米国肝臓学会2012報告（C型肝炎）

武蔵野赤十字病院　消化器科
泉　並木

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

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

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）

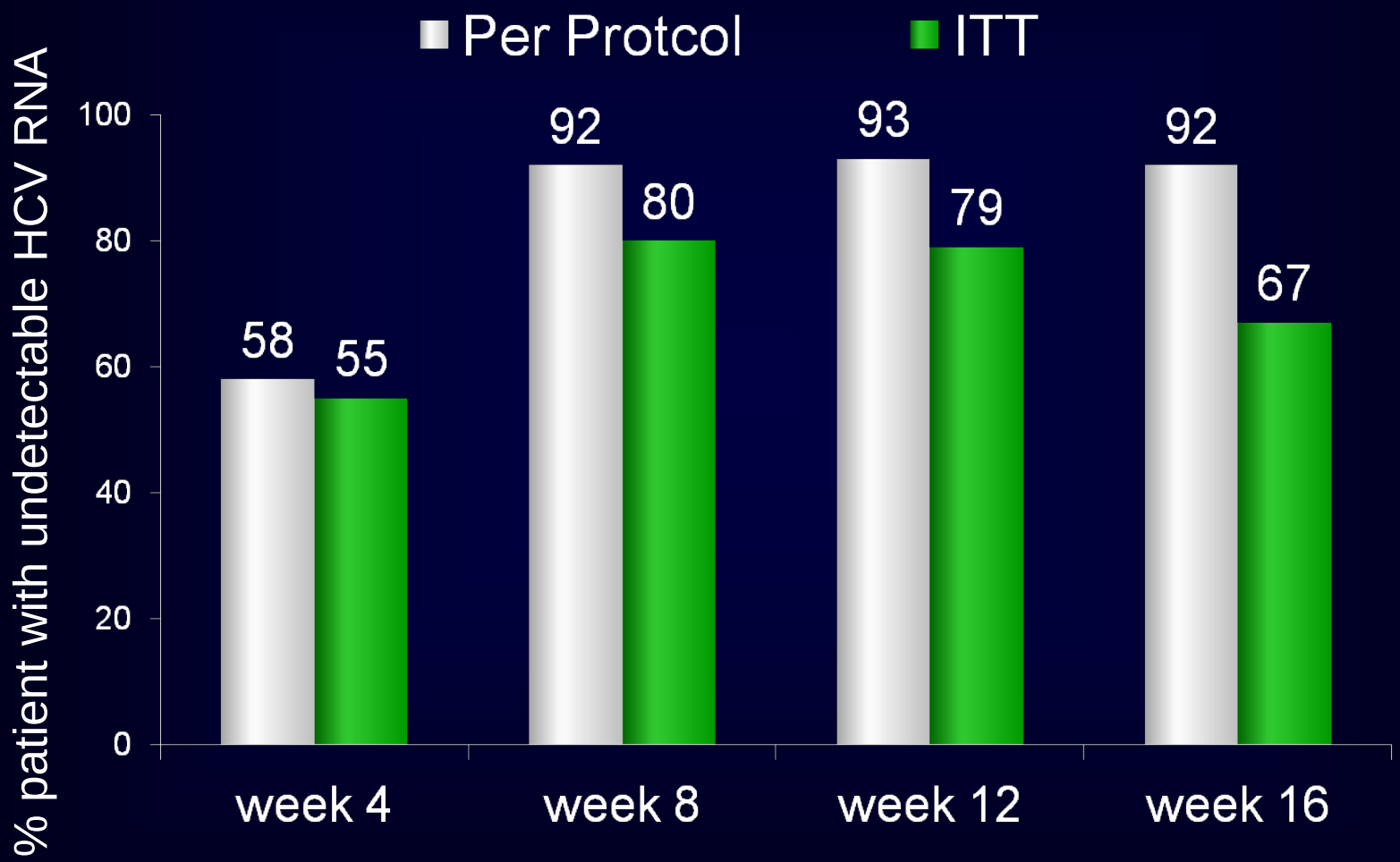
✓ 16週以上TVR or BOC/Peg/RBV投与した解析対象497例（2011年2月15日～2012年4月12日）

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



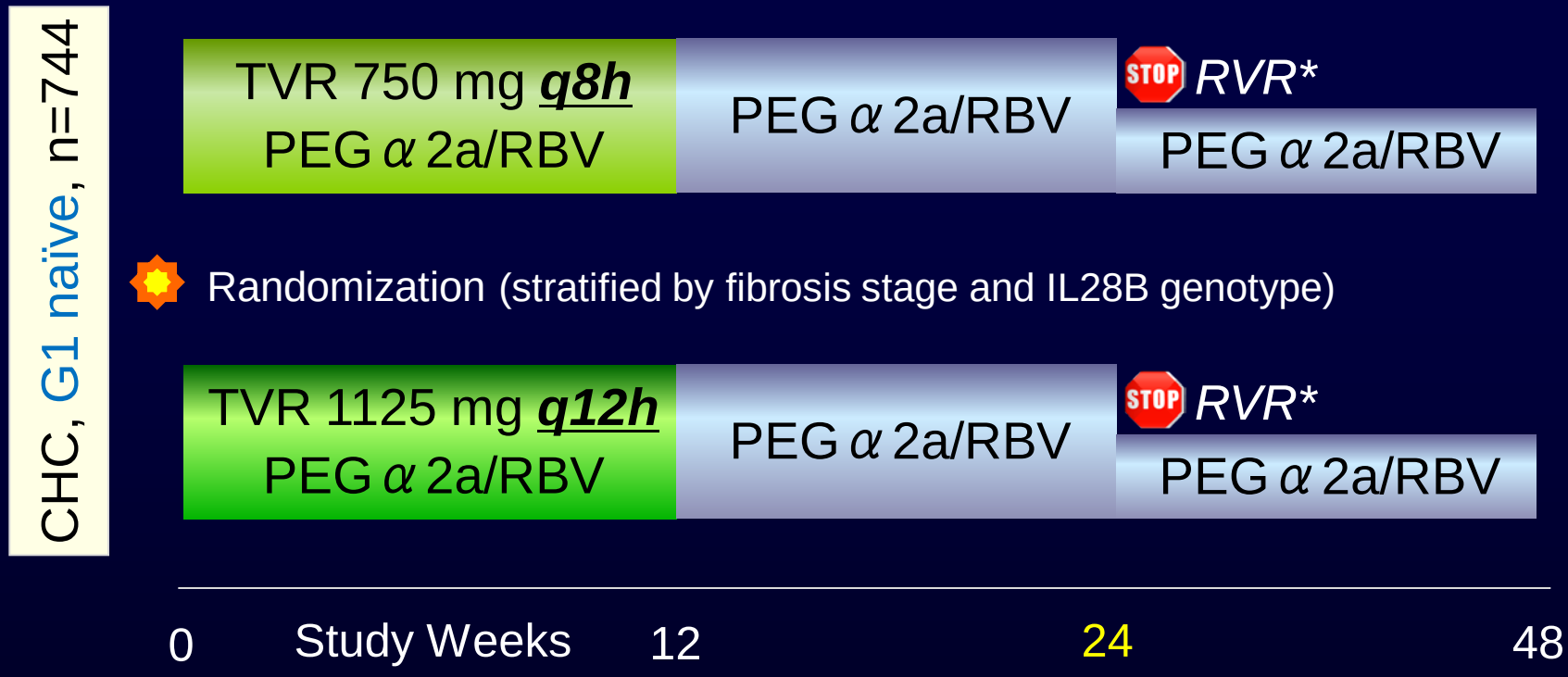
Hezode C, et al.; AASLD2012, oral #51

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-IFN α 2a/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-IFNα2a/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)

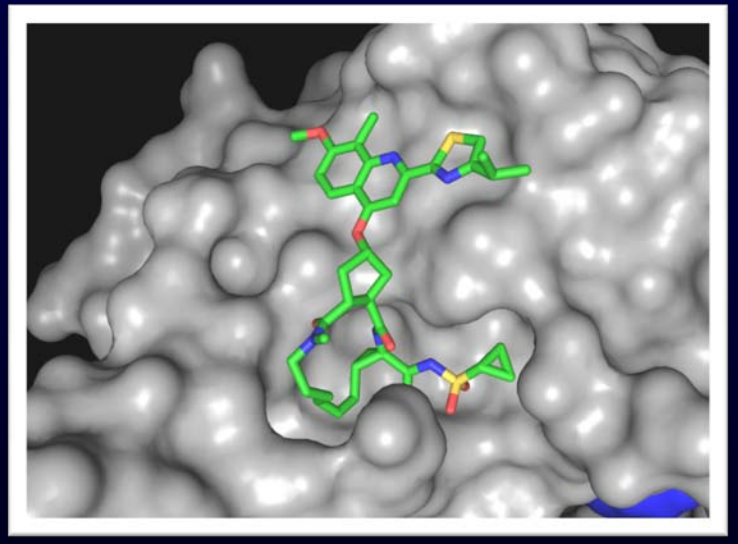
* met virologic stopping rule or viral breakthrough

‡ 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

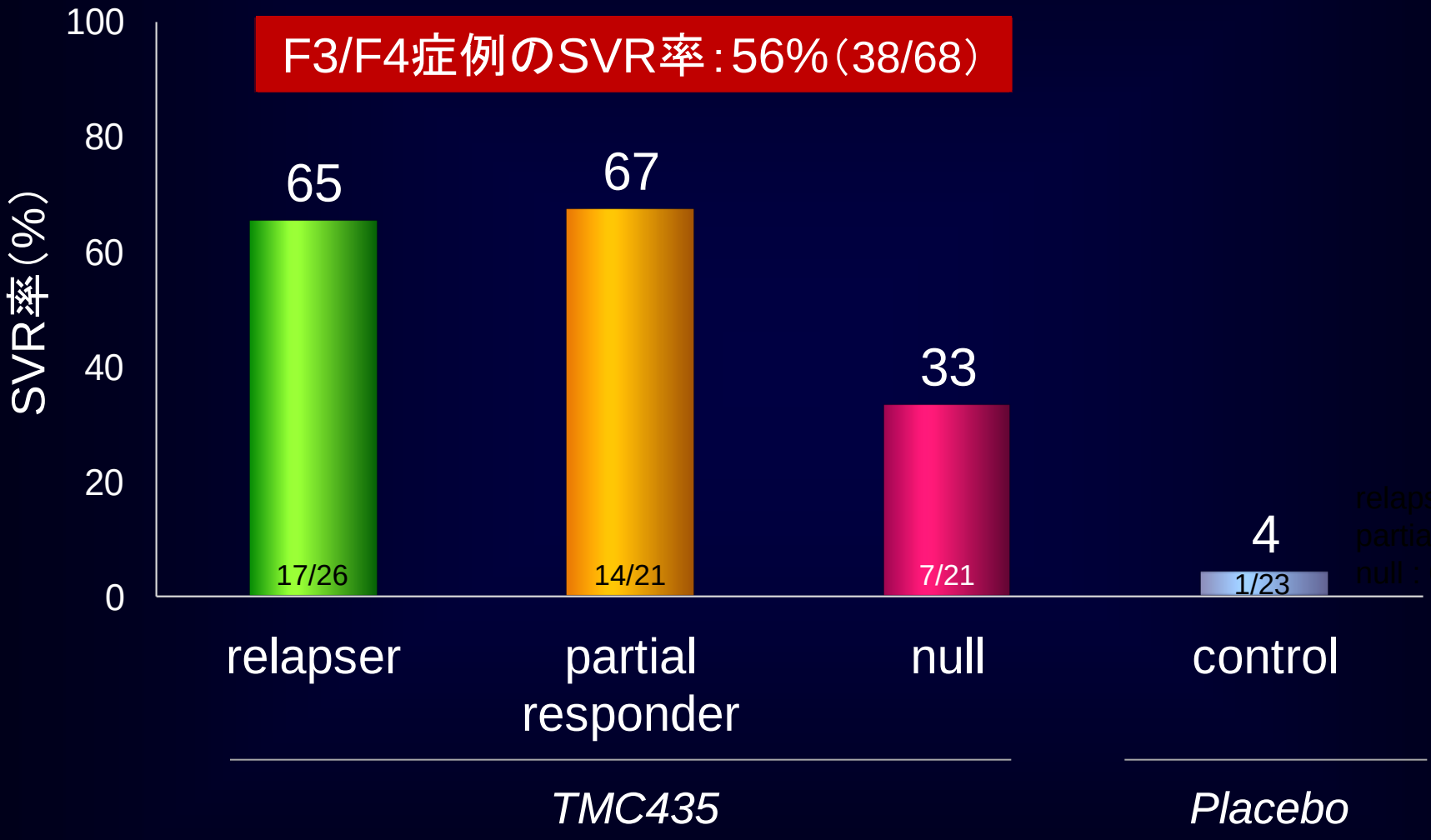
Simeprevir(TMC435) の主な有害事象

(*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

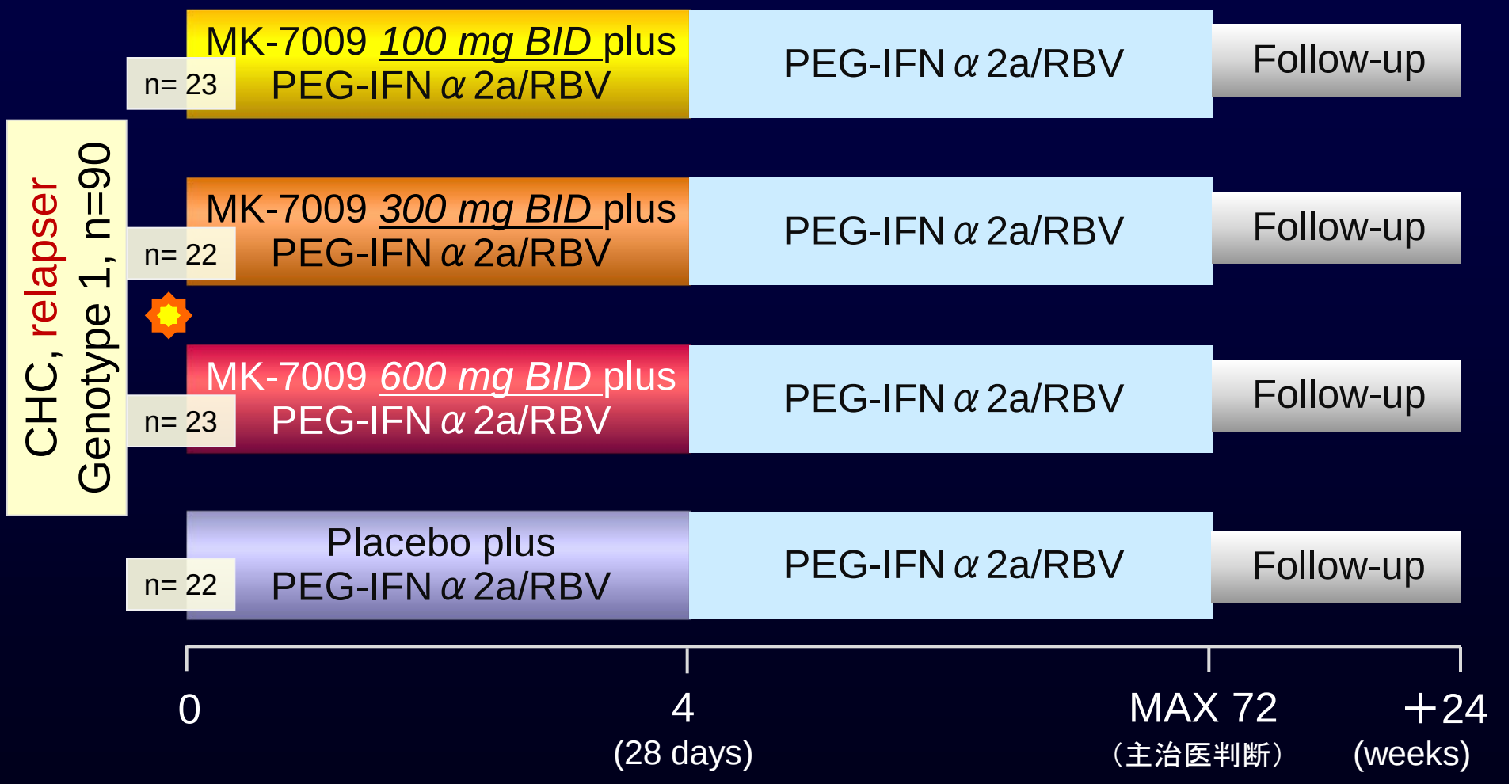
Poordad F et al, AASLD 2012, oral #83

NS3/4Aプロテアーゼ阻害薬

Vaniprevir (MK-7009)

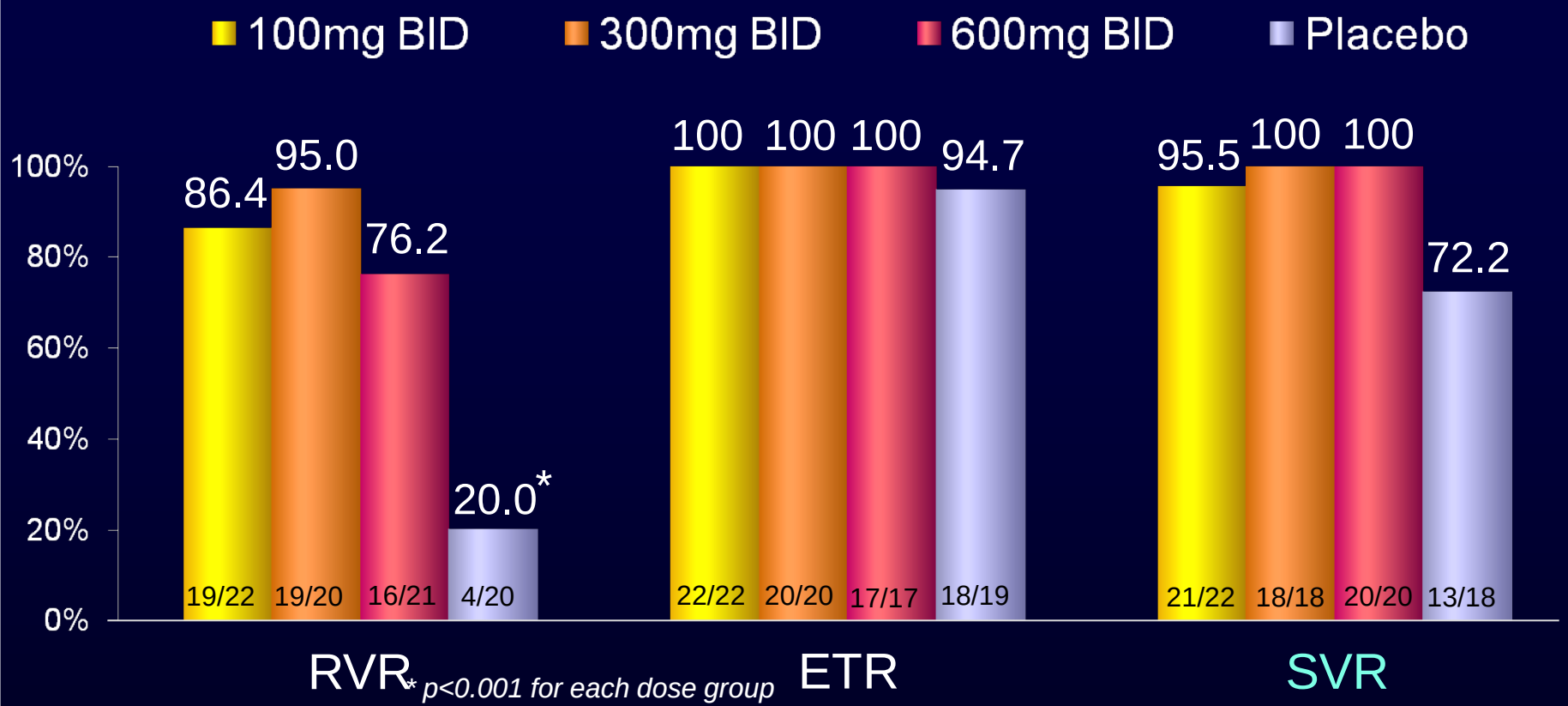
Vaniprevir (MK-7009) plus PEG-IFNα2a/RBV for 28 Days *in "Genotype 1 ≥5.0 Log IU/mL Japanese Relapser patients"*

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*

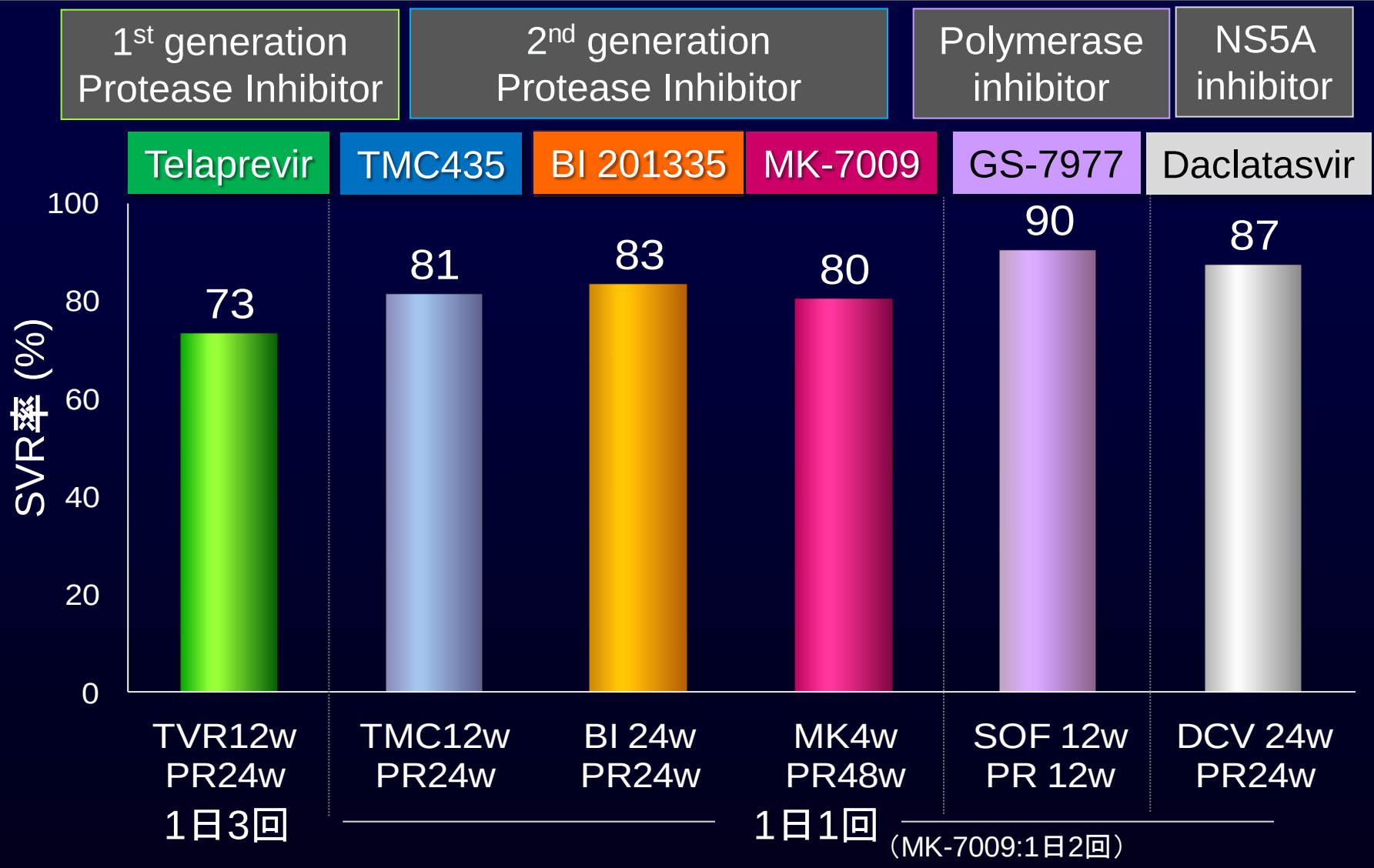
per protocol：7例除外 （MK-7009・RBV規定量以下の投与、低ウイルス量、除外基準違反、禁止薬物治療使用）

- ✓ 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

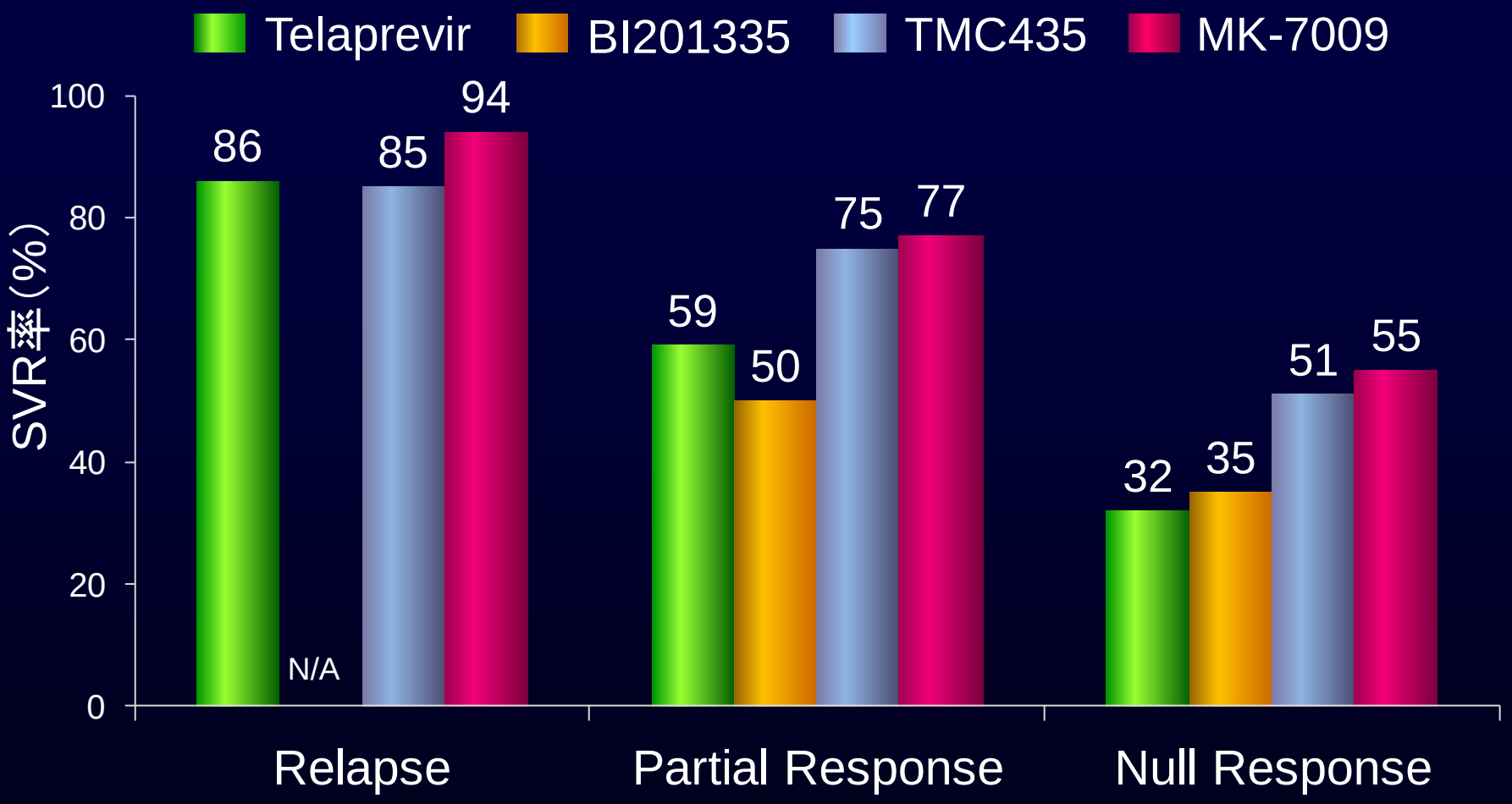


TVR: Okanoue et al .AASLD 2011
MK-7009: Manns et al . AASLD 2010
TMC 435: Fried et al. AASLD 2011
GS-7977(SOF): Hassanein et al, AASLD 2012
BI 201335: Sulkowski et al. AASLD 2011
Daclatasvir : Hézode et al, AASLD 2012

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)

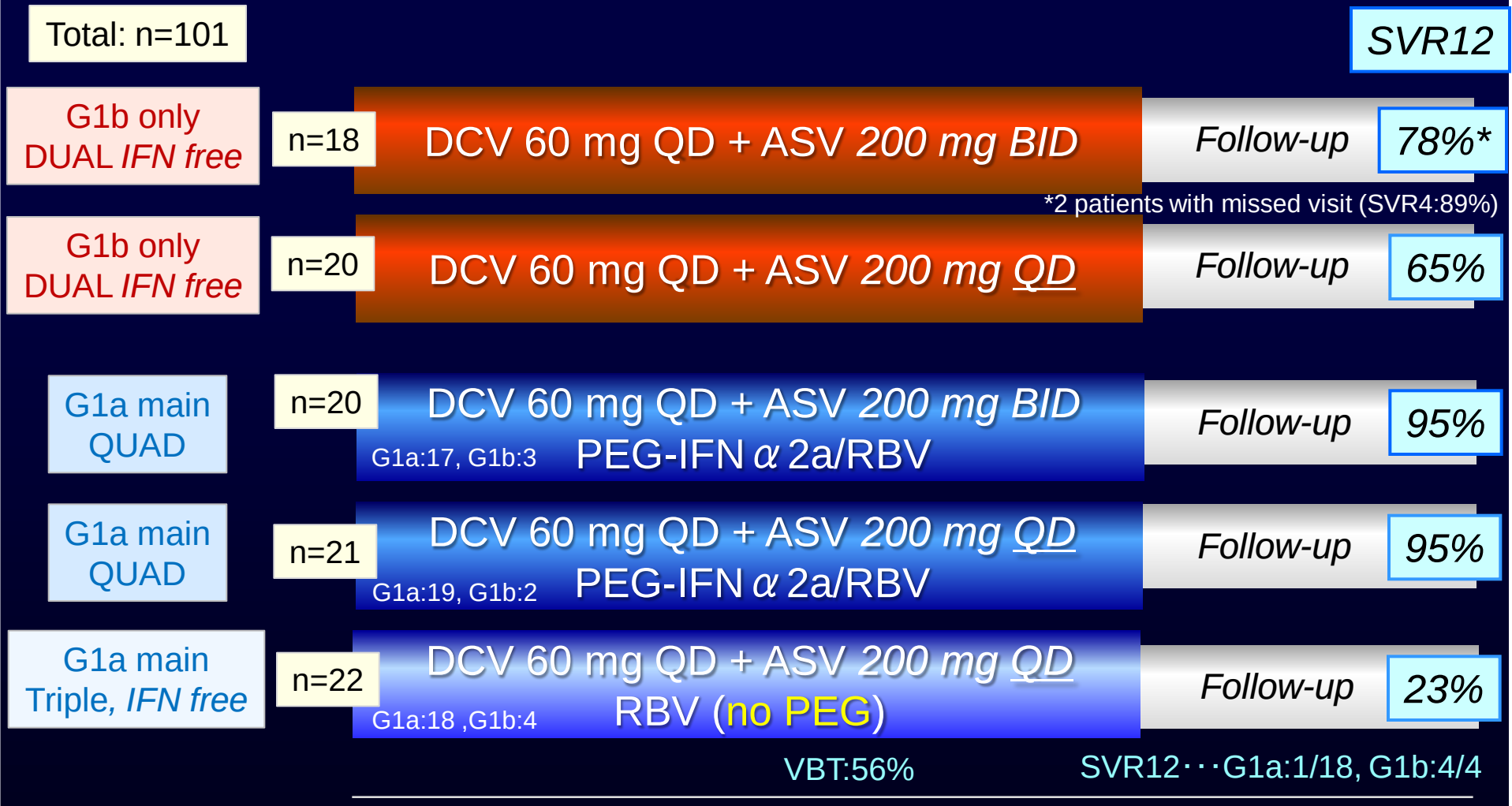
NS3/4Aプロテアーゼ阻害薬

Daclatasvir (BMS-790052)

NS5A阻害薬

BMS-650032（Asunaprevir）

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



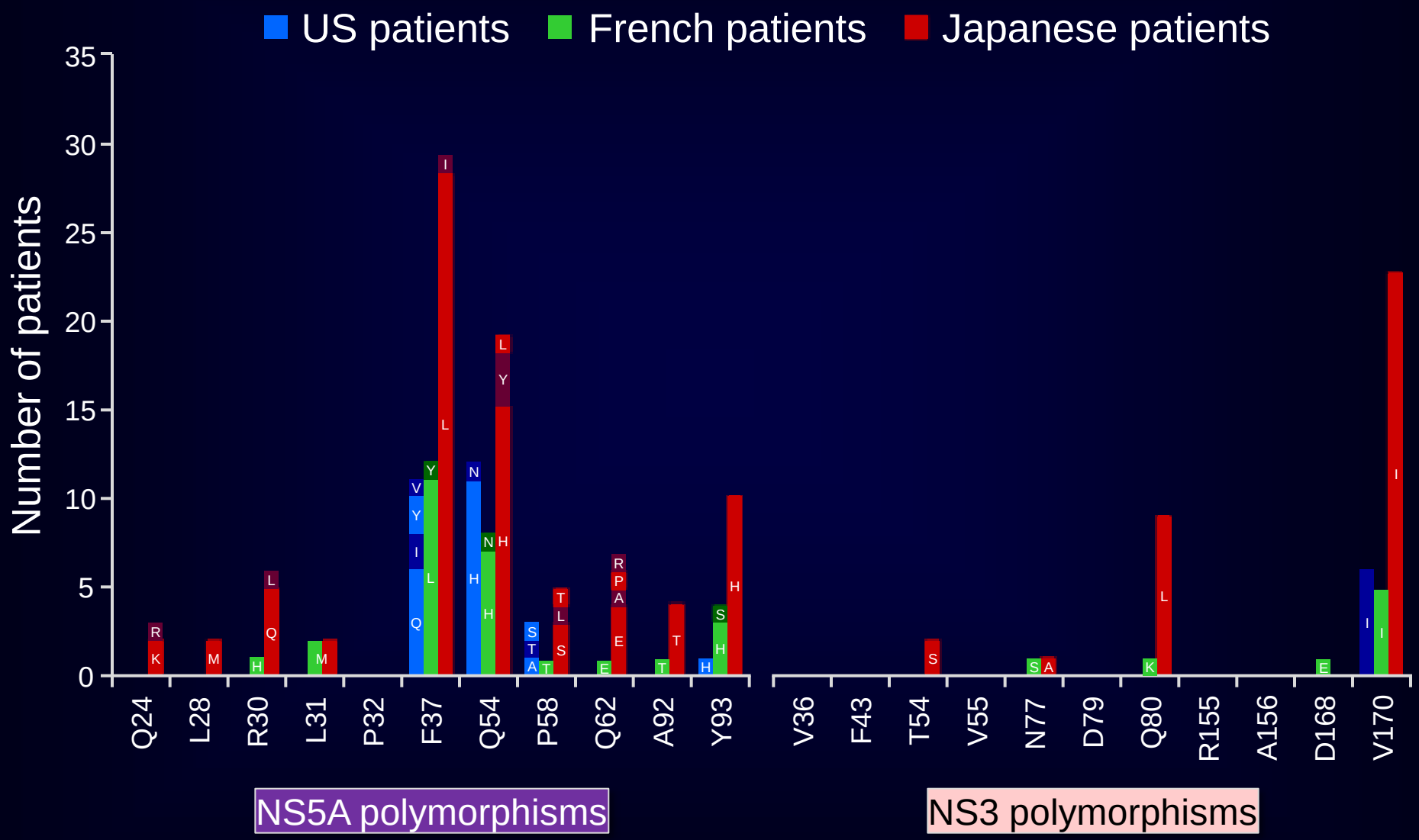
Phase IIa Study

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

NS3/4プロテアーゼ阻害薬

Faldaprevir(BI 201335)

NS5Bポリメラーゼ阻害薬

BI 207127

Faldaprevir

SOUND-C2 study

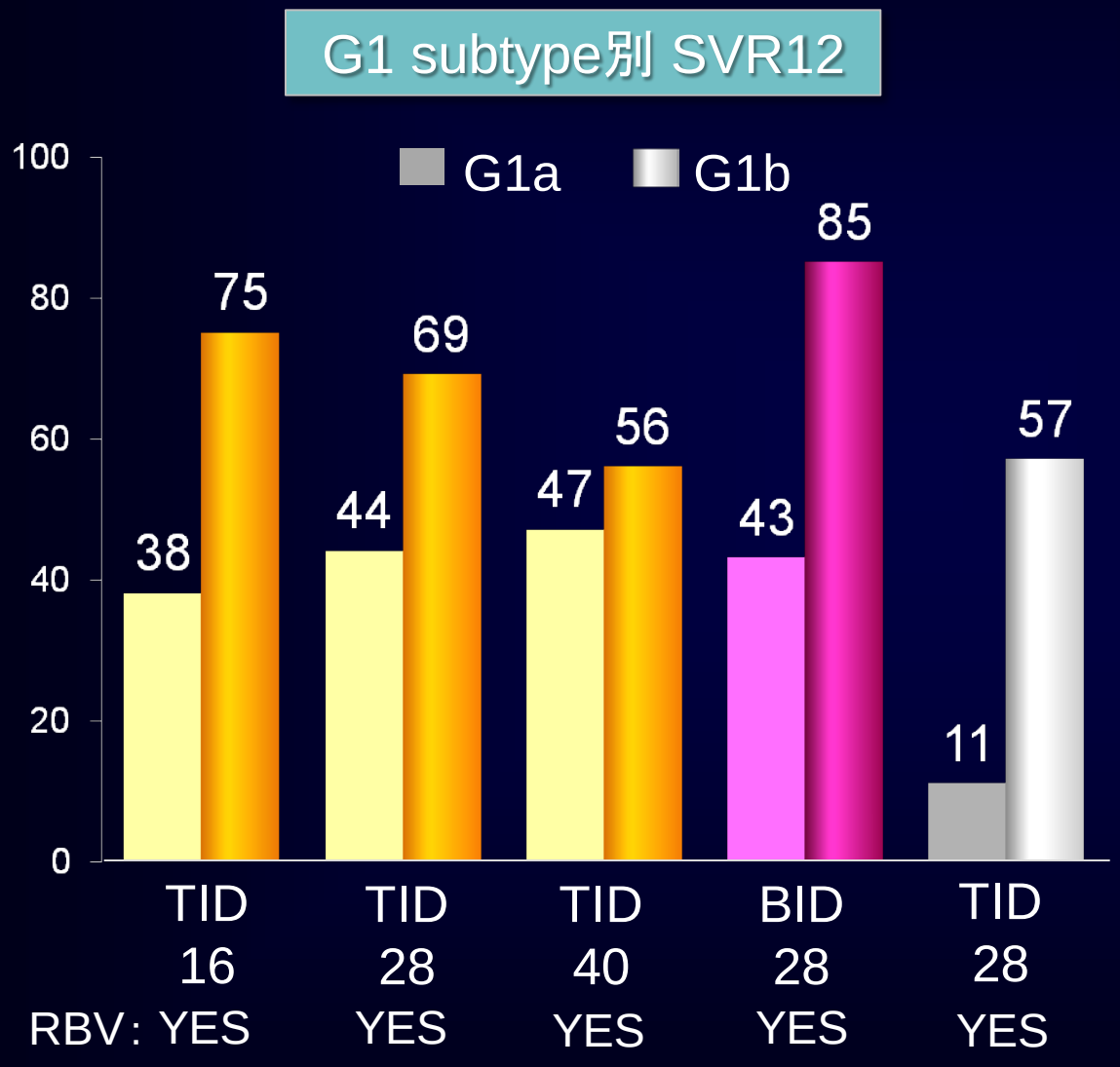
BI 201335/ BI 207127±RBV, G1 naive, *IFN Free*

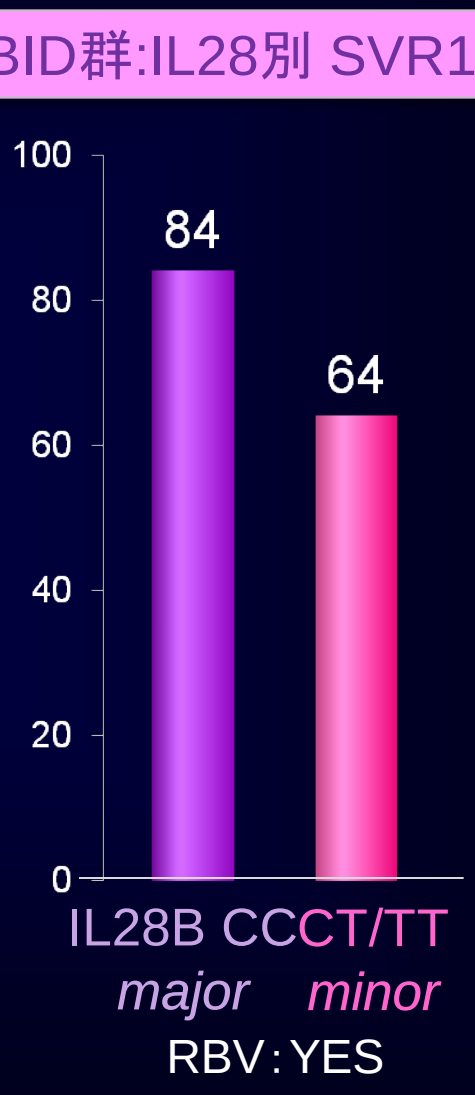
Cirrhosis: 10%（37/362）

BI 201335 = 120mg, BI 207127 = 600mg

S.Zeuzem et al.AASLD 2012 poster #778 & oral #232

Faldaprevir SOUND-C2 study, G1 naive
BI 201335/ BI 207127±RBV, *IFN Free :* SVR12





S.Zeuzem et al.AASLD 2012 poster #778 & oral #232

NS3/4Aプロテアーゼ阻害薬

ABT-450/ritonavir

NS5A阻害薬

ABT-267

NS5Bポリメラーゼ阻害薬

ABT-333

M11-652 study　*NS3/4A protease阻害薬*　*NS5A阻害薬*　*NS5B polymesase阻害薬*

3DAAs(ABT-450/r + ABT-267 + ABT-333) + RBV

8,12-week regimensの患者背景：平均年齢：50歳，G1a：66%(297/448)

G1 naive

8,12-week regimensのみ発表

			SVR12：全体	G1b
n=80	ABT-450/r＋267＋333＋RBV		87.5%	96%
n=79	ABT-450/r＋267＋333＋RBV		97.5%	100%
n=80	ABT-450/r＋267＋333＋RBV		–	–
n=41	ABT-450/r ＋333＋RBV	*no NS5A-i*	85.4%	100%
n=79	ABT-450/r＋267 ＋RBV	*no NS5B-i*	89.9%	100%
n=79	ABT-450/r＋267＋333	*no RBV*	87.3%	100%

G1 null-responder

n=45	ABT-450/r＋267＋333＋RBV		93.3%	100%
n=43	ABT-450/r＋267＋333＋RBV		–	–
n=45	ABT-450/r＋267 ＋RBV	*no NS5B-i*	88.9%	100%

0　Study Weeks　8　12　24

phase IIb

RBV dose : 1000/1200mg

K.V. Kowdley et al.; AASLD 2012 oral #LB-1

Nucleotide NS5Bポリメラーゼ阻害薬

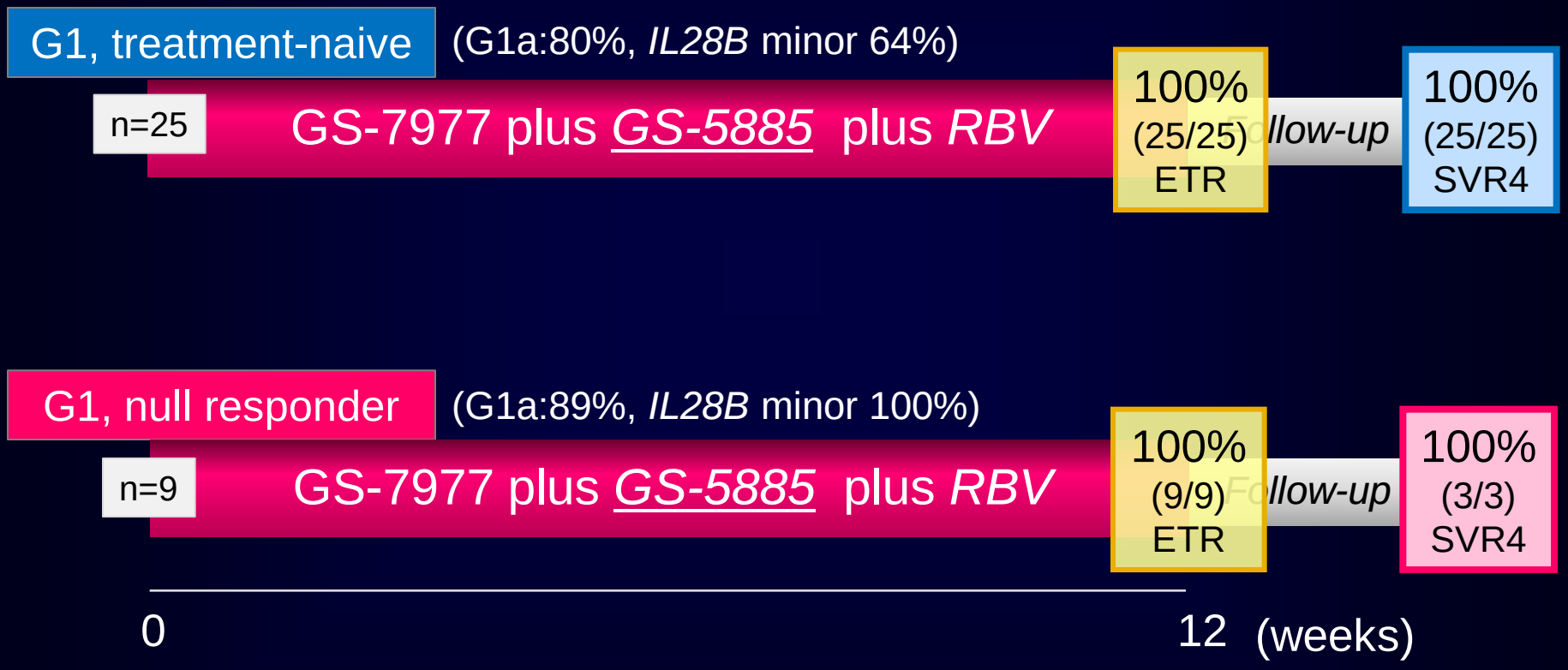
Sofosbuvir (GS-7977)

Sofosbuvir (GS-7977) plus RBV, Genotype 1,2,3
The ELECTRON Trial, IFN Free

no S282T containing mutations

Gane EJ et al. AASLD 2012 oral #229

Sofosbuvir (GS-7977)/GS-5885/RBV, Genotype 1
The ELECTRON Trial, IFN Free

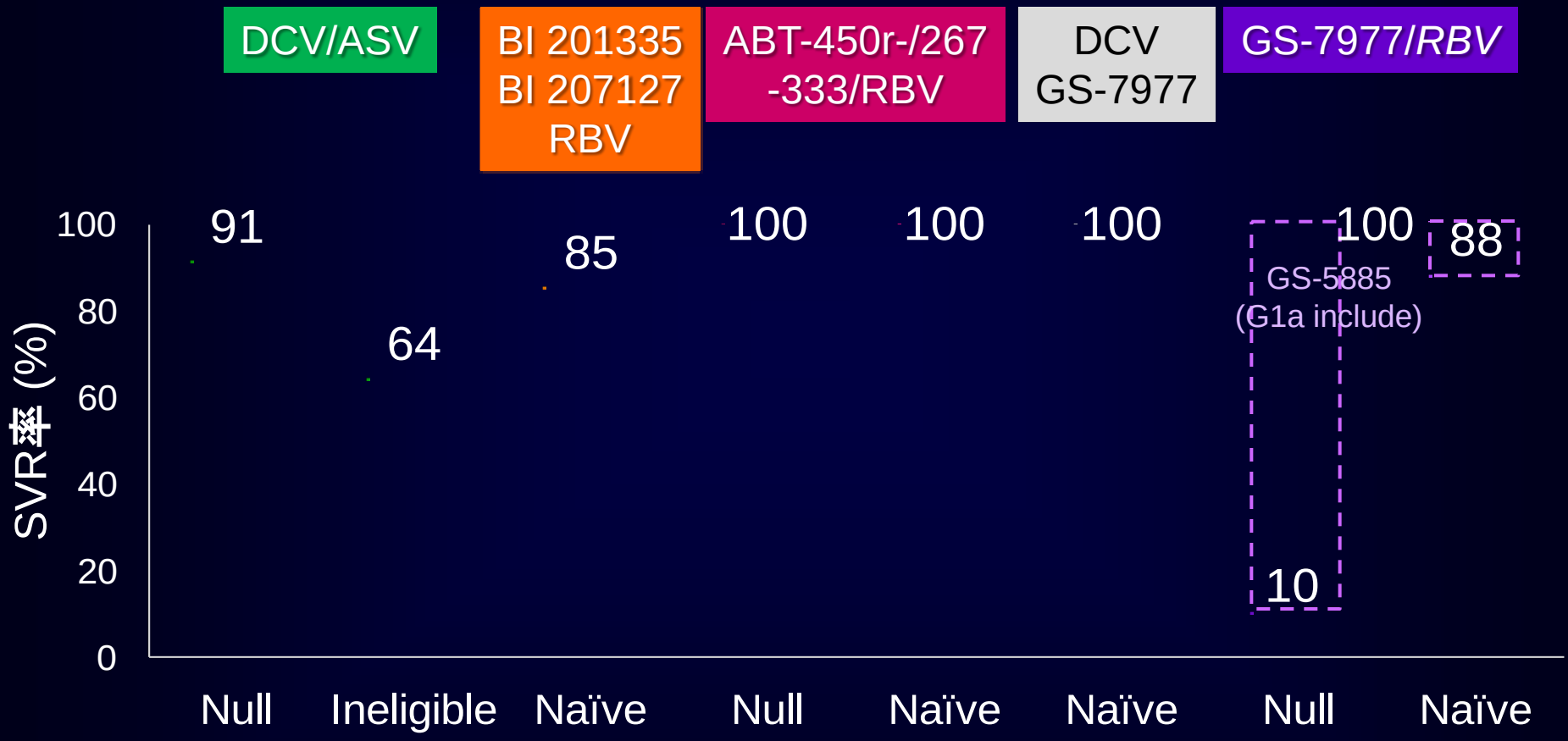


Gane EJ et al. AASLD 2012 oral #229

Genotype 1b：*IFN free*のSVR率

STUDY name： *phase 2b (JPN), SOUND-C2, M11-652, phase2a, ELECTRON*

EASL, AASLD 2011-12 presentations



DCV/ASV: Suzuki et al. EASL 2012

ABT-450r/-267-333/RBV: Kowdley et al .AASLD 2012

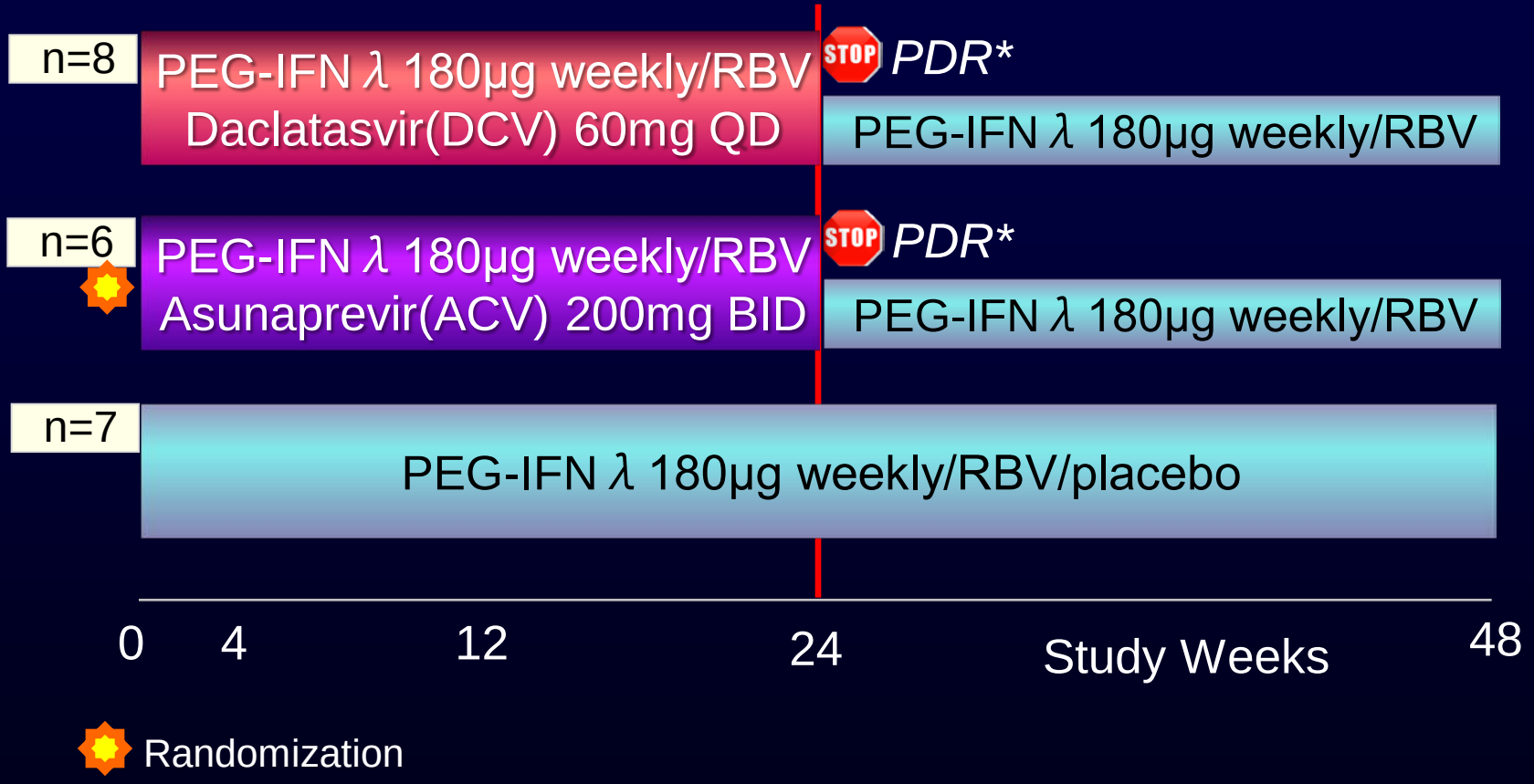
GS-7977(SOF)/DCV: Sulkowski et al. AASLD 2012

BI201335/BI207127: Zeuzem et al . EASL 2012&AASLD 2012

GS-7977(SOF)/RBV: Gane et al, AASLD 2012

D-LITE Japanese Sub-Study –
Peg-IFN Lambda plus DCV or ASV in Naïve *G1b* Patients

**PDR* = protocol-defined response: undetectable wk4 HCV RNA <25 IU/mL, wk 12 <10 IU/mL

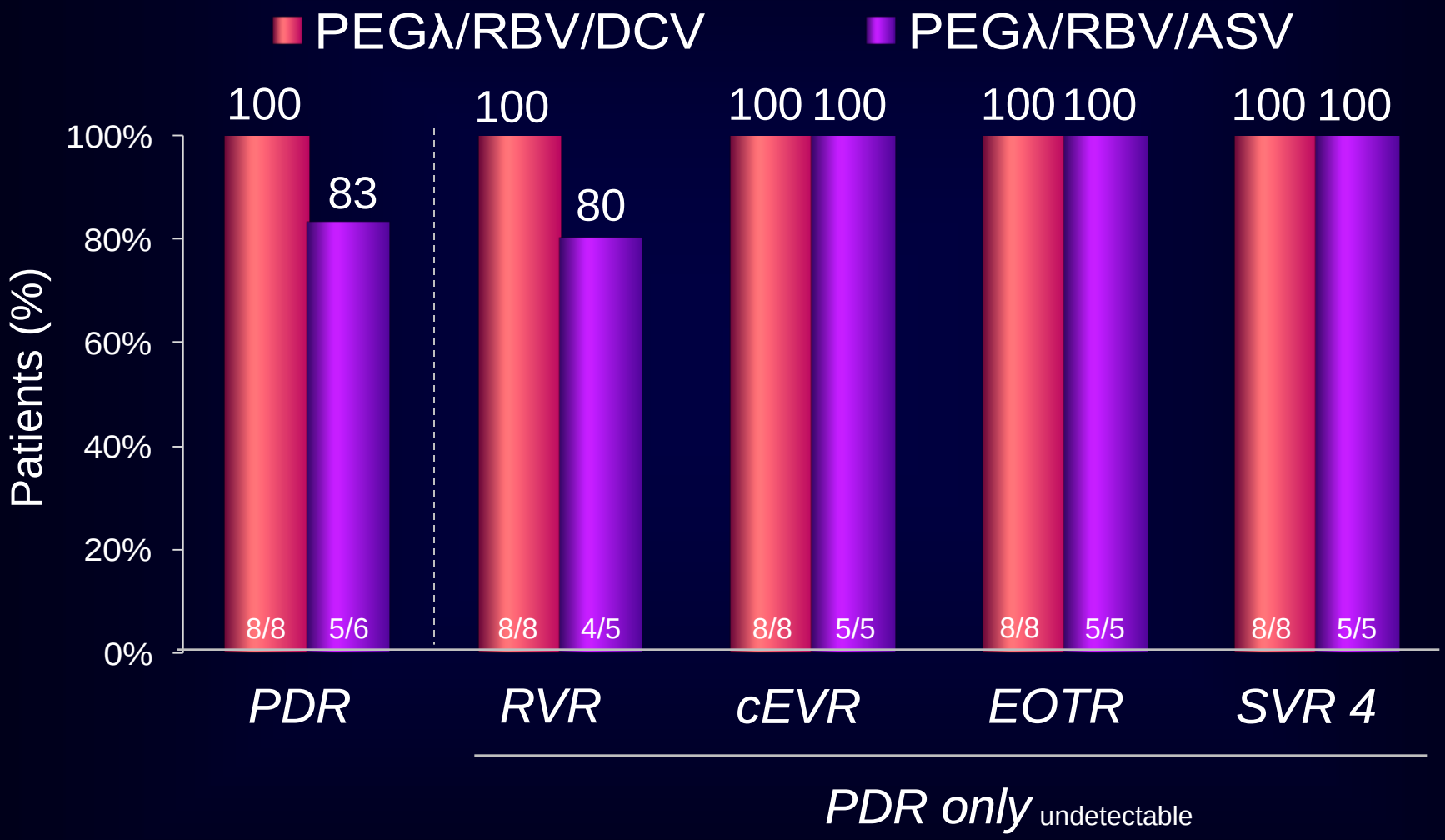


rs12979860 IL28B non-CC：各群2例

Izumi N et al. AASLD2012, oral #234, Auditorium

D-LITE Japanese Sub-Study – Virologic Response

Peg-IFN Lambda plus DCV or ASV in Naïve *G1b* Patients



undetectable

PDR: wk4 HCV RNA <25 IU/mL, wk 12 <10 IU/mL

Izumi N et al. AASLD2012, oral #234, Auditorium