第10回肝炎治療戦略会議

2012.11.27

米国肝臓学会2012報告（C型肝炎）

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資料２

C型肝炎のDAA製剤

DAAs=Direct Acting Antivirals
from AASLD 2012 presentations

NS3/4A プロテアーゼ阻害薬(17DAAs)	NS5B ポリメラーゼ阻害薬 核酸型 (6DAAs)	NS5B ポリメラーゼ阻害薬 非核酸型 (7DAAs)	NS5A 阻害薬 (7DAAs)
Telaprevir	Sofosbuvir (GS-7977)	ABT-333	Daclatasvir (BMS-790052)
Boceprevir	Mericitabine (RG7128)	BI 207127	ABT-267
Simeprevir (TMC435)	IDX 184	Tegobuvir (GS-9190)	GS-5885
Faldaprevir (BI 201335)	ALS-2200	VX-222	PPI-668
Vaniprevir (MK-7009)	BCX5191	ABT-072	IDX719
Asunaprevir (BMS-650032)	LG-7501	GS-9669	MK-8742
ABT-450		BMS-791325	ACH-3102
Danoprevir			
GS-9451			
GS-9256			
MK-5172			
ACH-1625			
BILN2961			
ACH-2684			

日本発売中
日本開発中/開発予定

出典:clinicaltrials.gov

海外*Phase III*

DAA/PEG-IFN/RBV併用療法

DAA　PEG　RBV

NS3/4Aプロテアーゼ阻害薬

Telaprevir
Simeprevir (TMC435)
Vaniprevir (MK-7009)
Faldaprevir (BI 201335)

NS5Bポリメラーゼ阻害薬

Sofosbuvir (GS-7977)

NS5A阻害薬

Daclatasvir (BMS-790052)

NS3/4Aプロテアーゼ阻害薬

Telaprevir

NS3/4Aプロテアーゼ阻害薬

AASLD 2012

Telaprevir

- *#51 Hezode C et al.* CUPIC study 安全性

  Safety and efficacy of telaprevir or boceprevir in combination with peginterferon alfa/ribavirin, in 455 cirrhotic non responders. Week 16 analysis of the French early access program (ANRS CO20-CUPIC) in real-life setting

- *#LB-15 Colombo M et al.* HEP3002 F3/F4での効果と安全性

  Treatment of Hepatitis C Genotype 1 Patients with Severe Fibrosis or Compensated Cirrhosis: The International Telaprevir Early Access Program

- *#968 Mousa O et al.* 安全性SAE

  Serious Adverse Events of the current HCV NS3/4A Protease Inhibitors (Telaprevir vs Boceprevir) and Non-Response to treatment.

- *#1754 狩野ほか* 腎機能低下

  Excessive dosage of telaprevir promotes anemia through a high blood concentration of telaprevir and renal function disorder in triple therapy

- *#1811 Mauss S et al.* F3/F4での安全性

  Safety and week 4 / 12 HCV RNA results of triple combination with telaprevir (TVR)/ peginterferon alfa-2a (P)/ ribavirin (R), in F3/F4 patients in real-life setting

- *#LB-8 Buti M et al.* 1日2回投与でいい

  OPTIMIZE trial: Non-inferiority of twice-daily telaprevir versus administration every 8 hours in treatment-naïve, genotype 1 HCV infected patients

Telaprevir or Boceprevirの市販後調査, France
CUPIC study：代償性肝硬変
Compassionate Use of Protease Inhibitors in viral C Cirrhosis

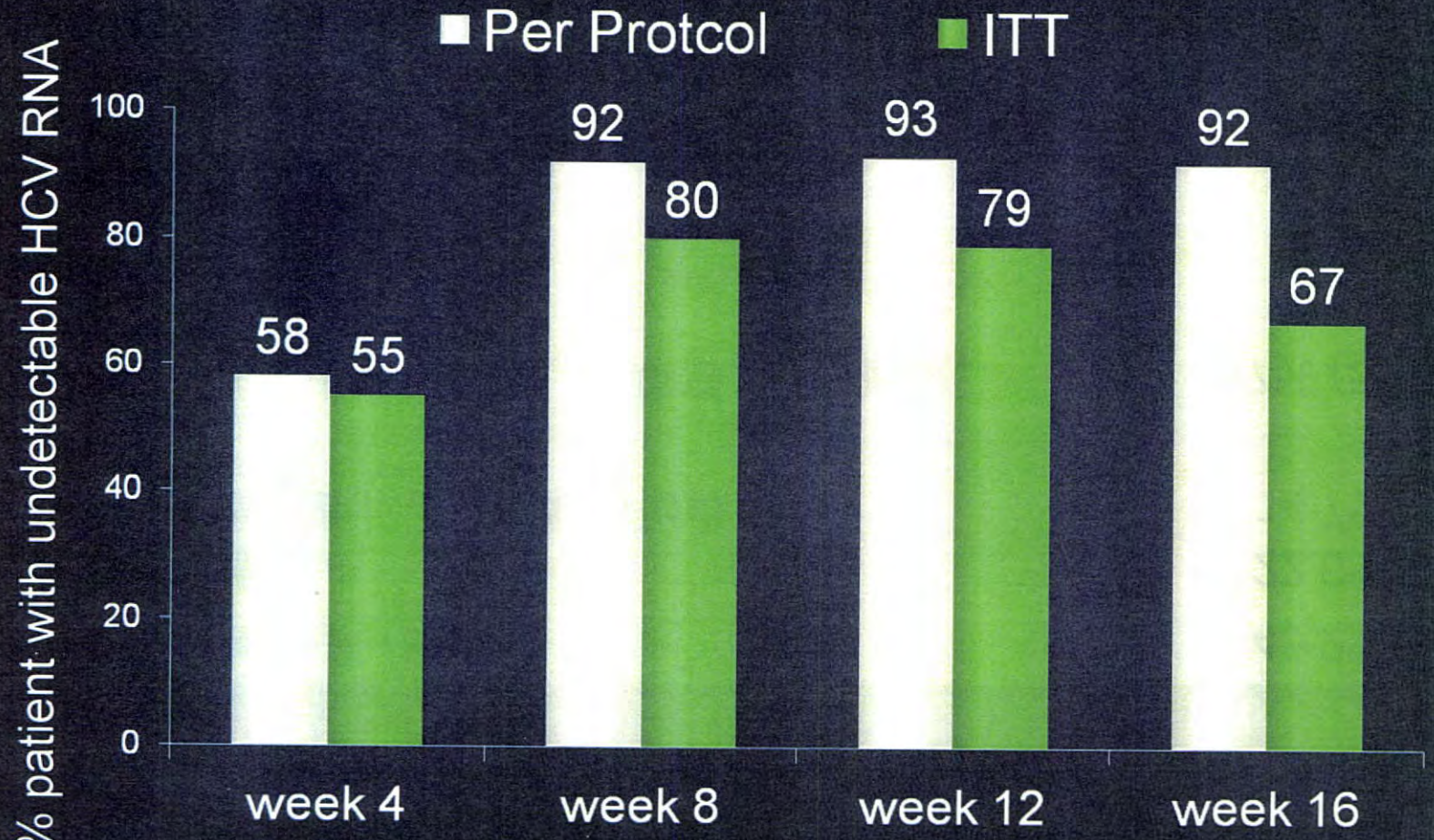
【対象】 フランスの市販後調査（French early access program），55施設
- ✓ HCV genotype 1，代償性肝硬変 (Child Pugh A)
- ✓ Non responders（Relapsers, Partial responders. Null responders は除外）
- ✓ 16週以上TVR or BOC/Peg/RBV投与した解析対象497例 （2011年2月15日～2012年4月12日）

n=292　　n=205

患者背景	Telaprevir (n=292)
男性比率，%	68
平均年齢，歳	57.2 (27-83)
平均Total Bil，*μmol/L*	15.4 (4.0-73.5)
平均Alb，*g/dL*	40.1 (20.7-52.0)
平均好中球数，$10^9/mm^3$	3.3 (0.8-9.7)
平均Hb量，*g/dL*	14.6 (9.0-19.7)
平均血小板数，$10^4/mm^3$	15.2 (1.8-60.4)

Hezode C, et al.; AASLD2012, oral #51

CUPIC study : Telaprevir/ PEG/ RBV
HCV RNA陰性化推移



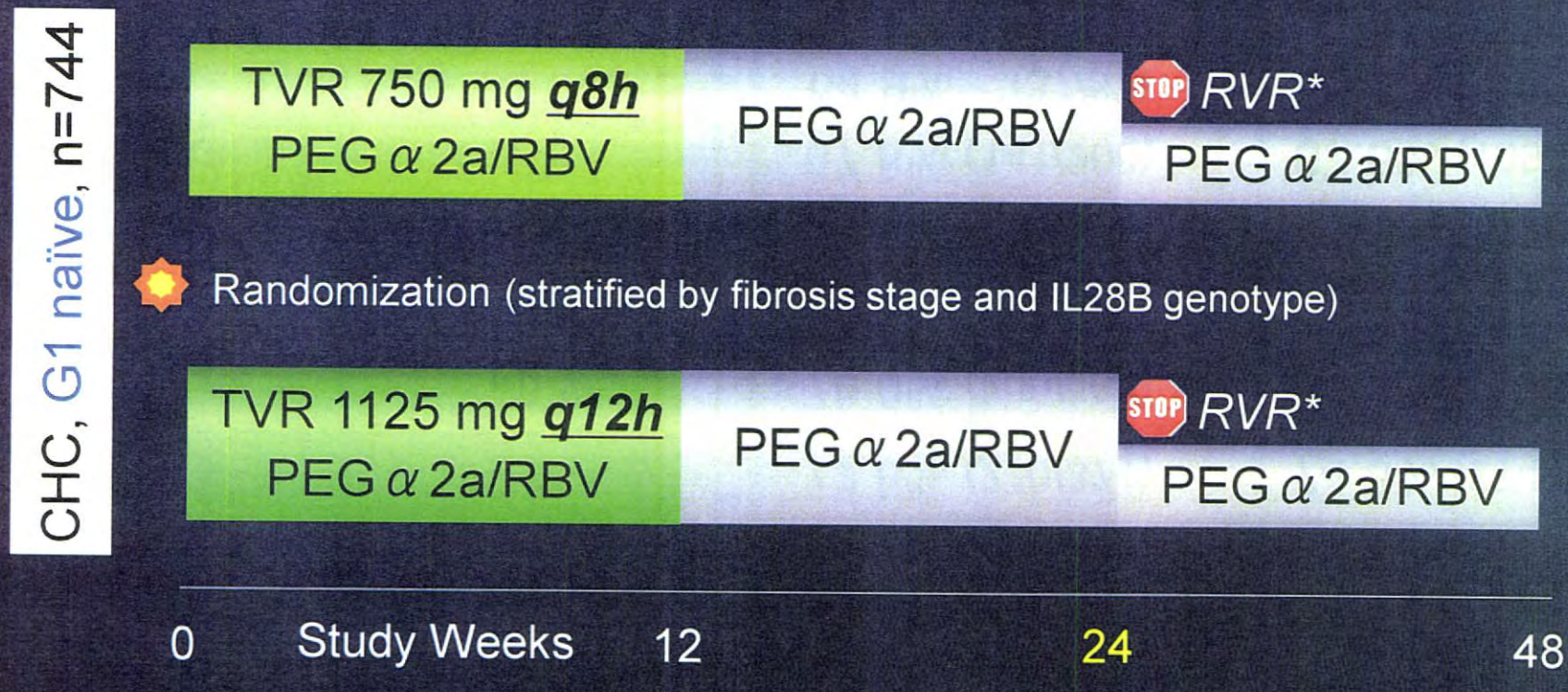
Hezode C, et al.; AASLD2012, oral #51

CUPIC study: Telaprevir/PEG/RBV 安全性 (16週時点)

Patients (at week 16)	Telaprevir (n=296)
✓重篤な有害事象 (SAEs)	45.2%
早期の治療中止	22.6%
重篤な有害事象による早期の治療中止	14.7%
✓死亡	
敗血症、敗血症性ショック、肺障害、心内膜症、食道静脈瘤出血	1.7% (5例)
Rash	
Grade 3	4.8%
腎不全	1.7%
貧血	
Grade 2 (8.0-<10.0g/dL)	18.8%
Grade 3/4 (<8.0g/dL)	11.6%
EPO使用	53.8%
輸血	16.1%

Hezode C, et al.; AASLD2012, oral #51

OPTIMIZE Study – Telaprevir q8 vs. q12 hrs PEG-IFNα2a/RBV – G1 naïve, Phase III



* RVR率はTVR q8hで67%，q12h(BID)で69%達成．　治療期間は24週

TVR:Telaprevir

Buti et al, AASLD 2012, poster #LB-8

OPTIMIZE Study – Telaprevir q8 vs. q12 hrs PEG-IFN α 2a/RBV – SVR12

- TVR q8h vs q12h 非劣勢が確認;non-inferior difference 1.5% (95% CI:-4.9%, 12.0%)
- 有害事象;両群間に差はなかった

Treatment outcome, n/n (%)		T12(q8h)/PR (n=371)	T12(q12h,BID)/PR (n=369)
SVR12		72.8% (270/371)	74.3% (274/369)
線維化別SVR12	F0-2	78.0% (209/268)	80.7% (213/264)
	F3-4	59.2% (61/103)	58.1% (61/105)
IL28B genotype別 SVR12	CC	86.8% (92/106)	92.4% (97/105)
	CT	67.8% (141/208)	67.5% (139/206)
	TT	64.9% (37/57)	65.5% (38/58)
治療中viral breakthrough*		9.7% (36/371)	10.3% (38/369)
治療後再燃率‡		6.5% (19/293)	7.7% (23/300)

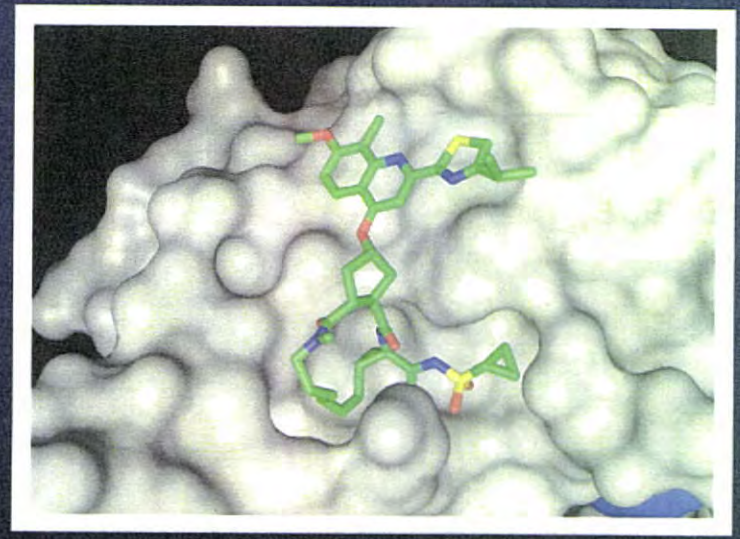
* met virologic stopping rule or viral breakthrough

‡ Assessed in patients with HCV RNA <25 IU/mL at the planned end of treatment

Buti et al, AASLD 2012, poster #LB-8

NS3/4Aプロテアーゼ阻害薬

Simeprevir (TMC435)



macrocyclic

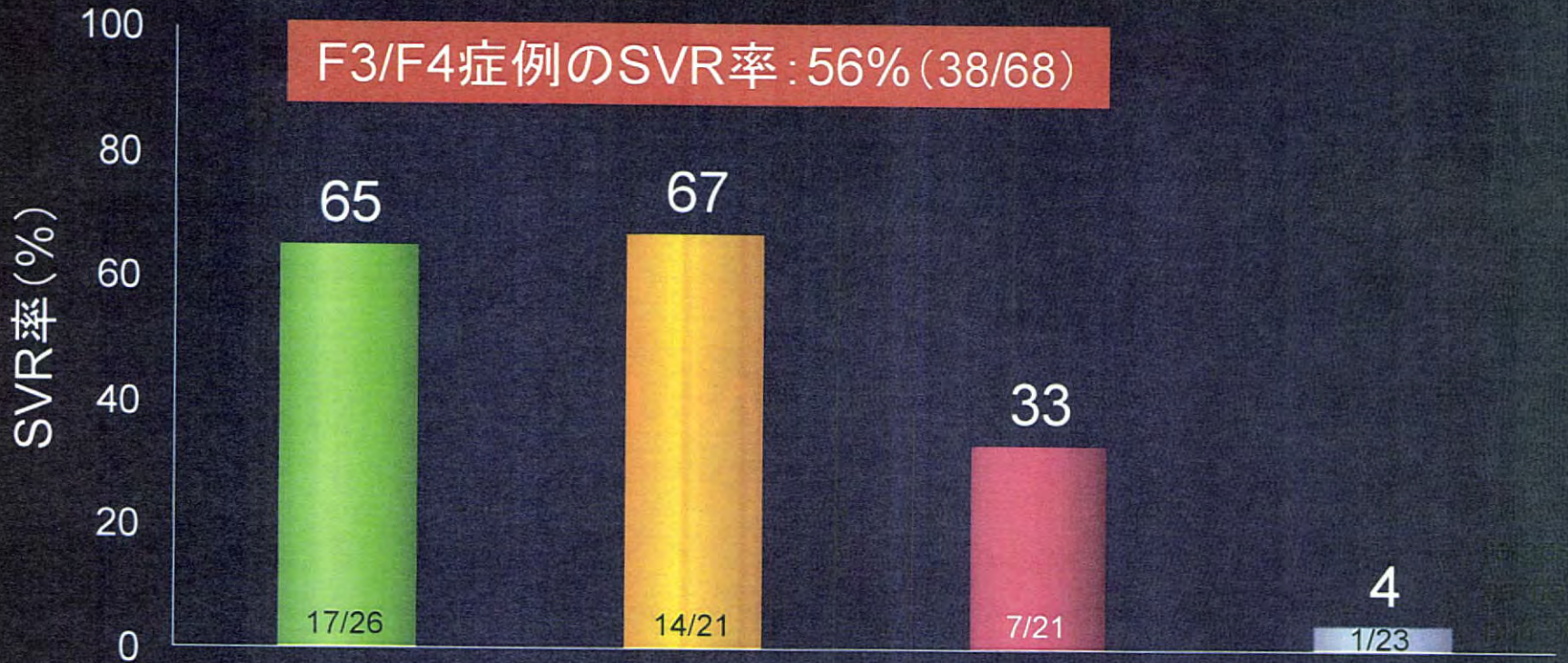
Simeprevir(TMC435) の主な有害事象

(*PILLAR and ASPIRE, phase IIb trials*)

Proportion of patients, %	TMC435 150 mg: *First 12 weeks*		TMC435 150 mg: *Overall treatment duration*	
	TMC435 150 mg & PR (n=355)	Placebo & PR (n=143)	TMC435 150 mg & PR (n=355)	Placebo & PR (n=143)
有害事象,全体	97.2%	95.1%	98.6%	97.2%
重篤な有害事象	2.3%	4.2%	7.6%	9.8%
有害事象による治療中止	2.8%	0.7%	4.8 %	2.1%
倦怠感	39.2%	42.7%	42.8%	46.2%
頭痛	39.7%	40.6%	41.1%	44.8%
掻痒感 (all types)	33.0%	24.5%	36.9%	34.3%
ｲﾝﾌﾙｴﾝｻﾞ様症状	25.9%	29.4%	26.2%	29.4%
発疹 (all types)	22.5%	16.1%	29.0%	23.8%
好中球数減少	20.3%	14.0%	26.2%	18.9%
吐き気	23.9%	23.8%	25.9%	25.2%

Fried MW et al, AASLD 2012, poster #769

Simeprevir (TMC435) : 再治療*ASPIRE study*
SVR24 rate in *F3 and F4* patients



#83 conclusionより
Phase IIIの結果は2013.1Qにopen

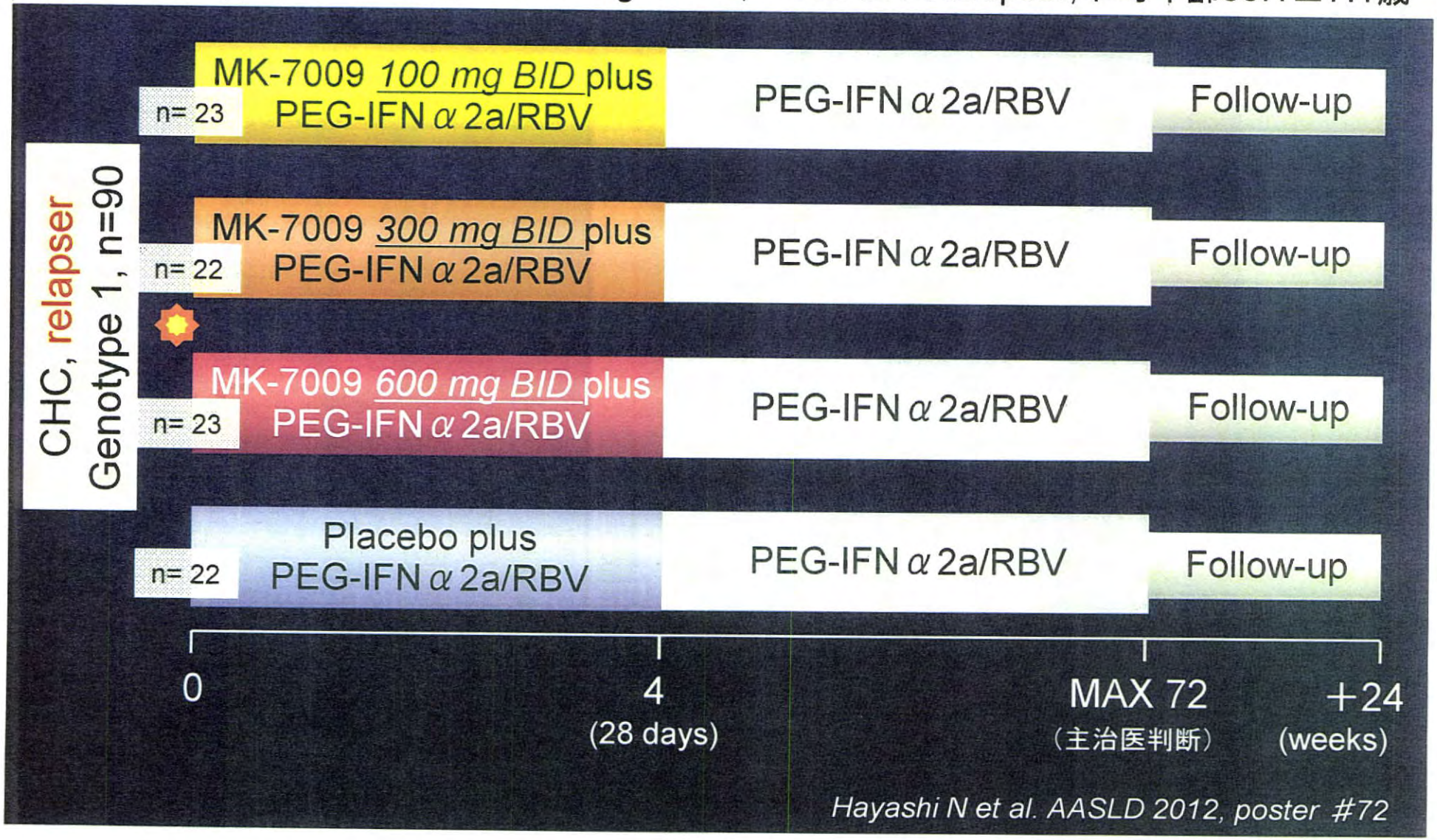
Poordad F et al, AASLD 2012, oral #83

NS3/4Aプロテアーゼ阻害薬

Vaniprevir (MK-7009)

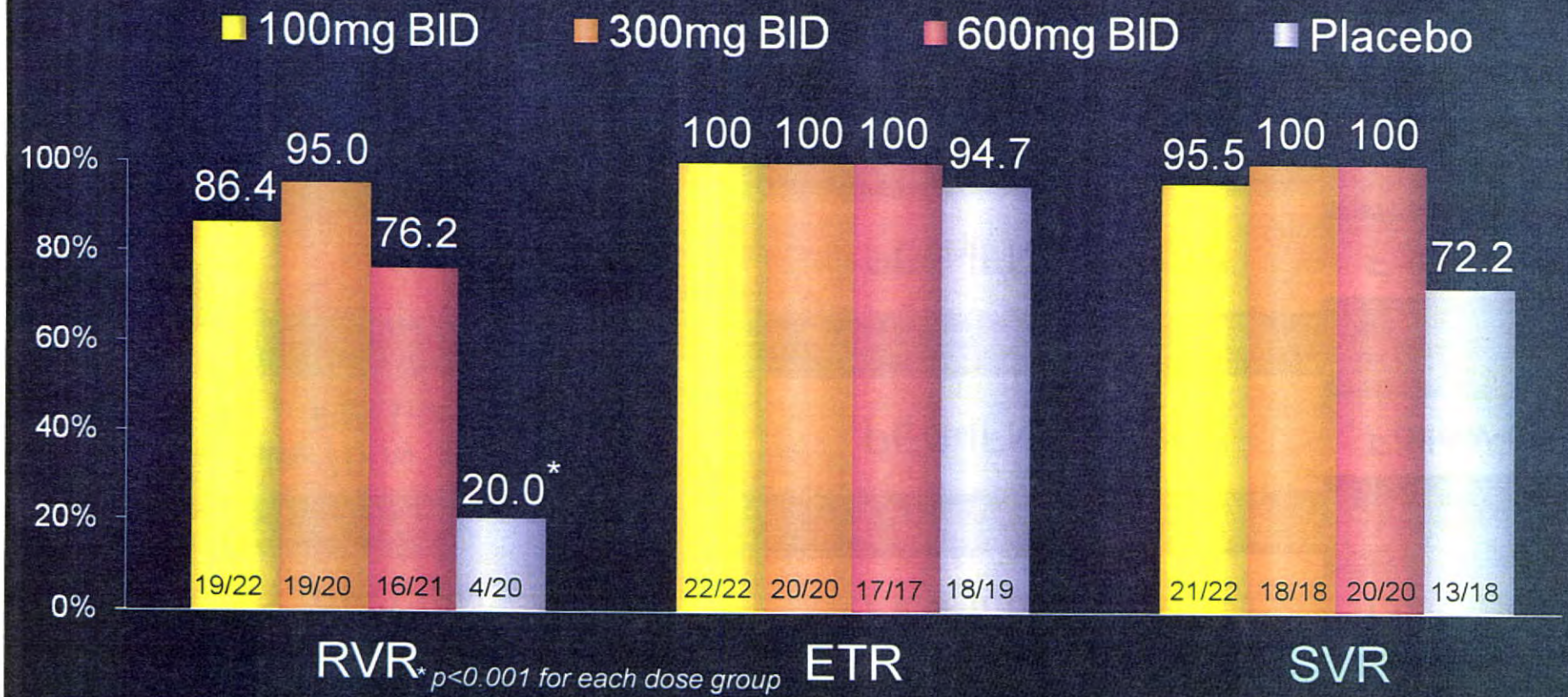
Vaniprevir (MK-7009) plus PEG-IFN α 2a/RBV for 28 Days *in "Genotype 1 ≥5.0 Log IU/mL Japanese Relapser patients"*

対象：*Genotype 1*, HCV RNA≥ 5.0 Log IU/mL, PEG/RBV Relapser,平均年齢55.1±7.1歳



Hayashi N et al. AASLD 2012, poster #72

Vaniprevir (MK-7009) plus PEG-IFNα2a/RBV for 28 Days *in G1 Japanese Relapser patients : RVR, ETR, SVR rate*



* *p<0.001 for each dose group*

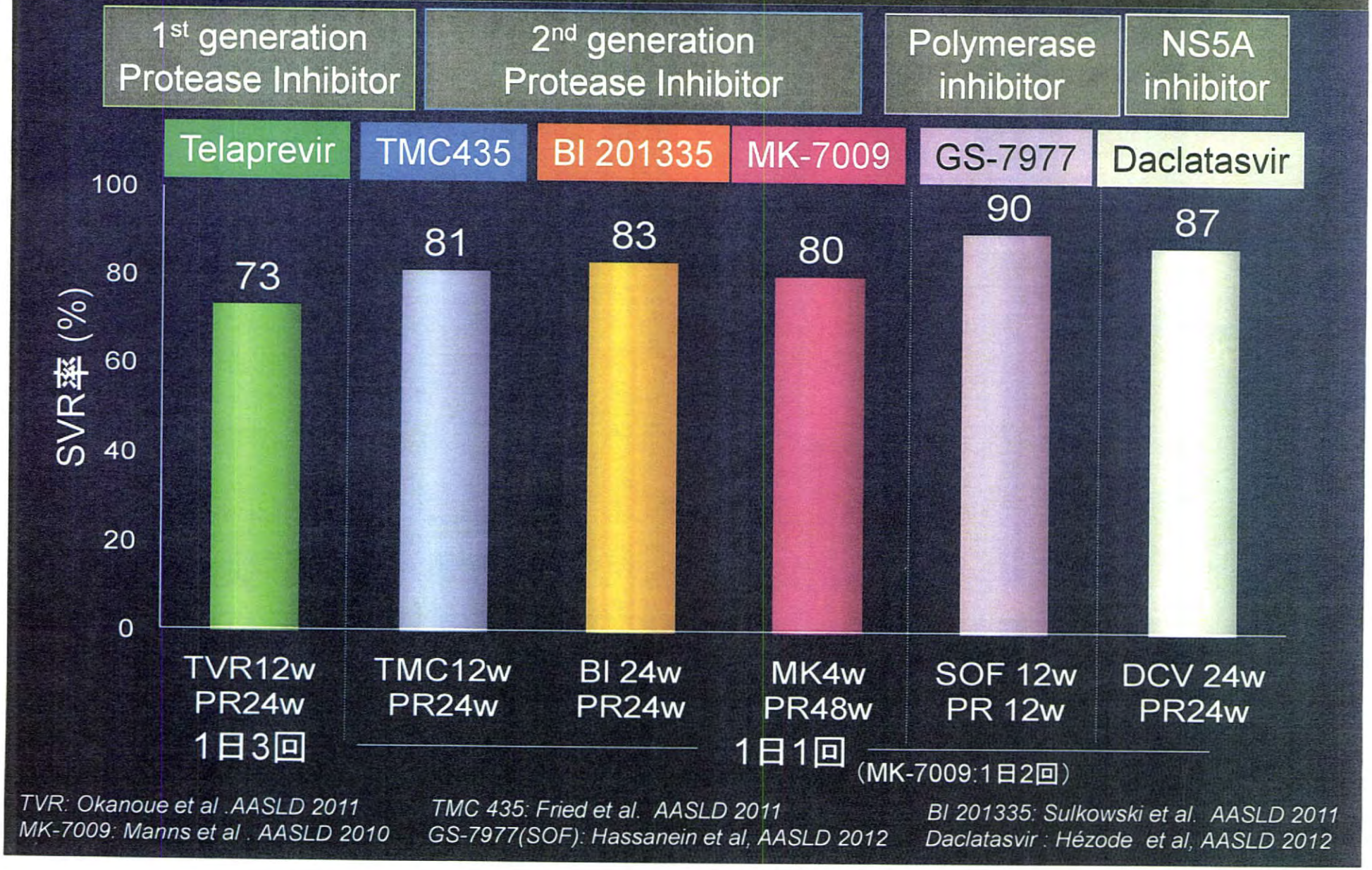
per protocol：7例除外 （MK-7009・RBV規定量以下の投与、低ウイルス量、除外基準違反、禁止薬物治療使用）

- ✓ **薬剤投与前の耐性変異**：88例中2例に認められたが（D168E：1例， A156T：1例）、**2例ともSVR。**
- ✓ **MK-7009での耐性変異なし。**
- ✓ MK-7009 100mg 1例のみ、治療終了後再燃。
- ✓ RVRデータより、phase IIIは300mg BID。

Hayashi N et al. AASLD 2012, poster #72

Genotype1：初回治療 DAA/PEG/RBV併用療法のSVR率

STUDY name : phase 3 (JPN), PILLAR, SILEN-C1, phase 2a, ATOMIC, COMMAND-1

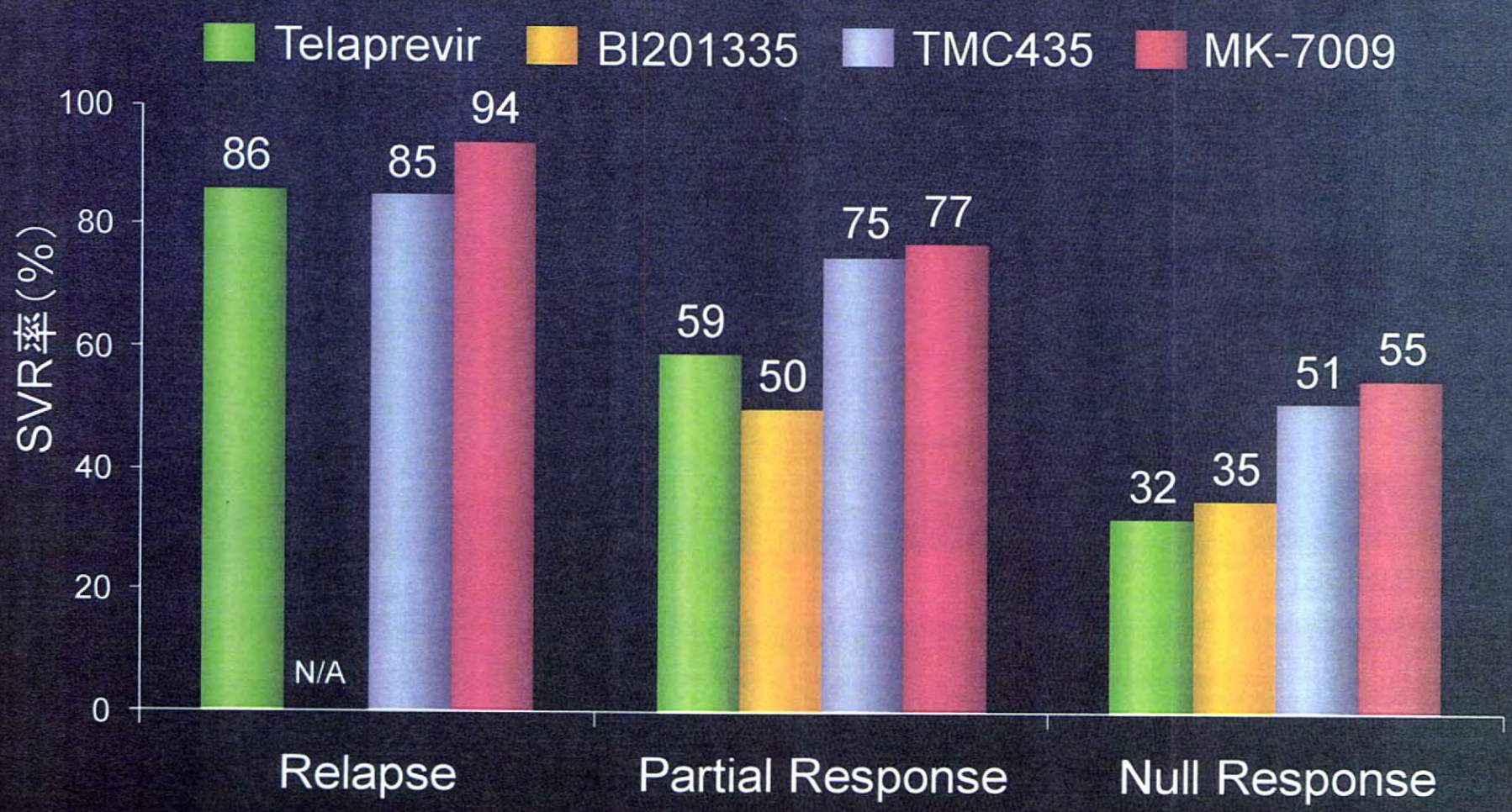


TVR: Okanoue et al .AASLD 2011
MK-7009: Manns et al . AASLD 2010
TMC 435: Fried et al. AASLD 2011
GS-7977(SOF): Hassanein et al, AASLD 2012
BI 201335: Sulkowski et al. AASLD 2011
Daclatasvir : Hézode et al, AASLD 2012

Genotype1：再治療 DAA/PEG/RBV併用療法のSVR率

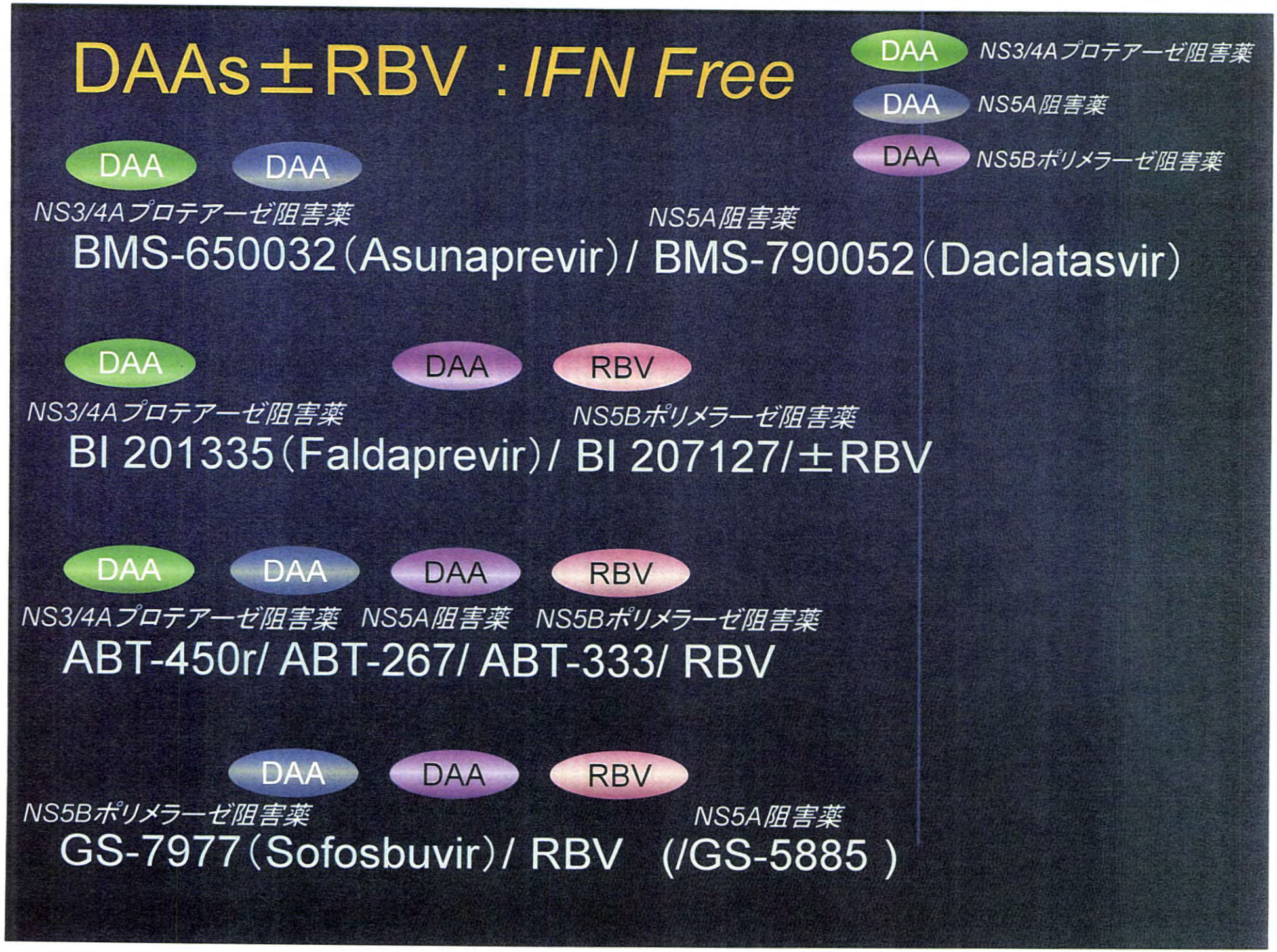
STUDY name : JPN P3(TVR), SILEN-C2(BI201335), ASPIRE(TMC435), P2b(MK-7009)

EASL,AASLD 2010-2012 presentations



Prior Relapser: undetectable HCV RNA at EoT and detectable within 24 weeks of follow-up
Prior Partial Responders: more than 2 log reduction in HCV RNA at W12 but not achieving undetectable at EoT
Prior Null Responders: less than 2 log reduction in HCV RNA at W12

All arm pooled


DAAs±RBV : IFN Free
DAA NS3/4Aプロテアーゼ阻害薬
DAA NS5A阻害薬
DAA NS5Bポリメラーゼ阻害薬
DAA
DAA
NS3/4Aプロテアーゼ阻害薬
NS5A阻害薬
BMS-650032（Asunaprevir）/ BMS-790052（Daclatasvir）
DAA
DAA
RBV
NS3/4Aプロテアーゼ阻害薬
NS5Bポリメラーゼ阻害薬
BI 201335（Faldaprevir）/ BI 207127/±RBV
DAA
DAA
DAA
RBV
NS3/4Aプロテアーゼ阻害薬
NS5A阻害薬
NS5Bポリメラーゼ阻害薬
ABT-450r/ ABT-267/ ABT-333/ RBV
DAA
DAA
RBV
NS5Bポリメラーゼ阻害薬
NS5A阻害薬
GS-7977（Sofosbuvir）/ RBV (/GS-5885)

NS3/4Aプロテアーゼ阻害薬

Daclatasvir (BMS-790052)

NS5A阻害薬

BMS-650032（Asunaprevir）

Daclatasvir(DCV) + Asunaprevir(ASV)
± PEG-IFN α-2a/RBV in Genotype 1 Null Responders

Total: n=101

			SVR12
G1b only DUAL *IFN free*	n=18	DCV 60 mg QD + ASV *200 mg BID*	Follow-up 78%*
			*2 patients with missed visit (SVR4:89%)
G1b only DUAL *IFN free*	n=20	DCV 60 mg QD + ASV *200 mg QD*	Follow-up 65%
G1a main QUAD	n=20	DCV 60 mg QD + ASV *200 mg BID* PEG-IFN α 2a/RBV (G1a:17, G1b:3)	Follow-up 95%
G1a main QUAD	n=21	DCV 60 mg QD + ASV *200 mg QD* PEG-IFN α 2a/RBV (G1a:19, G1b:2)	Follow-up 95%
G1a main Triple, *IFN free*	n=22	DCV 60 mg QD + ASV *200 mg QD* RBV (no PEG) (G1a:18 ,G1b:4)	Follow-up 23%

VBT:56%

SVR12･･･G1a:1/18, G1b:4/4

0 Study Weeks 24 48

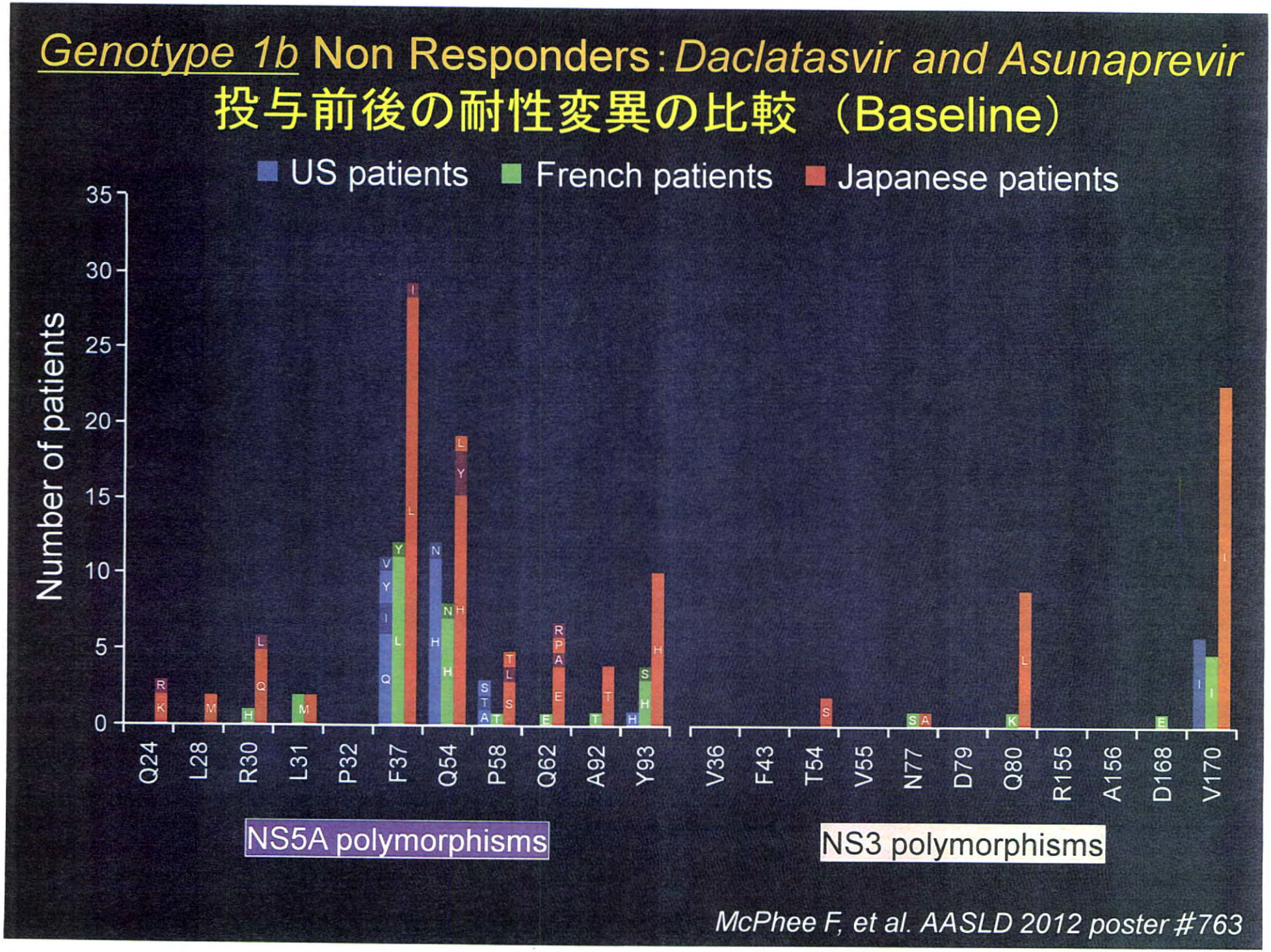
Phase IIa Study

AI447-011 study Randomization

Anna S. Lok et al, AASLD 2012, oral #79

Genotype 1b Non Responders: *Daclatasvir and Asunaprevir*

投与前後の耐性変異の比較 （Baseline）



McPhee F, et al. AASLD 2012 poster #763

Genotype 1b Non Responders: *Daclatasvir and Asunaprevir*
投与前後の耐性変異の比較 （after treatment）

country	patient	outcome	NS5A RAVs							NS3 RAVs		
			R30	L31	P32	Q54	P58	Q62	Y93	Q80	S122	D168
US	US2	VBT		V					H			Y
	US7	VBT		V			S	G/Y	H			Y
	US8	Relapse			Δ							V
France	FR2	VBT		V					H			V
	FR3	VBT		V					H			V
	FR8	VBT			Δ							V
	FR9	VBT	Q	M		H			H			E
	FR10	VBT		V					H			V
Japan	JP1	Relapse		M			L		H			V
	JP2	Relapse		V					H			V
	JP3	Relapse		V/M					H			V
	JP9	VBT		M		Y			H	L		V
	JP14	VBT		M			A		H			A
	JP15	Relapse		M					H			A
	JP16	VBT		M		Y			H		G	V

YELLOW had a pre-existing NS5A-Y93H variant. 60%(9/15)

McPhee F, et al. AASLD 2012 poster #763