Poster #797

High Correlation Between Week 4 and Week 12 as the Definition for Null Response to Peginterferon alfa (PEG) Plus Ribavirin (R) Therapy: Results From the IDEAL Trial

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Abstract

Background: The objective of this retrospective analysis was to investigate the correlation between HCV viral load declines at treatment weeks (TW) 4 and 12 in patients from the IDEAL trial in order to delineate a week 4 null response definition.

Methods: 3070 treatment-naive, HCV genotype 1 infected patients were treated for up to 48 weeks with ribavirin 800-1400mg/day plus PEG2b 1.5 or 1 mcg/kg/week, or PEG2a 180mcg/week plus ribavirin 1000-1200mg/day. Simple linear regression was used to assess the relationship between TW4 and TW12 log viral decline, and Pearson's correlation coefficient (r) was computed. Concordance in subjects who had data at both TWs 4 and 12 was assessed using a definition for null response of <1 log decline at TW4 vs <2 log at TW12. Testing for IL28B was performed in 1604 patients.

Results: There is a high positive correlation between HCV viral load decline at TWs 4 and 12 for patients receiving standard of care therapy: PEG2b 1.5/R (r=0.76), PEG2a/R (r=0.73), or PEG2b 1.0/R (r=0.78) (p<0.001 for each). Null response defined as a <2 log decline at TW12 corresponds to ~0.7-1.1 log decline at TW4 for PEG2b 1.5/R. Concordance of null or 'non-null' response defined by both TW4 and TW12 definitions was high for each of the treatment arms (Table) and for all 3 arms combined 89% (2459/2777) regardless of IL28b genotype, CC 98% (466/474) and CT/TT 83% (785/943). Nearly all patients who met the TW4 or TW12 definition for null response had the less favorable CT or TT allele.

Conclusions: TW4 viral load decline of <1 log approximates to that of <2 logs at TW12 and is an earlier predictor of null response. The TW4 definition of null response may have increased utility in aiding early treatment decisions.

Concordance of TW4 <1 log Viral Decline and TW12 <2 log Viral Decline from Baseline

		TW12 Response					
		ALL		IL28B* CC		IL28B* CT/TT	
TX	WK 4 Resp	Null†	Non-Null	Null†	Non-null	Null†	Non-null
PEG2b1.5/R	Null‡	150	56	5	0	68	29
	Non-null	55	639	0	141	30	182
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PEG2b1.0/R	Null‡	235	51	4	3	113	28
	Non-null	69	577	5	161	31	133
	Concordance	87%		95%		81%	

*Not all subjects had IL28B genotyping available.
†<2 log decrease from baseline.
‡<1 log decrease from baseline.

Note: This abstract has been modified since submission.

Background

- Current guidelines recommend that treatment-naive patients with chronic hepatitis C virus (HCV) genotype 1 infection be treated for a minimum duration of 12 weeks with peginterferon (PEG-IFN) alfa plus ribavirin (RBV) before a decision is made regarding continuation of therapy[1]
  - 97% to 100% of genotype 1 patients who fail to attain an early virologic response (<2-$\log_{10}$ decline in HCV-RNA at week 12 of treatment) will fail to attain sustained virologic response (SVR)[2,3]
  - Patients who do not attain early virologic response may be withdrawn from treatment[1]

Aim

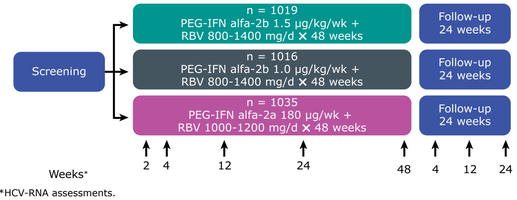
- To investigate the correlation between declines in HCV viral load at treatment weeks 4 and 12

Patients and Methods

Study Design

- IDEAL was a phase 3b, randomized, parallel-arm trial conducted at 118 academic and community centers in the United States (**Figure 1**)
  - Double-blinded for PEG-IFN alfa-2b dose
  - PEG-IFN alfa-2a and RBV administered open-label

Figure 1. IDEAL study design.



*HCV-RNA assessments.
PEG-IFN = peginterferon; RBV = ribavirin.

Patients

- Treatment-naive patients with chronic hepatitis C, genotype 1 infection, 18 to 70 years old, weighing 40 to 125 kg, and with compensated liver disease

Assessments and Definitions

- HCV-RNA levels were assessed at baseline, treatment weeks 2, 4, 12, 24, and 48, and follow-up weeks 4, 12, and 24
- SVR was defined as undetectable HCV-RNA at the end of follow-up (week 24 or, if missing, week 12)
  - HCV-RNA was measured using COBAS® TaqMan® (Roche; lower limit of quantitation, 27 IU/mL)
- Null response at treatment week 12 was defined as <2-$\log_{10}$ decline in HCV-RNA level compared with baseline
- Simple linear regression was used to assess the relationship between treatment-week-4 and week-12 $\log_{10}$ viral decline, and the Pearson correlation coefficient (r) was computed
  - Concordance was defined as the number of patients with either <1-$\log_{10}$ decline at week 4 and <2-$\log_{10}$ decline at week 12 or ≥1-$\log_{10}$ decline at week 4 and ≥2-$\log_{10}$ decline or undetectable at week 12 divided by the total number of patients with both treatment-week-4 and week-12 HCV-RNA levels available
- Testing for IL28B was performed in 1604 patients

Results

Treatment Week 4

- At treatment week 4, 25% (750/2944) of patients had <1-$\log_{10}$ decline in HCV-RNA from baseline
  - Patients who had a week-4 HCV-RNA <1-$\log_{10}$ decline from baseline had a low SVR rate of 4% (31/750)
    - 5% with PEG-IFN alfa-2b 1.5 µg/kg/wk + RBV
    - 5% with PEG-IFN alfa-2a 180 µg/wk + RBV
    - 3% with PEG-IFN alfa-2b 1.0 µg/kg/wk + RBV

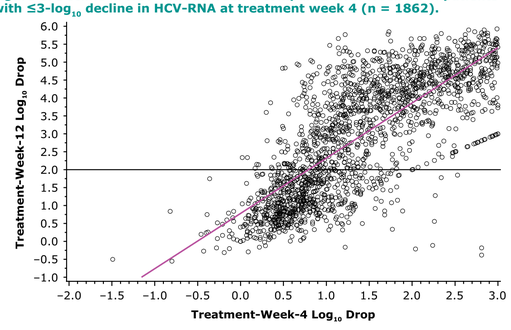
Treatment Week 12

- According to previous studies, 97% to 100% of genotype 1 patients with <2-$\log_{10}$ decline in HCV-RNA at week 12 failed to achieve SVR[1-3]
- Patients with an undetectable HCV-RNA at week 12 had an SVR rate of 79% (975/1239), and those with a detectable, ≥2-$\log_{10}$ decline in HCV-RNA from baseline had an SVR rate of 25% (220/889)

Correlation of HCV Viral Load Decline at Weeks 4 and 12

- There is a high positive correlation between HCV viral load decline at weeks 4 and 12 for patients receiving standard of care therapy ($P < .001$ for each treatment arm):
  - PEG-IFN alfa-2b 1.5 µg/kg/wk + RBV r = 0.76
  - PEG-IFN alfa-2a 180 µg/wk + RBV r = 0.73
  - PEG-IFN alfa-2b 1.0 µg/kg/wk + RBV r = 0.78
- To closely analyze the correlation between treatment weeks 4 and 12, a graph of the patients with ≤3-$\log_{10}$ decline in HCV-RNA from baseline to treatment week 4 is shown in **Figure 2**
  - For this subgroup (n = 1862), high positive correlation between HCV viral load decline at weeks 4 and 12 is also seen (r = 0.76)

Figure 2. Decline in HCV-RNA at week 4 compared with week 12 in patients with ≤3-$\log_{10}$ decline in HCV-RNA at treatment week 4 (n = 1862).



Concordance of HCV-RNA Decline at Weeks 4 and 12

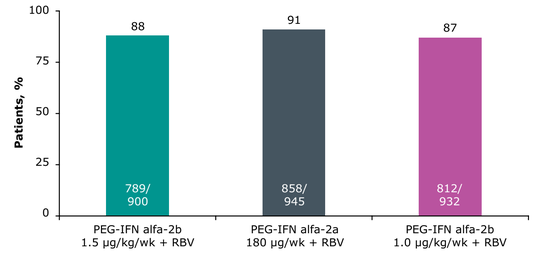
- For all 3 arms combined concordance of <1-$\log_{10}$ decline at week 4 and null response at week 12 or ≥1-$\log_{10}$ decline at week 4 and "non-null" response at week 12 was 89% (2459/2777)
  - Concordance of response defined by both week 4 and week 12 was high for each of the treatment arms (**Table 1** and **Figure 3**)
- Classification and regression tree analysis on all patients (n = 3070) determined that a 1.03-$\log_{10}$ decline in HCV-RNA at treatment week 4 most closely predicted null response (<2-$\log_{10}$ decline) at treatment week 12

Table 1. Concordance of Week-4 <1-$\log_{10}$ Viral Decline and Week-12 <2-$\log_{10}$ Viral Decline From Baseline Among Patients With Both Week-4 and -12 HCV-RNA Levels

		Week-12 Response	
	Week-4 Response	Null*	Non-Null
PEG-IFN alfa-2b 1.5 µg/kg/wk + RBV (n = 900)	<1-$\log_{10}$ decline	150	56
	≥1-$\log_{10}$ decline	55	639
PEG-IFN alfa-2a 180 µg/wk + RBV (n = 945)	<1-$\log_{10}$ decline	148	65
	≥1-$\log_{10}$ decline	22	710
PEG-IFN alfa-2b 1.0 µg/kg/wk + RBV (n = 932)	<1-$\log_{10}$ decline	235	51
	≥1-$\log_{10}$ decline	69	577

*<2-$\log_{10}$ decrease from baseline.
PEG-IFN = peginterferon; RBV = ribavirin.

Figure 3. Concordance between treatment-week-4 and -12 response among patients with both week-4 and -12 HCV-RNA levels.



PEG-IFN = peginterferon; RBV = ribavirin.

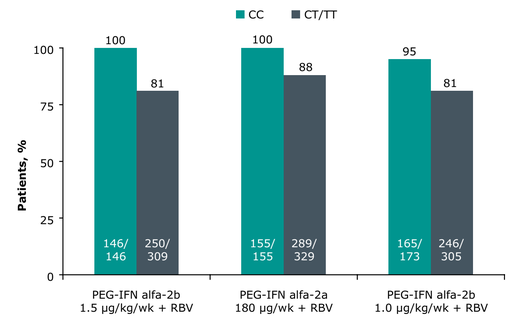
- Of the 705 patients with a week-4 viral load decline of <1 $\log_{10}$ and available week-12 HCV-RNA level, 71 patients did not meet week-12 or week-24 futility stopping rules, but only 28 (4%) ultimately achieved an SVR
- Among the patients with IL28B genotyping, concordance was 98% (466/474) in patients with the CC allele and 83% (785/943) in those with the CT/TT allele (**Table 2** and **Figure 4**)
  - 95% (409/430) of patients who had <1-$\log_{10}$ decline at week 4 and/or <2-$\log_{10}$ decline at week 12 had the less favorable CT or TT allele

Table 2. Concordance of Week-4 <1-$\log_{10}$ Viral Decline and Week-12 <2-$\log_{10}$ Viral Decline From Baseline With IL28B Genotyping*

		IL28B* CC		IL28B* CT/TT	
		Week-12 Response			
	Week-4 Response	Null†	Non-null	Null†	Non-null
PEG-IFN alfa-2b 1.5 µg/kg/wk + RBV	<1-$\log_{10}$ decline	5	0	68	29
	≥1-$\log_{10}$ decline	0	141	30	182
PEG-IFN alfa-2a 180 µg/wk + RBV	<1-$\log_{10}$ decline	4	0	70	31
	≥1-$\log_{10}$ decline	0	151	9	219
PEG-IFN alfa-2b 1.0 µg/kg/wk + RBV	<1-$\log_{10}$ decline	4	3	113	28
	≥1-$\log_{10}$ decline	5	161	31	133

*187 patients missing.
†<2-$\log_{10}$ decrease from baseline.
PEG-IFN = peginterferon; RBV = ribavirin.

Figure 4. Concordance between weeks 4 and 12 according to baseline IL28B genotype.*



*Among patients with both week-4 and week-12 HCV-RNA levels.
PEG-IFN = peginterferon; RBV = ribavirin.

Conclusions

- The negative predictive value of week-4 viral load decline of <1 $\log_{10}$ is 96%
- A treatment-week-4 viral load decline of <1 $\log_{10}$ approximates that of a <2-$\log_{10}$ decline at treatment week 12 and is an earlier predictor of null response based on correlation, concordance, and CART analyses
- The treatment-week-4 correlation with week-12 null response may have increased utility in aiding early treatment decisions

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2. Davis GL, et al. *Hepatology*. 2003;38(3):645-52.
3. Fried MW, et al. *N Engl J Med*. 2002;347(13):975-82.

Disclosures

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Supported by Schering-Plough Corporation, now Merck & Co. Inc., Whitehouse Station, NJ, USA.

Poster #797

High Correlatio Peginterferon

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Abstract

Background: The objective of this retrospective analysis was to investigate the correlation between HCV viral load declines at treatment weeks (TW) 4 and 12 in patients from the IDEAL trial in order to delineate a week 4 null response definition.

Methods: 3070 treatment-naive, HCV genotype 1 infected patients were treated for up to 48 weeks with ribavirin 800-1400mg/day plus PEG2b 1.5 or 1 mcg/kg/week, or PEG2a 180mcg/week plus ribavirin 1000-1200mg/day. Simple linear regression was used to assess the relationship between TW4 and TW12 log viral decline, and Pearson's correlation coefficient (r) was computed. Concordance in subjects who had data at both TWs 4 and 12 was assessed using a definition for null response of <1 log decline at TW4 vs <2 log at TW12. Testing for IL28B was performed in 1604 patients.

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*Not all subjects had IL28B genotyping available.
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- To investigate the correlation between declines in HCV viral load at treatment weeks 4 and 12

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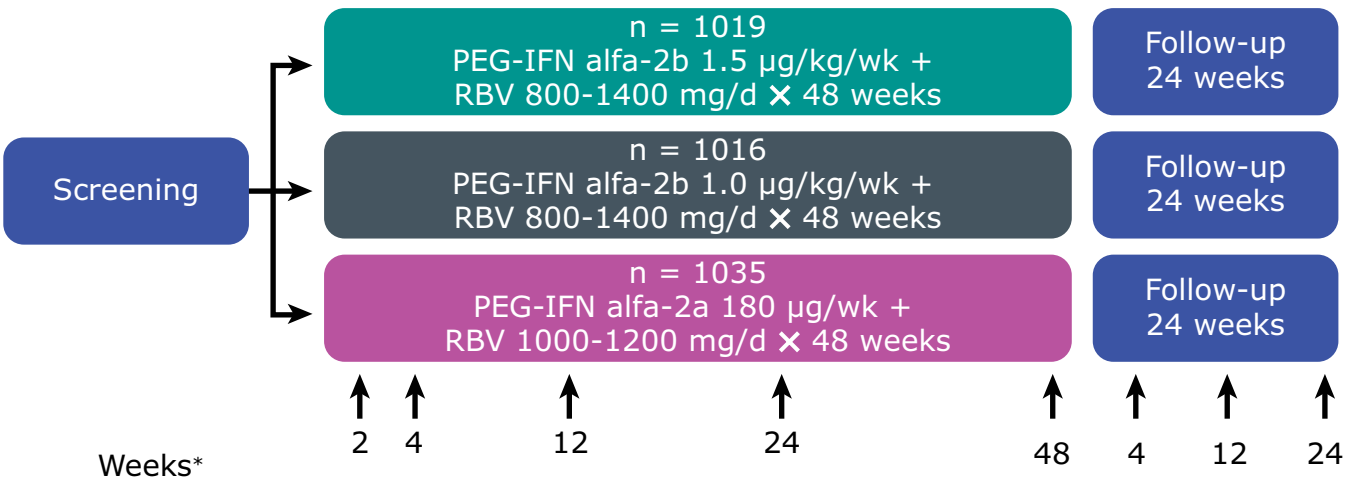
Figure 1. IDEAL study design.



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Results

Treatment Week 4

- At treatment week 4, 25% (750/2944) of patients had <1-$\log_{10}$ decline in HCV-RNA from baseline
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    - 3% with PEG-IFN alfa-2b 1.0 µg/kg/wk + RBV

Treatment Week 12

- According to previous studies, 97% to 100% of genotype 1 patients with <2-$\log_{10}$ decline in HCV-RNA at week 12 failed to achieve SVR[1-3]
- Patients with an undetectable HCV-RNA at week 12 had an SVR rate of 79% (975/1239), and those with a detectable, ≥2-$\log_{10}$ decline in HCV-RNA from baseline had an SVR rate of 25% (220/889)

Correlation of HCV Viral Load Decline at Weeks 4 and 12

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  - PEG-IFN alfa-2b 1.5 µg/kg/wk + RBV r = 0.76
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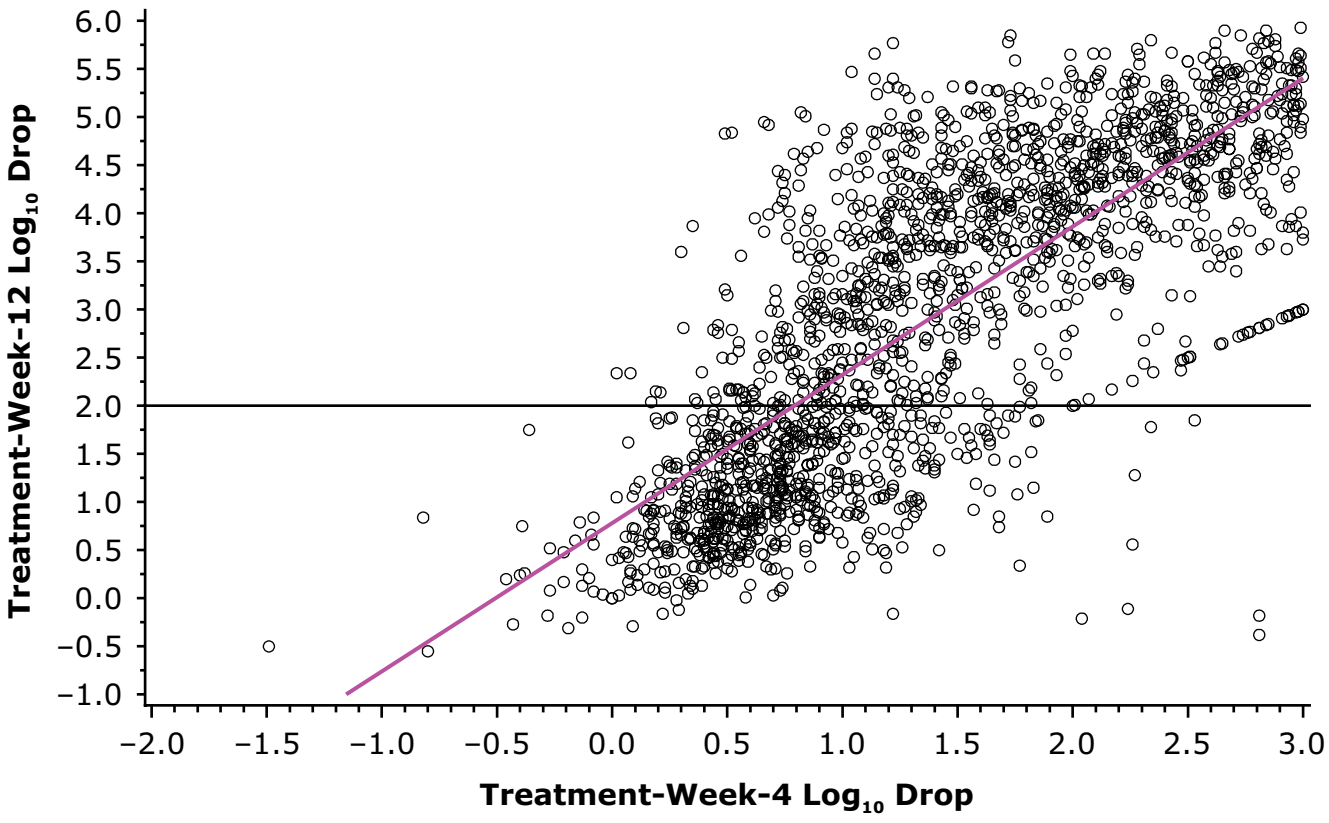
  - For this subgroup (n = 1862), high positive correlation between HCV viral load decline at weeks 4 and 12 is also seen (r = 0.76)

Figure 2. Decline in HCV-RNA at week 4 compared with week 12 in patients with ≤3-$\log_{10}$ decline in HCV-RNA at treatment week 4 (n = 1862).



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Concordance of HCV-RNA Decline at Weeks 4 and 12

- For all 3 arms combined concordance of <1-log_{10} decline at week 4 and null response at week 12 or ≥1-log_{10} decline at week 4 and "non-null" response at week 12 was 89% (2459/2777)
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- Classification and regression tree analysis on all patients (n = 3070) determined that a 1.03-log_{10} decline in HCV-RNA at treatment week 4 most closely predicted null response (<2-log_{10} decline) at treatment week 12

Table 1. Concordance of Week-4 <1-log_{10} Viral Decline and Week-12 <2-log_{10} Viral Decline From Baseline Among Patients With Both Week-4 and -12 HCV-RNA Levels

		Week-12 Response	
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PEG-IFN alfa-2b 1.5 µg/kg/wk + RBV (n = 900)	<1-log_{10} decline	150	56
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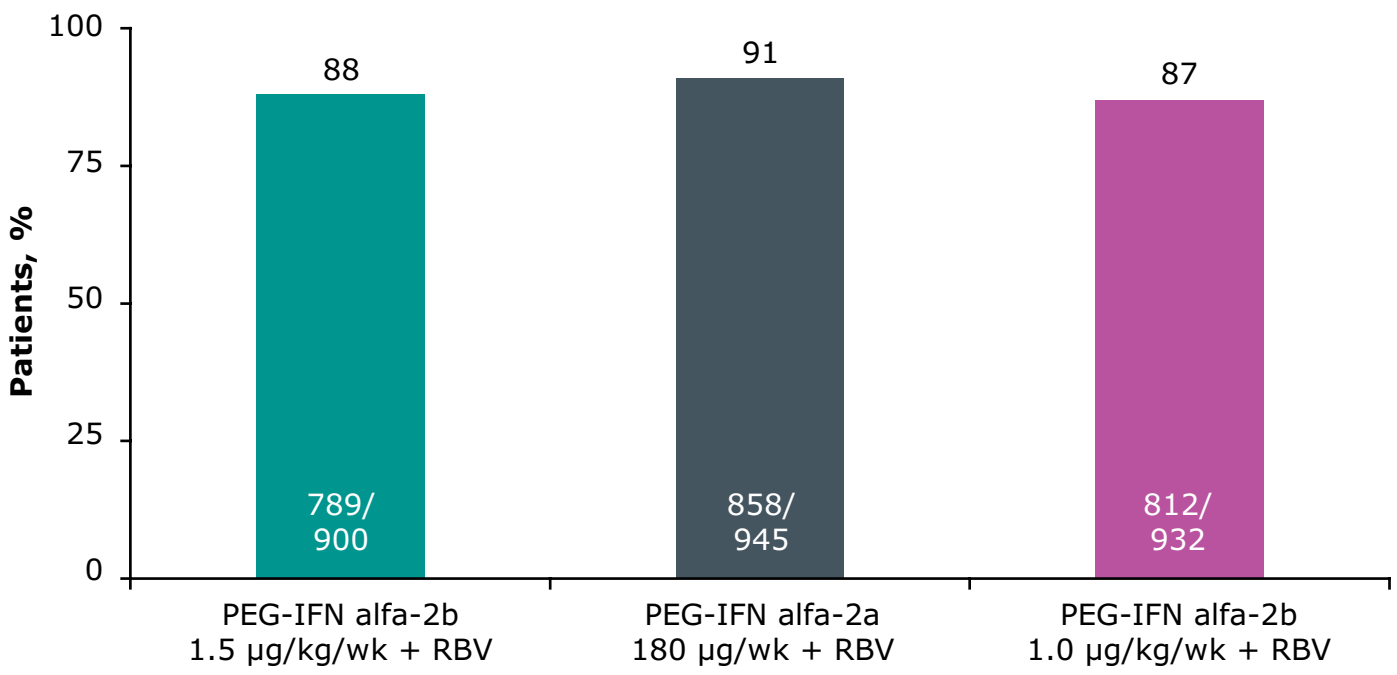
*<2-log_{10} decrease from baseline.
PEG-IFN = peginterferon; RBV = ribavirin.

Figure 3. Concordance between treatment-week-4 and -12 response among patients with both week-4 and -12 HCV-RNA levels.



PEG-IFN = peginterferon; RBV = ribavirin.

- Of the 705 patients with a week-4 viral load decline of <1 log_{10} and available week-12 HCV-RNA level, 71 patients did not meet week-12 or week-24 futility stopping rules, but only 28 (4%) ultimately achieved an SVR
- Among the patients with IL28B genotyping, concordance was 98% (466/474) in patients with the CC allele and 83% (785/943) in those with the CT/TT allele (**Table 2** and **Figure 4**)
  - — 95% (409/430) of patients who had <1-log_{10} decline at week 4 and/or <2-log_{10} decline at week 12 had the less favorable CT or TT allele

Table 2. Concordance of Week-4 <1-log_{10} Viral Decline and Week-12 <2-log_{10} Viral Decline From Baseline With IL28B Genotyping*

		IL28B* CC		IL28B* CT/TT	
		Week-12 Response			
	Week-4 Response	Null†	Non-null	Null†	Non-null
PEG-IFN alfa-2b 1.5 µg/kg/wk + RBV	<1-log_{10} decline	5	0	68	29
	≥1-log_{10} decline	0	141	30	182
PEG-IFN alfa-2a 180 µg/wk + RBV	<1-log_{10} decline	4	0	70	31
	≥1-log_{10} decline	0	151	9	219
PEG-IFN alfa-2b 1.0 µg/kg/wk + RBV	<1-log_{10} decline	4	3	113	28
	≥1-log_{10} decline	5	161	31	133

*187 patients missing.
†<2-log_{10} decrease from baseline.
PEG-IFN = peginterferon; RBV = ribavirin.

Null Response to the IDEAL Trial

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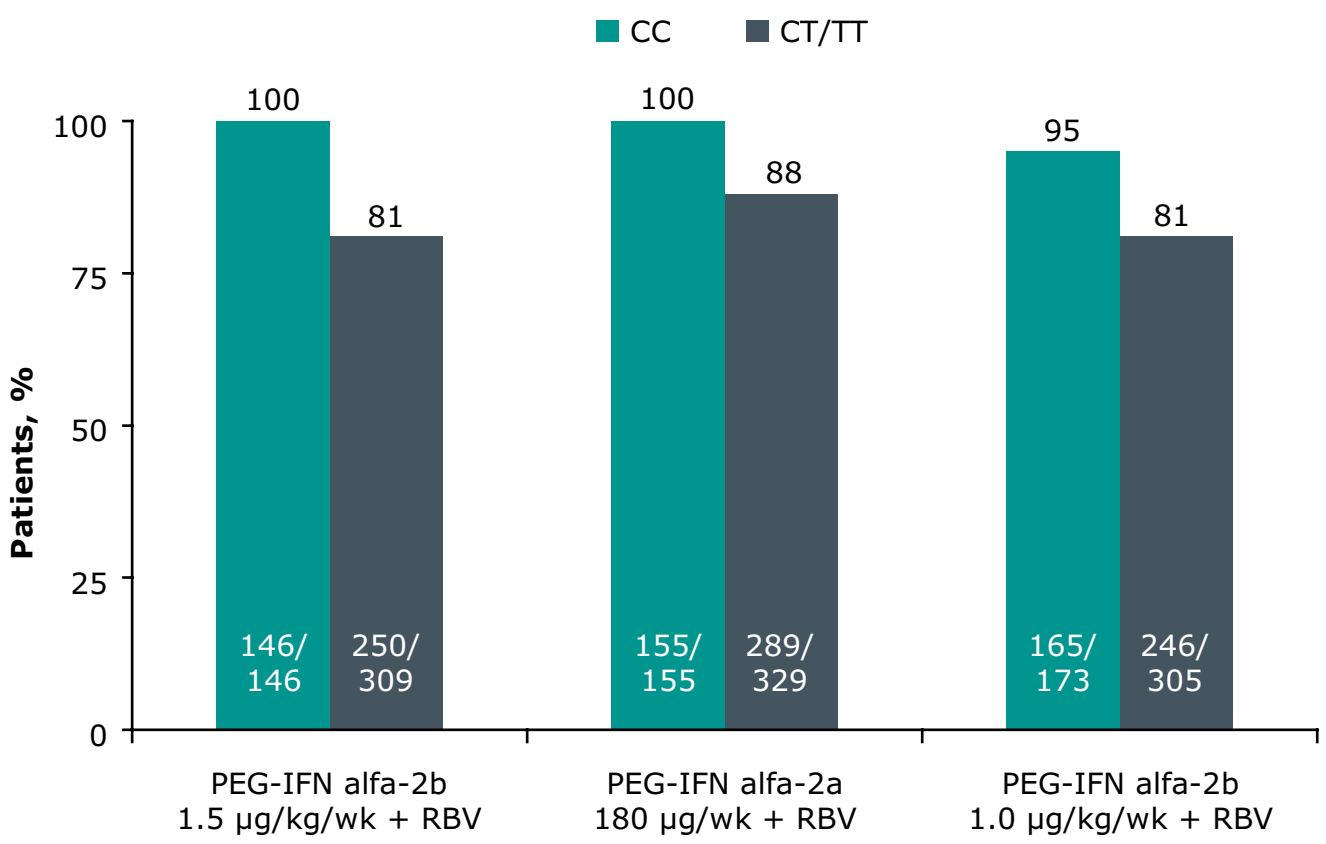
Figure 4. Concordance between weeks 4 and 12 according to baseline IL28B genotype.*



*Among patients with both week-4 and week-12 HCV-RNA levels.
PEG-IFN = peginterferon; RBV = ribavirin.

Conclusions

- The negative predictive value of week-4 viral load decline of <1 $\log_{10}$ is 96%
- A treatment-week-4 viral load decline of <1 $\log_{10}$ approximates that of a <2-$\log_{10}$ decline at treatment week 12 and is an earlier predictor of null response based on correlation, concordance, and CART analyses
- The treatment-week-4 correlation with week-12 null response may have increased utility in aiding early treatment decisions

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