Manejo de la Hepatitis C en el nuevo escenario

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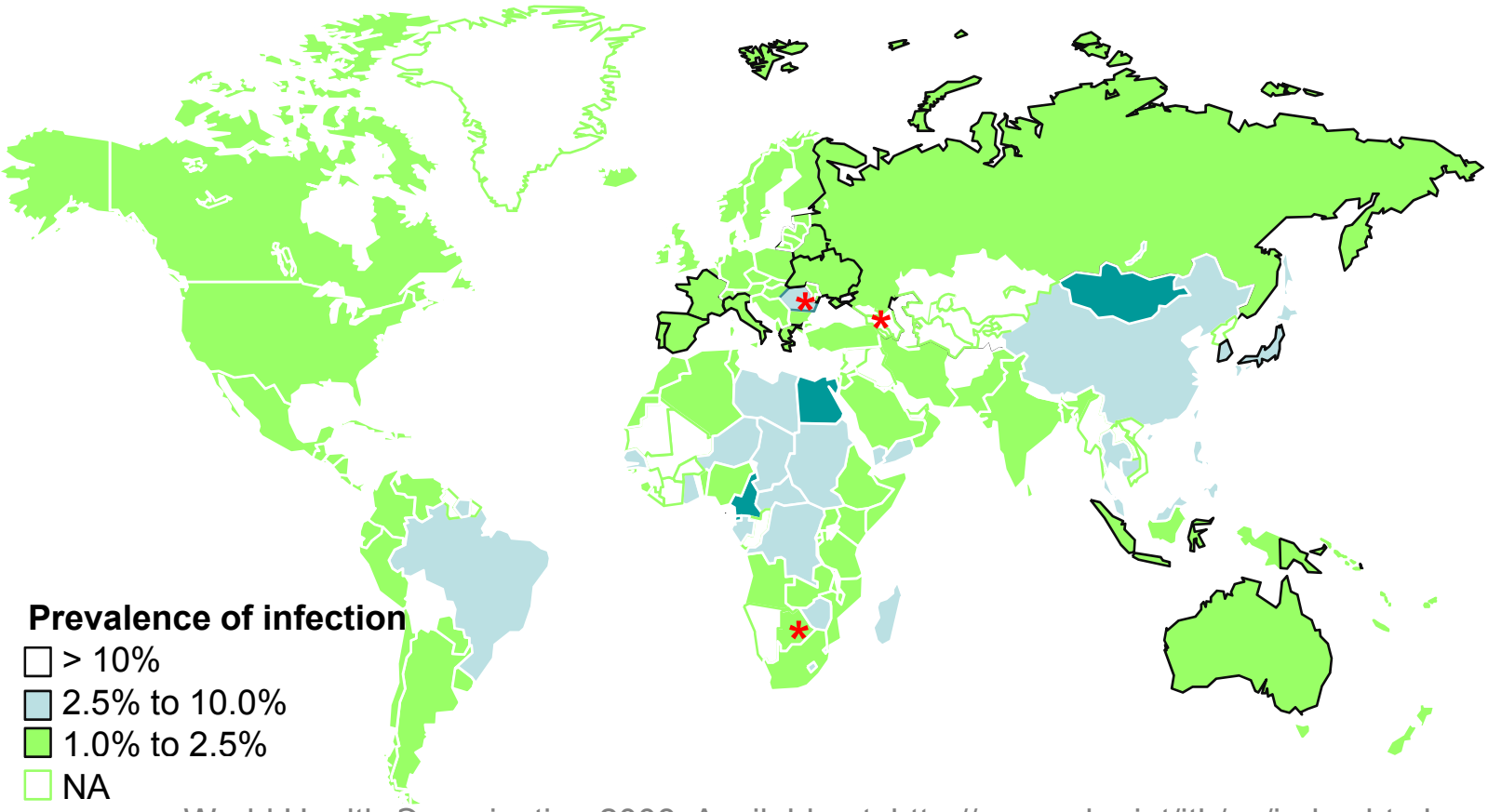
SaludMadrid

Comunidad de Madrid

Estimated 170 Million Persons With HCV Infection Worldwide

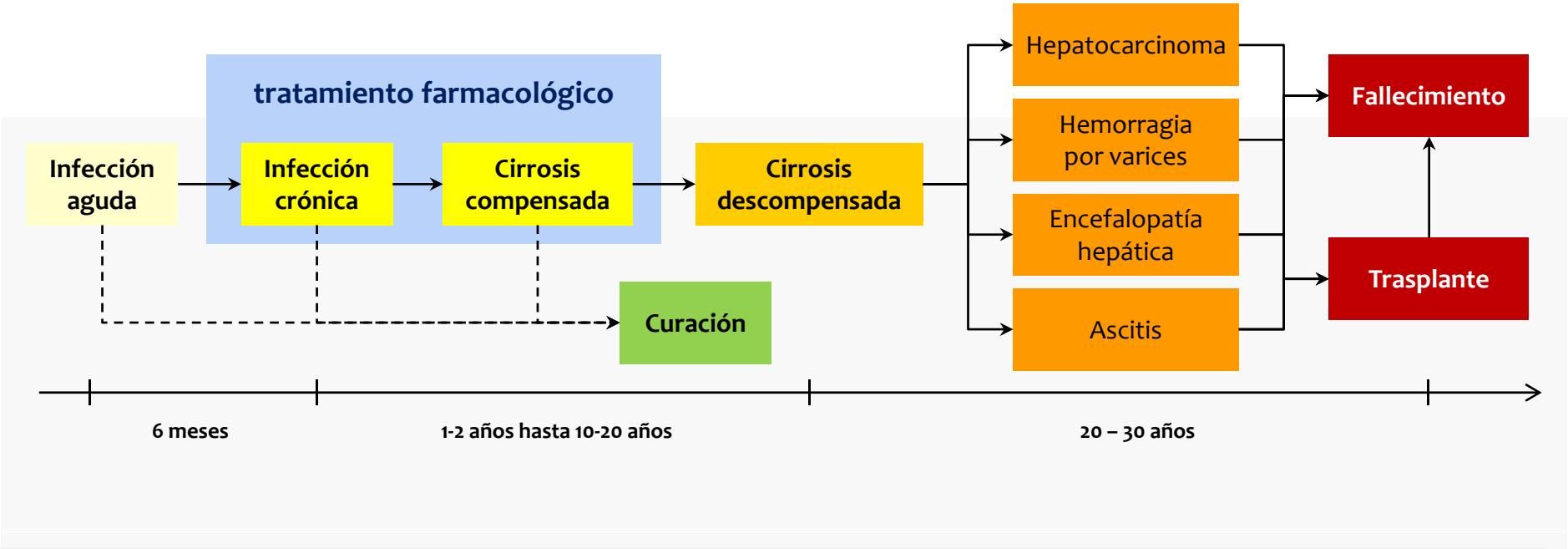
- 3-4 million newly infected each yr worldwide



World Health Organization 2008. Available at: http://www.who.int/ith/es/index.html.

¿Por qué es necesario tratar la hepatitis C?

- **Es una enfermedad curable** que puede evolucionar a **cirrosis**, estado a partir del cual se desarrollan el resto de complicaciones con un importante **impacto económico** y en la **vida del paciente**



"El objetivo del tratamiento es erradicar la infección por el VHC con el fin de prevenir las complicaciones de la enfermedad hepática que incluyen necroinflamación, fibrosis, cirrosis y hepatocarcinoma." [1]

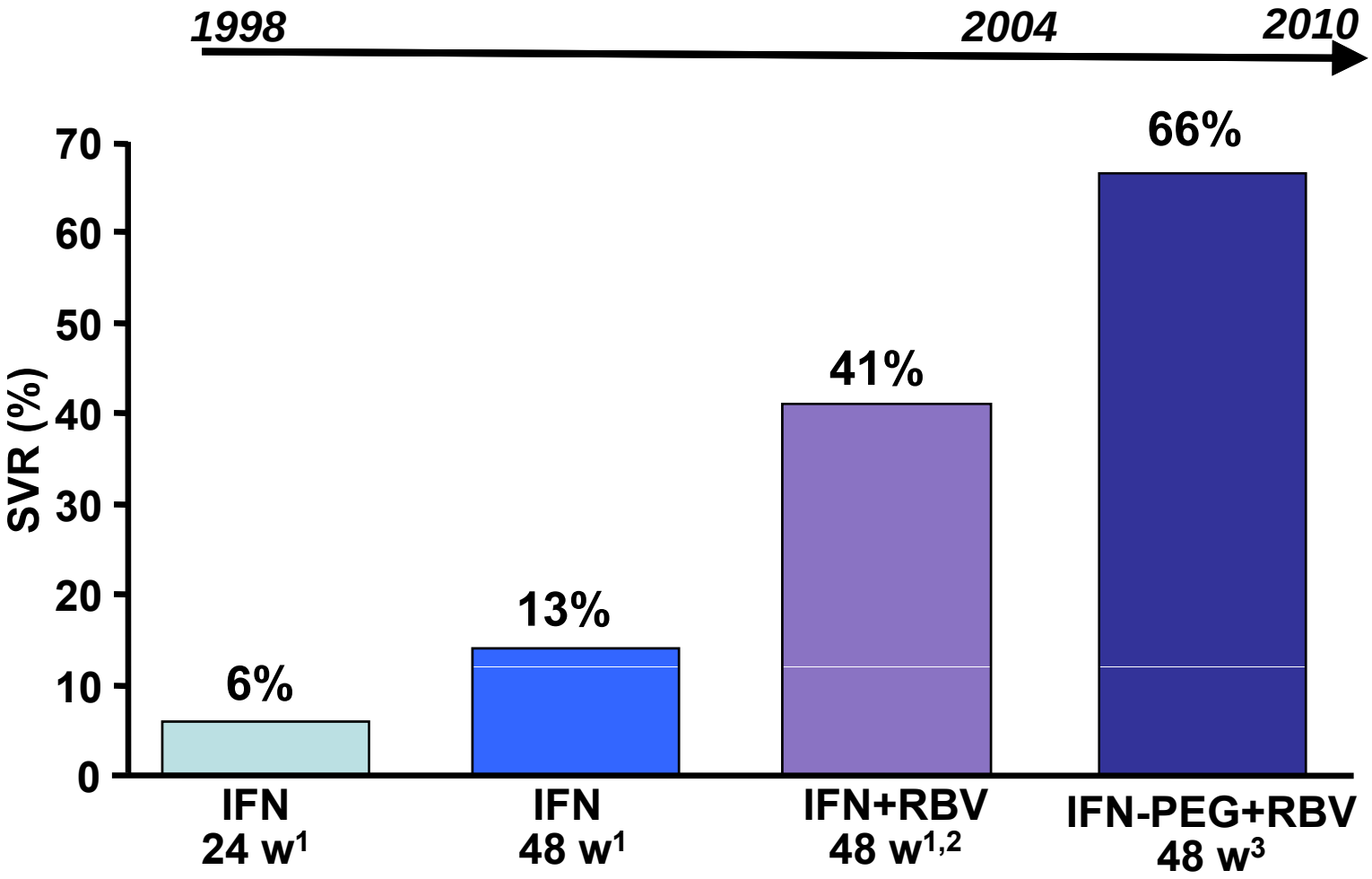
[1] *EASL Clinical Practice Guidelines: Management of HCV infection; Modelo adpatado de Enf Emerg 2003;5(2):90-96 M. Buti y M. Casado, Hoofnagle 1997, Thein 2008, Seef 1997*

SVR Associated With Improved Outcome

- SVR
  - Durable
  - Leads to improved histology
  - Leads to clinical benefits
    - Decreases decompensation
    - Prevents de novo esophageal varices
    - Decreases risk of hepatocellular carcinoma
    - Decreases mortality

Bruno S, et al. Hepatology. 2010;51:2069-2076. Veldt BJ, et al. Ann Intern Med. 2007;147:677-684.
Maylin S, et al. Gastroenterology. 2008;135:821-829.

Resultados del tratamiento de la hepatitis C



1. McHutchison J, et al. N Engl J Med 1998; 339: 1485
2. Poynard T, et al. Lancet 1998; 352: 1426
3. Zeuzem S, et al. J Hepatol 2005; 43: 250

Tratamiento de la hepatitis C genotipo 1 en 2012

IFN pegilado alfa

+

Ribavirina

+

Inhibidor de la proteasa:

Boceprevir

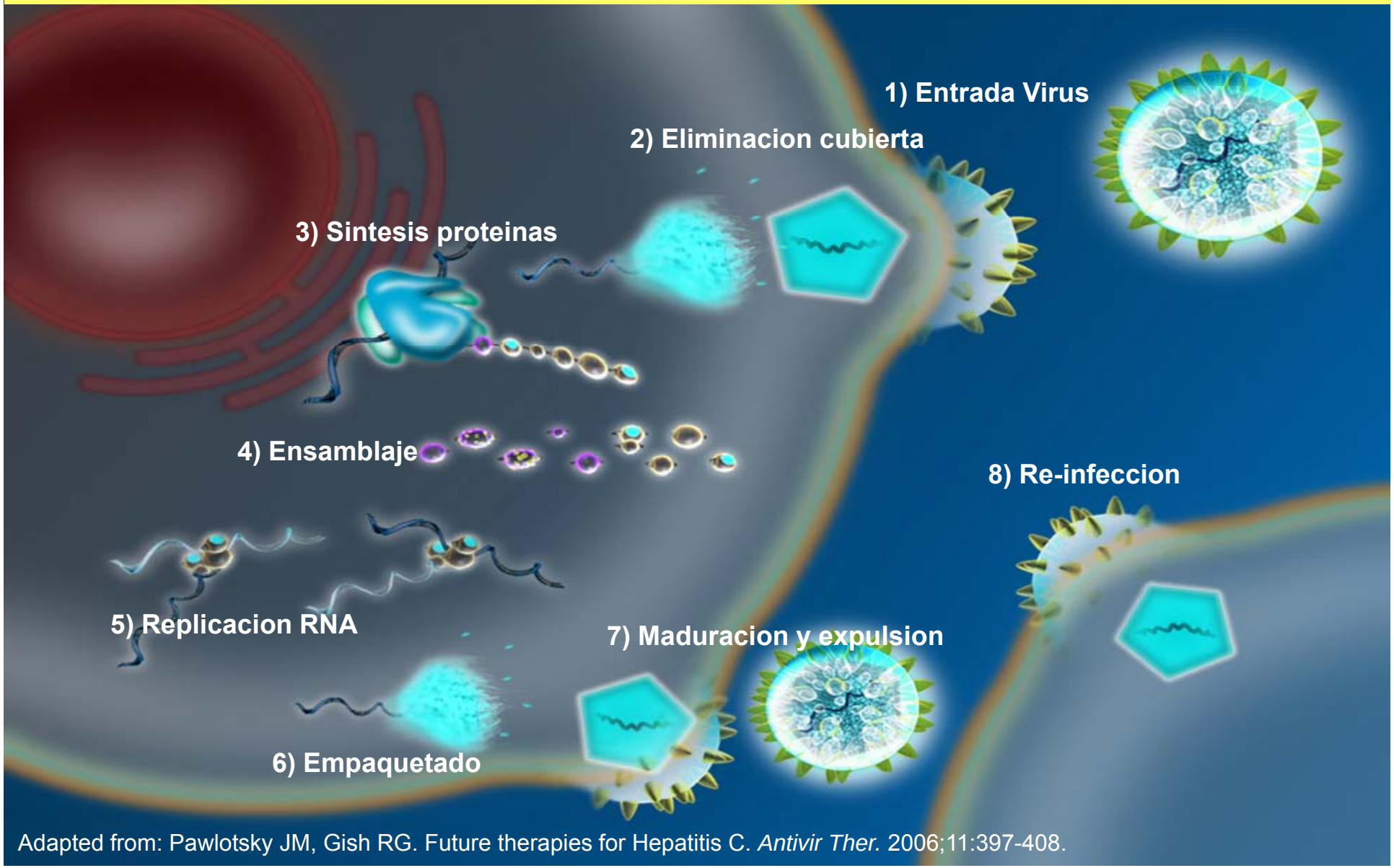
ó

Telaprevir

Tratamiento triple

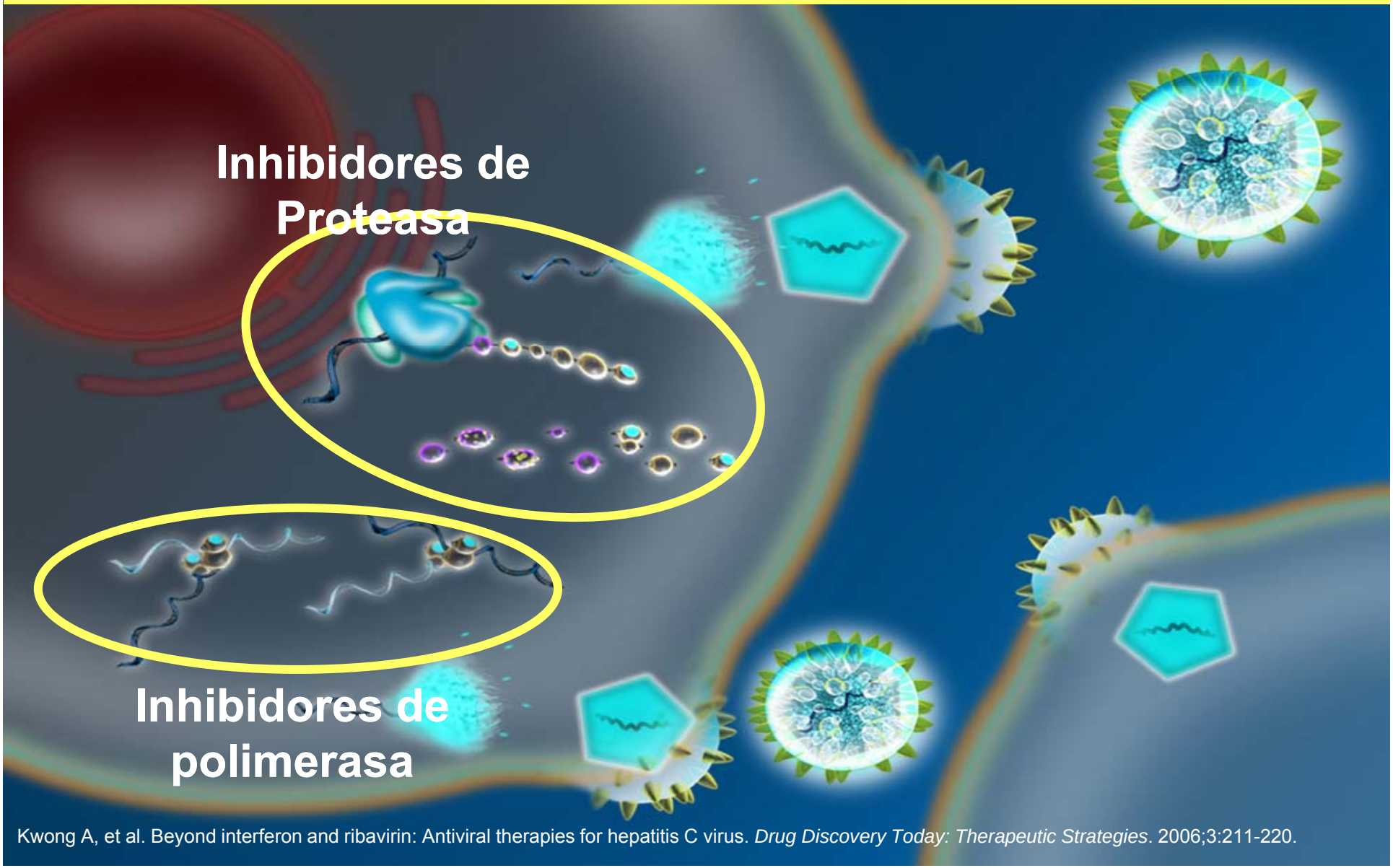
- ¿ Como hemos llegado hasta aquí?
- ¿ Cual es la situación actual?
- ¿ Que nos espera en un futuro?

Ciclo Vital del virus C



Adapted from: Pawlotsky JM, Gish RG. Future therapies for Hepatitis C. *Antivir Ther.* 2006;11:397-408.

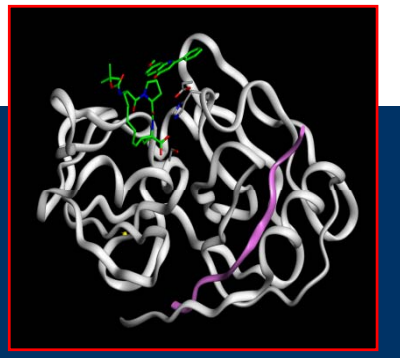
Dianas moleculares de nuevos farmacos



Kwong A, et al. Beyond interferon and ribavirin: Antiviral therapies for hepatitis C virus. *Drug Discovery Today: Therapeutic Strategies*. 2006;3:211-220.

Tratamiento de la hepatitis crónica C

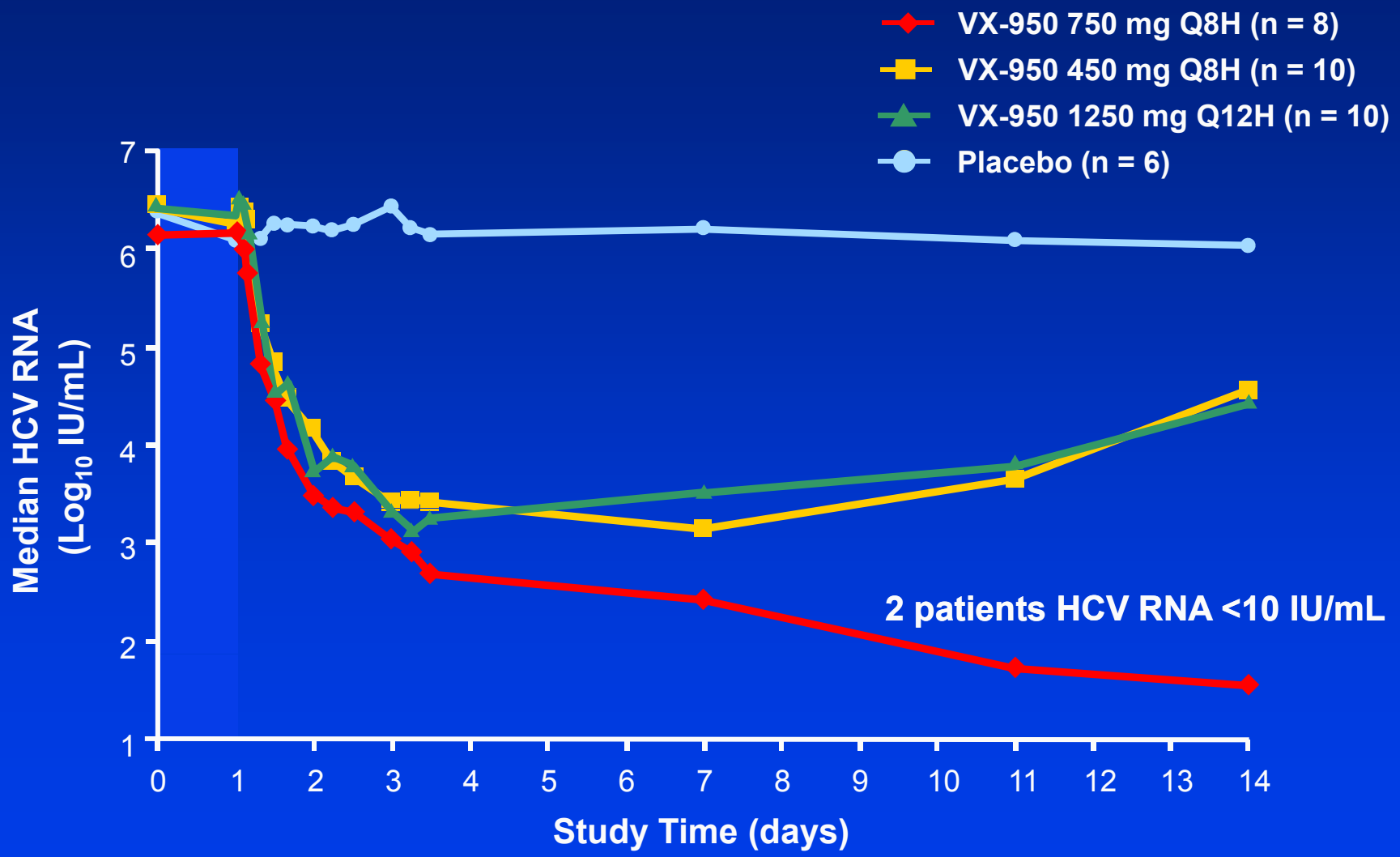
Eficacia virológica de 500 mg / 12 h



Gastroenterology 2004

Protease Inhibitor Telaprevir (VX-950) Monotherapy

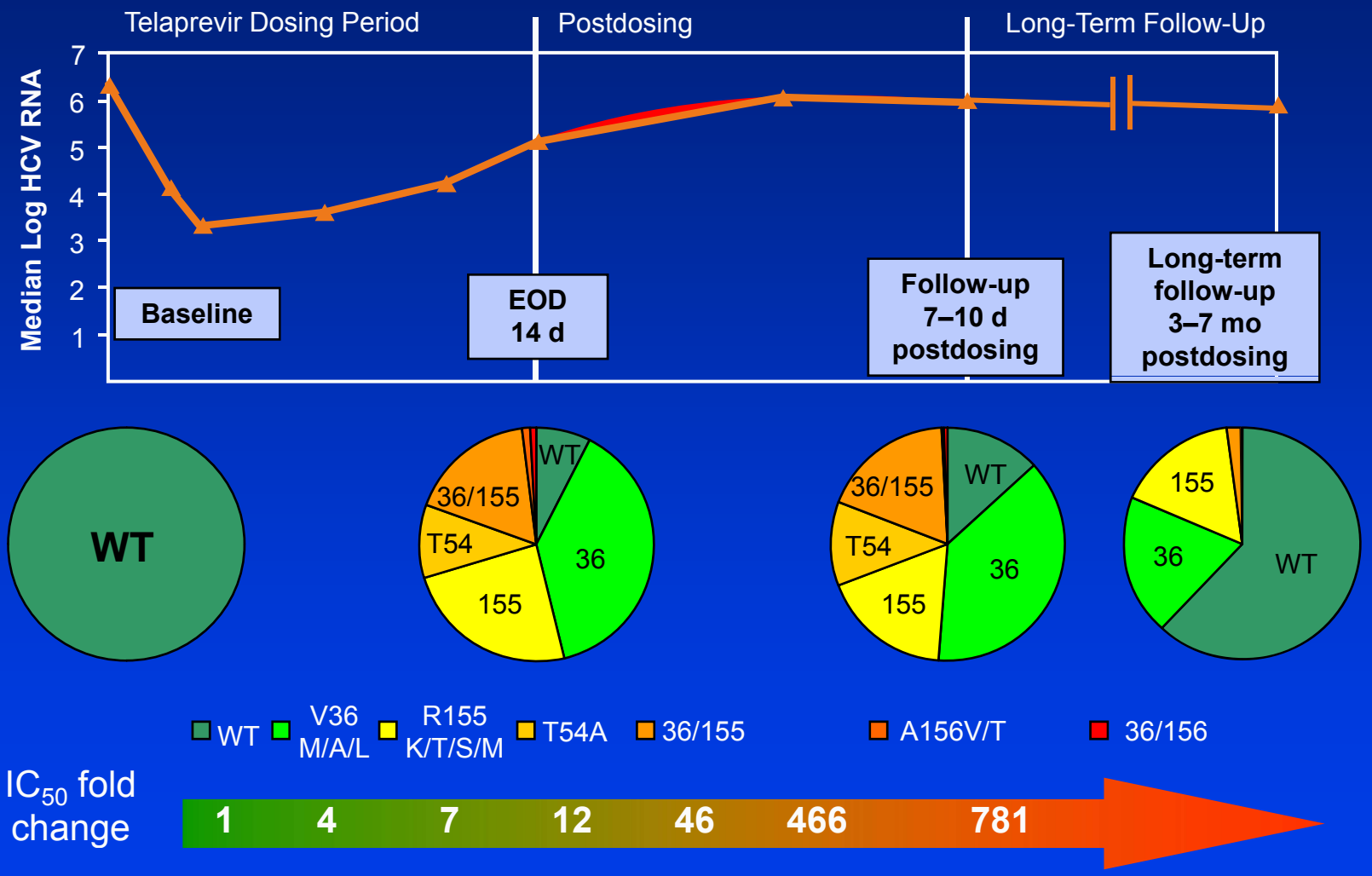
Proof of Principle



Reprinted from Reesink HW, et al. *Gastroenterology.* 2005;128:A-697, with permission from Elsevier.

Frequency of Variants Over Time

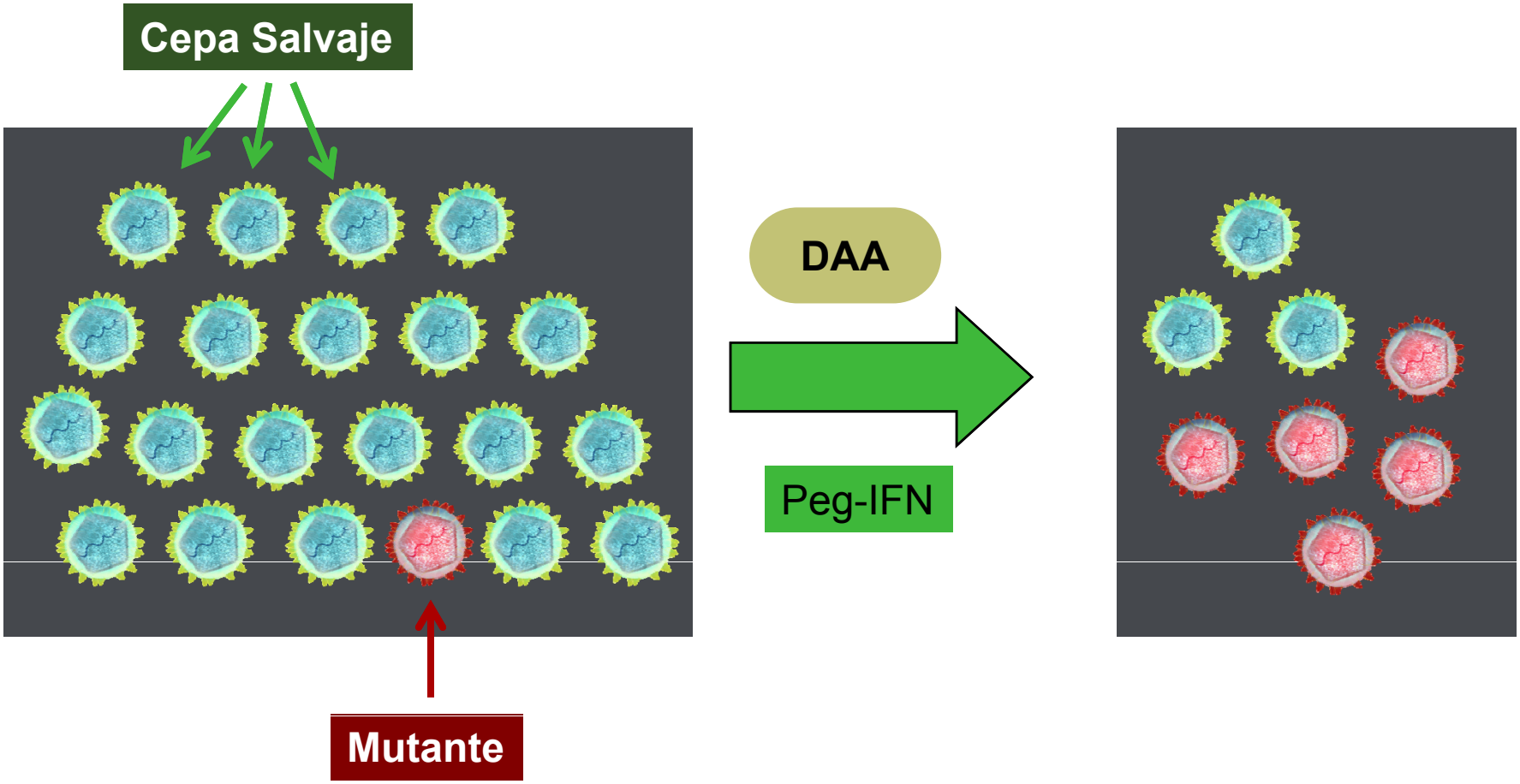
Breakthrough Group (n = 12)



EOD = end of dosing.

Sarrazin C, et al. *Gastroenterology.* 2007;132(5):1767. Courtesy of T. Kieffer, MD.

Añadir IFN al régimen de tratamiento reduce la probabilidad de desarrollar resistencias



Los nuevos AAD se han autorizado por la EMA después de una evaluación por procedimiento acelerado

NECESIDAD [1]

- *"Hepatitis C virus (HCV) is the **most common** infectious cause of chronic liver disease"*
- *"HCV is the most common **cause of liver transplantation** in Europe"*
- *"the **public health gain with telaprevir** therapy is likely considerable, and this benefit also applies to many of the individuals that will be **cured by telaprevir**"*

NOVEDAD [1]

- *"the addition of telaprevir to regimens with peginterferon alfa and ribavirin represents a **major advance** in the treatment of the genotype 1"*
- *"this greatly **increased efficacy and shortened treatment duration** represents a very **substantial improvement** in therapy for HCV genotype 1"*

EVALUACIÓN ACELERADA

*"En el caso de medicamentos de uso humano que tengan un **interés importante desde el punto de vista de la salud pública** y, en particular, desde el punto de vista de la **innovación terapéutica**, el solicitante podrá pedir, en el momento de presentar la solicitud de autorización de comercialización, la aplicación de un **procedimiento acelerado de evaluación**."* (Artículo 14.9. Reglamento (CE) No 726/200)

En los últimos 3 años **tan solo 4 productos** han sido evaluados por la EMA a través de un procedimiento acelerado

INCIVO®
telaprevir
Hepatitis C
Janssen

ZYTIGA®
abiraterona
Cáncer de próstata
Janssen

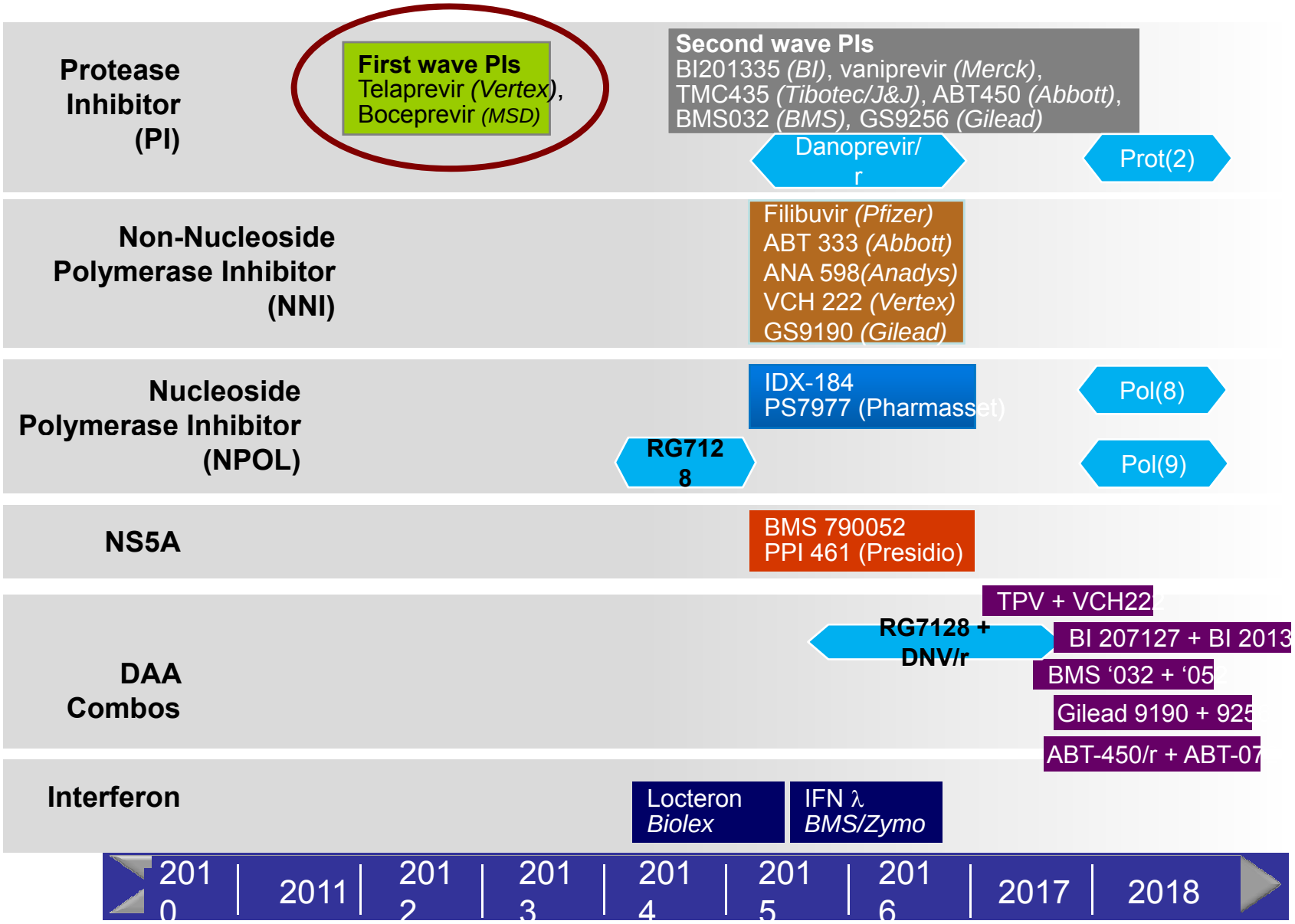
VPRIV®
velaglucerasa alfa
Enfermedad Gaucher [H]
Shire Pharmaceuticals

VICTRELIS®
boceprevir
Hepatitis C
Merck Sharp & Dome

2009 2010 2011

[1] CHMP Assessment Report EMA/CHMP/475470/2011

Select DAAs in Clinical Development



Los AADs representan una nuevo tiempo en el tratamiento de la hepatitis crónica C

RVS de hasta 79% en pacientes naïve

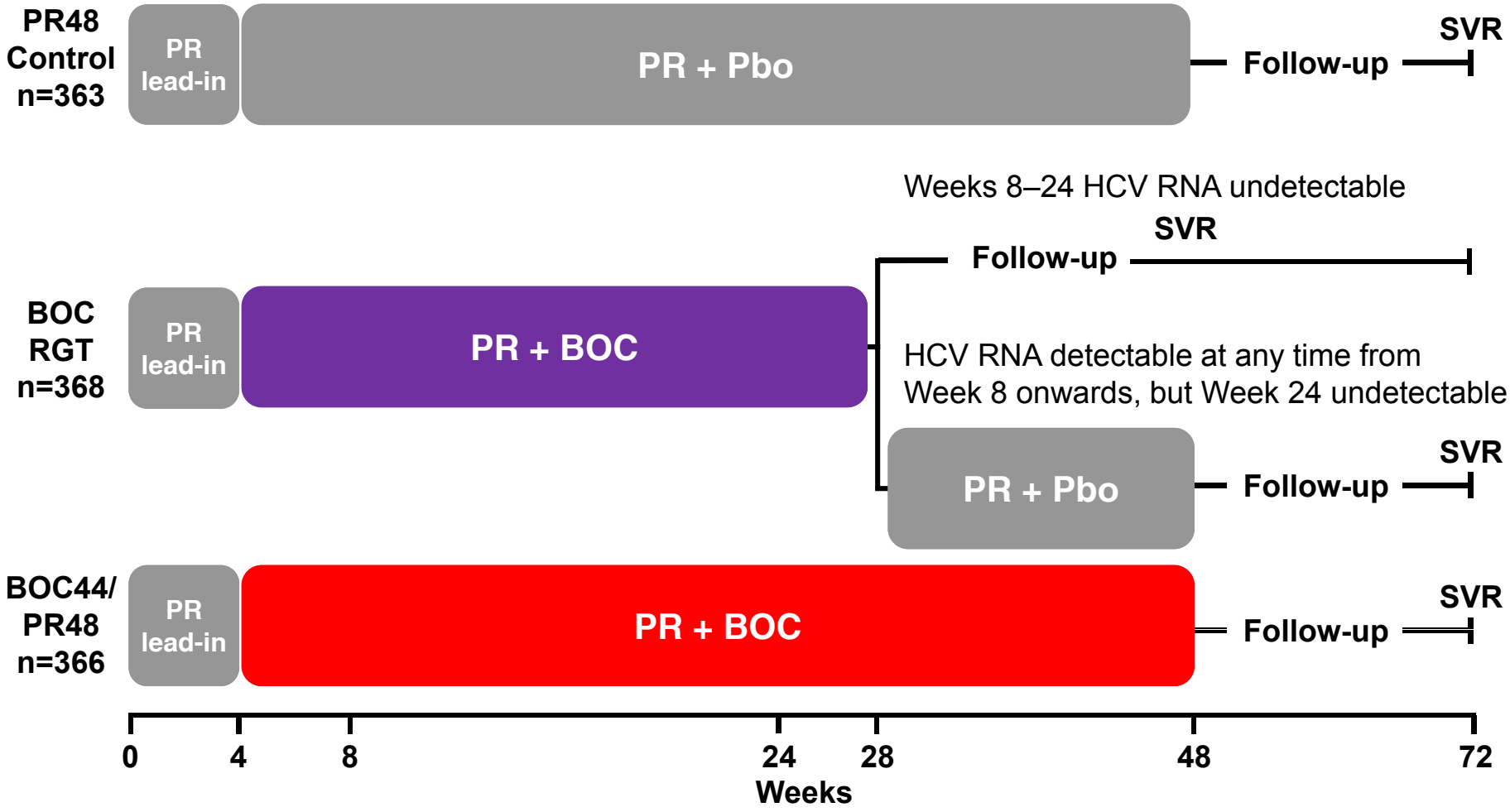
Reducción de la duración del tratamiento en la mayoría de los pacientes

Consideraciones en el manejo práctico

- ¿ Como hemos llegado hasta aquí?
- ¿ Cual es la situación actual?
- ¿ Que nos espera en un futuro?

Resultados del tratamiento triple en pacientes “naïve”

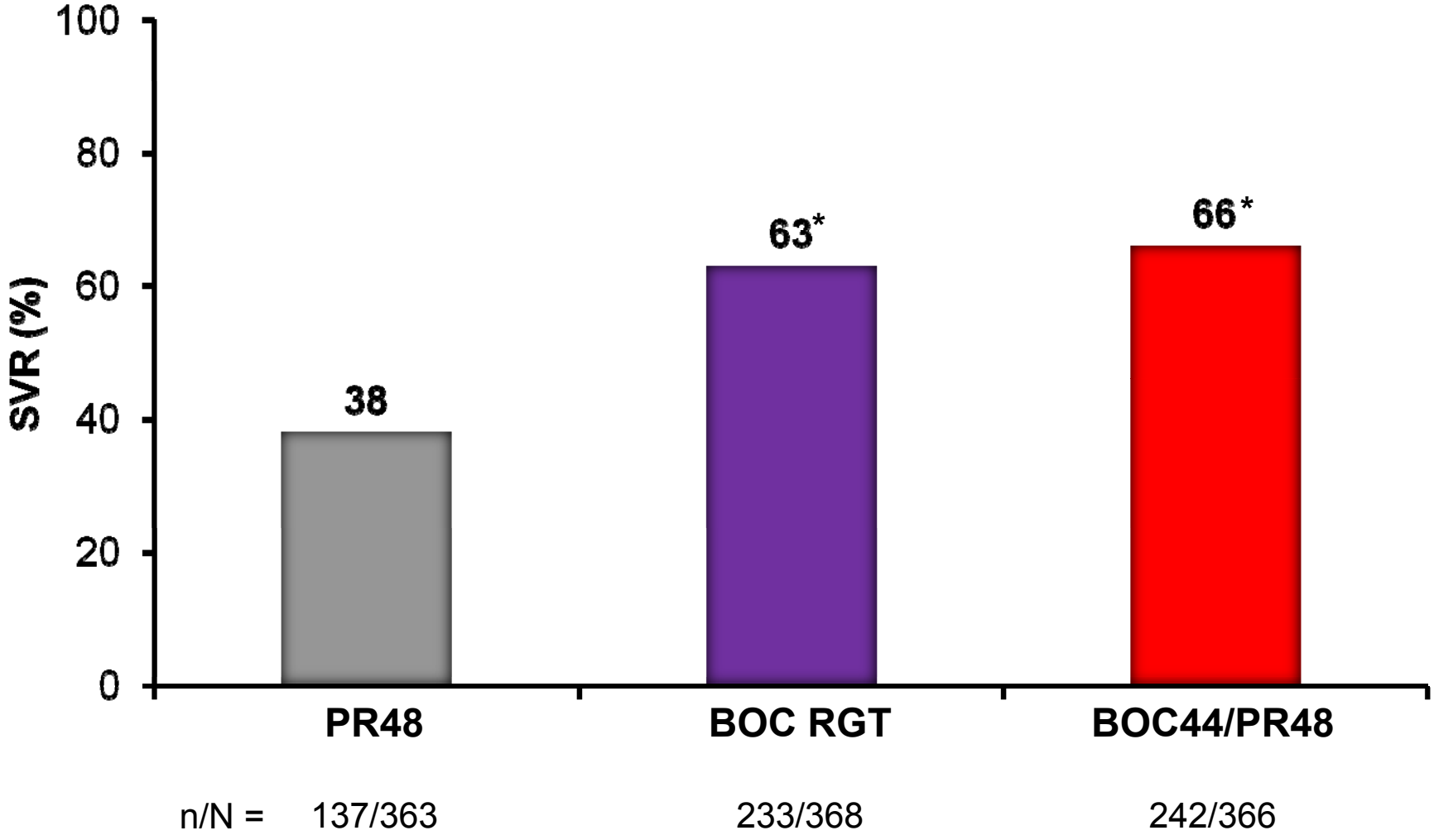
SPRINT-2 (boceprevir): study design (N=1097)



Peg-IFN alfa-2b dose: 1.5 µg/kg/week
RBV dose: 600–1400 mg/day in a divided daily dose

Poordad F, et al. N Engl J Med 2011;364:1195–206

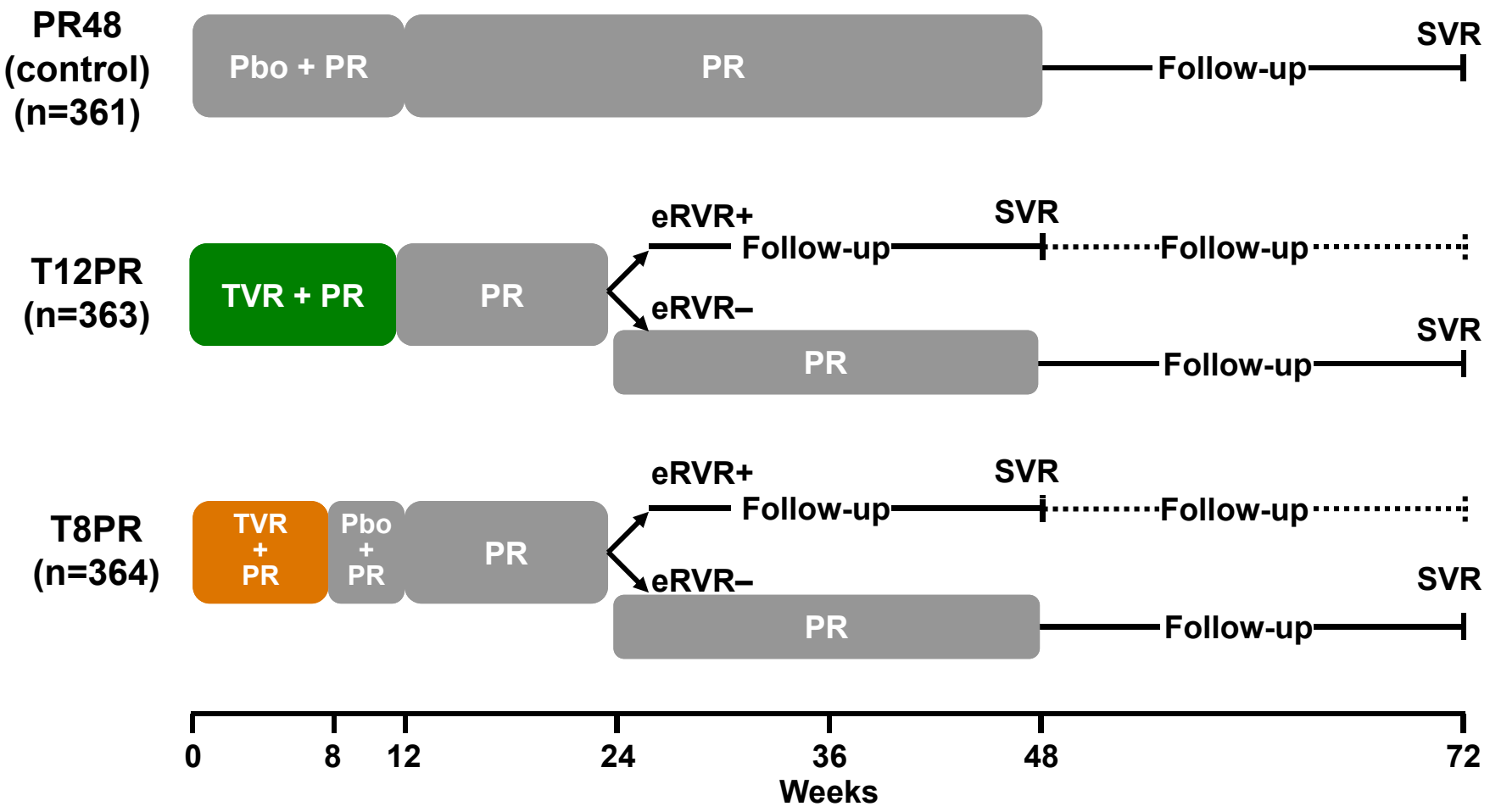
SPRINT-2: SVR rates with boceprevir-based therapy versus PR alone



*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

VICTRELIS (boceprevir) EU SmPC

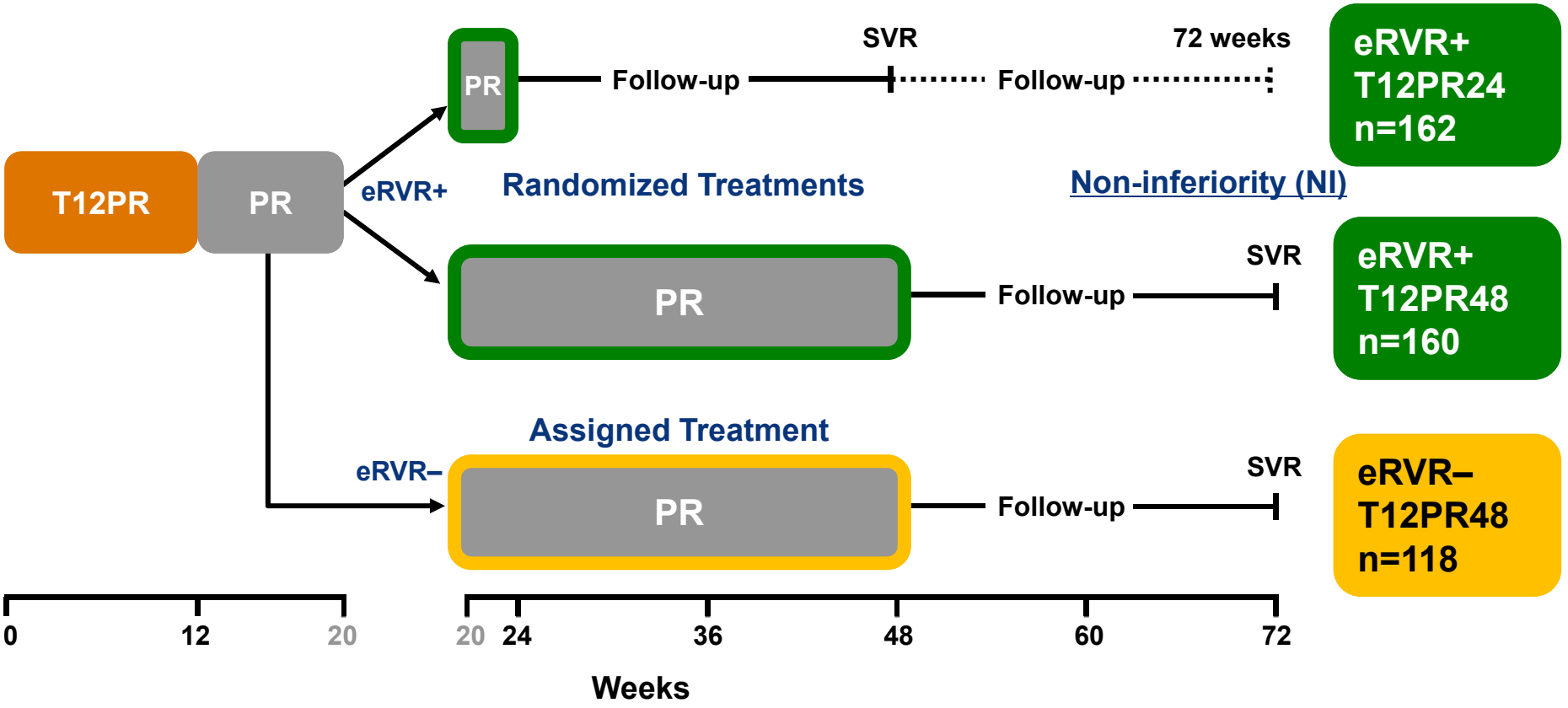
ADVANCE (telaprevir): study design (N=1088)



TVR dose: 750mg every 8 hours; Peg-IFN alfa-2a dose: 180 µg/week; RBV dose: 1000 or 1200 mg/day
eRVR: undetectable HCV RNA at Week 4 and 12

Jacobson IM, et al. N Engl J Med 2011;364:2405–16

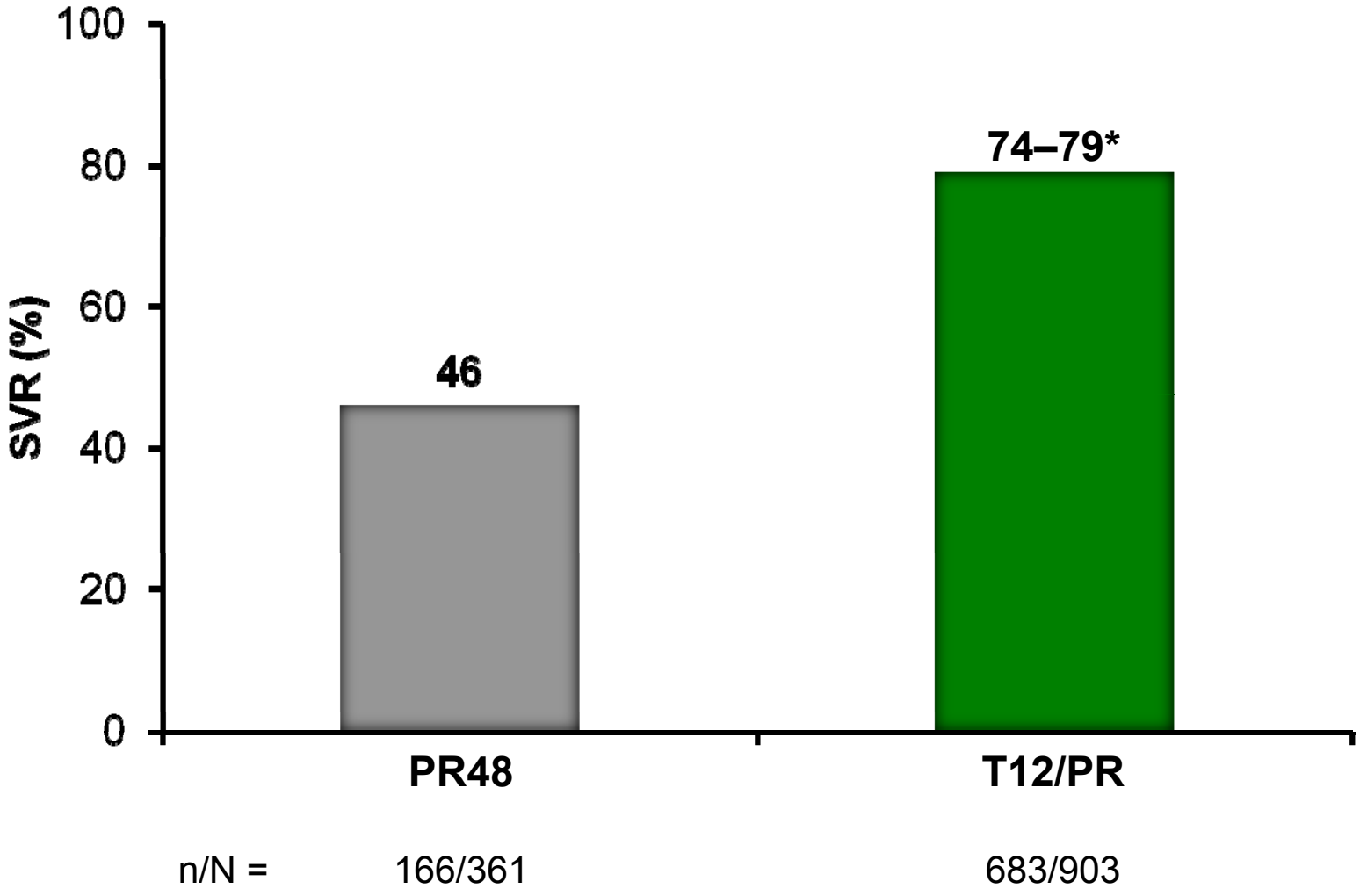
ILLUMINATE (telaprevir): study design (N=540)



TVR dose: 750mg every 8 hours; Peg-IFN alfa-2a dose: 180 µg/week; RBV dose: 1000 or 1200 mg/day
Patients discontinued for any reason before Week 20 randomization were categorized as 'Other' (N=100)
eRVR: undetectable HCV RNA at Week 4 and 12

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

ADVANCE and ILLUMINATE: SVR rates with telaprevir-based therapy versus PR alone

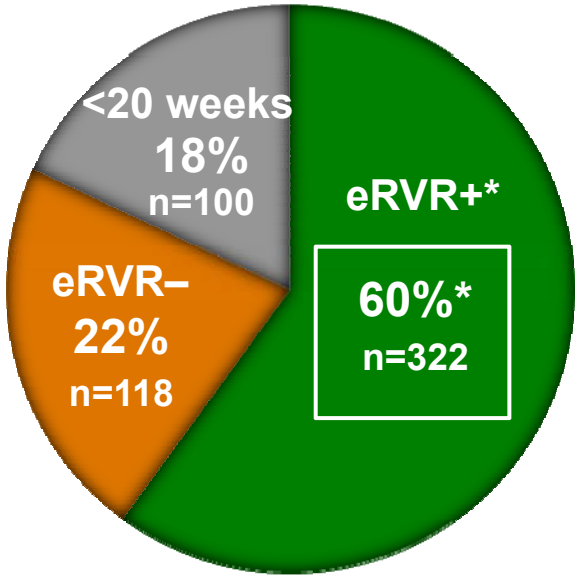


*p<0.0001 T12/PR vs PR48 (79% versus 46%) in ADVANCE
SVR, considered virologic cure, was defined as HCV RNA <25 IU/mL at last observation within the Week 72 visit window.
In case of missing data, the last HCV RNA data point from Week 12 of follow-up onwards was used

INCIVO (telaprevir) EU SmPC

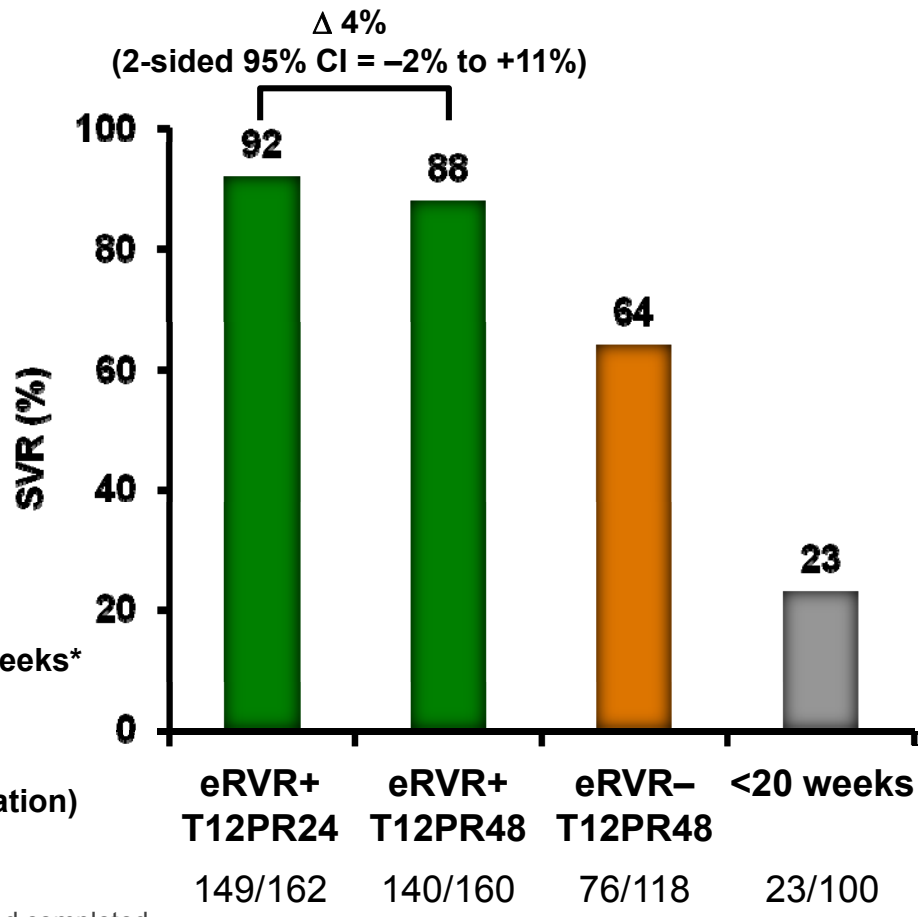
ILLUMINATE (telaprevir): SVR rates by treatment duration in patients treated with T12PR (N=540)

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)

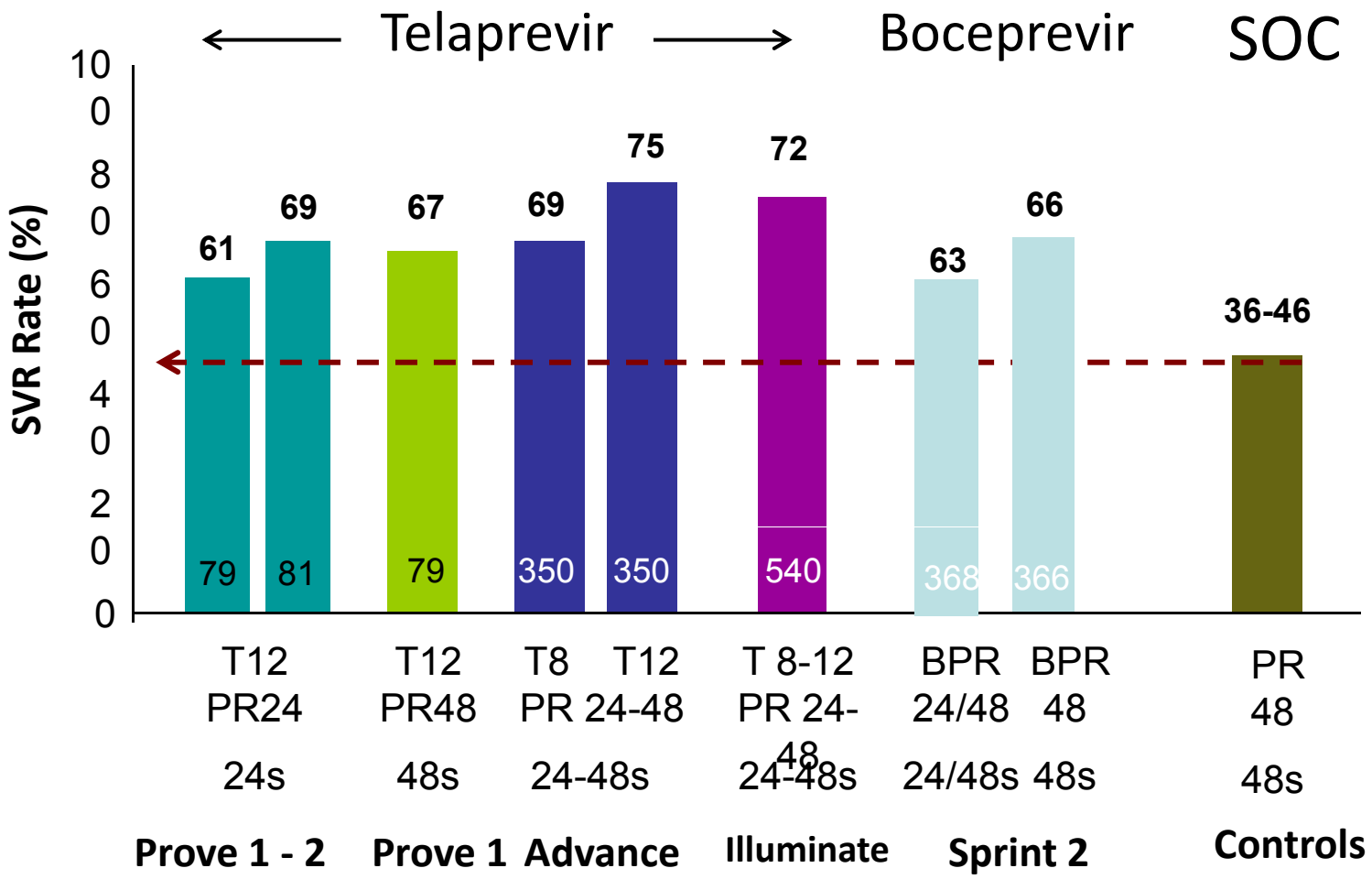
SVR rate



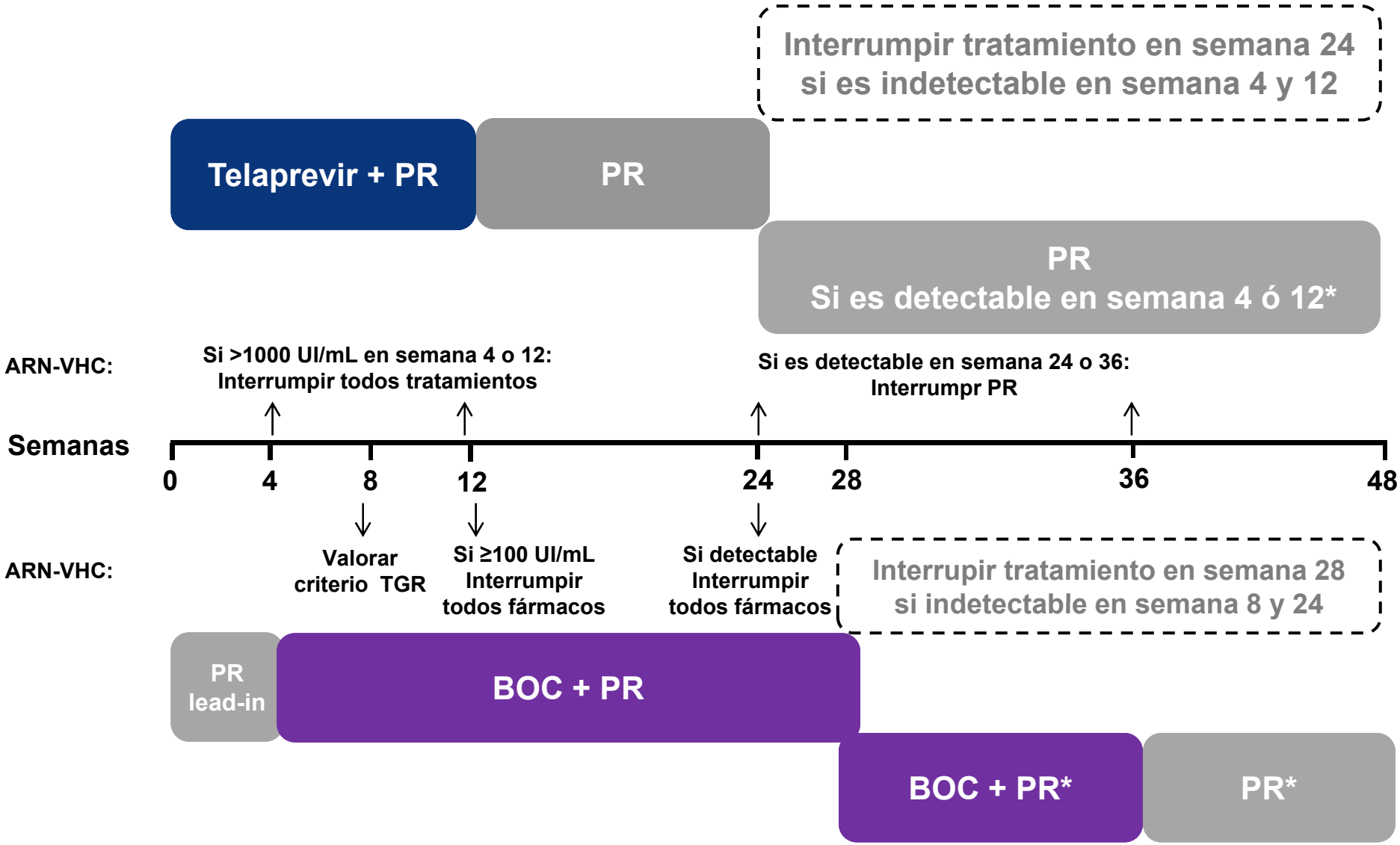
*Patients who achieved eRVR (undetectable HCV RNA at Weeks 4 and 12) and completed the Week 20 visit were randomized to receive an additional 4 or 28 weeks of PR alone
65% of patients achieved an eRVR (352/540); 322/352 were randomized and 30/352 patients discontinued before randomization at Week 20

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

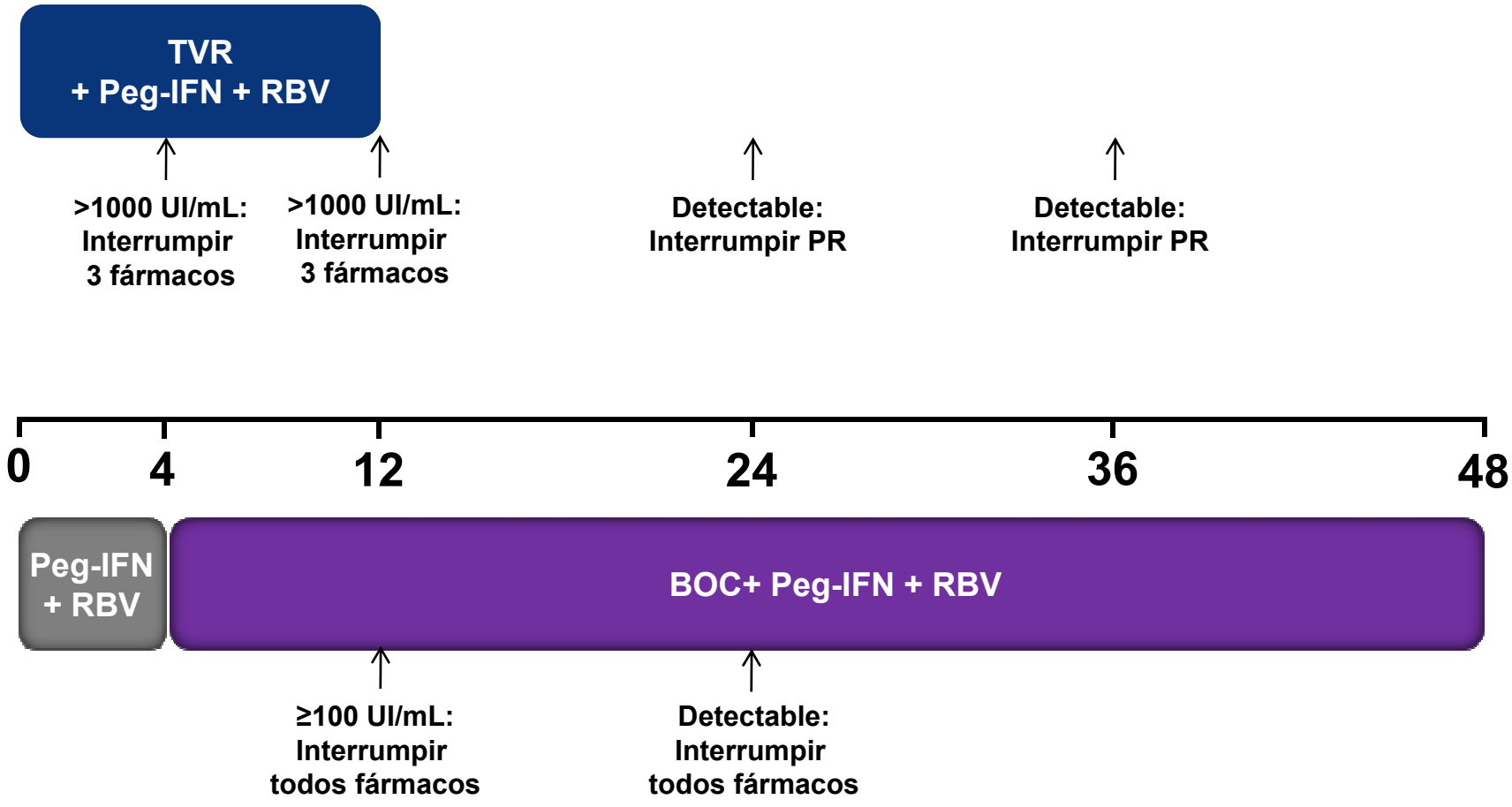
Treatment results in G1 hepatitis C naïve patients



Esquema tratamiento en pacientes VHC G1: pacientes naive sin cirrosis



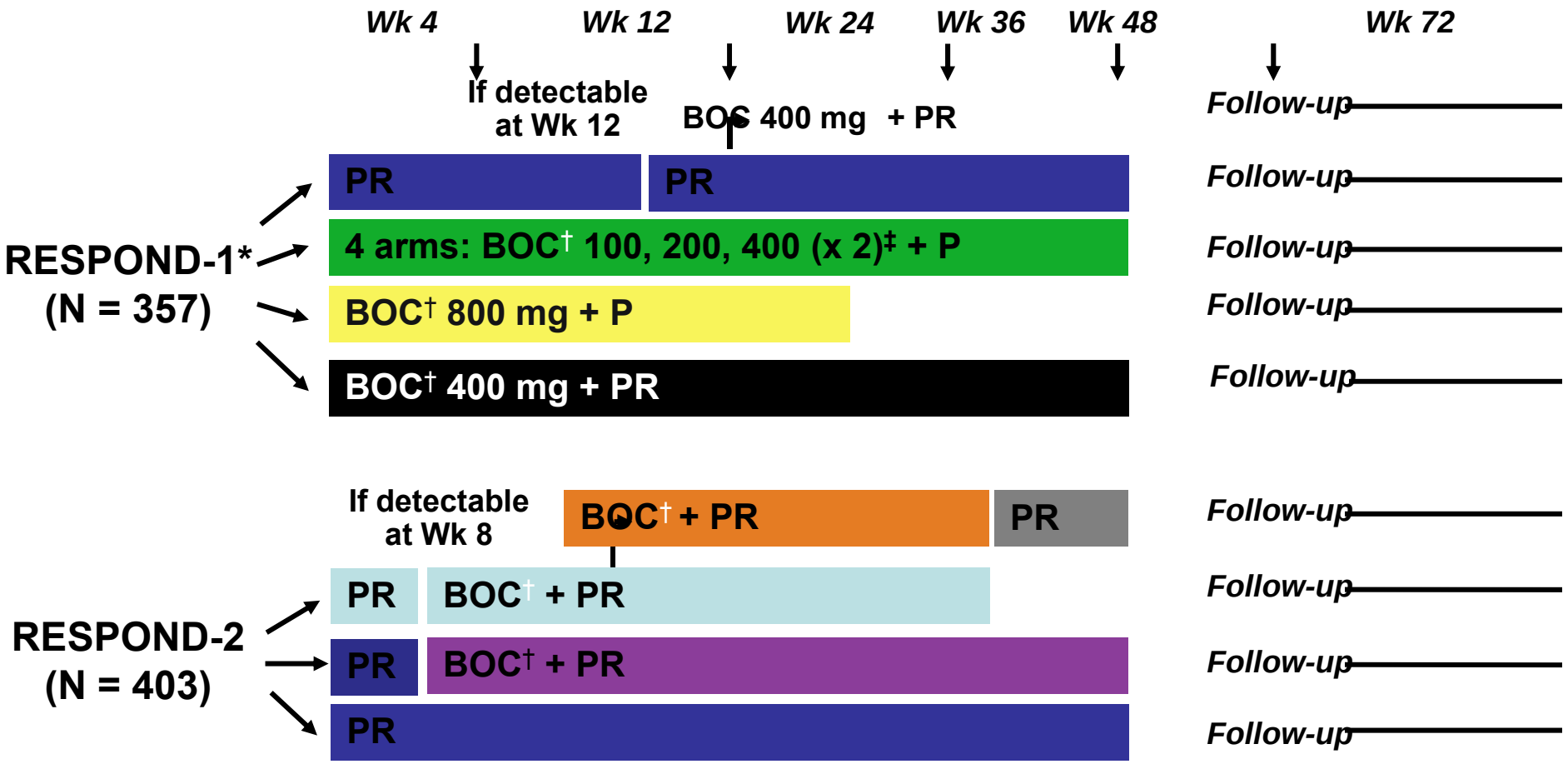
Esquema de tratamiento en pacientes con cirrosis compensada



Telaprevir EU SmPC; Boceprevir EU SmPC

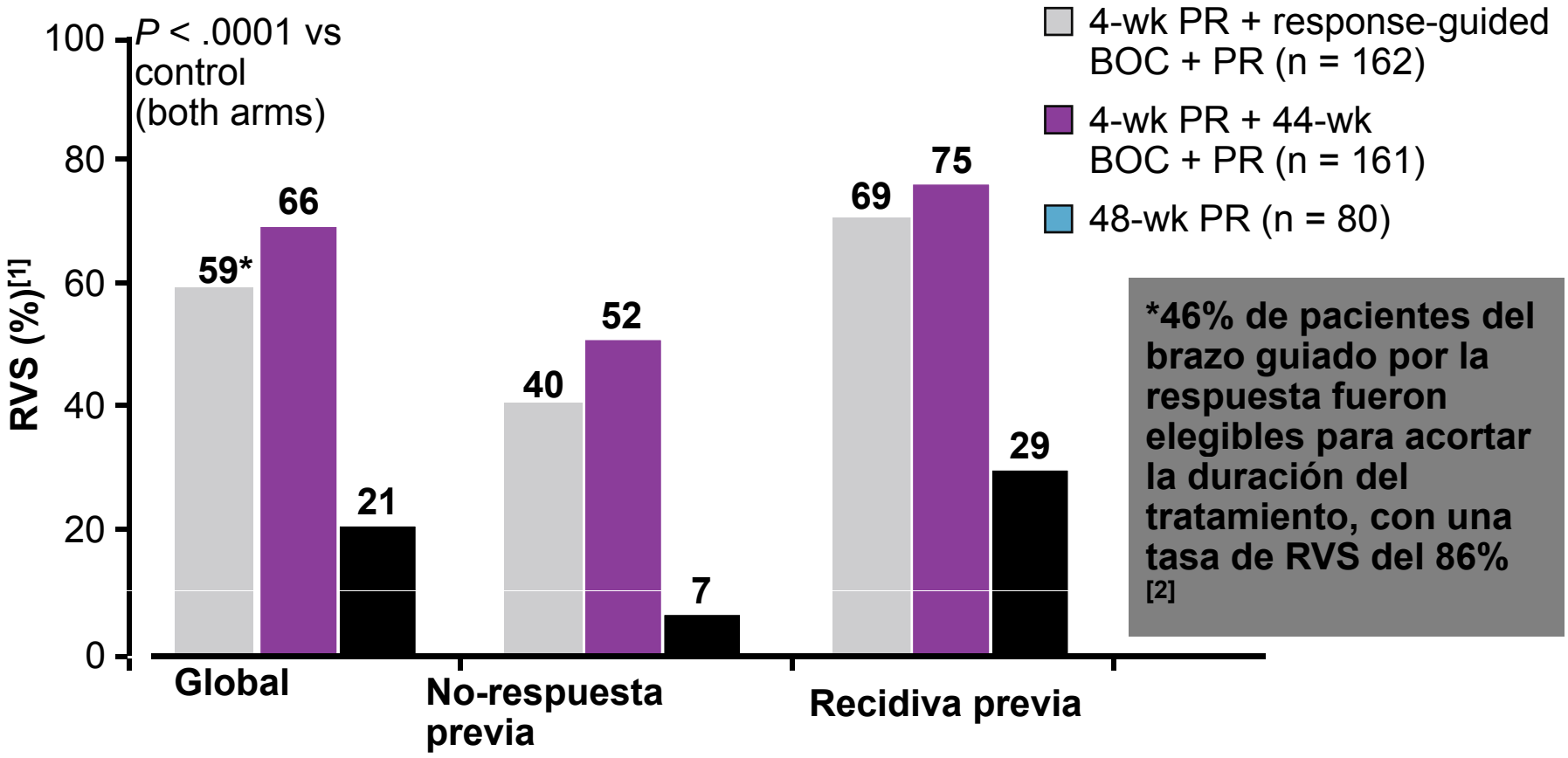
Resultados del tratamiento triple en pacientes con fallo a un tratamiento previo

Boceprevir: Estudios Clínicos en Pacientes con Fallo a PegIFN/RBV



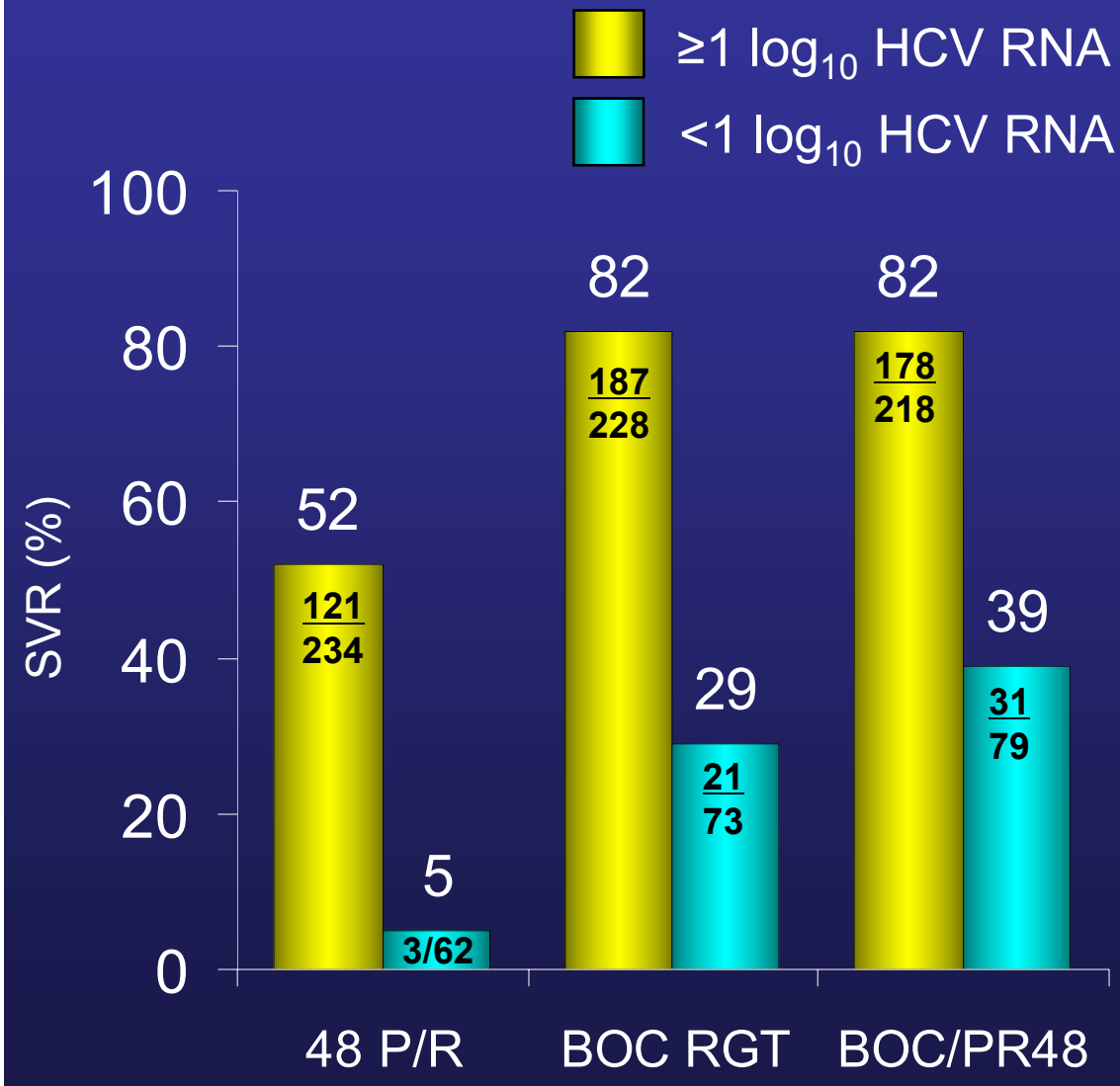
*All patients switched to BOC 800 mg + P/R at Wk 24 upon DSMB review.
†TID dosing. ‡One of the 400-mg arms was nonrandomized.

RESPOND-2: RVS según tipo de Respuesta al Tratamiento Previo



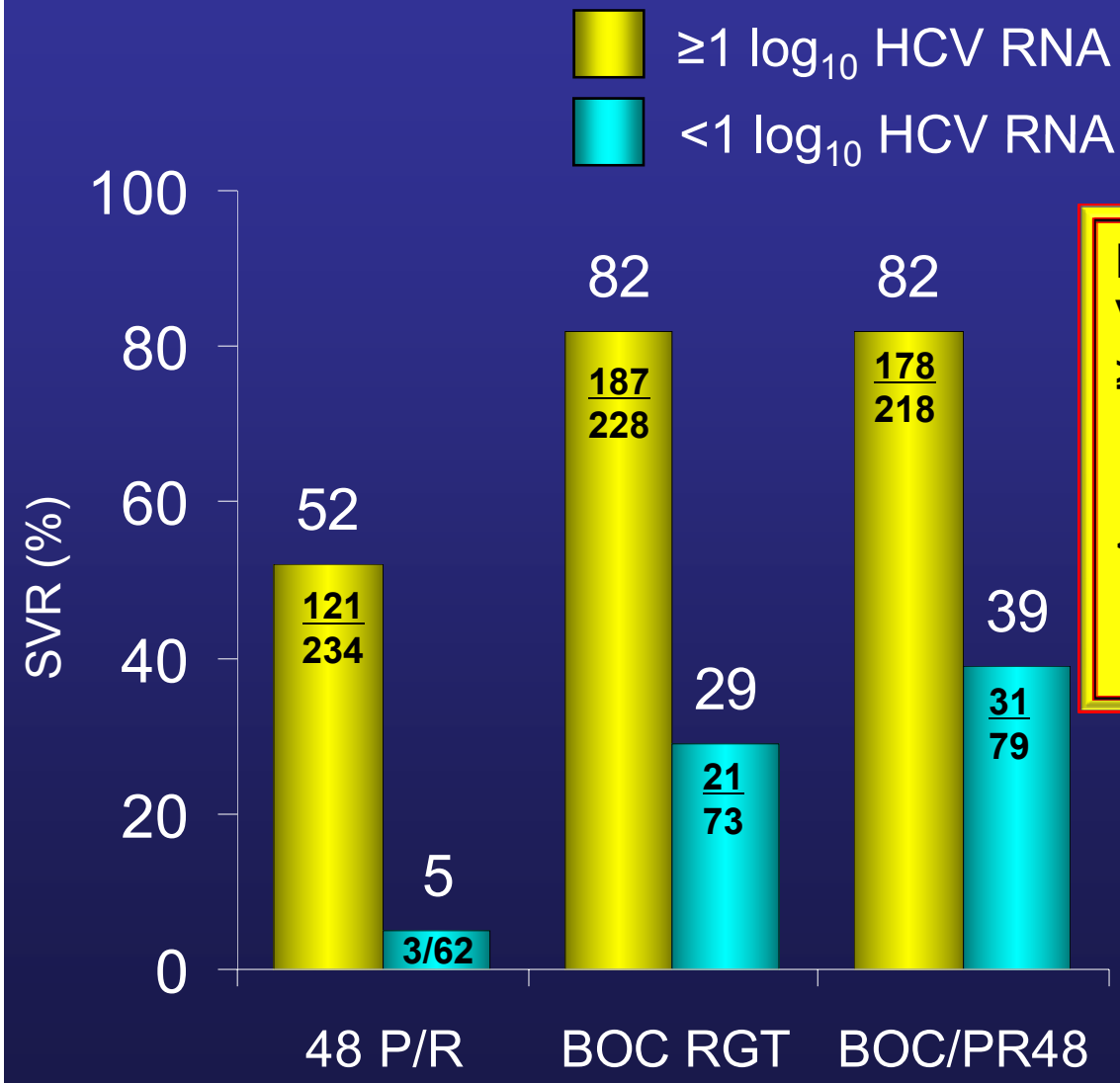
Bacon BR, et al. NEJM 2011

SVR Based on Week 4 PR Lead-In in Non-Black Patients



* Boceprevir resistance-associated variants determined with population sequencing

SVR Based on Week 4 PR Lead-In in Non-Black Patients



Boceprevir Resistance-associated Variants*:

≥ 1 $\log_{10}$ decline:

BOC RGT: 4% (9/232)

BOC/PR48: 4% (9/231)

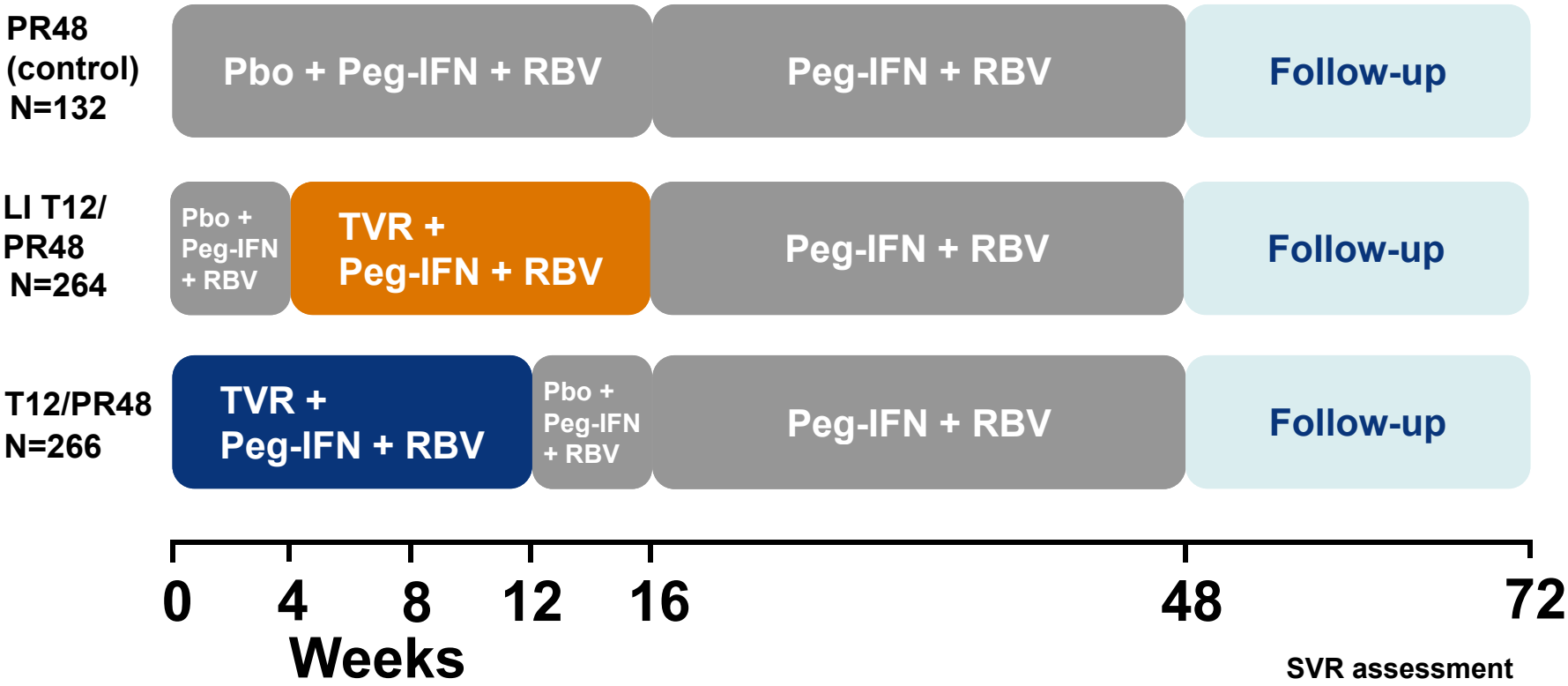
< 1 $\log_{10}$ decline:

BOC RGT: 47% (45/95)

BOC/PR48: 35% (33/94)

* Boceprevir resistance-associated variants determined with population sequencing

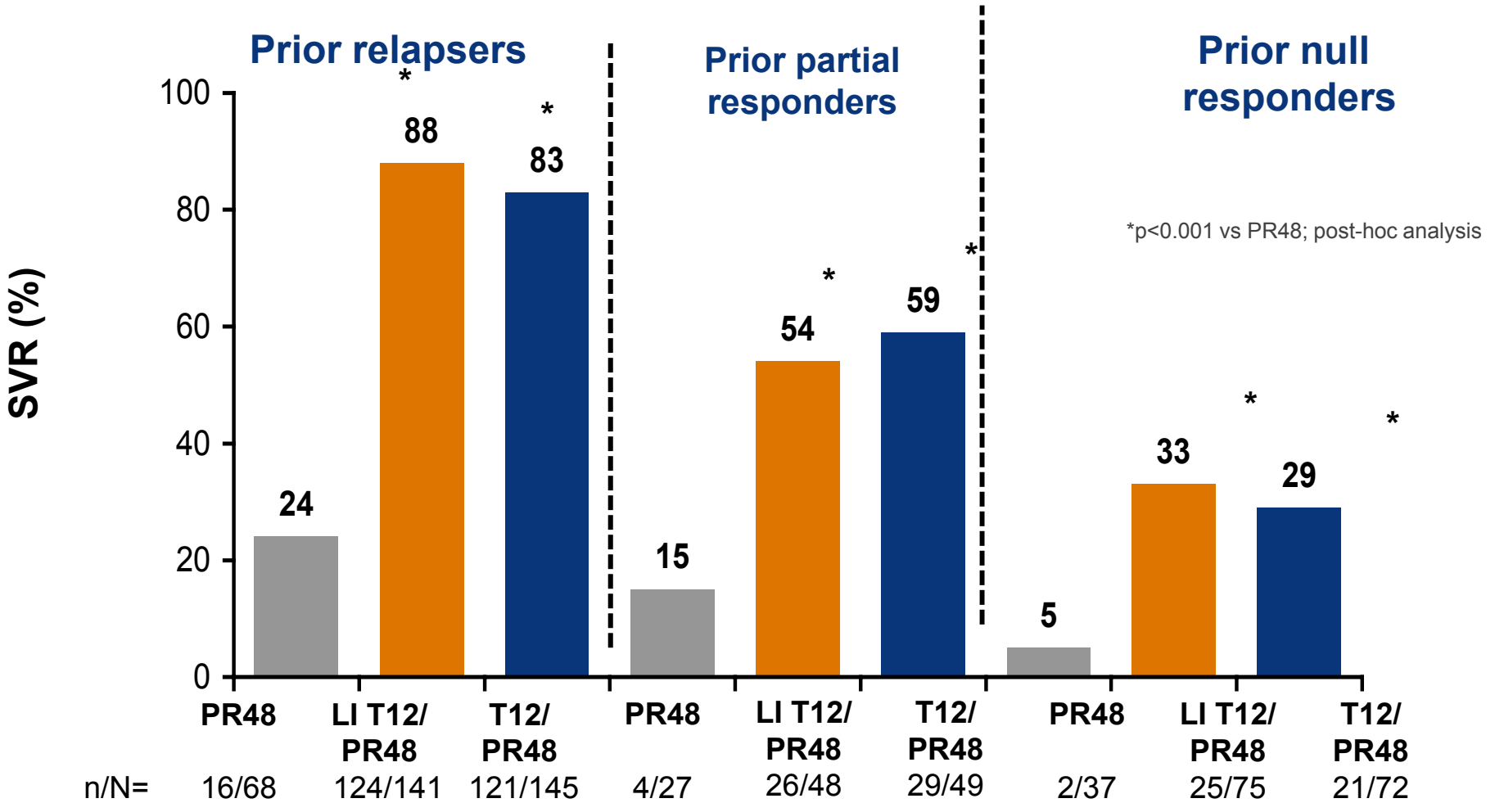
REALIZE (telaprevir): study design (N=662)



LI: lead-in; Pbo: placebo; TVR: telaprevir
Randomization was stratified by viral load and prior response category
Stopping rules applied for telaprevir (Weeks 4, 6, and 8) and Peg-IFN/RBV (Weeks 12, 24, and 36)
Peg-IFN alfa-2a = 180µg/week subcutaneously; RBV = 1000–1200mg/day
TVR = 750mg every 8 hours

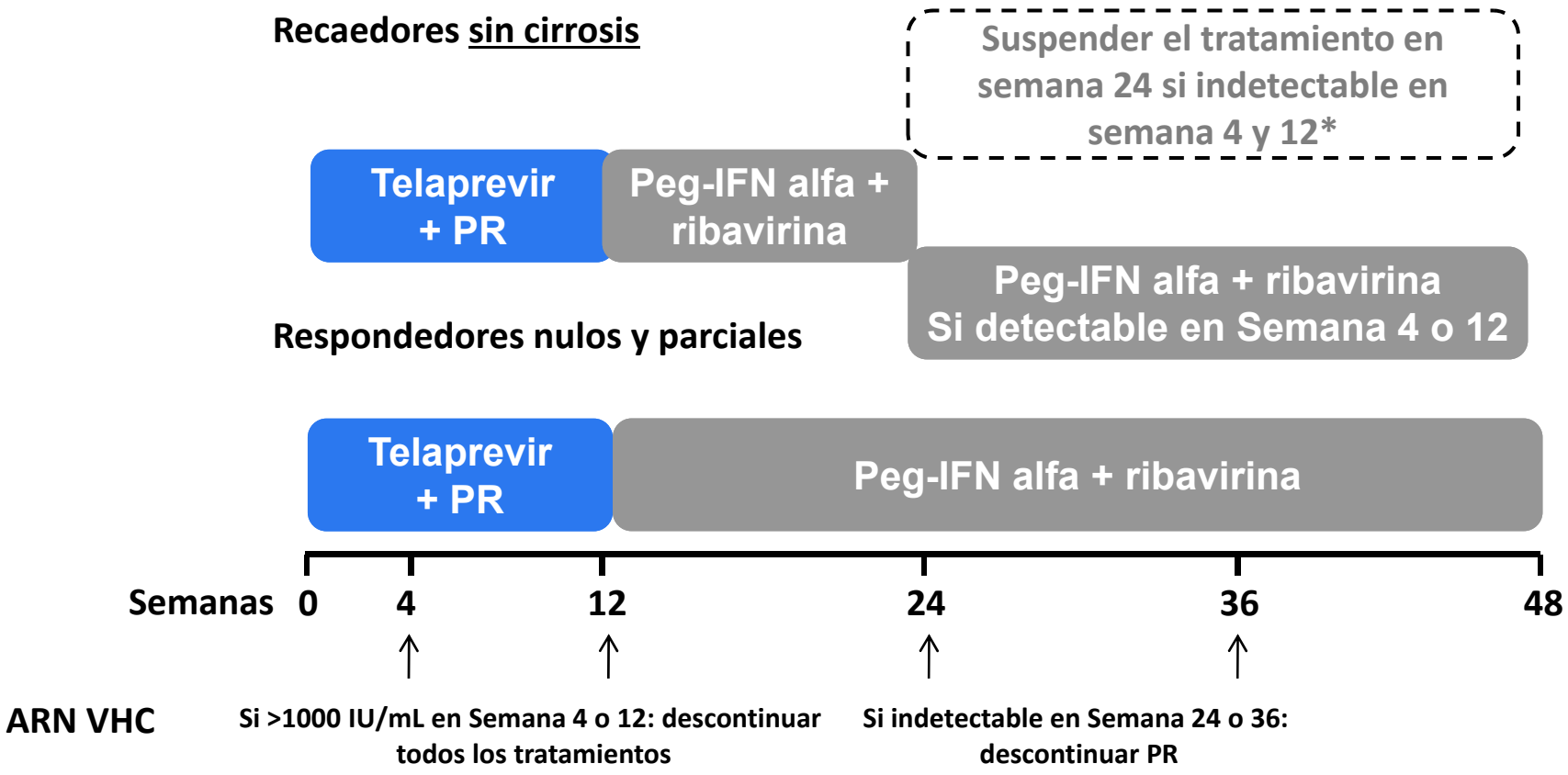
Foster GR, et al. Hepatol Int 2011;5(Suppl. 1):14

REALIZE (telaprevir): SVR in prior relapsers, partial responders and null responders



Foster GR, et al. Hepatol Int 2011;5(Suppl. 1):14

Régimen de Telaprevir en pacientes VHC genotipo 1: pacientes con fracaso al tratamiento previo



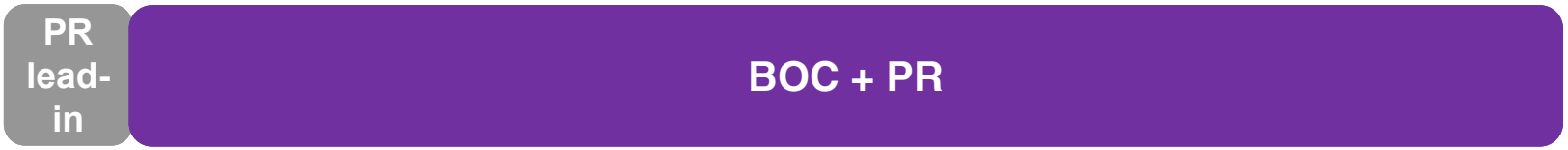
*In Phase III studies, a sensitive real-time PCR assay with a limit of quantification of 25 IU/mL and a limit of detection of 10–15 IU/mL was used to determine whether HCV RNA levels were undetectable. Detectable HCV RNA below the lower limit of assay quantification should not be used as a substitute for 'undetectable' for making decisions on treatment duration, as this may lead to an insufficient duration of therapy and higher relapse rates. In prior null responders, consideration should be given to conducting an HCV RNA test between Weeks 4 and 12 and if HCV RNA >1000 IU/mL all drugs should be stopped

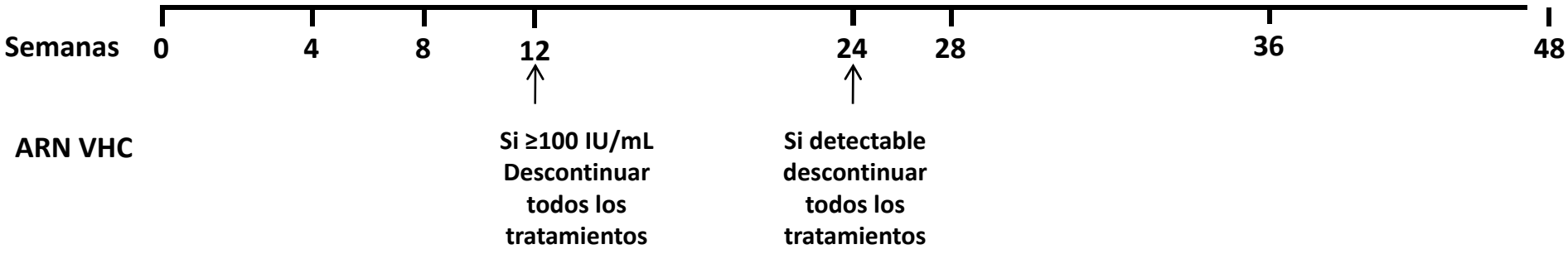
Telaprevir EU SmPC

Régimen de Boceprevir en pacientes VHC genotipo 1: pacientes con fracaso al tratamiento previo

Respondedores parciales y recaedores <u>sin cirrosis</u>

No respondedores





Boceprevir EU SmPC

Telaprevir Placebo-Controlled Phase 2/3 Studies: Summary of AEs during Telaprevir/Placebo Phase

% of patients	T12/PR (750 mg q8h) N=1346	Placebo/PR N=764	Leading to discontinuation of all study drugs*(%)
Skin and subcutaneous tissue disorders			
Pruritus (SSC)	51	26	0.6%
Rash (SSC)	55	33	1%
Gastrointestinal disorders			
Nausea	39	29	<0.5
Diarrhea	26	19	<0.5
Hemorrhoids	12	3	<0.5
Anorectal discomfort	8	2	<0.5
Anal pruritus	6	1	<0.5
Blood and lymphatic system disorders			
Anemia	29	12	0.8%

Other frequently reported AEs (preferred term) had a similar or lower incidence in the T12/PR than the placebo/PR groups, including (but not restricted to) neutropenia (8% versus 12% with control)

*Discontinuation of all study drugs in the T12/PR arms, not analyzed within SSC

SSC: special search category

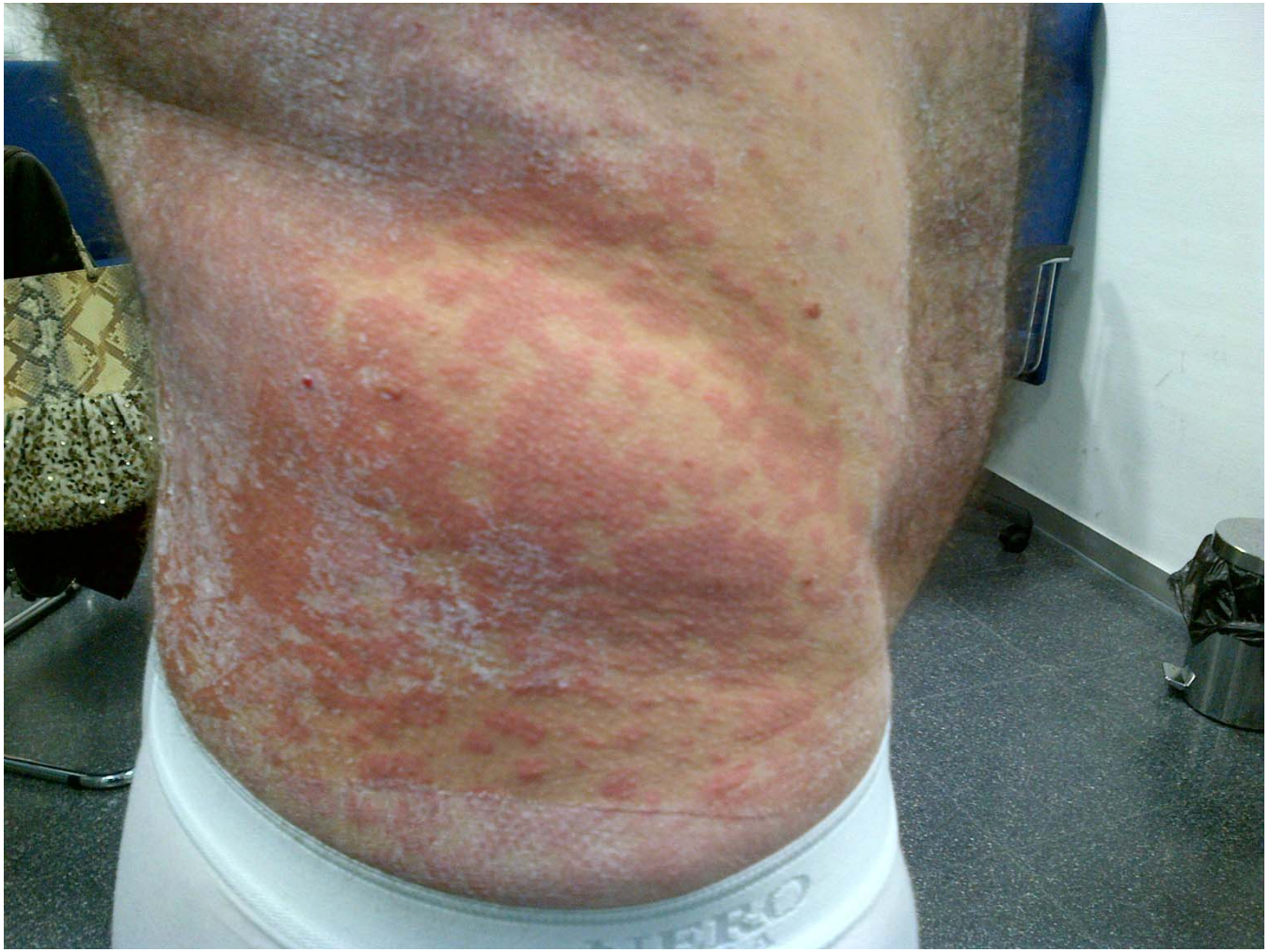
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/UCM252562.pdf

Boceprevir: Adverse Events and Discontinuations

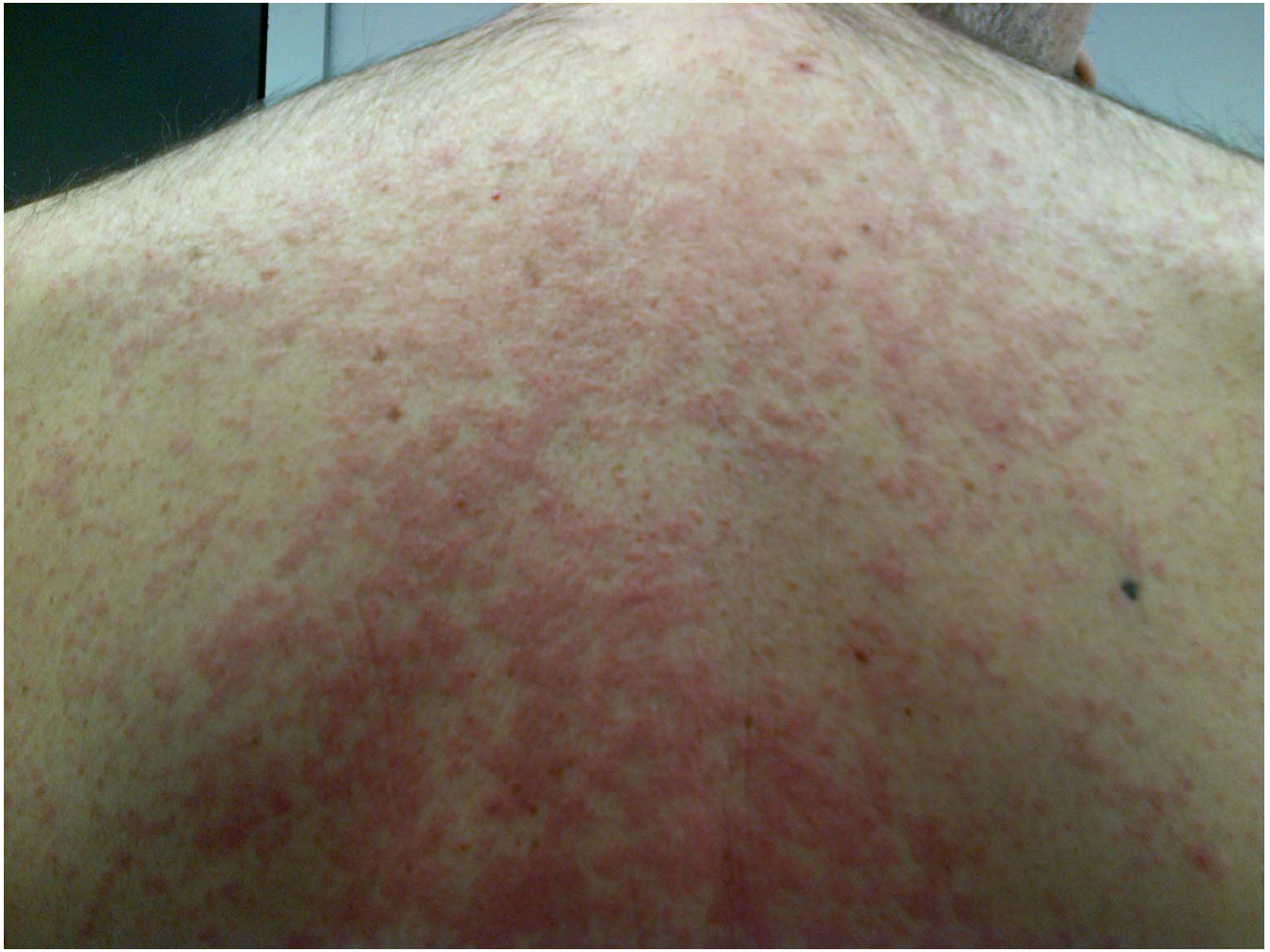
- Anemia and dysgeusia reported more frequently in BOC arms vs control in SPRINT-2[1-2]

Outcome	4-Wk PR + Response-Guided BOC/PR (n = 368)	4-Wk PR + 44-Wk BOC/PR (n = 366)	48-Wk PR (n = 363)
Adverse event, %			
▪ Anemia[1]	49	49	29
• EPO use	41	46	21
▪ Dysgeusia[2]	37	43	18
Discontinuations due to adverse events, %[1]	12	16	16
▪ Anemia[1]	2	2	1

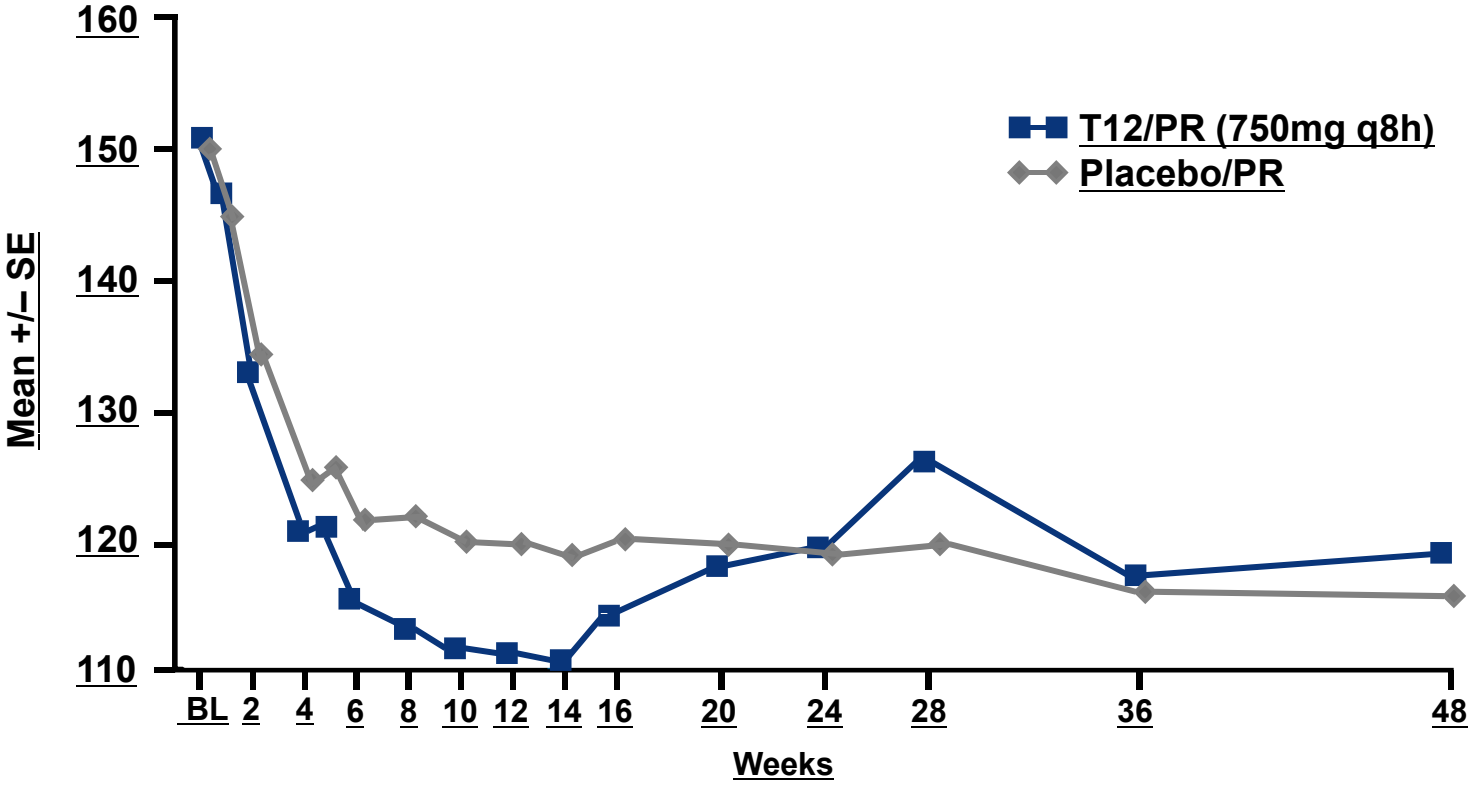
RASH T



RASH B



Hemoglobin Shifts on Telaprevir Treatment: Placebo-Controlled Phase 2 and 3 Studies



Number of patients

Week	BL	4	8	12	16	20	24	28	36	48
T12/PR (750mg q8h)	1345	1291	1248	1209	1074	1040	1016	498	544	525
Placebo/PR	764	742	721	677	625	584	565	459	399	379

http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/UCM252562.pdf

Anorectal Signs and Symptoms

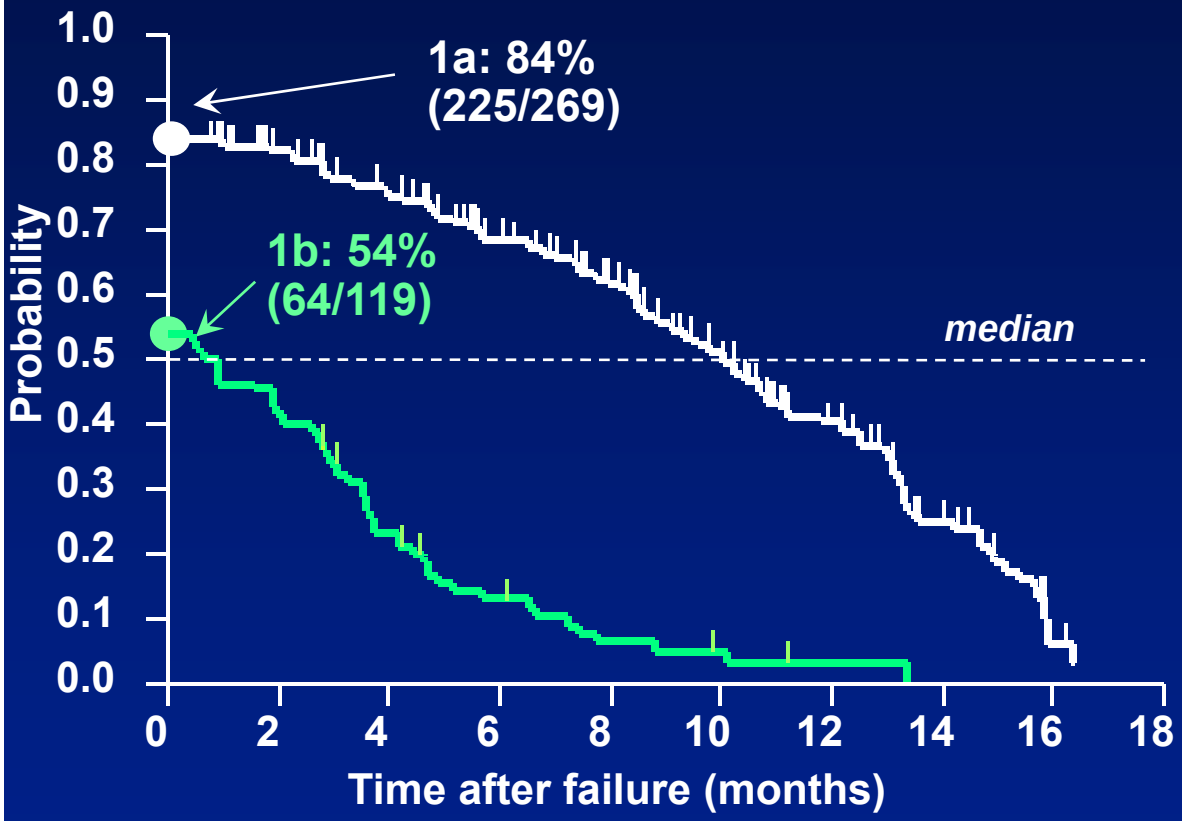
- First reported with telaprevir in PROVE1 as ‘hemorrhoids’
- Subsequently reported under various terms such as anal pruritus, anorectal discomfort as well as hemorrhoids
  - Onset is most commonly in the first 2 weeks of treatment
- Mechanism is unknown
  - Telaprevir is extensively metabolized and metabolites primarily excreted in the feces
  - No rectal findings in any of the toxicology studies
  - No evident association with either generalized pruritus or skin rash

Data on file

RESISTANCE

Triple Telaprevir + PEG/R

Population based sequencing, treatment failures, pooled Phase 3 studies



Probability of a patient being WT [3]

Time (months)	1a	1b
0	16%	46%
3	22%	66%
6	32%	87%
12	60%	98%
16	94%	100%

[3] Based on Kaplan-Meier estimation using population sequencing; hash marks in plot indicate censored observations

- **Frequency of resistant variants decline after the end of treatment**

Sullivan et al., EASL 2011

INTERACCIONES
Causantes de toxicidad de otros medicamentos (sustratos CYP3A4 y/o P gp)

- Telaprevir y Boceprevir incrementan x3 - x5 AUC Midazolam (sustrato CYP3A4)
- Telaprevir incrementa x8 AUC atorvastatina (CYP3A4 y Pgp): limitación dosis atorva, simvas, lovas….(sustituir x pravastatina)

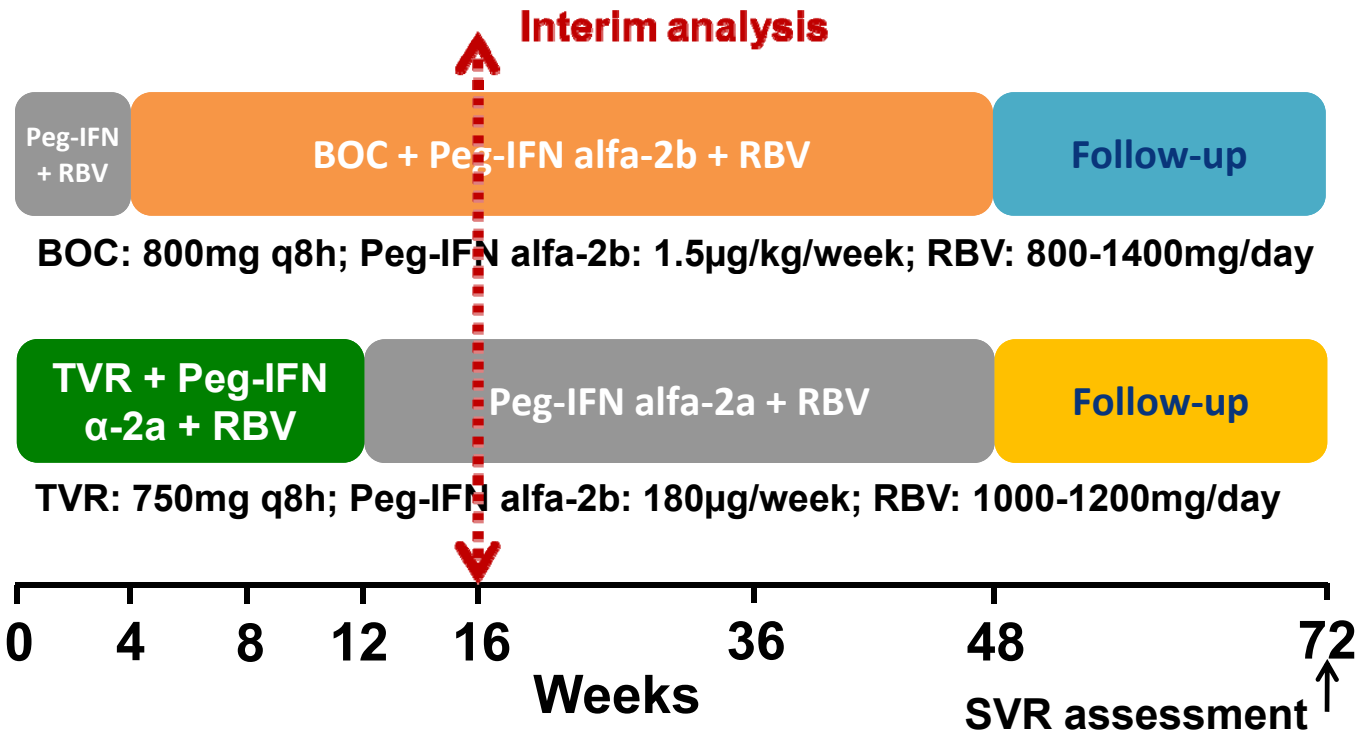
- ↑ ciclosporina, tacrolimus, sirolimus : monitorización
- ↑ Digoxina (Pgp)
- ↑ Colchicina (Pgp)
- ↑ Ergóticos
- ↑ Antiarrítmicos
- ↑ Macrolidos (CYP3A4) : QT
- ¿ Metadona ? (CYP3A4)
- ↑ Sildenafilo

CUPIC: patients

- HCV genotype 1 patients
- Compensated cirrhosis (Child Pugh A) genotype 1
- Non-responders
  - Relapsers
  - Partial responders ($\downarrow$ >2 $\log_{10}$ HCV RNA decline at Week 12)
  - Null responders theoretically excluded
- Treated in the French ATU

Hézode C, et al. HepDART 2011. Abstract 46

CUPIC: treatment regimen



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

Hézode C, et al. HepDART 2011. Abstract 46

CUPIC: TVR – patient characteristics

	Telaprevir n=176
Male, n (%)	127 (72)
Mean age, years	57.4
Median follow-up duration, days	112
Median telaprevir duration, days	85.0
Neutrophils, /mm^3	3100
Hemoglobin, g/dL	14.5
Platelets, /mm^3	150,000

Hézode C, et al. HepDART 2011. Abstract 46

CUPIC: TVR – patient characteristics

	Telaprevir n=176
Genotype 1b/1a, %	56 / 43
Mean baseline HCV RNA, log_{10} IU/mL	5.9
Prothrombin time, ratio	88%
Mean total bilirubin, µmol/L	15.5
Mean albumin, g/dL	39.5
Esophageal varices, %	19%
Previous treatment response, %	
Partial responders	40%
Relapsers	43%
Nulls responders	8%

Hézode C, et al. HepDART 2011. Abstract 46

CUPIC: TVR – preliminary safety findings

Patients, n (%)	Telaprevir (n=176)
Serious AEs	90 (51)*
Discontinuation due to serious AE	21 (12)
Death	3 (1.7)
Rash	
Grade 3	12 (6.8)
SCAR	0
Infection (Grade 3/4)	**8(4.5)**
Other AEs (Grade 3/4)	**84 (48)**
Anemia	
Grade 2 (8.0 – <10.0 g/dL)	58 (33)
Grade 3/4 (<8.0 g/dL)	23 (13)
EPO use	96 (55)
Transfusion	**32 (18)**
Neutropenia	
Grade 3 (500 – <1000/mm^3)	20 (11)
Grade 4 (<500/mm^3)	2 (1)
G-CSF use	5 (3)
Thrombopenia	
Grade 3 (25,000 – <50,000)	26 (15)
Grade 4 (<25,000)	12 (7)

*228 serious AEs in 90 patients; SCAR: severe cutaneous adverse reaction; EPO: erythropoetin; G-CSF: granulocyte-colony stimulating factor

Hézode C, et al. HepDART 2011. Abstract 46

CUPIC: BOC – patient characteristics

	Boceprevir n=134
Male, n (%)	95 (71)
Mean age, years	56.5
Median follow-up duration, days	115
Median boceprevir duration, days	84
Neutrophils, /mm^3	3200
Hemoglobin, g/dL	14.9
Platelets, /mm^3	140,000

Hézode C, et al. HepDART 2011. Abstract 46

CUPIC: BOC – preliminary safety findings

Patients, n (%)	Boceprevir (n=134)
Serious AEs	39 (29)*
Discontinuation due to serious AE	8 (6)
Death	1(1)
Rash	
Grade 3	0
SCAR	0
Infection (Grade 3/4)	2 (1,4)
Other AEs (Grade 3/4)	**41 (31)**
Anemia	
Grade 2 (8.0 – <10.0 g/dL)	41 (31)
Grade 3/4 (<8.0 g/dL)	8 (6)
EPO use	70 (52)
Transfusion	8 (6)
Neutropenia	
Grade 3 (500 – <1000/mm^3)	10 (7)
Grade 4 (<500/mm^3)	5 (4)
G-CSF use	7 (5)
Thrombopenia	
Grade 3 (25,000 – <50,000)	8 (6)
Grade 4 (<25,000)	3 (2)

*86 serious AEs in 39 patients; SCAR: severe cutaneous adverse reaction; EPO: erythropoetin; G-CSF: granulocyte-colony stimulating factor

Hézode C, et al. HepDART 2011. Abstract 46

Conclusions (1)

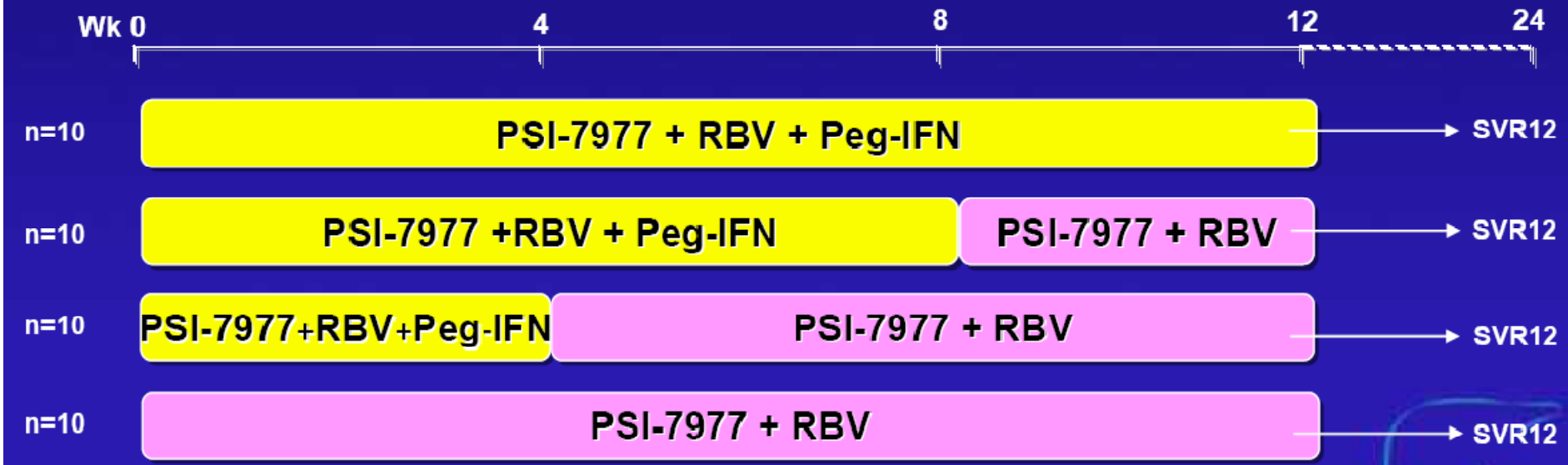
- The safety profile of DAAs among compensated cirrhotic patients treated in the CUPIC cohort is average, however, it is compatible with use in real-life practice
- High rate of SAEs (29–51%) and high rate of discontinuation due to severe AE (6–12%) compared with phase III trials results (9–14%)
- Based on preliminary results of the CUPIC cohort, patients with cirrhosis should be treated with caution and should be carefully monitored due to
  - High incidence of anemia with poor response to EPO

Hézode C, et al. HepDART 2011. Abstract 46

- ¿ Como hemos llegado hasta aquí?
- ¿ Cual es la situación actual?
- ¿ Que nos espera en un futuro?

PSI-7977 ELECTRON
Study Design for HCV GT2/3

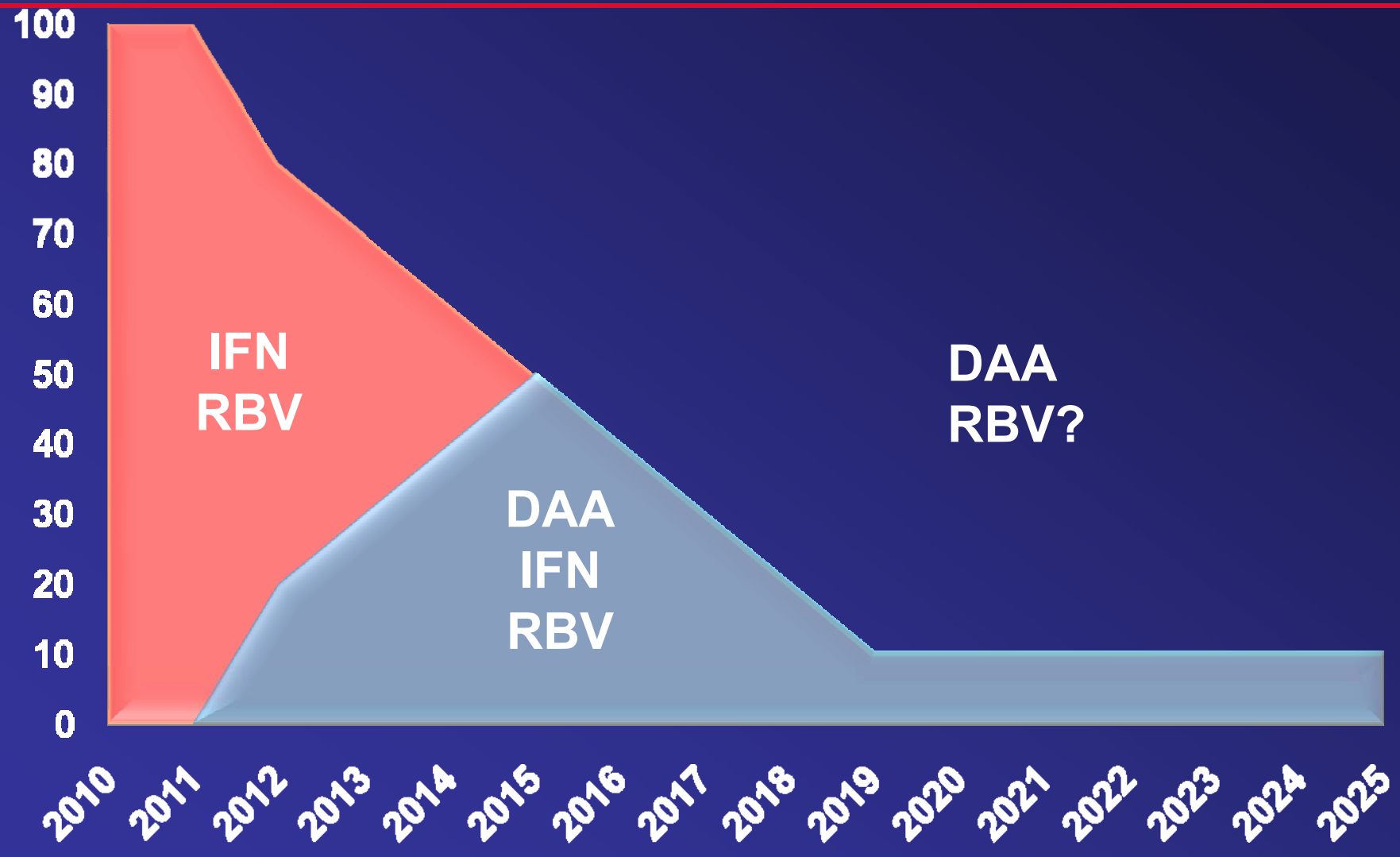
- Treatment-naïve, non-cirrhotic, age ≥18 years
- HCV RNA >50,000 IU/mL
- Allowed concurrent methadone use
- Stratified by HCV genotype and IL28B genotype
- Randomized 1:1:1:1 into IFN-sparing or IFN-free



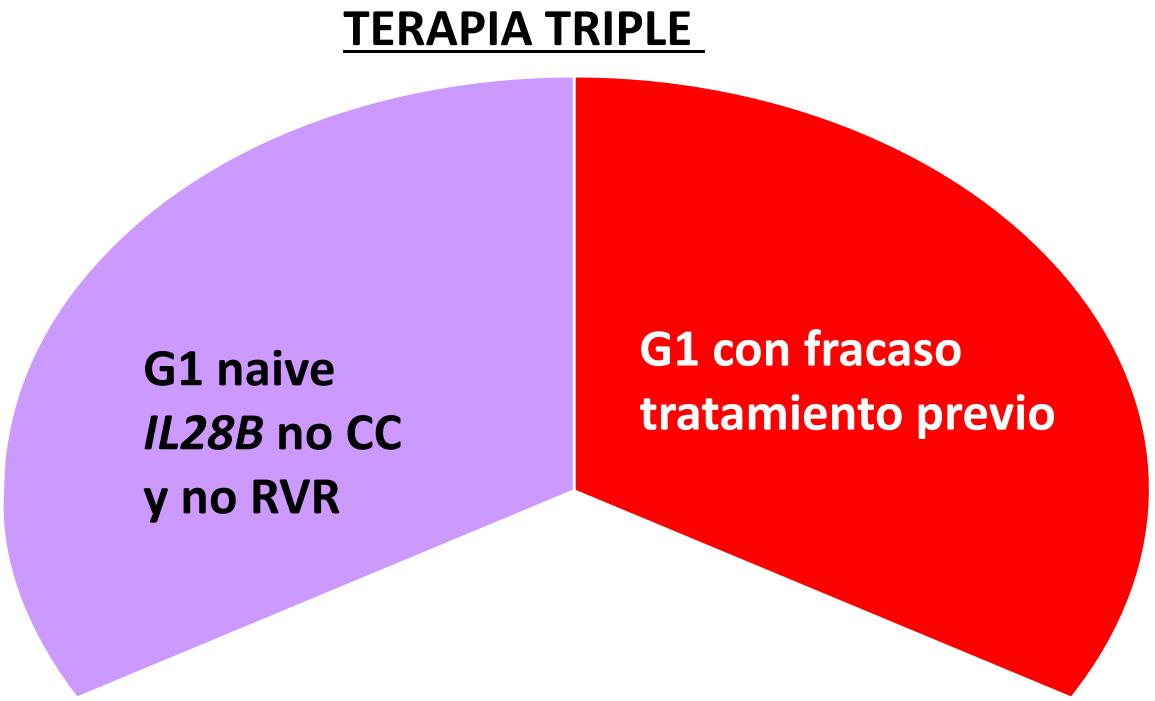
PSI-7977 ELECTRON
100% concordance of SVR12 with SVR24

Time wk	PSI-7977 RBV 12 weeks PEG		PSI-7977 RBV 8 weeks PEG		PSI-7977 RBV 4 weeks PEG		PSI-7977 RBV NO PEG	
	n	%<LOD	n	%<LOD	n	%<LOD	n	%<LOD
2	9/11	82	7/8	88	8/9	89	8/10	80
4	11/11	100	10/10	100	9/9	100	10/10	100
8	11/11	100	10/10	100	9/9	100	10/10	100
12	11/11	100	10/10	100	9/9	100	10/10	100
SVR4	11/11	100	10/10	100	9/9	100	10/10	100
SVR8	11/11	100	10/10	100	9/9	100	10/10	100
SVR12	11/11	100	10/10	100	9/9	100	10/10	100
SVR24	6/6	100	5/5	100	5/5	100	4/4	100

¿Podremos curar la hepatitis C sin IFN?

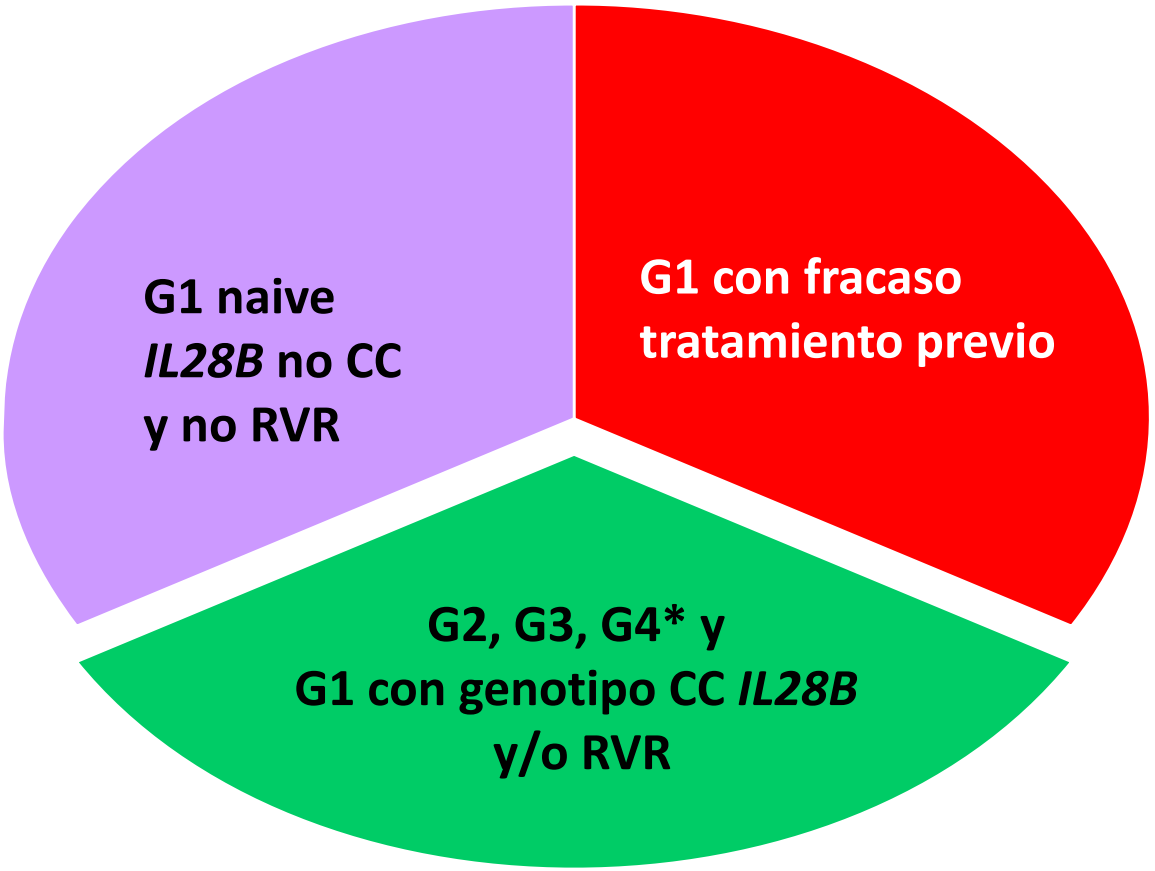


Posibles opciones terapéuticas para diferentes pacientes



Posibles opciones terapéuticas para diferentes pacientes

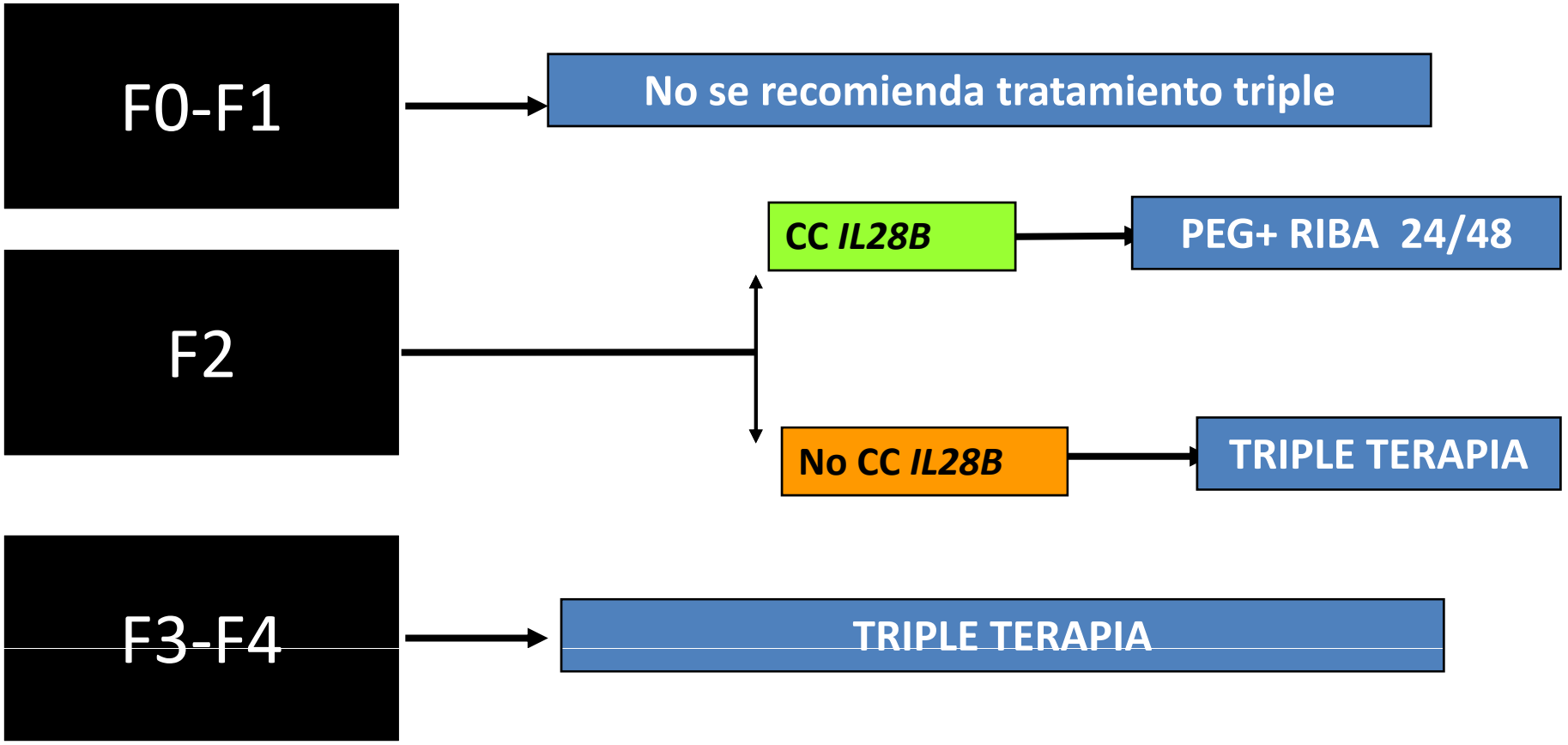
TERAPIA TRIPLE



TERAPIA DOBLE

*hasta disponibilidad AD activos frente G2, G3 y G4

Naives



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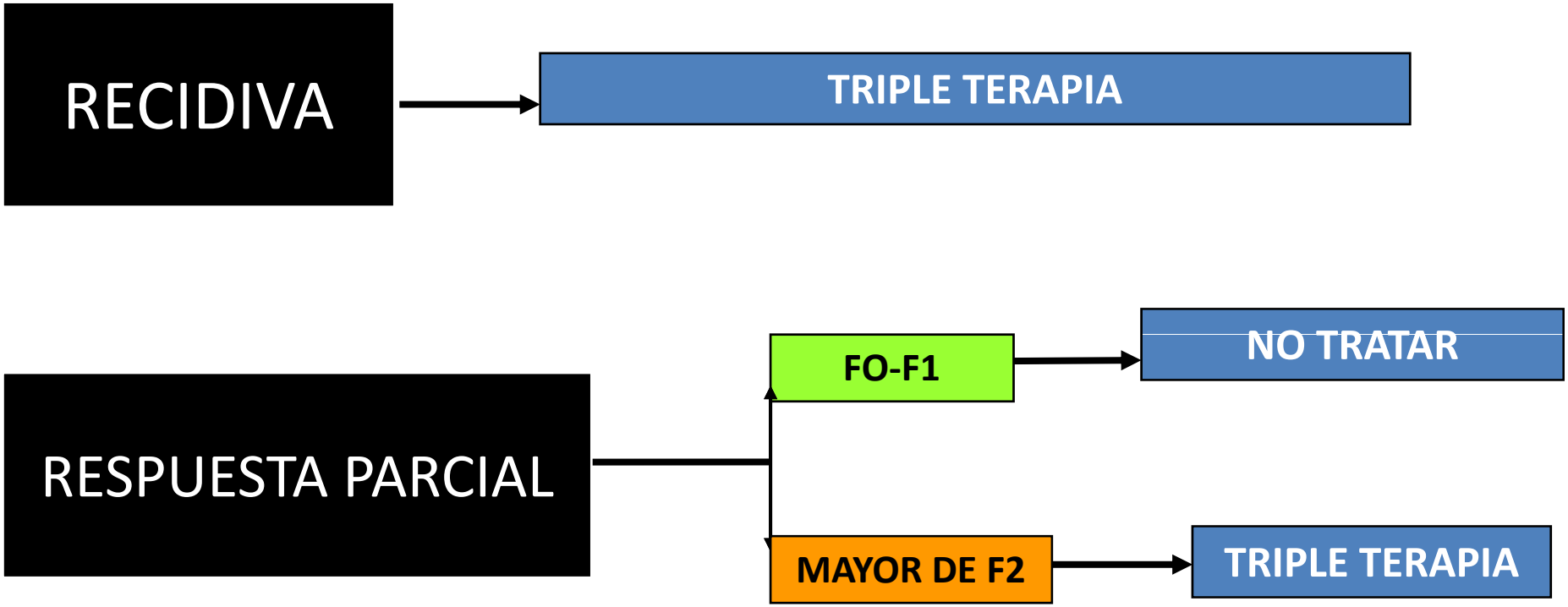
No respuesta previa



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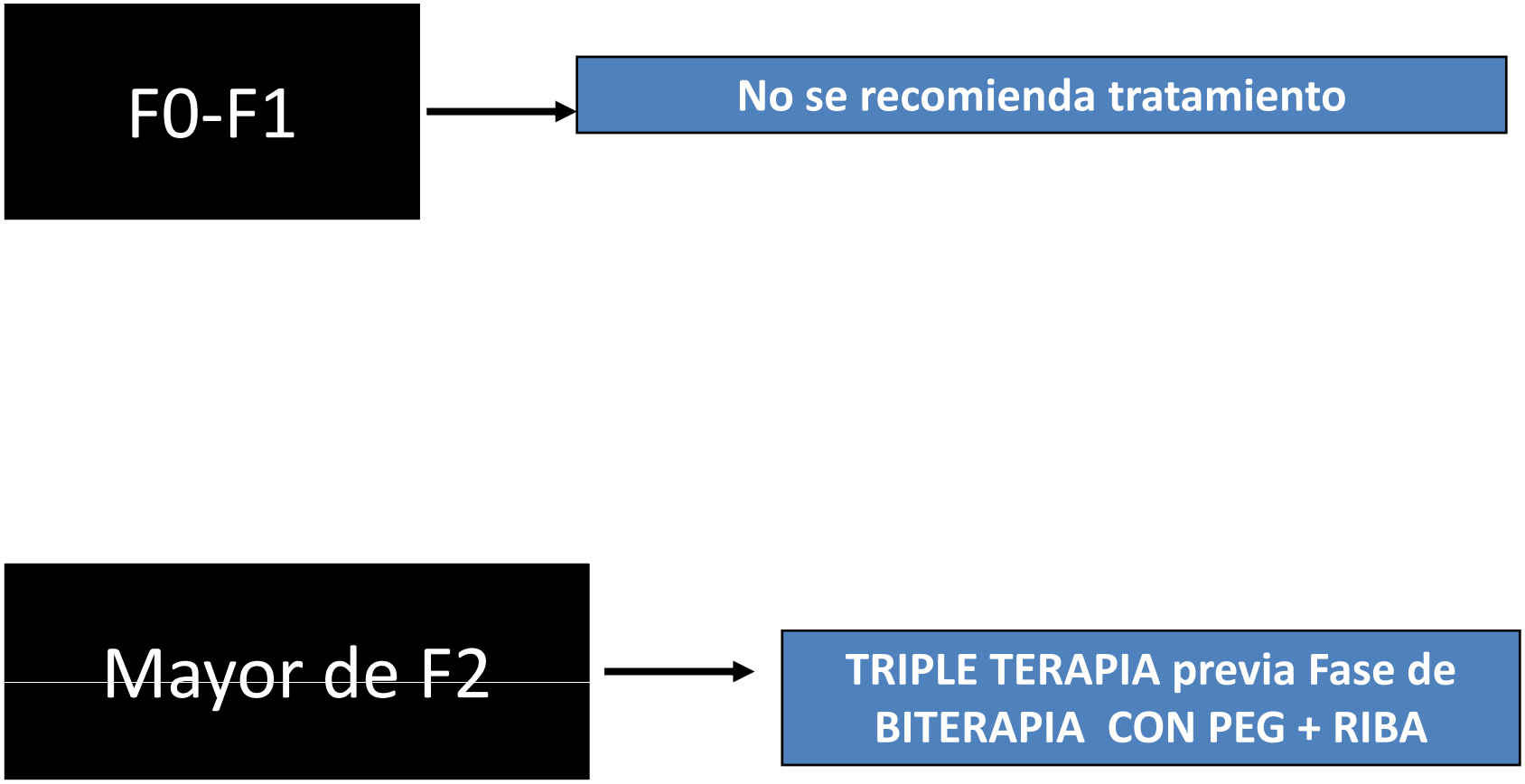
Respuesta Nula o desconocida



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CONCLUSIONES

- **Los nuevos inhibidores de la proteasa telaprevir y boceprevir cubren una importante necesidad médica en el tratamiento de los pacientes con hepatitis crónica C genotipo 1**
  - ✓ **Mayores tasas de curación incluso en los subgrupos dificiles de tratar**
  - ✓ **Menor duración del tratamiento en un porcentaje importante de pacientes**
  - ✓ **Inconvenientes :**
    - ✓ **Efectos secundarios**
    - ✓ **Interacciones**
    - ✓ **Importancia de las resistencias**
  - ✓ **Uso responsable de estos tratamientos**