Need to assess HCV resistance to DAAs: is it useful and when?

Philippe HALFON
MD, PhD

Associate Professor of Medicine

Internal Medicine and Infectious Diseases,
Hopital Europeen,
Marseille, France.
Progress in the Treatment of Hepatitis C

- IFN: 6% - 16%
- PEG-IFN: 18% - 23%
- IFN+RBV: 35% - 43%
- PEG-IFN+RBV: 47% - 63%
- DAAs: 90% - 100%

<table>
<thead>
<tr>
<th></th>
<th>HBV</th>
<th>HIV</th>
<th>HCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genome</td>
<td>DNA</td>
<td>RNA</td>
<td>RNA</td>
</tr>
<tr>
<td>Mutation rate</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Daily viral</td>
<td>$10^{13}$</td>
<td>$10^{10}$</td>
<td>$10^{12}$</td>
</tr>
<tr>
<td>production</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral Reservoir</td>
<td>cccDNA</td>
<td>Integrated cDNA</td>
<td>None</td>
</tr>
<tr>
<td>Therapeutic</td>
<td>Single</td>
<td>Multiple</td>
<td>Multiple</td>
</tr>
<tr>
<td>strategy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>recovery</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Mr. IFN
Drug targets in the HCV lifecycle

- RNA replication
- Nucleocapsid assembly
- Core of the virus released
- RNA uncoating
- Translation & polyprotein processing
- miR-122 inhibitor (LNA)
- Protease inhibitors
- NS5A inhibitors
- NS5B polymerase inhibitors
- RNA replication
- RNA synthesis
- Transport and release
- Liver cell

Early inhibitors
- Cyclophilin inhibitors
- CD81 Receptors
- Nucleocapsid assembly
- NS5A inhibitors

New Therapies & Targets
- Life Cycle Step
You are considering treatment options for a treatment non responder to PEG-IFN cirrhotic patient with genotype 1a HCV infection and an HCV RNA level of 7.4 x 10^6 IU/mL
If treating with DAA, which of the following would you recommend?

1. Sofosbuvir/ledipasvir for 12 wks + RBV
2. Sofosbuvir/ledipasvir for 24 wks
3. HCV baseline resistance NS5A+ NS5B analysis
4. Grazoprevir+Elbasvir for 16 wks
5. Grazoprevir+Elbasvir for 12 wks with NS5A analysis
6. Paritaprevir/ritonavir, ombitasvir +/- dasabuvir 12w
7. Sofosbuvir+Velpatasvir for 8 weeks
8. SOF + LDV + GS9451 ± GS9669 for 4 weeks
NS5A resistance associated substitutions observed with treatment

the most frequent substitutions for GT1a and GT1b respectively

substitution in non-SVR

<10%  $\geq$10%

**NS5A Class RAVs**: variants at any position associated with resistance to any NS5A inhibitor

<table>
<thead>
<tr>
<th>HCV Genotypes</th>
<th>NS5A Amino Acid Position</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>24</td>
</tr>
<tr>
<td>1a</td>
<td>K</td>
</tr>
<tr>
<td></td>
<td>→G/N/R</td>
</tr>
<tr>
<td>1b</td>
<td>Q</td>
</tr>
<tr>
<td></td>
<td>→G/N/R</td>
</tr>
<tr>
<td>2a</td>
<td>T</td>
</tr>
<tr>
<td></td>
<td>→T/A</td>
</tr>
<tr>
<td>3a</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td>→M/T</td>
</tr>
<tr>
<td>4a/d</td>
<td>K</td>
</tr>
<tr>
<td></td>
<td>→L/V</td>
</tr>
<tr>
<td>5a</td>
<td>Q</td>
</tr>
<tr>
<td>6a</td>
<td>Q</td>
</tr>
</tbody>
</table>

Five main major class NS5A RAVs
NS5A resistance < 10-fold
NS5A resistance 10 - <100-fold
NS5A resistance > 100-fold

*Resistance observed in combination with other RAVs*

_Halfon P et al_. Hepatology 2016
Baseline prevalence of RAVs NS5A (n = 5397 pts, cut-off 1%)

**Europe**
- 1a: 25% (130/517)
- 1b: 25% (105/416)

**Asia**
- 1a: 15% (4/27)
- 1b: 26% (150/570)

**Oceania**
- 1a: 27% (89/328)
- 1b: 26% (26/99)

**North America**
- 1a: 26% (686/2638)
- 1b: 23% (184/202)

**USA**
- Canada
- Porto Rico

**Belgique**
- Suisse
- République Tchèque
- Allemagne
- Espagne
- France
- Royaume Uni
- Italie
- Pays-Bas
- Pologne

**Chine**
- Inde
- Japon
- Corée
- Russie
- Taiwan

**Australie**
- Nouvelle Zélande

*G1a NS5A RAVs: K24G/N/R, K26E, M28A/G/T/V, Q30C/E/G/H/I/L/K/R/S/T/Y, L31I/F/M/V, P32L, S38F, H58D/L, A92K/T, Y93C/F/H/L/N/R/S/T/W*

Baseline and Post-baseline Resistance Analyses of Phase 2/3 Studies of Ledipasvir/Sofosbuvir ± RBV

<table>
<thead>
<tr>
<th>G 1a</th>
<th>SOF + LDV ± RBV 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>96,4 %</td>
<td>84,3 % Pas de RAVs NS5A à l’inclusion n = 1351</td>
</tr>
<tr>
<td>91,6 %</td>
<td>15,7 % RAVs NS5A n = 251</td>
</tr>
<tr>
<td>12</td>
<td>96,4 % SVR 12</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>G 1b</th>
<th>SOF + GS-5816 ± RBV ²</th>
</tr>
</thead>
<tbody>
<tr>
<td>98,4 %</td>
<td>83,6 % Pas de RAVs NS5A à l’inclusion n = 442</td>
</tr>
<tr>
<td>98,4 %</td>
<td>16,4 % RAVs NS5A n = 251</td>
</tr>
<tr>
<td>12</td>
<td>98,4 % SVR 12</td>
</tr>
</tbody>
</table>

Baseline RAVs NS5A before SOF/LDV is not predictive of failure 1

SVR12 Rates by Treatment Regimen (LDV/SOF) and Duration: TN Patients with Cirrhosis

Studies included for analysis:


**LDV/SOF+RBV 12 Wks**: GS-US-337-0102 (ION-1), GS-US-337-0113 (Japan 1), GS-US-337-0122 (ELECTRON-2);

**LDV/SOF 24 Wks**: GS-US-334-1274 (Bleeding Disorder)

Zeuzem et al., AASLD 2015

Sensitivity threshold at 1% (deep sequencing)
SVR12 Rates by Treatment Regimen and Duration: TE Patients with Cirrhosis

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>Duration</th>
<th>With NS5A RAVs</th>
<th>No NS5A RAVs</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDV/SOF+RBV</td>
<td>12 weeks</td>
<td>89/66</td>
<td>96/206</td>
</tr>
<tr>
<td></td>
<td>24 weeks</td>
<td>59/66</td>
<td>206/214</td>
</tr>
<tr>
<td>LDV/SOF</td>
<td>12 weeks</td>
<td>87/15</td>
<td>100/84</td>
</tr>
<tr>
<td></td>
<td>24 weeks</td>
<td>13/15</td>
<td>84/84</td>
</tr>
</tbody>
</table>

Studies included for analysis:

Sensitivity threshold at 1% (deep sequencing)
SYNERGY study: SOF + LDV + GS9451 ± GS9669 for 4 weeks

Baseline RAV is a strong negative factor of SVR in case of shorten therapy (4 weeks)

Virological response based on baseline RAV *

* SVR 12 (%)

RAV: high level (> 5x)

RAV: low level (< 5x)

p = 0.02

Baseline RAV is a strong negative factor of SVR in case of shorten therapy (4 weeks)
Grazoprevir+Elbasvir combination

Genotype 1a
(n = 154)

Proportion of patients with SVR (%)

Overall: 99%
NS5A RAV ≤ 5x fold loss of activities: 58%
NS5A RAV > 5x fold loss of activities: 22%

Génotype 1b
(n = 130)

Proportion de patients avec RVS (%)

Overall: 100%
NS5A RAV ≤ 5x loss of activities: 94%
NS5A RAV > 5x loss of activities: 94%

Grazoprevir+Elbasvir in G1a patients

Population Sequencing

EBR RAVs
- No RAVS: 414/438‡ (95%)
- 5%

NS5A Class RAVs
- No RAVS: 352/438‡ (80%)
- 20%

Next Generation Sequencing at 1% ST†

EBR RAVs
- No RAVS: 396/439‡ (90%)
- 10%

NS5A Class RAVs
- No RAVS: 289/439‡ (65%)
- 35%

Patients without RAVs
- Patients with RAVs

Grazoprevir + Elbasvir in G1a patients
12 weeks vs 16 weeks

SVR12 (% 95% CI)

<table>
<thead>
<tr>
<th></th>
<th>12 weeks</th>
<th>12 weeks</th>
<th>16 weeks</th>
<th>16 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>No RBV</td>
<td>97/105</td>
<td>98/104</td>
<td>97/105</td>
<td>104/106</td>
</tr>
<tr>
<td>+RBV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Do we Need to assess Baseline HCV resistance to DAAs:
is it useful and when?

1/ First and most important: Methodology for detection of RAVs must standardized (and automated)

2/ Usefulness of RAV testing will be patient population and treatment regimen dependent

- RAV testing most likely not required in patient populations with SVR rates > 99%

- RAV testing most likely be clinical useful and cost-effective in population with suboptimal SVR rates (definition < 95% / < 90% ?) & if population large enough
  - Regimens w/o a very high barrier to resistance drug
  - Treatment-experienced patients (in particular when exposed to DAAs)
  - Patients with cirrhosis
  - When the shortest possible treatment duration is economically important
If treating with DAA, which of the following would you recommend?

1. Sofosbuvir/ledipasvir for 12 wks + RBV
2. Sofosbuvir/ledipasvir for 24 wks
3. HCV baseline resistance NS5A+ NS5B analysis
4. Grazoprevir+Elbasvir for 16 wks
5. Grazoprevir+Elbasvir for 12 wks with NS5A analysis
6. Paritaprevir/ritonavir, ombitasvir +/- dasabuvir 12w
7. Sofosbuvir+Velpatasvir for 8 weeks
8. SOF + LDV + GS9451 ± GS9669 for 4 weeks
Outcomes Case 2

- You are considering treatment options for a treatment non responder to Ledipasvir/sofosbuvir cirrhotic patient with genotype 1a HCV infection and an HCV RNA level of 10 x 10^6 IU/mL
If retreating with DAA, which of the following would you recommend?

1. HCV baseline resistance NS5A+NS5B analysis
2. Sofosbuvir/ledipasvir for 24 wks+ RBV without HCV resistance analysis
3. Grazoprevir+Elbasvir +Sofosbuvir for 16 wks
4. ABT-493 +ABT-530 for 12 weeks
5. Sofosbuvir+Velpatasvir+Voxilaprevir for 12 weeks
6. Others
How to retreat the subgroup of experienced-patients with relapse or/and resistance to DAA?
Retreatment of patients with DAA treatment failures

- Patients who failed on a DAA-containing regimen should be retreated with an IFN-free regimen for 12 weeks with weight-based ribavirin if they have no, mild or moderate fibrosis (METAVIR score F0 to F2), for 24 weeks with ribavirin if they have extensive fibrosis (F3) or cirrhosis, unless otherwise specified below (B1).
- Patients who failed on sofosbuvir alone or sofosbuvir plus ribavirin or sofosbuvir plus pegylated IFN-a and ribavirin can be retreated with a combination of sofosbuvir and ledipasvir (genotypes 1, 4, 5 and 6), sofosbuvir with daclatasvir (all genotypes), sofosbuvir with velpatasvir, or sofosbuvir and daclatasvir (B1).

- Patients infected with HCV genotype 1 or 4 who failed on a regimen containing an NSSA inhibitor, such as ledipasvir, velpatasvir, ombitasvir, elbasvir or daclatasvir, should be retreated with a combination of sofosbuvir, ritonavir-boosted paritaprevir, ombitasvir and dasabuvir (genotype 1), with a combination of sofosbuvir, ritonavir-boosted paritaprevir and ombitasvir (genotype 4), with a combination of sofosbuvir, grazoprevir and elbasvir (genotypes 1 and 4) or with a combination of sofosbuvir, simeprevir and daclatasvir (genotypes 1 or 4), for 12 weeks (genotype 1b or 4 patients with METAVIR score F0 to F2) or 24 weeks (all patients with genotype 1a; genotype 1b and 4 patients with METAVIR score F3 or with compensated cirrhosis) with ribavirin. Treatment should be administered with caution in patients with extensive fibrosis (METAVIR score F3) or compensated cirrhosis due to a possible risk of severe adverse events of some of these combinations (B1).
- Patients infected with HCV genotype 2, 3, 5 or 6 who failed on a regimen containing an NSSA inhibitor, such as ledipasvir, velpatasvir or daclatasvir, should be retreated with a combination of sofosbuvir and velpatasvir for 24 weeks with ribavirin (B1).

Alternatively, patients without an urgent need for treatment can wait until more data and/or alternative therapeutic options become available (A1).

The utility of HCV resistance testing prior to retreatment in patients who failed on any of the DAA-containing treatment regimens is unknown. If reliable resistance testing is performed, retreatment can be guided by probabilities of response according to the resistance profile observed in the context of an experienced multidisciplinary team (B2).
Baseline and post-treatment hepatitis C NS5A resistance analysis in relapsed patients from a multicentric real-life cohort of 2995 patients exposed to NS5A inhibitors

- Only 81/2295 (2.7%) patients failed

- At the time of failure, Resistance to NS5A (> 10 fold résistance) was detected in 85% of the patients at the time of viral failure regardless of genotype

Halfon P. et al., AASLD 2016
Trimoulet P. et al. AFEF 2016 (oral presentation)
Geographical distribution of the 80 relapsers among the 2995 HCV-infected patients

- **Bordeaux**: 11/554
- **Toulouse**: 28/579
- **Lyon**: 26/975
- **Grenoble**: 8/185
- **Marseille**: 5/458
- **St-Laurent du Var**: 2/244
Patients treated using an NS5A Inhibitor
N=2995

Failure
N=80

Sanger sequencing
N=61

Baseline sequencing
N=35

31 Non Retreated
30 Retreated

17 Non Retreated
18 Retreated
Retreatment with Direct Active Antivirals of genotype 1, 3 and 4 chronic hepatitis C patients who previously failed an anti-NS5A-containing regimen in real world

From January 2014 to March 2016, 2995 patients infected with HCV were exposed to NS5A inhibitors in 6 French referent liver centers: 80 (2.7%) patients relapsed.

This “real-world” study included 30 patients among these 80 patients who had failed to achieve SVR on previous NS5A-based therapy.

These patients were retreated with different regimen combination including SOF + Daclatasvir (DAC) ± SIM (19%), SOF + Grazoprevir + Elbasvir (23%), SOF + Ledipasvir (LEDI) (6%), SOF + SIM (16%), SOF + Velpatasvir + GS9857 (20%), Ombitasvir (OBV) + Paritaprevir (PTV) + Ritonavir (RTV) + Dasabuvir (DAS) ± SOF (16%), with or without RBV for all regimens.
Retreatment with DAA of Hepatitis chronic C genotype 1, 3 and 4 in patients who previously failed a NS5A-containing regimen in real world

<table>
<thead>
<tr>
<th>First treatment</th>
<th>N</th>
<th>Second Treatment</th>
<th>N</th>
<th>Presence NS5A RAVs</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOF+LDV (12 or 24 Weeks)</td>
<td>6</td>
<td>SOF+DACL+RBV</td>
<td>1</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SOF+DACL+SIM</td>
<td>1</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SOF+GRAZO+ELBA±RBV</td>
<td>2</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SOF+SIM±RBV</td>
<td>6</td>
<td>Yes</td>
</tr>
<tr>
<td>SOF+LDV+RBV (12 Weeks)</td>
<td>11</td>
<td>SOF+SIM</td>
<td>1</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SOF+GRAZO+ELBA±RBV</td>
<td>2</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SOF+VELPA+GS9857</td>
<td>2</td>
<td>Yes(1)/No(1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SOF+OBV+PTV+RTV+DAS+RBV</td>
<td>1</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SOF+DACL+SIM</td>
<td>1</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SOF+LDV+RBV (24 Weeks)</td>
<td>2</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VIEKIRAX/EXVIERA+RBV</td>
<td>2</td>
<td>Yes(1)/No(1)</td>
</tr>
<tr>
<td>SOF+DACL (8, 12, or 24 Weeks)</td>
<td>8</td>
<td>SOF+DACL (24 Weeks)</td>
<td>1</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SOF+GRAZO+ELBA±RBV</td>
<td>3</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SOF+VELPA+GS9857</td>
<td>2</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SOF+OBV+PTV+RTV+DAS+RBV</td>
<td>1</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VIEKIRAX/EXVIERA+RBV</td>
<td>1</td>
<td>Yes</td>
</tr>
<tr>
<td>SOF+DACL+RBV (12 or 16 Weeks)</td>
<td>2</td>
<td>SOF+DACL (24 Weeks)</td>
<td>1</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SOF+VELPA+GS9857</td>
<td>1</td>
<td>Yes</td>
</tr>
<tr>
<td>PTV+OBV+RBV (12 Weeks)</td>
<td>1</td>
<td>SOF+DACL +RBV</td>
<td>1</td>
<td>Yes</td>
</tr>
<tr>
<td>DACL+PEG+RBV (12 Weeks)</td>
<td>1</td>
<td>SOF+SIM+RBV</td>
<td>1</td>
<td>Yes</td>
</tr>
<tr>
<td>ASUNA+DACL (20 or 24 Weeks)</td>
<td>2</td>
<td>SOF+SIM+RBV</td>
<td>1</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SOF+VELPA+GS9857</td>
<td>1</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Genotype 1

SVR12 by Baseline Resistance Associated Substitutions (RAS)

- No RAV: 100% SVR
- RAVs: 17 (85%)
  - No RAV: 3 (15%)
  - NS5A RAVs: 15/16 SVR (93%)
Genotype 1

Failure SOF + LDV (n = 11)

Failure SOF + DAC (n = 6)

G1 - SOF+LDV / SOF+DAC (n=17)

SVR12 = 94% (n = 15/16)

G1 - Retreatment after SOF+LDV / SOF+DAC failure

- NS5A RAV (%)
  - 82
  - 18

- No Rav (%)

- SOF+DAC±SIM (n=3)
- SOF+GRAZ+ELBA (n=4)
- SOF+LEDI (n=2, *One Ongoing)
- SOF+SIM (n=2, *One Ongoing)
- SOF+VELPA (n=2)
- Vekirax+Exviera+RBV (n=2)
Genotype 1

Failure ASU + DAC (n = 3)

SVR12 = 100% (n = 3/3)

G1 - Retreatment after ASU+DAC failure

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOF+SIM+RBV (n=1)</td>
<td>100</td>
</tr>
<tr>
<td>SOF+VELPA (n=1)</td>
<td>100</td>
</tr>
<tr>
<td>SOF+DAC+SIM (n=1)</td>
<td>100</td>
</tr>
</tbody>
</table>

G1 - ASU+DAC (n=3)
Patient CA

Asunaprevir + Daclatasvir

12 weeks

W2  W4

HVC Viral load (UI/mL)

LoQ (15 UI/ml)

12 weeks

Sofosbuvir + Daclatasvir + Simeprevir

K24Q+Q30R+L31V + H58P+Y93H

Y93H

Relapse

SVR4

1.106

2.106

3.106

4.106
Patient PEL

Sofosbuvir + Ledipasvir

12 weeks

HCV Viral load (UL/mL)

1.105
2.105
3.105
4.105

LoQ (15 UI/ml)

W2
EO
W4
EO
SVR4

No NS5A RAV

Relapse SVR4

Sofosbuvir + Simeprevir + Ribavirin

24 weeks

H58D

Relapse SVR4

EO
W4
EO
SVR4
Re-treatment of patient who relapsed after 8 weeks of sofosbuvir + ledipasvir

HCV RNA (log10 UI/ml)

SOF/LDV 8 sem.
Post-traitement

Re-traitemt SOF/LDV + RBV 24 sem.
Post-traitement

NS5A : L31M (25,5 %)
NS5B : no mutations

NS5A : Q30L (3,47 %) L31M (94,38 %)
L31V (4,67 %) Y93H (98,19 %)
NS5B : 282T (8,00 %)

NS5A : Q30L (4,5 %)
L31M (> 99 %)
Y93H (96,74 %)
NS5B : S282T (91,24 %)

< 25 UI/ml detectable
< 25 UI/ml non détectable

Lawitz E, États-Unis, AASLD 2013, Abs. 215/1844,
SVR 12 in 41 patients with failure SOF + LDV 8 – 12 weeks, retreated by LDV/SOF during 24 semaines

The chance of success using the same combination even extended are limited

Lawitz et al. EASL 2015. Abstract O005.
SVR 12 in 41 patients with failure SOF + LDV 8 – 12 weeks, retreated by LDV/SOF during 24 semaines

The number and type of mutations strongly impact the retreatment

Lawitz et al. EASL 2015. Abstract O005.
Retraitement of patients failed to NS5A Inhibitors

- HCV Abbott Real Time Assay (LOQ: 12 UI/ml)
- NS3, NS5A et NS5B sanger sequencing before retreatment using SOF/SMV

Hézode et al. AFEF 2015..
Retraitement of patients failed to NS5A Inhibitors

Genotype 1a patients are more impacted by previous NS5A failure

Hézode et al. AFEF 2015.
## POLARISIS Phase 3 Program

### DAA-Experienced

<table>
<thead>
<tr>
<th>Study</th>
<th>GT</th>
<th>Patients</th>
<th>Treatment</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>POLARIS-1</td>
<td>1 2 3 4 5 6</td>
<td>N = 415 NS5A-experienced ± cirrhosis</td>
<td>SOF/VEL/VOX</td>
<td>12 weeks (n=263)</td>
</tr>
<tr>
<td>POLARIS-4</td>
<td>1 2 3 4</td>
<td>N = 333 Non-NS5A-experienced ± cirrhosis</td>
<td>SOF/VEL/VOX</td>
<td>12 weeks (n=182)</td>
</tr>
<tr>
<td>POLARIS-2</td>
<td>1 2 3 4 5 6</td>
<td>N = 941 ± cirrhosis</td>
<td>SOF/VEL/VOX</td>
<td>8 weeks (n=501)</td>
</tr>
<tr>
<td>POLARIS-3</td>
<td>1 2 3 4 5 6</td>
<td>N = 219 Cirrhosis</td>
<td>SOF/VEL/VOX</td>
<td>8 weeks (n=110)</td>
</tr>
</tbody>
</table>

### DAA-Naïve

<table>
<thead>
<tr>
<th>Study</th>
<th>GT</th>
<th>Patients</th>
<th>Treatment</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>POLARIS-1</td>
<td>1 2 3 4 5 6</td>
<td>N = 415 NS5A-experienced ± cirrhosis</td>
<td>Placebo</td>
<td>(n=152)</td>
</tr>
<tr>
<td>POLARIS-2</td>
<td>1 2 3 4 5 6</td>
<td>N = 941 ± cirrhosis</td>
<td>SOF/VEL</td>
<td>12 weeks (n=151)</td>
</tr>
<tr>
<td>POLARIS-3</td>
<td>1 2 3 4 5 6</td>
<td>N = 219 Cirrhosis</td>
<td>SOF/VEL</td>
<td>12 weeks (n=440)</td>
</tr>
</tbody>
</table>

SVR12 Results by Genotype

POLARIS-1: SOF/VEL/VOX for 12 Weeks in NS5A Inhibitor-Experienced HCV GT 1–6

Bourliere M, AASLD 2016, Oral 194
Two patients had S282T at baseline, both achieved SVR12.

*12 patients were excluded due to incomplete RAS data; RASs were analyzed using a 15% cut off

Bourlier M, AASLD 2016, Oral 194
POLARIS-4: SOF/VEL/VOX or SOF/VEL for 12 Weeks in Non-NS5A Inhibitor DAA-Experienced HCV GT 1–4

SVR12 Results by Genotype

SVR12 by Baseline Resistance Associated Substitutions (RAS)

All 22 patients with BL NS5B RAS achieved SVR12
No treatment-emergent RASs were observed in the patient who relapsed following SOF/VEL/VOX

*10 patients were excluded due to unavailable RAS data; RASs were analyzed using a 15% cut off;
SVR12 by Baseline Resistance Associated Substitutions (RAS)

SOF/VEL 12 weeks
48% Baseline RASs (70/145)*

All 8 patients with BL NS5B RAS achieved SVR12

*6 patients were excluded due to unavailable RAS data; RASs were analyzed using a 15% cut off

In a wide variety of DAA-experienced patients across all genotypes, SOF/VEL/VOX for 12 weeks resulted in:

- 96% SVR in NS5A experienced patients
- 97% in DAA-experienced patients
- Including patients with multiple unfavorable characteristics including multiple RASs across NS5A and NS3/4A
- Baseline RASs did not impact treatment outcome for SOF/VEL/VOX with SVR rates of 94-100%
- No treatment-emergent RASs were observed among patients who relapsed with SOF/VEL/VOX

SOF/VEL/VOX for 12 weeks provides a simple, well tolerated, and effective single tablet, once daily, RBV-free treatment for DAA-experienced patients, including NS5A and non-NS5A failures
ABT-493 and ABT-530 in G1 patients who have failed DAA-containing regimens: The MAGELLAN-I study

ABT-493 dose
ABT-530 dose
RBV dose
n=6
200 mg
80 mg
(n=6)
300 mg
120 mg
(n=22)
300 mg
120 mg
(n=22)
ABT-493
ABT-530
RBV
800 mg
300 mg
120 mg
300 mg
120 mg
Arm stopped early; inadequate results of dose-finding studies in pts across all genotypes

Male, n (%)
3 (50)
20 (91)
18 (82)
Black race, n (%)
2 (33)
5 (23)
10 (45)
Hispanic/Latino, n (%)
1 (17)
1 (5)
2 (9)
Age, median years (range)
59 (39–61)
56 (39–64)
59 (46–70)
BMI, median kg/m² (range)
27 (25–37)
28 (22–34)
28 (19–37)
HCV RNA, median log10 IU/mL (range)
6.1 (5.5–6.7)
6.7 (5.0–7.3)
6.6 (5.5–7.2)
HCV G1a, n (%)
4 (67)
20 (91)
18 (82)
Fibrosis stage
F0–F1
4 (67)
17 (77)
11 (50)
F2
1 (17)
0
6 (27)
F3
1 (17)
5 (23)
5 (23)

SVR12
Day
0
Wk 12
Wk 24
Wk 36

Male, n (%)
3 (50)
20 (91)
18 (82)
Black race, n (%)
2 (33)
5 (23)
10 (45)
Hispanic/Latino, n (%)
1 (17)
1 (5)
2 (9)
Age, median years (range)
59 (39–61)
56 (39–64)
59 (46–70)
BMI, median kg/m² (range)
27 (25–37)
28 (22–34)
28 (19–37)
HCV RNA, median log10 IU/mL (range)
6.1 (5.5–6.7)
6.7 (5.0–7.3)
6.6 (5.5–7.2)
HCV G1a, n (%)
4 (67)
20 (91)
18 (82)
Fibrosis stage
F0–F1
4 (67)
17 (77)
11 (50)
F2
1 (17)
0
6 (27)
F3
1 (17)
5 (23)
5 (23)

1 LTFU after Week 6 with HCV RNA undetectable
2 patients LTFU after completing treatment (1 death); both achieved SVR8
ABT-493 and ABT-530 in G1 patients who have failed DAA-containing regimens: The MAGELLAN-I study

**Safety**
- AEs: HA (28%), fatigue (26%), nausea (20%), insomnia (12%)  
- No grade ≥2 ALT elevation  
- Grade 2 ↑ bili in 3 pts (RBV arm)  
- No early d/c  
- No SAE

**Treatment experience by DAA class:**
- 25 (50%) NS5A-experienced  
- 42 (84%) PI-experienced

**SVR12 rates in pts w/ BL RAVs**
- 100% SVR12 in 10 pts with Y93 NS5A RAVs  
- 100% SVR12 in 26 pts w/ Q80 or R155 NS3 RAVs  
- 100% SVR12 in 17 pts w/ prior failure of a SOF-containing regimen

ABT-493 + ABT-530 achieved high SVR in G1 DAA-experienced pts  
BL RAVs had no impact on outcome, await data in cirrhosis (part 2)  
RBV did not enhance SVR

*3 pts with no BL RAVs were LTFU (excluded from the mITT analysis). BL RAVs based on deep sequencing 1% threshold.
HCV genotype 1 German resistance surveys (1)

**Genotype 1**

Failure: SOF + SMV (n = 31)

Retreatment with a strategy including a NS5A Inhibitor Regimen

- SOF/LDV ± RBV (n = 9)
- SOF/LDV ± RBV (n = 17)
- PrOD ± RBV (n = 3)
- PrOD ± RBV (n = 1)

Intermediate Study
SVR 12 = 93.5% (n = 28/30)

Vermehren J, Allemagne, AASLD 2016, Abs. 894
Genotype 3 German HCV resistance surveys (4)

- Failure SOF + RBV (n = 20)
- Failure SOF + DCV (n = 4)
- SOF + DCV + RBV (n = 6)
- SOF/LDV + RBV (n = 1)

Retreatment with a strategy including a NS5A Inhibitor Regimen

Intermediate analysis: RVS12 = 100 % (n = 7/7)

Failure SOF + DCV: 50 % of SVR (2/4)

Vermehren J, Allemagne, AASLD 2016, Abs. 894, actualisé
Genotyping and characterisation of HCV strains before retreatment

Relapse

Looking for a cause
- Compliance
- DDI
- early stop
- Sub-optimal treatment

Retreatment based on Guidelines
Virological expertise

Retreatment as a naïve patient

Education: Measures avoiding recontamination

Recontamination

HCV resistance assessment as close as possible to the initiation of 2° Retreatment

Do we Need to assess HCV resistance to DAAs: is it useful and when?
Retreatment of non-3 patients
Treatment duration of 24 weeks + RBV + 2 or 3 DAA depends on the types of mutations

Don’t use paritaprevir/ritonavir, ombitasvir +/- dasabuvir in patients with cirrhosis
Genotype 3 with baseline RAVs

Surveys/ Triple therapy/ Clinical trial

Relapse post-G3 treatment based on cirrhosis

Sofosbuvir + NS5A inhibitor + ribavirine
24 wks in compensated cirrhosis

Whole genome sequencing?
HCV whole genome analysis

1- Typage précis + description nouvelles souches

2- Détection des mutations de résistance en 1 seule analyse + mut compensatoires
the Sequel System: The Scalable Platform for SMRT Sequencing
HCV whole genome analysis

802 unique genomic sequences covering the recombination breakpoint with at least 30 2k-upstream and 30 1b-downstream nucleotides
How to retreat the subgroup of experienced-patients with relapse or/and resistance to DAA?

- HCV resistance have to be done as close as possible to the initiation of 2° Retreatment
- Don’t use the same class regimen even for 24 weeks to retreat these patients
- The benefice of extension to 24 weeks + RBV have to be extensively studied
- Triple therapy seems very effective in retreatment regardless the presence of RAVs
- Clinical trials combination with new drugs are mandatory
Merci pour votre attention

Nice...
We have so many options!
- Deep whole genome
- Low pass whole genome
- Deep whole exome
- Genomewide array
- Exome array

How would you like to be sequenced?