HCV Resistance – Clinical Aspects

Sanjay Bhagani
Royal Free Hospital/UCL
London
DAAs in 2018, and beyond...

Protease-Inhibitors „...previrs“
- Paritaprevir/r
- Asunaprevir
- Grazoprevir
- Glecaprevir

Non-Nucs

Polymerase-Inhibitors „...buvirs“
- Voxilaprevir
- Grazoprevir
- Simeprevir
- Sofosbuvir
- Uprifosbuvir
- AL-335

NS5A-Inhibitors „...asvirs“
- Ombitasvir
- Daclatasvir
- Elbasvir
- Pibrentasvir
- Sofosbuvir
- Ledipasvir
- Velpatasvir
Changing characteristics of patients treated with DAA over time

Prospective, multicenter cohort of DAA-based therapy from 9 sites in Germany

Baseline characteristics of HCV patients started DAA therapy over time

There has been a shift to younger, treatment-naïve and patients with IVDU

Antiviral effectiveness has increased over time, but there has been an increase in LTFU

Christensen, EASL 2018, THU-358
Italian Real-World Data

Effectiveness of 12 weeks SOF/VEL without RBV in Patients with or without Cirrhosis

Real world study of 909 GT 1-4 patients treated with SOF/VEL for 12 weeks

**Baseline Demographics**

<table>
<thead>
<tr>
<th>N=909</th>
<th>Male, %</th>
<th>Mean age (18-90)</th>
<th>GT %</th>
<th>Fibrosis %</th>
<th>PWID, %</th>
<th>Prior PegIFN Tx, %</th>
<th>Diabetes, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, %</td>
<td>59</td>
<td></td>
<td>1</td>
<td>39</td>
<td>24</td>
<td>19</td>
<td>18</td>
</tr>
<tr>
<td>Mean age</td>
<td>63.4</td>
<td>(18-90)</td>
<td>2</td>
<td>41</td>
<td>31</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>GT %</td>
<td></td>
<td></td>
<td>3</td>
<td>17</td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td>4</td>
<td>3</td>
<td>22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrosis %</td>
<td></td>
<td></td>
<td>F0-F1</td>
<td>24</td>
<td>19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F0-F1</td>
<td></td>
<td></td>
<td>F2</td>
<td>31</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F2</td>
<td></td>
<td></td>
<td>F3</td>
<td>24</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F3</td>
<td></td>
<td></td>
<td>F4</td>
<td>22</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PWID, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior PegIFN Tx, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**SVR 12 Rates**

<table>
<thead>
<tr>
<th></th>
<th>Overall (ITT)</th>
<th>GT 1</th>
<th>GT 2</th>
<th>GT 3</th>
<th>GT 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVR 12, %</td>
<td>99</td>
<td>99</td>
<td>99</td>
<td>99</td>
<td>99</td>
</tr>
<tr>
<td>N=909</td>
<td>903</td>
<td>350</td>
<td>152</td>
<td>370</td>
<td>155</td>
</tr>
<tr>
<td>N=909</td>
<td>909</td>
<td>353</td>
<td>154</td>
<td>371</td>
<td>156</td>
</tr>
<tr>
<td>Advanced Fibrosis/Cirrhosis</td>
<td>99</td>
<td>99</td>
<td>99</td>
<td>99</td>
<td>100</td>
</tr>
<tr>
<td>N=909</td>
<td>152</td>
<td>154</td>
<td>156</td>
<td>157</td>
<td>86</td>
</tr>
<tr>
<td>N=909</td>
<td>155</td>
<td>156</td>
<td>87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=29</td>
<td>29</td>
<td>29</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=11</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

12 weeks SOF/VEL without RBV achieves high SVR rates regardless of fibrosis stage and genotype

Mangia, EASL 2018, THU-323
‘Real World’ co-infected patients – ANRS CO13 HepaVIH cohort

Piroth, J Hepatol. 2017
Patient 1 (MM)

- HIV+ MSM
- Well-controlled HIV-infection
  - On Truvada/Raltegravir
  - CD4 650, vl < 40 c/mL
- Acute G1a HCV diagnosed in November 2017
- Failure to clear virus spontaneously predicted by ‘week 4 rule’
- Keen on early treatment
- Enrols on RCT of 6 vs. 12 weeks of SOF/VEL
- Week 6 HCV RNA – undetectable
- ‘Relapse’ by week 4 end of treatment
- G1a, clonal sequencing E/NS3/4 regions - >90% homology to original virus
Patient 2 (MN)

- HIV+ MSM
- Well-controlled HIV/HBV co-infection
  - Truvada + Dolutegravir (previous raltegravir)
- Acquires HCV (G1a) in 2007 – relapse post 24 weeks of PegIFN and ribavirin for early HCV
- 2014 – C-P A cirrhosis, platelets 105, albumin 35, AFP 15
- NHS E treatment – 12 weeks of PRoD + R
- ‘Breakthrough’ at week 8
• Who is likely to fail?
• Who is likely to fail with RASs?
• What mutations are most likely and what is their significance?
• What options are available to treat patients with resistance?
Considerations for DAA Regimen Failure

- **Therapy**
  - DAA classes
  - RBV
  - Duration

- **Patient**
  - Cirrhosis
  - BMI
  - Renal disease

- **Resistance**

- **Others**
  - Adherence
  - Drug interactions
Impact of Multiple Negative Predictors on Response

- Retrospective analysis of phase II/III studies of SOF + RBV ± pegIFN in pts with GT1-3 HCV (N = 871)

**Negative Predictors:**
- Treatment experienced
- Cirrhosis
- HCV RNA
- Male
- ≥ 75 kg
- IL28B non-CC
- NS5A RASs?

**Number of Negative Predictors**

**HCV TARGET: Predictors of HCV DAA Failure**

- Prospective, observational cohort study of real-world clinical practice
  - N = 4099 pts with GT1 HCV treated with oral therapy including ≥ 2 DAAs
  - SVR: 93.7%; no SVR: 6.3%

- Factors independently associated with lack of SVR
  - Logistic linear regression: cirrhosis, time of treatment start
  - Multivariate logistic regression: cirrhosis, low albumin, low platelet count, high total bilirubin, male sex, older age

- Inverse probability weighting by propensity scores identified lower likelihood of SVR with SMV + SOF vs LDV/SOF or OBV/PTV/RTV + DSV (all ± RBV)
  - Limited data available on Q80K presence

- 19 of 22 pts retreated with LDV/SOF or OBV/PTV/RTV + DSV ± RBV achieved SVR

Do baseline RASs have an impact?

• Very much dependent on the ‘barrier to resistance’ of initial regimen
  – In association with viral load, genotype, length of therapy, patient characteristics

Exemplified by
• Grazoprevor/Elbasvir for G1a patients
• PrOD + R for compensated cirrhotic G1a patients
NS5A RAVS had no impact on SVR in patients with HCV GT1b infection

*any variant at positions 28, 30, 31, and 93
†Resistance analysis population which includes all patients with baseline sample sequence and an outcome of virologic failure or SVR
# Resistance Associated Variants: NS5A

(Resistance analysis population†)

<table>
<thead>
<tr>
<th>Genotype 1a RAVS</th>
<th>RAV Status in Patients with Baseline Sequence % (n/m)</th>
<th>SVR12 All Patients % (N/n)</th>
<th>SVR12 NS5A RAVs ≤5-fold potency loss</th>
<th>SVR12 NS5A RAVs &gt;5-fold potency loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline NS5A RAVS</td>
<td>12% (19/154)</td>
<td>58% (11/19)</td>
<td>90%</td>
<td>22%</td>
</tr>
<tr>
<td>No baseline NS5A RAVs</td>
<td>86% (112/130)</td>
<td>100% (112/112)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Genotype 1b RAVS</th>
<th>RAV Status in Patients with Baseline Sequence % (n/m)</th>
<th>SVR12 All Patients % (N/n)</th>
<th>SVR12 NS5A RAVs ≤5-fold potency loss</th>
<th>SVR12 NS5A RAVs &gt;5-fold potency loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline NS5A RAVS</td>
<td>14% (18/130)</td>
<td>94% (17/18)</td>
<td>100%</td>
<td>94%</td>
</tr>
<tr>
<td>No baseline NS5A RAVs</td>
<td>86% (112/130)</td>
<td>100% (112/112)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

All patients with virologic failure had baseline HCV RNA of > 800,000 IU/mL
TURQUOISE-II Results: ITT SVR12 Rates by HCV Subtype

<table>
<thead>
<tr>
<th>HCV Subtype</th>
<th>12-week arm</th>
<th>24-week arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT 1a</td>
<td>88.6%</td>
<td>94.2%</td>
</tr>
<tr>
<td>GT 1b</td>
<td>98.5%</td>
<td>100%</td>
</tr>
</tbody>
</table>

3D + RBV

124/140 114/121
67/68 51/51

Adapted from the Fred Poordad presentation at ILC/EASL on April 12, 2014
TURQUOISE-II Results: ITT SVR12 Rates by Surrogates of Portal Hypertension and Hepatic Function

![Graph showing SVR12 rates by surrogates of portal hypertension and hepatic function.](image_url)

Adapted from the Fred Poordad presentation at ILC/EASL on April 12, 2014
Different treatment recommendations for these relatively lower genetic-barrier regimens

- **G/E for G1a**
  - Baseline RAS testing if vl >800 000 IU/mL
  - If Ns5a RAS with >5 fold efficacy effect (substitutions at positions 28, 30, 31, 58 and 93) OR not available – G/E + R for 16 weeks

- **PrOD + R for G1a compensated cirrhotics**
  - 24 weeks if platelets <90, albumin <35 or AFP >20
Resistance Analysis from the ASTRAL Program

**ASTRAL 1–3 (SOF/VEL)**

**GT1–6**

<table>
<thead>
<tr>
<th>NS5A Class RAVs</th>
<th>15% Cut Off</th>
</tr>
</thead>
<tbody>
<tr>
<td>99%</td>
<td>701/709</td>
</tr>
<tr>
<td>69%</td>
<td>n=709</td>
</tr>
<tr>
<td>31%</td>
<td>n=314</td>
</tr>
<tr>
<td>98%</td>
<td>309/314</td>
</tr>
</tbody>
</table>

**VEL-Specific RAVs**

<table>
<thead>
<tr>
<th>15% Cut Off</th>
</tr>
</thead>
<tbody>
<tr>
<td>99%</td>
</tr>
<tr>
<td>92%</td>
</tr>
<tr>
<td>8%</td>
</tr>
<tr>
<td>95%</td>
</tr>
</tbody>
</table>

**ASTRAL 4 (SOF/VEL + RBV)**

**GT1–4**

<table>
<thead>
<tr>
<th>NS5A Class RAVs</th>
<th>15% Cut Off</th>
</tr>
</thead>
<tbody>
<tr>
<td>96%</td>
<td>65/68</td>
</tr>
<tr>
<td>80%</td>
<td>n=68</td>
</tr>
<tr>
<td>20%</td>
<td>n=17</td>
</tr>
<tr>
<td>100%</td>
<td>17/17</td>
</tr>
</tbody>
</table>

**VEL-Specific RAVs**

<table>
<thead>
<tr>
<th>15% Cut Off</th>
</tr>
</thead>
<tbody>
<tr>
<td>96%</td>
</tr>
<tr>
<td>94%</td>
</tr>
<tr>
<td>6%</td>
</tr>
<tr>
<td>100%</td>
</tr>
</tbody>
</table>

**Patients with baseline RAVs**

**Patients without baseline RAVs**

Hezode, EASL 2016, Poster THU-216
Prevalence of RAVs in DAA-Naïve Patients

European RAVs Database

**GT1a**

- **NS3**
  - Frequency of RAVs: 34% (pts. with RAVs)
  - EC50 fold change: 10
  - Variants: Q80K/R, R155K/T, G169A, D168N

**GT1b**

- **NS3**
  - Frequency of RAVs: 3% (pts. with RAVs)
  - EC50 fold change: (not specified)

- **NS5A**
  - Frequency of RAVs: 13% (pts. with RAVs)

- **NS5B**
  - Frequency of RAVs: 53% (pts. with RAVs)
  - EC50 fold change: (not specified)

Dietz, EASL 2016, Oral PS-007
## Resistance Characteristics of HCV Antiviral Classes

<table>
<thead>
<tr>
<th>Class</th>
<th>Antiviral Potency</th>
<th>GT Activity</th>
<th>Resistance Barrier</th>
<th>FDA Approvals</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS3 protease inhibitor</td>
<td>+++ to ++++</td>
<td>1, 4</td>
<td>Low to high</td>
<td>Simeprevir (2013)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(± 2, 3, 6)</td>
<td></td>
<td>Paritaprevir (2014)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Grazoprevir (2016)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Voxilaprevir (2017)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Glecaprevir (2017)</td>
</tr>
<tr>
<td>NS5B nucleotide</td>
<td>++++</td>
<td>1-6</td>
<td>Very high</td>
<td>Sofosbuvir (2013)</td>
</tr>
<tr>
<td>NS5B non-nucleoside</td>
<td>++</td>
<td>1</td>
<td>Low</td>
<td>Dasabuvir (2014)</td>
</tr>
<tr>
<td>NS5A inhibitor</td>
<td>++++</td>
<td>1, 4, 6</td>
<td>Low to high</td>
<td>Ledipasvir (2014)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(± 2, 3)</td>
<td></td>
<td>Daclatasvir (2015)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ombitasvir (2014)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Elbasvir (2016)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Velpatasvir (2016)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pibrentasvir (2017)</td>
</tr>
</tbody>
</table>
Key HCV Resistance Concepts

• HCV resistance-associated substitutions
  – Enriched in pts experiencing DAA treatment failure
  – Has an impact on treatment response in specific situations
• HCV resistance is NOT absolute
• Some pt characteristics are just as important as RASs
• Future regimens appear to obviate the need for most resistance testing at baseline
Durability of Treatment-Emergent NS5A RASs

EBR/GZR ± RBV

Detectable RASs (%)

Wks Post VF

# Broad Cross-Resistance With “Early-Generation” NS5A Inhibitors

<table>
<thead>
<tr>
<th>Fold Change</th>
<th>Genotype 1a</th>
<th>Genotype 1b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M28T</td>
<td>Q30R</td>
</tr>
<tr>
<td>Ledipasvir</td>
<td>20x</td>
<td>&gt; 100x</td>
</tr>
<tr>
<td>Ombitasvir</td>
<td>&gt; 1000x</td>
<td>&gt; 100x</td>
</tr>
<tr>
<td>Daclatasvir</td>
<td>&gt; 100x</td>
<td>&gt; 1000x</td>
</tr>
<tr>
<td>Elbasvir</td>
<td>20x</td>
<td>&gt; 100x</td>
</tr>
<tr>
<td>Velpatasvir</td>
<td>&lt; 10x</td>
<td>&lt; 3x</td>
</tr>
<tr>
<td>Pibrentasvir</td>
<td>&lt; 3x</td>
<td>&lt; 3x</td>
</tr>
<tr>
<td>Ruzasvir</td>
<td>&lt; 10x</td>
<td>&lt; 10x</td>
</tr>
</tbody>
</table>

*Slide credit: clinicaloptions.com*
NS5A Resistance Selection Rate Upon Virologic Failure

- Varies by regimen and duration
- PI based:
  - EBR/GZR: 94%[1]
  - OBV/PTV/RTV + DSV: 68%[2]
- Nucleotide based:
  - LDV/SOF: 75%[3]
  - SOF/VEL: 93% (14/15; majority GT3)[4]
  - SOF/VEL/VOX (≤ 6 wks): 0% (n = 15)[5]
  - SOF + EBR/GZR (≤ 8 wks): 37% (n = 30)[6]

### References

References in slidenotes.

### NS5A RAS Detection Among Pts With VF in LDV/SOF Phase II/III Trials[3]

<table>
<thead>
<tr>
<th>Treatment Duration (Wks)</th>
<th>Pts With NS5A RASs at VF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>37.5</td>
</tr>
<tr>
<td>8</td>
<td>66.7</td>
</tr>
<tr>
<td>12</td>
<td>94.7</td>
</tr>
<tr>
<td>24</td>
<td>100</td>
</tr>
<tr>
<td>n/N =</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>3/14</td>
</tr>
<tr>
<td>21</td>
<td>14/21</td>
</tr>
<tr>
<td>19</td>
<td>18/19</td>
</tr>
<tr>
<td>3</td>
<td>3/3</td>
</tr>
</tbody>
</table>
HCV Resistance – concepts (2)

- NS5a substitutions persist
- Cross-resistance amongst first/second generation NS5a inhibitors
- Short(er) duration of therapy less likely to result in selection of RASs in regimens with high(er) barrier – especially in the presence of SOF
So what about our two patients?

Where they destined to fail?
Are they likely to have RASs?
Patients MM and MN

**MM**
- G1a
- Early HCV – viral load 2 million IU/ml
- Short duration therapy with Sof + Vel

**MN**
- G1a
- Compensated cirrhosis
- Viral load 120 000 IU/ml
- Platelets 100, albumin 35, AFP <20
- 12 weeks PrOD + R
Patients MM and MN

**MM**
- G1a
- Early HCV – viral load 2 million IU/ml
- Short duration therapy with Sof + Vel
- Efficacy of short duration therapy with Sof + Vel in patients with a high viral load?

**MN**
- G1a
- Compensated cirrhosis
- Viral load 120 000 IU/ml
- Platelets 100, albumin 35, AFP <20
- 12 weeks PrOD + R
- No ‘bad prognostic’ features for 12 weeks therapy
- Adherence?
Resistance Testing MM and MN

**MM**
- G1a
- Early HCV
- Short duration Sof + Vel
- NO baseline or treatment emergent RASs

**MN**
- G1a
- Compensated cirrhosis
- 12 weeks PrOD + R
- NO baseline RASs
  - Treatment Emergent
    - NS3 – R155K, D168E
    - NS5a – M28V, Q30R
So how do we re-treat our two patients?
RESCUE/A5348: RBV and Longer Tx Duration for Overcoming Resistance, Optimizing Retreatment

Previous SOF Failure Without NS5A Exposure
37% (30/82) with previous SMV + SOF failure

- 37% (30/82) with previous SMV + SOF failure
- No impact of BL NS5A or NS5B RASs


- 6/10 VFs SOF + SMV failures; 7/10 cirrhotic
- No impact of BL NS5A or NS5B RASs
Roles of RBV and Longer Tx Duration in Overcoming Resistance, Optimizing Retreatment

- Single-arm trial
- HCV-infected pts without SVR in previous phase II trials of SOF/VEL (n = 41) or SOF/VEL + VOX (n = 28)
- Cirrhosis: 26%; previous relapse: 99%
- 20% GT2
- Only 18% of GT1 with NS5A RASs
- Previous treatment: 41% VEL 25 mg, 74% < 12 wks

MAGELLAN-1, Part 2 Study: Objective and Study Design

Objective

- Determine the efficacy and safety of G/P for 12 or 16 weeks in patients with chronic HCV GT1, 4, 5 or 6 infection and prior DAA failure, including those with compensated cirrhosis

Treatment Period

1:1 Randomized

12 weeks
N = 44

16 weeks
N = 47

G/P

0

Patients with cirrhosis: 50% enrollment maximum
NS5A-naïve patients: 40% enrollment maximum

Weeks

Poordad F, et al. 52nd EASL; Amsterdam, Netherlands; April 19-23, 2017. Abst. PS-156.
MAGELLAN-1, Part 2: Registrational Study
MAGELLAN-1, Part 2 Study: Results
SVR12 by DAA Class in Prior Therapy

Overall SVR12:
- 12-week: 89% (39/44)
- 1 OTVF; 4 relapse
- 16-week: 91% (43/47)
- 1 OTVF; 0 relapse

Prior Treatment History
- PI: TVR, SMV, BOC
- NS5A: LDV, DCV
- NS5A+PI: OBV and PTV, or other combinations
- OTVF, on-treatment virologic failure

Poordad F, et al. 52nd EASL; Amsterdam, Netherlands; April 19-23, 2017. Abst. PS-156.
Sofosbuvir-Velpatasvir-Voxilaprevir in NS5A-Experienced GT 1-6 POLARIS-1: Study Design

<table>
<thead>
<tr>
<th>Week</th>
<th>0</th>
<th>12</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=263</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=152</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GT 1-6 with NS5A inhibitor experience*  
\( n = 415 \)

- **Sofosbuvir-Velpatasvir-Voxilaprevir**
- **Placebo**

- **GT 1 patients** randomized 2:1 ratio (active:placebo). Stratified by presence of cirrhosis (target ≥30%).
- Genotypes 2-6 were assigned to active arm (and not randomized).
- Placebo recipients were eligible for deferred treatment with sofosbuvir-velpatasvir-voxilaprevir

**Drug Dosing**

Sofosbuvir-Velpatasvir-Voxilaprevir (400/100/100 mg): fixed dose combination; one pill once daily  
Placebo: one pill once daily

Sofosbuvir-Velpatasvir-Voxilaprevir in NS5A-Experienced GT 1-6

POLARIS-1: Prior NS5A Treatment

Sofosbuvir-Velpatasvir-Voxilaprevir in NS5A-Experienced GT 1-6

POLARIS-1: Results

POLARIS-1: SVR12 Results by Genotype

MAGELLAN-3: GLE/PIB + SOF + RBV for 12-16 Wks for Retreatment After Failure of GLE/PIB

- Ongoing, open-label phase IIIb study
  - Primary endpoint: SVR12

Noncirrhotic patients with GT1, 2, 4, 5, 6 HCV infection ± HIV coinfection with VF on/after GLE/PIB and no previous NS5AI or PI* (N = 2)

Cirrhotic and noncirrhotic patients with GT1-6 HCV infection ± HIV coinfection with VF on/after GLE/PIB ± previous NS5AI or PI**† (N = 21)

*All patients received GLE/PIB in previous clinical study and either completed treatment or discontinuation ≥ 1 mo before screening. †Includes patients with GT3 ± cirrhosis and ± previous NS5AI or PI, cirrhotic patients with any HCV GT ± previous NS5AI or PI, and patients with any HCV GT ± cirrhosis with previous NS5AI or PI. Dosing: GLE/PIB 300/120 mg QD + SOF 400 mg QD + RBV 1000-1200 mg BID.

MAGELLAN-3: Efficacy of GLE/PIB + SOF + RBV in Patients Who Experienced GLE/PIB Failure

- Baseline RAS:
  - NS5A RAS detected in 18 (78%) of 23 patients
    - 12-wk arm: 2/2
    - 16-wk arm: 16/21
  - NS3 + NS5A RAS detected in 5/23 patients, all in 16-wk arm
- VF occurred in 1 patient in 16-wk arm
  - GT1a HCV infection, cirrhosis, previous LDV/SOF, NS5A RAS (Q30K + Y93H), and no NS3 RAS at MAGELLAN-3 BL

HCV-retreatment post failure

- Treatment decisions ideally guided by RAS testing
- SOF/VEL/VOX 12 weeks OR G/P + SOF for 12 weeks are ideal retreatment options including compensated cirrhotics
- SOF/VEL + R for 24 weeks may be a re-treatment option in de-compensated cirrhotics
So what about MM and MN?

**MM**
- G1a
- Early HCV
- Short duration SOF/VEL
- NO baseline or treatment emergent RASs
- SOF/VEL 12 weeks

**MN**
- G1a
- Compensated cirrhosis
- 12 weeks PrOD + R
- NO baseline RASs
- Treatment Emergent
  - NS3 – R155K, D168E
  - NS5a – M28V, Q30R
- SOF/VEL/VOX 12 weeks
EASL Recommendations on Treatment of Hepatitis C 2018

European Association for the Study of the Liver

- Testing for HCV resistance prior to treatment is not recommended (B1).

- HCV resistance testing prior to retreatment in patients who failed after any of the DAA-containing treatment regimens is useful to guide retreatment by probabilities of response, according to the resistance profile observed in the context of a multidisciplinary team including experienced treaters and virologists (B2).
And they lived happily ever after...?

Questions?