What every clinician should now about HCV resistance

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Disclosures

Consultancies / Advisory boards:
Abbott, Abbvie, BMS, Gilead, Janssen, Merck/MSD, Roche

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Abbott, Gilead, Janssen, Qiagen, Roche, Siemens

Speaker:
Abbott, Abbvie, Achillion, BMS, Gilead, Janssen, Merck/MSD, Qiagen, Roche, Siemens
Overview

- Natural frequency of resistance associated variants
- Resistance associated with differences between HCV genotypes / subtypes
- Importance of RAVs for all oral DAA treatment naïve patients
- Importance of RAVs for DAA combination failure patients
- Frequency and importance of chimera
Natural frequency of resistance
Differences for targets and between HCV geno- and subtypes

NS3 protease

Genotype 1a
(geographical distribution of Q80K)

35%

59; 34.7%

111; 65.3%

Genotype 1b

3.5%

1; 0.7%

3; 2.1%

137; 96.5%

Genotype 2: V36L, Q80G, S122R
Genotype 3: V36L, D168Q

as natural variants

Dietz et al., PlosOne 2015; Lenz et al., J Hepatol 2013
Natural frequency of resistance
Differences for targets and between HCV geno- and subtypes

Genotype 1a
- 7%
- Genotype 2: L31M in 48%
- Genotype 3: A30X in 19% + Y93H in 9%
- Genotype 4r: M28V/I

Genotype 1b
- 18%
- as natural variants

Dietz et al., PlosOne 2015; Doehle et al., AASLD 2014
Association of RAVs and IL28B genotype
SVR rates according to NS5A sequence analysis and IL28B

NS3 protease plus NS5A inhibitor
unexpected lower SVR rates in IL28B CC

Manns et al., Lancet 2014
Highly significant association of Y93 RAVs with IL28B CC genotype

Y93H in Genotype 1b and IL28B rs12979860

<table>
<thead>
<tr>
<th>Frequency of RAV</th>
<th>Primary Cohort</th>
<th>Replication Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>21/78 (27%)</td>
<td>15/44 (34%)</td>
</tr>
<tr>
<td></td>
<td>p = 0.0005</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>25/245 (10%)</td>
<td>8/87 (9%)</td>
</tr>
</tbody>
</table>

Peiffer et al., Hepatology 2015, epub
Overview

- Natural frequency of resistance associated variants
- Resistance associated with differences between HCV genotypes / subtypes
  - Importance of RAVs for all oral DAA treatment naïve patients
  - Importance of RAVs for DAA combination failure patients
- Frequency and importance of chimera
Importance of HCV geno-/subtypes

Antiviral activities in patients and in vitro (no head-to-head studies)

**NS3-protease inhibitors (patients)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>GT1</th>
<th>GT2</th>
<th>GT3</th>
<th>GT4</th>
<th>GT5</th>
<th>GT6</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMV 200mg QD</td>
<td>4.0</td>
<td>2.5</td>
<td>3.0</td>
<td>4.0</td>
<td>5.0</td>
<td>2.0</td>
</tr>
<tr>
<td>PTV/r 100/100mg QD</td>
<td>4.5</td>
<td>3.0</td>
<td>5.0</td>
<td>4.5</td>
<td>5.0</td>
<td>3.0</td>
</tr>
<tr>
<td>GZR 100mg QD</td>
<td>5.0</td>
<td>4.5</td>
<td>5.0</td>
<td>5.0</td>
<td>5.0</td>
<td>4.0</td>
</tr>
</tbody>
</table>

**NS3-protease inhibitors (in vitro)**

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>GT1a</th>
<th>GT1b</th>
<th>GT2a</th>
<th>GT2b</th>
<th>GT3</th>
<th>GT4a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simeprevir (SMV)</td>
<td>10.0</td>
<td>8.0</td>
<td>6.0</td>
<td>5.0</td>
<td>7.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Paritaprevir (PTV)</td>
<td>12.0</td>
<td>10.0</td>
<td>8.0</td>
<td>7.0</td>
<td>9.0</td>
<td>5.0</td>
</tr>
<tr>
<td>Grazoprevir (GZR)</td>
<td>10.0</td>
<td>8.0</td>
<td>6.0</td>
<td>5.0</td>
<td>7.0</td>
<td>4.0</td>
</tr>
</tbody>
</table>

mean max. HCV RNA log10 decline in monotherapy studies; nM EC50 values from chimeric HCV replicon studies, no head-to-head comparison

Sarrazin; J Hepatol 2015 in press
Importance of HCV geno-/subtypes
Antiviral activities in patients and in vitro (no head-to-head studies)

NS5A-inhibitors (patients)

mean max. HCV RNA log10 decline

0 1 2 3 4 5

DCV 60mg QD
LDV 90mg QD
OMV 25mg QD
EBR 50mg QD

GT1
GT2
GT3
GT4
GT5
GT6

NS5A-inhibitors (in vitro)

replicon EC50 nM

0 0,1 0,2 0,3 0,4 0,5

Daclatasvir (DCV)
Ledipasvir (LDV)
Ombitasvir (OMV)

GT1a
GT1b
GT2a
GT3
GT4a
GT5a
GT6a

mean max. HCV RNA log10 decline in monotherapy studies;
nM EC50 values from chimeric HCV replicon studies,
no head-to-head comparison
Importance of HCV geno-/subtypes

Antiviral activities in patients and in vitro (no head-to-head studies)

NS5B-inhibitors (patients)

- **Mean max. HCV RNA log_{10} decline**
- **SOF 400mg QD**
- **DSV 400mg BID**

NS5B-inhibitors (in vitro)

- **Replicon EC_{50} nM**
- **Sofosbuvir (SOF)**
- **Dasabuvir (DSV)**

**Mean max. HCV RNA log_{10} decline in monotherapy studies; nM EC_{50} values from chimeric HCV replicon studies, no head-to-head comparison**
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- Natural frequency of resistance associated variants
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- Importance of RAVs for all oral DAA treatment naïve patients
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- Frequency and importance of chimera
Importance of resistance associated variants
DAA combination treatment naïve patients (GT1)

**NS3 protease plus NS5A inhibitor**

*no head to head studies, different resistance analysis*

- ASV + DCV (GT1b, TN+TE, ph 3)
  - 24 wks
  - SVR without bl. RAVs: 92%
  - SVR with bl. RAVs: 39%

- SMV + DCV (GT1, phase 2)
- GZR + EBR (GT1a, TN, phase 3)
  - 12 wks
- GZR + EBR ± R (GT1a, TE, phase 3)
  - 12-16 wks

**Frequency of pts. with baseline RAVs**

- 13%

*References*

- Manns et al., Lancet 2014
- Zeuzem et al., CROI 2014
- Zeuzem et al., EASL 2015
- Kwo et al., EASL 2015
- Sarrazin; J Hepatol 2015 epub
Importance of resistance associated variants
DAA combination treatment naïve patients (GT1)

**NS3 protease plus NS5A inhibitor**

*no head to head studies, different resistance analysis*

<table>
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<tr>
<th>Treatment</th>
<th>24 wks SVR (%)</th>
<th>12-24 wks SVR (%)</th>
</tr>
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<tbody>
<tr>
<td>ASV + DCV (GT1b, TN+TE, ph 3)</td>
<td>92</td>
<td>39</td>
</tr>
<tr>
<td>SMV + DCV (GT1b, TN+TE, ph 2)</td>
<td>91</td>
<td>55</td>
</tr>
</tbody>
</table>

Frequency of pts. with baseline RAVs: 13%

Manns et al., Lancet 2014; Zeuzem et al., CROI 2014; Zeuzem et al., EASL 2015; Kwo et al., EASL 2015; Sarrazin; J Hepatol 2015 epub
Importance of resistance associated variants
DAA combination treatment naïve patients (GT1)

NS3 protease plus NS5A inhibitor
no head to head studies, different resistance analysis

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<td>SMV + DCV (GT1b, TN+TE, ph 2)</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>GZR + EBR (GT1a, TN, phase 3)</td>
<td>98</td>
<td>6%</td>
</tr>
<tr>
<td>GZR + EBR ± R (GT1a, TE, phase 3)</td>
<td>99</td>
<td>10%</td>
</tr>
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SVR without bl. RAVs | SVR with bl. RAVs

Manns et al., Lancet 2014; Zeuzem et al., CROI 2014; Zeuzem et al., EASL 2015; Kwo et al., EASL 2015; Sarrazin; J Hepatol 2015 epub
Importance of resistance associated variants
DAA combination treatment naïve patients (GT1)

NS3 protease plus NS5B NUC

no head to head studies, different resistance analysis

- SVR without bl. Q80K: 97%
- SVR with bl. Q80K: 96%

SMV + SOF (GT1a, TN+TE, phase 3)

12 weeks

Frequency of pts. with baseline RAVs: 40%

Lawitz et al., EASL 2015; Kwo et al., EASL 2015; Sarrazin; J Hepatol 2015 in press
Importance of resistance associated variants
DAA combination treatment naïve patients (GT1)

NS3 protease plus NS5B NUC
no head to head studies, different resistance analysis

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<thead>
<tr>
<th></th>
<th>SVR without bl. Q80K</th>
<th>SVR with bl. Q80K</th>
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<tr>
<td>SMV + SOF</td>
<td>84</td>
<td>97</td>
</tr>
<tr>
<td>(GT1a, TN+TE, phase 3)</td>
<td>73</td>
<td>96</td>
</tr>
</tbody>
</table>

8 weeks
12 weeks
no cirrhosis

Frequency of pts. with baseline RAVs
42% 40%

Lawitz et al., EASL 2015; Kwo et al., EASL 2015; Sarrazin; J Hepatol 2015 in press
Importance of resistance associated variants
DAA combination treatment naïve patients (GT1)

NS3 protease plus NS5B NUC
*no head to head studies, different resistance analysis*

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<tr>
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<td>96</td>
</tr>
<tr>
<td>8 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SMV + SOF</td>
<td>97</td>
<td>92</td>
</tr>
<tr>
<td>(GT1a, TN+TE, phase 3)</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>12 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SMV + SOF</td>
<td>92</td>
<td>74</td>
</tr>
<tr>
<td>(GT1a, TN+TE, phase 3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 weeks</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

no cirrhosis

Frequency of pts. with baseline RAVs

- Smv + Sof (GT1a, TN+TE, phase 3): 42%
- Smv + Sof (GT1a, TN+TE, phase 3): 40%
- Smv + Sof (GT1a, TN+TE, phase 3): 47%

Lawitz et al., EASL 2015; Kwo et al., EASL 2015; Sarrazin; J Hepatol 2015 in press
Importance of resistance associated variants
DAA combination treatment naïve patients (GT1)

NS5A inhibitor plus NS5B NUC
no head to head studies, different resistance analysis

Wyles et al., CROI 2015/NEJM 2015; Poordad et al., EASL 2015; Sarrazin et al., AASLD 2014; Sarrazin et al., EASL 2015; Sarrazin; J Hepatol 2015 in press

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Importance of resistance associated variants
dAA combination treatment naïve patients (GT1)

**NS5A inhibitor plus NS5B NUC**
no head to head studies, different resistance analysis

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SVR without bl. RAVs</th>
<th>SVR with bl. RAVs</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCV + SOF (GT1-3/HIV, TN, phase 3) 8 wks</td>
<td>78%</td>
<td>67%</td>
</tr>
<tr>
<td>DCV + SOF (GT1-4/HIV, TN+TE, phase 3) 12 wks</td>
<td>98%</td>
<td>96%</td>
</tr>
<tr>
<td>DCV + SOF + R (GT1-4, Child A-C, phase 3) 12 wks</td>
<td>87%</td>
<td>71%</td>
</tr>
<tr>
<td>LDV + SOF (GT1, TN, phase 2/3) 8 wks</td>
<td>95%</td>
<td>83%</td>
</tr>
<tr>
<td>LDV + SOF (GT1, TN+TE, phase 2/3) 12 wks</td>
<td>97%</td>
<td>87%</td>
</tr>
<tr>
<td>LDV + SOF + R (GT1, cirrhosis, phase 2/3) 12-24 wks</td>
<td>98%</td>
<td>87%</td>
</tr>
</tbody>
</table>

Frequency of pts. with baseline RAVs
18% 16% 24% 12% 12% 12%

Wyles et al., CROI 2015/NEJM 2015; Poordad et al., EASL 2015; Sarrazin et al., AASLD 2014; Sarrazin et al., EASL 2015; Sarrazin; J Hepatol 2015 in press
Importance of resistance associated variants
DAA combination treatment naïve patients (GT1)

NS3 PI plus NS5A inhibitor plus NS5B NonNUC

*no head to head studies, different resistance analysis*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SVR (%)</th>
<th>Frequency of pts. with baseline RAVs</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTV/r+OMV+DSV+R (GT1a, TN, phase 2)</td>
<td>87</td>
<td>39%</td>
</tr>
<tr>
<td>PTV/r+OMV+DSV±R (GT1a, TN+TE, phase 2)</td>
<td>92</td>
<td>52%</td>
</tr>
</tbody>
</table>

Krishnan et al., AAC 2015; EMA CHMP Assessment Report 20. Nov 2014; Sarrazin; J Hepatol 2015 in press
Importance of resistance associated variants
DAA combination treatment naïve patients (GT1)

NS3 PI plus NS5A inhibitor plus NS5B NonNUC

no head to head studies, different resistance analysis

SVR (%)

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>SVR without bl. RAVs</th>
<th>SVR with bl. RAVs</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTV/r+OMV+DSV+R</td>
<td>87</td>
<td>74</td>
</tr>
<tr>
<td>PTV/r+OMV+DSV±R</td>
<td>92, 87</td>
<td></td>
</tr>
<tr>
<td>ASV+DCV+BCV</td>
<td>93</td>
<td>74</td>
</tr>
<tr>
<td>ASV+DCV+BCV±R</td>
<td>92, 87</td>
<td></td>
</tr>
</tbody>
</table>

Frequency of pts. with baseline RAVs

- 39%
- 52%
- 11%
- 10%

Krishnan et al., AAC 2015; EMA CHMP Assessment Report 20. Nov 2014; Sarrazin; J Hepatol 2015 in press
Importance of resistance
Ledipasvir/sofosbuvir (Child A cirrhosis)

n=513 patients with cirrhosis (integrated analysis)

GT1 overall (15% Cutoff)

- 98% SVR12
- 87% no NS5A RAVs at baseline (n=445)
- 13% NS5A RAVs at baseline (n=66)
- p=0.004

GT1a (1% Cutoff)

- 98% SVR12
- 87% no NS5A RAVs at baseline (n=263)
- 13% NS5A RAVs at baseline (n=40)
- p=0.002

RAVs

<table>
<thead>
<tr>
<th>HCV genotype</th>
<th>2.5–100-fold resistance</th>
<th>&gt;100-fold resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b</td>
<td>L31M, P32L, L31I, L31V</td>
<td>P58D, A92K, Y93H</td>
</tr>
</tbody>
</table>
Importance of resistance
Ledipasvir/sofosbuvir (Child Pugh A cirrhosis)
SVR12 rates by resistance level of Baseline NS5A RAVs

GT1a Treatment naïve

<table>
<thead>
<tr>
<th>Baseline NS5A RAVs</th>
<th>&gt;100-fold resistance</th>
<th>&lt;100-fold resistance</th>
<th>No NS5A RAVs at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>11/12</td>
<td>3/3</td>
<td>70/70</td>
</tr>
<tr>
<td>P = 0.0019</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GT1a Treatment experienced

<table>
<thead>
<tr>
<th>Baseline NS5A RAVs</th>
<th>&gt;100-fold resistance</th>
<th>&lt;100-fold resistance</th>
<th>No NS5A RAVs at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10/15</td>
<td>11/11</td>
<td>187/193</td>
</tr>
</tbody>
</table>

Sarrazin C et al. EASL 2015, Poster P773
Importance of resistance associated variants
DAA combination treatment naïve patients (GT3)

Genotype 3
NS5A inhibitor plus NS5B NUC

- **DCV + SOF (TN+TE, phase 3)**
  - SVR (%)
    - All: 89
    - No cirrhosis: 96
    - Cirrhosis: 63

Frequency of pts. with baseline RAVs

Nelson et al., Hepatology 2015; Sarrazin; J Hepatol 2015 in press
Importance of resistance associated variants
DAA combination treatment naïve patients (GT3)

Genotype 3
NS5A inhibitor plus NS5B NUC

![Bar chart showing SVR percentages for different treatments and conditions]

- DCV + SOF (TN+TE, phase 3)
  - All: 89%
  - No cirrhosis: 96%
  - Cirrhosis: 63%

- DCV + SOF (TN+TE, phase 3) A30X
  - All: 67%
  - No cirrhosis: 100%
  - Cirrhosis: 33%

Frequency of pts. with baseline RAVs: 10%

Nelson et al., Hepatology 2015; Sarrazin; J Hepatol 2015 in press
Importance of resistance associated variants
DAA combination treatment naïve patients (GT3)

Genotype 3
NS5A inhibitor plus NS5B NUC

- DCV + SOF (TN+TE, phase 3)
- DCV + SOF (TN+TE, phase 3) A30X
- DCV + SOF (TN+TE, phase 3) Y93H

SVR (%)

Frequency of pts. with baseline RAVs

Nelson et al., Hepatology 2015; Sarrazin; J Hepatol 2015 in press
Overview

- Natural frequency of resistance associated variants
- Resistance associated with differences between HCV genotypes / subtypes
- Importance of RAVs for all oral DAA treatment naïve patients
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- Frequency and importance of chimera
Persistence of resistance associated variants
Persistence rates for NS3, NS5A and NS5B variants

Follow up after failure to 3D (n=67 GT1a, n=7 GT1b)
follow-up 24 and 48 wks., pop. based seq. (if no RAVs cloning)

Rate of patients with RAVs after failure to 3D (%)

Rate of patients with RAVs at failure to 3D
- all
- recommended tx

Rate of patients with RAVs at 24 and 48 wks FU
- FU24
- FU48
Persistence of resistance associated variants
S282T resistance for sofosbuvir

- Detection of Treatment-Emergent S282T Variant Is Rare
- n = 12,012 in SOF or LDV/SOF clinical studies
- n = 1025 with virologic failure
- n = 901* with deep sequencing
- n = 10 with S282T detected
  - 1% SOF virologic failures
  - <0.1% SOF-treated patients

N=10 patients with S282T
- n=4 GT1a, n=1 GT1b, n=1 GT2, 3, 4, 5, 6
- n=5 DAA experienced / n=5 TN/TE
- 8/9 IL28B non-CC
- 5/10 cirrhosis
- reversion to wild type within several weeks

Gane et al., AASLD 2015, #O057
Efficacy of salvage therapies after DAA failure (Genotype 1)

**Initial therapy** (ION-1, ION-2, ION-3, LONESTAR, and TRILOGY-1)

- **n = 30**
  - LDV/SOF±R
- **n = 11**
  - LDV/SOF ± R/PI

**Relapse**

**Re-treatment**

- **n = 41**
  - LDV/SOF

Lawitz et al., EASL 2015
Re-treatment of DAA combination failure patients

24 wks. SOF/LDV after virolog. failure to SOF/LDV +/- RBV

n=41, cirrh. n=19, failure to 8 (n=30) or 12 weeks (n=11)

SOF/LDV +/- RBV

---

All 11 patients without NS5A RAVs received 8 weeks of prior treatment

EASL Clinical Practice Guidelines Hepatitis C 2015
Re-Treatment of DAA failures:
Sofosbuvir plus changed DAA-class, plus RBV, 24 wks
Salvage Therapy
SMV/SOF after NS5A-based DAA Therapy

- n=16, GT1 or GT4 with failure to DCV/PEG/R (n=13), DCV/ASV(PEG/R (n=3)
- 56% cirrhosis
- Treatment with SMV/SOF for 12 wks

SVR12 (%)

<table>
<thead>
<tr>
<th>GT1a</th>
<th>GT1b</th>
<th>GT4</th>
<th>all</th>
</tr>
</thead>
<tbody>
<tr>
<td>80</td>
<td>100</td>
<td>100</td>
<td>87</td>
</tr>
</tbody>
</table>

NS5A RAVs
n=12
Relapse: n=2

NS3 RAVs
n=8
Q80K, R155K, V170L
Relapse: n=2 (ASV exposed!)

1 patient did not reach SVR12 yet
Salvage Therapy
LDV/SOF after DAA triple or SMV/SOF

- n=32, GT1, no cirrhosis, 3-4 DAA (LDV/SOF + PI +/- NonNUC) 4-6 wks
- Baseline RAVs in 85% by NGS
- Treatment LDV/SOF for 12 wks

Wilson et al., AASLD 2015, #O92

- n=46, GT1, relapse to SMV/SOF
- Baseline RAVs?
- Treatment LDV/SOF +/- RBV for 12 or 24 wks

Pungpapong et al., AASLD 2015, #1038
Salvage Therapy
3D + SOF after DAA failure (Quarz 1)

- n=22, GT1 (n=20 GT1a) with failure to 3D (n=14), 2D (n=2), TVR (n=2), SOF-based (n=3), SMV/SAV (n=1)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HCV GT1a OBV/PTV/r + DSV + SOF + RBV 12 Weeks (N = 14)</th>
<th>HCV GT1a OBV/PTV/r + DSV + SOF + RBV 24 Weeks (N = 6)</th>
<th>HCV GT1b OBV/PTV/r + DSV + SOF 12 Weeks (N = 2)</th>
</tr>
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<tbody>
<tr>
<td>Prior DAA experience, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapse</td>
<td>11 (79)</td>
<td>6 (100)</td>
<td>1 (60)</td>
</tr>
<tr>
<td>Breakthrough</td>
<td>3 (21)</td>
<td>0</td>
<td>1 (60)</td>
</tr>
<tr>
<td>Prior DAA regimen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OBV/PTV/r</td>
<td>2 (14)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>OBV/PTV/r + DSV</td>
<td>8 (57)</td>
<td>6 (100)</td>
<td>0</td>
</tr>
<tr>
<td>SIM + SOF</td>
<td>0</td>
<td>0</td>
<td>1 (60)</td>
</tr>
<tr>
<td>SIM + SAM + RBV</td>
<td>0</td>
<td>0</td>
<td>1 (60)</td>
</tr>
<tr>
<td>SOF + RBV</td>
<td>1 (7)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>SOF + PR</td>
<td>1 (7)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TPV + PR</td>
<td>2 (14)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Resistance-associated variants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NS3-Q80K²</td>
<td>9 (64)</td>
<td>5 (83)</td>
<td>0</td>
</tr>
<tr>
<td>NS3-D168E/V</td>
<td>2 (14)</td>
<td>1 (17)</td>
<td>0</td>
</tr>
<tr>
<td>NS5A-M287TV</td>
<td>8 (57)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NS5A-Q30E/H/R</td>
<td>7 (50)</td>
<td>2 (33)</td>
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<td>NS5A-L31M</td>
<td>0</td>
<td>0</td>
<td>1 (60)</td>
</tr>
<tr>
<td>NS5A-H58D</td>
<td>0</td>
<td>1 (17)</td>
<td>0</td>
</tr>
<tr>
<td>NS5A-Y93C/F/H</td>
<td>2 (14)</td>
<td>0</td>
<td>1 (60)</td>
</tr>
<tr>
<td>NS5B-S556G</td>
<td>4 (29)</td>
<td>2 (33)</td>
<td>1 (60)</td>
</tr>
<tr>
<td>NS5B-M414/T</td>
<td>2 (14)</td>
<td>0</td>
<td>0</td>
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<tr>
<td>NS5B-Y448H</td>
<td>1 (7)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Poordad et al., AASLD 2015, #LB20
Salvage Therapy
3D + SOF after DAA failure (Quarz 1)

- n=22, GT1 (n=20 GT1a) with failure to 3D (n=14), 2D (n=2), TVR (n=2), SOF-based (n=3), SMV/SAV (n=1)

Figure 1. QUARTZ-I: Open-label, Phase 2, Multicenter Study Design
Salvage Therapy
3D + SOF after DAA failure (Quarz 1)

- n=22, GT1 (n=20 GT1a) with failure to 3D (n=14), 2D (n=2), TVR (n=2), SOF-based (n=3), SMV/SAV (n=1)
- 3D+SOF (1b) for 12 wks or 3D+SOF+RBV for 12 wks (24 wks cirrhosis) (1a)

Figure 2. Virologic Response During and After Treatment

12 weeks treatment
24 wks pending (currently 6/6 SVR4)

Poordad et al., AASLD 2015, #LB20
Overview

- Natural frequency of resistance associated variants
- Resistance associated with differences between HCV genotypes / subtypes
- Importance of RAVs for all oral DAA treatment naïve patients
- Importance of RAVs for DAA combination failure patients
- Frequency and importance of chimera
Importance of chimera

HCV viral recombination

LiPA Assay 2.0

nucleotide polymerase-inhibitor

Sofosbuvir

➢ St. Petersburg variant

Prevalence of chimera

**Georgia**

Prevalence Lipa Assay

- **Genotype 1**: 44.4%
- **Genotype 2**: 29.1%
- **Genotype 3**: 26.3%

76% of GT2 are GT2k/1b by sequencing

Karchava et al., Hep Research 2015
Treatment response in Genotype 2 chimera
Sofosbuvir plus RBV

GT2 patients from SOF/R
12-16 wks. approval studies

Experience
FFM resistance data base

Hedskog C et al., Hepatology 2015; data on file FFM Resistenzdatenbank
Summary

- Different frequencies of baseline RAVs according to DAA target, HCV geno-/subtype, geographical region
- Antiviral activities of DAAs with high variation between HCV geno-/subtypes
- Importance of pre-existing baseline resistance
  - reduced SVR rates especially in the presence of additional stress factors (high level of resistance, certain HCV subtypes /GT1a, shortened treatment duration / 8 wks., patients with cirrhosis)
- DAA failure patients
  - different persistence rates of RAVs (NS3 vs NS5A and nonNUC NS5B)
  - re-treatment with the same regimen seems to be inefficient
  - resistance testing, change of DAA class, extension to 24 wks., add RBV
- Viral chimera
  - mainly HCV genotype 2/1 recombinants / other chimera are rare
  - prevalence between 2 and 70% of GT2 pts. with geographical variation
  - response to sofosbuvir plus RBV significantly reduced