Hepatitis C en 2013
¿ Tratar o Esperar ?

Servicio de Enfermedades Infecciosas
Hospital Carlos III
Madrid

Caveats on hepatitis C therapy decision making

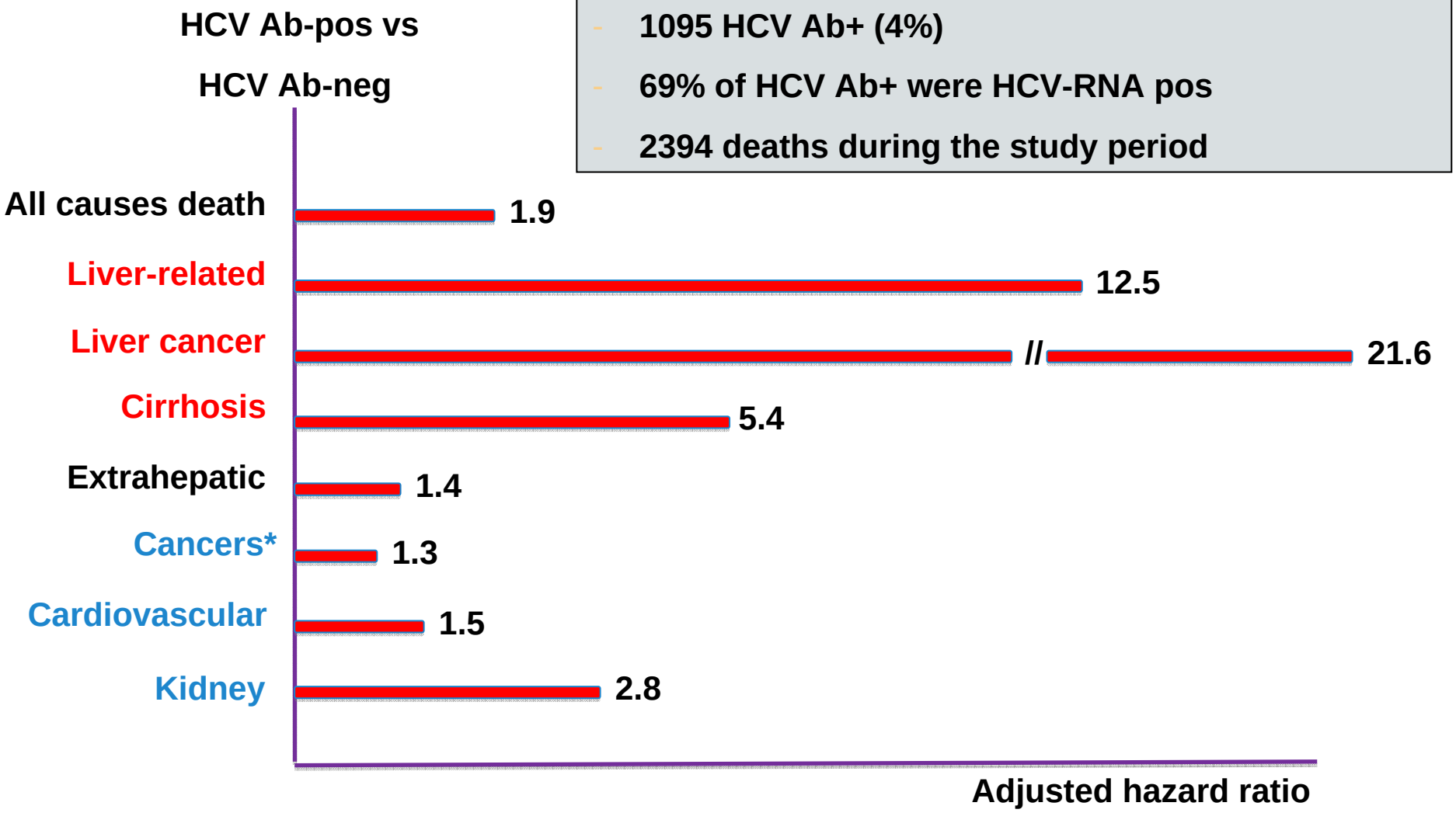
- We treat persons with a liver. They have feelings and responsabilities, including family and profession.

- Chronic HCV infection produces a slow progressive hepatic illness; however, it is not just liver disease.

- Current triple therapy has doubled treatment response rates but does not cure everyone.

REVEAL-HCV

- 23,820 adults followed for a mean of 16.2 years
- 1095 HCV Ab+ (4%)
- 69% of HCV Ab+ were HCV-RNA pos
- 2394 deaths during the study period



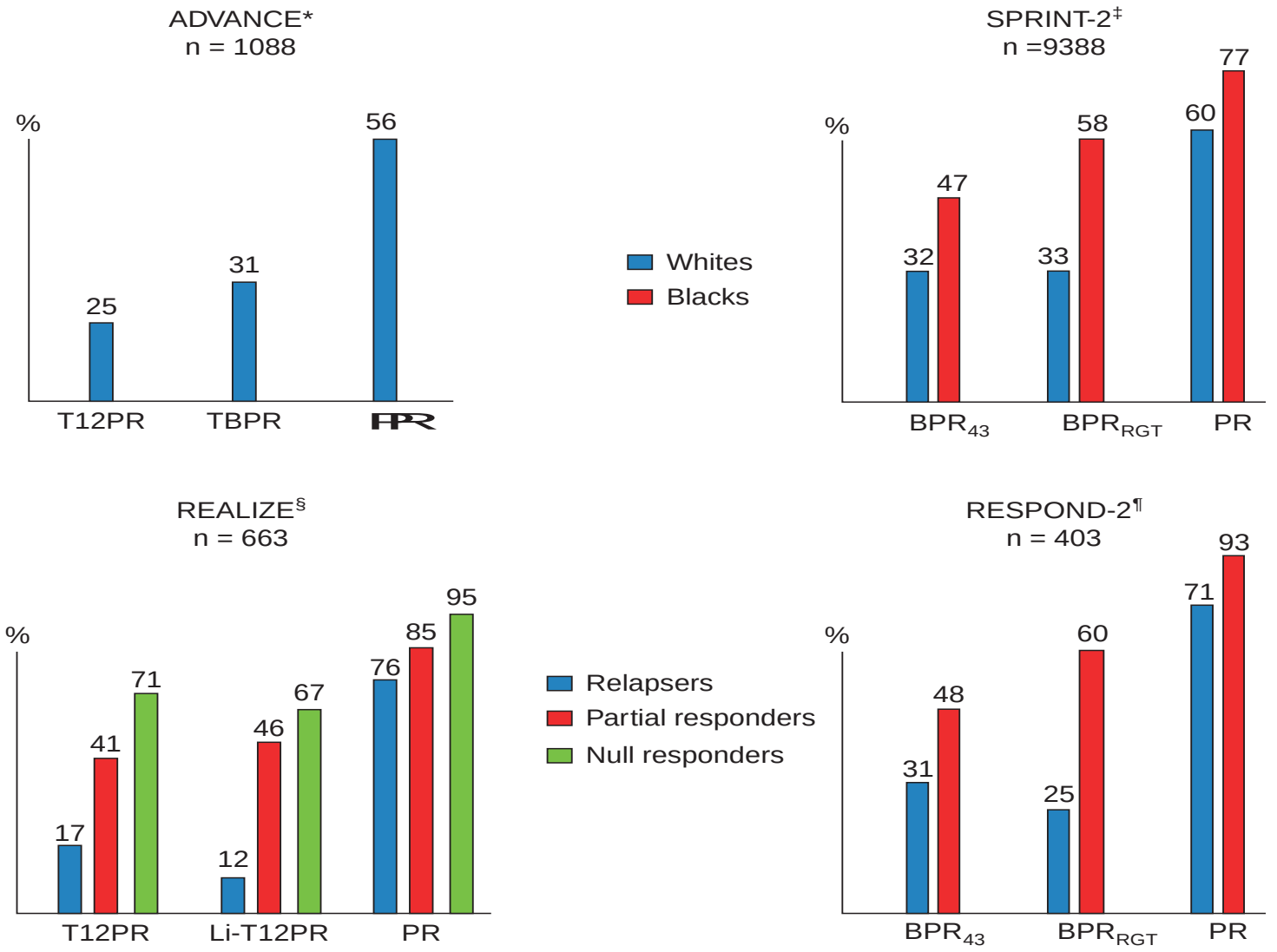
**esophagus, prostate & thyroid*

Lee et al. J Infect Dis 2012; 206: 469-77.

Treatment failure with new hepatitis C drugs

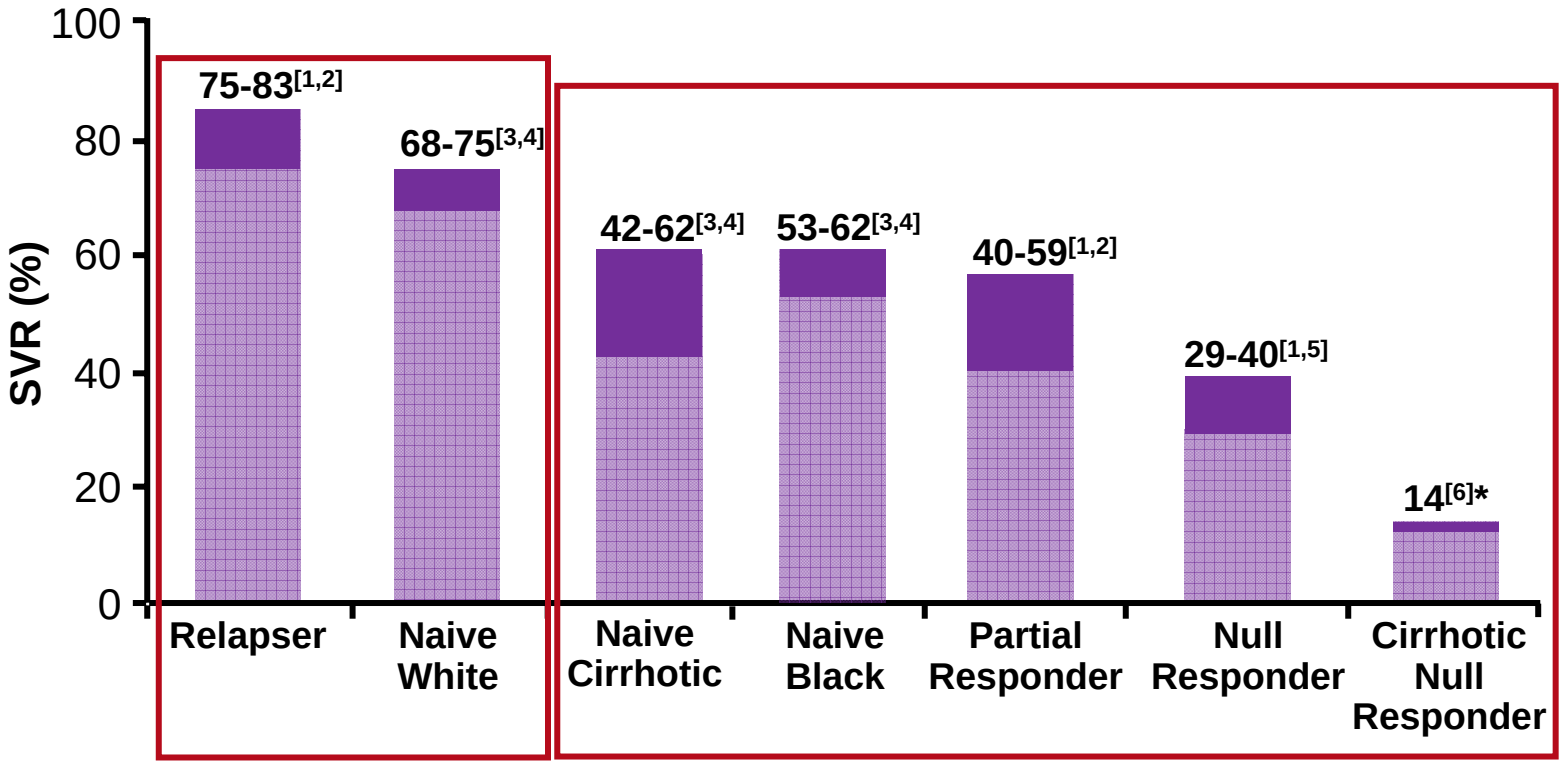
Vincent Soriano†, Eugenia Vispo, Eva Poveda, Pablo Labarga & Pablo Barreiro
Hospital Carlos III, Infectious Diseases Department, Madrid, Spain

Expert Opin Pharmacother 2012; 13: 313-23.



Limited Efficacy With Telaprevir & Boceprevir

Room for Improvement in All Patient Groups



*Pooled TVR arms of REALIZE trial.

1. Zeuzem S, et al. N Engl J Med. 2011;364:2417-2428. 2. Bacon BR, et al. N Engl J Med. 2011;364:1207-1217. 3. Jacobson IM, et al. N Engl J Med. 2011;364:2405-2416. 4. Poordad F, et al. N Engl J Med. 2011;364:1195-1206. 5. Bronowicki J, et al. EASL 2012. Abstract 11. 6. Zeuzem S, et al. EASL 2011. Abstract 5.

HCV treatment now

Pros

- Higher response rate
- Shorter treatment duration

Cons

- Still limited efficacy
- Common & serious adverse effects
- Drug interactions
- Adherence
- Contraindicated in IFN and/or intolerant
- Activity limited to G1
- Scarce information in special patient groups (HIV, transplant, cirrhotics)

Adverse Events Are Common With Current PI Therapy

Outcome, %	ADVANCE[1]		SPRINT-2[2]	
	T12 + PR	PR	BOC + PR RGT	PR
Discontinued due to adverse events	10	7	12	16
Discontinued due to rash	7	1	N/A	N/A
Anemia, g/dL				
▪ < 10.0	36	14	45	26
▪ < 8.5	9	2	5	4
Use of EPO	Not permitted		43	24

1. Jacobson IM, et al. AASLD 2010. Abstract 211.
2. Poordad F, et al. N Engl J Med. 2011;364:1195-1206.

Safety Concerns Increased in Patients With Advanced Liver Disease

- CUPIC trial: early access program with telaprevir and boceprevir from France enrolling treatment-experienced patients with cirrhosis
  - Wk 16 interim analysis of 497 patients
- High rate of serious adverse events: **33% to 45%**
- High rate of anemia
  - Grade 2: 19% to 23%
  - Grade 3/4: 4% to 12%
- High rate of premature discontinuation: 23% to 26%

Hezode C, et al. AASLD 2012. Abstract 51.

Higher Discontinuation Rates in Real-World Settings Than in Clinical Trials

- Retrospective studies from the US: data from medical records review and included patients with genotype 1 HCV infection[1,2]

- 2 centers in Dallas and Miami with 12-wk follow-up[1]
- Exclusions: transplantation, dialysis, or HIV coinfected
- Of 498 patients identified
  - 18% began triple therapy
  - **21%** discontinued triple therapy before Wk 12

- Mount Sinai Medical Center and Montefiore with 12-wk follow-up[2]
- Of 174 patients who initiated TVR-based triple therapy
  - 33% discontinued TVR prematurely
  - **21%** discontinued treatment due to adverse events

1. Chen EY, et al. AASLD 2012. Abstract 133. 2. Bichoupan K, et al. AASLD 2012. Abstract 1755.

Drug–Drug Interactions

- Several drugs contraindicated; many more require dose adjustment or caution*

Drug Class	Contraindicated with BOC[1]	Contraindicated with TVR[2]
Alpha 1-adrenoreceptor antagonist	Alfuzosin	Alfuzosin
Anticonvulsants	Carbamazepine, phenobarbital, phenytoin	N/A
Antimycobacterials	Rifampin	Rifampin
Ergot derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Dihydroergotamine, ergonovine, ergotamine, methylergonovine
GI motility agents	Cisapride	Cisapride
Herbal products	*Hypericum perforatum* (St John's wort)	*Hypericum perforatum*
HMG CoA reductase inhibitors	Lovastatin, simvastatin	Lovastatin, simvastatin
Oral contraceptives	Drospirenone	N/A
Neuroleptic	Pimozide	Pimozide
PDE5 inhibitor	Sildenafil or tadalafil when used for tx of pulmonary arterial hypertension	Sildenafil or tadalafil when used for tx of pulmonary arterial hypertension
Sedatives/hypnotics	Triazolam; orally administered midazolam	Orally administered midazolam, triazolam

Challenges With Adherence to Complex Regimens

- Triple therapy regimens are complex, presenting challenges to medication adherence
  - TID dosing
  - Food requirements
- Data show pegIFN/RBV adherence decreases over time[1]
  - Addition of PIs may exacerbate this trend

1. Lo Re V 3rd, et al. Ann Intern Med. 2011;155:353-360.

Several Patient Populations With Continued Need in Current Era

- Contraindication or poor tolerance to pegIFN or RBV
- Safety and efficacy of boceprevir and telaprevir not fully established
  - Organ transplant recipients
  - Patients with end-stage liver disease
  - Patients with HIV and/or HBV coinfection
  - Pediatric patients
- Patients with decompensated cirrhosis
- Although pegIFN/RBV effective for non–genotype 1, comes with all troubles associated to IFN use
- Patients with poor IFN responsiveness
- Patients unable to adhere to complex, lengthy regimens

Investigational HCV Regimens in Phase III Clinical Trials

Regimens With 1 DAA + PegIFN alfa/RBV

- Faldaprevir (BI, PI)
- Daclatasvir (BMS, NS5A)
- Sofosbuvir (GS, NI)
- Simeprevir (Tibo, PI)
- Vaniprevir (MSD, PI)

Alternative Dosing

- TVR BID (approved PI)

Regimens With 2 DAAs + PegIFN alfa/RBV

- Daclatasvir + asunaprevir

New IFNs

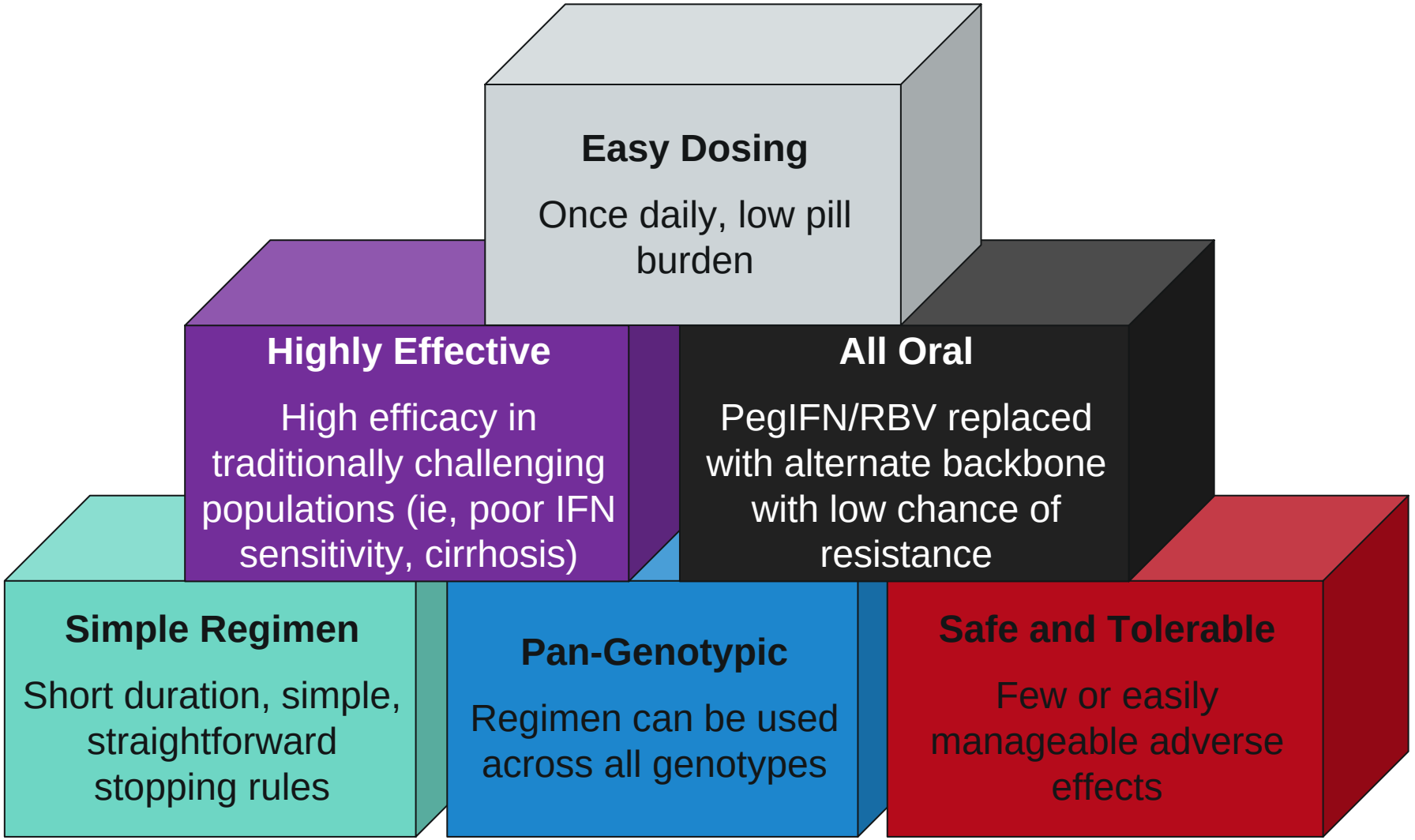
- PegIFN lambda-1a + RBV
- PegIFN lambda-1a + daclatasvir + RBV
- PegIFN lambda-1a + RBV + TVR

IFN-Free Regimens

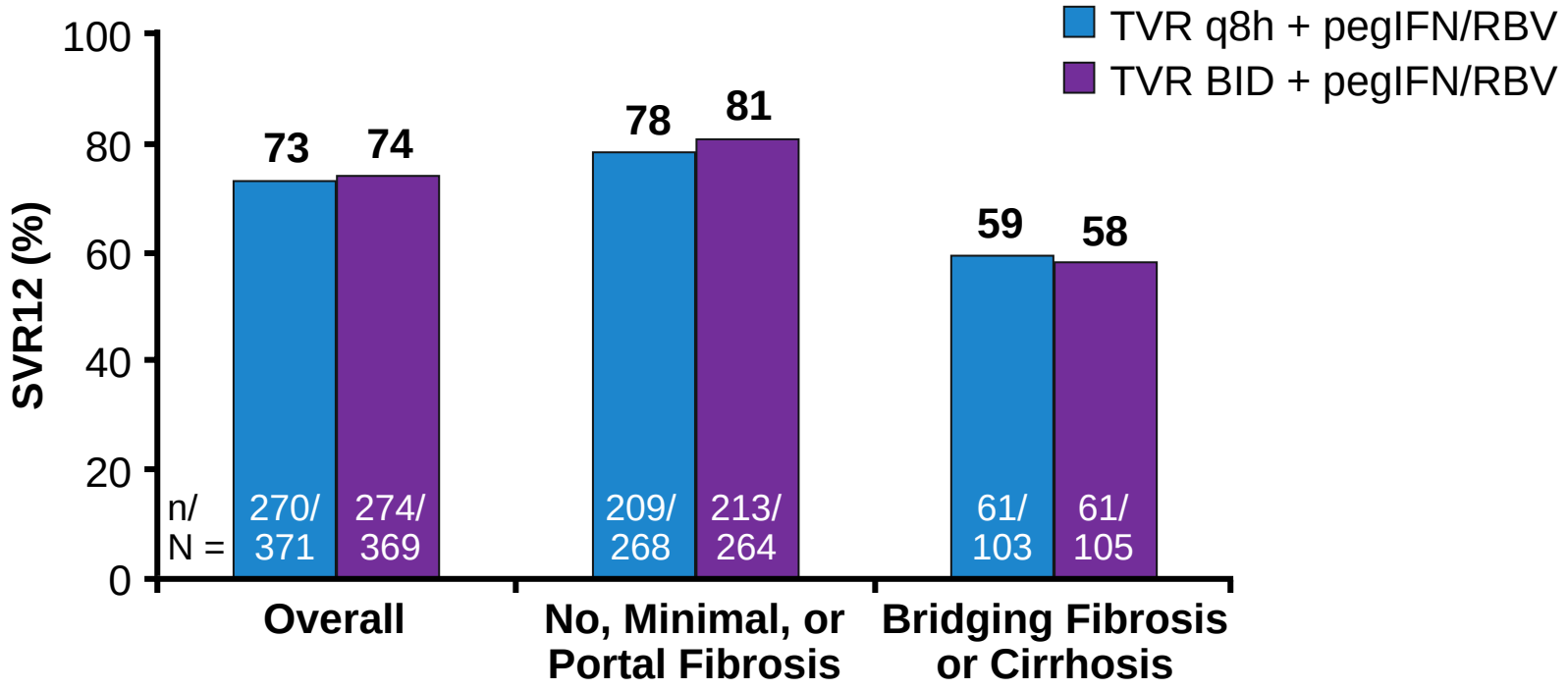
- Sofosbuvir + RBV
- Sofosbuvir + GS-5885 (NS5A) ± RBV
- Asunaprevir (PI) + daclatasvir
- ABT-450 (PI)/r + ABT-267 (NS5A) + ABT-333 (NNI) + RBV
- Faldaprevir (PI) + BI 207127 (NNI) + RBV

ClinicalTrials.gov. January 27, 2013.

Ideal HCV Regimen?



Improved Dosing With Current Therapy: TVR BID Noninferior to TID in Tx-Naive GT1

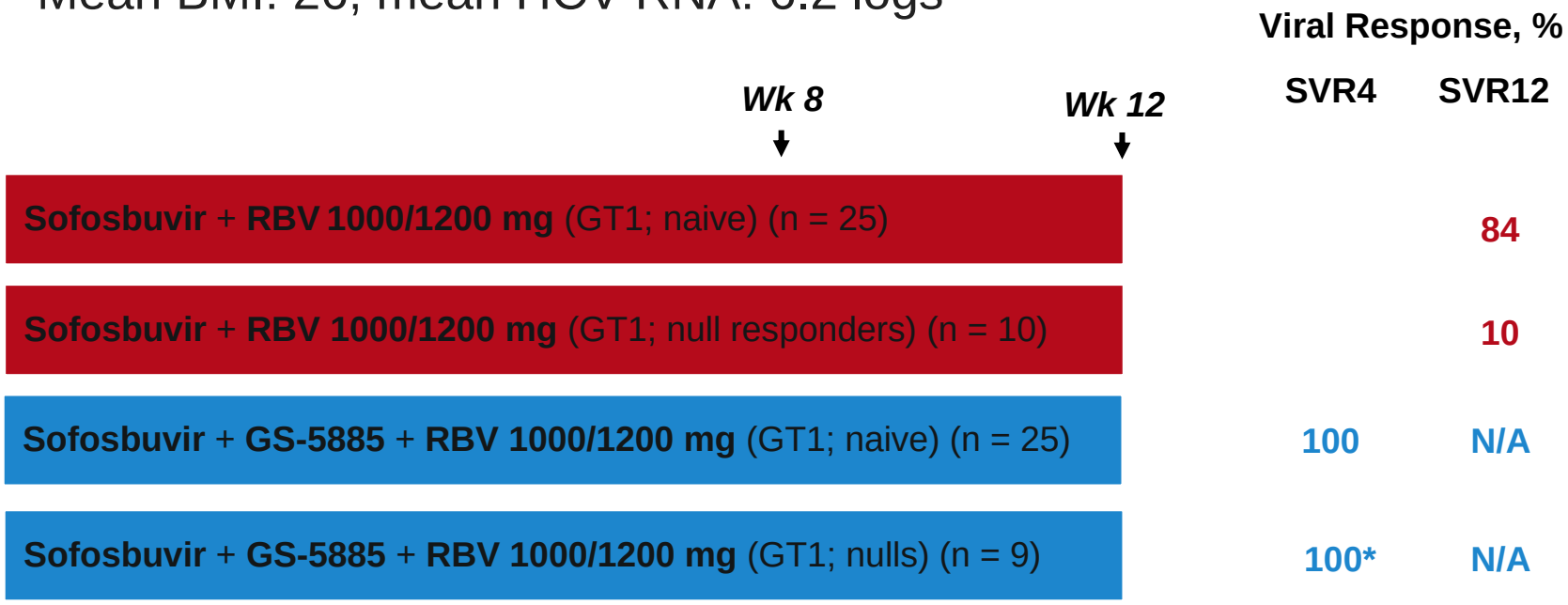


- Adverse events similar between treatment arms
- No differences in efficacy with 2 strategies in patients with more advanced disease

Buti M, et al. AASLD 2012. Abstract LB-8.

ELECTRON: Sofosbuvir ± GS-5885 + RBV in Naive and Previous Null Responders

- Pts with poor prognostic indicators: GT1a (86%), male (54%), nonwhite (12%), *IL28B* CT/TT (68%)
- Mean BMI: 26; mean HCV RNA: 6.2 logs



Gane EJ, et al. N Engl J Med 2013.

The New Waves of HCV Therapy

- **Wave 1 (2011-2013): First-generation PI added to pegIFN/RBV**
  - Naives → consider Rx with pegIFN/RBV/PI only for advanced stage
  - Experienced → offer Rx in relapsers & partial responders
  - Nulls → offer Rx only in advanced stage and prior good tolerance

Only G1

- **Wave 2 (2013-2016): a paradigm shift**

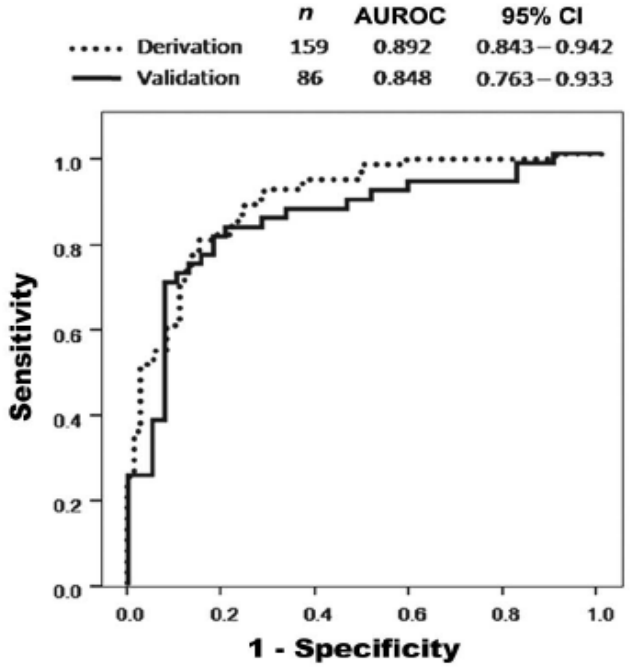
All genotypes

  - Oral cocktails of DAAs
  - Potential substitution of better-tolerated IFNs
  - Substitution of second-generation PIs (better PK, tolerability)
  - Arrival of N5A inhibitors
  - 4-drug regimens for pegIFN/RBV/PI failures

Modeling the Probability of Sustained Virological Response to Therapy with Pegylated Interferon plus Ribavirin in Patients Coinfected with Hepatitis C Virus and HIV

Clinical Infectious Diseases 2010;51(10):1209–1216

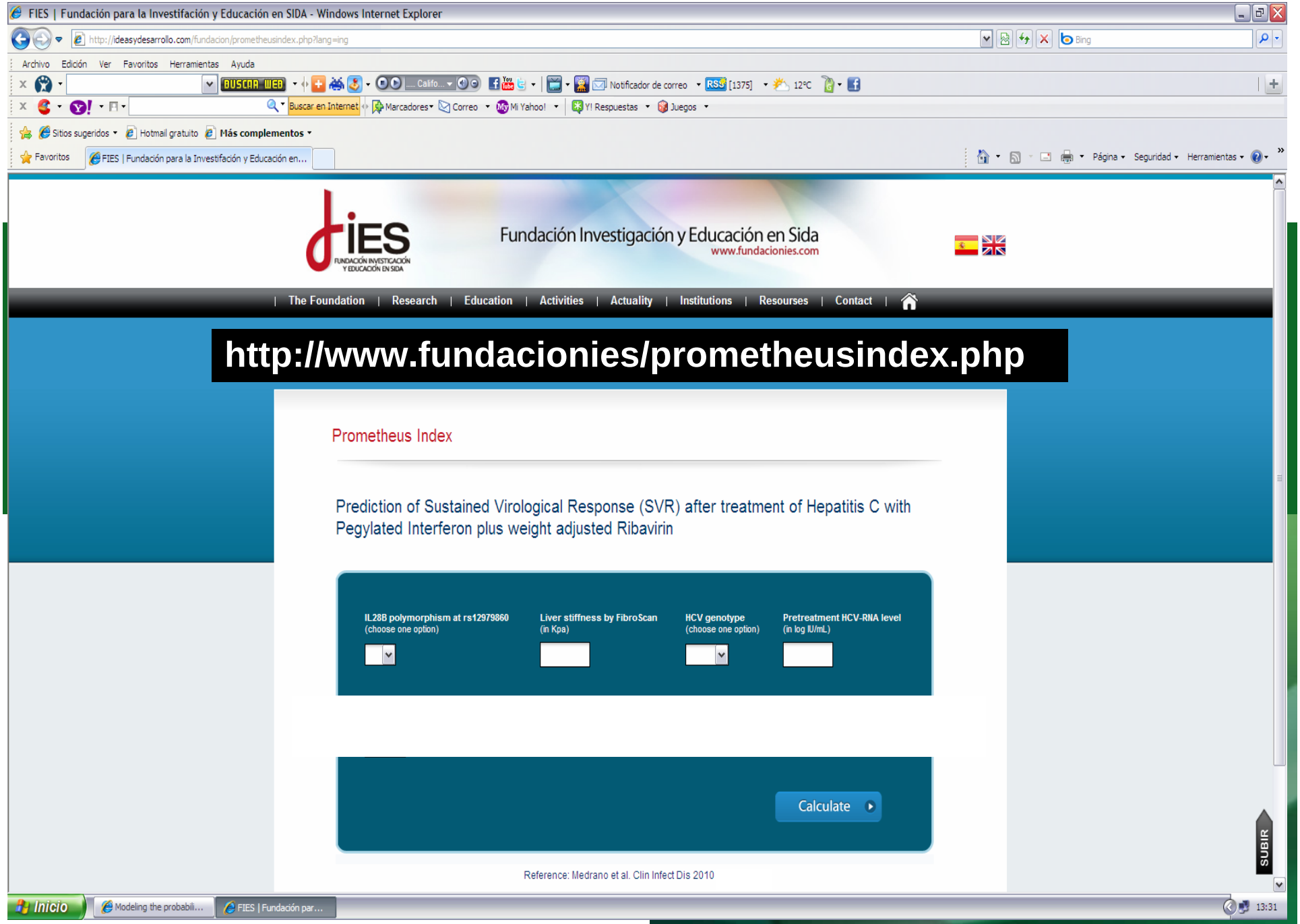
Jose Medrano,[1] Karin Neukam,[3] Norma Rallón,[1] Antonio Rivero,[4] Salvador Resino,[2] Susanna Naggie,[6] Antonio Caruz,[5] Aida Calvino,[2] Juan Macías,[3] Jose Miguel Benito,[1] Carlos Sánchez-Piedra,[1] Eugenia Vispo,[1] Pablo Barreiro,[1] John McHutchison,[6] Juan Antonio Pineda,[3] and Vincent Soriano[1]



Prometheus index

- HCV genotype
- Fibrosis stage (KPa)
- Serum HCV-RNA
- IL28B SNPs

http://www.fundacionies/prometheusindex.php


FIES | Fundación para la Investifación y Educación en SIDA - Windows Internet Explorer
http://ideasydesarrollo.com/fundacion/prometheusindex.php?lang=ing
Fundación Investigación y Educación en Sida
www.fundacionies.com
The Foundation | Research | Education | Activities | Actuality | Institutions | Resourses | Contact
http://www.fundacionies/prometheusindex.php
Prometheus Index
Prediction of Sustained Virological Response (SVR) after treatment of Hepatitis C with Pegylated Interferon plus weight adjusted Ribavirin
IL28B polymorphism at rs12979860 (choose one option)
Liver stiffness by FibroScan (in Kpa)
HCV genotype (choose one option)
Pretreatment HCV-RNA level (in log IU/mL)
Calculate
Reference: Medrano et al. Clin Infect Dis 2010
SUBIR

Summary

- First improvements in treatment may be related to less frequent dosing (eg, BID TVR) and improved tolerability (eg, QD DAA + pegIFN/RBV)
- Deep pipeline for DAA-based regimens and superb prospects for all oral regimens
- Combinations of several DAA classes can achieve SVR
- High-barrier resistance compounds highly desirable for simplified regimens but may be matched by combinations of DAA classes
- RBV still appears to be critical in achieving freedom from IFN, particularly in less-than-optimal regimens
- IL28B and Subtype also plays an important role
  - 1a non-CC < 1a CC, 1b
- DAA regimens in cirrhotics and other special populations require further study

Treat Now vs Wait

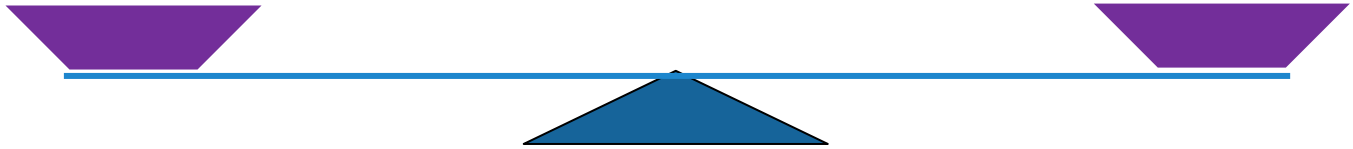
Many Issues to Consider

Treat now

- Triple therapy increases SVR
- Earlier treatment (younger age & less fibrosis) has higher success
- Successful treatment arrests progression of liver disease
- Shorter treatment duration
- Patient's willingness

Defer

- First-generation PIs complex, associated with adverse events
- Unclear if current treatment failure affects future treatment?
- Next DAA will provide higher SVR, including in challenging populations
- Next DAA regimens will be simpler, QD or BID, with fewer adverse effects, eventually IFN-free
- Next DAA wil be active on non–genotype 1



Agradecimientos

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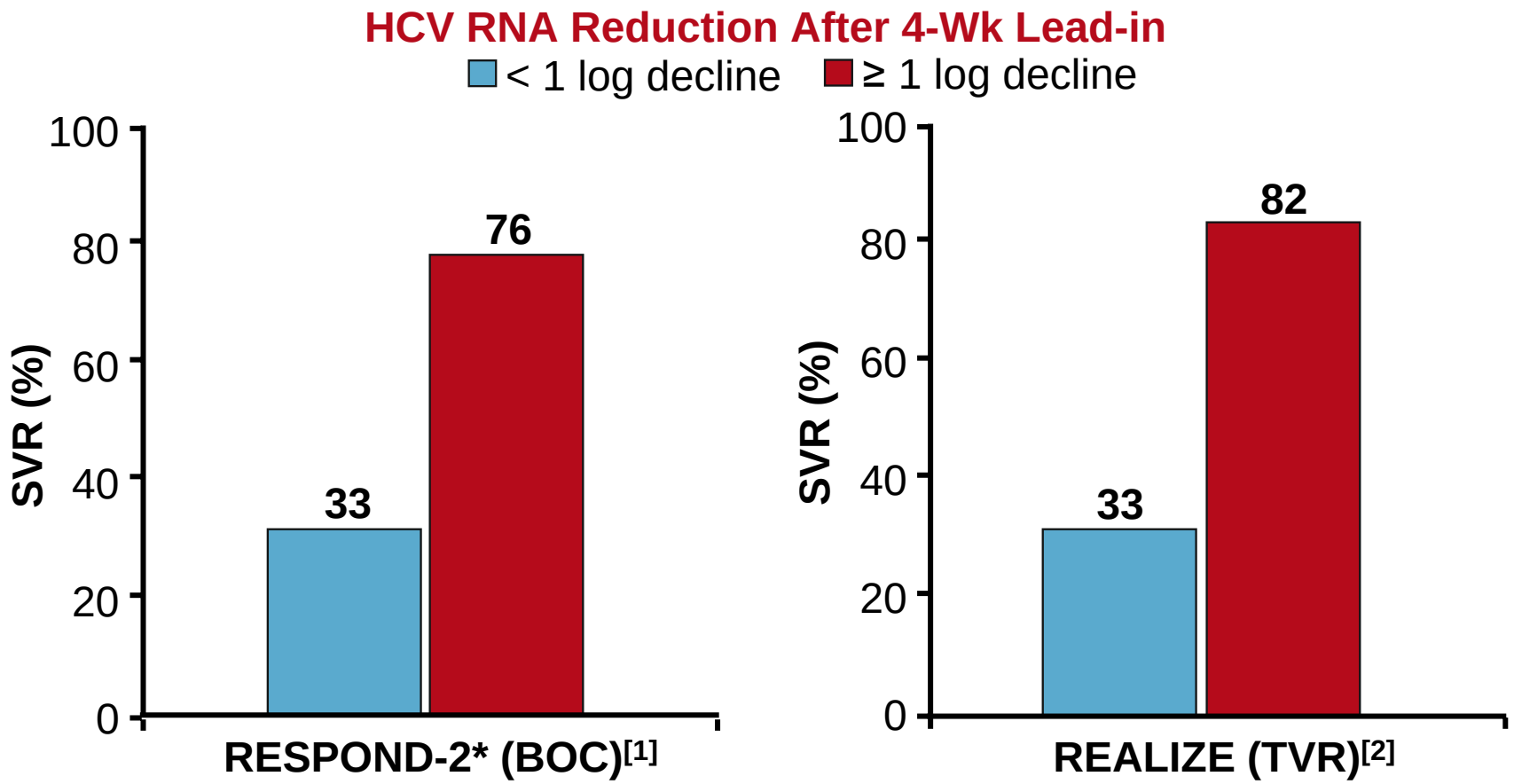
- Eva Poveda
- Zulema Plaza
- Rocío Sierra
- Carmen de Mendoza
- Jose Miguel Benito
- Norma Rallon

Likelihood of SVR With Current Therapies Related to IFN Responsiveness

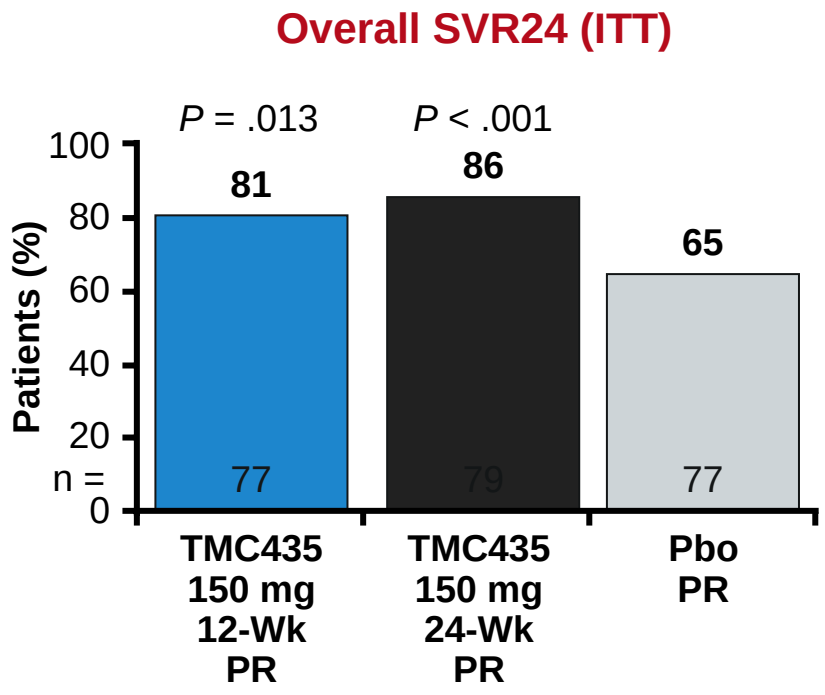


*Pooled data from RGT and arm 3.

1. Vierling JM, et al. EASL 2011. Abstract 481. 2. Foster G, et al. EASL 2011. Abstract 6.

Safety and Efficacy of Simeprevir QD + PegIFN/RBV in GT1 Treatment-Naive Pts

- Addition of simeprevir (TMC435) to pegIFN/RBV significantly improved SVR rates vs pegIFN/RBV alone at Wk 24

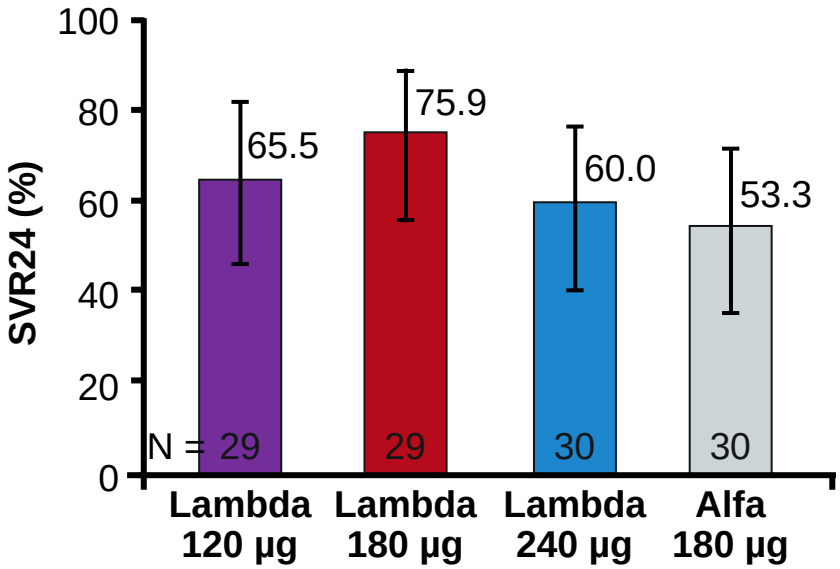


Safety Outcome, %	All TMC435 Arms (n = 309)	Placebo + PR 48W (n = 77)
Study tx permanently discontinued for AE	3.6	5.2
Grade 3/4 AE	32.0	35.1
Serious AE	6.5	13.0
Most frequent AEs in TMC435-treated pts		
▪ Fatigue	42.4	48.1
▪ Flu-like illness	31.7	37.7
▪ Pruritus	31.1	45.5
▪ Headache	46.0	51.9
Other AEs of interest		
▪ Rash	21.0	23.4
▪ Anemia	20.4	20.8
▪ Neutropenia	24.3	20.8

Fried MW, et al. AASLD 2011. Abstract LB-5.

Safety and Efficacy of PegIFN lambda-1a vs PegIFN alfa-2a in GT 2/3 Tx-Naive Pts

- EMERGE study: each group received pegIFN + RBV for 24 wks

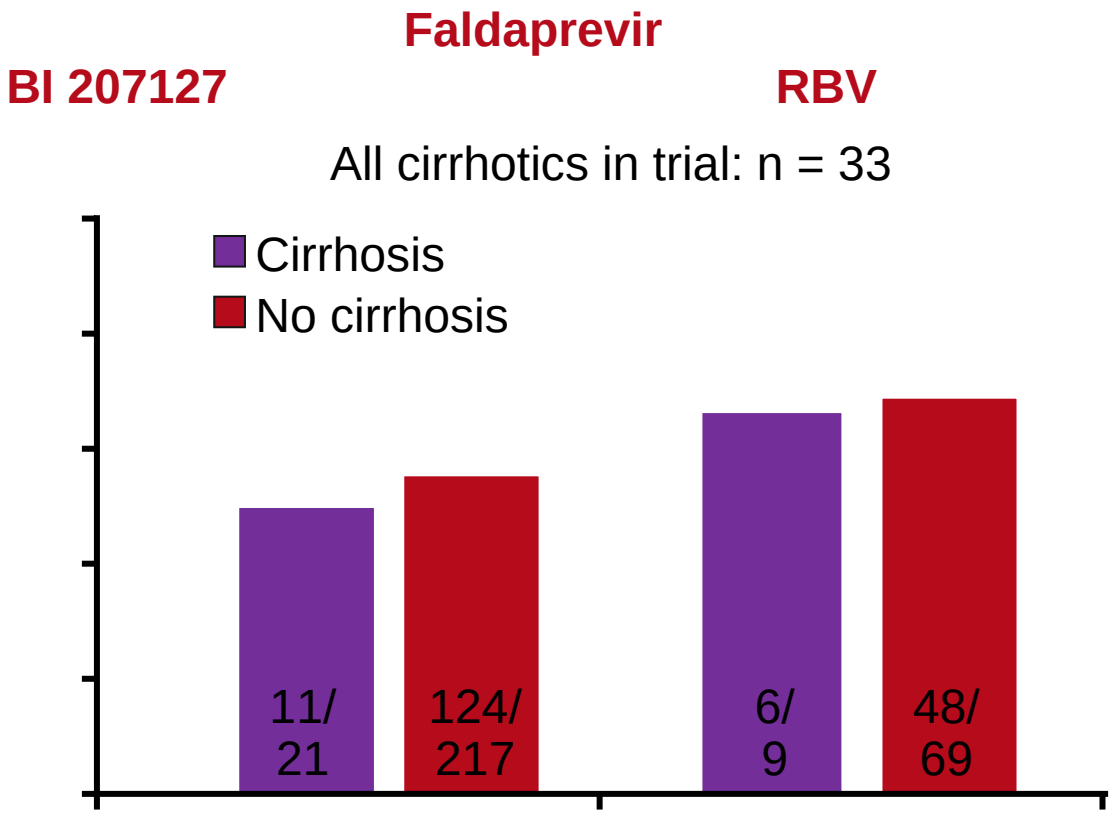


Hematologic Adverse Event, %	Lambda 180 µg (n = 29)	Alfa 180 µg (n = 30)
Hemoglobin low < 10 g/dL *or* Δ > 3.4 g/dL	6.9	44.8
RBV dose reduction (hemoglobin associated)	0	23.3
Neutrophils low < 750 cells/mm^3	0	27.6
Platelets low < 100,000 cells/mm^3	0	24.1
PegIFN dose reduction (hematologic abnormality)	0	23.3

- PegIFN lambda-1a 180 µg/wk dosage chosen for phase III trials

Zeuzem S, et al. EASL 2012. Abstract 10.

Efficacy in GT1 Tx-Naive Pts With Cirrhosis: Faldaprevir + BI 207127 + RBV

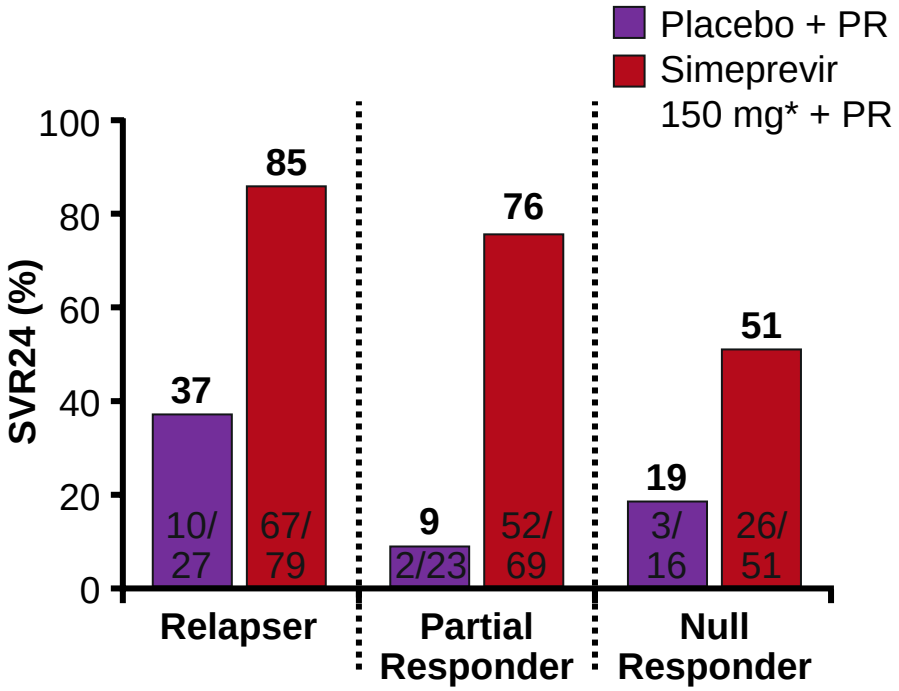


*Treatment arms with different durations combined.

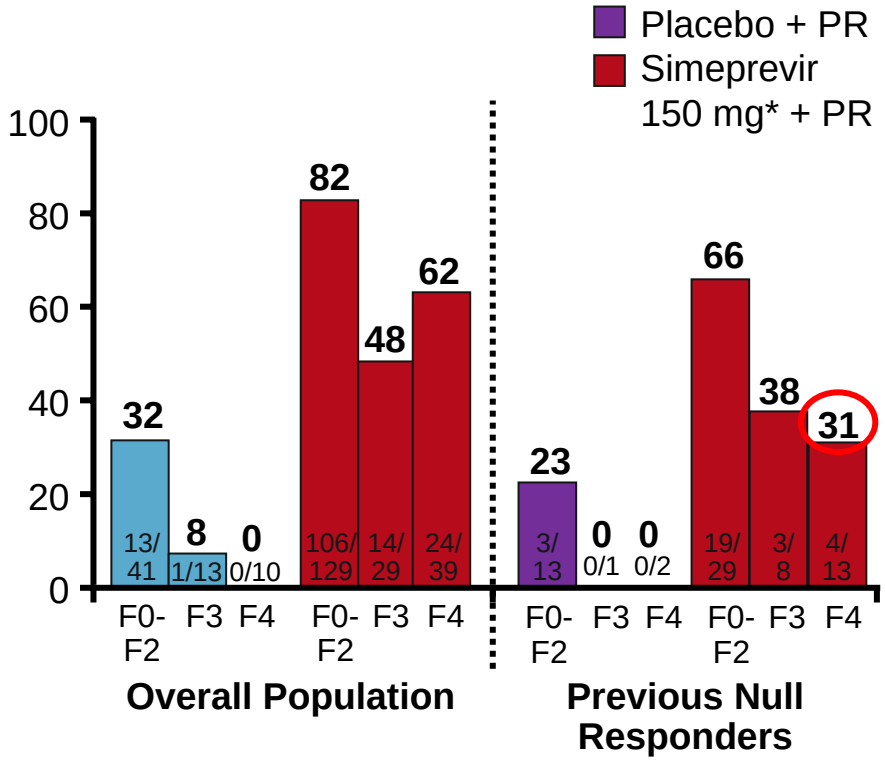
Soriano V, et al. AASLD 2012. Abstract 84.

Efficacy in Txt-Experienced Pts, Advanced Disease: Simeprevir + PegIFN/RBV

Treatment-Experienced GT1 Patients Achieving SVR24 by Previous Response



Treatment-Experienced GT1 Patients Achieving SVR24 by METAVIR Score

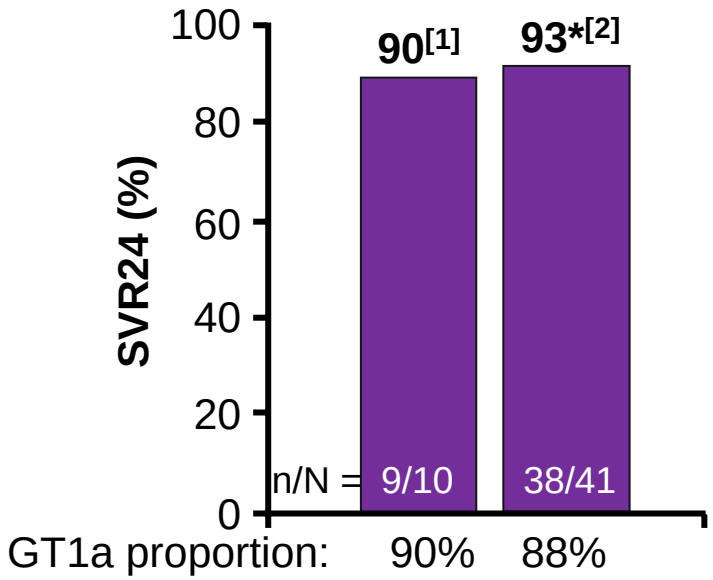


*Treatment arms with different durations combined.

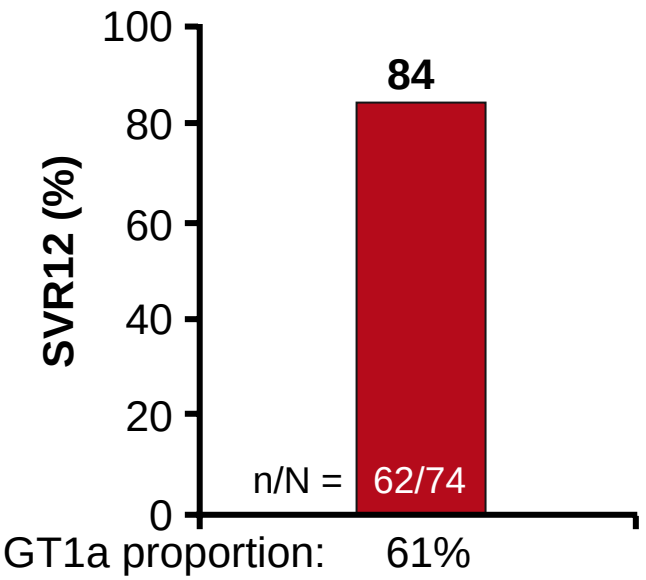
Jacobson IM, et al. IDSA 2012.

2 DAAs + PegIFN/RBV in GT1 Previous Null Responders

Daclatasvir (NS5A) + Asunaprevir (PI) + PegIFN/RBV x 24 Wks



Danoprevir/RTV (PI) + Mericitabine (Nuc) + PegIFN/RBV x 24 Wks[3]

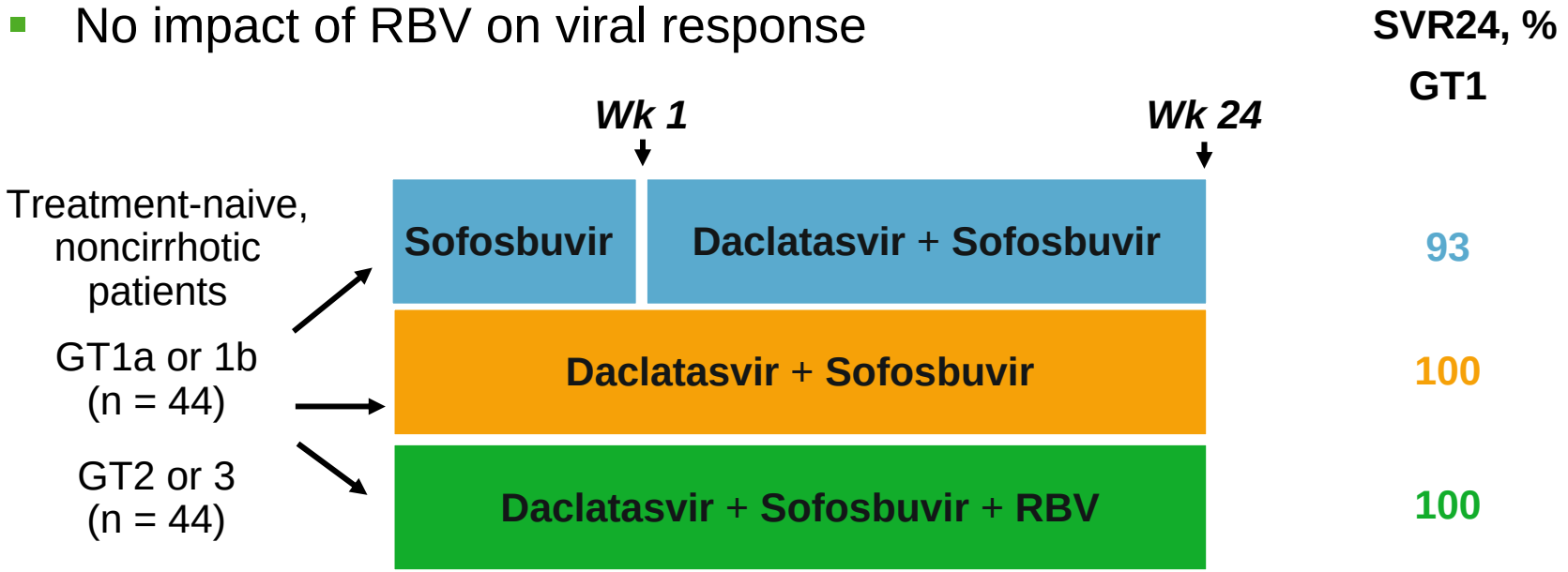


*Asunaprevir QD and BID combined.

1. Lok A, et al. N Engl J Med. 2012;366:216-224. 2. Lok A, et al. AASLD 2012. Abstract 79.
3. Feld JJ, et al. AASLD 2012. Abstract 81 .

Daclatasvir Plus Sofosbuvir in GT1 Treatment-Naive Patients

- Pts with poor prognostic indicators: GT1a (73%), male (52%), black (20%), *IL28B* CT/TT (64%); advanced liver disease: 14%
- Mean HCV RNA: 6.6 logs
- No impact of RBV on viral response

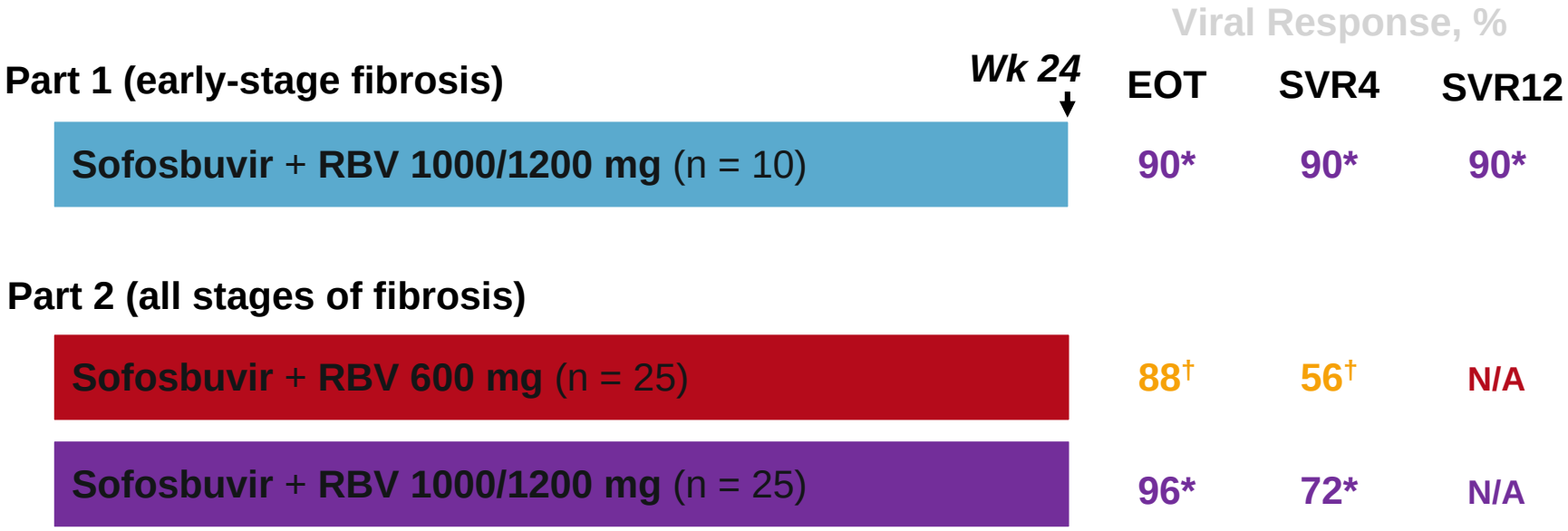


Sofosbuvir dosed 400 mg QD. Daclatasvir dosed 60 mg QD. RBV dosed by body weight for GT1 patients (1000-1200 mg/day); 800 mg/day for GT2/3 patients.

Sulkowski M, et al. AASLD 2012. Abstract LB-2.

NIH SPARE: Interim Data on Sofosbuvir and RBV in Difficult-to-Treat GT1 Pts

- Pts with poor prognostic indicators: GT1a (70%), male (63%), black (83%), *IL28B* CT/TT (80%); advanced liver disease: 22%
- Median BMI: 26-30; median HCV RNA: 6.05-6.85 logs

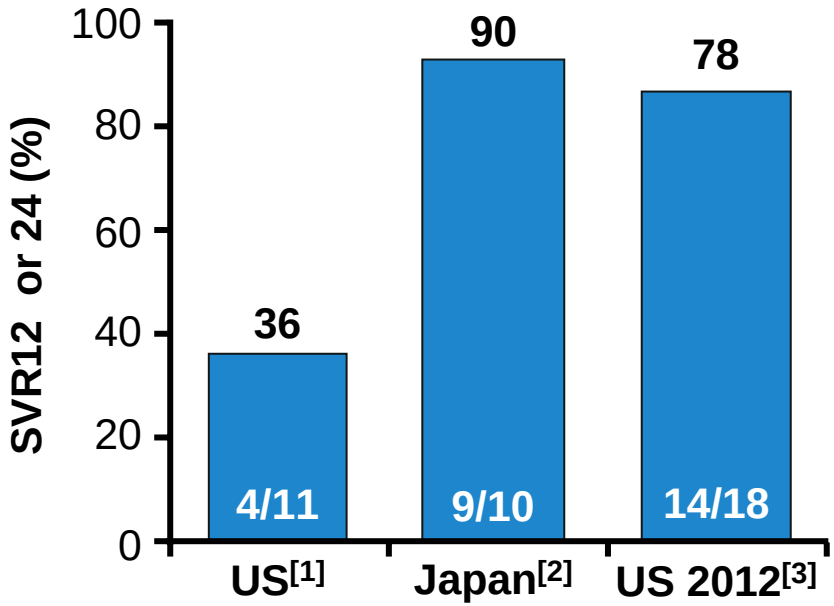


*1 drop out by Wk 3. †3 drop outs by Wk 8.

Osinusi A, et al. AASLD 2012. Abstract LB-4.

IFN-Free Therapy in Prior Null Responders

Daclatasvir (NS5A) + Asunaprevir (PI) x 24 Wks (IFN Free)



US Study
9/11 GT1a

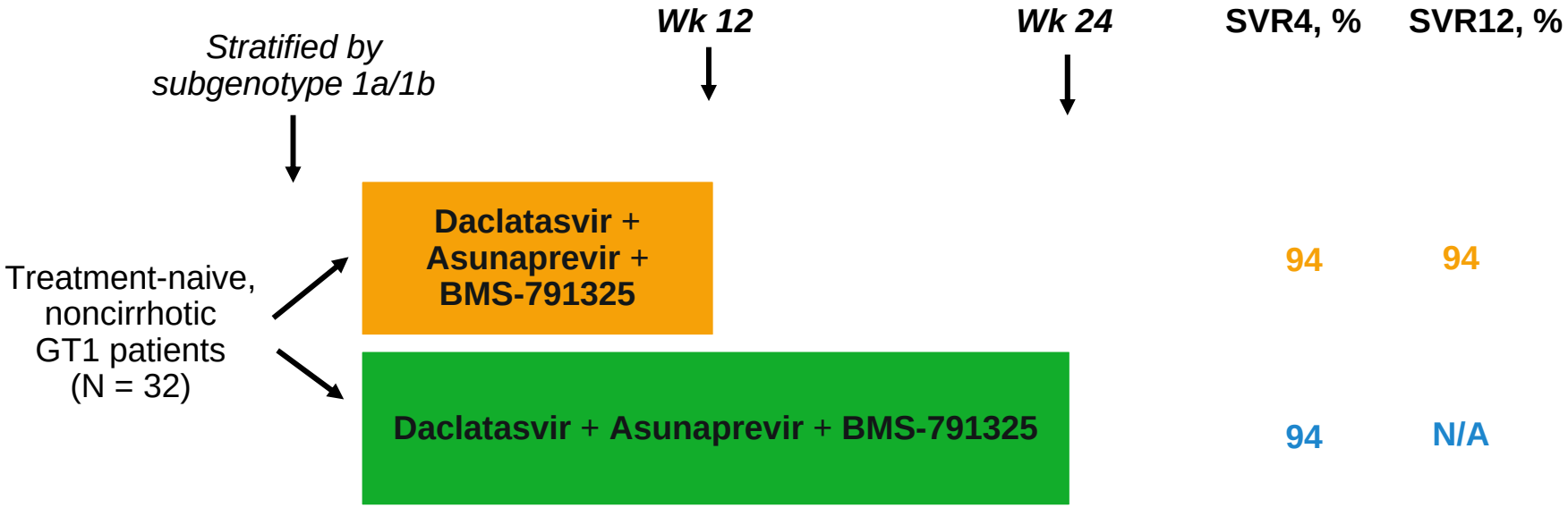
Japanese Study
10/10 GT1b

US 2012
GT1b only

1. Lok A, et al. N Engl J Med. 2012;366:216-224. 2. Chayama K, et al. AASLD 2011. Abstract LB-4.
3. Lok A, et al. AASLD 2012. Abstract 79.

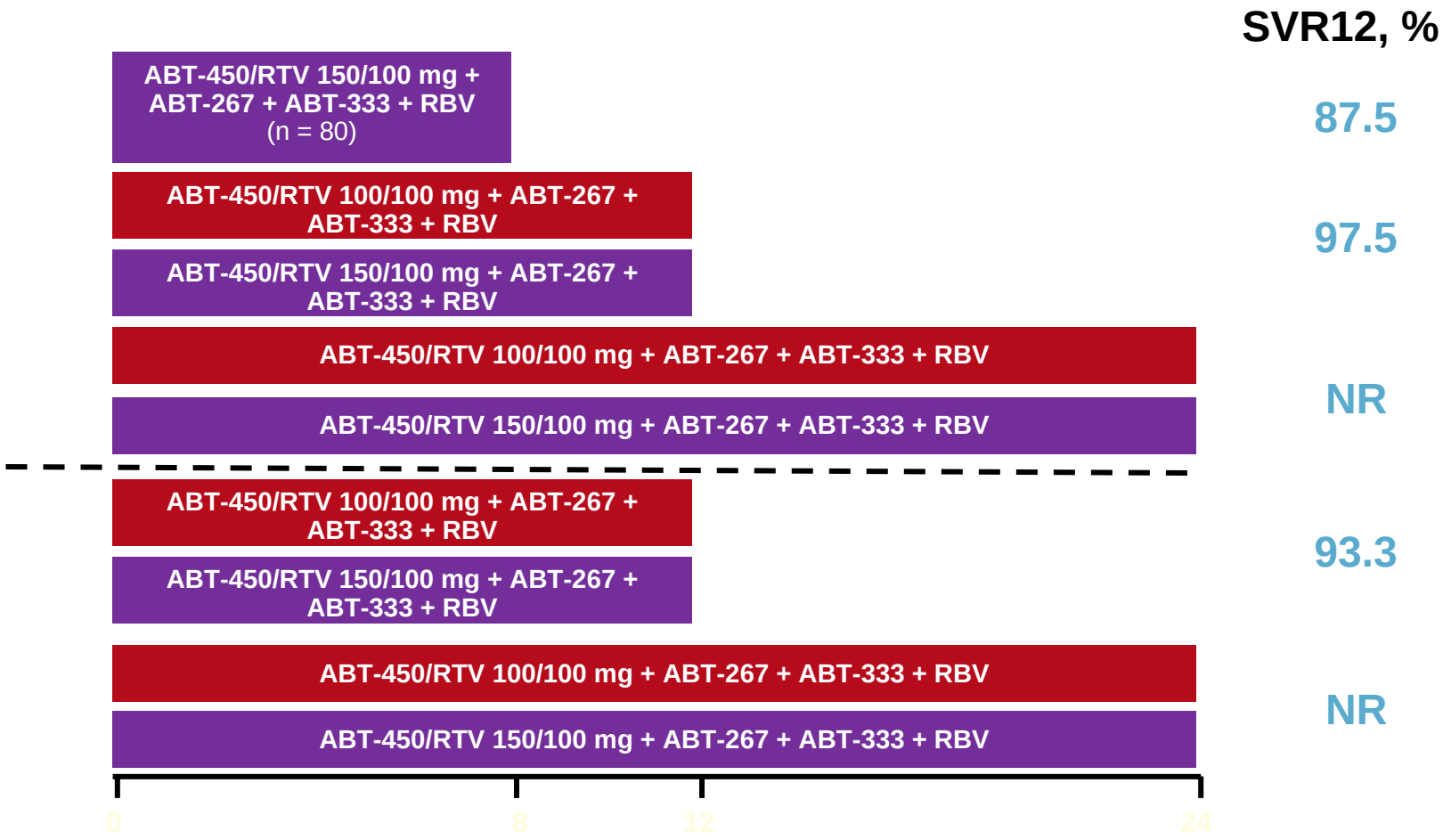
Daclatasvir + Asunaprevir + BMS-791325 in GT1 Treatment-Naive Pts: 12 vs 24 wks

- Pts with poor prognostic indicators: GT1a (75%), male (53%), black (25%), *IL28B* CT/TT (72%); advanced liver disease: 6%
- Mean HCV RNA: 6.3 logs



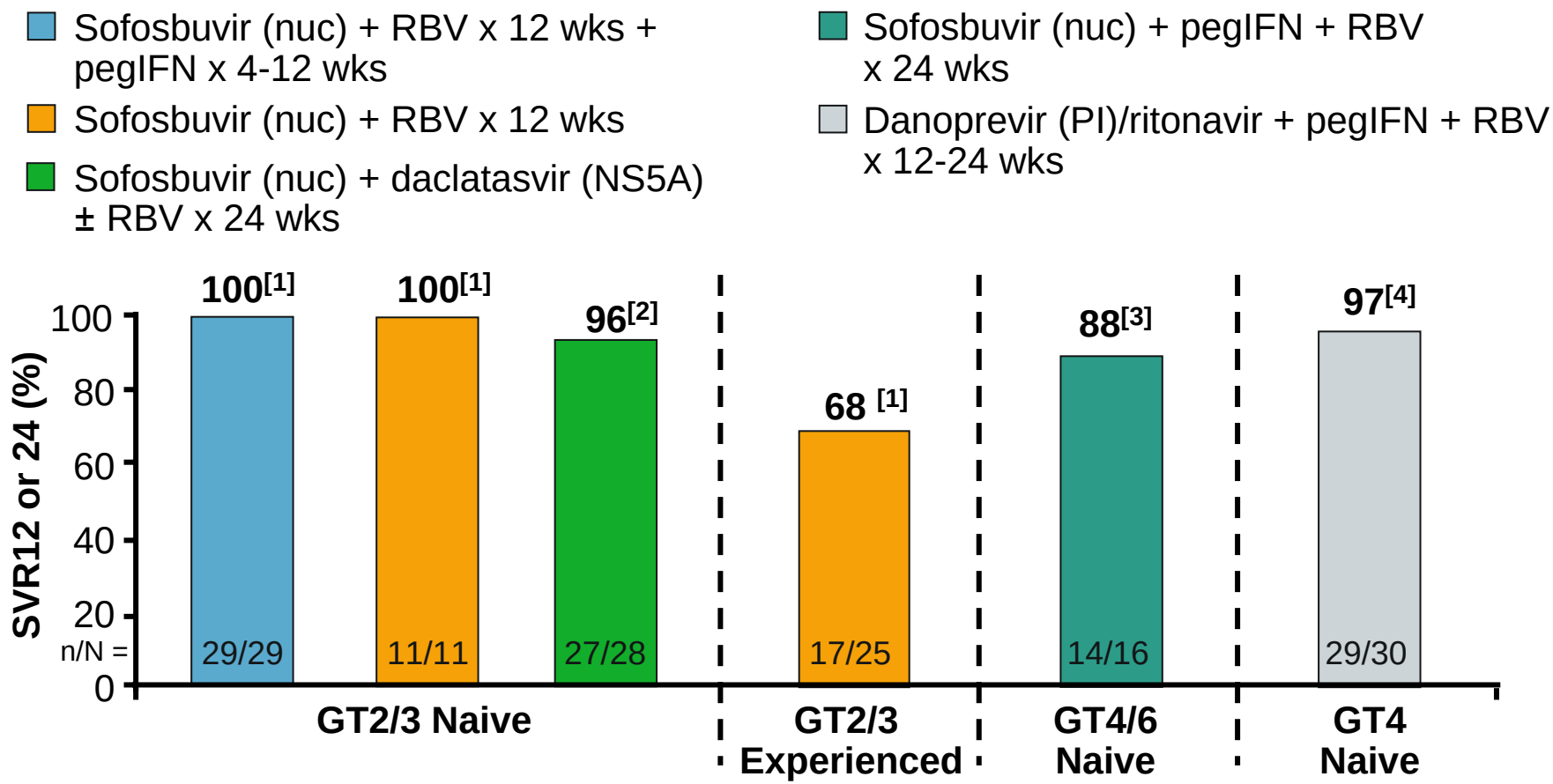
Everson G, et al. AASLD 2012. Abstract LB-3.

IFN-Free Regimens With ABT-450/RTV, ABT-267, ABT-333, and RBV



Kowdley K, et al. AASLD 2012. Abstract LB-1.

Efficacy in Non–GT 1 Patients



1. Gane EJ, et al. AASLD 2012. Abstract 229. 2. Sulkowski M, et al. AASLD 2012. Abstract LB-2.
3. Hassanein T, et al. AASLD 2012. Abstract 230. 4. Hezode C, et al. AASLD 2012. Abstract 760.