OSPEDALE NIGUARDA
CA' GRANDA

New drugs and strategies for HCV treatment

Massimo Puoti

SC Malattie Infettive

AO Ospedale Niguarda Cà Granda, Milano

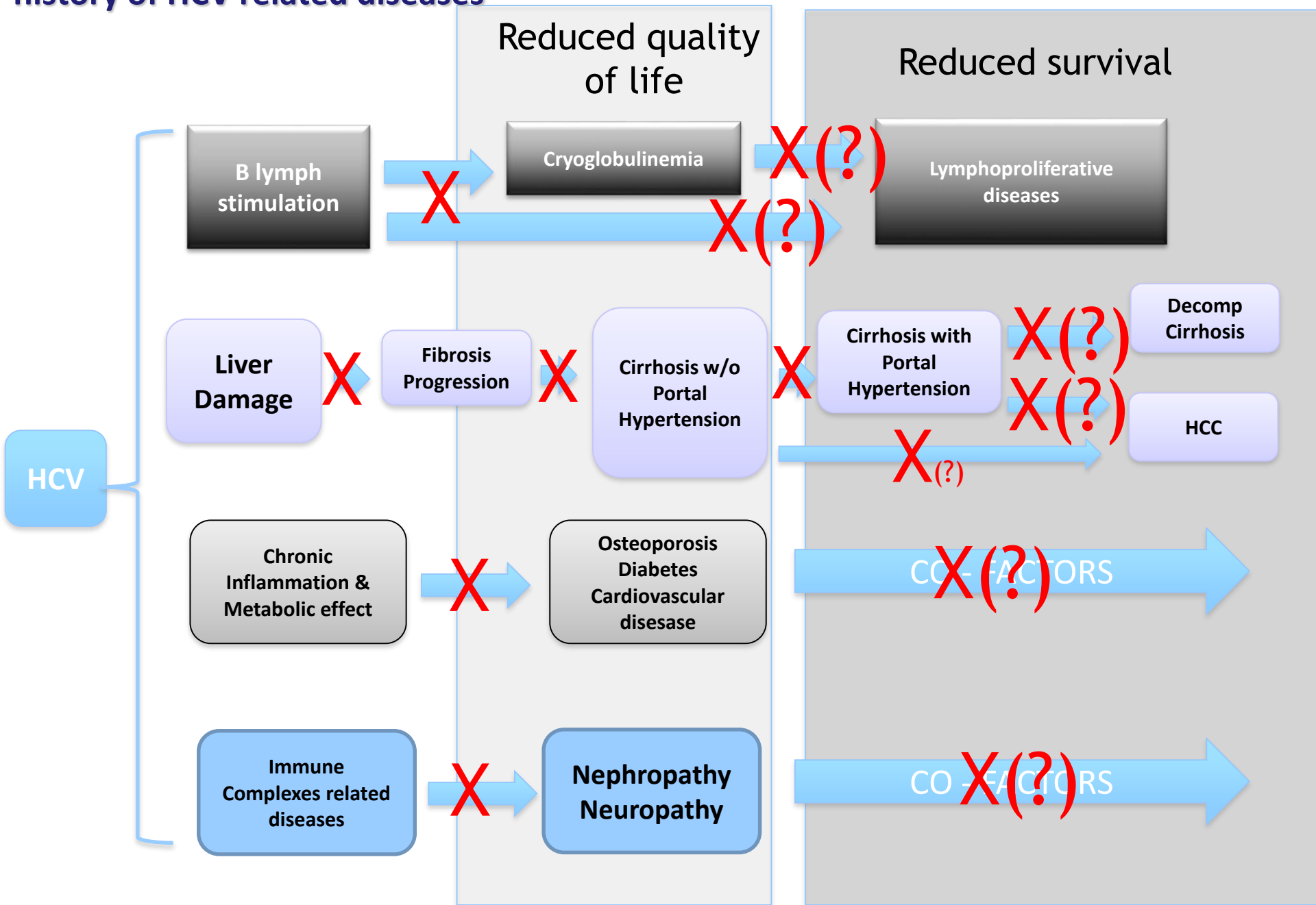
New drugs and strategies for HCV treatment

- Tools & strategies
- Upcoming Results
- The future

New drugs and strategies for HCV treatment

- Tools & strategies
- Upcoming Results
- The future

Role of HCV eradication (Sustained Virologic Response X) in the natural history of HCV related diseases



Sustained Virologic Response: a gamebreaker for HCV patients

- Improvement in non cirrhotics
  - Non progression to cirrhosis
  - Reduced incidence of extrahepatic manifestations
    - B Cells Lymphomas
    - Cryoglobulinemia
    - Diabetes
  - Neurocognitive function improvement
  - Overall survival
- Improvement in compensated cirrhotics
  - Reduced incidence of Clinical decompensation and Variceal bleeding
  - Reduced incidence of Hepato Cellular Carcinoma (HCC)
  - Cirrhosis Regression in pts w/o Portal Hypertension
  - Liver related survival
- Improvement in decompensated cirrhotics ???

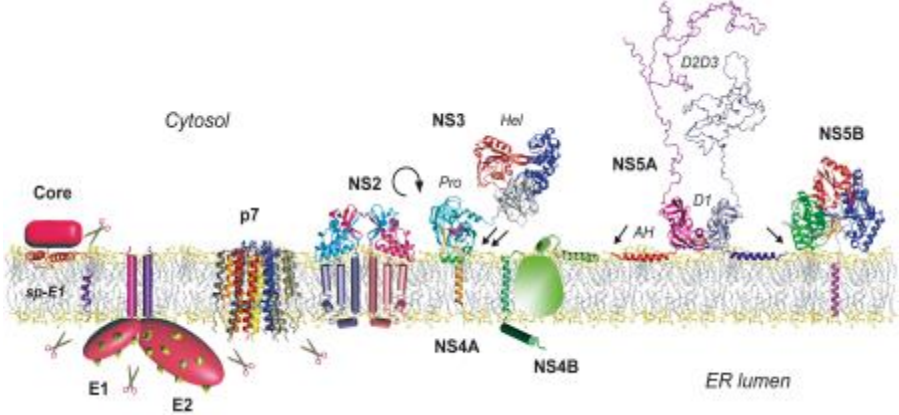
Aghemo A et al J Hepatol 2012; 57: 1326-35

The number needed to treat to prevent mortality and cirrhosis-related complications within 5 years among patients with cirrhosis and HCV genotype 1 infection (eligible for Interferon)

SVR %	NNT to prevent all causes mortality (95% CI)	NNT to prevent cirrhosis related complications (95% CI)
35%	**61 (54-101)**	**18 (16-24)**
50%	**43 (38-71)**	**13 (11-17)**
85%	**25 (23-42)**	**8 (7-10)**
95%	**23 (20-37)**	**7 (6-9)**

From Van der Meer AJ et al. J Viral Hepatitis 2013 modified

HCV targets for therapy



"entry inhibitors"
mAbs anti-E2/CD81,
PRO 206 Ezetimibe

Receptors binding
And endocytosis

Fusion and
decapsidation

(+) RNA

Traslation

miRNA
ISIS 14803 (antisense)
AVI- 4066 (antisense)
Heptazyme (ribozyme)
VGX-410C (small molecules IRES inhibitor) TT 033 (sIRNA)
eIF2α phosphorilation inhibitors:
Nitazoxanide

Transport and release

Virion assembly

Inhibitors of viral assembly and relaese :
Celgosivir
NS5A I

Translation and processing of polyprotein

Protease inhibitors

NS2-NS3 protease

RNA replication

Replication inhibitors:
- **NS5B**
  - **NNI,**
  - **NI**
- **NS5A I**
- **Ciclophyllin B**

Drugs active on viral enzymes
Drugs active on host cell enzymes

NS3 protease

Membrane

Serine protease domain

RNA-dipendent RNA polymerase

Lindenbach BD & Rice CM. Nature 2005;436:933–938; Moradpour D & Penin F. Curr Top Microbiol Immunol 2013;369:113–142.

HCV: probability of the presence of viral variants

Hepatitis C virus: ~9600 nucleotides
Error rate during replication: ~10^{-4} – 10^{-5} per copied nucleotide
Viral turnover: ~10^{12} virions produced every day

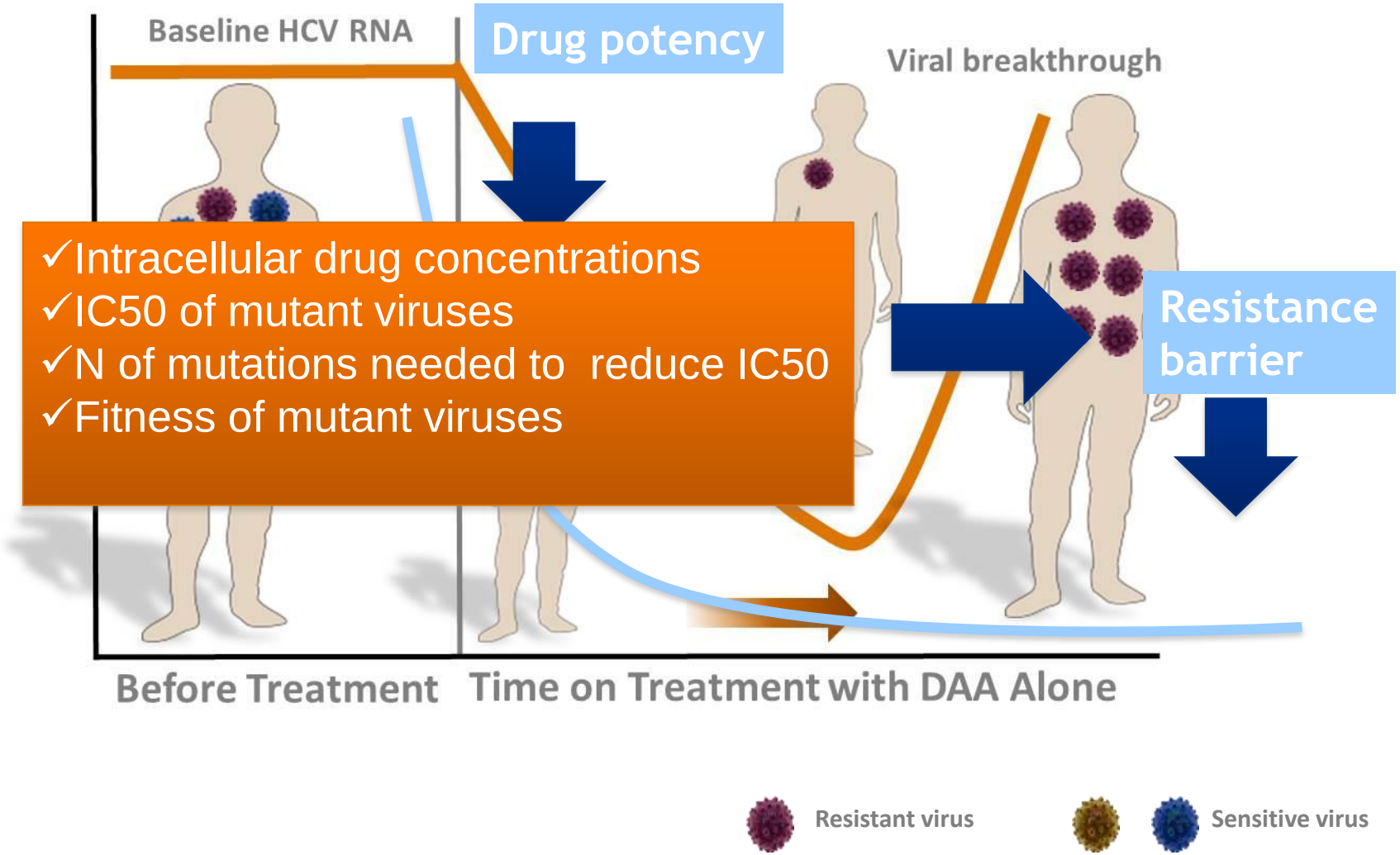
Number of nucleotide change	Probability of generation after one round of replication	Number of virions with nucleotide change(s) produced per day	Number of all possible nucleotide mutants	Fraction of all possible mutants created per day
0	91%	9.1×10^{11}		
1	8.7%	8.7×10^{10}	2.9×10^{4}	1
2	0.4%	4.2×10^{9}	4.1×10^{8}	1
3	0.001%	1.3×10^{8}	4.0×10^{12}	3.4×10^{-5}

Not all variants survive

- Dead mutations (variants that can not replicate)
- Immune sensitive mutations (variants eliminated by the immune system)

Rong L, et al. Sci Transl Med 2010;2:30ra32; Neumann AU, et al. Science 1998;282:103–107
Domingo E, et al.. Viral Hepatitis Rev 1996;2:247–261; Cuevas JM, et al. J Virol 2009;83:5760–5764

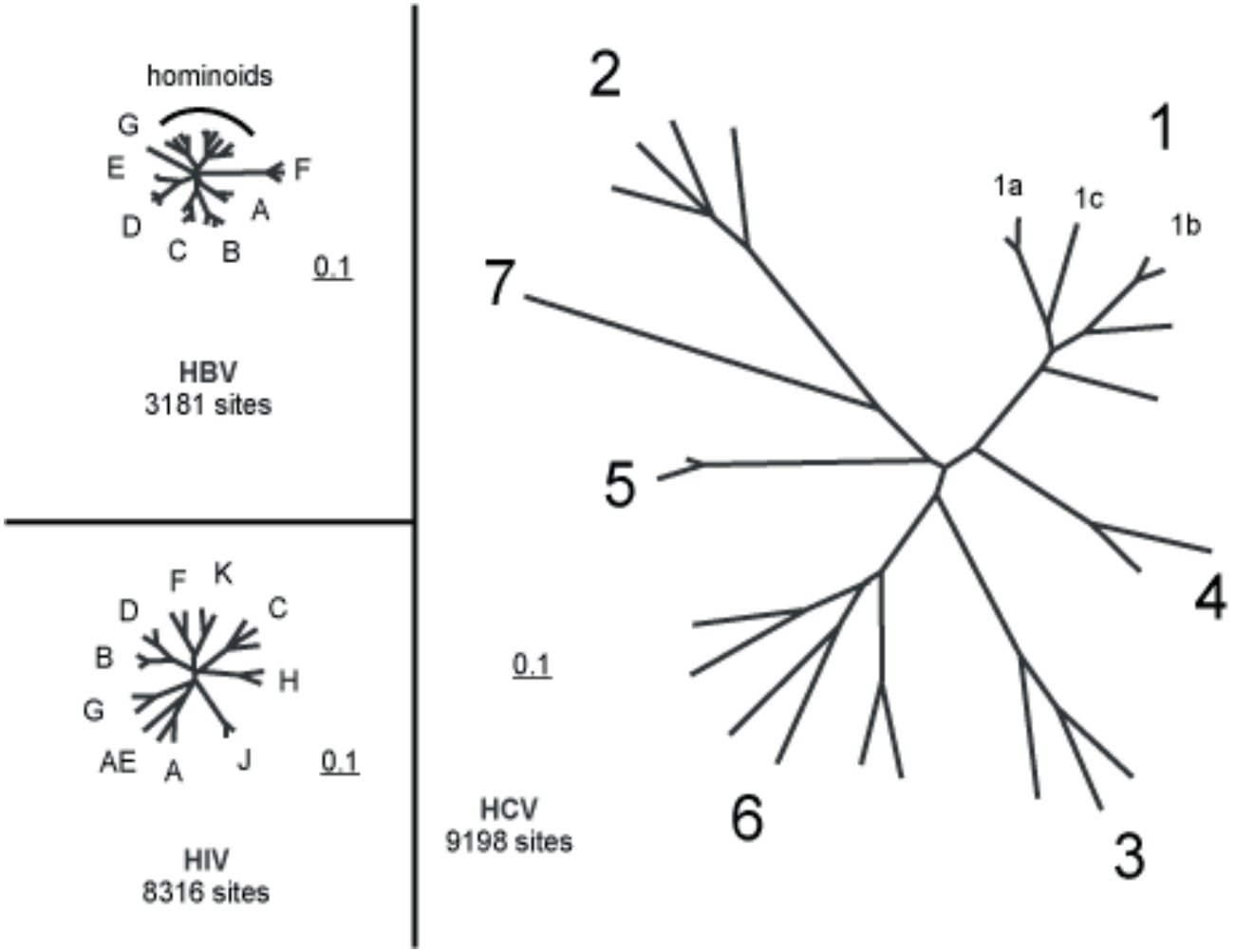
Emergence of pre-existing resistant variants during treatment with DAA



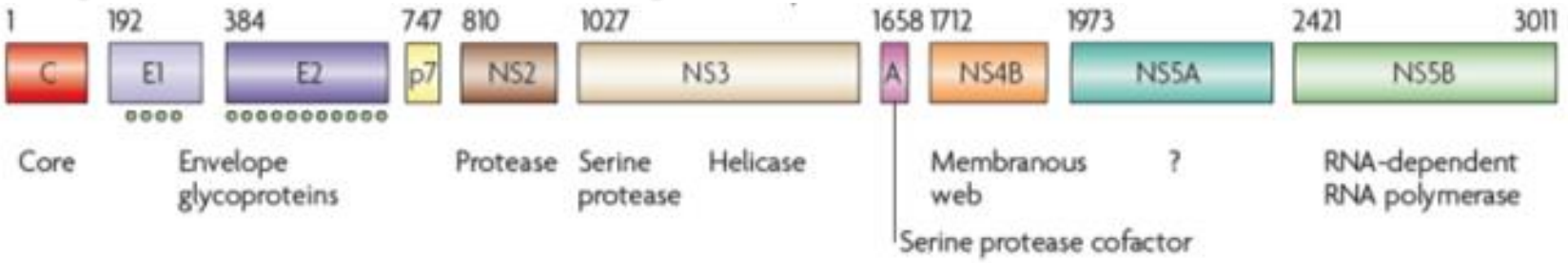
DAA classes and subclasses

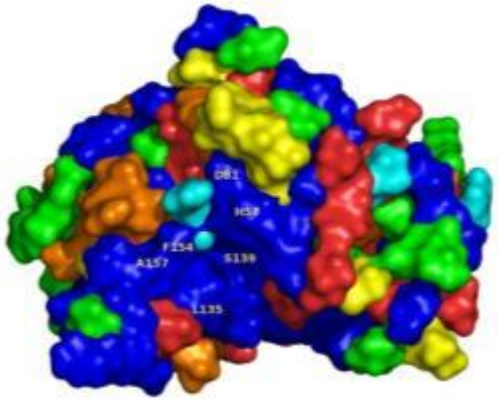
Drug Class	Subclass	Potency	Resistance barrier
Protease inhibitors "- previr"	1st Generation first wave i.e. Telaprevir/Boceprevir	**Medium-Low**	**Low**
	1st Generation 2nd wave i.e. Simeprevir/Asunaprevir Paritaprevir/r	**Medium**	**Low**
	2nd Generation Grazoprevir (in vivo) ABT 493 (in vitro)	**High**	**High except HCVG3**
NS5a inhibitor " ..asvir"	1st Generation Daclatasvir, Ledipasvi,r Ombitasvir, Elbasvir	**High**	**Medium- High except HCV G3 & 1a**
	2nd Generation GS 5816 (in vivo) ABT530 (in vitro)	**High**	**High**
Ppolymerase inhibitors "..buvir" NN	Dasabuvir Beclobuvir	**Low-Medium**	**Low**
Nucleos/tides	2nd Generation : Sofosbuvir	**High**	**High**

Consequences of HCV variability at population level: HCV genotypes

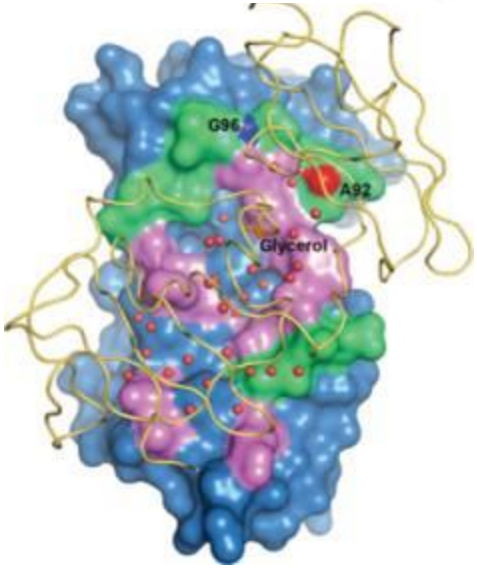


HCV protein variability

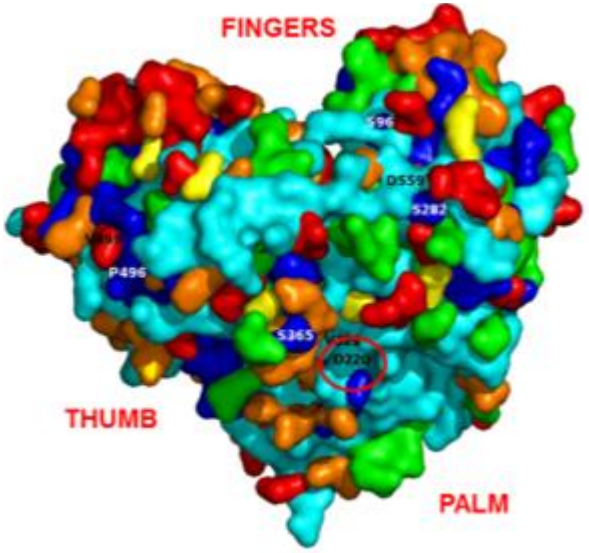




47% amino acid of HCV PROTEASE NS3 are conserved among All HCV-genotypes



46.1% amino acid of HCV NS5A are conserved among All HCV-genotypes



54.8% amino acid of HCV POLYMERASE NS5B are conserved among All HCV-genotypes

Amino acid variability:

0% | ≤1% | 1-5% | 5-10% | 10-25% | >25%

Cento V, et al. PLoS ONE 2012;7(7):e39652

Love RA, et al. J Vir 2009;83(9):4395–4403

Amino acid variability:

0% | ≤1% | 1-5% | 5-10% | 10-25% | >25%

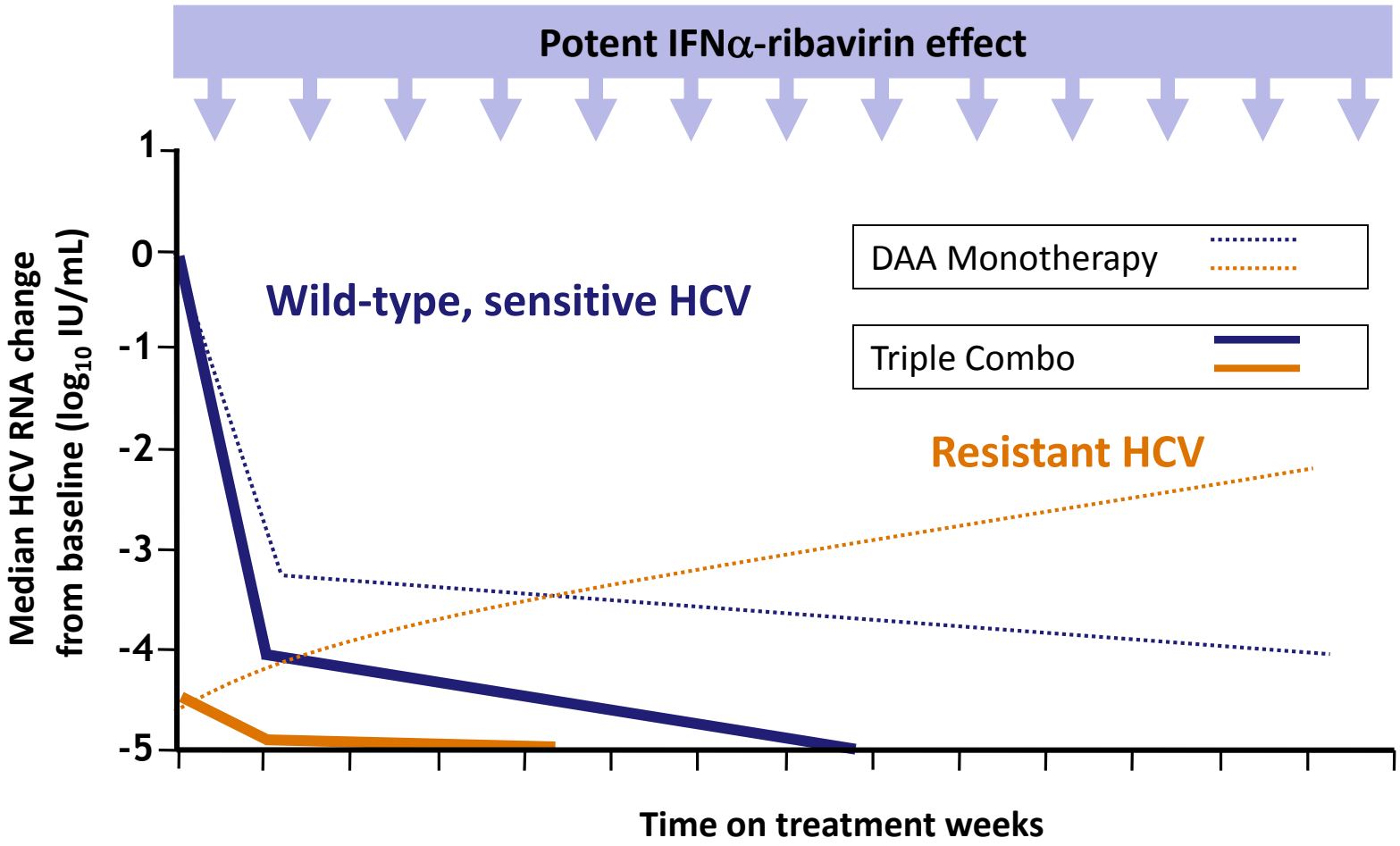
Di Maio VC, et al. Antimicrob Agents Chemother 2014;58(5):2781–97

DAA classes and subclasses: antiviral potency and resistance barrier according to HCV genotype

Drug Class	Subclass	1 b	1a	2	3	4
Protease inhibitors	1st Generation first wave i.e. Telaprevir/Boceprevir	●	●	●	●	●
	1st Generation 2nd wave i.e. Faldaprevir/Simeprevir	●	●	●	●	●
	2nd Generation MK5172 ABT 493	●	●	●	●	●
NS5a Inhibitor	1st Generation Daclatasvir Ledipasvir Ombitasvir	●	●	●	●	●
	2nd Generation MK 8742 GS 5816 ABT 530	●	●	●	●	●
NN Polymerase Inhibitors	Dasabuvir Deleobuvir	●	●	●	●	●
Nucleos/tides Polymerase inhibitors	2nd Generation : Sofosbuvir	●	●	●	●	●

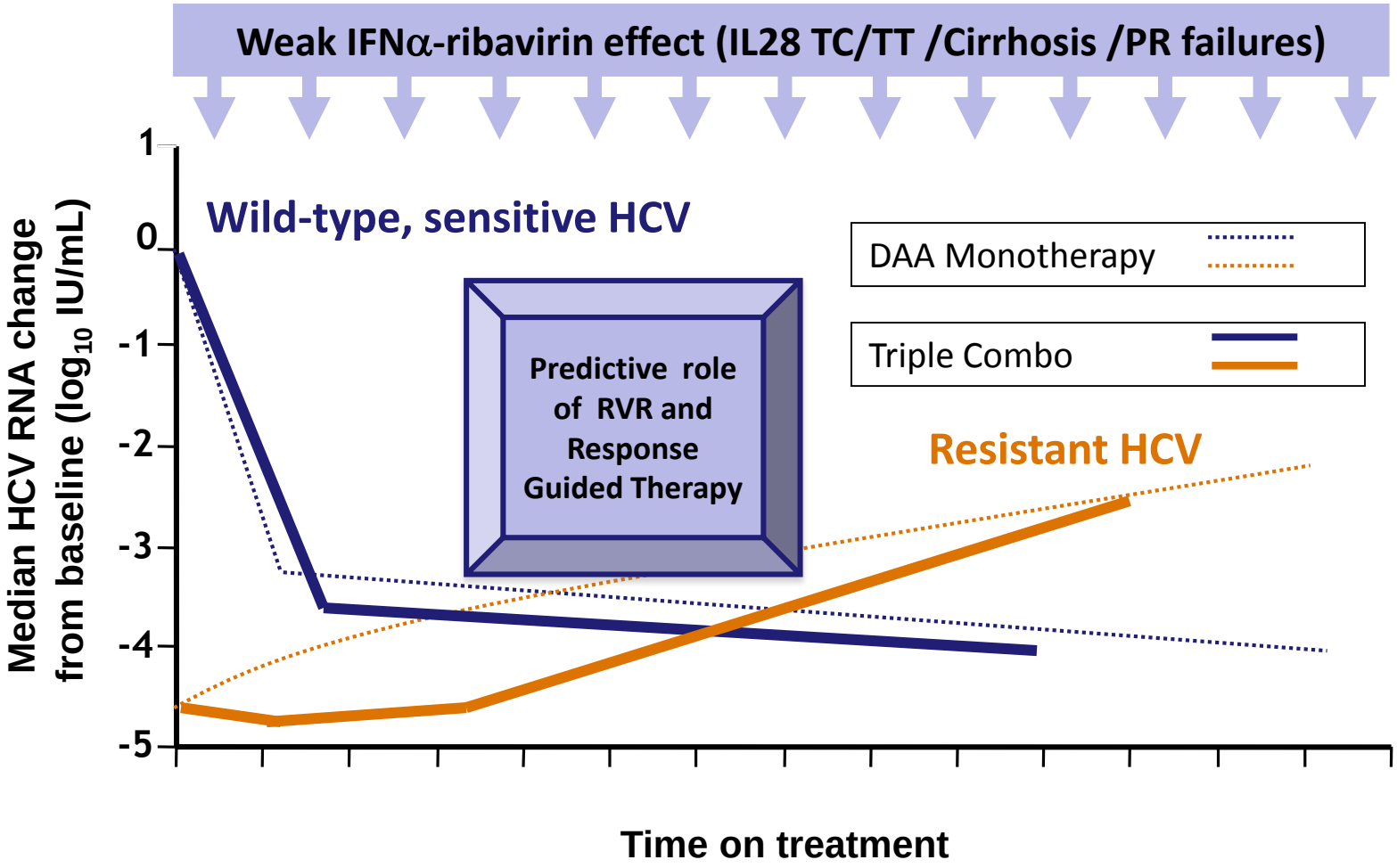
● High ● Moderate ● Low ● Very low

Combo with PEGIFN + RBV of 1 DAA low resistance barrier (Boceprevir, Simeprevir and Daclatasvir)



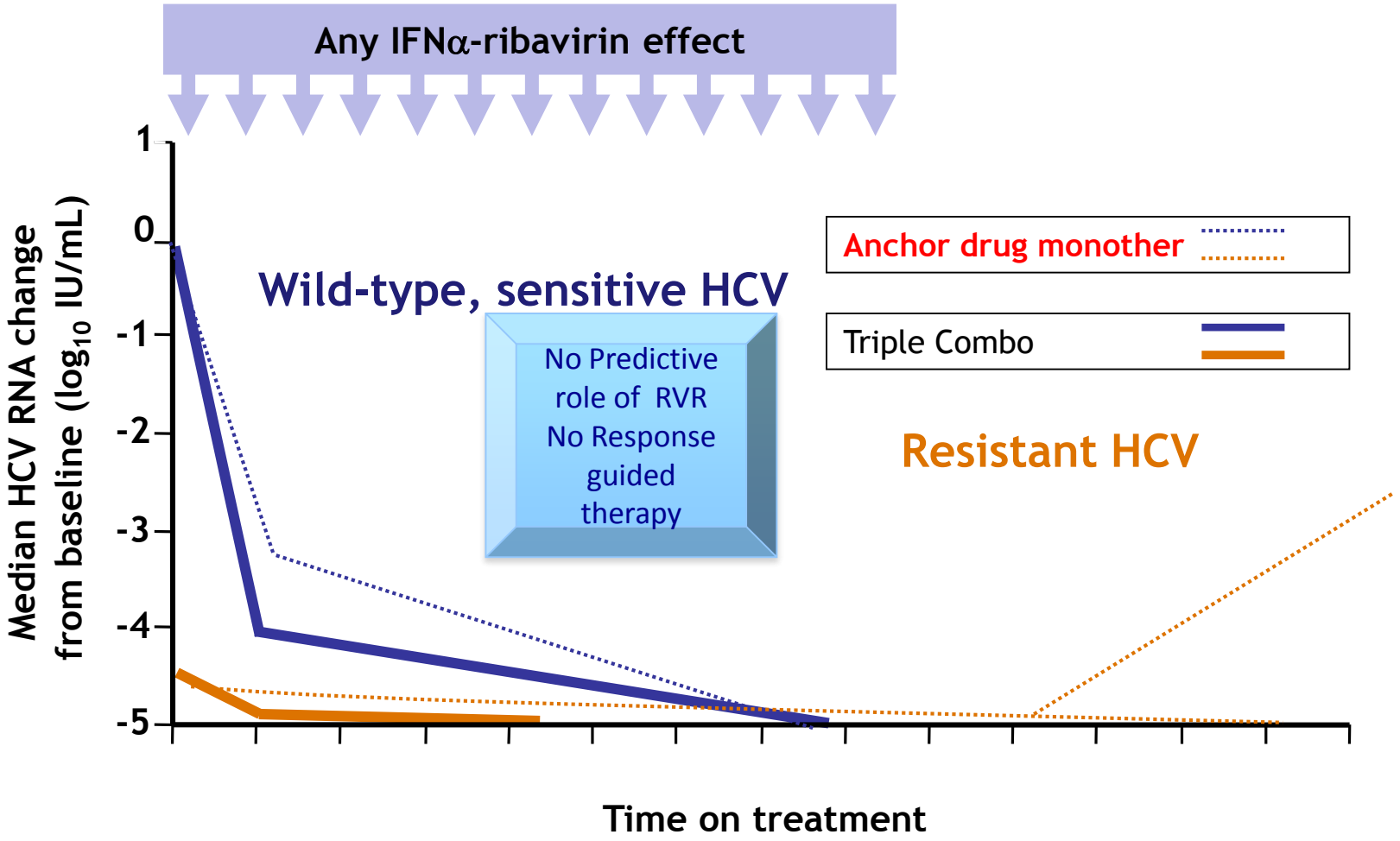
Sarrazin C et al J Hepatol. 2012;56 Suppl 1:S88-100.

Combo with PEGIFN + RBV of 1 DAA low resistance barrier (Boceprevir, Simeprevir and Daclatasvir)



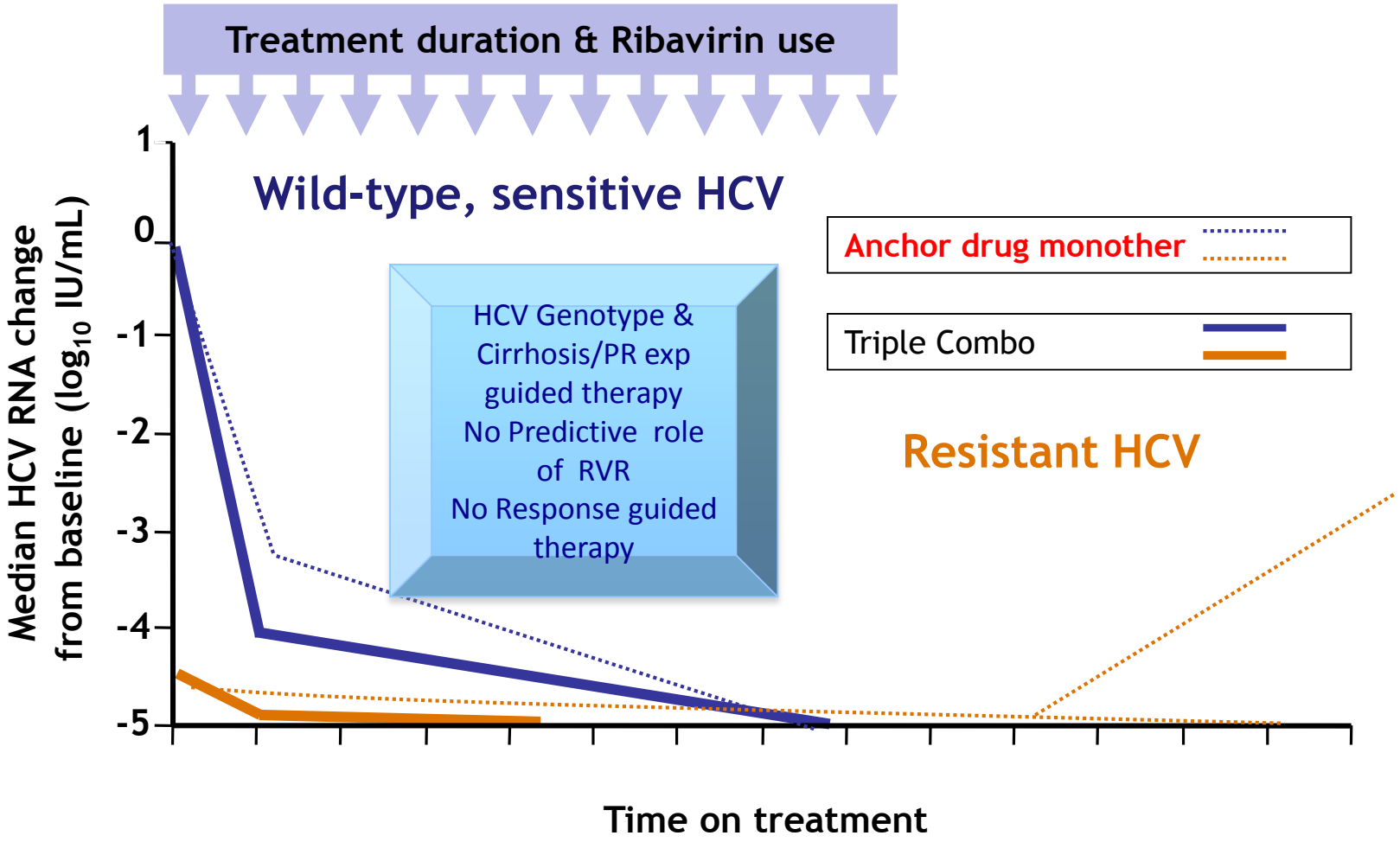
Sarrazin C et al J Hepatol. 2012;56 Suppl 1:S88-100.

Combo with PEG IFN & RBV + 1 high resistance barrier DAA (Sofosbuvir)



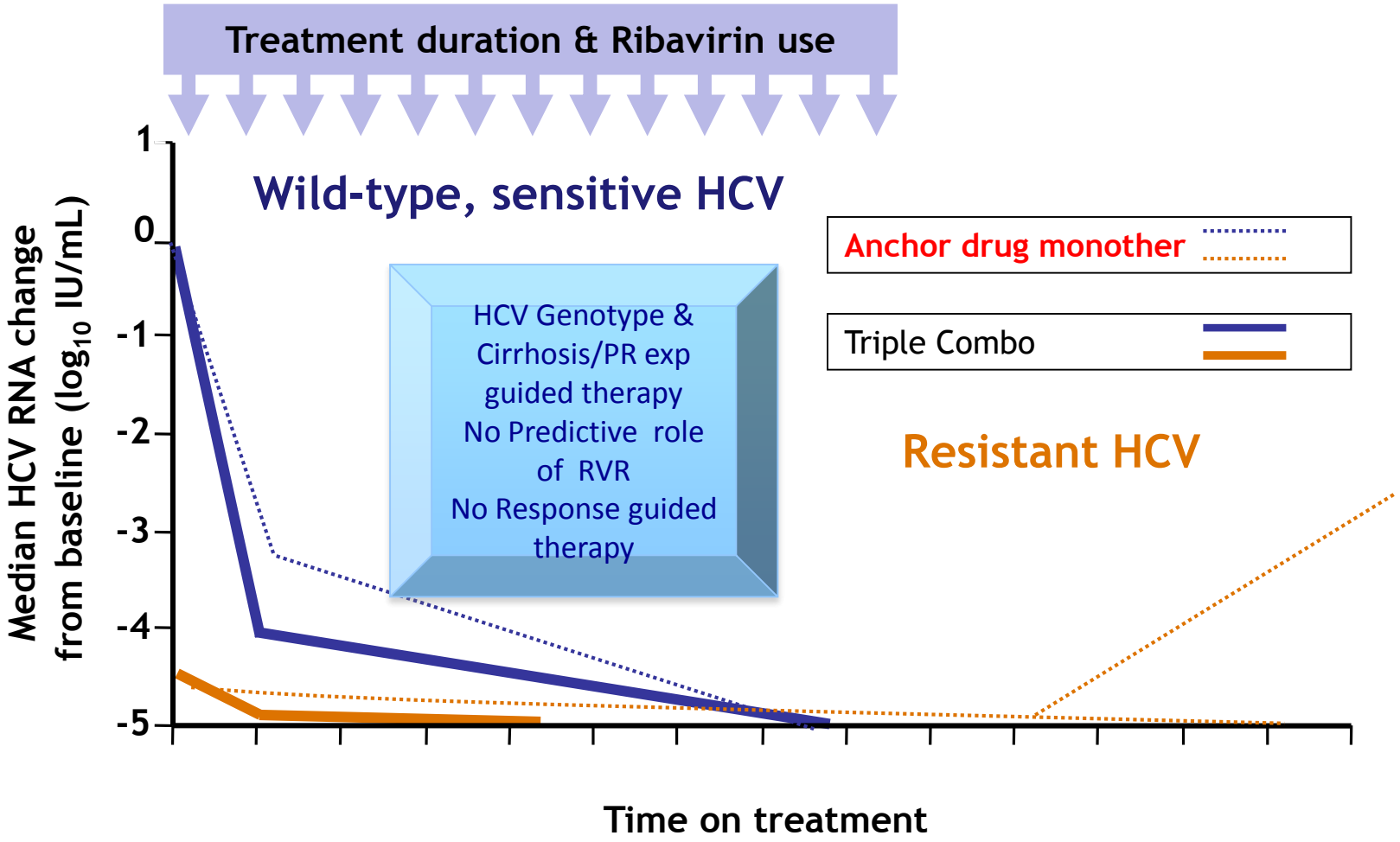
Sarrazin C et al J Hepatol. 2012;56 Suppl 1:S88-100.

1 high resistance barrier DAA (Sofosbuvir) ± Ribavirin ± 1 DAA x 12-24 weeks



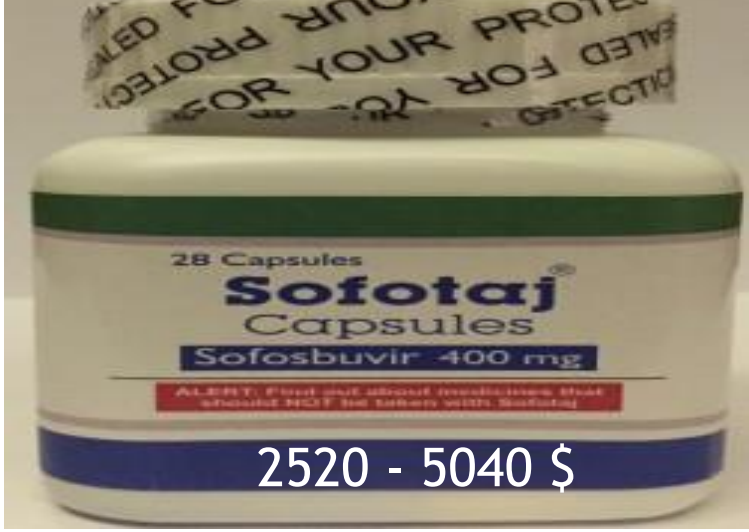
Sarrazin C et al J Hepatol. 2012;56 Suppl 1:S88-100.

2-3 low resistance barrier DAA ± Ribavirin x 12-24 weeks



Sarrazin C et al J Hepatol. 2012;56 Suppl 1:S88-100.

Anti HCV Drugs Prices x treatment cycle



Drug	US Price $	EU lowest price €	Price for Italian NHS €
Sofosbuvir	84-168.000	39-68.000	X?-37.000
Daclatasvir		15.6 – 31.200	?
Simeprevir	54.000		18.000 (?)
Harvoni	94-188.000	45-90.000	?
Viekira Pack	83-166.000		?

Strategies of DAA based HCV eradication

- IFN/Riba based
  - IFN/Riba based (HCV G1 & 4)
    - IFN + 1 DAA with low resistance barrier
- Sofosbuvir based
  - IFN/riba + Sofosbuvir (1 DAA high resistance barrier)
  - Sofosbuvir (high resistance barrier) + RBV
  - Sofosbuvir (high resistance barrier) + 1 DAA ± RBV
- Sofosbuvir free
  - 3 (2) DAAs low resistance barrier
- Sofosbuvir based "pangenotypic"
  - Sofosbuvir + 1/2 DAA Pangenotypic
- Sofosbuvir free "pangenotypic"
  - 2 DAA pangenotypic

Phase IV

Adjusted for HCV Genotype Previous Tx for HCV Cirrhosis Fine tuning by RBV & Tx duration

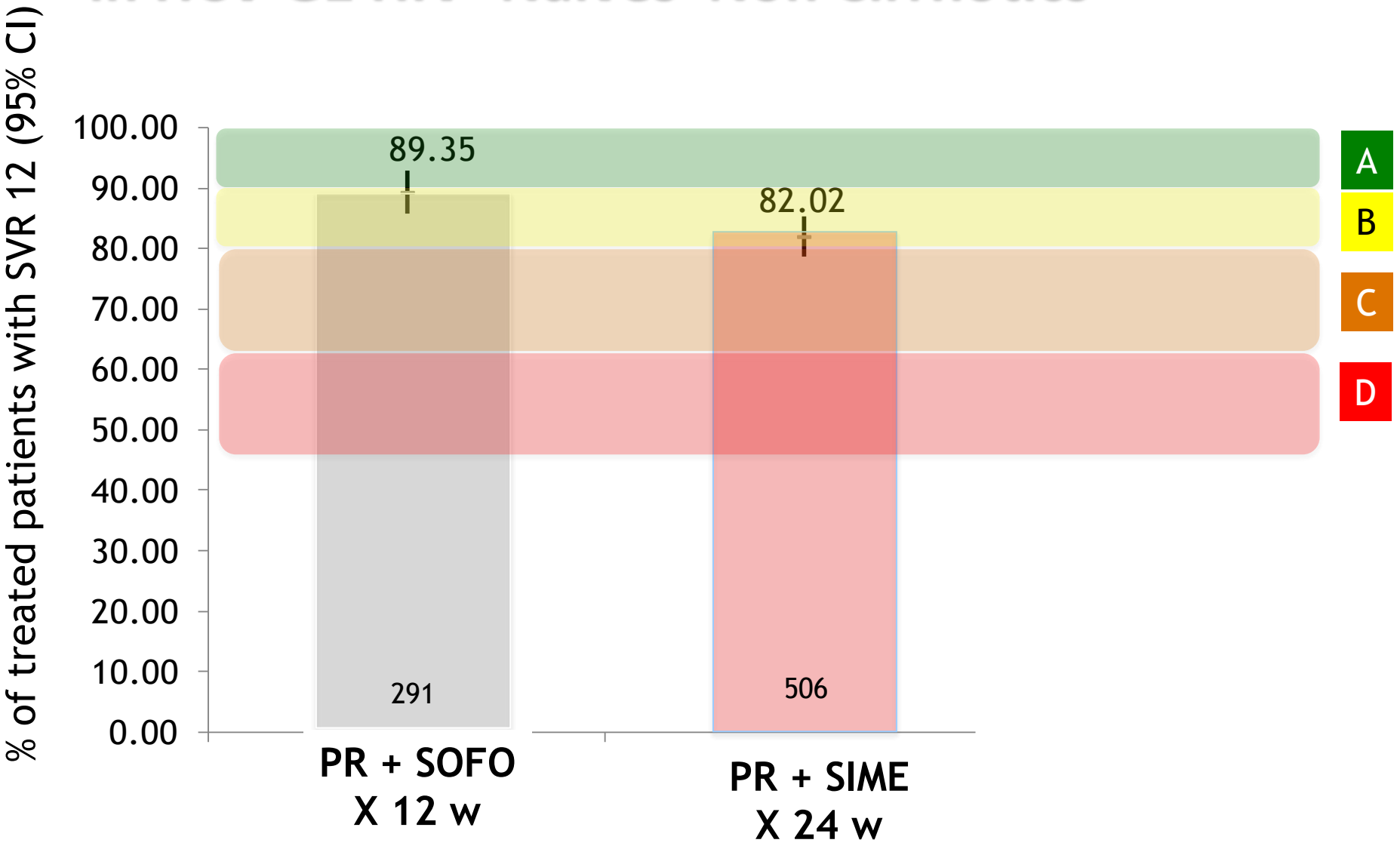
Phase II-III

One pill for all

New drugs and strategies for HCV treatment

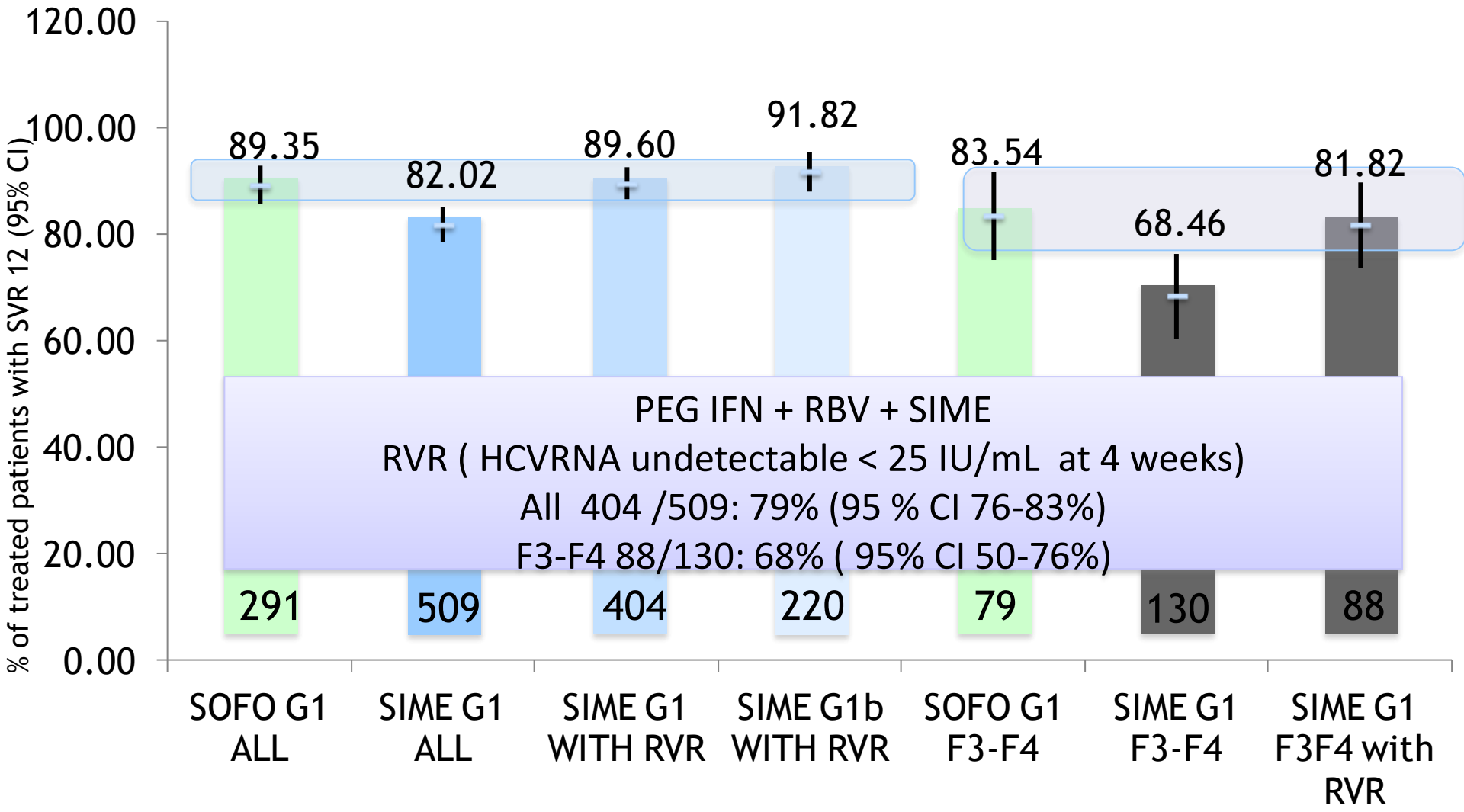
- Tools & strategies
- Upcoming Results
- The future

Summary of SVR rates to IFN based regimens in HCV G1 HIV- Naives Non Cirrhotics



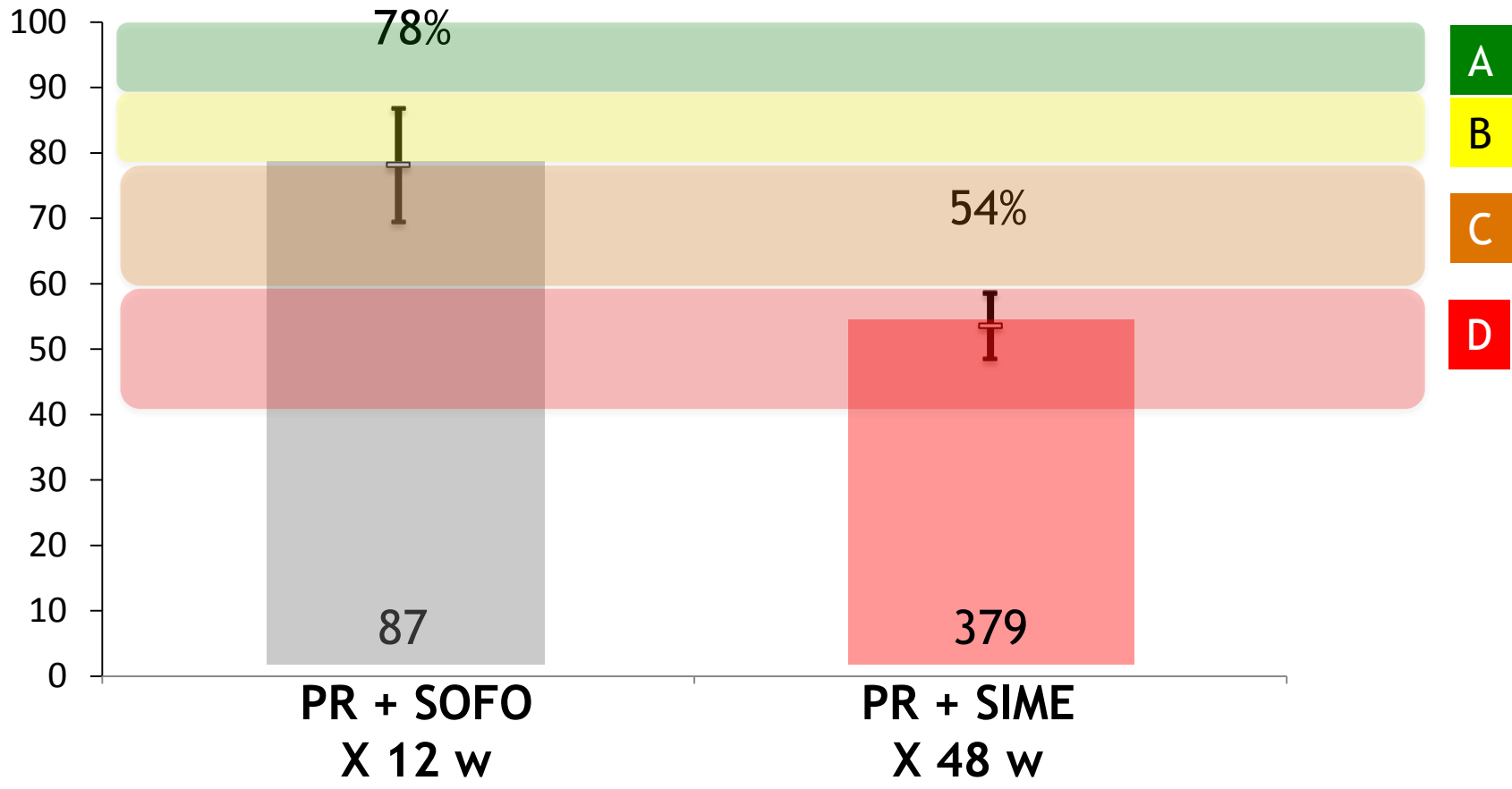
Lawitz E, et al. NEJM 2013; Jacobson et al. AASLD 2013; Yoshida et al. AASLD 2013.

PEG IFN + RBV + SOFO vs PEG IFN + RBV + SIME SVR12 according to Rapid Viral Response (RVR) to PEG IFN + RBV + SIME and fibrosis stage



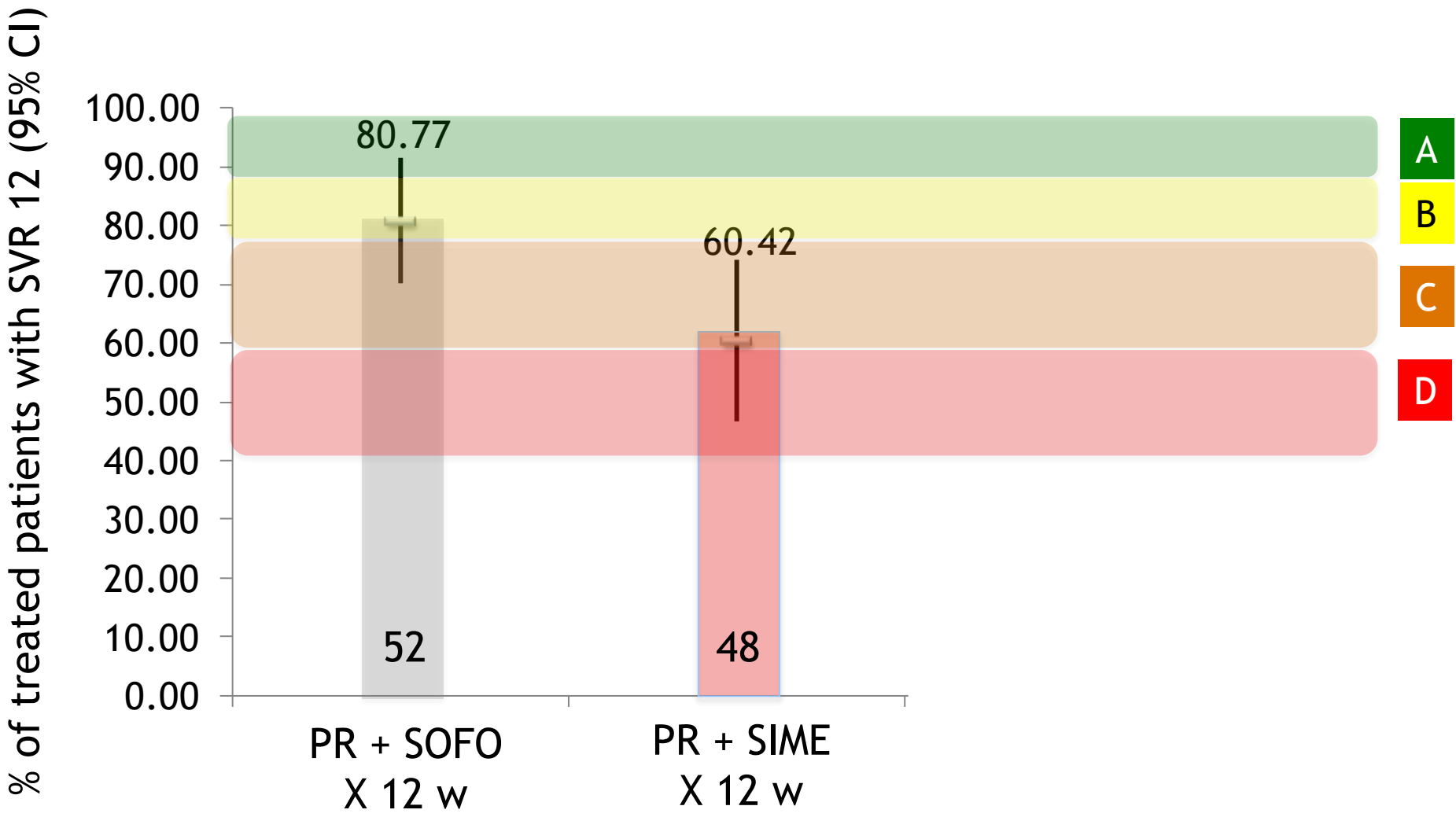
Lawitz E, et al. NEJM 2013; Jensen et al. AASLD 2013; Yoshida et al. AASLD 2013.

Summary of SVR rates to IFN based regimens in HCV G1 HIV- Experienced Non Cirrhotics



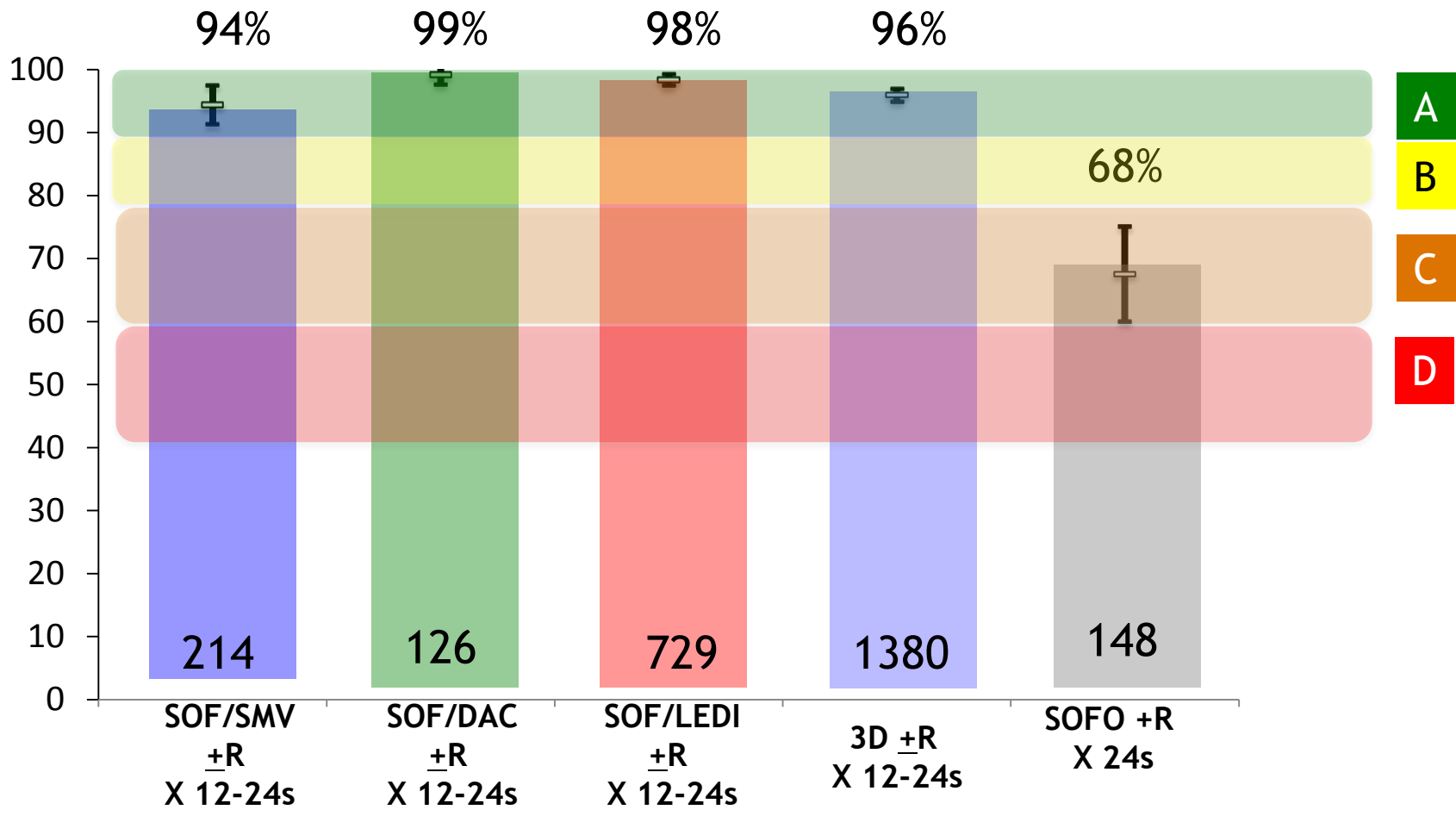
PR + SOFO Pol Easl 2014; TRIO AASLD 2014
PR SIME: ATTAIN study Reddy APASL 2013

Summary of SVR rates to IFN based regimens in HCV G1 HIV- Naives Cirrhotics



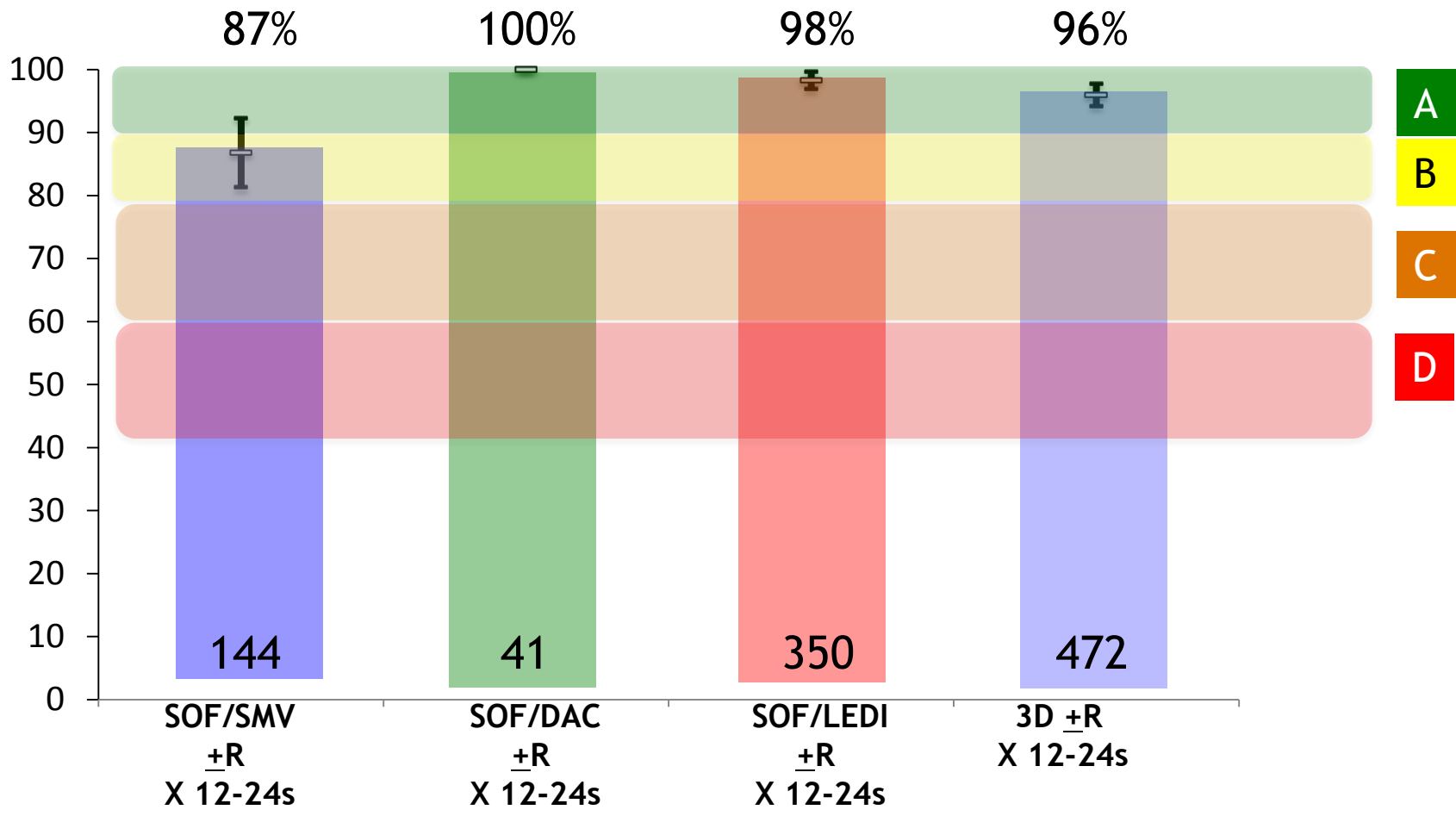
Lawitz E, et al. NEJM 2013; Jensen et al. AASLD 2013; Yoshida et al. AASLD 2013.

Summary of SVR rates to IFN free regimens in HCV G1 HIV- and HIV+ Naives non Cirrhotics



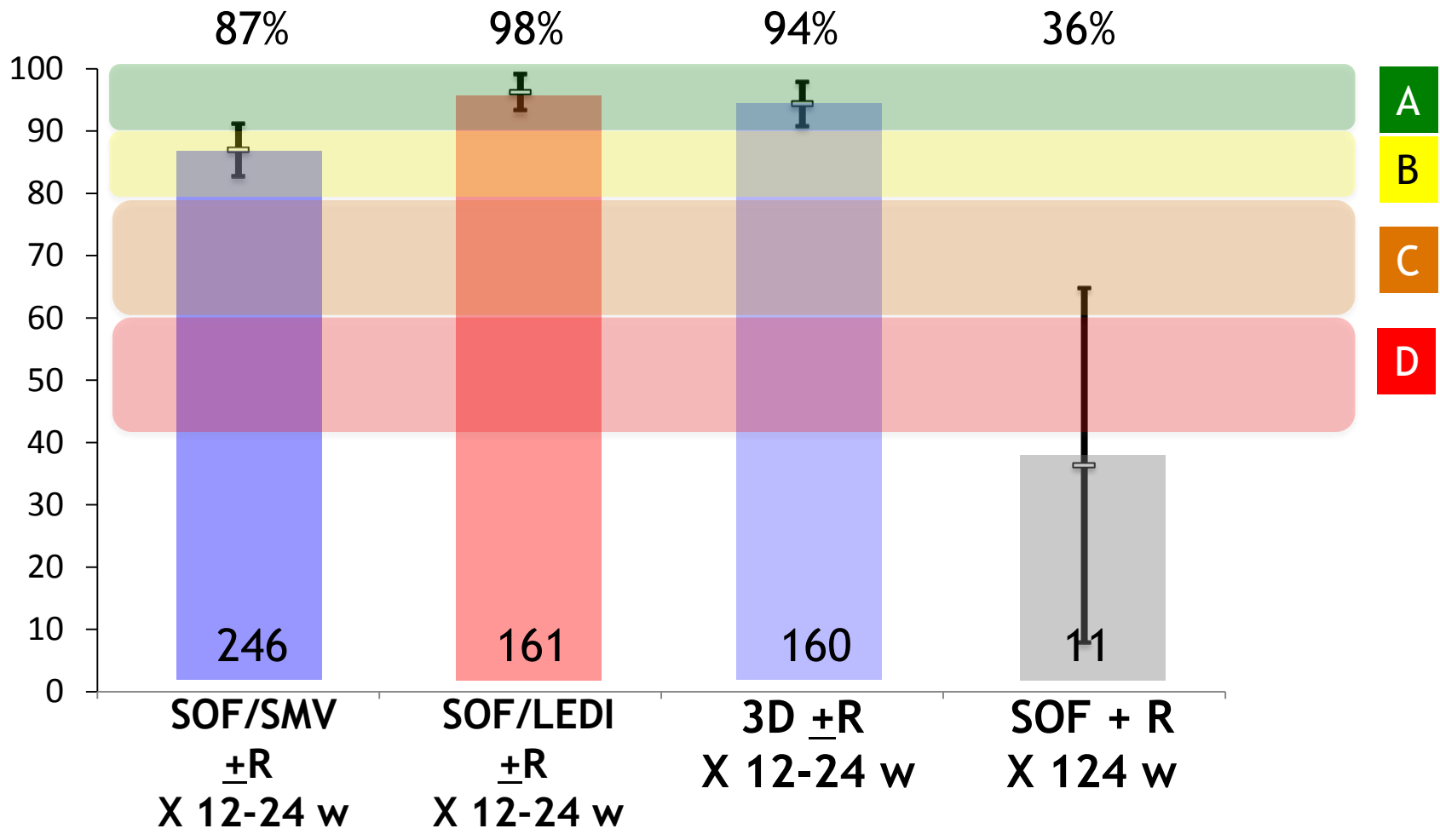
SIM/SOF study Cosmos, cohorts: TRIO, TARGET
SOF/LED studies ION-1 ION-3
3D: studies PEARL SAPPHIRE
SOFO + R: SPC Sovaldi

Summary of SVR rates to IFN free regimens in HCV G1 HIV- Experienced non Cirrhotics



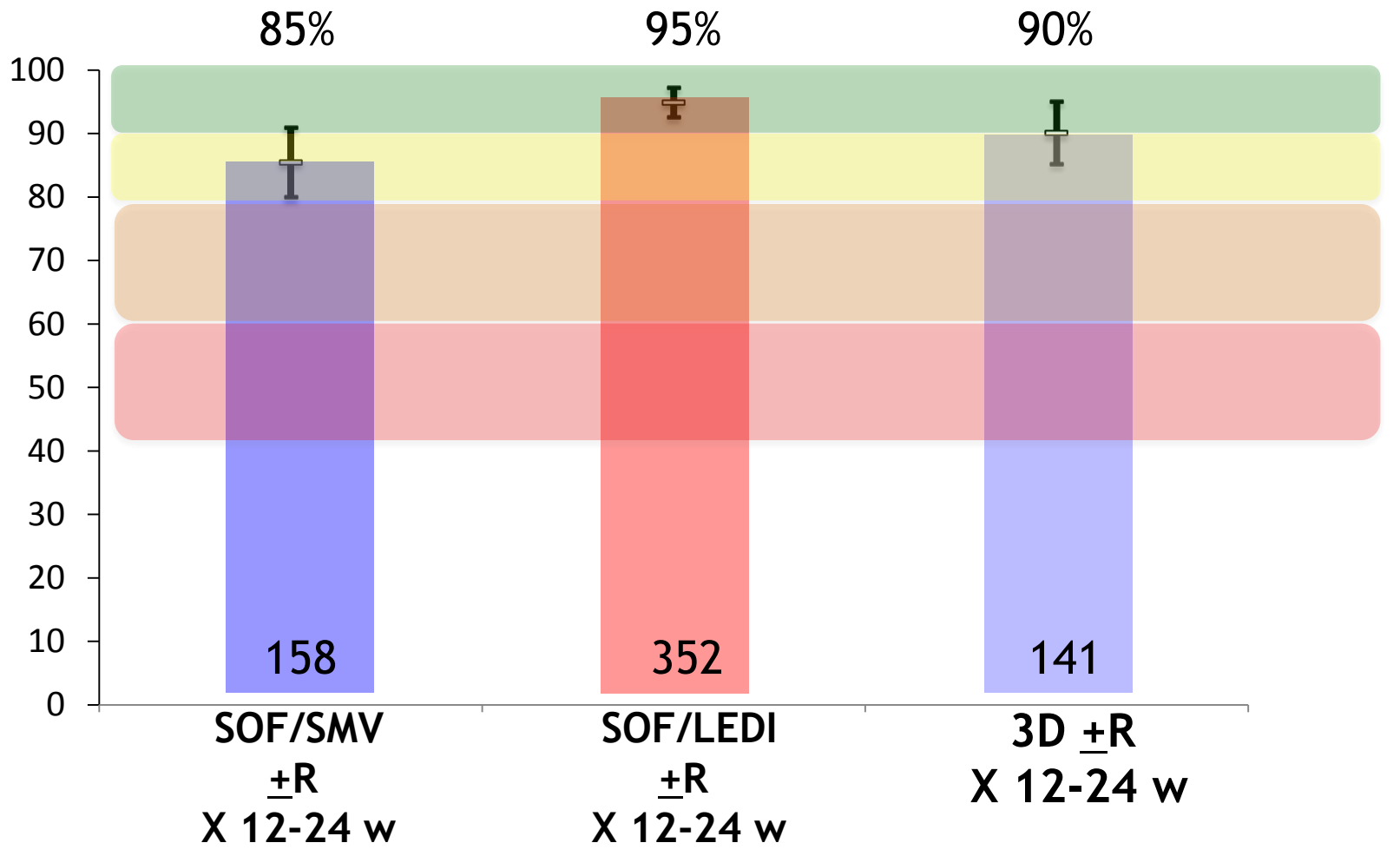
SIM/SOF study Cosmos, cohorts: TRIO, TARGET
SOF/LED studies ION-1 ION-3
3D: studies PEARL SAPPHIRE
SOFO + R: SPC Sovaldi

Summary of SVR rates to IFN free regimens in HCV G1 HIV- Naives Cirrhotics



SIM/SOF study Cosmos, cohorts: TRIO, TARGET
SOF/LED study meta analysis AASLD 2014
3D: studies Turquoise II

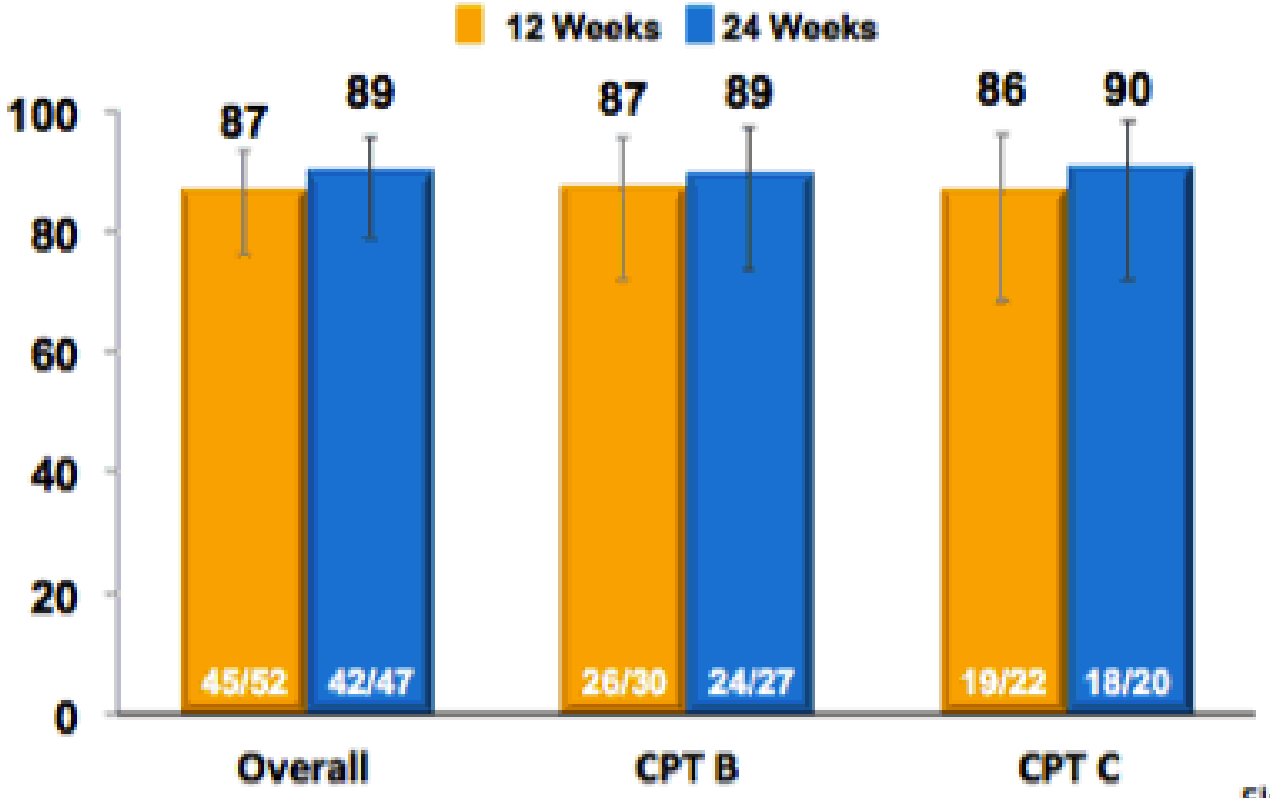
Summary of SVR rates to IFN free regimens in HCV G1 HIV- Experienced Cirrhotics



SIM/SOF study Cosmos, cohorts: TRIO, TARGET
SOF/LED study meta analysis AASLD 2014
3D: studies Turquoise II

Ledipasvir/Sofosbuvir + RBV in Patients with Decompensated Cirrhosis: Preliminary Results of a Prospective, Multicenter Study

- Randomized to SOF + LDV + RBV (600 mg w/escalation) for 12 or 24 weeks
- Patients with GT 1 or 4 and decompensated cirrhosis
  - Most patients with MELD > 10 (MELD= 16-20 in 10-46%)
  - Median Albumin= 2.6- 3.0 g/L; Median platelets = 71-88 K

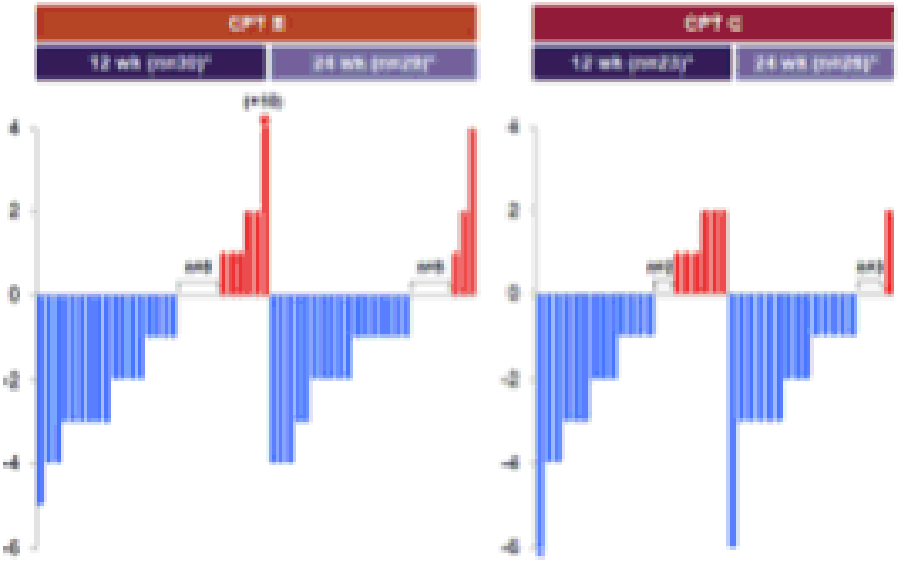


Flamm, Abst# 239

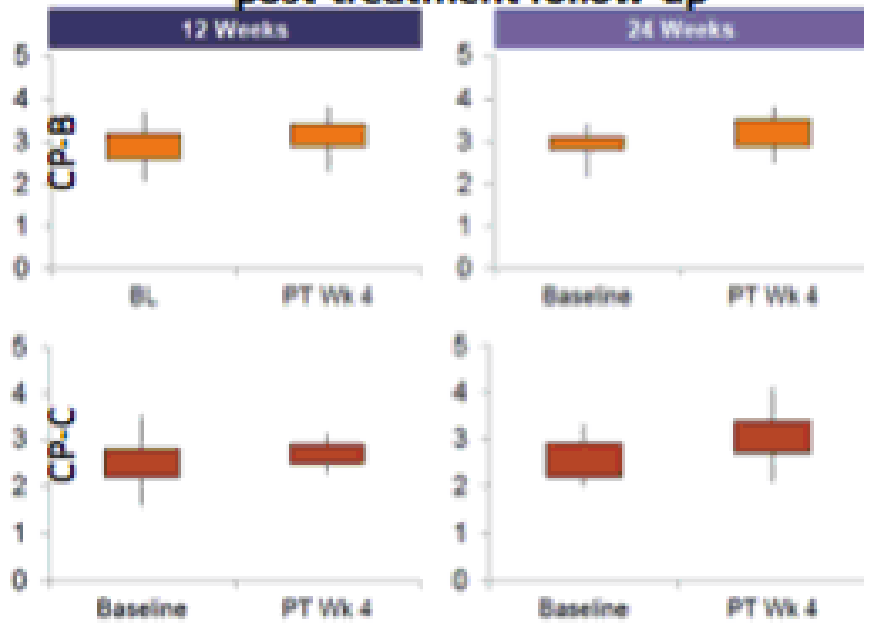
Ledipasvir/Sofosbuvir + RBV in Patients with Decompensated Cirrhosis: Preliminary Results of a Prospective, Multicenter Study

- **Safety: Only 3 early discontinuation due to AE**
- **SAE= 10%-42% (only 4 considered treatment-related)**
- **5 deaths: Septic shock (4), renal failure/cardiac arrest**

Most patients had a decrease in MELD

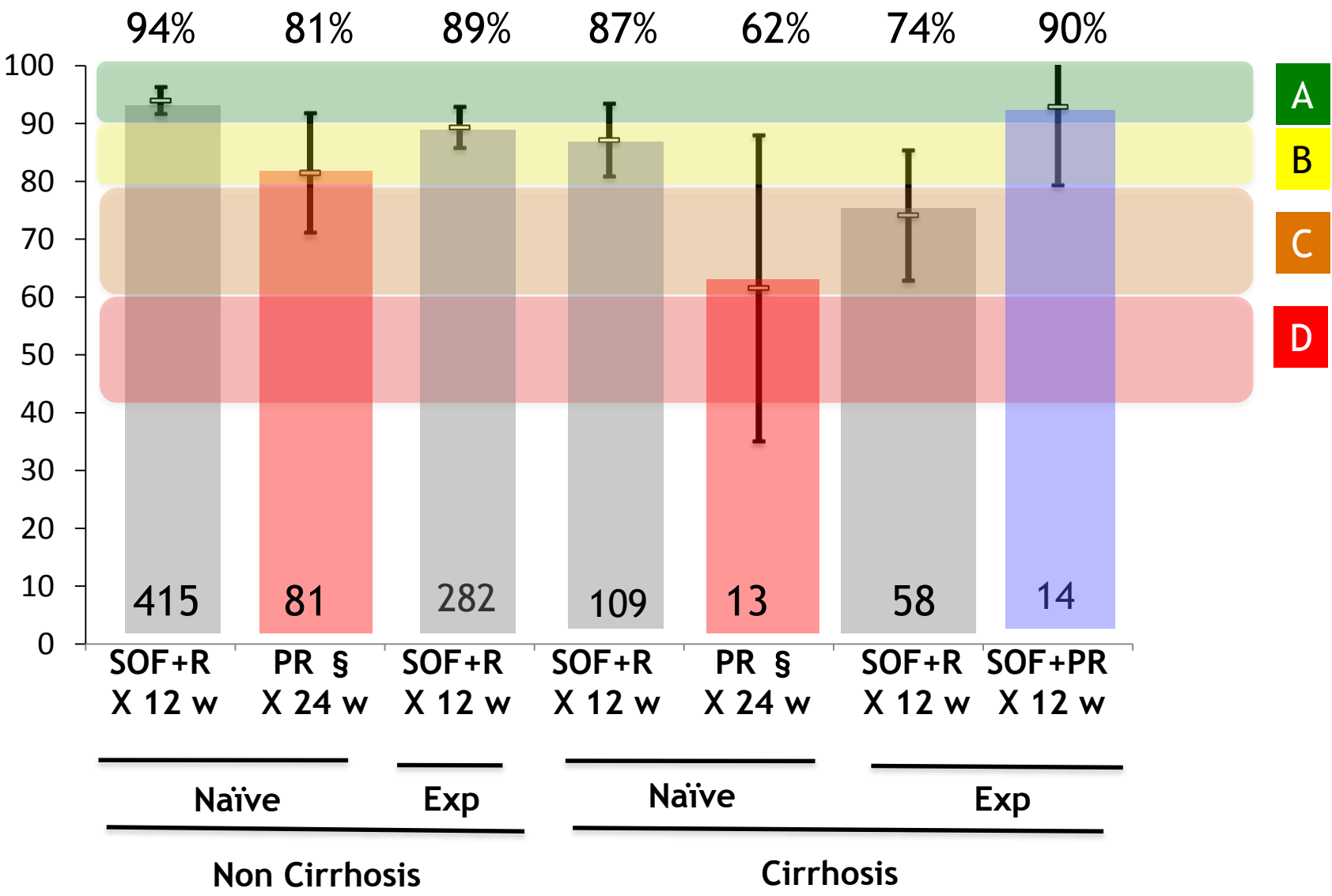


Albumin increased during post-treatment follow-up



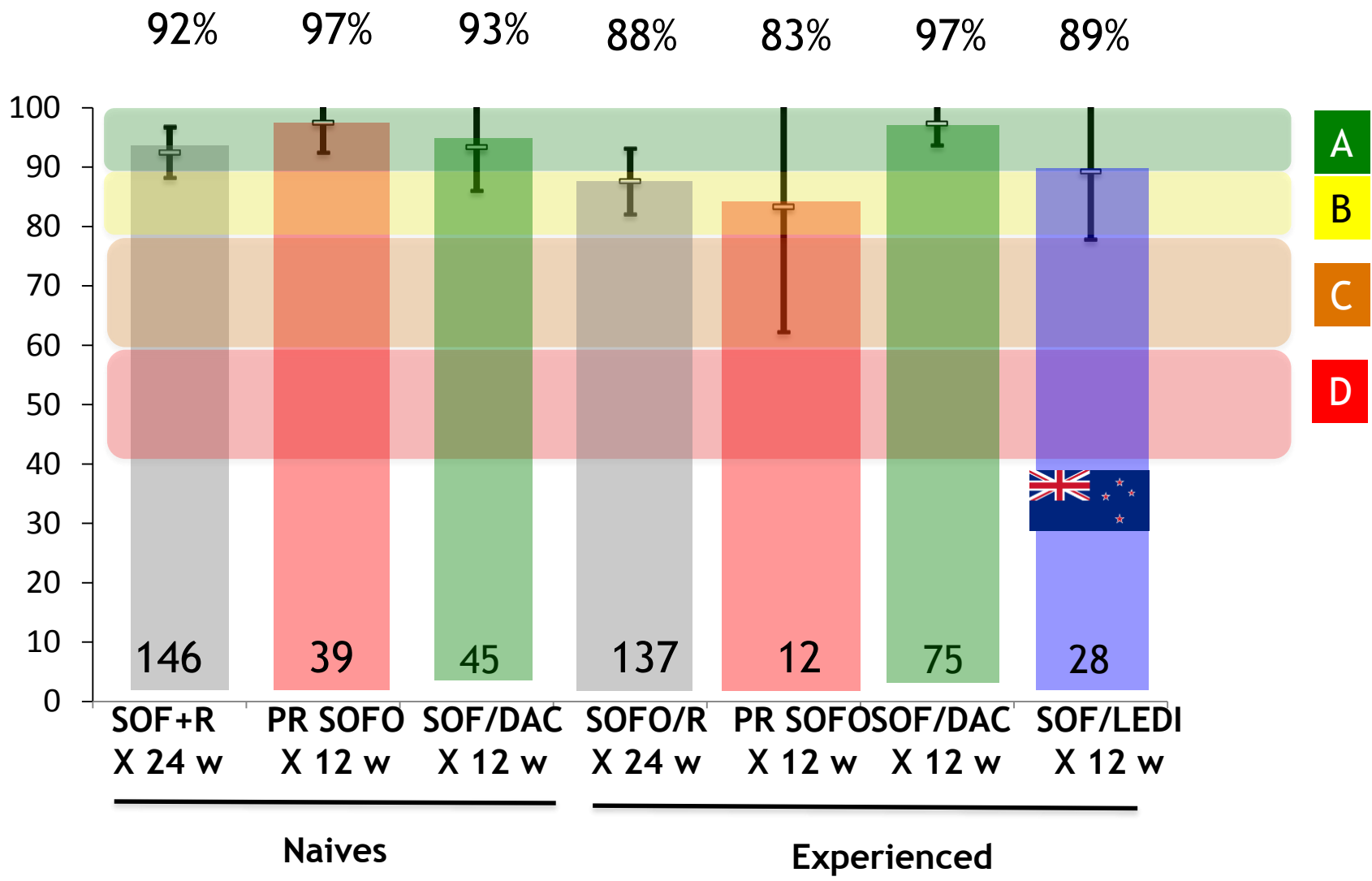
Flamm, Abst# 239

Summary of SVR rates in HCV G2 HIV-



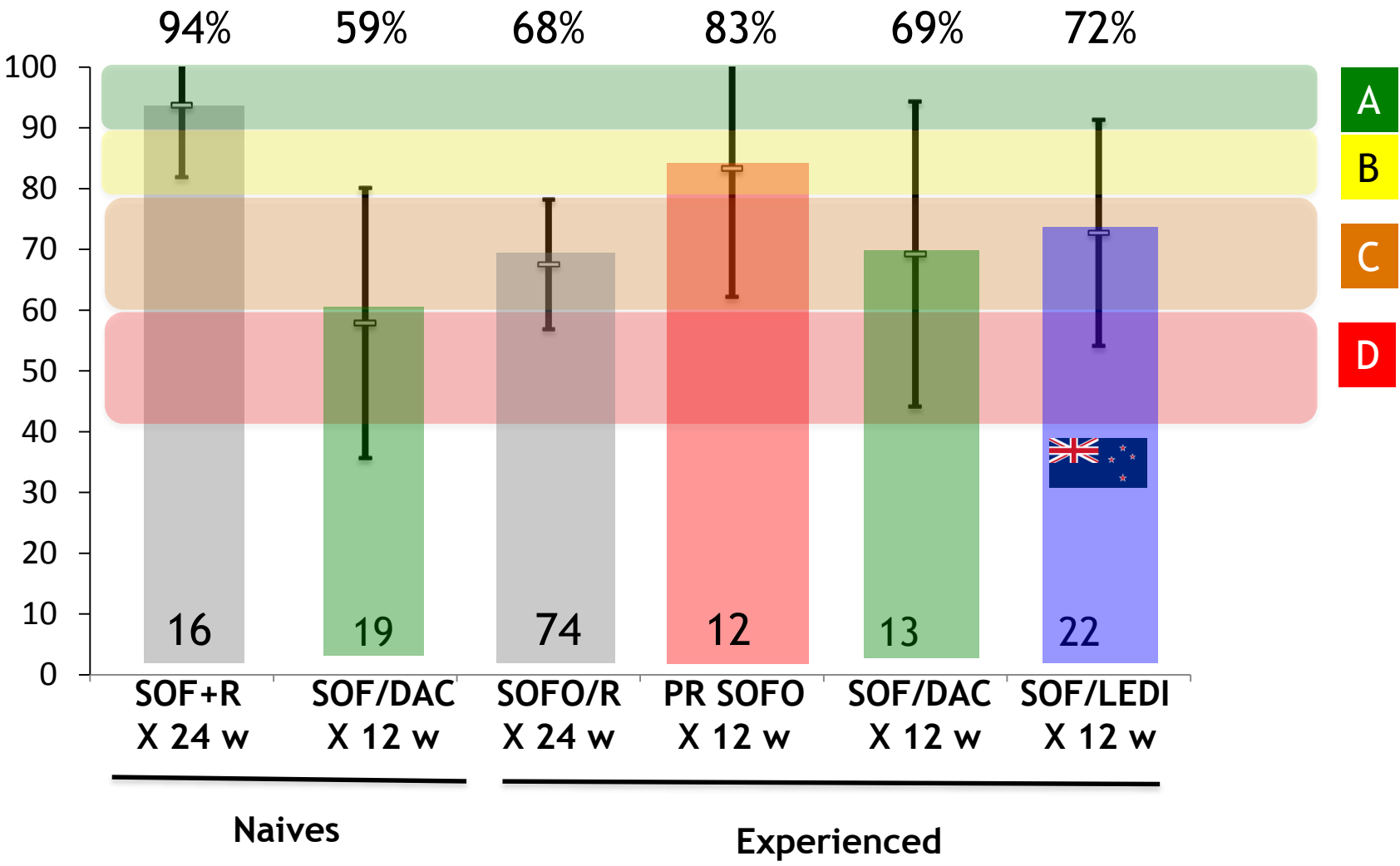
Registrative studies: Fusion, Fission Positron, Valence, Lonestar, cohorts: TRIO, TARGET

Summary of SVR rates in HCV G3 non cirrhosis HIV-& HIV+



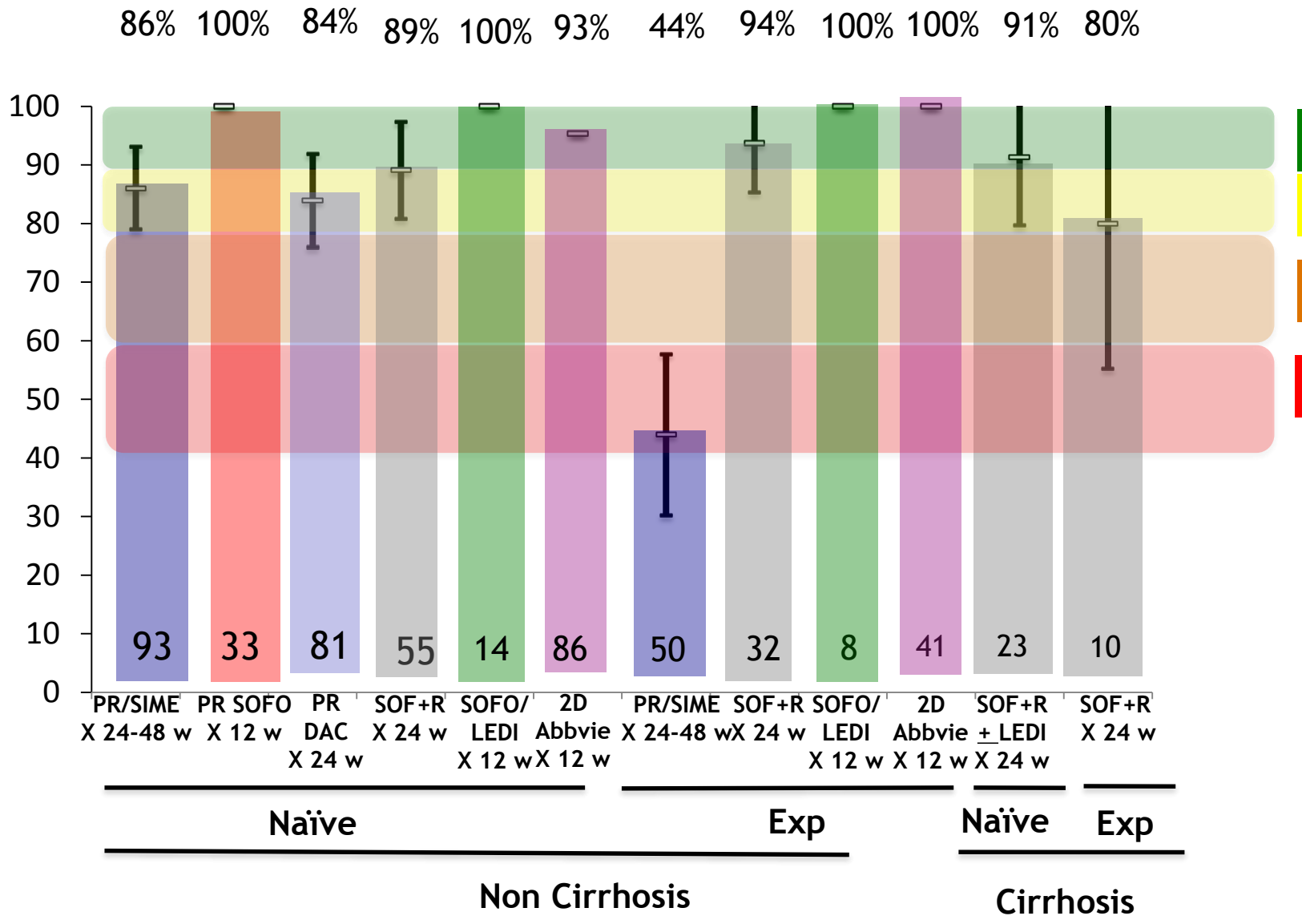
Registrative studies: Fusion, Fission Positron, Valence, Lonestar, Ally 3, Gane et al AASLD 2014

Summary of SVR rates in HCV G3 cirrhosis HIV-& HIV+



Registrative studies: Fusion, Fission Positron, Valence, Lonestar, Ally 3, Gane et al AASLD 2014

Summary of SVR rates in HCV G4 HIV- & HIV+

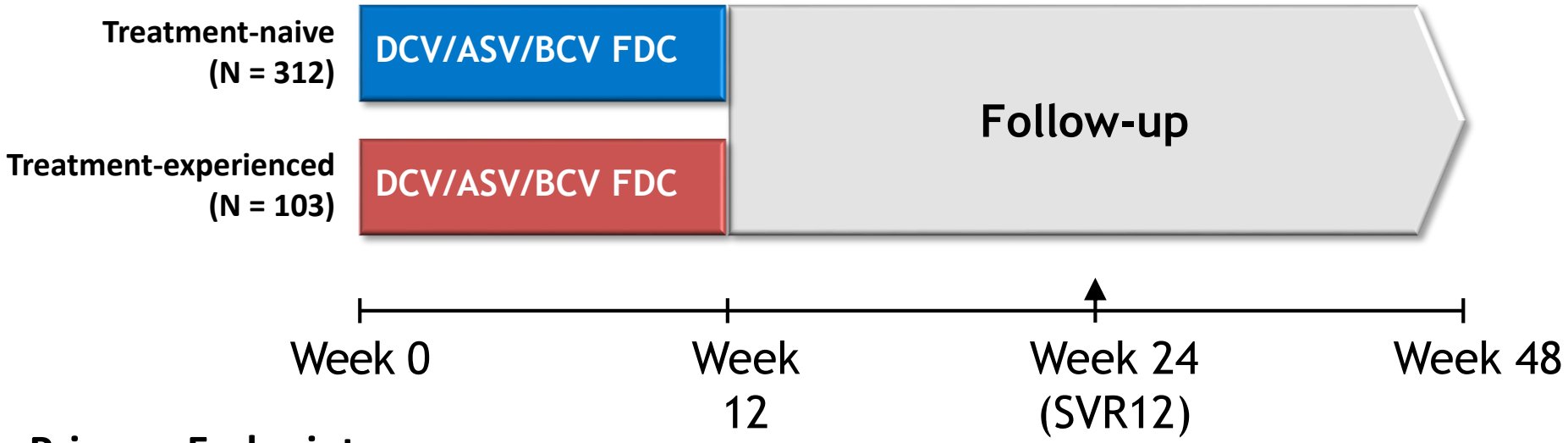


Registrative studies;RESTORE III Neutrino,PEARL -I Osinusi et al AASlD 2014, Gamal E et al AASLD 2014

New drugs and strategies for HCV treatment

- Tools & strategies
- Upcoming Results
- The future

UNITY-1 Study Design (AI443-102)



Primary Endpoint

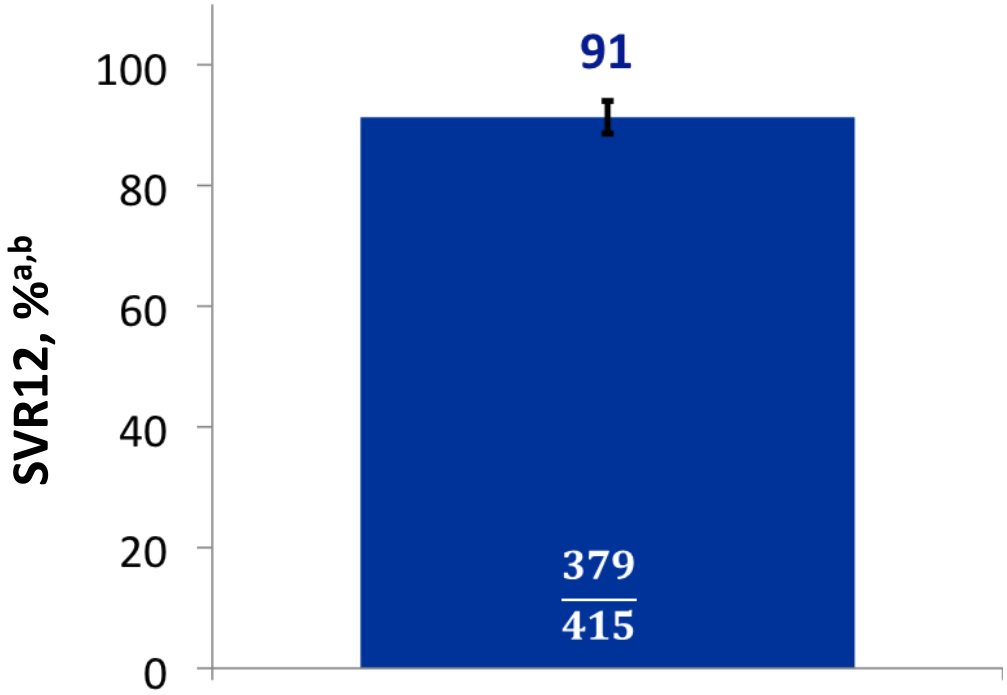
- SVR12 in treatment-naive patients
  - HCV RNA < lower limit of quantitation (LLOQ) at posttreatment Week 12
  - Demonstrate SVR12 is significantly greater than historical threshold of 79% (based on an analysis of sofosbuvir plus peginterferon/ribavirin data)
  - Assessed using the Roche HCV COBAS TaqMan® test v2.0 (LLOQ, 25 IU/mL)

Treatment regimen

- Twice-daily, fixed-dose combination tablet (DCV-TRIO)
  - DCV 30 mg / ASV 200 mg / BCV 75 mg

Poordad F *et al*. *AASLD* 2014. Poster

Overall SVR12 Rate

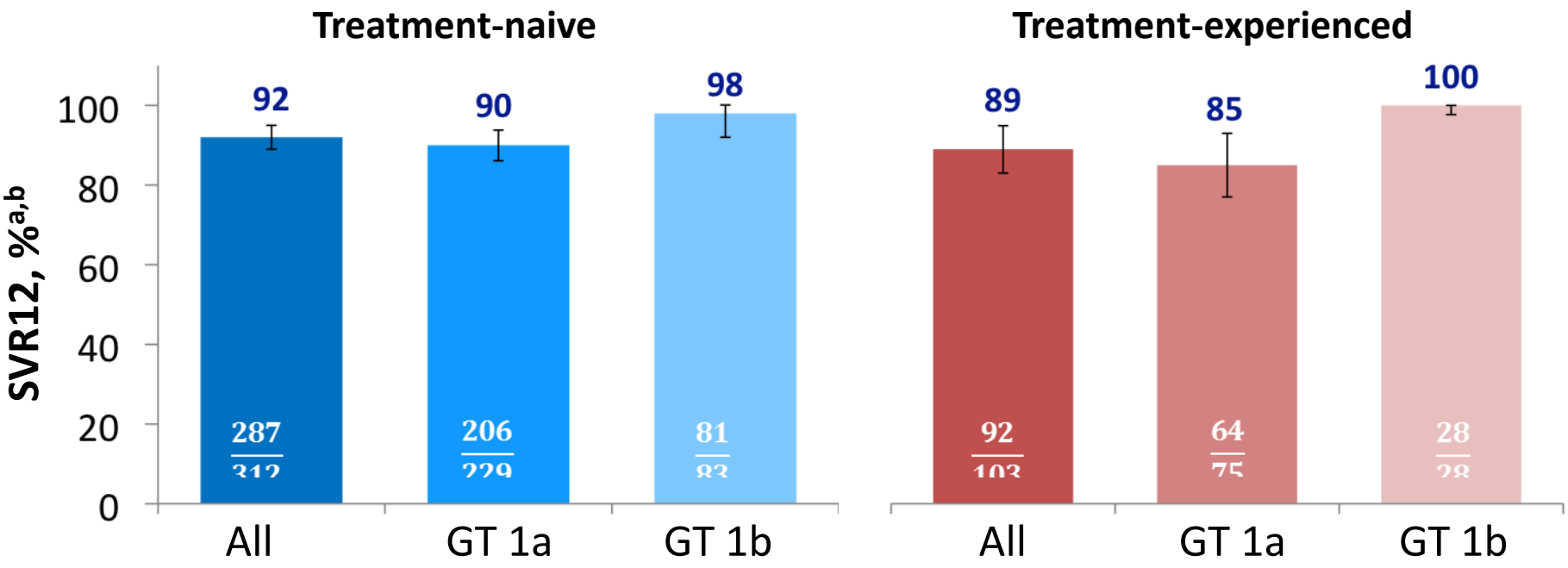


- Overall, SVR12 was achieved by 91% of HCV genotype 1-infected patients

[a] HCV RNA < LLOQ (25 IU/mL); patients with missing SVR12 data counted as treatment failures.
[b] Error bars reflect 95% CI.

Poordad F *et al*. *AASLD* 2014. Poster

SVR12 Rates by Patient Population

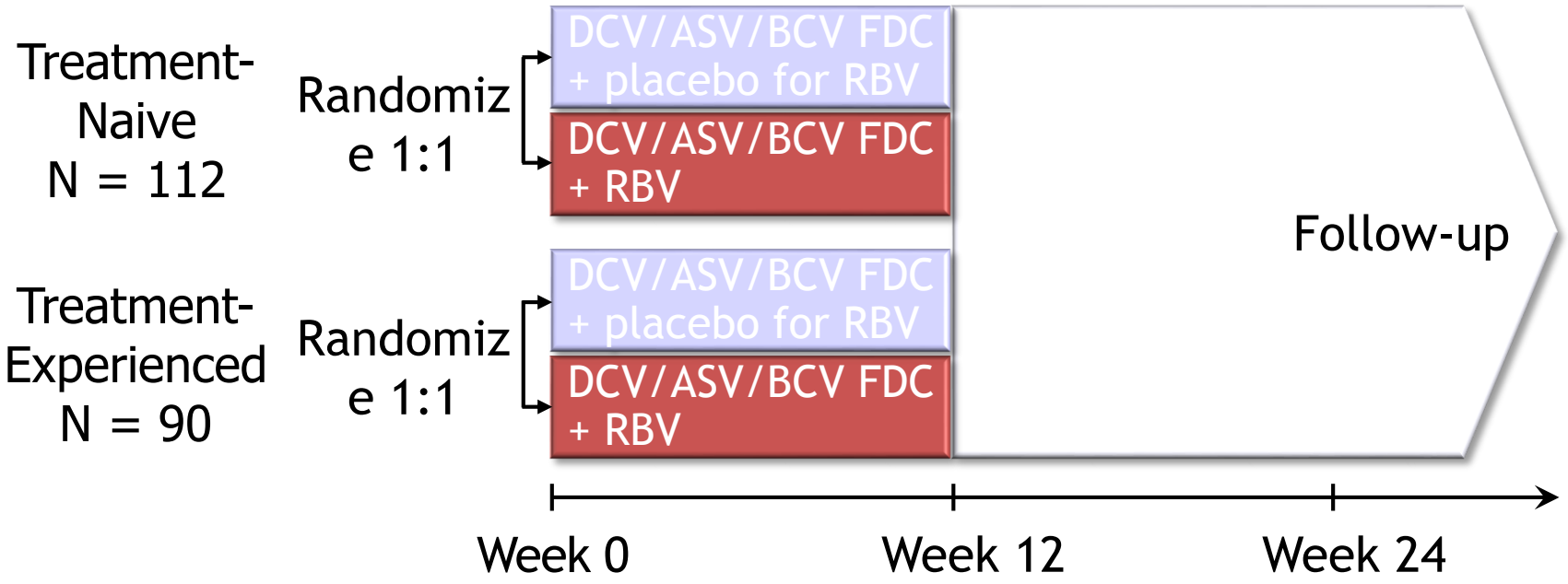


- The SVR12 rate in treatment-naive HCV GT 1 patients (92%) was significantly higher than the historical threshold rate (79%)
  - The lower bound 95% confidence interval (89%) exceeded the threshold value
- A significantly higher SVR12 rate was observed in treatment-experienced HCV GT 1 patients (89%) compared with the historical threshold rate (48%)
- High SVR12 rates (98–100%) were observed in treatment-naive and treatment-experienced patients infected with HCV GT 1b

[a] HCV RNA < LLOQ (25 IU/mL); patients with missing SVR12 data counted as treatment failures.
[b] Error bars reflect 95% CI.

Poordad F *et al*. *AASLD* 2014. Poster LB-7

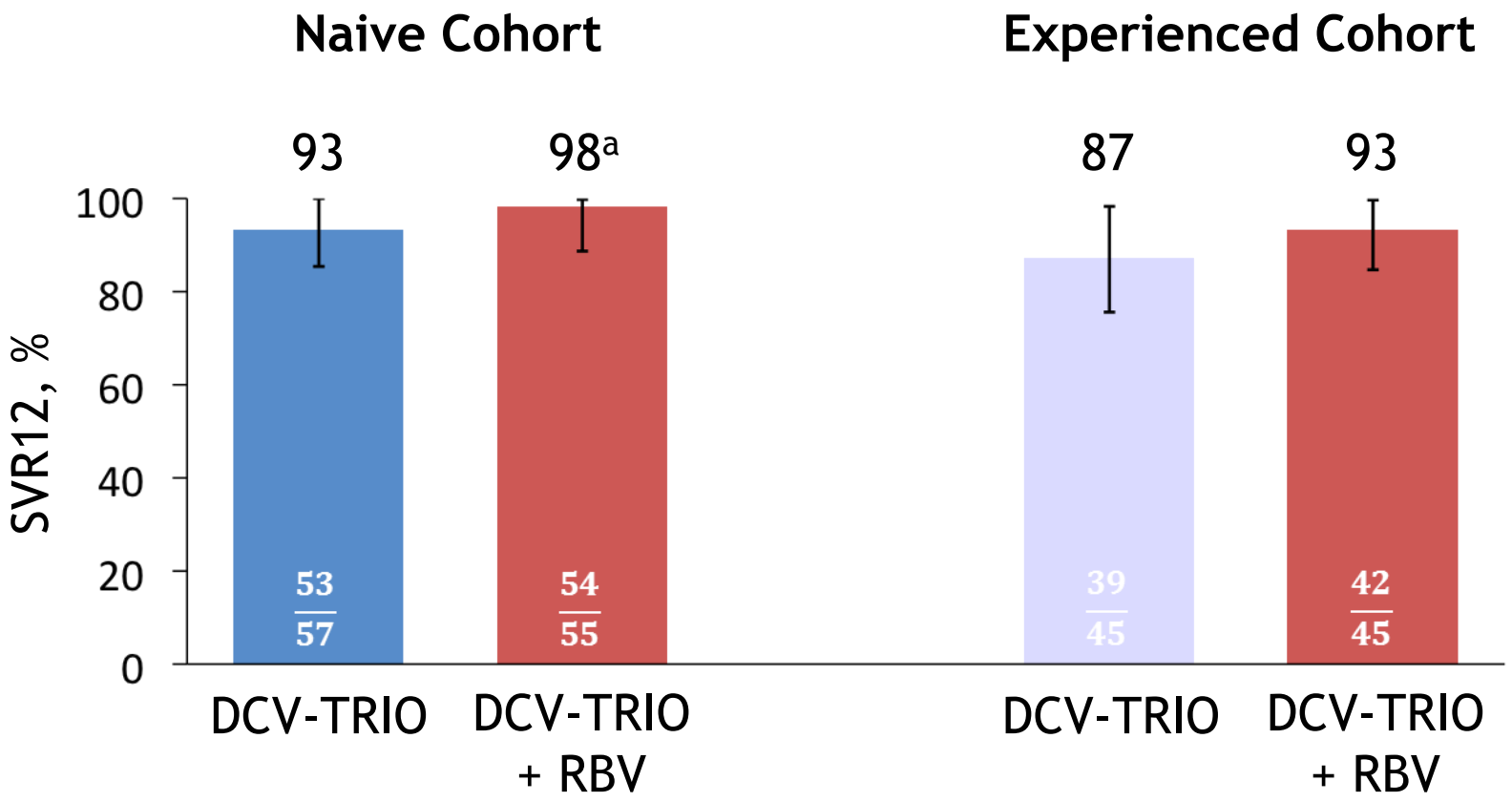
UNITY-2: Randomized, Double-Blind, Phase 3 Study



- Primary efficacy assessment: SVR12
  - HCV RNA < LLOQ (25 IU/mL) TD or TND at posttreatment Week 12
- Twice-daily fixed-dose combination (FDC)
  - DCV 30 mg / ASV 200 mg / BCV 75 mg
  - With or without weight-based ribavirin twice-daily

TD, target detected; TND, target not detected

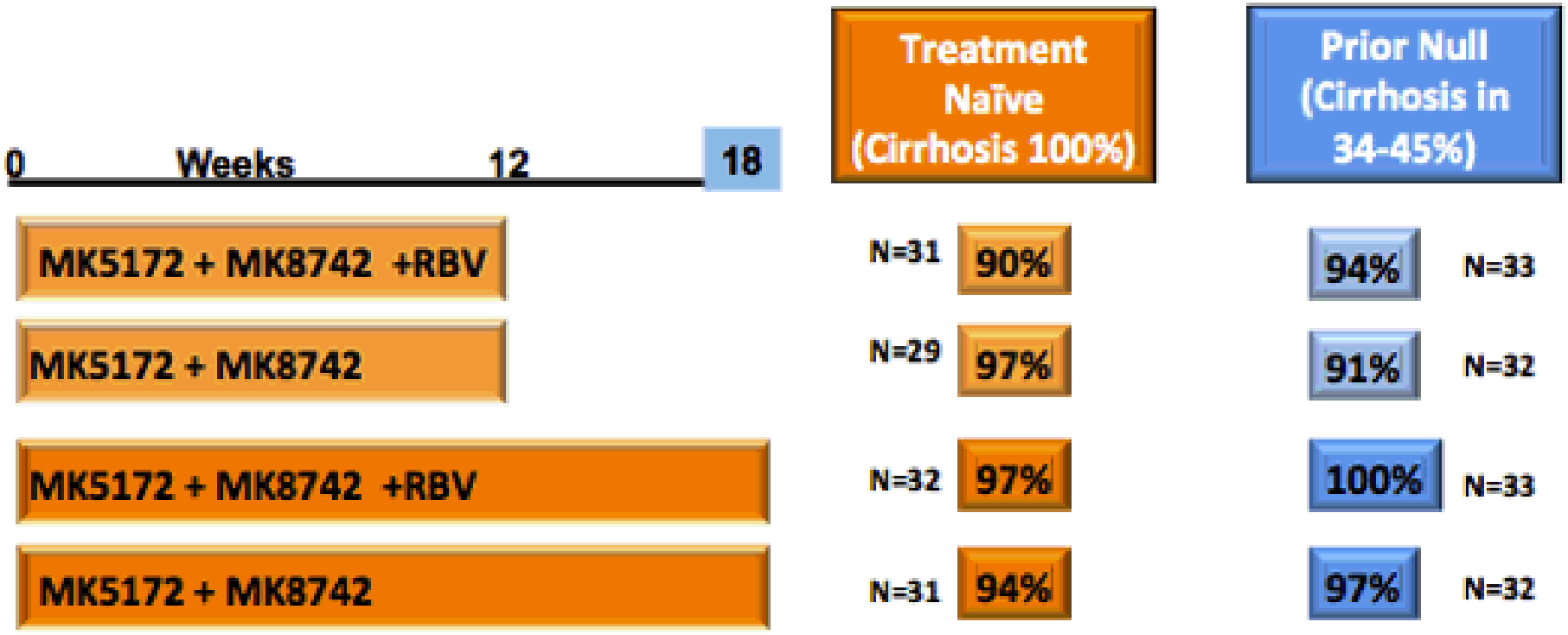
SVR12 (mITT)



[a]One patient with HCV RNA <LLOQ TND at end of therapy and posttreatment Week 4 had missing data at posttreatment Week 12.

Error bars indicate 97.5% confidence intervals.

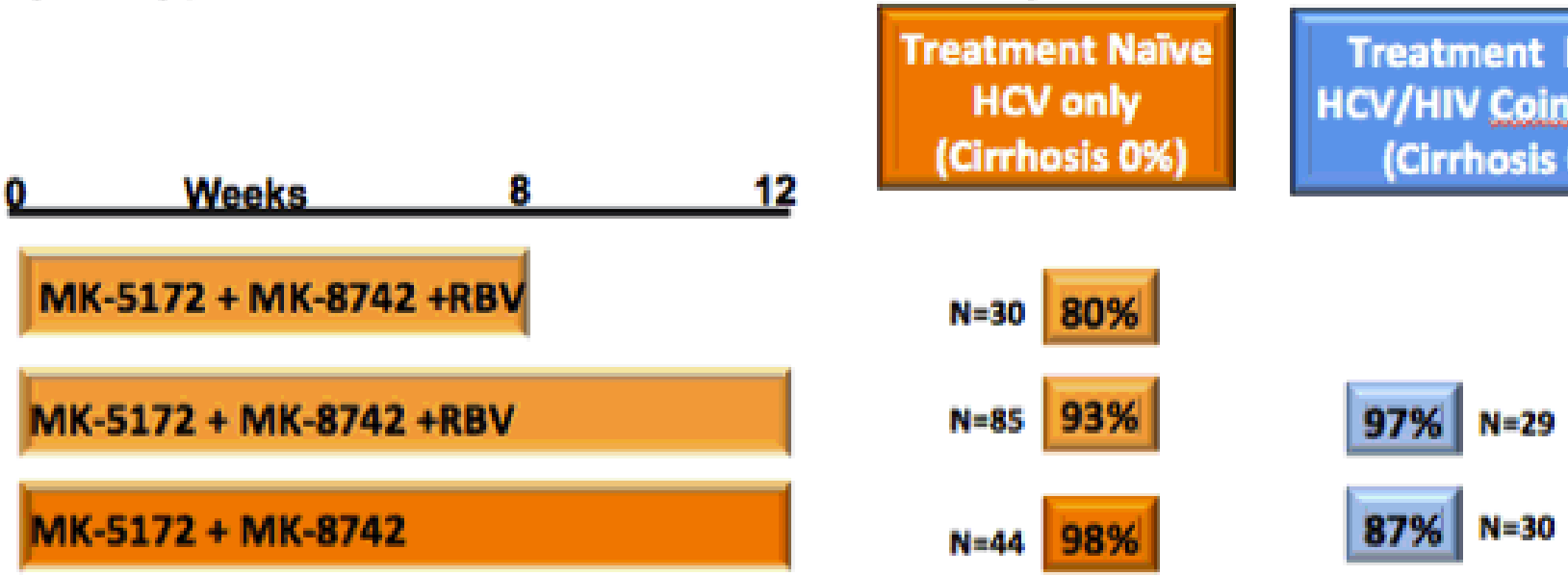
Efficacy and Safety of MK-5172 (Grazoprevir) and MK-8742 (Elbasvir) ± RBV in HCV G1 with Cirrhosis or Previous Null Response: C-WORTHY



- No substantial difference in SVR in subgroup analysis
- Virologic failure was rare overall (Relapse > VBT)
- Relapse numerically higher in RBV-free arms
- Well-tolerated with only 5 early D/C due to AE

Lawitz, Abst# 196

Efficacy and safety of MK-5172 + MK-8742 ± RBV in HCV and HIV/HCV co-infected treatment-naïve, non-cirrhotic patients with hepatitis C virus genotype 1 infection: The C-WORTHY study

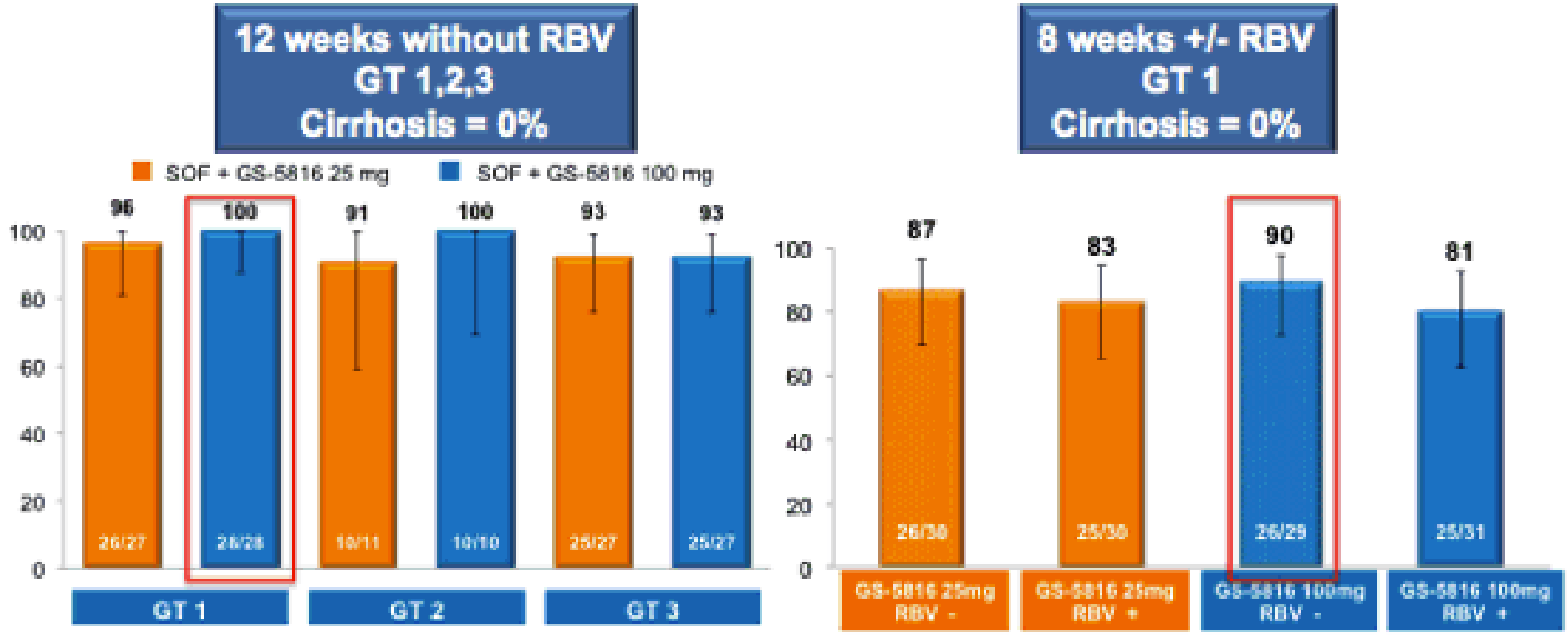


- Similar efficacy in HCV mono vs HCV/HIV co-infection
- 12-week regimens with high rates of SVR
- Relapse numerically higher in 8 week arm
- HIV suppression remained stable
- No discontinuation due to AE or lab abnormalities

Sulkowski, Abst# 236

Safety and Efficacy of Sofosbuvir+ GS-5816 ± Ribavirin for 8 or 12 Weeks in Treatment Naïve Patients with GT 1-6 HCV Infection

- Aim: Dose finding for new NS5A inhibitor and to evaluate treatment duration
- All patients received sofosbuvir + GS-5816 ± RBV

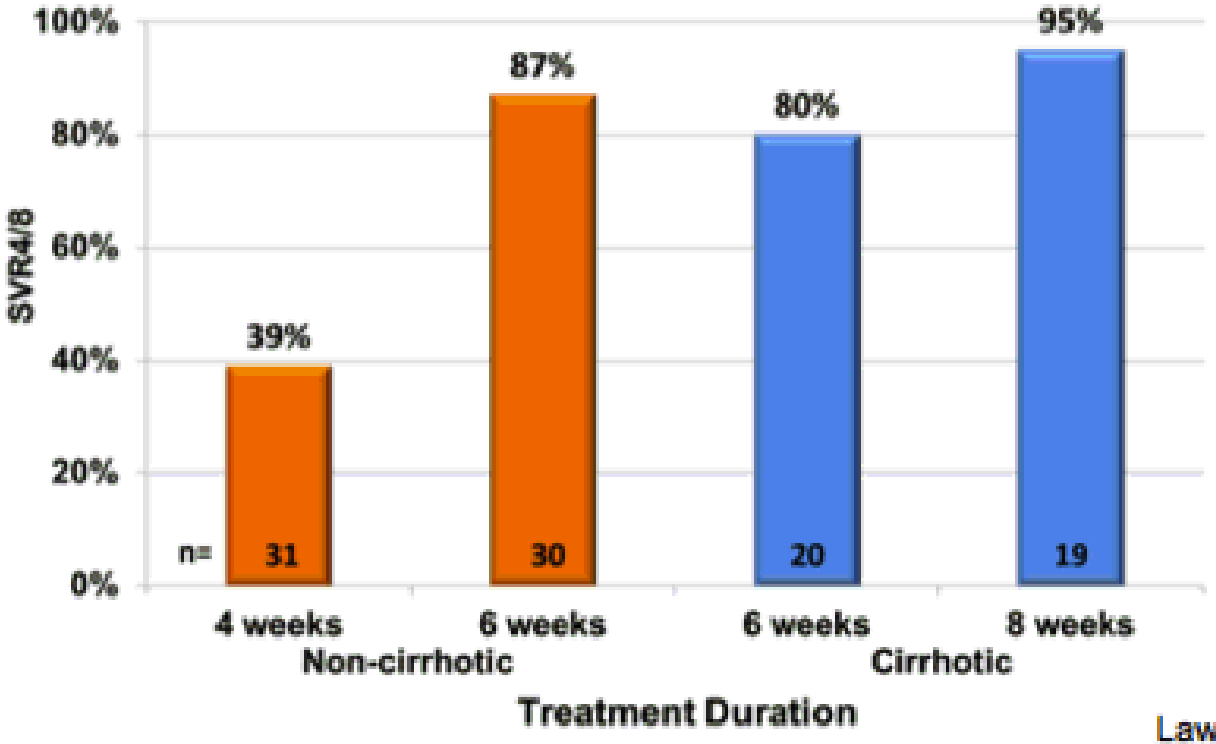


- Higher relapse rates in 8 wks vs 12 wks
- RBV did not mitigate risk of relapse w/ 8 week duration
- Virological failure associated with NS5A RAVs

T.T. Tran, Abst# 80

C-SWIFT: MK-5172+MK-8742+Sofosbuvir in Treatment Naïve Patients with HCV GT1, with or without Cirrhosis for Durations of 4,6, or 8 weeks

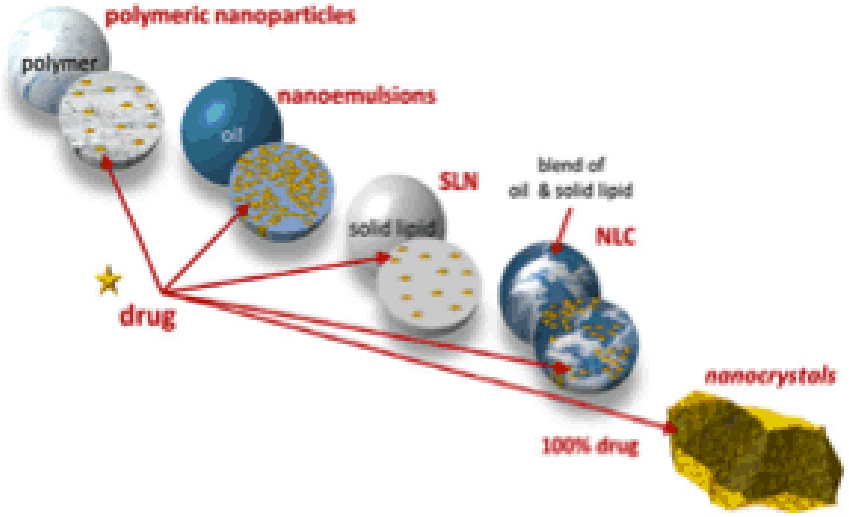
- Optimized regimen of PI + NS5A + NUC
- Evaluated 3 very short durations of therapy (4, 6, or 8 weeks)
- Non-cirrhotics: 4-6 weeks; Cirrhotics: 6-8 weeks
- Treatment failure due exclusively to relapse
- Detailed evaluation of baseline RAVs and PK



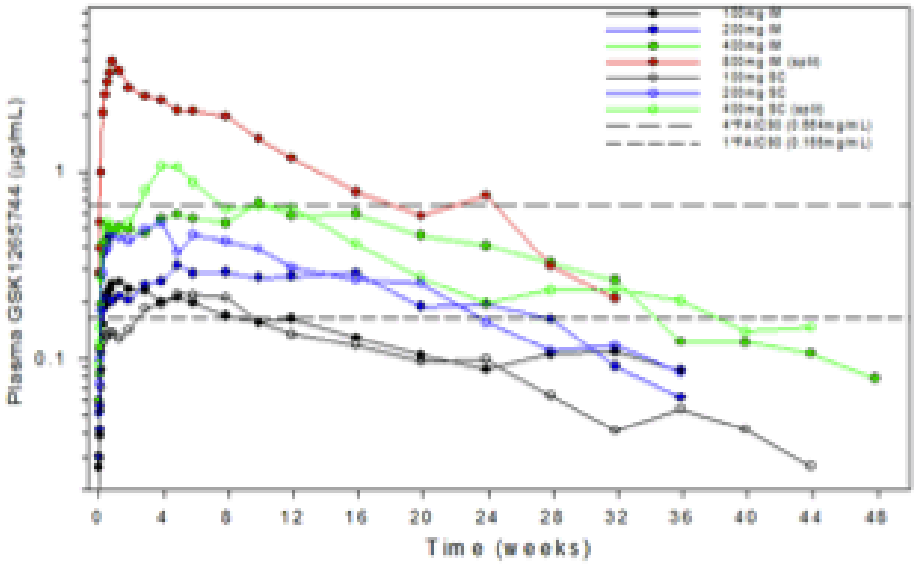
Lawitz, Abstr# LB-33

Long-acting nanoformulations of antiviral drugs for treatment and prevention of infection

- Drug nanocrystal suspended in liquid = nanosuspension
  - Nano-dimensions vastly increase drug dissolution rate
  - Allows high drug loading compared to matrix approaches



Rilpivirine and Cabotegravir (GSK1265744) are clinical-stage candidates



Cabotegravir (analogue to dolutegravir) as a single IM (gluteal) or SC (abdominal) injection provides detectable drug in plasma for 48 Weeks

Margolis DA, Brinson CC, Eron JJ, et al. 2014 CROI; Abstract 91LB

Key messages

- HCV Eradication
  - It is feasible in the single patient
    - Early treatment improvement of quality of life and life expecyancy
    - Late treatment : improved survival?
  - Three very successful strategies: tailored treatment → difficult access to treatment (price and complexity)
    - Peg IFN based
    - Sofosbuvir based
    - Sofosbuvir free
  - Lower efficacy in HCV G3 with poorer results in cirrhotics PEGIFN experienced --> add RBV + a DAA increase duration SOFO + NS5A + RBV x 24 weeks
  - Future perspectives → improvement in efficacy & access to treatment
    - One pill (injection?) for all
    - Short courses
    - Price reduction

Where we go: the future 10 commandments for the magic drug

1. HIGH **E**FFICACY
2. LOW **R**ESISTANCE (high genetic barrier)
3. FOR **A**LL GENOTYPES
4. SHORT **D**URATION
5. TOLERAB**I**LITY
6. PHARMA**C**OKINETIC (low pill burden)
7. ONLY OR**A**L REGIMEN or 1 SHOT INJECTION (IFN free)
8. DRUG IN**T**ERACTION
9. AVAILABLE: C**I**RRHOSIS, ELD, HIV-HCV…
10. C**O**ST REDUCTIO**N** (access program)

HCV ERADICATION WORLDWIDE

Courtesy of T Asselah.