HCV protease inhibitors in the treatment of naive and experienced patients

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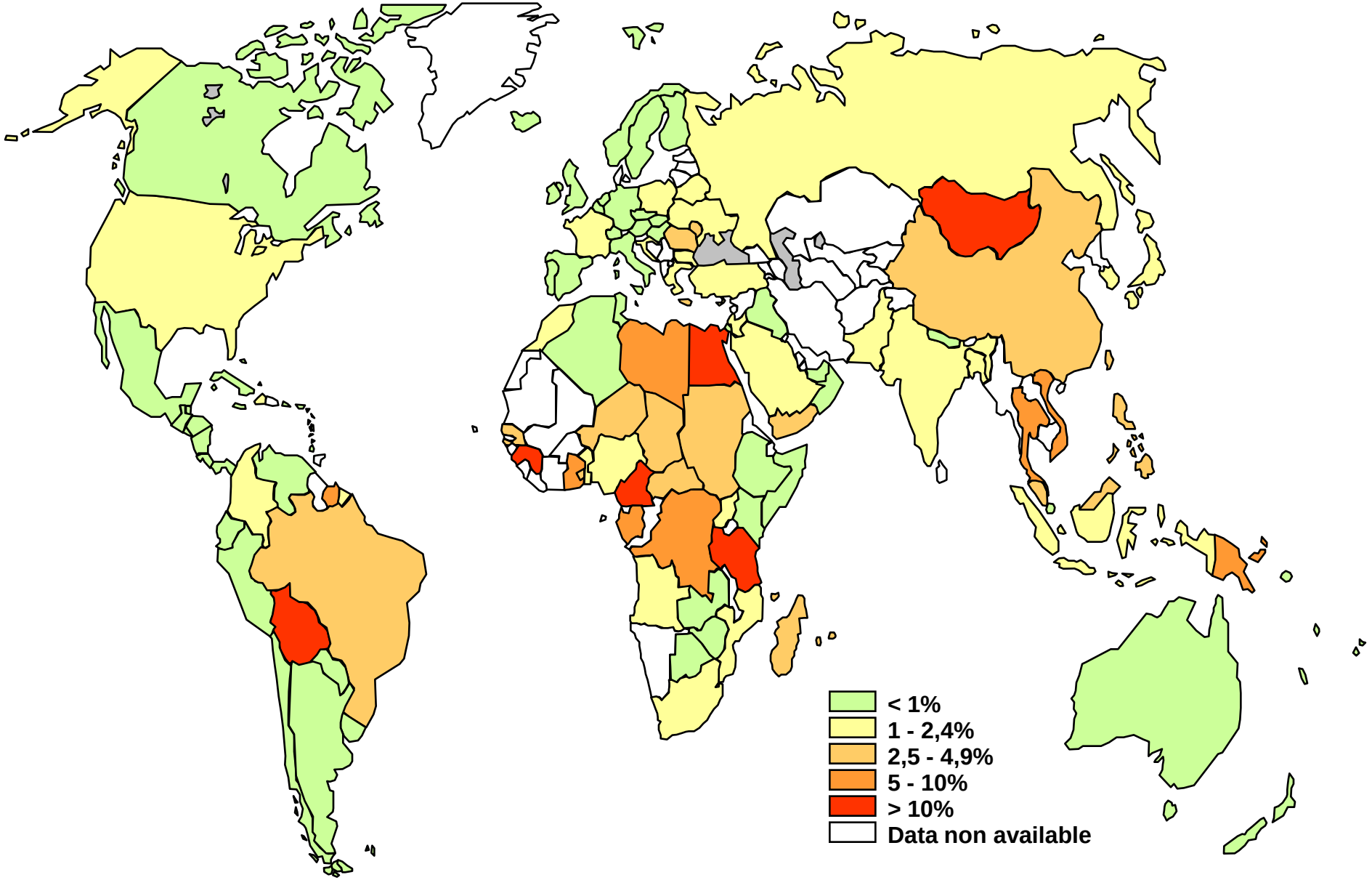
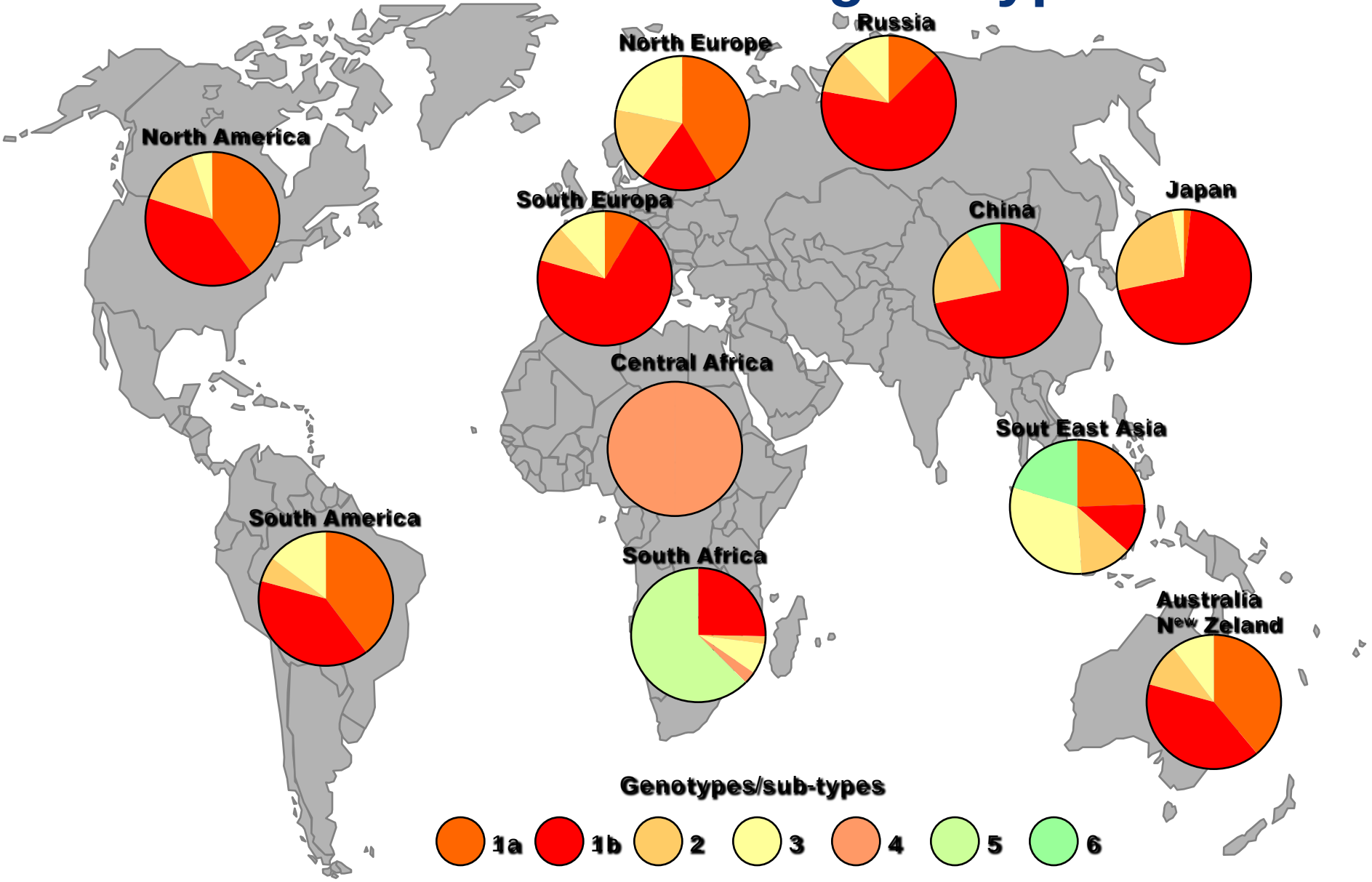
2nd Congress of Federation of Arab Societies of Clinical Microbiology and Infectious Diseases
22nd Tunisian Congress of Infectious Diseases

World prevalence of HCV



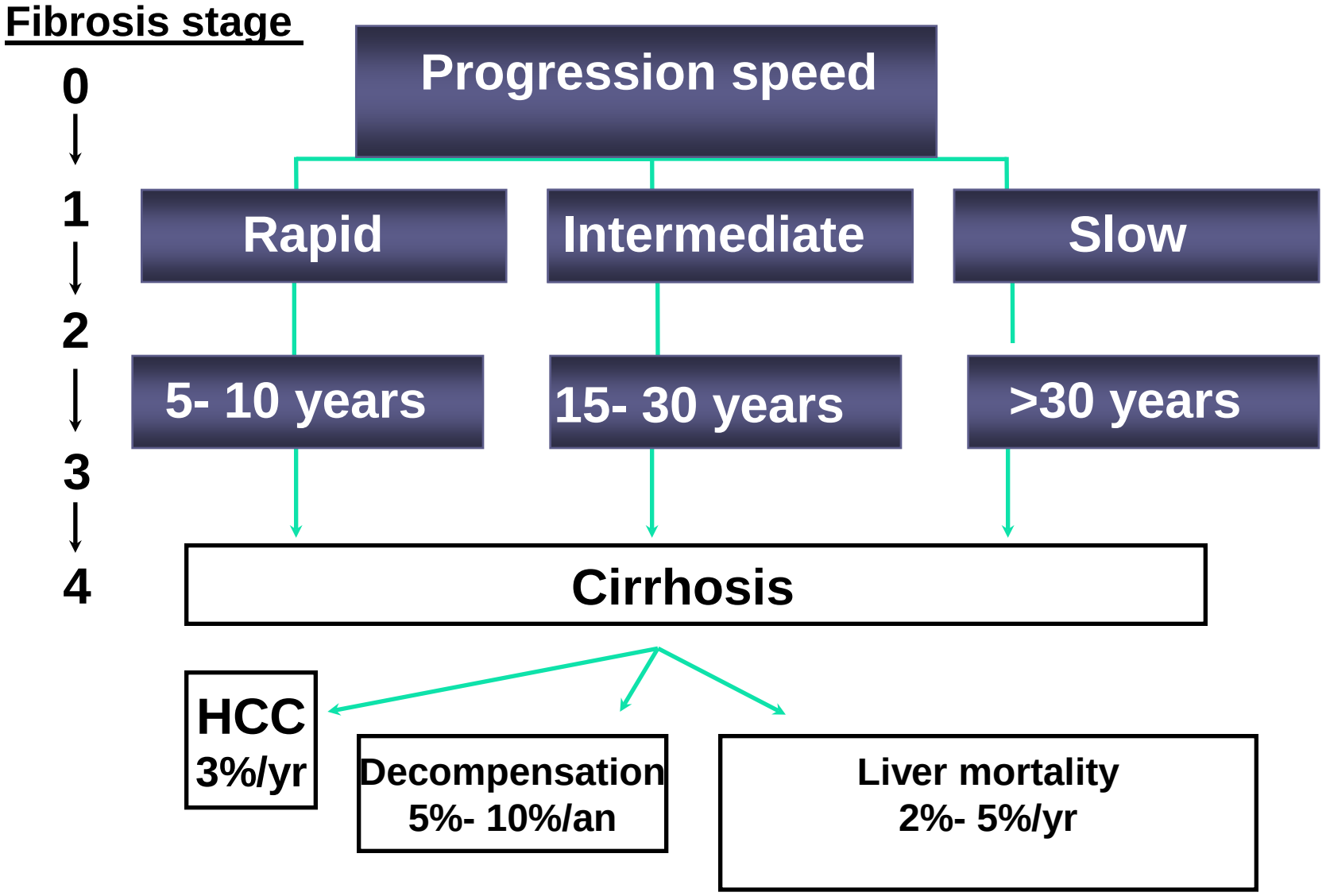
WHO (97)

Distribution of HCV genotypes

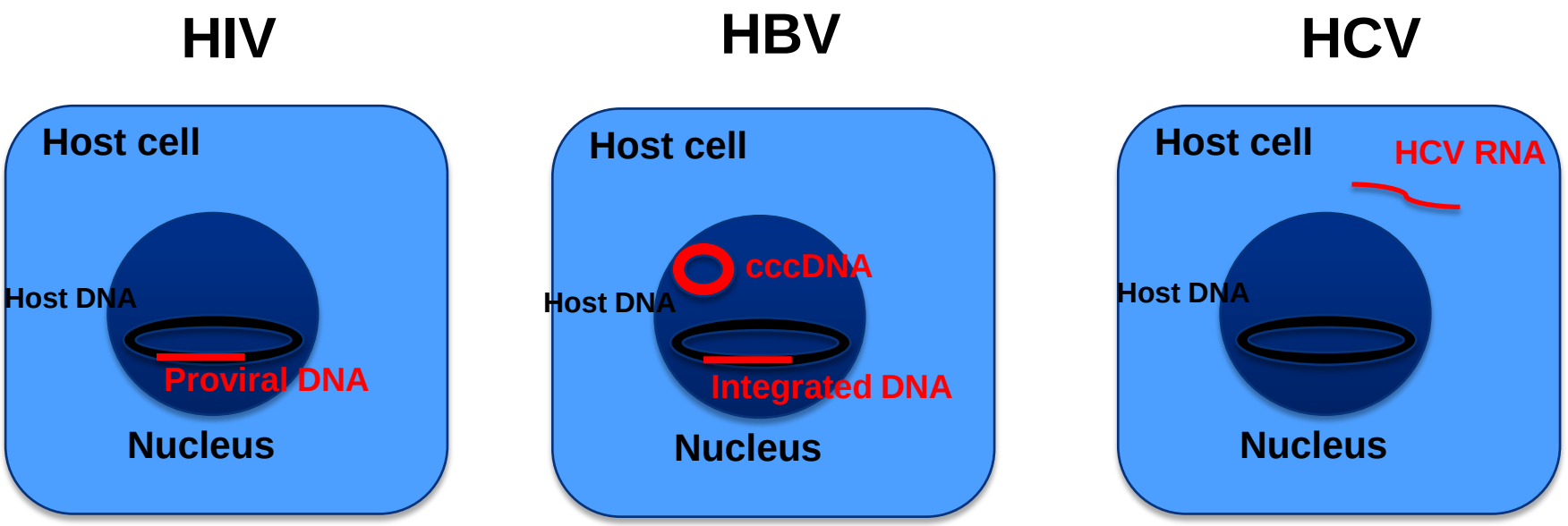


Forns et Bukh (98)

Chronic hepatitis C progression



Therapeutic objectives for HIV, HBV and HCV



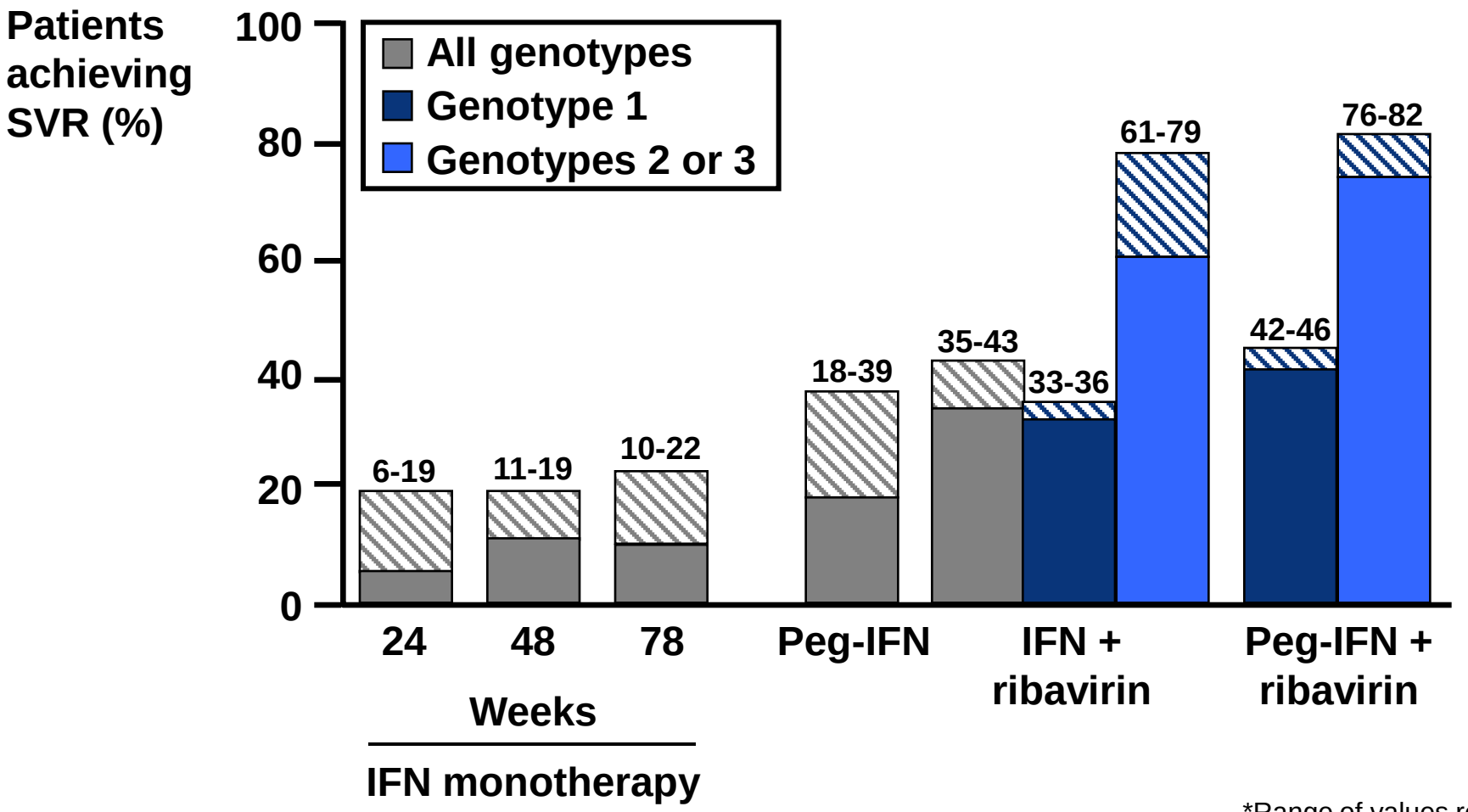
Life long suppression of viral replication

Long term suppression of viral replication

Definitive viral clearance and SVR

Kieffer et al. J Antimicrob Chemother 2010; Sorriano et al. J Antimicrob Chemother 2009; Clavel et al. New Engl J Med 2004; Zoulim &Locarnini Gastroenterology 2009; Sarrazin & Zeuzem Gastroenterology 2010

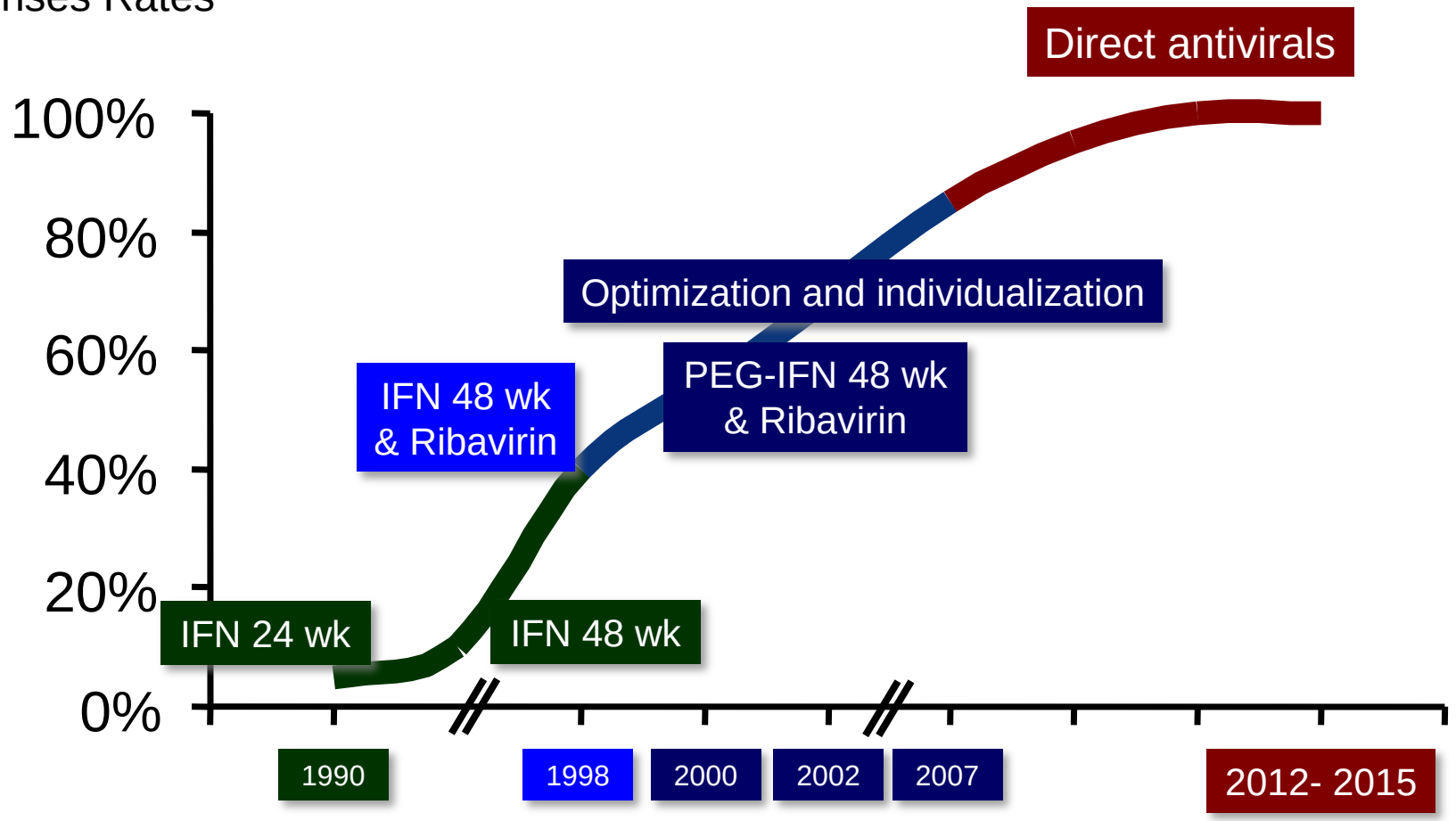
Combinaison of peg interferon and ribavirin: first step towards cure …



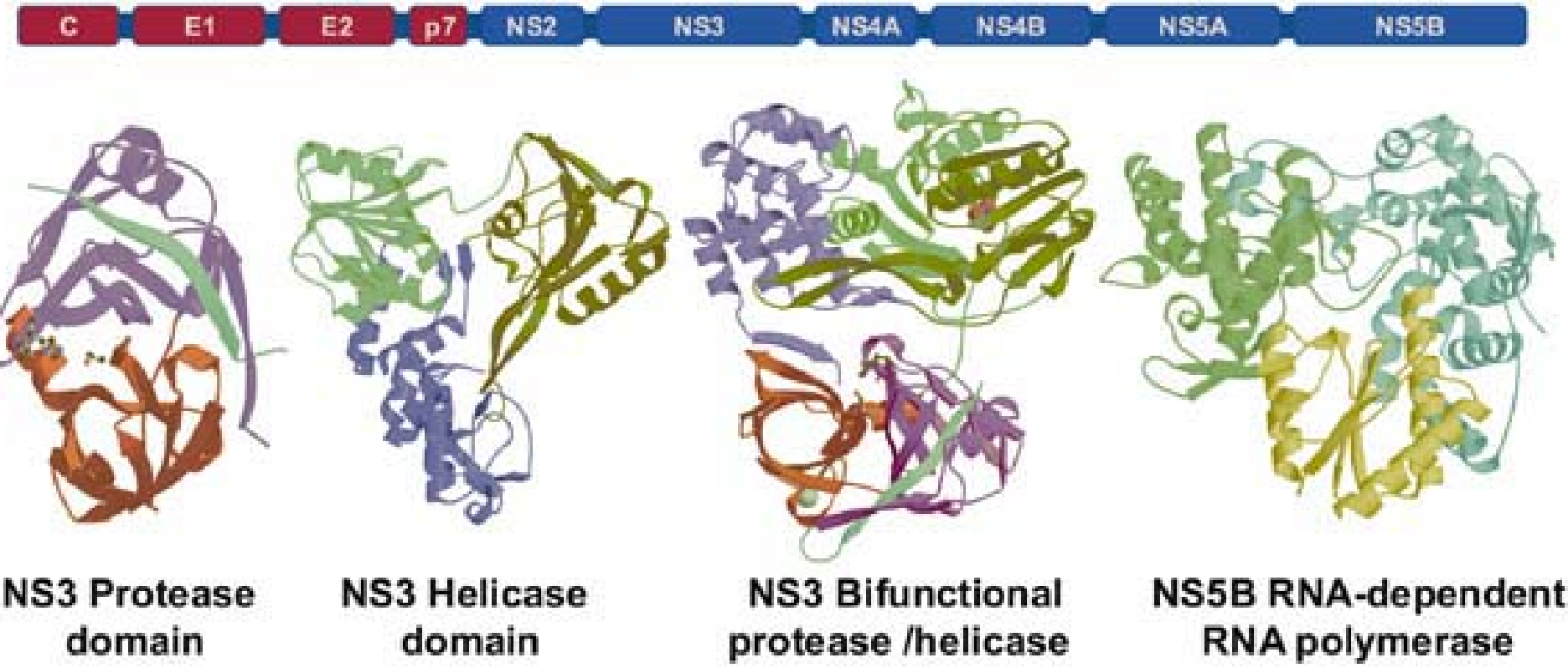
*Range of values reported;
lower bar represents lower value;

Future of anti HCV therapy

Sustained Virological Responses Rates



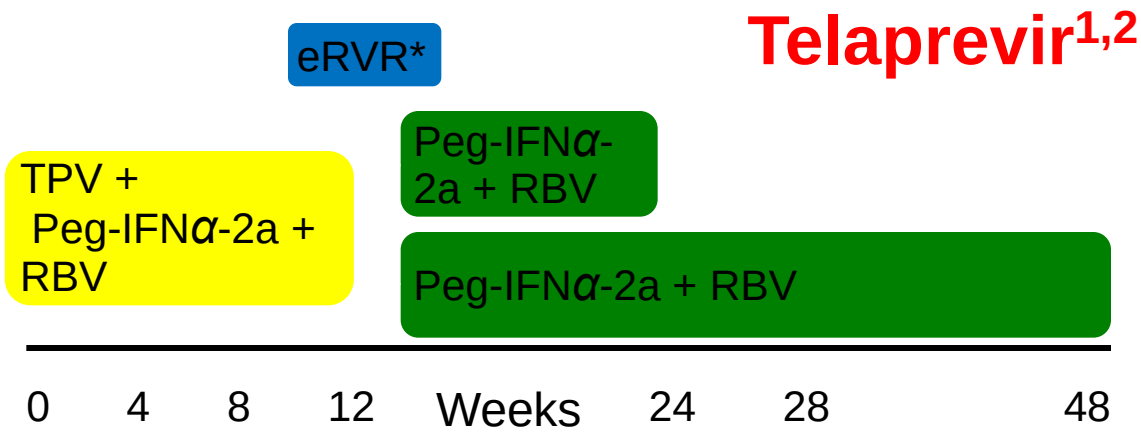
Better knowledge of HCV enzymes targeted by specific inhibitors



Di Bisceglie et al., Hepatology 2002

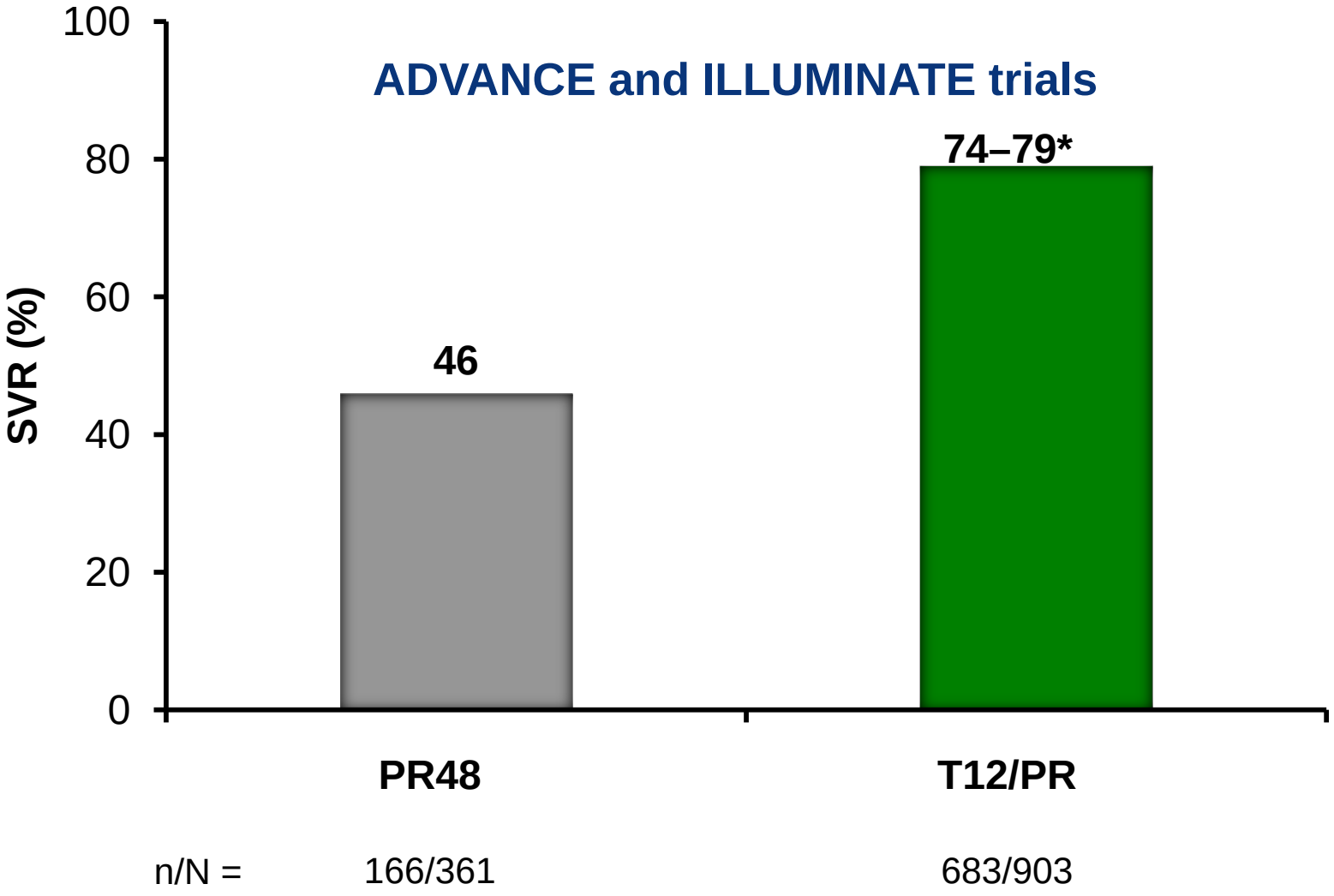
Efficacy of with HCV protease inhibitors with peg interferon and ribavirin in NAIVE patients infected with genotype 1

Telaprevir in GT1 treatment-naive patients



1. Jacobson IM, et al. Hepatology 2010; 52 (S1) [abstract 211]
2. Sherman KE, et al. Hepatology 2010; 52 (S1) [abstract LB-2]

SVR rate with telaprevir and peginterferon/RBV versus PR

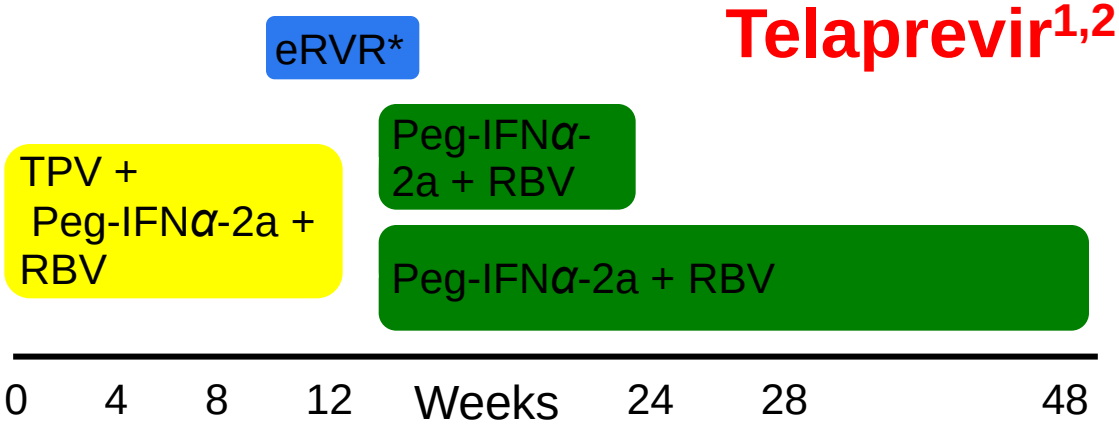


*p<0.0001 T12/PR vs PR48 (79% versus 46%) in ADVANCE

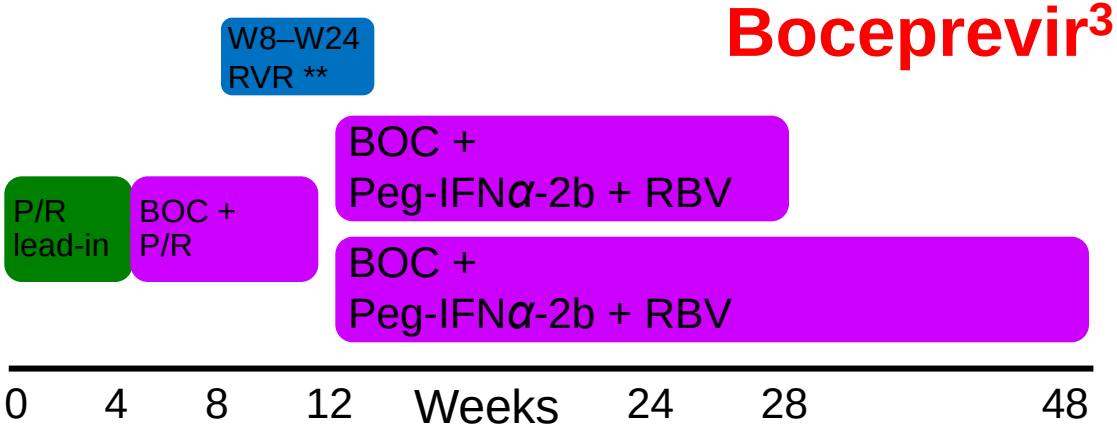
SVR, considered virologic cure, was defined as HCV RNA <25 IU/mL at last observation within the Week 72 visit window. In cases of missing data, the last HCV RNA data point from Week 12 of follow-up onwards was used

TPV and BOC in GT1 treatment-naive patients

Telaprevir[1,2]

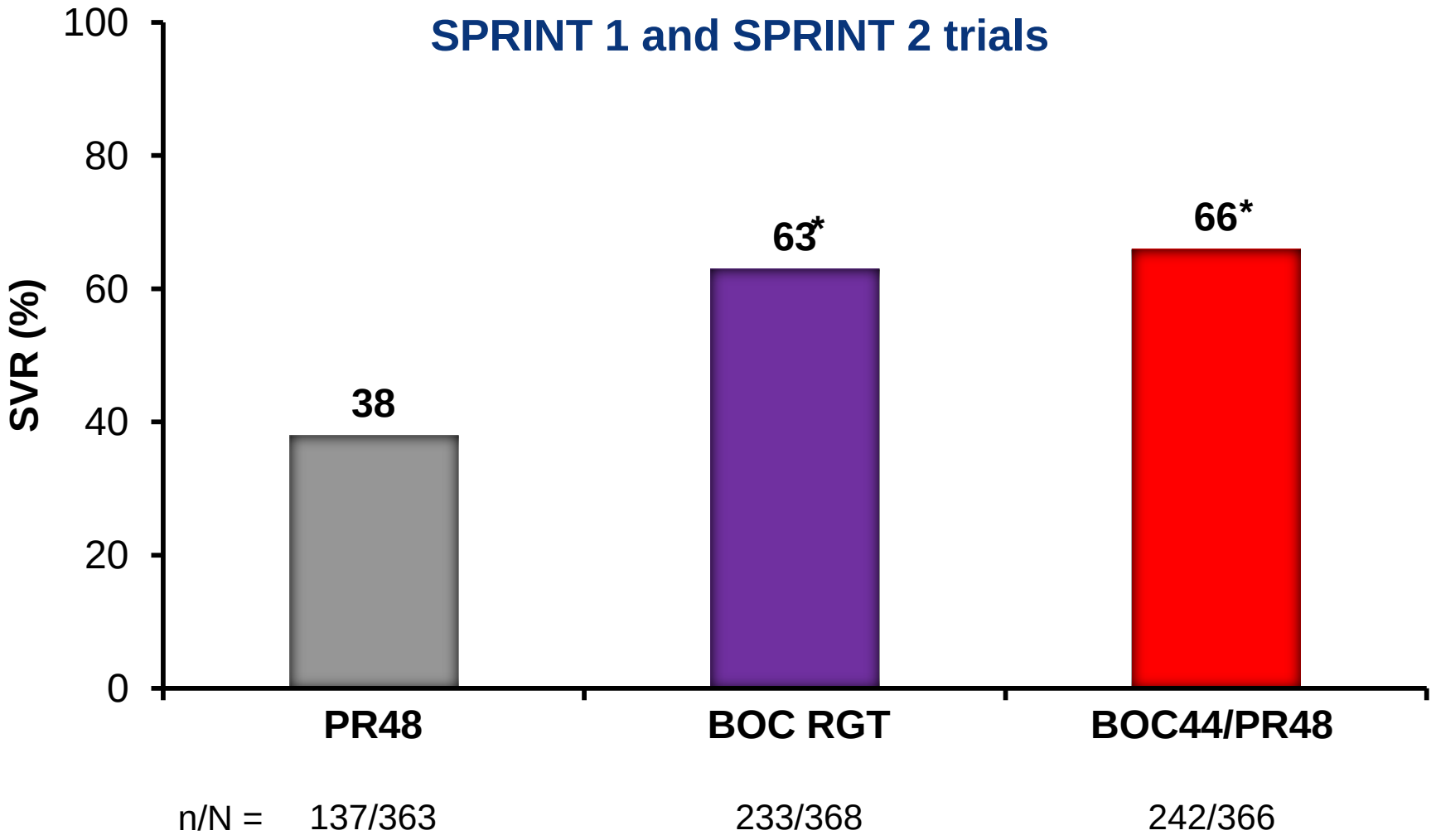


Boceprevir[3]



1. Jacobson IM, et al. Hepatology 2010; 52 (S1) [abstract 211];
2. Sherman KE, et al. Hepatology 2010; 52 (S1) [abstract LB-2];
3. Poordad F, et al. Hepatology 2010; 52 (S1) [abstract LB-4]

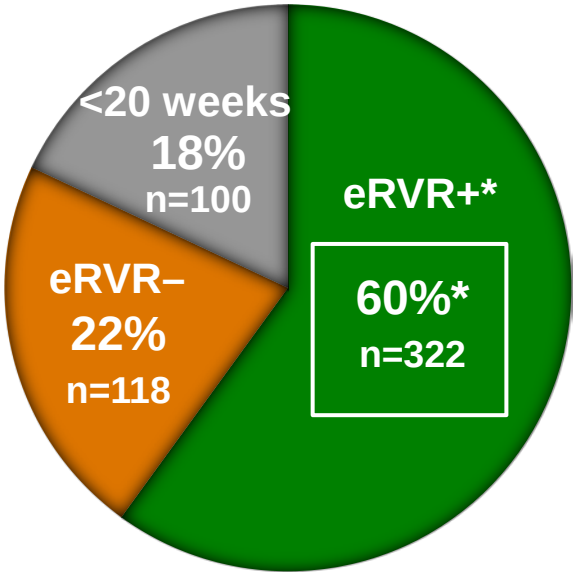
SVR rate with boceprevir and peginterferon/RBV versus PR



*p<0.001 for both boceprevir arms versus PR48
SVR was defined as undetectable HCV RNA at the last available value in the period at or after follow-up Week 24.
If there was no such value, the follow-up Week value was carried forward

Impact of rapid virologic response on SVR : leading to different durations of treatment
Exemple of telaprevir

Treatment duration according to eRVR status

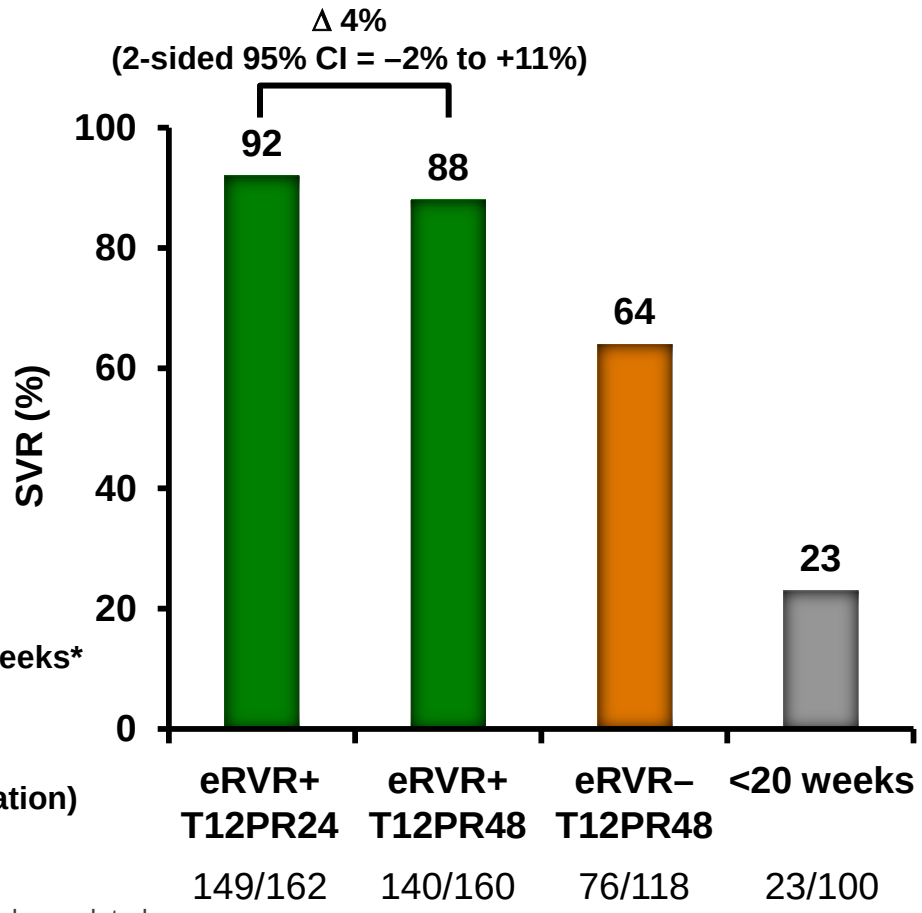


Eligible for 24 weeks and randomized to 24 or 48 weeks*

48 weeks

<20 weeks (due to premature treatment discontinuation)

SVR rate



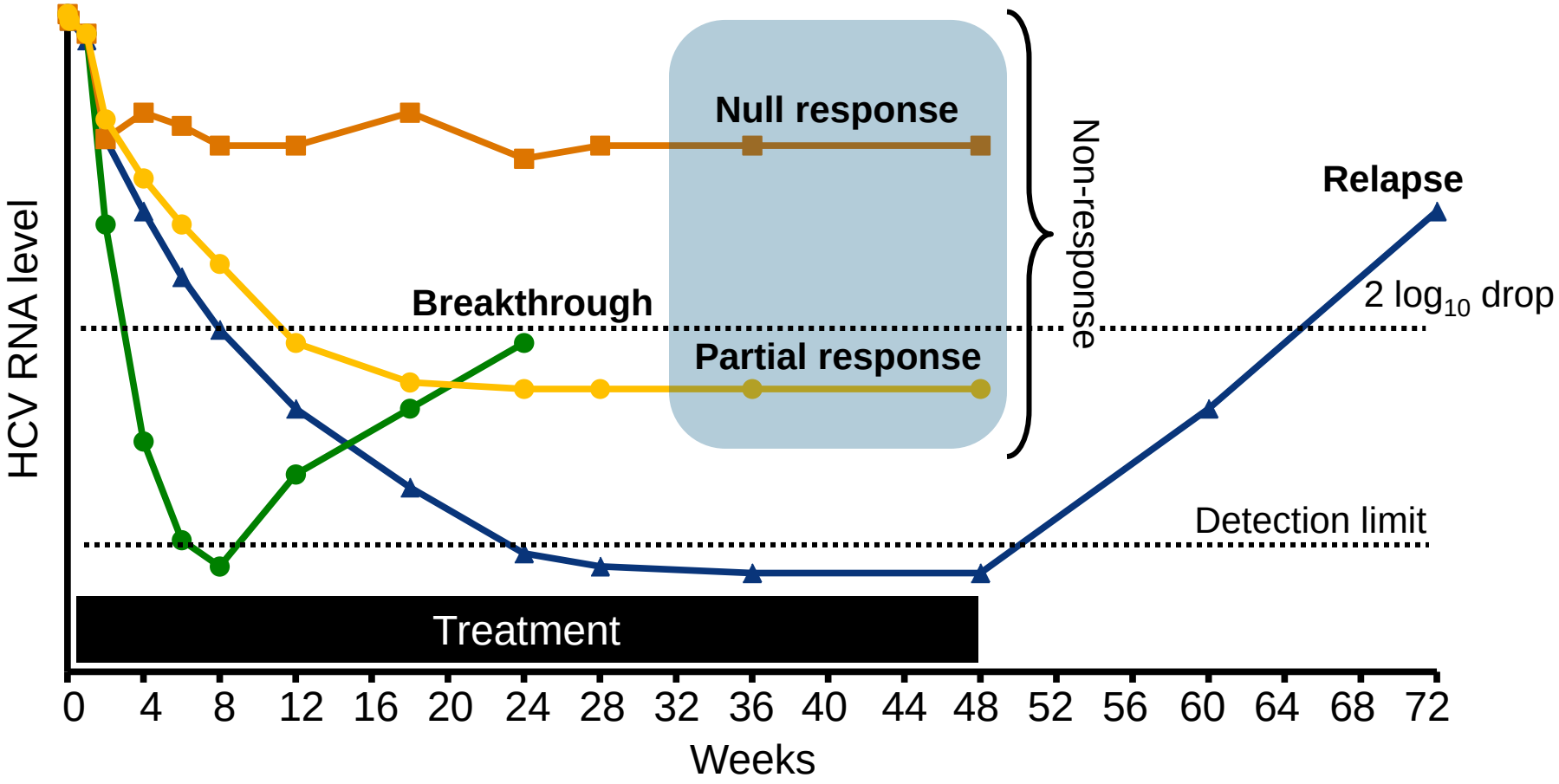
*Patients who achieved eRVR (undetectable HCV RNA at Weeks 4 and 12) and completed the Week 20 visit were randomized to receive an additional 4 or 28 weeks of PR alone

65% of patients achieved an eRVR (352/540); 322/352 were randomized and 30/352 patients discontinued before randomization at Week 20

Sherman KE, et al. N Engl J Med 2011;365:1014–24

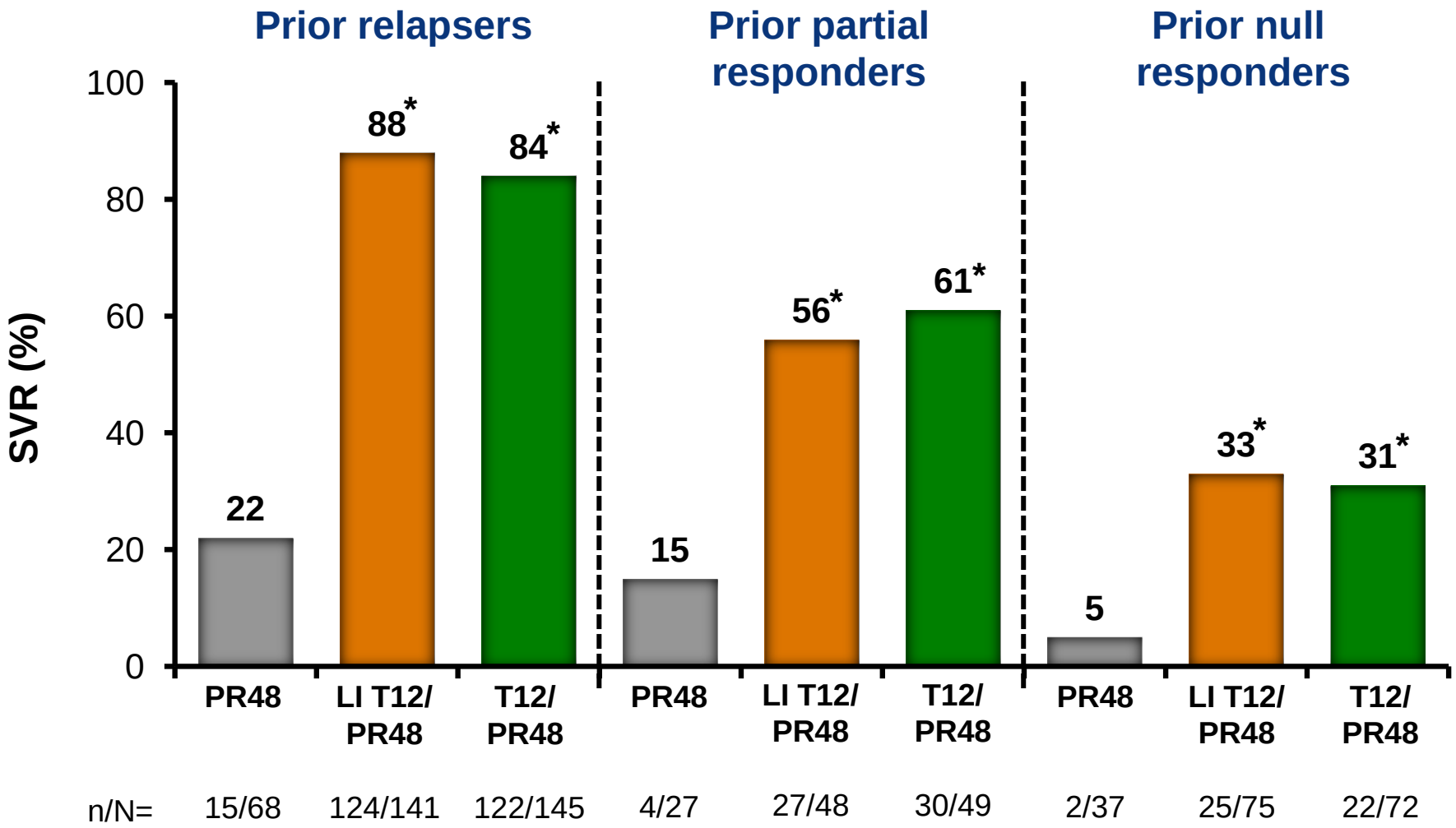
Efficacy of with HCV protease inhibitors with peg interferon and ribavirin in patients infected with genotype 1, non responders to peg IFN/RBV

Definitions of non responses to Peg-IFN/RBV



Adapted from Shiffman M. Curr Gastroenterol Rep 2006;8:46–52
Neumann A, et al. Science 1998;282:103–7; De Bruijne J, et al. Neth J Med 2008;66:311–22

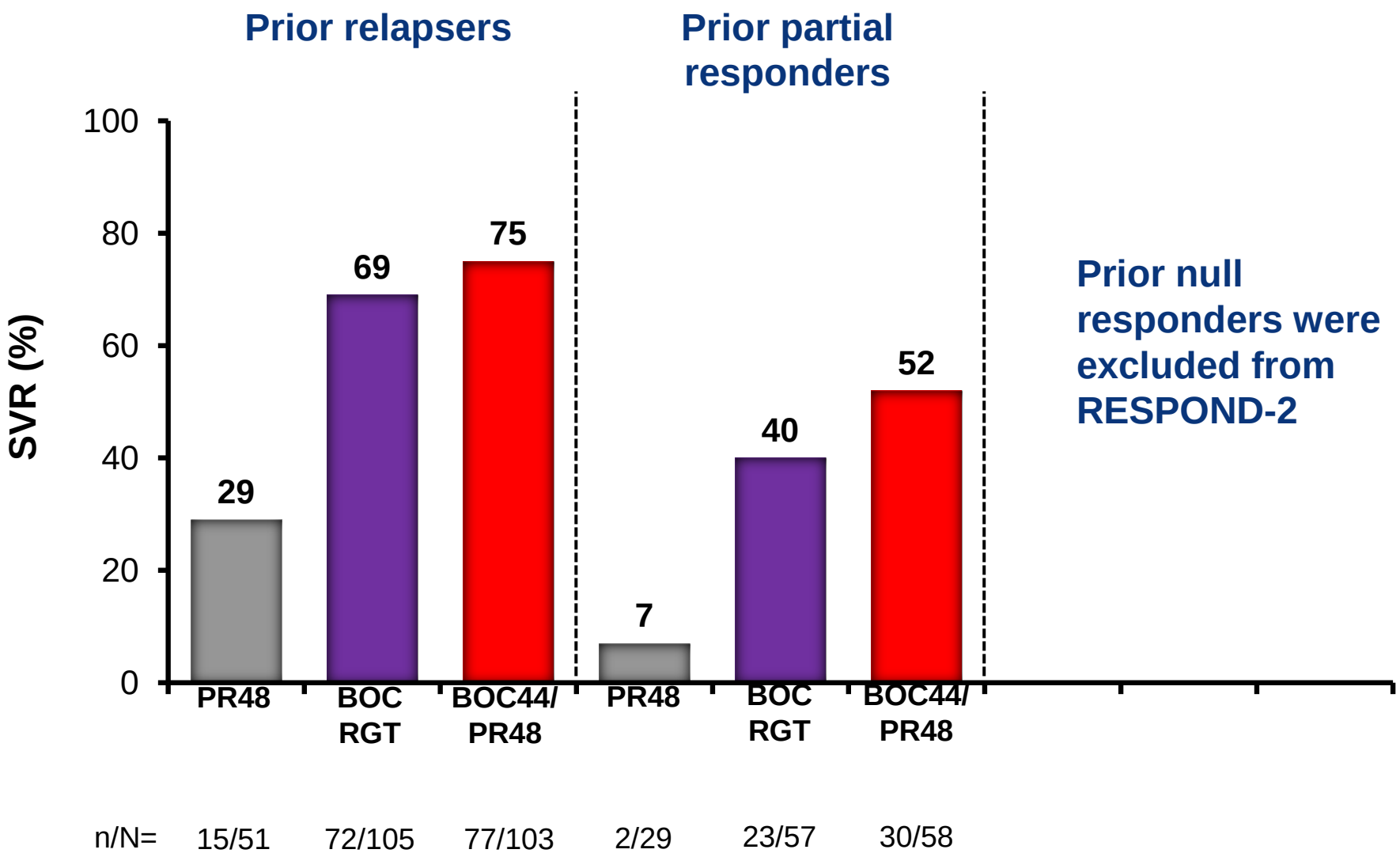
SVR to telaprevir with PR in relapsers, partial responders and null responders to PR



*p<0.001 vs PR48

SVR, considered virologic cure, was defined as HCV RNA <25 IU/mL at last observation within the Week 72 visit window. In case of missing data, the last HCV RNA data point from Week 12 of follow-up onwards was used

SVR to boceprevir with PR in relapsers and partial responders to PR

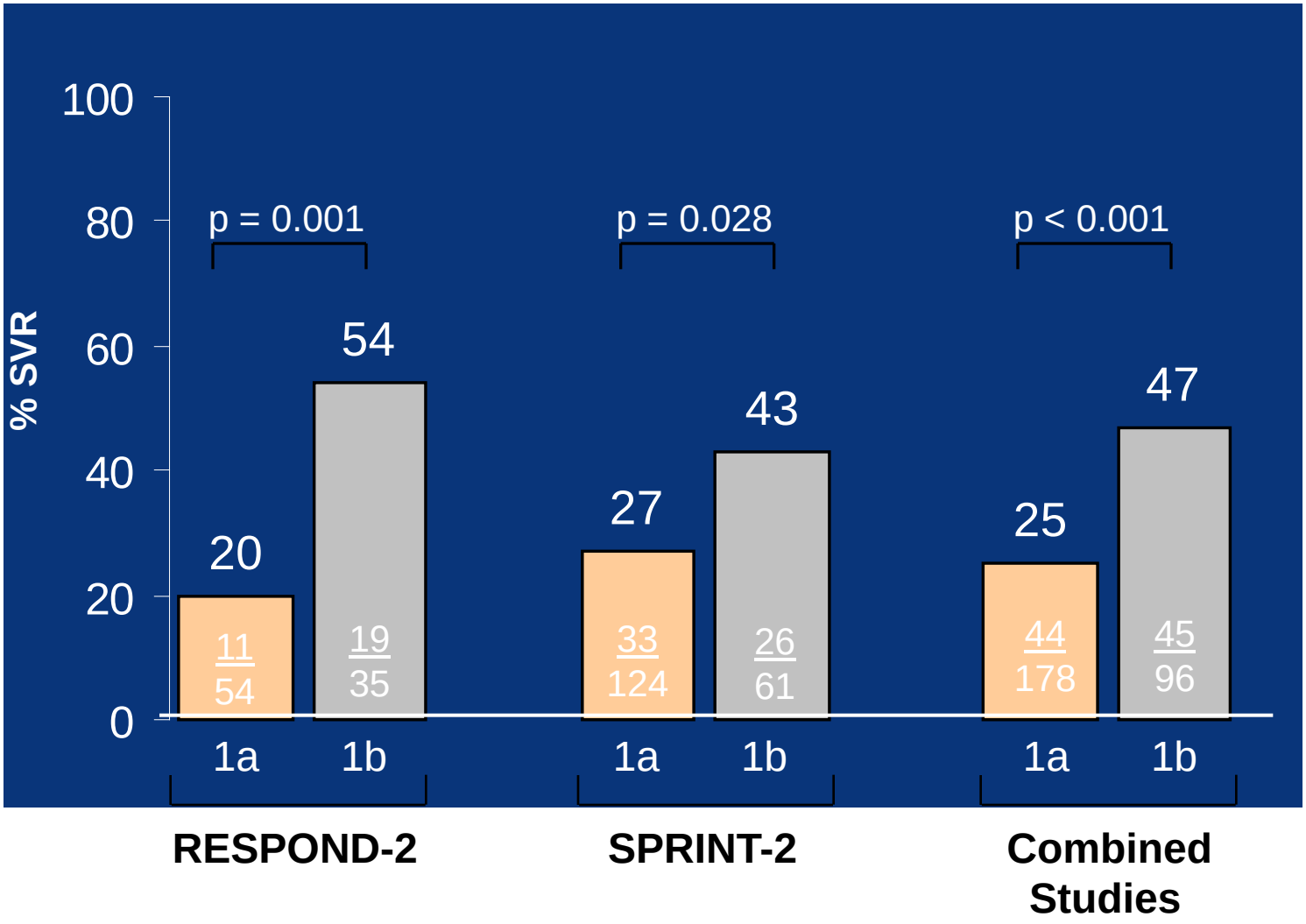


SVR was defined as undetectable HCV RNA at the last available value in the period at or after follow-up Week 24. If there was no such value, the follow-up Week 12 value was carried forward

Three main baseline predictors of SVR under tritherapy with PI

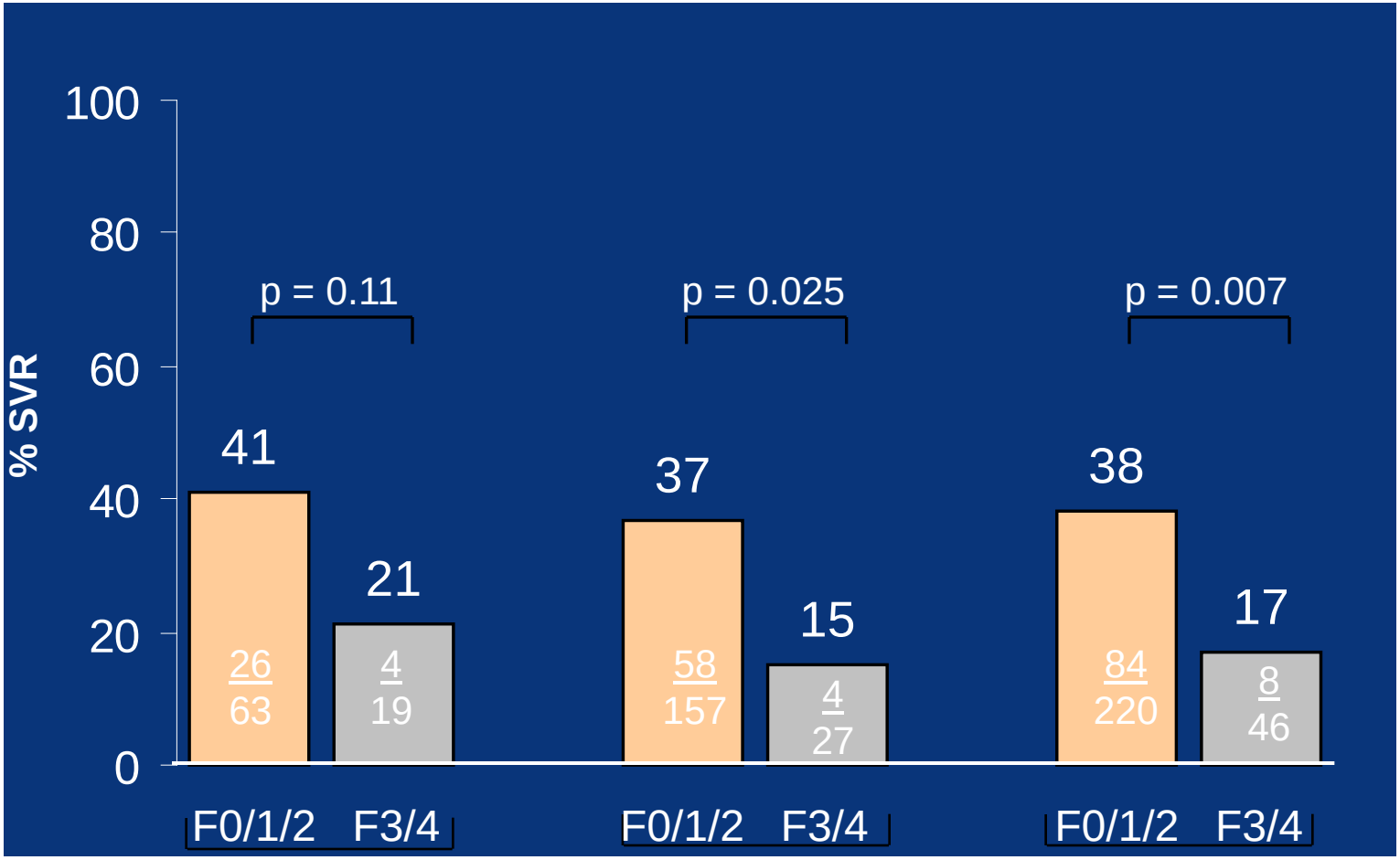
- **HCV viral load**
- **HCV G1 subtype: 1b > 1a**
- **Fibrosis stage**

HCV G1 subtype as a Predictor of SVR (BOC Arms Combined)



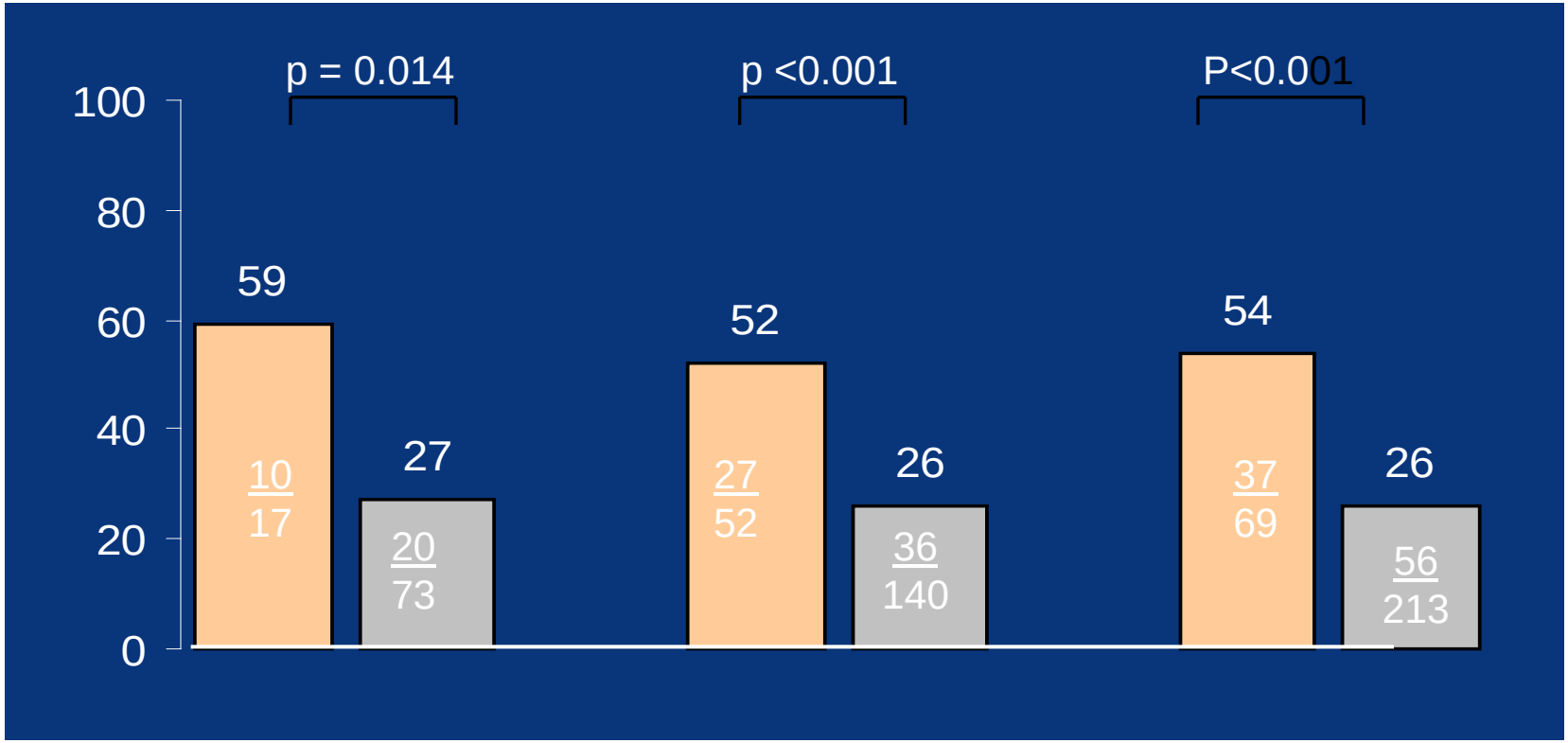
Bacon, AASLD, 2011

Fibrosis Score as a Predictor of SVR (BOC Arms Combined)



Bacon, AASLD, 2011

HCV Viral Load as a Predictor of SVR (BOC Arms Combined)



Bacon, AASLD, 2011

SAFETY OF TELAPREVIR OR BOCEPREVIR IN COMBINATION WITH PEGINTERFERON ALFA/RIBAVIRIN, IN CIRRHOTIC NON RESPONDERS FIRST RESULTS OF THE FRENCH EARLY ACCESS PROGRAM (ANRS CO20-CUPIC)

C Hézode[1], C Dorival[2], F Zoulim[3], T Poynard[4], P Mathurin[5], S Pol[6], D Larrey[7], P Cacoub[4], V de Ledinghen[8], M Bourlière[9], PH Bernard[10], G Riachi[11], Y Barthe[2], H Fontaine[6], F Carrat[2], JP Bronowicki[12] for the CUPIC study group (ANRS CO 20)

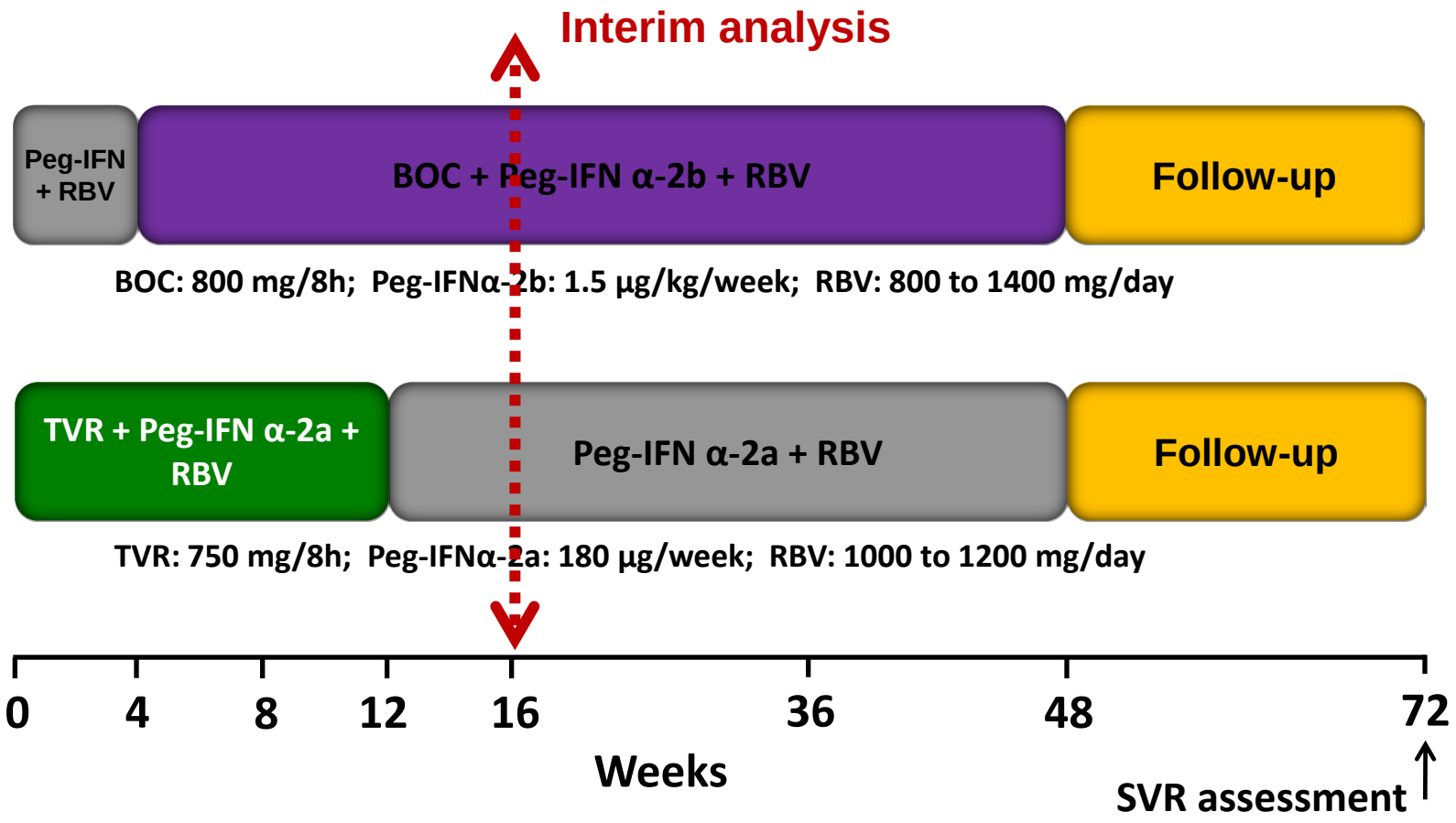
Hôpital Henri Mondor, Créteil[1], UMR-S 707, Paris[2], INSERM U871, Lyon[3], Hôpital de la Pitié-Salpêtrière, Paris[4], Hôpital Claude Huriez, Lille[5], Hôpital Cochin, Paris[6], Hôpital Saint-Eloi, Montpellier[7], Hôpital Haut-Lévèque, Pessac[8], Fondation Hôpital Saint Joseph, Marseille[9], Hôpital Saint André, Bordeaux[10], Hôpital Charles Nicolle, Rouen[11], Hôpital de Brabois, Nancy[12], France

CUPIC Patients

- HCV genotype 1 patients
- Compensated cirrhosis (Child Pugh A)
- Non-responders
  - Relapsers
  - Partial responders

    (↓ >2 $\log_{10}$ HCV RNA decline at Week 12)
  - Null responders theoretically excluded
- Treated in the French early access program

Treatment regimen



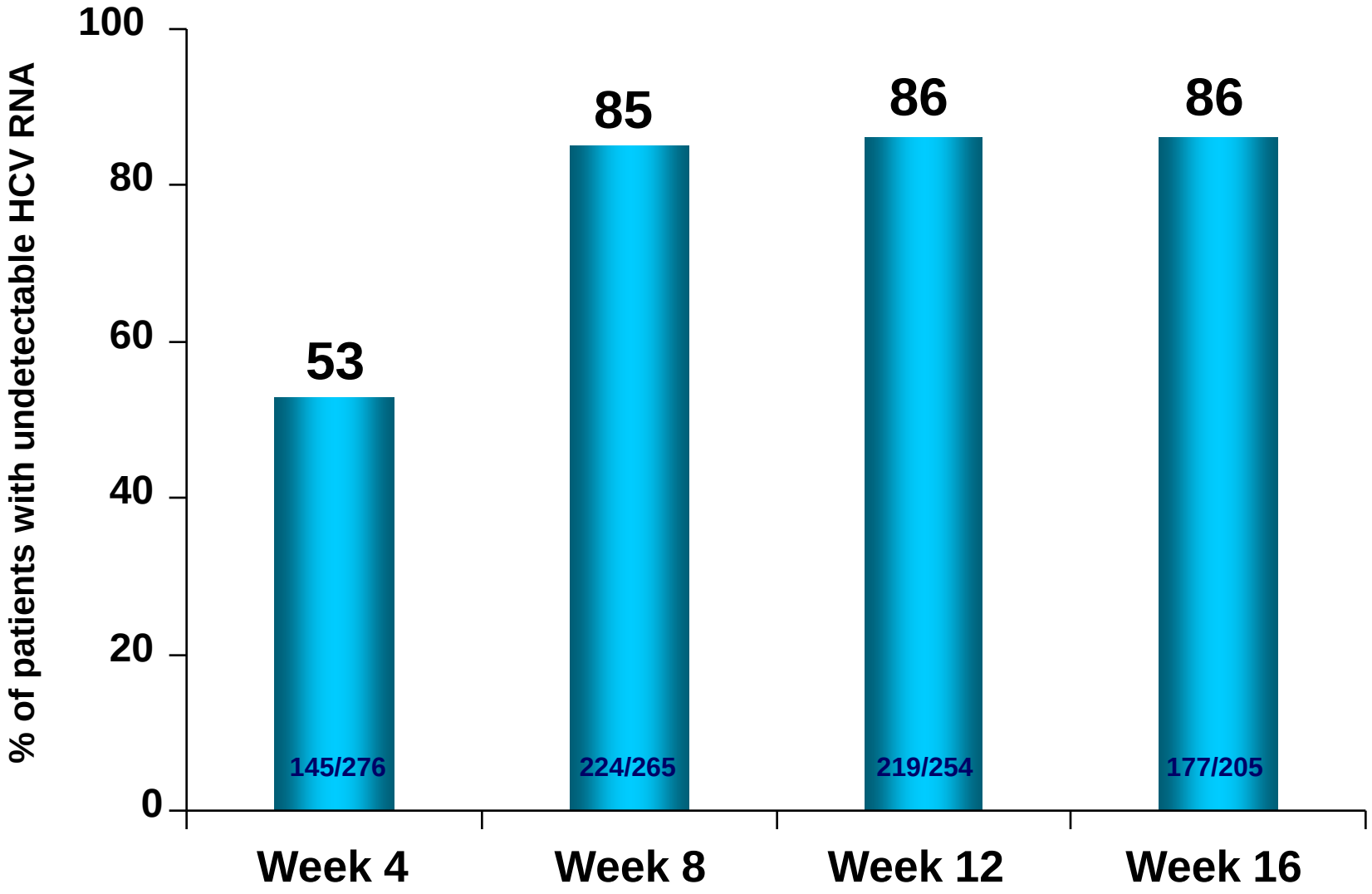
http://www.afssaps.fr/var/afssaps_site/storage/original/application/4b8c53711bab9d8f7d4c3f947caa90f6.pdf
http://www.afssaps.fr/var/afssaps_site/storage/original/application/fa78af08e029caf9d82bcd9d3e77eb09.pdf

Preliminary safety findings

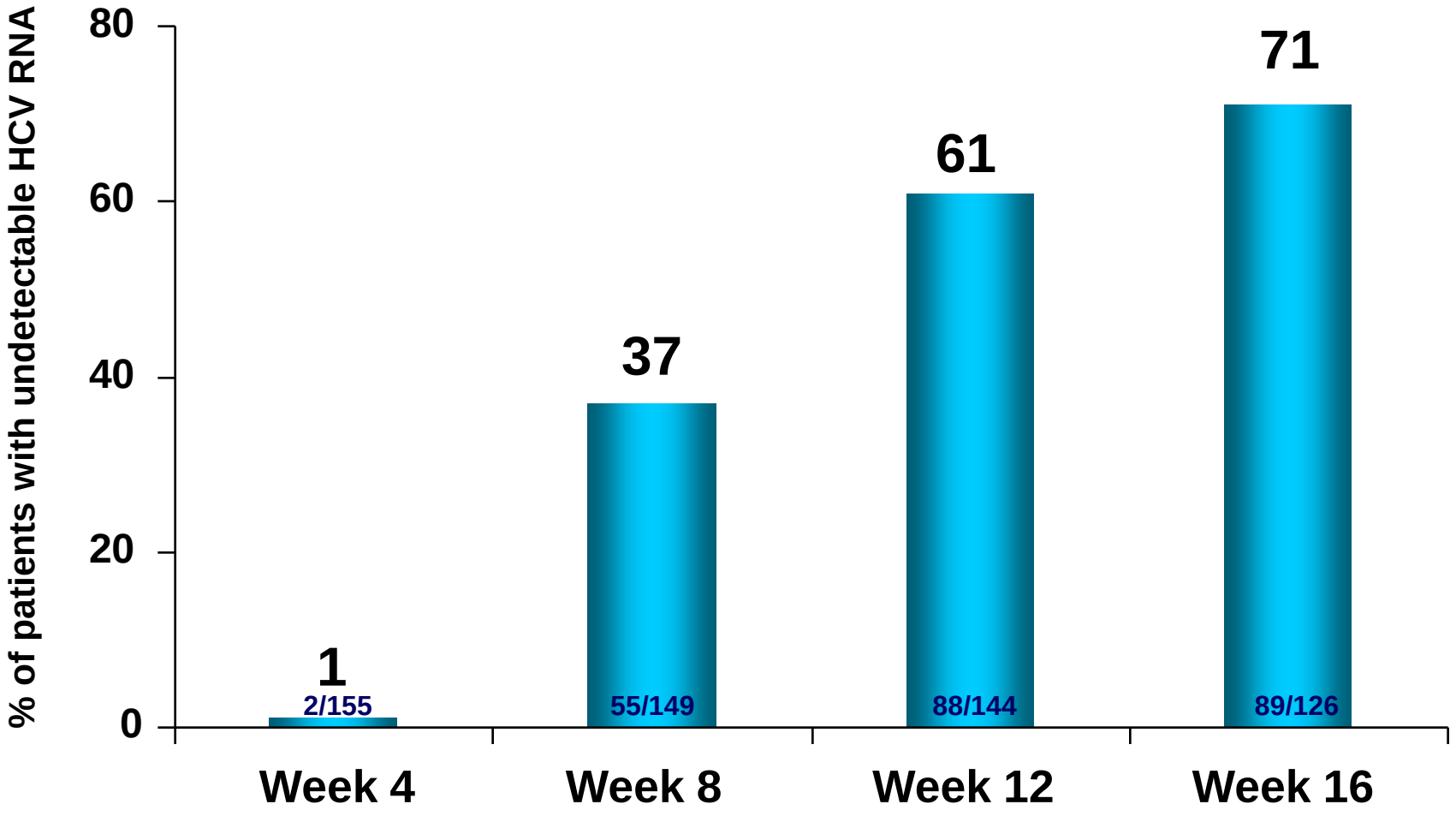
Patients, (% patients with ≥1 event)		Telaprevir n=296	Boceprevir N=159
Serious adverse events (SAEs)*		48.6%	38.4%
Premature discontinuation		26.0%	23.9%
Death		2.0%	1.3%
Infection (Grade 3/4)		8.8%	2.5%
Anemia (Grade 3/4)		19.6%	22.6%
EPO use		56.8%	66.0%
Transfusion		15,2%	10.7%
Rash	Grade 3	6.8%	0%
	Grade 4	0.7%	0%
Pruritus (Grade 3/4)		3.7%	

*407 SAEs in 144 patients; SCAR: severe cutaneous adverse reaction

Telaprevir: preliminary efficacy data



Boceprevir: preliminary efficacy data



Practical use of boceprevir and telaprevir in France

- Indications : treatment of hepatitis C, genotype 1, in association with PR, in patients with compensated liver disease, naive or non responders to previous anti HCV treatment.

BOCEPREVIR (VICTRELIS°)

- 4 capsules 200 mg x 4/d
- Lead-in : PegIFN+RBV for 1 month
- BOC+PegIFN+RBV until W44, or W28 (if eRVR+)

TELAPREVIR (INCIVO°)

- 2 capsules 750 mg, TID, with meal
- Duration : 12 weeks
- Followed by PR until W48 or 24 (if eRVR+)

The future?

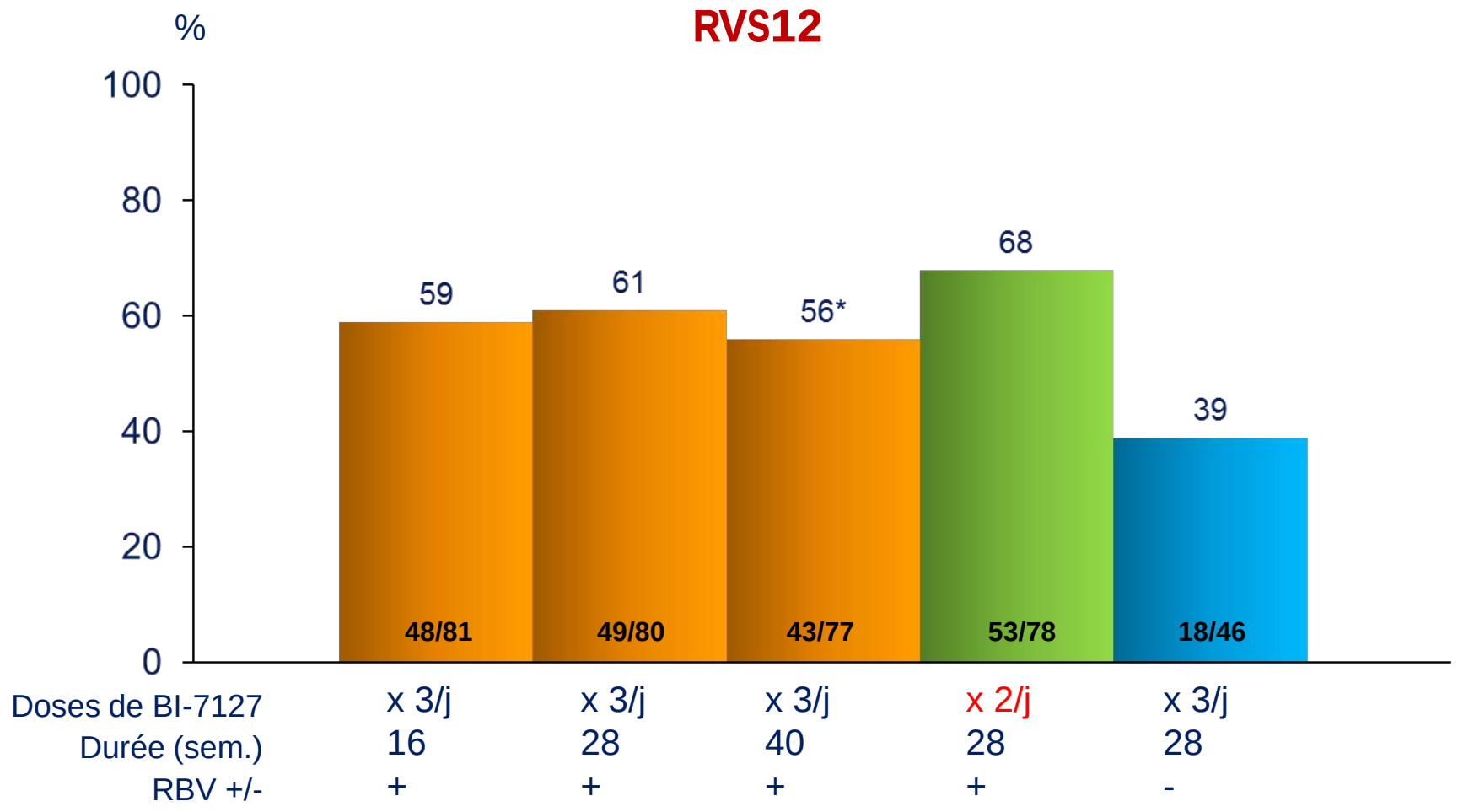
- **Combinations of direct active drugs (DADs)**
  - High barrier of resistance
  - With and without interferon
- **Short duration of treatment :** 24, 12, 8 weeks
- **Pangenotypic or genotype specific**
- **Questions unresolved**
  - Interactions
  - Place of ribavirin

Novel anti HCV drugs

NS3 Protease	NS5B Polymerase		NS5A	Cyclophilin
	Nucleos(t)ide (NPOL)	Non-nucleoside (NNI)		
Telaprevir Boceprevir Danoprevir TMC435 BI 201335 asunaprevir BMS-650032 ABT-450 GS-9451 GS-9256 MK-5172 ACH-1625 VX-985 CTS-1027	Mericitabine GS7977 IDX 184	Tegobuvir Filibuvir ANA598 BI 207127 ABT-333 VX-222 ABT-072 BMS-791325	daclatasvir BMS 824393 CF102	Alisporivir SCY-465

Traitement without interferon in genotype 1b naive patients

- BI-201335 (prot inhib) + BI-207127 (NS5B pol inhib) +/- RBV



*RVS4

Zeuzem S, EASL 2012, Abs. 101

ELECTRON : bitherapy GS-7977/ribavirin

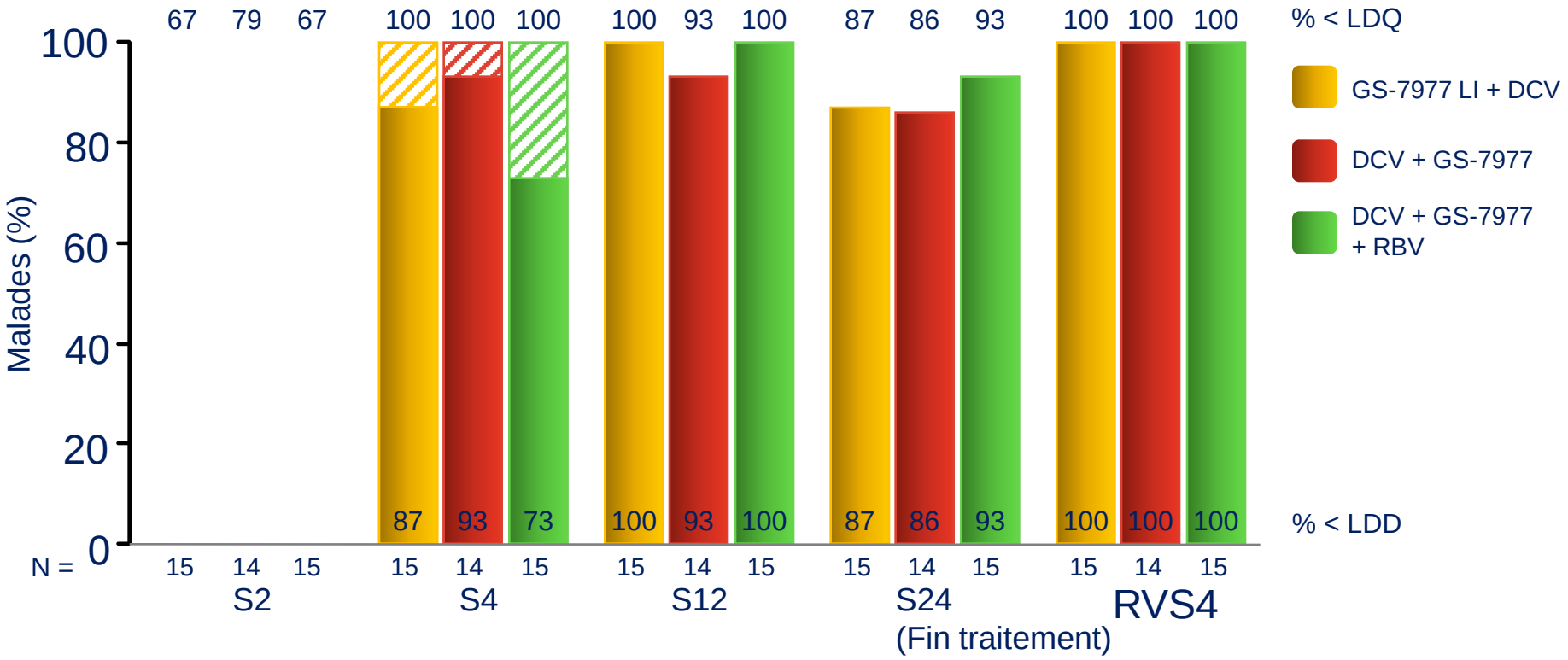
Virologic response

	Genotypes 2/3 Naive 8 weeks n (%)	Genotype 1 Null responders 12 weeks n (%)	Genotype 1 Naive 12 weeks n (%)	Genotypes 2/3 Non responders 12 weeks n (%)
W2	10/10 (100)	7/10 (70)	17/24 (71)	21/25 (84)
SVR4	10/10 (100)	1/9 (11)	22/25 (88)	12/15 (80)
SVR12	10/10 (100)	-	-	-

8 weeks for GT 2/3 naive but 12 weeks not suffisant for GT1 null responders

Gane EJ, EASL 2012, Abs. 1113

Efficacy of daclatasvir and GS-7977 +/- ribavirine in genotype 1 naive patients



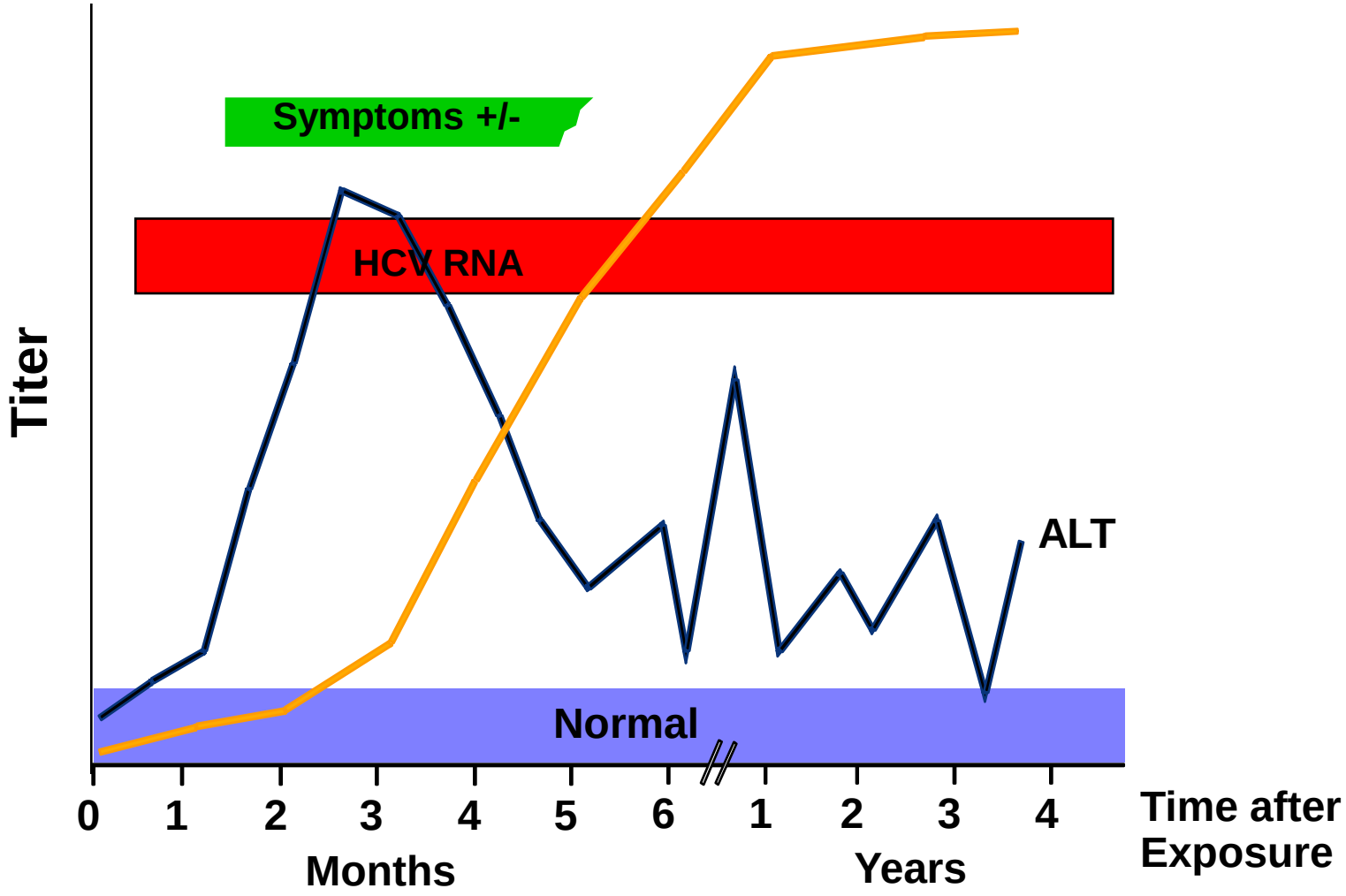
➔ 100 % (44/44) of G1 patients had an RVS W4 with the combination DCV + GS7977

Sulkowski M, EASL 2012, Abs. 1422

Conclusions

- First generation protease inhibitors associated with pegylated interferon and ribavirin
  - 30% increase of SVR rate, in naive and non responders patients
  - GT1 only
  - Low efficacy if cirrhosis and null responders
  - Severe side effects
- Future
  - Several new molecules with high genetic barrier
  - dual or triple triple therapy with ou without RBV
  - End of life for interferon in HCV disease

Course of acute infection towards chronicity



Telaprevir: preliminary safety findings

Patients, n (% patients with at least one event)	Telaprevir n=296
Serious adverse events (SAEs)*	144 (48.6%)
Premature discontinuation Due to SAEs	77 (26.0%) 43 (14.5%)
Death *Septicemia, Septic shock, Pneumopathy, Oesophageal varices Bleeding, Encephalopathy, Lung carcinoma*	6 (2.0%)
Infection (Grade 3/4)	26 (8.8%)
Asthenia (Grade 3/4)	14 (4.7%)
Rash Grade 3 Grade 4 (SCAR)	 20 (6.8%) 2 (0.7%)
Pruritus (Grade 3/4)	11 (3.7%)
Hepatic decompensation (Grade 3/4)	13 (4.4%)

*407 SAEs in 144 patients; SCAR: severe cutaneous adverse reaction

Telaprevir: preliminary safety findings

Patients, n (% patients with at least one event)	Telaprevir (n=296)
Anemia	
Grade 2 (8.0 – <10.0 g/dL)	58 (19.6%)
Grade 3/4 (<8,0 g/dL)	30 (10.1%)
EPO use	168 (56.8%)
Blood transfusion	45 (15.2%)
Neutropenia	
Grade 3 (500 – <1000/mm^3)	12 (4.0%)
Grade 4 (<500/mm^3)	2 (0.7%)
G-CSF use	7 (2.4%)
Thrombopenia	
Grade 3 (25 000 – <50 000)	35 (11.8%)
Grade 4 (<25 000)	4 (1.3%)
Thrombopoïetin Use	5 (1.7%)

EPO: érythropoïétine; G-CSF: granulocyte-colony stimulating factor

Boceprevir: preliminary safety findings

Patients, n (% patients with at least one event)	Boceprevir (n=159)
Serious adverse events (SAEs)*	61 (38.4%)
Premature discontinuation Due to SAE	38 (23.9%) 12 (7.4%)
Death *Bronchopulmonary infection, Sepsis*	 2 (1.3%)
Infection (Grade 3/4)	4 (2.5%)
Asthenia (Grade 3/4)	9 (5.7%)
Rash Grade 3 Grade 4 (SCAR)	 0 0
Pruritus (Grade 3/4)	1 (0.6%)
Hepatic decompensation (Grade 3/4)	7 (4.4%)

*158 SAEs in 61 patients; SCAR: severe cutaneous adverse reaction

Boceprevir: preliminary safety findings

Patients, n (% patients with at least one event)	Boceprevir (n=159)
Anemia	
Grade 2 (8.0 – <10.0 g/dL)	36 (22.6%)
Grade 3/4 (<8,0 g/dL)	16 (10.1%)
EPO use	105 (66.0%)
Blood transfusion	17 (10.7%)
Neutropenia	
Grade 3 (500 – <1000/mm^3)	7 (4.4%)
Grade 4 (<500/mm^3)	1 (0.6%)
G-CSF use	6 (3.8%)
Thrombopenia	
Grade 3 (25 000 – <50 000)	10 (6.3%)
Grade 4 (<25 000)	1 (0.6%)
Thrombopoïetin Use	3 (1.9%)

EPO: érythropoïétine; G-CSF: granulocyte-colony stimulating factor

Main classes of anti HCV inhibitors

- **Protease inhibitors**
  - 1st generation and approved: **telaprevir, boceprevir**
  - 2nd generation
- **Polymerase inhibitors**
  - Nucleosidic inhibitors
  - Non nucleosidic inhibitors
- **NS5A inhibitors**
- **Entry inhibitors**
- **Immunomodulators**