2014 7th Paris Hepatitis Conference
Organised by Pr Patrick Marcellin
13 & 14 January 2014
Palais des Congrès, Paris

Future strategies with new DAAs

Ola Weiland
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New direct antiviral drugs

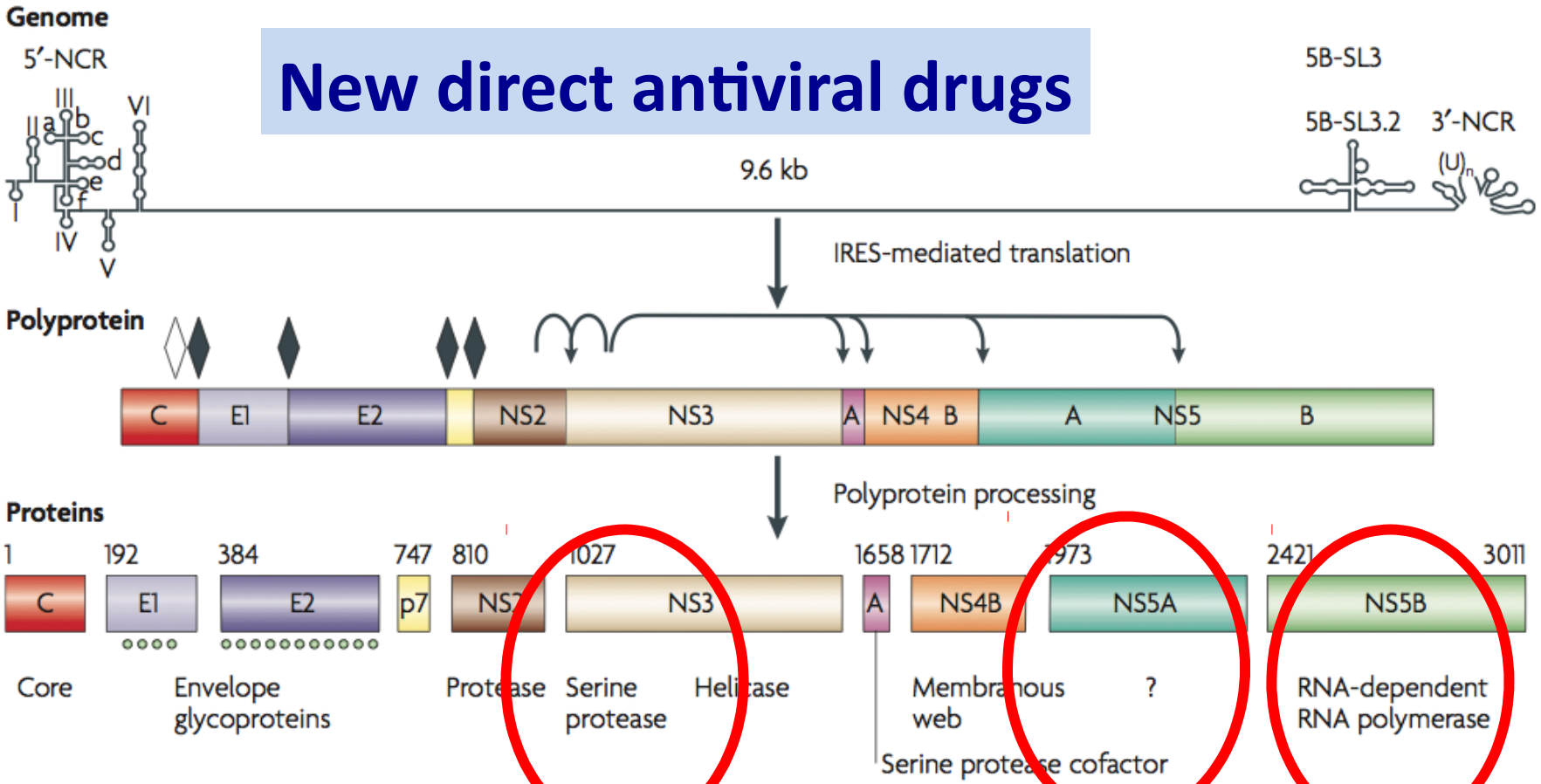

Figure 3 | **Genetic organization and polyprotein processing of hepatitis C virus (HCV).** The 9.6-kb positive-strand RNA genome is schematically depicted at the top. Simplified RNA secondary structures in the 5′- and 3′-non-coding regions (NCRs) and the core gene, as well as the NS5B stem-loop 3 *cis*-acting replication element (5B-SL3) are shown. Internal ribosome entry site (IRES)-mediated translation yields a polyprotein precursor that is processed into the mature structural and non-structural proteins. Amino-acid numbers are shown above each protein (HCV H strain; genotype 1a; GenBank accession number AF009606). Solid diamonds denote cleavage sites of the HCV polyprotein precursor by the endoplasmic reticulum signal peptidase. The open diamond indicates further C-terminal processing of the core protein by signal peptide peptidase. Arrows indicate cleavages by the HCV NS2–3 and NS3–4A proteases. Dots in E1 and E2 indicate the glycosylation of the envelope proteins (4 and 11 *N*-linked glycans, respectively, in the HCV H strain). Note that polyprotein processing, illustrated here as a separate step for simplicity, occurs co- and post-translationally.

Multiple Direct Acting Antivirals

Protease

Polymerase

HCV PIs	NS5A Inhibitors	NS5B Nucs	NS5B Non-nucs
Viral enzyme Active site	Non-enzyme Replication complex	Viral enzyme Active site	Viral enzyme Allosteric site
Telaprevir	Daclatasvir	Sofosbuvir	ABT-333
Boceprevir	Ledipasvir	VX-135	Deleobuvir
Simeprevir	ABT-267	IDX20963	BMS-791325
Faldaprevir	GS-5816	ACH-3422	PPI-383
Asunaprevir	ACH-3102		GS-9669
ABT-450	PPI-668		TMC647055
MK-5172	GSK2336805		
Sovaprevir	Samatasvir		
ACH-2684	MK-8742		

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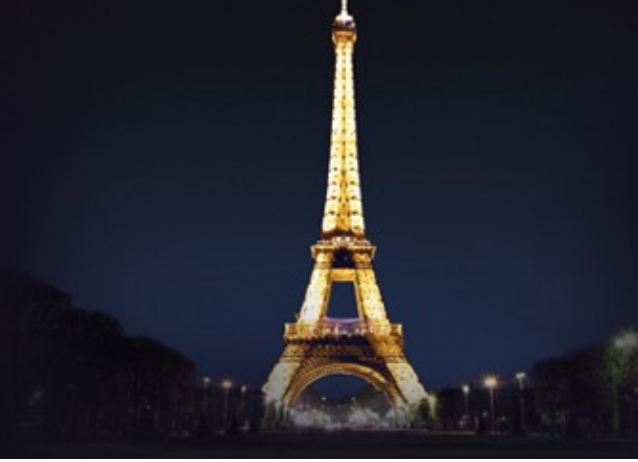


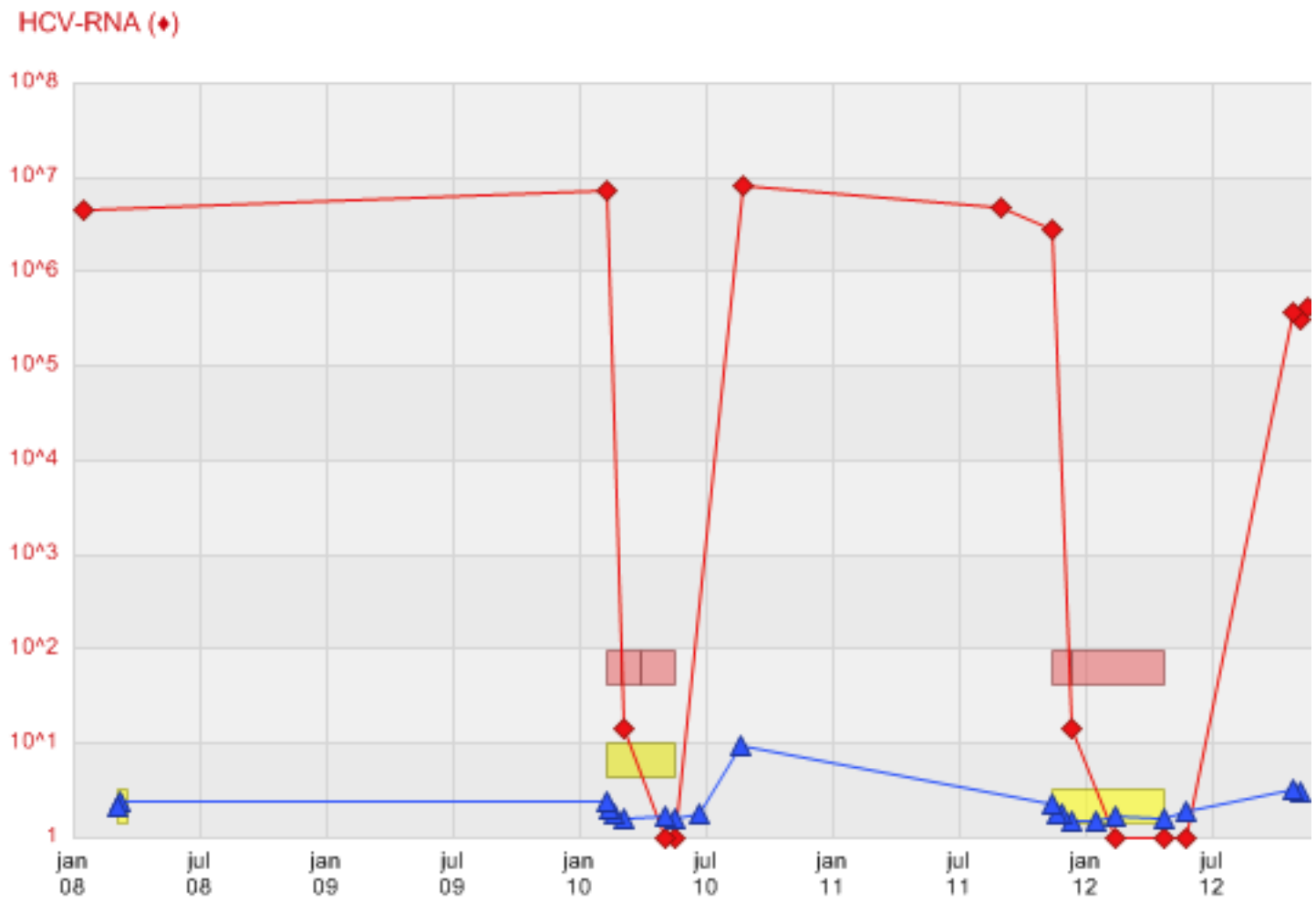
Case no 1 male with genotype 2b

Male with gt 2b chronic HCV

- **Male with gt 2b relapse after peg-IFN + RBV during 24 weeks and**

- **Again after 48 weeks treatment**

Male with gt 2b chronic HCV



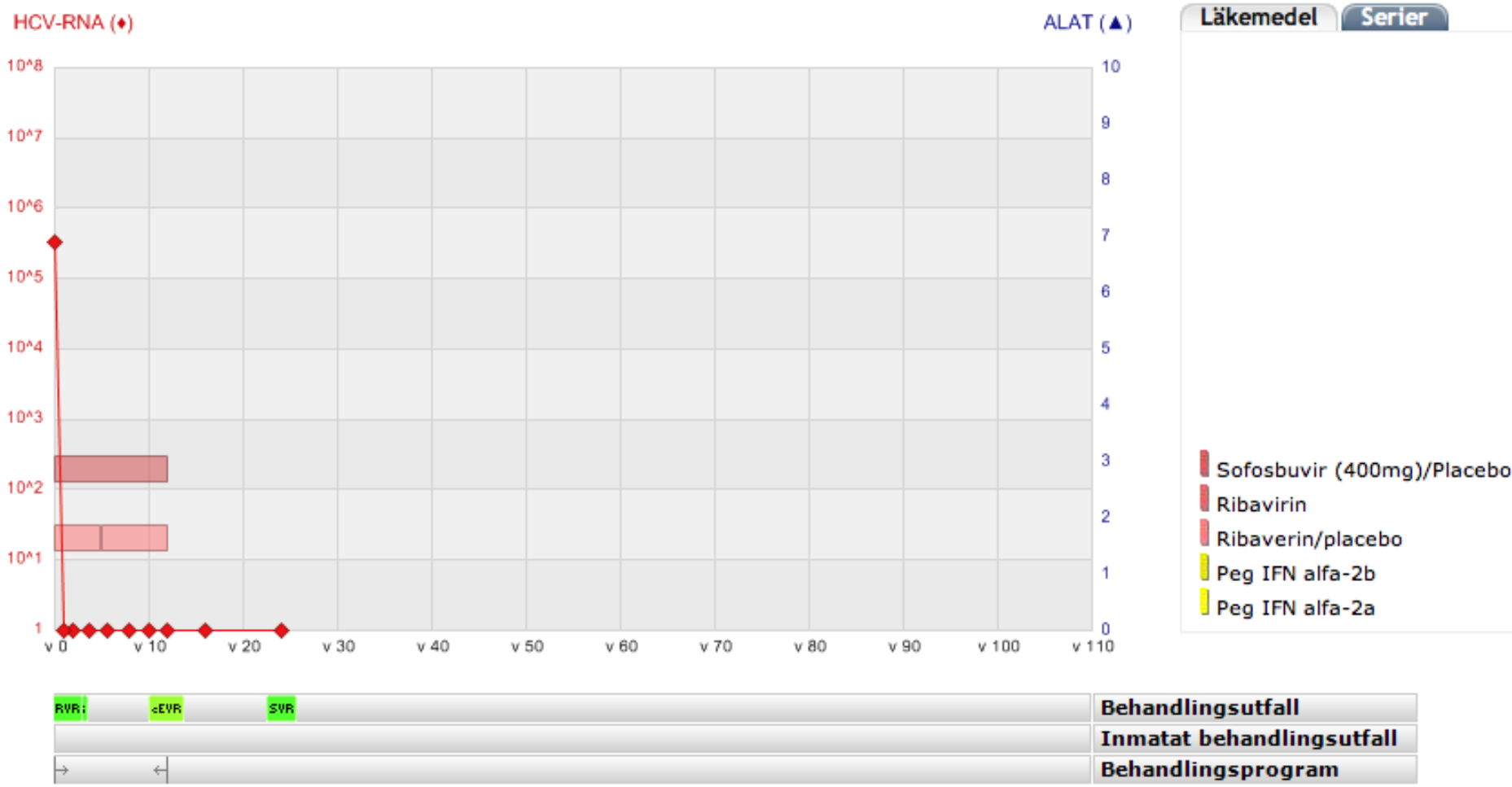
Male with gt 2b chronic HCV- treatment options

- **NUC (Sofosbuvir) + RBV**
- **NUC (Sofosbuvir) + NS5A inh (Daclatasvir)**
- **NUC (Sofosbuvir) + PI (Simeprevir)**

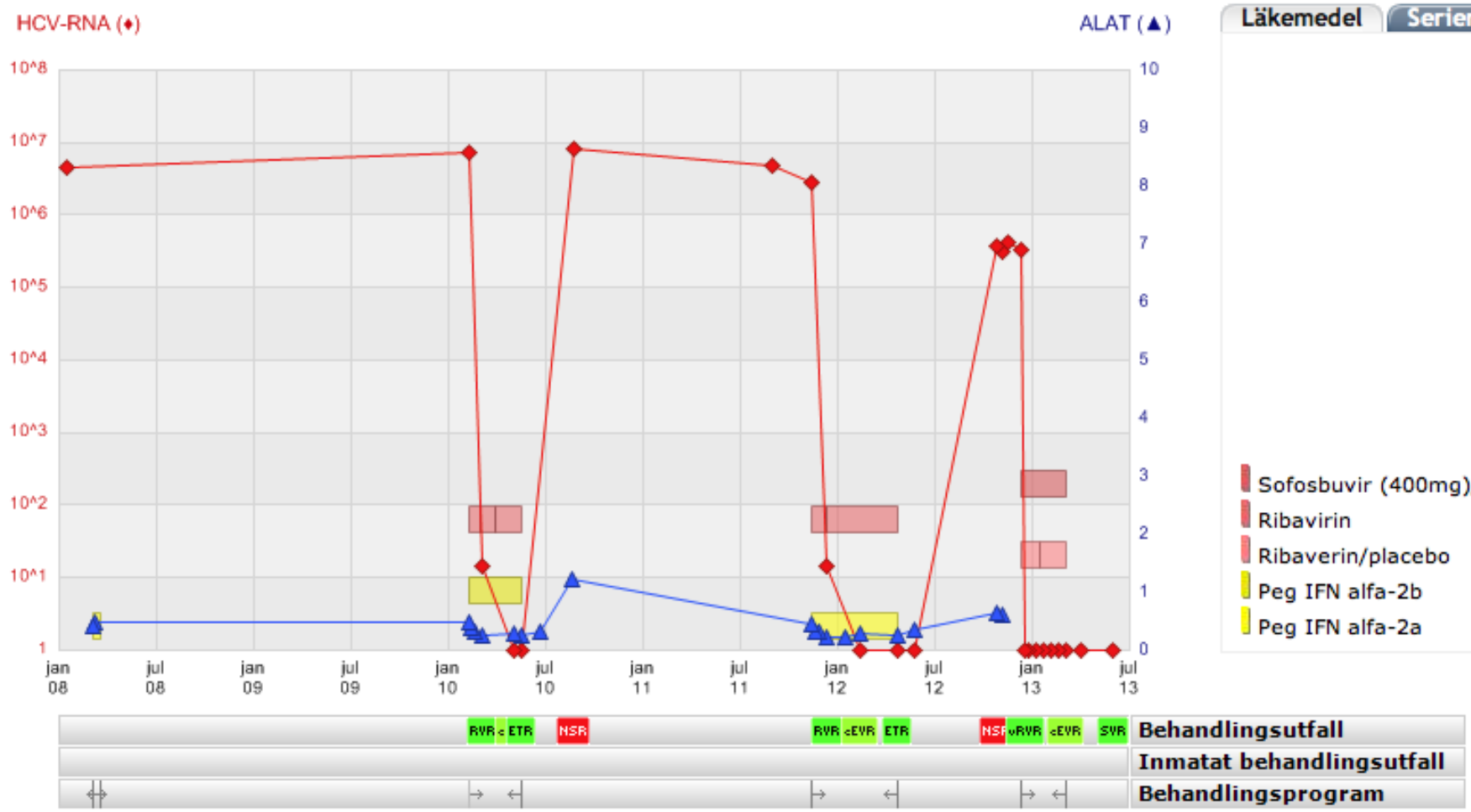
Male with gt 2b chronic HCV

- **Treatment given with Sofosbuvir + ribavirin**
- **12 weeks duration**
- **No adverse events during treatment**

Male with gt 2b chronic HCV



Man med gt 2b kronisk HCV



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Factors which influence IFN free treatment

- IL28B CC versus non CC
- Genotype 1 subtype (b > a)
- Earlier rx response (relapse > NR)
- Compliance
- Antiviral activity
- Barrier against resistance

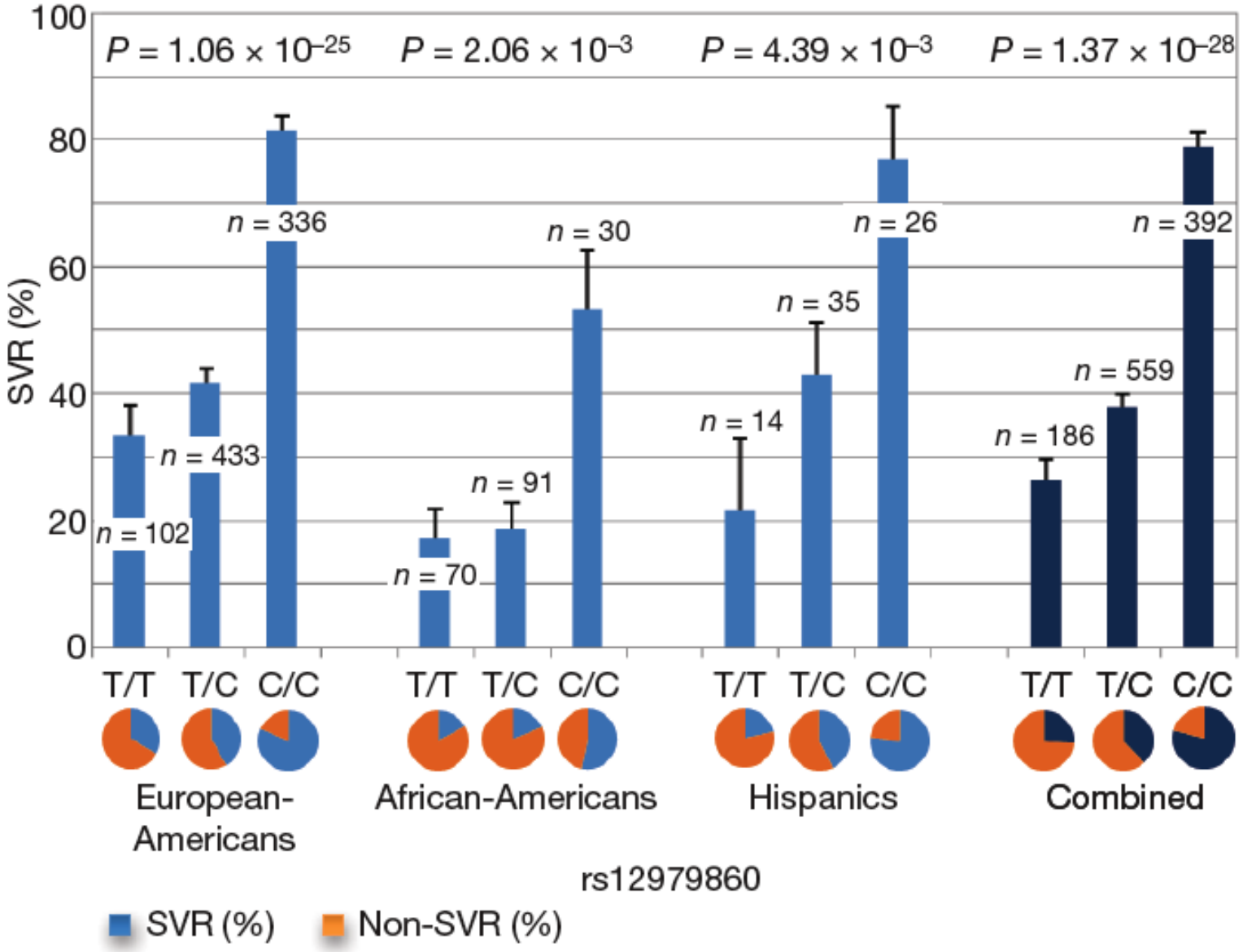

Figure 1 | Percentage of SVR by genotypes of rs12979860. Data are percentages + s.e.m.

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NNUCs -

- Low resistance barrier
- Mean - low antiviral potency

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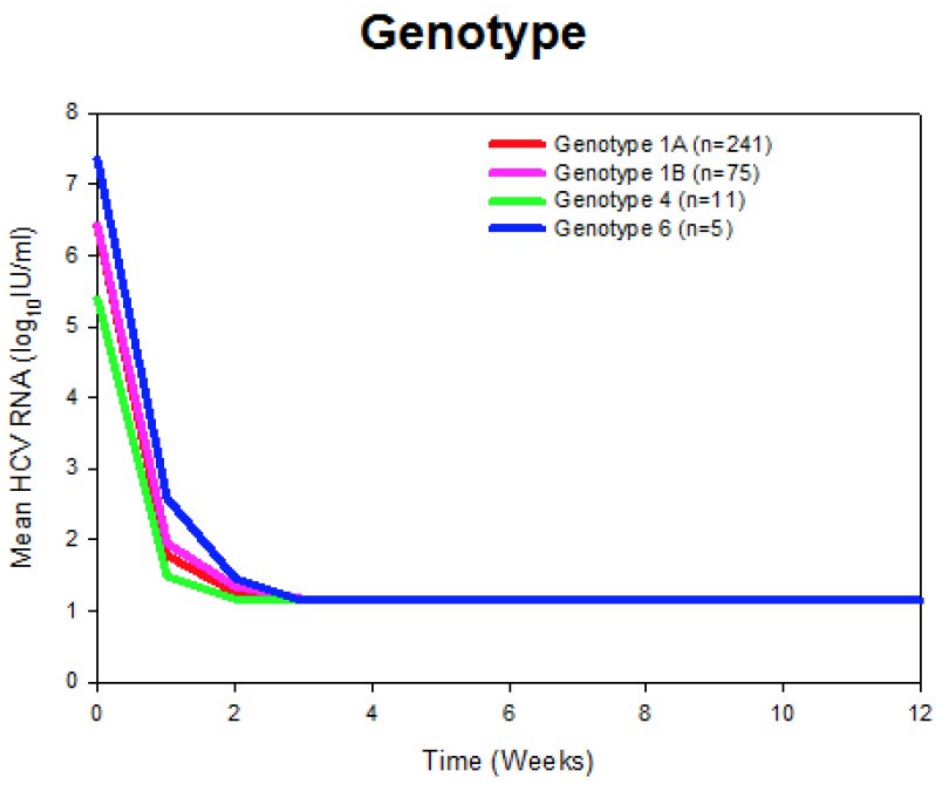
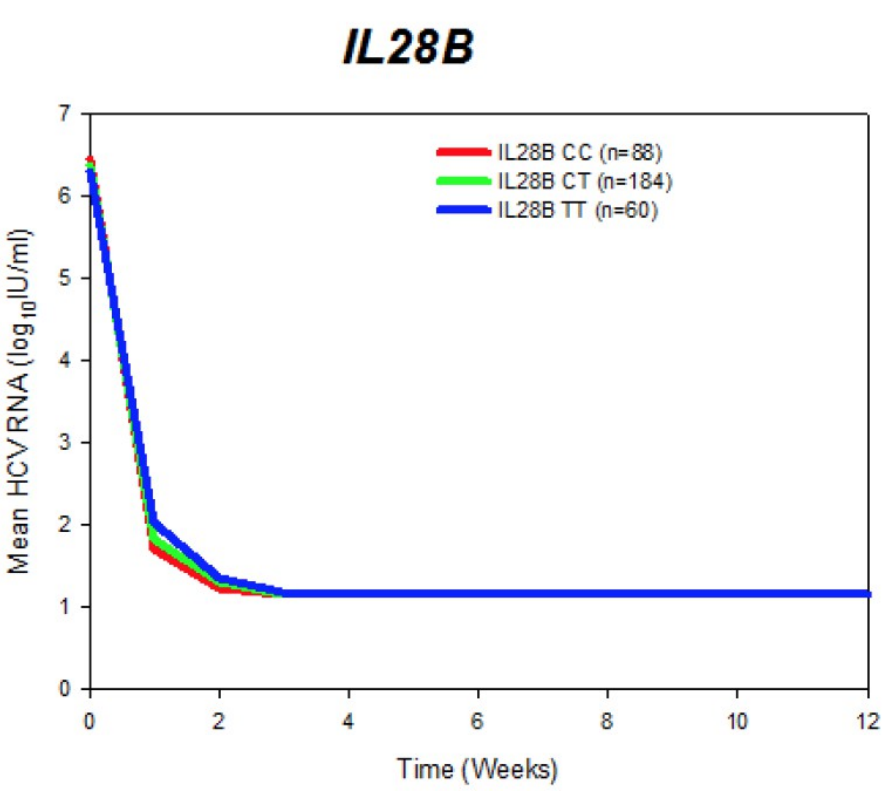
NUC - Sofosbuvir

- High resistance barrier
- High antiviral potency
- All genotypes covered

Sofosbuvir plus RBV (ATOMIC study): Viral kinetics by HCV genotype and IL28b





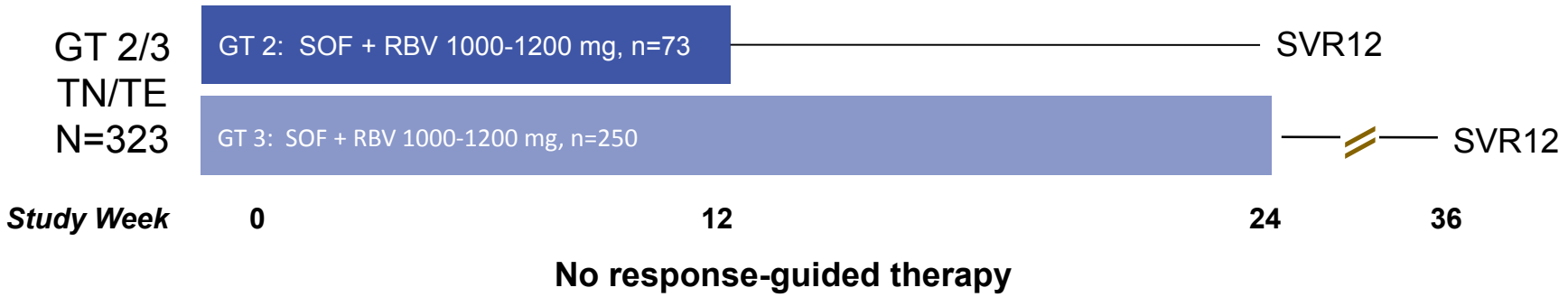
Similar viral dynamics regardless of genotype or *IL28B* status

Hassanein T, et al. AASLD 2012; Boston. #230.

SOF + RBV for 12 Weeks for HCV GT 2 and 24 Weeks for GT 3

Phase 3 VALENCE Trial Design

Phase 3, randomized, safety and efficacy study of all-oral sofosbuvir (SOF) + ribavirin (RBV) for 12 or 24 weeks in treatment-naïve (TN) or -experienced (TE) patients infected with HCV genotype (GT) 2 or 3



- Primary endpoint: sustained virologic response (SVR)12
- Expanded inclusion criteria
  - Targeted 20% enrollment of patients with cirrhosis
  - No upper limit to age or body mass index (BMI)
  - Opiate replacement therapy permitted
  - Platelets > 50,000/mm3

Zeuzem S, et al. AASLD 2013. Washington, DC. #1085

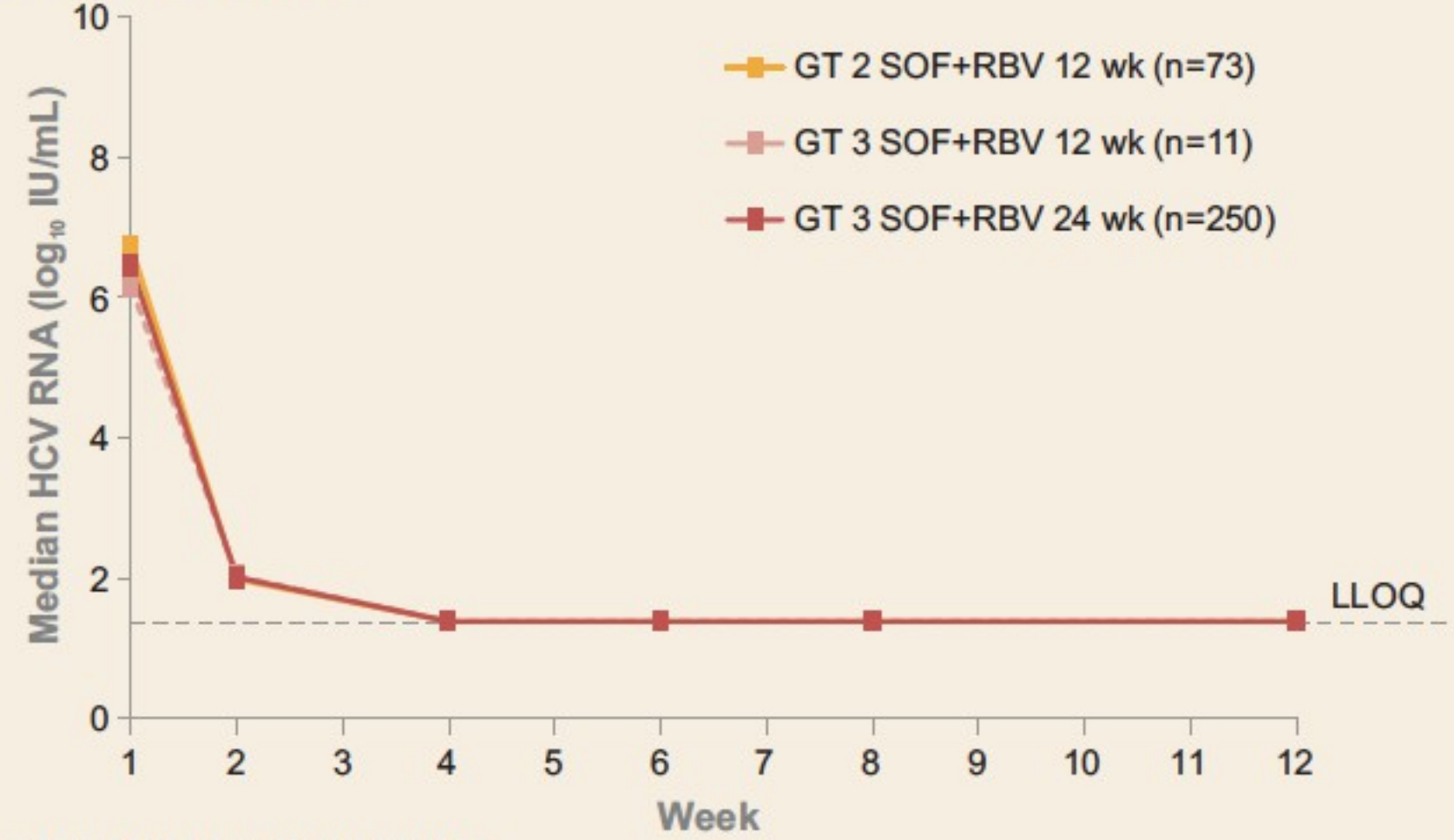
SOF + RBV for 12 Weeks for HCV GT 2 and 24 Weeks for GT 3

VALENCE Demographics

	GT 2	GT 3
	SOF + RBV 12 wk (n=73)	SOF + RBV 24 wk (n=250)
Mean age (range), y	58 (28–74)	48 (19–69)
Male, %	55	62
White, %	89	94
Mean BMI (range), kg/m2	26 (20–35)	25 (17–41)
IL28B CC, %	33	34
Mean baseline (BL) HCV RNA (range), log10 IU/mL	6.5	6.3
Cirrhosis, %	14	23
Treatment-experienced, %	56	58
Prior nonresponse, %	24	28
Prior relapse, %	68	65

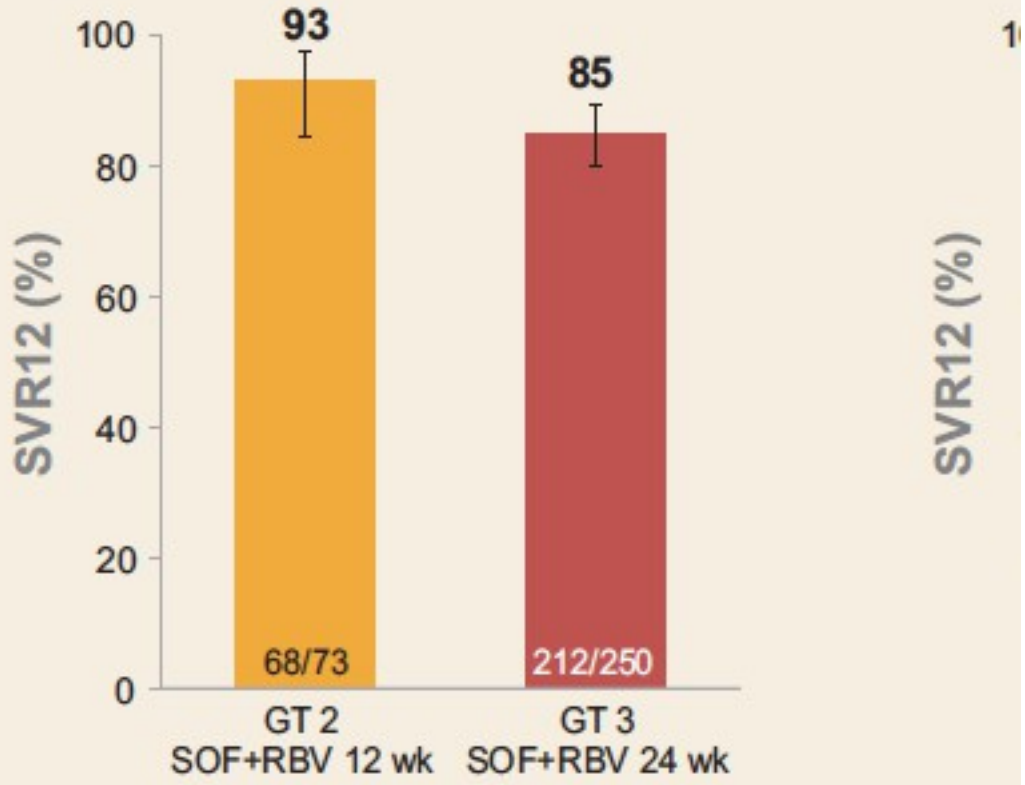
Zeuzem S, et al. AASLD 2013. Washington, DC. #1085

Viral Kinetics



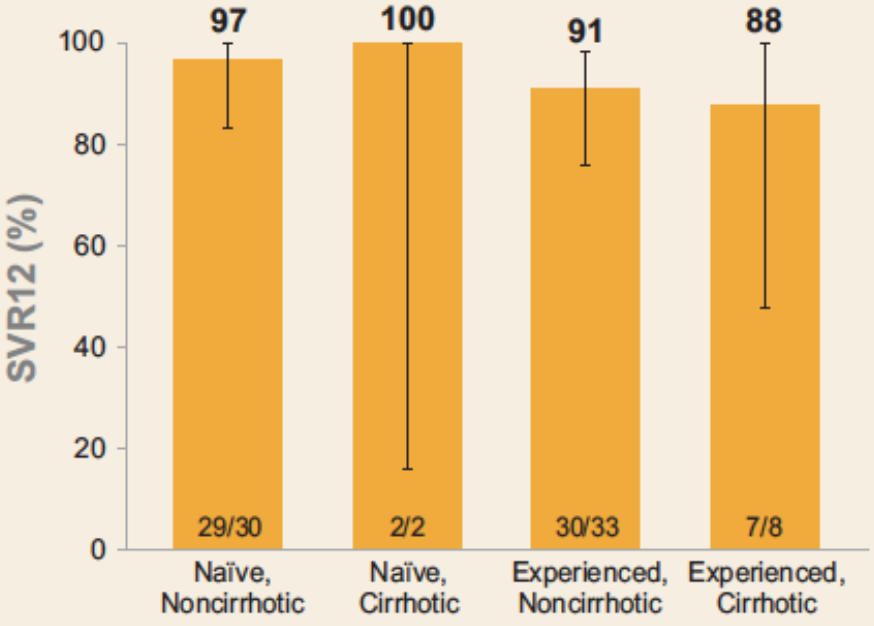
LLOQ, lower limit of quantification (25 IU/mL).

SVR12 in GT 2 and 3 Patients*



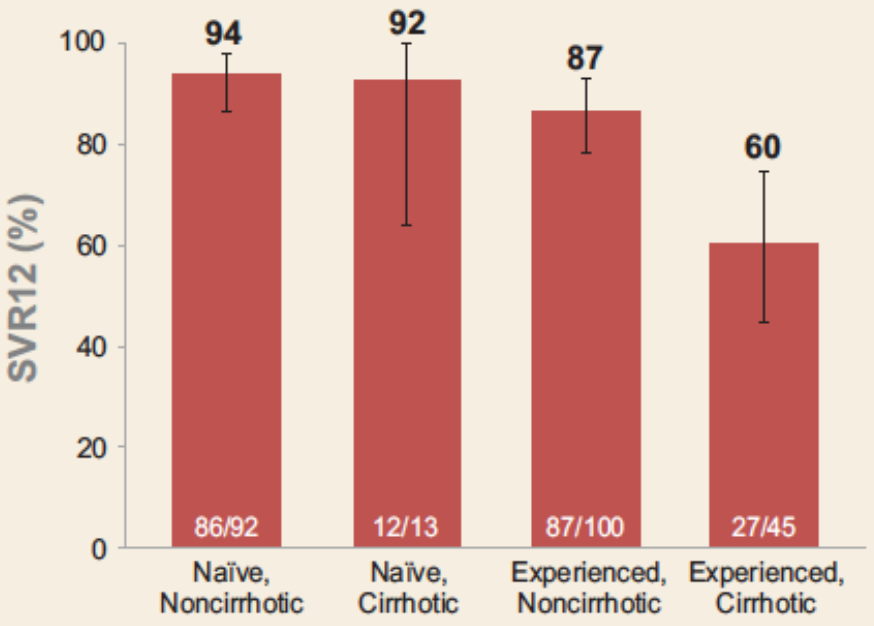
*3 of 11 patients (27%) with HCV GT 3 who received 12 weeks of SOF+RBV achieved S

SVR12 in GT 2 Patients Treated for 12 Weeks



hieved SVR12.

SVR12 in GT 3 Patients Treated for 24 Weeks



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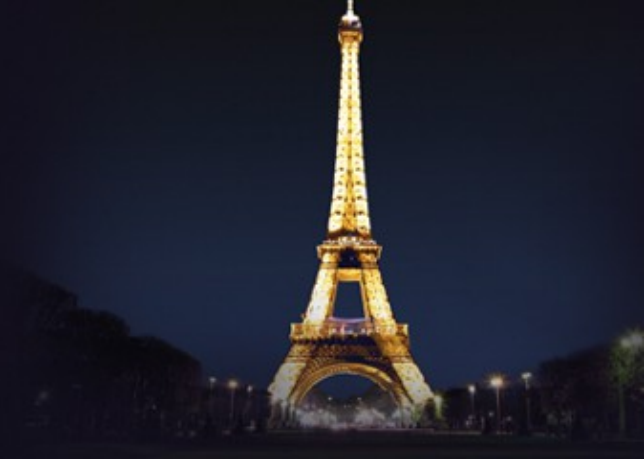
Conclusions Sofosbuvir + ribavirin for gt 2 and 3

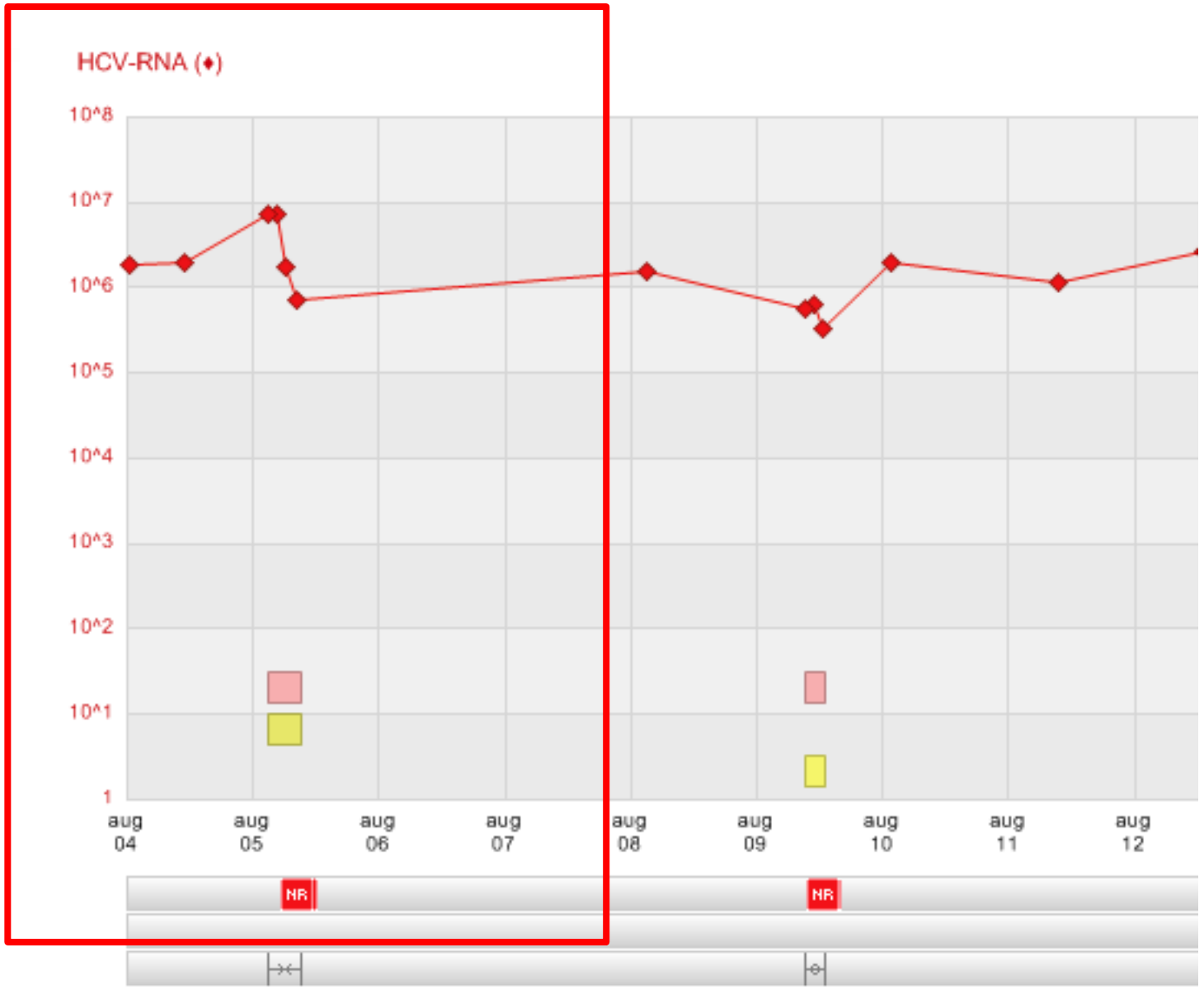
- For gt 2 12 weeks treatment
- For gt 3 24 weeks treatment needed
- Offers SVR in 90% of naive patients
- Less effective in experienced gt 3a with cirrhosis
- Safety as with ribavirin



Case no 2 female with genotype 1a

Female born 1952 (GN)

- Treatment with peg-IFN + RBV in the success study offered
- Nonresponse with HCV RNA drop from 9 M IU/mL at baseline to 1,7 M week 12
- Depression with loss of energy, tiredness, sleeping problems
- Hemoglobin drop 30 G/L
- Dry skin


HCV-RNA (♦)
10^8
10^7
10^6
10^5
10^4
10^3
10^2
10^1
1
aug 04
aug 05
aug 06
aug 07
aug 08
aug 09
aug 10
aug 11
aug 12
NR
NR

Female born 1952 (GN)

- Treatment stopped week 12
- New treatment with natural IFN (Multiferon) + RBV 2009
- Now Fibrosis stage IV / cirrhosis compensated
- Nonresponse again
- Many AE:s

Female born 1952 (GN)

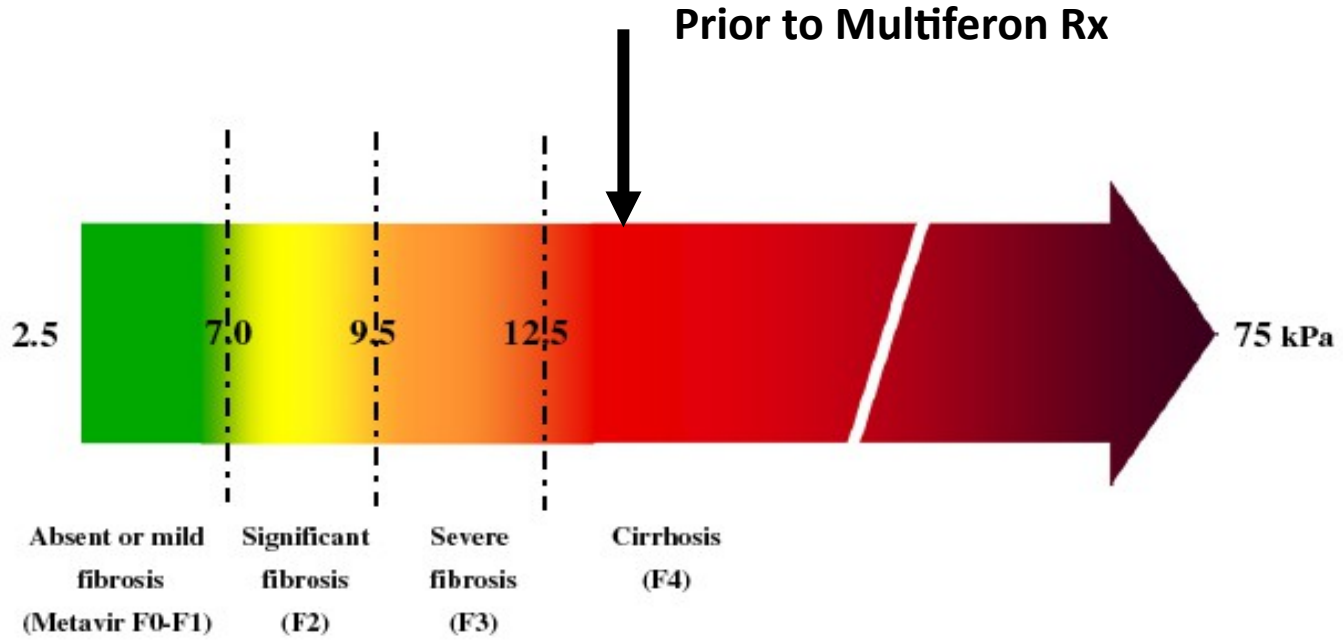
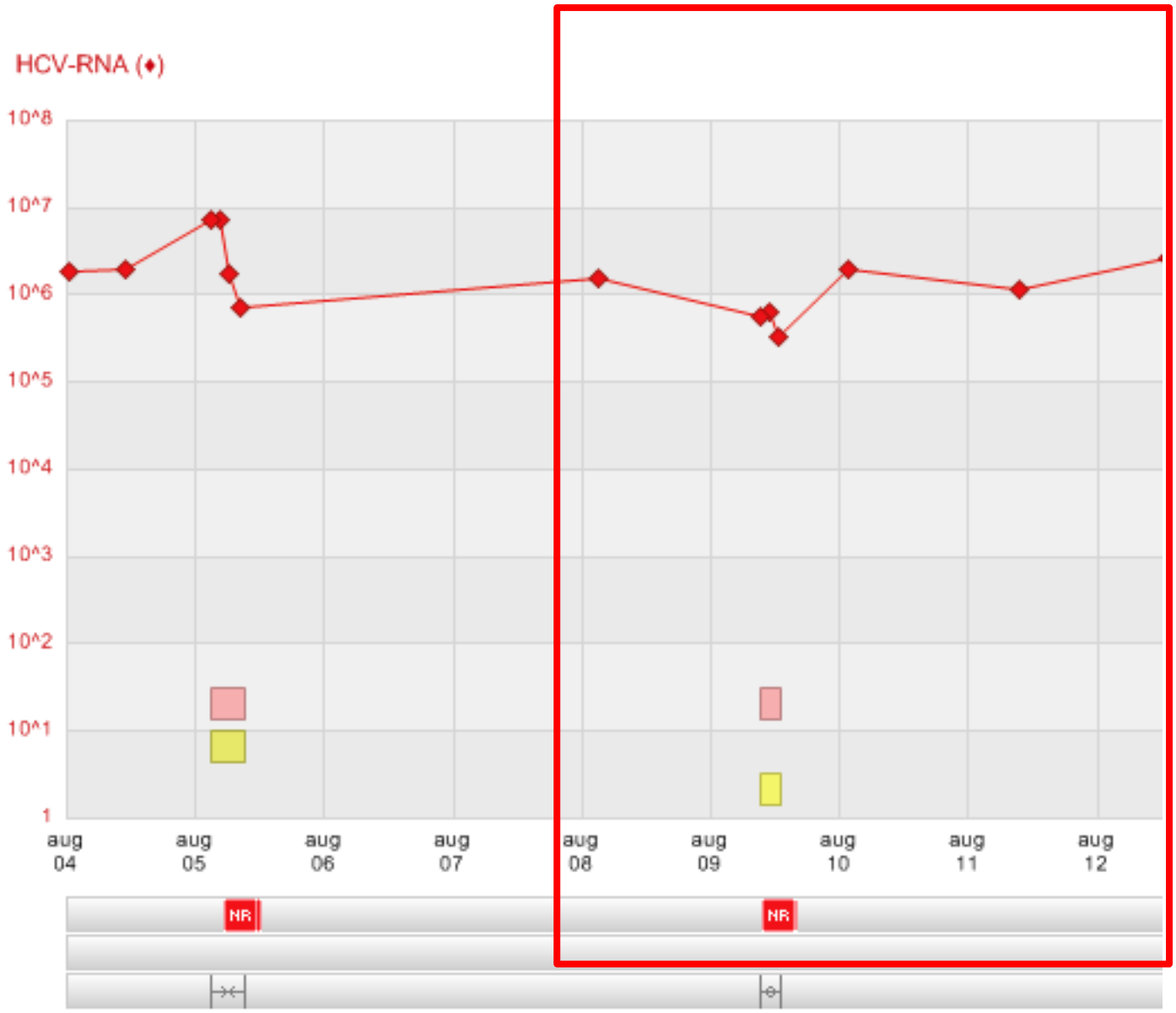


Fig. 6. Clinical significance of liver stiffness cut-offs in chronic liver diseases. When liver stiffness values range between 2.5 and 7 kPa, mild or absent fibrosis is likely, whereas when liver stiffness values are above 12.5 kPa, cirrhosis is likely.

Castera et al J Hepatol 2008;48:835-47


HCV-RNA (♦)
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NR
NR

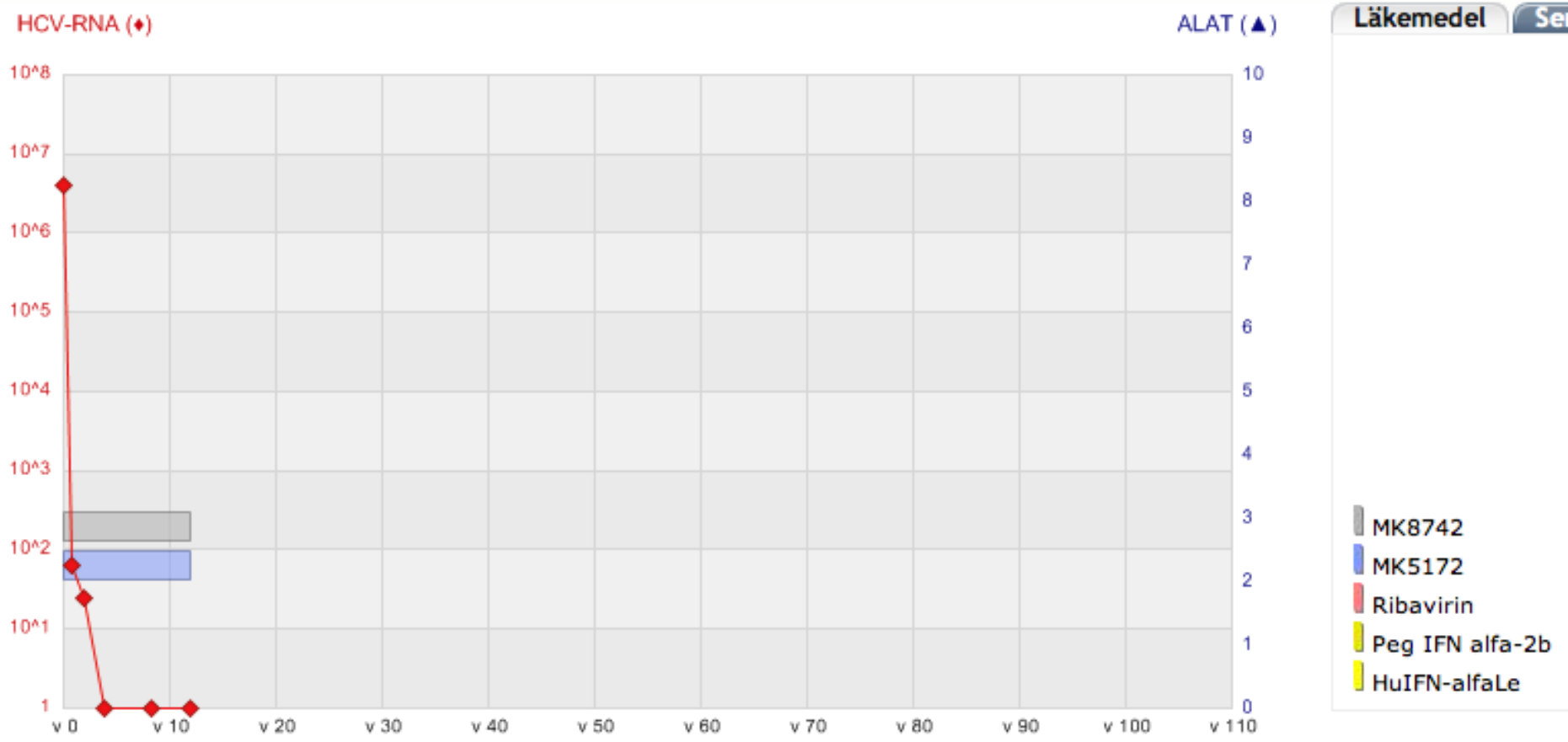
Female born 1952 (GN)

- NR to peg-IFN + RBV
- IFN intolerant which provokes depression
- GT 1a, IL28B snp TT
- Advanced fibrosis/ cirrhosis

- What to do?

Female born 1952 (GN) what treatment can be given

- NUC (Sofosbuvir) + RBV
- NUC (Sofosbuvir) + NS5A inh (Daclatasvir)
- NUC (Sofosbuvir) + PI (Simeprevir)
- PI 2nd gen (Asunaprevir) + NS5A inh (Daclatasvir)
- PI/r + NS5A inh + NNUC +/- RBV (AbbVie)
- PI 3rd gen (MK5172) + NS5A inh (MK8742)


HCV-RNA (♦)
ALAT (▲)
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10^5
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10^1
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9
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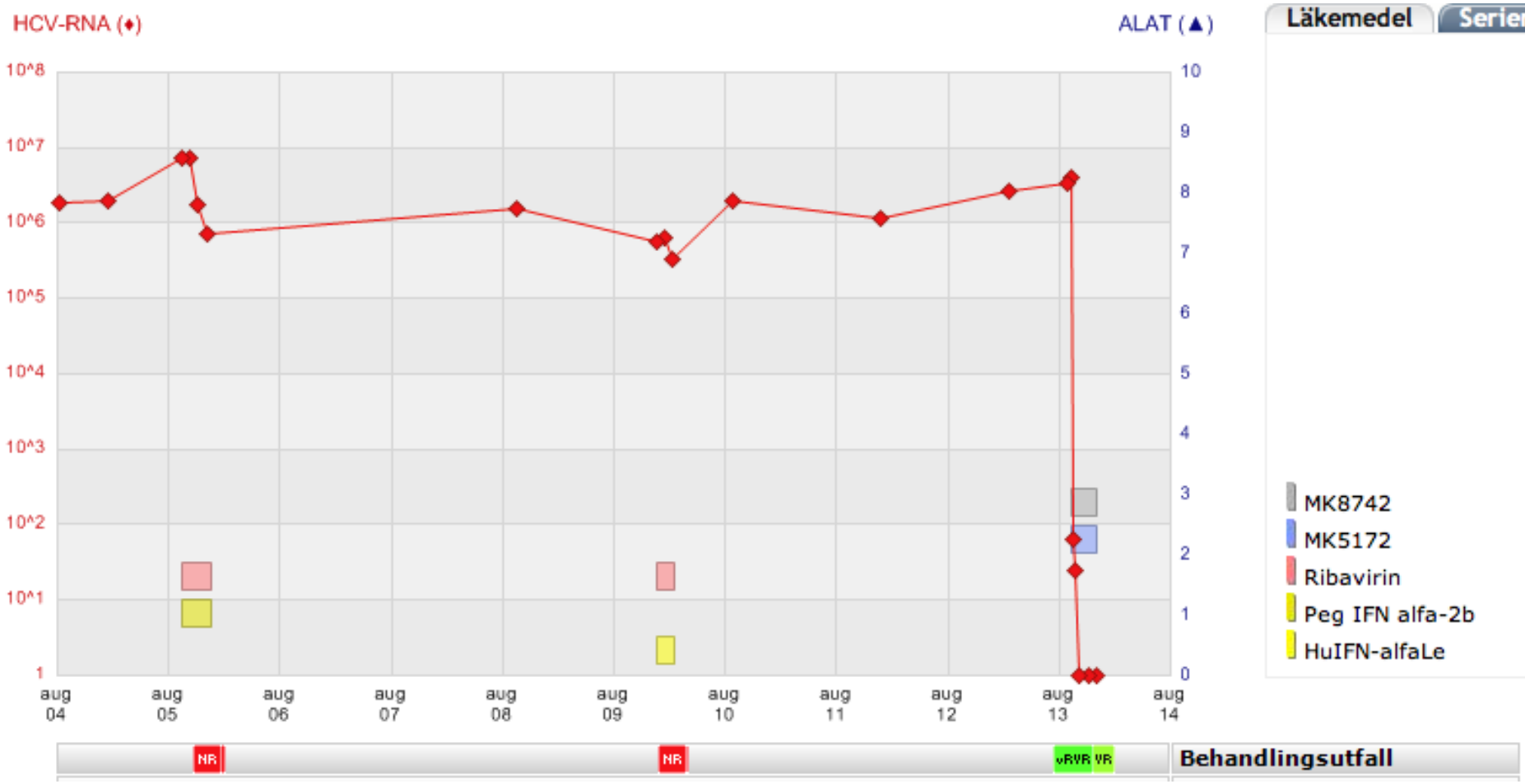
v 0
v 10
v 20
v 30
v 40
v 50
v 60
v 70
v 80
v 90
v 100
v 110
Läkemedel
Se
MK8742
MK5172
Ribavirin
Peg IFN alfa-2b
HuIFN-alfaLe


HCV-RNA (♦)
ALAT (▲)
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MK8742
MK5172
Ribavirin
Peg IFN alfa-2b
HuIFN-alfaLe
NR
NR
vRVR
VR
Behandlingsutfall

Female born 1952 (GN)

- Treatment was given with
- PI 3rd gen (MK5172) + NS5A inh (MK8742) 12 weeks
- Rapid response HCV RNA neg before Rx week 4
- Few AE:s
- ETR after 12 weeks
- SVR 1 week post Rx so far

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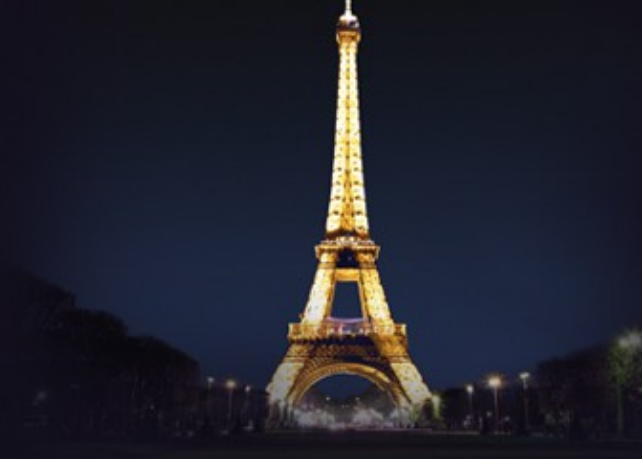


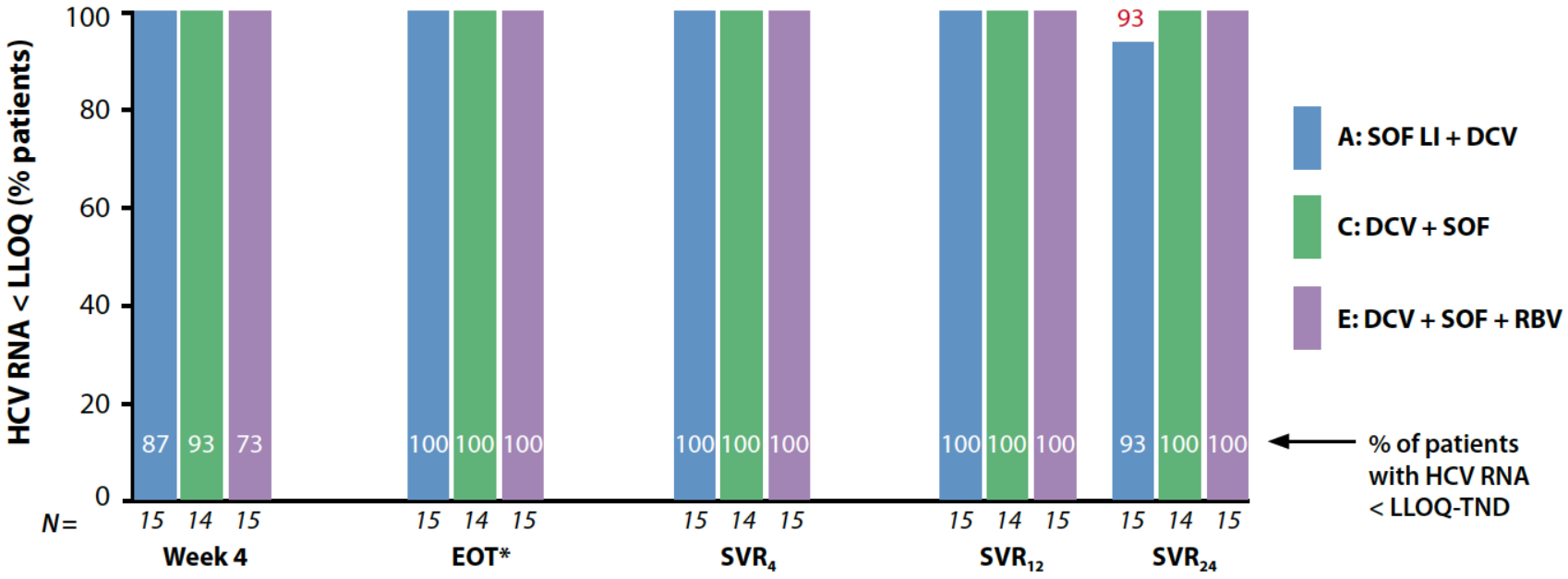
Case no 3 female with genotype 4a

Combination of 2 DAAs with 1 with high resistance barrier

- NUC (Sofosbuvir)
- +
- NS5A inh (Daclatasvir)
- Or +
- PI (Simeprevir)
- +/- RBV

Sofosbuvir + Daclatasvir +/- RBV LB

Figure 2. Virologic response during an after treatment with Sofosbuvir (SOF) with and without lead in (LI) + Daclatasvir (DCV) 12 or 24 weeks in Group E and H with ribavirin added.



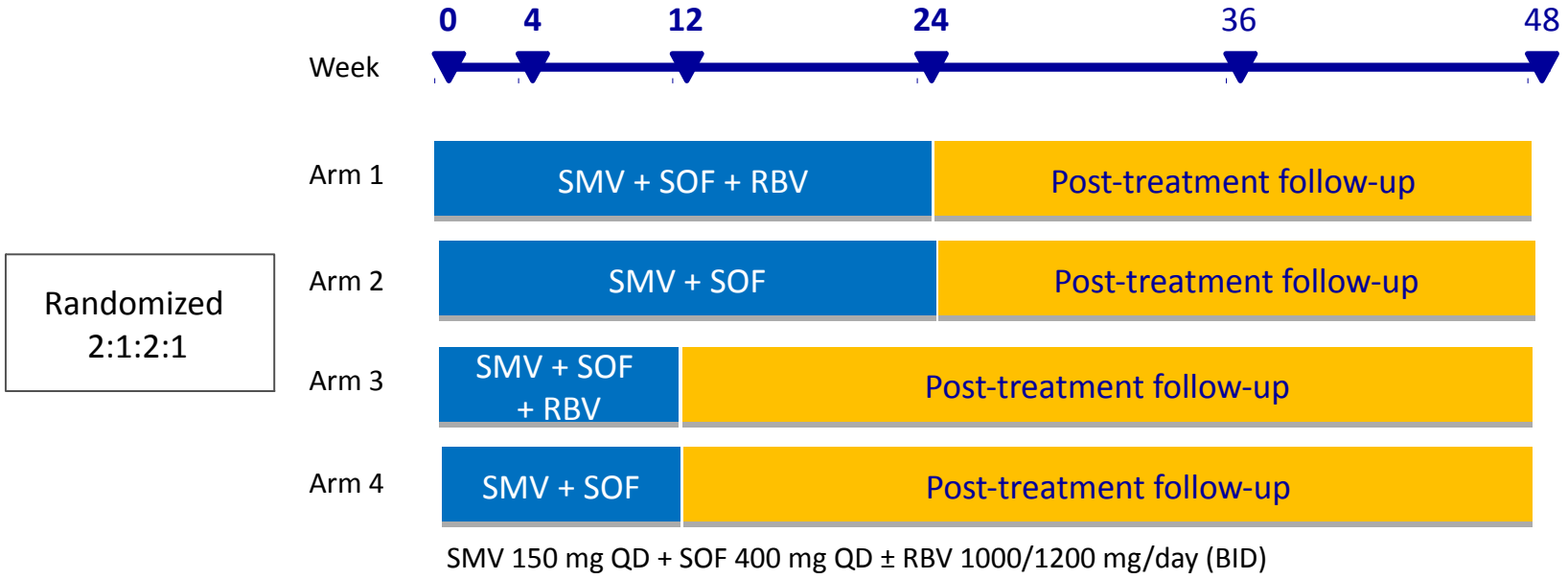
- **Group A**: 1 patient with history of IDU became viremic at PT Week 24: posttreatment viral sequence clearly different from pretreatment virus, consistent with reinfection.

* End-of-treatment (EOT) includes patients who discontinued early, with last visit considered EOT.

Sulkowsky LB2 AASLD Boston 2012

COSMOS: Study design

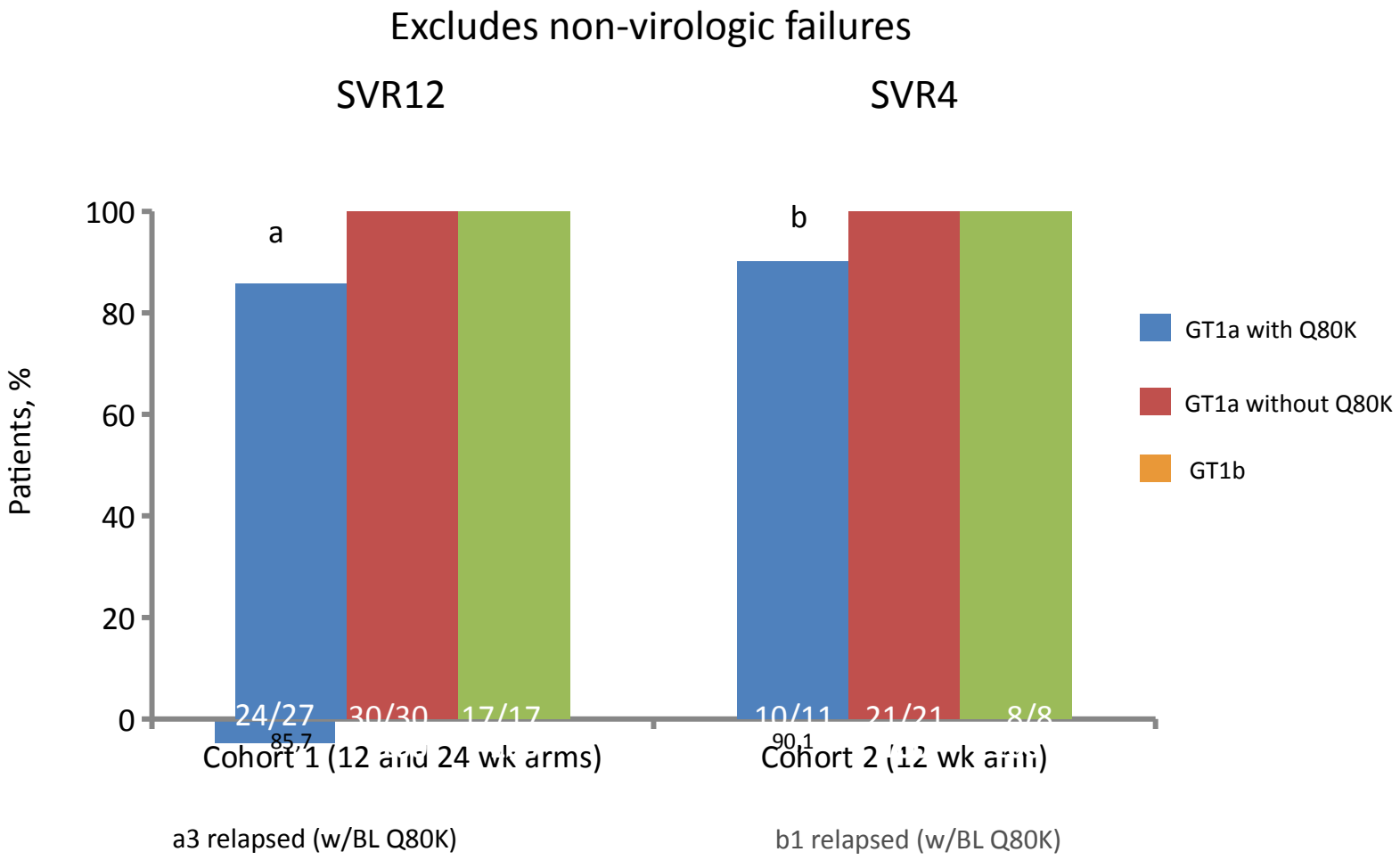
- Cohort 1: Prior null responders (METAVIR F0-F2)
- Cohort 2: Treatment-naïve and prior null responders (METAVIR F3-F4)



- Stratification: Cohort 1: HCV geno/subtype and *IL28B*
  Cohort 2: HCV geno/subtype and population (naïve/null)
- Planned interim analysis: Cohort 1: Final SVR12 for all arms
  Cohort 2: Interim SVR4 for 12 week arms

BID, twice daily; HCV, Hepatitis C virus; QD, once daily; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained virologic response; SVR4, sustained virologic response 4 weeks after planned treatment end; SVR12, sustained virologic response 12 weeks after planned treatment end

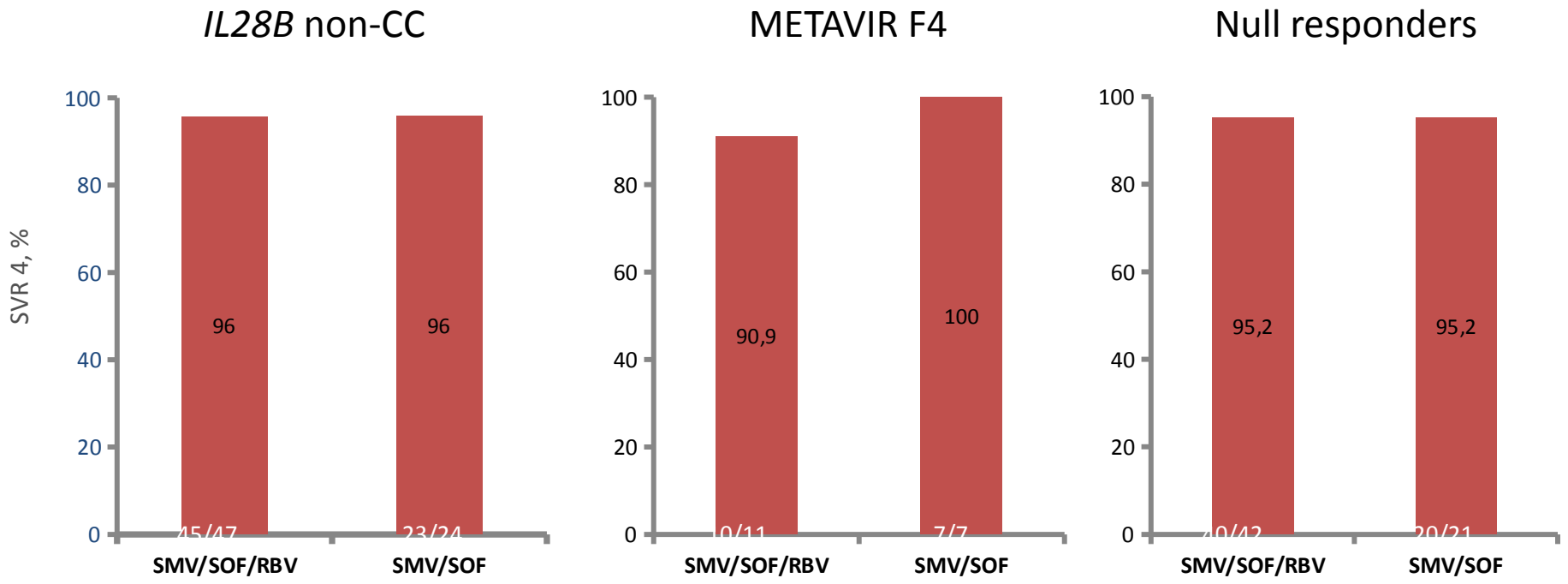
SVR rates according to HCV subtype: Cohorts 1 and 2



BL, baseline; GT, genotype; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR4, sustained virologic response 4 weeks after end of treatment; SVR12, sustained virologic response 12 weeks after end of treatment

SVR4 (Cohort 1 and Cohort 2)
12-week treatment arms: Impact of RBV

Excludes non-virologic failures



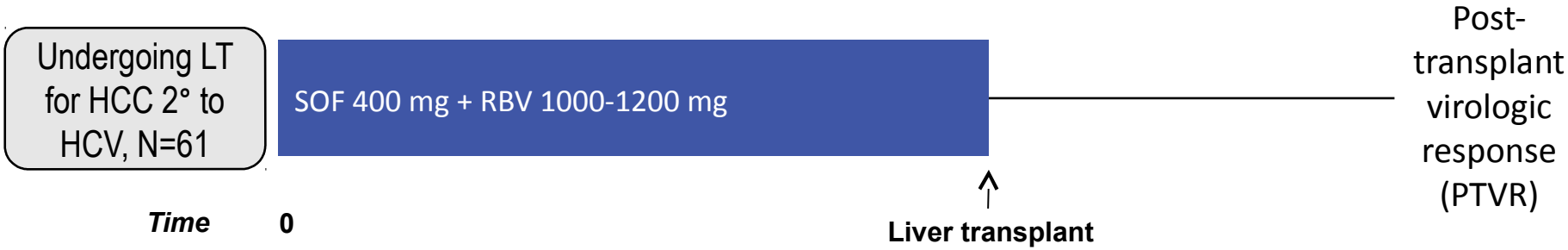
- There were 9 naïve and 9 null responder METAVIR F4 patients

RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir

Pre-Transplant SOF + RBV to Prevent HCV Recurrence Post-Transplant

Phase 2 Pre-Liver Transplant Pilot Study

Phase 2, open-label study of SOF + RBV for up to 48 weeks in patients with HCV listed for liver transplant for hepatocellular carcinoma (HCC)



- Recurrence of HCV is universal and there is no standard of care prior to liver transplantation
- Objective: prevention of HCV recurrence following orthotopic liver transplant (OLT)
  - PTVR at Week 12
- Study criteria
  - Meeting MILAN criteria undergoing LT for HCC 2º to HCV
    - Model for End-Stage Liver Disease (MELD) < 22 and HCC-weighted MELD ≥ 22
  - Child-Pugh-Turcotte score ≤ 7

Curry MP, et al. AASLD 2013. Washington, DC. Oral #213

Pre-Transplant SOF + RBV to Prevent HCV Recurrence Post-Transplant

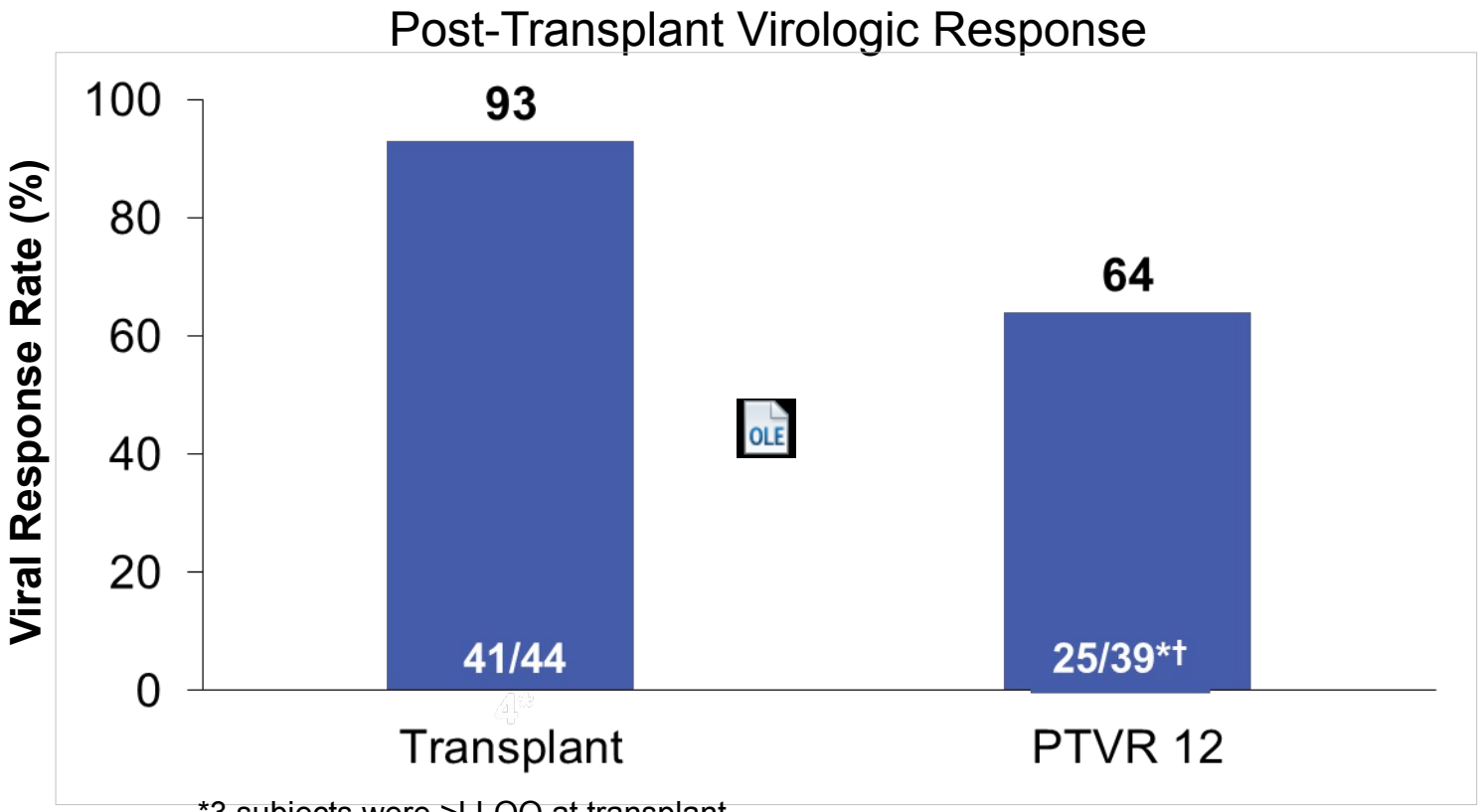
Patient Demographics

	SOF + RBV (n=61)
Male, n (%)	49 (80)
Median age, y (range)	59 (46–73)
White, n (%)	55 (90)
BMI < 30 kg/m2, n (%)	43 (70)
HCV RNA > 6 log10 IU/mL, n (%)	41 (67)
Genotype, n (%) 1a 1b 2 3a 4	 24 (39) 21 (34) 8 (13) 7 (12) 1 (2)
Non-CC allele, n (%)	47/60 (78)
CTP score, n (%) 5 6 7 8	 26 (43) 18 (30) 14 (23) 3 (5)
Median MELD score, (range)	8 (6–14)
Prior HCV treatment, n (%)	46 (75)

Curry MP, et al. AASLD 2013. Washington, DC. Oral #213

Pre-Transplant SOF + RBV to Prevent HCV Recurrence Post-Transplant

Virologic Response



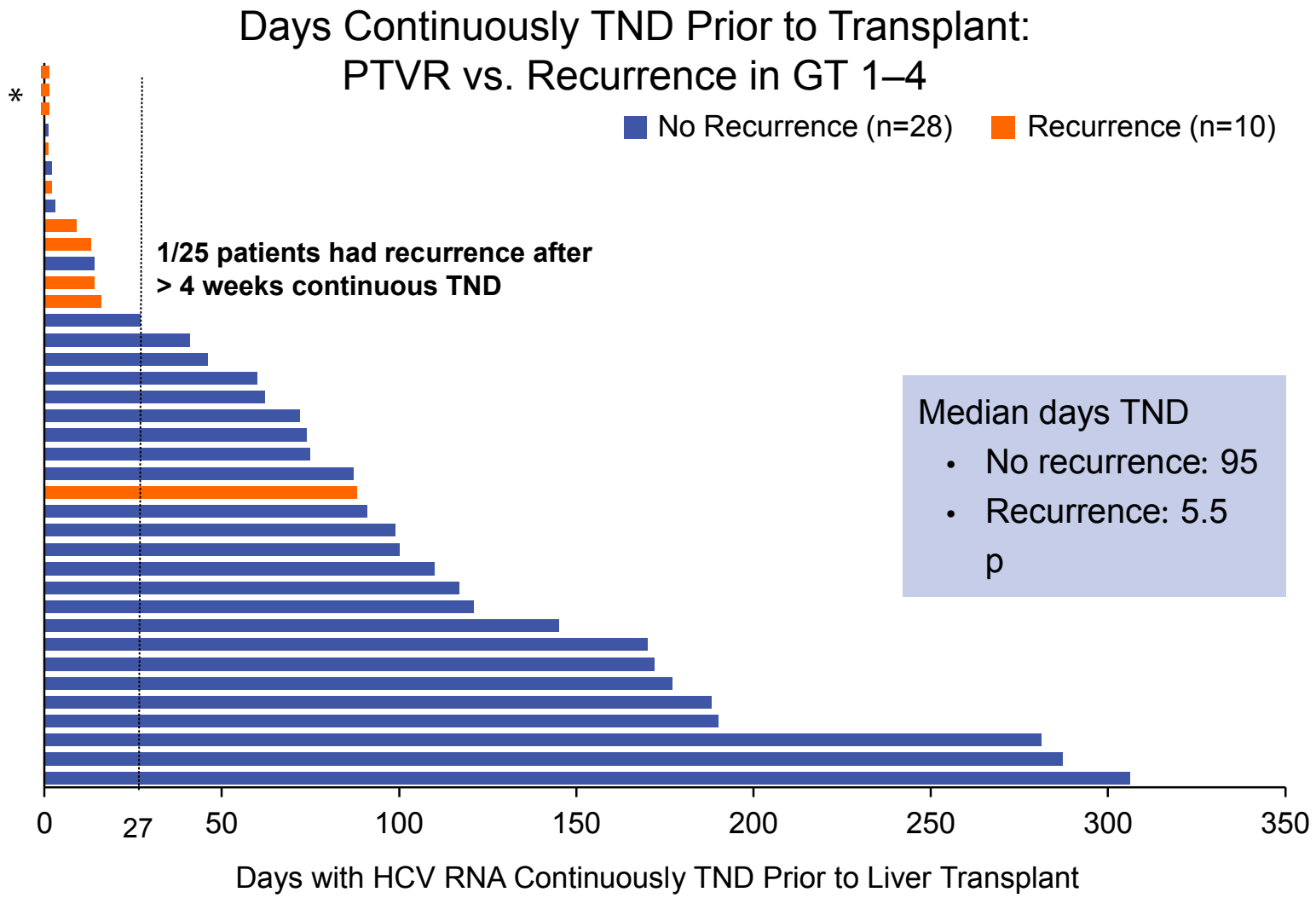
*3 subjects were >LLOQ at transplant.
†1 subject has not reached pTVR12, 1 subject LTFU at Week 8 post transplant.

SOF + RBV was effective and well-tolerated in patients with well compensated cirrhosis, and prevented post-transplant HCV recurrence in 64% of patients who had HCV RNA < 25 IU/mL prior to transplant

Curry MP, et al. AASLD 2013. Washington, DC. Oral #213

Pre-Transplant SOF + RBV to Prevent HCV Recurrence Post-Transplant

No Recurrence vs. Recurrence in GT 1–4



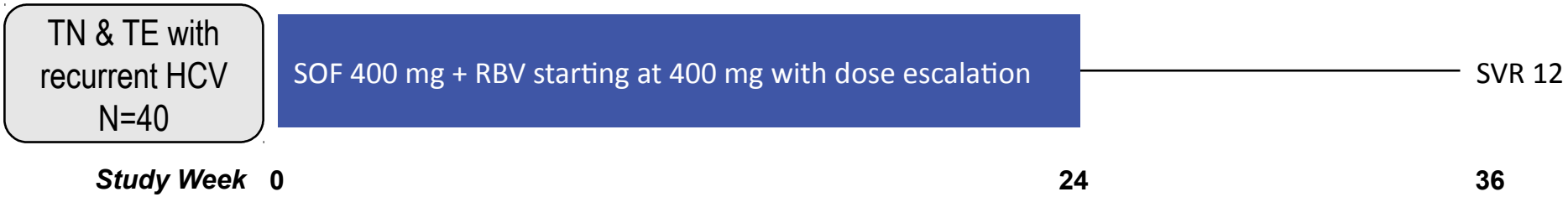
*3 patients with recurrent HCV had 0 consecutive days TND before transplant.

Curry MP, et al. AASLD 2013. Washington, DC. Oral #213

SOF + RBV for Established Recurrent HCV Post-Liver Transplant

Phase 2 Post-Liver Transplant Study

Prospective, multicenter, open-label, IFN-free pilot study of SOF + RBV for up to 24 weeks in naïve and treatment-experienced patients with recurrent HCV infection



- Recurrence of HCV in the transplanted liver is universal in patients who are serum HCV RNA-positive at the time of transplantation
- Primary endpoint: SVR12 in patients with recurrent HCV post-LT
- Study inclusion criteria
  - Liver transplant ≥ 6 months and ≤ 150 months
  - CPT ≤ 7 and MELD ≤ 17
  - (Exclusion prednisone > 5 mg/day)

Charlton MR, et al. AASLD 2013. Washington, DC. Oral #LB-2

SOF + RBV for Established Recurrent HCV Post-Liver Transplant

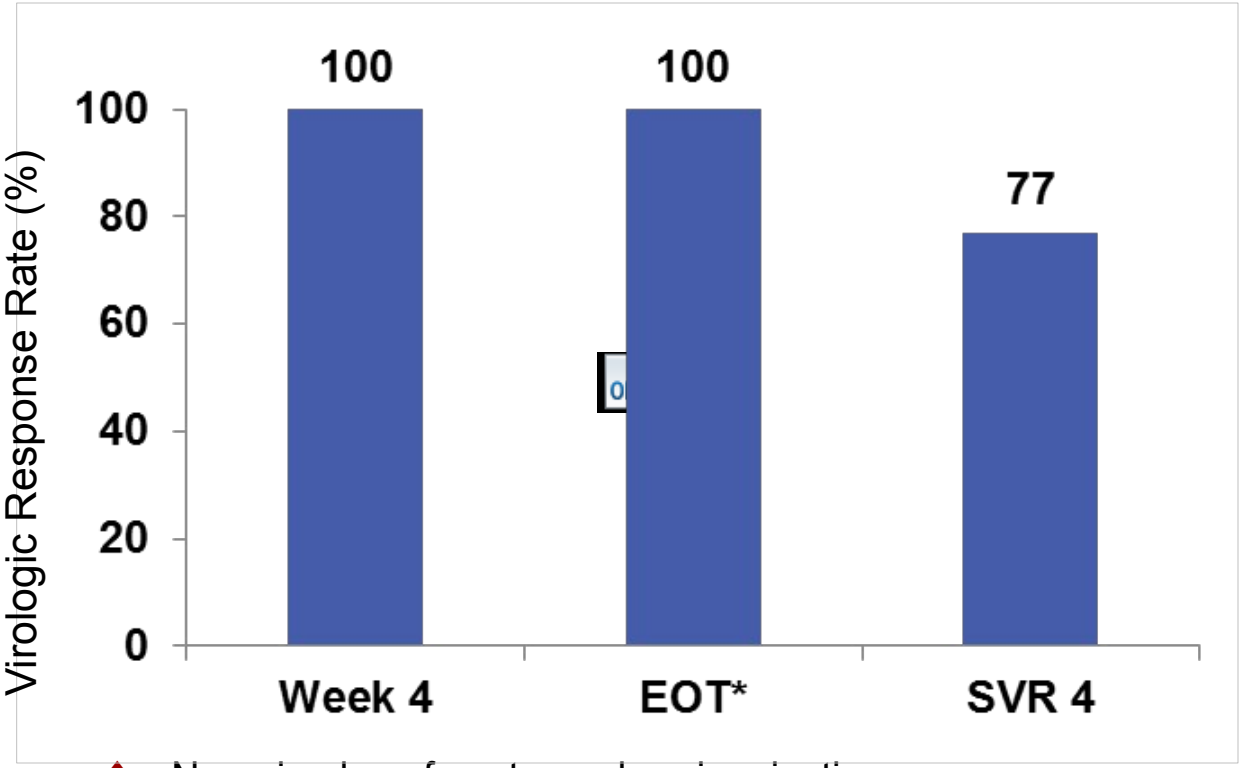
Baseline Characteristics

	SOF + RBV (N=40)
Male, n (%)	31 (78)
Median age, y (range)	59 (49-75)
White, n (%)	34 (85)
BMI <30 kg/m2, n (%)	30 (75)
Mean HCV RNA $\log_{10}$ IU/mL (range)	6.55 (4.49-7.59)
Genotype, n (%) 1a 1b 2 3 4	 22 (55) 11(28) 0 6 (15) 1 (3)
IL28B, n (%) CC CT TT	 13 (33) 16 (40) 11 (28)
Metavir-equivalent fibrosis stage, n (%) None or minimal (F0) Portal Fibrosis (F1-F2) Bridging Fibrosis (F3) Cirrhosis (F4)	 1 (3) 14 (35) 9 (23) 16 (40)
Prior HCV Treatment, n (%)	35 (88)
Median years since liver transplantation (range)	4.3 (1.02-10.6)

Charlton MR, et al. AASLD 2013. Washington, DC. Oral #LB-2

SOF + RBV for Established Recurrent HCV Post-Liver Transplant

Virologic Response Interim Results



*1 patient still on treatment,
†4 patients have not reached SVR4 visit.

- No episodes of acute or chronic rejection
- No interactions between immunosuppressants and SOF
  - 4 patients increased tacrolimus dosing due to improved liver function

Administration of an all-oral regimen of SOF + RBV after liver transplantation in patients with HCV recurrence is effective and well-tolerated

EOT, end of treatment

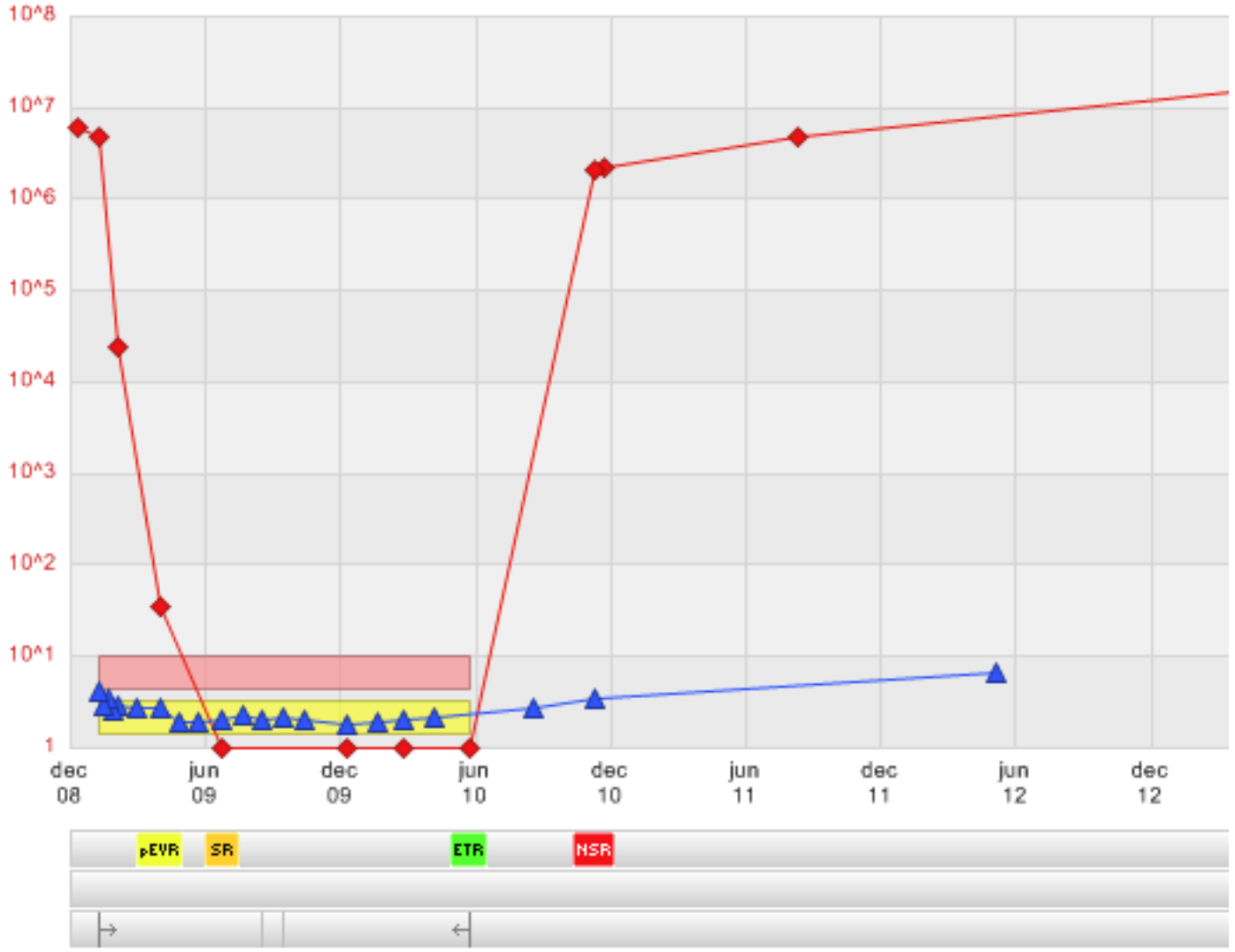
Charlton MR, et al. AASLD 2013. Washington, DC. Oral #LB-2

Extra case female with genotype 1b

Female with gt 1b chronic HCV

- Relapse after 72 weeks treatment with peg-IFN + RBV
- Many side effects during this treatment
- IL28B TT
- Fibrosis stage 3

Female with gt 1b chronic HCV



Female with gt 1b chronic HCV- Treatment options

- Peg-IFN + RBV + NUC (Sofosbuvir)
- Peg-IFN + RBV + PI (Simeprevir)
- PI + NS5A inh (Asunaprevir + Daclatasvir)
- NUC + PI (Sofosbuvir + Simeprevir)
- NUC + NS5A inh (Sofosbuvir + Daclatasvir)
- PI/r + NS5A inh+ NNUC +/- RBV (AbbVie)

Combination of 3 DAAs with weak resistance barrier ABT PI/r+ ABT NS5A inh + ABT NNUC +/-Ribavirin

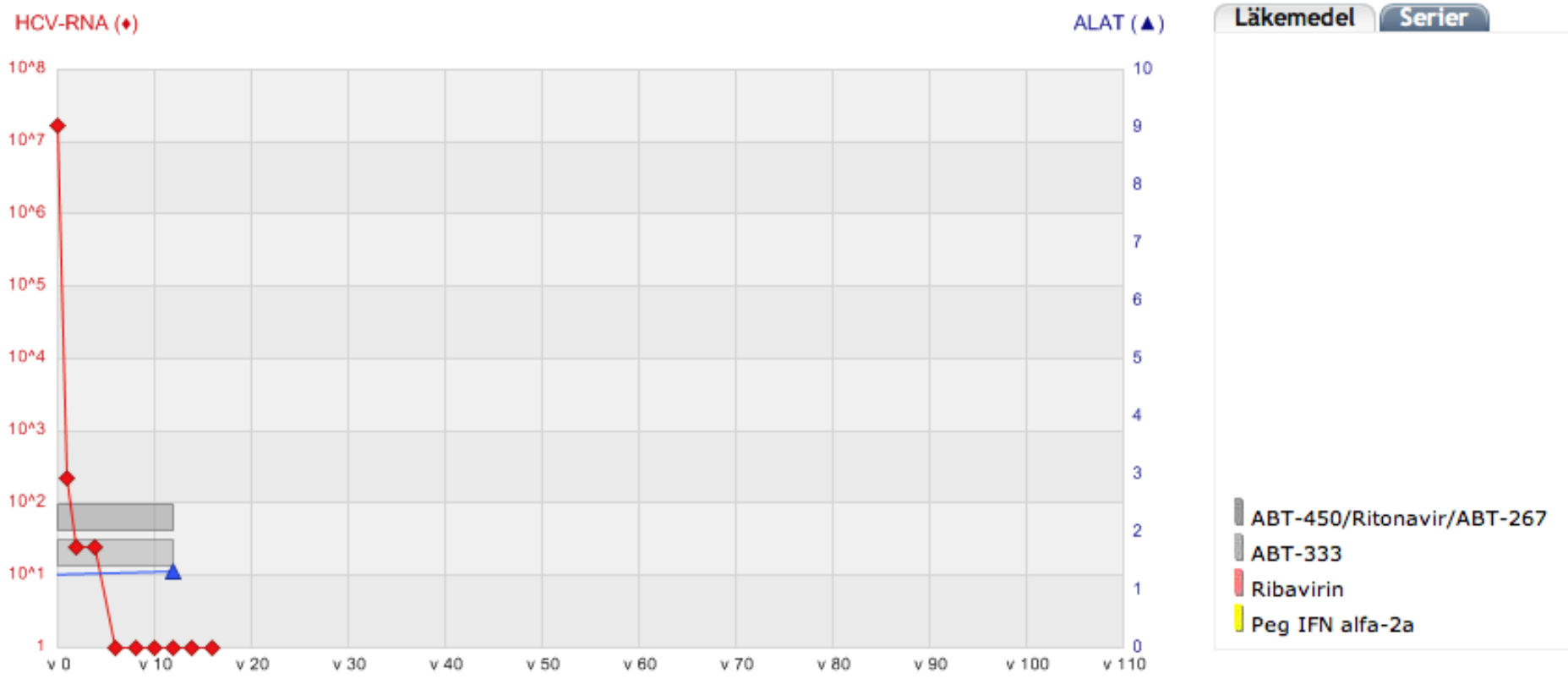
- Protease inh with ritonavir
- NS5A inh
- NNUC
- +/- RBV

Female with gt 1b chronic HCV

- **ABT PI/r + ABT NS5A inh + ABT NNUC 12 weeks treatment**

- **No AE:S during treatment**

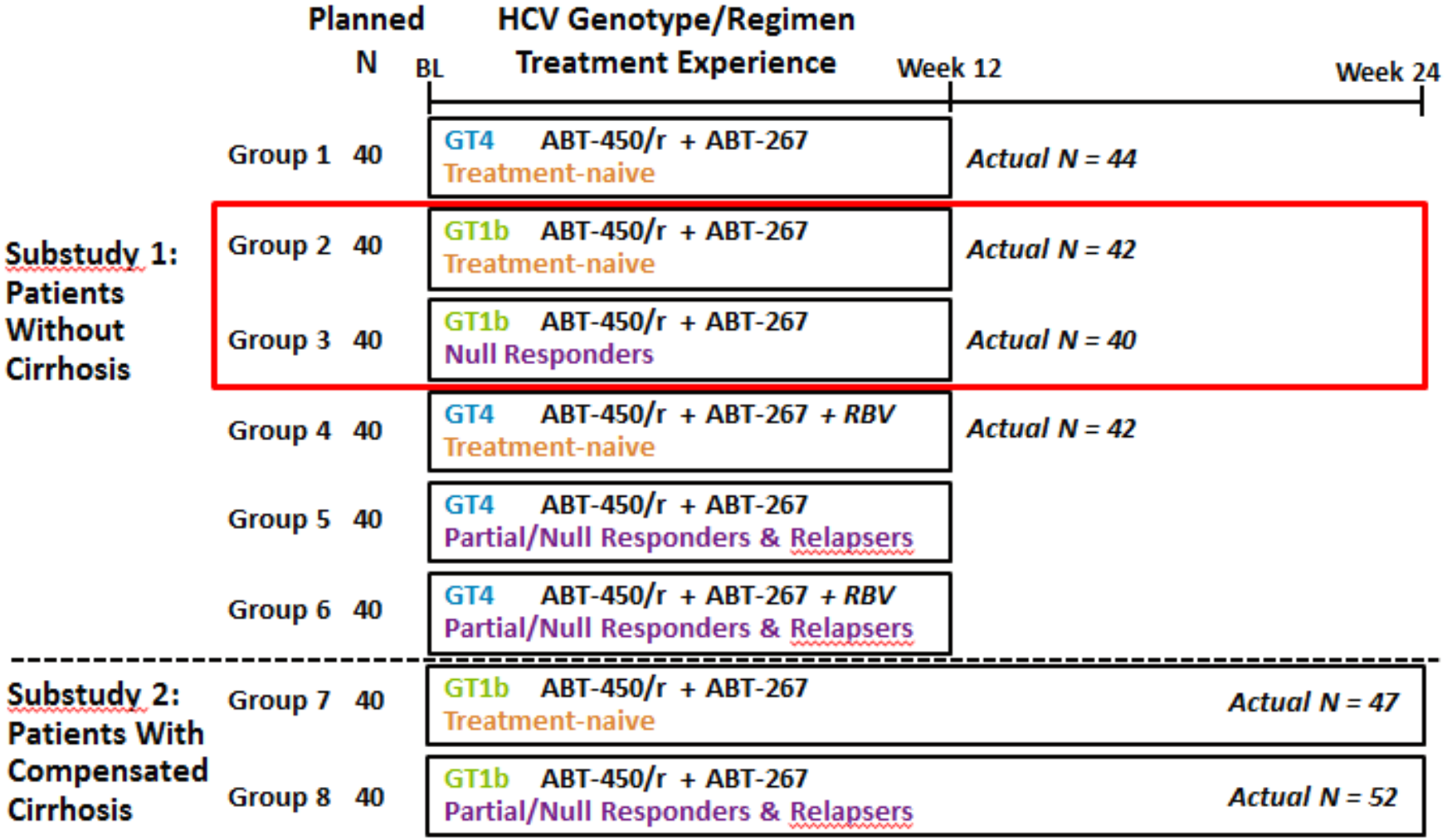
Female with gt 1b chronic HCV



Female with gt 1b chronic HCV

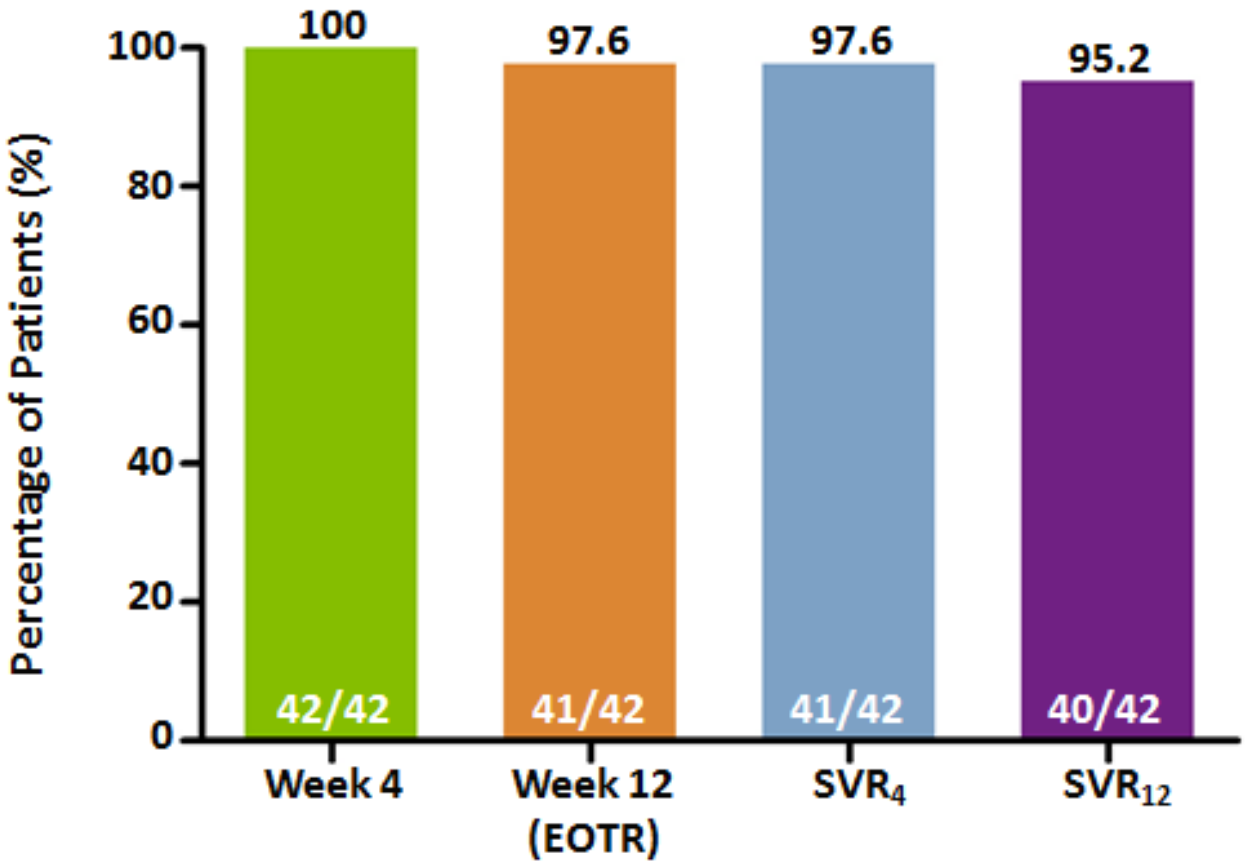
- **ABT PI/r + ABT NS5A inh + ABT NNUC 12 weeks treatment**
- **Very reapid response**
- **No AE:s**
- **SVR achieved**

PEARL-I Study Design



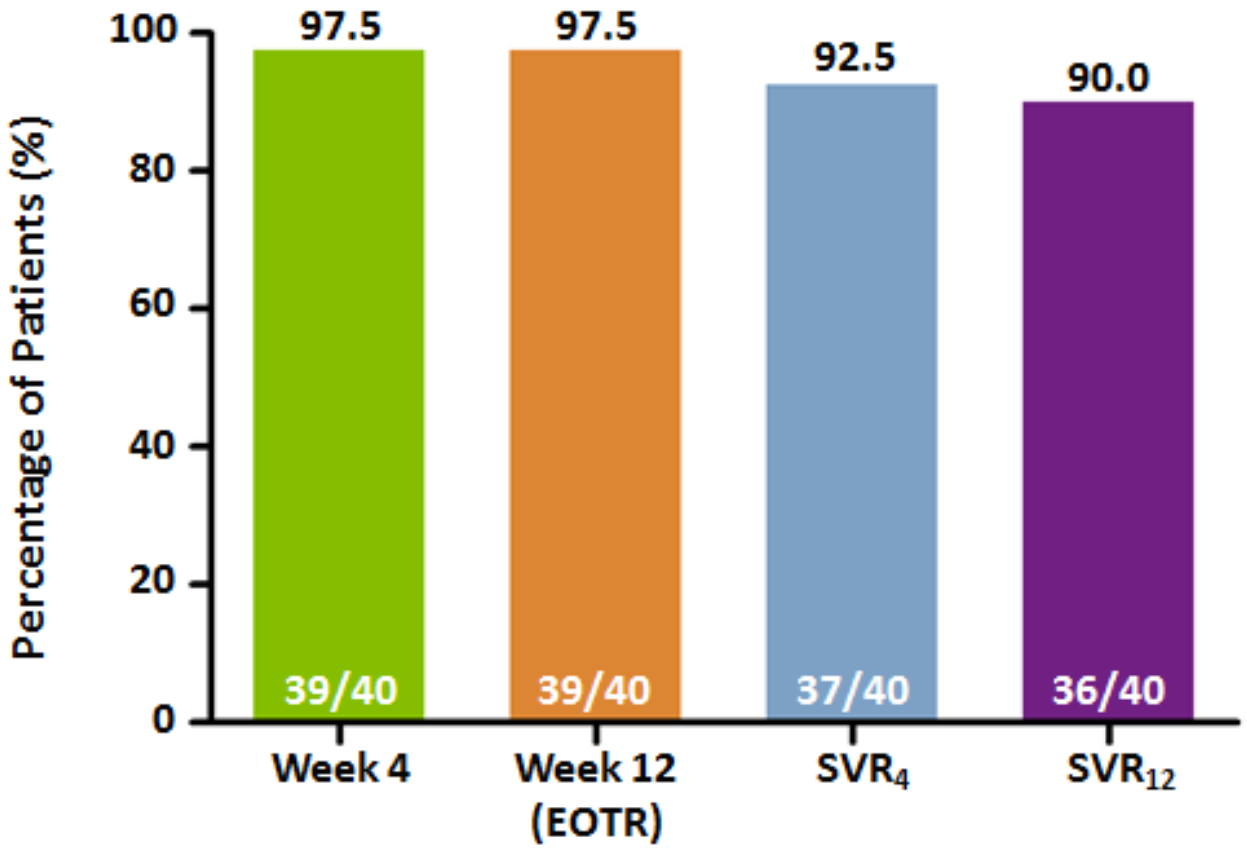
ABT-450/r 150/100 mg QD; ABT-267 25 mg QD; RBV weight based, 1000 mg or 1200 mg daily divided BID
Patients followed through 48 weeks post-treatment.

Efficacy: Treatment-Naïve Patients, ITT



Two patients did not achieve SVR_{12} due to loss to follow-up

Efficacy: Prior Null Responders, ITT



One patient experienced breakthrough and three patients relapsed

Available All-Oral Combinations

Company	NI	PI	NS5A	NNI	Cyclophilin
AbbVie		✔	✔	✔	
BMS		✔	✔	✔	
Gilead	✔	✔	✔	✔	
Vertex	✔	✔		✔	
Boehringer-Ingelheim		✔	✔	✔	
Roche	✔	✔		✔	
Novartis					✔
Merck		✔	✔		
Janssen		✔			
Achillion		✔	✔		

IFN-Free Combination Options

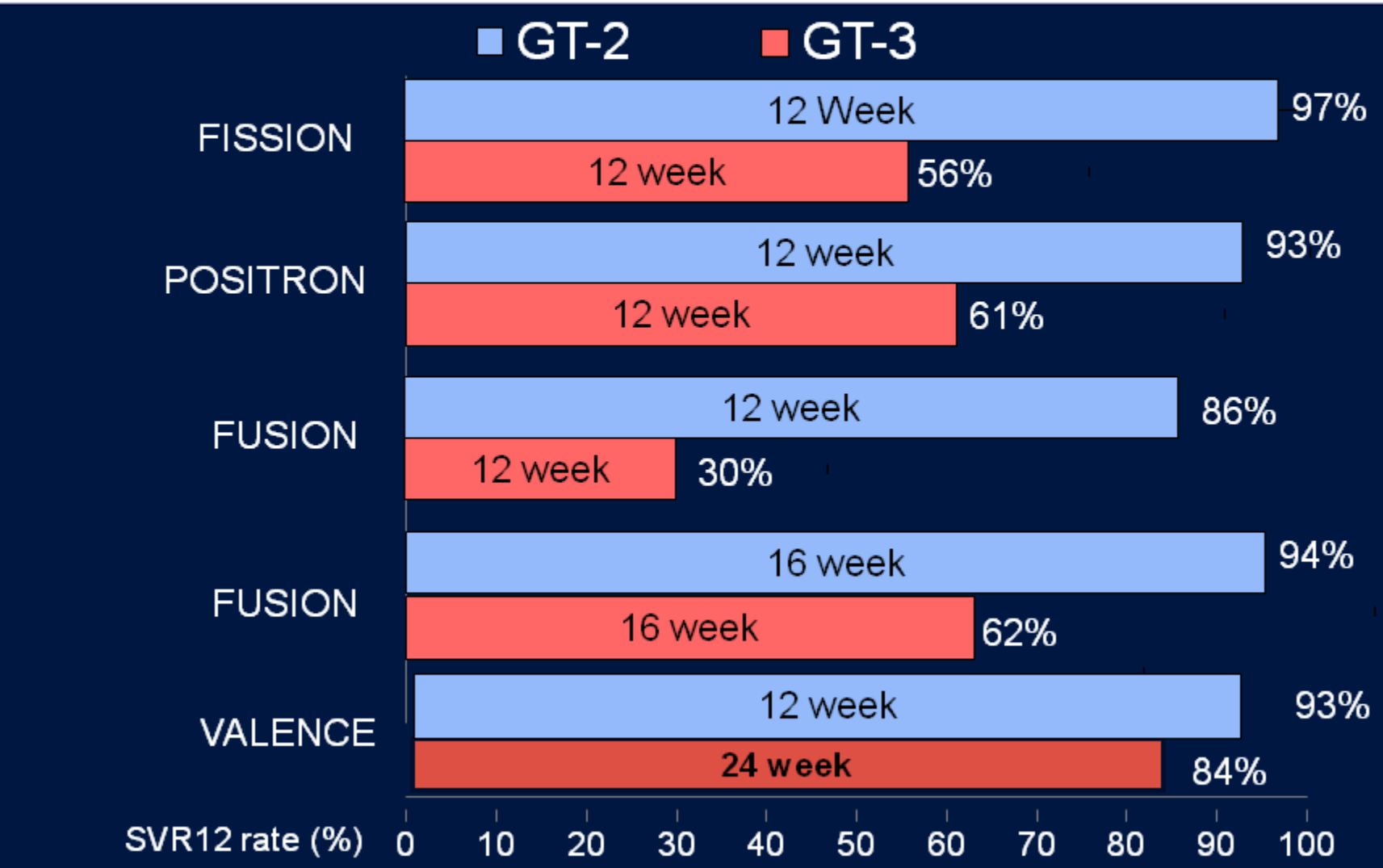
	NI	PI	NS5A	NNI	RBV
Nucleos(t)ide analogue-based strategies					
Gilead	**Sofosbuvir**		**Ledipasvir**	**GS-9669**	**±**
Vertex/others	**VX-135**	**Simeprevir**	**Daclatasvir**		**±**
Roche	**Mericitabine**	**Danoprevir/r**	**Setrobuvir**		**±**
Nucleoside-free triple combo strategies					
Abbvie		**ABT-350/r**	**ABT-267**	**ABT-333**	**±**
BMS		**Asunaprevir**	**Daclatasvir**	**BMS791325**	**±**
BI/Presidio		**Faldaprevir**	**PPI-668**	**Deleobuvir**	**±**
Nucleoside-free, second-generation double combo strategies					
Merck		**MK-5172**	**MK-8742**		**±**
Achillion		**ACH-2684**	**ACH-3102**		**±**

Conclusion

Very soon oral IFN-free regimens will predominate for HCV treatment including:

- **Nucleotide analogue-based regimens**
- **Nucleotide analogue-free regimens with 3 drugs with low resistance barrier**
- **Nucleotide analogue-free regimens with 2 drugs, including at least one with high resistance barrier**

Sofosbuvir + RBV in HCV GT 2/3
Genotype 2 ≠ 3



Lawitz E, et al. *N Engl J Med* 2013;368:1878-87.

Jacobson IM, et al. *N Engl J Med* 2013;368:1867-7714

Genotype 1 Treatment Options
Phase 3 Landscape