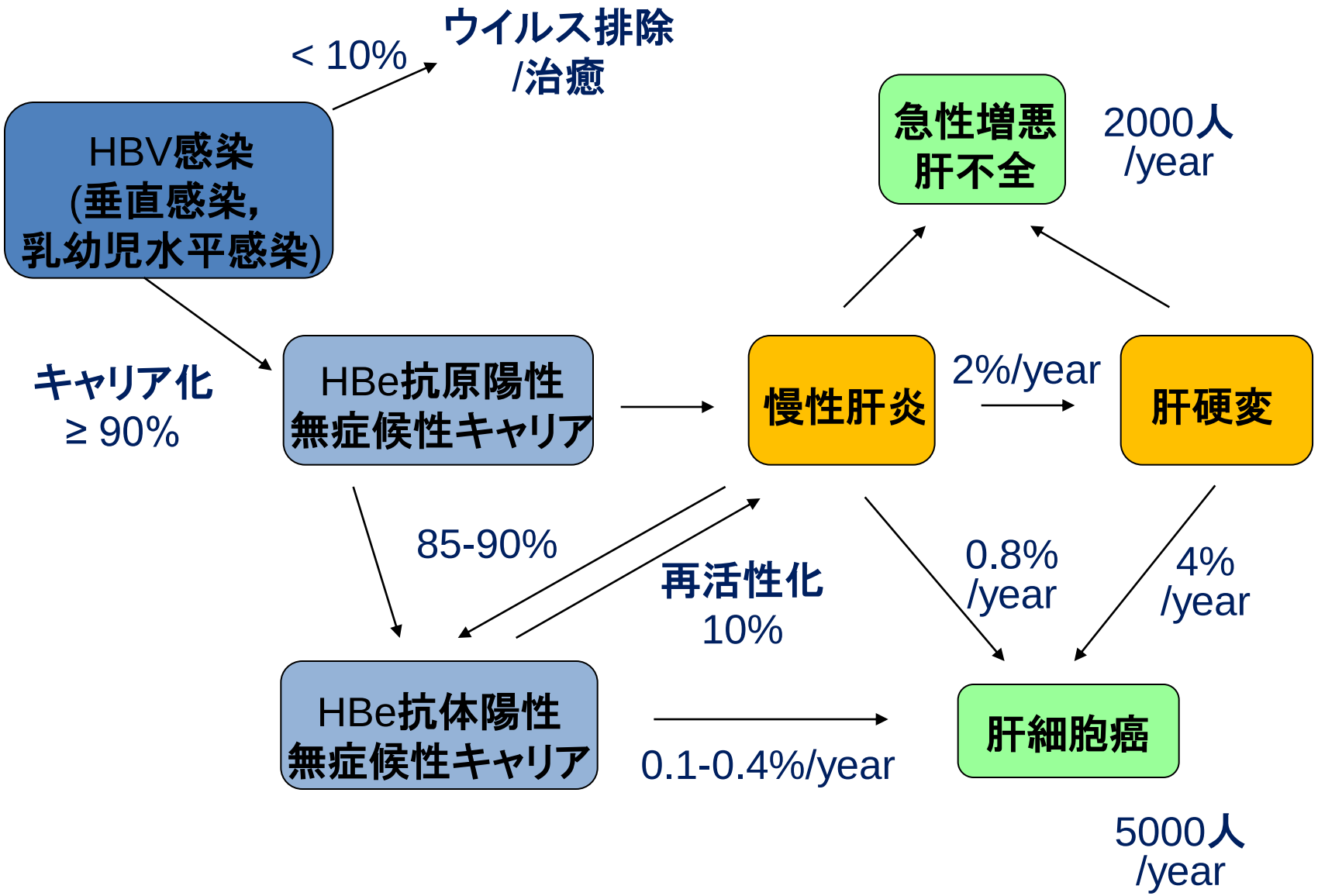
ウイルス肝炎治療の現状と治療薬開発の方向性

関西労災病院病院長
林　紀夫

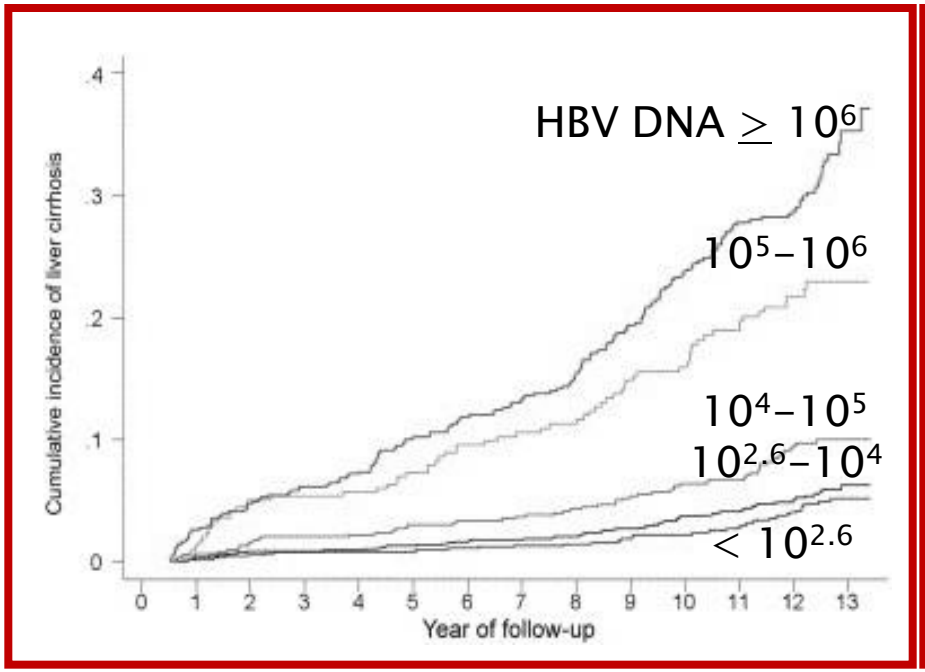

B 型 肝 炎

HBVキャリアの臨床経過

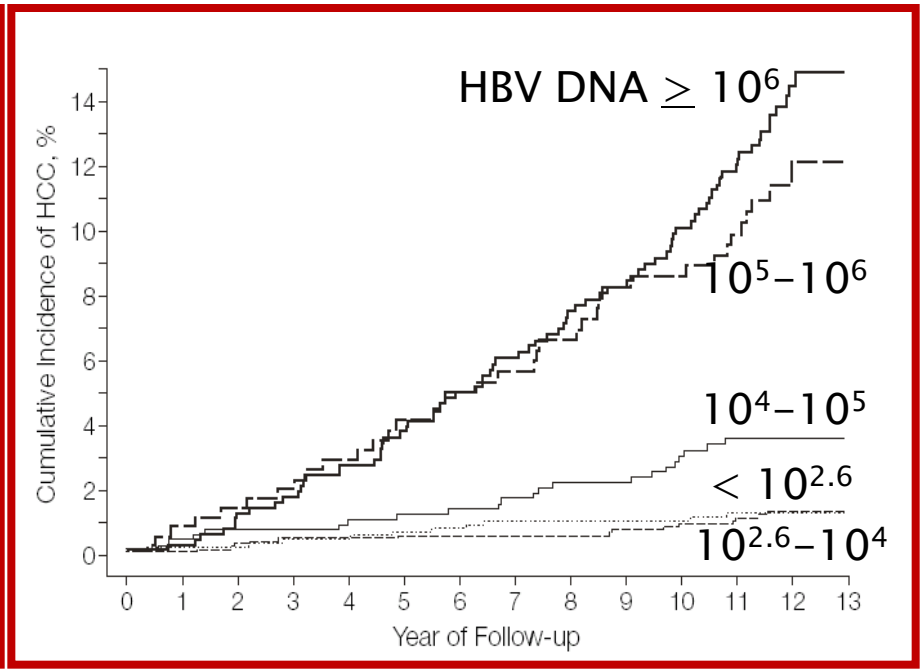


HBVキャリアにおける累積肝硬変・肝癌発症率（海外のprospective cohort studyの結果）

Incidence of cirrhosis (n = 3582)

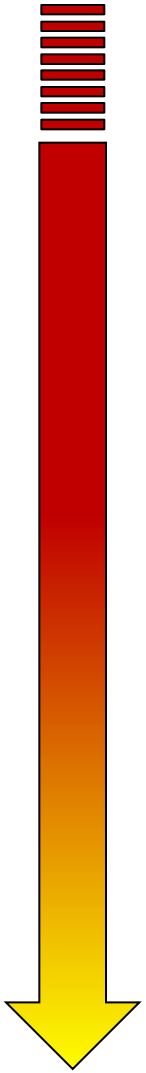


Incidence of HCC (n = 3653)



1) Iloeje et al., Gastroenterology 2006, 130; 678.
2) Chen et al. JAMA 2006, 295; 65.

B型慢性肝疾患に対する抗ウイルス製剤認可の過程



核酸アナログ製剤

2000.9　ラミブジン

2004.10　アデホビル
（ラミブジン耐性症例のみ）

2006.9　エンテカビル

2008.6　アデホビル
（naïve症例）

??　テルビブジン
テノホビル
クレブジン　etc.

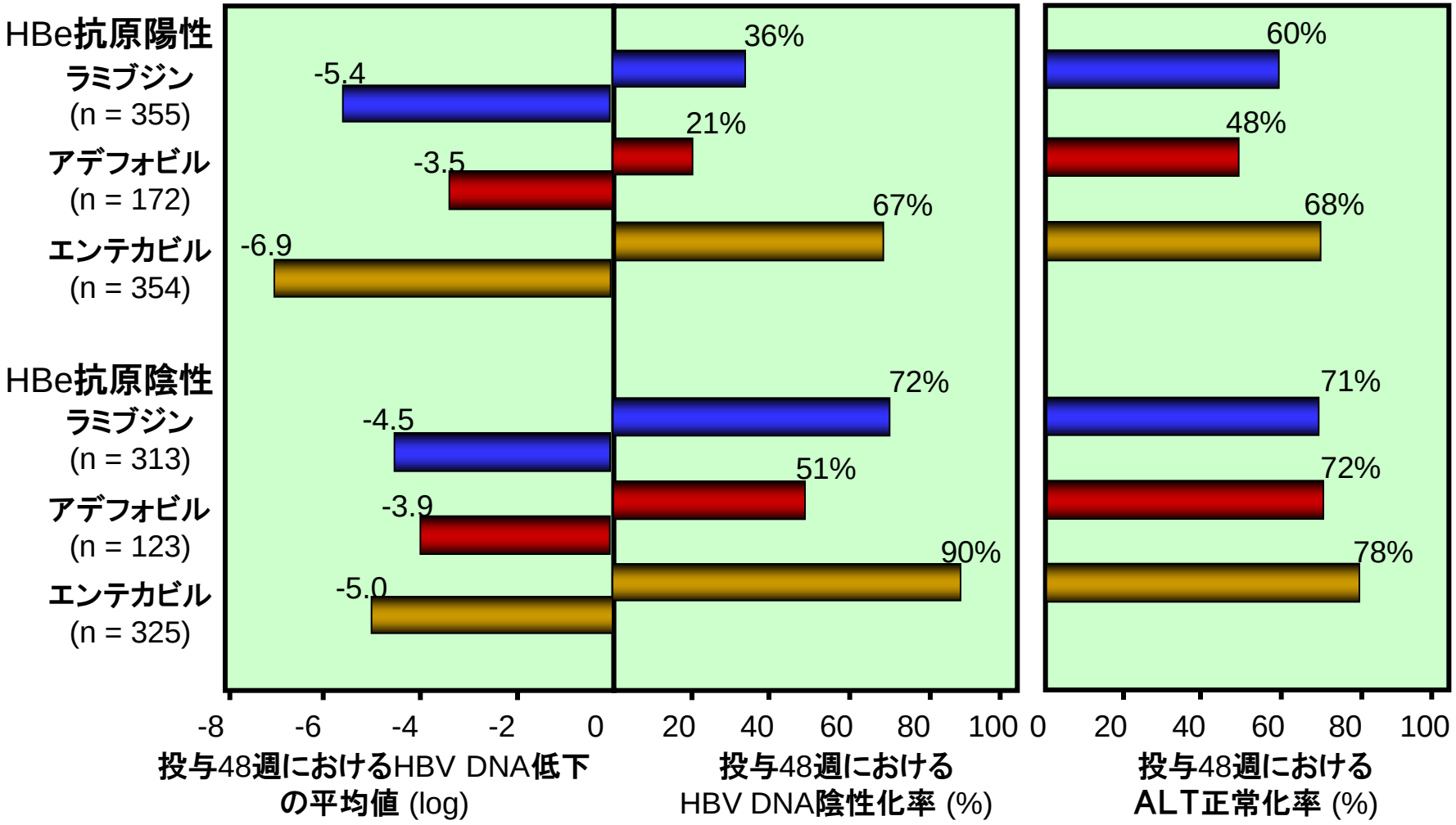
インターフェロン

1988.3　インターフェロン
28日投与

2002.1　インターフェロン
半年投与

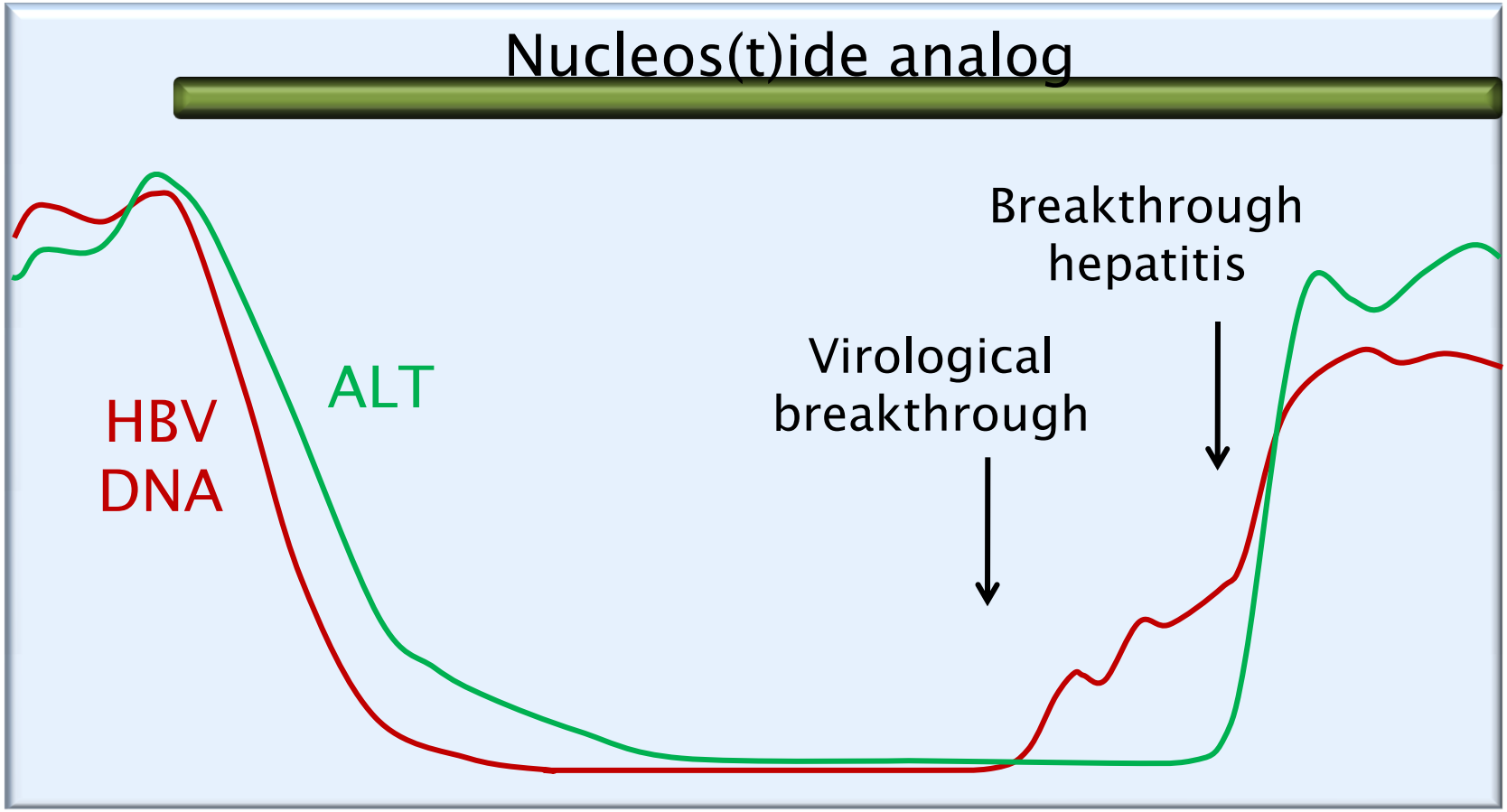
2010.9　PEGインターフェロン

海外の大規模臨床試験におけるB型慢性肝炎に対する各種核酸アナログの治療効果

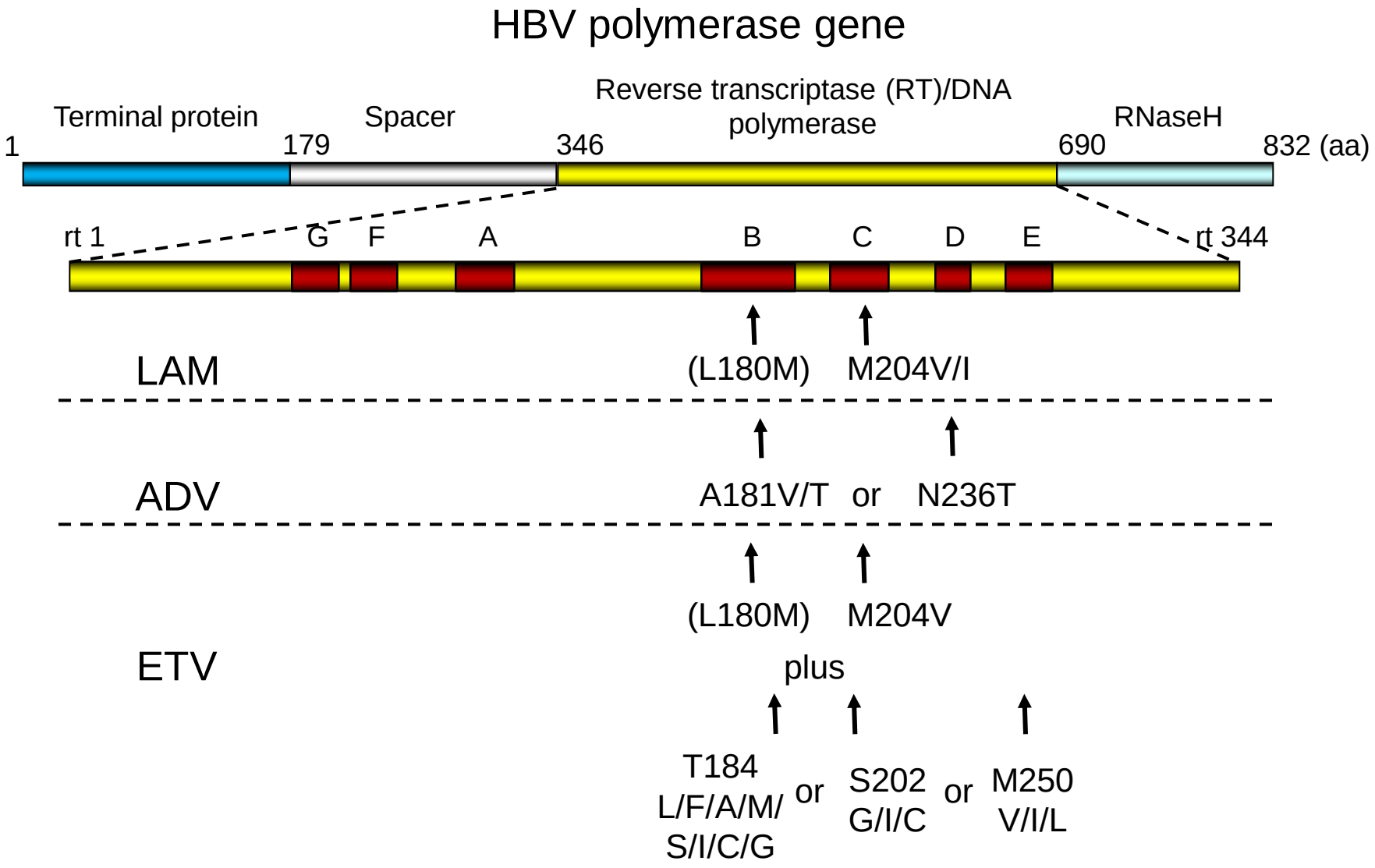


1. Hadziyannis SJ, et al. N Engl J Med 2003; 348: 800-7. 2. Marcellin P, et al. N Engl J Med 2003; 348: 808-16.
3. Chang TT, et al. N Engl J Med 2006; 354: 1001-10. 4. Lai CL, et al. N Engl J Med 2006; 354: 1011-20.

核酸アナログの抗HBV効果



HBVポリメラーゼ遺伝子の構造ならびに各種核酸アナログ耐性関連HBV変異

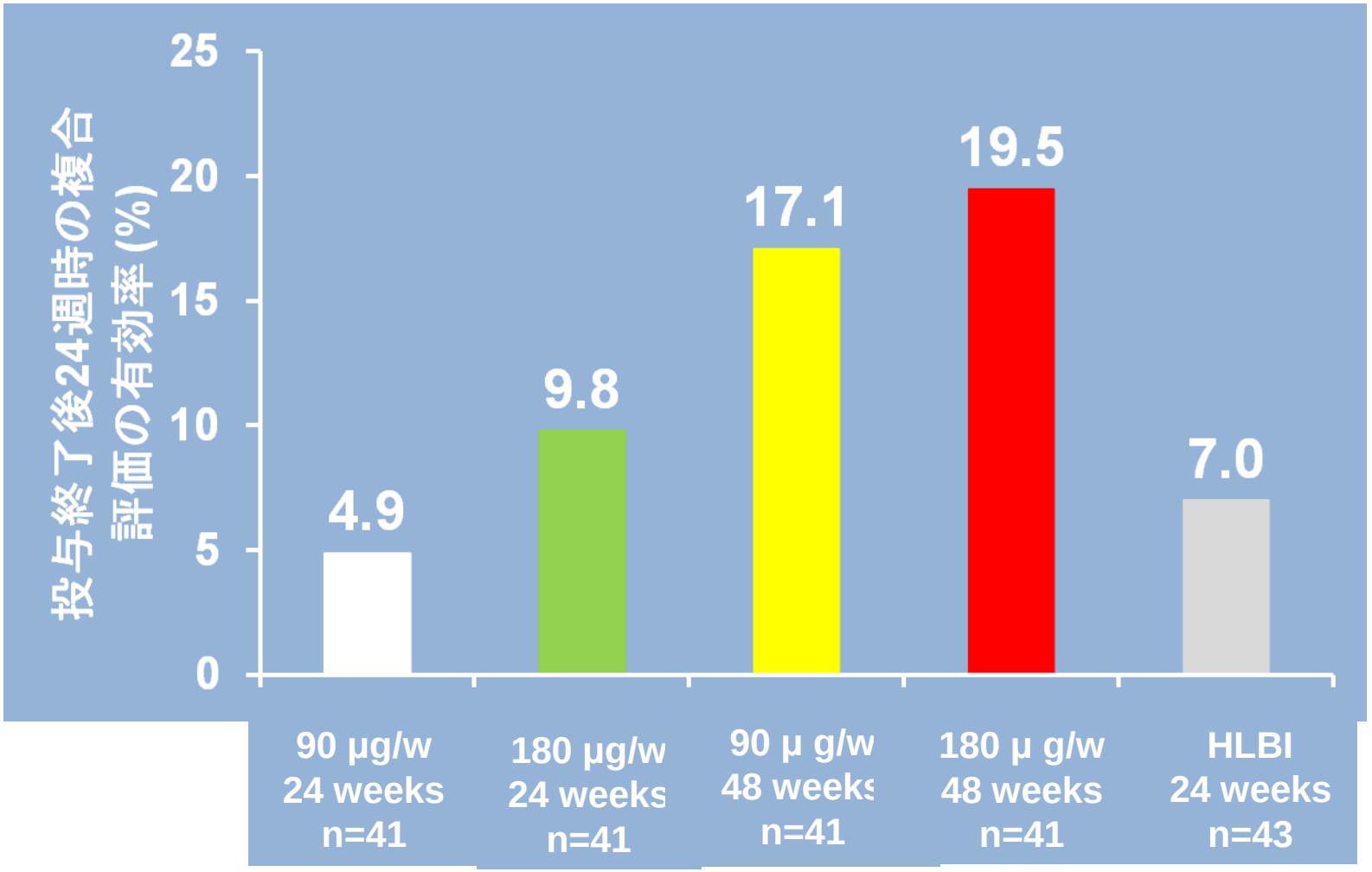


核酸アナログ耐性変異ウイルスの累積出現頻度

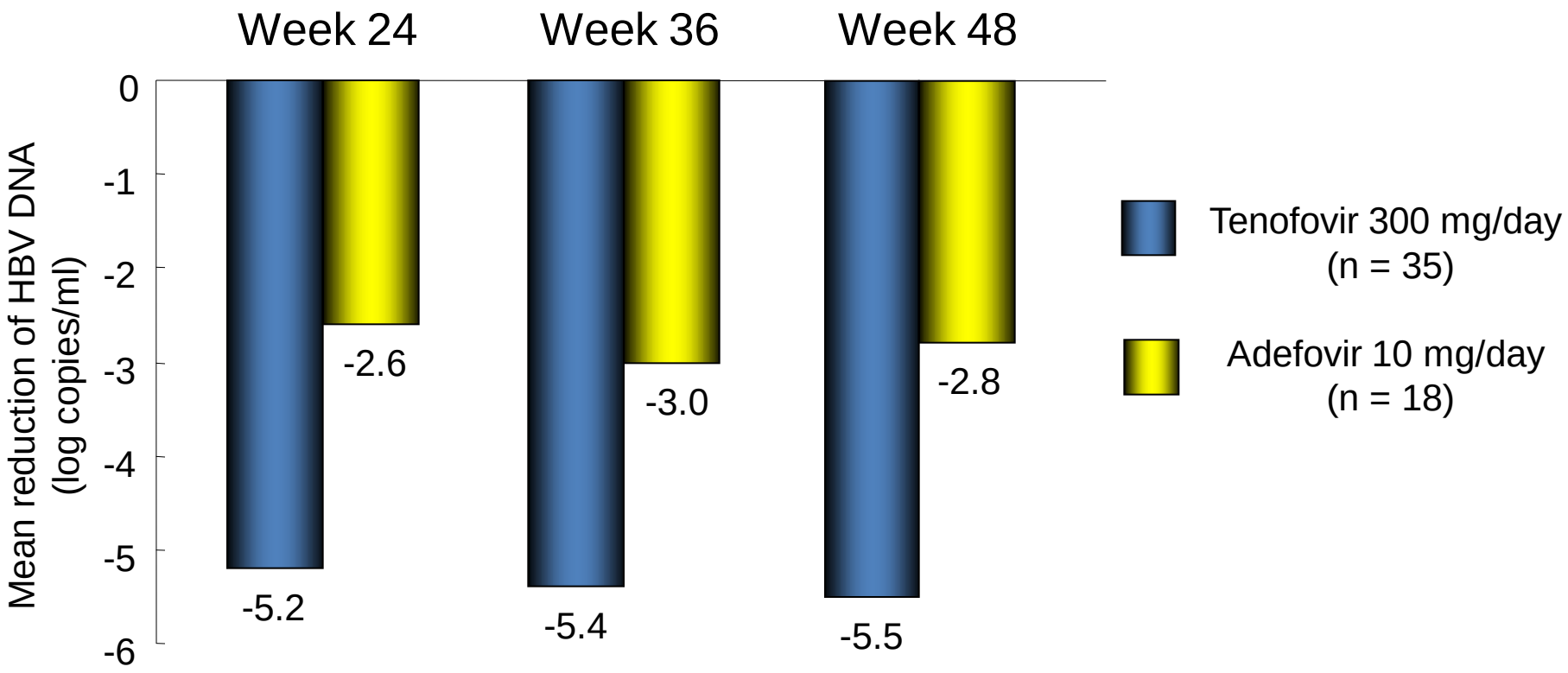
Drugs	Duration of therapy	Emergence rate of drug-resistant mutant virus
ラミブジン	1 yr	24%
	2 yr	42%
	3 yr	53%
	4 yr	70%
アデフォビル (nucleoside-naïve)	1 yr	0%
	3 yr	6%
	5 yr	29%
アデフォビル (lamivudine-resistant)		
switch from LAM to ADV	1 yr	18%
ADV plus LAM	3 yr	rare
エンテカビル (nucleoside-naïve)	3 yr	< 1%
エンテカビル (lamivudine-resistant)	3 yr	15%

投与群別有効率（複合評価*）

***:複合評価**：HBe-セロコンバージョンかつHBV-DNA 陰性化（5.0 Log コピー／mL 未満）かつALT 正常化（40 U/L以下）



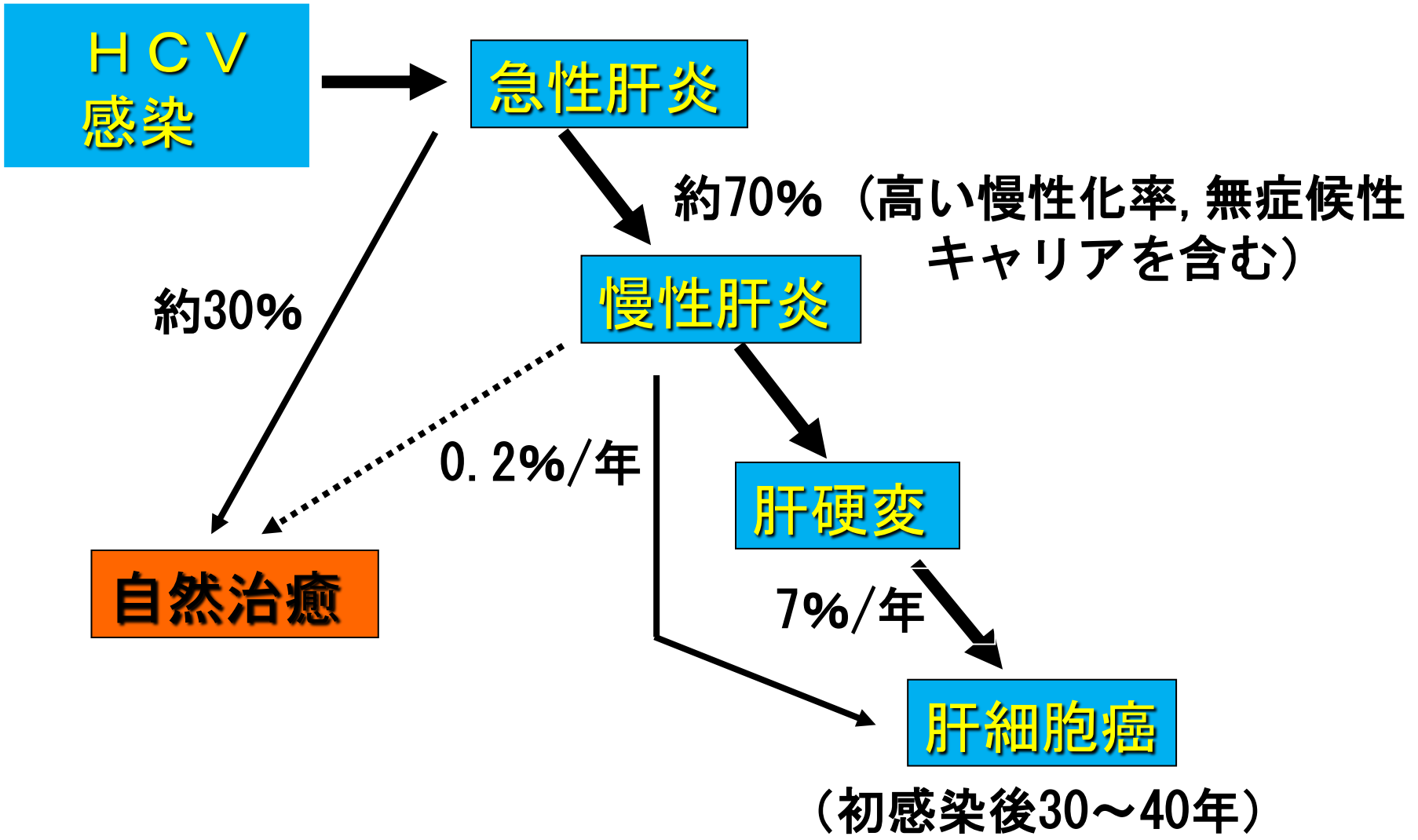
ラミブジン耐性症例に対するアデホビル ならびにテノホビルの抗HBV効果の比較



van Bömmel F, et al. Hepatology 2004; 40: 1421-5.

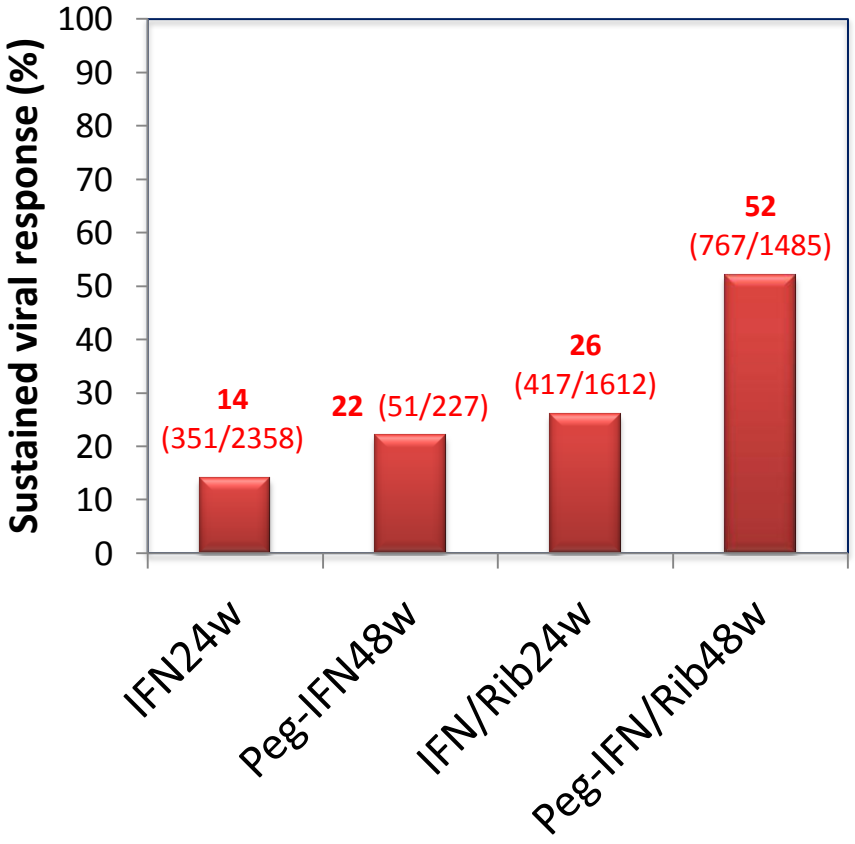

C 型 肝 炎

C型肝炎感染後の自然経過

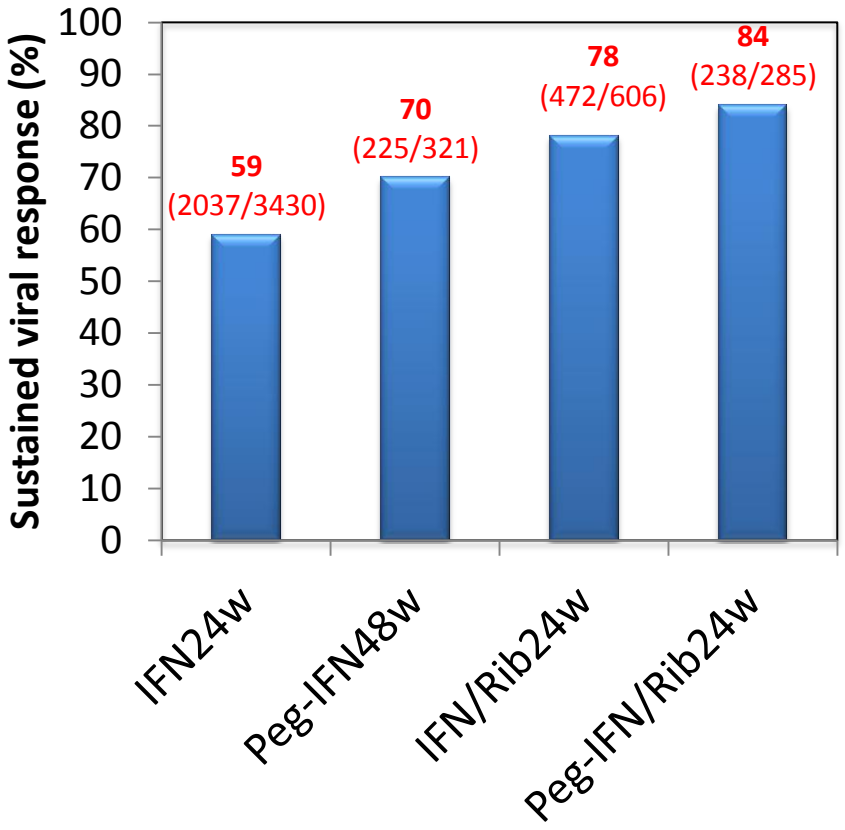


IFNの短期治療 （PPS解析）

1型高ウイルス量



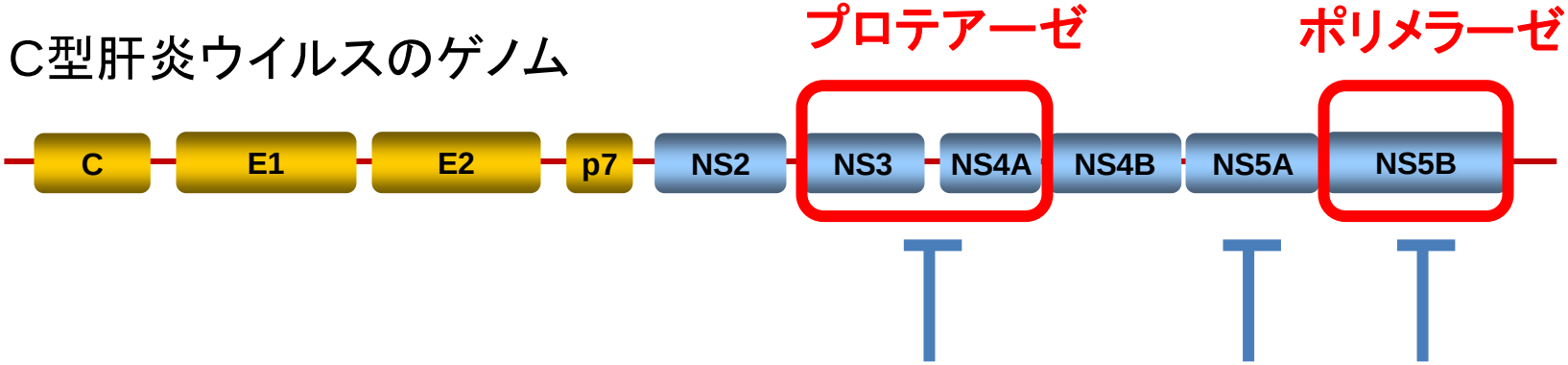
1型高ウイルス量以外



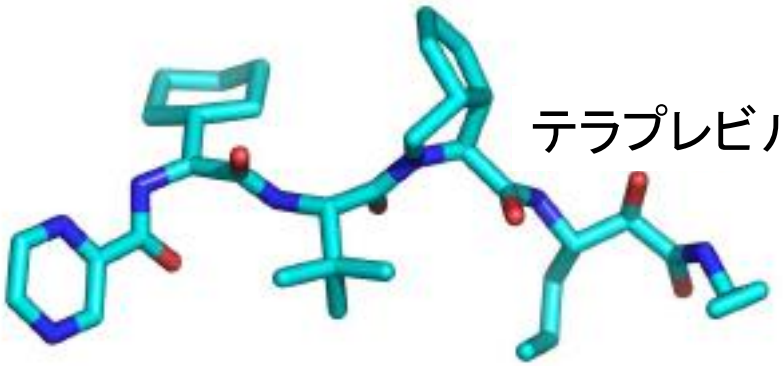
新たなC型肝炎治療薬

これからの治療: C型肝炎ウイルス特異的抗ウイルス薬

C型肝炎ウイルスのゲノム



(Telaprevir)MP-424　BMS-790052 R7128
MK-7009　GS9190
TMC435



テラプレビル

新たなC型肝炎治療薬の開発

新しいIFN製剤

Peg-IFN λ

TLRアゴニスト

CPG10101
Isatorbine

HCV選択的抗ウイルス剤

プロテアーゼ阻害剤

Telaprevir
Boceprevir
TMC435
MK-7009
Vaniprevir
MK-5172
Danoprevir
BI 201335
GS 9256
BMS-650032
ABT-450
GS-9451

ポリメラーゼ阻害剤

R 7128
PSI-7977
BI 207127
ABT-333
IDX184
PSI-938
Tegovuvir
ANA-598

NS5A阻害剤

BMS-790052
GS-5885

サイクロフィリン阻害剤

Alisporivir
SCY-465

C型肝炎の今後の治療

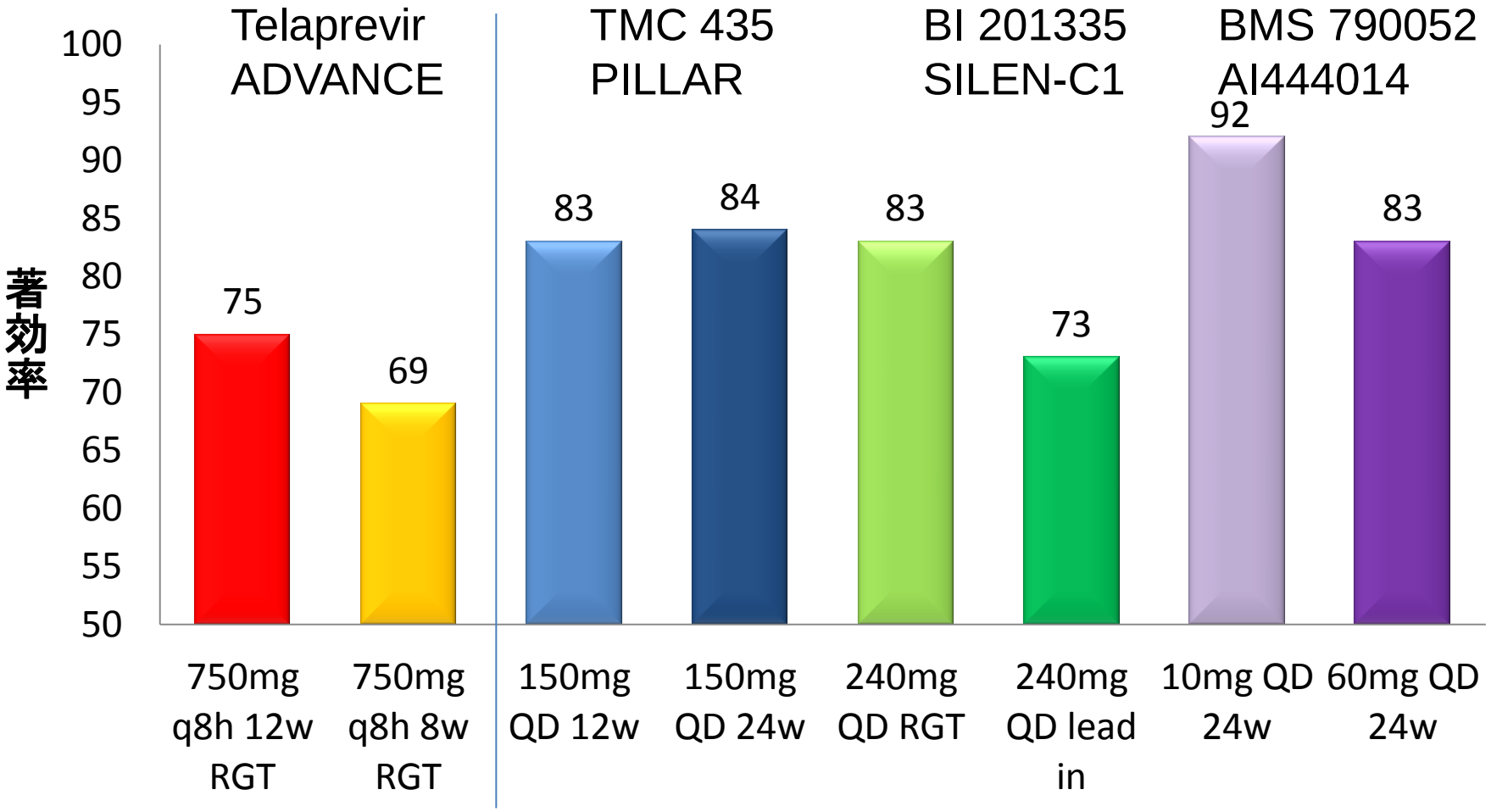
Peg-IFN + リバビリン + 新しい抗HCV剤

プロテアーゼ阻害剤 + ポリメラーゼ阻害剤 NS5A阻害剤 +/- その他の抗HCV剤

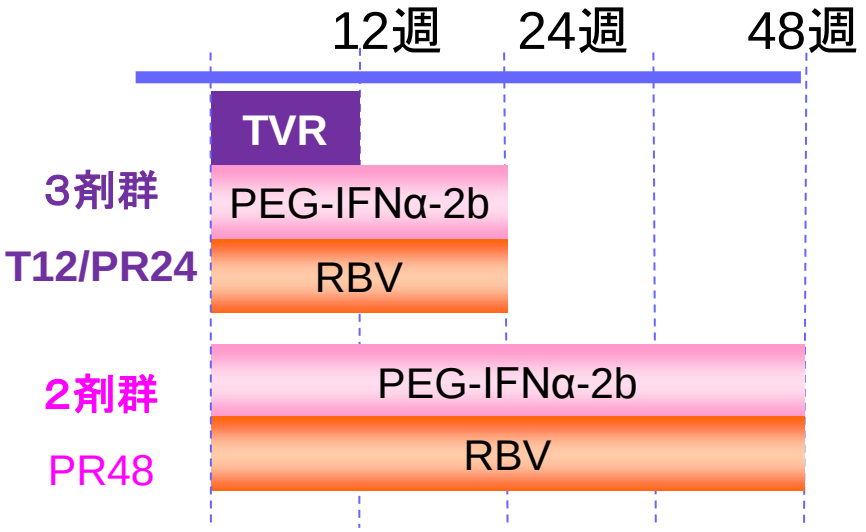
Peg－IFN＋リバビリン+新しい抗HCV剤:

プロテアーゼ阻害剤
ポリメラーゼ阻害剤
NS5A阻害剤

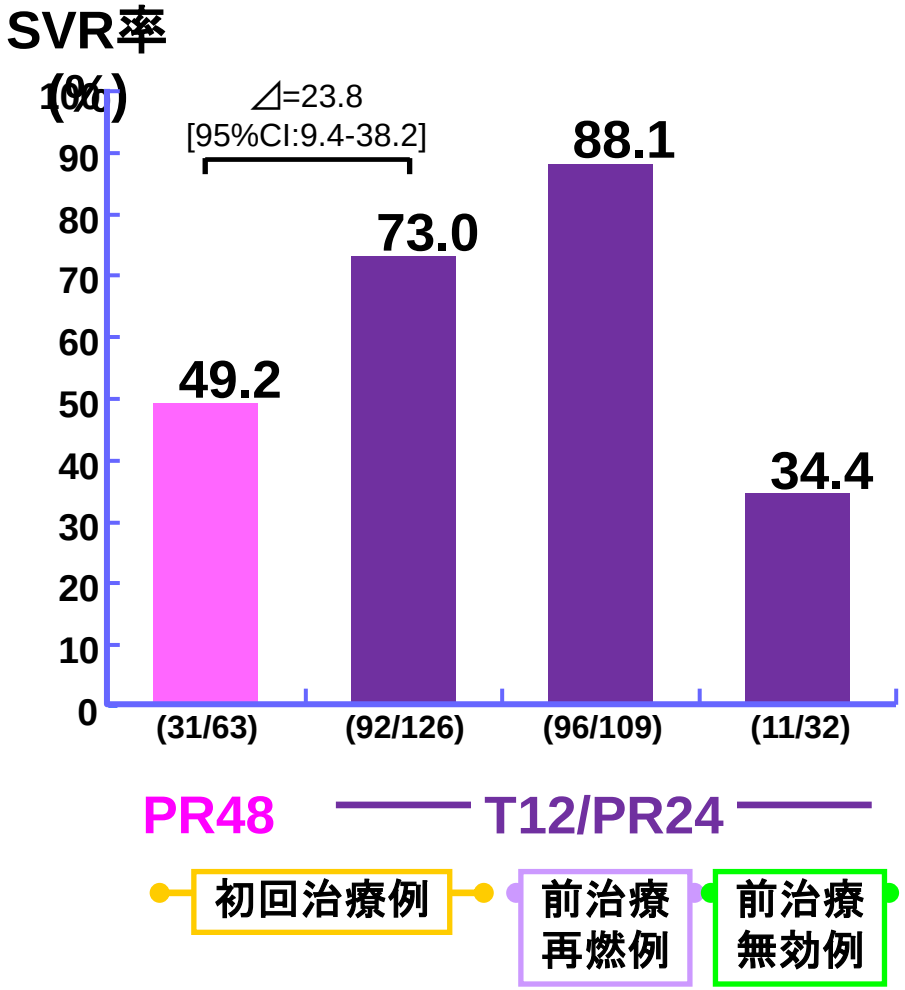
新しい抗ウイルス剤の著効率



テラプレビルによる3剤治療
（1型高ウイルス量）



65歳以下、Hb>13g･dl



MP-424 (Telaprevir 国内第3相試験)

プロテアーゼ阻害剤に対するHCV変異

	V36A/M	T54A	V55A	Q80R/K	R155K/T/Q	A156S	A156V/T	D168A/V/T/H	V170A
Telaprevir (linear)			*			*			*
Boceprevir (linear)							*		
SCH900518 (linear)									
BILN-2061 (macrocyclic)									
ITMN191 (macrocyclic)						*	*		
MK7009 (macrocyclic)						*			
TMC435350 (macrocyclic)									
BI-201335 (linear)									
MK5172 (macrocyclic)									
GS-9256 (macrocyclic)									
ABT 450 (macrocyclic)									
BMS-791325 (macrocyclic)									

Table . Amino acid positions within the NS3/4A protease associated with resistance mutations to different NS3 protease inhibitors and a cross-resistance table of different NS3 protease inhibitors based on mutations selected in patients from clinical studies and/or from in vitro studies./Mutations associated with resistance in vitro. Resistance mutations of NS3 protease inhibitors with a P4-fold increase in EC50 are shown in red (Resistant) and resistance mutations described 64-fold change in EC50; are shown in white (S = susceptible) EC50 = 50% effective concentration (replicon HCV-1b).

Philippe Halfon. Journal of Hepatology 2011 in press

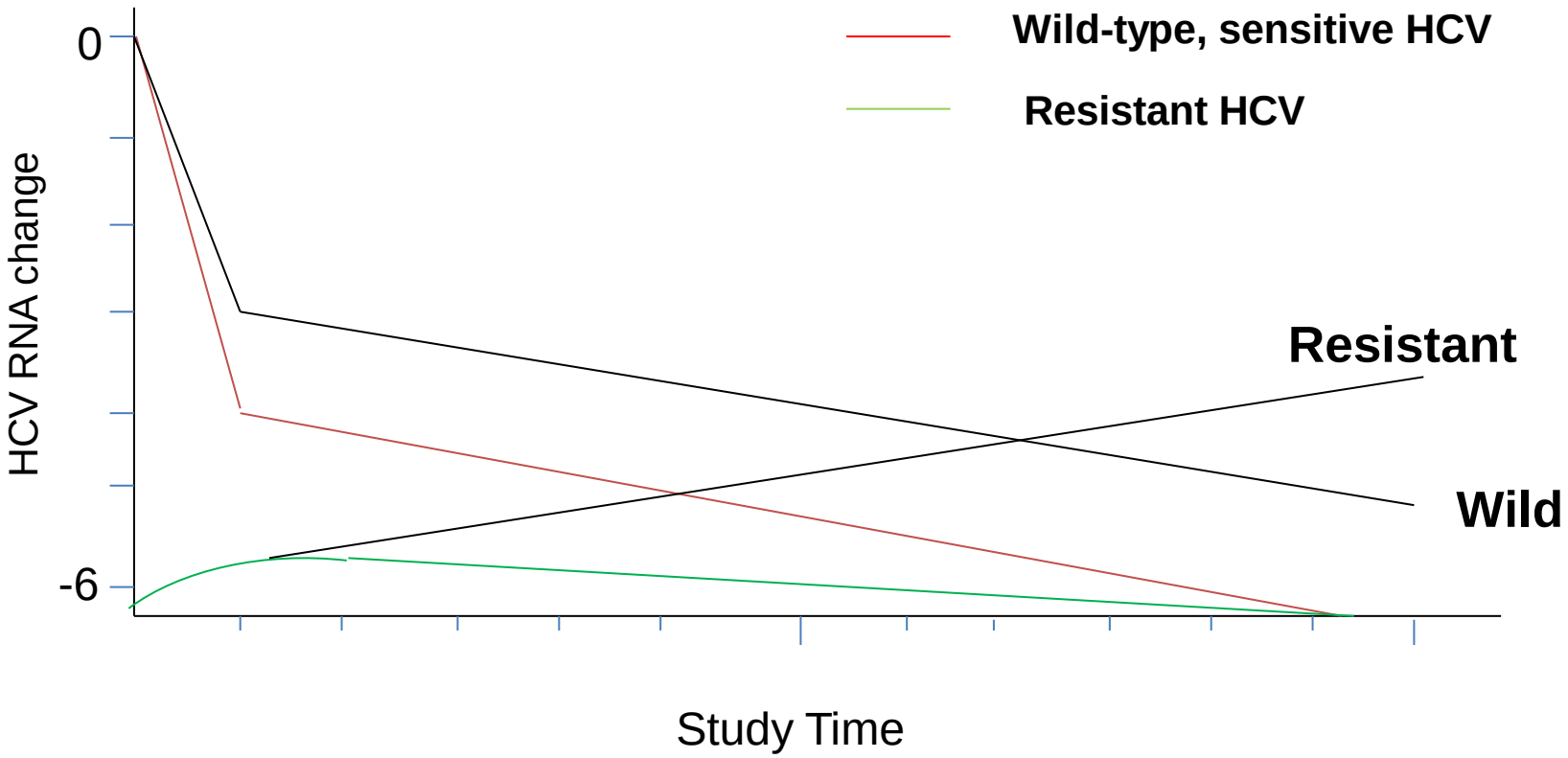
テラプレビル臨床試験におけるHCV変異

Variant	% of sequenced patients	
	Subtype 1a	Subtype 1b
WT	16%	46%
V36M	10%	3%
R155K	20%	0%
V36M+R155K	46%	0%
V36A	3%	16%
T54A	<1%	22%
A156S/T	3%	13%

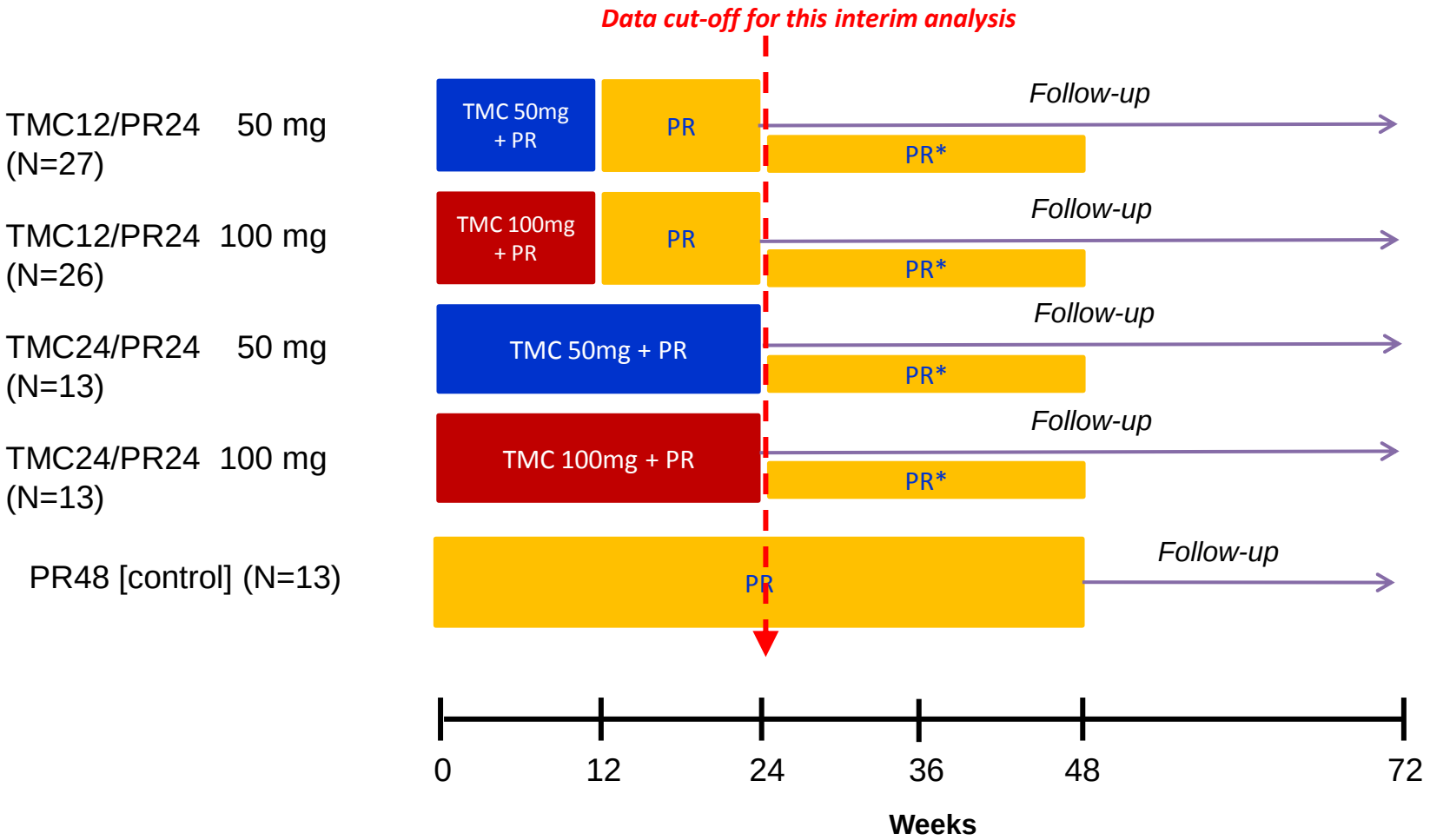
J.C Sullivan. EASL 2011 oral #8

3剤併用療法におけるHCVダイナミックス

IFNα+ribavirin effect

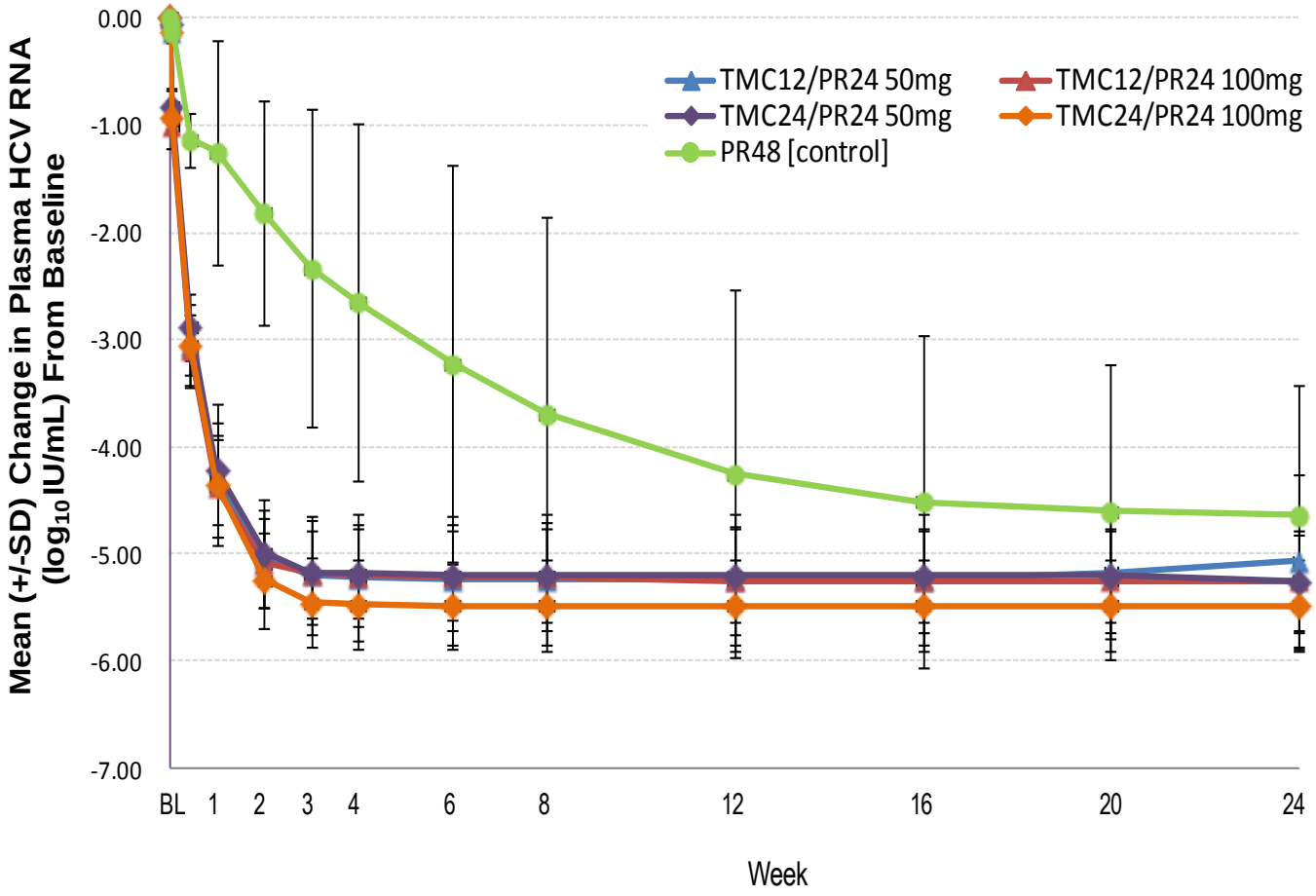


TMC435の第Ⅱ相臨床試験 (DRAGON)

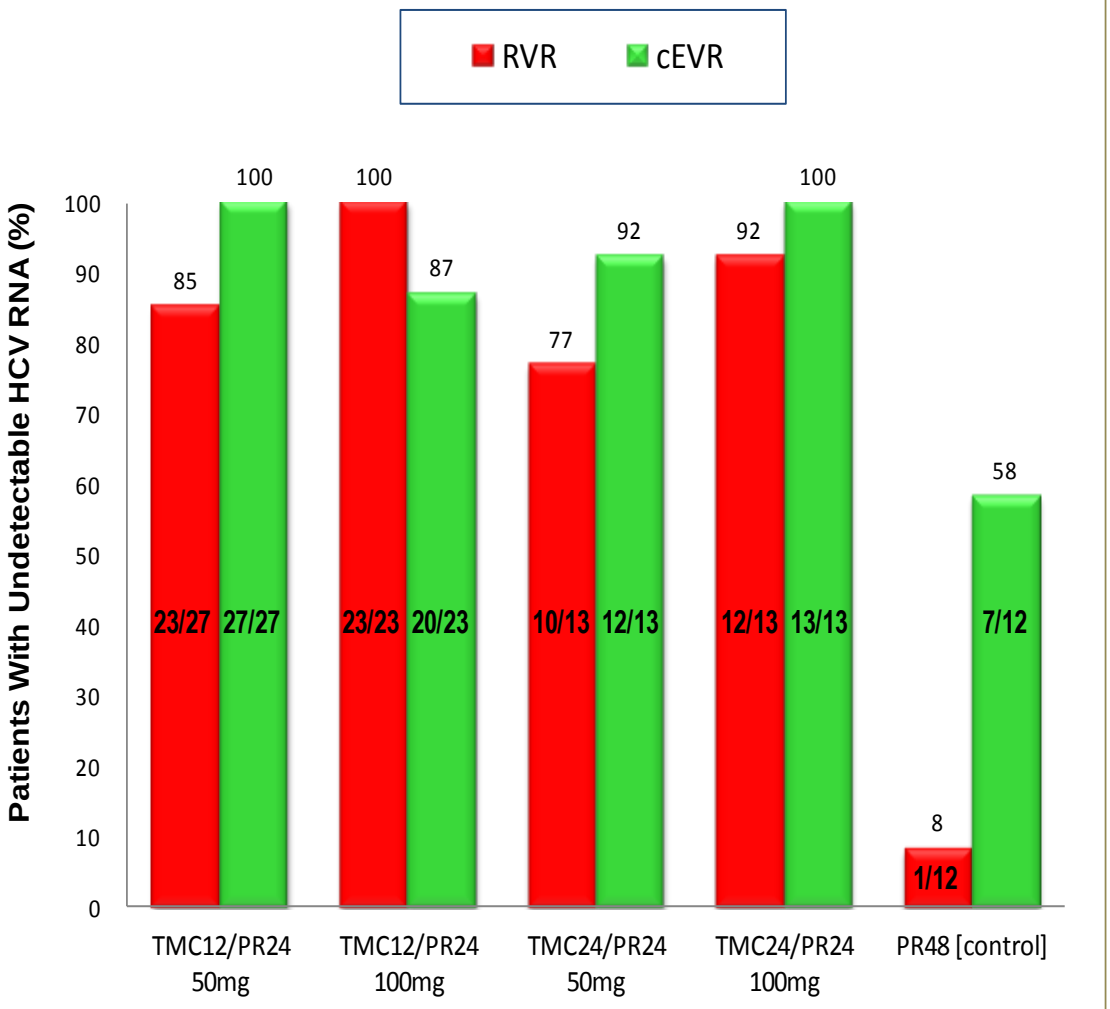


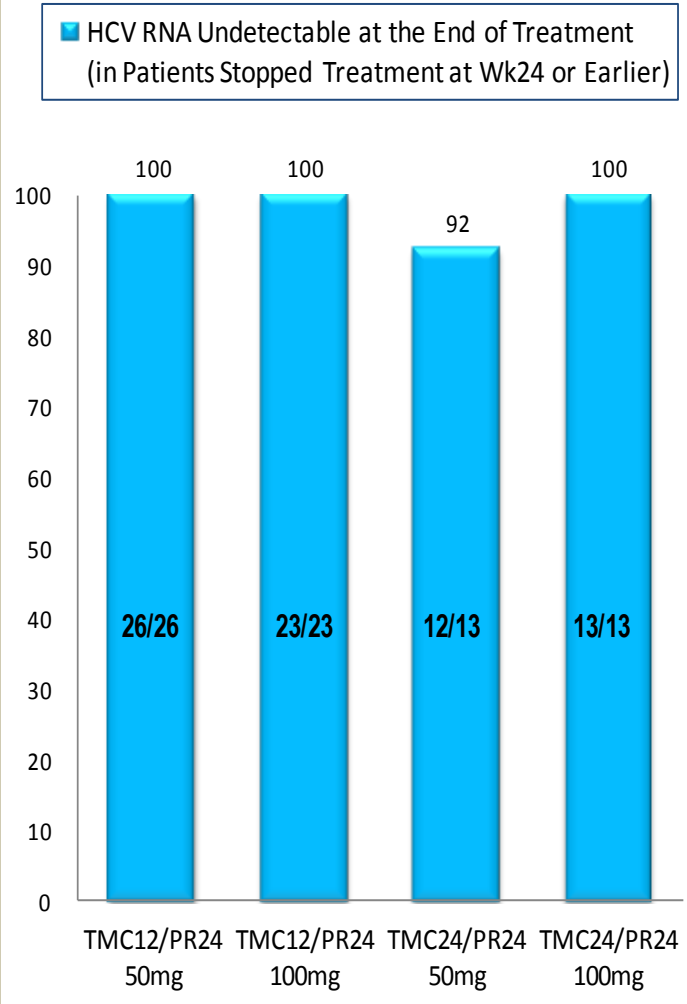
*: Patients who did not achieve HCV RNA < 15IU/mL and undetectable HCV RNA (< 15IU/mL undetectable) at week 4, 12,16 and 20 continue PR until week 48; (P) Peg-IFN = pegylated interferon alfa-2a 180 µg/wk; (R) RBV = ribavirin weight based 600 to 1,000 mg/day

HCV RNAの減少率


Mean (+/-SD) Change in Plasma HCV RNA (log10 IU/mL) From Baseline
0.00
-1.00
-2.00
-3.00
-4.00
-5.00
-6.00
-7.00
BL
1
2
3
4
6
8
12
16
20
24
Week
TMC12/PR24 50mg
TMC12/PR24 100mg
TMC24/PR24 50mg
TMC24/PR24 100mg
PR48 [control]

RVR率とcEVR率

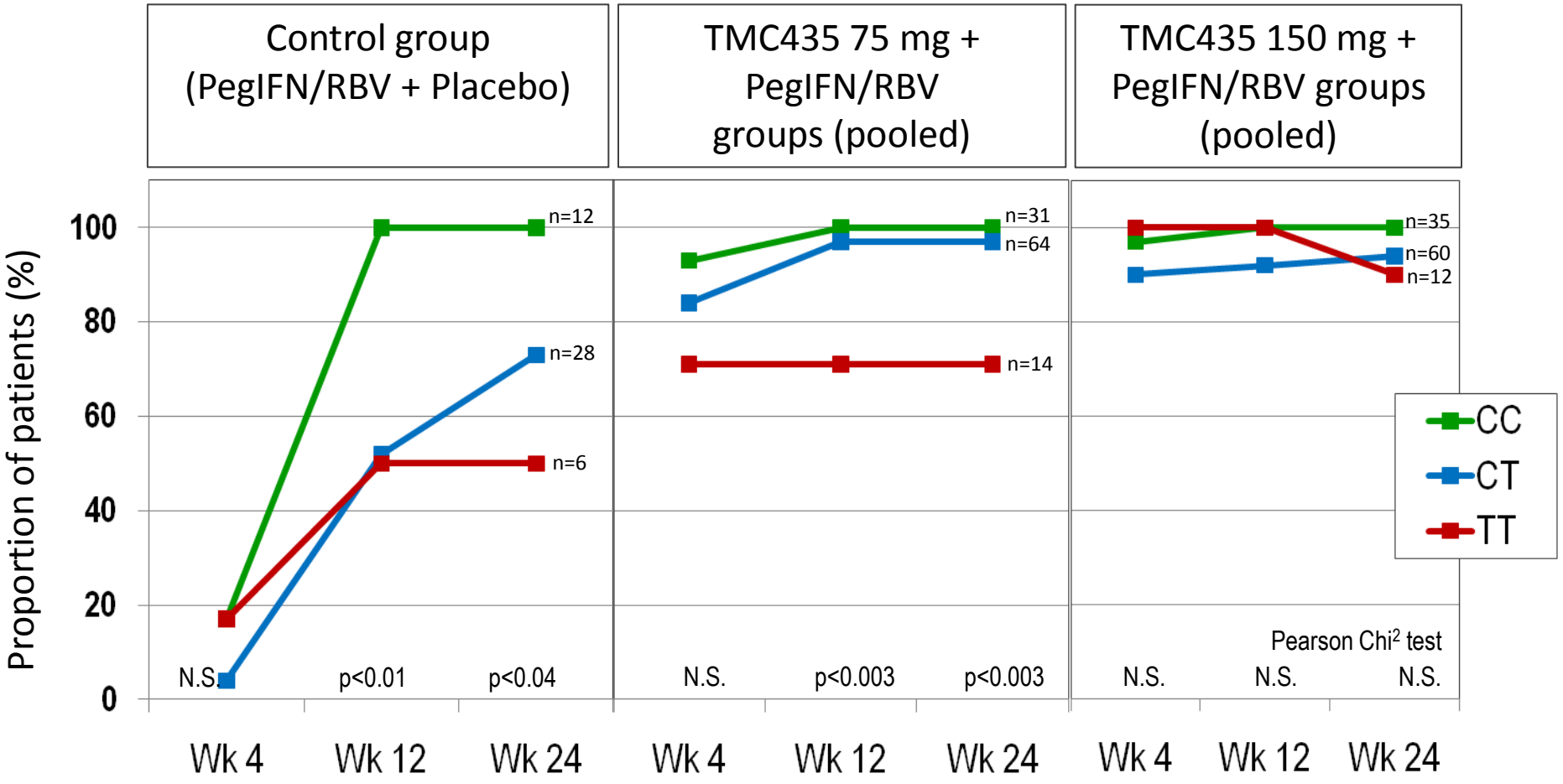




RVR: HCV RNA undetectable at Week 4　cEVR: HCV RNA undetectable at Week 12
The subjects who stopped all medications are handled as those not achieved HCV RNA undetectable
The end of treatment (at Wk48) for group 5 (PR48): data not available yet

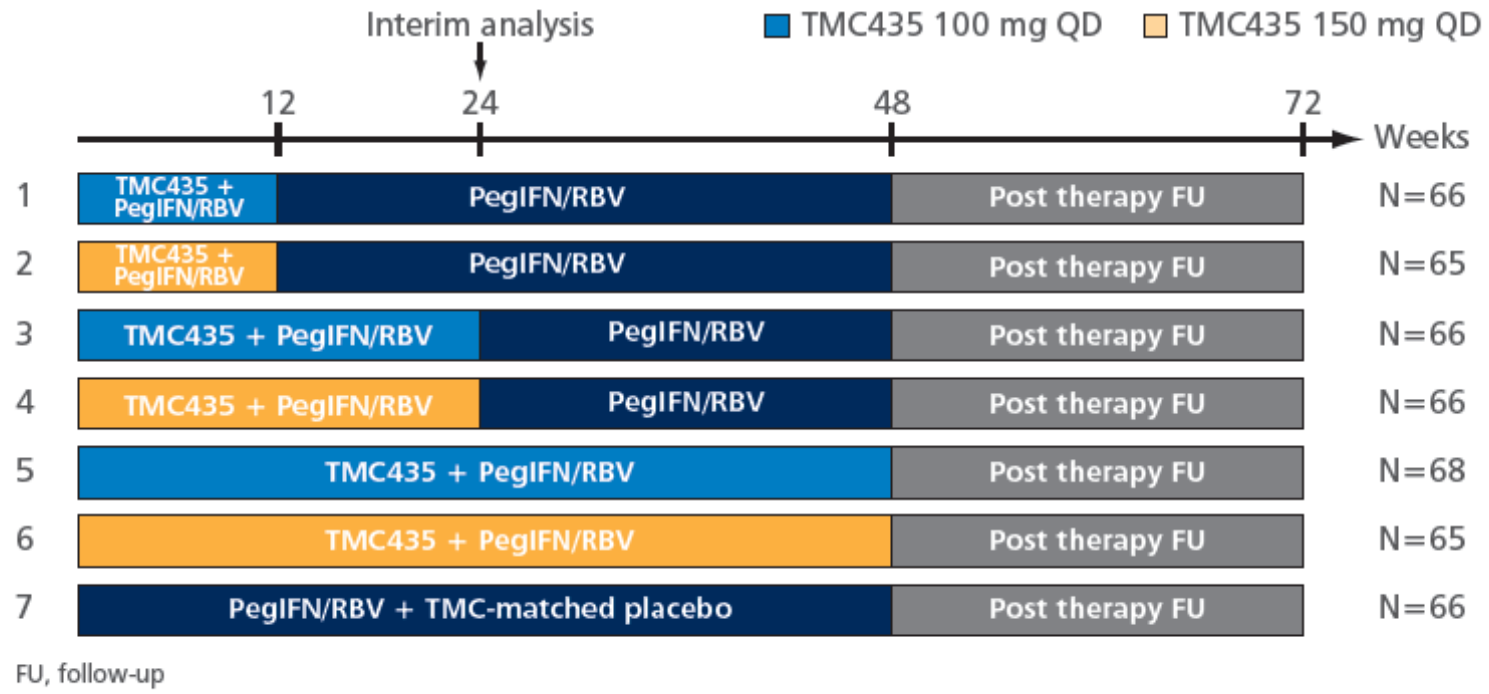
IL28B別のウイルス陰性化率

Virologic response: HCV RNA <25 IU/ml (detectable or undetectable)



ＴＭＣ４３５の既治療に対する臨床試験
（ASPIRE 試験）

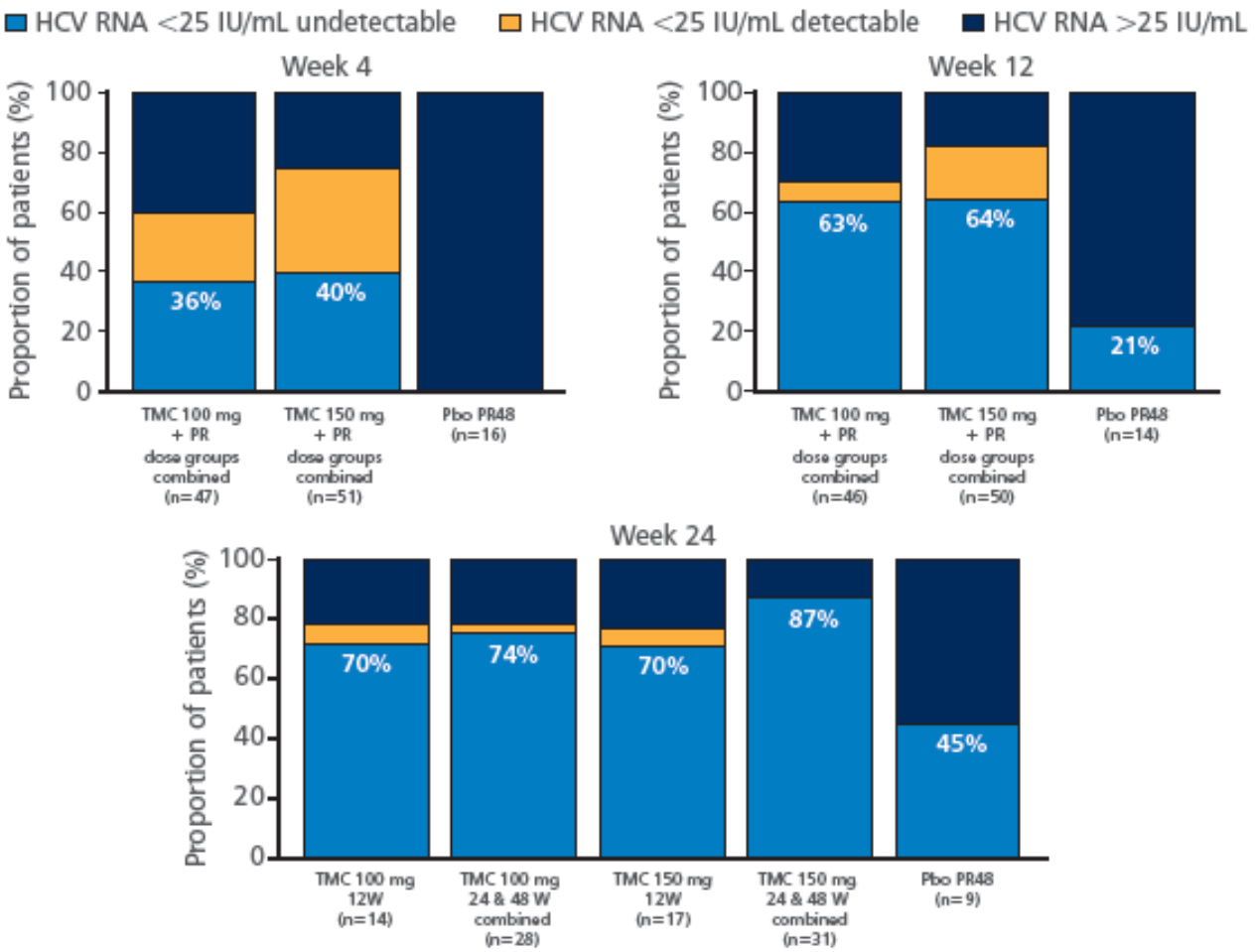
FIGURE 1: ASPIRE study design.



FU, follow-up

ＮＲ症例のウイルス陰性化率

FIGURE 3c: Observed virologic response rate at Weeks 4, 12, 24, by treatment group: Null responders.

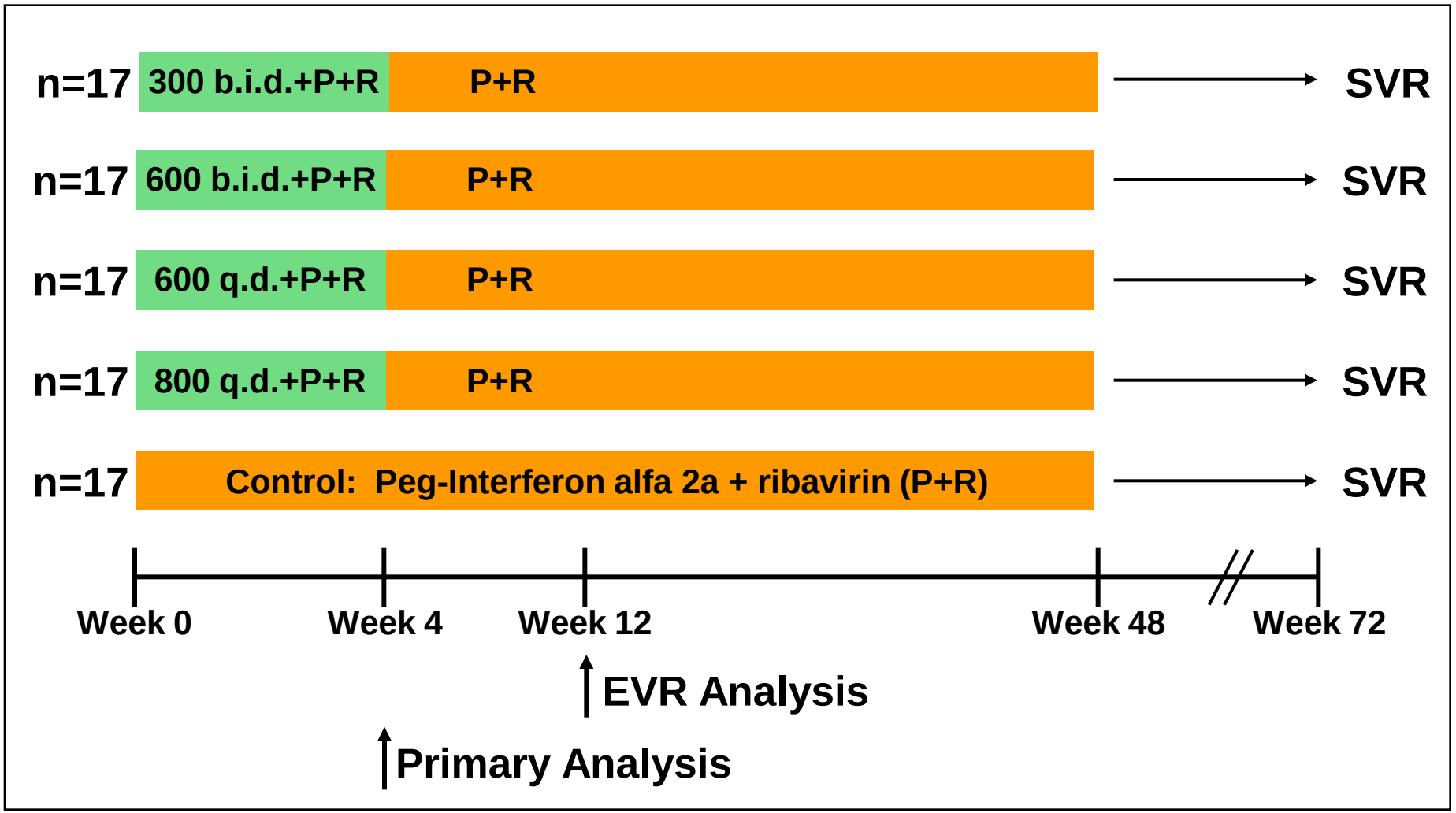


Pbo PR48, Placebo in addition to PegIFN/RBV for 48 Weeks; PegIFN, peginterferon; RBV, ribavirin; TMC, TMC435

既治療症例におけるTMC435の治療効果

%(nN)	TMC435 12PR48 N=66	TMC435 24PR48 N=68	TMC435 48PR48 N=65	All TMC435 N=199	Placebo PR48 N=66
Relapser					
EoT	92 (24/26)	93 (25/27)	92 (24/26)	92 (73/79)	70 (19/27)
SVR4	84 (21/25)	93 (25/27)	85 (22/26)	87 (68/78)	50 (12/24)
Partial Responder					
EoT	78 (18/23)	83 (20/24)	86 (19/22)	83 (57/69)	17 (4/23)
SVR4	64 (14/22)	86 (18/22)	82 (18/22)	77 (50/65)	11 (2/18)
Null Responder					
EoT	65 (11/17)	71 (12/17)	77 (13/17)	71 (36/51)	25 (4/16)
SVR4	56 (9/16)	60 (9/15)	56 (9/16)	57 (27/47)	23(3/13)

MK-7009: Study Design



Primary hypothesis: RVR rates for at least 1 MK-7009-treated group superior to control

MK-7009のRVRとSVR

MK-7009 Dose group	RVR (Full Analysis set)	% RVR	SVR (Full Analysis Set)	% SVR
300mg bid	12/18	67	11/18	61
600 mg bid	16/20	80	16/20	80
600 mg qd	12/17	71	14/18	78
800 mg qd	16/19	84	16/19	84
placebo	1/19	5	12/19	63

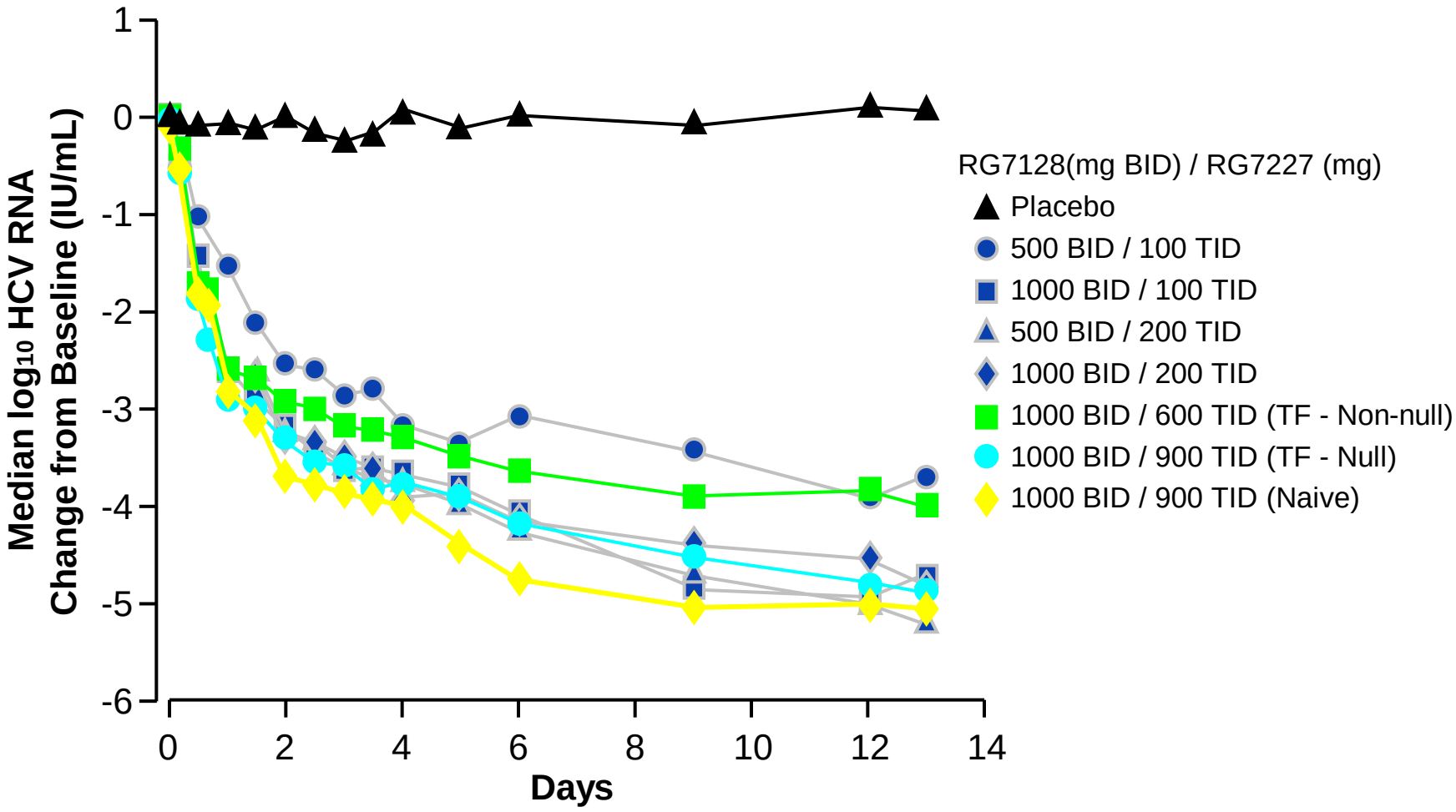
- SVR for QD and high BID doses of MK7009 numerically higher than placebo
  - Placebo SVR rate higher than expected /historical rate

Michael P. Manns et. al., AASLD2010 #82

新しい抗HCV剤+新しい抗HCV剤:

プロテアーゼ阻害剤
ポリメラーゼ阻害剤
NS5A阻害剤

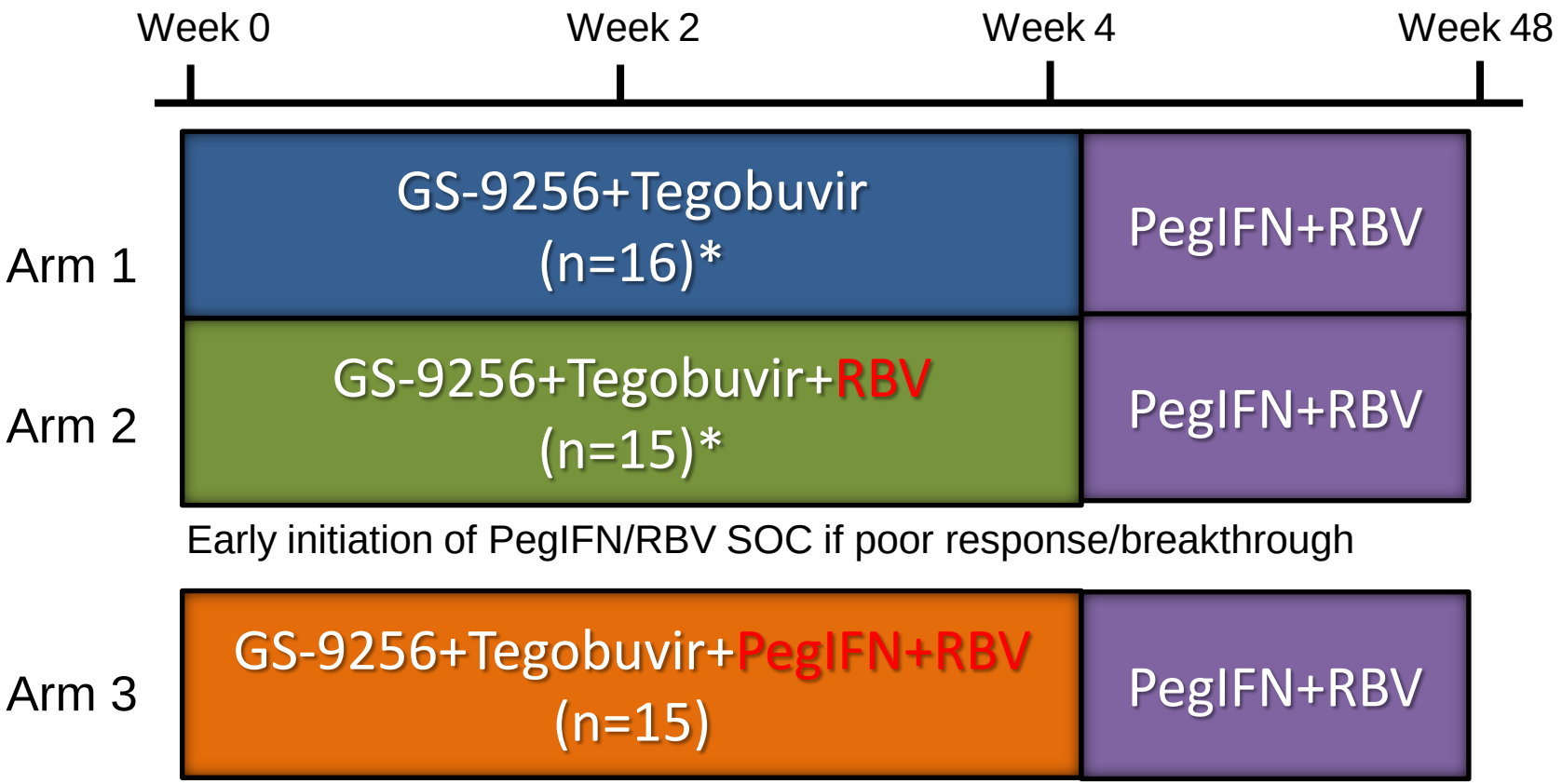
ポリメラーゼ阻害剤(RG7128)とプロテアーゼ阻害剤(RG7227)の同時投与による抗ウイルス効果



DAAsの開発状況

	NS3 PI	NS5A Inh	NS5B Nuc	NS5B NN
Roche	Danoprevir		R7128	
Vertex	Telaprevir			VX-222
BMS	BMS650032	BMS790052		
Boehringer	BI201335			BI207127
Gilead	GS-9256			GS-9190
Idenix	IDX320		IDX184	
Abbott	ABT450			ABT072
Pharmasset			PSI-938+PSI-7977	

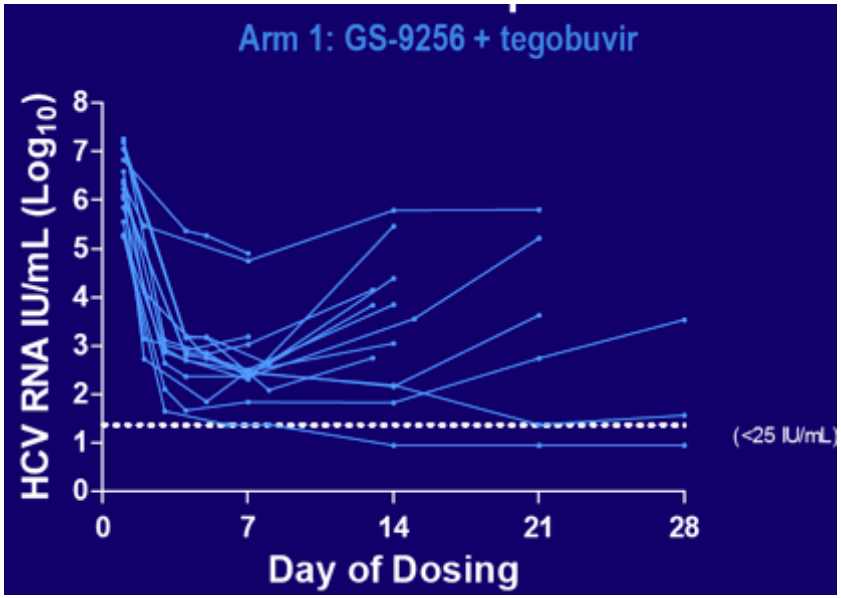
GS-9256+Tegobuvir Study

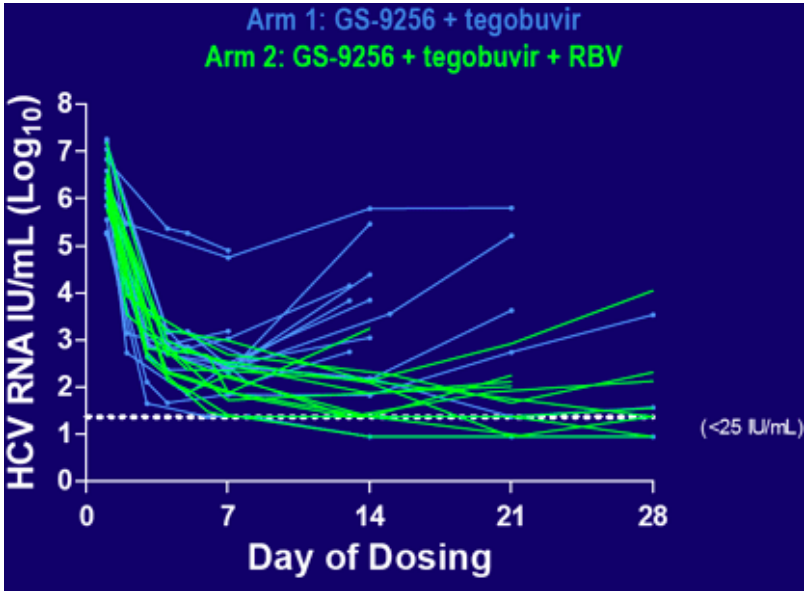


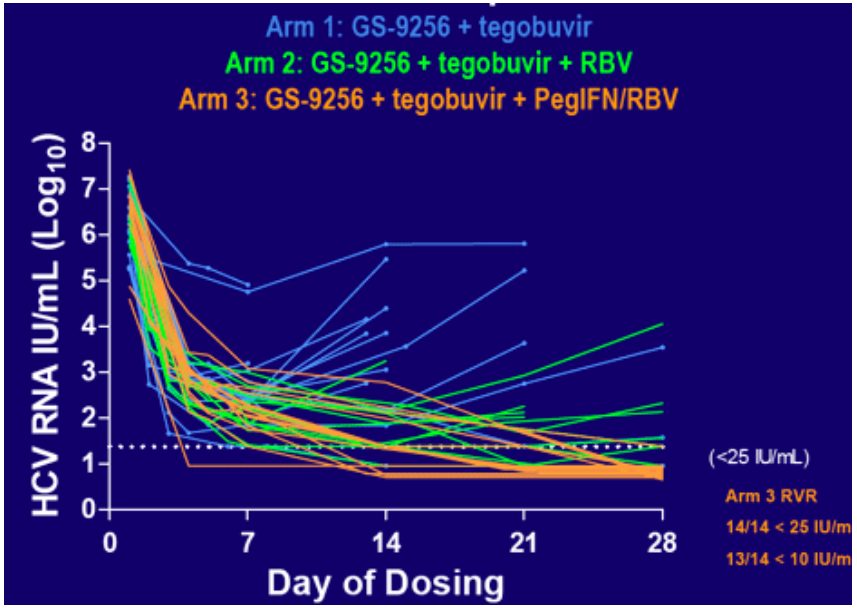
- GS 9256 75mg BID, Tegobuvir 40 mg BID,
- RBV 1000-1200 mg/day, Peginterferon alfa-2a 180 mcg SC QW
- Safety and virologic monitoring 2-3* per week
- Serial PK evaluated at week 3 or 4

Zeuzem, et.al. AASLD, oral, #LB-1

GS-9256+Tegobuvirの抗ウイルス効果







NS5A阻害剤（BMS-790054）+プロテアーゼ阻害剤（BMS-650032）の臨床試験

Subjects: **genotype 1, null responders**(< 2log decline in HCV RNA following 12 weeks of treatment with PegIFN/RBV)

Group A: BMS-790054+BMS-650032 (n=11)

Group B: BMS-790054+BMS-650032 +PegIFN/RBV(n=10)

Follow-up: up to 48 weeks posttreatment

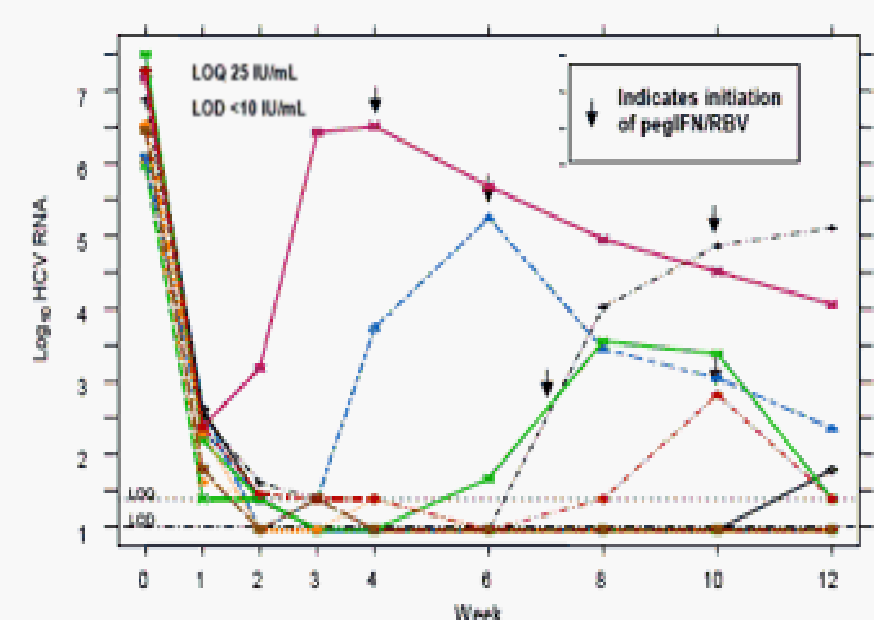
24-week duration of therapy

- BMS-790052 (NS5A inhibitor) 60mg PO QD
- BMS-650032 (NS3 protease inhibitor) 600mg PO BID
- PegIFN alfa-2a 180 μg SC pnce weekly
- RBV 1000-1200 mg daily in 2 divided doses, according to body wight

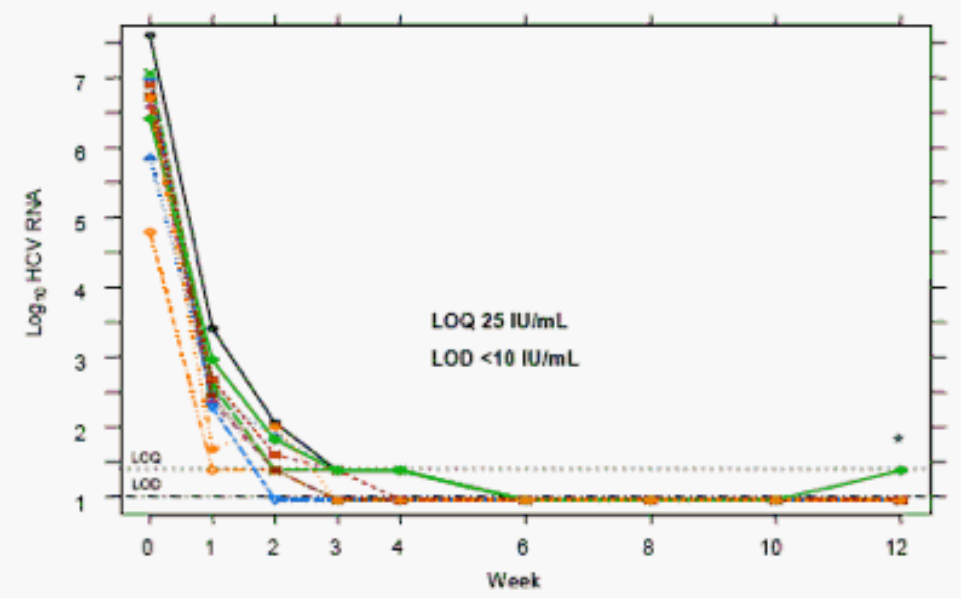
PO=orally; SC=Subcutaneously

HCV RNAの変化

Group A:
BMS-790054+BMS-650032



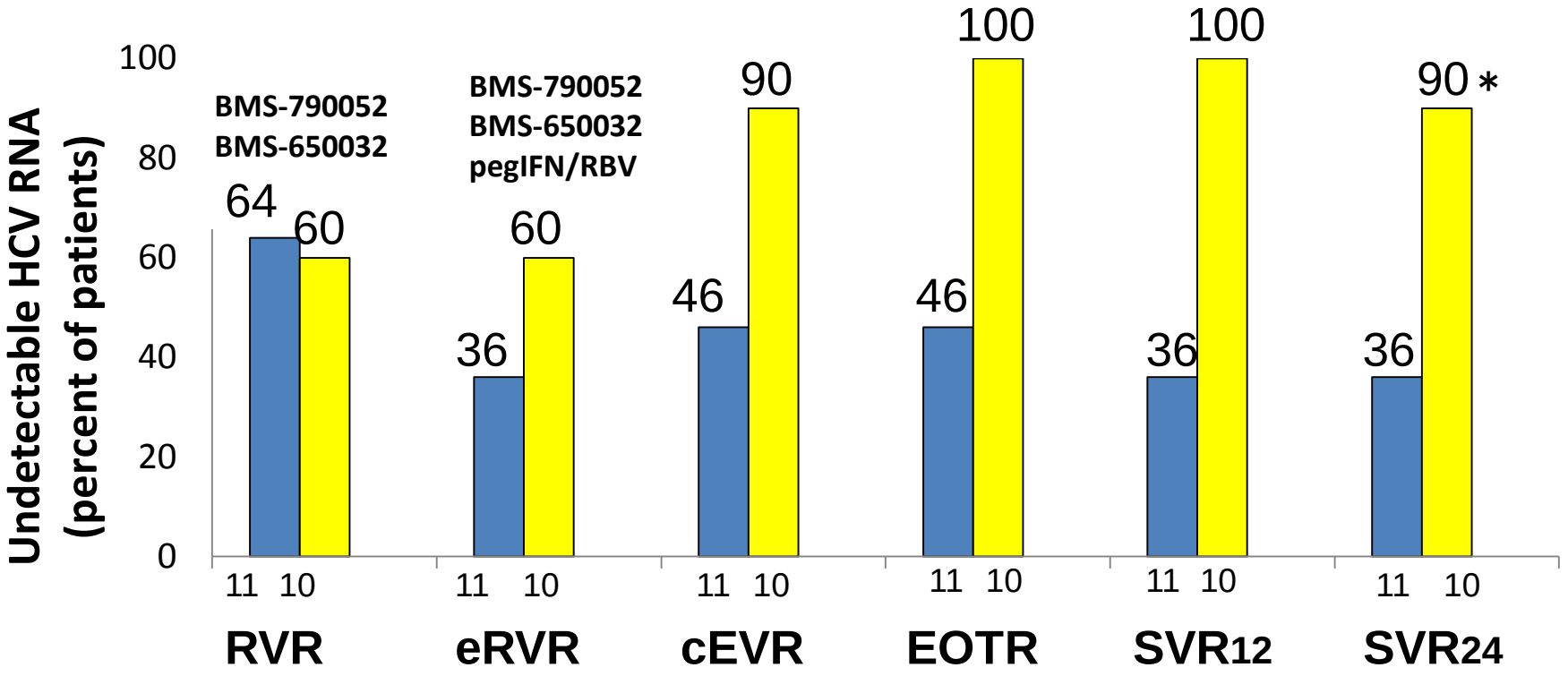
Group B:
BMS-790054+BMS-650032+Peg/RBV



Lok AS, et.al : AASLD 2010, Abstract LB-8.

著効率

BMS-790052 NS5Ainhibitor 60mg QD
BMS-650032 Protease-inhibitor 600mg BID
Null-responder genotype 1 patients(n=21)

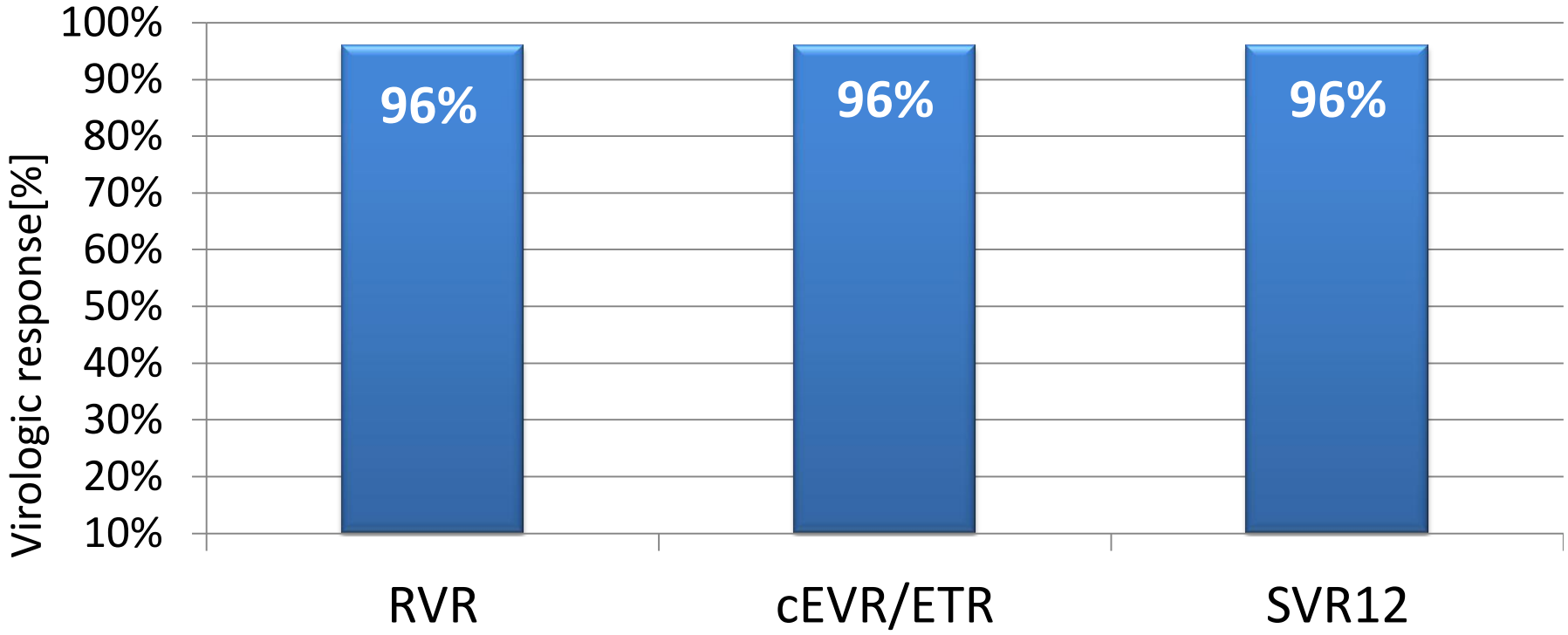


Viral breakthrough in 6 pts in Gr.A between wks 2 and 12 (NS3+NS5B variants in all patients detected)
Viral relapse occurred in 1 patient from DUAL at post-treatment week 4
QUAD:1patient had HCV-RNA<LLOQ at FU24 but neg. 35day later

Lok et al, EASL 2011, oral

Genotype 2/3症例におけるPSI-7977+PEG/Rの治療効果

- Treatment naïve HCV genotype 2/3 infected patients (n=25)[1 patient lost to follow- up after first dose]
- PSI-7977 400mg QD plus PEG/R for 12weeks



No viral breakthrough
No AE leading to discintinuation

Lalezari et al.,EASL2011