

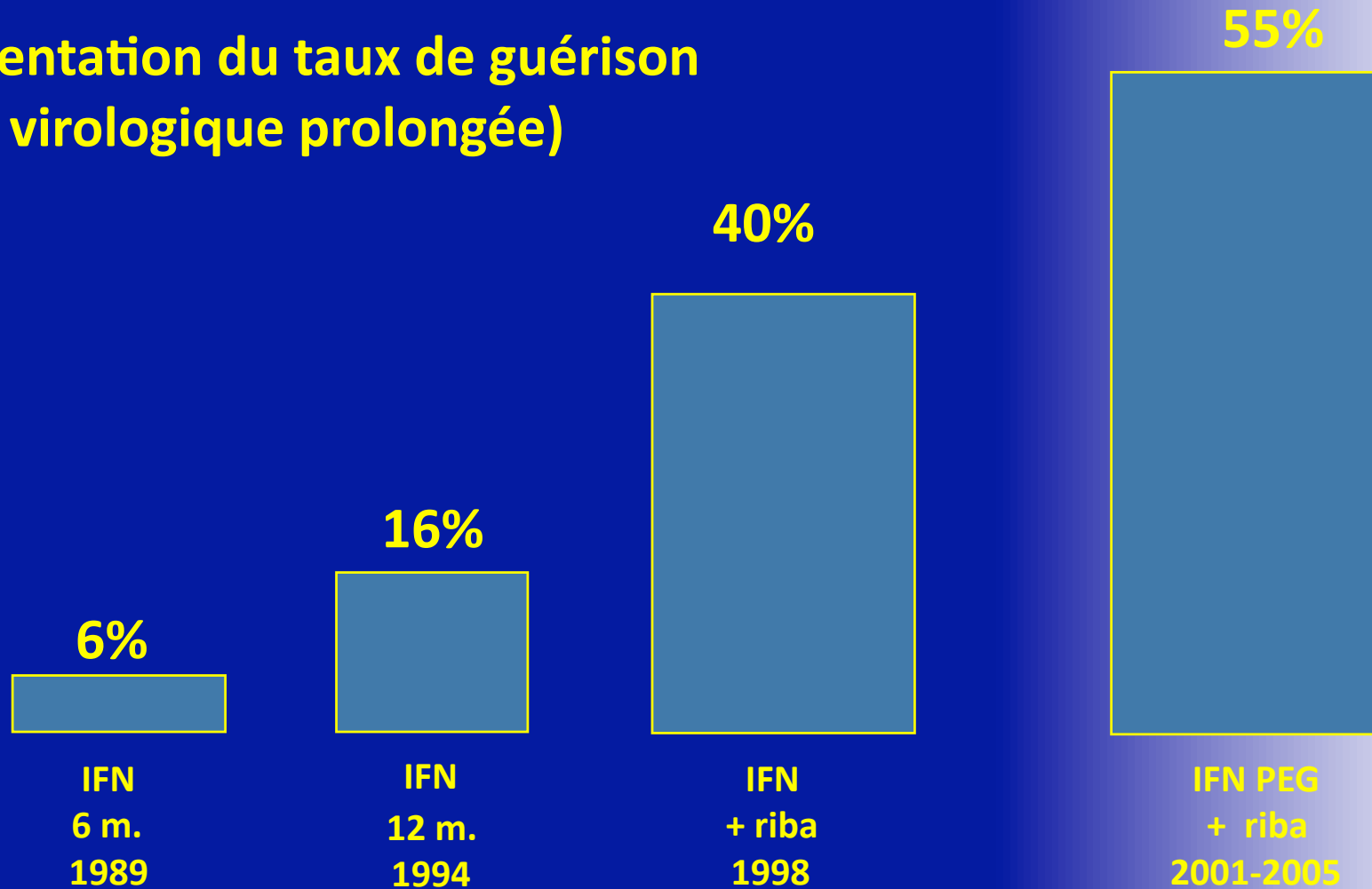
*5^e Réunion annuelle de pathologie digestive
Hôpital Cochin - Hôtel Dieu
6 février 2009*

VHC: nouveaux traitements

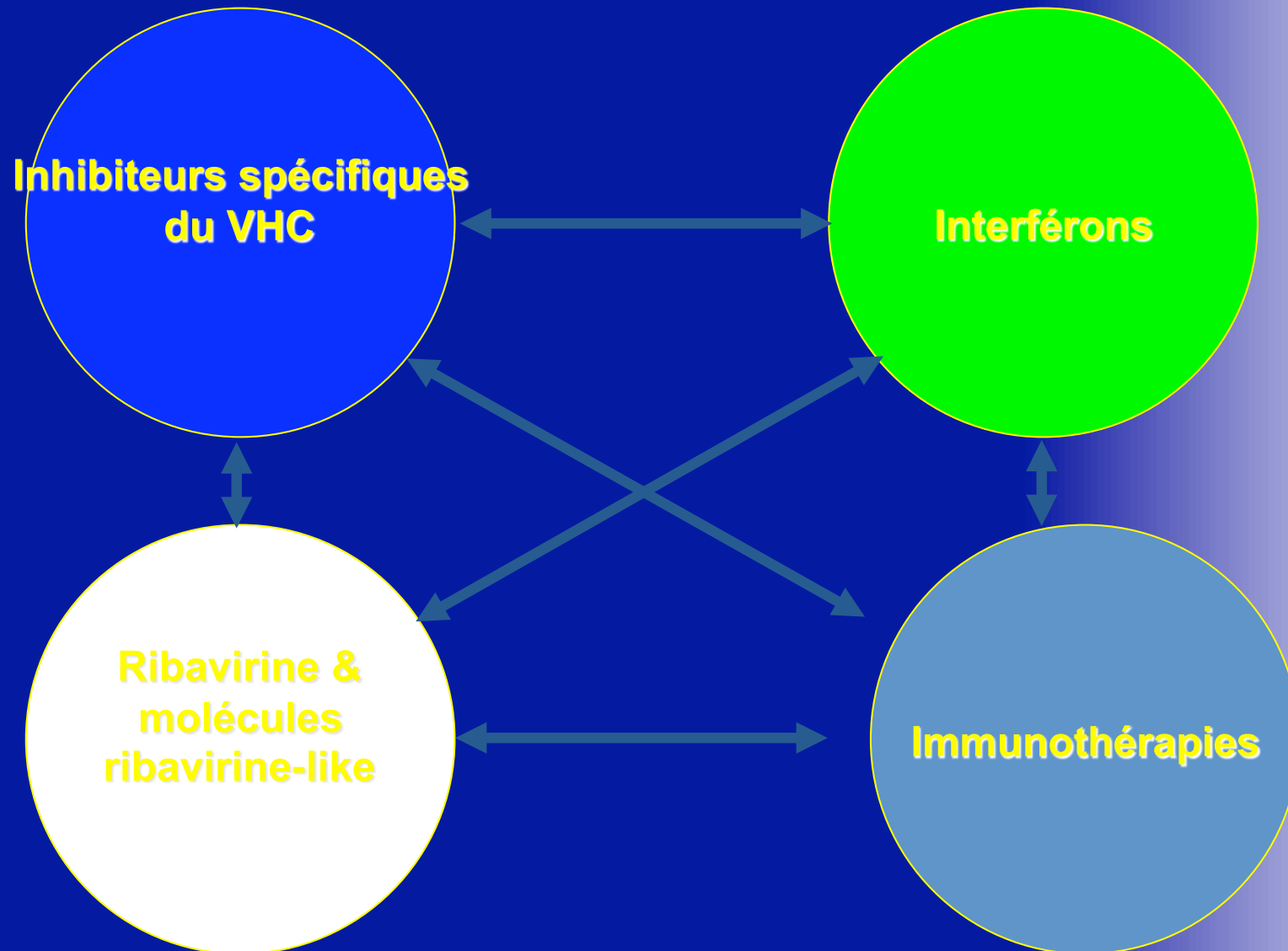
Stanislas Pol, MD, PhD
Université Paris Descartes
Unité d'Hépatologie & Inserm U-567
Hôpital Cochin, Paris, France

Évolution et Optimisation des traitements antiviraux C

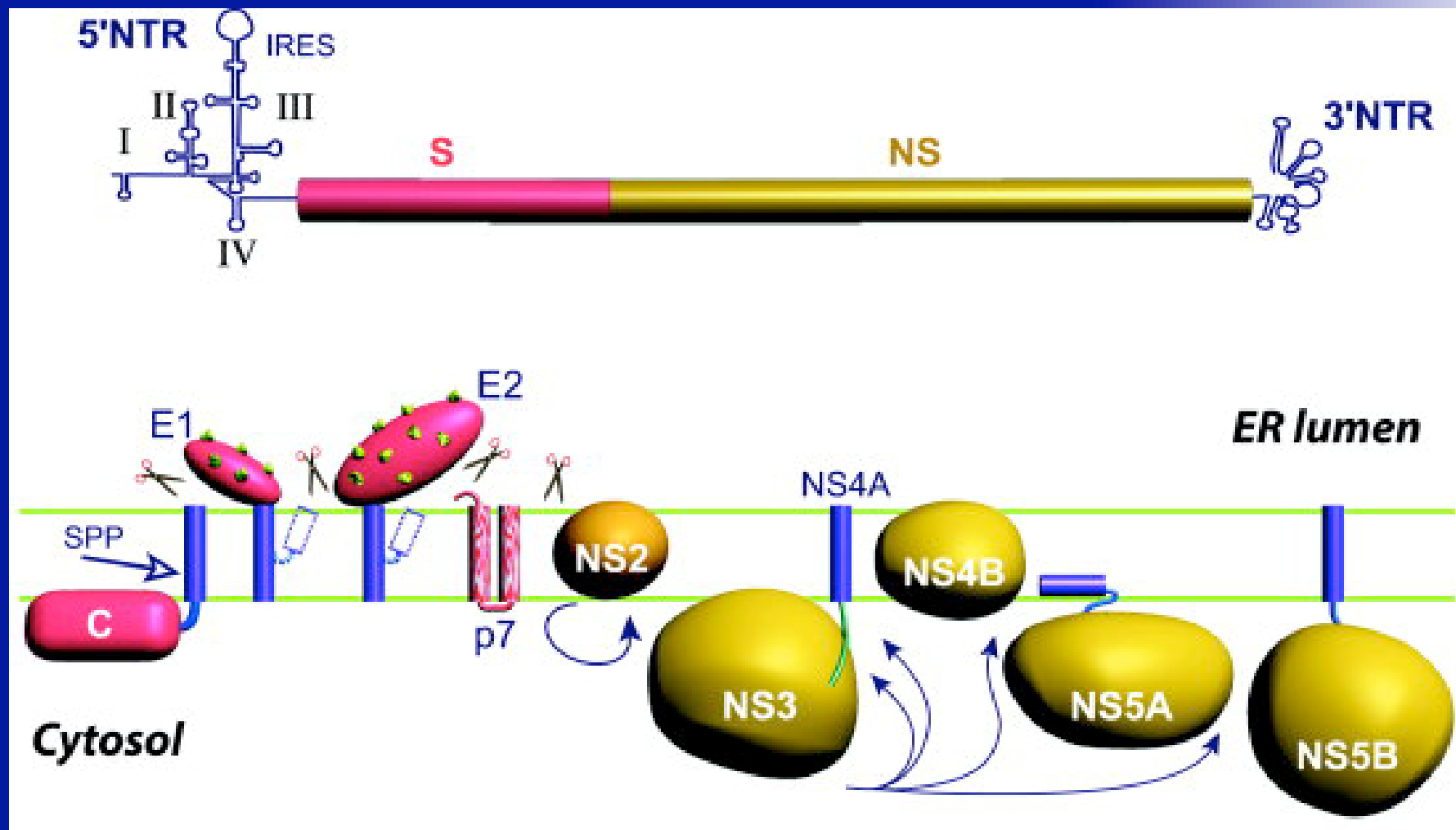
→ augmentation du taux de guérison
(réponse virologique prolongée)



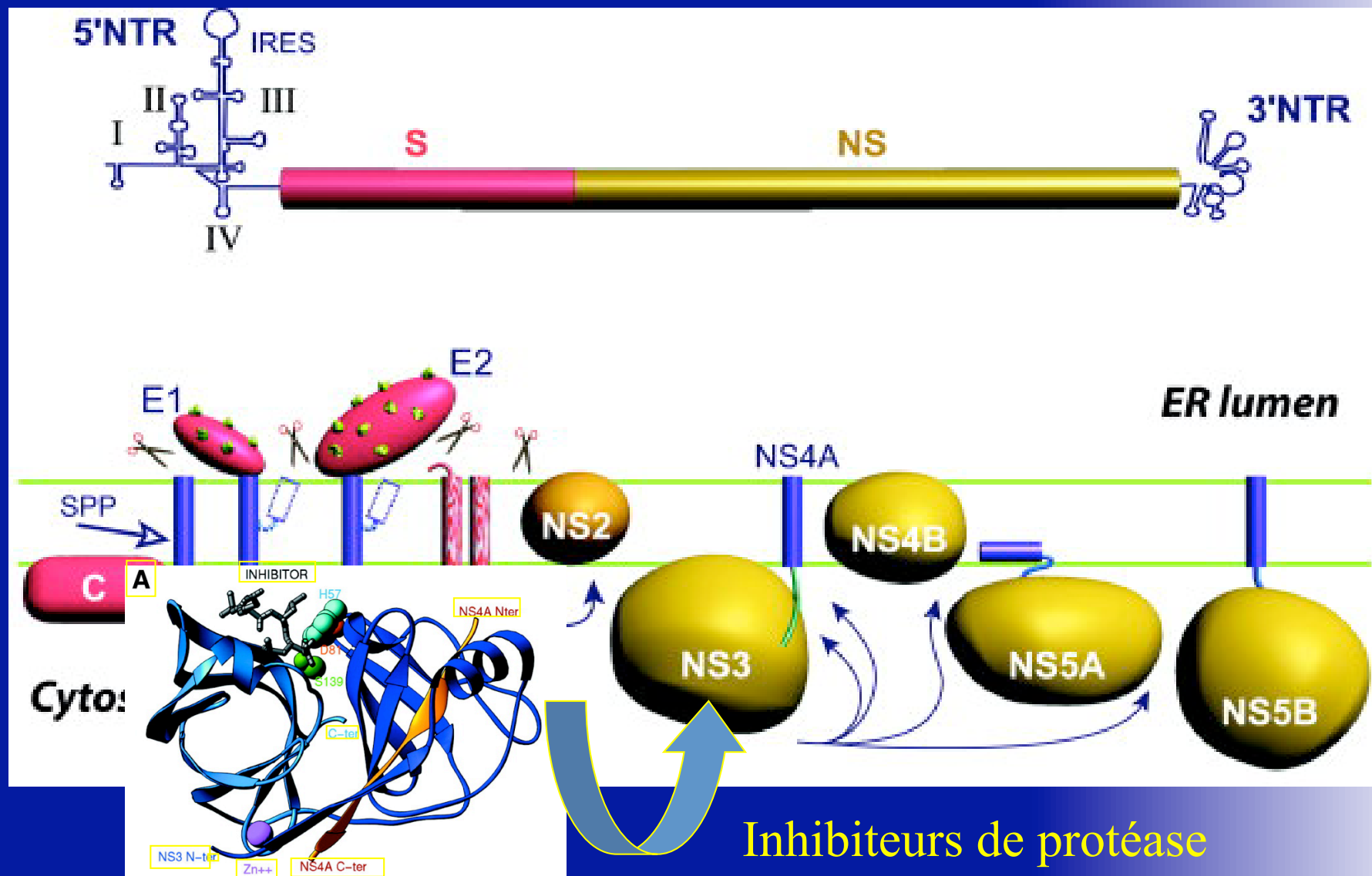
Les évolution des traitements antiviraux C



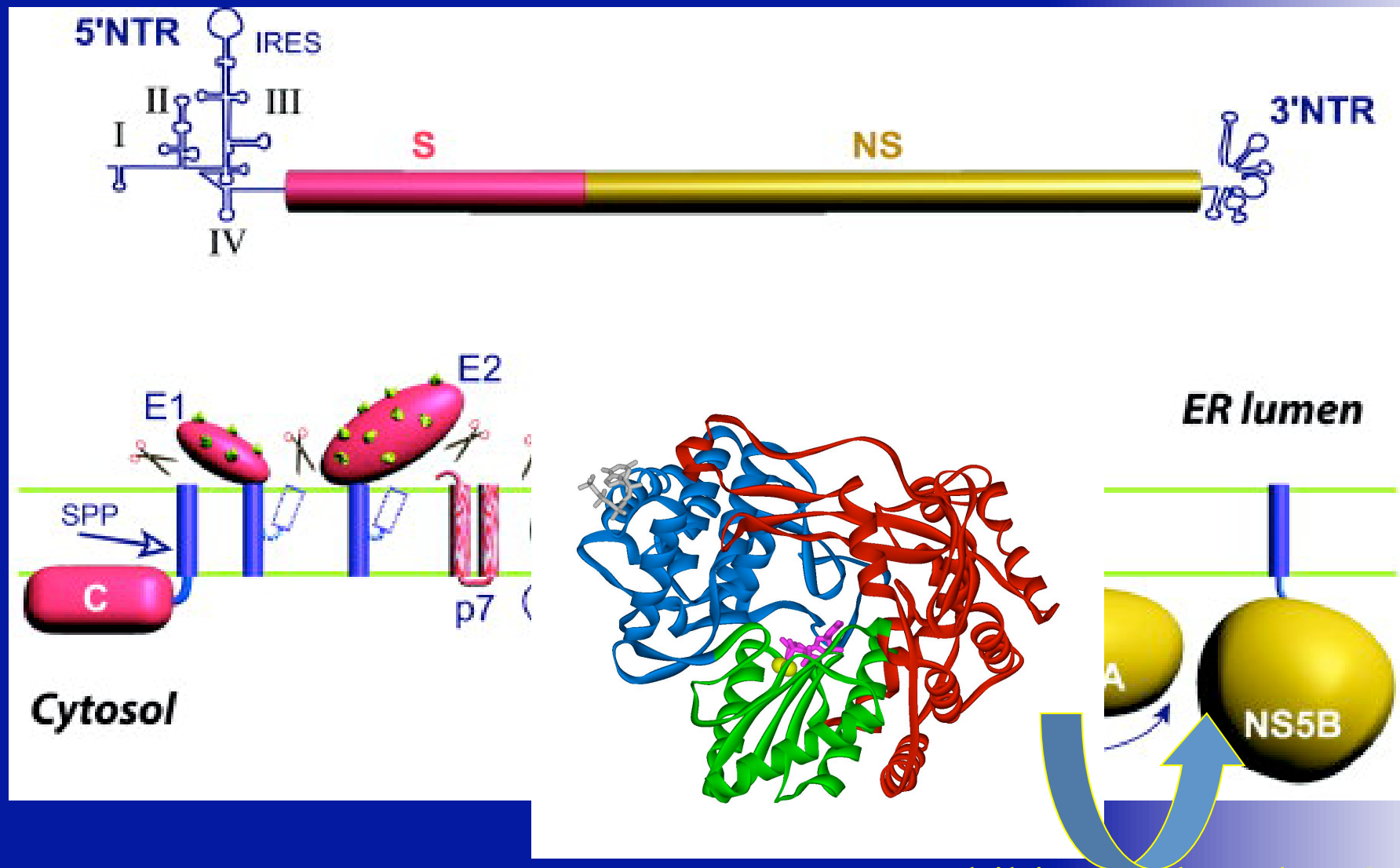
Les inhibiteurs spécifiques du VHC (STAT-C)



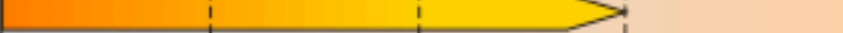
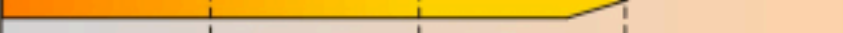
Les inhibiteurs spécifiques du VHC (STAT-C)



Les inhibiteurs spécifiques du VHC (STAT-C)



Inhibiteurs de polymérase

Drug name	Drug class	Preclinical	Phase I	Phase II	Phase III
Telaprevir (VX-950) (Janssen, tibotec)	<i>NS3/4 serine protease inhibitors</i>				
Boceprevir (SCH 503034) (Schering-Plough)	<i>NS3/4 serine protease inhibitors</i>				
BI201335 (Bohringer)	<i>NS3/4 serine protease inhibitors</i>				
TMC435350 (Tibotec, Medivir)	<i>NS3/4 serine protease inhibitors</i>				
R7227 (prodrug of ITMN-191) (Roche, Intermune)	<i>NS3/4 serine protease inhibitors</i>				
MK7009 (Merck)	<i>NS3/4 serine protease inhibitors</i>				
R1626 (prodrug of R1479) (Roche)	<i>NS5B RNA-dependent RNA-polymerase inhibitors</i> <u>Nucleoside analogues</u>				
R7128 (prodrug of PSI-6130) (Roche)	<i>NS5B RNA-dependent RNA-polymerase inhibitors</i> <u>Nucleoside analogues</u>				
GS-9190 (Gilead Sciences)	<i>NS5B RNA-dependent RNA-polymerase inhibitors</i> <u>Non-nucleoside analogues</u>				
A-831 (Astra Zeneca, Arrow)	<i>NS5A inhibitors</i>				

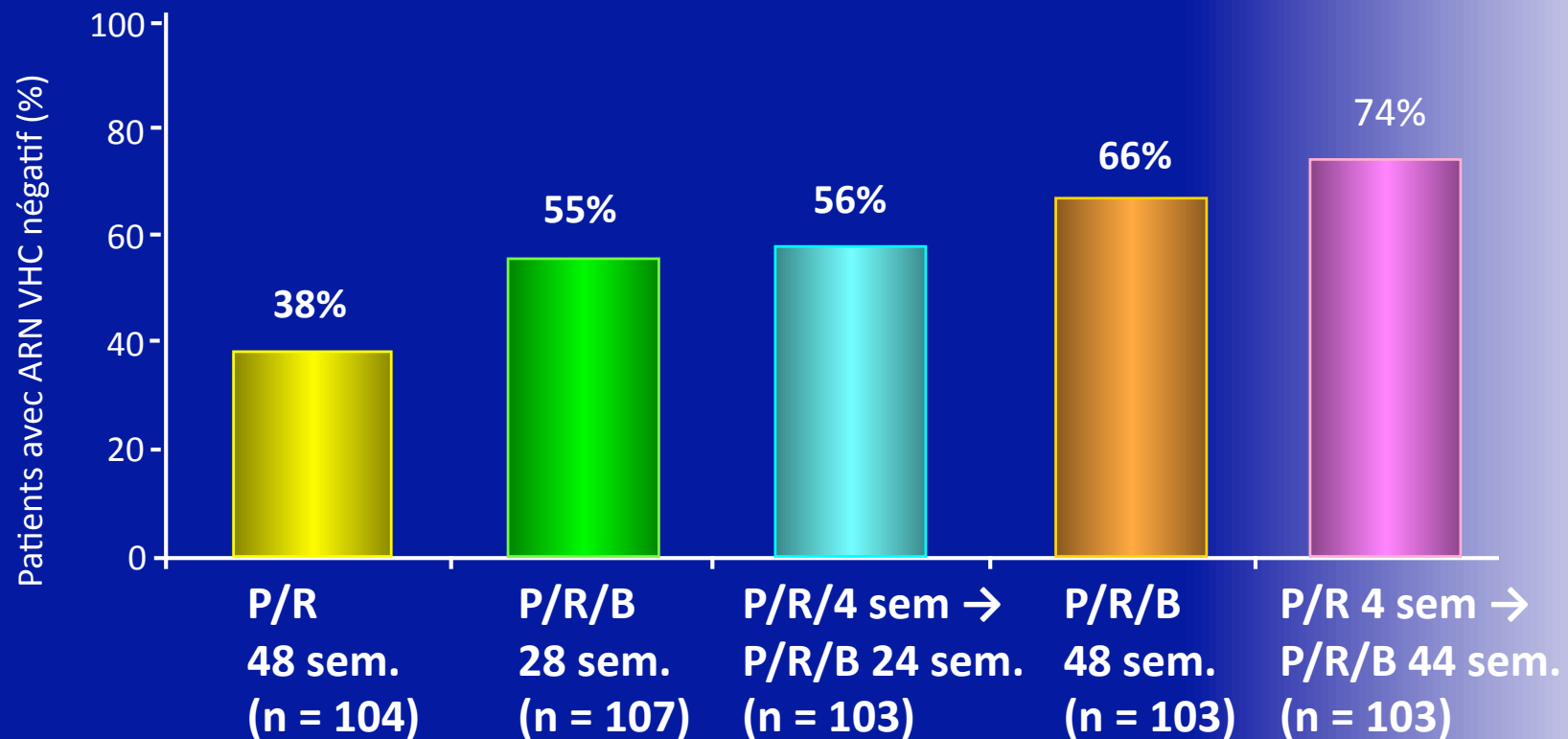
SPRINT-1 : boceprevir chez les malades naïfs de génotype 1

- Étude de phase II, randomisée, contrôlée
- Patients de génotype 1 naïfs de tout traitement



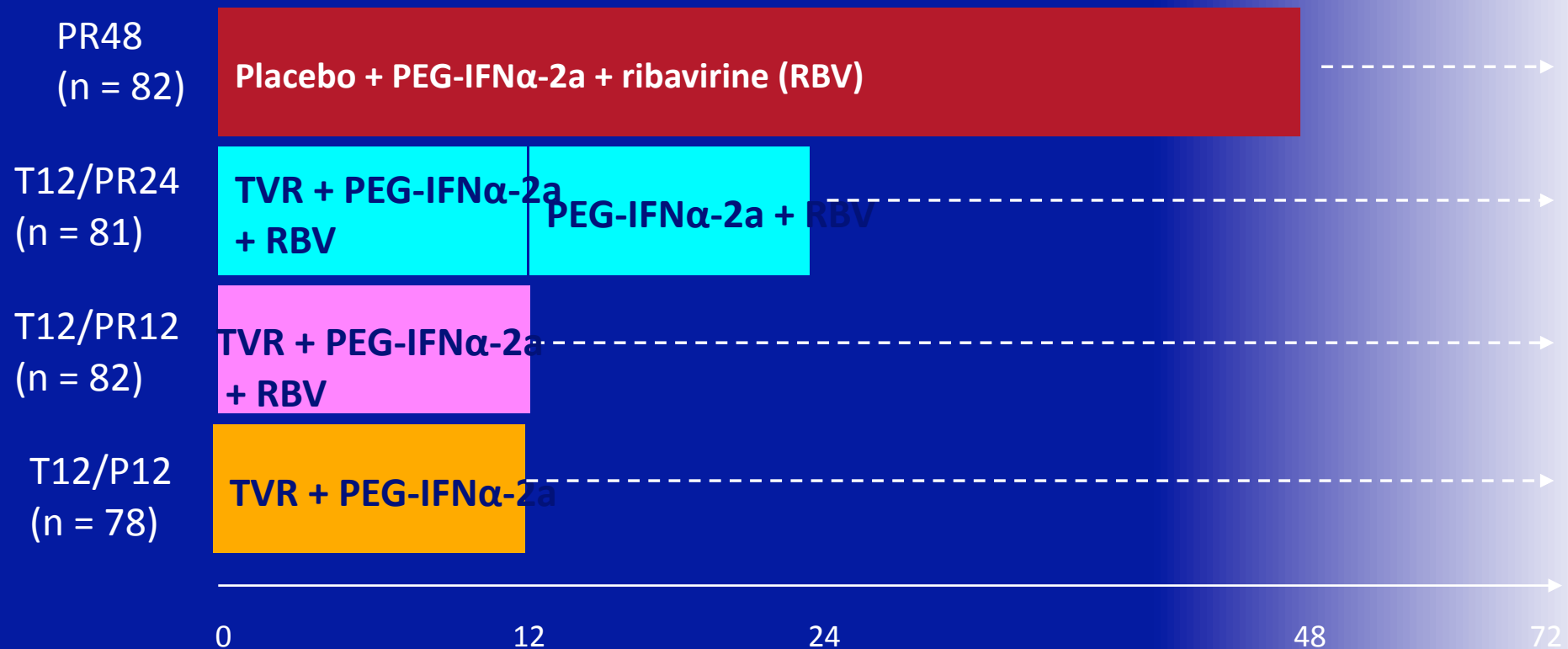
SPRINT-1 : boceprevir chez les patients naïfs de génotype 1

Réponse virologique 12 ou 24 semaines après arrêt du traitement (ITT)



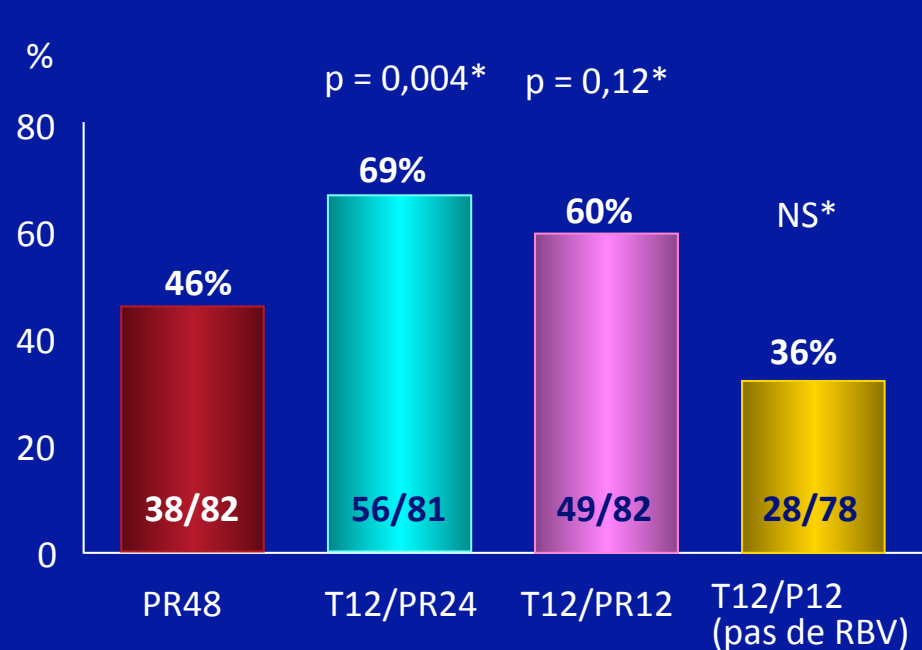
Télaprévir : étude européenne PROVE2

- Étude de phase IIb, randomisée, contrôlée, multicentrique chez 323 patients européens naïfs, génotype 1, sans cirrhose
- Télaprévir (TVR) 750 mg/8 heures, PEG-IFN 180 µg/sem, RBV 1 000-1 200 mg/j



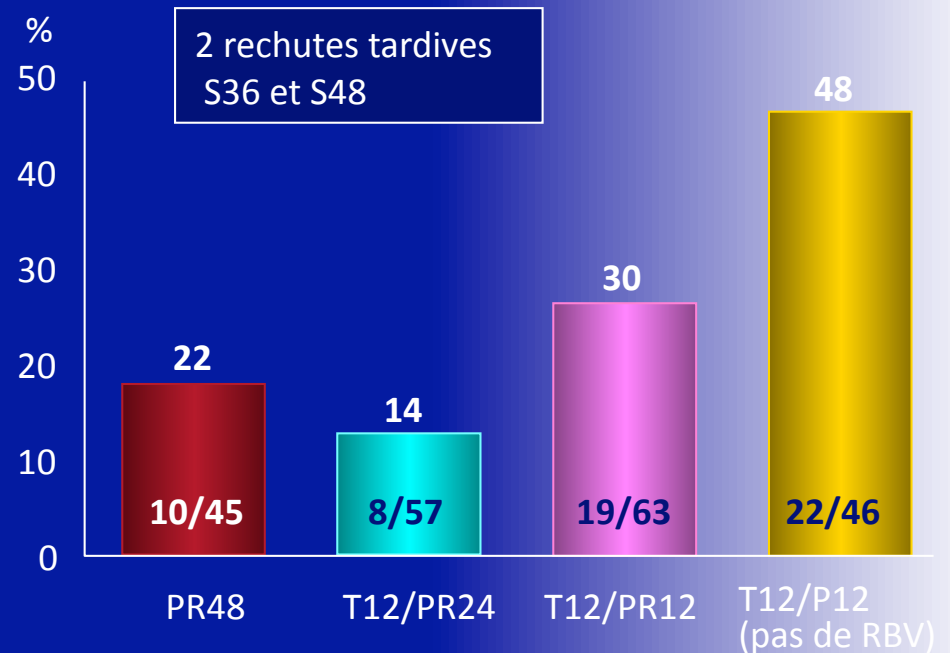
Télaprévir : étude européenne PROVE2

Réponse virologique soutenue



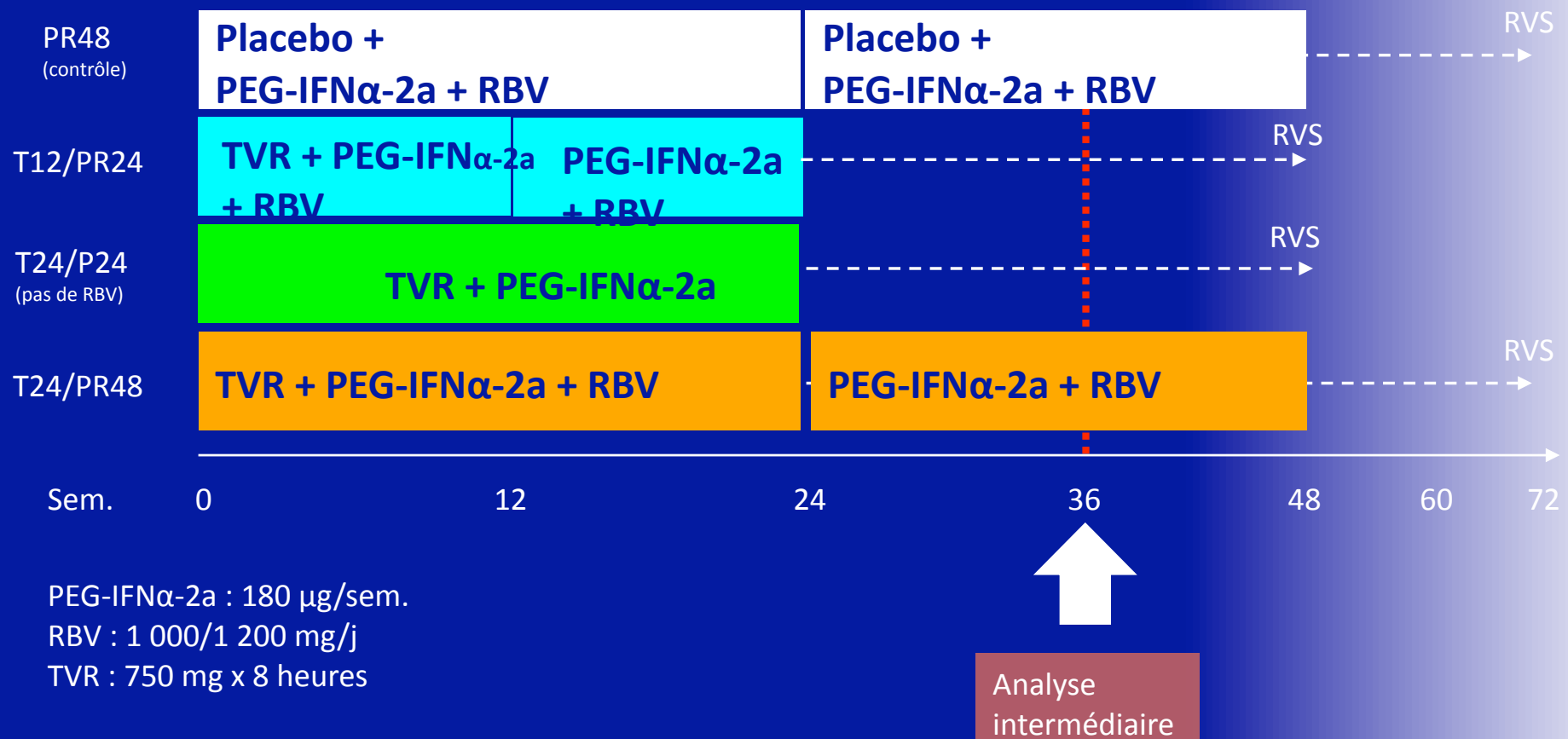
* versus PR48

Rechute (%)



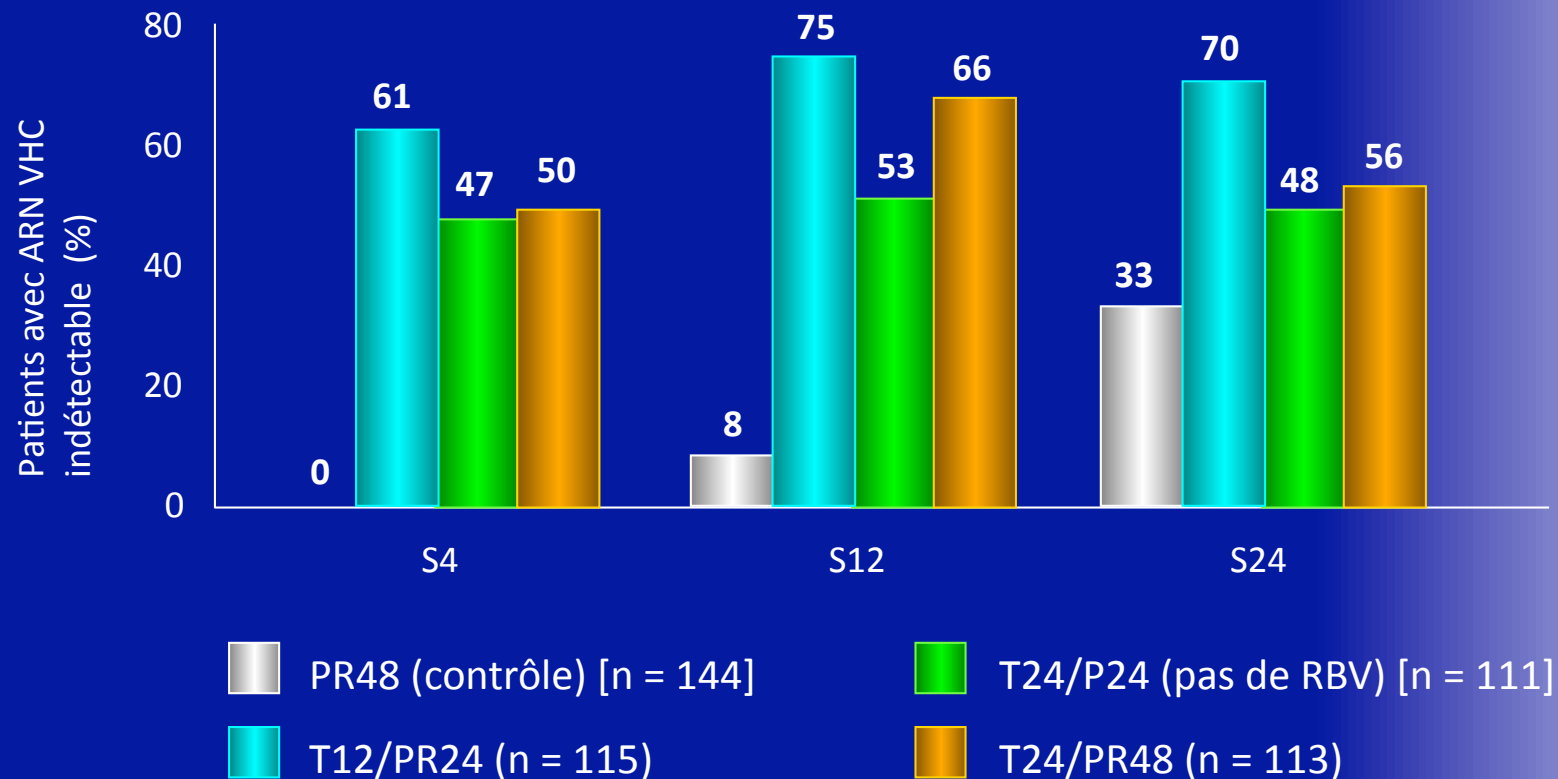
PROVE3 : téléprévoir chez les non répondeurs/rechuteurs génotype 1

- Étude randomisée contrôlée de phase IIb : 453 patients génotype 1 non répondeurs à une bithérapie pégylée



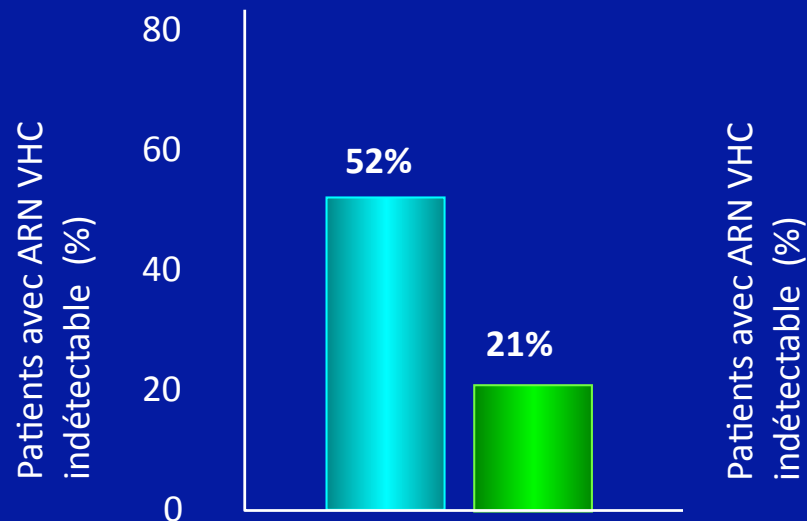
PROVE3 : téléprévir chez les non répondeurs/rechuteurs génotype 1

Réponse virologique sous traitement (ARN VHC indétectable)



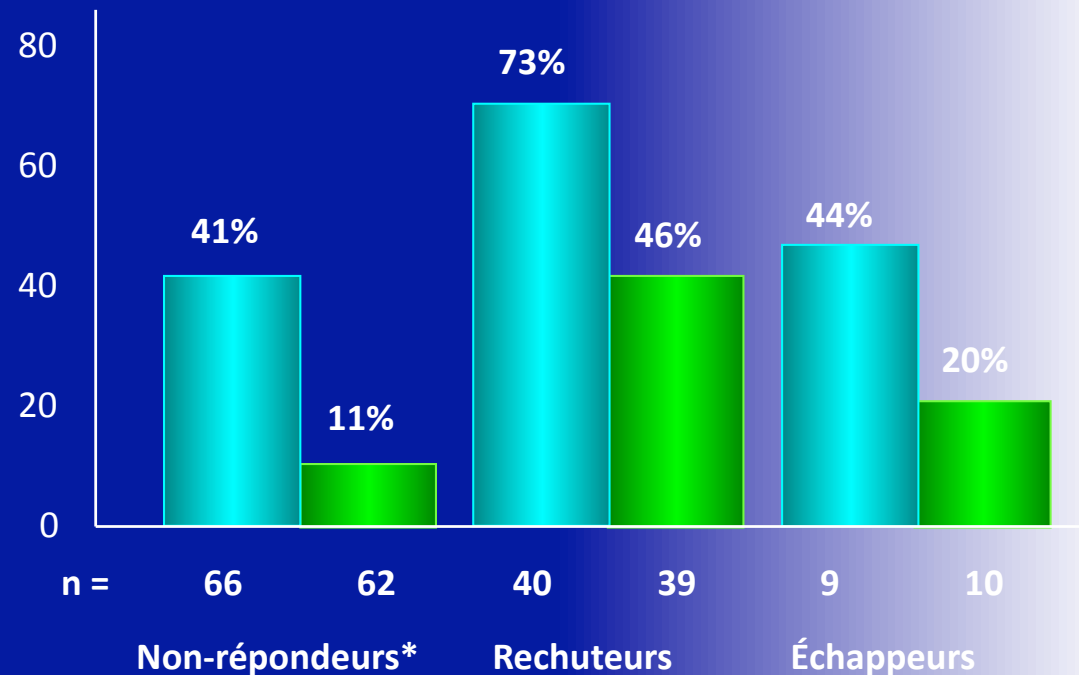
PROVE3 : téléprévir chez les non répondeurs/rechuteurs génotype 1

Réponse virologique
12 semaines après arrêt
de traitement (ITT)



T12/PR24 (n = 115)

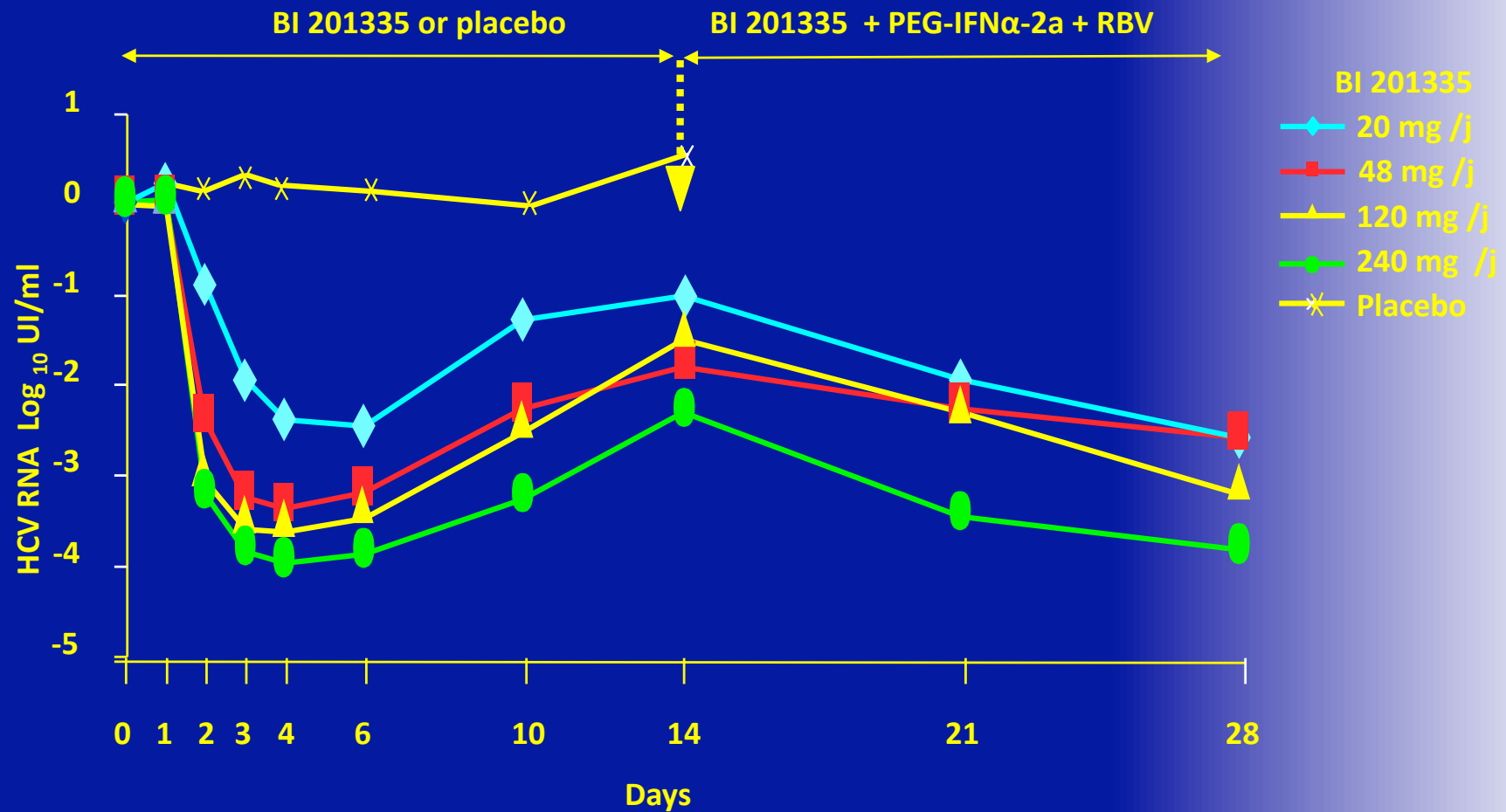
Réponse virologique
12 semaines après arrêt
de traitement (ITT)
selon la réponse antérieure



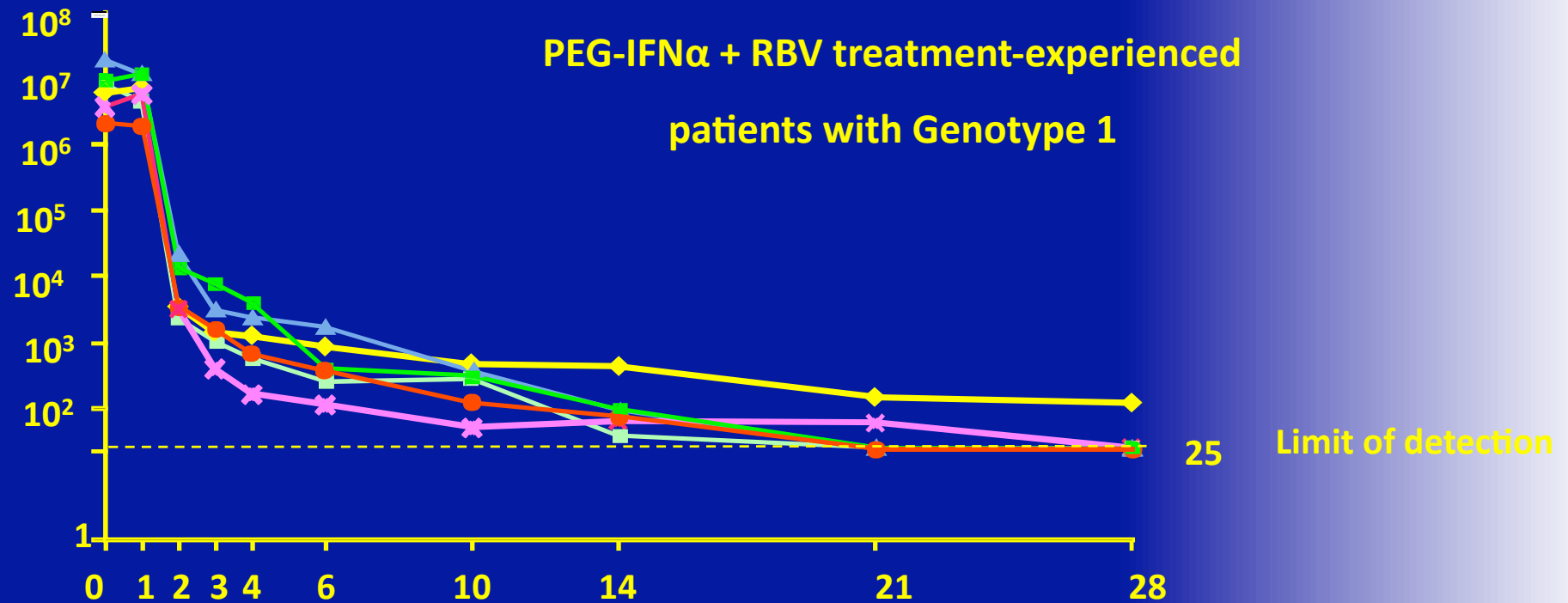
T24/P24 (pas de RBV) [n = 111]

* Vrais non-répondeurs et
non-répondeurs partiels¹⁴

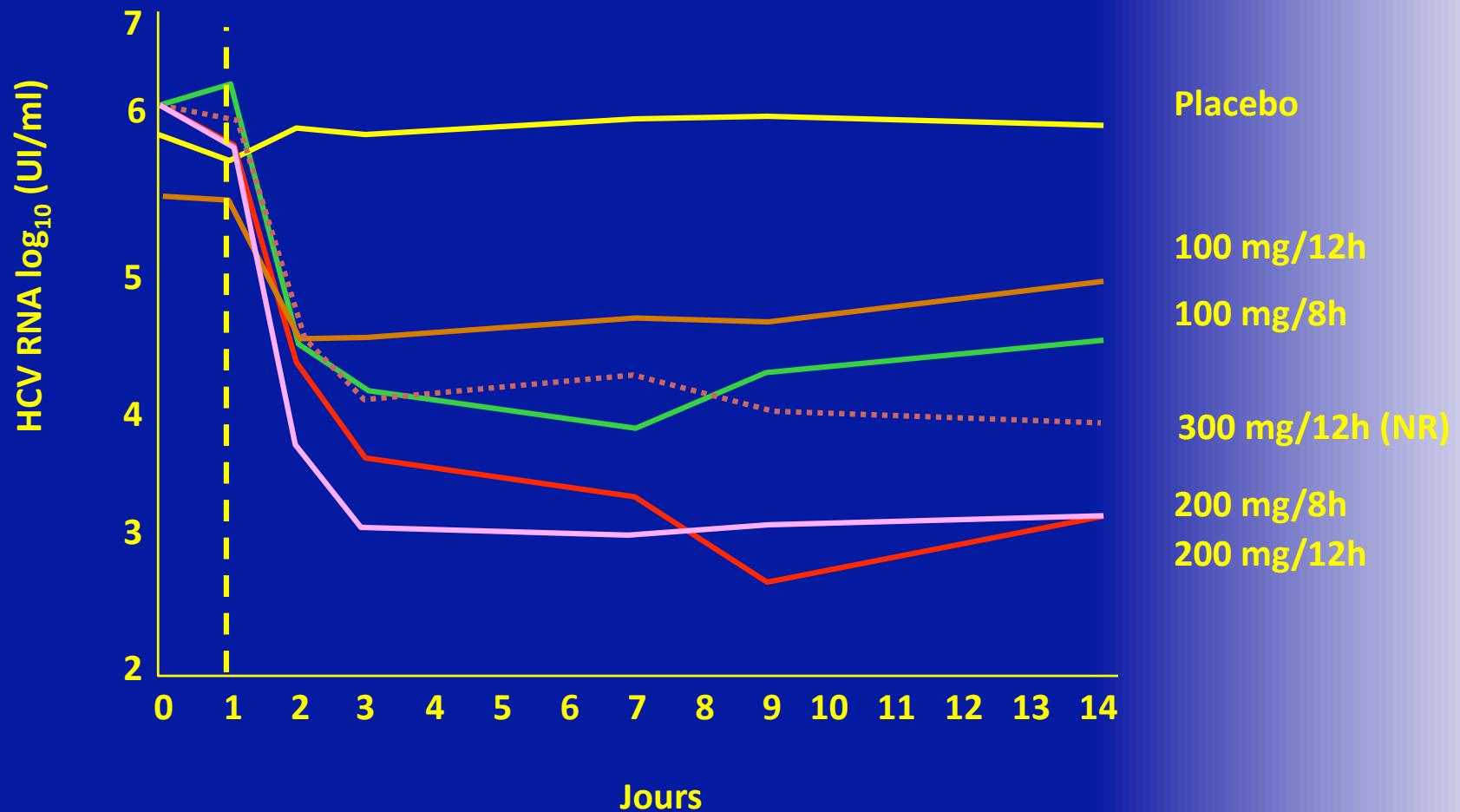
BI 201335 (Bohringer)



BI 201335 (Bohringer)



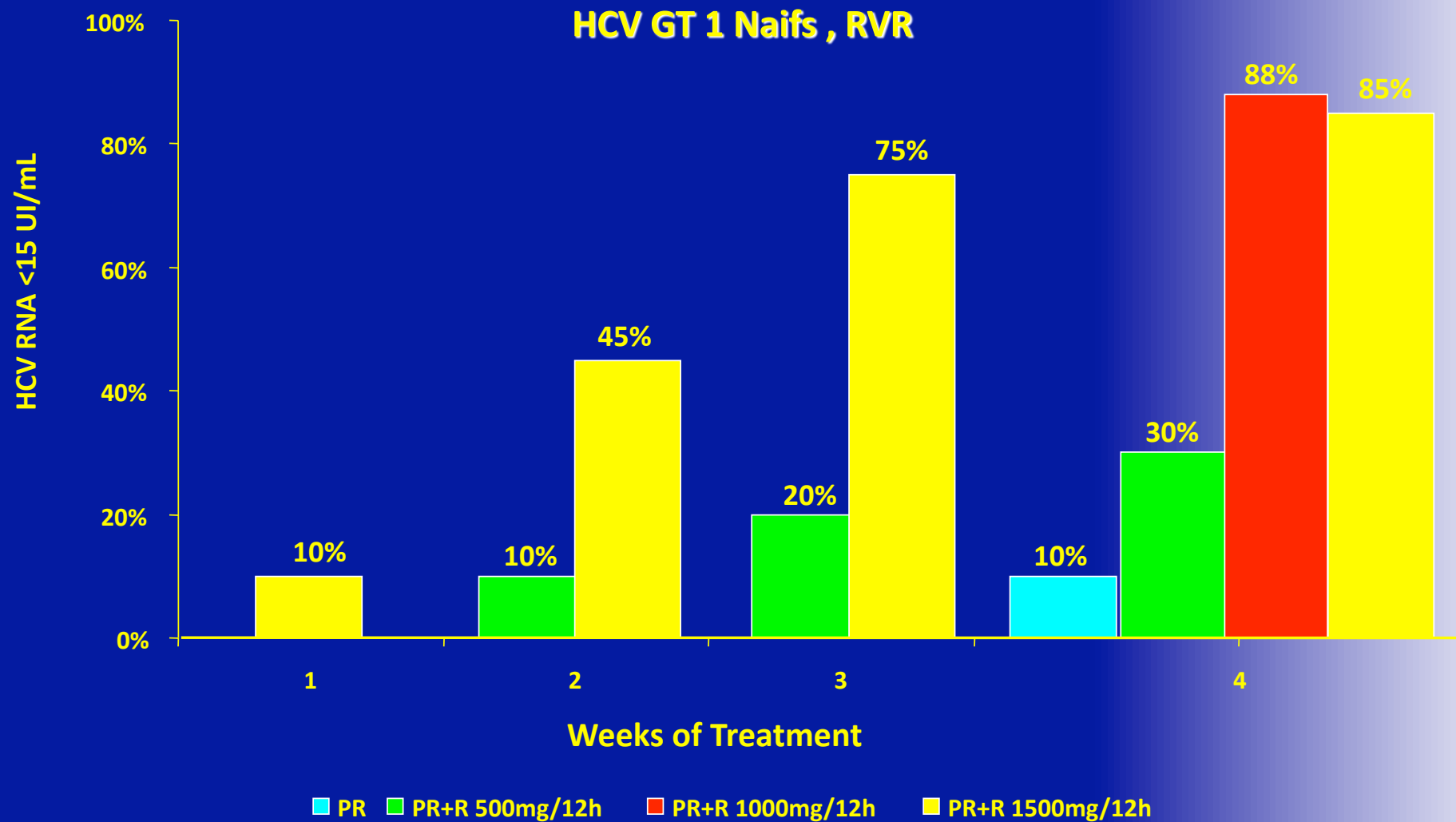
ITMN-191 (Intermune)



(NR) : non-responders to PEG-IFN α + RBV

AASLD 2008 - Forestier et al., A1847

R7128 (Pharmasset-Roche)



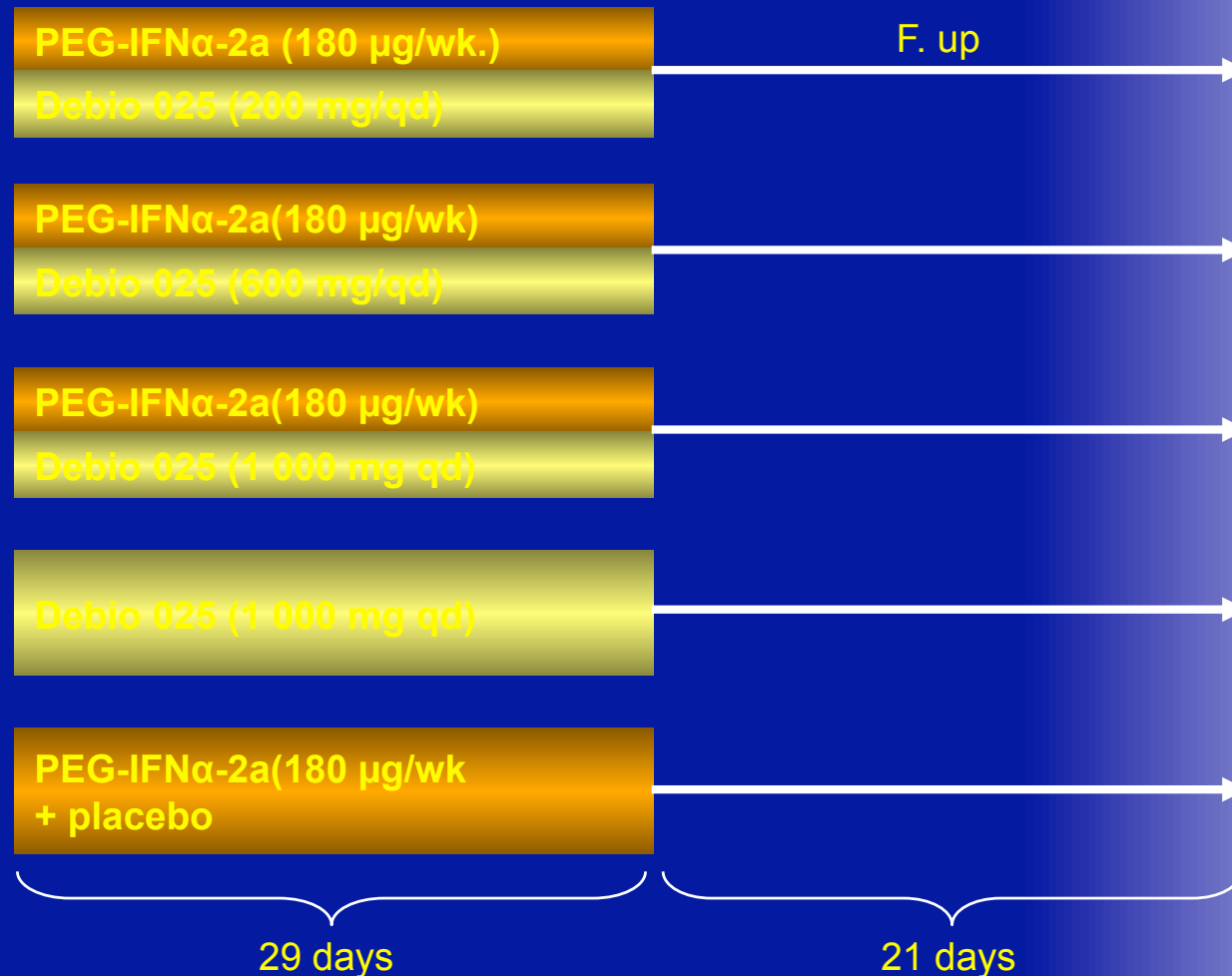
Lalezari et al. EASL 2008. Pharmasset. Press Release Sept 2008

Les antiviraux non »STAT-C«

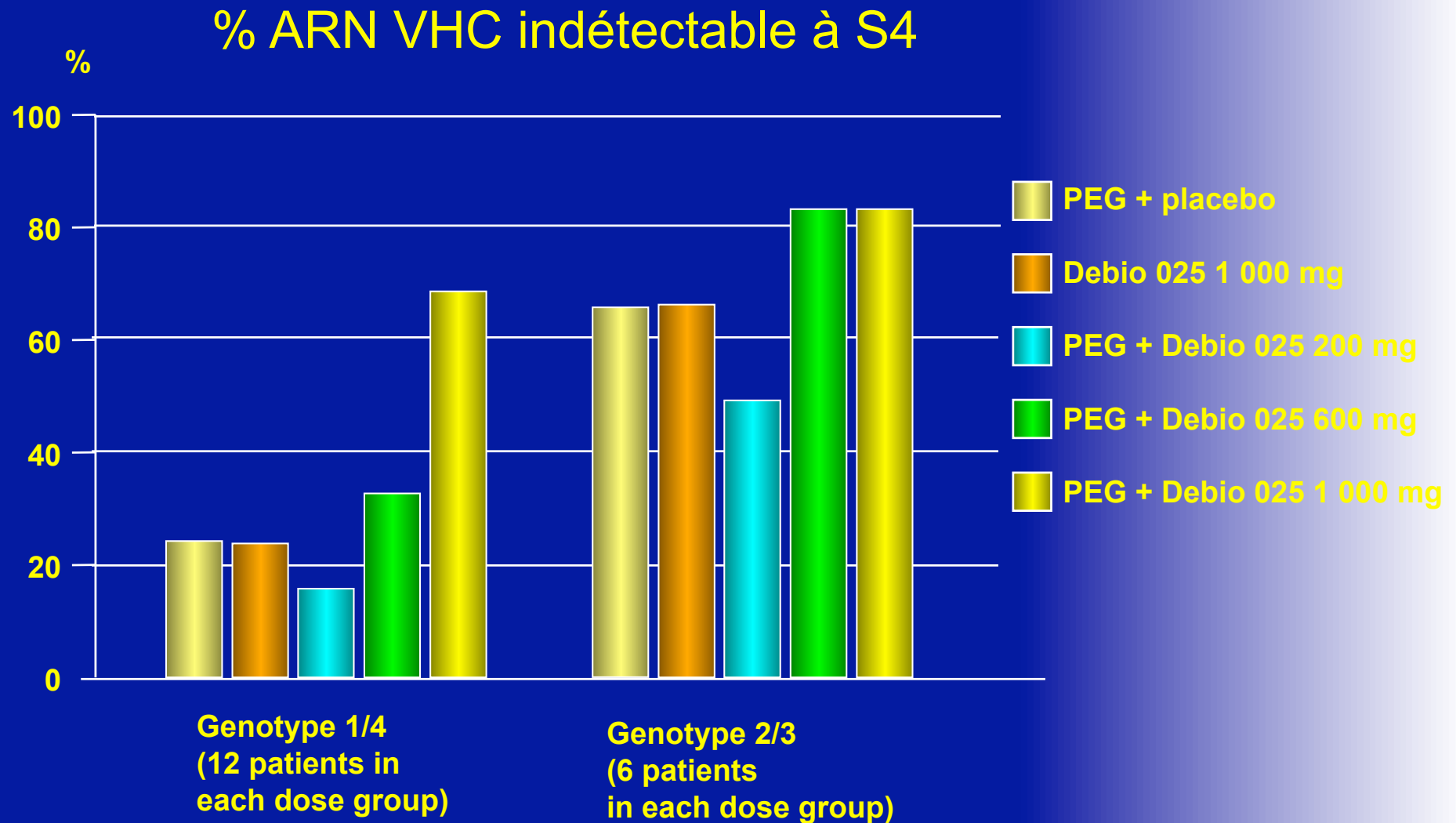
COMPANY	DRUG	Research	Preclin	P 1	P 2	P 3	NDA
Human Genome Sciences	AlbInterferon						
SciClone Pharma/Sigmatau	Zadaxin - thymalfasin						
SciClone Pharma	SCV-07 (immunomodulator)						
Migenix	Celgosivir (α glucosidase inhibitor)						
Intarcia	Omega Interferon						
NABI	Polyclonal antibody (Civacir)						
Transition Therapeutics	IET Interferon Enhancing Therapy						
Romark Laboratories	Alinia						
Biolex / OctoPlus	Locteron (controlled release IFN)						
VioQuest Pharmaceuticals	Lenocta (sodium stibogluconate)						
Conatus	CTS-1027 MMP inhibitor						
Enzo Biochem	Immune Regulator ECH18						
Immunomedics	IMMU 105						
Amarillo Bioscience	Low Dose Oral Interferon						
ZymoGenetics	PEG-Interferon lambda						
Novelos	NOV-205 immunomodulating						
Idera	IMO-2125 TLR9 Agonist						
Anadys	ANA773 TLR7 agonist						
Debiopharm	Debio 025 Cyclophilin Inhibitor						
Medarex / Ono	MDX-1106 (ONO-4538) anti-PD1						IND for HCV aproved
Cytheris	CYT107 Interleukin-7						
REPLICor	REP 9C broad-spectrum entry inhibitor						
Nautilus	Oral Belerofon						
Genodyssee	GEA007.1 IFN alpha variant						
Valeant	Taribavirin						

Inhibiteur de la cyclophylline: Debio 025

- Phase IIa, double-blinded, randomized, trial
- 90 HCV naive patients : GT 1/4 (n=60) and 2/3 (n=30)

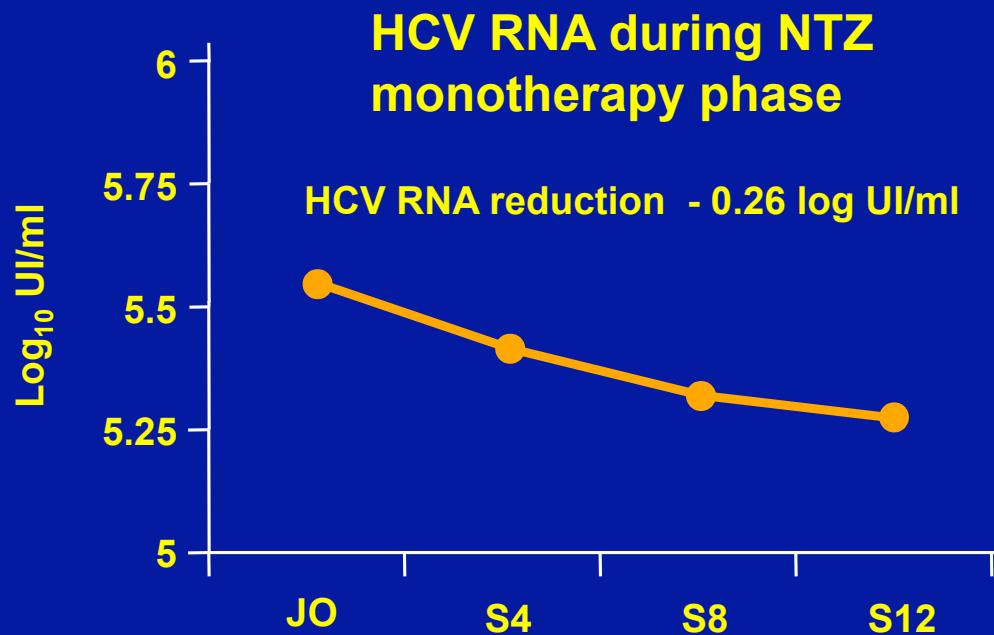


Inhibiteur de la cyclophylline: Debio 025



Nitazoxanide (NTZ)

STEALTH C-1 : HCV GT 4 Naive Patients

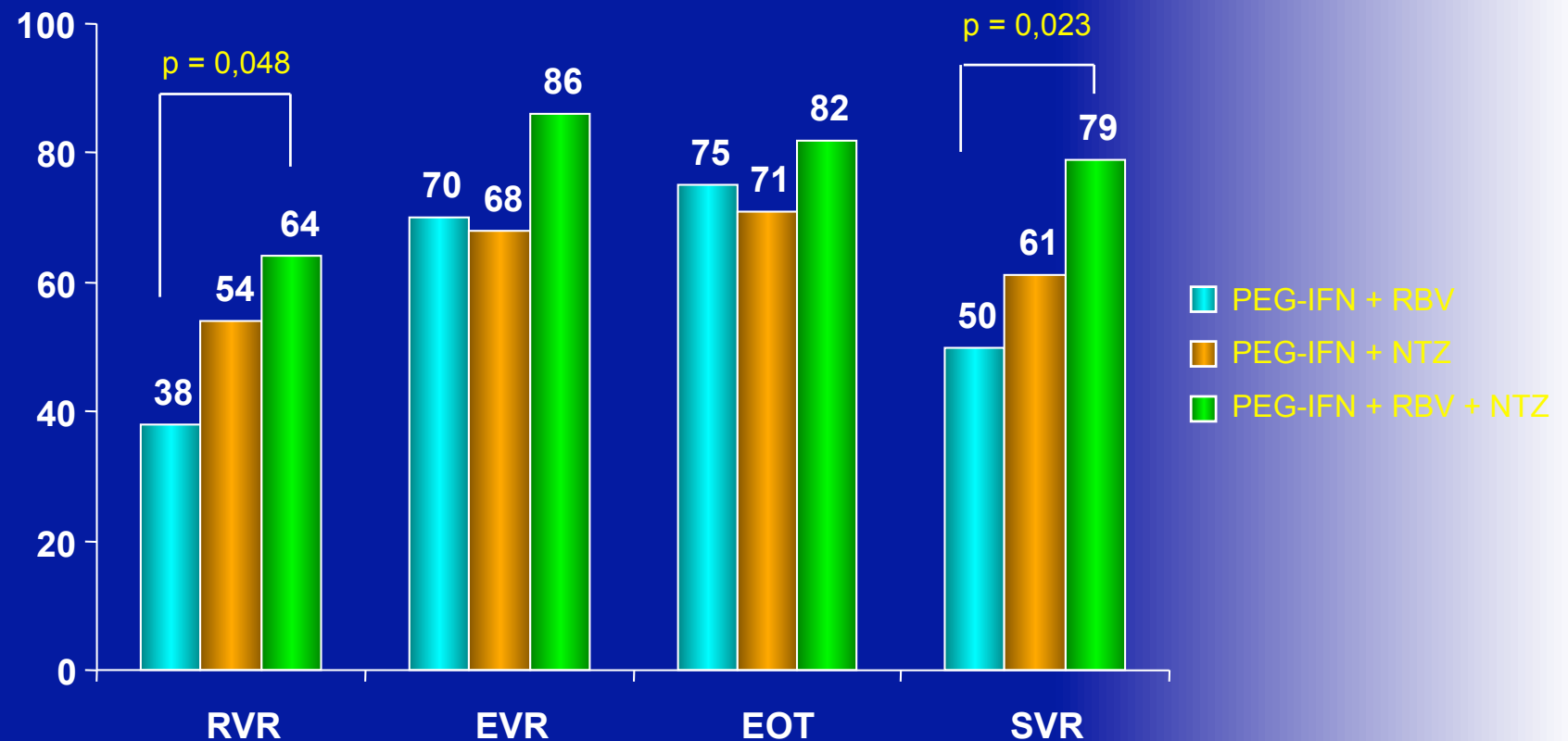


- 5: HCV RNA reduction > 1 log
- 1 patient undetectable

Nitazoxanide (NTZ)

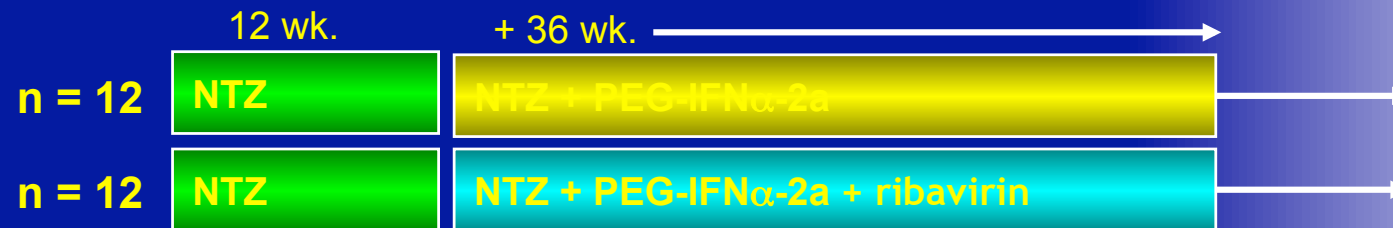
STEALTH C-1 : HCV GT 4 Naive Patients

Virologic Response

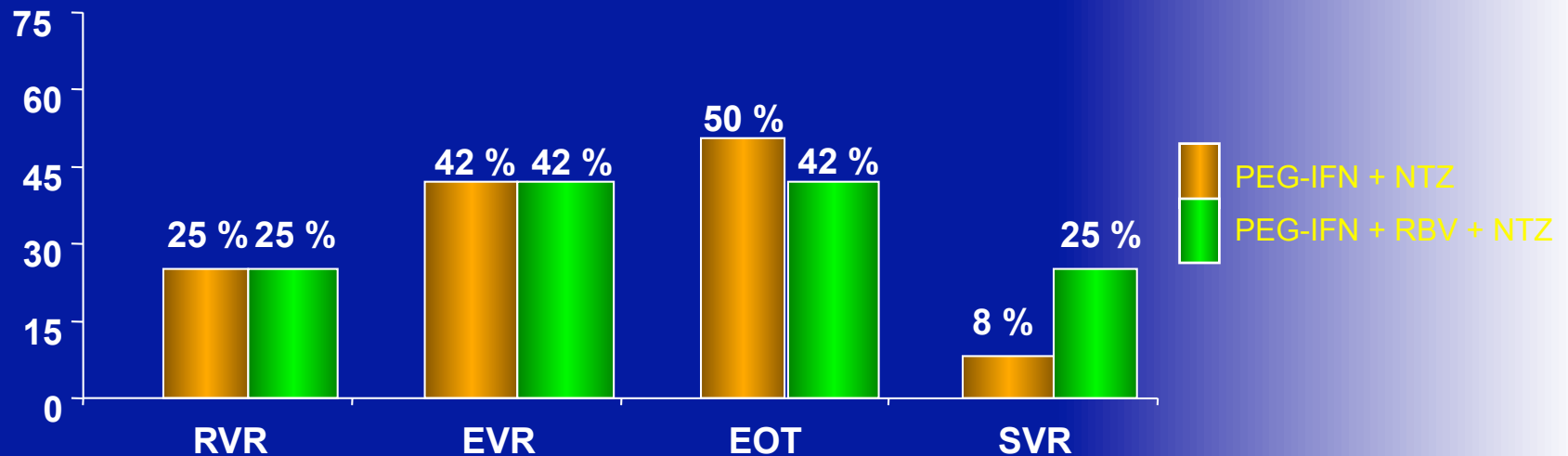


Nitazoxanide (NTZ)

STEALTH C-1 : HCV GT 4 NR Patients

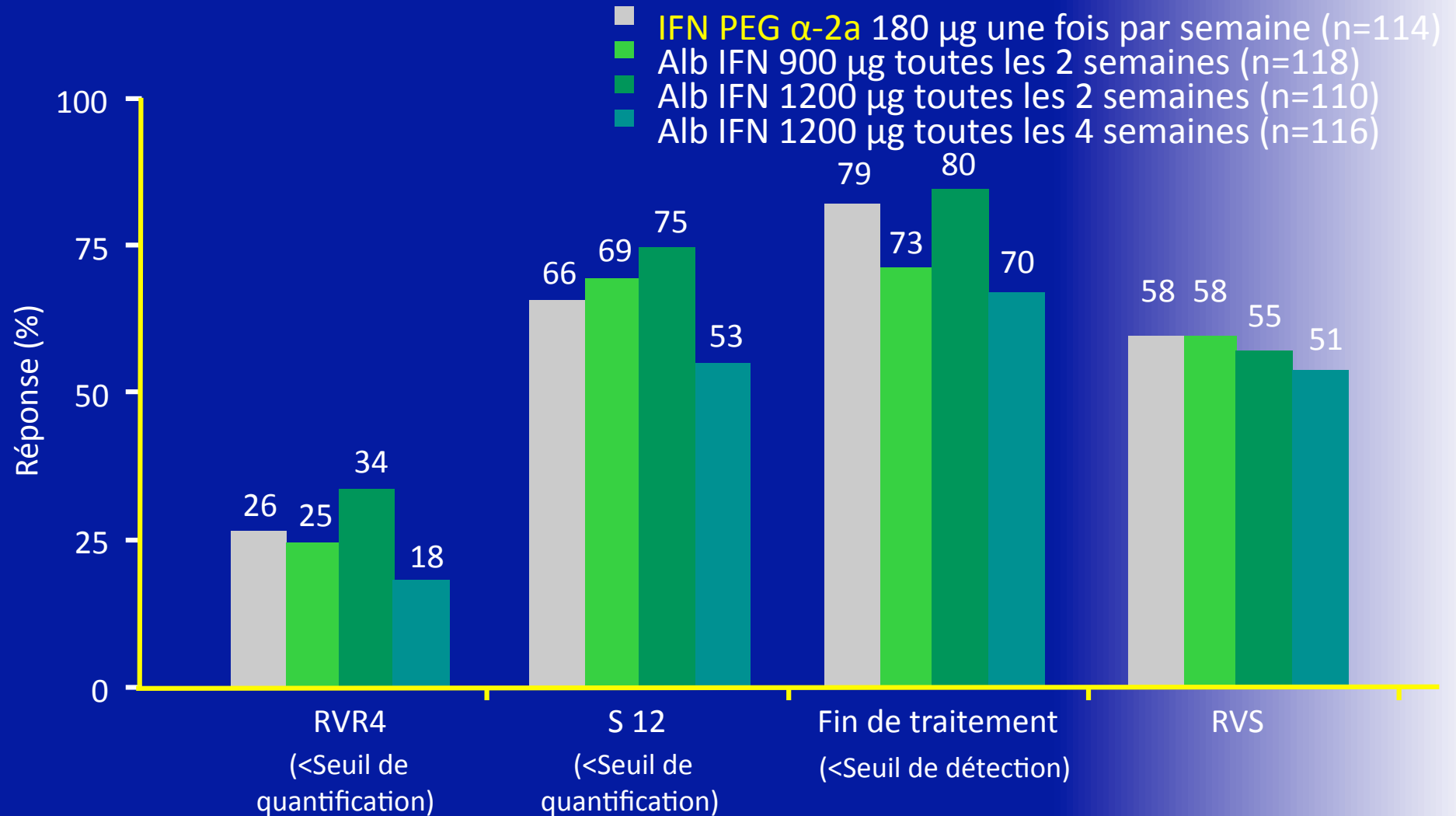


Virologic Response

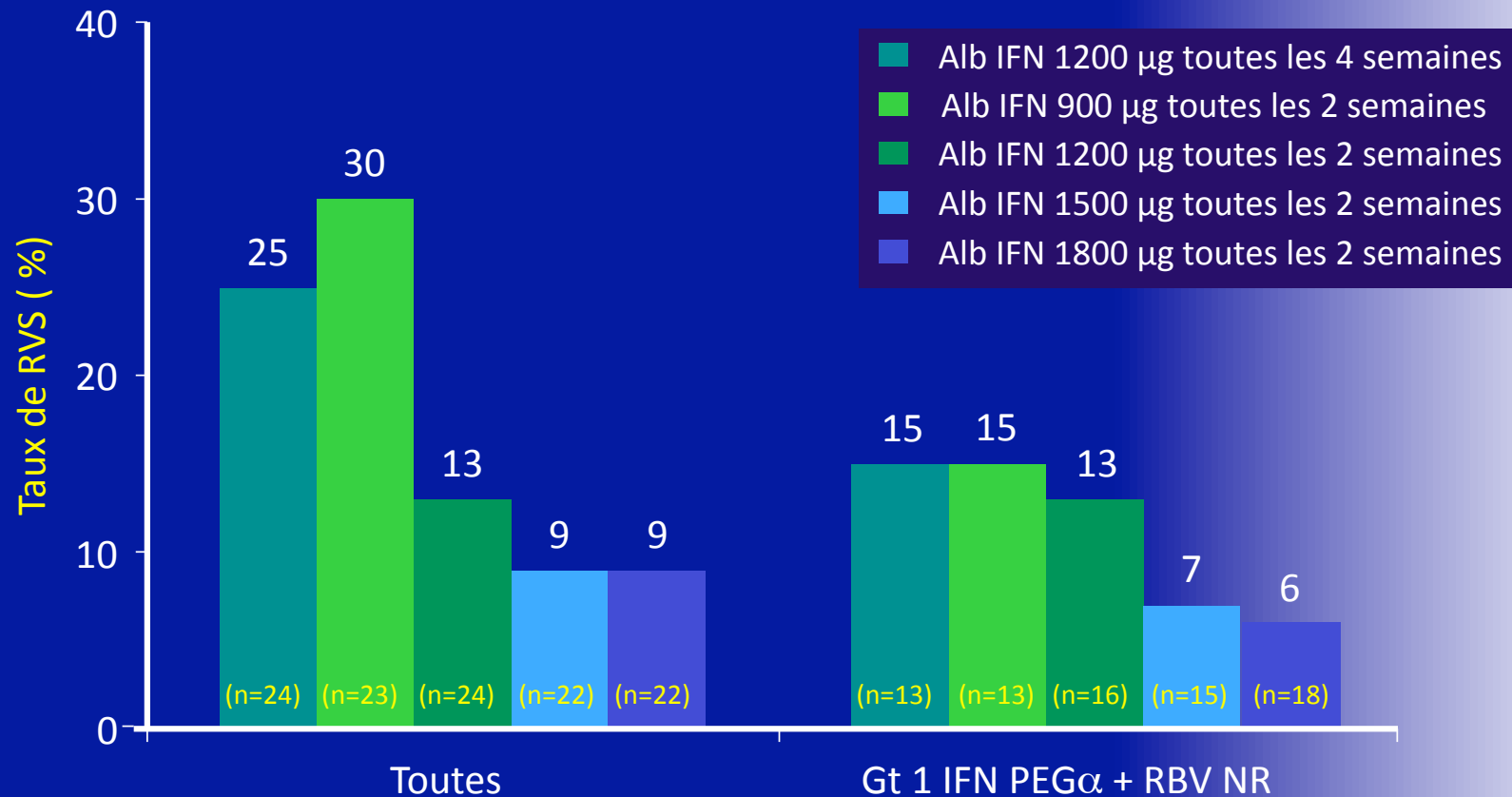


Rossignol F. et al. EASL 2008

Alb IFN: Patients Naïfs, Génotypes 1 (Phase II)



Alb IFN: Patients Non-Répondeurs



- Taux de RVS globale: 17,4% (20/115)
- Gt 1, non-répondeurs (NR) à la RBV + IFN PEG α, taux de RVS: 10,7% (8/75)

Scenarii futurs

2012

2017

2020

2022?

IFN - RBV

STAT-C

Inhibiteurs de la
cyclophyliline ?

STAT-C
inhibiteurs
d'entrée ?

Combinaisons de STAT-C

Vaccinothérapie?

Cytokines ?
Autres
immuno-
modulateurs

Traitements sans IFN?