How to Optimize Current Therapy of Genotype 2 Patients

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Disclosures

Dr. Adrián Gadano has received research support, lecture fees and took part in clinical trials for:

- Roche
- Novartis
- BMS
- Gilead
- Janssen
- MSD
- GSK
- AbbVie

HCV-2: best friend in the HCV family…

- Distribution worldwide. High prevalence in some countries (Italy, South Korea, Argentina…).
- Easiest to treat genotype.
- New highly effective and safe therapies are changing the landscape (SOF-RBV).
- Conventional therapy may be optimized according to baseline and on-treatment predictors of response (Peg-RBV).

HCV-2: Treat or Wait ?

What do the Guidelines say ?

(1) All patients with compensated disease should be considered for therapy (A2).

(2) Treatment should be initiated promptly in patients with advanced fibrosis (METAVIR score F3–F4), and strongly considered in patients with moderate fibrosis (METAVIR score F2) (B2).

(3) In patients with less severe disease, indication for therapy is individual (C2).

EASL Guidelines HCV. J Hepatol 2011

As oral regimens with improved tolerability and efficacy are released, the optimal management in patients with mild disease may be to defer treatment until they become available.

HCV-2: Two different scenarios at the time of deciding therapy

- **Past and Current therapy: Peg/RBV**

  (still most countries)

- **New therapy: SOF/RBV**

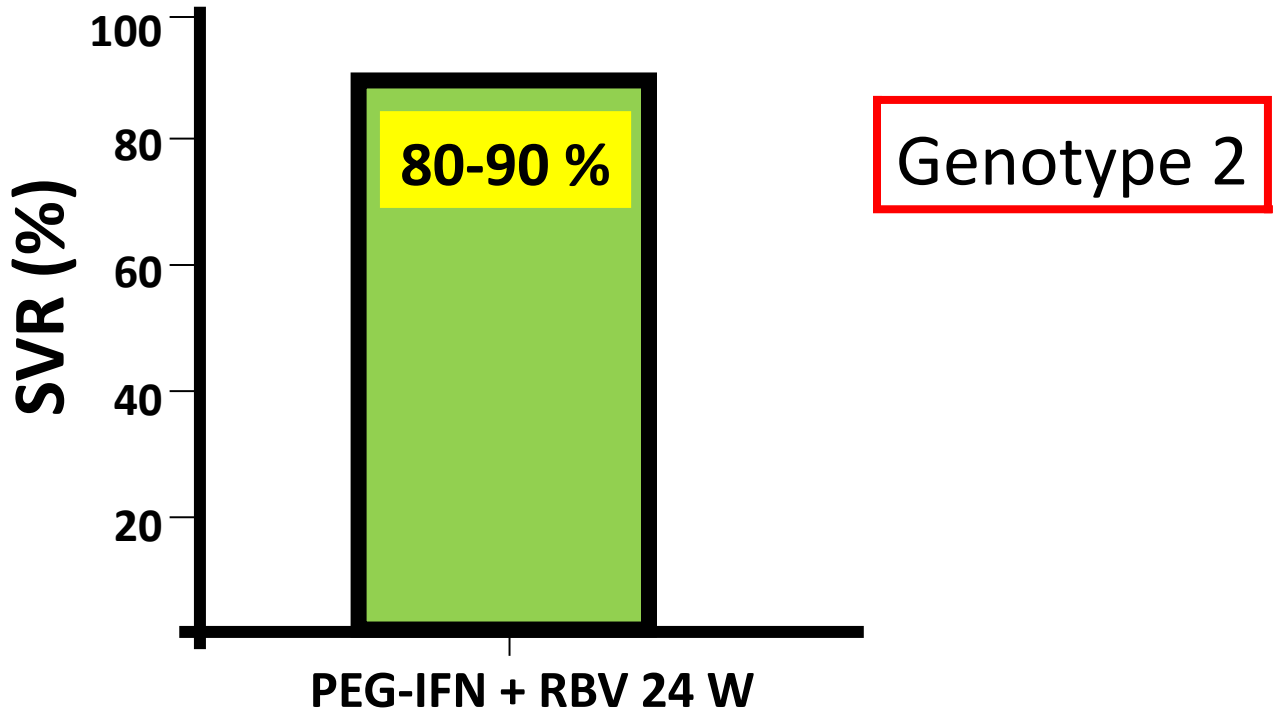
  (only few countries…)

Why treating HCV-2 patients with Peg/RBV now ?

- Many HCV-2 patients cannot wait ! (F3, F4). (also extrahepatic disease).
- Access to DAAs still uncertain in most parts of the world.
- High SVR rates with Peg-RBV (possible short duration).

Treatment Guidelines for HCV-2 patients

Peg IFN plus RBV for 24 weeks



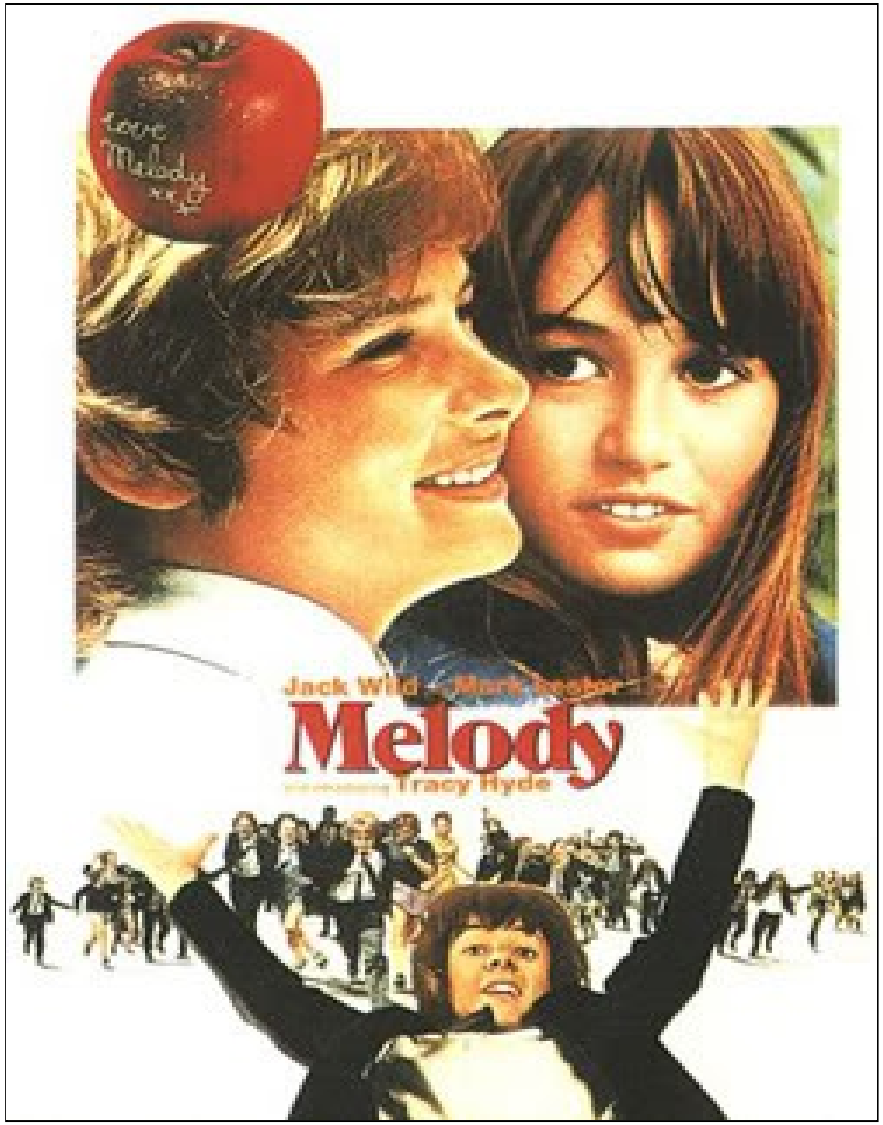
EASL Guidelines HCV. J Hepatol 2011

“Optimized” Therapy for HCV-2

- HCV-2 is different from HCV-3 in terms of response to therapy.

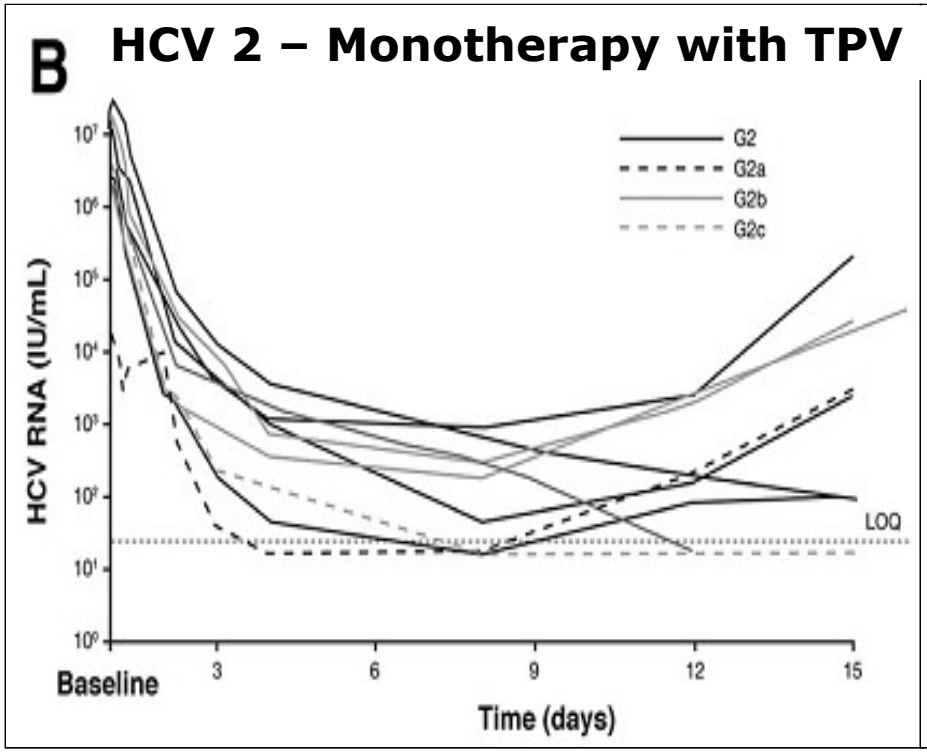
- Is it possible to shorten treatment without loosing efficacy ? In which patients ?

- Do we need to extend therapy in “difficult to treat” patients ? Which are these patients ?

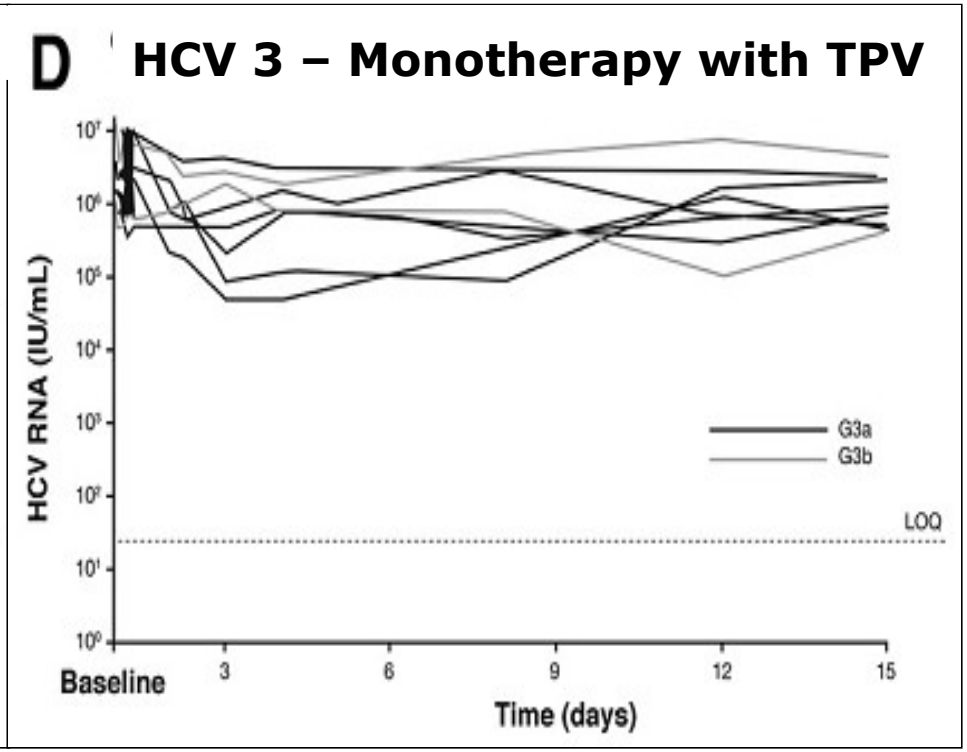

Melody
Tracy Hyde


G3
G2

Telaprevir in patients with HCV genotypes 2 and 3



HCV 2



HCV 3

Foster et al. Gastroenterol 2011

“Optimized” Therapy for HCV-2

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Shorten therapy? → YES, in patients with predictors of good response…

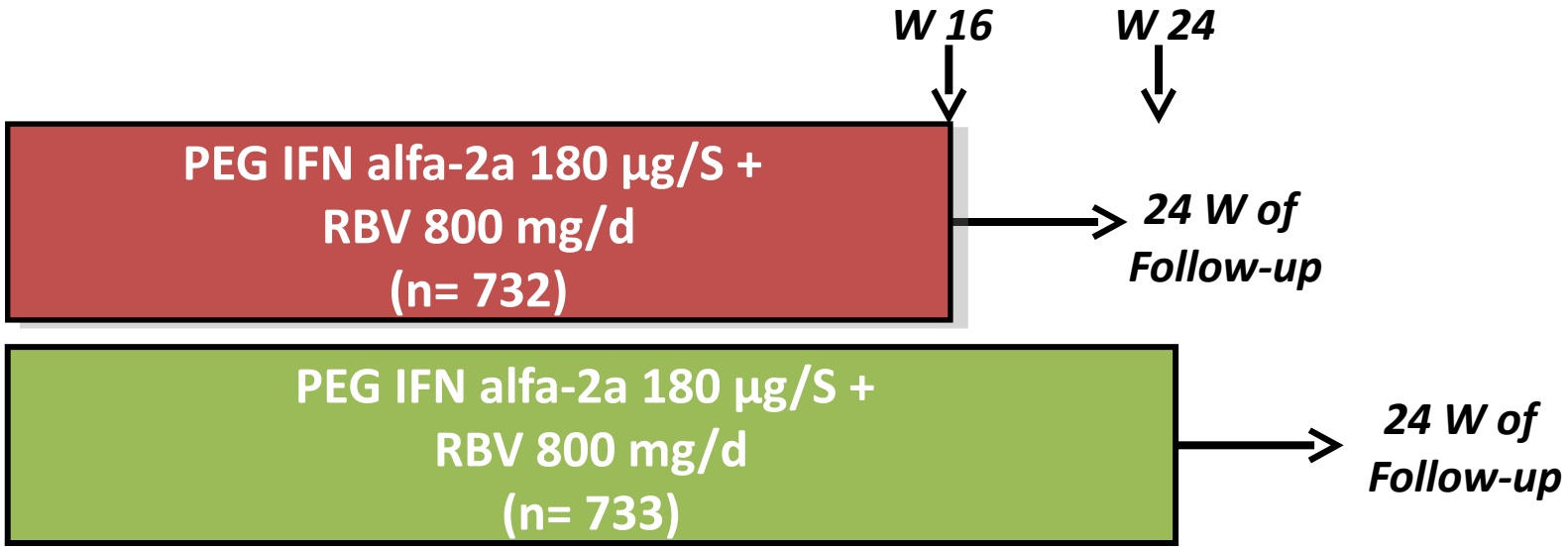
Which are the predictors of response ?

- Baseline: → **Cirrhosis**
  - BMI/IR
  - Viral load
  - IL28B (in non RVR)
- On treatment: → **RVR**

EASL Guidelines HCV. J Hepatol 2011

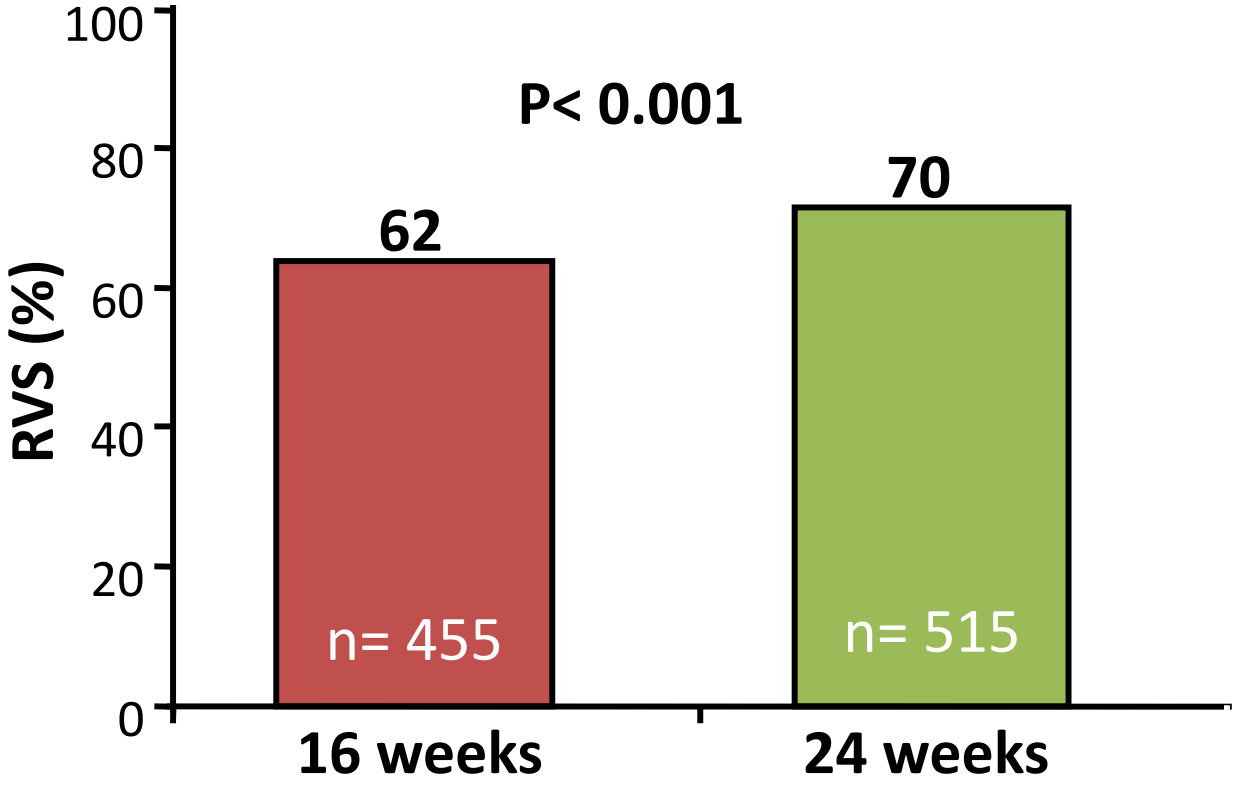
ACCELERATE: Treatment duration in HCV-2 and 3

20-25% → Bridging fibrosis or cirrhosis



Shiffman et al. N Engl J Med 2007

ACCELERATE: Treatment duration in HCV-2 and 3



Shiffman et al. N Engl J Med 2007

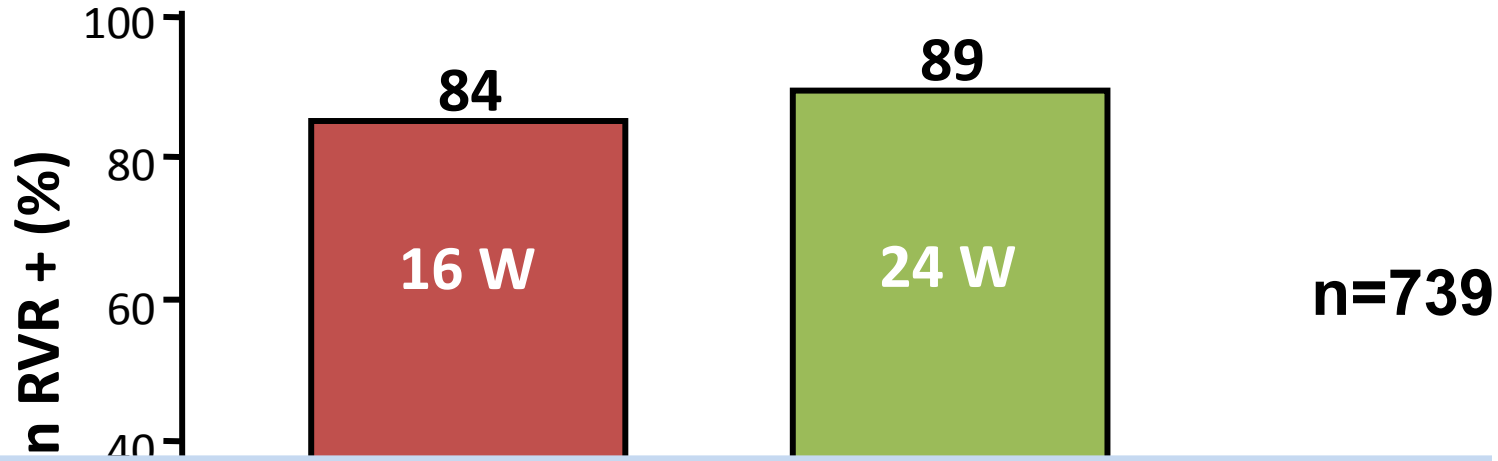
RVR is the strongest predictor of treatment outcome in HCV-2 patients

Reference	Patients	RVR	Non-RVR
Mangia	213	76% (40/53)	78% (45/58)
Schiffman	347	85% (210/247)	53% (53/100)
Rumi	230	83% (151/182)	52% (25/48)
Yu	150	95% (95/100)	77% (10/13)
Marcellin	1025	76% (662/858)	45% (70/157)

Grassi E, Liver Int 2013

SVR in patients with HCV-2 that experienced RVR

RVR + / Weight-Based Dose of RBV (1000-1200 mg)



However, short therapy is not recommended in patients with baseline predictors of treatment failure such as bridging fibrosis/cirrhosis, high baseline viraemia, high BMI and insulin resistance

(RR 1.02, 95%, CI: 0.97–1.06, NS)

Di Martino et al. Hepatology 2011

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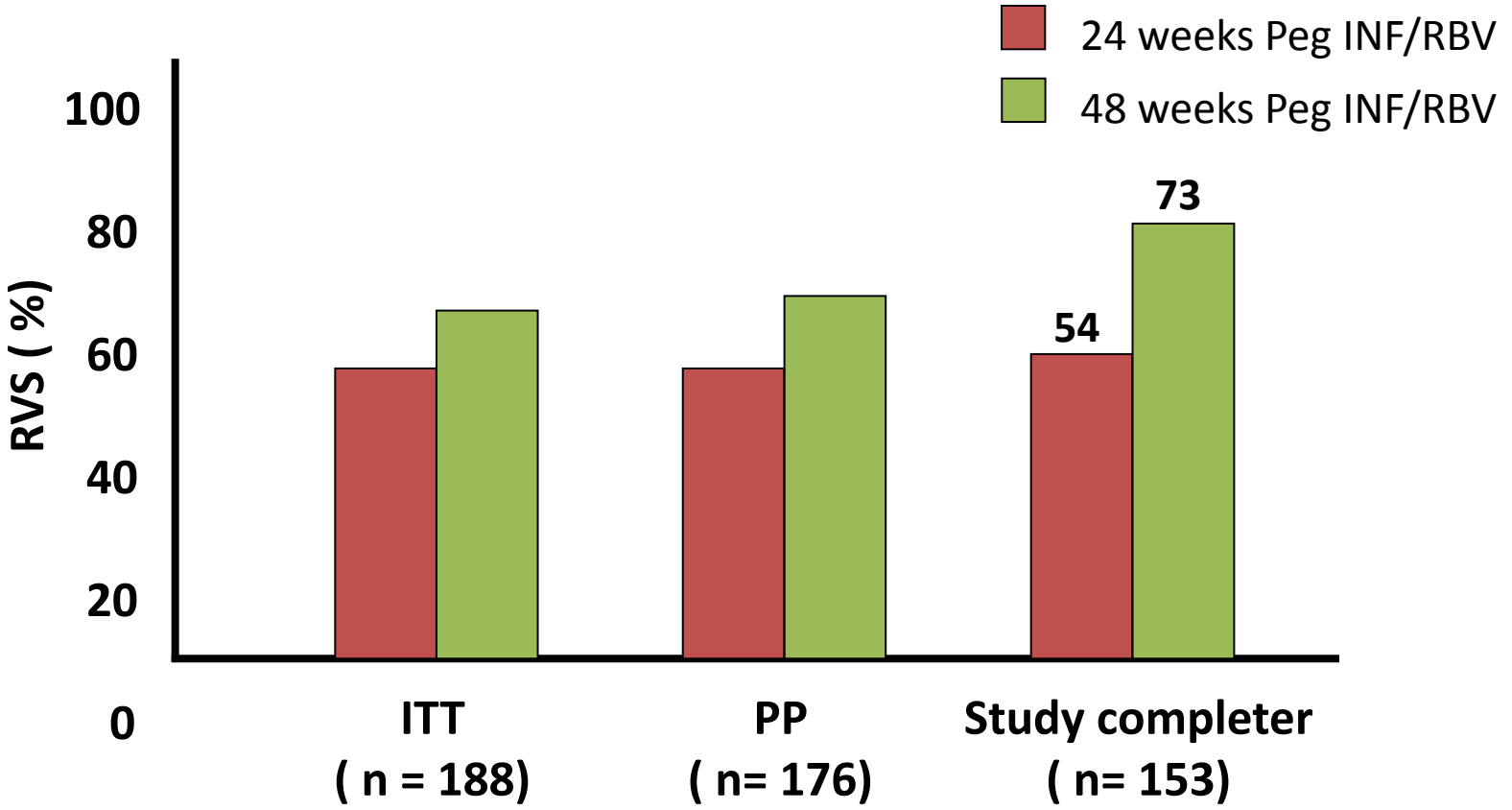
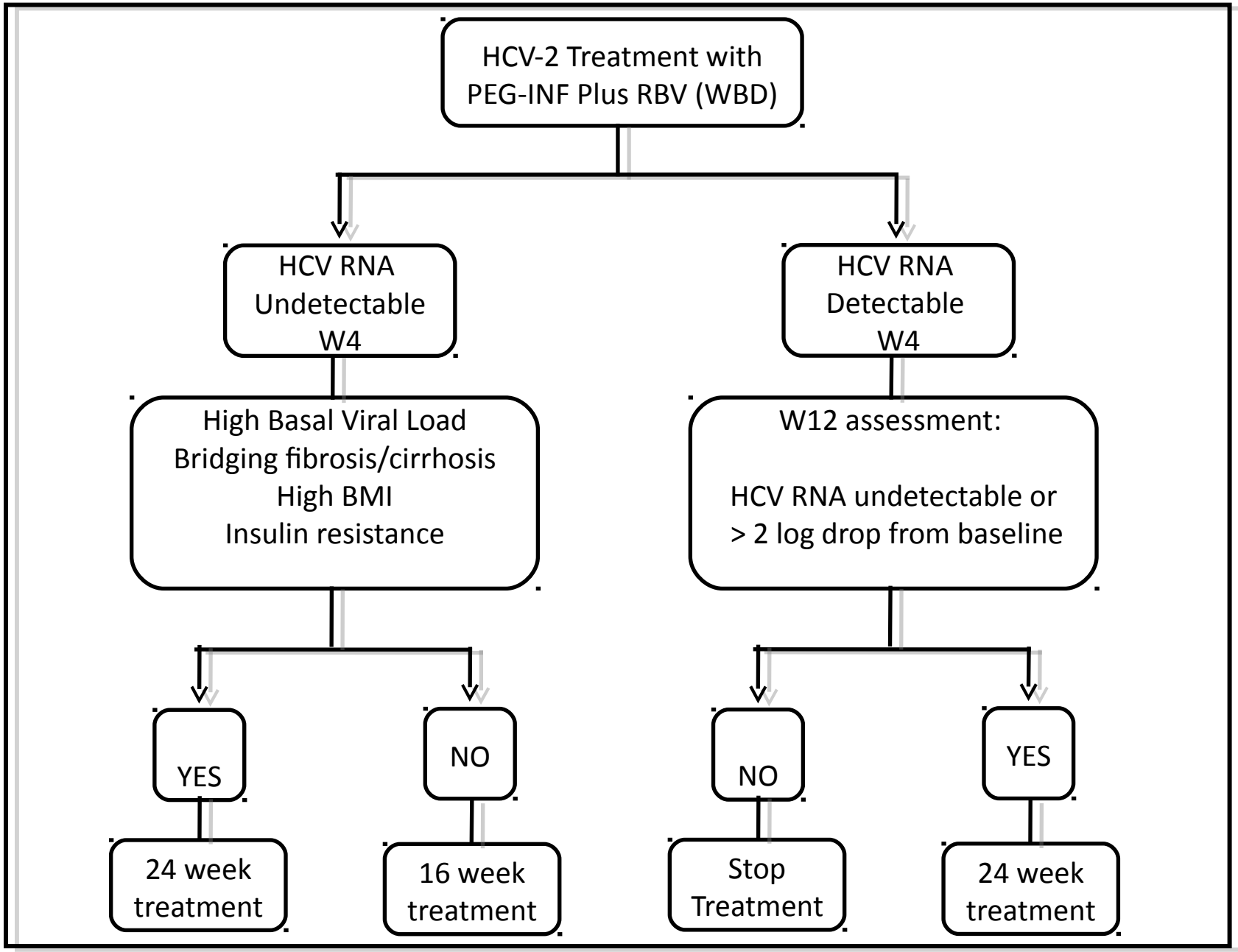
48 weeks therapy in HCV 2/3 patients without RVR but with EVR: N-CORE



Poor evidence to recommend extended treatment in patients with negative predictors of response

Cheinquer et al, AASLD 2012



Marciano & Gadano, Liver Int 2014

Options for HCV G2 patients that did not respond to previous therapy

Patients may be re-treated with Peg-IFN + RBV (WBD)
if they need immediate therapy and if measures to improve response can be introduced:

- Improve Adherence
- Correction of cofactors
  - Body weight, IR…
- Growth factors, Antidepressants

48 weeks recommended

Or → Wait for new drugs…

HCV-2: Two different scenarios at the time of deciding therapy

- Past and current therapy: Peg/RBV

(still most countries)

- New therapy: SOF/RBV

(only in few countries…)

U.S. Food and Drug Administration
Protecting and Promoting Your Health

Approval of Sovaldi (sofosbuvir) tablets for the treatment of chronic hepatitis C.

On December 6, 2013, FDA approved SOVALDI (sofosbuvir) tablets for the treatment of chronic hepatitis C (CHC) infection as a component of a combination antiviral treatment regimen.
Sovaldi is the first drug that has demonstrated safety and efficacy to treat certain types of HCV infection without the need of IFN.

Recommended Regimens and Treatment Duration for SOVALDI Combination Therapy in HCV Mono-infected and HCV/HIV-1 Co-infected Patients

	Treatment	**Duration**
Patients with genotype 1 or 4 CHC	SOVALDI + peginterferon alfa + ribavirine	12 weeks
Patients with genotype 2 CHC	**SOVALDI + ribavirine**	**12 weeks**
Patients with genotype 3 CHC	SOVALDI + ribavirine	24 weeks

The pangenotypic nucleotide polymerase inhibitor

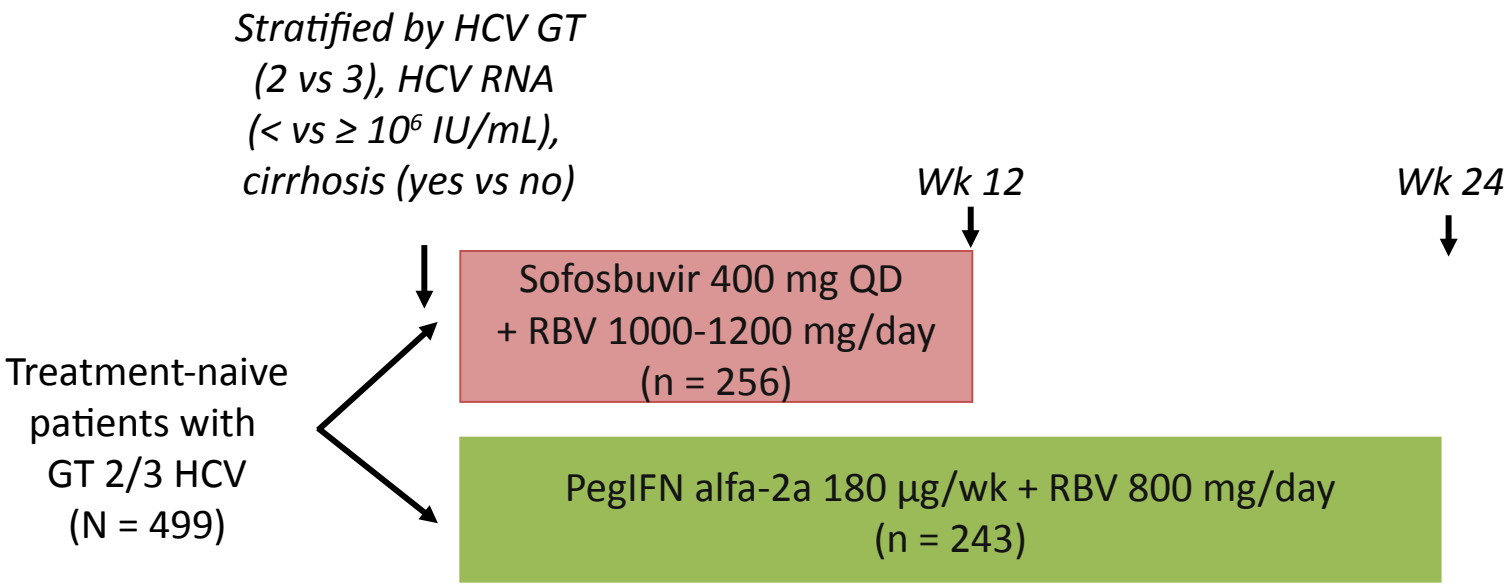
Sofosbuvir has been evaluated for the treatment of HCV G2

infection in 4 phase III studies:

FISSION, POSITRON, FUSION and VALENCE

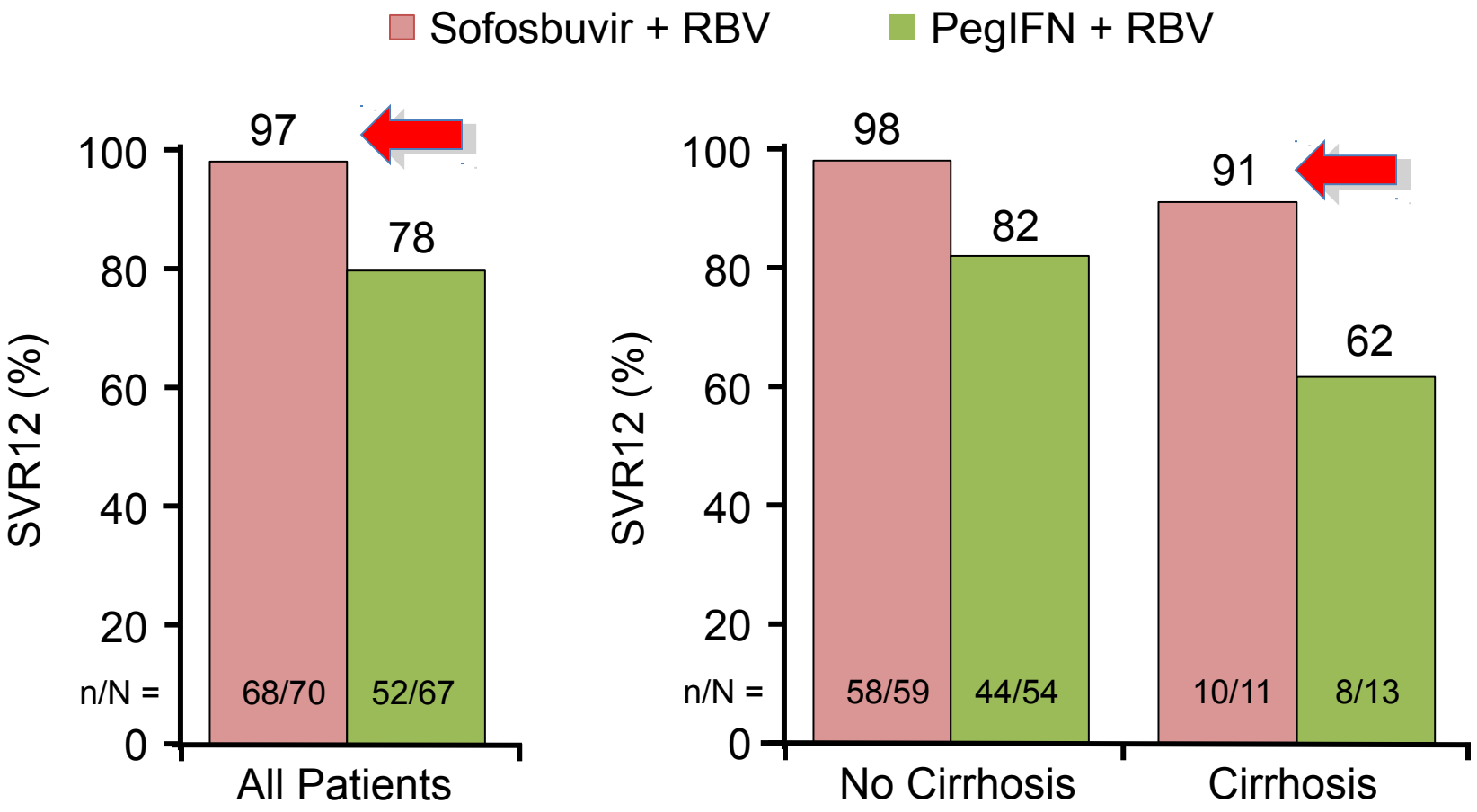
FISSION: Sofosbuvir/RBV vs PegIFN/RBV in HCV-Naive GT 2/3

- Randomized, controlled, open-label phase III noninferiority trial
  - 20% had cirrhosis; 72% had GT 3 HCV



Lawitz E, et al. NEJM 2013

FISSION: SVR12 in HCV-Naive G2 and in Patients With and Without Cirrhosis



Treatment failure in SOF + RBV → Relapse.

No resistance to sofosbuvir (DS)

Lawitz E, et al. NEJM 2013

FISSION: Better tolerance with Sofosbuvir/RBV vs PegIFN/RBV

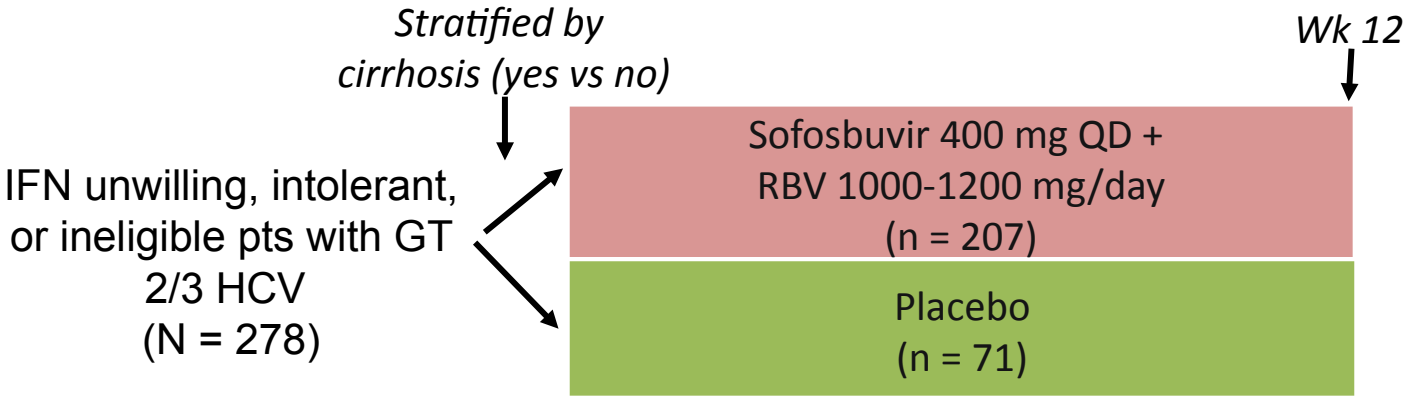
- Grade ≥ 3 AEs: 7% with SOF/RBV vs 19% for pegIFN/RBV
- Discontinuations due to AEs: 1% for SOF/RBV vs 11% for pegIFN/RBV

AEs Occurring in ≥ 15% in Either Arm, %	SOF/RBV (n = 256)	PegIFN/RBV (n = 243)	*P* Value
Fatigue	36	55	< .0001
Headache	25	44	< .0001
Nausea	18	29	.0057
Insomnia	12	29	< .0001
Rash	9	17	.0052
Diarrhea	9	17	.0075
Irritability	10	17	.0328
Decreased appetite	7	18	.0001
Myalgia	8	17	.0060
Pruritus	7	17	.0009
Influenzalike symptoms	3	18	< .0001
Chills	3	18	< .0001

Lawitz E, et al. NEJM 2013

POSITRON: Sofosbuvir + RBV, in HCV G2/3, IFN-Intolerant/Ineligible/Unwilling

- Randomized, double-blind, placebo-controlled phase III trial



Baseline Factor, n (%)	Sofosbuvir + RBV (n = 207)	Placebo (n = 71)
GT 2	109 (53)	34 (48)
Cirrhosis	31 (15)	13 (18)
Interferon unwilling	102 (49)	30 (42)
Interferon ineligible	88 (43)	33 (47)
Interferon intolerant	17 (8)	8 (11)

Jacobson I, et al. NEJM 2013

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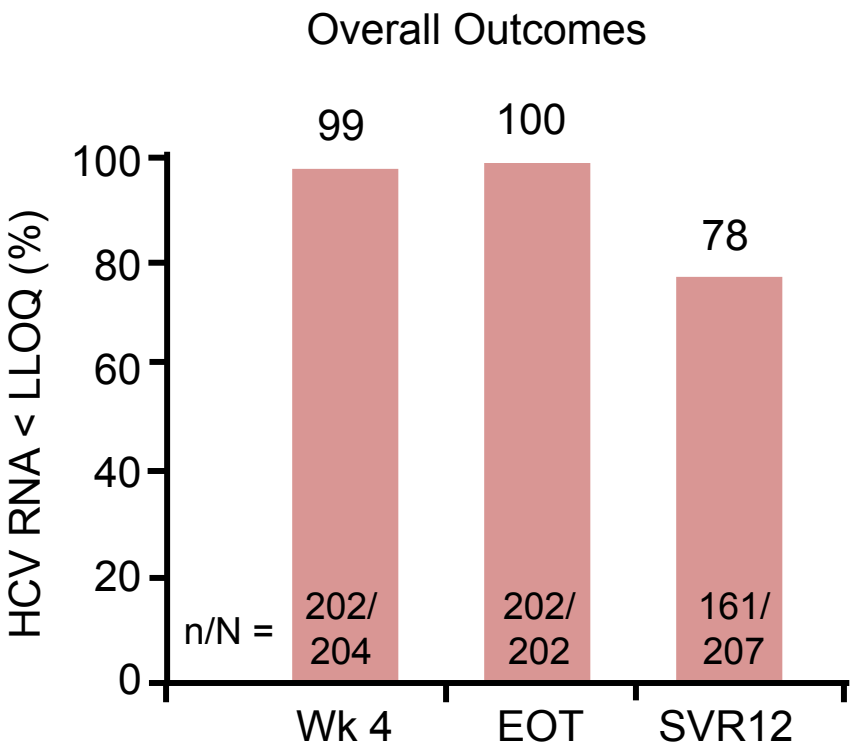
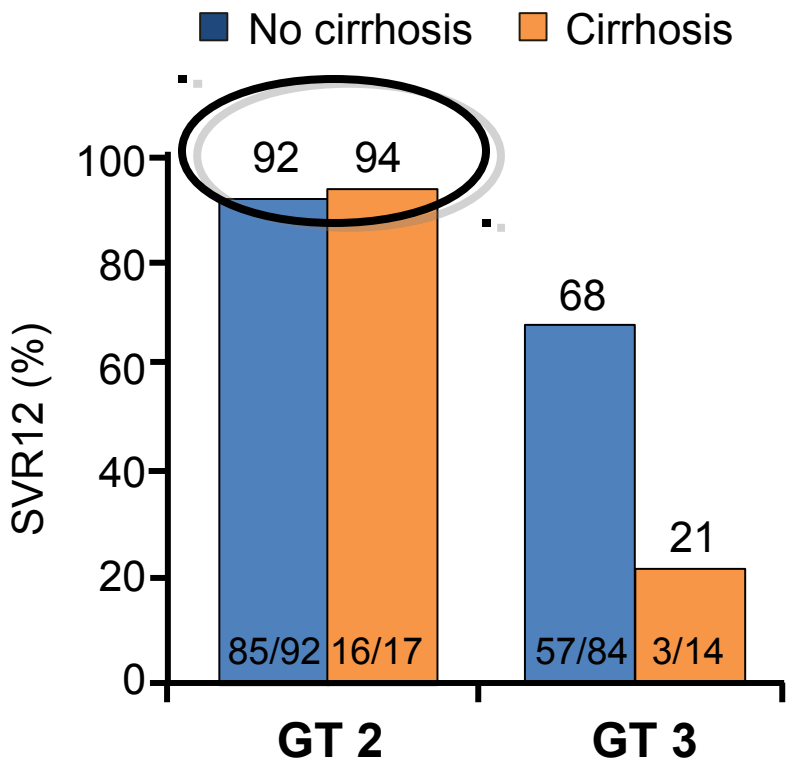


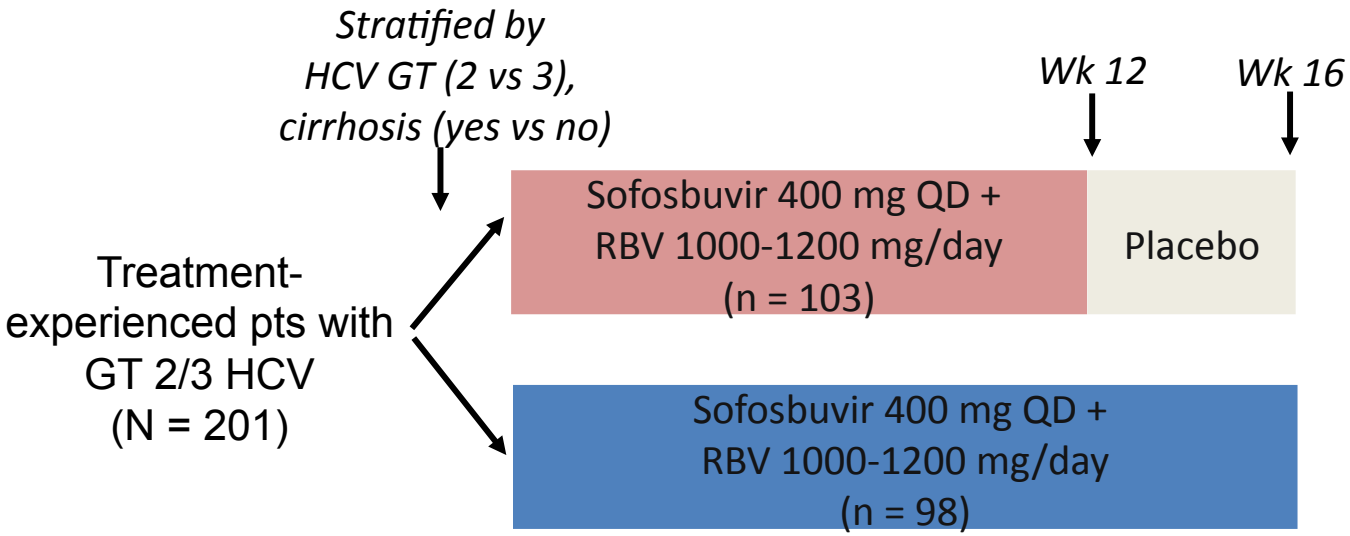


- SVR12 0% for placebo

Jacobson I, et al. NEJM 2013

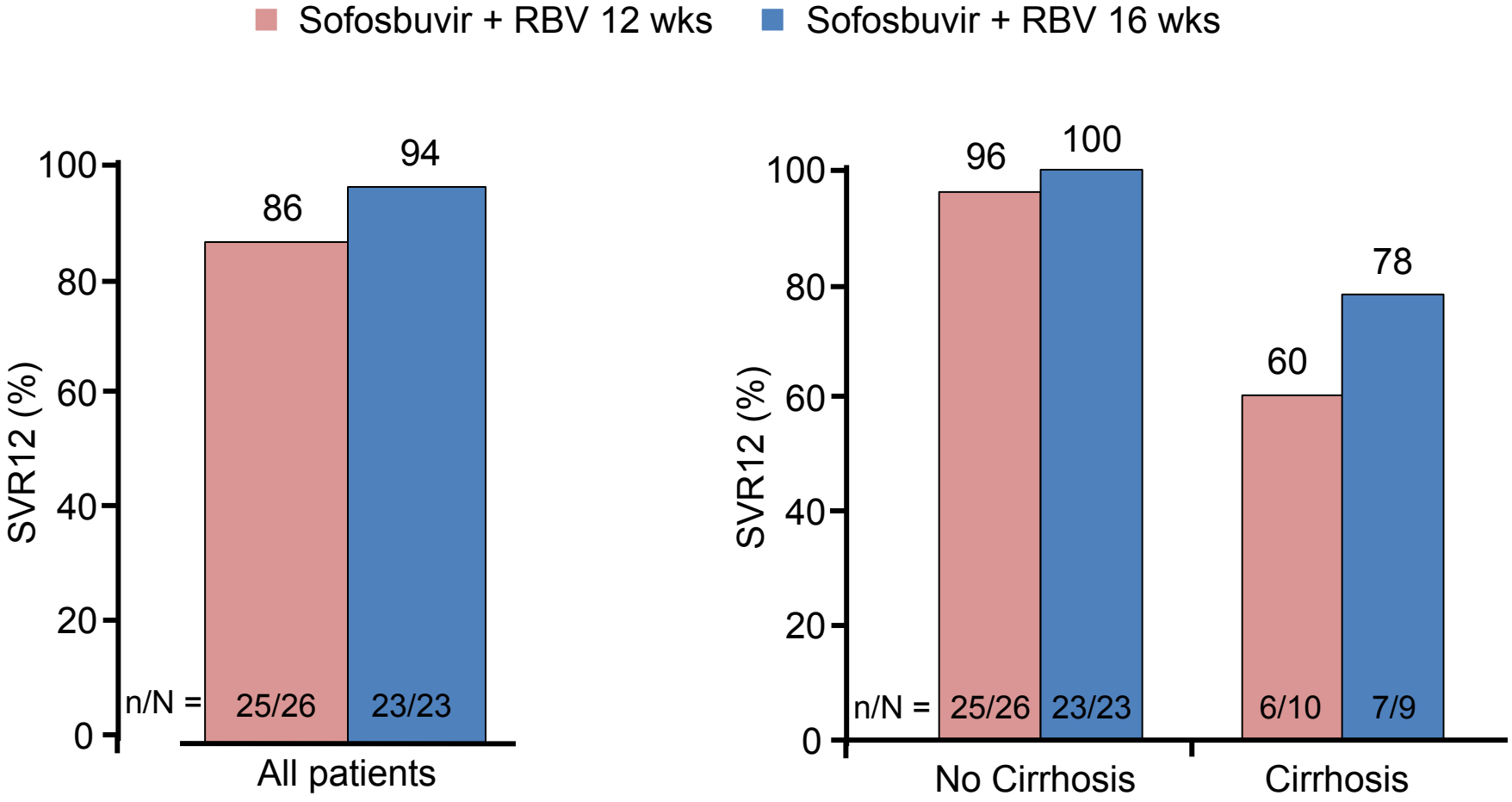
FUSION: Sofosbuvir + RBV, 12 or 16 weeks in treatment-experienced with HCV G2/3

- Randomized, double-blind, placebo-controlled phase III trial
  - 62% to 64% had GT 3 HCV, 33% to 35% had cirrhosis, 75% to 76% were previous relapsers



Jacobson I, et al. NEJM 2013

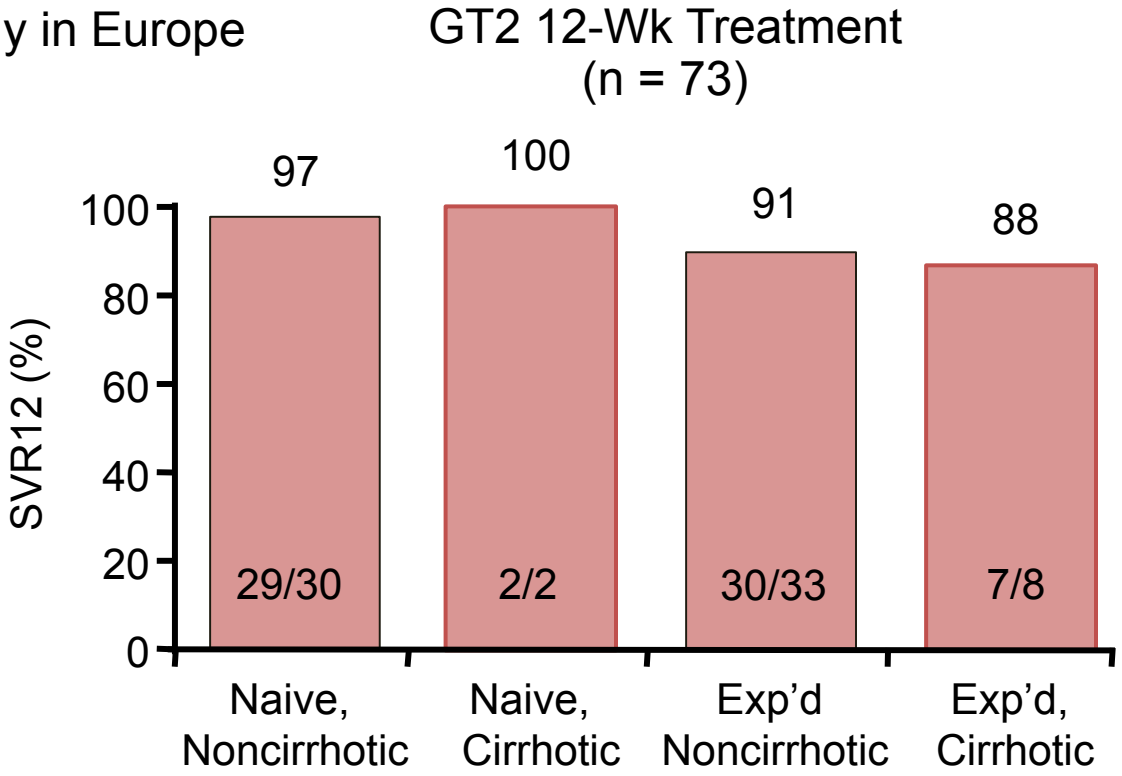
FUSION: SVR12 in G2 patients with and without cirrhosis



Jacobson I, et al. NEJM 2013

VALENCE: SVR12 With 12 Wks of SOF + RBV in Naive and Exp'd G2 Pts

Phase III study in Europe



- No increase in AEs seen with longer duration treatment
  - AEs seen consistent with RBV

Zeuzem S, et al. AASLD 2013

The New York Times

F.D.A. Approves Pill to Treat Hepatitis C

By ANDREW POLLACK

December 7, 2013, Saturday

"Today's approval represents a significant shift in the treatment paradigm for some patients with chronic hepatitis C," said Dr. Edward Cox, director of the office of antimicrobial products at the F.D.A.

But the greater convenience and effectiveness comes at a price.

Gilead said the wholesale cost of Sovaldi, which is known generically as sofosbuvir, would be $28,000 for four weeks — or $1,000 per daily pill. That translates to $84,000 for the 12 weeks of treatment recommended for most patients, and $168,000 for the 24 weeks needed for a hard-to-treat strain of the virus.

Sovaldi, from Gilead Sciences…

Conclusions

- The combination of Sofosbuvir and Ribavirin for 12 weeks is highly effective and safe and is currently the treatment of choice for patients with HCV G2.

- In countries where Sofosbuvir is not available, PEG IFN + RBV for 24 weeks is the recommended therapy.

  → In patients without baseline predictors of treatment failure that experience RVR and receive WBD-RBV, treatment may be shortened to 16 weeks.

Unresolved issues…for HCV G2

- Facilitate access to the new therapies ?
- Is there room for other players ?
- How to treat non responders to SOF-RBV ?

  → retreat for longer period of time ?
  → back to IFN (+ SOF/RBV) ?
  → wait for other IFN-free combination ?

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Thank you !!!!