Hepatitis C virus: Global Update

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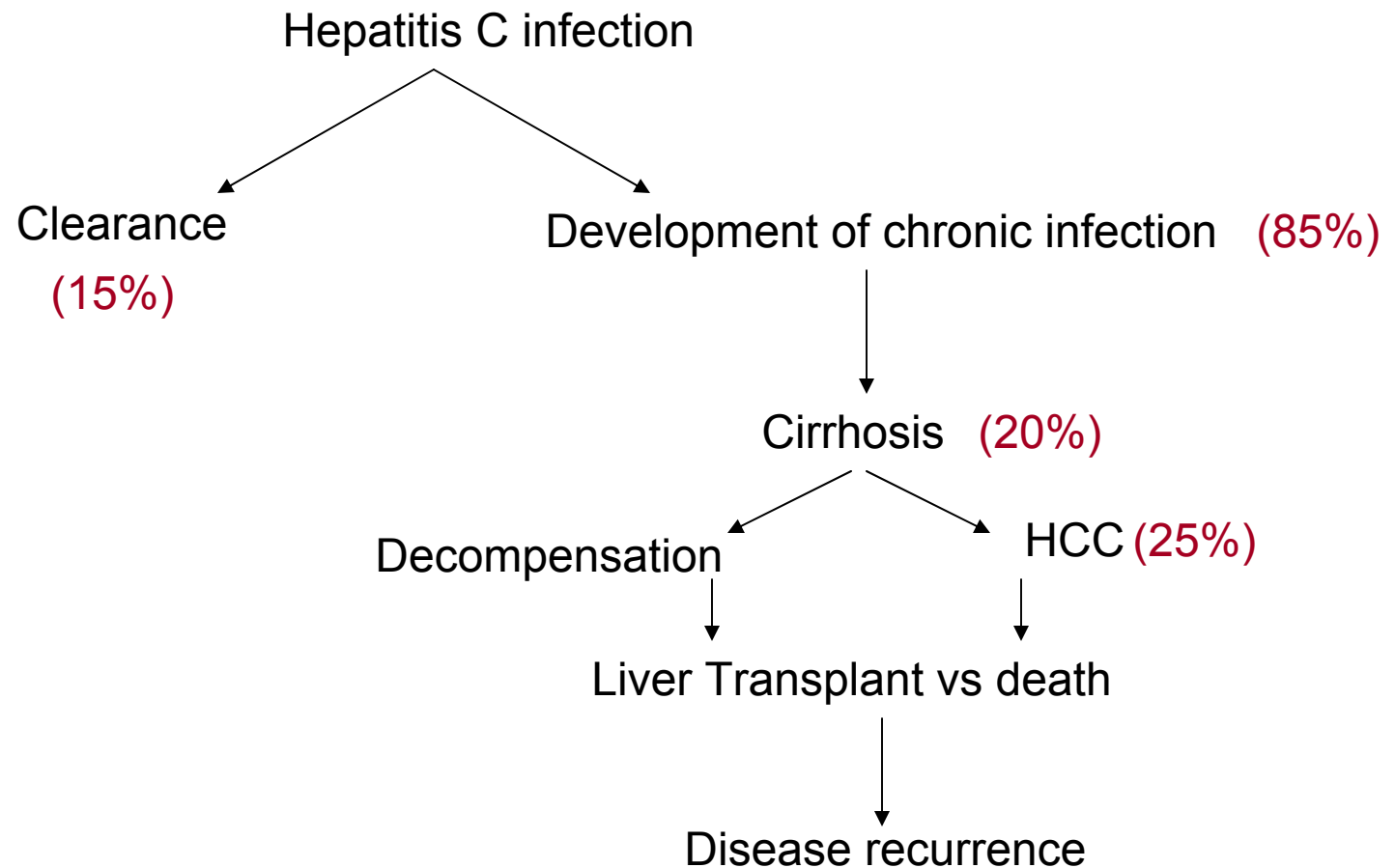
DISCLOSURES:

Consultant to Sanofi, Aventis, PDL, Oridion

Advisory Board: Vertex, Gilead

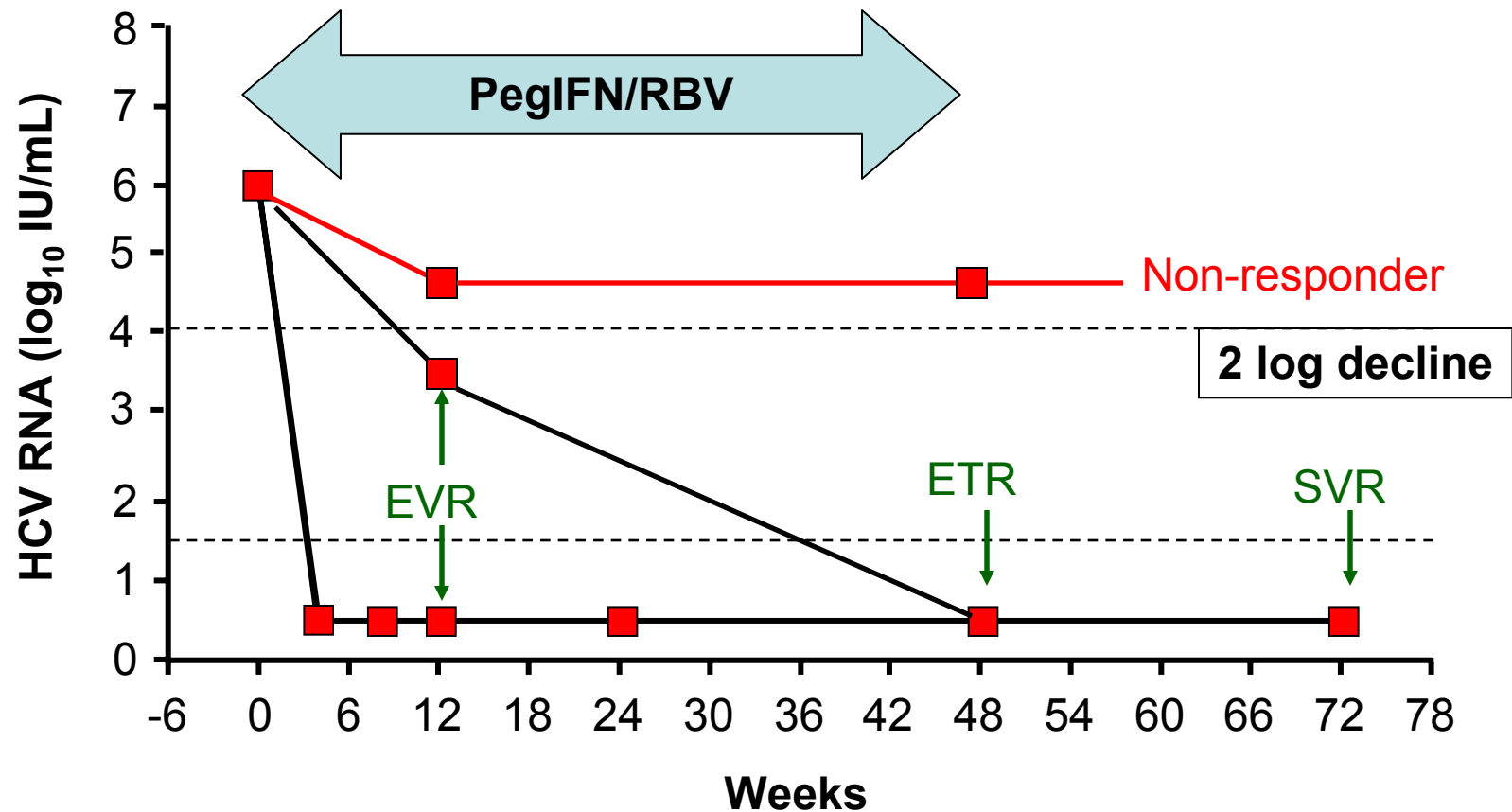DSMB: Vertex

Hepatitis C: Natural history

Hepatitis C infection

Clearance (15%)

Development of chronic infection (85%)

Cirrhosis (20%)

Decompensation

HCC (25%)

Liver Transplant vs death

Disease recurrence

Kamal SM, et al. Gastroenterology. 2006;130:632-638.
Liang et al, Ann Intern Med, 2000

Impact of treatment of acute HCV with PEG-interferon

Virologic Outcome	Treatment Initiated at Week 8, n (%)	Treatment Initiated at Week 12, n (%)	Treatment Initiated at Week 20, n (%)
Intent-to-treat analysis	(n = 43)	(n = 43)	(n = 43)
End-of-treatment response	42 (97.6)	41 (95.3)	38 (88.3)*
Sustained response	41 (95.3)	40 (93.2)	33 (76.6)†

Kamal et al, Gastroenterology, 2006, 130: 632-638

Response patterns: importance of early virologic response (EVR)

Factors affecting sustained virologic response

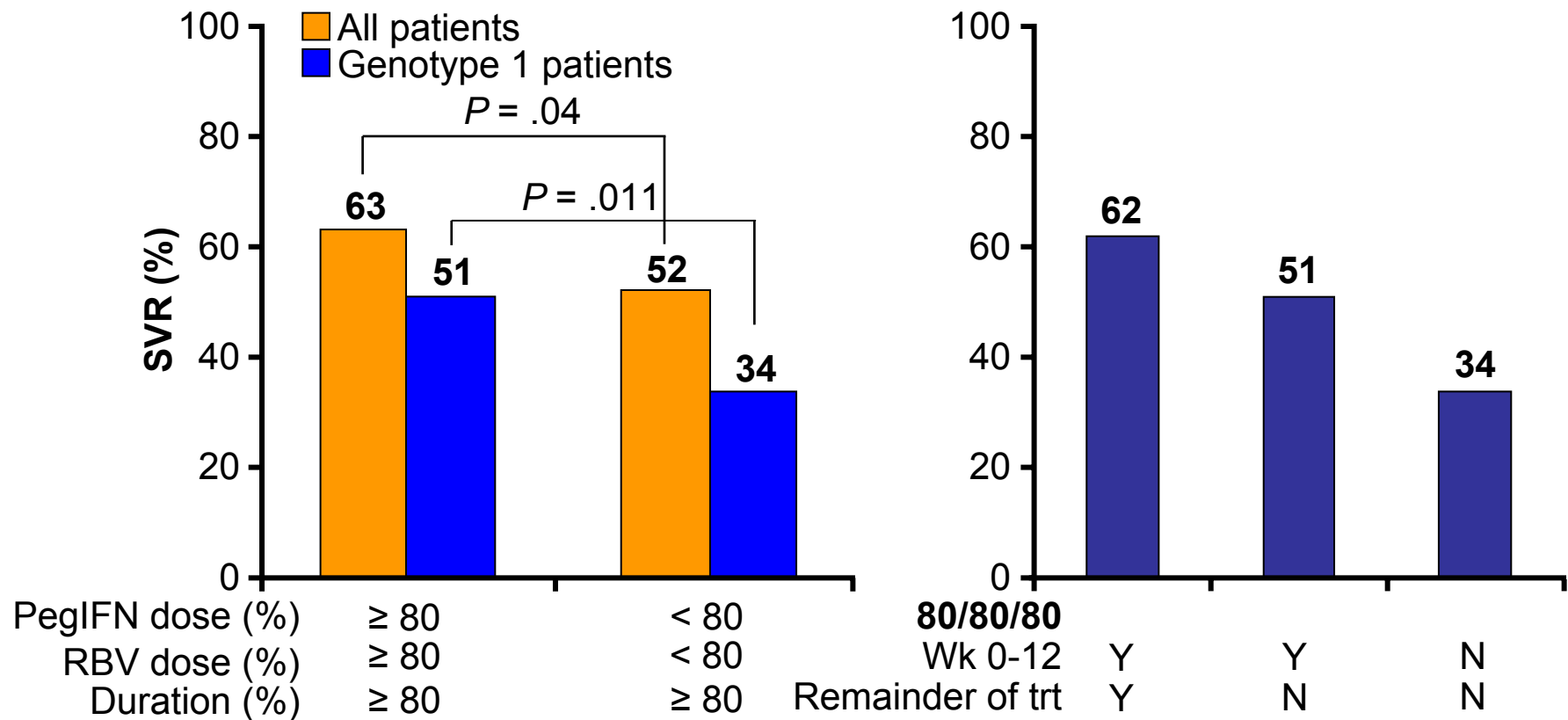- **Modifiable**
  - compliance
  - dose
  - duration
  - viral response
  - insulin resistance

- **Non-modifiable**
  - increasing age
  - race
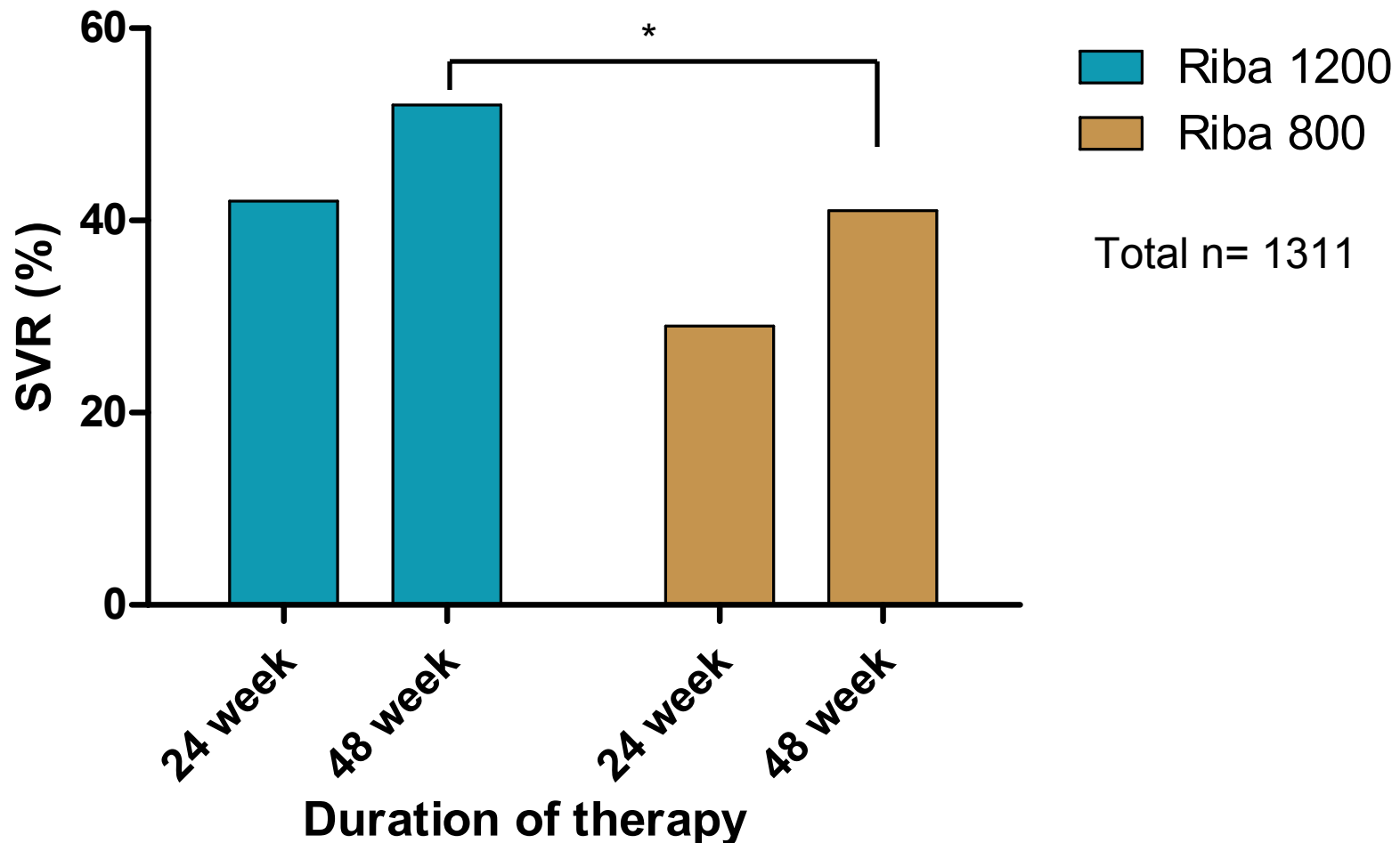 - virus genotype
  - virus load
  - liver histology

Importance of Maintaining Dose
Retrospective analysis of pegIFN alfa-2b/RBV phase trials

McHutchison JG, et al. Gastroenterology. 2002;123:1061-1069.

Ribavirin: effect of dosing on outcomes of genotype 1 infection
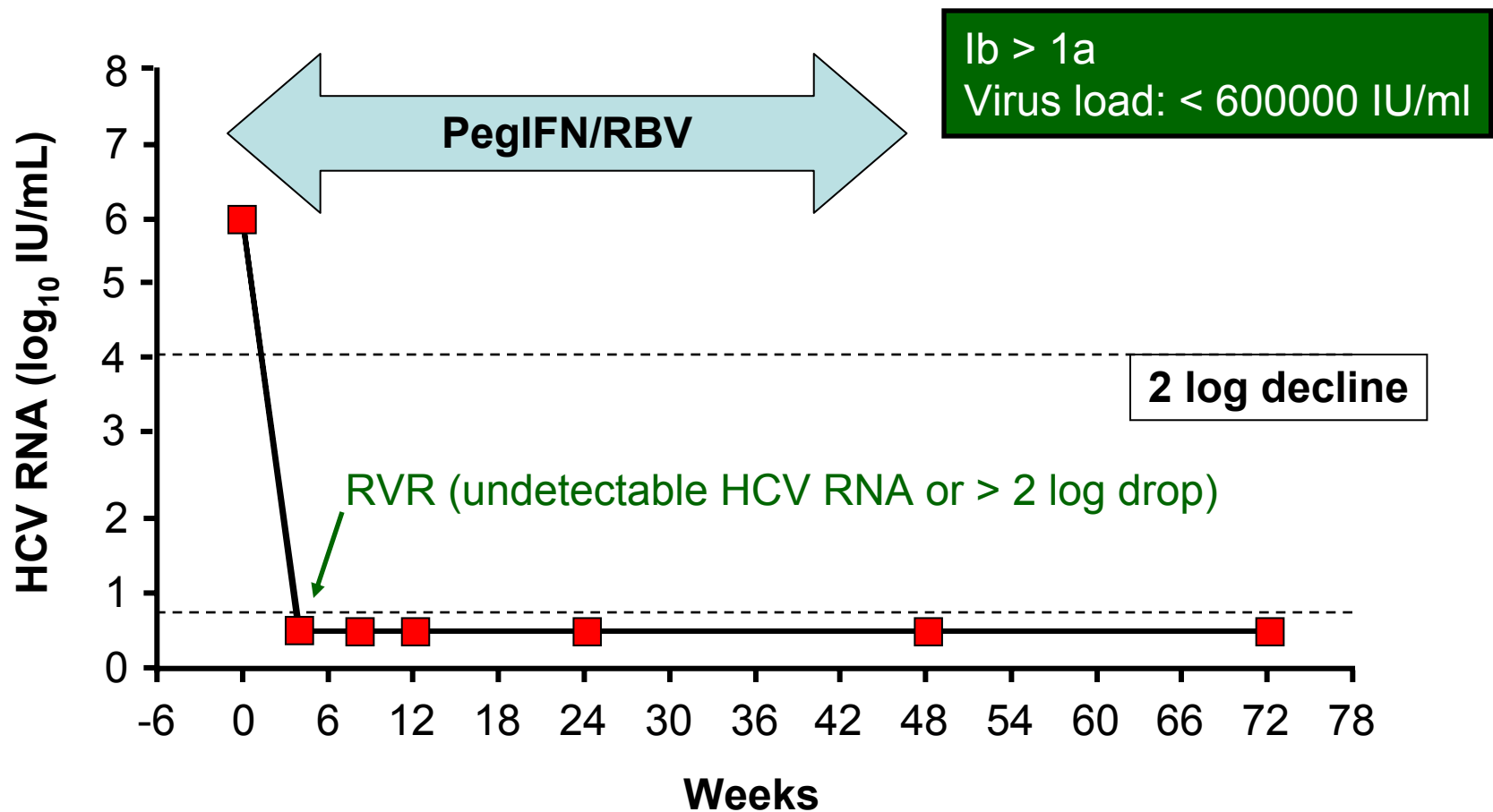

Hadziyannis et al, Ann Intern Med, 2004, 140:346-355

Recommendations for starting Rx

- Evaluate issues related to compliance and address before starting Rx

- PEG-IFN (1.5 µg/Kg for 2b, 180 µg/wk for 2a)

- Ribavirin:
  - 800 mg/day for 24 wk for genotype 2/3
  - 1000-1200 mg/day for 24 wk for genotype 1

Response patterns
(rapid virologic response)

Ib > 1a
Virus load: < 600000 IU/ml

PegIFN/RBV

2 log decline

RVR (undetectable HCV RNA or > 2 log drop)

HCV RNA ($\log_{10}$ IU/mL)

Weeks

Jensen et al, Hepatology 2006; 43:954-960

Importance of RVR

Legend: ETR (blue), SVR (tan)

WK 4:	Undetectable	< 2 log10	< 2 log10	any decrease
WK 12:	undetectable	undetectable	> 2 log 10	any decrease
WK 24:	undetectable	undetectable	undetectable	detectable

Ferenci et al, J Hepatol, 2005; 43:425-433

Shortened duration of therapy for genotype 2/3 based on RVR

* ACCELERATE trial: 16 vs 24 wk SVR for negative RVR= 27 vs 49% (p< 0.001)

Author	IFN µg/wk	Riba Mg/day	SVR (12-16 wk)	SVR (24 wk)	P value
Von Wagner	180	800-1200	82	80	n.s.
Dalgard	1.5 ug/kg	800-1400	90	NA	NA
Mangia	1 ug/kg	1000-1200	85	NA	NA
Shiffman*	180	800	82	90	P< 0.005

Take home messages:
-If HCV RNA is + at 4 wks, do not shorten Rx
-If RVR +, may be OK to cut Rx short at 16 wks if side effects are bad

Extending duration of therapy

Berg et al, Gastroenterology, 2006; 130:1086-1097

Individualizing Rx

- Check HCV PCR at 4, 12, 24, 48 and 72 wks

- If RVR present:
  - continue Rx for 48 wks for genotype 1
  - continue Rx for 24 wks for genotype 2/3 unless side effects are severe (16wks)

- If RVR absent but EVR present:
  - continue as above

- If EVR absent:
  - consider discontinuation
  - in selected cases, consider extending Rx to 24 wks; if ETR +, extend Rx for 72 wks

Response patterns: Relapse

Is 24 weeks treatment duration the gold standard in genotype 2/3?

- Easy to treat
  - Genotype 2
  - Low viral load
  - Age 30 years
  - No cirrhosis

- Not easy to treat
  - Genotype 3
  - High viral load
  - Age 60 years
  - Cirrhosis

Relapse rate <5%

Relapse rate >25%

RBV Exposure and SVR: Genotype 1 and Treatment Completers

- *Retrospective analysis of pegIFN alfa-2a/RBV phase III trials*

Legend: SVR ($P = .006$), Relapse

Y-axis: Patients (%)

Data values:
- 0-60: SVR 33, Relapse 54
- (second group): SVR 57, Relapse 32
- > 80-97: SVR 62, Relapse 22
- > 97: SVR 67, Relapse 19

X-axis: Cumulative RBV Exposure

Reddy KR, et al. Clin Gastroenterol Hepatol. 2007;5:124-129.

High-Dose RBV and Epoetin: Study Design

- Prospective, randomized trial

Week 0   Week 48   Week 72

Treatment-naive, HCV genotype 1, and liver biopsy consistent with chronic hepatitis C

N = 150

PegIFN + RBV ~13.3 mg/kg/d (n = 50)

PegIFN + RBV ~13.3 mg/kg/d + **EPO** (n = 50)

PegIFN + RBV ~15.2 mg/kg/d + **EPO** (n = 50)

Off-treatment follow-up

Shiffman ML, et al. Hepatology. 2007;46:371-379.

High-Dose RBV and Epoetin: Virologic Response and Relapse

Outcome	PegIFN + RBV ~13.3 mg/kg/d	PegIFN + RBV ~13.3 mg/kg/d + EPO	PegIFN + RBV ~15.2 mg/kg/d + EPO
End of treatment response	51	37	54
SVR	34	22	49*
Relapse	36	40	8*

*P < .05 vs weight-based ribavirin dosing groups.

Package inserts for all three commercial EPO products recommend that Hb level not exceed 12g/dL

Shiffman ML, et al. Hepatology. 2007;46:371-379.

Response patterns: nonresponse

Maintenance IFN for HCV— HALT-C Final Results

- Low dose peginterferon alfa-2a arm (90 µg/week) vs control group had
  - Greater reductions in HCV RNA and ALT ($P < .0001$)
  - Greater reductions in necroinflammation ($P < .001$)
- No reduction in fibrosis
- No significant difference between arms in any primary outcome
  - 34.1% vs 33.8%: HR 1.01 (95% CI, 0.81-1.26)

Study Arm	Baseline Fibrosis*	Any primary outcome, %	Death, %	HCC, %	CTP score ≥ 7, %
Peginterferon alfa-2a 90 µg/week (n = 517)	3/4	36.6	2.6	2.6	3.2
	5/6	30.1	2.4	1.9	17.8
Control (n = 533)	3/4	35.5	0.6	1.6	3.2
	5/6	31.1	2.7	4.6	14.6

Other ways to boost SVR and reduce non-response

- High dose PEG-IFN + riba
- IMPD (ribavirin target) inhibitors
  - viramidine
- Newer and other interferons:
  - albuferon
  - consensus interferon
- Treat insulin resistance
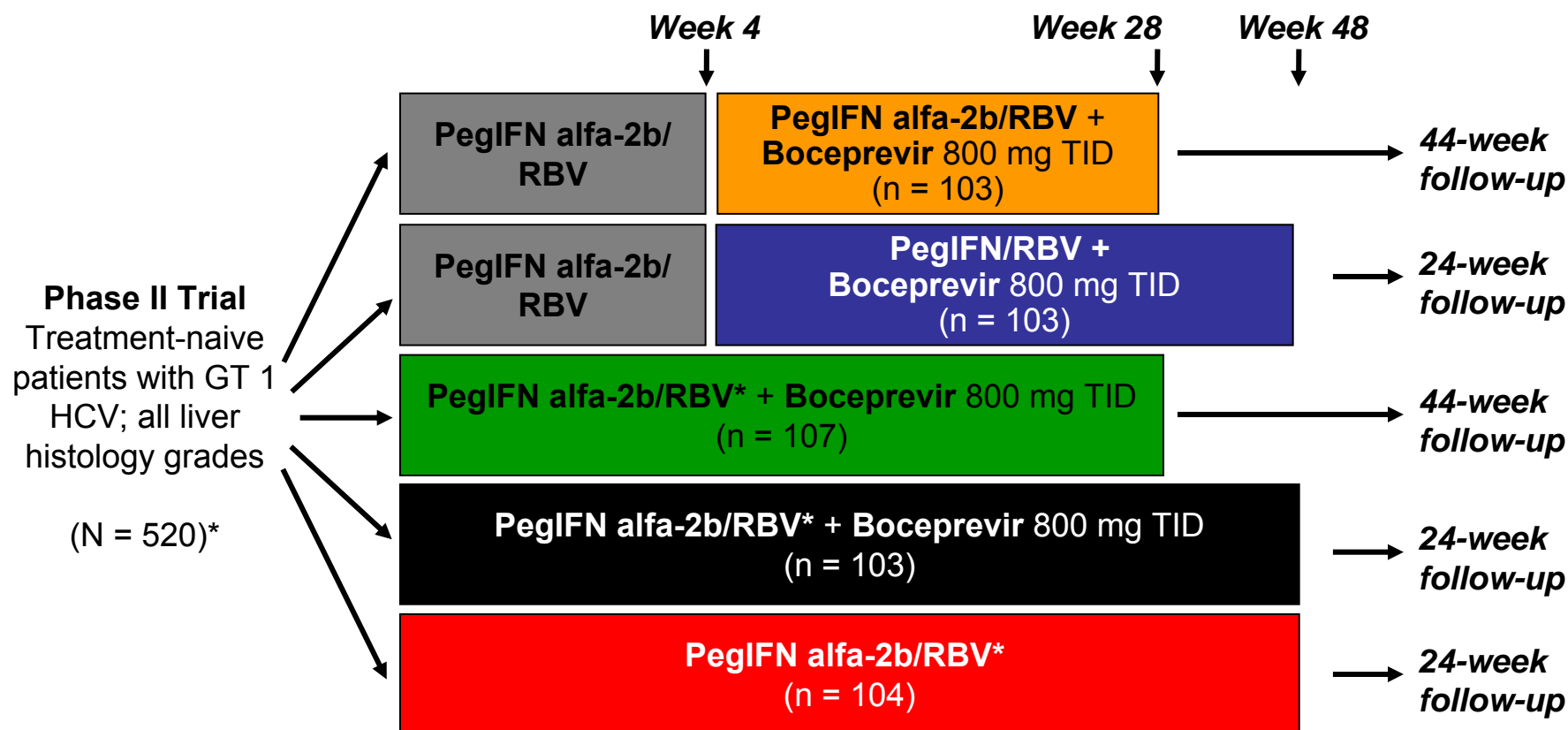- Newer agents (protease and polymerase inhibitors)
- Other agents (nitozaxanide)

Impact of NAFLD on virologic response to anti-HCV therapy

Sanyal et al, Am J Gastroenterol, 2003

SPRINT-1: Boceprevir + PegIFN/RBV in Treatment-Naive GT1 Patients

Week 4   **Week 28**   **Week 48**

Phase II Trial
Treatment-naive patients with GT 1 HCV; all liver histology grades

(N = 520)*

PegIFN alfa-2b/ RBV	**PegIFN alfa-2b/RBV + Boceprevir 800 mg TID (n = 103)** → *44-week follow-up*
PegIFN alfa-2b/ RBV	**PegIFN/RBV + Boceprevir 800 mg TID (n = 103)** → *24-week follow-up*

PegIFN alfa-2b/RBV* + Boceprevir 800 mg TID (n = 107) → *44-week follow-up*

PegIFN alfa-2b/RBV* + Boceprevir 800 mg TID (n = 103) → *24-week follow-up*

PegIFN alfa-2b/RBV* (n = 104) → *24-week follow-up*

*This is a 2-part study; part 2 includes 2 additional arms that are not included in this interim analysis.

Kwo P, et al. AASLD 2008. Abstract LB16.

SPRINT-1: Boceprevir + PegIFN/RBV in Treatment-Naive GT1 Patients

Sustained Virologic Response*

*SVR12 for 48-wk arms and SVR24 for 28-wk arms.

Kwo P, et al. AASLD 2008. Abstract LB16.

PROVE 2: Virologic Responses in Rx naive GT1 subjects

Outcome Undetectable HCV RNA, %	PegIFN/RBV 48 (Control) (n = 82)	TVR Arms		
		TVR/PegIFN/RBV 12 → PegIFN/RBV 12 (n = 81)	TVR/PegIFN/ RBV 12 (n = 82)	TVR/PegIFN 12 (No RBV) (n = 78)
• Week 4	13	69	80	50‡
• Week 12	43	73	80	62
• SVR	46	69*	60†	36‡
Relapse, % (n/N)	22 (10/45)	14 (8/57)	30 (19/63)	48 (22/46)

*P = .004
†P = .12
‡P > .20

Zeuzem S, et al. AASLD 2008. Abstract 243.

PROVE 3: Virologic Response in prior relapsers/nonresponders and breakthrough cases

Response	Control Arm (n = 114)	TVR Arms		
		24 Week (n = 115)	48 Week (n = 113)	No RBV (n = 111)
RVR, %	0	61	50	47
EVR, %	8	75	66	53
Undetectable HCV RNA at Week 24, %	33	70	56	48
Virologic breakthrough, % • Weeks 1-12, n • Weeks 13-24, n	3 0 3	12 9 5	12 9 5	32 29 6
SVR12, % Previous nonresponders Previous relapsers Previous breakthroughs	N/A	52 41 73 44	N/A	21 11 46 20

McHutchison J, et al. AASLD 2008. Abstract 269.

TVR + PegIFN/RBV in Nonresponders and Relapsers: Virologic Response

- Open-label study: nonresponders and relapsers to 48 weeks of pegIFN/RBV from PROVE 1-3 trials
  - TVR + pegIFN alfa-2a for 12 weeks, then pegIFN/RBV for 12-36 weeks

HCV RNA Negative (MITT Analysis)*, %	Previous Response		
	Null Response[†] (n = 48)	Partial Response[‡] (n = 33)	Relapse[§] or Breakthrough[‖] (n = 23)
Week 4	40	85	91
Week 12	61	90	94
Week 24	43	82	71

*< 10 IU/mL. [†]< 1 $\log_{10}$ drop by Week 12 or < 2 $\log_{10}$ drop by Week 24 in HCV RNA. [‡]≥ 2 $\log_{10}$ drop in HCV RNA at Week 12, but detectable at Week 24. [§]End of treatment response, then HCV RNA positive after. [‖]Detectable HCV RNA after being undetectable.

Shiffman M, et al. AASLD 2008. Abstract 1852.

4-Week Lead-in With NTZ for Treatment-Naive GT4 Patients

HCV RNA Undetectable, %	Open Label Study	STEALTH C-1		
	PegIFN + NTZ (4-wk NTZ lead-in) (n = 44)	PegIFN + RBV (n = 40)	PegIFN + NTZ (12-wk NTZ lead-in) (n = 28)	PegIFN + RBV + NTZ (12-wk NTZ lead-in) (n = 28)
Week 4	59	38	54	64
Week 12	82	70	68	86
Treatment end	86	75	71	82
SVR (overall)	80*	50	61	79
• GT 4 (n = 40)	**78**	--	--	--

*P = .006 vs PegIFN/RBV; P = NS vs PegIFN + NTZ with 12-wk lead-in; P = NS vs PegIFN/RBV + NTZ with 12-wk lead-in.

Rossignol JF, et al. AASLD 2008. Abstract 87.

A Potential Evolution Scenario HCV Therapy for Genotype 1

The addition of small molecules with additive benefit

Y-axis: **Sustained Virologic Response in G1 (SVR)**, scale 0 to 100

- **10%** — 1st Stage 1989-1998
- **35%** — ribavirin + (2nd Stage 1998-2001)
- **42-50%** — + PEG-IFN (3rd Stage 2001- present)
- **Estimated 65-70%** — + Pol Inhibitor or Prot Inhibitor +/- (4th Stage 2008-2009)
- **Estimated 85-90%** — + Pol Inhibitor + Prot Inhibitor ... Oral immune modulators, Other direct antivirals (5th Stage 2011-2014)
- **All Oral Therapy** — 6th Stage 2014+