The New Elements of HCV Care: Practical Skills to Optimize Protease Inhibitor–Based Therapy

This program is supported by an educational grant from MERCK

CLINICAL CARE OPTIONS HEPATITIS

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Fred Poordad, MD, has disclosed that he has received grants for research support from Abbott, Anadys, Achillion, Bristol-Myers Squibb, Gilead Sciences, Genentech, Merck, and Vertex and has received consulting fees from Abbott, Anadys, Achillion, Bristol-Myers Squibb, Gilead Sciences, Genentech, Idenix, Merck, Pharmasset, and Vertex.

Graham R. Foster, FRCP, PhD, has disclosed that he has received grants for research support from Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Janssen, and Roche; has received consulting fees from Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck, Novartis, Pharmasset, and Roche; and has received fees for non-CME services from Gilead Sciences, Janssen, Merck, and Roche.

Paul Y. Kwo, MD, has disclosed that he has received research support from Abbott, Anadys, Bayer, Bristol-Myers Squibb, Conatus, GlaxoSmithKline, Gilead Sciences, Merck, Novartis, Roche, and Vertex; has received consulting fees from Abbott, Anadys, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Johnson & Johnson, Merck, Novartis, and Vertex; and has received fees for non-CME services from Bristol-Myers Squibb, Gilead Sciences, Merck, and Roche.

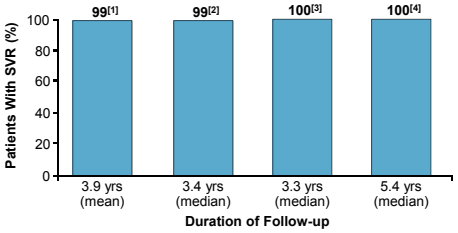
The Hepatitis C Epidemic

- Worldwide prevalence of chronic hepatitis C: 170 million[1]
- US prevalence of chronic hepatitis C[2,3]
  - 5.0 million exposed
  - 3.5 million with chronic viremia
- Most patients with hepatitis C asymptomatic until irreversible liver damage occurs[4]
- Diagnosis depends on high index of suspicion and proper screening
- Forthcoming guidelines from CDC for screening (birth cohort)

1. World Health Organization hepatitis C fact sheet 2011. 2. Chak E, et al. Liver Int. 2011;31:1090-1101. 3. Armstrong GL, et al. Ann Intern Med. 2006;144:705-714. 4. Ghany MG, et al. Hepatology. 2009;49:1-40.

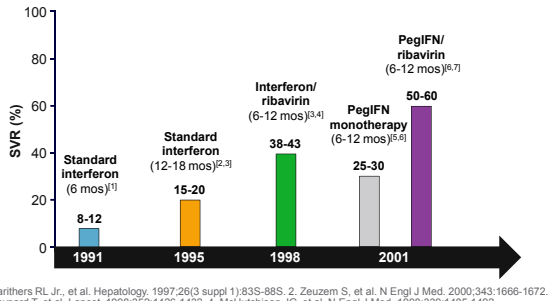
SVR Equivalent to Viral Cure

- Nearly 100% of patients who achieve SVR remain undetectable during long-term follow-up[1-4]



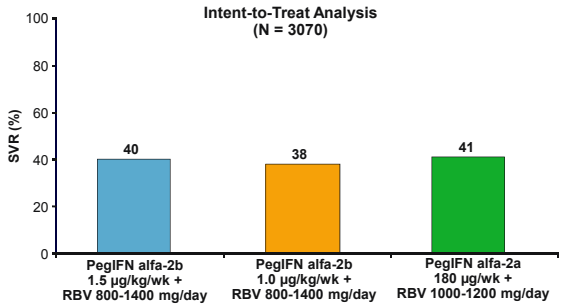
1. Swain MG, et al. Gastroenterology. 2010;139:1593-1601. 2. Giannini EG, et al. Aliment Pharmacol Ther. 2010;31:502-508. 3. Maylin S, et al. Gastroenterology. 2008;135:821-829. 4. George SL, et al. Hepatology. 2009;49:729-738.

Treatment of Chronic Hepatitis C



1. Carithers RL Jr., et al. Hepatology. 1997;26(3 suppl 1):83S-88S. 2. Zeuzem S, et al. N Engl J Med. 2000;343:1666-1672. 3. Poynard T, et al. Lancet. 1998;352:1426-1432. 4. McHutchison JG, et al. N Engl J Med. 1998;339:1485-1492. 5. Lindsay KL, et al. Hepatology. 2001;34:395-403. 6. Fried MW, et al. N Engl J Med. 2002;347:975-982. 7. Manns MP, et al. Lancet. 2001;358:958-965.

IDEAL Study: PegIFN alfa-2a vs alfa-2b in Treatment-Naive Genotype 1 HCV Patients



McHutchison JG, et al. N Engl J Med. 2009;361:580-593.

2 Protease Inhibitors Approved for Genotype 1 HCV Infection

Protease Inhibitor	Additional Regimen Components	Considerations
Boceprevir 800 mg TID (q7-9hrs)[1,2]	PegIFN alfa + weight-based RBV	▪ Naive to previous therapy ▪ Previous treatment failure ▪ Compensated cirrhosis ▪ RGT ▪ Take with food
Telaprevir 750 mg TID (q7-9hrs)[2,3]	PegIFN alfa + weight-based RBV	▪ Naive to previous therapy ▪ Previous treatment failure ▪ Compensated cirrhosis ▪ RGT ▪ Take with food (not low fat)

For patients with genotype 2/3 infection, HCV therapy with pegIFN/RBV remains the standard of care

1. Boceprevir [package insert]. 2011. 2. Ghany MG, et al. Hepatology. 2011;54:1433-1444.
3. Telaprevir [package insert]. 2011.

Phase III Protease Inhibitor Studies

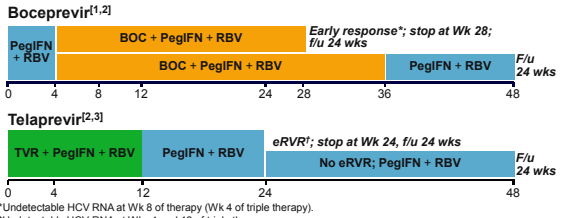
- Telaprevir
  - Treatment-naive
    - ADVANCE[1]
    - ILLUMINATE[2]
  - Treatment-experienced
    - REALIZE[3]
- Boceprevir
  - Treatment-naive
    - SPRINT-2[4]
  - Treatment-experienced
    - RESPOND-2[5]

1. Jacobson IM, et al. N Engl J Med. 2011;364:2405-2416. 2. Sherman KE, et al. N Engl J Med. 2011;365:1014-1024. 3. Zeuzem S, et al. N Engl J Med. 2011;364:2417-2428. 4. Poordad F, et al. N Engl J Med. 2011;364:1195-1206. 5. Bacon BR, et al. N Engl J Med. 2011;364:1207-1217.

Treatment-Naive Patients

New Standard of Care for Genotype 1 Treatment-Naive Patients

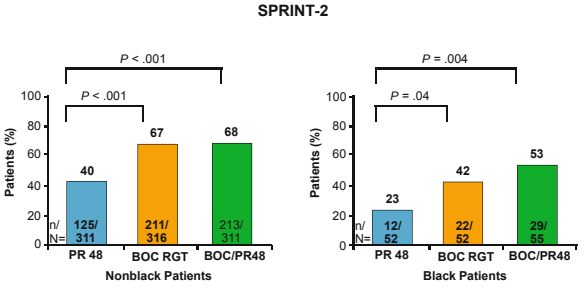
- **Recommendation:** Optimal treatment for all genotype 1 treatment-naive patients is BOC or TVR + pegIFN/RBV
  - BOC and TVR should not be used without pegIFN/RBV



*Undetectable HCV RNA at Wk 8 of therapy (Wk 4 of triple therapy).
†Undetectable HCV RNA at Wks 4 and 12 of triple therapy.

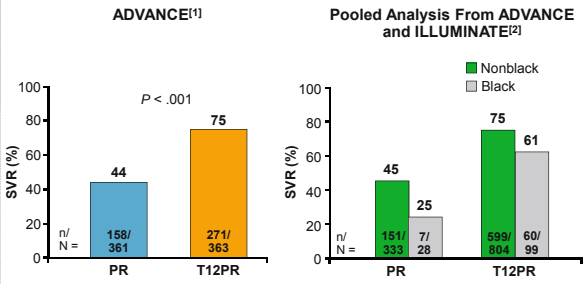
1. Boceprevir [package insert]. May 2011. 2. Ghany MG, et al. Hepatology. 2011;54:1433-1444.
3. Telaprevir [package insert]. May 2011.

SVR Rates With BOC + PegIFN/RBV in Genotype 1 Treatment-Naive Patients



Poordad F, et al. N Engl J Med. 2011;364:1195-1206.

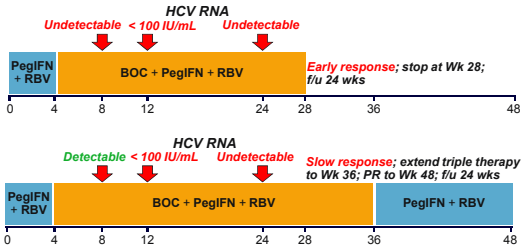
SVR Rates With TVR + PegIFN/RBV in Genotype 1 Treatment-Naive Patients



1. Jacobson IM, et al. N Engl J Med. 2011;364:2405-2416.
2. Dusheiko GM, et al. EASL 2011. Abstract 1788.

Response-Guided Therapy Paradigm With BOC + PegIFN/RBV in Tx-Naive Patients

- **Recommendation:** Noncirrhotic patients can be considered for response-guided therapy with BOC

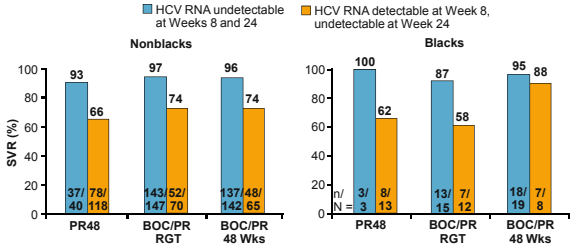


Boceprevir [package insert]. May 2011. Ghany MG, et al. Hepatology. 2011;54:1433-1444.

Impact of Early Response to Boceprevir-based Therapy

SPRINT-2: BOC + PegIFN/RBV in GT1 Treatment-Naive Patients

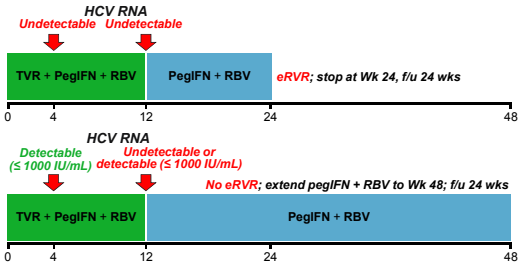
- 57% of patients eligible for shorter therapy



Poordad F, et al. N Engl J Med. 2011;364:1195-1206.

Response-Guided Therapy Paradigm With TVR + PegIFN/RBV in Tx-Naive Patients

- **Recommendation:** Noncirrhotic patients can be considered for response-guided therapy with TVR

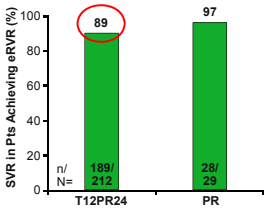


Telaprevir [package insert]. May 2011. Ghany MG, et al. Hepatology. 2011;54:1433-1444.

Response-Guided Approach With TVR in Tx-Naive Patients Supported by 2 Studies

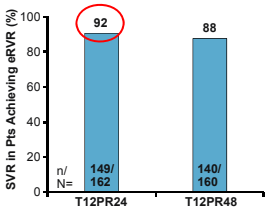
ADVANCE: TVR + PegIFN/RBV in Treatment-Naive Genotype 1

- 58% of patients eligible for shortened therapy[2]



ILLUMINATE: Response-Guided TVR + PegIFN/RBV in Treatment-Naive Genotype 1

- 65% of patients eligible for shortened therapy[1]



1. Jacobson IM, et al. N Engl J Med. 2011;364:2405-2416.
2. Sherman KE, et al. N Engl J Med. 2011;365:1014-1024.

Futility Rules for BOC or TVR + PegIFN/RBV in Tx-Naive Patients

- **Recommendation:** All therapy should be discontinued in patients with the following:

BOC[1,2]		
Time Point	**Criteria**	**Action**
Wk 12	HCV RNA ≥ 100 IU/mL	Discontinue all therapy
Wk 24	HCV RNA detectable	Discontinue all therapy

TVR[1,3]		
Time Point	**Criteria**	**Action**
Wk 4 or 12	HCV RNA > 1000 IU/mL	Discontinue all therapy
Wk 24	HCV RNA detectable	Discontinue pegIFN/RBV

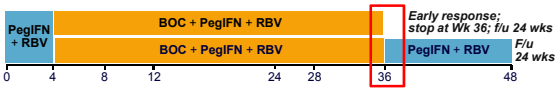
Assay should have a lower limit of HCV RNA quantification of ≤ 25 IU/mL and a limit of HCV RNA detection of approximately 10-15 IU/mL.

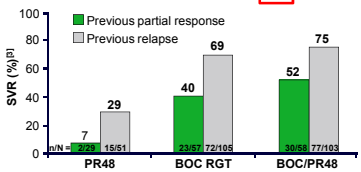
1. Boceprevir [package insert]. May 2011. 2. Ghany MG, et al. Hepatology. 2011;54:1433-1444.
3. Telaprevir [package insert]. May 2011.

Treatment-Experienced Patients

Retreatment With BOC + PegIFN/RBV in Treatment-Experienced Patients

- **Recommendation:** BOC approved for previous relapsers, partial, and null responders[1]
  - AASLD guidelines say BOC "recommended" for previous relapsers and partial responders; advise caution in null responders given lack of definitive information from phase III studies[2]

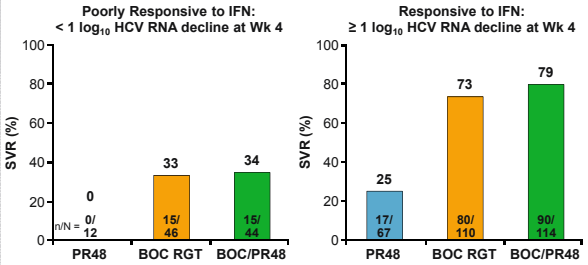




1. Boceprevir [package insert]. 2011. 2. Ghany MG, et al. Hepatology. 2011;54:1433-1444.
3. Bacon BR, et al. N Engl J Med. 2011;364:1207-1217.

SVR in Poorly IFN-Responsive Patients by Wk 4 PR Lead-in Response

RESPOND-2: BOC + PegIFN/RBV in GT 1 Treatment-Experienced Patients

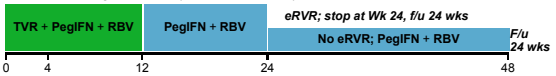


Bacon BR, et al. N Engl J Med. 2011;364:1207-1217.

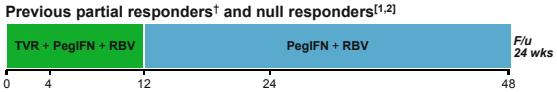
Retreatment With TVR + PegIFN/RBV in Treatment-Experienced Patients

- **Recommendation:** TVR approved for previous relapsers, partial, and null responders[1]
  - AASLD guidelines say TVR "recommended" for previous relapsers and partial responders; "may be considered" for previous null responders[2]

Previous relapsers*[1,2] (same as naives)



Previous partial responders† and null responders[1,2]



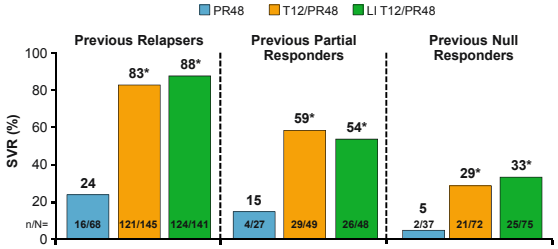
*Response-guided therapy not studied in relapsers in registration trials.
†AASLD guidelines say RGT "may be considered" for prior partial responders[2] but package insert recommends 48 weeks of therapy[1]

1. Telaprevir [package insert]. 2011. 2. Ghany MG, et al. Hepatology. 2011;54:1433-1444.

SVR in Previous Relapsers, Partial Responders, Null Responders

REALIZE: TVR + PegIFN/RBV in G1 Previous Relapsers and Partial/Null Responders

Lead-in examined but found not to influence response and not included in TVR label

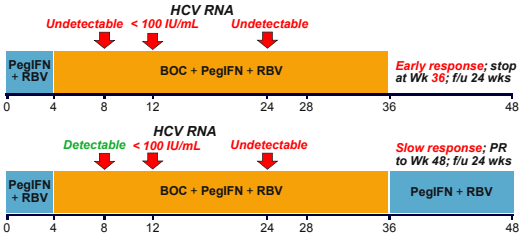


*P < .001 vs PR48.

Zeuzem S, et al. N Engl J Med. 2011;364:2417-2428.

Response-Guided Therapy Paradigm With BOC + PegIFN/RBV in Tx-Exp Patients

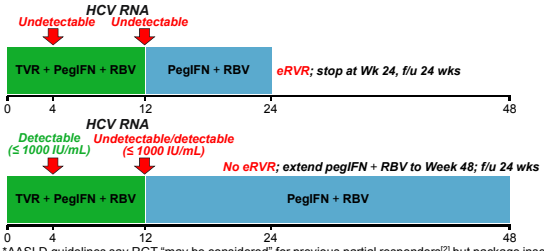
- **Recommendation:** Response-guided therapy can be considered for previous relapsers, may be considered for previous partial responders, but not for previous null responders



Boceprevir [package insert]. May 2011. Ghany MG, et al. Hepatology. 2011;54:1433-1444.

Response-Guided Therapy Paradigm With TVR + PegIFN/RBV in Tx-Exp Patients

- **Recommendation:** Response-guided therapy recommended for previous relapsers, but not for previous partial or null responders*[1]



*AASLD guidelines say RGT "may be considered" for previous partial responders[2] but package insert recommends 48 wks of therapy.[1]

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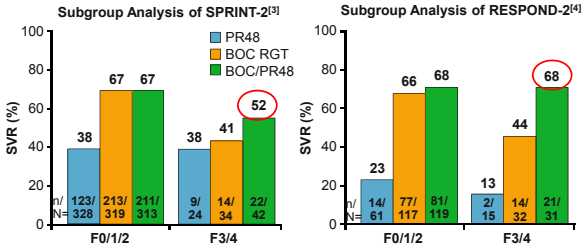
Assay should have a lower limit of HCV RNA quantification of ≤ 25 IU/mL and a limit of HCV RNA detection of approximately 10-15 IU/mL.

1. Boceprevir [package insert]. May 2011. 2. Ghany MG, et al. Hepatology. 2011;54:1433-1444.
3. Telaprevir [package insert]. May 2011.

Other Management Considerations

SVR by Advanced Fibrosis/Cirrhosis in Patients Receiving BOC + PegIFN/RBV

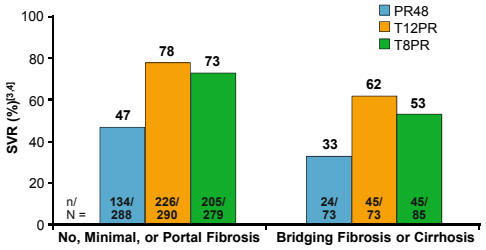
- **Recommendation:** All cirrhotic patients receiving BOC + PR should receive 48 weeks of therapy[1,2]



1. Boceprevir [package insert]. May 2011. 2. Ghany MG, et al. Hepatology. 2011;54:1433-1444.
3. Poordad F, et al. NEJM. 2011;364:1195-1206. 4. Bacon BR, et al. NEJM. 2011;364:1207-1217.

SVR by Advanced Fibrosis/Cirrhosis in Patients Receiving TVR + PegIFN/RBV

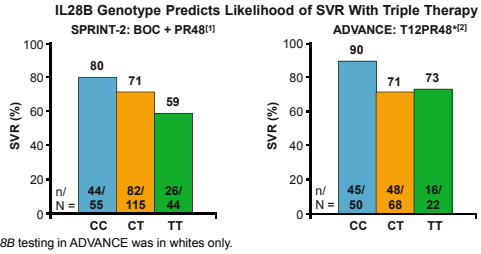
- **Recommendation:** All cirrhotic patients receiving TVR + PR may benefit from 48 weeks of therapy[1,2]



1. Telaprevir [package insert]. May 2011. 2. Ghany MG, et al. Hepatology. 2011;54:1433-1444.
3. Jacobson IM, et al. AASLD 2010. Abstract 211. 4. Jacobson IM, et al. NEJM. 2011;364:2405-2416.

IL28B Genotype Predicts Likelihood of Achieving SVR

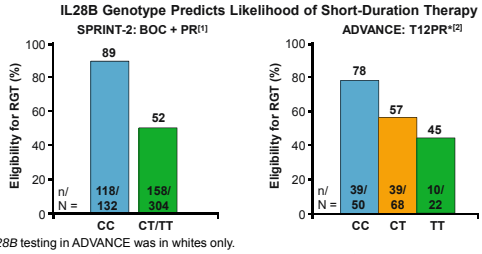
- **Recommendation:** *IL28B* genotype testing may be considered prior to therapy if more information about probability of response or treatment duration desired



**IL28B* testing in ADVANCE was in whites only.*
1. Poordad F, et al. EASL 2011. Abstract 12. 2. Jacobson IM, et al. EASL 2011. Abstract 1369.

IL28B Genotype Predicts Likelihood of Eligibility for Shortened Therapy

- **Recommendation:** *IL28B* genotype testing may be considered prior to therapy if more information about probability of response or treatment duration desired



**IL28B* testing in ADVANCE was in whites only.*
1. Poordad F, et al. EASL 2011. Abstract 12. 2. Jacobson IM, et al. EASL 2011. Abstract 1369.

IL28B Genotype Should Not Be Used to Exclude Patients From Therapy

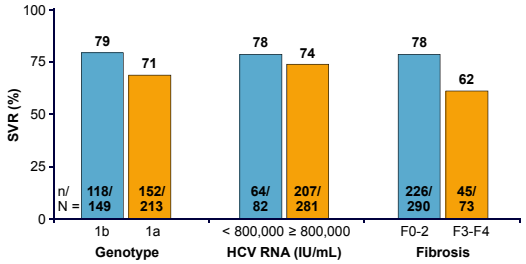
- If patients have favorable CC genotype
  - Likelihood of SVR is high with PR alone, but triple therapy may allow shorter therapy and, in one TVR study, higher SVR rates[1]
- If patients have unfavorable CT/TT genotype
  - Likelihood of SVR is higher with triple therapy than with PR
    - 59% to 71% in SPRINT-2[2]
    - 71% to 73% in ADVANCE*[1]
- Limited value of *IL28B* genotyping in treatment-experienced patients
  - Most have unfavorable TT or CT genotype

**IL28B* testing in ADVANCE was in white Americans only.*

1. Jacobson IM, et al. EASL 2011. Abstract 1369. 2. Poordad F, et al. EASL 2011. Abstract 12.

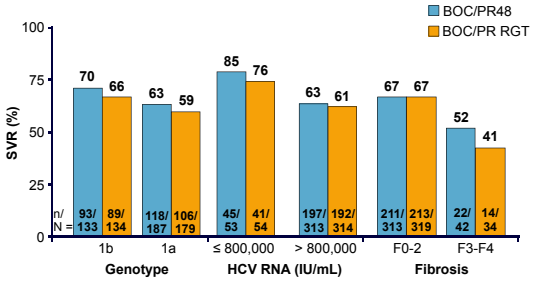
ADVANCE: Influence of Baseline Patient and Virus Factors on SVR

- Data from T12PR arm only



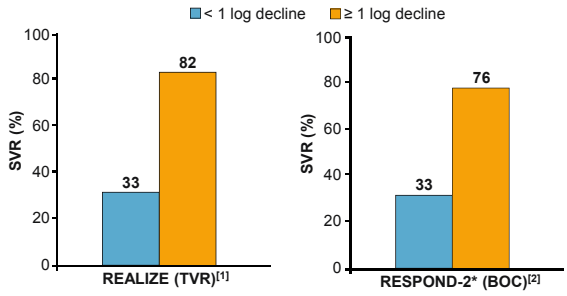
Marcellin P, et al. EASL 2011. Abstract 451.

SPRINT-2: Influence of Baseline Patient and Virus Factors on SVR



Poordad F, et al. N Engl J Med. 2011;364:1195-1206. Reddy KR, et al. EASL 2011. Abstract 466.

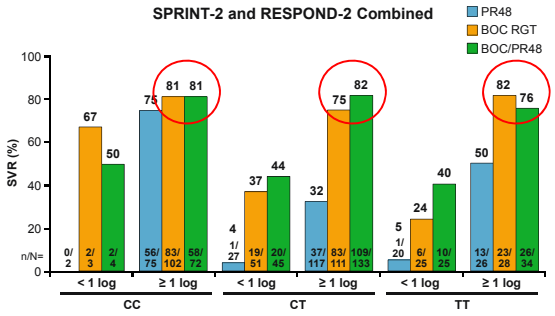
Predictive Value of Response to Lead-in in Treatment-Experienced Patients



1. Foster G, et al. EASL 2011. Abstract 6.
2. Vierling JM, et al. EASL 2011. Abstract 481.

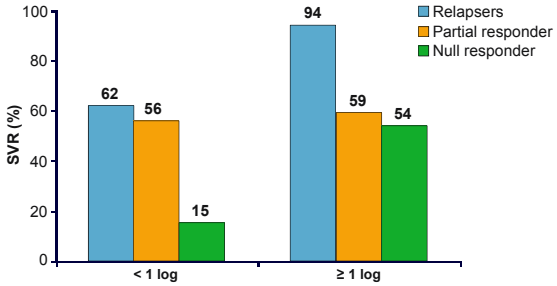
*Pooled data from RGT and BOC/PR48.

Early IFN Response (Lead-in) Further Defines Likelihood of SVR for Non-CC Pts



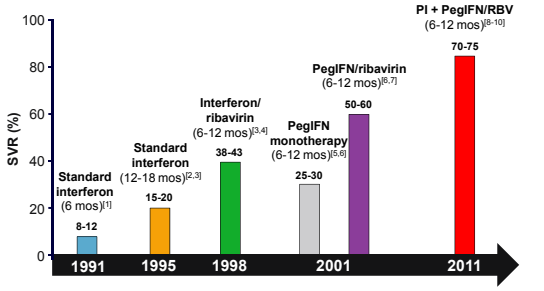
Poordad F, et al. EASL 2011. Abstract 12.

REALIZE: SVR by Response at Wk 4 in Lead-in Arm



Foster GR, et al. EASL 2011. Abstract 6.

Treatment of Chronic Hepatitis C



1. Carithers RL Jr., et al. Hepatology. 1997;26(3 suppl 1):83S-88S. 2. Zeuzem S, et al. N Engl J Med. 2000;343:1666-1672. 3. Poynard T, et al. Lancet. 1998;352:1426-1432. 4. McHutchison JG, et al. N Engl J Med. 1998;339:1485-1492. 5. Lindsay KL, et al. Hepatology. 2001;34:395-403. 6. Fried MW, et al. N Engl J Med. 2002;347:975-982. 7. Manns MP, et al. Lancet. 2001;358:958-965. 8. Poordad F, et al. N Engl J Med. 2011;364:1195-1206. 9. Jacobson IM, et al. N Engl J Med. 2011;364:2405-2416. 10. Sherman KE, et al. N Engl J Med. 2011;365:1014-1024.

MANAGING THE SIDE EFFECTS OF THE HEPATITIS C TREATMENT

Boceprevir + PR: Adverse Events

- Significantly higher rates of anemia, neutropenia, and dysgeusia in BOC arms vs control

Adverse Event, %	PR48 (n = 467)	BOC + PR RGT/48 (n = 1225)
Anemia*	30	50
Neutropenia	19	25
Dysgeusia	16	35

*Anemia was managed with RBV reduction and/or epoetin alfa (43% of BOC + PR and 24% of PR).

Boceprevir [package insert]. May 2011.

Telaprevir + PR: Adverse Events

- Higher rates of rash, anemia, and anorectal signs/symptoms in TVR arms vs control

Adverse Event, %	PR48 (n = 493)	TVR + PR RGT/48* (n = 1797)
Rash	34	56
Anemia†	17	36
Anorectal events	7	29

*Pooled results from TVR arms.
†Anemia was managed with RBV dose modification; epoetin alfa was not permitted.

- In most subjects, rash was mild to moderate
  - Severe rash in 4%; discontinuation due to rash in 6% of subjects
    - Occurred early, usually first 4 wks, but can occur at any time during TVR exposure
    - < 1% had SJS or DRESS (11 cases DRESS and 3 cases SJS)

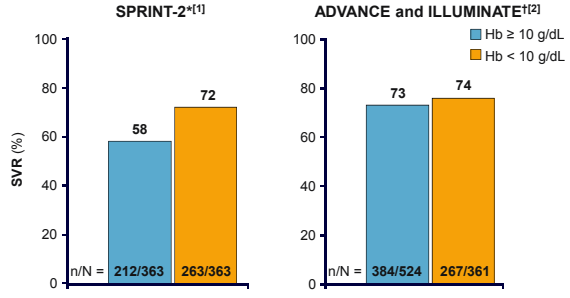
Telaprevir [package insert]. May 2011. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/UCM252562.pdf

Adverse Effect Management: Anemia

- **Recommendation:** Anemia should be managed initially by reducing the RBV dose[1]
- Dose reduction of RBV is acceptable
- Dose reduction of DAA is not acceptable
- Do not discontinue pegIFN/RBV and continue DAA
- DAA should not be stopped and then restarted
- Monitor closely if Hb falls < 10 g/dL
- ESA agents are unlabeled for HCV anemia and should not be used if Hb > 12 g/dL

1. Ghany MG, et al. Hepatology. 2011;54:1433-1444.

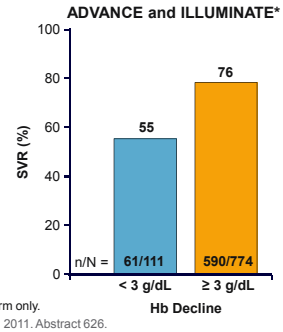
Predictive Value of Anemia for SVR With BOC or TVR



*Data from BOC/48 and BOC RGT arms.
†Data from T12/PR arm only.

1. Sulkowski M, et al. EASL 2011. Abstract 476. 2. Poordad F, et al. DDW 2011. Abstract 626.

Predictive Value of Hb Decline > and < 3 g/dL From Baseline for SVR With TVR

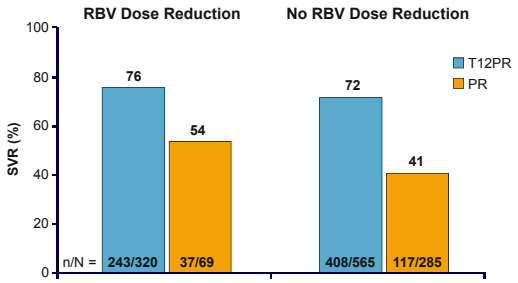


*Data from T12/PR arm only.

Poordad F, et al. DDW 2011. Abstract 626.

The New Elements of HCV Care:
Practical Skills to Optimize HCV Protease Inhibitor–Based Therapy

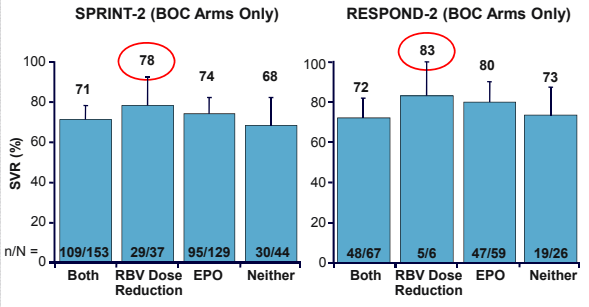
Telaprevir: SVR Rates by RBV Dose Reduction in ADVANCE and ILLUMINATE



Poordad F, et al. DDW 2011. Abstract 626.

The New Elements of HCV Care:
Practical Skills to Optimize HCV Protease Inhibitor–Based Therapy

Boceprevir: SVR in Pts With Hb < 10 g/dL by EPO and/or RBV Dose Reduction



Sulkowski M, et al. DDW 2011. Abstract 1865.

The New Elements of HCV Care:
Practical Skills to Optimize HCV Protease Inhibitor–Based Therapy

Adverse Effect Management: Rash and Anorectal Symptoms

- Rash management
  - Mild to moderate rash can be treated with oral antihistamines, topical steroids
    - Systemic steroids are ***not*** recommended
  - Stop all 3 drugs for severe rash, DRESS, or SJS
  - Important to have "go-to" dermatologist; vigilance with rash is key
- Anorectal symptom management
  - Fiber, loperamide, hydrocortisone, and pramoxine topical cream

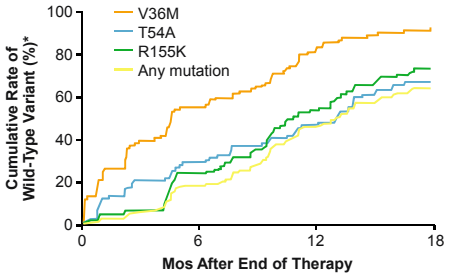
Telaprevir [package insert]. May 2011.

Resistance-Associated Variants Develop When SVR Not Achieved

- **Recommendation:** Patients with virologic failure on one PI should not be retreated with the other
- Similar mutations selected in resistance-associated variants detectable in patients failing BOC or TVR
- Clinical significance of resistance-associated variants unknown
- Predominant strain returns to wild type in majority within 2 yrs
  - Slower process in subtype 1a
- **Recommendation:** Follow stopping rules strictly to minimize selection of resistance-associated variants

Boceprevir [package insert]. May 2011. Telaprevir [package insert]. May 2011.
Ghany MG, et al. Hepatology. 2011;54:1433-1444.

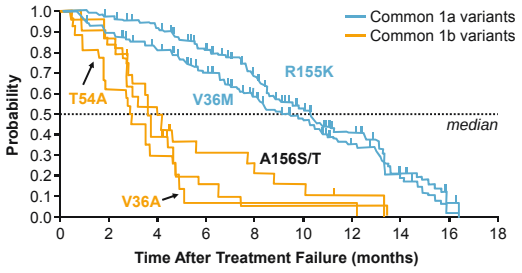
Loss of Detectable Resistance in Patients Stopping BOC + PegIFN/RBV



*Data from phase II studies.

Vierling JM, et al. EASL 2010. Abstract 2016.

Loss of Detectable Resistance in Patients Stopping TVR + PegIFN/RBV



Sullivan J, et al. EASL 2011. Abstract 8.

Contraindications and Cautions for Use of HCV Protease Inhibitors

- Contraindications for BOC and TVR therapy
  - Patients with previous SAEs leading to premature pegIFN/RBV discontinuation
  - Pregnant women or men whose female partners are pregnant
  - Coadministration with other drugs highly dependent on CYP3A4/5 for clearance
  - Coadministration with potent CYP3A4/5 inducers that may significantly reduce BOC or TVR plasma concentrations, leading to reduced efficacy
- Safety and pharmacokinetics have not been studied in patients with decompensated cirrhosis or in liver transplant recipients, patients coinfected with HBV or HIV, or persons younger than 18 yrs of age
- Assess carefully for all drug-drug interactions prior to commencing therapy

Boceprevir [package insert]. May 2011. Telaprevir [package insert]. May 2011.
Ghany MG, et al. Hepatology. 2011;54:1433-1444.

Drug-Drug Interactions With PIs

- HCV PIs are CYP3A4 inhibitors
  - ~ One half of FDA-approved drugs are metabolized by CYP3A4
- Until the drug is specifically studied, magnitude of the impact of PI on its level is not known
- HCV PI metabolism differs
  - Boceprevir: primarily aldo-ketoreductase and partially CYP3A4/5
  - Telaprevir: CYP3A4
- Exercise caution with ALL coadministered medications

Contraindications to BOC and TVR as Listed in Prescribing Information*

Drug Class	Contraindicated With BOC[1]	Contraindicated With TVR[2]
Alpha 1-adrenoreceptor antagonist	Alfuzosin	Alfuzosin
Anticonvulsants	Carbamazepine, phenobarbital, phenytoin	N/A
Antimycobacterials	Rifampin	Rifampin
Ergot derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Dihydroergotamine, ergonovine, ergotamine, methylergonovine
GI motility agents	Cisapride	Cisapride
Herbal products	*Hypericum perforatum* (St John's wort)	*Hypericum perforatum*
HMG CoA reductase inhibitors	Lovastatin, simvastatin	Atorvastatin, lovastatin, simvastatin
Oral contraceptives	Drospirenone	N/A
Neuroleptic	Pimozide	Pimozide
PDE5 inhibitor	Sildenafil or tadalafil when used for tx of pulmonary arterial hypertension	Sildenafil or tadalafil when used for tx of pulmonary arterial hypertension
Sedatives/hypnotics	Triazolam; orally administered midazolam	Orally administered midazolam, triazolam

*Studies of drug-drug interactions incomplete.

1. Boceprevir [package insert]. May 2011. 2. Telaprevir [package insert]. May 2011.

Summary: Updated AASLD Guidelines on Treatment of HCV Genotype 1 Infection

- Optimal treatment is BOC or TVR, each in combination with pegIFN/RBV
  - All treatment-naive and -experienced patients can be considered for treatment with BOC and TVR
    - Caution is advised when using BOC in null responders given lack of definitive information from phase III studies*
  - All patients can be considered for shortened duration of therapy except patients with cirrhosis and null responders (who should receive 48 wks of therapy)†
  - Stopping rules outlined in package inserts should be strictly adhered to in order to avoid antiviral resistance
- Anemia should be managed with RBV dose reductions
- Patients failing one PI should not be retreated with the other
- *IL28B* genotype testing may be considered prior to therapy if more information about probability of response or treatment duration desired

*Package insert says if BOC tx of previous null responders is considered, it should be 48 wks of therapy.
†Package insert recommends 48 wks of therapy with TVR for previous partial responders.

Ghany MG, et al. Hepatology. 2011;54:1433-1444.

Go Online for More Educational Programming on the New HCV Protease Inhibitors!

Case vignettes highlighting important management decisions for HCV-infected patients with the new protease inhibitors.

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