

米国肝臓学会2012報告(C型肝炎)

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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)

非核酸型
(7DAAs)

NS5A 阻害薬
(7DAAs)

Telaprevir

Boceprevir

Simeprevir

(TMC435)

Faldaprevir

(BI 201335)

Vaniprevir

(MK-7009)

Asunaprevir

(BMS-650032)

ABT-450

Danoprevir

GS-9451

GS-9256

MK-5172

ACH-1625

BILN2961

ACH-2684

Sofosbuvir

(GS-7977)

Mericitabine

(RG7128)

IDX 184

ALS-2200

BCX5191

LG-7501

ABT-333

BI 207127

Tegobuvir

(GS-9190)

VX-222

ABT-072

GS-9669

BMS-791325

Daclatasvir

(BMS-790052)

ABT-267

GS-5885

PPI-668

IDX719

MK-8742

ACH-3102

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

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)

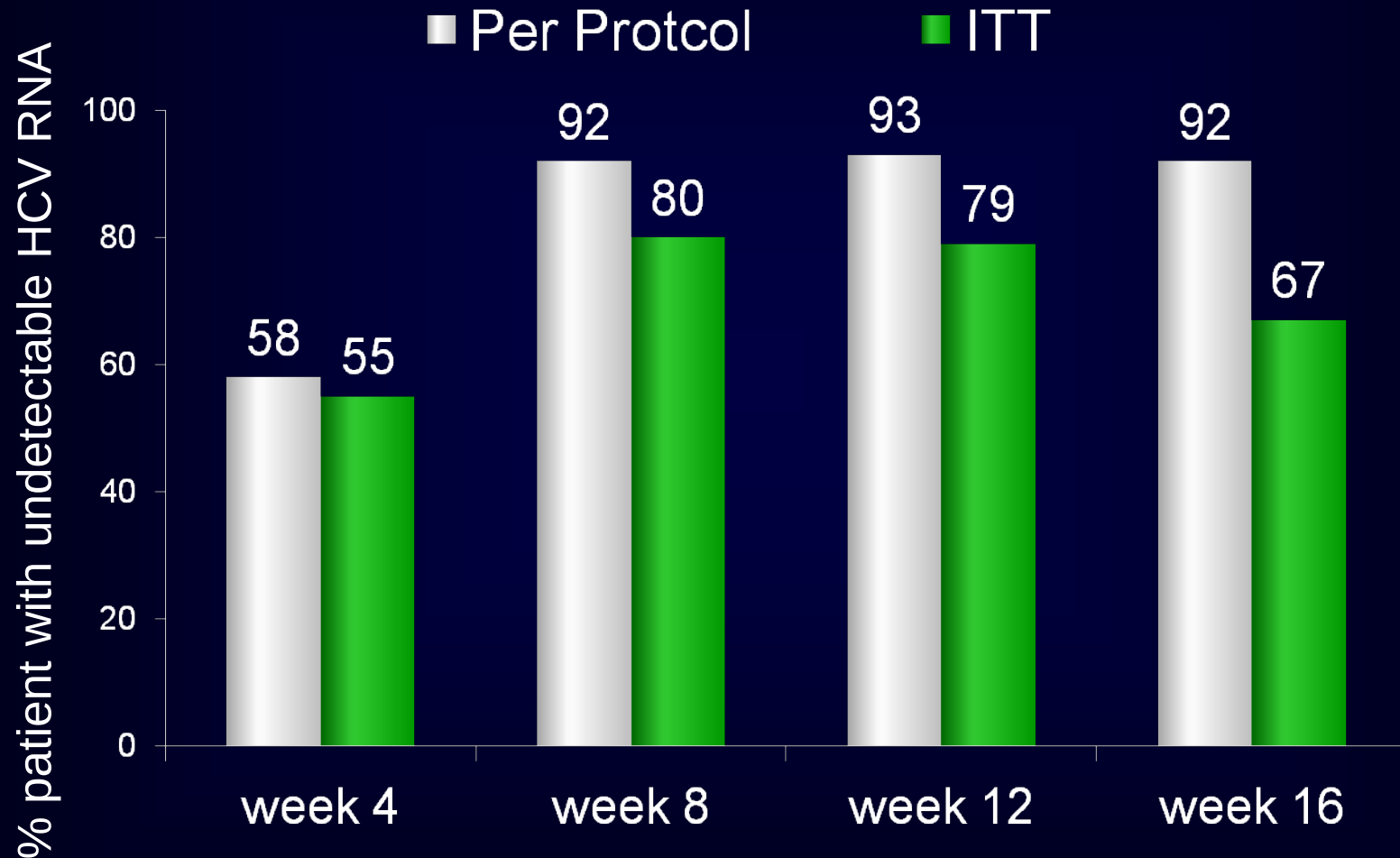
n=292

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, $\mu\text{mol/L}$	15.4 (4.0-73.5)
平均Alb, g/dL	40.1 (20.7-52.0)
平均好中球数, $10^9/\text{mm}^3$	3.3 (0.8-9.7)
平均Hb量, g/dL	14.6 (9.0-19.7)
平均血小板数, $10^4/\text{mm}^3$	15.2 (1.8-60.4)

CUPIC study: Telaprevir/ PEG/ RBV

HCV RNA陰性化推移

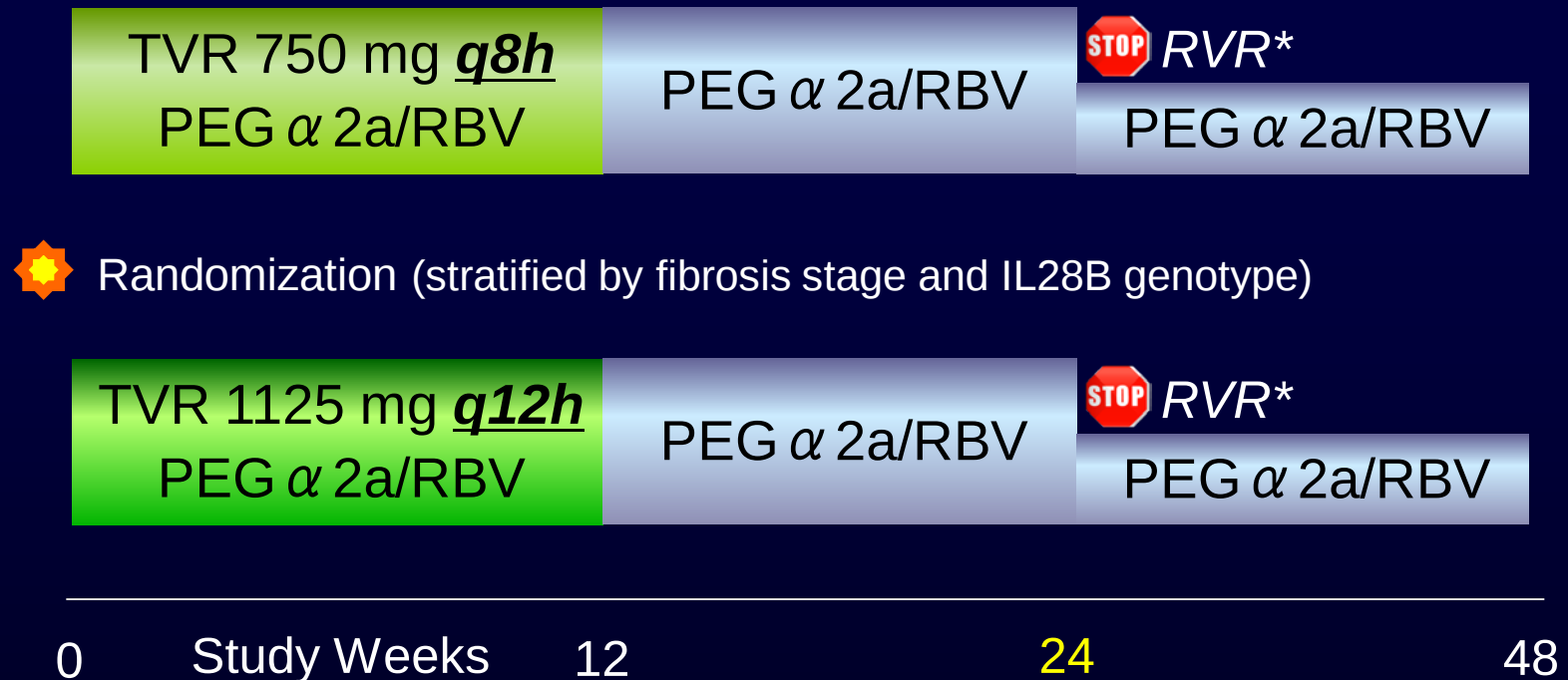


CUPIC study: Telaprevir/PEG/RBV 安全性 (16週時点)

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%

OPTIMIZE Study – Telaprevir q8 vs. q12 hrs PEG-IFN α 2a/RBV – G1 naïve, Phase III

CHC, G1 naïve, n=744



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

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)

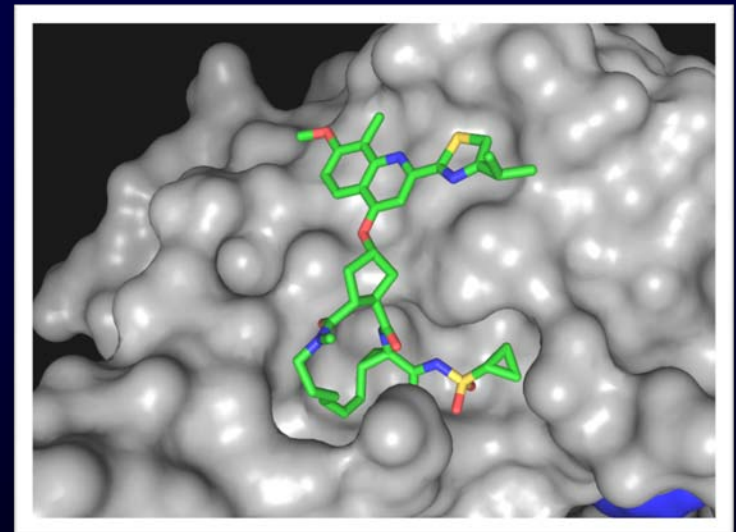
* met virologic stopping rule or viral breakthrough

‡ 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)



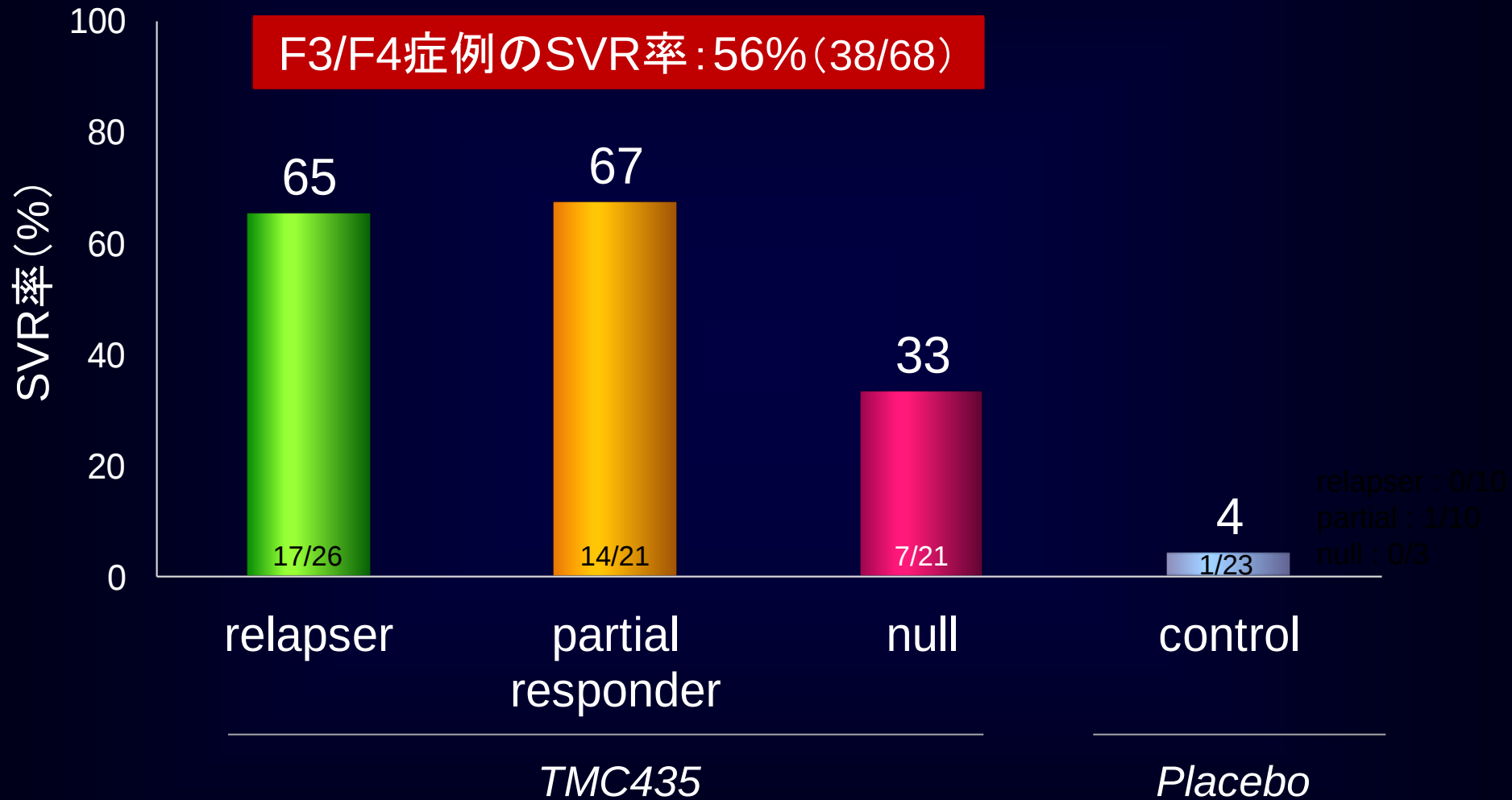
macrocyclic

Simeprevir(TMC435) の主な有害事象

(PILLAR and ASPIRE, phase IIb trials)

Proportion of patients, %	TMC435 150 mg: <i>First 12 weeks</i>		TMC435 150 mg: <i>Overall treatment duration</i>	
	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%
インフルエンザ様症状	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%

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



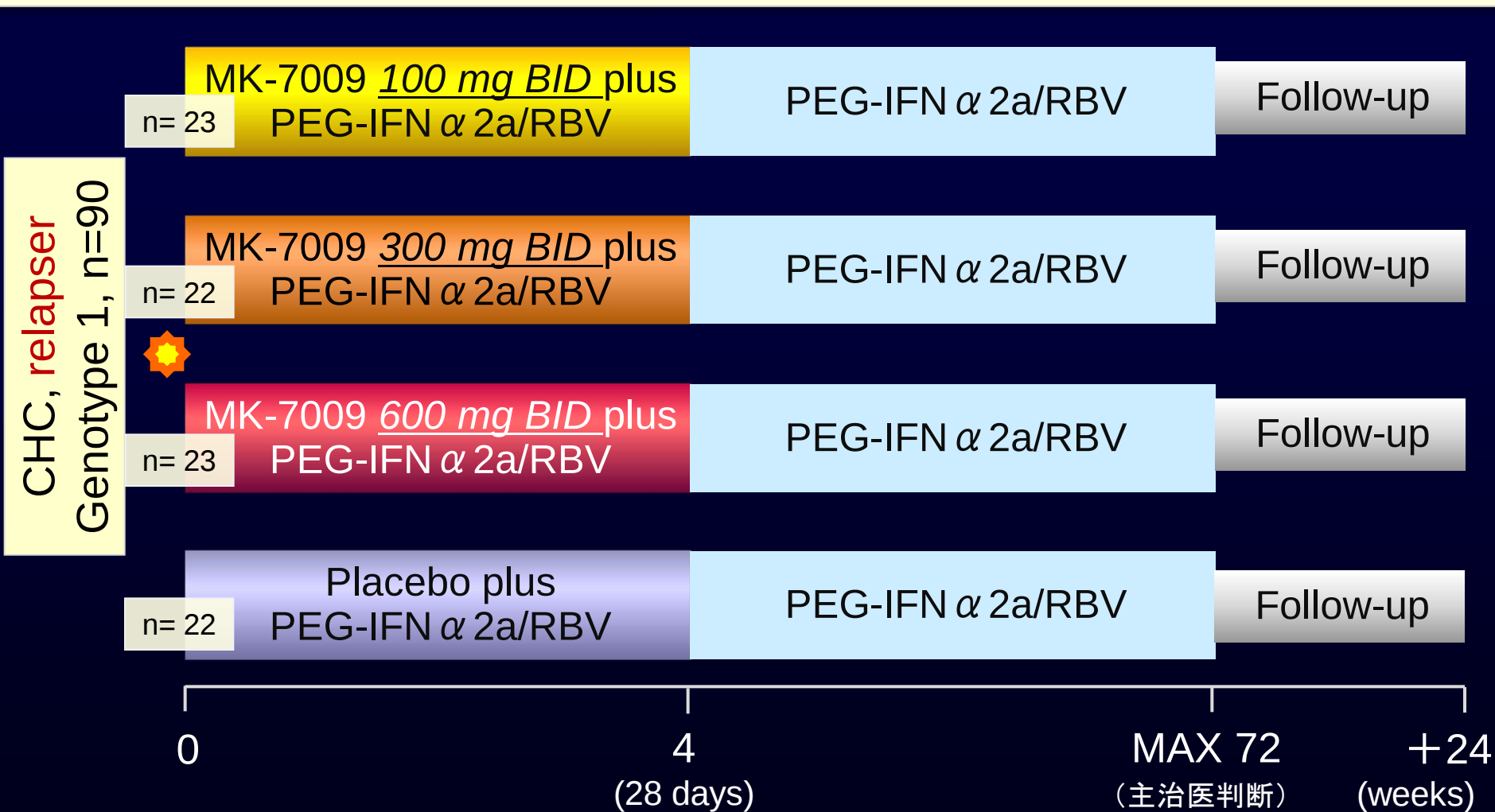
#83 conclusionより
Phase IIIの結果は2013.1Qにopen

NS3/4Aプロテアーゼ阻害薬

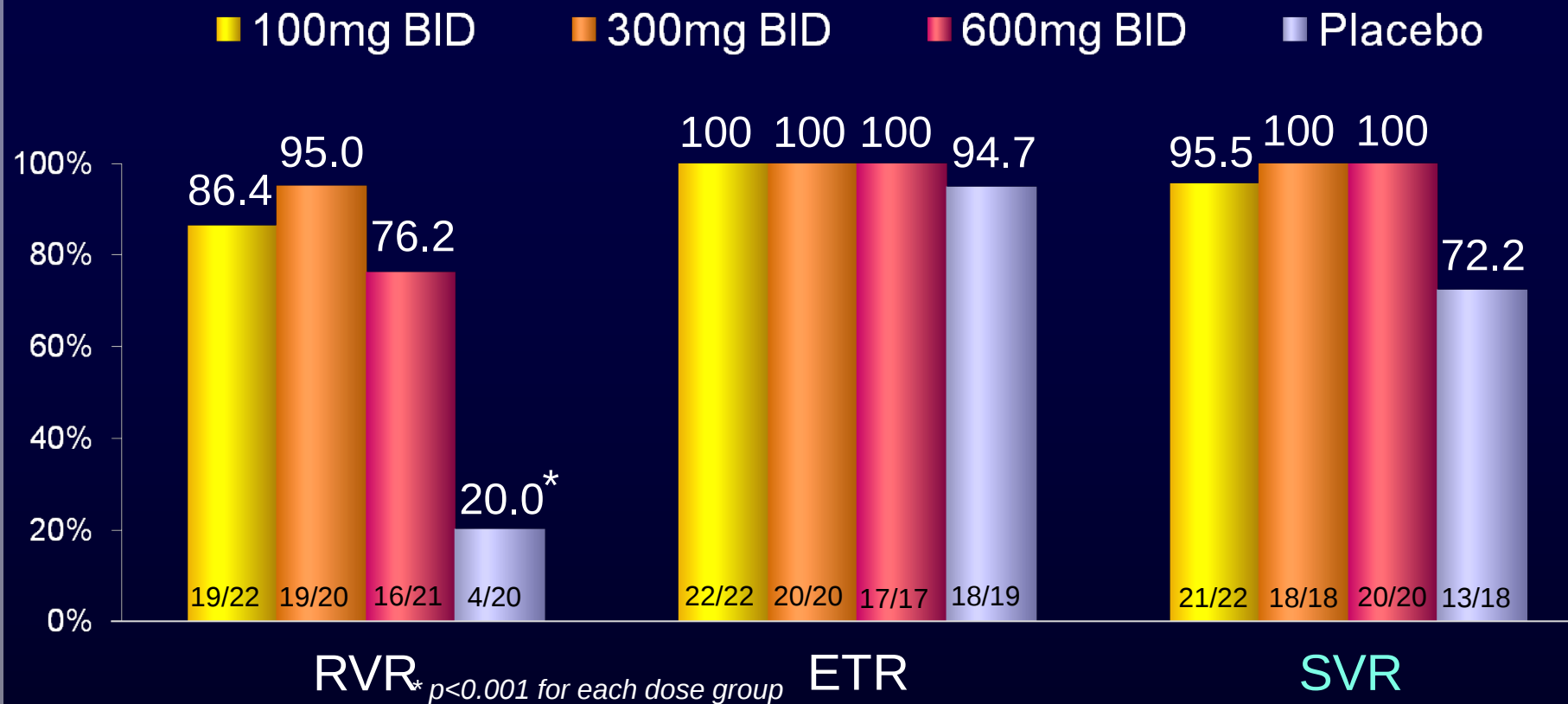
Vaniprevir (MK-7009)

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



Vaniprevir (MK-7009) plus PEG-IFN α 2a/RBV for 28 Days in G1 Japanese Relapser patients : RVR, ETR, SVR rate

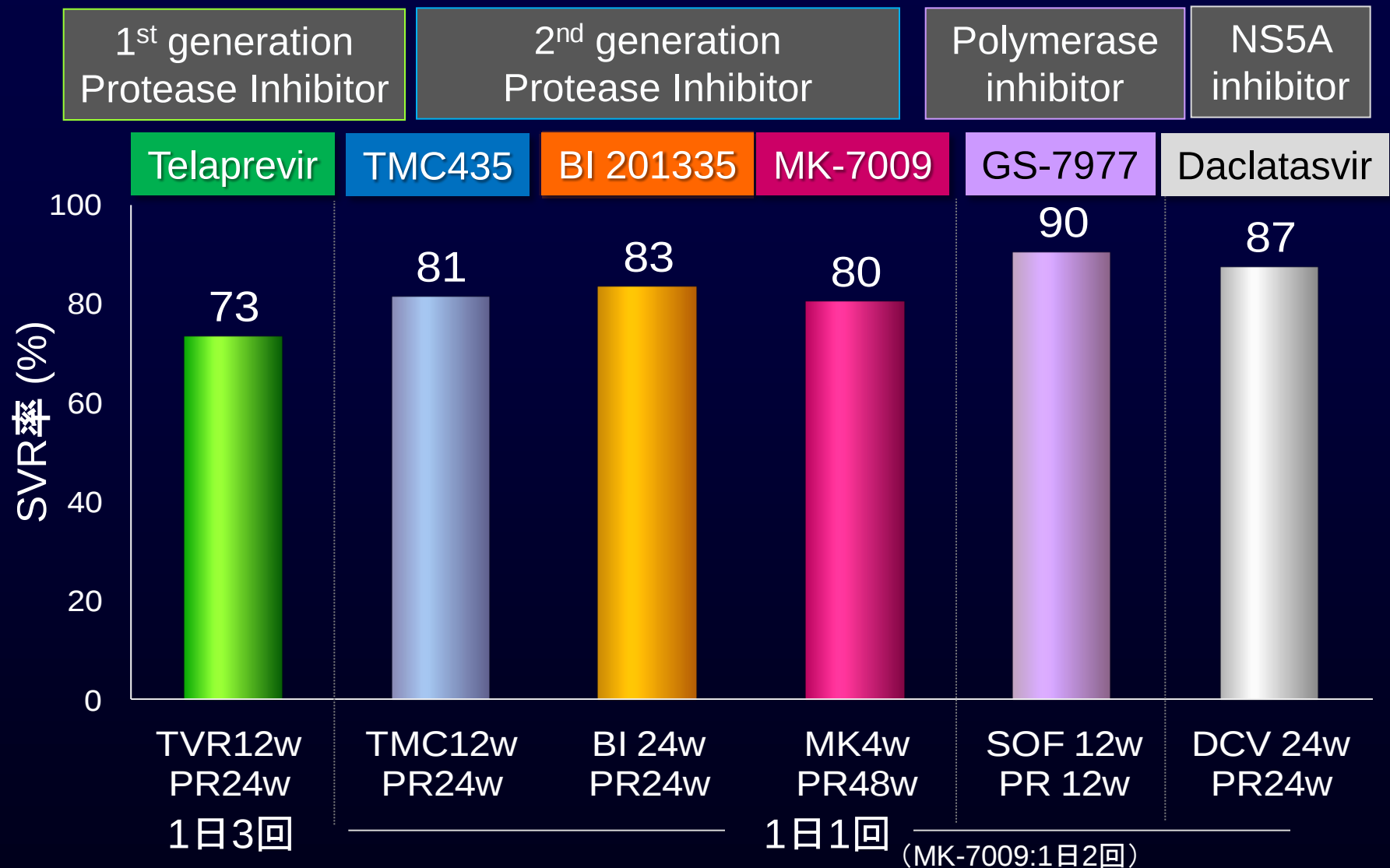


per protocol : 7例除外 (MK-7009・RBV規定量以下の投与、低ウイルス量、除外基準違反、禁止薬物治療使用)

- ✓ 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。

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

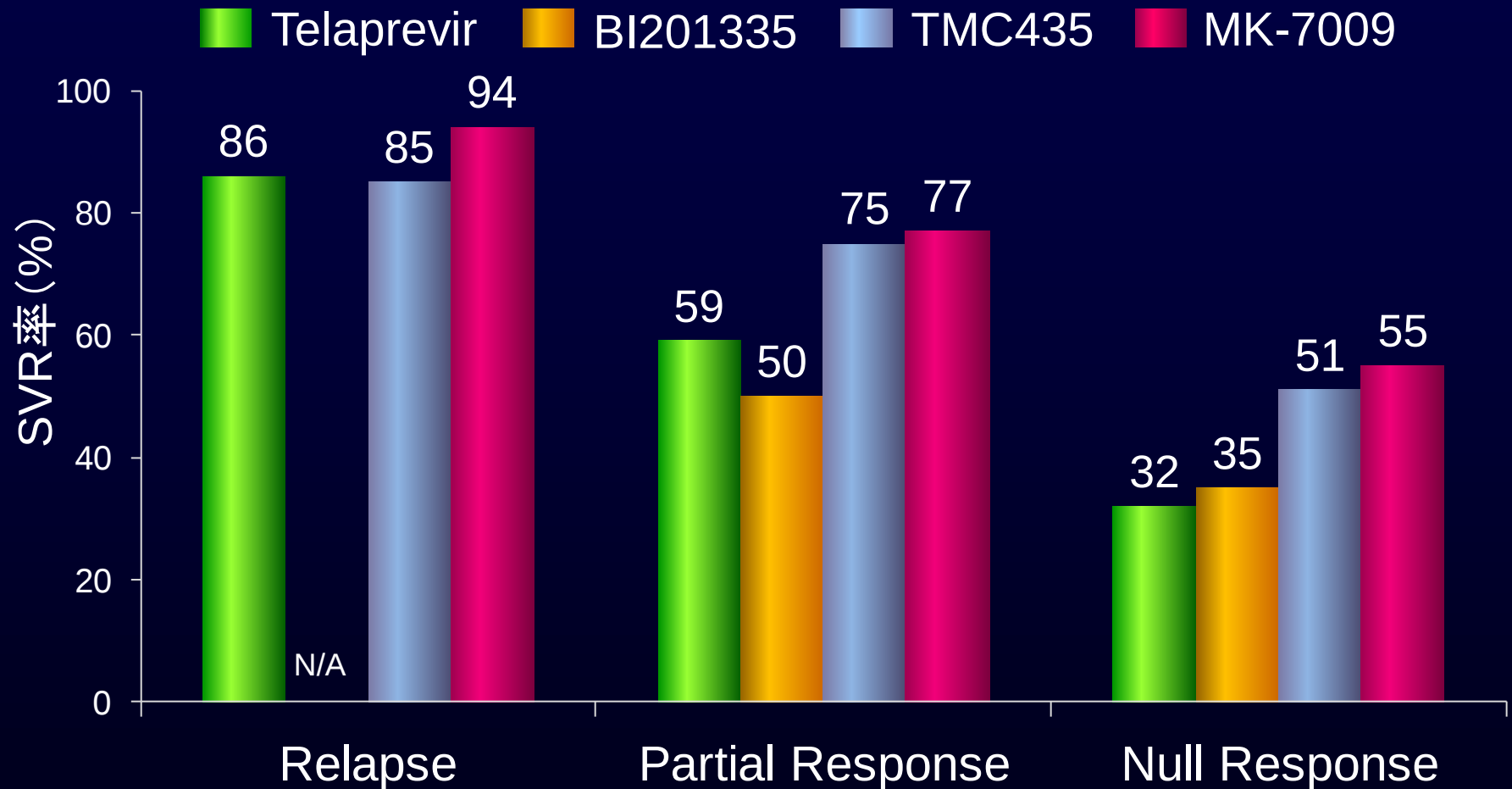
TMC 435: Fried et al. AASLD 2011
GS-7977(SOF): Hassanein et al, AASLD 2012

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

DAA±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
NS3/4Aプロテアーゼ阻害薬

DAA

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*

G1a:17, G1b:3 PEG-IFN α 2a/RBV

Follow-up

95%

G1a main
 QUAD

n=21

DCV 60 mg QD + ASV 200 mg QD

G1a:19, G1b:2 PEG-IFN α 2a/RBV

Follow-up

95%

G1a main
 Triple, IFN free

n=22

DCV 60 mg QD + ASV 200 mg QD

G1a:18 ,G1b:4 RBV (no PEG)

Follow-up

23%

VBT:56%

SVR12...G1a:1/18, G1b:4/4

0

Study Weeks

24

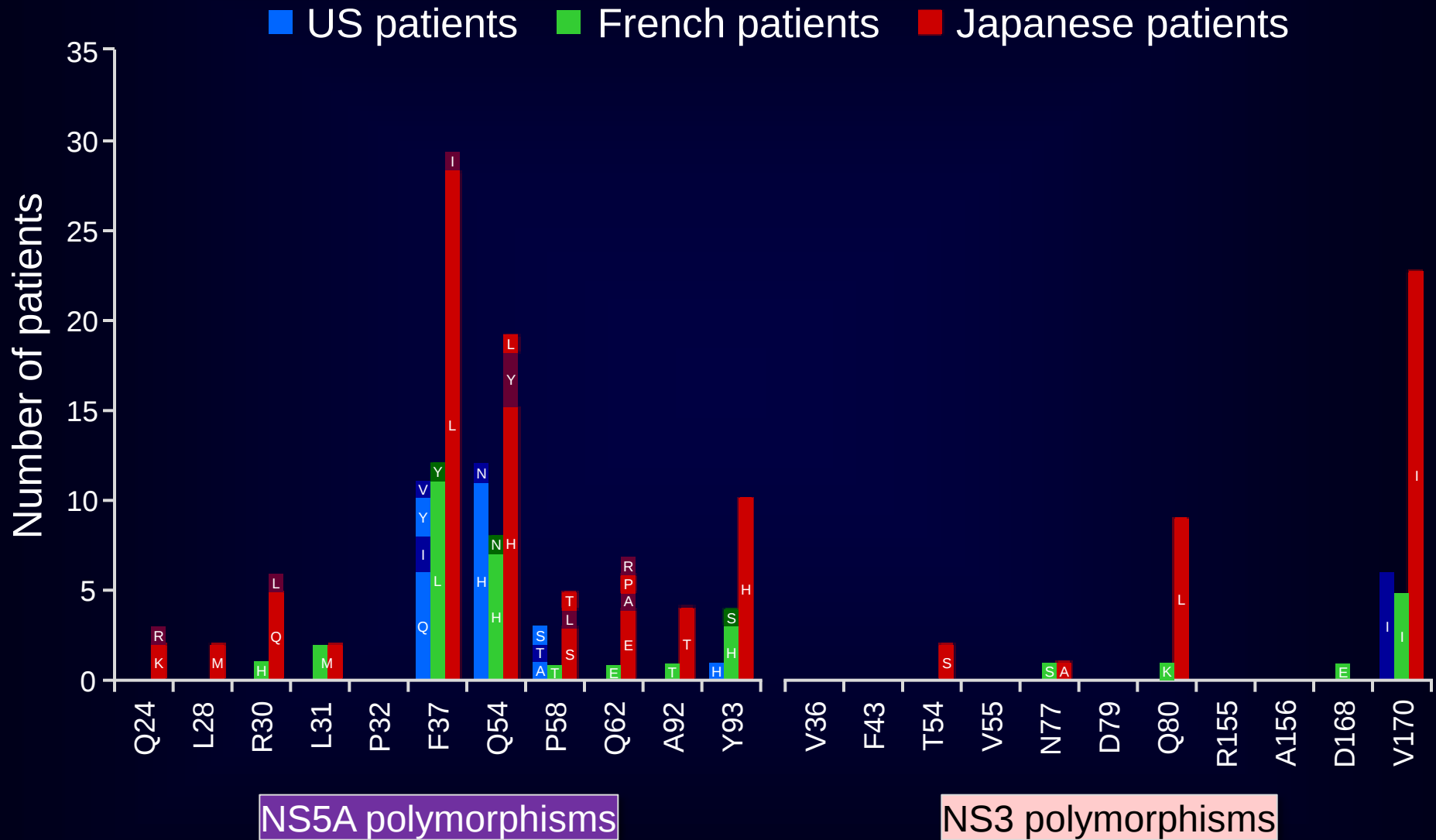
48

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)



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	VB		V					H			Y
	US7	VB		V			S	G/Y	H			Y
	US8	Relapse			Δ							V
France	FR2	VB		V					H			V
	FR3	VB		V					H			V
	FR8	VB			Δ							V
	FR9	VB	Q	M		H			H			E
	FR10	VB		V					H			V
Japan	JP1	Relapse		M			L		H			V
	JP2	Relapse		V					H			V
	JP3	Relapse		V/M					H			V
	JP9	VB		M		Y			H	L		V
	JP14	VB		M			A		H			A
	JP15	Relapse		M					H			A
	JP16	VB		M		Y			H		G	V



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

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 naïve, IFN Free



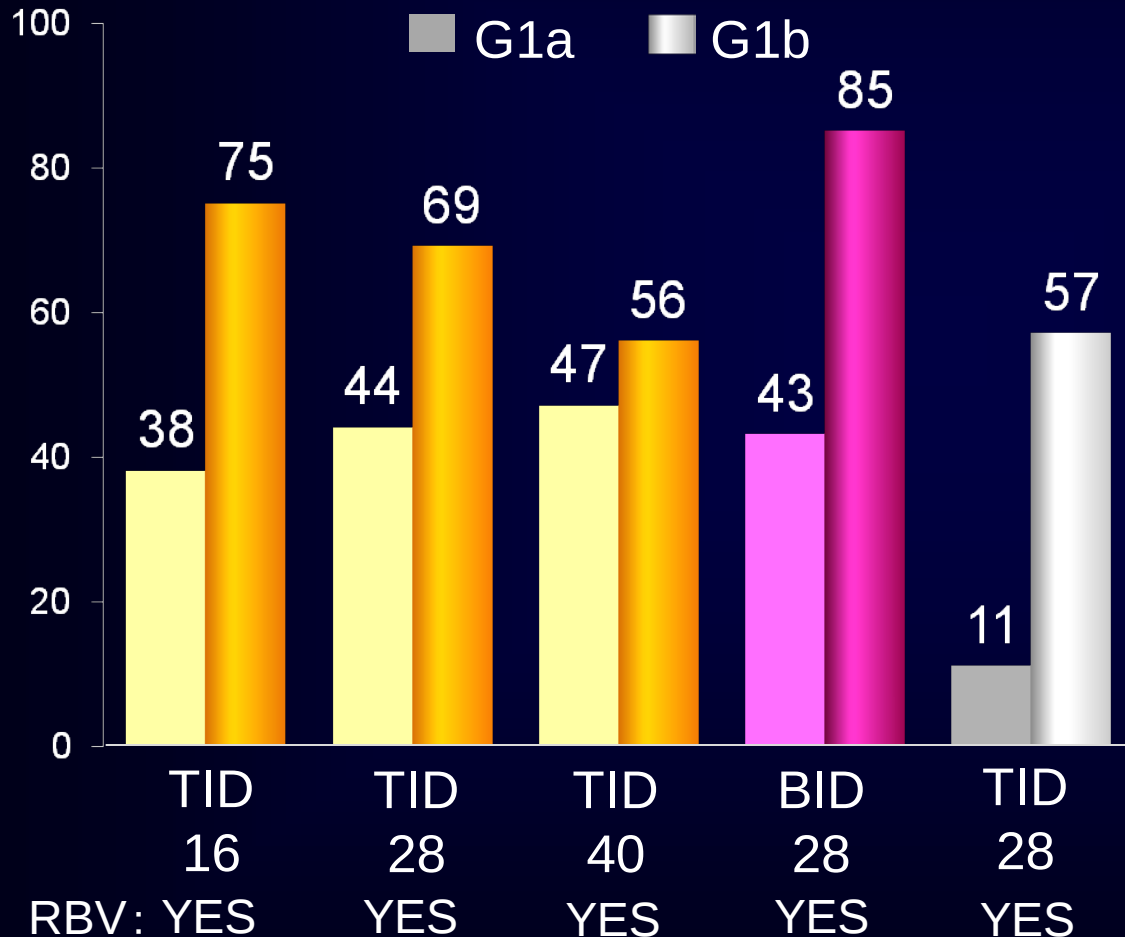
Cirrhosis: 10% (37/362)

BI 201335 = 120mg, BI 207127 = 600mg

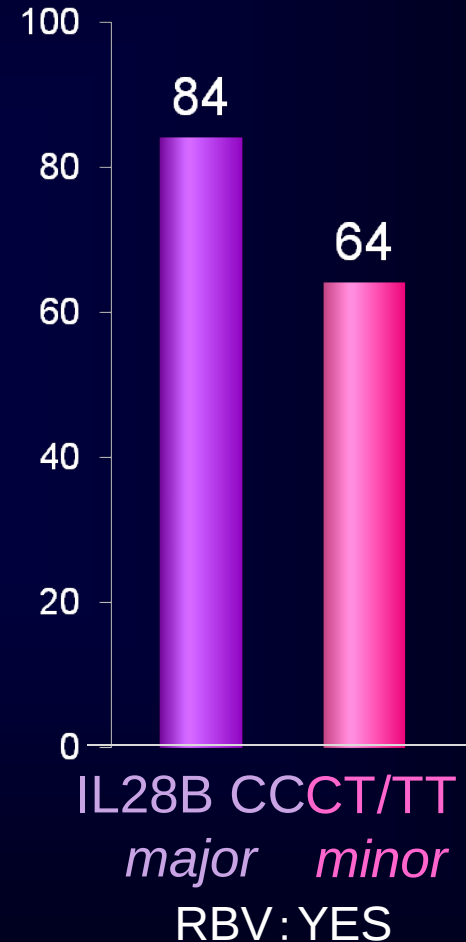
S.Zeuzem et al.AASLD 2012 poster #778 & oral #232

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

G1 subtype別 SVR12



BID群:IL28別 SVR12



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 polymerase 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%

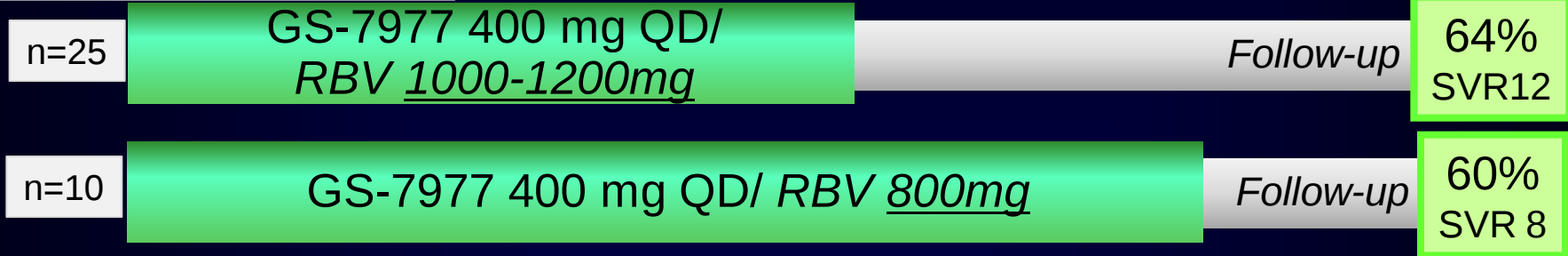
Nucleotide NS5Bポリメラーゼ阻害薬

Sofosbuvir (GS-7977)

Sofosbuvir (GS-7977) plus RBV, Genotype 1,2,3

The ELECTRON Trial, IFN Free

G2/3, treatment-naïve



G2/3, treatment-experience



G1, treatment-naïve (G1a:88%, IL28B minor 56%)



G1, null responder (G1a:90%, IL28B minor 80%)



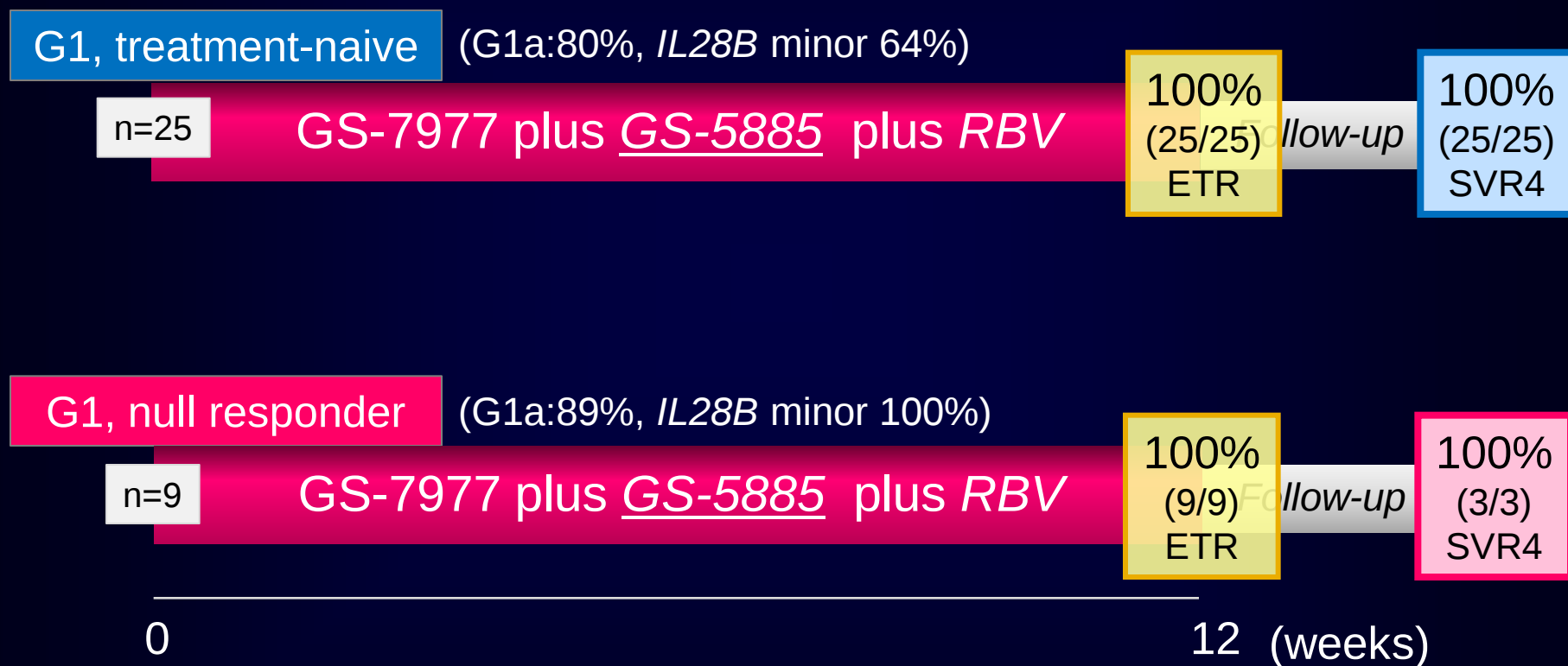
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8

12 (weeks)

Sofosbuvir (GS-7977)/GS-5885/RBV, Genotype 1

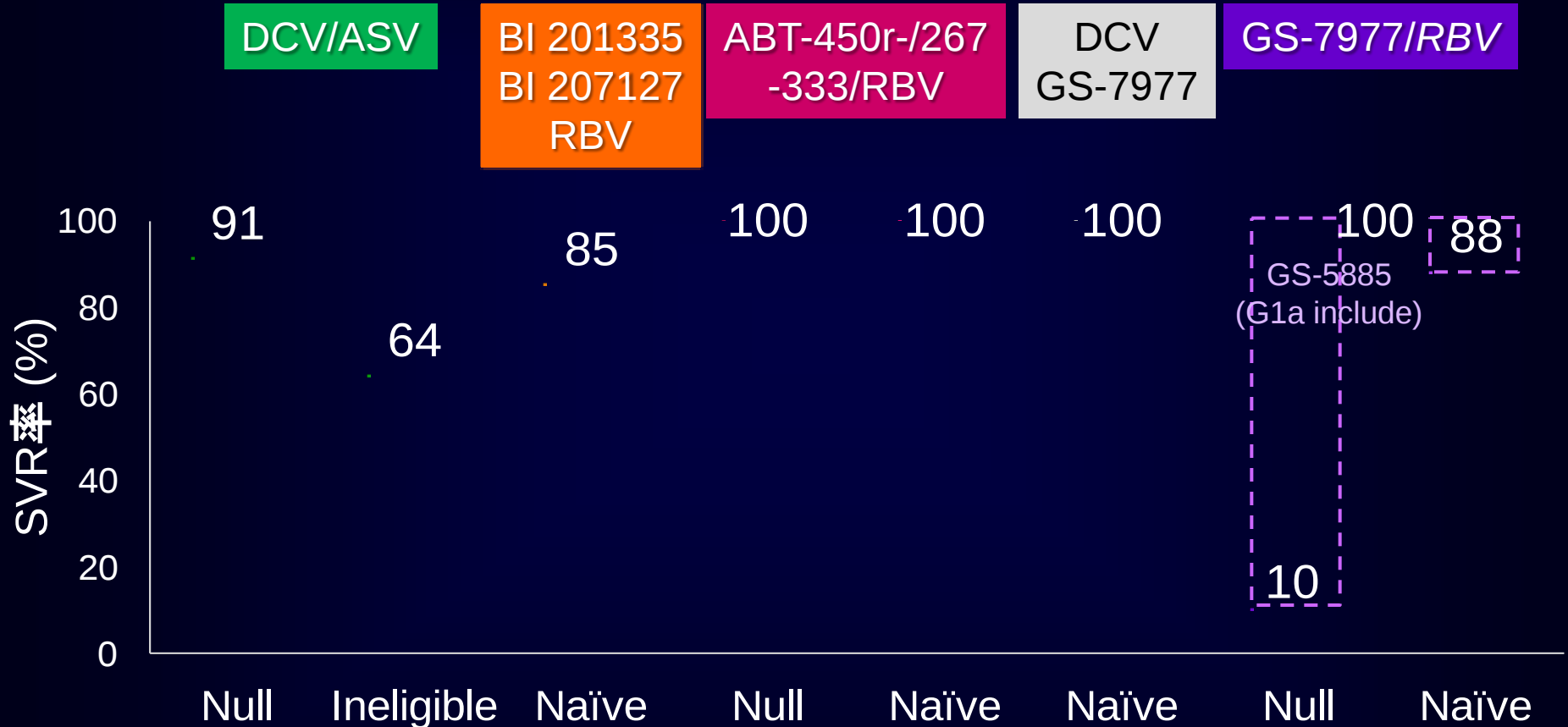
The ELECTRON Trial, IFN Free



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

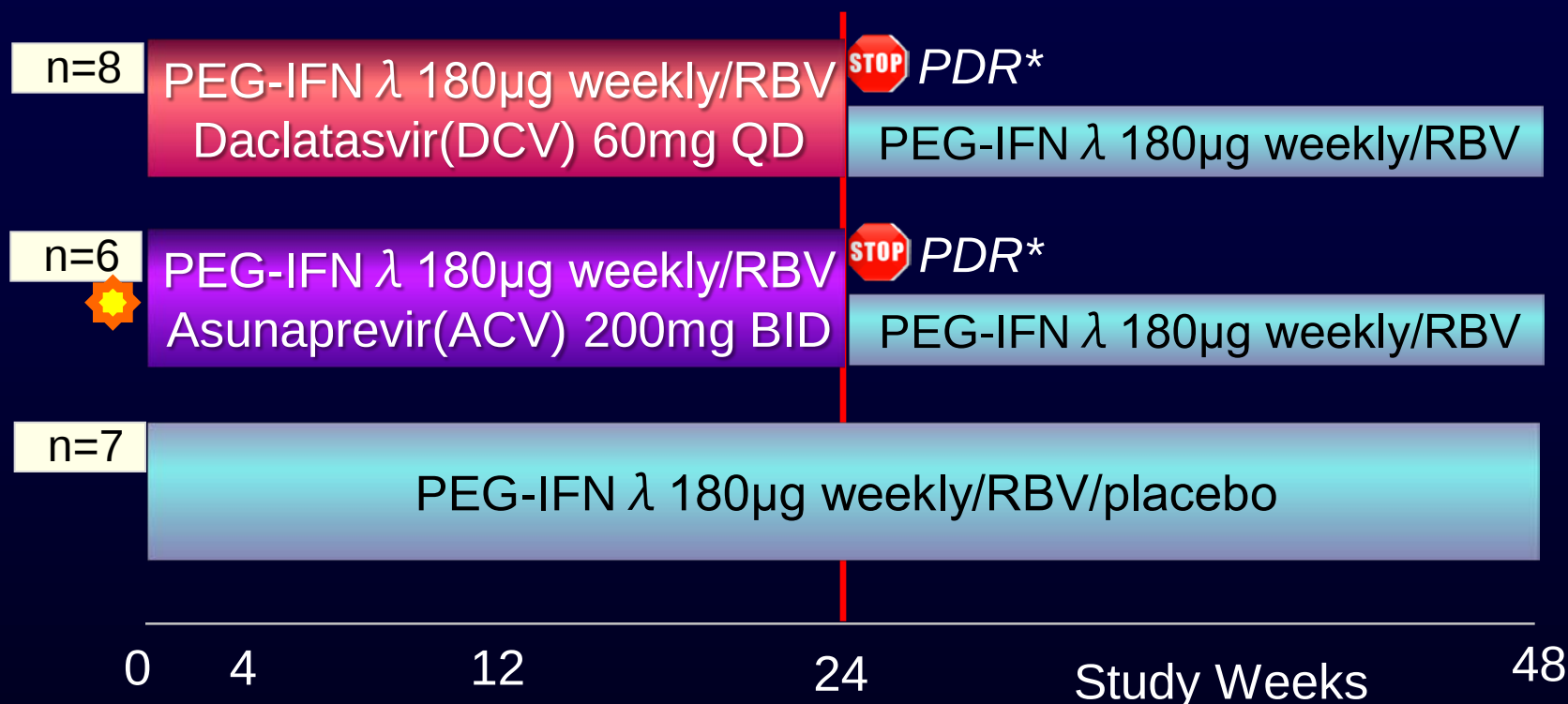
GS-7977(SOF)/DCV: Sulkowski et al. AASLD 2012

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

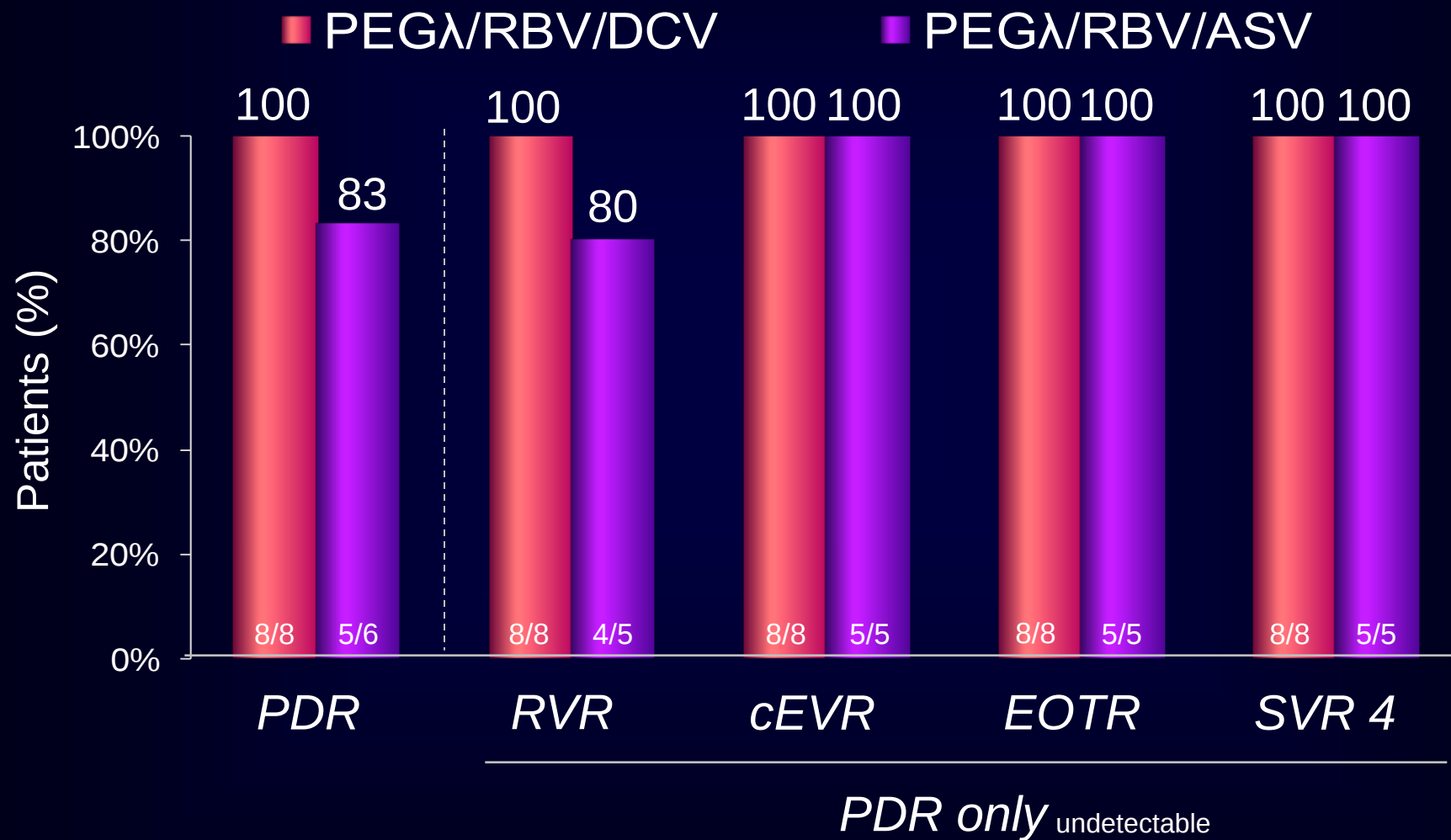


 Randomization

rs12979860 IL28B non-CC: 各群2例

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