/mL

No pts in the PBO group had HCV RNA <15 IU/mL at any timepoint

Feld JJ, et al. AASLD 2015, San Francisco. #LB-2
Phase 3 evaluation of SOF/VEL FDC for 12 weeks in naive and experienced G1, 2, 4, 5, 6 patients with and without cirrhosis: ASTRAL-1 study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo for 12 wks (n = 116)</th>
<th>SOF-VEL for 12 wks (n = 624)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients discontinuing treatment due to AE</td>
<td>2 (2)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Patients with SAEs</td>
<td>0</td>
<td>15 (2)†</td>
</tr>
<tr>
<td>Patients with any AE</td>
<td>89 (77)</td>
<td>485 (78)</td>
</tr>
<tr>
<td>Common adverse events*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>33 (28)</td>
<td>182 (29)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>23 (20)</td>
<td>126 (20)</td>
</tr>
<tr>
<td>Hematologic events, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin concentration &lt;10 g/dL</td>
<td>0</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Lymphocyte count &lt;350 to &lt;500 per mm³</td>
<td>0</td>
<td>3 (&lt;1)</td>
</tr>
<tr>
<td>Neutrophil count 500 to &lt;750 per mm³</td>
<td>0</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Platelet count 25,000 to &lt;50,000/mm³</td>
<td>0</td>
<td>1 (&lt;1)</td>
</tr>
</tbody>
</table>

*Adverse events occurring in ≥20% of patients in any arm

- Treatment with the once daily, all-oral, single tablet regimen of SOF/VEL for 12 weeks is well tolerated and results in high SVR12 rates in tx-naive / -experienced G1, 2, 4, 5, and 6 patients with and without cirrhosis

Feld JJ, et al. AASLD 2015, San Francisco. #LB-2
ASTRAL-3 Phase 3 Study: SOF/VEL FDC for 12 weeks compared to SOF + RBV for 24 weeks in G3 HCV infected patients

Foster GR, et al. NEJM 2015

<table>
<thead>
<tr>
<th></th>
<th>SOF/VEL 12 weeks n=277</th>
<th>SOF + RBV 24 weeks n=275</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y (range)</td>
<td>49 (21‒76)</td>
<td>50 (19‒74)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>170 (61)</td>
<td>174 (63)</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>250 (90)</td>
<td>239 (87)</td>
</tr>
<tr>
<td>Mean BMI, kg/m² (range)</td>
<td>26 (17‒48)</td>
<td>27 (17‒56)</td>
</tr>
<tr>
<td>Cirrhosis, n (%)</td>
<td>80 (29)</td>
<td>83 (30)</td>
</tr>
<tr>
<td>Treatment experienced, n (%)</td>
<td>71 (26)</td>
<td>71 (26)</td>
</tr>
<tr>
<td>IL28B CC, n (%)</td>
<td>105 (38)</td>
<td>111 (40)</td>
</tr>
<tr>
<td>HCV RNA, log_{10} IU/mL (range)</td>
<td>6.2 (3.7‒7.5)</td>
<td>6.3 (3.6‒7.5)</td>
</tr>
</tbody>
</table>
ASTRAL-3 Phase 3 Study: SOF/VEL FDC for 12 weeks compared to SOF + RBV for 24 weeks in G3 HCV infected patients

SVR12 by cirrhosis and treatment history

- 95% SVR12 rate in G3 infection
  - Superior to SOF + RBV for 24 weeks
  - 91% SVR12 in cirrhosis
- Well tolerated and lacked toxicities associated with RBV
- Simple, safe, highly effective, RBV-free

Resistance analysis

- 97% SVR12
- 84% No BL NS5A RAVs
- 16% BL NS5A RAVs

Foster GR, et al. NEJM 2015
SOF/VEL FDC for treatment of HCV in patients with decompensated liver disease: The Phase 3 ASTRAL-4 study

Charlton MR, et al. AASLD 2015, San Francisco. #LB-13

- 267 treatment naive or experienced G1–6 with Child B cirrhosis
  - 65% treatment experienced
  - MELD <15 = 95%
  - Ascites 65–75%; encephalopathy 58–66%

<table>
<thead>
<tr>
<th></th>
<th>Wk 0</th>
<th>Wk 12</th>
<th>Wk 24</th>
<th>Wk 36</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOF/VEL</td>
<td>83/90</td>
<td>94/90</td>
<td>86/90</td>
<td></td>
</tr>
<tr>
<td>SOF/VEL + RBV</td>
<td>75/87</td>
<td>82/87</td>
<td>77/90</td>
<td></td>
</tr>
<tr>
<td>SOF/VEL</td>
<td>75/87</td>
<td>82/87</td>
<td>77/90</td>
<td></td>
</tr>
</tbody>
</table>

**SVR12 (%)**

- Overall: 83/90, 94/90, 86/90
- G1: 75/87, 82/87, 77/90
- G3: 7/14, 11/13, 6/12
- G2, 4, and 6: 100/100, 86/86

**Breakthrough, n**
- Overall: 1
- G1: -
- G3: 7
- G2, 4, and 6: -

**Relapse, n**
- Overall: 1
- G1: 1
- G3: 1
- G2, 4, and 6: -

**LTFU, n**
- Overall: 1
- G1: 2
- G3: 3
- G2, 4, and 6: -

**Death, n**
- Overall: 3
- G1: 2
- G3: 2
- G2, 4, and 6: 1

**Safety**
- d/c due to AE 3%; death 3% (9)
- AE more frequent with RBV
- Fatigue (29%); nausea (23%); HA (22%); anemia (13%; 31% in RBV arm)
- RBV dose: Hb <10 = 23%; Hb <8.5 = 7%
- RBV decreased in 37% and d/c in 17%
- Bili <3 x ULN

Charlton MR, et al. AASLD 2015, San Francisco. #LB-13
HCV – New Antivirals

• The drugs

• The patients
HCV – The Patients

• Four populations:-
  • Decompensated cirrhosis
  • Cirrhosis
  • Transmitters
  • Stable mild/moderate
English EAP Program
Inclusion Criteria

- Decompensated cirrhosis with ascites/variceal bleed/encephalopathy
- CTP score $\geq 7$
- Non-hepatic manifestation likely to lead to irreversible damage in 12 months and intolerant to or failed Peg/Riba
- Exceptional circumstances by panel review
SVR12 defined as HCV RNA at 12 weeks post-treatment < 30 IU/ml
Functional Outcome Change in MELD: Baseline – Follow up week 4

Comparative MELD scores available for 220 patients (3 patients who died are not plotted)
HCV – The Patients

• Even the sickest patients benefit

• Care needed to select the right patient
HCV – The Patients

• Even the sickest patients benefit

• Care needed to select the right patient

What to do

• DISCUSS – transplant centre/MDT

• These tricky patients need consensus and experience
HCV – The Patients

• Cirrhosis – excellent response with new drugs
Non-cirrhotics G2 and 3

• Offer Peg/Riba

• All oral drugs will not be affordable any time soon!
Non-cirrhotics G1

- ‘Harvoni’ and ‘Viekirax/Exviera’ are NICE approved
- You can not treat everyone immediately
- You need to set up local prioritisation
Who should be prioritized for HCV antiviral treatment?
A cost-effectiveness analysis including individual and population prevention benefits

- Dynamic HCV transmission and disease progression cost-effectiveness model to compare prioritization of HCV treatment using IFN-free DAAs
- Willingness to pay threshold (WTP) at £30,000 (~$50,000) per QALY gained

After treating cirrhotics in population with 20% or 40% chronic prevalence among people who inject drugs (PWID) it is more cost effective to prioritize treatment to PWID at earlier disease stages because of substantial prevention benefits

- Treating HCV in PWID is highly cost effective

Martin NK, et al. AASLD 2014, Boston. #1752
HCV – who needs therapy now?

• Logically we should treat transmitters next

BUT

• Transmitters have no political clout
• Transmitters are expensive to treat
HCV - The New Drugs

• Exciting times

• Most patients can now be cured, many will get all oral therapies

• We need to prioritise sensibly