Difficult to treat patients : patients with cirrhosis

Marc Bourliere , MD
Hôpital Saint Joseph
Marseille France

6th Paris Hepatitis Conference
Paris
January 14th 2013

Disclosures

- Board member for : Schering-Plough, Merck, Janssen, Gilead, Boehringer Ingelheim, BMS, Novartis, Roche, Abbott, GSK, Vertex
- Speaker for : Roche, Schering-Plough, Merck, Janssen, Gilead, BMS

TREATMENT EFFICACY WITH PI IN GENOTYPE 1 PATIENTS WITH CIRRHOSIS

Virological efficacy of Boceprevir or Telaprevir in cirrhotic patients

Naive genotype 1 patients

40

Boceprevir

SVR **range from 31/42 %**

108

Telaprevir

SVR range from **42/73 %**

Treatment-experienced patients

39

Relapsers

SVR range from **50%** to **83 %**

Partial-Responders

SVR range from **30 %** to **46 %**

2

Null-responders

SVR : **1/2**

139

Relapsers

SVR : 84%

Partial-responders

SVR : 34%

Null-responders

SVR : 14%

Poordad F et al. N Engl J Med 2011: 364: 1195-1206
Bacon BR. et al. N Engl J Med 2011; 364:1207-1217.
Bronowicki JP. et al. J Hepatol 2012: 56: S6 .

Sherman KE et al. N Engl J Med 2011; 365: 1014-1024.
Jacobson IM et al. N Engl J Med 2011; 364 : 2405-16.
Zeuzem S. et al. N Engl J Med 2011;364:2417–28

Key Findings from phase III trials

- RVR is less frequent in cirrhotic
  - (25% vs 46% boc naive)
  - (25% vs 43% Boc TE)
  - (46-49% vs 58-60% TVR naïve)
- Relapse rate is more frequent
  - (12-18% vs 9% boc naive)
  - (21% vs 11% boc TE)
  - (10% vs 4% in PR and NR TVR TE)
- SVR is always higher for 48 weeks
- Predictive factor of response:
  - Previous PR response

SVR in real life

CUPIC data

CUPIC cohort

- **Primary objective**
  - **Determine the rate of SVR**

- **Interim analysis**
  - **Evaluate safety and tolerability at week 16 of antiviral therapy**

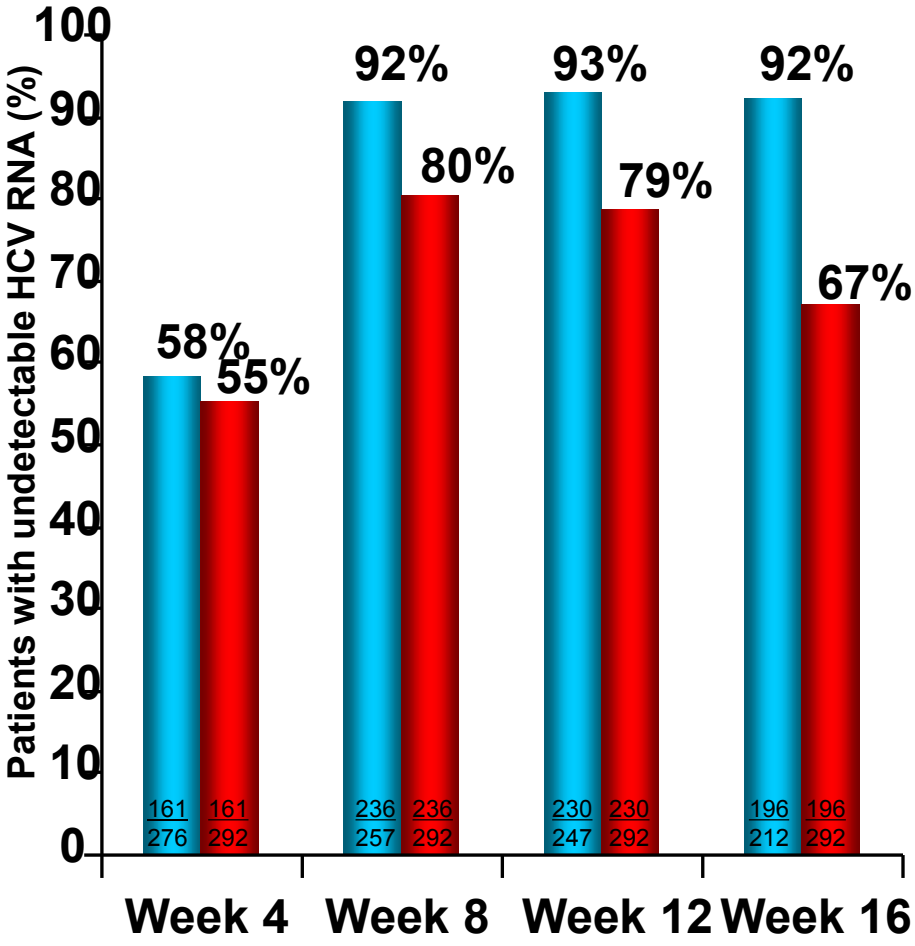
From February 15th 2011 to April 12th 2012:

674 patients were included in 56 sites

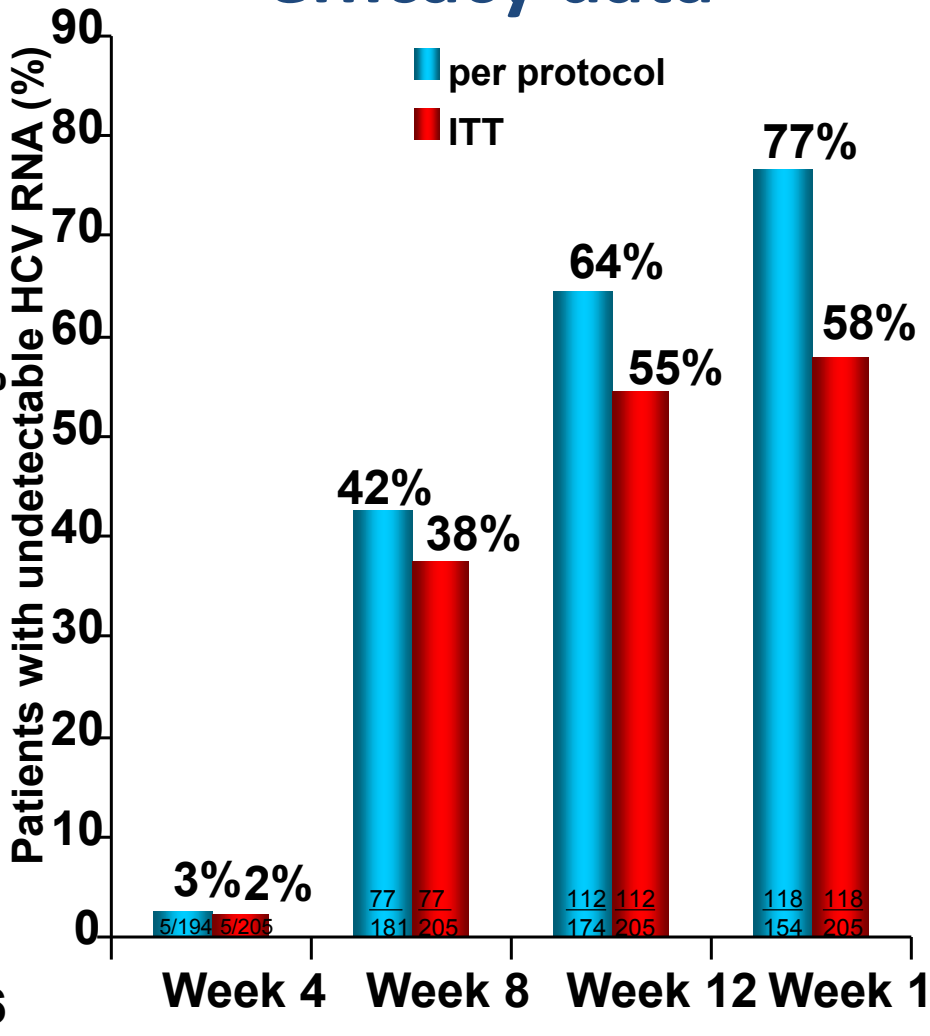
497 patients were included in this analysis

Hézode C, France, AASLD 2012, Abs. 51 actualisé

Telaprevir: week 16 efficacy data

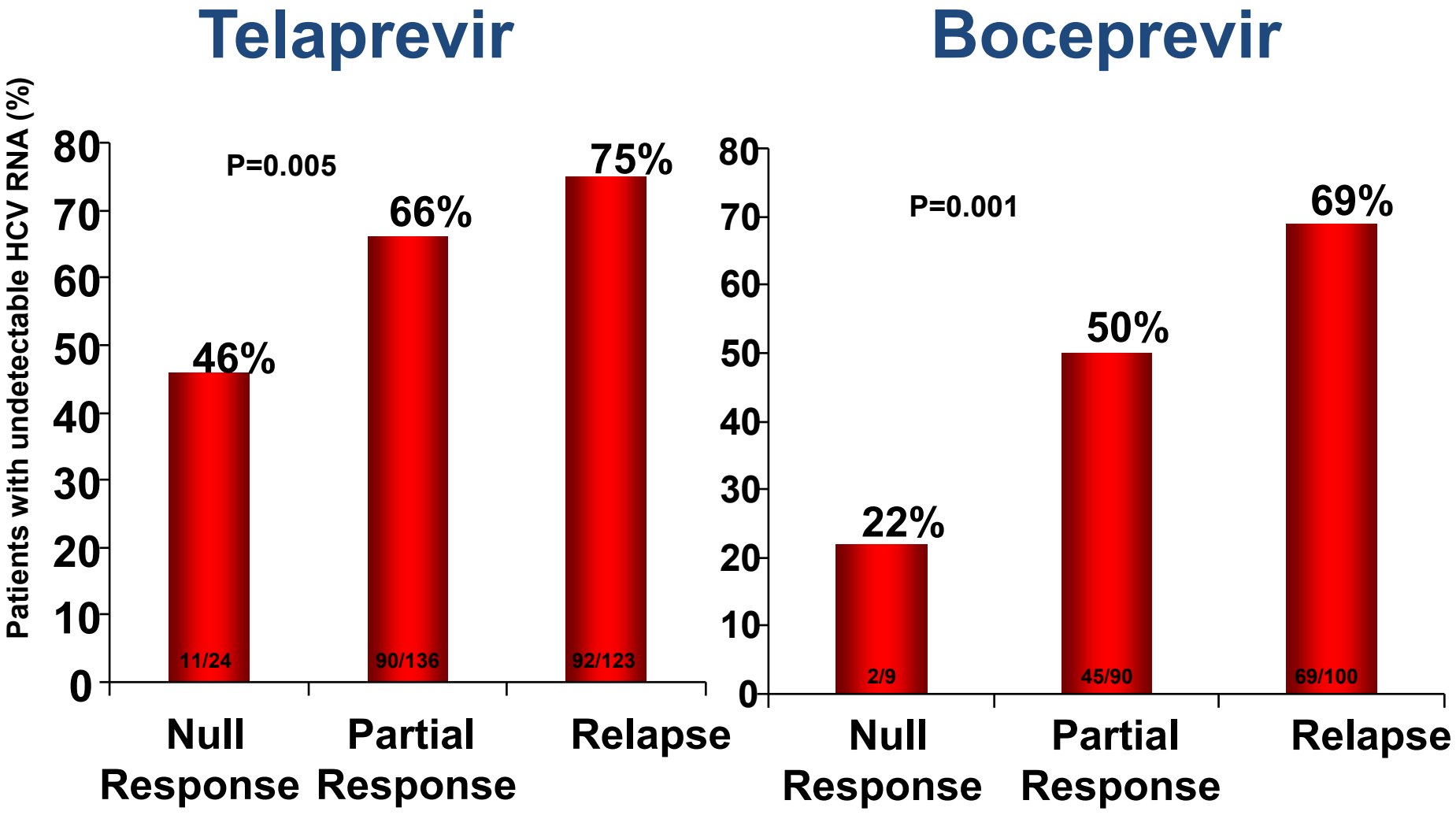


Boceprevir: week 16 efficacy data



Hézode C, France, AASLD 2012, Abs. 51 actualisé

Week 16 efficacy according to prior treatment response (ITT)



Hézode C, France, AASLD 2012, Abs. 51 actualisé

SVR DATA WILL BE AVAILABLE FOR EASL 2013

Fontaine H et al . EASL 2013 ?

Safety ?

Challenge in treating these patients

Which side effects occurred?

Safety issue in phase III trials

- **In Phase III trial safety issue were reported :**
  - **Rash, pruritus and anemia with Telaprevir (TVR)**
  - **Anemia and dysgeusia with Boceprevir (BOC)**

- **Few patients with cirrhosis were included :**

  - **Telaprevir :**
    - **ADVANCE[1] = 47**
    - **ILLUMINATE[2] = 61**
    - **REALIZE[3] = 139**

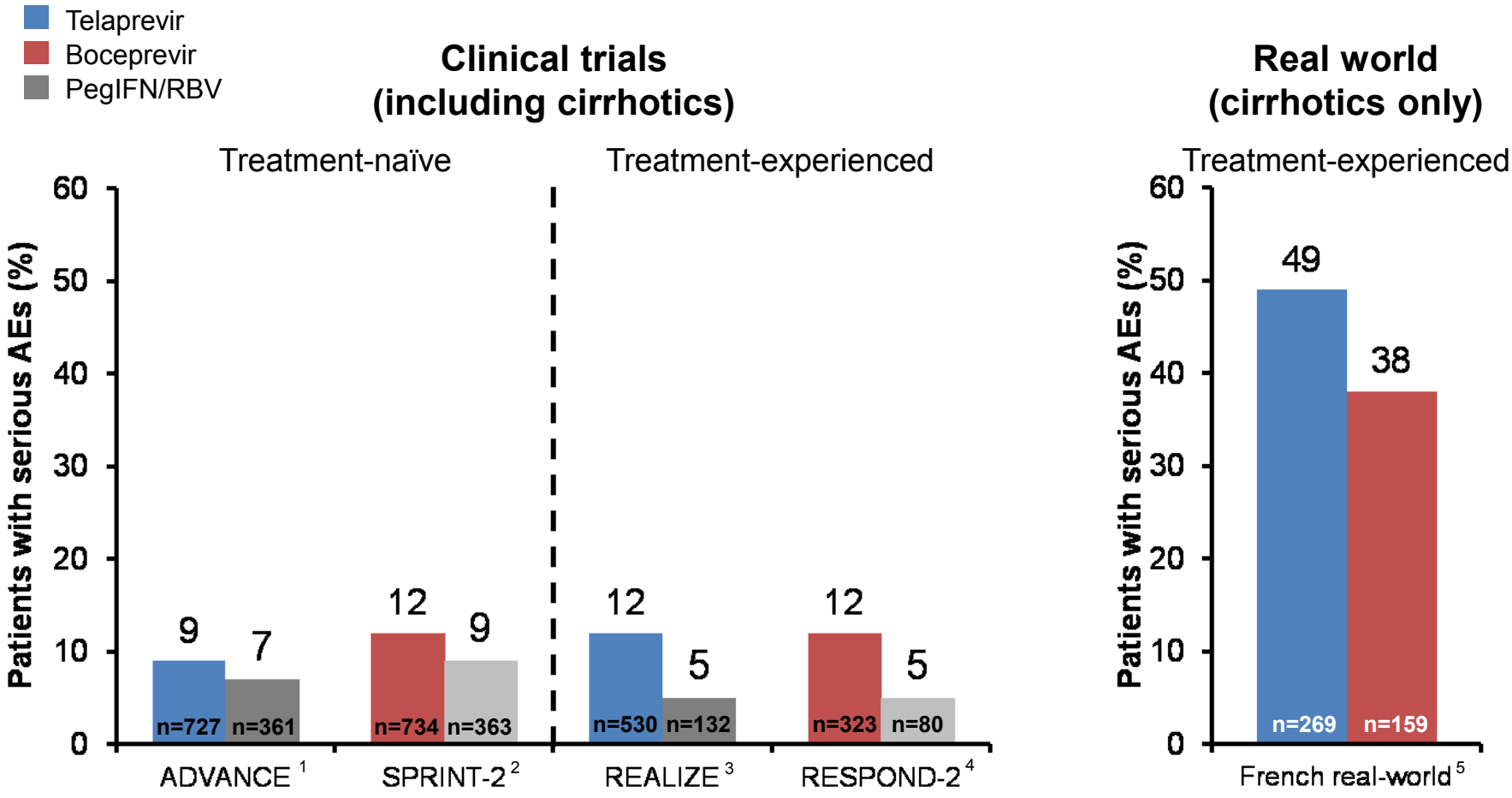
    } **247**

  - **Boceprevir :**
    - **SPRINT-2[4] = 40**
    - **RESPOND-2[5] = 39**

    } **79**

1. Jacobson IM, et al, N Engl J Med 2011;364:2405-16
2. Sherman KE, et al, N Engl J Med 2011;365:1014-24
3. Zeuzem S, et al, N Engl J Med 2011;364:2417-28
4. Poordad F, et al, N Engl J Med 2011;364:1195-206
5. Bacon BR, et al, N Engl J Med 2011;364:1207-17

Clinical Trials *vs* Real World



(courtesy F. Poordad)

Triple therapy: Increased rates of SAEs observed in CUPIC at week 16

Patients, n (% patients with at least one event)	Telaprevir n=292	Boceprevir n=205
Serious adverse events (SAEs)*	132 (45.2%)	67 (32.7%)
Premature discontinuation Due to SAEs	66 (22.6%) 43 (14.7%)	54 (26.3%) 15 (7.3%)
Death	5 (2.6%)	1 (0.5%)
Infection (Grade 3/4)	19 (6.5%)	5 (2.4%)
Hepatic decompensation (Grade 3/4)	6 (2.0%)	6 (2.9%)
Asthenia (Grade 3/4)	16 (5.5%)	12 (5.8%)
Rash Grade 3/SCAR	14 (4.8%)	0
Renal failure	5 (1.7%)	0

Hezode et al AASLD 2012 Abs 51

Hézode C, France, AASLD 2012, Abs. 51 actualisé<

Explanation for these side effects observed ?

Baseline characteristics

	Telaprevir n=292	Boceprevir n=205
Mean Prothrombin Time, range (ratio)	86.3 (27-100)	87.3 (23-100)
Mean Total Bilirubin, range (µmol/L)	15.4 (4.0-73.5)	15.0 (4.0-78.0)
Mean Albumin, range (g/dL)	40.1 (20.7-52.0)	40.4 (27.0-50.3)
Child-Pugh A / B (%)	98 / 2	99 / 1
Mean MELD score, SD	8.1 (2.8)	8.1 (3.0)
MELD score <10 / 10 - <13 / ≥13 (%)	81 / 13 / 6	83 / 12 / 5
Esophageal varices (%)	33	40
Realize / Respond-2 exclusion criteria (%)	33 / 46	29 / 40

Hézode C, France, AASLD 2012, Abs. 51 actualisé

CUPIC: patients characteristics

	Telaprevir n=296	Boceprevir n=159	Death n=11
Male (%)	68	67.5	45.4
Age (years)	57.0	56.8	58.9
Prothrombin Time (ratio)	88	88	74.8
Total Bilirubin (µmol/L)	15	15	15.4
Albumin (g/dL)	40	41	32.6
Esophageal varices (%)	15	16	40
Platelets (/mm^3)	150 000	150 000	110 000

Courtesy of Dr Serfaty

Predictive factors for death, severe infection or hepatic decompensation

Univariate analysis: baseline factors related to severe complications*

Factors	OR	95%CI	p-value
Hemoglobin level (≤12 g/dL for female; ≤13 g/dL for male)	5.05	2.28-11.19	<0.0001
Thrombopenia ≤100,000/mm^3	5.52	2.63-11.58	<0.0001
Neutropenia ≤900/mm^3	3.43	1.09-10.82	0.035
Albumin <35 g/L	10.23	4.67-22.43	<0.0001
Total bilirubin (per µmol/L increase)	1.04	1.015-1.066	0.0016
Prothrombin Time ≤70%	3.09	1.24-7.72	0.015
MELD score (per unit increase)	1.14	1.04-1.25	0.0043
Child-Pugh B score	5.23	1.01-27.06	0.049
Esophageal varices	3.44	1.33-9.09	0.01
REALIZE exclusion criteria	4.72	2.21-10.05	<0.0001
RESPOND-2 exclusion criteria	4.3	1.89-9.78	0.0005
HCV RNA level (per $\log_{10}$ increase)	1.36	1.03-1.81	0.03

* Death, severe infection and hepatic decompensation, n=32

Hézode C, France, AASLD 2012, Abs. 51 actualisé

Multivariate analysis: baseline predictors of severe complications*

Predictors	OR	95%CI	p-value
Platelet count ≤100,000/mm^3	3.11	1.32-7.73	0.0098
Albumin level <35 g/L	6.33	2.66-15.07	<0.0001

* Death, severe infection and hepatic decompensation, n=32

Hézode C, France, AASLD 2012, Abs. 51 actualisé

Anemia management

In cirrhotic

Triple therapy: Increased rates of SAEs and more difficult management of anaemia

Patients, n (% patients with at least one event)	Telaprevir n=292	Boceprevir n=205
Anemia		
Grade 2 (8.0 – ≤9.0 g/dL)	55 (18.8%)	48 (23.4%)
Grade 3/4 (<8,0 g/dL)	34 (11.6%)	9 (4.4%)
EPO use	157 (53.8%)	95 (46.3%)
Blood transfusion	47 (16.1%)	13 (6.3%)
RBV dose reduction	38 (13.0%)	22 (10.7%)
Neutropenia		
Grade 4 (<500/mm^3)	2 (0.7%)	7 (3.4%)
G-CSF use	7 (2.4%)	9 (4.4%)
Thrombopenia		
Grade 4 (<20,000/mm^3)	9 (3.1%)	3 (1.5%)
Thrombopoïetin Use	4 (1.4%)	2 (1.0%)

Hezode et al AASLD 2012 Abs 51

Predictors of severe anaemia < 8 g/dl or BT

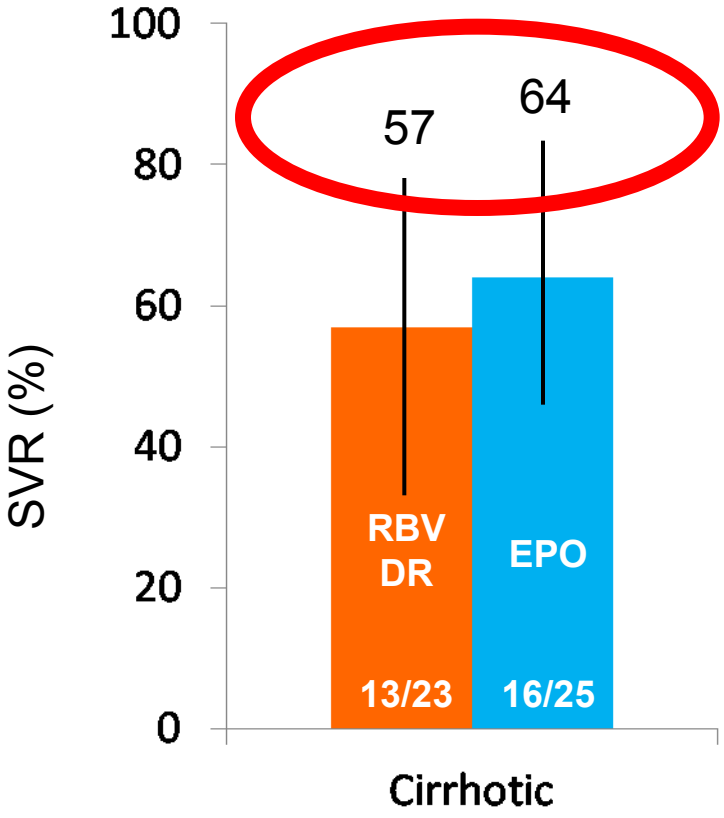
Multivariate analysis: baseline factors related to anaemia<8g/dl or blood transfusio

Predictors	OR	95%CI	p-value
Gender: Female	2.19	1.11-4.33	0.023
No lead-in phase	2.25	1.15-4.39	0.018
Age ≥65 years	3.04	1.54-6.02	0.0014
Hemoglobin level ≤12 g/dL for female ≤13 g/dL for male	5.30	2.49-11.25	<0.0001

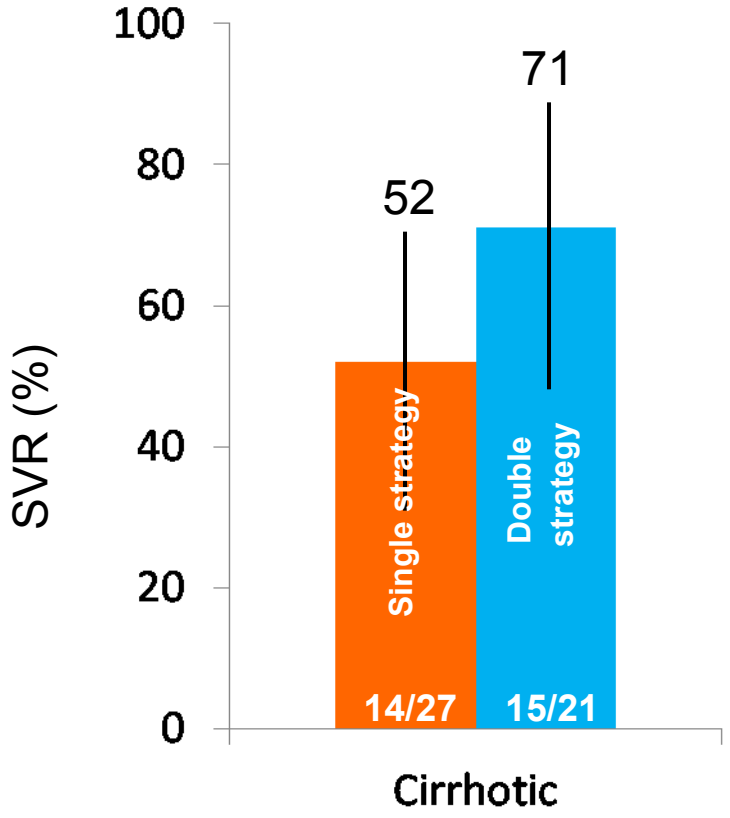
Hezode et al AASLD 2012 Abs 51

Management of anaemia : some concern in cirrhotic : RBV DR vs EPO ?

SVR according to RBV DR or EPO use



SVR according to the need of single or double strategy

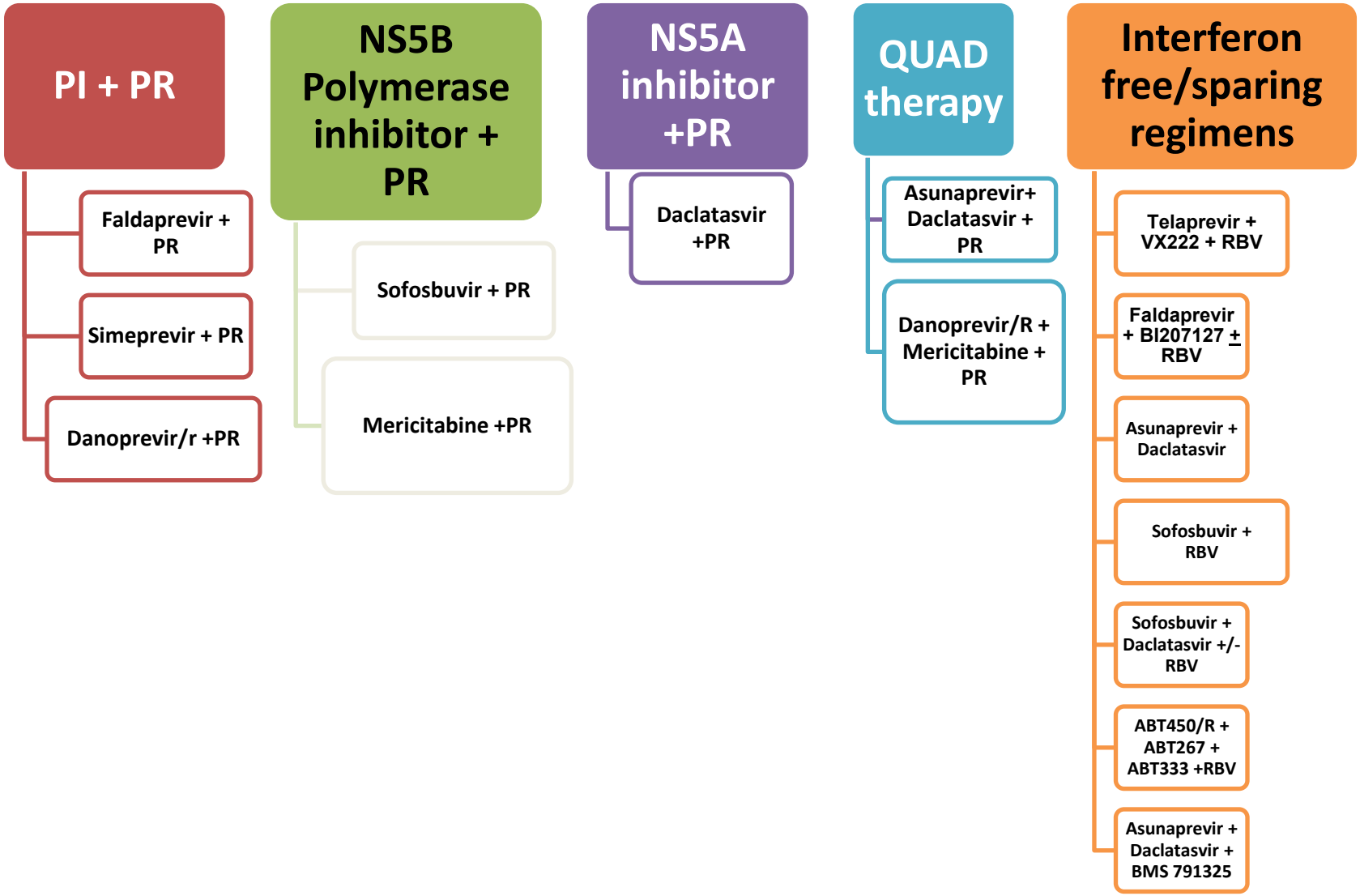


RBV DR : RBV dose reduction

Lawitz E, et al. AASLD 2012, Abs. 50

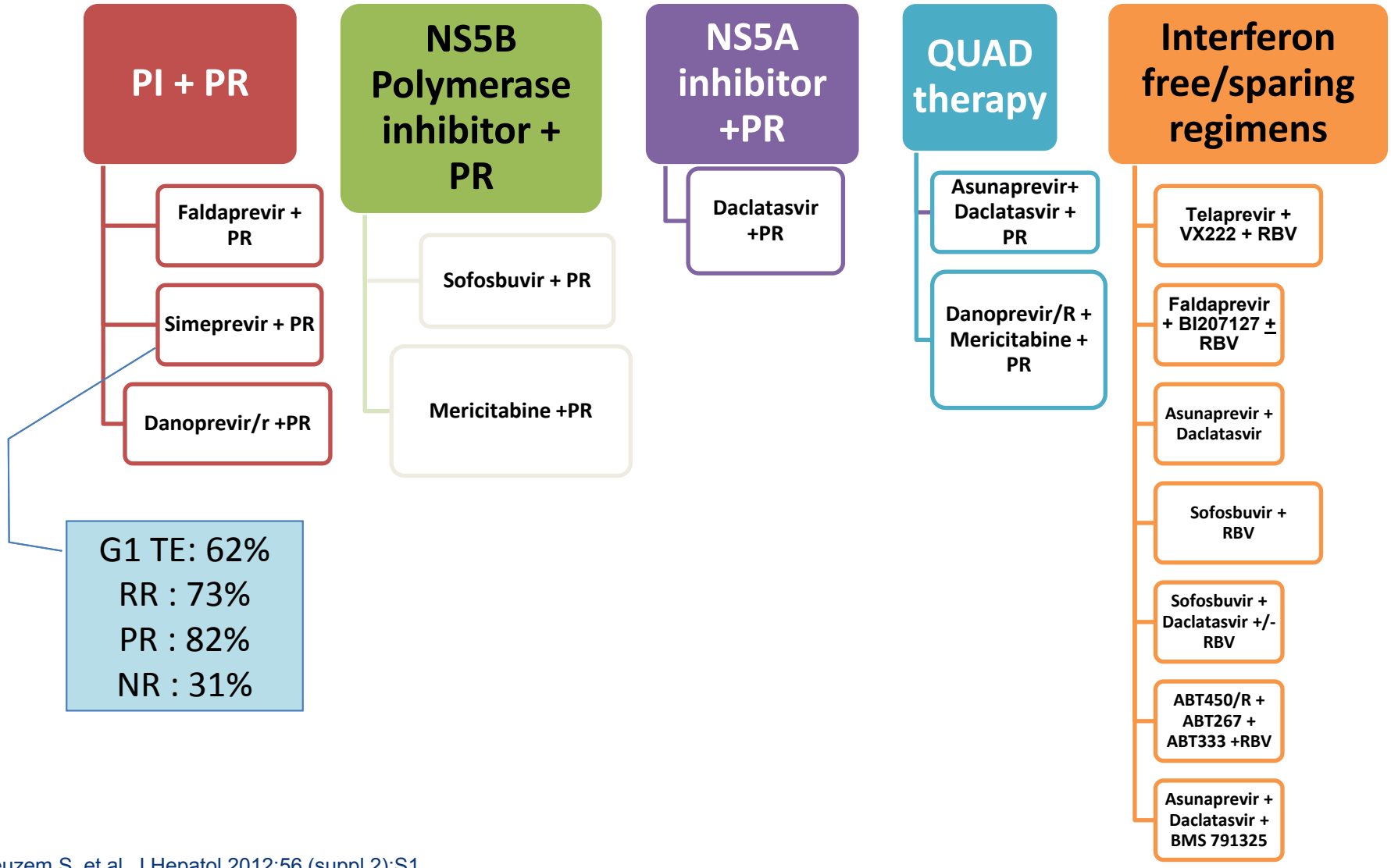
BEYOND FIRST GENERATION PI

HCV treatment: beyond first generation PIs



PI: protease inhibitor; PR: peginterferon + ribavirin;l

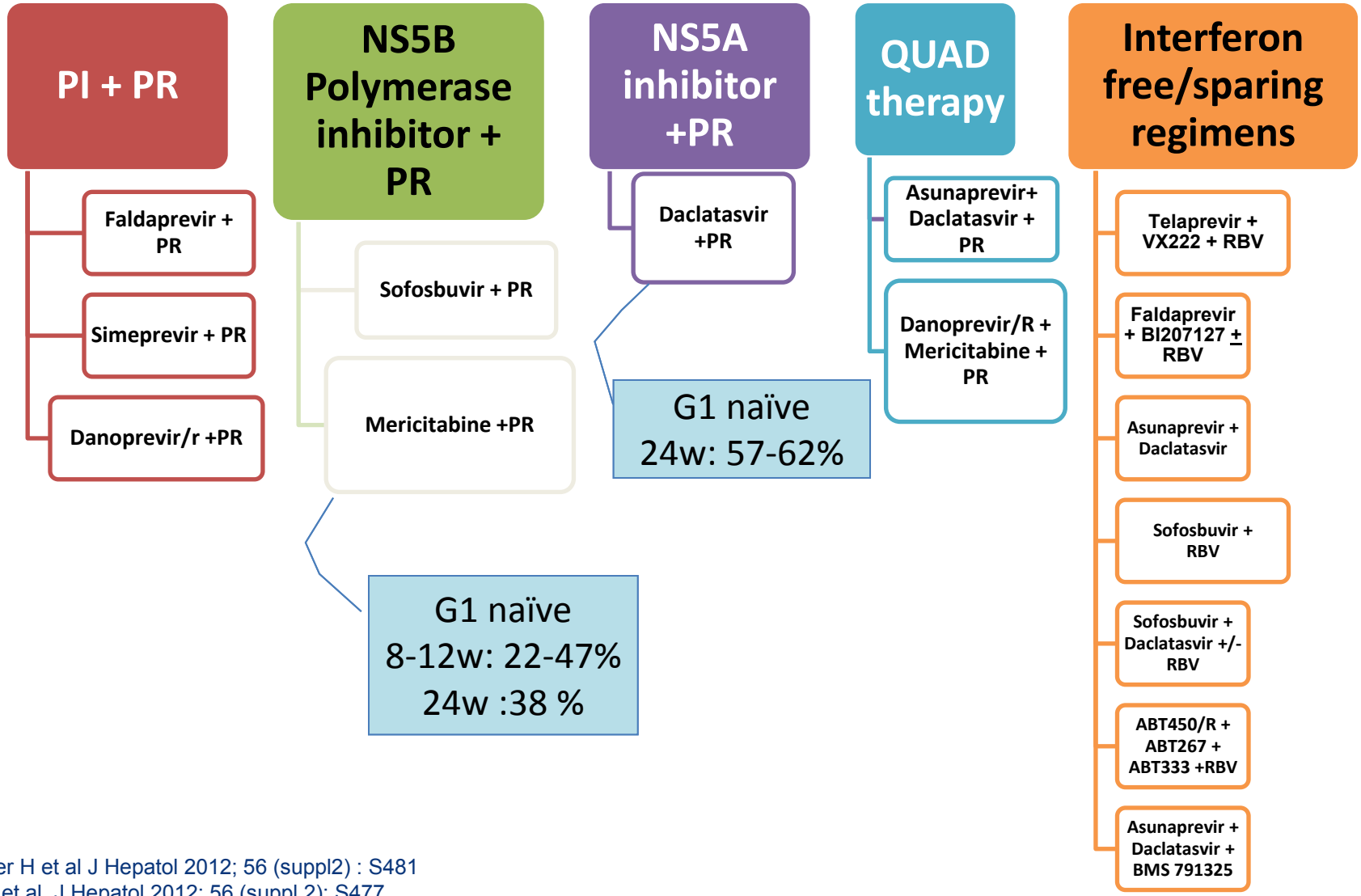
HCV treatment: beyond first generation Pis SVR in cirrhotic



Zeuzem S, et al. J Hepatol 2012;56 (suppl 2):S1

PI: protease inhibitor; PR: peginterferon + ribavirin

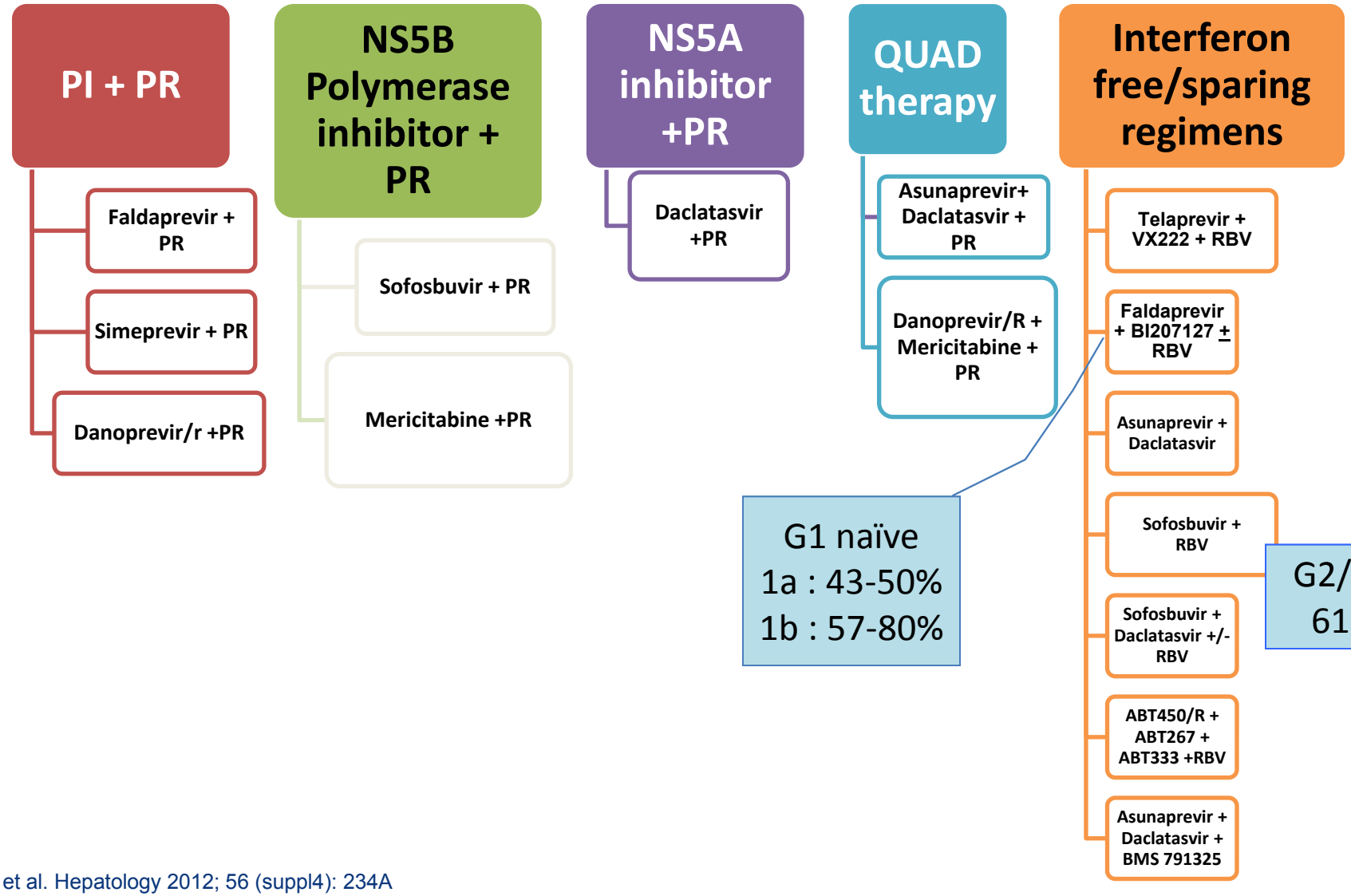
HCV treatment: beyond first generation Pis SVR in cirrhotic



Wedemeyer H et al J Hepatol 2012; 56 (suppl2) : S481
Pockros P et al. J Hepatol 2012; 56 (suppl 2): S477
Hezode C et al. Hepatology 2012; 56 (suppl 4): 553A

PI: protease inhibitor; PR: peginterferon + ribavirin

HCV treatment: beyond first generation Pis SVR in cirrhotic

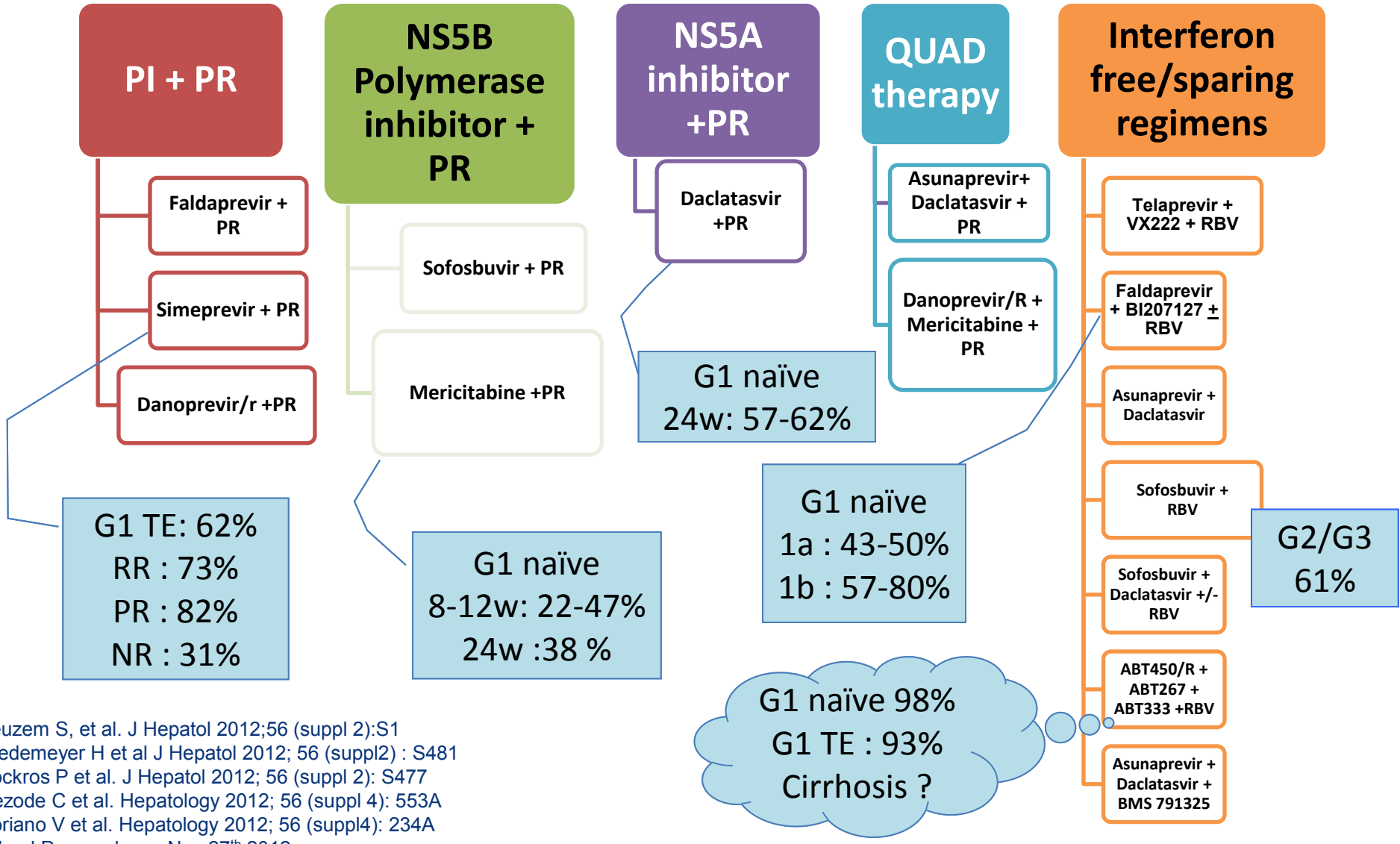


Soriano V et al. Hepatology 2012; 56 (suppl4): 234A
Gilead Press release Nov 27th 2012

PI: protease inhibitor; PR: peginterferon + ribavirin

HCV treatment: beyond first generation Pis

SVR in cirrhotic



Zeuzem S, et al. J Hepatol 2012;56 (suppl 2):S1
Wedemeyer H et al J Hepatol 2012; 56 (suppl2) : S481
Pockros P et al. J Hepatol 2012; 56 (suppl 2): S477
Hezode C et al. Hepatology 2012; 56 (suppl 4): 553A
Soriano V et al. Hepatology 2012; 56 (suppl4): 234A
Gilead Press release Nov 27th 2012

PI: protease inhibitor; PR: peginterferon + ribavirin

Conclusion

- Using first generation PI in real world is a major step forward in HCV treatment :
  - increase SVR in cirrhotic GT-1 patients
  - is associated with more frequent SAEs and needs closer monitoring
- Beyond PI, new DAAs combination increases SVR in cirrhotic patients and IFN-free DAAs regimen demonstrates significant potency in cirrhotic patients