HCV Debrief 2010

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- **Intellectual Property:** None

Unlabeled use of commercial products will be discussed in this presentation.

Anticipated Directions for 2011

- Approval of first DAAs: Telaprevir and Boceprevir
- Widespread use of these drugs in US and EU
- Improve SVR rates to 75% of Rx-naïve G1 patients
- Potential for misuse of new drugs:
  - Poor understanding of treatment populations
  - Inadequate viral assay testing
  - Poor side effect management
  - Lack of monitoring for antiviral resistance

Viral Hepatitis Debrief

Purpose

- Move the field forward by synthesizing the new data from annual meeting
- Avoid casual or incorrect use of new medications
- AASLD's website will produce enduring materials
- These educational materials will be made available to all physicians by AASLD

Hepatitis Debrief

Outline

1. Changes in pre-treatment diagnostic testing
2. Lessons from phase 3 trials presented at this meeting
3. Monitoring for resistance during treatment
4. Combinations of small molecules
5. Special populations
6. Expanded Access Programs
7. What will be different next year

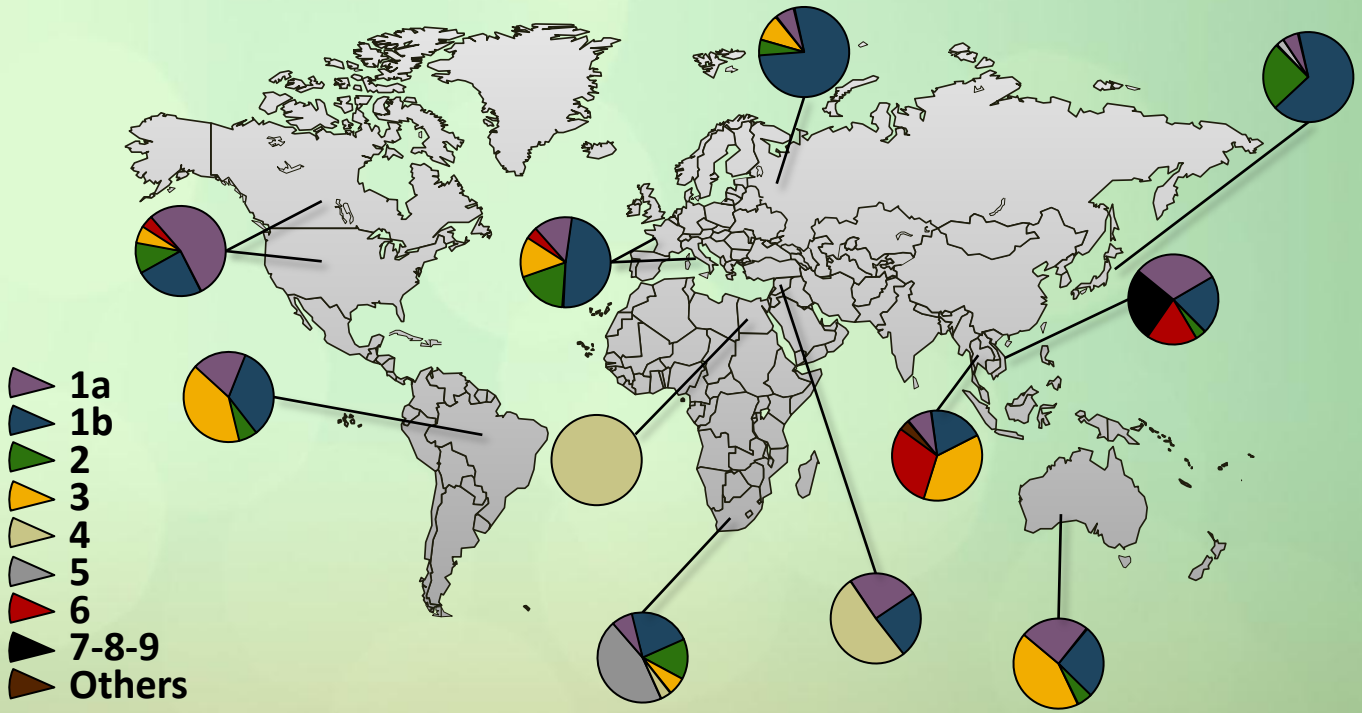
HCV Treatment: A Lexicon of Acronyms

- DRM: drug-resistant mutations
- IL28B: IL28B polymorphism (rs12979860) genotype test
- LLQ: lower limit of quantitation
- LLD: lower limit of detection
- NA: nucleoside analog polymerase inhibitors
- NNI: nonnucleoside polymerase inhibitors
- MV: minority variants
- PI: protease inhibitors
- UDPS: ultradeep pyrosequencing
- vBT: viral breakthrough
- RGT: response-guided therapy

HCV RNA Assays

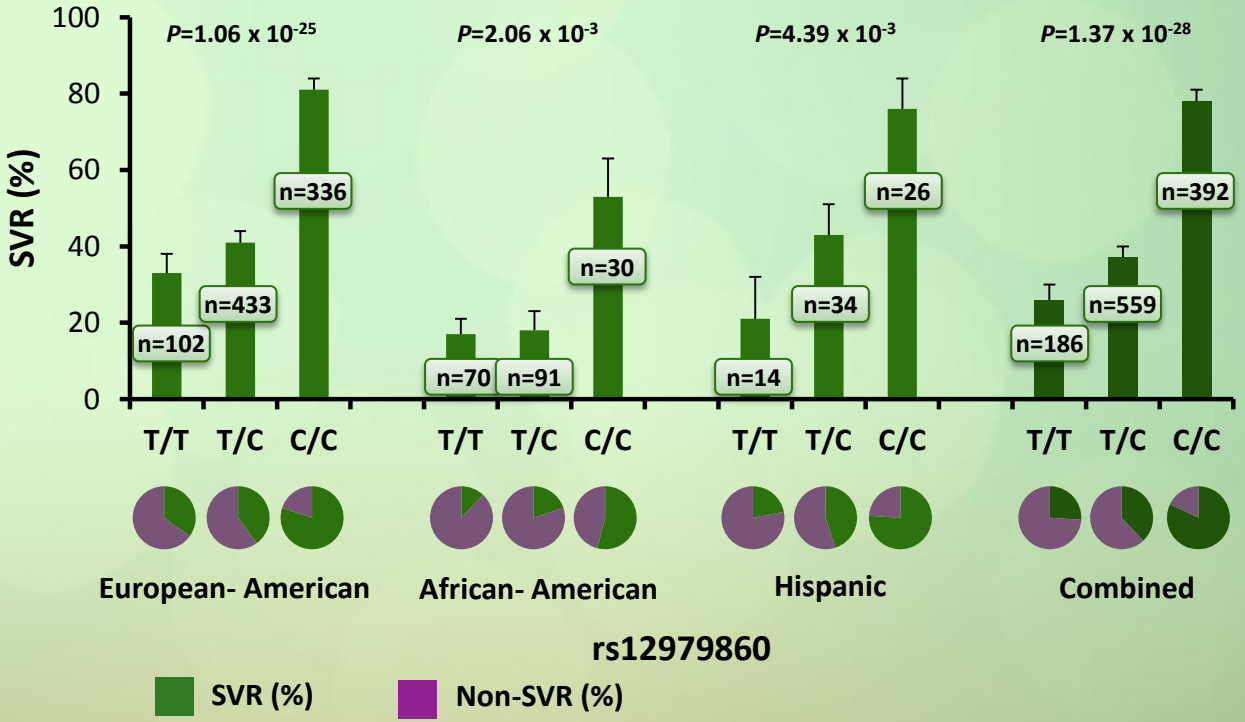
- Definition of HCV negativity during treatment will need to be consistent for labeling
- Absolute titer of HCV RNA that will be used for PI to determine RGT has not yet been stated
- “Undetectable” (LLOD) will likely replaced by “Unquantifiable” (LLOQ)
- For instance, the LLOQ <25 IU/mL by Roche COBAS Taqman HCV test at will likely be used to define eRVR rather than LLOD COBAS assay

Worldwide Distribution of HCV Genotypes



Zein N. Clin Microbiol Rev. 2000;13:223-235. Reproduced with permission.
http://cmr.asm.org/cgi/content/full/13/2/223?view=long&pmid=10755999.

Sustained Viral Response by II28B Genotypes



Ge DL et al. Nature 2009

IL28B Genotype Testing

- 16 oral presentations and 57 posters at this meeting with IL28B in their title
- Important pretreatment predictor for PEGIFN+RBV therapy regardless of genotype, viral load and other predictors
- In recent HCV infection, early therapeutic intervention could be recommended in unfavorable IL28B genotypes
- Indications for IL28B testing with DAAs in combination with PEGIFN/RBV currently are unclear

Grebely J, Petoumenos K, Hellard M, et al. Hepatology 2010.

IL28B Genotype Testing

- Genotyping of rs12979860 (C>T) in the IL28B locus using TaqMan 5’ allelic discrimination assay (not GWAS)
- Multiple vendors licensed: LabCorp, Quest, Roche Molecular, etc.
- Simple to interpret results of CC, CT or TT genotype
- Performed on buccal swab or whole blood in EDTA collection tube
- 5- to 7-day turnaround time for results
- Use of existing CPT billing codes (83891,83898,83896X2,83912)

ITPA Deficiency Testing

- 2 SNPs in the inosine triphosphate pyrophosphatase (ITPA) gene (rs1127354 and rs7270101) have been associated with deficient ITPA activity
- Clear risk factor for early onset anemia in patients receiving DAAs+SOC therapy which includes RBV
- May be useful to modify therapy or add erythropoeitin to increase adherence to RBV
- Screening for ITPA deficiency currently not available but may soon be

Abstracts 909, 910, 929 and 964.

36 Small Molecules for HCV: Clinical Trials at AASLD 2010

15 Linear and Macrocyclic NS3/4 Pis:

Drug	Company	Phase	Abstract
Telaprevir	Vartex and Johnson & Johnson	III	221, 227, 805, 828, 899, 1051, LB-2, LB-11
Boceprevir (SCH-603034)	Merck/Schering-Plough	III	216, 801, 933, 1871, LB-4, LB-15
TMC435	Tibolac, Medivir, Johnson & Johnson	IIb	298, 812, 895, 1873, LB-5
BI 201335	Boehringer, Ingelhaim	II	804, LB-7
Vaniprevir (MK-7009)	Merck	II	82
Narlaprevir (SCH-900518)	Merck/Schering-Plough	IIa	832
Danoprevir (ITMN-191, RG7227)	InterMune and Roche	II	32, 802, 1884
BMS-850032	Bristol-Myer Squibb	I	LB-8
ACH-1625 (linear, non-covalent)	Achillon	Ib	1880
GS 9256	Gilead	I	824, 1867, 18761, LB-1
ABT-450	Abbott and Enanta	I	1855, LB-10
IDX320	Idenix	I	LB-16
GS-9451	Gilead	I	820
ACH-2684	Achillion	Pre-clinical	1859
MK-6172	Merck	I	807, 1885

36 Small Molecules for HCV: Clinical Trials at AASLD 2010

5 NS5B NPI's

Drug	Company	Phase	Abstract
R7128	Pharmasset and Roche	II	81, 799
IDX	Idenix	IIa	34
PSI-7977	Pharmasset	IIb	806, 810, 1861
PSI-938	Pharmasset	IIb	1890
INX-198	Inhibitex	I	1874, 1888, 1889

5 NNPI's

Drug	Company	Phase	Abstract
GS-9190	Gilead	II	833
Filibuyir I	Pfizer	II	818, 834
ANA-598	Anadys	Ib	31, 1852
ABT-333	Abbott	I	519
IDX-375	Idenix	Ia	1891

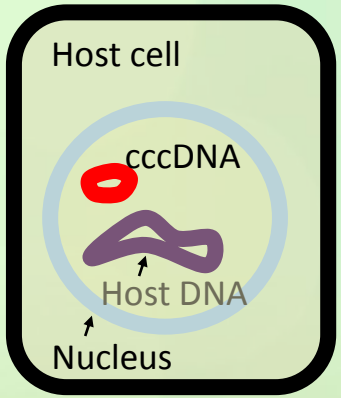
36 Small Molecules for HCV: Clinical Trials at AASLD 2010

4 NS5A's

Drug	Company	Phase	Abstract
BMS-790052	BMS	II	827, 1881, LB-8
PPI-461	Presidio	I	LB-12
GS-5885	Gilead	I	1883
BMS-824393	BMS	I	1858
Cyclophylin Inhibitors			
SCY-635	Scynexis	IIa	36
Theapeutic Vaccines			
GI-5005	Globeimmune	II	LB-6, 1973
Caspace Inhibitors			
GS-9450	Gilead	II	862, 1995

Hepatitis C Differs from HIV and HBV
No Long-term or Latent Reservoir

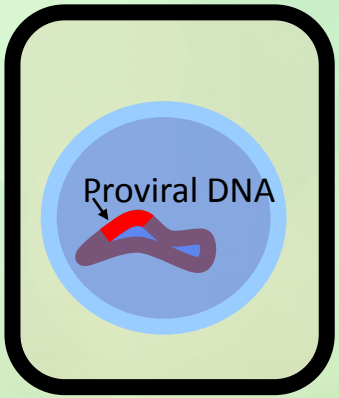
HBV



TREATMENT

Long-term suppression of viral replication

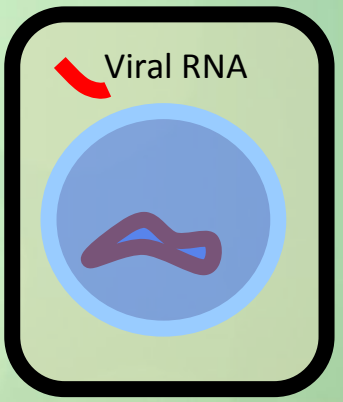
HIV



TREATMENT

Long-term suppression of viral replication[2,3]

HCV



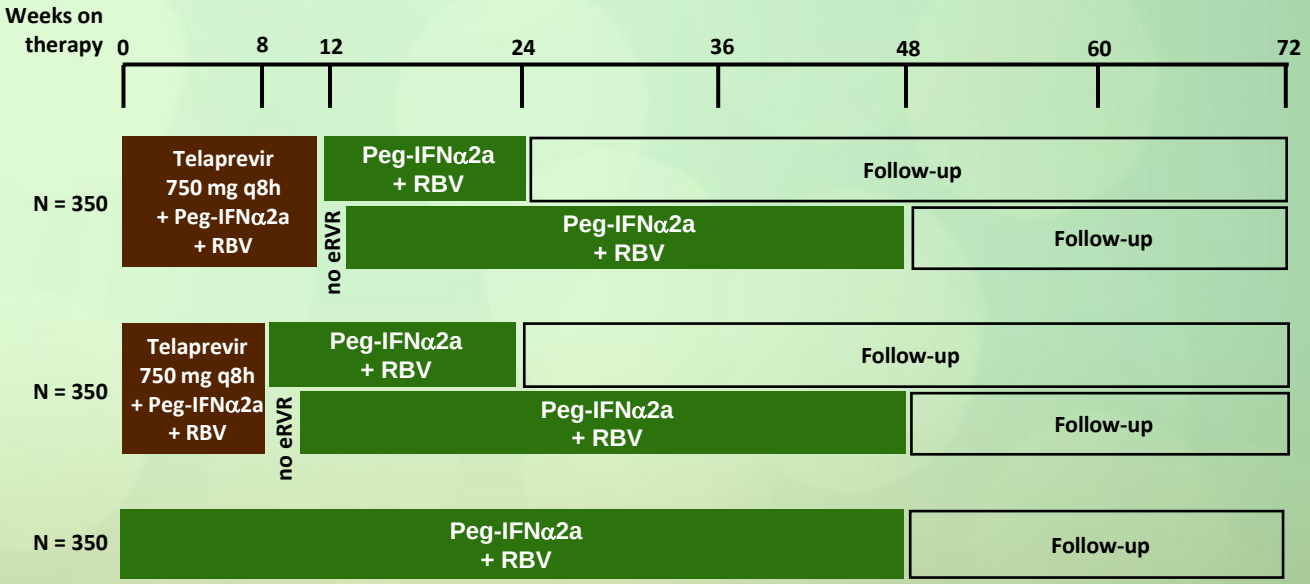
TREATMENT

Viral Eradication = Cure

cccDNA = covalently closed circular DNA

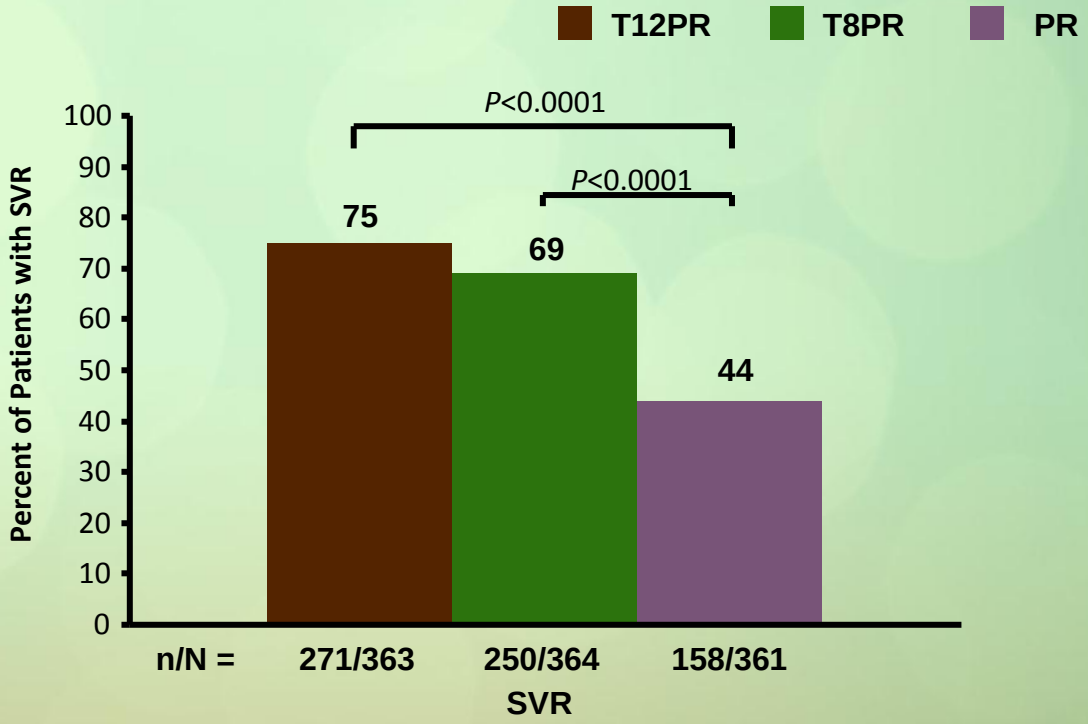
1. Pawlotsky JM. J Hepatol 2006;44:S10-S13; 2. Siliciano JD, Siliciano RF. J Antimicrob Chemother 2004;54:6-9;
3. Lucas GM. J Antimicrob Chemother 2005;55:413-416

Telaprevir Ph3 Trial: ADVANCE – GT1 Naïve

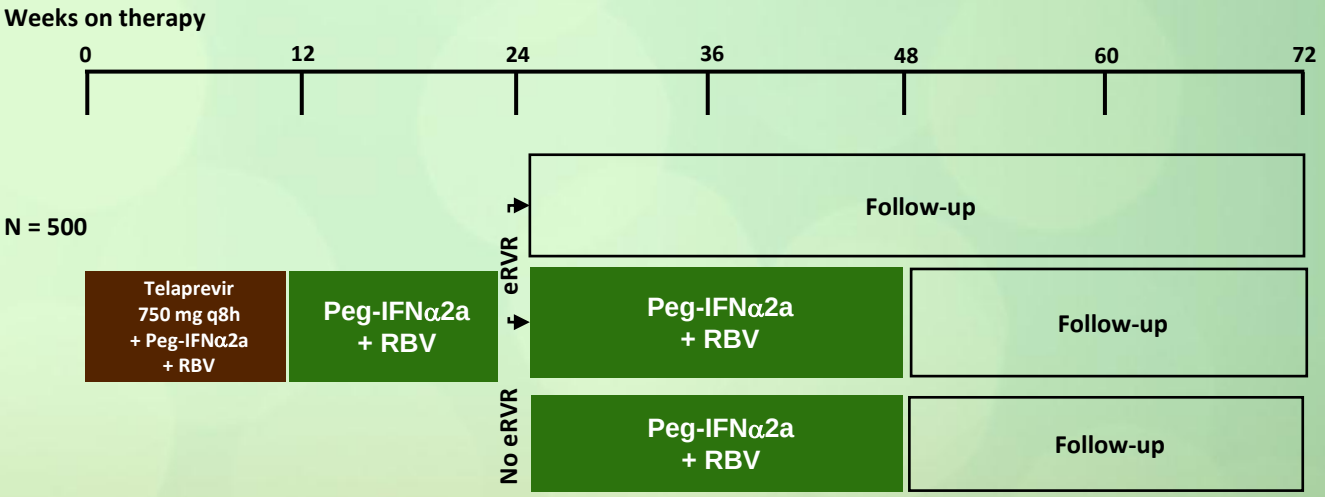


*eRVR = undetectable HCV RNA at week 4 and week 12
Telaprevir patients who achieve extended EVR (i.e., RVR + EVR) stop treatment after 24 weeks.

ADVANCE: SVR Rates

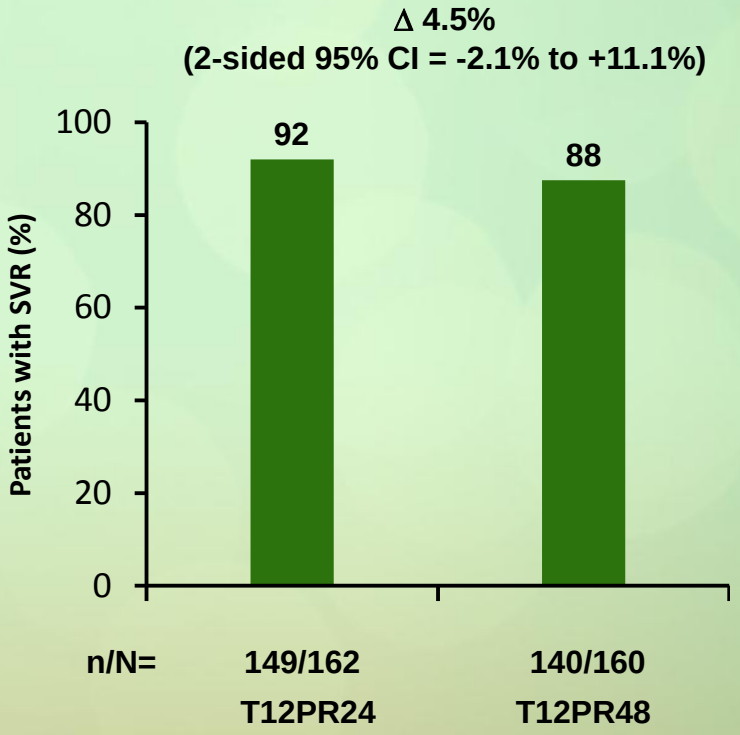


Telaprevir Ph3 Trial: ILLUMINATE – GT1 Naïve

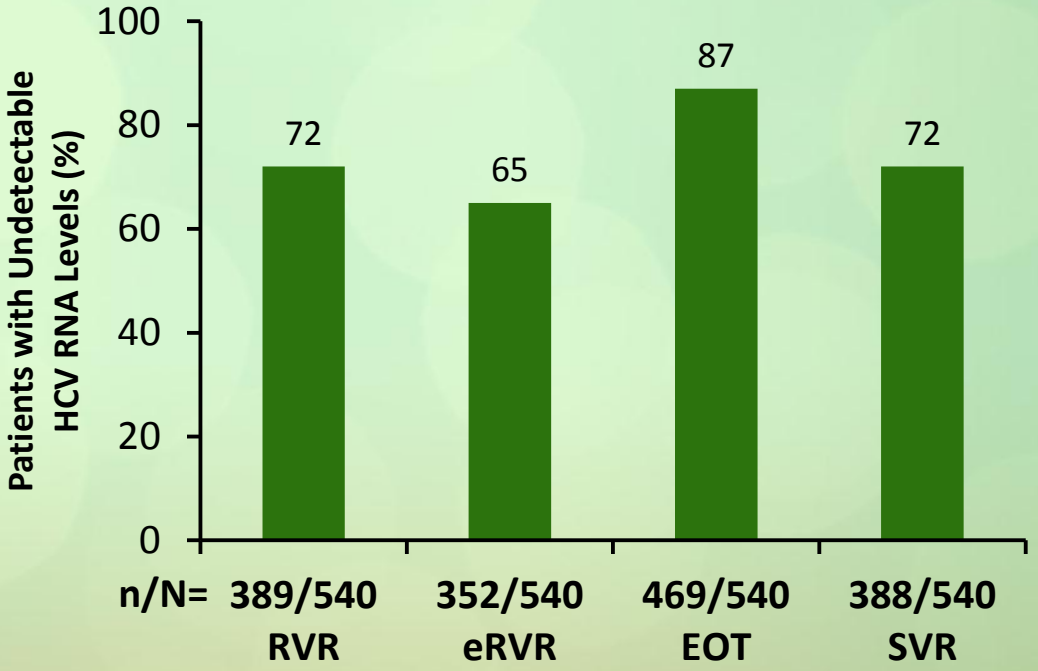


*eRVR = undetectable HCV RNA at week 4 and week 12

ILLUMINATE: SVR Rates – Noninferiority of 24-Week Regimen



ILLUMINATE: Undetectable HCV RNA Over time – ITT Population



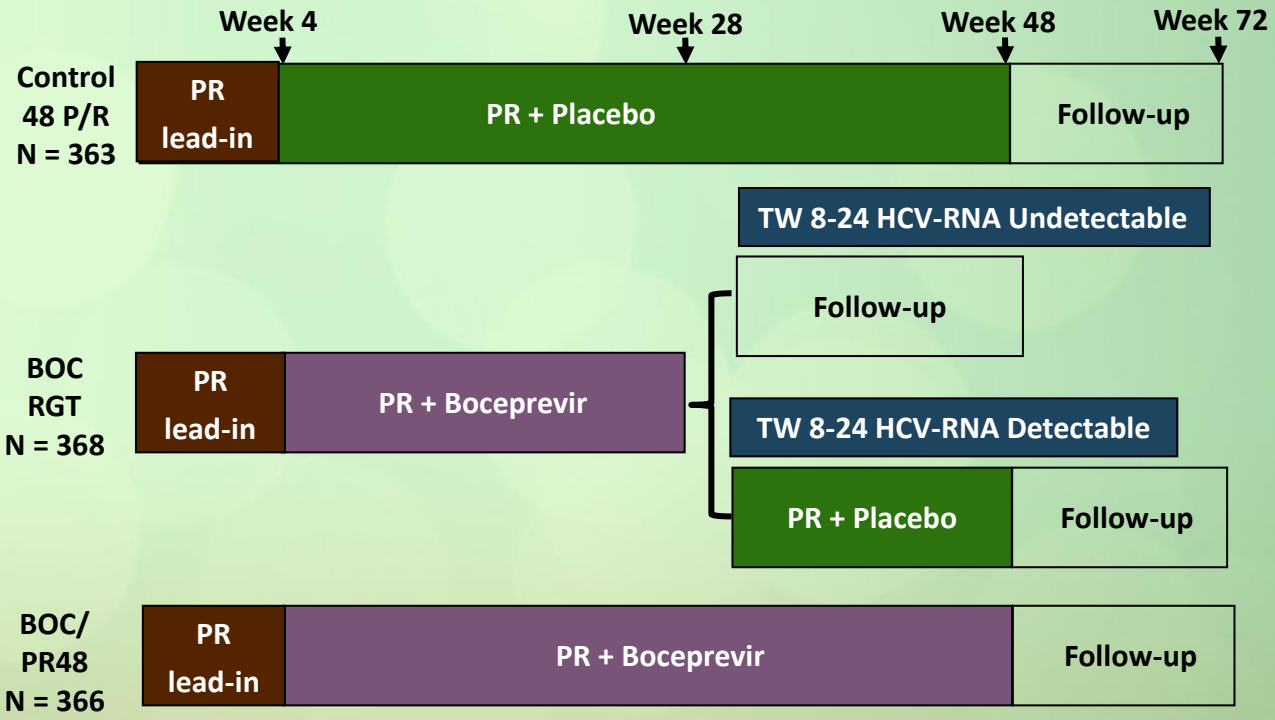
Sherman KE, et al. AASLD, 2010: Abstract LB-2.

Lessons From Advance[1] and Illuminate[2] Trials

- Response-guided therapy is non-inferior to 48 weeks of therapy in pts with an eRVR (defined as undetectable at week 4 and 24)
- Response-guided therapy will be possible in roughly 2/3 of Rx-naïve patients
- Shortened duration of therapy will reduce treatment D/Cs mainly due to a reduction in fatigue and anemia AEs
- Although rash is a common AE it should result in treatment D/C only rarely
- 12 weeks of TVR is required for the optimal virologic response
- Significantly improved SVRs seen in Black, Latino and cirrhotic patients

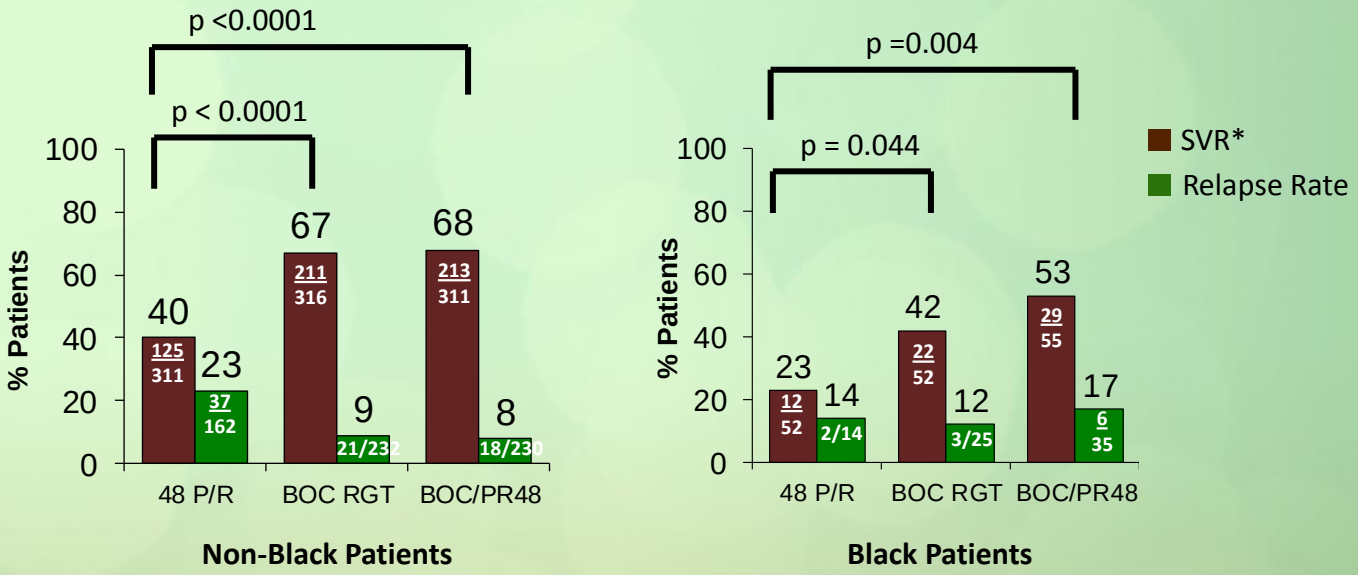
1. Jacobson IM, McHutchison JG,Dusheiko GM, et al. AASLD 2010: Abstract 211.
2. Sherman KE, Flamm SL, Afdhal NH, et al. AASLD 2010:LB-2.

SPRINT 2: Study Design



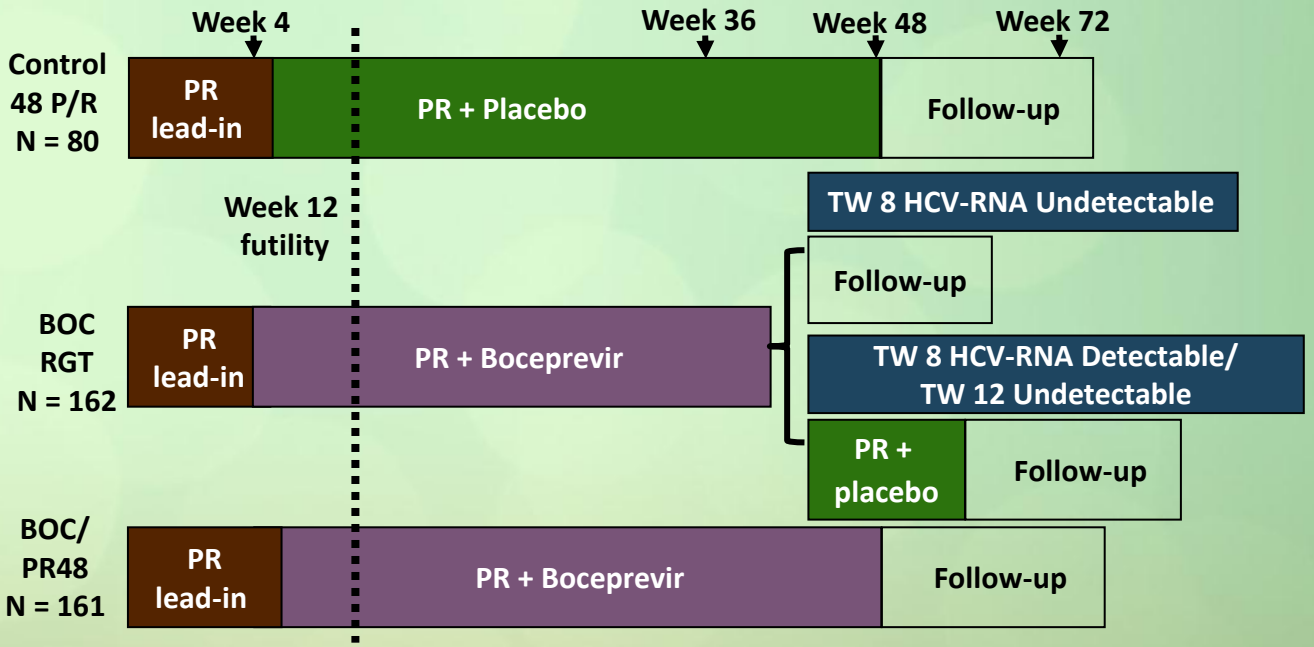
Peginterferon (P) administered subcutaneously at 1.5 µg/kg once weekly, plus ribavirin (R) using weight based dosing of 600-1400 mg/day in a divided daily dose
Boceprevir dose of 800 mg thrice daily

SPRINT 2: SVR and Relapse Rates (ITT)



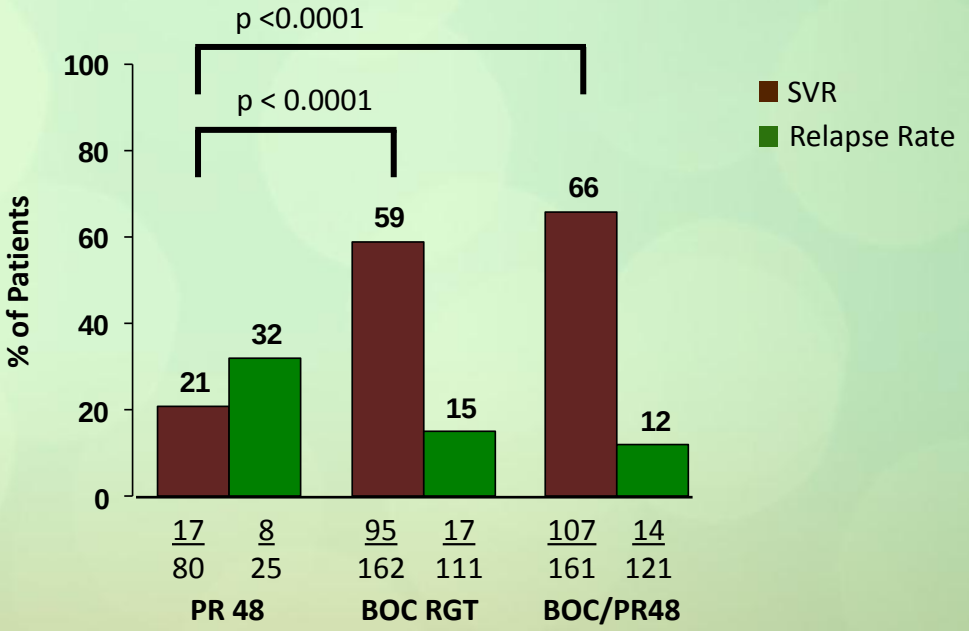
*SVR was defined as undetectable HCV RNA at the end of the follow-up period. The 12-week post-treatment HCV RNA level was used if the 24-week post-treatment level was missing (as specified in the protocol). A sensitivity analysis was performed counting only patients with undetectable HCV RNA documented at 24 weeks post-treatment and the SVR rates for Arms 1, 2 and 3 in Cohort 1 were 39% (122/311), 66% (207/316) and 68% (210/311), respectively and in Cohort 2 were 21% (11/52), 42% (22/52) and 51% (28/55), respectively.

RESPOND-2 Study Arms and Dosing Regimen



HCV-RNA measured by the Cobas TaqMan assay (Roche). Patients with detectable HCV-RNA (LLD=9.3 IU/mL) at week 12 were considered treatment failures. Peginterferon (P) administered subcutaneously at 1.5 µg/kg once weekly, plus Ribavirin (R) using weight based dosing of 600-1400 mg/day in a divided daily dose. Boceprevir dose of 800 mg thrice daily

RESPOND-2 SVR and Relapse Rates Intention to Treat Population



12-week HCV RNA level used if 24-week post-treatment level was missing. A sensitivity analysis where missing data was considered as non-responder, SVR rates for Arms 1, 2 and 3 were 21% (17/80), 58% (94/162) and 66% (106/161), respectively.

Lessons From Sprint-2[1] and Respond-2[2]

- BOC regimens will require a 4-week lead-in (LI) period with PEGIFN+RBV
- Response-guided therapy (defined as undetectable at weeks 8 and 28) will be possible in Rx-naïve patients
- 24 weeks of BOC is required for optimal virologic response in Rx-naïve patients
- LI + 32 weeks of therapy with BOC/PEGIFN/RBV+-12 wks PEGIFN/RBV will be necessary for prior treatment-failure patients
- Black patients will have a benefit with the addition of BOC over SOC

Poordad F,McCone J,Bacon BR, et al. AASLD 2010:LB-4. 2. Bacon BR, Gordon SC,Lawitz E, et al. AASLD 2010: Abstract 216.

Lessons From Extend* Study

- SVR after TVR-based therapy was durable (122 /123 undetectable) during a median 22 months follow-up
- In Rx-failures after TVR-based therapy variants associated with decreased sensitivity to TVR were no longer detectable in 89% of patients
- Suggests a reversion back to WT but the time period for this may be variable and dependent on which DRM has emerged

*Zeuzem S, Sulkowski MS, Zoulim F, et al. AASLD 2010:Abstract 227.

Monitoring for Viral Breakthrough and Resistant Variants

- Most cases occur during the first 12 weeks of treatment
- More often among 1a than those with 1b (24% vs 11%)
- HCV variants with substitutions at amino acids 36, 54, 155, and 156 within the NS3 protease
- Majority of patients who discontinued harbored the V36M/R155K double mutation

McHutchison JG, Manns MP, Muir AJ, et al. N Engl J Med. 2010;362:1292-1303.

Monitoring for Viral Breakthrough and Resistant Variants

Clinicians using telaprevir or boceprevir may need to verify the viral subtype prior to treatment initiation and frequently test for virologic breakthrough during the first 12 weeks of therapy to monitor for the emergence of drug-resistant variants, particularly in patients with HCV genotype 1a. The absolute intervals for monitoring will likely be clarified at the time of package labeling but will probably be at least every 4 weeks until Week 12.