Actualización en nuevas terapias para la hepatitis C

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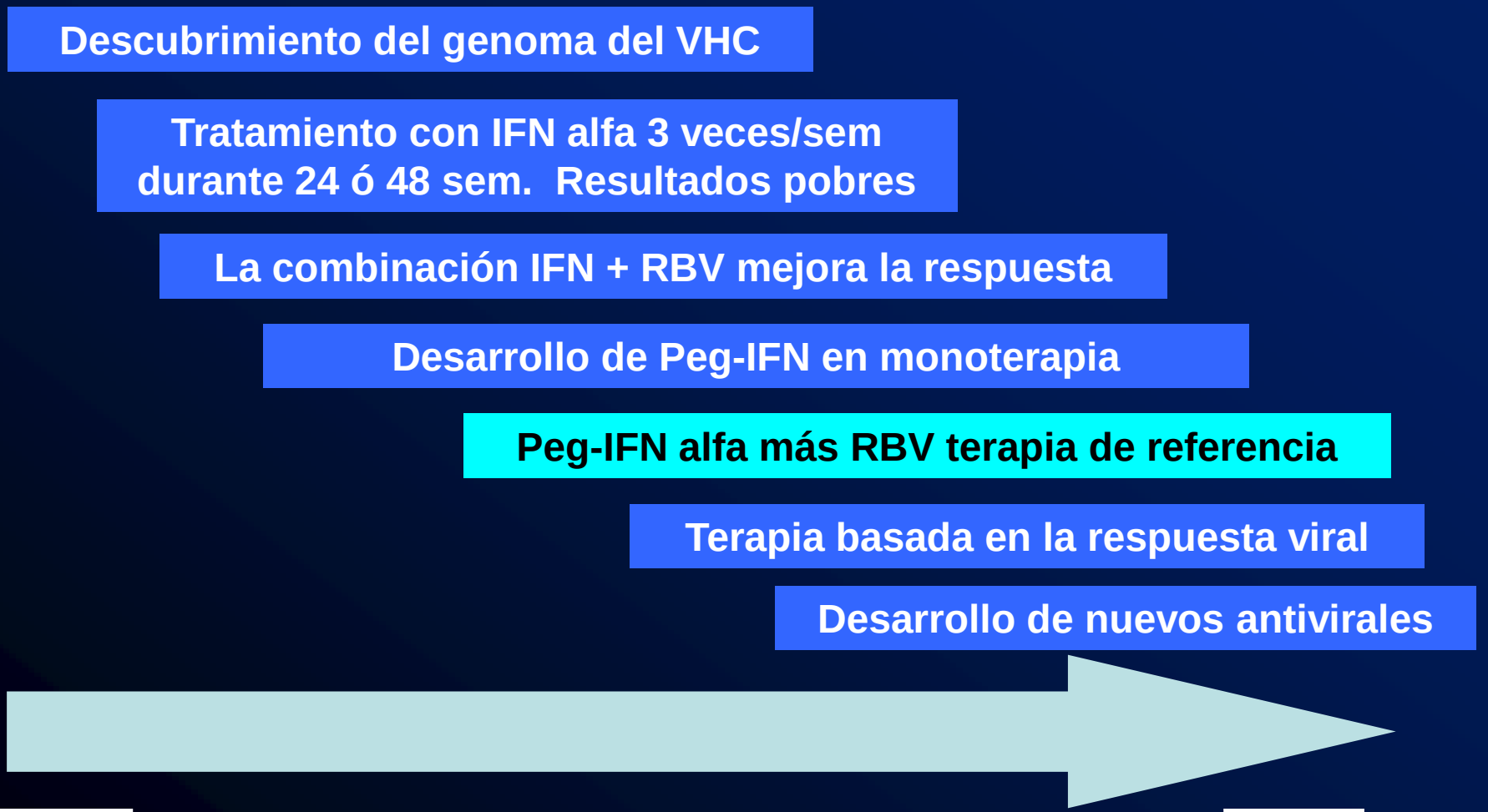
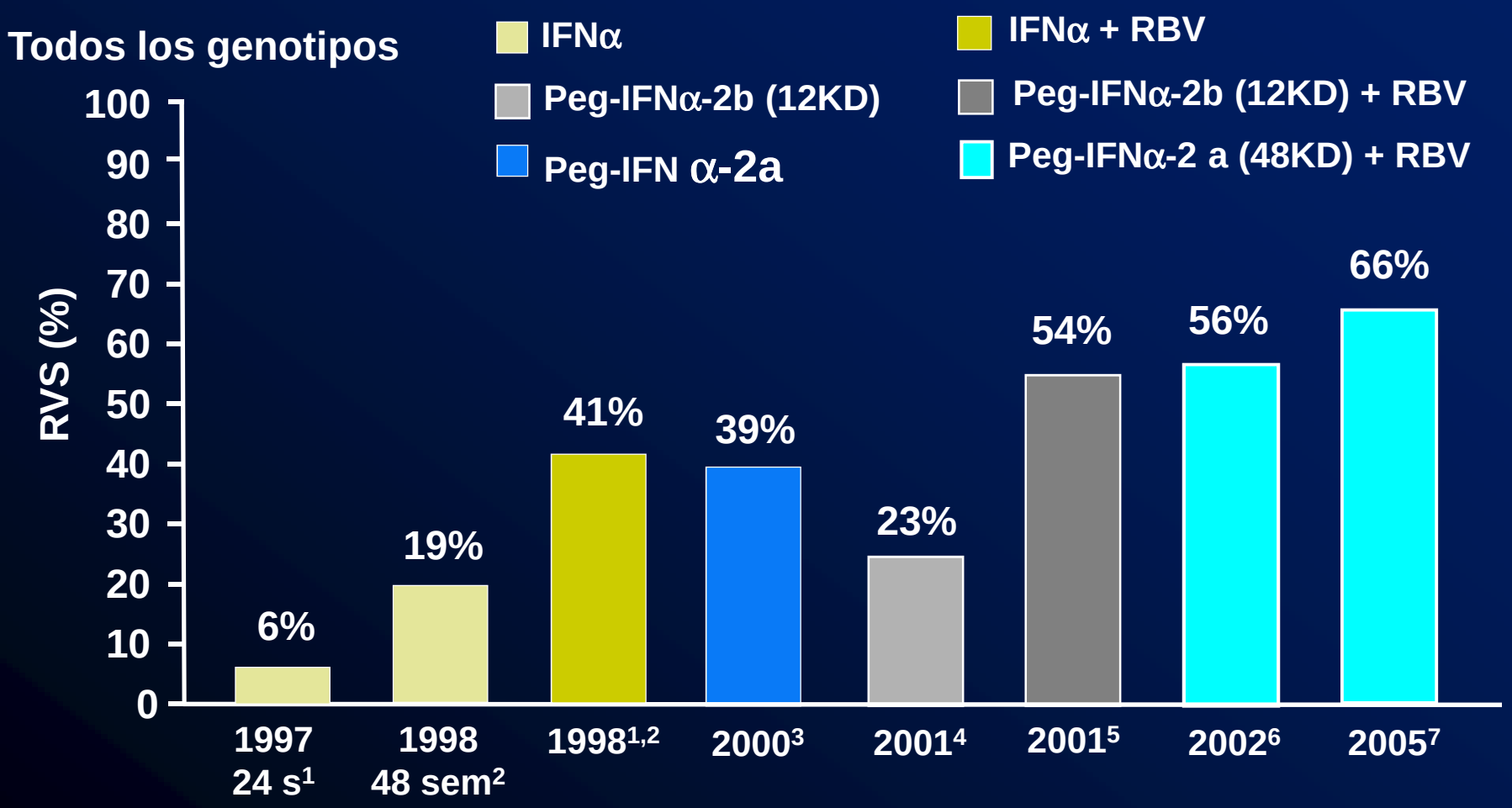
JORNADAS 2011 DE ACTUALIZACIÓN EN ATENCIÓN FARMACÉUTICA AL PACIENTE CON PATOLOGÍAS VÍRICAS.
SOCIEDAD ESPAÑOLA DE FARMACIA HOSPITALARIA
Madrid, 13 de mayo de 2011

Evolución del tratamiento de la hepatitis C



Evolución de la tasa de respuesta



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. N Engl J Med 2000; 343: 1666 4. Lindsay K, et al. Hepatology 2001; 34: 395 5. Manns M, et al. Lancet 2001; 358: 958 6. Fried M, et al. N Engl J Med 2002; 347: 975 7. Zeuzem S, et al. J Hepatol 2005; 43: 250

Respuesta virológica: definiciones

- **Respuesta fin de tratamiento (RFT)**
- Niveles indetectables de ARN-VHC al final del tratamiento (24 semanas para genotipo 2/3 del VHC, 48 semanas para genotipo 1 del VHC)
- **Respuesta virológica sostenida (RVS)**
- Niveles indetectables de ARN-VHC al final del seguimiento (24 semanas después de terminado el tratamiento)
- **No respuesta**
- Disminución de ARN-VHC < 2 logs en el tercer mes y/o ARN-VHC (+) en el 6º mes de tratamiento
- **Recaída**
- ARN-VHC negativo al final del tratamiento, pero de nuevo positivo durante el período de seguimiento

Definiciones de respuesta viral rápida y temprana

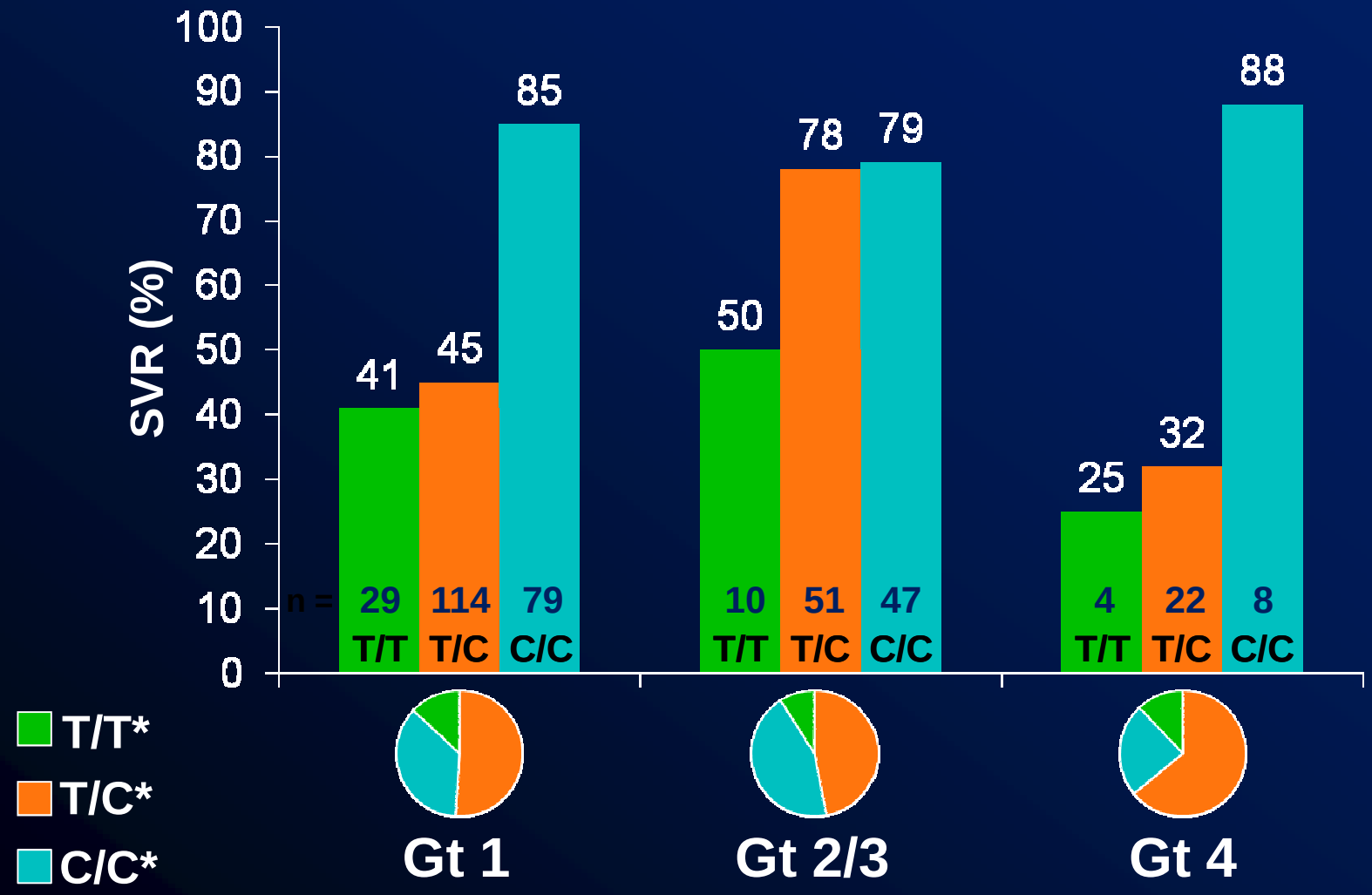
Respuesta	Definición
RVR*	RNA VHC negativo (<15 IU/mL) en la semana 4
RVT**	
ñ Completa (RVTc)	No RVR pero RNA VHC negativo (<15 IU/mL) en la semana 12
ñ Parcial (RVTp)	No RVR, RNA VHC positivo en la semana 12 pero con descenso ≥ 2 $\log_{10}$
No-RVT	Descenso RNA VHC <2 $\log_{10}$ en la semana 12

* RVR = respuesta viral rápida
** RVT = respuesta viral temprana

HCV Treatment: A Lexicon of Acronyms

- DAAs: direct antiviral agents
- IL28B: IL28B polymorphism (rs12979860) genotype test
- NA: nucleoside analog polymerase inhibitors
- NNI: nonnucleoside polymerase inhibitors
- PI: protease inhibitors
- MV: minority variants
- UDPS: ultradeep pyrosequencing
- vBT: viral breakthrough
- RGT: response-guided therapy
- eRVR: extended rapid virological response
- DRM: drug-resistant mutations

Genetics Predict Response: *IL28B* Genotype C/C Confers Higher SVR Rates



*Genotype of rs12979860 on chromosome 19 (Ge D et al. *Nature.* 2009;461:399-401).
Strättermayer A et al. EASL 2010.

Hepatitis C: escenario en 2011

- Aprobación de los primeros DAAs: telaprevir y boceprevir
- Amplia utilización de estos medicamentos en la UE y EE UU
- Incremento de la RVS hasta el 75% en pacientes *naïves* G1
- Problemas potenciales con el uso de estos nuevos fármacos:
  - Selección adecuada de los pacientes
  - Control y monitorización inapropiados
  - Manejo de los efectos adversos
  - Resistencias

Tratamiento de la hepatitis C

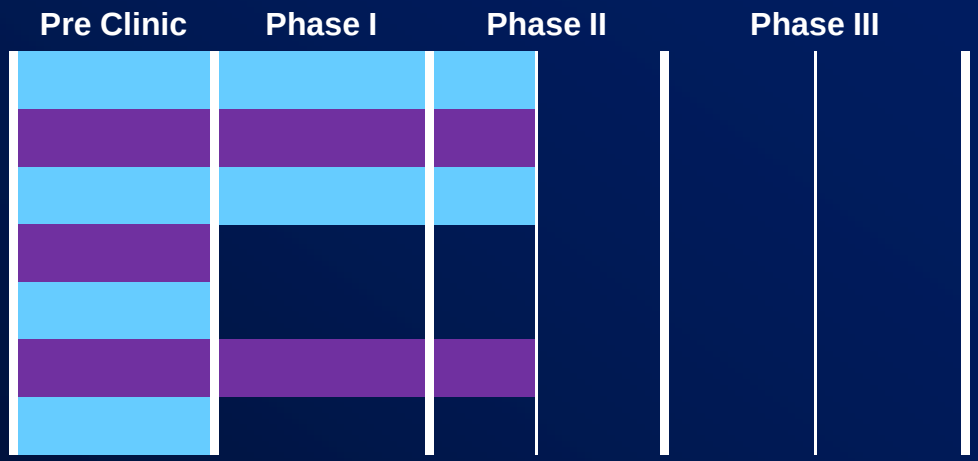
- Tratamiento actual (PEG-IFN + Riba)
- Nuevos tratamientos
  - *Standard of care* en 2012
    - *Naïves*
    - No respondedores
  - Nuevos antivirales
    - Nuevos IFNs
    - Inhibidores de la proteasa
    - Inhibidores de la polimerasa
    - Combinaciones “libres” de IFN

Select DAAs in Clinical Development

	Phase I	Phase II	Phase III
Protease Inhibitors	ABT-450 ACH-1625 GS 9451 MK-5172 VX-985	BMS-650032 CTS-1027 Danoprevir GS 9256 IDX320 Vaniprevir	BI 201335 Boceprevir Telaprevir TMC435
Nonnucleoside polymerase inhibitors	BI 207127 IDX375	ABT-333 ABT-072 ANA598 BMS-791325 Filibuvir Tegobuvir VX-759 VX-222	
Nucleoside polymerase inhibitors		IDX184 PSI-7977 RG7128-Mericitabine	
NS5A inhibitors	A-831 PPI-461	BMS-790052 BMS-824393 CF102	

Anti-HCV drugs in development

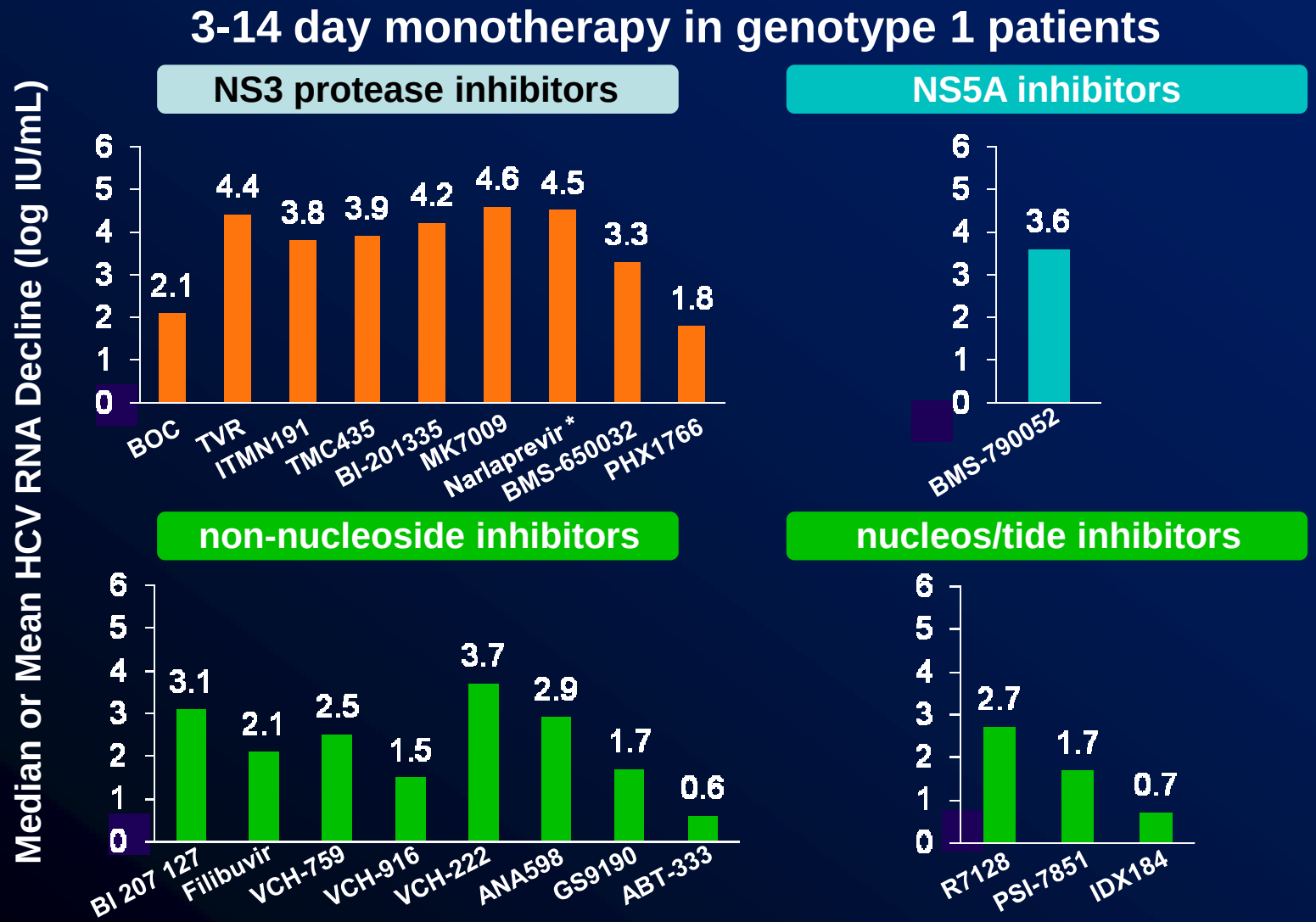
Cyclo sporine analogue	SCY-635 (Scynexis)
Cyclo sporine analogue	**Debio-025 (Debiopharm)**
Cyclo sporine analogue	NIM-811 (Novartis)
Entree inhibitor	PRO-206 (Progenics)
Cyclo sporine analogue	JTK-652 (Amsterdam)
TLR agonist	ANA 773 (Anadys)
Cyclo sporine analogue	EP-CyP282 (Enanta)



New treatments in AASLD 2010 & EASL 2011

- 36 Drugs
  - 15 Protease Inhibitors
  - 10 Polymerase Inhibitors
  - 9 Other
- 240 Abstracts

Antiviral Activity of DAA Vary Among and Within Classes

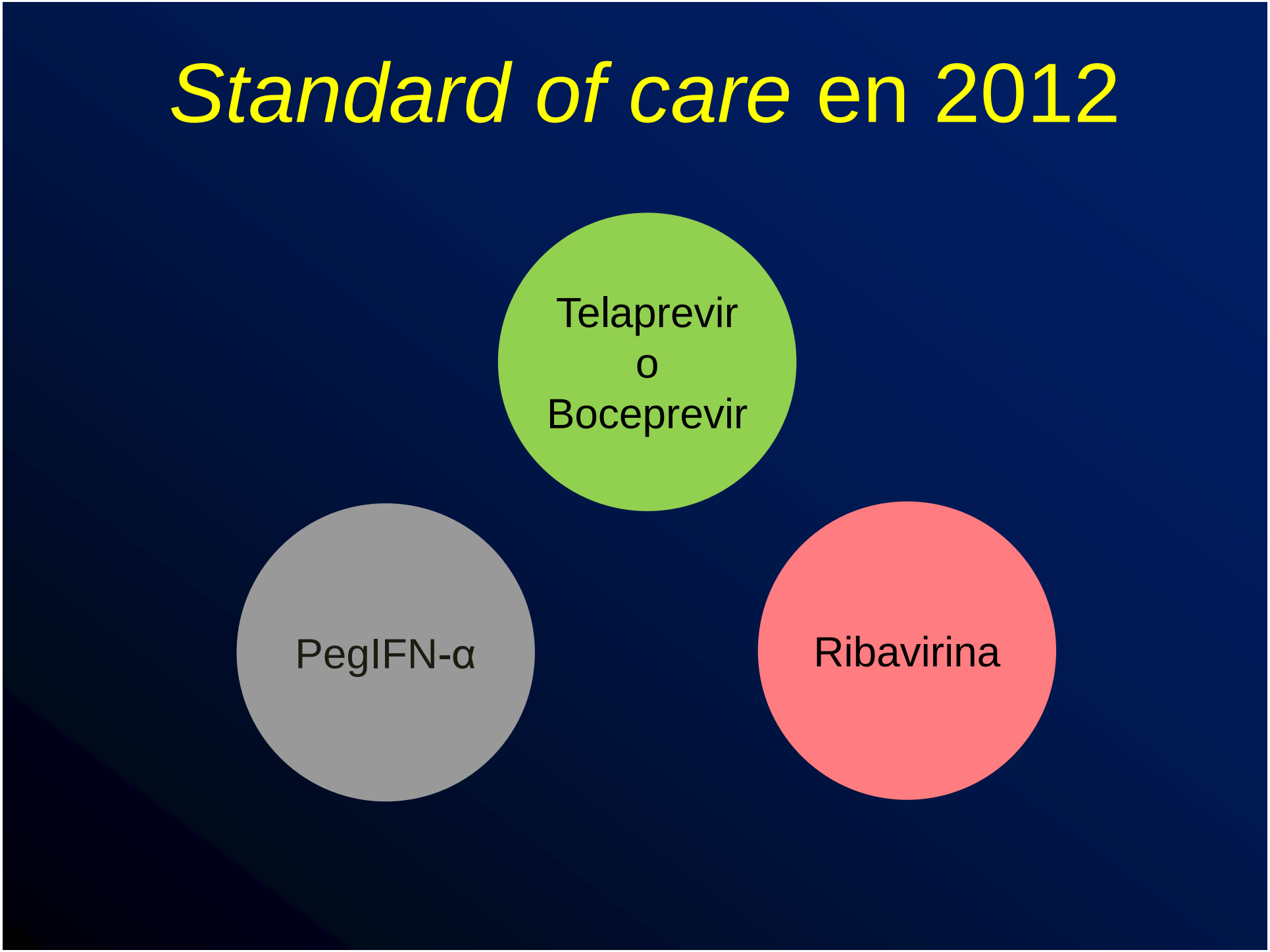


BCP, boceprevir; TVP, telaprevir. *Clinical development stopped. Sarrazin C, Zeuzem S. *Gastroenterology.* 2010;138:447-62.

Efficacy & Genetic Barrier

Type of drugs	Genetic Barrier/ AV Efficacy	*Other*
Protease Inhibitors	Low/ High	Genotype 1
Polymerase Inhibitors Nucleoside Analogs	High / Low-Medium	Few in develop All genotypes
Polymerase Inhibitors Non Nucleoside	Low/ Medium	Genotype 1
Ciclofilin Inhibitors	No/ Low	All?
NS5A Inhibitors	High/Medium-High	All?

Standard of care en 2012



Boceprevir and Telaprevir

- Boceprevir, a potent inhibitor of HCV NS3/4A protease
- Telaprevir, a potent inhibitor of HCV NS3/4A protease
- Both being tested in combination with standard-of-care pegIFN alfa-2/RBV in phase III studies in chronic HCV infection

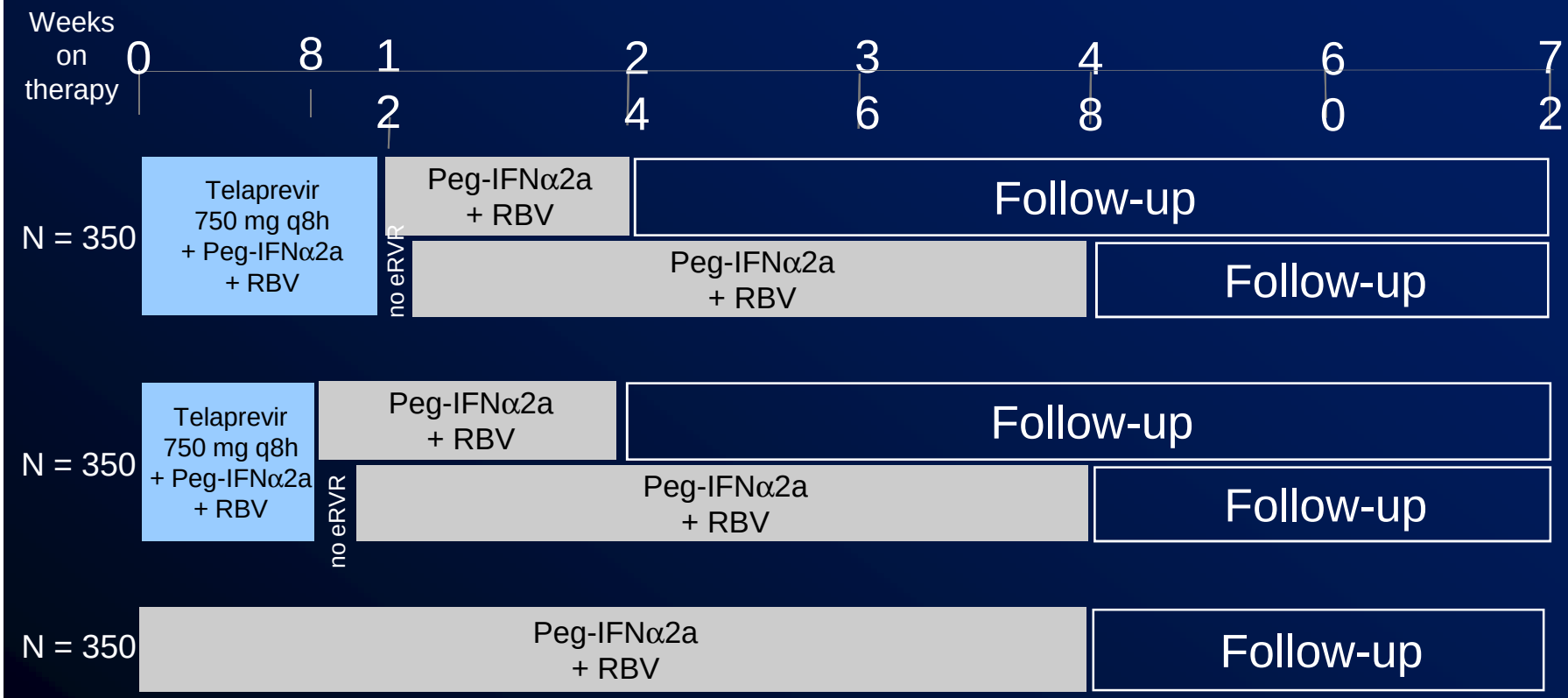
Boceprevir

- SPRINT-2: naive GT1 patients
- RESPOND-2: nonresponder GT1 patients (partial responders and relapsers)

Telaprevir

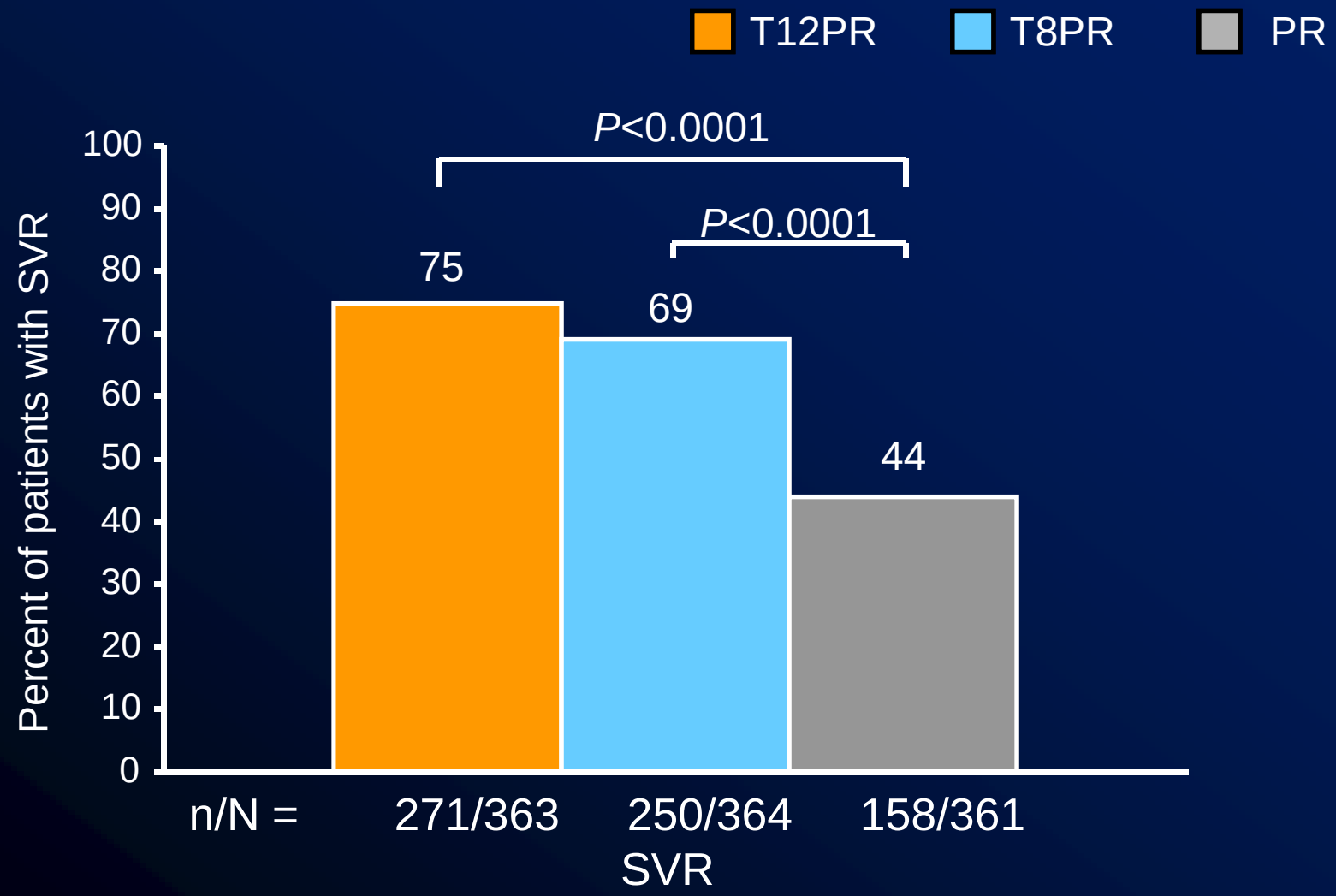
- ADVANCE: naive GT1 patients
- ILLUMINATE: response-guided therapy in naive GT1 paitents
- REALIZE: nonresponder GT1 patients (null responders, partial responders, relapsers)

Telaprevir Phase 3 Trial: ADVANCE – GT1 Naïve



*eRVR = undetectable HCV RNA at week 4 and week 12
Telaprevir patients who achieve extended EVR (i.e., RVR + EVR) stop treatment after 24 weeks.

ADVANCE: SVR rates



Jacobson I, et al. AASLD 2010: Abstract 211.

Telaprevir: Discontinuations

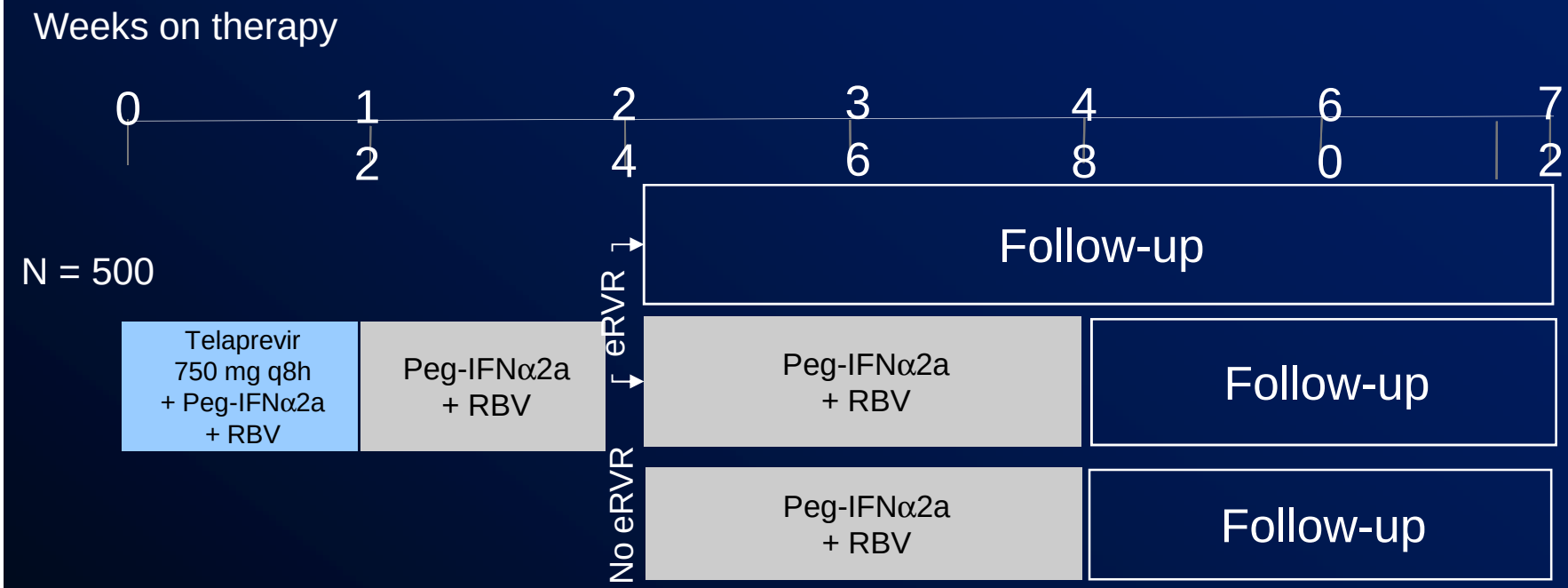
- Discontinuations due to adverse events in Phase III ADVANCE:

Outcome, %	8-Wk TVR/PR + 16/40-Wk PR (n = 364)	12-Wk TVR/PR + 12/36-Wk PR (n = 363)	48-Wk PR (n = 361)
Discontinuation of TVR/placebo due to rash	7	11	1
Discontinuation of all drugs due to AEs	8	7	4
▪ Anemia	3.3	0.8	0.6

Jacobson IM, et al. AASLD 2010. Abstract 211.

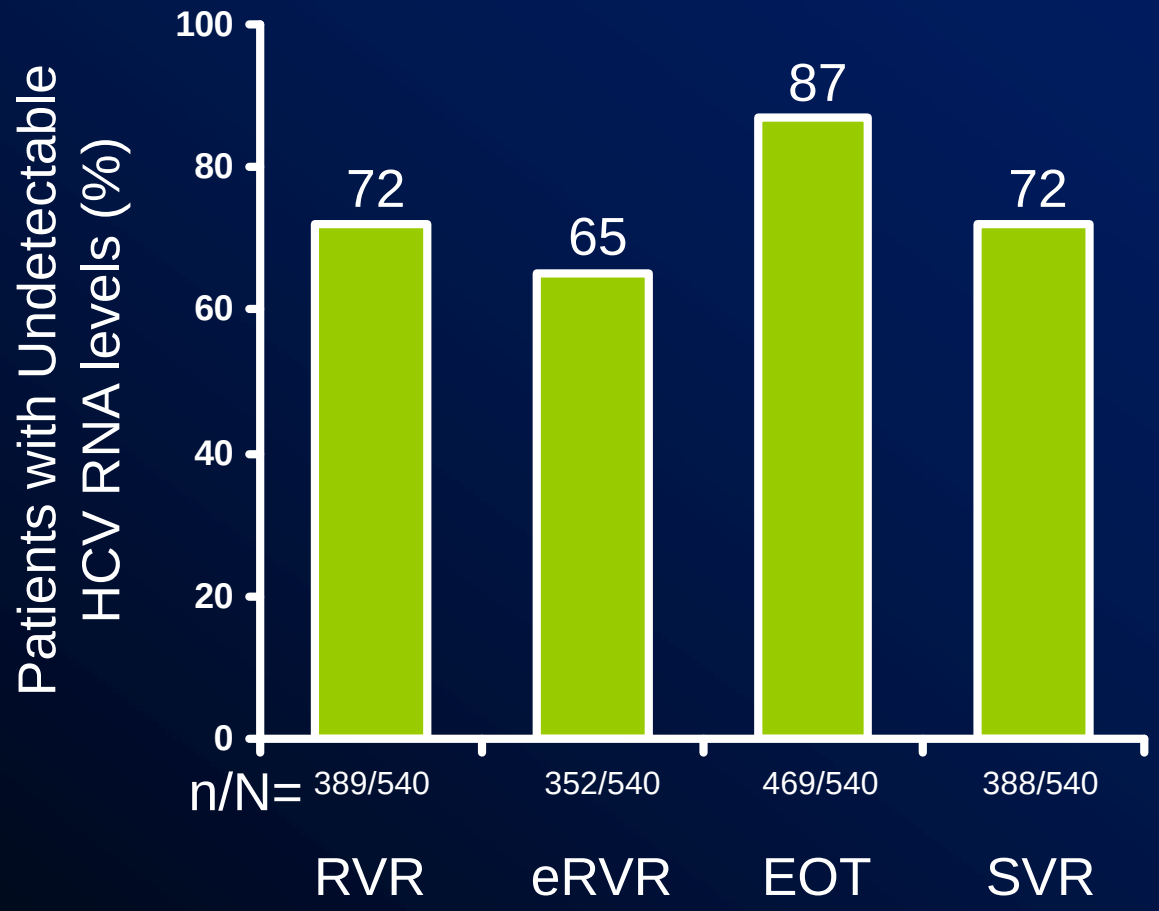
Telaprevir Ph3 Trial: ILLUMINATE – GT1 Naïve

Non-inferiority trial requested by the FDA to specifically demonstrate that treating GT1 Naïve patients for 24 weeks was not a disadvantage compared to treating them for 48 weeks



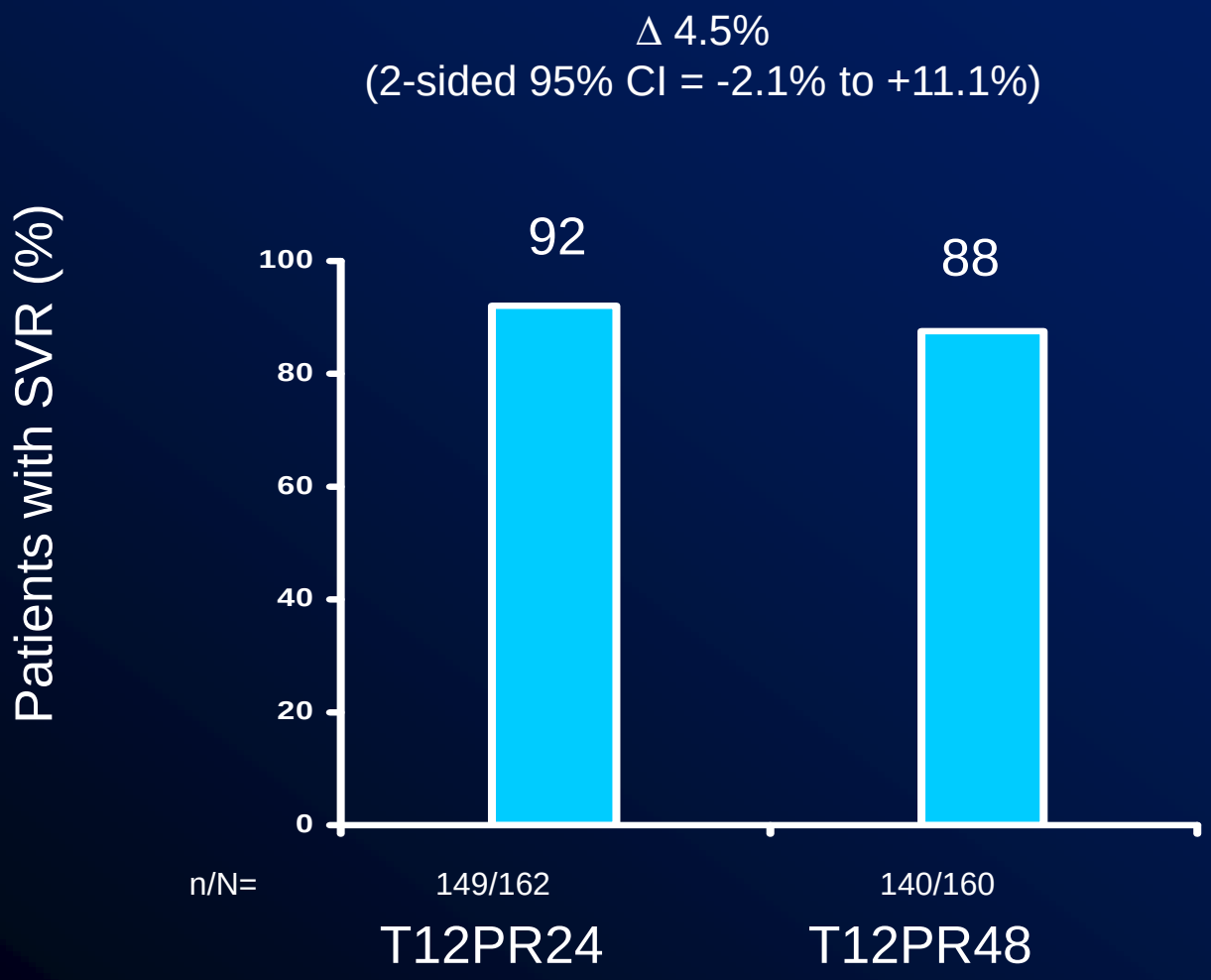
eRVR = undetectable HCV RNA at week 4 and week 12

ILLUMINATE:
Undetectable HCV RNA over time – ITT Population



Sherman KE, et al. AASLD 2010: Abstract LB-2.

ILLUMINATE
SVR Rates - Noninferiority of 24-week Regimen



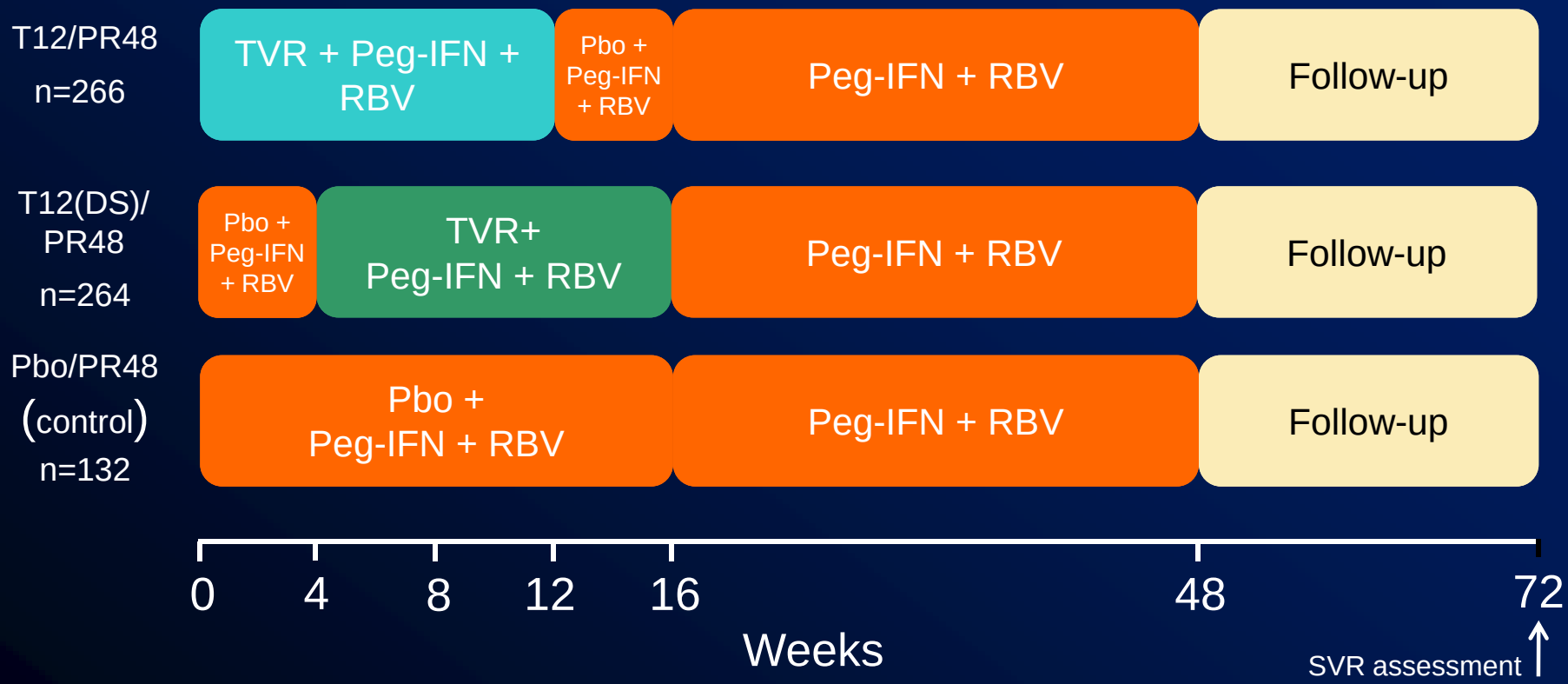
Sherman KE, et al. AASLD, 2010: Abstract LB-2.

Resumen de los estudios Advance[1] e Illuminate[2] (Telaprevir-Fase III pacientes naïve Gt 1)

- El tratamiento “guiado” por la respuesta viral (RGT) durante 24 semanas es igual de eficaz que el de 48 semanas de duración en pacientes con eRVR (semanas 4-12).
- La RGT es posible en 2/3 de los pacientes
- La duración más corta del tratamiento facilita el cumplimiento y la tolerancia, y reduce los efectos secundarios.
- La duración óptima del tratamiento con TVR es de12 semanas

1. Jacobson IM, McHutchison JG,Dusheiko GM, et al. AASLD 2010: Abstract 211.
2. Sherman KE, Flamm SL, Afdhal NH, et al. AASLD 2010:LB-2.

REALIZE Study Design (N=662)*



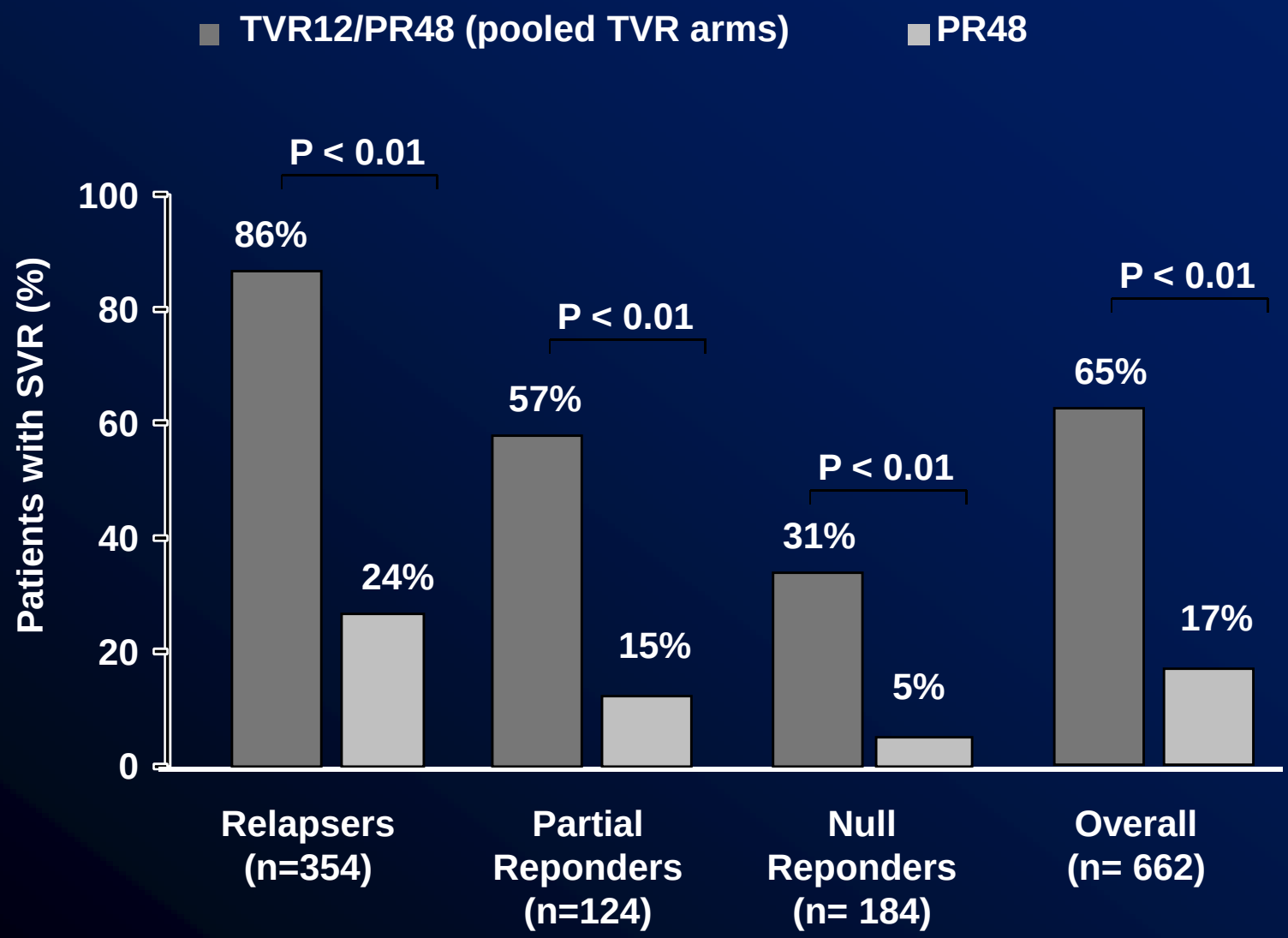
*Randomization stratified by viral load and prior response; stopping rules applied for TVR (Weeks 4, 6, and 8) and Peg-IFN/RBV (Weeks 12, 24, and 36)

Peg-IFN = 180µg/week; RBV 1000–1200mg/day; TVR = 750mg every 8 hours ClinicalTrials.gov identifier: NCT00703118

Pbo = placebo; DS = delayed start

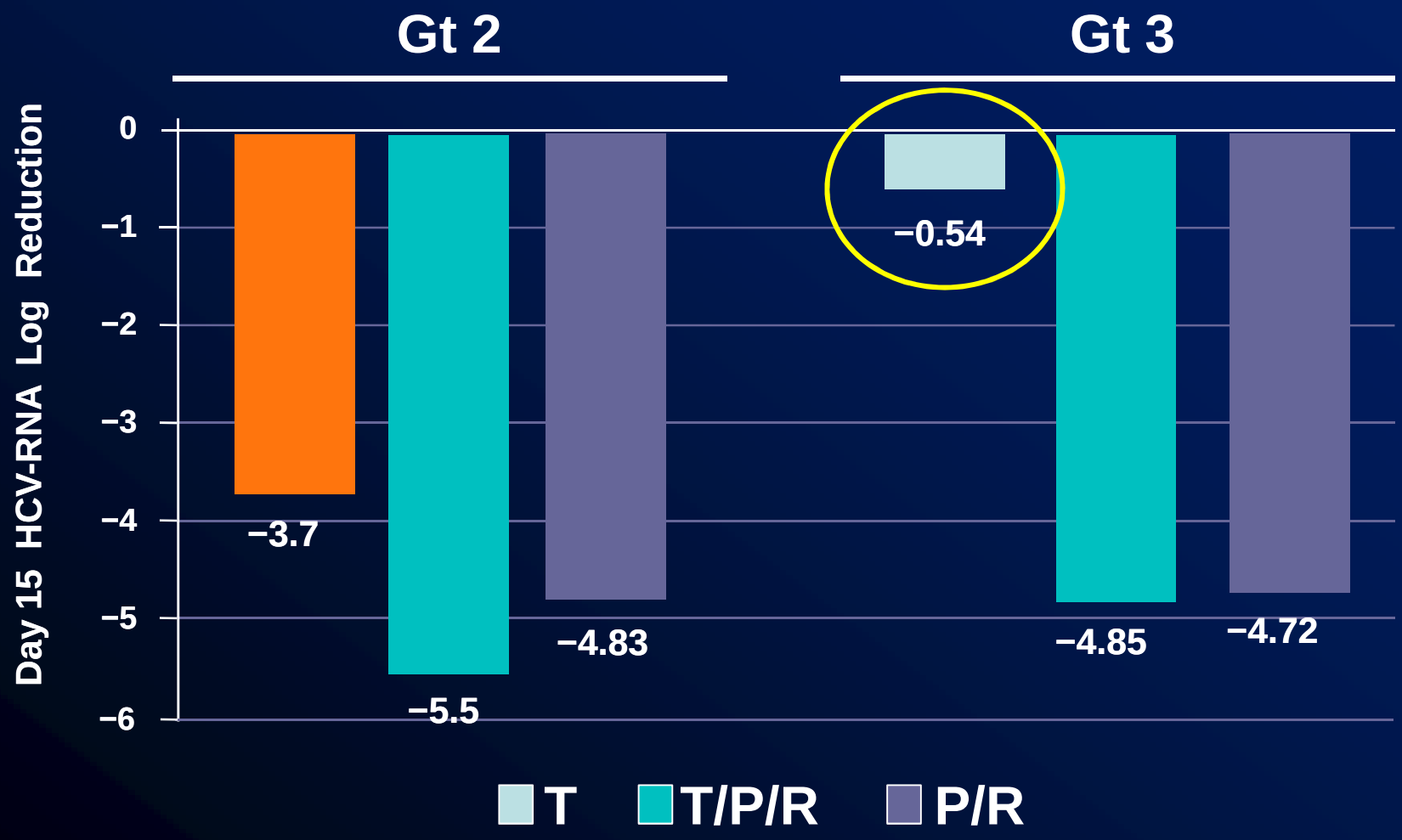
Zeuzem, et al. EASL 2011

SVR by Treatment Arms (ITT Analysis)



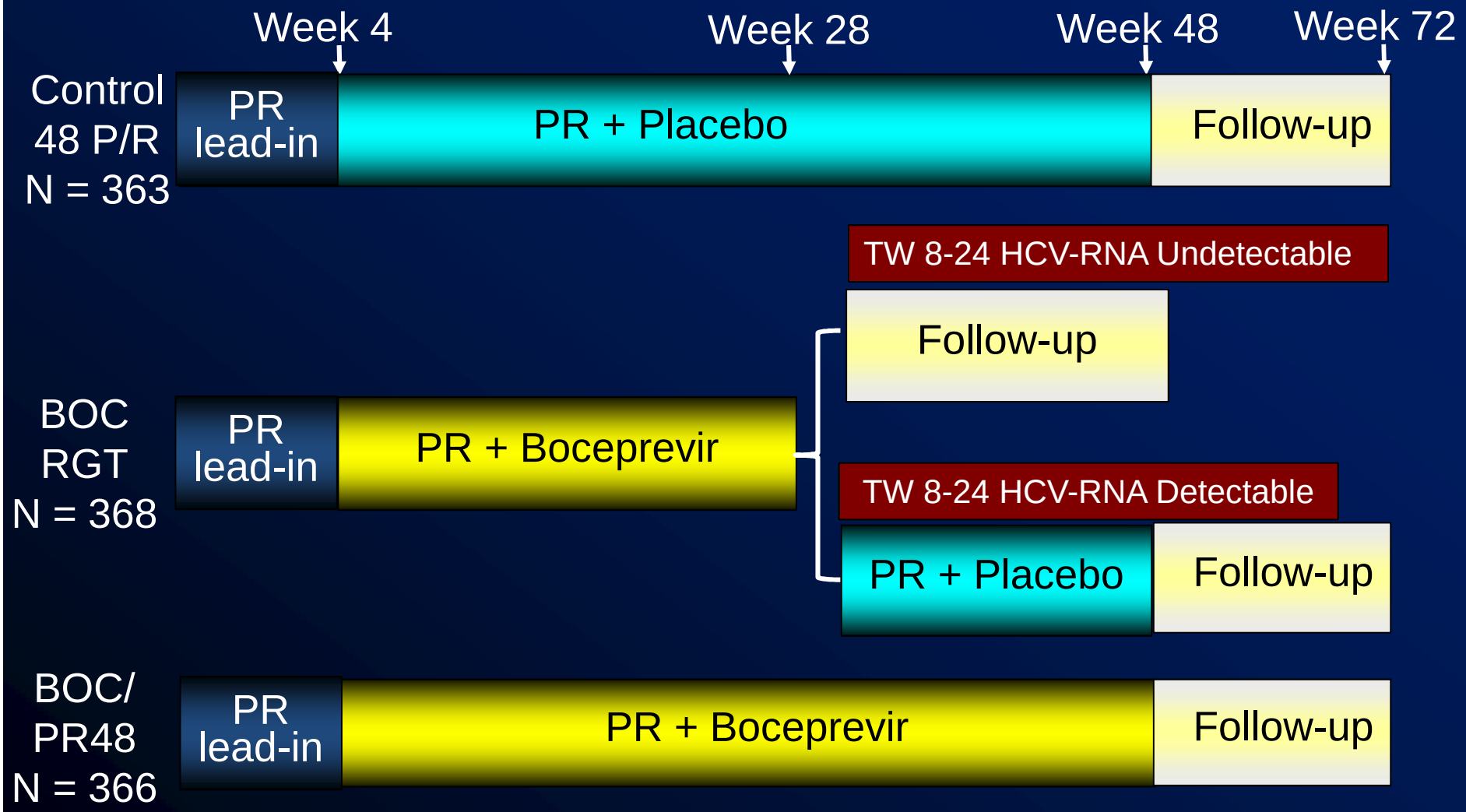
Zeuzem EASL 2011

Telaprevir in Genotype non-1 (C209)



P, Peg-IFNα-2a 180 µg/wk; R, ribavirin 800 mg/d; T, telaprevir q8h.
Foster G et al. EASL 2010.

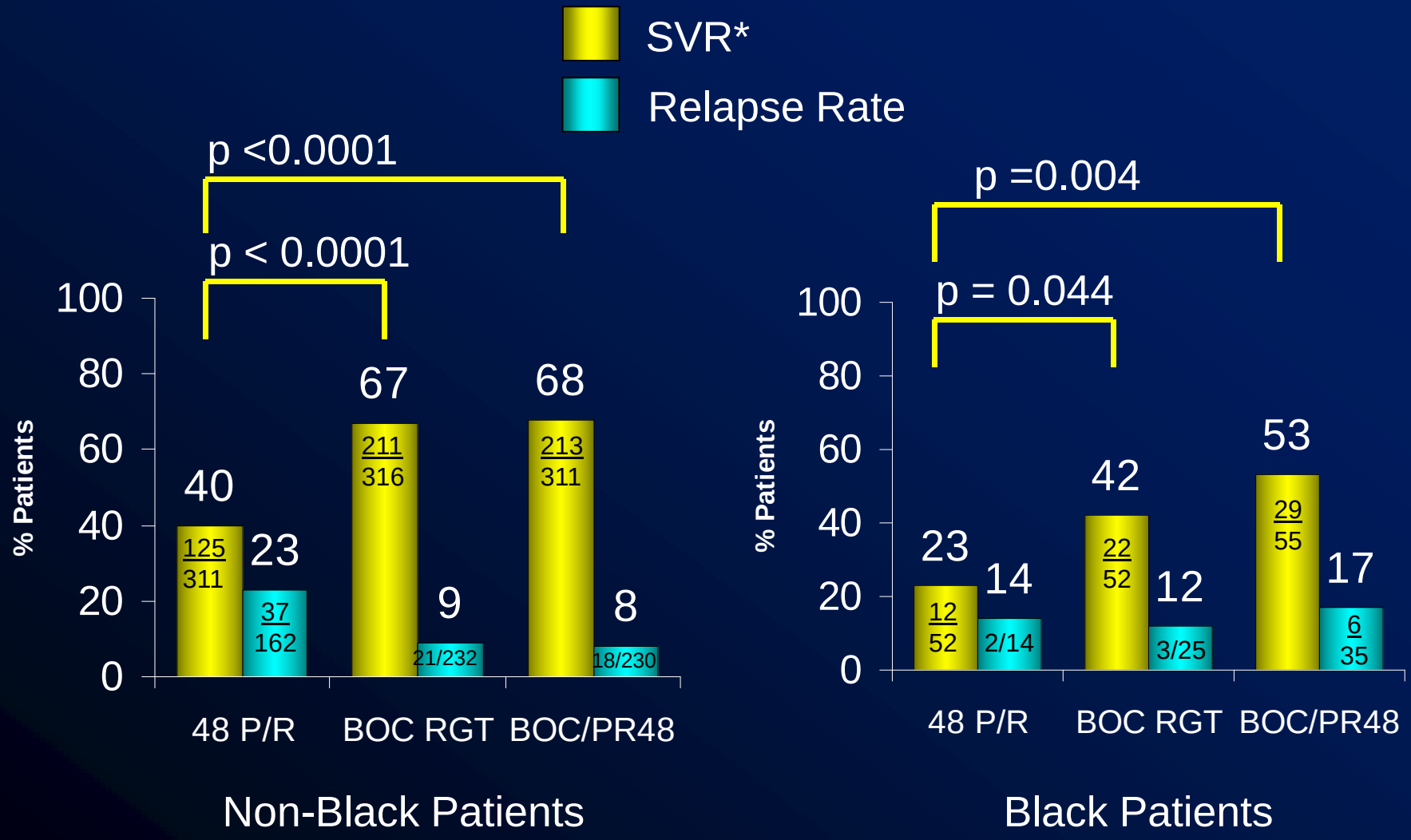
SPRINT 2: Study Design



Peginterferon (P) administered subcutaneously at 1.5 µg/kg once weekly, plus ribavirin (R) using weight based dosing of 600-1400 mg/day in a divided daily dose. BOC 800 mg 3 times daily

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

SPRINT 2: SVR and Relapse Rates (ITT)



*SVR was defined as undetectable HCV RNA at the end of the follow-up period. The 12-week post-treatment HCV RNA level was used if the 24-week post-treatment level was missing (as specified in the protocol). A sensitivity analysis was performed counting only patients with undetectable HCV RNA documented at 24 weeks post-treatment and the SVR rates for Arms 1, 2 and 3 in Cohort 1 were 39% (122/311), 66% (207/316) and 68% (210/311), respectively and in Cohort 2 were 21% (11/52), 42% (22/52) and 51% (28/55), respectively.

Poordad et al. NEJM 2011

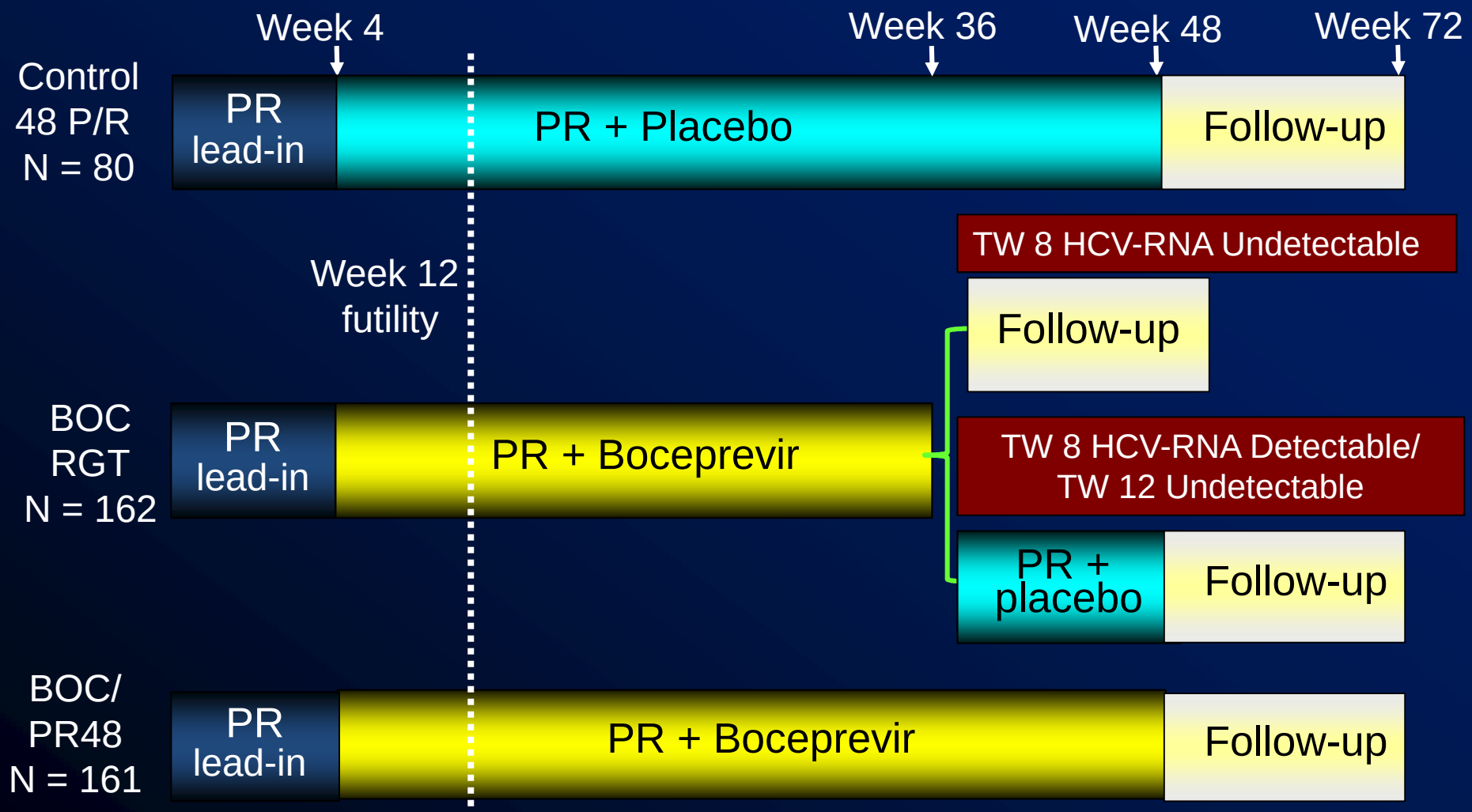
Boceprevir: Adverse Events and Discontinuations

- 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

1. Poordad F, et al. NEJM 2011.

RESPOND-2 Study Arms and Dosing Regimen

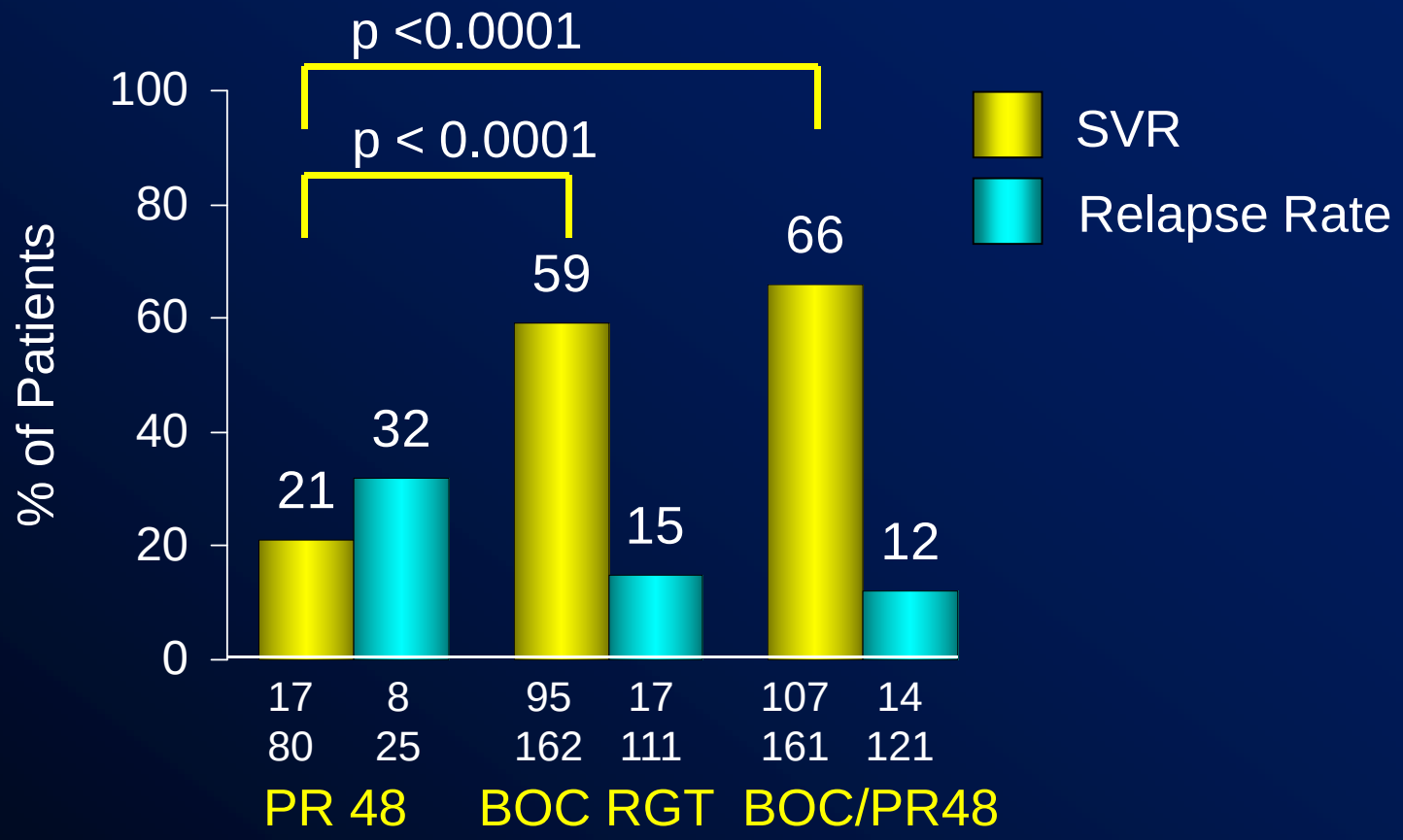


HCV-RNA measured by the Cobas TaqMan assay (Roche). Patients with detectable HCV-RNA (LLD=9.3 IU/mL) at week 12 were considered treatment failures.

Peginterferon (P) administered subcutaneously at 1.5 µg/kg once weekly, plus Ribavirin (R) using weight based dosing of 600-1400 mg/day in a divided daily dose
Boceprevir dose of 800 mg thrice daily

Bacon et al. N Engl J Med 2011; 364: 1217-17.

RESPOND-2 SVR and Relapse Rates
Intention to treat population



SVR rates in BOC RGT and BOC/PR48 arm not statistically different (OR, 1.4; 95% CI [0.9, 2.2])

12-week HCV RNA level used if 24-week post-treatment level was missing. A sensitivity analysis where missing data was considered as non-responder, SVR rates for Arms 1, 2 and 3 were 21% (17/80), 58% (94/162) and 66% (106/161), respectively.

Resumen de los estudios Sprint-2[1] y Respond-2[2]

- Las pautas de tratamiento con BOC requieren un periodo de 4 semanas de *lead-in* (LI) con PEGIFN+RBV
- La RGT (viremia C indetectable en las semanas 8 y 24) es posible en la mitad de los pacientes naïve
- Se requiere un mínimo de 24 semanas de BOC para la respuesta viral óptima en pacientes naïve
- Se requiere LI + un periodo mínimo de 32 semanas de tratamiento con BOC/PEGIFN/RBV para los pacientes con fallo a un tratamiento previo con PEGIFN/RBV

1. Poordad F, et al. NEJM 2011; 364: 1195-206.
2. Bacon B et al. NEJM 2011; 364: 1207-17

Similarities and Differences in Phase III Studies of TVR and BOC in GT1 Naive Pts

Parameter	TVR[1]	BOC[2]
PR lead-in?	No	Yes: 4 wks
PegIFN alfa formulation	2a	2b
PI dosing requirements	TID; administer with fatty meal	TID
Duration of PI triple therapy	8-12 wks followed by 12-40 wks PR	24-44 wks after 4 wks PR lead-in
Qualification for shortened therapy (response guided)	Undetectable HCV RNA until Wk 12 of triple therapy	Undetectable HCV RNA until Wk 24 of triple therapy
Qualified for shortened therapy, %	58 (24 wks)	44 (28 wks)
SVR, %	69-75	63-66
Relapse, %	9	9
Adverse events more frequent in PI arms	Rash, anemia, pruritus, nausea	Anemia, dysgeusia

Jacobson IM, et al. AASLD 2010. Abstract 211. 2. Poordad F, et al. N Engl J Med 2011; 364: 1195-206 .

Tratamiento de la hepatitis C

- Tratamiento actual (PEG-IFN + Riba)
- Nuevos tratamientos (DAA)
  - *Standard of care* en 2012
    - *Naïves*
    - No respondedores
  - Nuevos antivirales
    - Nuevos IFNs
    - Inhibidores de la proteasa
    - Inhibidores de la polimerasa
    - Combinaciones “libres” de IFN

Interferons in Development

- Albinterferon alfa-2b (albIFN; HGS - Novartis):
  - Every-2-week injections (phase 3 completed; clinical development stopped in EU and USA)
  - Every-4-week injections (phase 2; clinical development stopped in EU and USA))
- Locteron (Biolex, Octoplus): phase 2b
- Omega IFN (Intarcia): phase 2
- Peginterferon Lambda (IL-29; ZymoGenetics/BMS): phase 2
  - Type III IFN binding to unique receptor

Second-Generation Protease Inhibitors

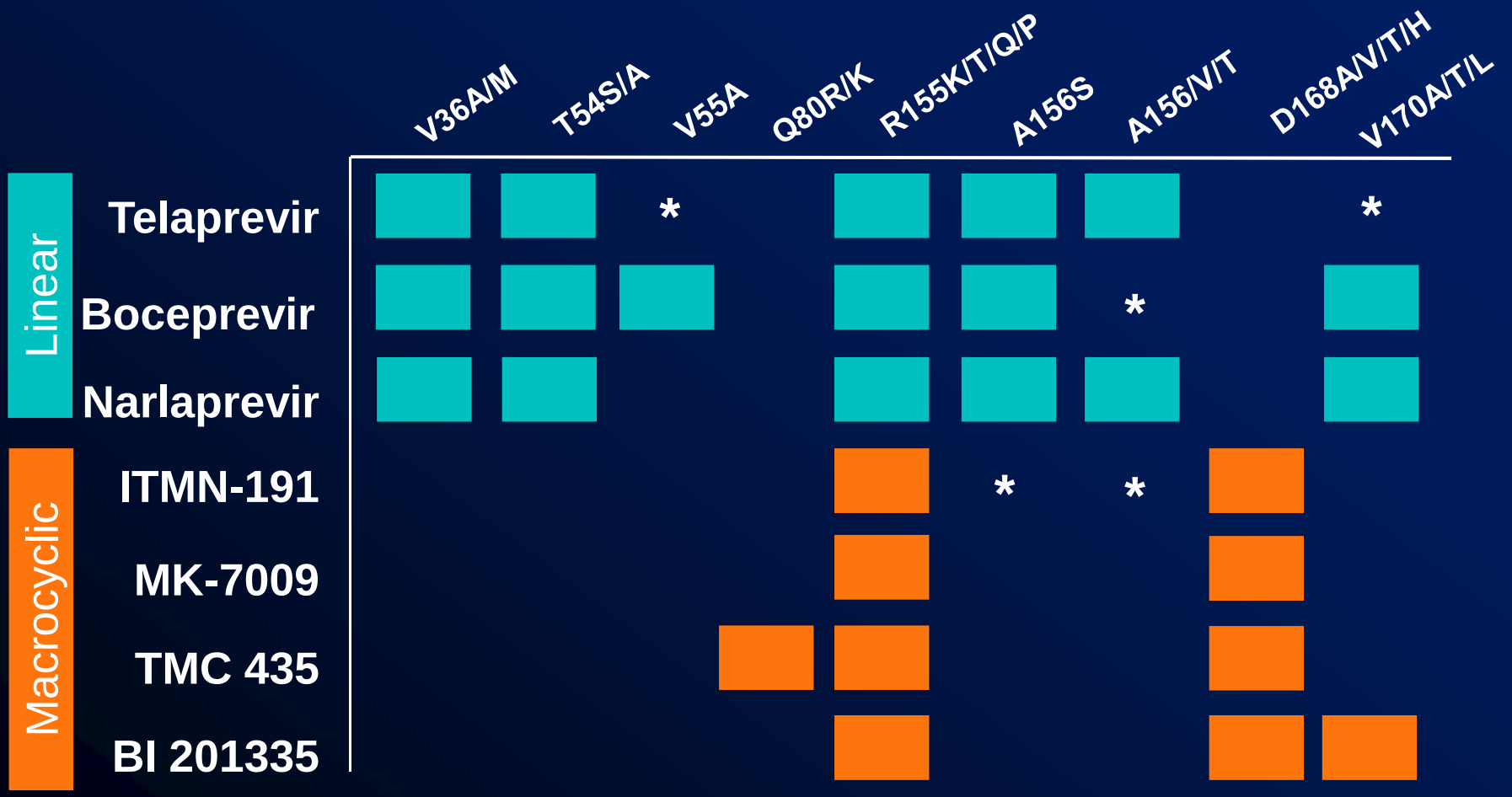
- TMC435: Tibotec
- Danoprevir: ITM/Roche
- BI-201335: Boehringer Ingelheim
- Vaniprevir: Merck

Activity of Other Protease Inhibitors Combined With PR in Phase II Studies

Protease Inhibitor	Trial, Phase	Patients Meeting Efficacy Measure, % (SOC)
BI 201335-NR[1]	SILEN-C2, II	eEVR: 42-47 (NO) SVR12: 32-47 (NO)
Danoprevir-NR[2]	II	RVR: 37*-87** (NO) cEVR: 50*-77** (NO)
TMC435-NR[3]	ASPIRE, IIb	RVR: 40-68-93 (NO) eEVR: 75-90-97 (NO)
Vaniprevir (MK-7009)[4]	Protocol 007, IIa	RVR: 67-84 (5)* cEVR: 74-85 (47)* SVR: 61-84 (63)

1 . Sulkowski M, et al. EASL 2011. 2. Rouzier, et al. EASL 2011. *G1a. **G1b
3. Zeuzem,et al. EASL 2011. Abstract LB.. 4. Manns MP, et al. AASLD 2010. Abstract 82. *Significant

Cross-resistance of NS3 Protease Inhibitors



*Mutations associated with in vitro resistance but not described in patients.

Susser S et al. *Hepatology.* 2009;50:1709-18; Sarrazin C, Zeuzem S. *Gastroenterology.* 2010;138:447-62.

What Do We Currently Know About Resistance to Protease Inhibitors?

- Minor resistant populations preexist at baseline in virtually all HCV-infected patients[1]
- Resistant variants rapidly selected with monotherapy[2]
  - R155K requires 1 nucleotide change in GT1a but 2 nucleotide changes in GT1b; virtually all resistance has been seen in GT1a[3]
- Emergence of resistance reduced when protease inhibitor combined with potent antivirals without cross-resistance, such as pegIFN, or pegIFN plus RBV[3,4]
- Failure to achieve SVR during triple-combination therapy associated with selection of resistant HCV variants[3]
- Boceprevir mutations can persist at least 3 yrs after exposure. However, telaprevir resistance mutations undetectable 2 yrs after treatment discontinuation in 89% of patients in EXTEND study[4]

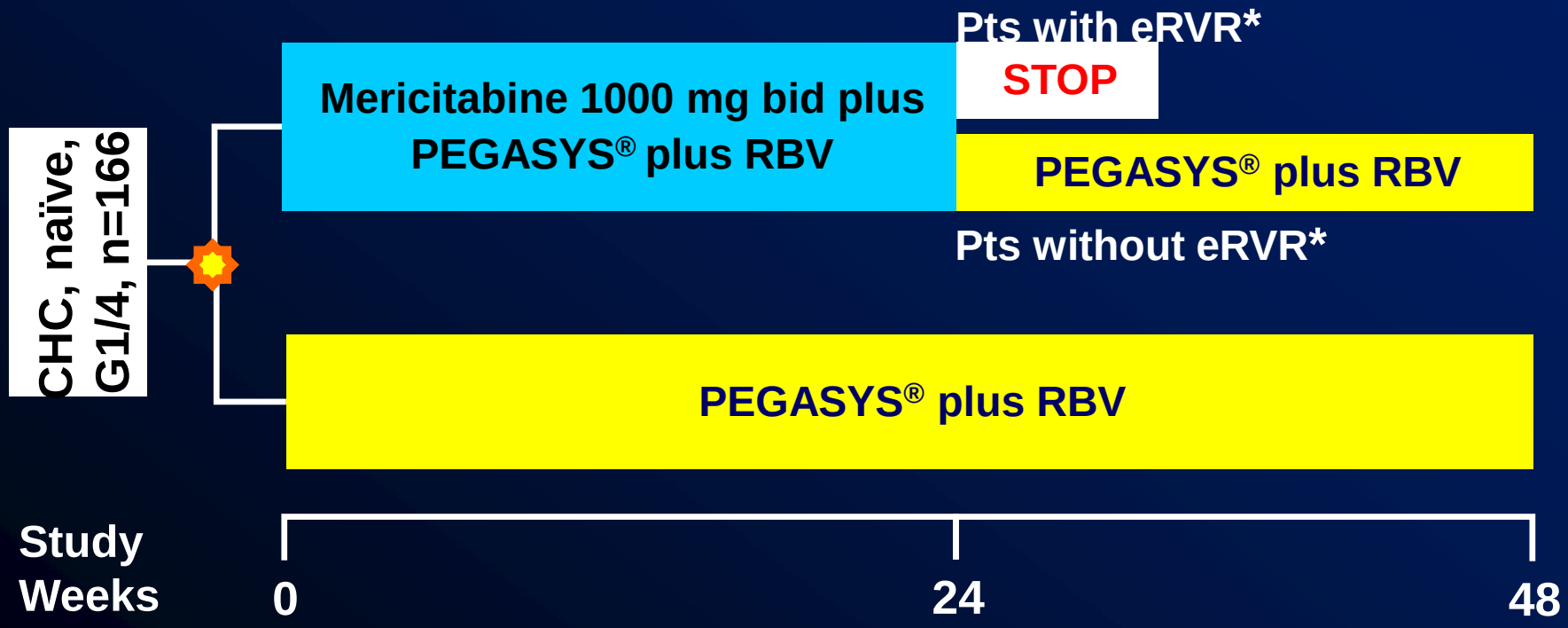
1. Bartenschlager R, et al. J Gen Virol. 2000;81:1631-1648. 2. Ozeki I. J Hepatol. 2009;50:S350.
3. McHutchison JG, et al. N Engl J Med. 2009;360:1827-1838. 4. Zeuzem S AASLD 2010.

Polymerase Inhibitors: Main Characteristics

	Summary	Advantages	Disadvantages
Nucleoside Inhibitors (Mericitabine; IDX 184)	• Analogs of natural substrates • Binds active site of NS5B, terminates viral RNA chain generation	• High genetic barrier for resistance • Equally active in all genotypes	• Relatively lower antiviral efficacy • Few in pipeline
Non-nucleoside Inhibitors (GS 9190; BI 207127; filibuvir)	• Binds to various allosteric sites, inducing conformational changes in polymerase	• Multiple target sites identified • Low-to-medium antiviral efficacy	• Low genetic barrier • HCV genotype/subtype dependent • Efficacy influenced by polymorphisms?

Sarrazin C, Zeuzem S. *Gastroenterology.* 2010;138:447-62.

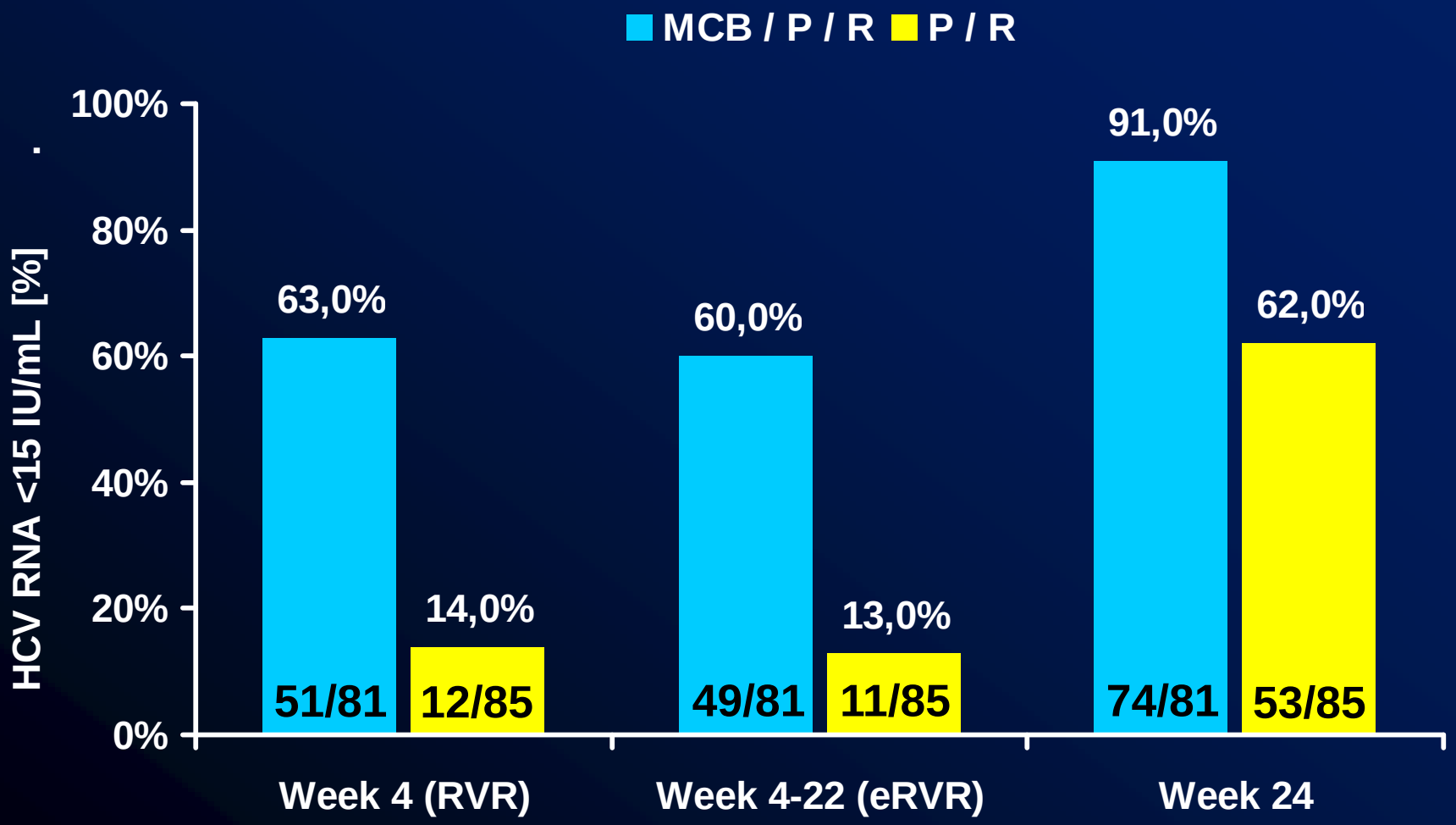
JUMP-C – Mericitabine + PEGASYS® + RBV in Naïve G1/4 Patients



* eRVR (HCV RNA <15 IU/mL from weeks 4-22)

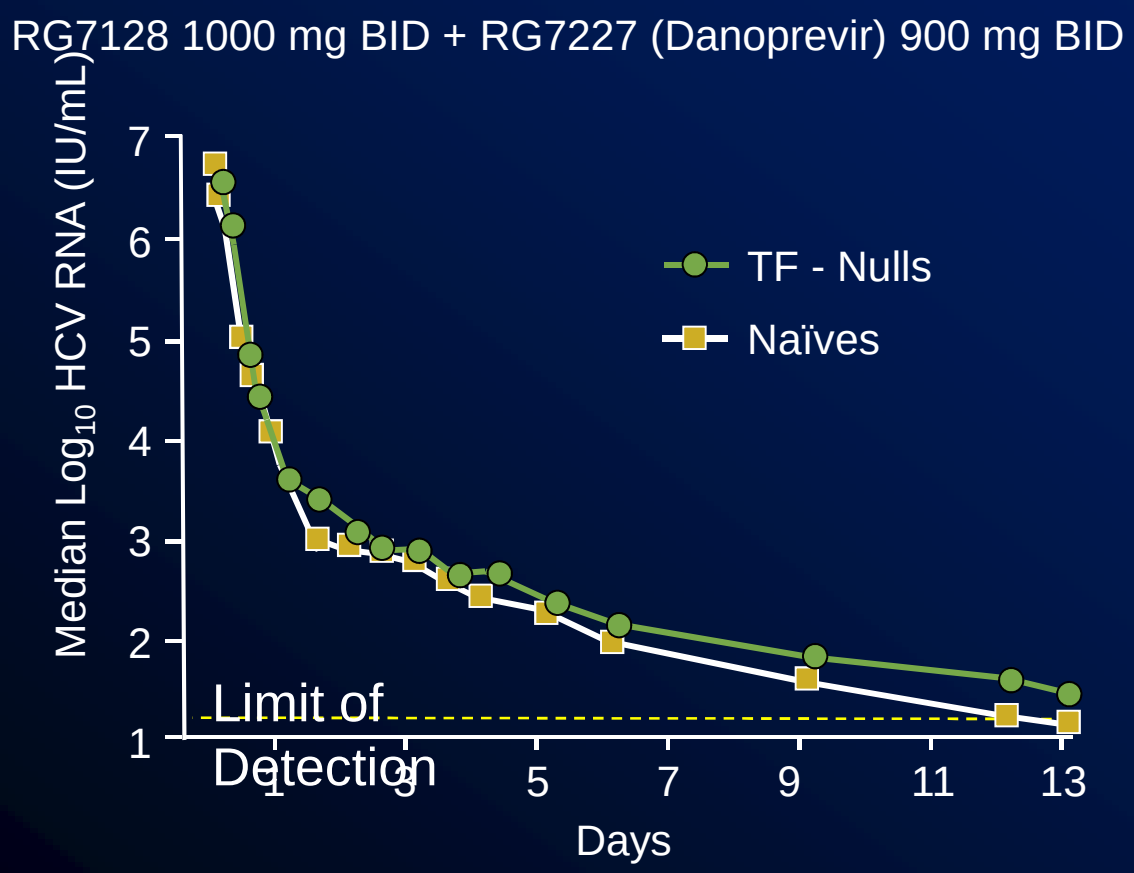
Pockros et al, EASL 2011, late-breaker oral

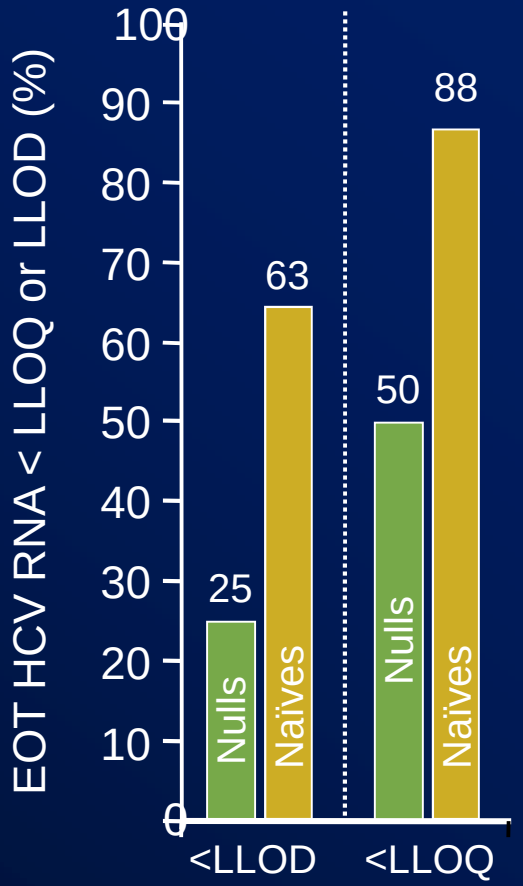
JUMP-C – Virological Response – On Treatment Interim Results



Pockros et al, EASL 2011, late-breaker oral

Other strategies: PI + Polymerase Inhibitor. Potent Antiviral Activity in HCV G1 Interferon-Naïve and Null Responders with a BID Regimen of RG7128 + Danoprevir: INFORM-1





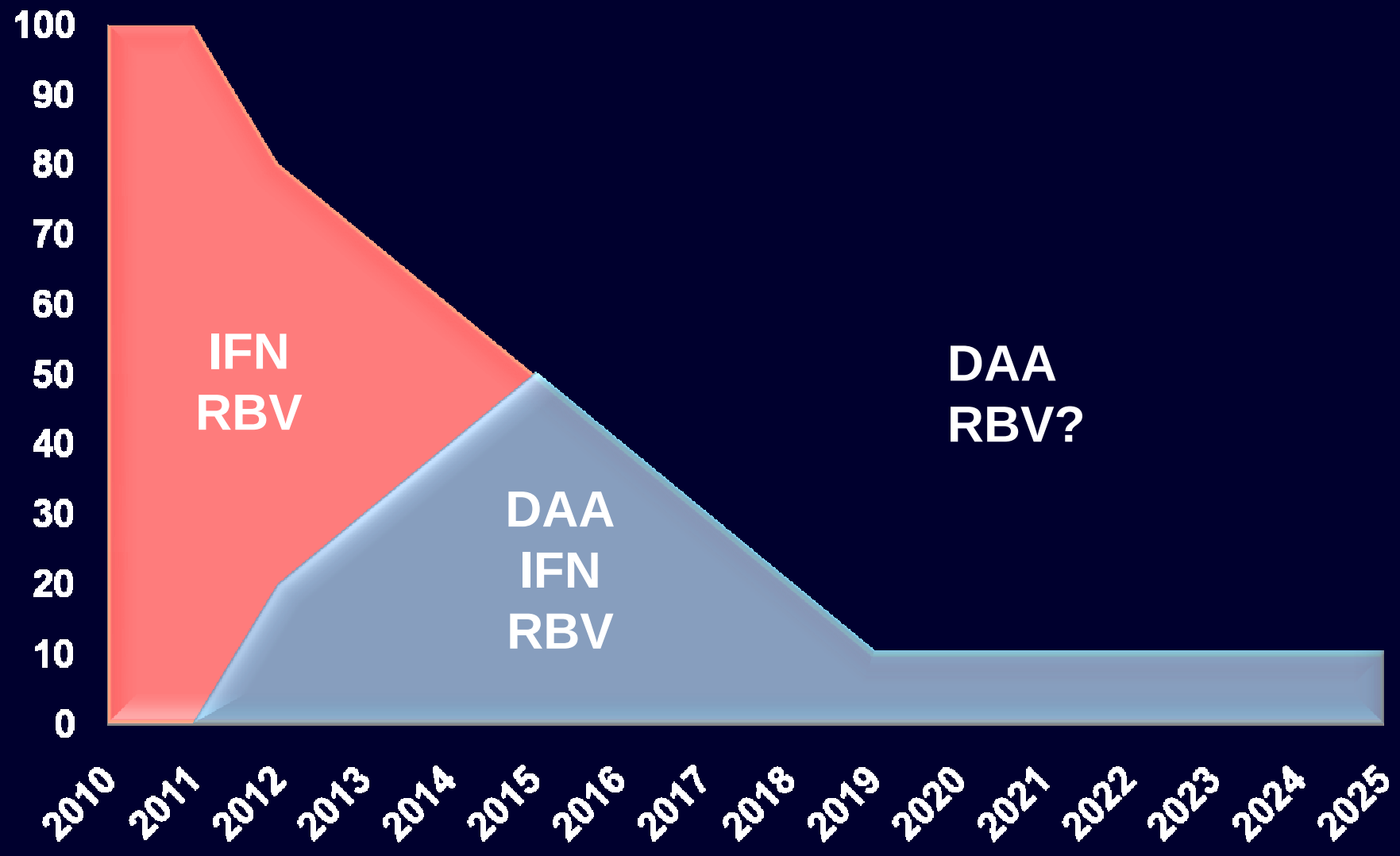
LLOD: Lower limit of detection
LLOQ: Lower limit of quantification

Gane EJ, et al. Lancet 2010.

Combination Therapies with 2 or More DAAs Presented at AASLD 2010

DRUG COMBOS	CLASS	COMPANY	PHASE	ABSTRACT
BMS-650032+ BMS-790052	PI+NS5a	BMS	2a	LB-8
Danoprevir (RG7227)+ RG7128	PI+NI	Roche/ Genetech	2b	32, 81
GS-9190+ GS-92568	PI+NNI	Gilead	2a	LB-1
BI-201335+ BI-207127	PI+NNI	Boehringer Ingelheim	2a	LB-7

¿Podremos curar la hepatitis C sin IFN?



“A theory is something nobody believes, except the person who made it. An experiment is something everybody believes, except the person who made it”

Albert Einstein