A CONTINUING MEDICAL EDUCATION ACTIVITY

THE 46TH ANNUAL MEETING OF THE EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER (EASL)

Online Expert Poster Review and Discussion

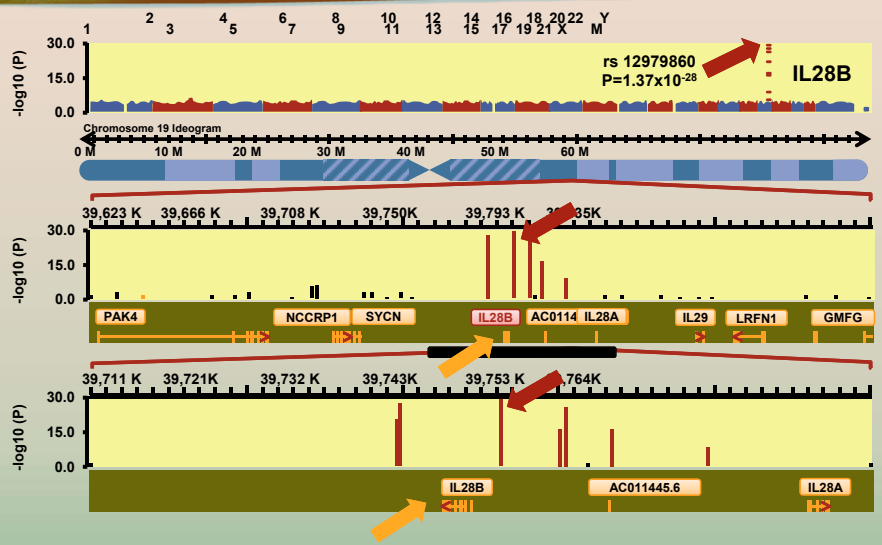
Jointly sponsored by the Postgraduate Institute for Medicine and ViralEd, LLC.

IL28B Polymorphism Predicts Virologic Response in Patients with Hepatitis C Genotype 1 Treated with Boceprevir Combination Therapy

F. Poordad, J.-P. Bronowicki, S.C. Gordon, S. Zeuzem, I.M. Jacobson, M.S. Sulkowski, T. Poynard, T.R. Morgan, M. Burroughs, V. Sniukiene, N. Boparai, C.A. Brass, J.K. Albrecht, and B.R. Bacon

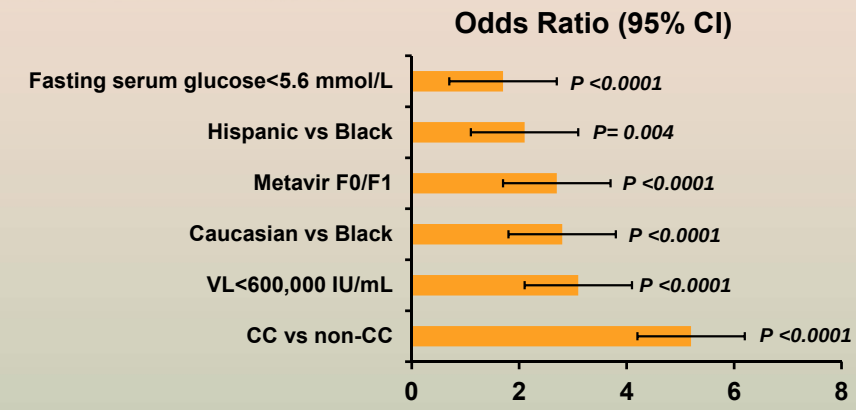
46th EASL Congress, Berlin, Germany
March 30-April 3, 2011
Abstract 12

A Polymorphism Upstream of the IL28B Gene is Strongly Associated with SVR



Ge et al, Nature, 2009 (7262) p399-401

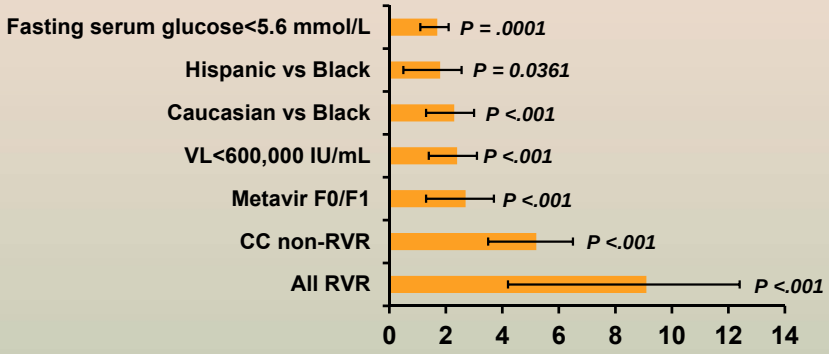
IL-28B Polymorphism is the Strongest Baseline Predictor of SVR Using Peginterferon/Ribavirin



Covariates - rs12979860 (2-level), ethnicity (4-level), age (≤ 40), gender, BMI (< 30), VL (≤ 600,000), ALT (≤ ULN), fasting glucose (< 5.6), hepatic steatosis (N/Y[>0%]), fibrosis (METAVIR F012), RBV (>13 mg/kg/d)

Thompson AJ, et al Gastroenterology 2010 (139) p120-129

RVR is Stronger than All Baseline Predictors of SVR Using Peginterferon/Ribavirin



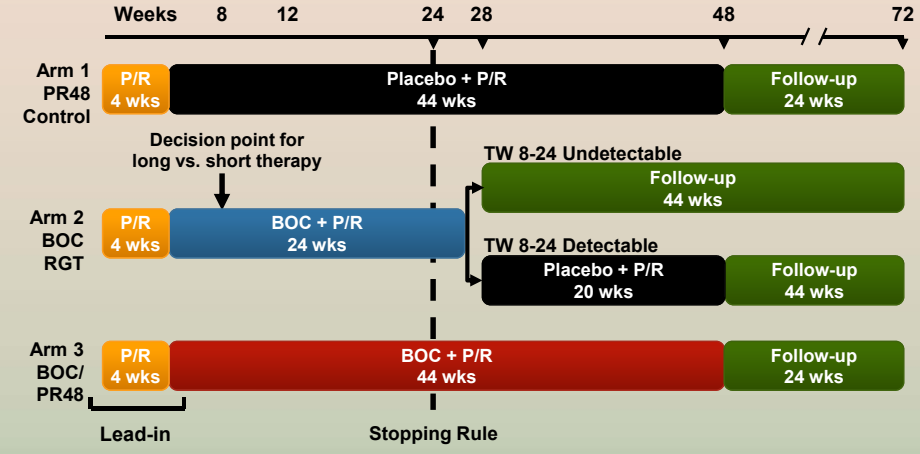
Comparison of RVR vs no RVR + non-CC genotype
Comparison of no-RVR + CC genotype vs no-RVR + non-CC genotype
Co-variates : RVR vs no RVR + CC genotype vs no RVR + non-CC genotype (3-level), ethnicity (4-level), age (≤ 40), gender, BMI (< 30), VL (≤ 600,000), ALT (≤ ULN), fasting glucose (< 5.6), hepatic steatosis (N/Y[>0%]), fibrosis (METAVIR F012), RBV (>13 mg/kg/d)

Thompson AJ, et al Gastroenterology 2010 (139) p120-129

Study Objectives

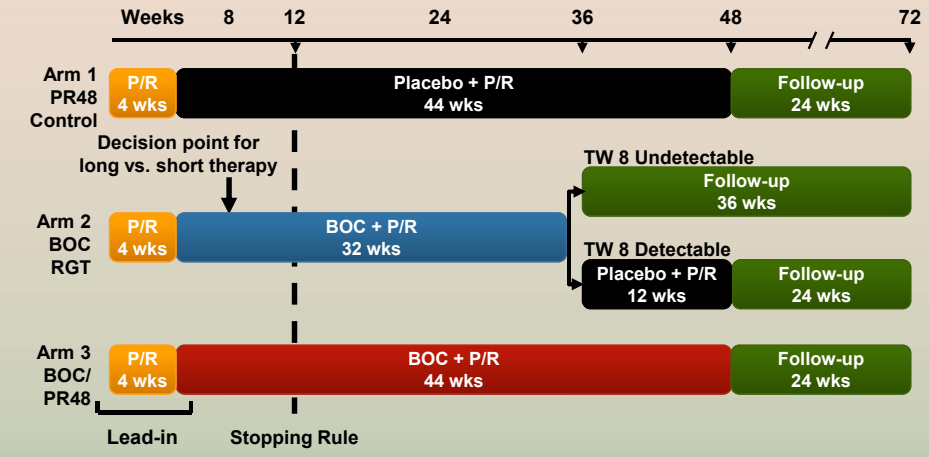
- Evaluate IL-28B polymorphism as a predictor of SVR in SPRINT-2 and RESPOND-2
  - As a baseline predictor with or without lead-in response (week 4)

SPRINT-2 Treatment-Naïve Patients Study Design



Stopping Rule: Patients with detectable HCV-RNA at week 24 were discontinued from treatment for futility. 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. BOC administered 800 mg TID.

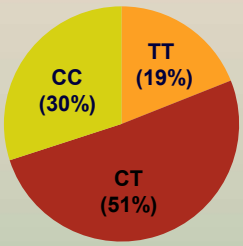
RESPOND-2 Previous Treatment Failure Patients Study Design



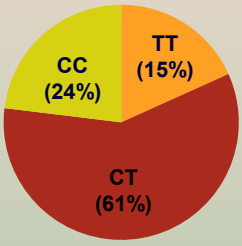
Stopping Rule: Patients with detectable HCV-RNA at week 24 were discontinued from treatment for futility. Peginterferon (P) administered subcutaneously at 1.5 µg/kg once weekly, plus Ribavirin (R) using weight based dosing of 600-1400 mg/day in a divided daily dose. BOC administered 800 mg TID.

Distribution of IL-28B Polymorphisms

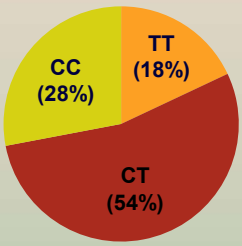
- IL28B polymorphisms assessed with DNA Sanger Sequencing
  - rs12979860/rs12980275/rs8103143
- Patients analyzed were consented prospectively and received at least one dose of BOC or placebo (63%)



SPRINT 2
62% (653/1048)

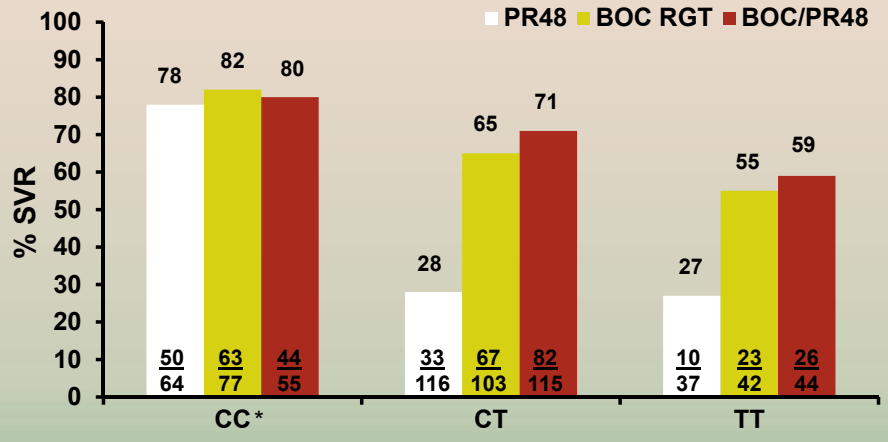


RESPOND 2
66% (259/394)



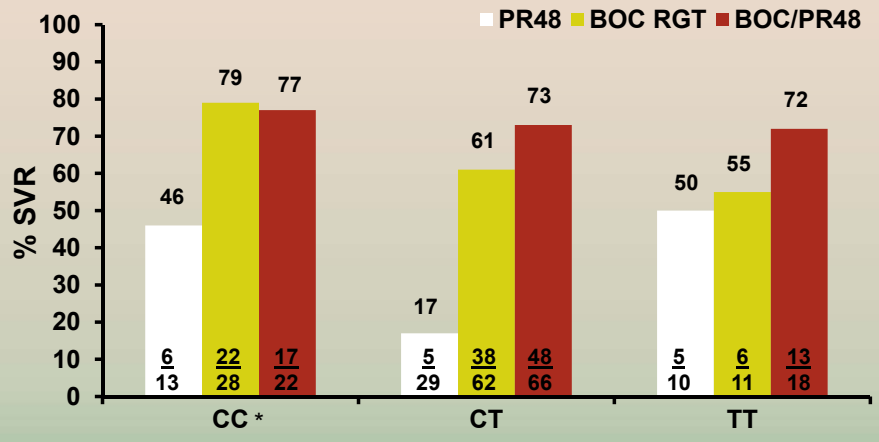
Total
63% (912/1442)

SPRINT-2: SVR by IL28B Polymorphism



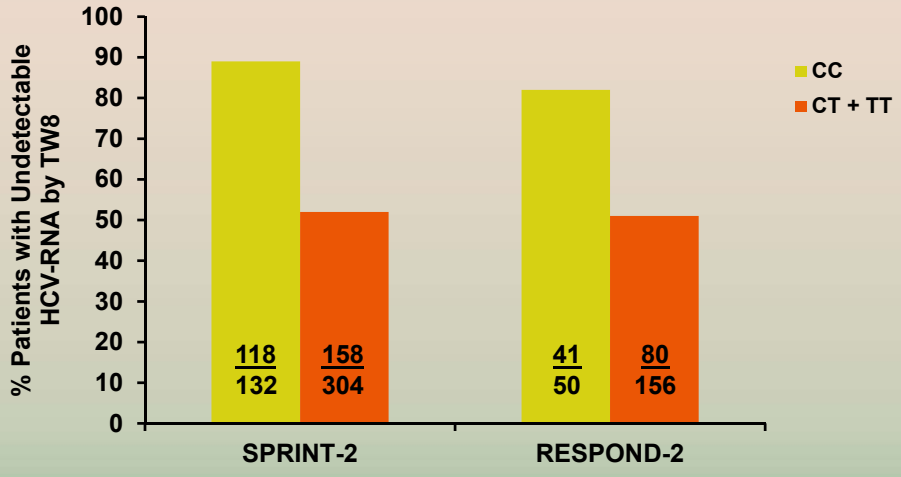
*~90% eligible for short duration therapy

RESPOND-2: SVR by IL28B Polymorphism



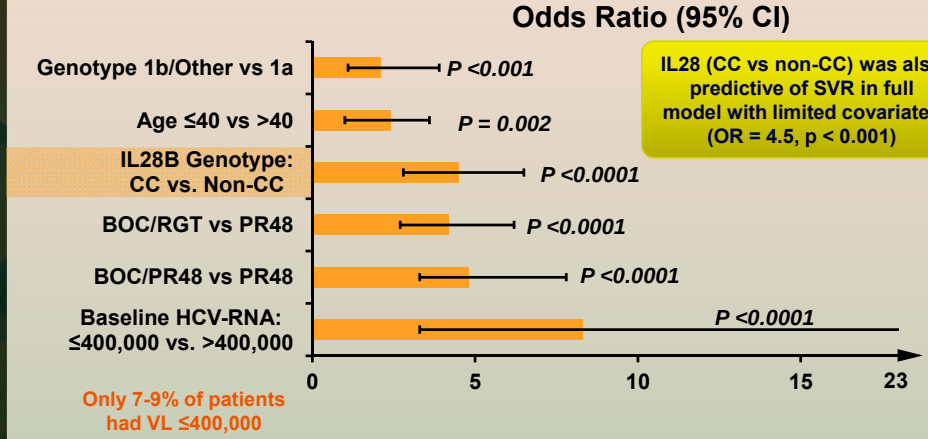
*~80% eligible for short duration therapy

IL-28B CC Polymorphism Predicts Week 8 Response* with Boceprevir



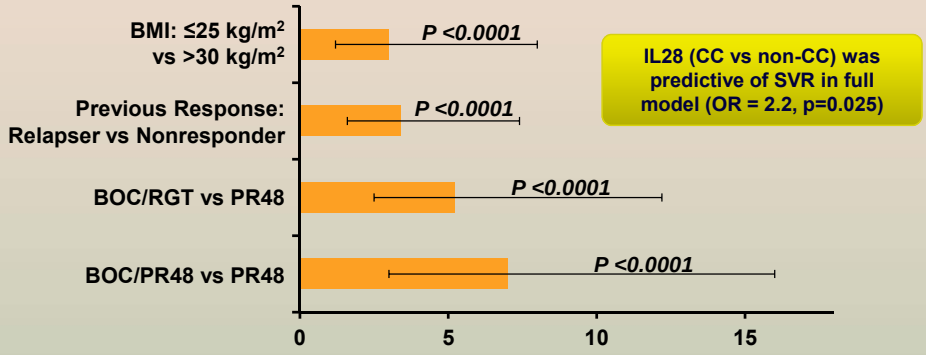
*Decision point for short vs. long treatment duration with RGT

SPRINT-2: IL-28B CC Polymorphism as a Predictor of SVR (Multiple Stepwise Logistic Regression Model)



Only covariates remaining significant at α=0.05 after adjustment for the other variables were retained in the model as shown in the figure. Factors entered but not retained in the model were, region, race, gender, weight, BMI, steatosis, platelets, ALT, statin use, and fibrosis

RESPOND-2: IL-28B CC Polymorphism as a Predictor of SVR (Multiple Stepwise Logistic Regression Model)



Only covariates remaining significant at α=0.05 after adjustment for the other variables were retained in the model as shown in the figure. Factors entered but not retained in the model were IL28 polymorphism, HCV 1 subtype, race, gender, age, weight, platelets, fibrosis, steatosis, previous treatment (peginterferon alfa-2a vs peginterferon alfa-2b), ALT, baseline viral load, statin use and region

IL28B is a Strong Baseline Predictor of Interferon Response at End of Lead-in (≥1 Log Decline at TW 4)

RESPOND-2 (effect)	Odds Ratio (95% CI)	p-value
IL28B Genotype: CC vs. Non-CC	4.5 (1.5 – 13.7)	0.007
Previous Response: Relapser vs Nonresponder	3.2 (1.6 – 6.4)	<0.001
BOC/PR48 vs PR48	0.2 (0.05 – 0.7)	0.01
BOC/RGT vs PR48	0.14 (0.4 – 0.5)	0.004
SPRINT-2 (effect)	**Odds Ratio (95% CI)**	**p-value**
IL28B Genotype: CC vs. Non-CC	15.8 (6.3 – 39.8)	<0.001
Baseline HCV-RNA: ≤400,000 vs. >400,000	4.3 (1.3 – 14.6)	0.02
Steatosis 0 vs >0	2.6 (1.6 – 0.7)	0.0003
Race (non-black vs black)	2.1 (1.2 – 3.7)	0.007
Gender (female vs male)	1.7 (1.1 – 2.6)	0.03
BMI: ≤25 kg/m² vs >30 kg/m²	0.4 (0.2 to 0.7)	0.001

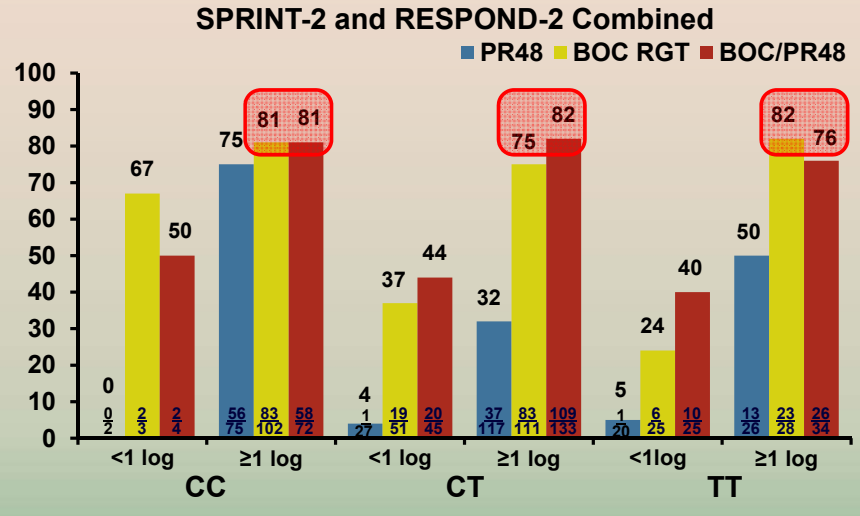
Only covariates remaining significant at α=0.05 after adjustment for the other variables were retained in the model as shown in the table.

IL28B is No Longer an Important Predictor of SVR when Lead-in Response is Considered

RESPOND-2 (effect)	Odds Ratio (95% CI)	*P*-value
BOC/PR48 vs PR48	11.4 (4.6 to 28.0)	<.0001
BOC/RGT vs PR48	7.9 (3.3 to 18.9)	<.0001
Previous Response: Relapser vs Nonresponder	2.2 (1.2 to 4.3)	0.01
Log decline in HCV-RNA at TW 4 (continuous variable)	**1.8 (1.3 to 2.4)**	**<.0001**
BMI: ≤25 kg/m^2 vs >30 kg/m^2	3.4 (1.4 to 8.2)	0.01
SPRINT-2 (effect)	**Odds Ratio (95% CI)**	***P*-value**
BOC/PR48 vs PR48	7.0 (4.1, 12.0)	< 0.0001
BOC/RGT vs PR48	6.0 (3.5, 10.2)	< 0.0001
Baseline HCV-RNA: ≤400,000 vs. >400,000 IU/mL	5.8 (1.9, 17.5)	0.002
Log decline in HCV-RNA at TW 4 (continuous variable)	**2.6 (2.1, 3.0)**	**< 0.0001**
Genotype: 1b/others vs 1a	2.3 (1.5, 3.6)	< 0.001
BMI: 25-30 kg/m^2 vs. >30 kg/m^2	2.3 (1.4, 3.9)	0.002
BMI: ≤25 kg/m^2 vs. >30 kg/m^2	1.9 (1.1, 3.3)	0.02

Only covariates remaining significant at α=0.05 after adjustment for the other variables were retained in the model as shown in the table.

Early Interferon Response (Lead-in) Further Defines Likelihood of Success for Non-CC Patients



Summary

- IL-28B CC polymorphism is a strong predictor of week 4 and 8 viral response in both SPRINT 2 and RESPOND 2 trials
- CC polymorphism: ~80-90% of naïve and treatment experienced patients qualify for shorter duration of PR/BOC
- On treatment interferon response (lead-in) is a stronger predictor of SVR than any single baseline variable including IL-28B polymorphism
- IL-28B used with lead-in response are powerful predictors of SVR

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Telaprevir Substantially Improved SVR Rates Across All IL28B Genotypes in the ADVANCE Trial

IM Jacobson, I Catlett, P Marcellin, NH Bzowej, AJ Muir, N Adda, L Bengtsson, S George, S Seepersaud, R Ramachandran, K Sussky, RS Kauffman, M Botfield

46th EASL Congress, Berlin, Germany
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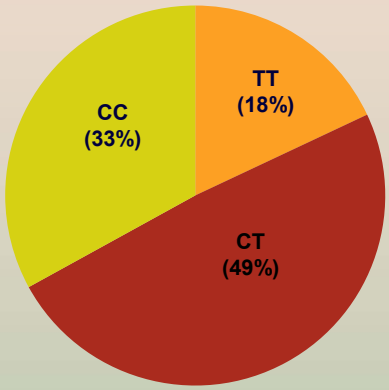
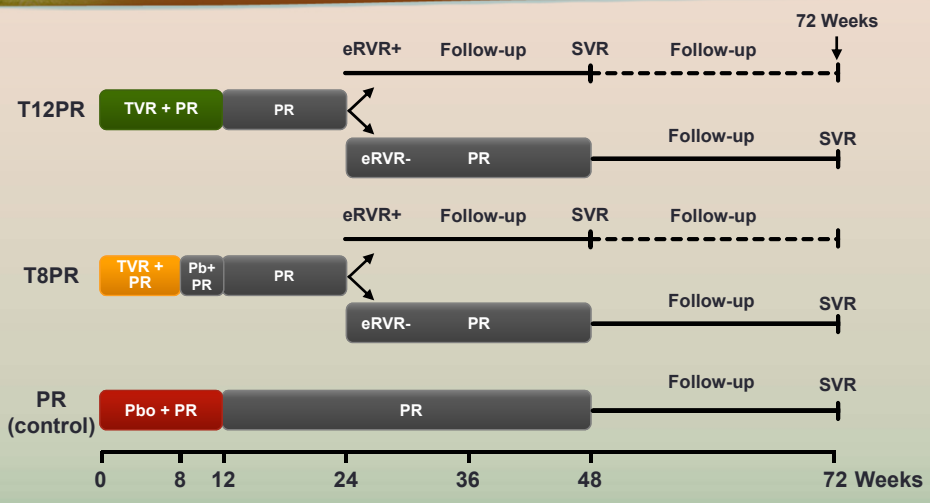
Abstract 13

Distribution of IL28B Genotypes in ADVANCE

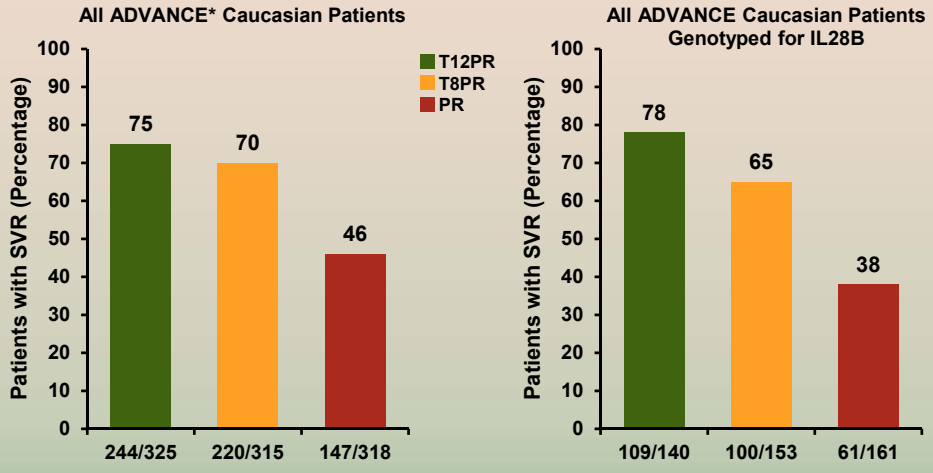


Samples from 42% (454/1088) of ADVANCE patients were available in the IL28B dataset.

Study Design of ADVANCE Trial

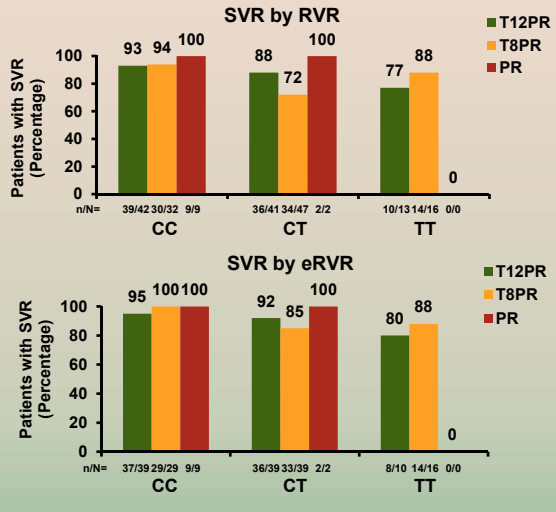


SVR Rates



*Overall SVR rates were 73%, 69%, and 44% in the T12PR, T8PR, and PR, respectively.

SVR Rates in ADVANCE in Patients Genotyped for IL28B Who had RVR or eRVR



- Among patients treated telaprevir-based regimen who had eRVR, 91% achieved SVR (97% of CC, 88% of TT) and were assigned to 24 weeks of therapy
- Among patients treated with a telaprevir-based regimen who did not have eRVR, 43% achieved SVR (63% of CC, 33% of CT, 46% of TT) and were assigned to 48 weeks of therapy

Conculsions

- Telaprevir in combination with peginterferon alfa-2a/ribavirin increased SVR across all IL28B genotypes
- The greatest increment in efficacy occurred in CT/TT patients. CC patients also had improvement in SVR rates up to 90% in T12 PR, with 78% of patients receiving 24 weeks of total therapy
- Patients with the CC genotype who were treated with telaprevir had the highest rate of RVR and eRVR
  - CC patients nearly always achieved SVR if they attained RVR or eRVR
  - CT and TT patients with RVR or eRVR were highly likely to attain SVR
  - Among patients no having eRVR, CT/TT patients had lower SVR rates than CC patients
- Further studies, including non-Caucasians, are needed to confirm these findings