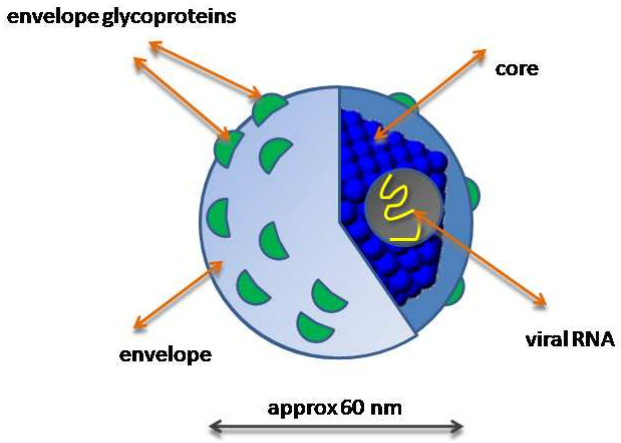
Network di Microbiologia e Virologia del Nord Est

LE INFEZIONI DA VIRUS DELL'EPATITE C (HCV)

Trento, 14 ottobre 2011

Stato dell'arte, prospettive future delle terapia antivirali e caratteristiche del paziente eleggibile

Claudio Paternoster
Malattie Infettive - Trento



Structure of Hepatitis C Virus

Treatment of Chronic Non-A, Non-B Hepatitis with Recombinant Human Alpha Interferon

Jay H. Hoofnagle, M.D., Kevin D. Mullen, M.D., D. Brian Jones, M.D., Vinod Rustgi, M.D., Adrian Di Bisceglie, M.D., Marion Peters, M.D., Jeanne G. Waggoner, B.A., Yoon Park, R.N., and E. Anthony Jones, M.D.

ABSTRACT

We treated **10 patients** who had chronic non-A, non-B hepatitis with recombinant human alpha interferon in varying doses (0.5 to 5 million units) daily, every other day, or three times weekly for up to 12 months. In 8 of the 10 patients, elevated serum aminotransferase levels decreased rapidly during therapy and eventually fell into the normal or nearly normal range. In two of these patients, the interferon therapy was stopped after four months, and in both cases, a prompt return of aminotransferase activities to pretreatment values occurred. Prolonged treatment was associated with a sustained improvement in aminotransferase levels; in three cases, biopsy specimens obtained after one year of therapy showed marked improvement in hepatic histology, even though low doses of alpha interferon had been used.

These preliminary findings, although not adequately controlled, suggest that long-term, low-dose alpha interferon therapy may be effective in controlling the disease activity in some patients with chronic non-A, non-B hepatitis.

A prospective controlled trial is now needed to assess the role of interferon therapy in this disease.

N Engl J Med 1986; 315:1575-1578

1986 **1989**

Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome

QL Choo, G Kuo, AJ Weiner, LR Overby, DW Bradley and M Houghton

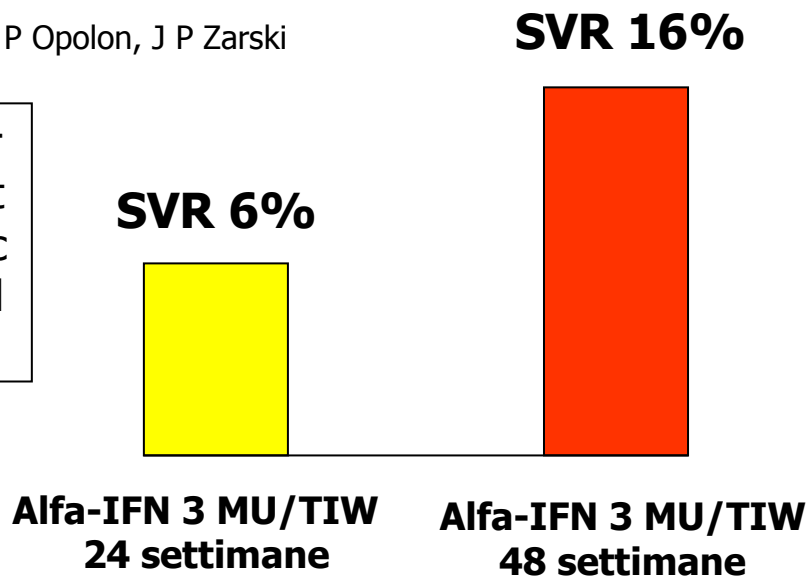
Science, 21 April 1989:
Vol. 244 no. 4902 pp.359-362

Meta-analysis of interferon randomized trials in the treatment of viral hepatitis C: Effects of dose and duration

Poynard, V Leroy, M Cohard, T Thevenot, P Mathurin, P Opolon, J P Zarski

The best efficacy/risk ratio was in favor of **3 MU three times per week** for at least 12 months in patients with chronic hepatitis C who had never been treated with interferon.

Hepatology, 1996; 24:778



1986 1989 IFN IN MONOTERAPIA

Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome

QL Choo, G Kuo, AJ Weiner, LR Overby, DW Bradley and M Houghton

Science, 21 April 1989:
Vol. 244 no. 4902 pp.359-362

Interferon Alfa-2b Alone or in Combination with Ribavirin as Initial Treatment for Chronic Hepatitis C

John G. McHutchison, M.D., Stuart C. Gordon, M.D., Eugene R. Schiff, M.D., Mitchell L. Shiffman, M.D., William M. Lee, M.D., Vinod K. Rustgi, M.D., Zachary D. Goodman, M.D., Ph.D., Mei-Hsiu Ling, Ph.D., Susannah Cort, M.D., and Janice K. Albrecht, Ph.D. for THE HEPATITIS INTERVENTIONAL THERAPY GROUP

N Engl J Med 1998; 339:1485-1492

Randomised trial of interferon 2b plus ribavirin for 48 weeks or for 24 weeks versus interferon 2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus

Thierry Poynard, Patrick Marcellin, Samuel S Lee, Christian Niederau, Gerald S Minuk, Gaetano Ideo, Vincent Bain, Jenny Heathcote, Stefan Zeuzem, Christian Trepo, Janice Albrecht, for the International Hepatitis Interventional Therapy Group (IHIT)

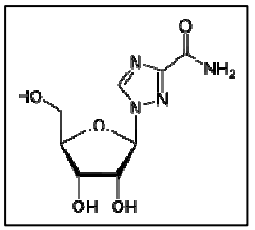
Lancet 1998; 352: 1426–32

1986 IFN IN MONOTERAPIA | **1998** | **IFN + RIBAVIRINA**

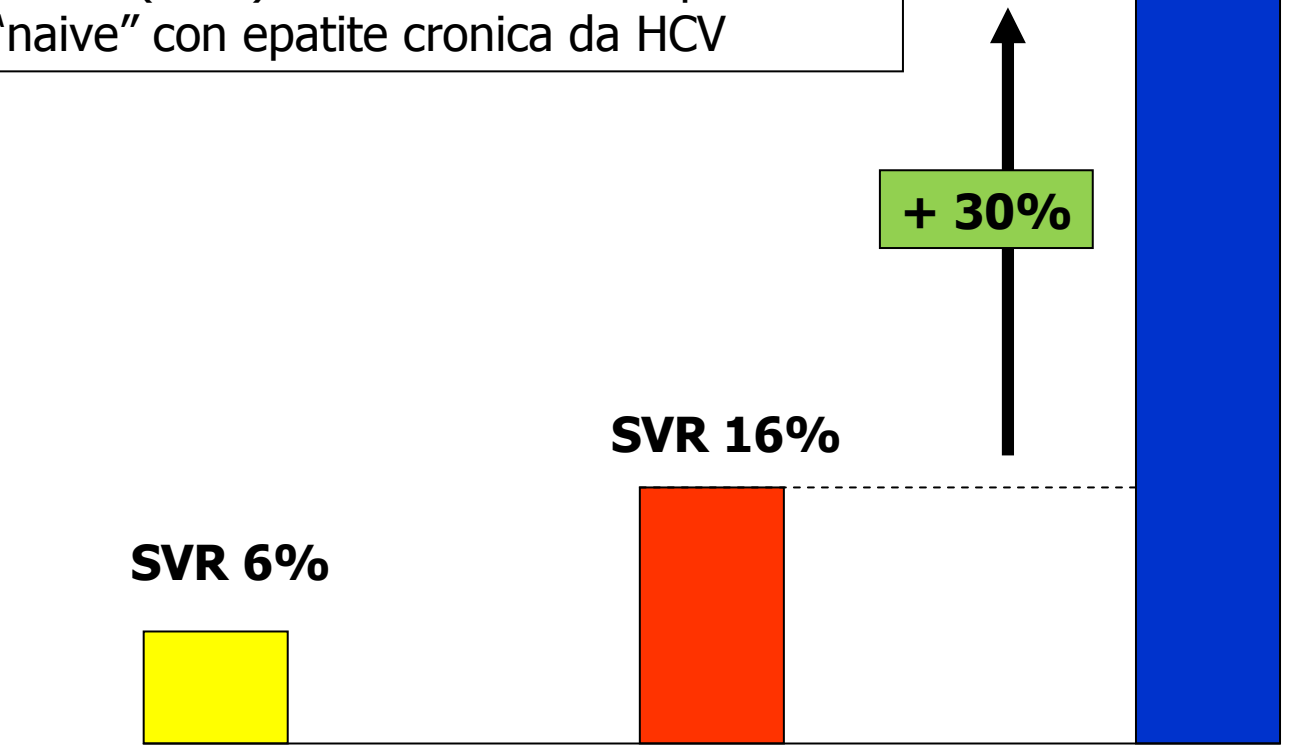
Conclusions: In patients with chronic hepatitis C, initial therapy with interferon and ribavirin **was more effective** than treatment with interferon alone.

Interpretation: An interferon 2b plus ribavirin combination is more effective than 48 weeks of interferon 2b monotherapy and has an acceptable safety profile. Patients with few favourable factors benefit more from extending the duration of combination therapy to 48 weeks.

Effetto della **ribavirina** sulla risposta virologica sostenuta (**SVR**) al trattamento dei pazienti "naive" con epatite cronica da HCV



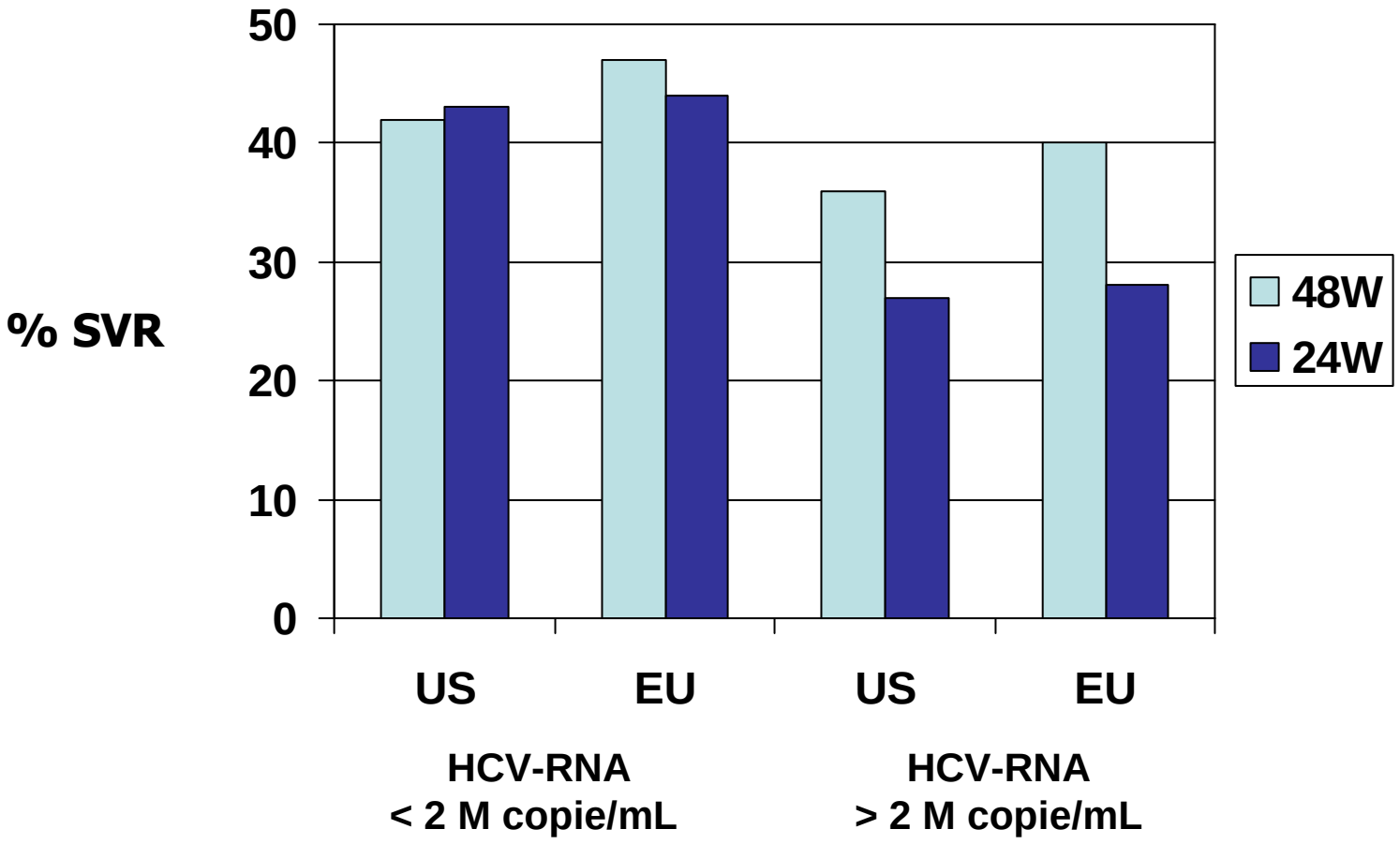
Ribavirina



1986 IFN IN MONOTERAPIA 1998 IFN + RIBAVIRINA

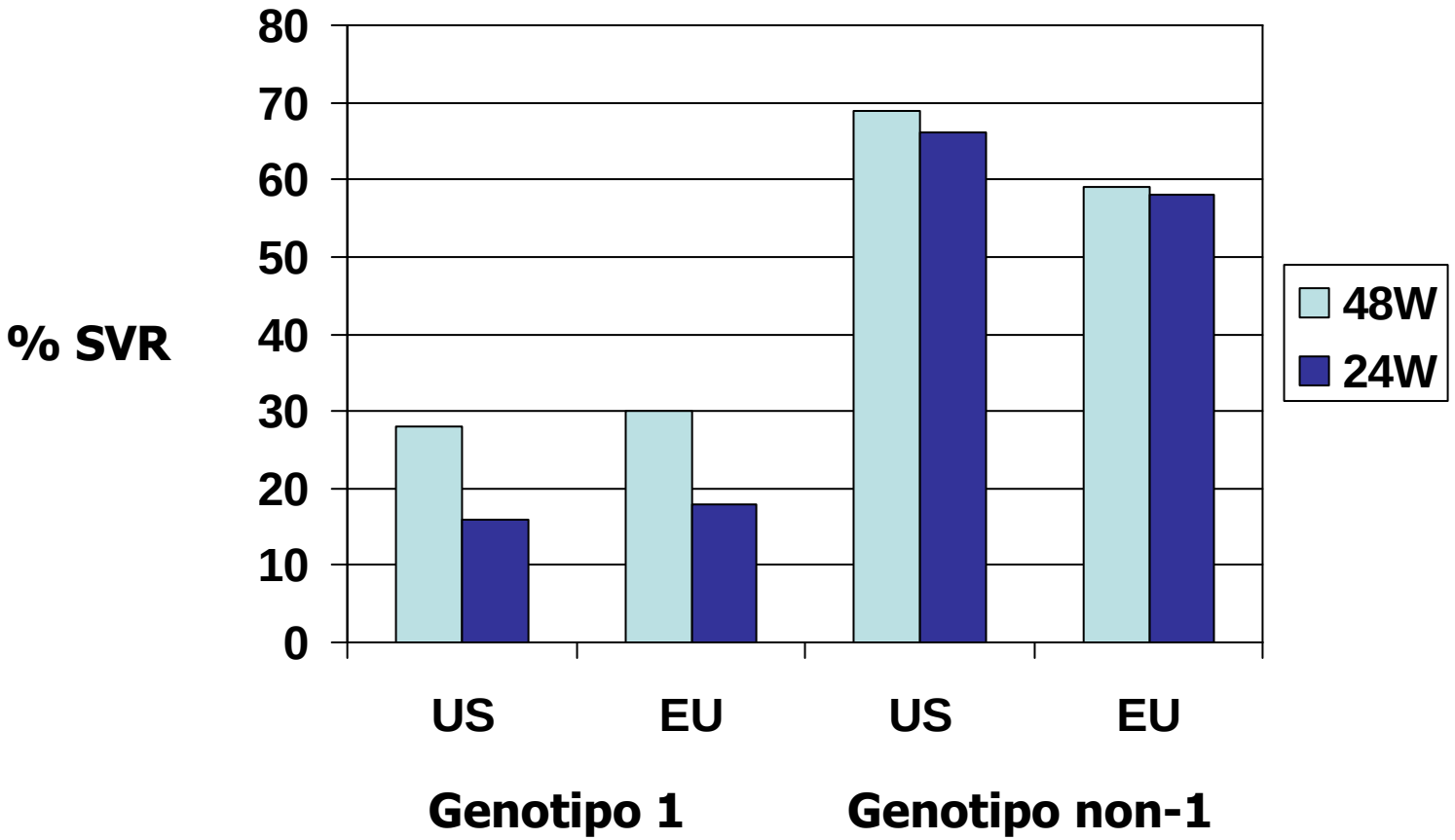
Poynard T et al. Lancet 1998
McHutchison JG et al. N Engl J Med 1998

Effetto della carica virale e della durata del trattamento sulla % di risposta virologica sostenuta



US trial: McHutchison JG et al. N Engl J Med 1998
EU trial: Poynard T et al. Lancet 1998

Effetto del genotipo virale e della durata del trattamento sulla % di risposta virologica sostenuta



US trial: McHutchison JG et al. N Engl J Med 1998
EU trial: Poynard T et al. Lancet 1998

Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial

Manns MP et al. Lancet 2001; 358: 958-65

Interpretation: In patients with chronic hepatitis C, the most effective therapy is the combination of peginterferon alfa-2b 1·5 μg/kg per week plus ribavirin. The benefit is mostly achieved in patients with HCV genotype 1 infections.

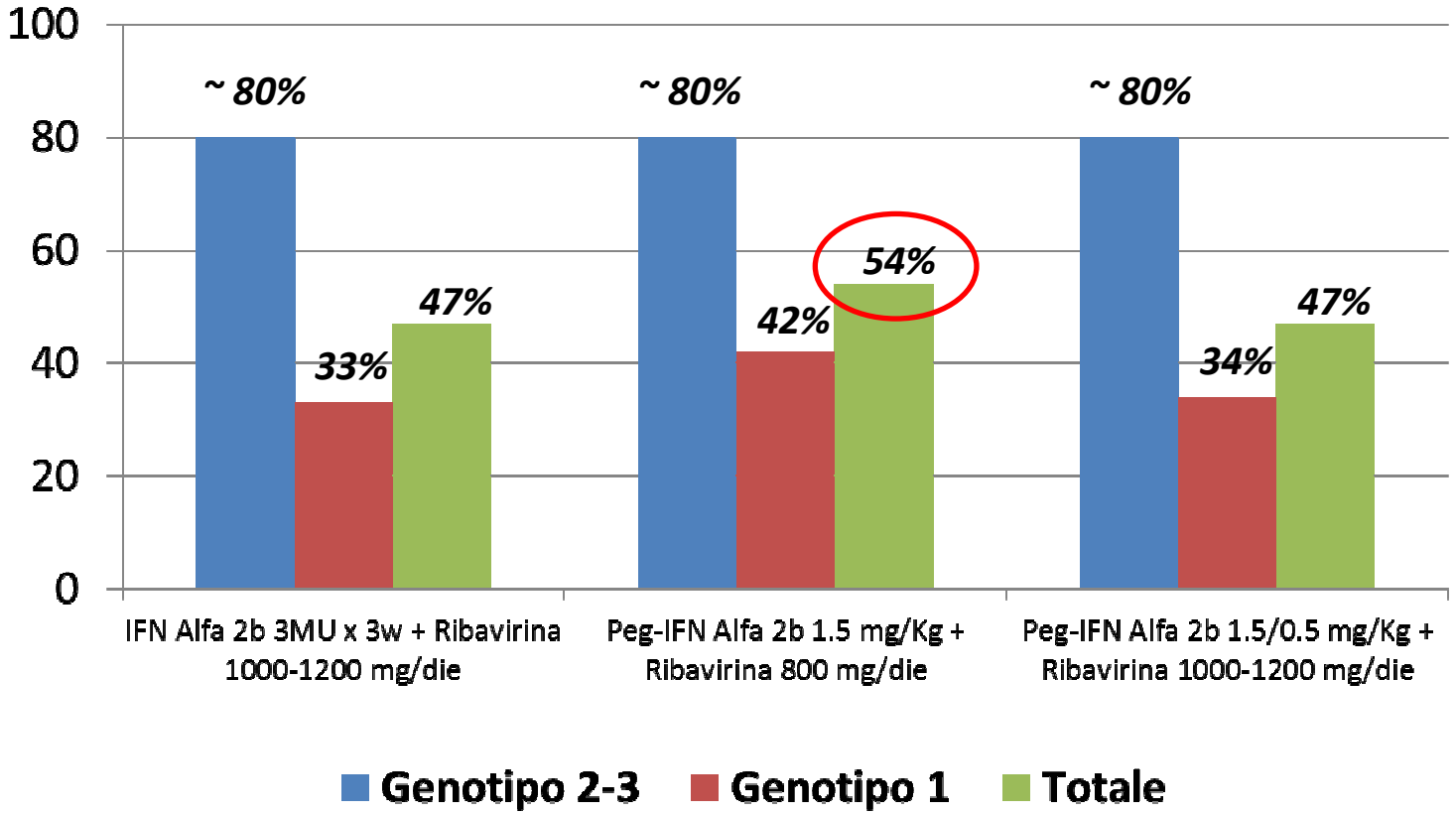
1986 IFN 1998 IFN + RBV 2001 PEG-IFN + RBV

PEGINTERFERON ALFA-2a PLUS RIBAVIRIN FOR CHRONIC HEPATITIS C VIRUS INFECTION

Fried MW et al. N Engl J Med 2002; 347: 975-82

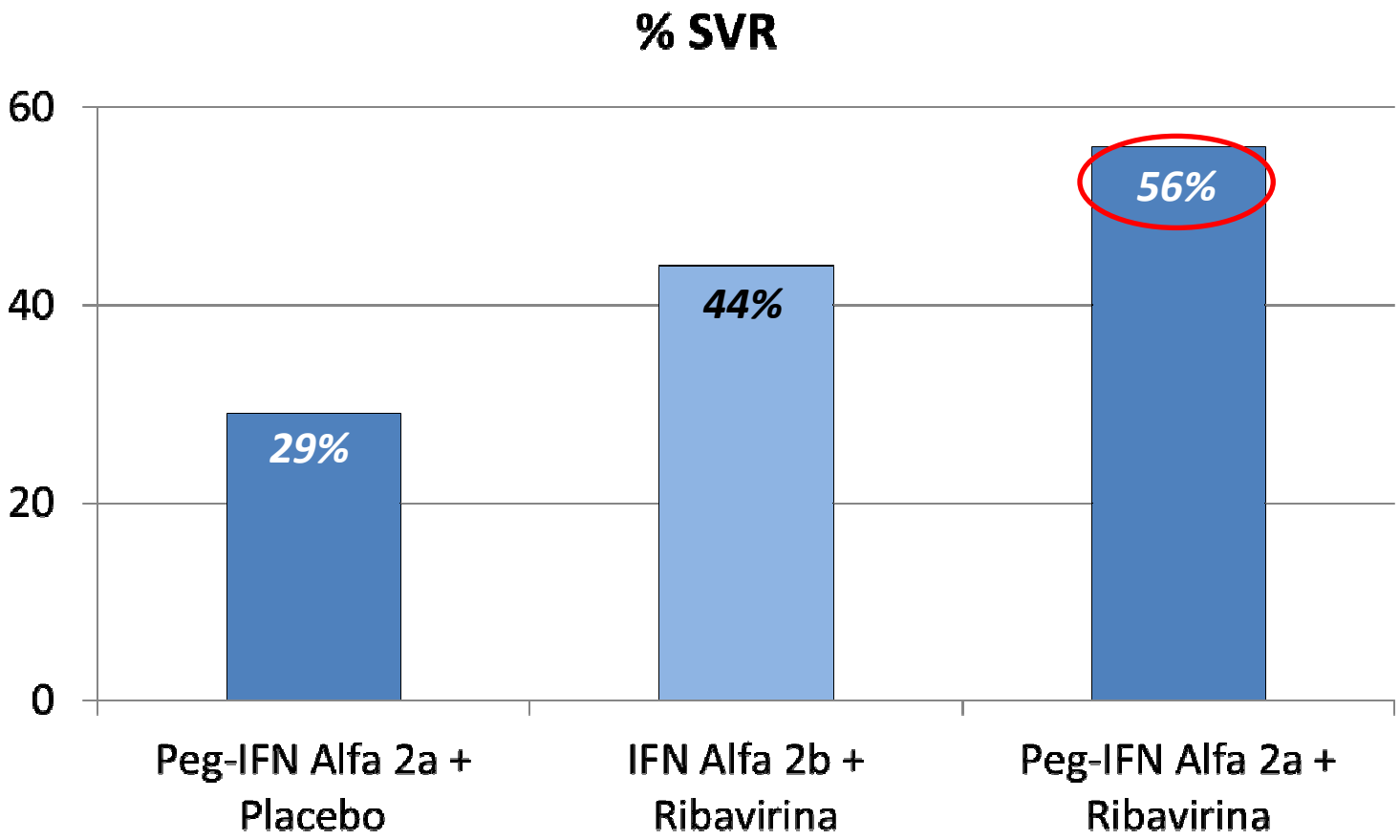
Conclusions: In patients with chronic hepatitis C, once-weekly peginterferon alfa-2a plus ribavirin was tolerated as well as interferon alfa-2b plus ribavirin and produced significant improvements in the rate of sustained virologic response, as compared with interferon alfa-2b plus ribavirin or peginterferon alfa-2a alone.

Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial



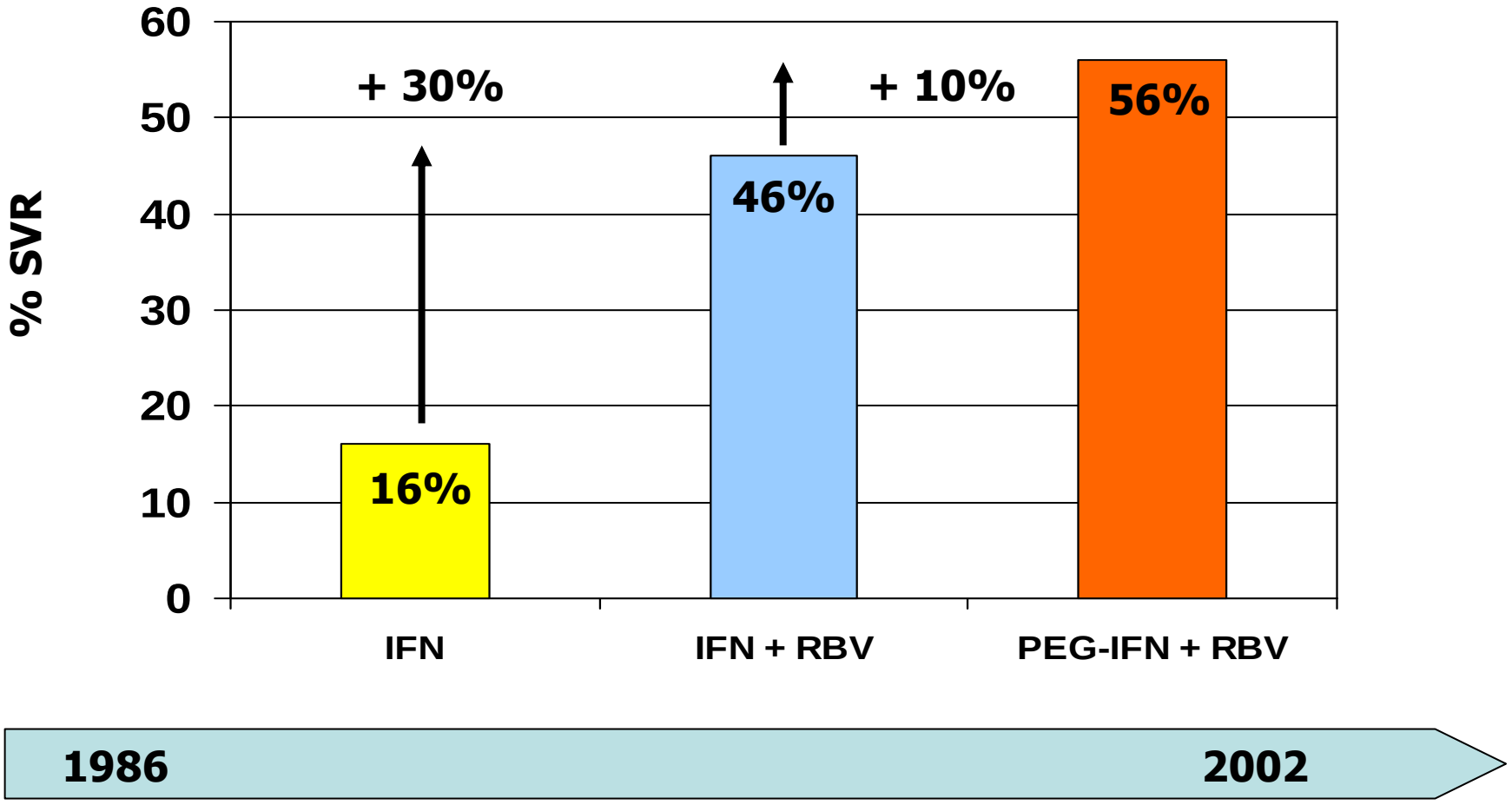
Manns MP et al. Lancet 2001; 358: 958 - 65

PEGINTERFERON ALFA-2a PLUS RIBAVIRIN FOR CHRONIC HEPATITIS C VIRUS INFECTION



Fried MW et al.N Engl J Med, Vol. 347, No. 13 · September 26, 2002

Progressi nella terapia dell'epatite cronica da HCV



Manns MP et al. Lancet 2001
Fried MV et al. N Engl J Med 2002

Peginterferon-2a and Ribavirin Combination Therapy in Chronic Hepatitis C

A Randomized Study of Treatment Duration and Ribavirin Dose

Stephanos J. Hadziyannis, MD; Hoel Sette Jr., MD; Timothy R. Morgan, MD; Vijayan Balan, MD; Moises Diago, MD; Patrick Marcellin, MD; Giuliano Ramadori, MD; Henry Bodenheimer Jr., MD; David Bernstein, MD; Mario Rizzetto, MD; Stefan Zeuzem, MD; Paul J. Pockros, MD; Amy Lin, MS; and Andrew M. Ackrill, PhD, for the PEGASYS International Study Group*

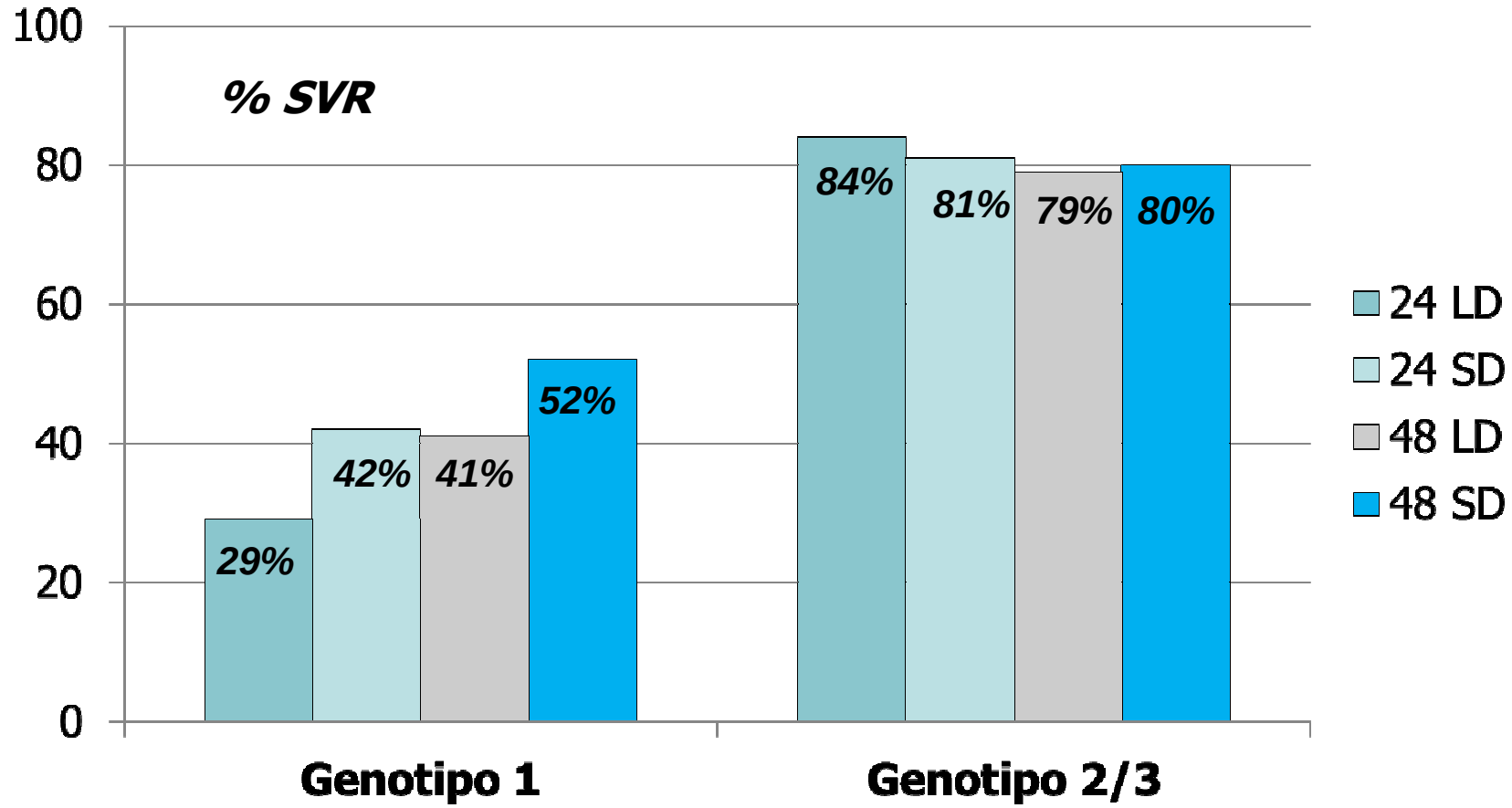
Conclusion: Treatment with peginterferon-2a and ribavirin may be individualized by genotype. Patients with HCV **genotype 1** require treatment for **48 weeks** and a standard dose of ribavirin; those with HCV **genotypes 2 or 3** seem to be adequately treated with a low dose of ribavirin for **24 weeks**.

1986 **IFN → IFN + RBV → PEG-IFN + RBV** **2004**

Ann Intern Med. 2004;140:346-355.

Peginterferon-2a and Ribavirin Combination Therapy in Chronic Hepatitis C

A Randomized Study of Treatment Duration and Ribavirin Dose



***LD** = RBV 800 mg/day*
***SD** = RBV 1000–1200 mg/day*

Hadziyannis S, et al. Ann Intern Med 2004; 140: 346

Trattamento "standard" dell'epatite cronica da HCV

Genotipo	Dosaggio Peg-IFN	Dosaggio Ribavirina	Durata
1-4	Peg-IFN α-2a 180 µg/settimana Peg-IFN α-2b 1.5 µg/kg settimana	15 mg/kg/die (800-1400 mg/die)	48 settimane
2-3	Peg-IFN α-2a 180 µg/settimana Peg-IFN α-2b 1.5 µg/kg settimana	800 mg/die	24 settimane

Manns MP et al. Lancet 2001 - Fried MV et al. N Engl J Med 2002 - Hadziyannis S et al. Ann Intern Med. 2004

Infezione da HCV: obiettivi del trattamento

Obiettivi primari

- Eradicazione virale (SVR*)
- Arrestare la progressione della fibrosi

Obiettivi secondari

- Ridurre la progressione della fibrosi/cirrosi
- Prevenire lo scompenso epatico
- Prevenire lo sviluppo di HCC

***SVR**= HCV-RNA negativo dopo 6 mesi dal termine del trattamento.
SVR = Risoluzione dell'infezione in > 99% dei pazienti

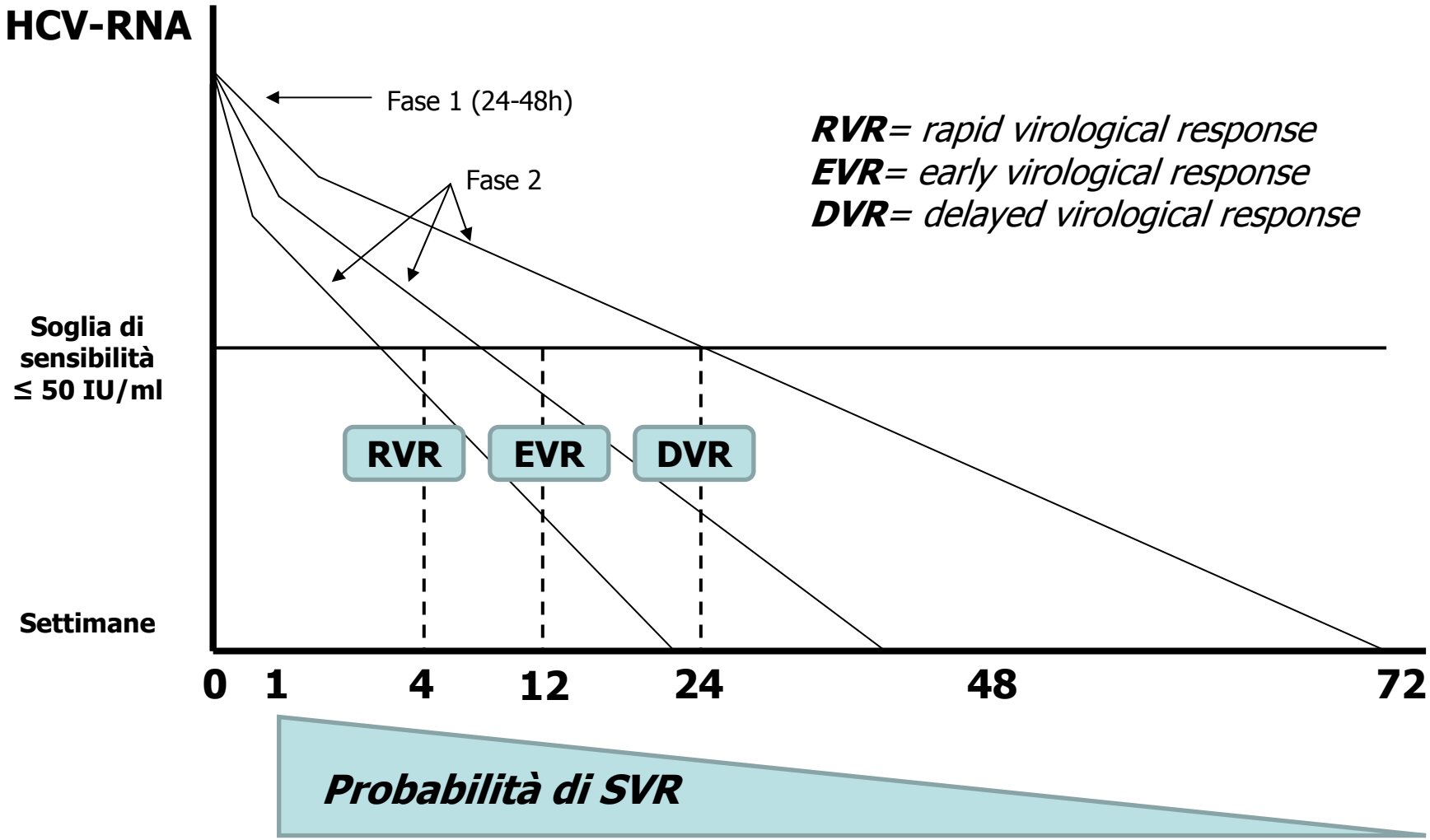
Swain MG et al. A sustained virologic response is durable in patients with chronic hepatitis C treated with peginterferon alfa-2a and ribavirin. Gastroenterology 2010; 139:1593

Caratteristiche del paziente candidato al trattamento

Pazienti nei quali il trattamento è generalmente raccomandato	Pazienti per i quali il trattamento può essere considerato	Pazienti in cui il trattamento è controindicato
▪ Età > 18 anni ▪ HCV-RNA misurabile ▪ Fibrosi ≥ 2 (METAVIR) ▪ Malattia epatica compensata ✓ Bilirubina totale < 1.5 g/dL ✓ INR < 1.5 ✓ Albumina > 3.4 g/dL ✓ PLT > 75.000/mcL ✓ Assenza di ascite ed encefalopatia ▪ Emoglobina > 13 g/dL ▪ Neutrofili > 1.500/mcL ▪ Creatinina < 1.5 mg/dL ▪ Desiderio del paziente di essere trattato e capacità di aderire al trattamento ▪ Assenza di controindicazioni	▪ Pazienti non-responders o relapsers ad un precedente trattamento con IFN standard (± ribavirina) o Peg-IFN in monoterapia ▪ Fibrosi minima o assente alla biopsia epatica ▪ Epatite acuta da HCV ▪ Coinfezione HIV/HCV ▪ Età < 18 anni ▪ Trapiantati di fegato ▪ IRC che non richiede dialisi ▪ Tossicodipendenti in trattamento metadonico e/o ex etilisti in programma di recupero ▪ Cirrosi epatica (Child A-B)	▪ Depressione maggiore non controllata dal trattamento ▪ Trapianto di rene, cuore, polmone ▪ Epatite autoimmune o altre patologie autoimmuni che possono essere esacerbate dall'IFN ▪ Patologia tiroidea non controllata dal trattamento ▪ Severe condizioni concomitanti: ipertensione severa, scompenso cardiaco, cardiopatia ischemica significativa, diabete scompensato, grave BPCO ▪ Ipersensibilità nota a IFN o RBV ▪ Età < 2 anni ▪ Gravidanza in atto

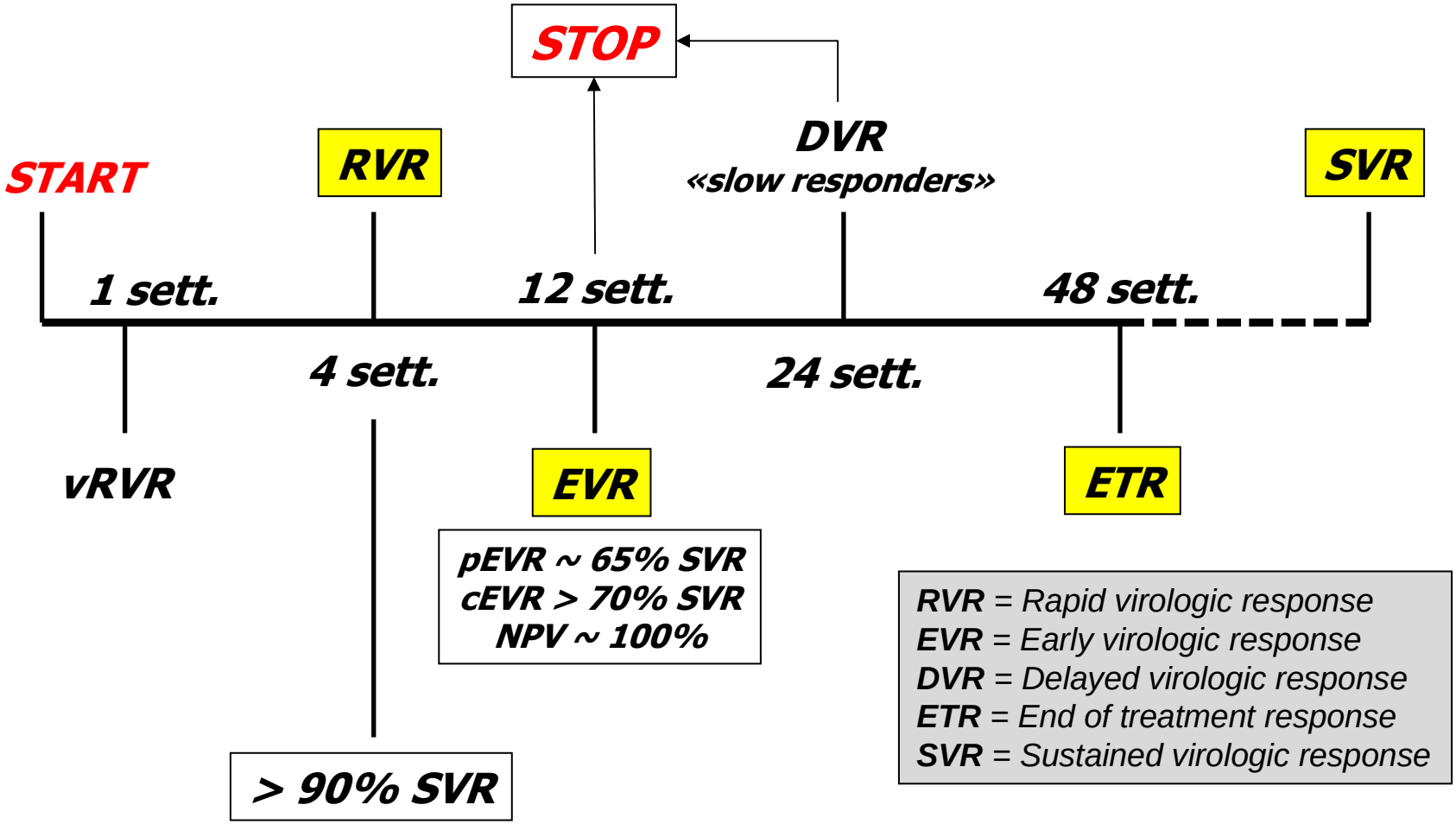
Linee guida AASLD 2009

Probabilità di SVR in relazione alla risposta virologica nelle prime settimane di trattamento



Journal of Hepatology 2011

Terapia guidata dalla risposta terapeutica
Response-guided therapy (RGT)



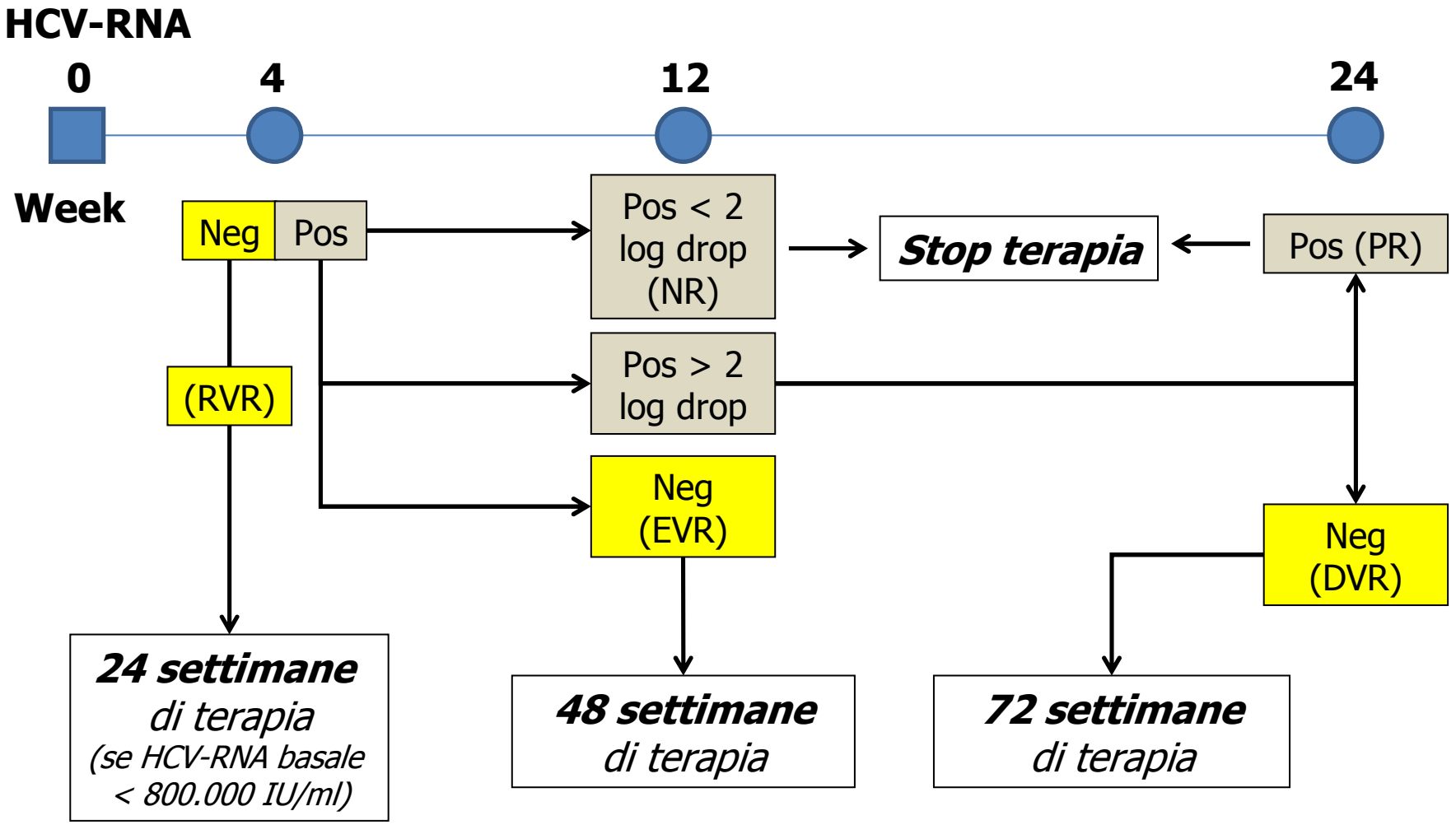
Treatment of hepatitis C virus infection: Updated Swedish Consensus reccomendations

Risposta virologica	Definizione	Genotipo 1-4	Genotipo 2-3
vRVR	HCV-RNA < 1000 UI/mL 1^ sett.		12-16 sett.
RVR	HCV-RNA negativo 4^ sett.	24 sett.	24 sett.
cEVR	HCV-RNA negativo 12^ sett.	48 sett.	≥ 24 sett.
pEVR	Riduzione HCV-RNA ≥ 2 log10 12^ sett.	considera 72 sett.	considera ≥ 48 sett.

Sospendere il trattamento nei pazienti che non ottengono una pEVR o con HCV-RNA positivo alla 24^ settimana

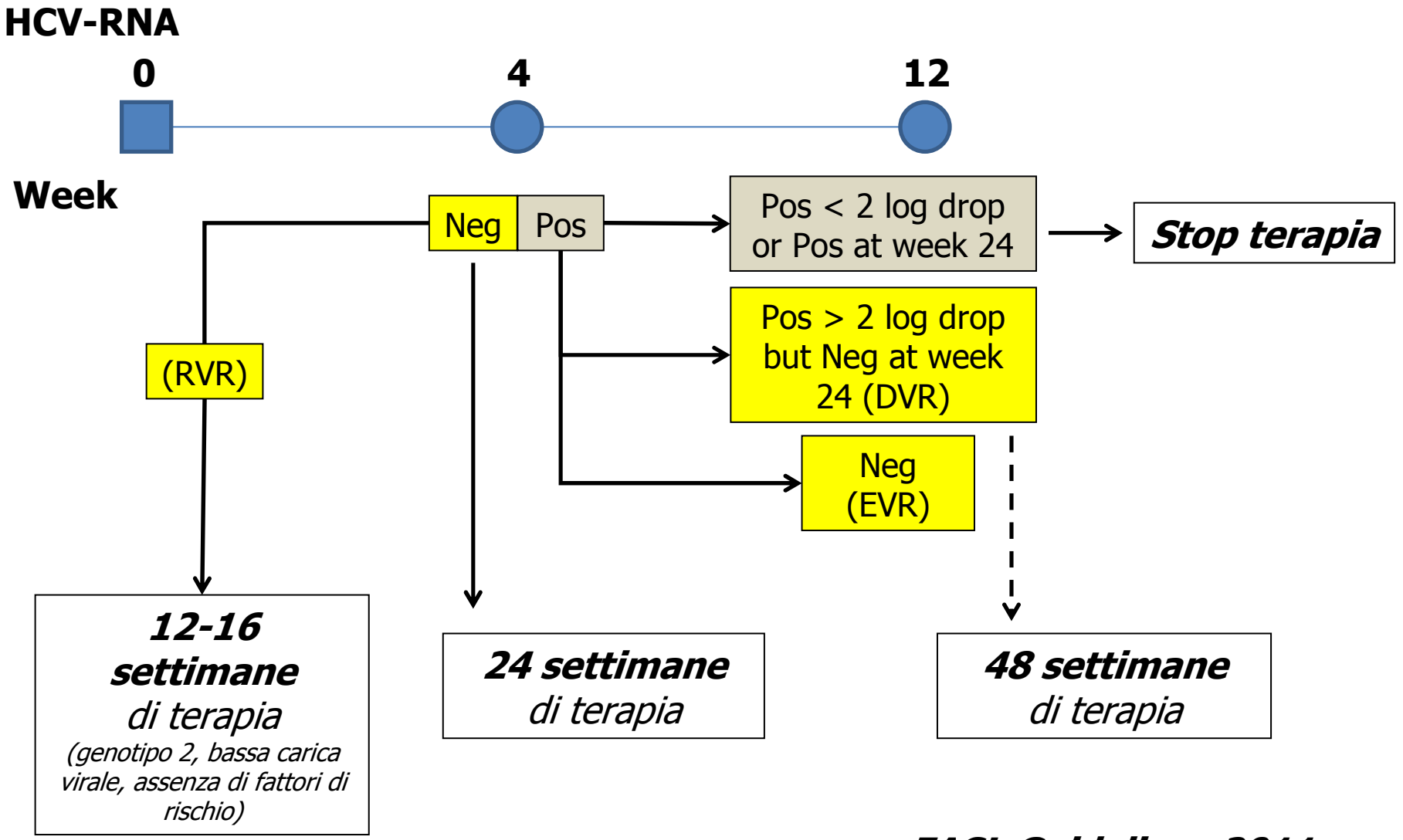
Lagging M et al. Scand J Infect Dis 2009;41:389-402

Response-guided therapy in patients with genotype 1



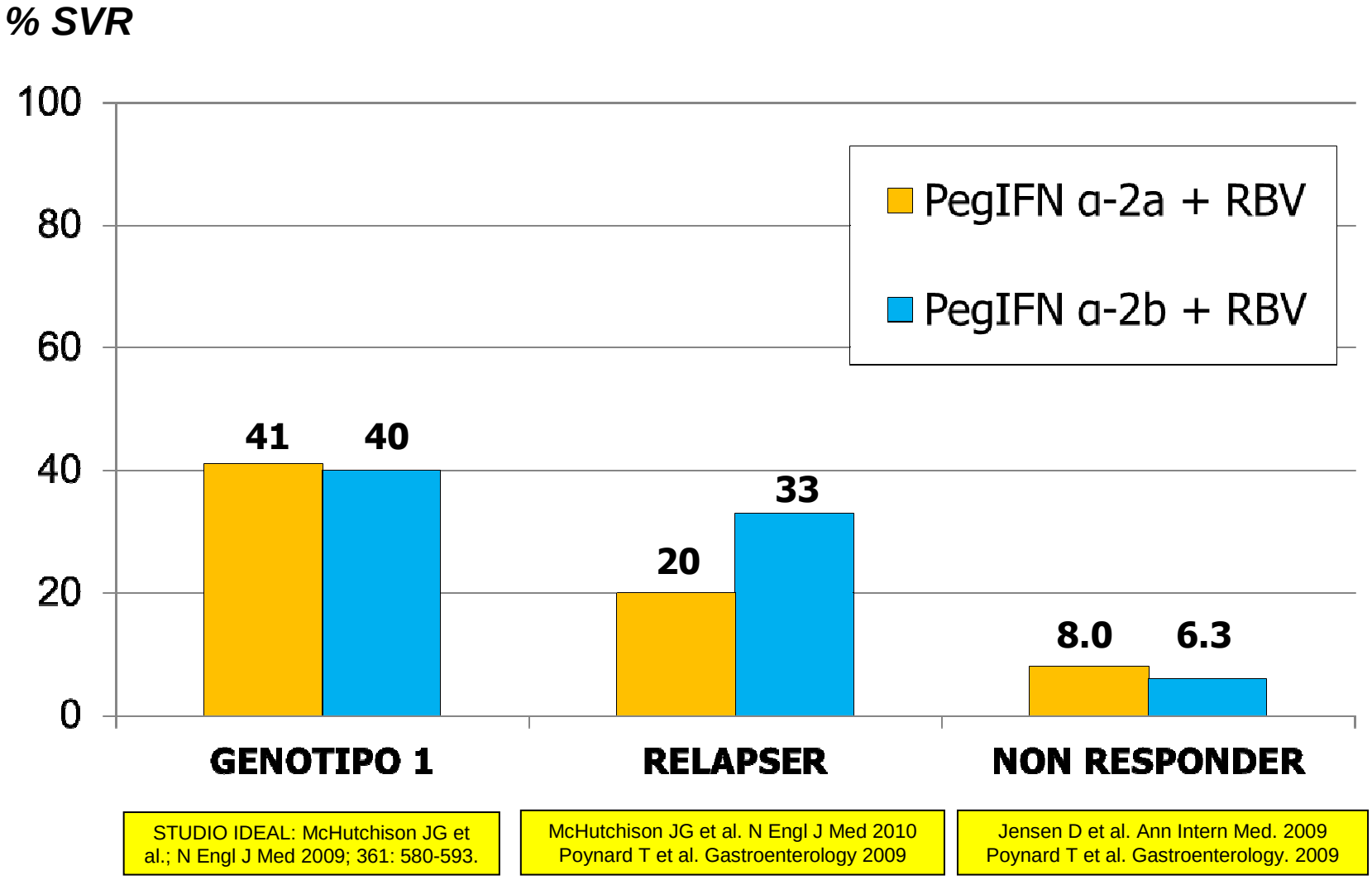
EASL Guidelines 2011

Response-guided therapy in patients with genotype 2 and 3

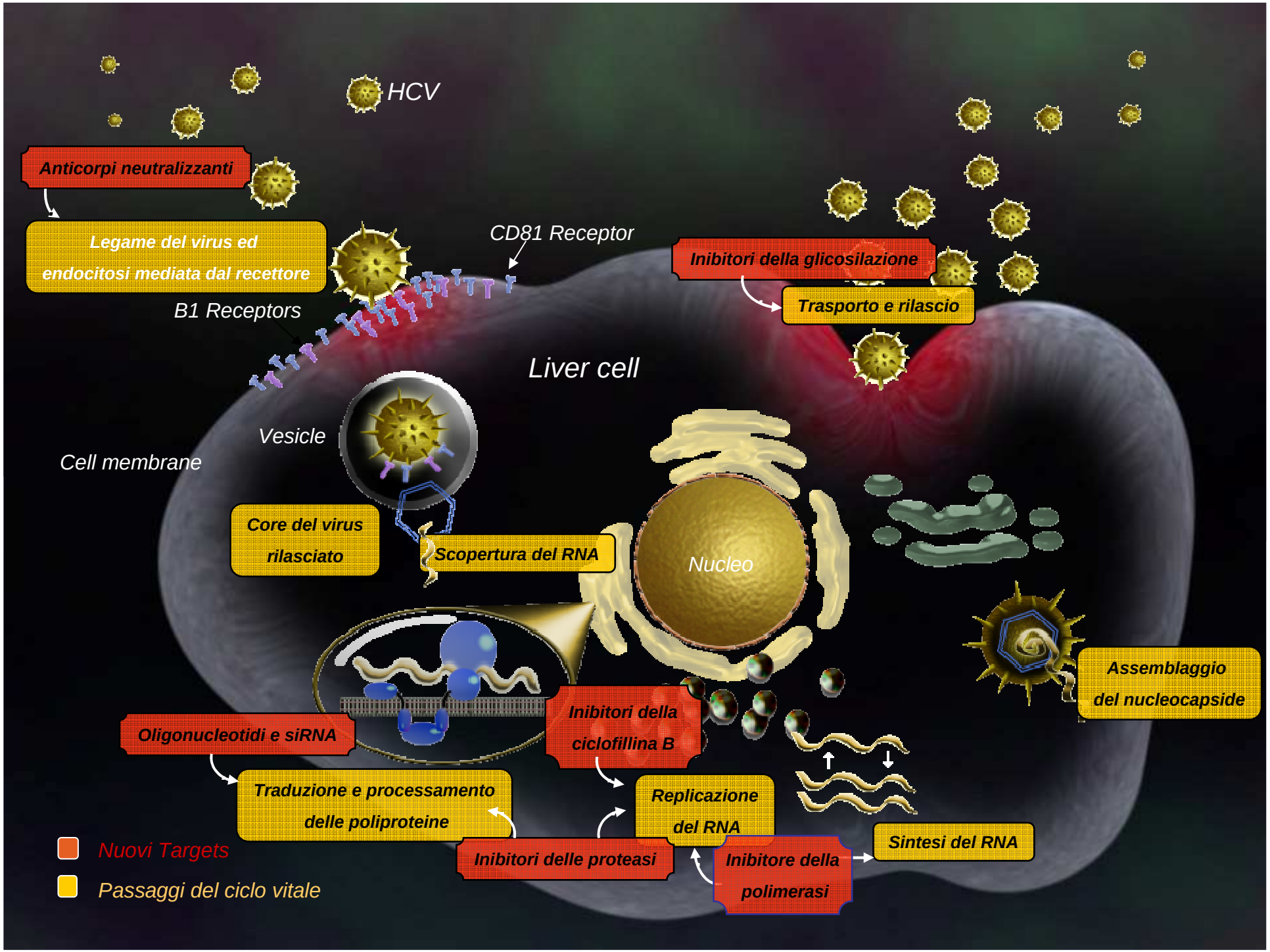


EASL Guidelines 2011

Terapia dell'infezione da HCV: principali problemi irrisolti



Nuove prospettive terapeutiche nel trattamento dell'epatite cronica da HCV

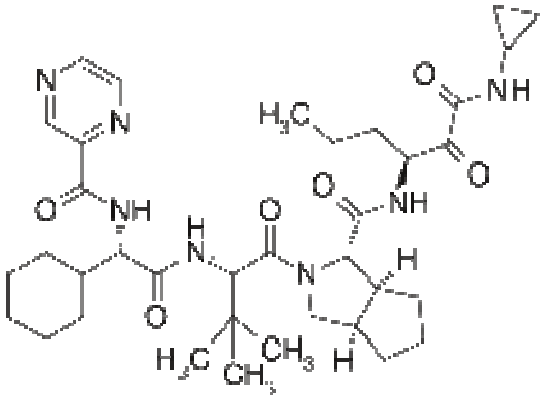

HCV
Anticorpi neutralizzanti
Legame del virus ed endocitosi mediata dal recettore
CD81 Receptor
B1 Receptors
Inibitori della glicosilazione
Trasporto e rilascio
Liver cell
Vesicle
Cell membrane
Core del virus rilasciato
Scopertura del RNA
Nucleo
Assemblaggio del nucleocapside
Oligonucleotidi e siRNA
Inibitori della ciclofillina B
Traduzione e processamento delle poliproteine
Replicazione del RNA
Inibitori delle proteasi
Inibitore della polimerasi
Sintesi del RNA
Nuovi Targets
Passaggi del ciclo vitale

Nuove prospettive terapeutiche nel trattamento dell'epatite cronica da HCV

STAT-C: Specifically Targeted Antiviral Therapy for Hepatits C

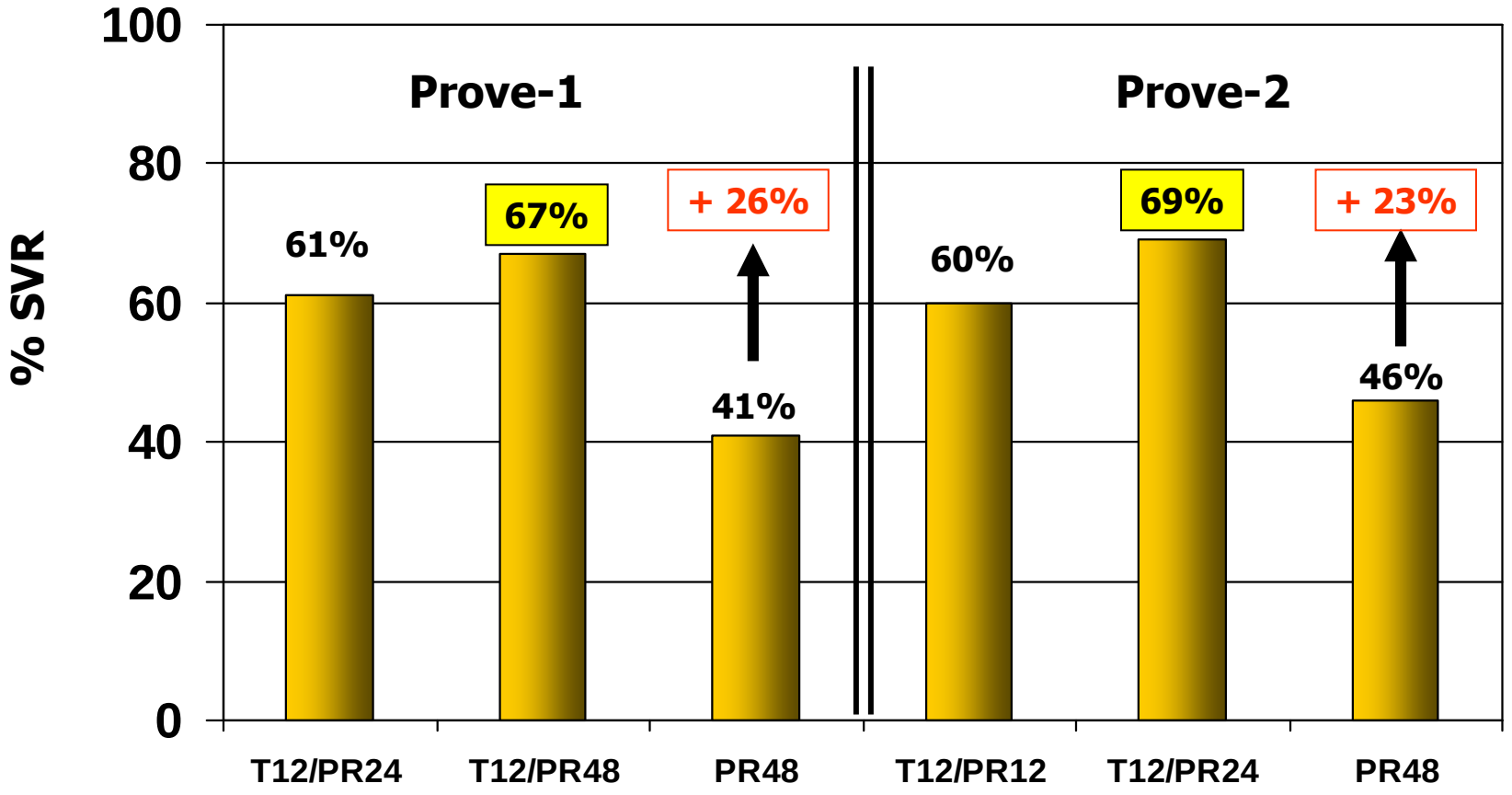
Target	Farmaco
Proteasi	**Telaprevir** (Vertex/JJ) **Boceprevir** (Schering) ITMN-191 (Intermune/Roche)
Polimerasi	R1626 (Roche) R7128 (Pharmassett/Roche) MK-0608 (Merck) BILB 1941(Boehringer-Ingelheim) GS 9190 (Gilead) VCH 759 (ViroChem) A-837093 (Abbott)
Inibitori della ciclofillina B	DEBIO-025 (DebioPharm) NIM 811 (Novartis)

TELAPREVIR



- **Inibitore specifico della proteasi serinica NS3/4A di HCV**
- **Approvato FDA maggio 2011 per l'utilizzo clinico negli USA**
- **Formulazione: compresse 375 mg**
- **Posologia: 750 mg (2 cp) ogni 8 ore per os**

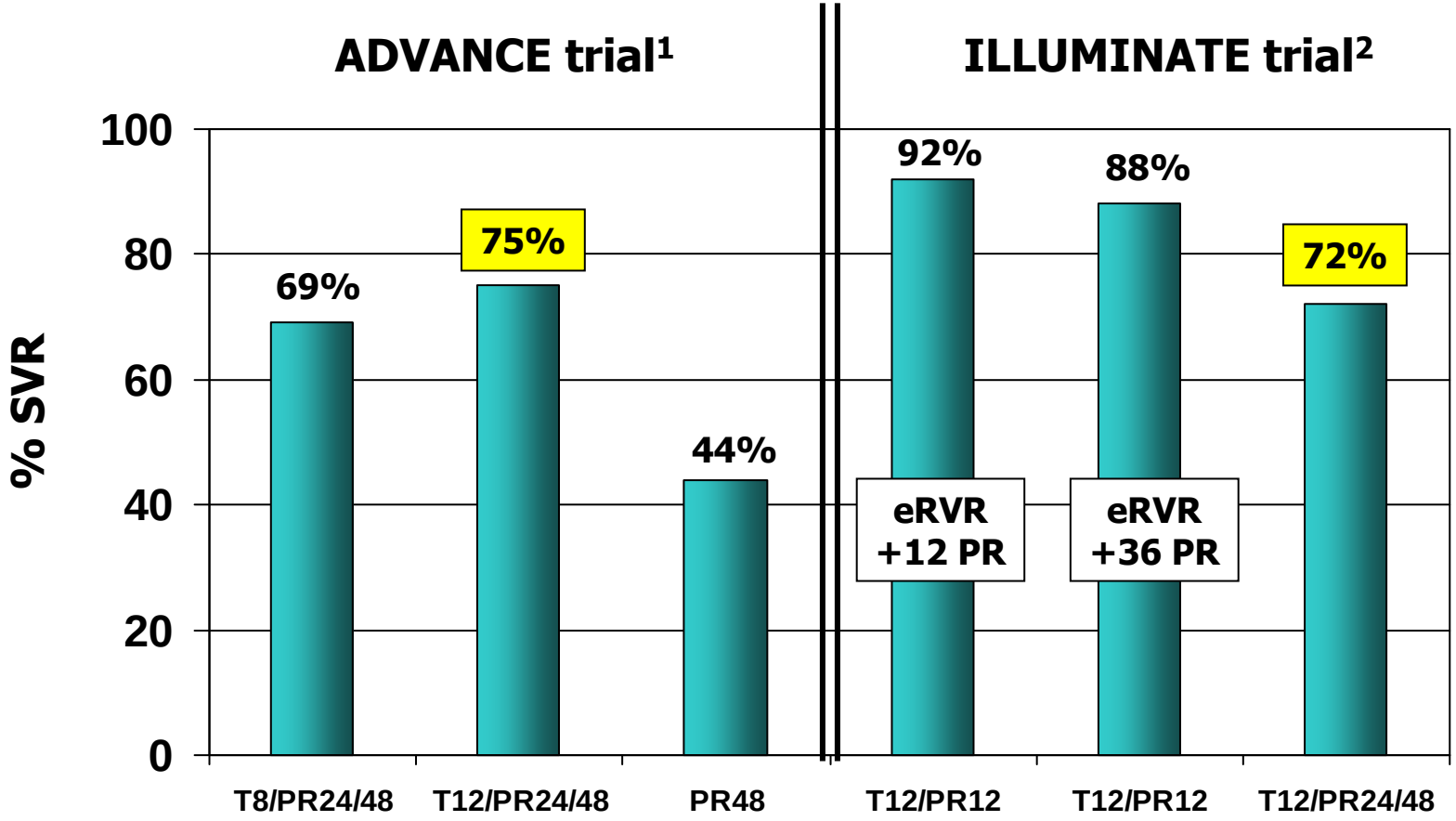
Dati di risposta virologica sostenuta (SVR) nei pazienti naive trattati con Telaprevir (studi fase II)



T= Telaprevir
P= Peg-Interferon
R= Ribavirina

[1]*McHutchinson JC et al. N Engl J Med 2009; 360:1827*
[2]*Hezode C et al. N Engl J Med 2009; 360:1839*

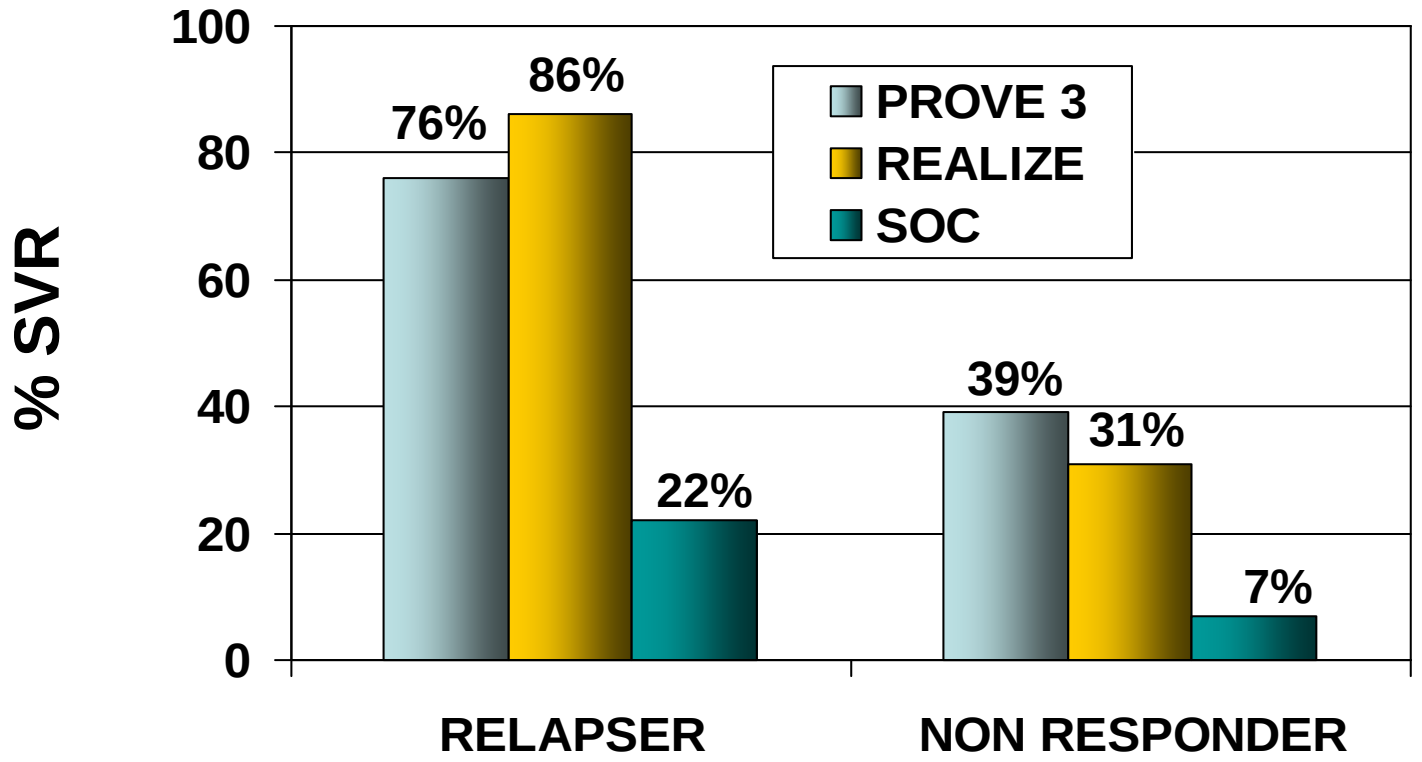
Dati di risposta virologica sostenuta (SVR) nei pazienti naive trattati con Telaprevir (studi fase III)



eRVR = HCV-RNA < 25 IU/mL alla 4^ e alla 12^ settimana di trattamento

[1]Jacobsonn IM et al. ADVANCE study. Hepatology 2010
[2]HSherman KE et al. ILLUMINATE study. Hepatology 2010

Dati di risposta virologica sostenuta (SVR) nei pazienti non responder/relapser trattati con Telaprevir



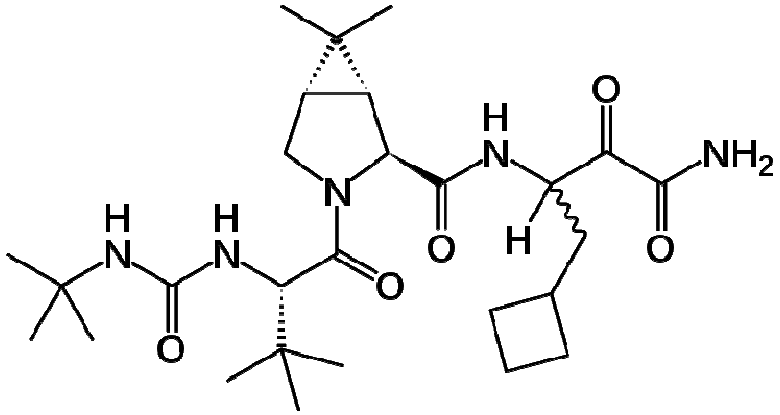
McHutchinson JG et al. Telaprevir for previously treated chronic HCV infection. N Engl J Med 2010; 362:1292

Telaprevir: schema di trattamento raccomandato

Pazienti naive e relapser			
HCV-RNA*	**Triplice terapia** **Telaprevir + Peg-IFN + Ribavirina**	**Duplice terapia** **Peg-IFN + Ribavirina**	**Durata totale del trattamento**
Negativo settimana 4 e 12	Prime 12 settimane	Ulteriori 12 settimane	**24 settimane**
Positivo ≤ 1000 UI/mL settimana 4 o 12	Prime 12 settimane	Ulteriori 36 settimane	**48 settimane**
Pazienti non responder o partial responder			
Tutti i pazienti	Prime 12 settimane	Ulteriori 36 settimane	**48 settimane**

** Se HCV-RNA > 1000 UI/mL alla settimana 4 o 12 sospendere tutto il trattamento*
** Se HCV-RNA positivo alla settimana 24 sospendere Peg-IFN + Ribavirina*

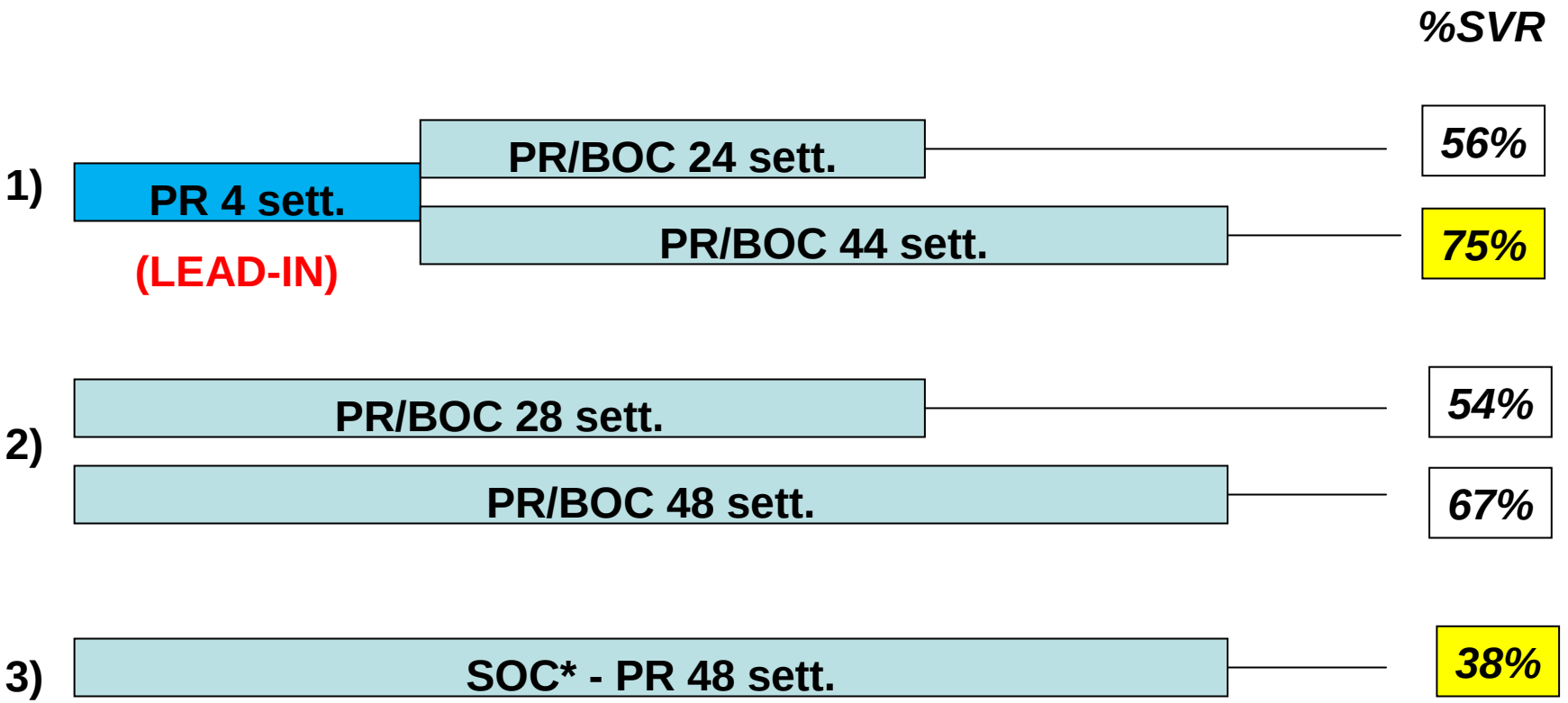
BOCEPREVIR



- **Inibitore competitivo della proteasi NS3 di HCV1**
- **Approvato FDA maggio 2011 per l'utilizzo clinico negli USA**
- **Formulazione: capsule 200 mg**
- **Posologia: 800 mg (4 cp) ogni 8 ore per os (con cibo)**

Boceprevir – HCV SPRINT trials

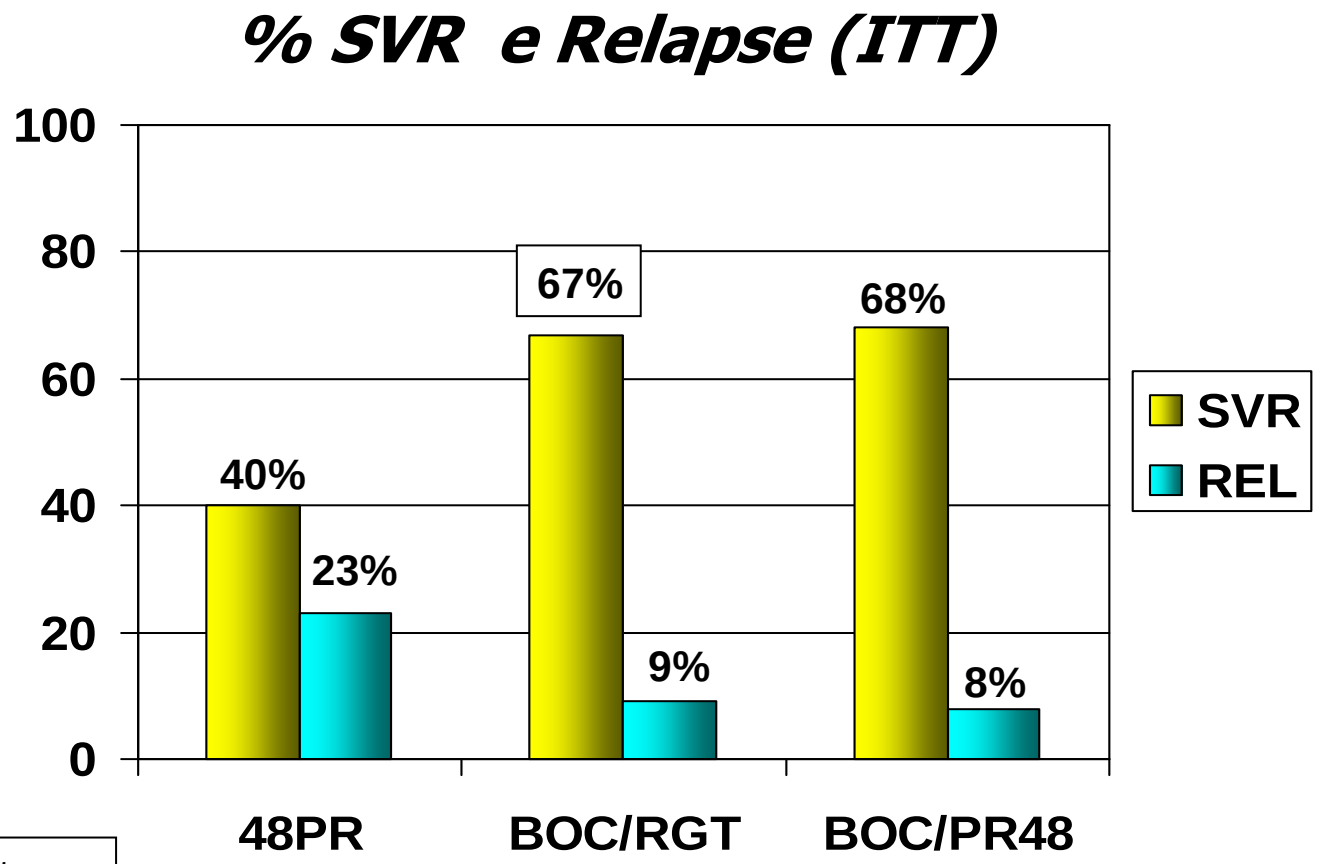
HCV SPRINT-1 (fase II): 559 pz. naive gen. 1



*SOC=Standard of care

Kwo PY et al. Lancet 2010; 376:705

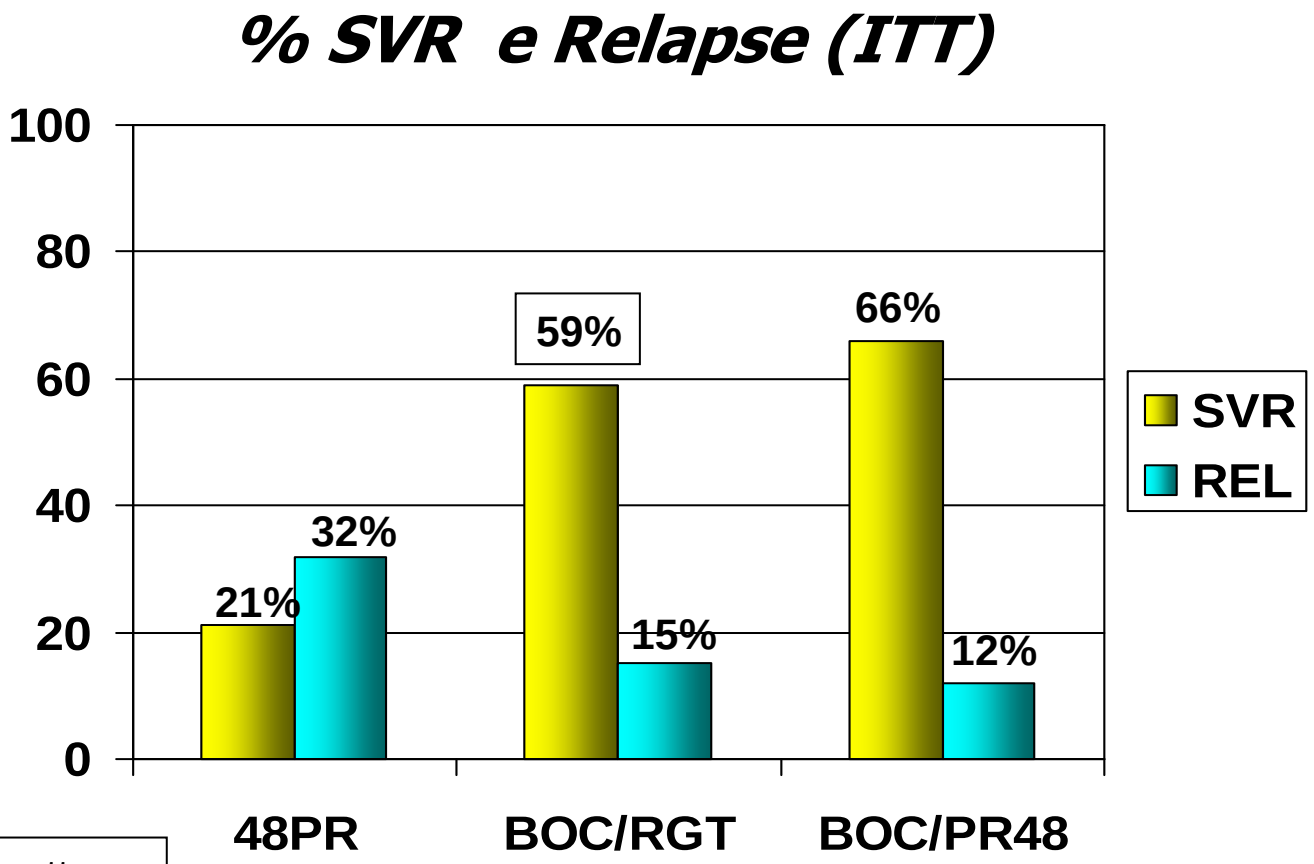
Dati di risposta virologica sostenuta (SVR) nei pazienti naive trattati con Boceprevir (Studio SPRINT-2/fase III)



RGT: PR 4 sett.
+ PR/BOC 24 sett.
± PR 20 sett.

Poordard F et al. N Engl J Med 2011; 364:1195

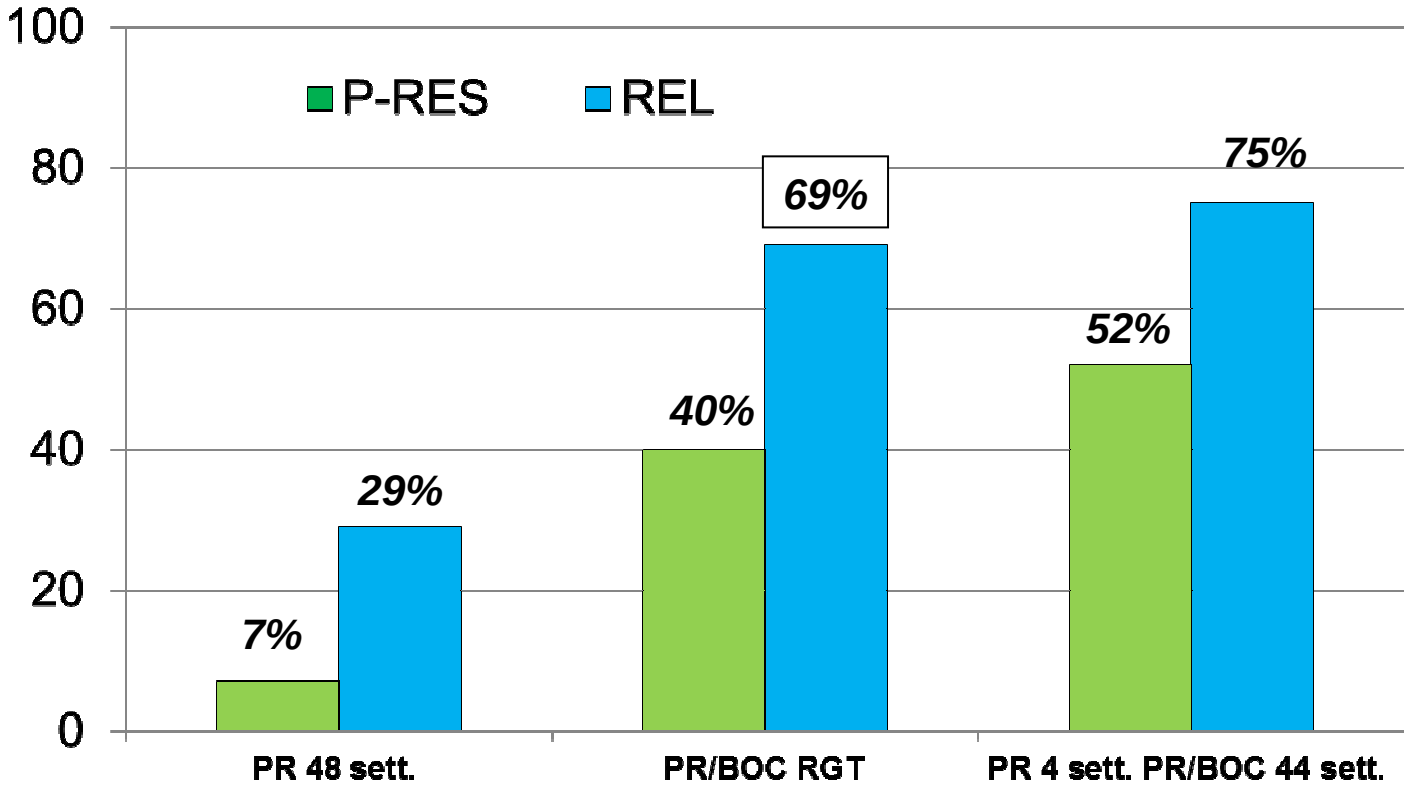
Dati di risposta virologica sostenuta (SVR) nei pazienti partial responder/relapser trattati con Boceprevir (Studio RESPOND-2/fase III)



RGT: PR 4 sett.
+ PR/BOC 32 sett.
± PR 12 sett.

Bacon et al. N Engl J Med 2011; 364:1207

Dati di risposta virologica sostenuta (SVR) nei pazienti partial responder/relapser trattati con Boceprevir (Studio RESPOND-2/fase III)



RGT: PR 4 sett.
+ PR/BOC 32 sett.
± PR 12 sett.

Bacon et al. N Engl J Med 2011; 364:1207

Boceprevir: schema di trattamento raccomandato

<table>
<tr><th colspan="5">Pazienti naive</th></tr>
<tr><td rowspan="2">Lead-in

Peg-IFN + Ribavirina per 4 settimane</td><td>HCV-RNA negativo settimana 8-24</td><td colspan="2">Boceprevir + Peg-IFN + RBV 24 settimane</td><td>28 settimane</td></tr>
<tr><td>HCV-RNA positivo settimana 8 negativo settimana 24</td><td>Boceprevir + Peg-IFN + RBV 32 settimane</td><td>Peg-IFN + RBV 12 settimane</td><td>48 settimane</td></tr>
</table>

Se HCV-RNA negativo alla settimana 4 valutare trattamento solo con Peg-IFN + Ribavirina
Se HCV-RNA ≥ 100 UI/mL alla settimana 12 sospendere il trattamento
Se HCV-RNA positivo alla settimana 24 sospendere il trattamento

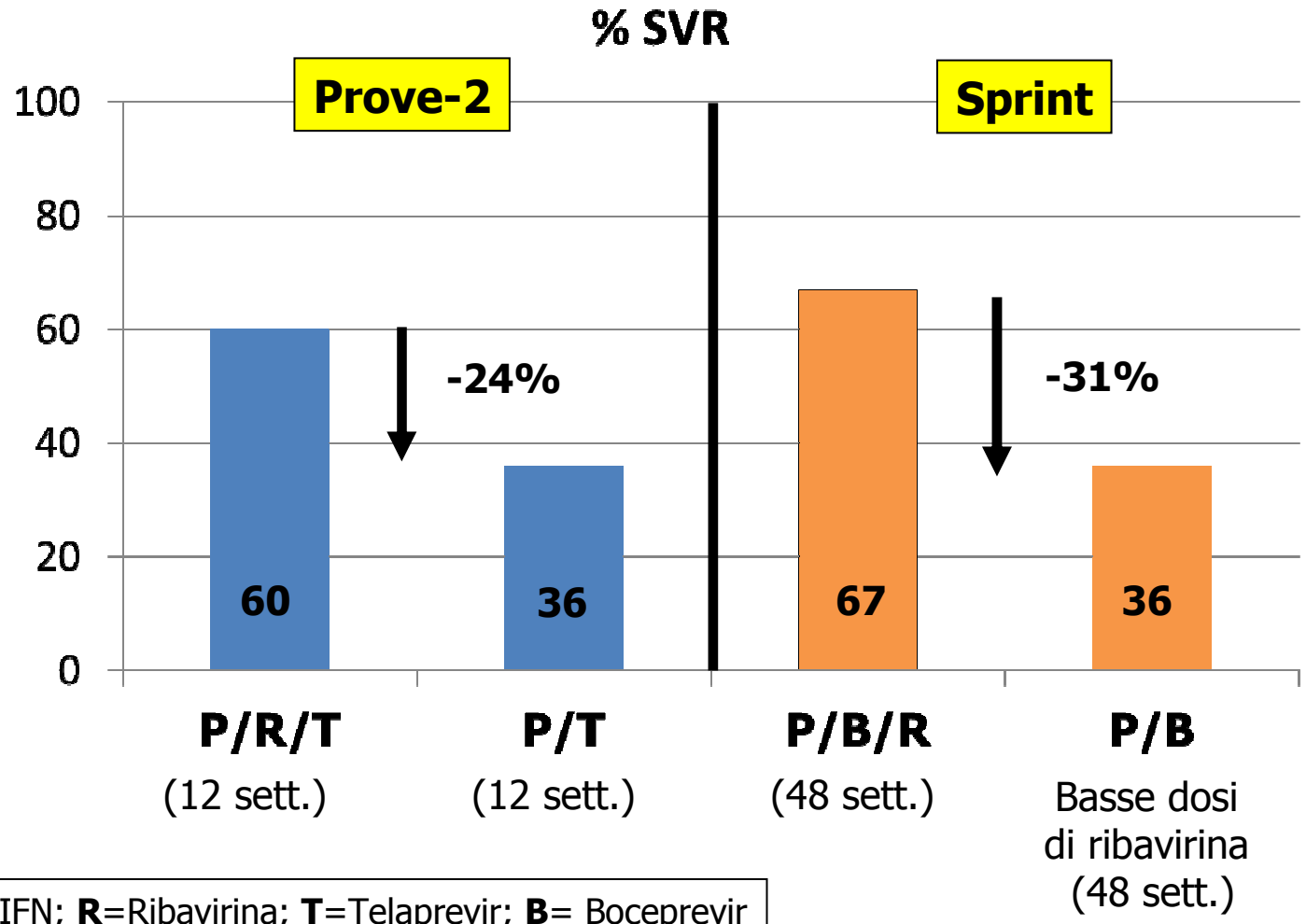
Boceprevir: schema di trattamento raccomandato

<table>
<tr><th colspan="5">Pazienti partial responder o relapser</th></tr>
<tr><td rowspan="2">Lead-in

Peg-IFN + Ribavirina per 4 settimane</td><td>HCV-RNA negativo settimana 8-24</td><td colspan="2">Boceprevir + Peg-IFN + RBV 32 settimane</td><td>36 settimane</td></tr>
<tr><td>HCV-RNA positivo settimana 8 negativo settimana 24</td><td>Boceprevir + Peg-IFN + RBV 32 settimane</td><td>Peg-IFN + RBV 12 settimane</td><td>48 settimane</td></tr>
</table>

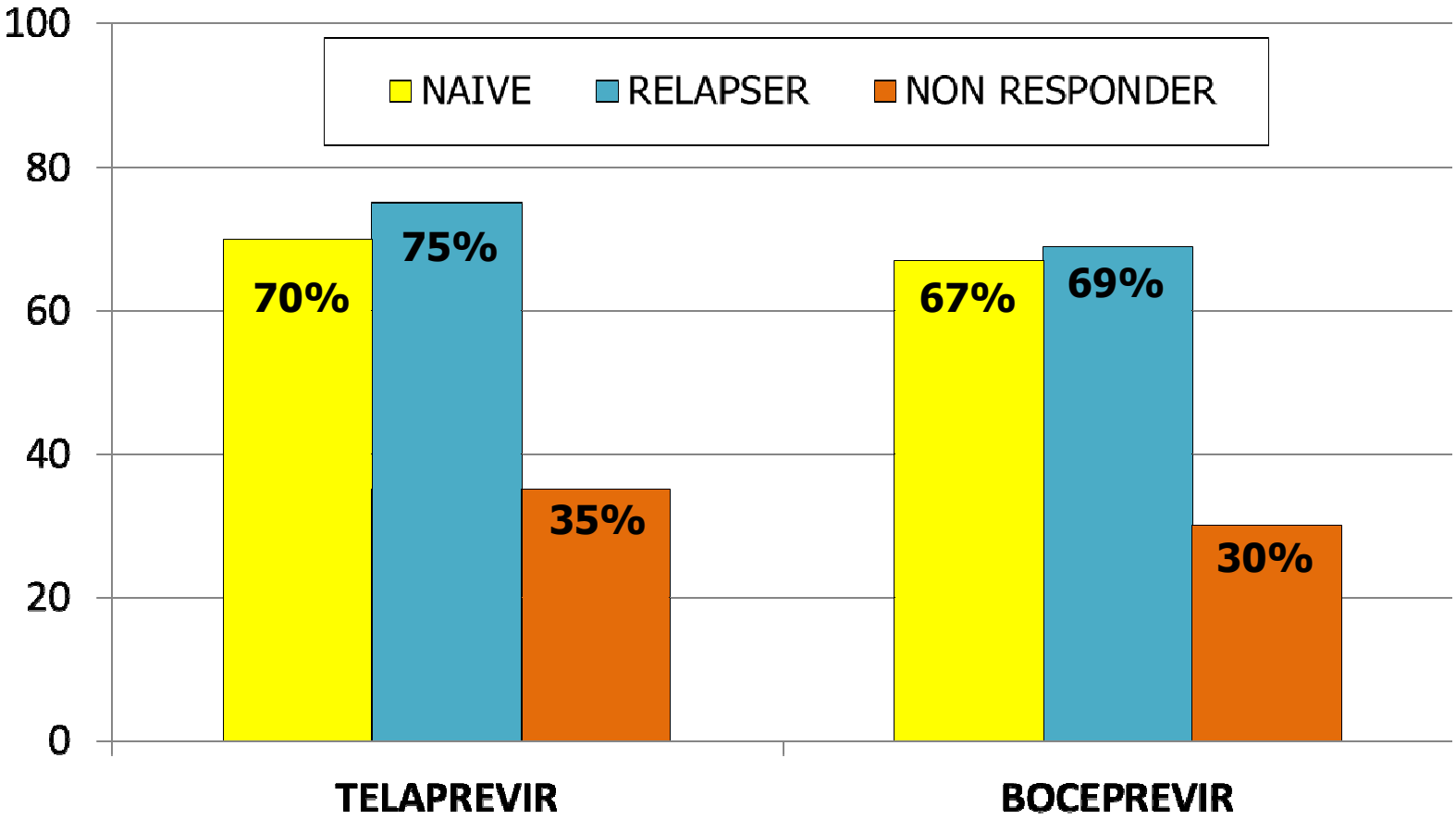
Se HCV-RNA ≥ 100 UI/mL alla settimana 12 sospendere il trattamento
Se HCV-RNA positivo alla settimana 24 sospendere il trattamento

Importanza della ribavirina in combinazione con gli inibitori della proteasi



P=Peg-IFN; **R**=Ribavirina; **T**=Telaprevir; **B**= Boceprevir

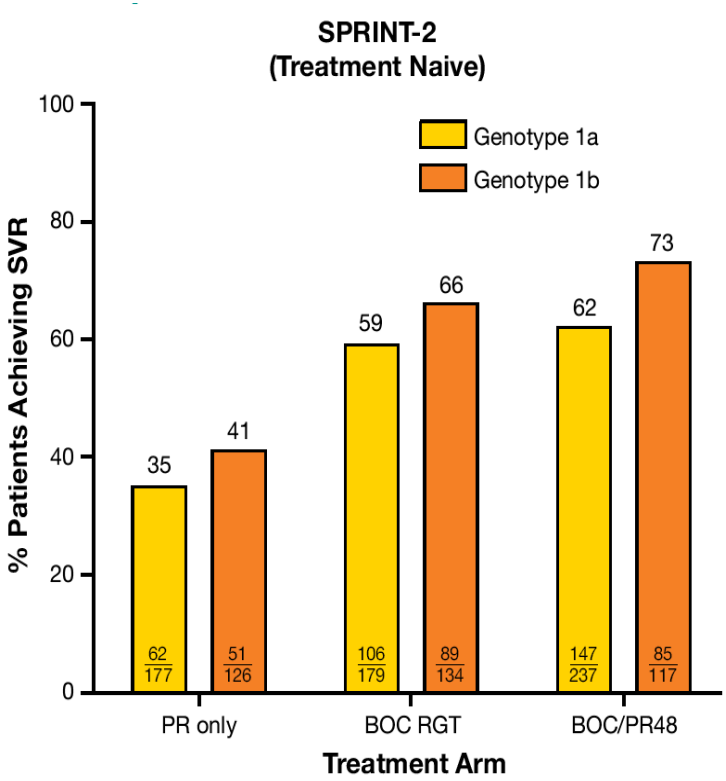
Tassi di risposta virologica sostenuta al trattamento con inibitori della proteasi sulla base degli studi clinici pubblicati

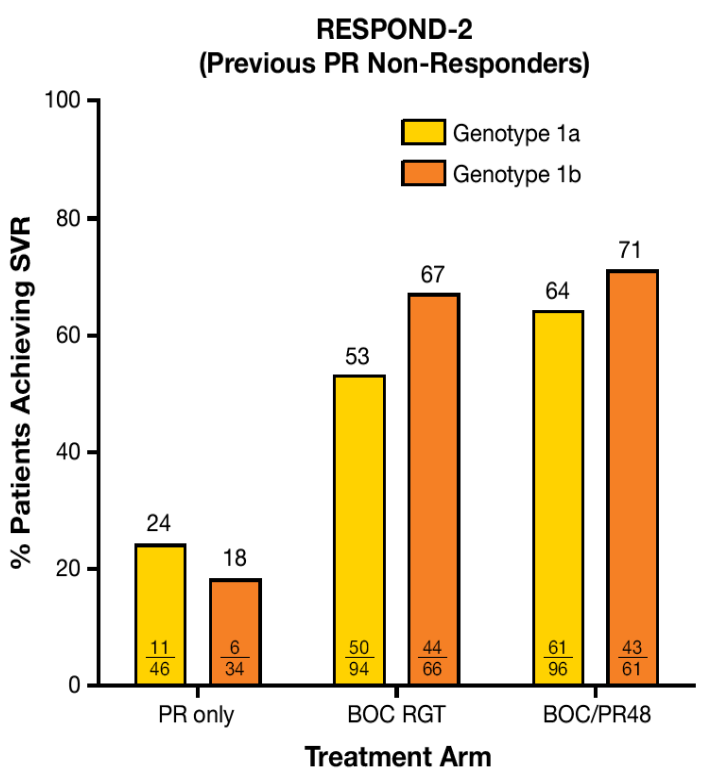


Poordad F, et al. AASLD 2010. Abstract LB-4. Jacobson IM, et al. AASLD 2010. Abstract 211. Bacon BR, et al. AASLD 2010. Abstract 216. Foster GR, et al. APASL 2011. Abstract 1529.

SPRINT-2/RESPOND-2

SVR rates were higher in G1b patients vs G1a

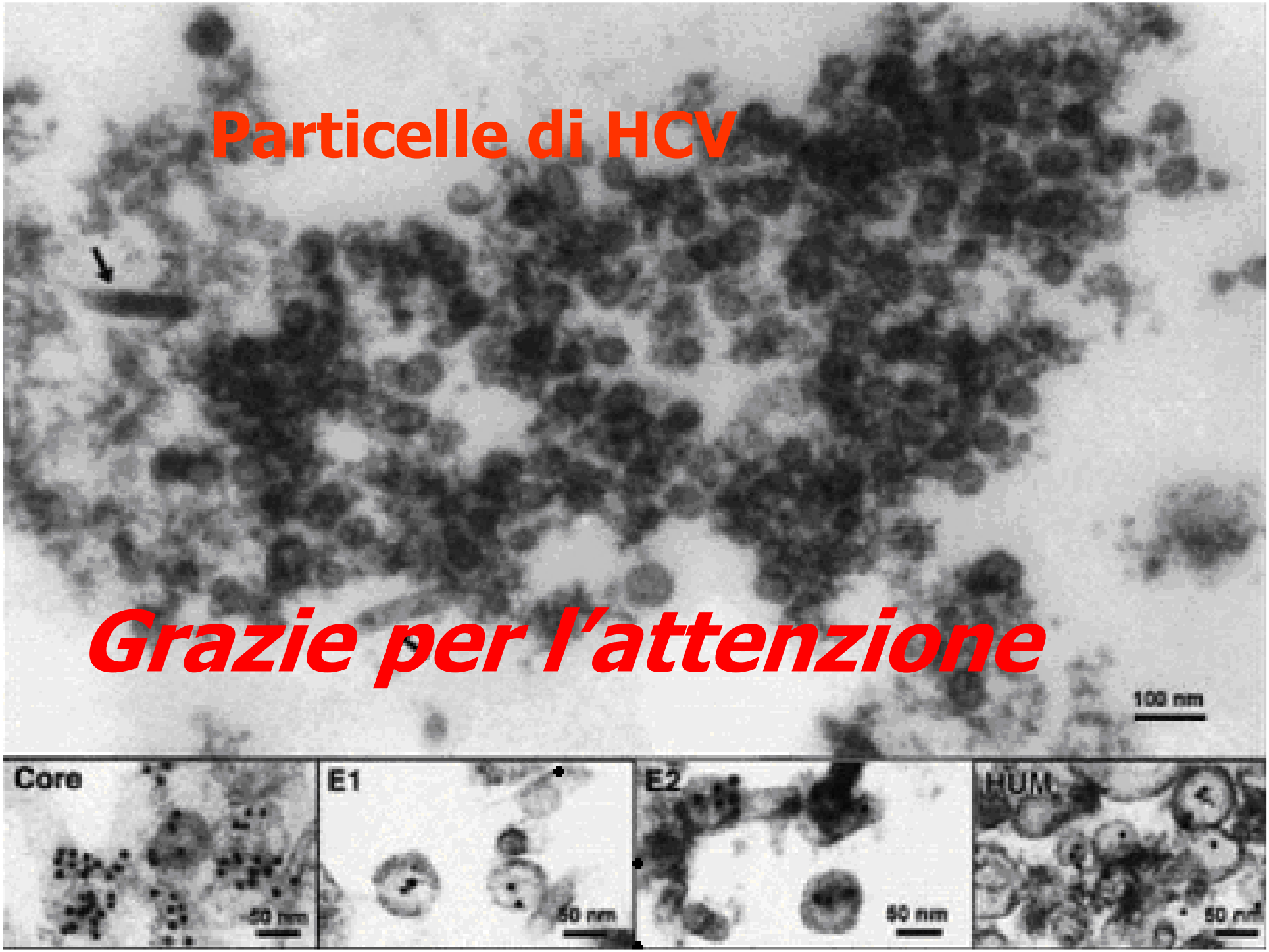




Brass C. et al. EASL 2011. J Hepatol 2011: 54: S471 (abstract 1194)

Nuove prospettive terapeutiche nel trattamento dell'epatite cronica da HCV

PRO:	**CONTRO:**
▪ Aumento SVR ▪ Qualche speranza per i non-responders ▪ Riduzione della durata del trattamento	▪Problemi legati all'aderenza ▪Costi elevati ▪Complessità dello schema terapeutico ▪**Tossicità** (rash cutaneo da telaprevir – anemizzazione da boceprevir) ▪Resistenza virale


Particelle di HCV
Grazie per l'attenzione
100 nm
Core
50 nm
E1
50 nm
E2
50 nm
HUM
50 nm

ERROR: undefined
OFFENDING COMMAND: Stato

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(11)
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