Objectives

• Epidemiology
• Screening for Chronic Hepatitis C – New CDC Guidelines
• Current Standard of Care
• Treatment Options in the Future – BIG Changes on the Horizon
• Will not discuss: Who to Treat and When to Treat
Current Burden of the HCV Epidemic

• Estimated 140-170 million persons with HCV infection worldwide[1]
  – 3-4 million newly infected each yr worldwide
• At least 3.9 million people in United States infected with HCV[2]
  – Causes ~ 12,000+ deaths annually
• ~ 7.3-8.8 million people infected with HCV in study of 22 European focus countries[3]
  – 86,000 deaths estimated to be caused by HCV in Europe in 2002

Hepatitis C Associated Mortality

- Liver Cancer
  - Incidence has tripled since the early 1980s
  - 50% to 60% of liver cancer patients are infected with HCV
  - Fastest growing cancer-related deaths

- Liver transplants
  - HCV is the most common indication for adult transplants
  - The majority of adult pts waiting for liver transplant are aged 50 to 64 yrs old

Hepatitis C is the leading cause of cirrhosis, liver cancer, and liver transplants in the U.S.
Screening for Chronic Hepatitis C

• The undiagnosed represent a major break in the link to care
• A large proportion of patients with chronic HCV infection in the US remain undiagnosed
  – Estimates indicate at least 50% unaware of HCV-positive status\textsuperscript{[1,2]}
• Estimated proportion of individuals with HCV infection who remain undiagnosed in Europe varies between countries\textsuperscript{[3]}
  – France: 44%
  – United Kingdom: 69%
  – Northern Spain: 84%
  – Germany: 90%
  – Poland: 98%

Economic Burden of the HCV Epidemic

• Few countries have conducted studies to estimate HCV-related costs
  – Most studies have unreliable estimates

• In the US, total medical costs from HCV infection expected to increase from $30 billion in 2009 to > $85 billion in 2024
  – Estimate based on pegIFN/RBV treatment; potential impact of DAAs not reflected

Consequences of HCV

• Chronic HCV infection is a leading cause of liver disease\textsuperscript{[1]}
  – 10% to 20% of patients will develop cirrhosis over 10-20 yrs
  – 1% to 5% of patients with HCV cirrhosis will develop HCC
  – 25% of the ~ 500,000 new HCC cases identified globally each yr are attributable to HCV\textsuperscript{[2]}

• HCV-related complications estimated to increase ~ 2-fold within the next 10 yrs\textsuperscript{[3]}

• Other diseases/manifestations associated with HCV infection\textsuperscript{[4]}
  – Mixed cryoglobulinemia vasculitis, lymphoproliferative disorders, diabetes, renal disease, rheumatoid arthritis–like polyarthritis, sicca syndrome, depression, cognitive impairment

Current AASLD Guidelines for Screening and Counseling

1. As part of a comprehensive health evaluation, all persons should be screened for behaviors that place them at high risk for HCV infection (Class I, level B).

2. Persons who are at risk should be tested for the presence of HCV infection (Class I, level B).

3. Persons infected with HCV should be counseled on how to avoid HCV transmission to others (Class I, level C).
Current AASLD Guidelines for Screening and Counseling

4. Patients suspected of having acute or chronic HCV infection should first be tested for anti-HCV (Class I, Level B).

5. HCV RNA testing should be performed in:
   a) Patients with a positive anti-HCV test (Class I, Level B)
   b) Patients for whom antiviral treatment is being considered, using a sensitive quantitative assay (Class I, Level A)
   c) Patients with unexplained liver disease whose anti-HCV test is negative and who are immunocompromised or suspected of having acute HCV infection (Class I, Level B).
CDC Guidelines for Chronic Hepatitis C

• Baby Boomers (those born between 1945 and 1965) account for 76.5% of HCV cases in the U.S.

• An estimated 33% of undiagnosed baby boomers with HCV currently have advanced fibrosis (F3-F4, bridging fibrosis or cirrhosis)

The CDC recommends one-time HCV testing for people born between 1945 and 1965, regardless of other risk factors for HCV. These recommendations by the CDC are meant to augment and not replace the existing risk-based testing guidelines.

• All patients diagnosed with HCV should be evaluated for follow-up care as determined by their HCP
SVR (Sustained Virologic Response) Associated With Improved Outcome

• SVR
  – Durable, considered CURED
  – Leads to improved histology
  – Leads to clinical benefits
    • Decreases decompensation
    • Prevents de novo esophageal varices
    • Decreases risk of hepatocellular carcinoma
    • Decreases mortality

Treatment for Hepatitis C – Now and in the Future

A Major Advance in Treatment

<table>
<thead>
<tr>
<th>Year</th>
<th>SVR (%)</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991</td>
<td>6</td>
<td>Standard IFN</td>
</tr>
<tr>
<td>1998</td>
<td>34</td>
<td>RBV</td>
</tr>
<tr>
<td>2001</td>
<td>42</td>
<td>PegIFN</td>
</tr>
<tr>
<td>2011</td>
<td>55</td>
<td>Peg/Riba/DAA</td>
</tr>
</tbody>
</table>

DAAs
A Major Step Forward: SVR Rates With BOC or TVR in GT1 Treatment-Naive Patients

SVR Rates With BOC or TVR in GT1 Treatment-Experienced Patients

Limited Efficacy With Telaprevir and Boceprevir in Some Patient Groups

*Pooled TVR arms of REALIZE trial.

Likelihood of SVR With Current Therapies Related to IFN Responsiveness

HCV RNA Reduction After 4-Wk Lead-in

- < 1 log decline
- ≥ 1 log decline

Challenges of Current PI-Based Therapy

- Efficacy
  - Very dependent on the IFN response
- Tolerability
  - Additional AEs beyond pegIFN/RBV
- Regimens
  - Complicated (lead-in, RGT)/pill burden
- DDIs
  - Many with both agents to common drugs
- Genotype/special populations
  - Limited activity in non-GT1, limited data HIV/OLTx, ESRD
## Adverse Events Are Common With Current PI Therapy

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T12 + PR</td>
<td>PR</td>
</tr>
<tr>
<td>Discontinued due to adverse events</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Discontinued due to rash</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Anemia, g/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ &lt; 10.0</td>
<td>36</td>
<td>14</td>
</tr>
<tr>
<td>▪ &lt; 8.5</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Use of EPO</td>
<td>Not permitted</td>
<td>43</td>
</tr>
</tbody>
</table>

Adverse Effects
Preliminary Real-World Safety Findings: CUPIC—PIs in Patients With Cirrhosis

<table>
<thead>
<tr>
<th>Safety Outcome, n (%)</th>
<th>TVR-Based Treatment</th>
<th>BOC-Based Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 292)</td>
<td>(n = 205)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>132 (45.2)</td>
<td>67 (32.7)</td>
</tr>
<tr>
<td>Premature discontinuation</td>
<td>66 (22.6)</td>
<td>54 (26.3)</td>
</tr>
<tr>
<td>▪ From serious AEs</td>
<td>43 (14.7)</td>
<td>15 (7.3)</td>
</tr>
<tr>
<td>Death*</td>
<td>5 (2.6)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Infection (grade 3/4)</td>
<td>19 (6.5)</td>
<td>5 (2.4)</td>
</tr>
<tr>
<td>Rash</td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Grade 3/SCAR</td>
<td>14 (4.8)</td>
<td>0</td>
</tr>
<tr>
<td>Hepatic decompensation</td>
<td>6 (2.0)</td>
<td>6 (2.9)</td>
</tr>
<tr>
<td>Blood transfusions</td>
<td>47 (16.1)</td>
<td>13 (6.3)</td>
</tr>
</tbody>
</table>


Higher Discontinuation Rates in Real-World Settings Than in Clinical Trials

498 GT1 Patients Evaluated\(^1\)

174 GT1 Patients Started TVR-Based Triple Therapy\(^2\)

Efficacy Limitations

• Dependent on response to pegIFN/RBV
• Limited efficacy in poor IFN responders
  – Cirrhosis, *IL28B* non-CC, black patients
  – Prior nonresponders, particularly nulls
• Treatment failure—high rate of resistance
  – May affect future treatment options
Tolerability

• Multiple AEs
• Some severe, but mostly manageable
• Creates issues with capacity and experience
• “Discouraging” to some low volume treaters
• Very difficult and discouraging for patients – especially treatment failures
Difficult and different regimens –
Lead-in/no lead-in, RGT

For our patients . . .
Pill Burden

BOC = 12/day with RBV 4-6/day

Food Requirement
TVR 6/day with RBV 4-6/day
Strategies to Impact the HCV Epidemic

• Increase rate of HCV diagnosis and treatment
  – Enhance screening
  – Enhance treatment delivery

• Develop novel treatments that achieve higher SVR rates in all patients
  – Overcome host factors
  – Shorten therapy
  – Decrease side effects
The future looks bright, but some challenges remain . . .
What Are the Key Elements of an Ideal HCV Regimen?

- **Simple Regimen**
  - Short duration, simple, straightforward stopping rules

- **Easy Dosing**
  - Once daily, low pill burden

- **Highly Effective**
  - High efficacy in traditionally challenging populations (ie, poor IFN sensitivity, cirrhosis)

- **Pan-Genotypic**
  - Regimen can be used across all genotypes

- **Safe and Tolerable**
  - Few or easily manageable adverse effects

- **All Oral**
  - PegIFN/RBV replaced with alternate backbone with low chance of resistance
HCV Lifecycle and Targets

## Characteristics of HCV DAA Classes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Protease Inhibitors</th>
<th>Nucleos(t)ide Polymerase Inhibitors</th>
<th>Nonnucleoside Polymerase Inhibitors</th>
<th>NS5A Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potency</td>
<td>High; variable among HCV genotypes</td>
<td>Moderate-high; consistent across genotype, subtype</td>
<td>Variable; variable among HCV genotypes</td>
<td>High; multiple HCV genotypes</td>
</tr>
<tr>
<td>Barrier to resistance</td>
<td>Low 1a &lt; 1b</td>
<td>High 1a = 1b</td>
<td>Very low 1a &lt; 1b</td>
<td>Low 1a &lt; 1b</td>
</tr>
<tr>
<td>Drug interaction potential</td>
<td>High</td>
<td>Low</td>
<td>Variable</td>
<td>Low to moderate</td>
</tr>
<tr>
<td>Toxicity</td>
<td>Rash; anemia; ↑ bilirubin</td>
<td>Mitochondrial; nuc interactions (ART)</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td>Pharmacokinetics</td>
<td>Variable; QD to TID</td>
<td>QD</td>
<td>Variable; QD to TID</td>
<td>QD</td>
</tr>
<tr>
<td>Comments</td>
<td>2nd-generation PIs: better barrier, pangenotypic</td>
<td>Single target; good tolerability in agents progressing in PhIII</td>
<td>Many targets</td>
<td>Multiple antiviral MOA</td>
</tr>
</tbody>
</table>
Investigational HCV Regimens in Phase III Clinical Trials

Regimens With 1 DAA + PegIFN alfa/RBV
- Faldaprevir (BI 201335, PI)
- Daclatasvir (BMS-790052, NS5A)
- Sofosbuvir (GS-7977, NI)
- Simeprevir (TMC-435, PI)
- Alisporivir (CYP)
- Vaniprevir (MK-7009, PI)

Regimens With 2 DAAs + PegIFN alfa/RBV
- Daclatasvir + asunaprevir

New IFNs
- PegIFN lambda-1a + RBV
- PegIFN lambda-1a + daclatasvir + RBV
- PegIFN lambda-1a + RBV + TVR

IFN-Free Regimens
- Sofosbuvir + RBV
- Sofosbuvir + GS-5885 (NS5A) (FDC) ± RBV
- Asunaprevir (PI) + daclatasvir
- ABT-450 (PI)/RTV/ABT-267 (NS5A) (FDC) + ABT-333 (NNI) + RBV
- Faldaprevir (PI) + BI 207127 (NNI) + RBV

Alternative Dosing
- TVR BID (approved PI)
# Some of the Investigational HCV Agents

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Dosing</th>
<th>Genotypic Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS3/4A protease inhibitor</td>
<td>ABT-450/RTV</td>
<td>100/100 mg, 150/100 mg, or 200/100 mg QD</td>
<td>Genotype 1</td>
</tr>
<tr>
<td>NS3 protease inhibitor</td>
<td>Asunaprevir</td>
<td>200 mg BID</td>
<td>Genotype 1</td>
</tr>
<tr>
<td>NS3 protease inhibitor</td>
<td>GS-9451</td>
<td>200 mg QD</td>
<td>Genotype 1</td>
</tr>
<tr>
<td>NS3/4A protease inhibitor</td>
<td>MK-5172</td>
<td>100 mg, 200 mg, 400 mg, or 800 mg QD</td>
<td>Genotype 1</td>
</tr>
<tr>
<td>NS3/4A protease inhibitor</td>
<td>Vaniprevir (MK-7009)</td>
<td>300 mg or 600 mg BID</td>
<td>Genotype 1</td>
</tr>
<tr>
<td>NS5A nonnucleoside inhibitor</td>
<td>ABT-267</td>
<td>25 mg QD</td>
<td>Genotype 1</td>
</tr>
<tr>
<td>NS5B nonnucleoside polymerase inhibitor</td>
<td>ABT-333</td>
<td>400 mg BID</td>
<td>Genotype 1</td>
</tr>
<tr>
<td>NS5B nonnucleoside polymerase inhibitor</td>
<td>BMS-791325</td>
<td>75 mg or 150 mg BID</td>
<td>Genotype 1</td>
</tr>
<tr>
<td>NS5B nonnucleoside polymerase inhibitor</td>
<td>GS-9669</td>
<td>500 mg QD</td>
<td>Genotype 1</td>
</tr>
<tr>
<td>NS5B nucleotide polymerase inhibitor</td>
<td>GS-0938</td>
<td>300 mg QD</td>
<td>Genotypes 1-4</td>
</tr>
<tr>
<td>NS5B nucleotide polymerase inhibitor</td>
<td>Sofosbuvir  (GS-7977)</td>
<td>400 mg QD</td>
<td>Pangenotypic</td>
</tr>
<tr>
<td>NS3/4A protease inhibitor</td>
<td>MK-5172</td>
<td>100 mg, 200 mg, 400 mg, or 800 mg QD</td>
<td>Genotype 1</td>
</tr>
<tr>
<td>NS5A inhibitor</td>
<td>Ledipasvir (GS-5885)</td>
<td>30 mg or 90 mg QD</td>
<td>Genotype 1</td>
</tr>
</tbody>
</table>
Non-Genotype 1: Options Increasing

- Sofosbuvir (Nuc) + RBV x 12 wks + pegIFN x 4-12 wks
- Sofosbuvir (Nuc) + RBV x 12 wks
- Sofosbuvir (Nuc) + Daclatasvir (NS5A) ± RBV x 24 wks
- Danoprevir (PI)/ritonavir + pegIFN + RBV x 12-24 wks

Major caveat: no patients with cirrhosis included

SVR12 or 24 (%)

<table>
<thead>
<tr>
<th>GT2/3 Naive</th>
<th>GT2/3 Experienced</th>
<th>GT4/6 Naive</th>
<th>GT4 Naive</th>
</tr>
</thead>
<tbody>
<tr>
<td>29/29</td>
<td>11/11</td>
<td>27/28</td>
<td>29/30</td>
</tr>
<tr>
<td>68[^1]</td>
<td>17/25</td>
<td>14/16</td>
<td></td>
</tr>
<tr>
<td>88[^3]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>97[^4]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NEUTRINO: Sofosbuvir + P/R for 12 Wks in Treatment-Naive GT 1/4/5/6 HCV Patients

- Open-label, single-arm study of sofosbuvir 400 mg QD + P/R for 12 wks in treatment-naive patients with GT 1/4/5/6 HCV
  - 17% had cirrhosis; 89% had GT 1, 9% had GT 4, < 1% had GT 5, 2% had GT 6 HCV

![Bar chart showing HCV LLOQ%](chart)

P/R: pegIFN alfa-2a 180 µg/wk + RBV 1000-1200 mg/day

NEUTRINO: SVR12 With Sofosbuvir + P/R According to Genotype and Fibrosis Level

SVR12 According to Genotype

<table>
<thead>
<tr>
<th>Genotype</th>
<th>SVR12 (%)</th>
<th>n/N</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT 1</td>
<td>89</td>
<td>261/292</td>
</tr>
<tr>
<td>GT 4</td>
<td>96</td>
<td>27/28</td>
</tr>
<tr>
<td>GT 5,6</td>
<td>100</td>
<td>7/7</td>
</tr>
</tbody>
</table>

SVR12 According to Fibrosis Level

<table>
<thead>
<tr>
<th>Fibrosis Level</th>
<th>SVR12 (%)</th>
<th>n/N</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Cirrhosis</td>
<td>92</td>
<td>252/273</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>80</td>
<td>43/54</td>
</tr>
</tbody>
</table>

FISSION: Sofosbuvir/RBV vs PegIFN/RBV in Treatment-Naive GT 2/3 HCV Patients

Randomized, controlled, open-label phase III noninferiority trial
20% to 21% had cirrhosis; 72% had GT 3 HCV

Stratified by HCV GT (2 vs 3),
HCV RNA (< vs ≥ 10^6 IU/mL),
cirrhosis (yes vs no)

Treatment-naive patients with GT 2/3 HCV (N = 499)

Sofosbuvir 400 mg QD + RBV 1000-1200 mg/day
(n = 256)

PegIFN alfa-2a 180 µg/wk + RBV 800 mg/day
(n = 243)

Wk 12

Wk 24

FISSION: Sofosbuvir/RBV Noninferior to P/R in Tx-Naive GT 2/3 HCV Patients

Sofosbuvir + RBV

PegIFN + RBV

On Treatment

FISSION: SVR12 According to Genotype and Fibrosis Level

FISSION: Better Tolerability Profile With Sofosbuvir/RBV vs PegIFN/RBV

- Grade ≥ 3 AEs: 7% with SOF/RBV vs 19% for pegIFN/RBV
- Discontinuations due to AEs: 1% for SOF/RBV vs 11% for pegIFN/RBV

<table>
<thead>
<tr>
<th>AEs Occurring in ≥ 15% in Either Arm, %</th>
<th>SOF/RBV (n = 256)</th>
<th>PegIFN/RBV (n = 243)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>36</td>
<td>55</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Headache</td>
<td>25</td>
<td>44</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Nausea</td>
<td>18</td>
<td>29</td>
<td>.0057</td>
</tr>
<tr>
<td>Insomnia</td>
<td>12</td>
<td>29</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Rash</td>
<td>9</td>
<td>17</td>
<td>.0052</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9</td>
<td>17</td>
<td>.0075</td>
</tr>
<tr>
<td>Irritability</td>
<td>10</td>
<td>17</td>
<td>.0328</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>7</td>
<td>18</td>
<td>.0001</td>
</tr>
<tr>
<td>Myalgia</td>
<td>8</td>
<td>17</td>
<td>.0060</td>
</tr>
<tr>
<td>Pruritus</td>
<td>7</td>
<td>17</td>
<td>.0009</td>
</tr>
<tr>
<td>Influenzalike symptoms</td>
<td>3</td>
<td>18</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Chills</td>
<td>3</td>
<td>18</td>
<td>&lt; .0001</td>
</tr>
</tbody>
</table>
FUSION: Sofosbuvir + RBV for 12 or 16 Wks in Treatment Experienced GT 2/3 HCV Pts

- Randomized, double-blind, placebo-controlled phase III trial
  - 62% to 64% had GT 3 HCV, 33% to 35% had cirrhosis, 75% to 76% were previous relapsers

FUSION: SVR12 With Sofosbuvir + RBV by Genotype and Fibrosis Level

ELECTRON: Sofosbuvir ± GS-5885 + RBV in Naive and Previous Null Responders

- Pts with poor prognostic indicators: GT1a (86%), male (54%), nonwhite (12%), *IL28B* CT/TT (68%)
- Mean BMI: 26; mean HCV RNA: 6.2 logs

<table>
<thead>
<tr>
<th>Wk 8</th>
<th>Wk 12</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sofosbuvir + RBV 1000/1200 mg (GT1; naive) (n = 25)</strong></td>
<td><strong>Sofosbuvir + GS-5885 + RBV 1000/1200 mg (GT1; naive) (n = 25)</strong></td>
</tr>
<tr>
<td><strong>Sofosbuvir + RBV 1000/1200 mg (GT1; null responders) (n = 10)</strong></td>
<td><strong>Sofosbuvir + GS-5885 + RBV 1000/1200 mg (GT1; nulls) (n = 9)</strong></td>
</tr>
<tr>
<td><strong>Viral Response, %</strong></td>
<td><strong>SVR4</strong></td>
</tr>
<tr>
<td><strong>84</strong></td>
<td><strong>N/A</strong></td>
</tr>
<tr>
<td><strong>10</strong></td>
<td><strong>100</strong></td>
</tr>
<tr>
<td><strong>100</strong></td>
<td><strong>100</strong>*</td>
</tr>
</tbody>
</table>

*Data reported for 3 pts only. Data collection ongoing.*
QUEST-1: Simeprevir + P/R RGT in Treatment-Naive GT 1 HCV

- Randomized, double-blind, placebo-controlled phase III trial
  - 12% to 13% had cirrhosis, 56% to 57% had GT 1a HCV

*RResponse-guided therapy: Patients with HCV RNA < 25 IU/mL at Wk 4 and HCV RNA undetectable at Wk 12 received a total of 24 wks of therapy. Those not achieving this on-treatment response received 48 wks of therapy. P/R, peginterferon alfa-2a 180 µg/wk + ribavirin 1000-1200 mg/day.*
QUEST-1: Virologic Response to Simeprevir + P/R Treatment

Virologic outcomes
- SMV + P/R
- P/R

HCV RNA Undetectable (%)

<table>
<thead>
<tr>
<th></th>
<th>Wk 4</th>
<th>SVR12</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMV</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>P/R</td>
<td>12</td>
<td>50</td>
</tr>
</tbody>
</table>

SMV Arm: Total Duration of RGT

SVR12 by RGT Group
- 85% of pts in SMV arm met RGT criteria

<table>
<thead>
<tr>
<th></th>
<th>24 Wks</th>
<th>48 Wks</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMV</td>
<td>203/224</td>
<td>6/28</td>
</tr>
<tr>
<td>P/R</td>
<td>21</td>
<td></td>
</tr>
</tbody>
</table>
Daclatasvir + Asunaprevir + BMS-791325 in GT1 Treatment-Naive Pts: 12 vs 24 wks

- Pts with poor prognostic indicators: GT1a (75%), male (53%), black (25%), *IL28B* CT/TT (72%); advanced liver disease: 6%
- Mean HCV RNA: 6.3 logs

<table>
<thead>
<tr>
<th>Stratified by subgenotype 1a/1b</th>
<th>Wk 12</th>
<th>Wk 24</th>
<th>SVR4, %</th>
<th>SVR12, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-naive, noncirrhotic GT1 patients (N = 32)</td>
<td>Daclatasvir + Asunaprevir + BMS-791325</td>
<td>Daclatasvir + Asunaprevir + BMS-791325</td>
<td>94</td>
<td>94</td>
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<td>N/A</td>
</tr>
</tbody>
</table>
AVIATOR Study: ABT-450/r + ABT-267 + ABT-333 + RBV

Phase 2
Open-label, genotype 1
HCV RNA >50K IU/mL
Absence of cirrhosis
No HIV or HBV

Treatment Naive
- ABT-450/r 150/100 mg qd + ABT-267 + ABT-333 + RBV (n=80)
- ABT-450/r 100/100 or 200/100 mg qd + ABT-267 + RBV (n=41)
- ABT-450/r 150/100 mg qd + ABT-267 + ABT-333 (n=79)
- ABT-450/r 100/100 or 150/100 mg qd + ABT-267 + ABT-333 + RBV (n=79)
- ABT-450/r 100/100 or 150/100 mg qd + ABT-267 + ABT-333 + RBV (n=80)

Null responders
- ABT-450/r 200/100 mg qd + ABT-267 + RBV (n=45)
- ABT-450/r 100/100 or 150/100 mg qd + ABT-267 + ABT-333 + RBV (n=45)
- ABT-450/r 100/100 or 150/100 mg qd + ABT-267 + ABT-333 + RBV (n=43)

Primary outcome: SVR24.
AVIATOR Study: Treatment Naïve SVR24 Rates (ITT)

No clinically meaningful differences based on gender, HCV subtype, IL28B genotype, baseline HCV RNA, or fibrosis stage.

AVIATOR Study (Null Responders): SVR24 Rate (ITT)

No clinically meaningful differences based on gender, HCV subtype, IL28B genotype, baseline HCV RNA, or fibrosis stage.

AVIATOR Study: Virologic Relapse and Overall Safety

• Virologic relapse in prior null responders ranged from 2.5% (24-week arm) to 11% (12-week arm)
• Discontinuations due to adverse events was infrequent: 2.4%
  – Adverse events considered related to treatment (n=4/6)
    • Hepatitis cholestatic, feeling jittery, homicidal ideation, decreased creatinine clearance
• Most common adverse events
  – Headache (31%), fatigue (30%), nausea (23%), insomnia (20%), diarrhea (15%)
  – Bilirubin increase: 2.4%
  – Anemia (hemoglobin 6.5 to <8 g/dL): 2.4%
Improvements in Dosing Strategies and Tolerability

- Which strategy fits your patients’ needs?
  - Which patients are looking for smaller improvements and which must wait for ideal regimen?

- **BID dosing with current PIs**
  - Less frequent dosing, improved tolerability, no food requirement, fewer DDIs

- **1-2 DAAs + RBV**
  - QD-BID dosing, shorter duration, IFN free, more tolerable

- **QD DAA (single drug or FDC)**
  - IFN/RBV free
  - Short duration, pangenotypic, very tolerable, few DDIs

- **IFN-free DAA combo**
  - QD-BID dosing, IFN free, more tolerable

- **QD DAA + PR, RGT**
  - Less frequent dosing, improved tolerability, no food requirement, fewer DDIs
Summary of the Future

• First improvements in treatment may be related to less frequent dosing (eg, BID TVR) and improved tolerability (eg, QD DAA + pegIFN/RBV)
• Deep pipeline for DAA-based regimens and superb prospects for all oral SOC
• Combinations of several classes can achieve SVR
• High-barrier compounds highly desirable for simplified regimens but may be matched by combinations of DAA classes
• RBV still appears to be critical in achieving freedom from IFN, particularly in less-than-optimal regimens
• Subtype also plays an important role
  – 1a non-CC < 1a CC, 1b
• DAA regimens in cirrhotics and other special populations require further study
Our Current Balancing Act

Treat now
- Triple therapy increases SVR
- Earlier treatment has higher success rates
- Successful treatment may arrest progression of liver disease
- Uncertainty about timelines for approval and reimbursement

Defer
- First-generation PIs complex, associated with adverse events
- Does current treatment failure affect future treatment?
- Potential for higher SVR, including in challenging populations
- Potential for simpler regimens, QD or BID, fewer adverse effects, eventually IFN-free
- Activity in non-genotype 1

Hang in there!!