OSPEDALE NIGUARDA
CA' GRANDA

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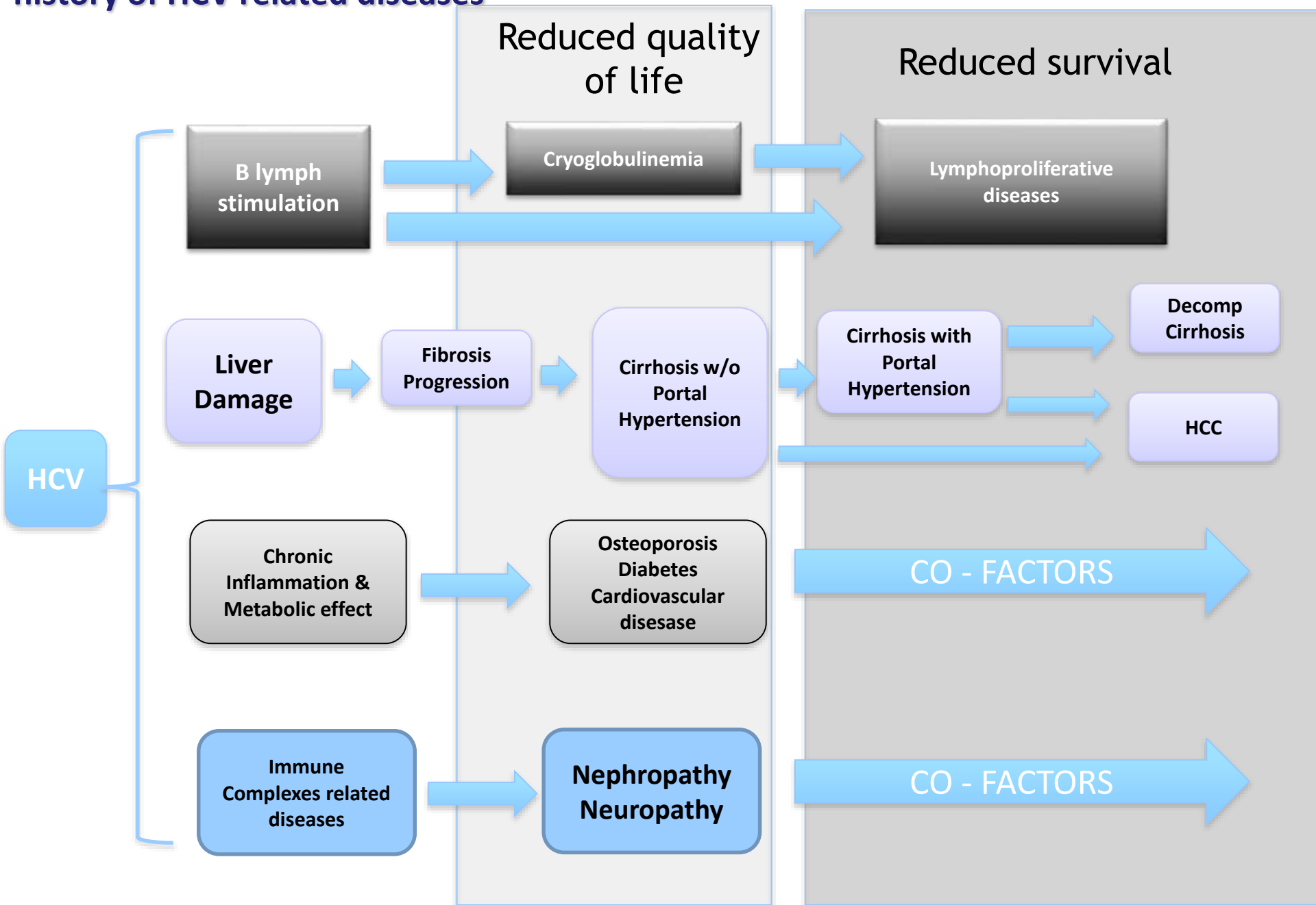
Il trattamento dell'epatite C stato dell'arte

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



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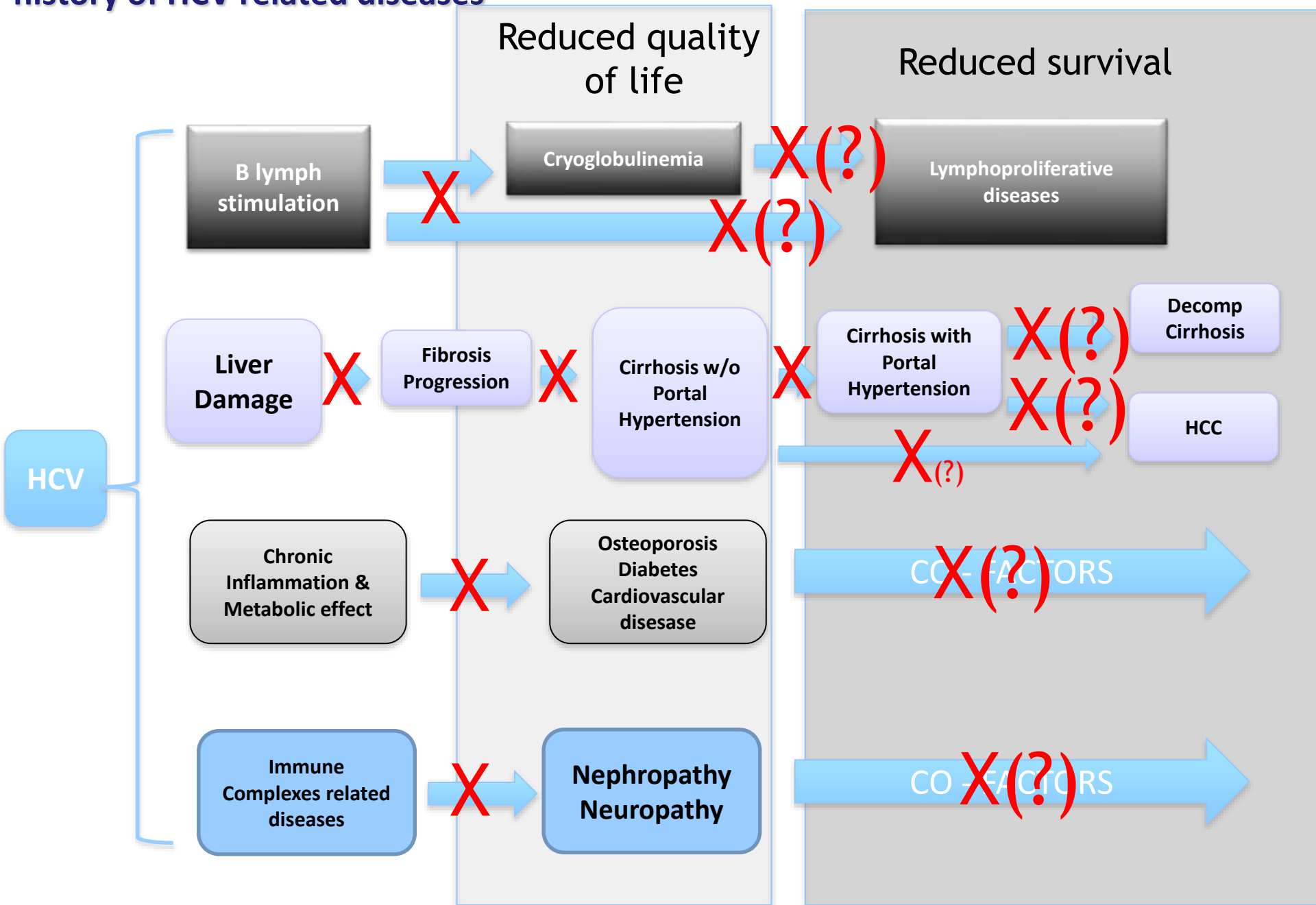

Il trattamento dell'epatite C: stato dell'arte

- Basi virologiche del trattamento
- Strategie di terapia
- Terapia anti HCV : AD 2015
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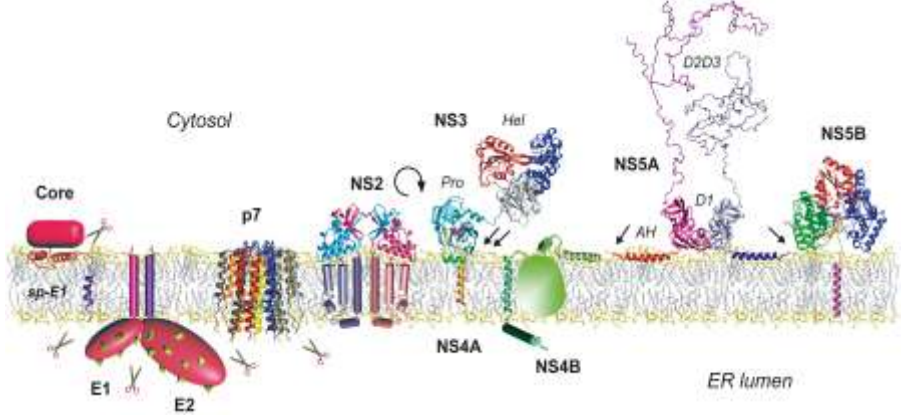
HCV targets for therapy



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

Receptors binding
And endocytosis

Fusion and
decapsidation

(+) RNA

Trasltion

Transport and release

Virion assembly

Inhibitors of viral assembly and relaese :
Celgosivir
NS5A I

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

Protease inhibitors

Translation and processing of polyprotein

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

1. Lindenbach BD & Rice CM. Unravelling hepatitis C virus replication from genome to function. *Nature* 2005;Moradpour D and Penin F. Curr Top Microbiol Immunol

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}

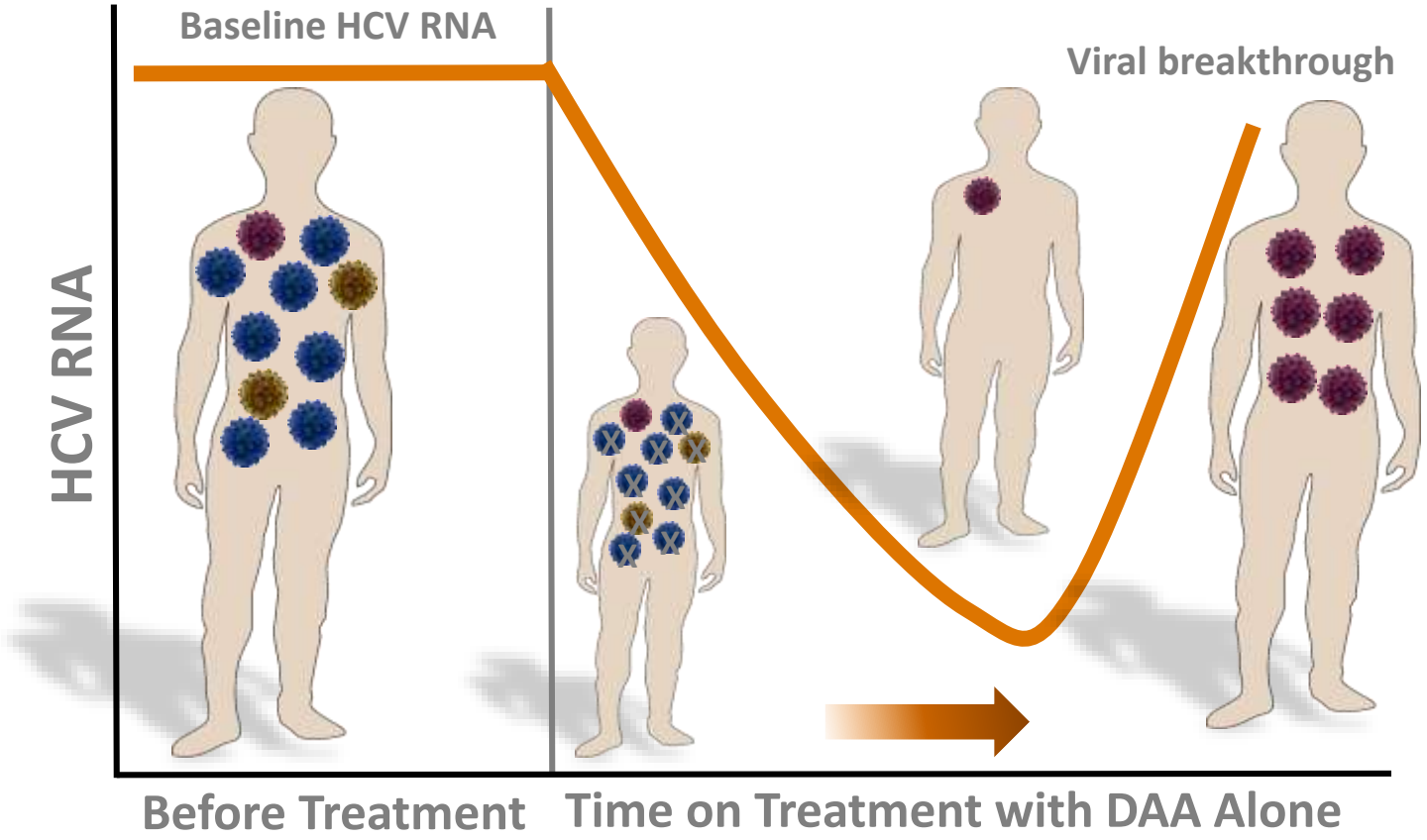
- HCV genome ~ 9600 nucleotides; the average number of changes per genome is 0.096 per replication cycle
- Before treatment, a new virion has a probability of 91% to carry an unmutated genome and 8.7% to carry one substitution

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;282:103–7
Domingo E, et al. Viral Hepatitis Rev 1996;2:247–61; Cuevas JM, et al. J Virol 2009;83:5760–4

Emergence of Pre-existing Resistant Variants During Treatment with DAA



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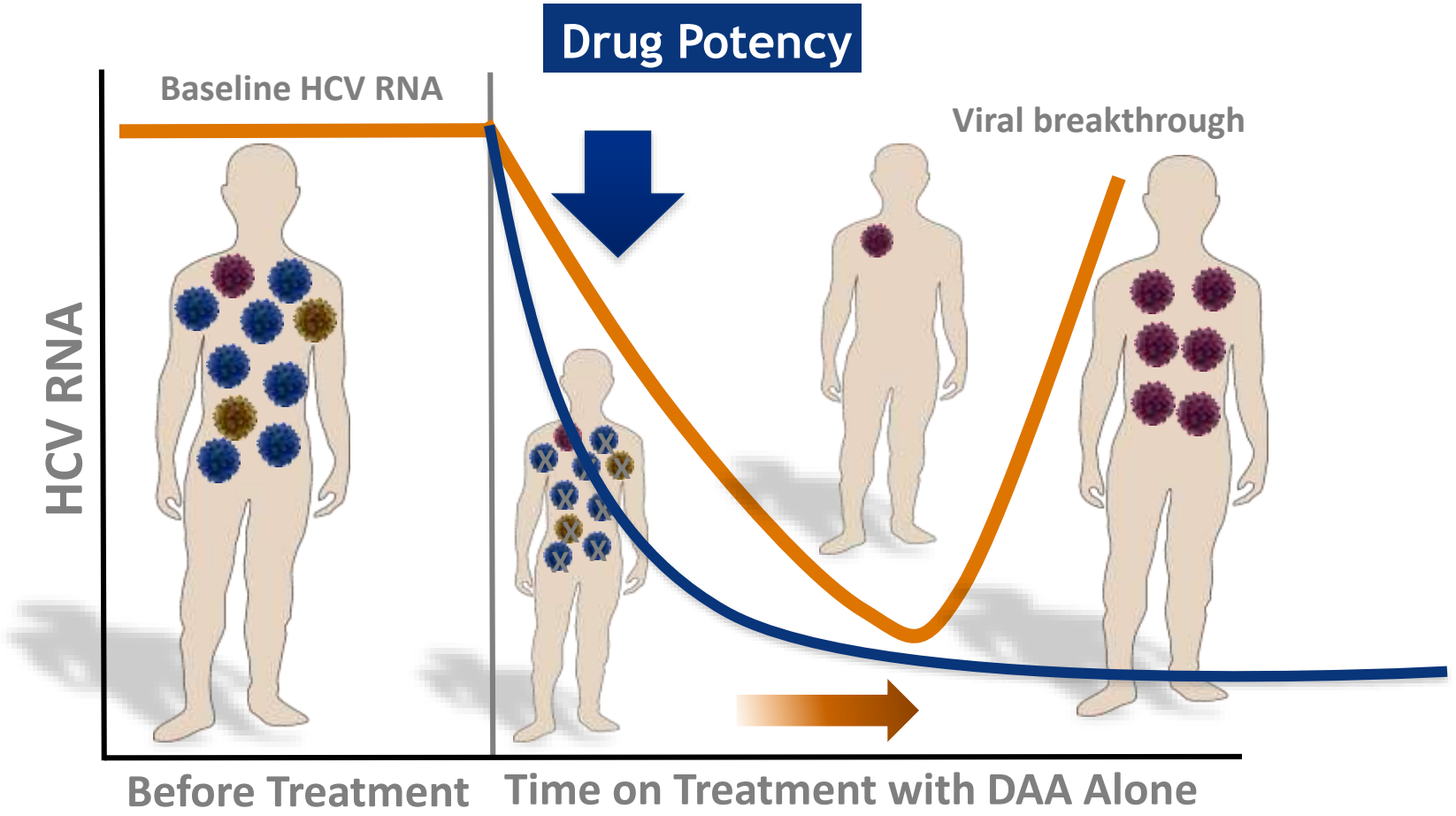

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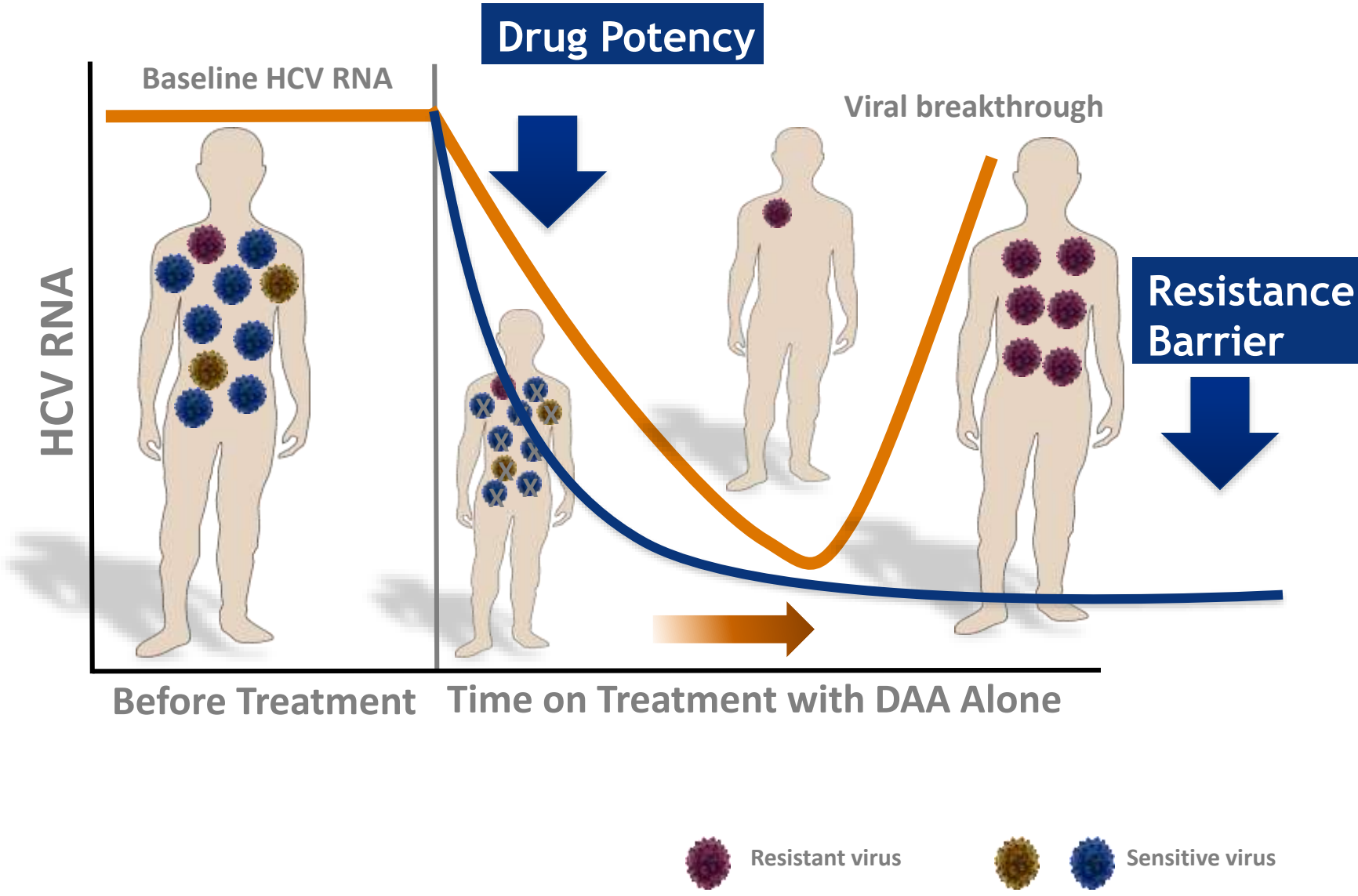

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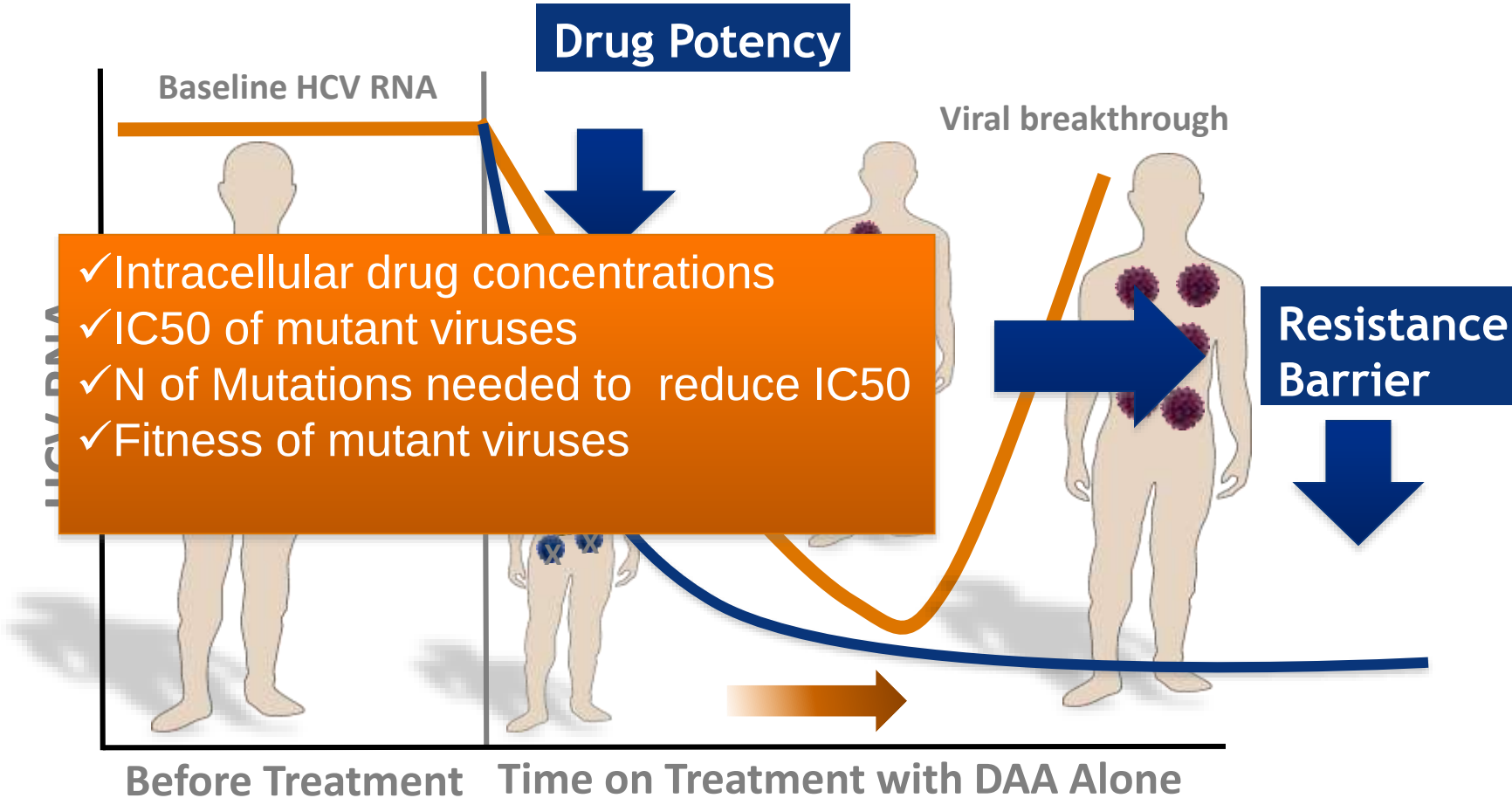

DAA classes and subclasses

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**
NS5a inhibitor " ..asvir"	1st Generation Daclatasvir, Ledipasvir Ombitasvir, Elbasvir	**High**	**Medium- High**
	2nd Generation Velpatasvir (GS-5816), ABT530 (in vitro)	**High**	**High**
Ppolymerase inhibitors "..buvir" NN	Dasabuvir Beclobuvir	**Low-Medium**	**Low**
Nucleos/tides	2nd Generation : Sofosbuvir	**High**	**High**

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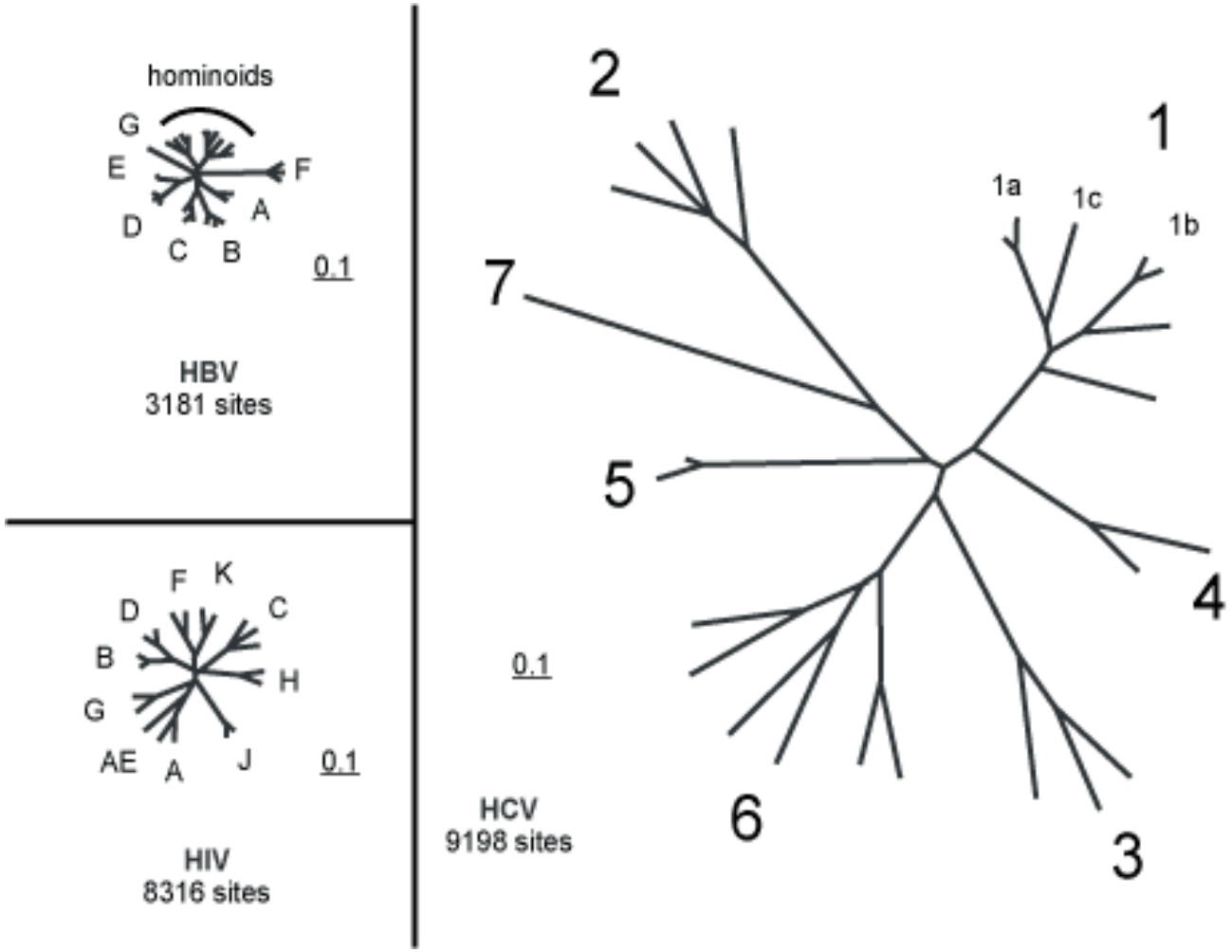
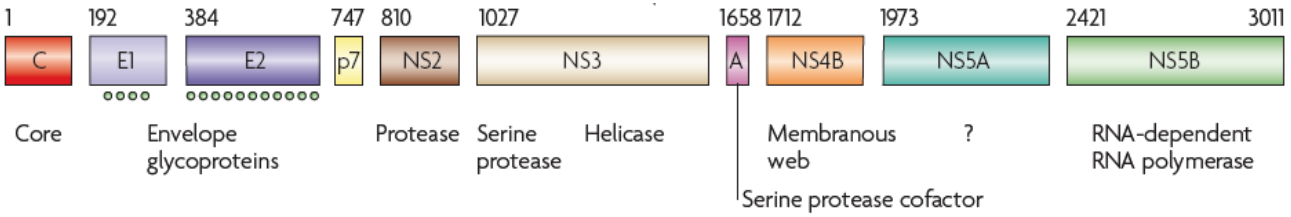
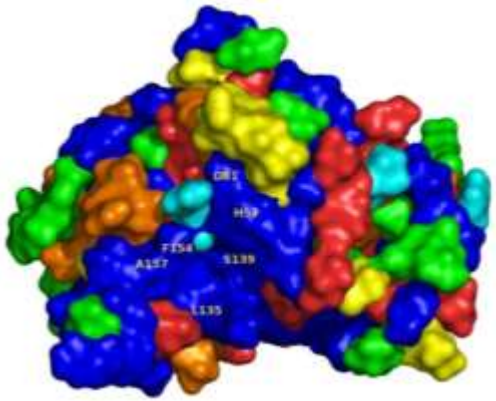
CONSEQUENCES OF HCV VARIABILITY AT POPULATION LEVEL: HCV GENOTYPES

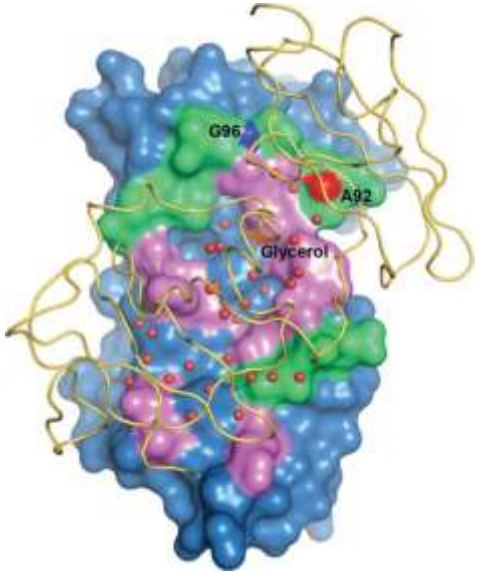


HCV protein variability

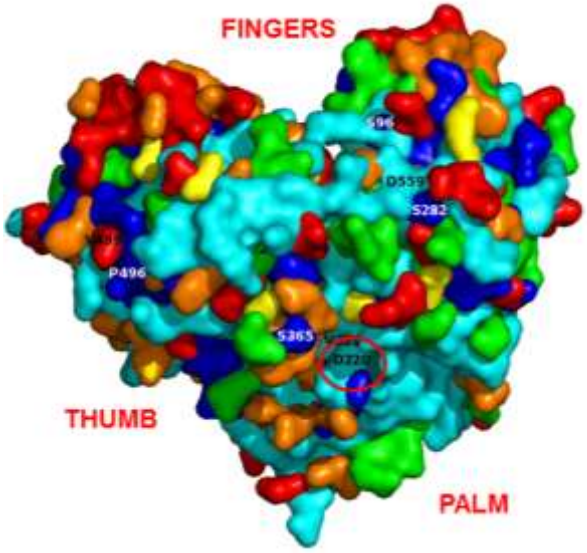




47% amino acid of HCV PROTEASE NS3 are conserved among All HCV-genotypes



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 et al., PLoS ONE 2012

Love et al., J Vir 2009

Amino acid variability:

0% ≤1% 1-5% 5-10% 10-25% >25%

Di Maio et al., submitted 2013

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. Simeprevir Paritaprevir/r	●	●	●	●	●
	2nd Generation Grazoprevir ABT 493	●	●	●	●	●
NS5a Inhibitor	1st Generation Ledipasvir Ombitasvir Elbasvir	●	●	●	●	●
	Daclatasvir 2nd Generation Valpatasvir ABT 530	●	●	●	●	●
NN Polymerase Inhibitors	Dasabuvir	●	●	●	●	●
Nucleos/tides Polymerase inhibitors	2nd Generation : Sofosbuvir	●	●	●	●	●

● High ● Moderate ● Low ● Very low

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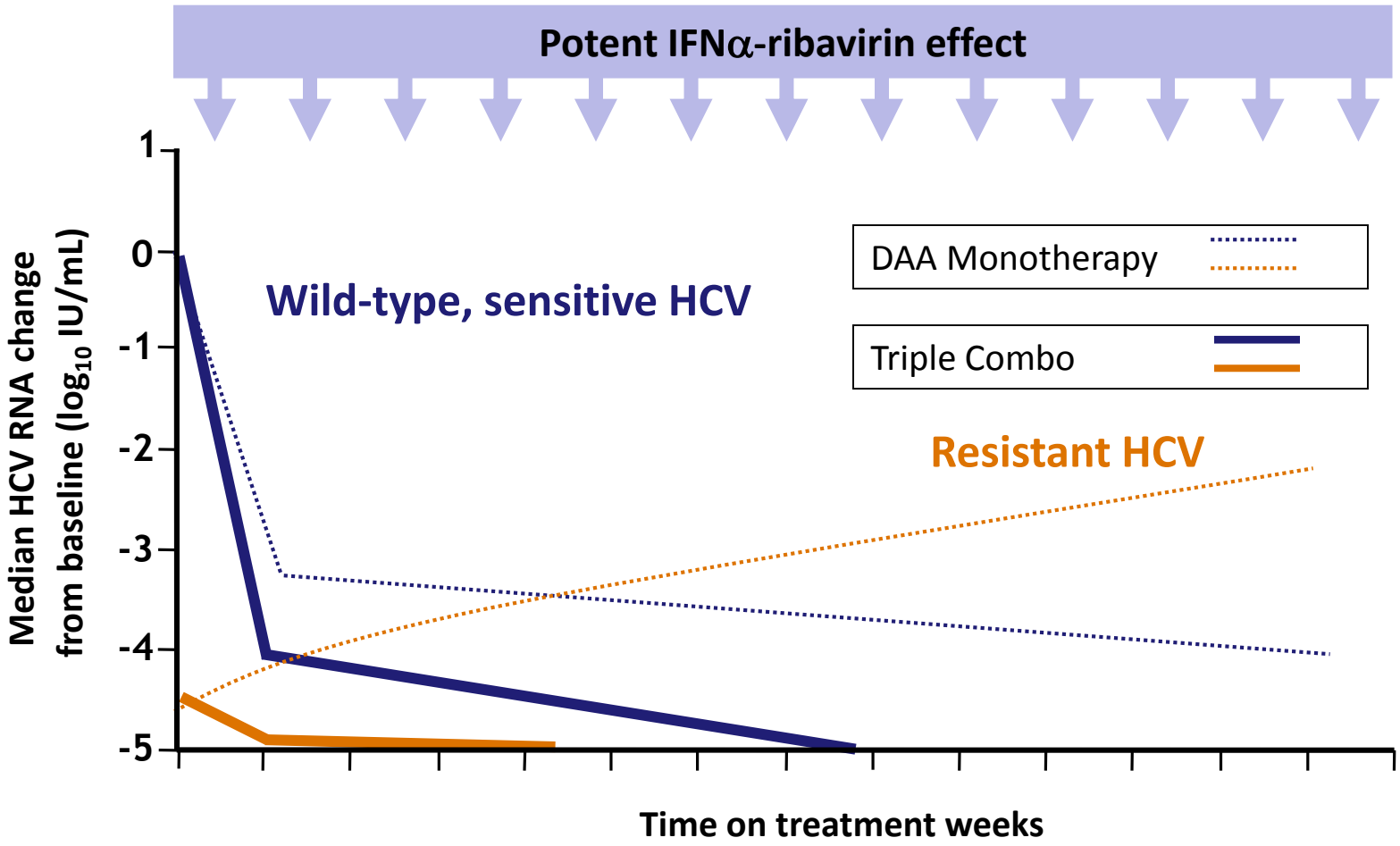
Combo with PEGIFN + RBV of 1 DAA low resistance barrier (Boceprevir, Simeprevir and Daclatasvir)



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

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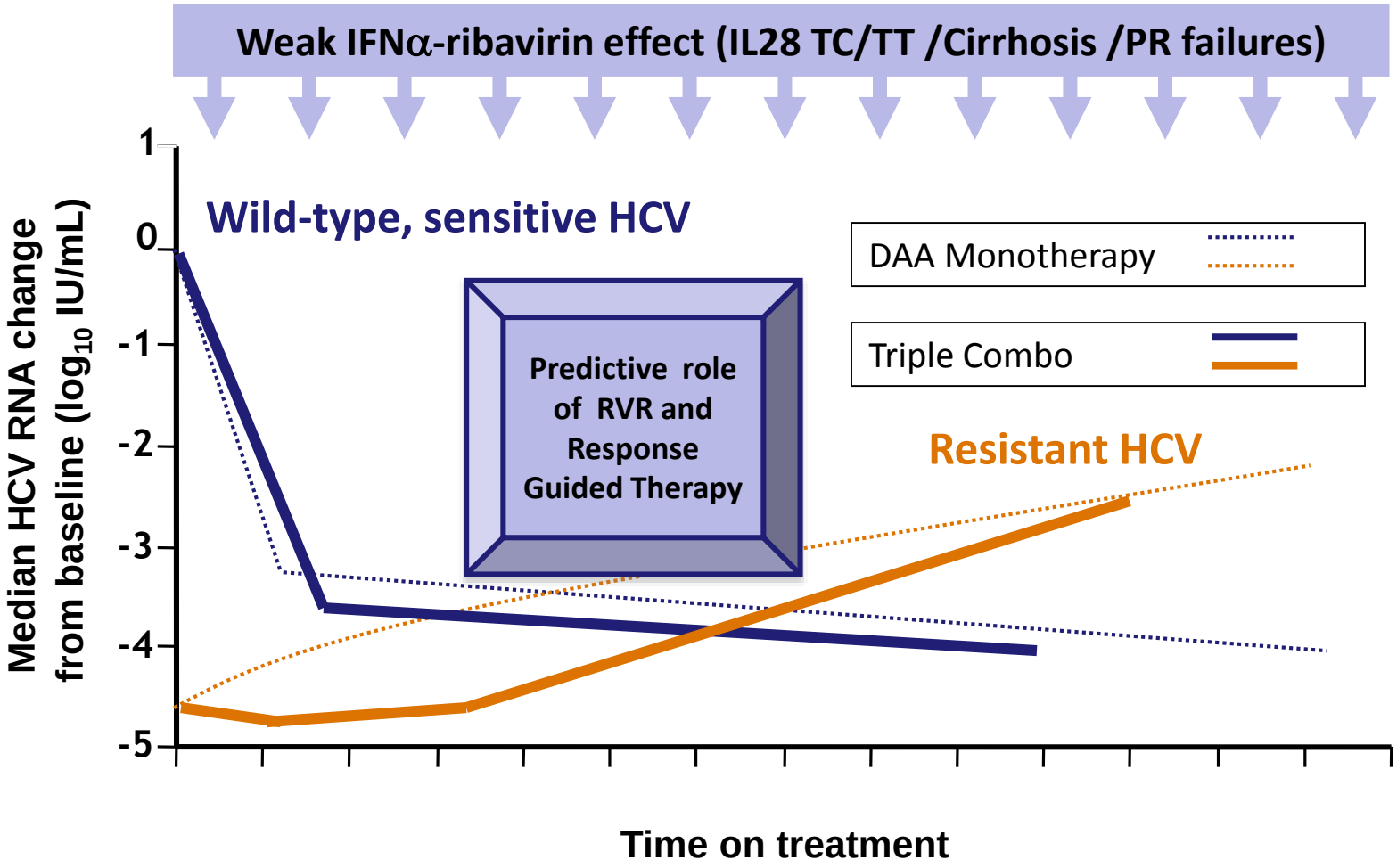
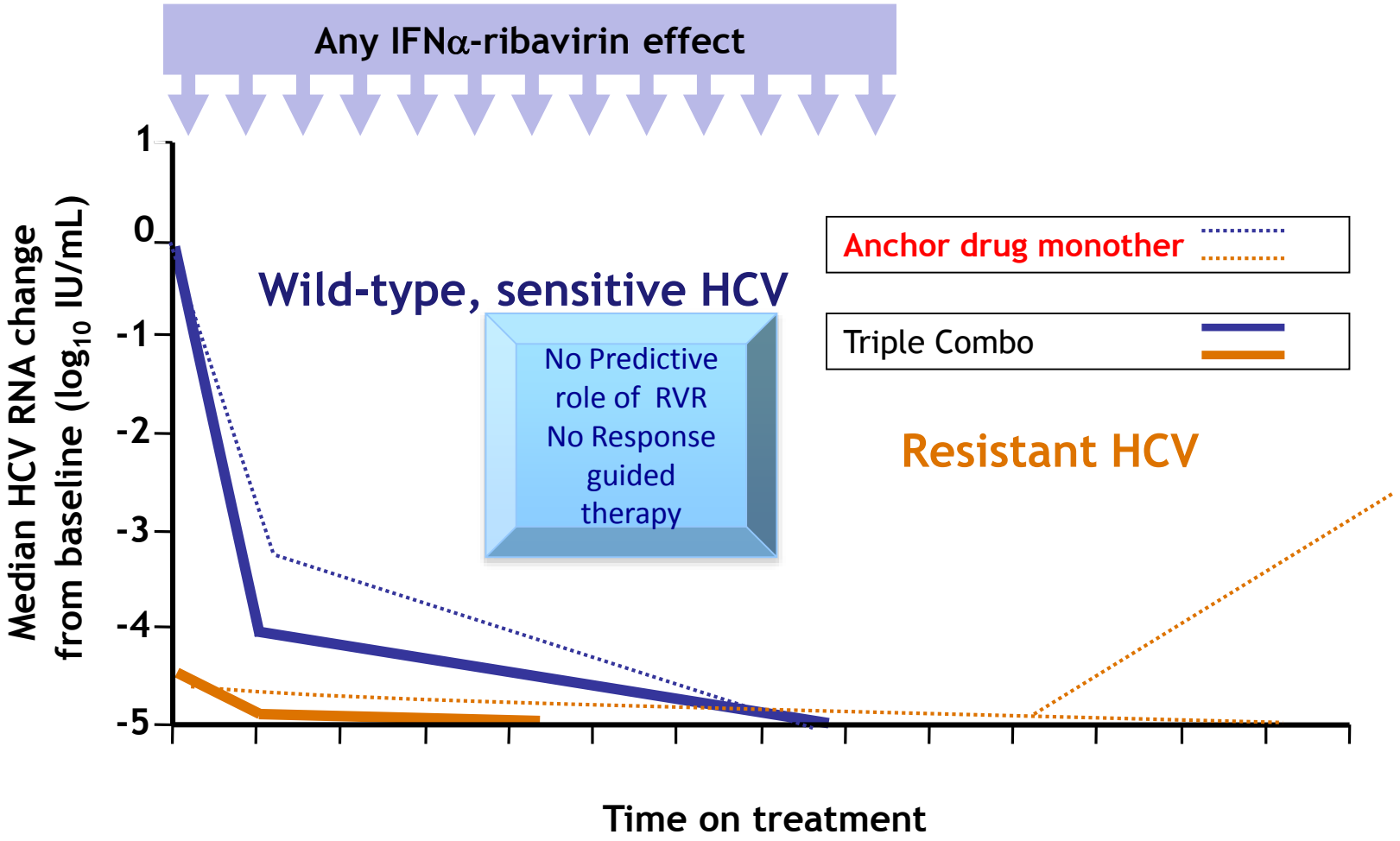


Sarrazin C et al J Hepatol. 2012;56 Suppl 1:S88-100.

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



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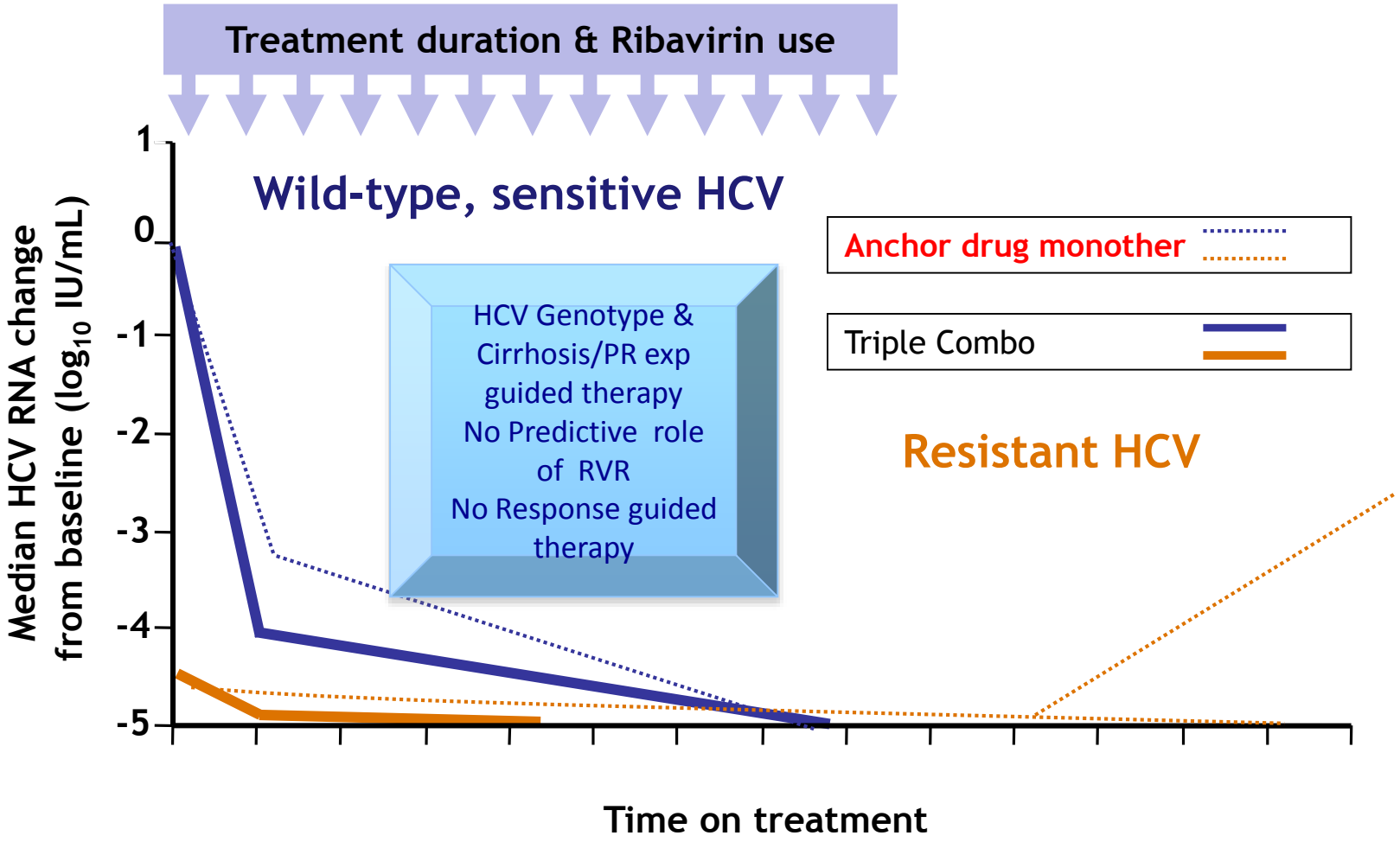
1 high resistance barrier DAA (Sofosbuvir) ± Ribavirin ± 1 DAA x 12-24 weeks



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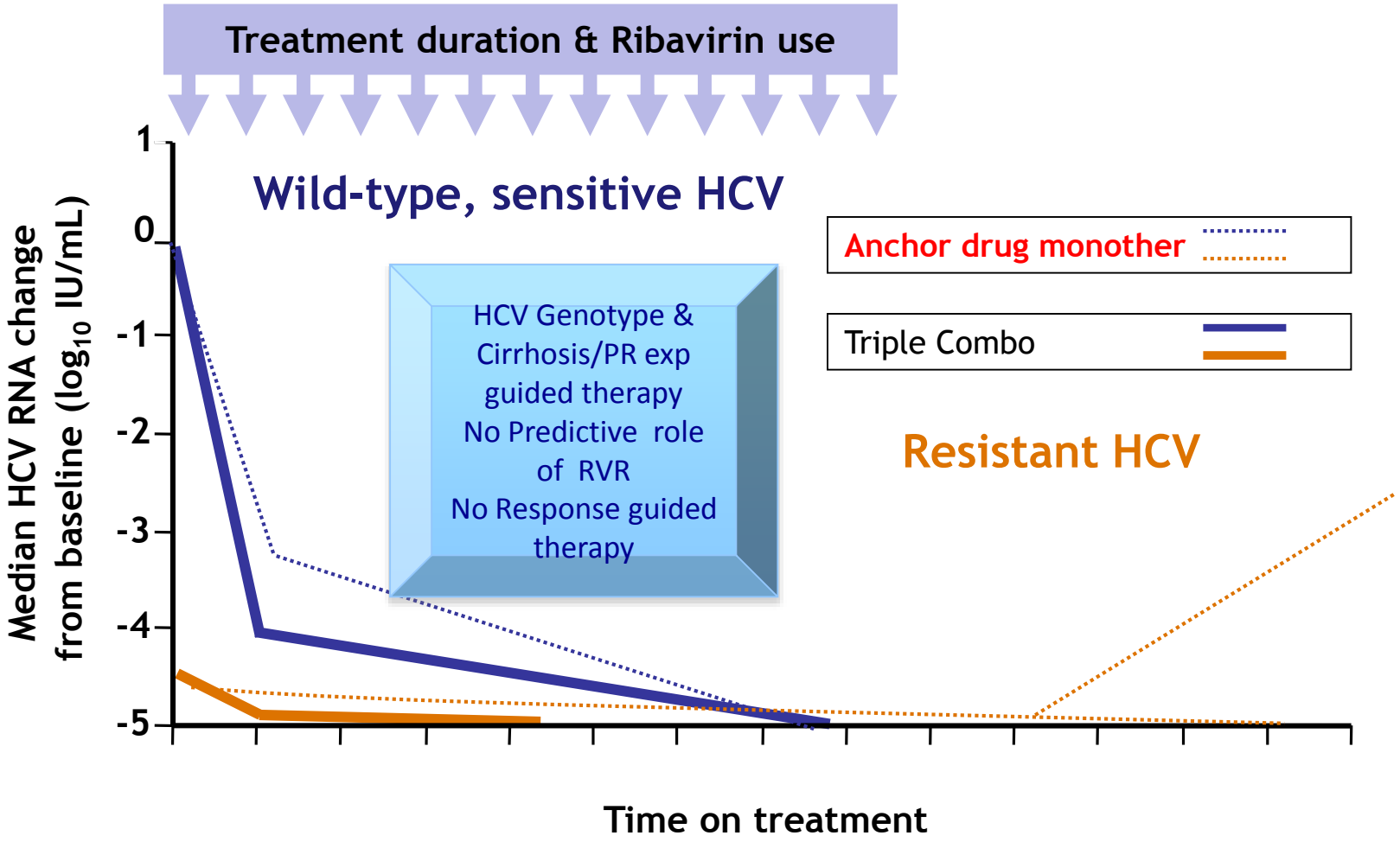
3 Low - 2 high resistance barrier DAA ± Ribavirin x 12-24 weeks



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

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

Still challenging

Phase IV

Adjusted for HCV Genotype.

Fine tuning by RBV & Tx duration In PR failures & Cirrhosis

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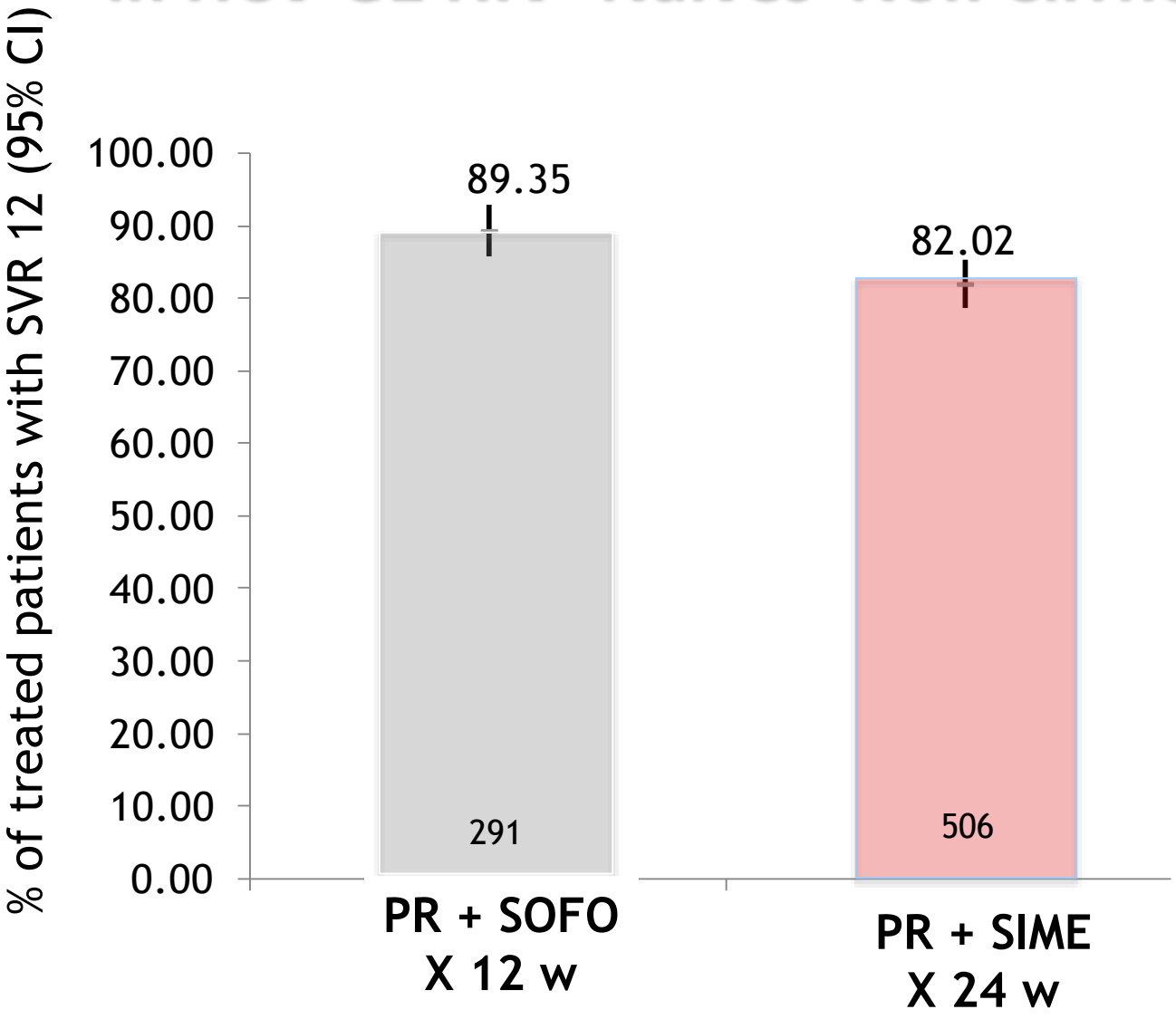
Summary of SVR rates to IFN based regimens in HCV G1 HIV- Naives Non Cirrhotics



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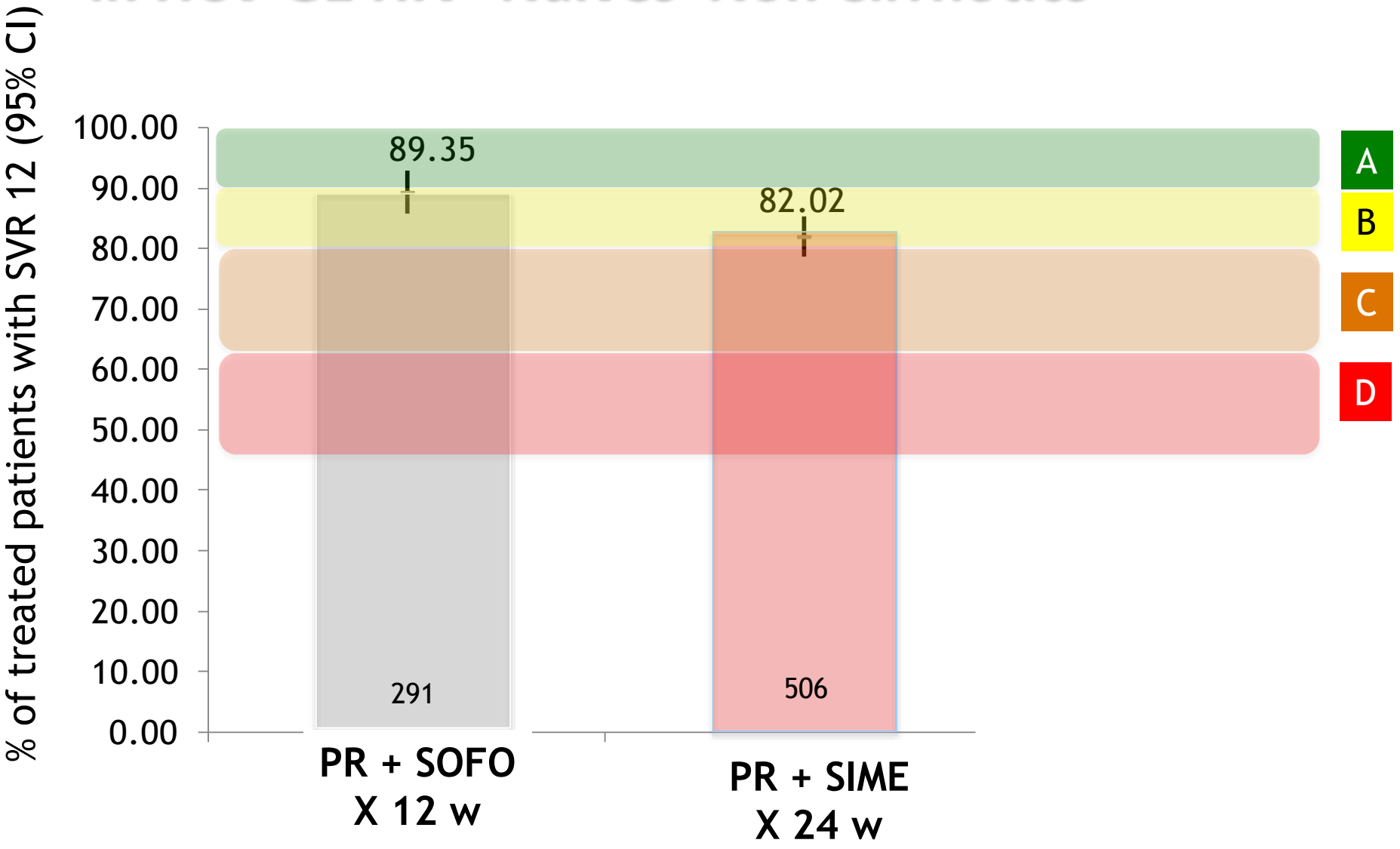

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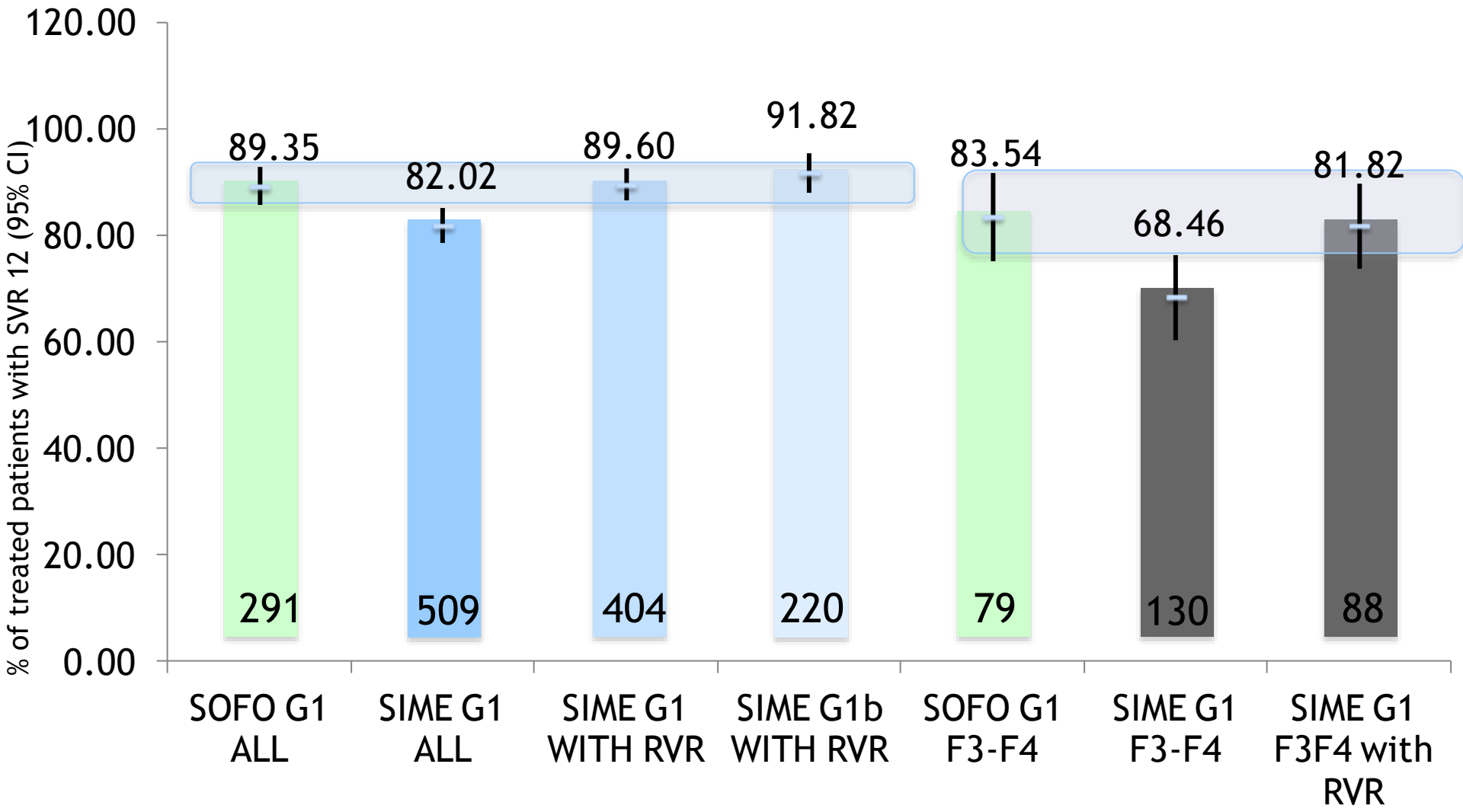
PEG IFN + RBV + SOFO vs PEG IFN + RBV + SIME SVR12 according to Rapid Viral Response (RVR) to PEG IFN + RBV + SIME and fibrosis stage



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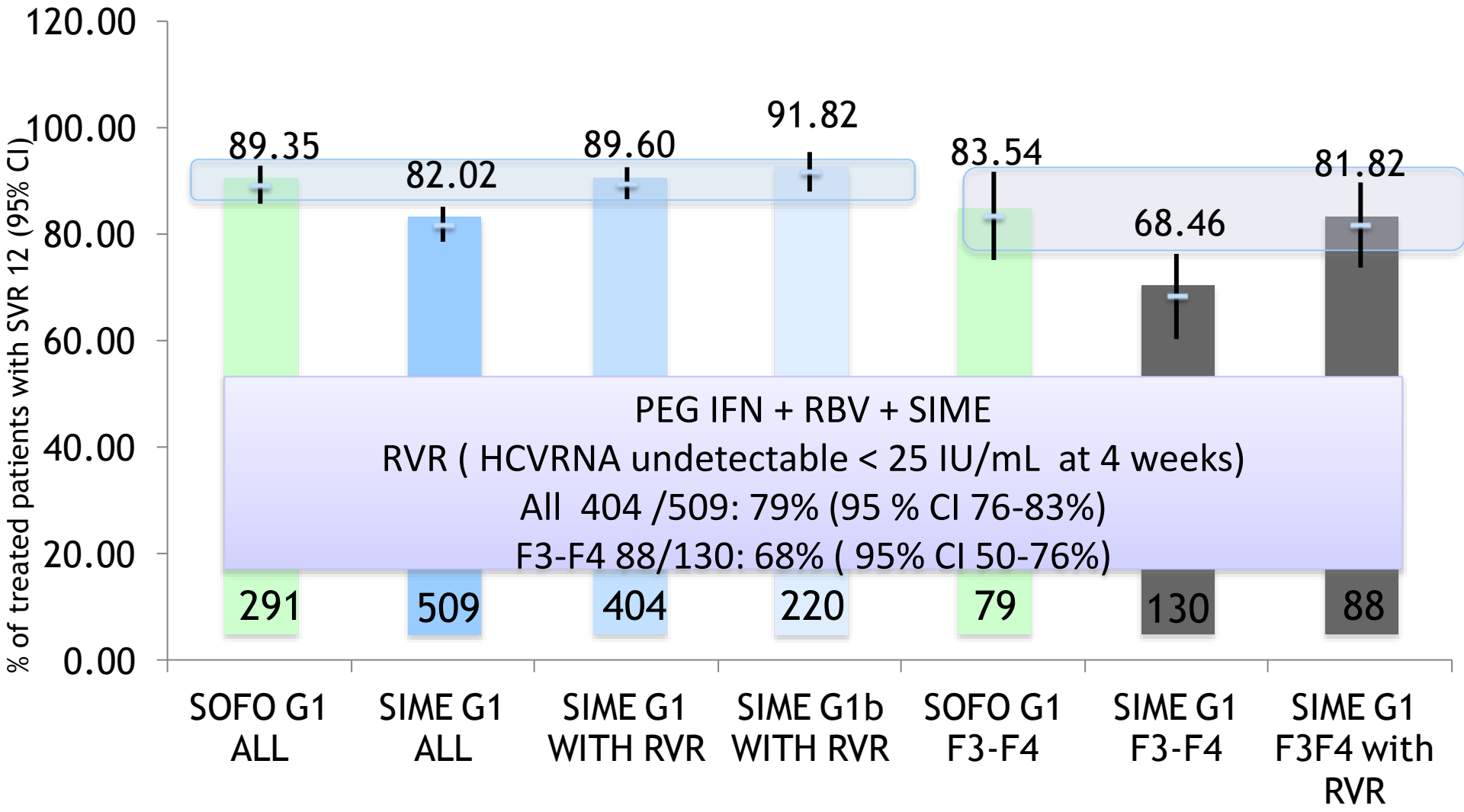

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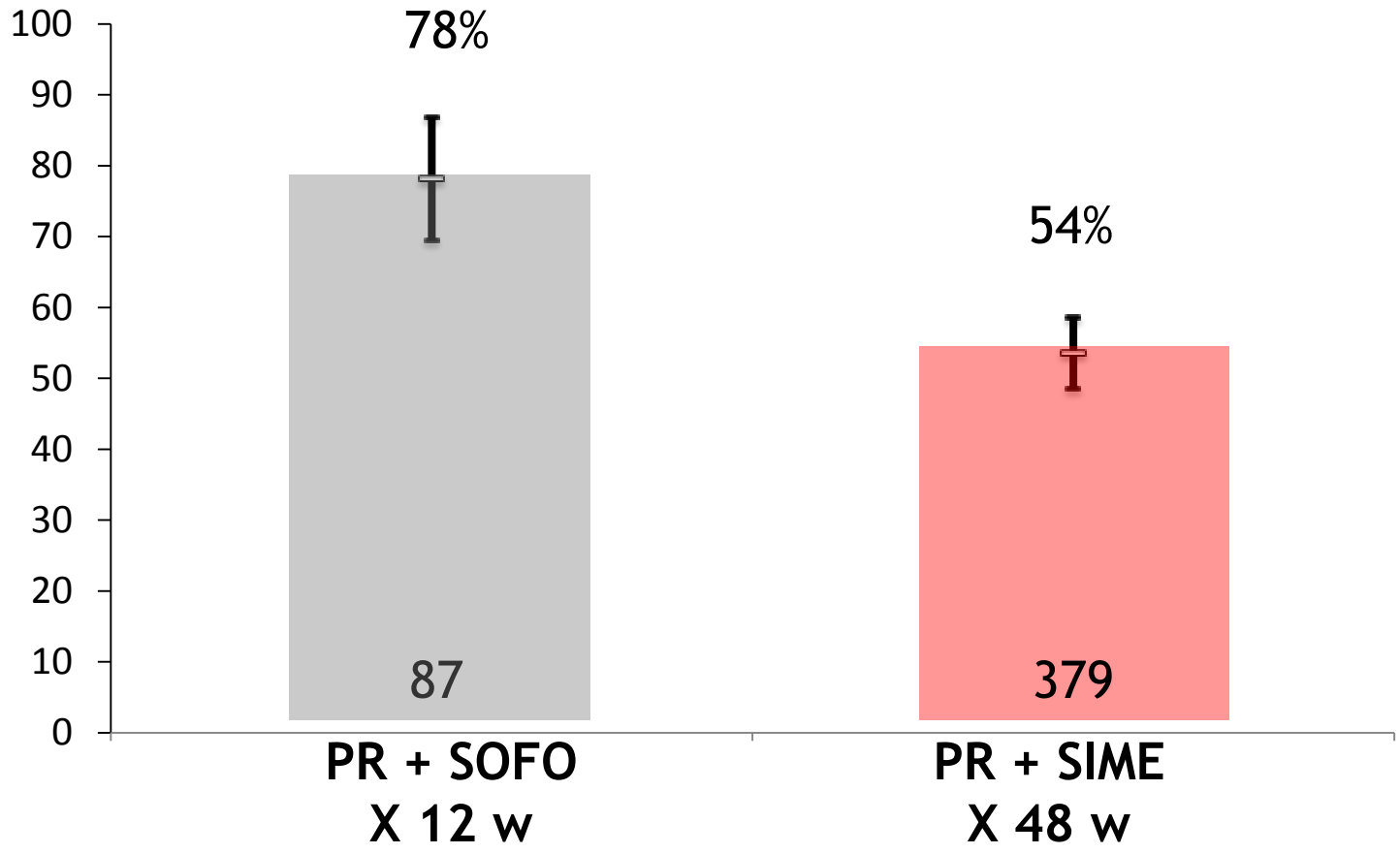

PR + SOFO Pol Easl 2014; TRIO AASLD 2014
PR SIME: ATTAIN study Reddy APASL 2013

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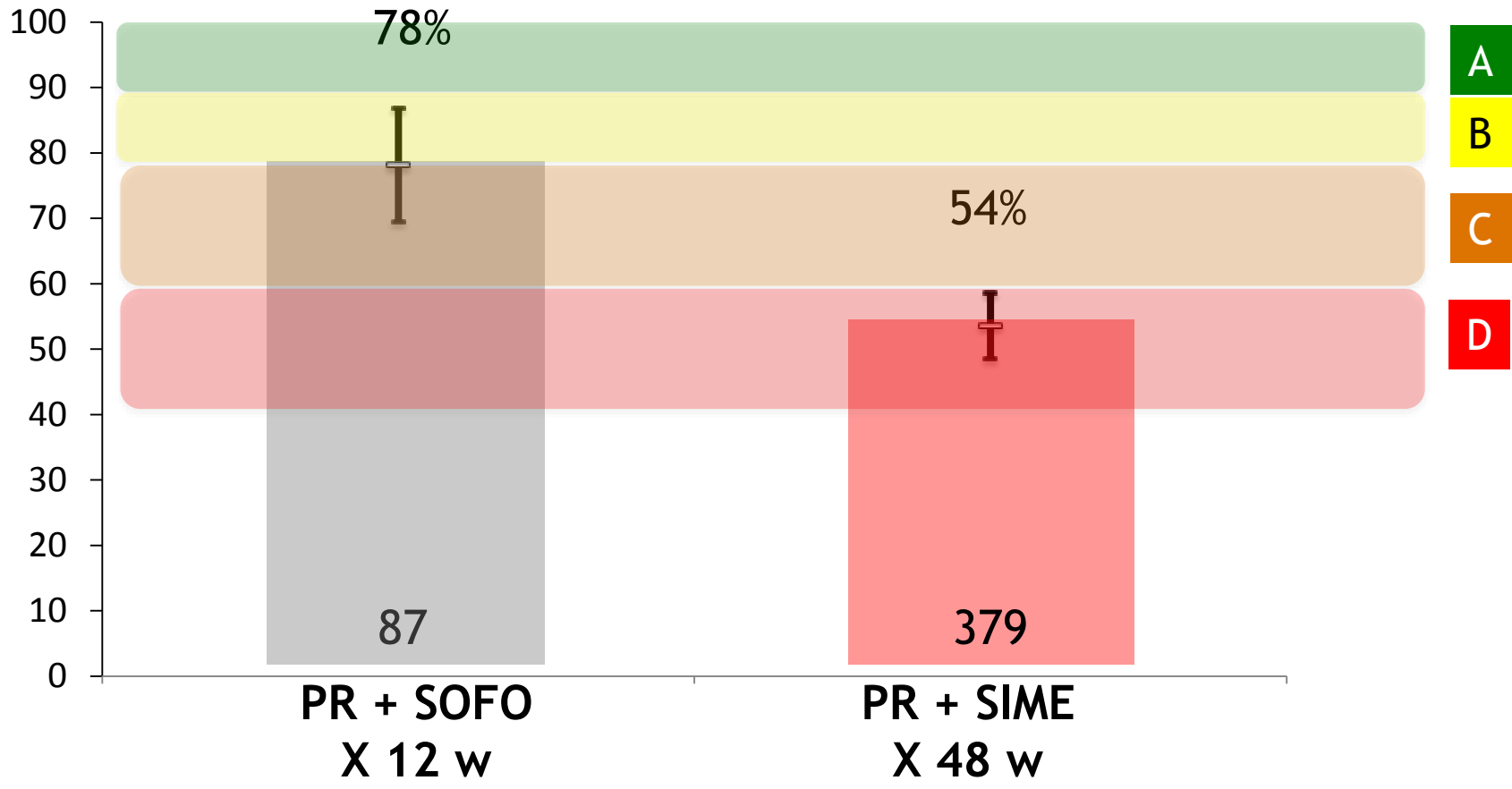

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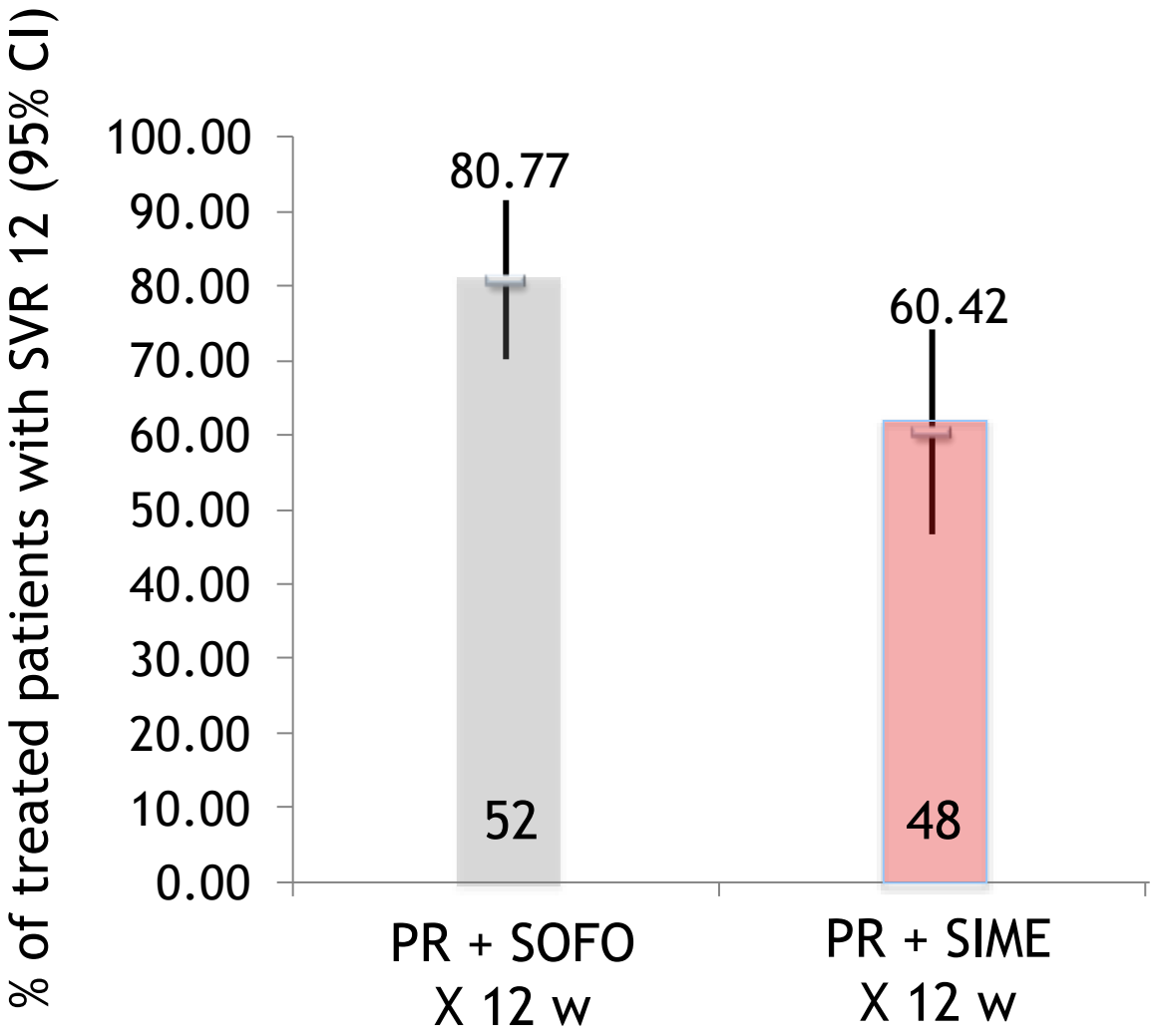

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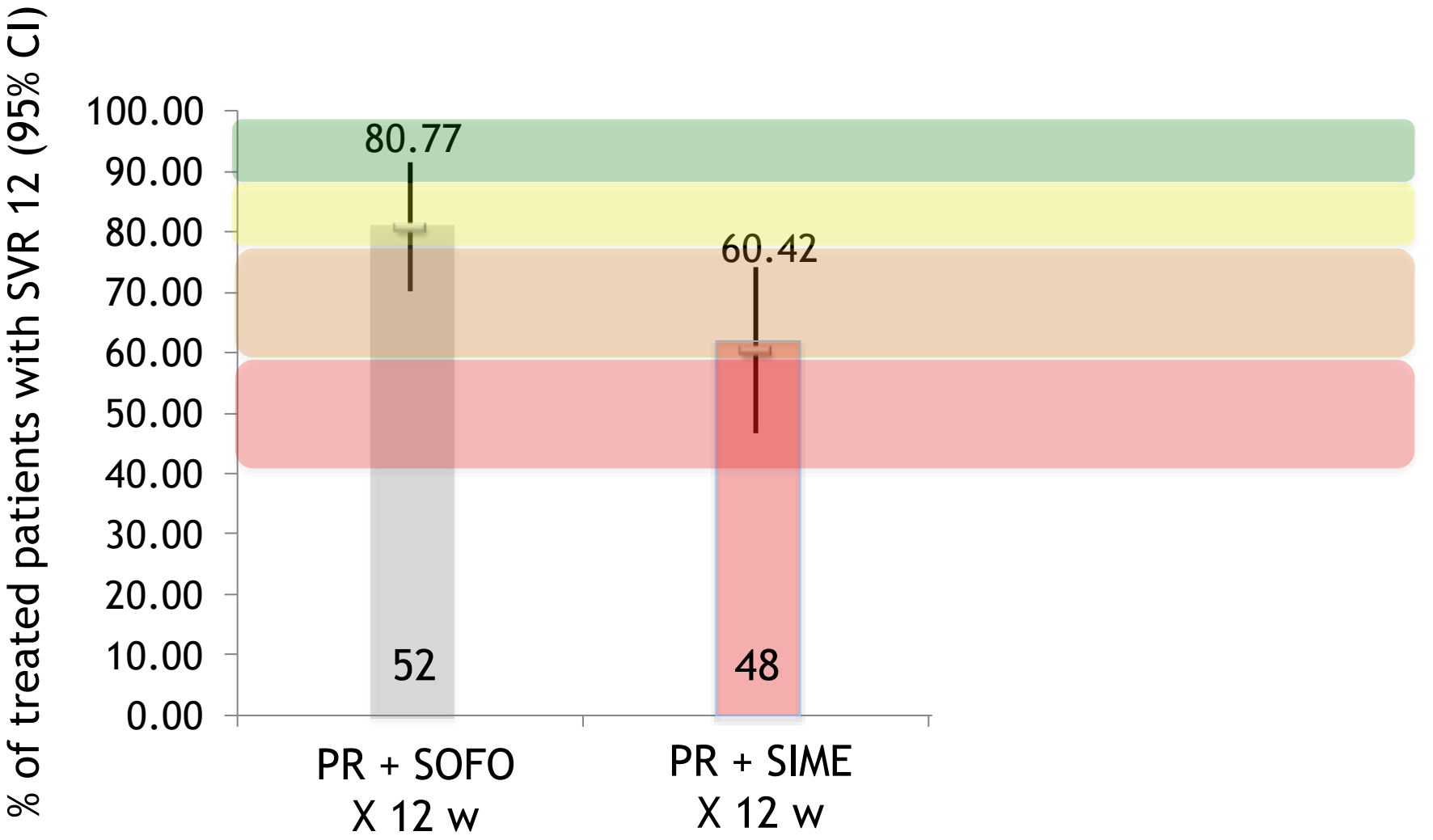

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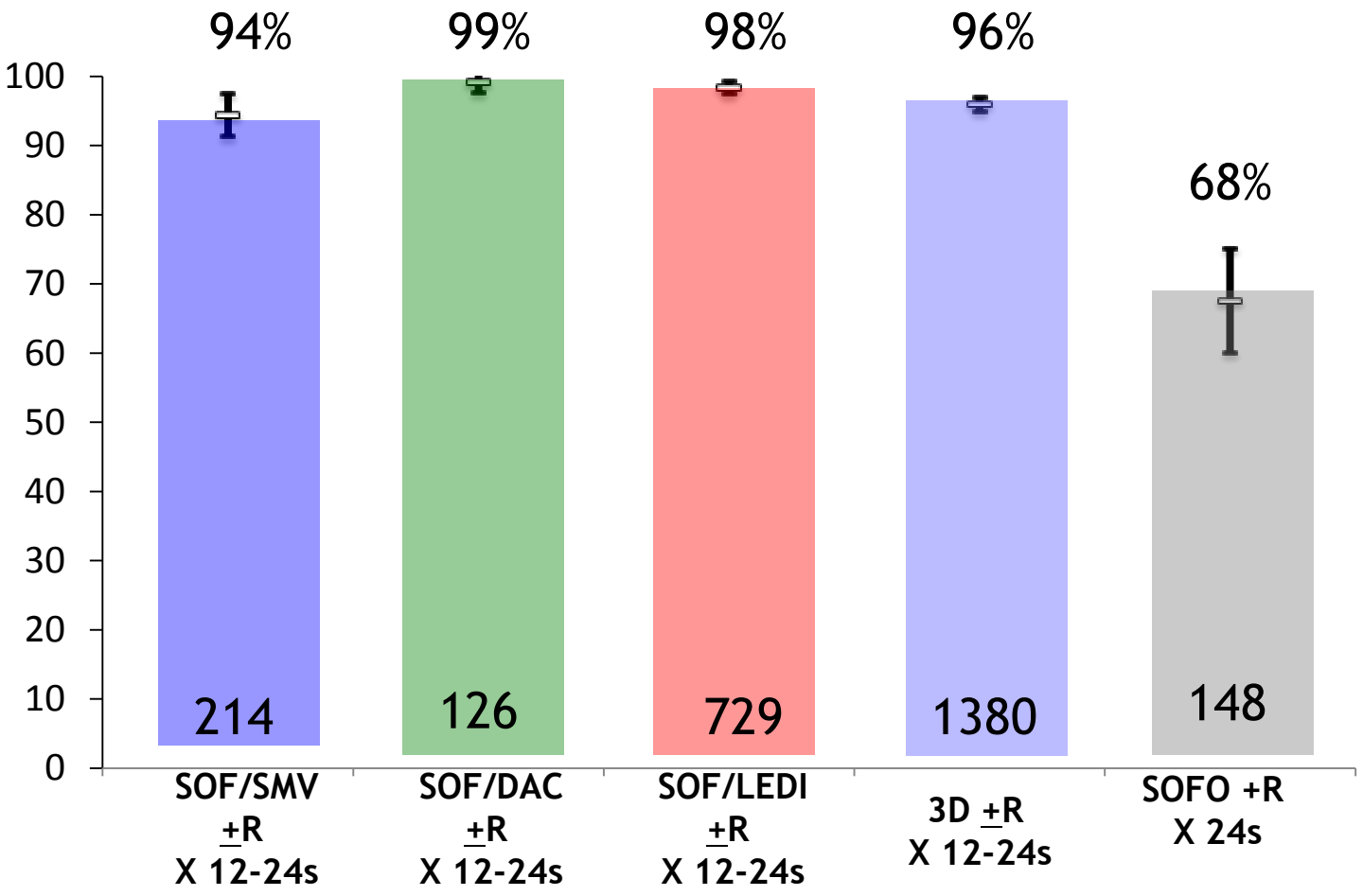

SIM/SOF study Cosmos, cohorts: TRIO, TARGET
SOF/LED studies ION-1 ION-3
3D: studies PEARL SAPPHIRE
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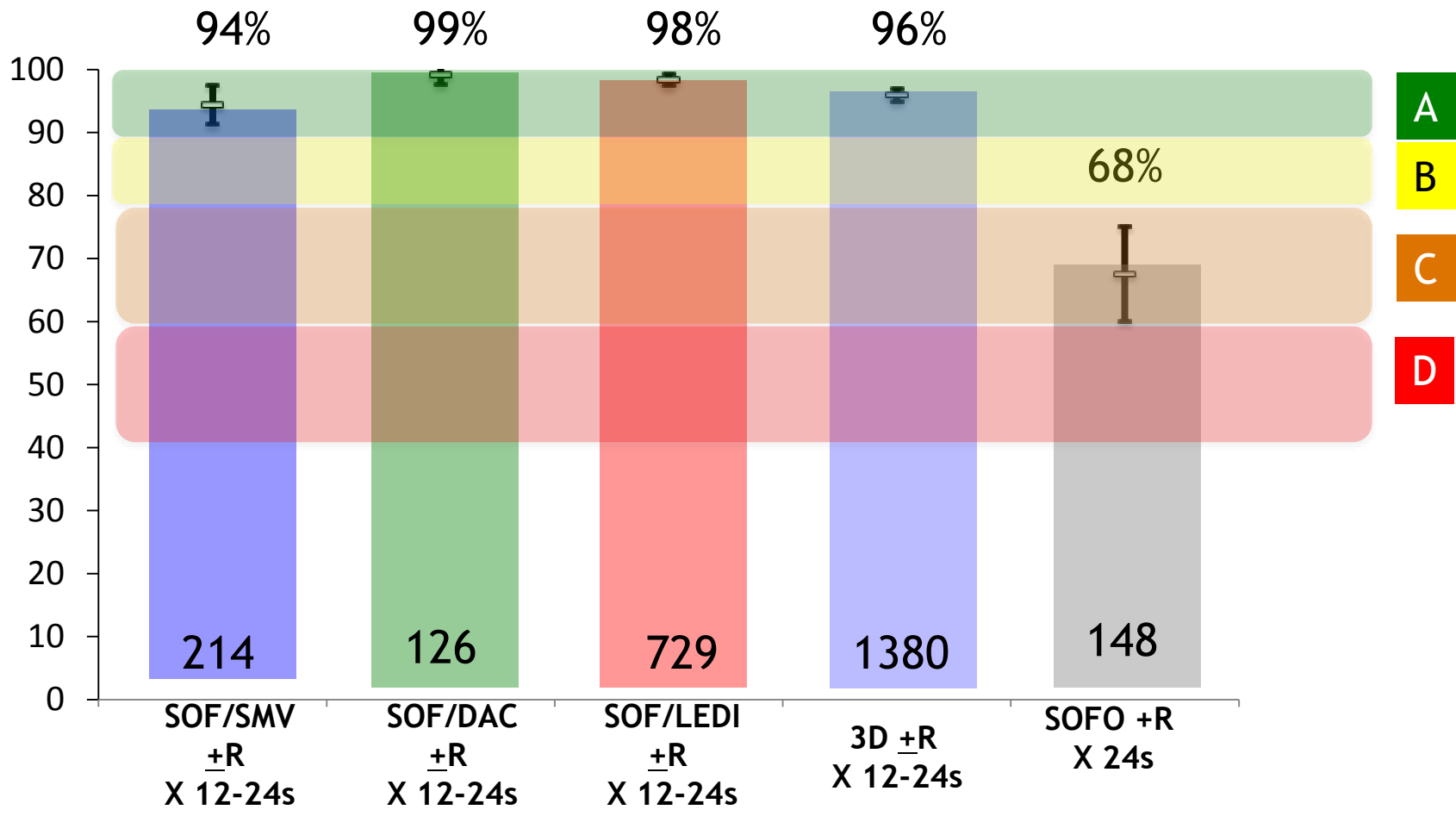

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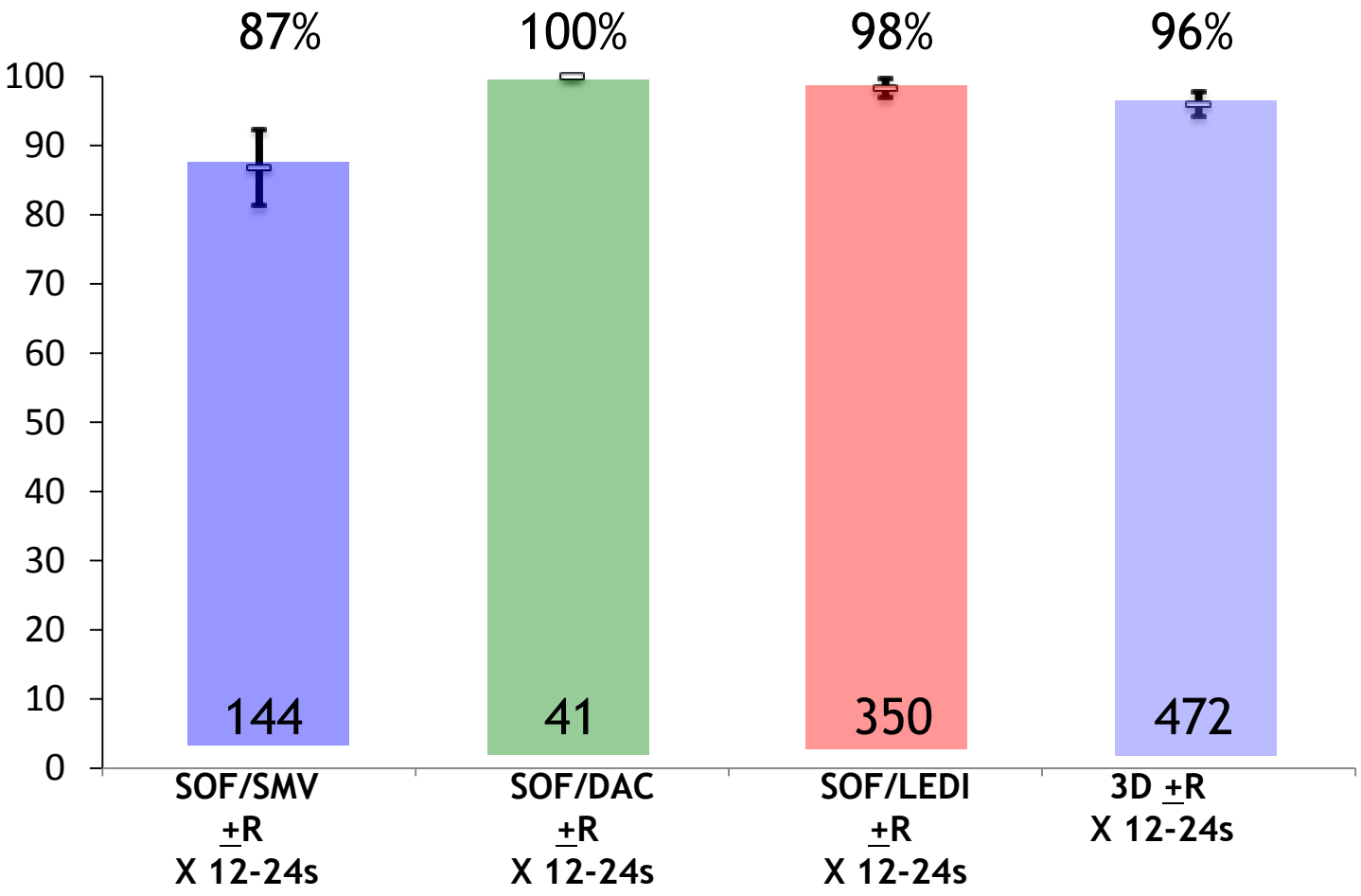

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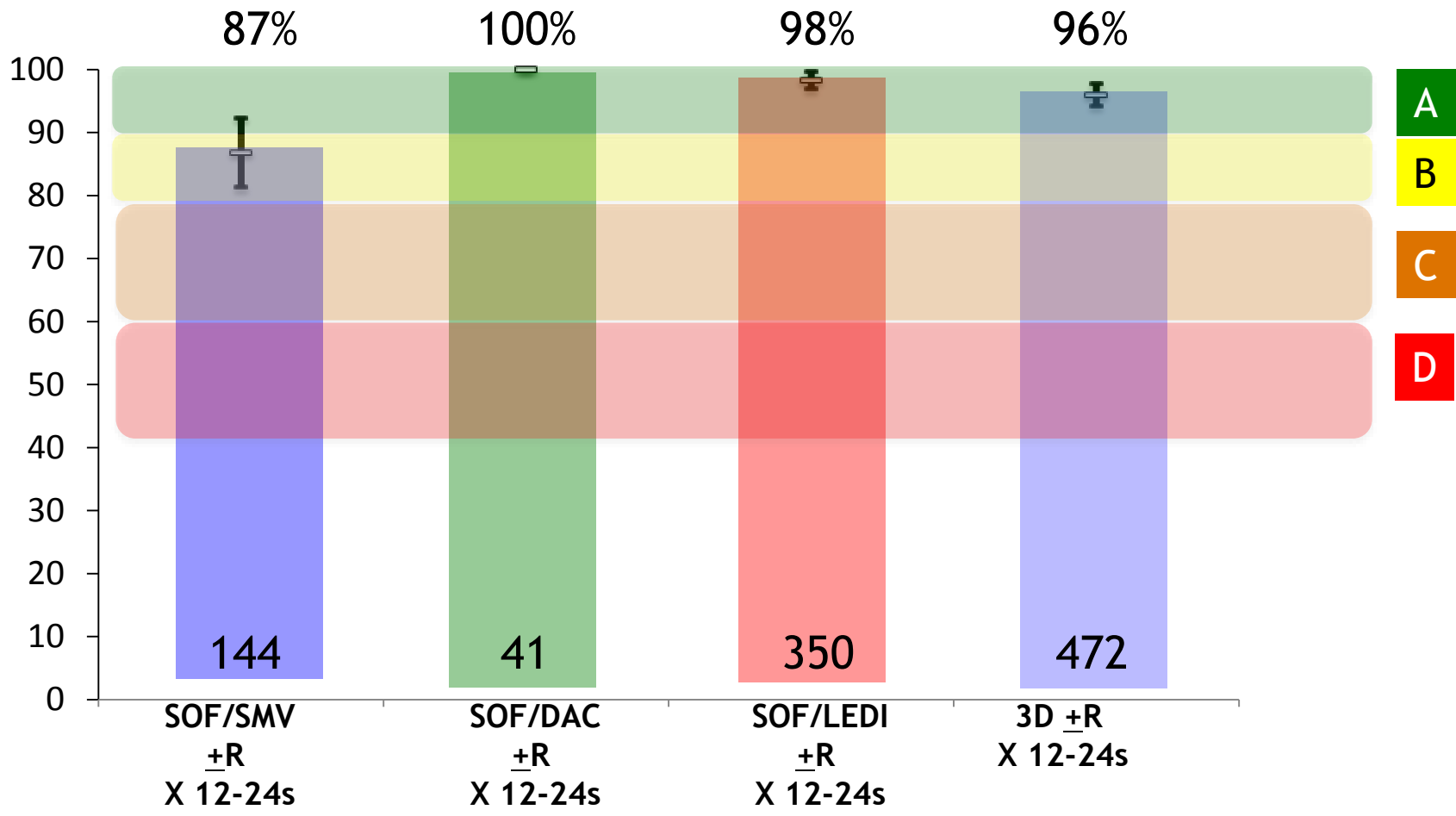

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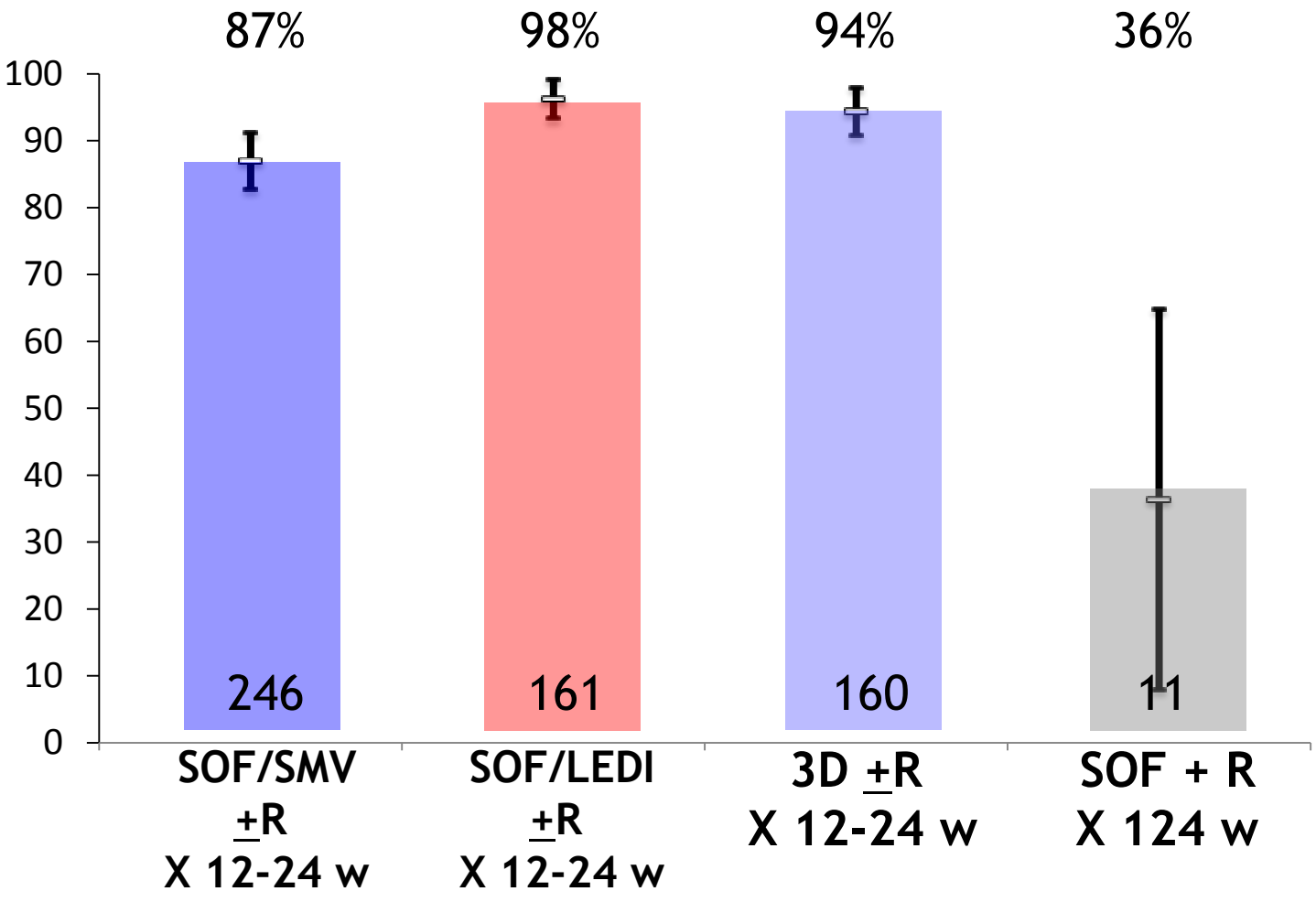

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SOF/LED study meta analysis AASLD 2014
3D: studies Turquoise II

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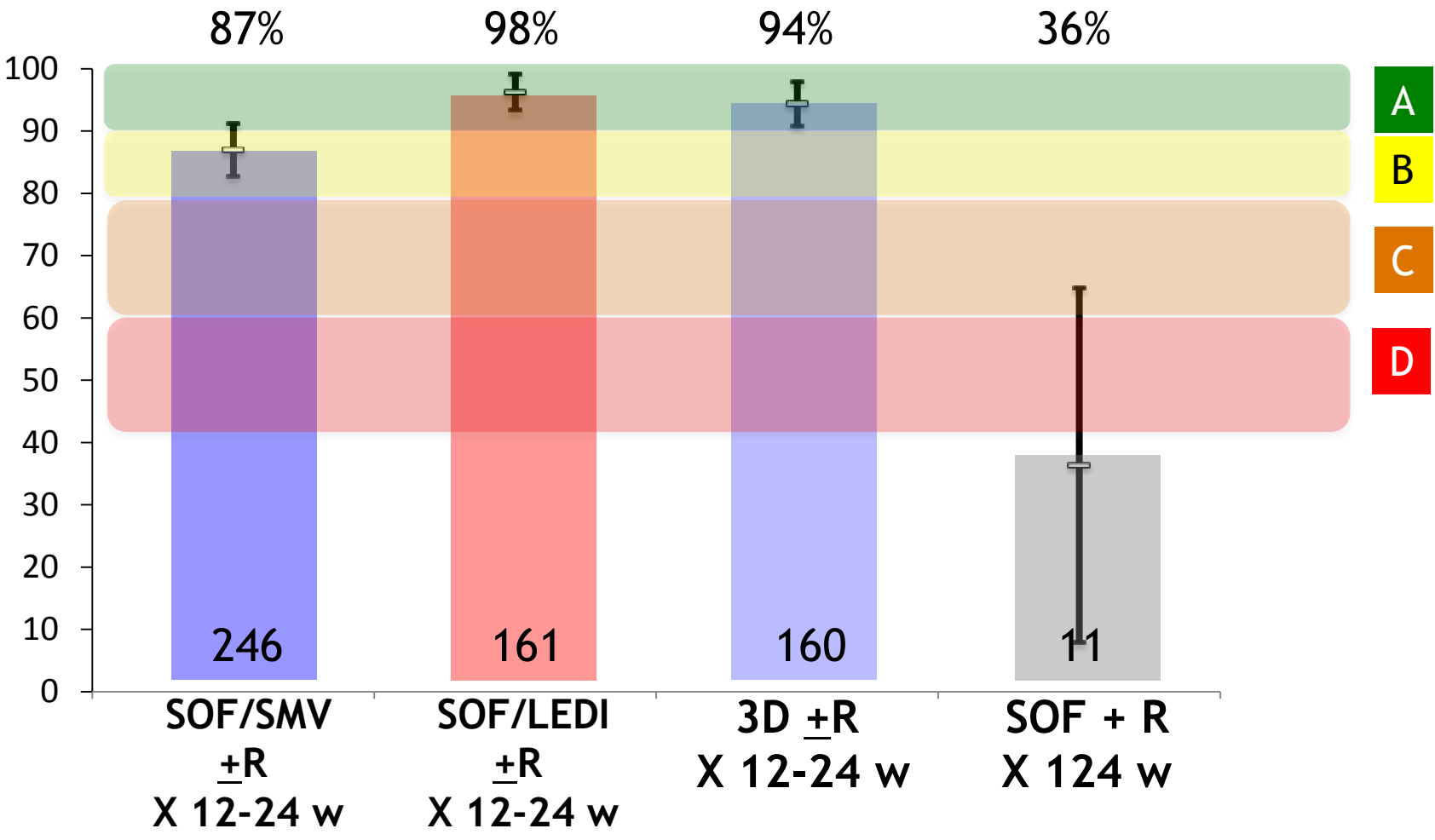

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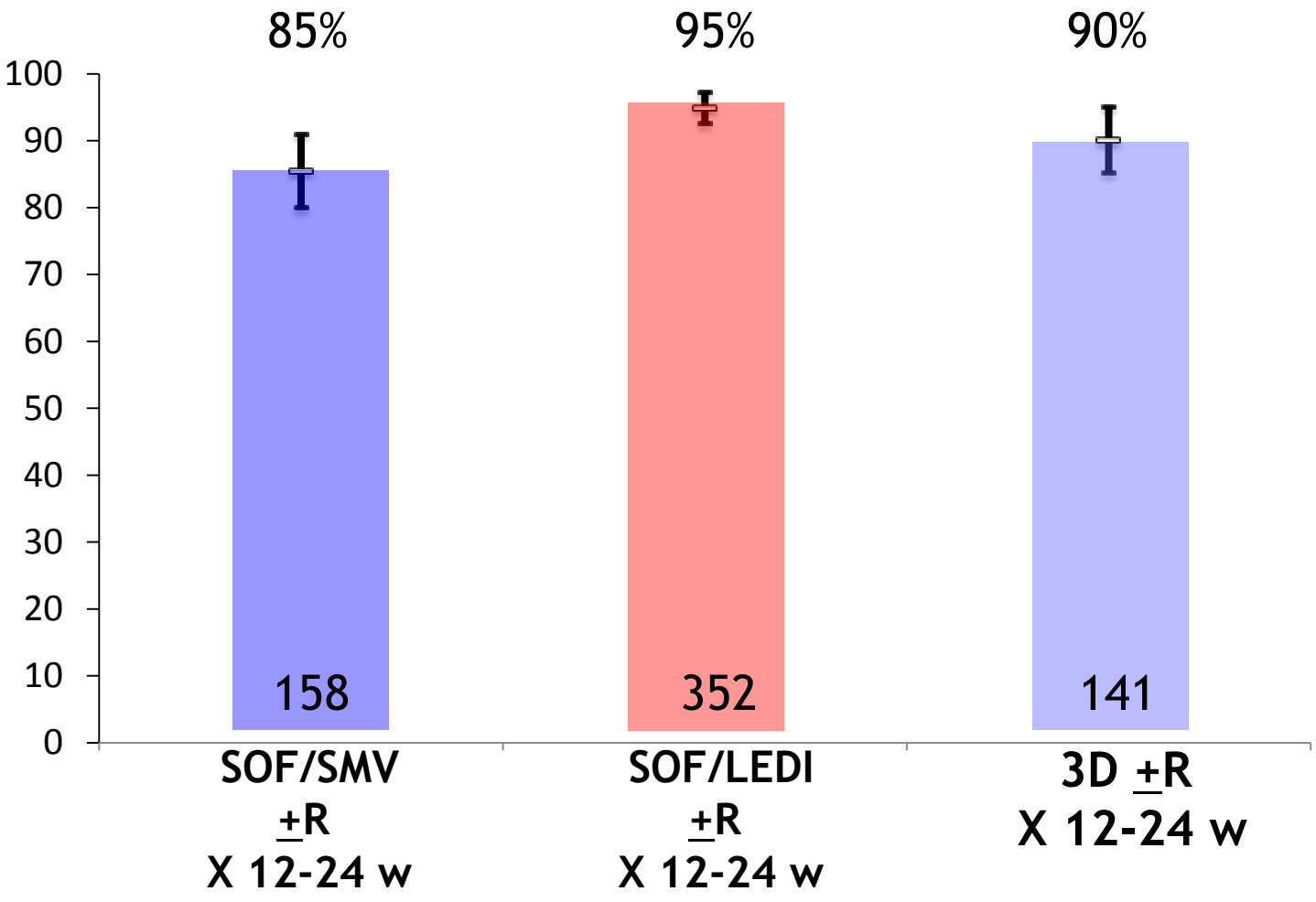

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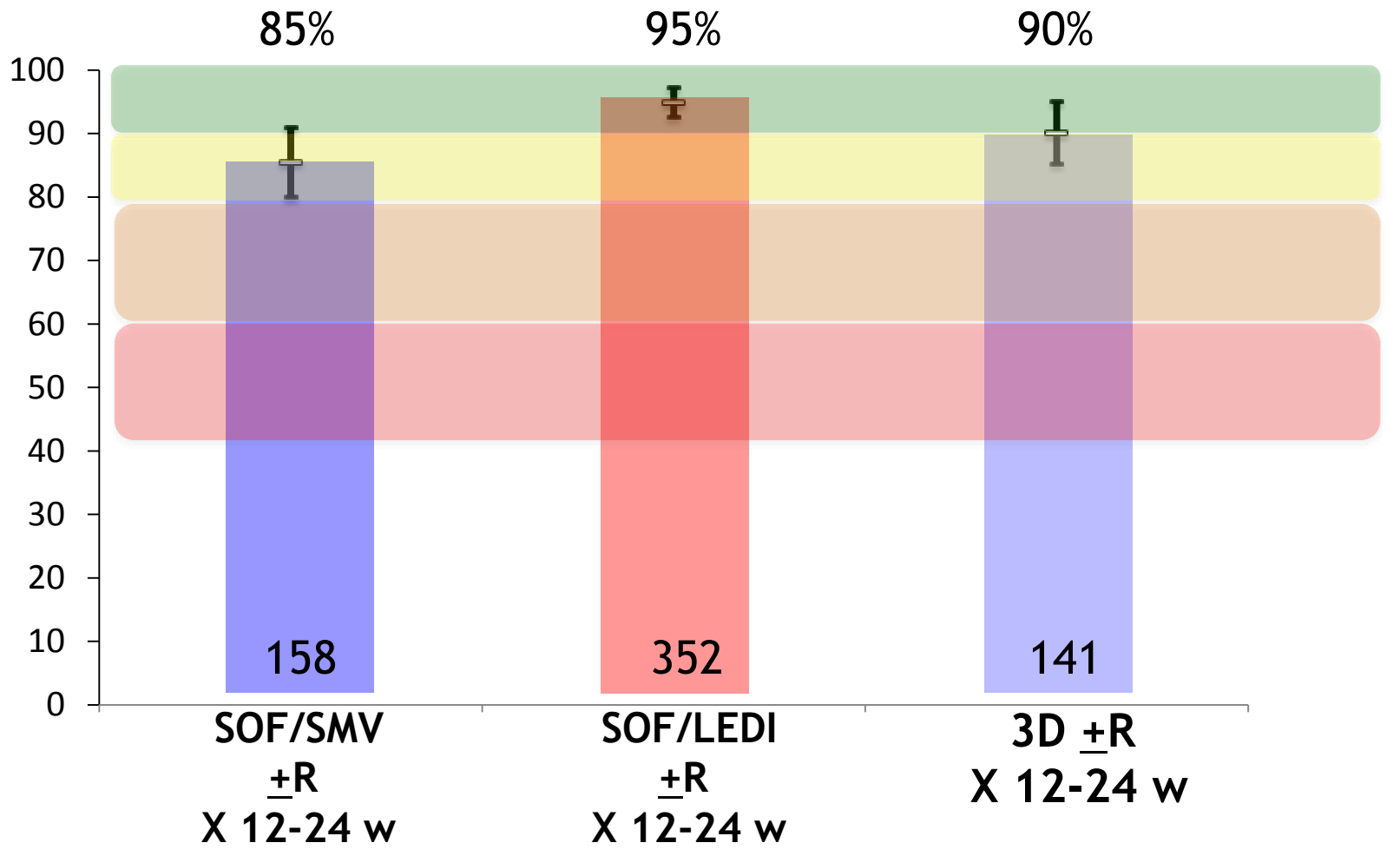

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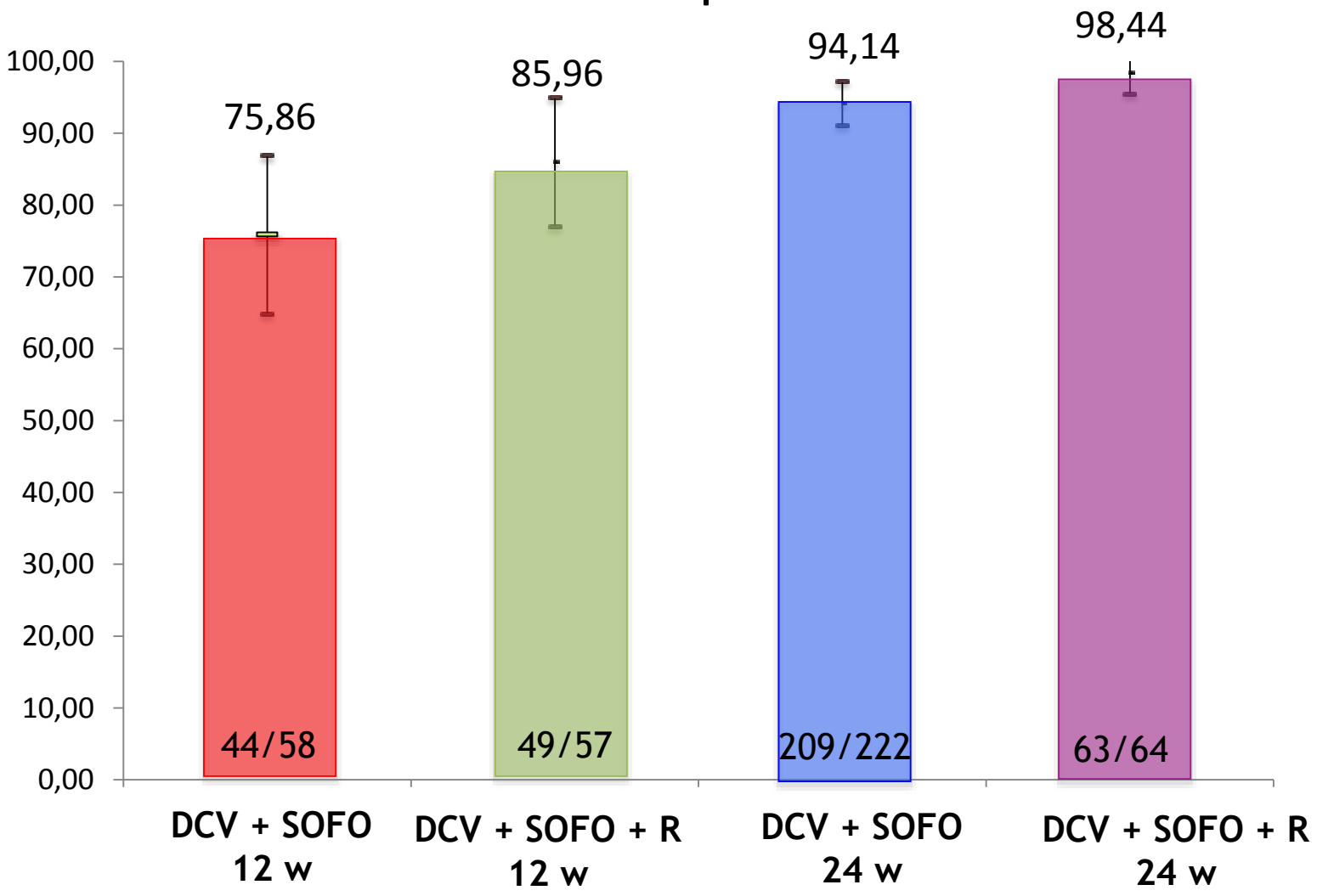
Summary of UK NHS & ANRS compassionate use studies
DCV + SOF in HCV G1 & 4
Cirrhotic patients



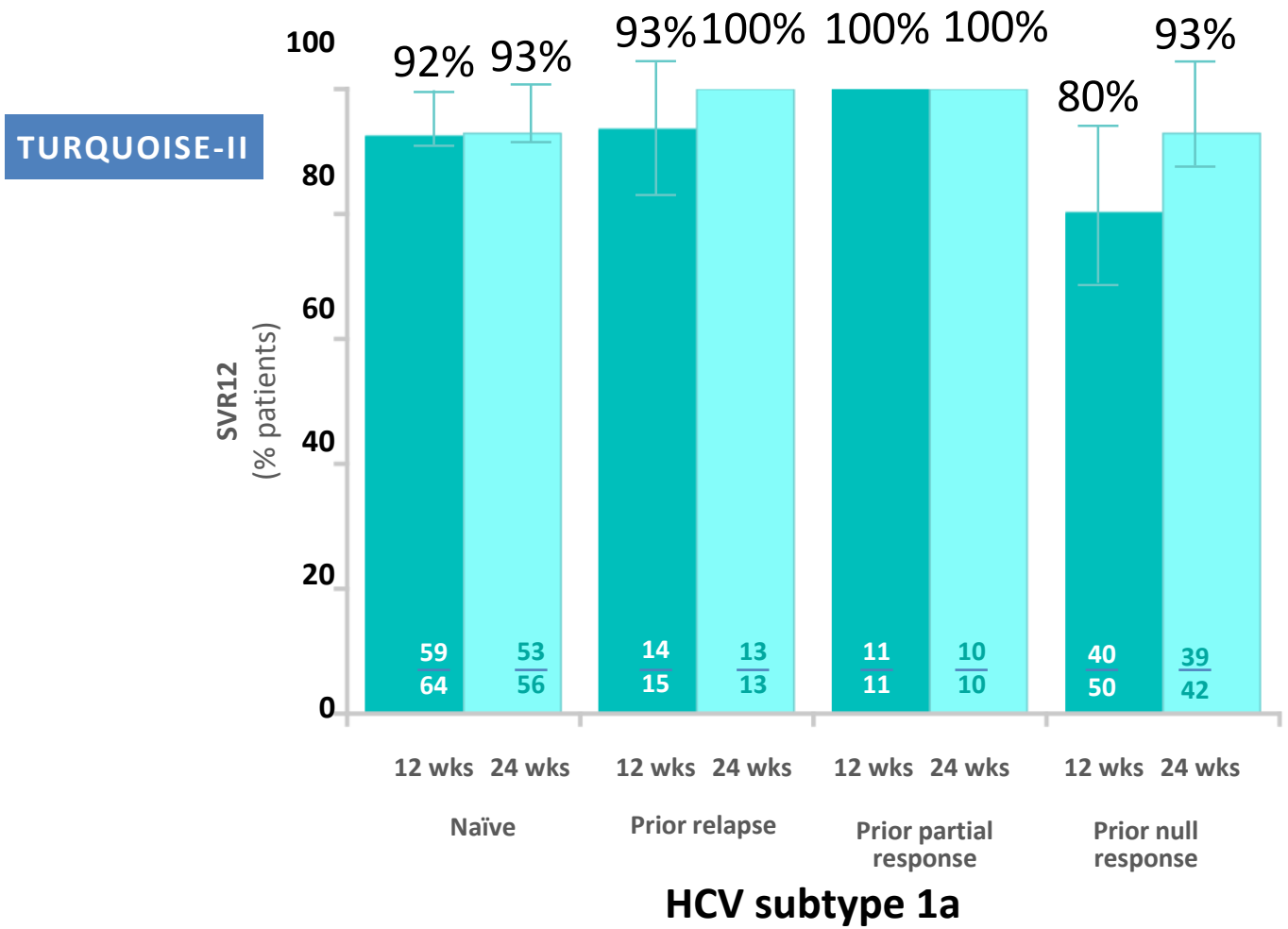
Foster G et al EASL 2015; Pol S et al EASL 2015; Fontaine H et al EASL 2015

SOF/LDV ± RBV in compensated cirrhotics: SVR12 by Treatment Regimen

SVR12 by treatment regimen		Total	Treatment naïve	Treatment experienced
Overall SVR12		96%	98%	95%
Duration	12 wk	95%	97%	94%
	24 wk	98%	99%	98%
Regimen	LDV/SOF	95%	96%	95%
	LDV/SOF + RBV	97%	99%	96%
Duration/ ± RBV	LDV/SOF 12 wk	92%	96%	90%
	LDV/SOF + RBV 12 wk	96%	98%	96%
	LDV/SOF 24 wk	98%	97%	98%
	LDV/SOF + RBV 24 wk	100%	100%	100%

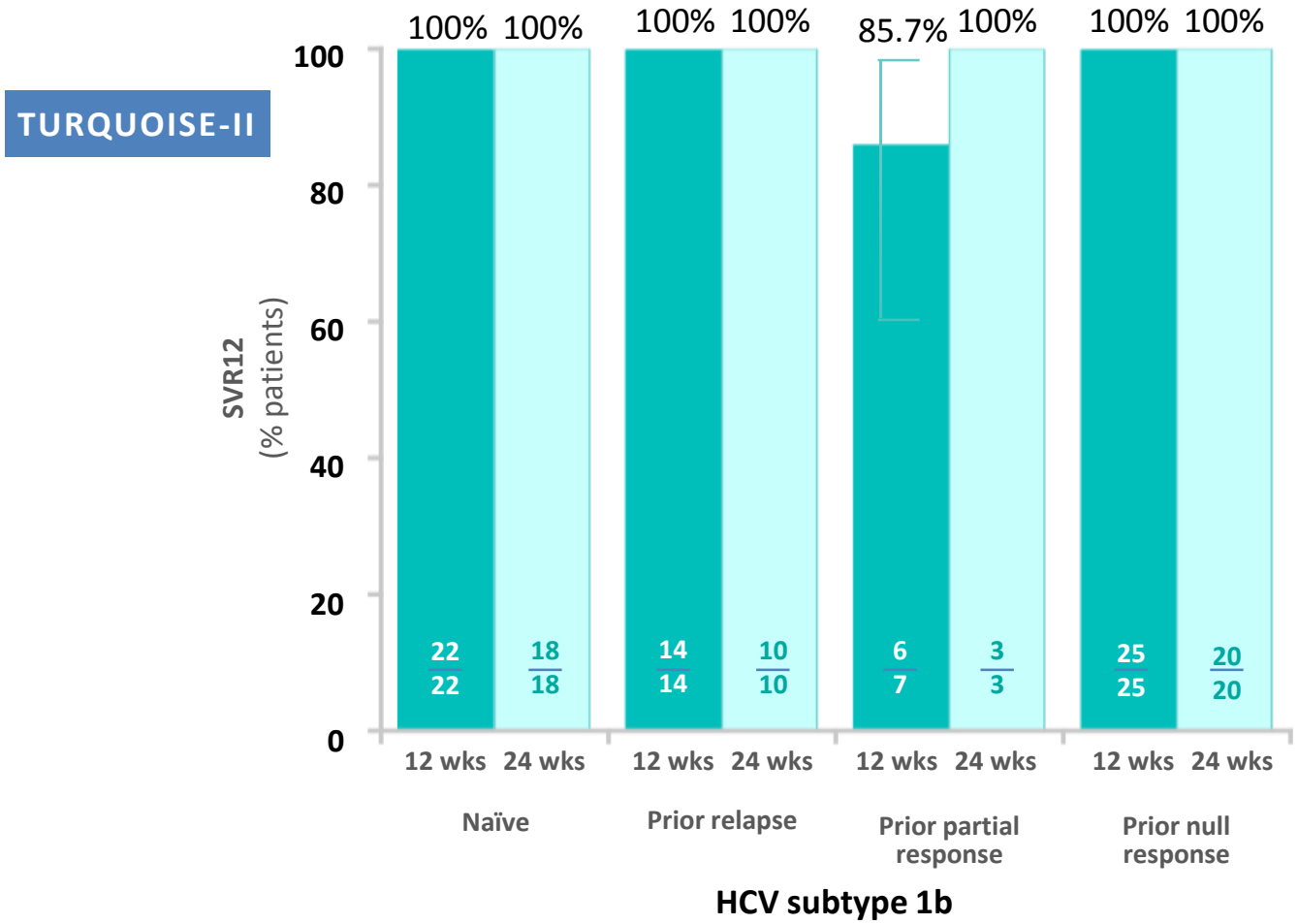
Bourlière et al., AASLD 2014, abstract# 82 (oral)

3D: SVR12 rates in treatment-naïve and P/R-experienced cirrhotic patients with GT1a HCV



ombitasvir/paritaprevir/ritonavir Summary of product characteristics.
dasabuvir Summary of product characteristics. .

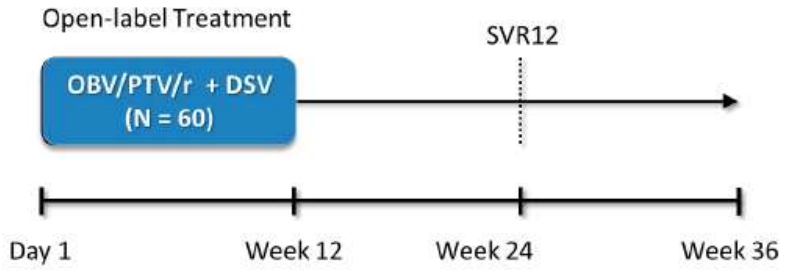
3D:SVR12 rates in treatment-naïve and P/R-experienced cirrhotic patients with GT1b HCV



1. ombitasvir/paritaprevir/ritonavir Summary of product characteristics.
2. dasabuvir Summary of product characteristics.

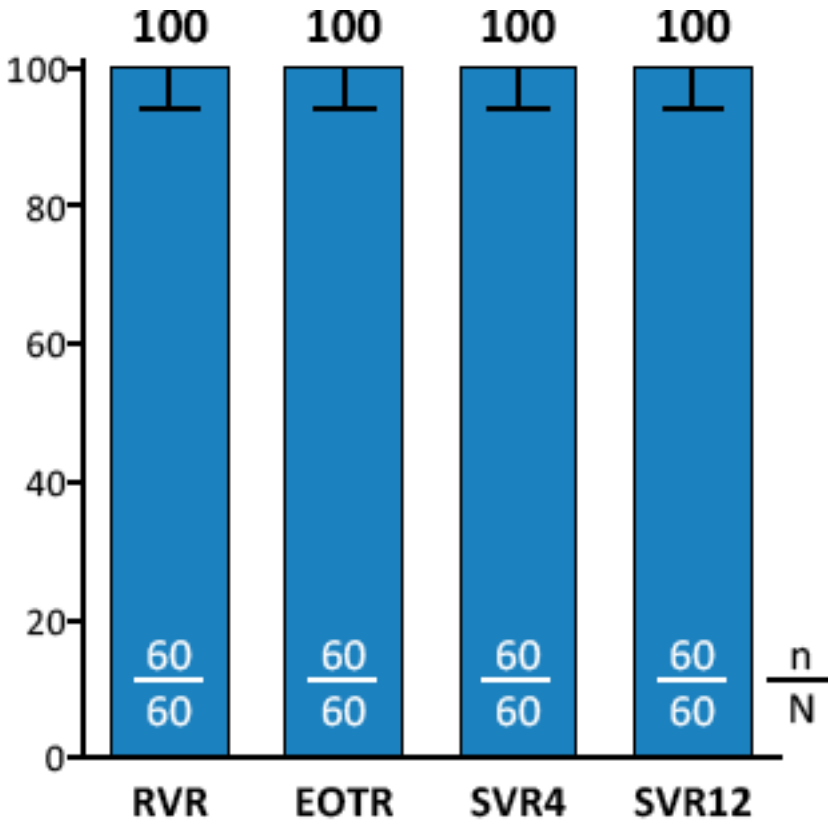
Turquoise –III OBV/PTV/r + DSV in HCV G1b cirrhotics naives and experienced

TURQUOISE-III Study Design (N = 60)



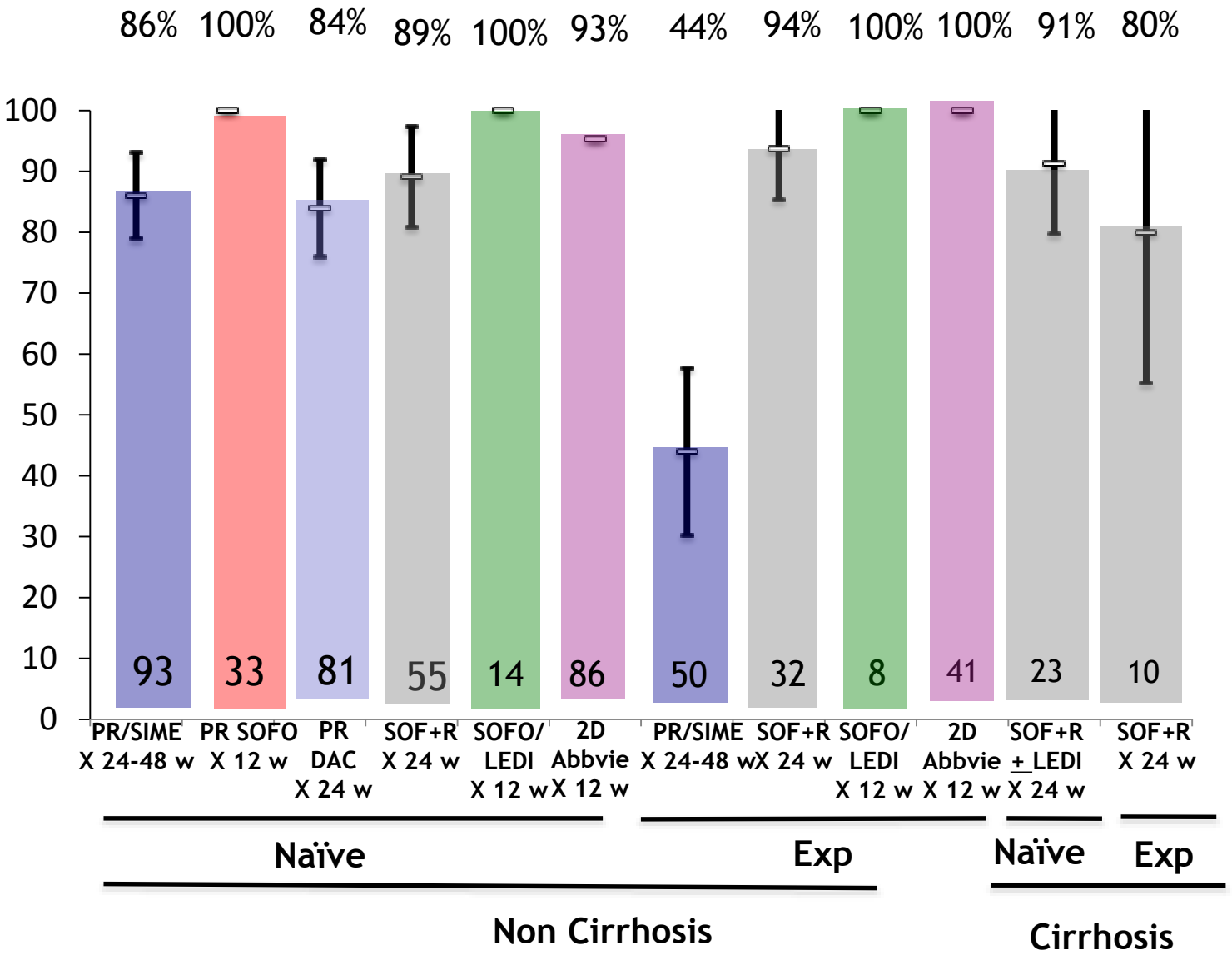
TURQUOISE-III: Key Eligibility Criteria

- HCV GT1b infection (plasma HCV RNA >1000 IU/mL)
- Age ≥18 years
- Child-Pugh A cirrhosis without history of decompensation
- HCV treatment-naïve or pegIFN/RBV-experienced
- Haemoglobin ≥10 g/dL
- Total bilirubin ≤3.0 mg/dL
- Albumin ≥2.8 g/dL
- Platelet count ≥25 × 10^9/L
- Creatinine clearance ≥30 mL/min



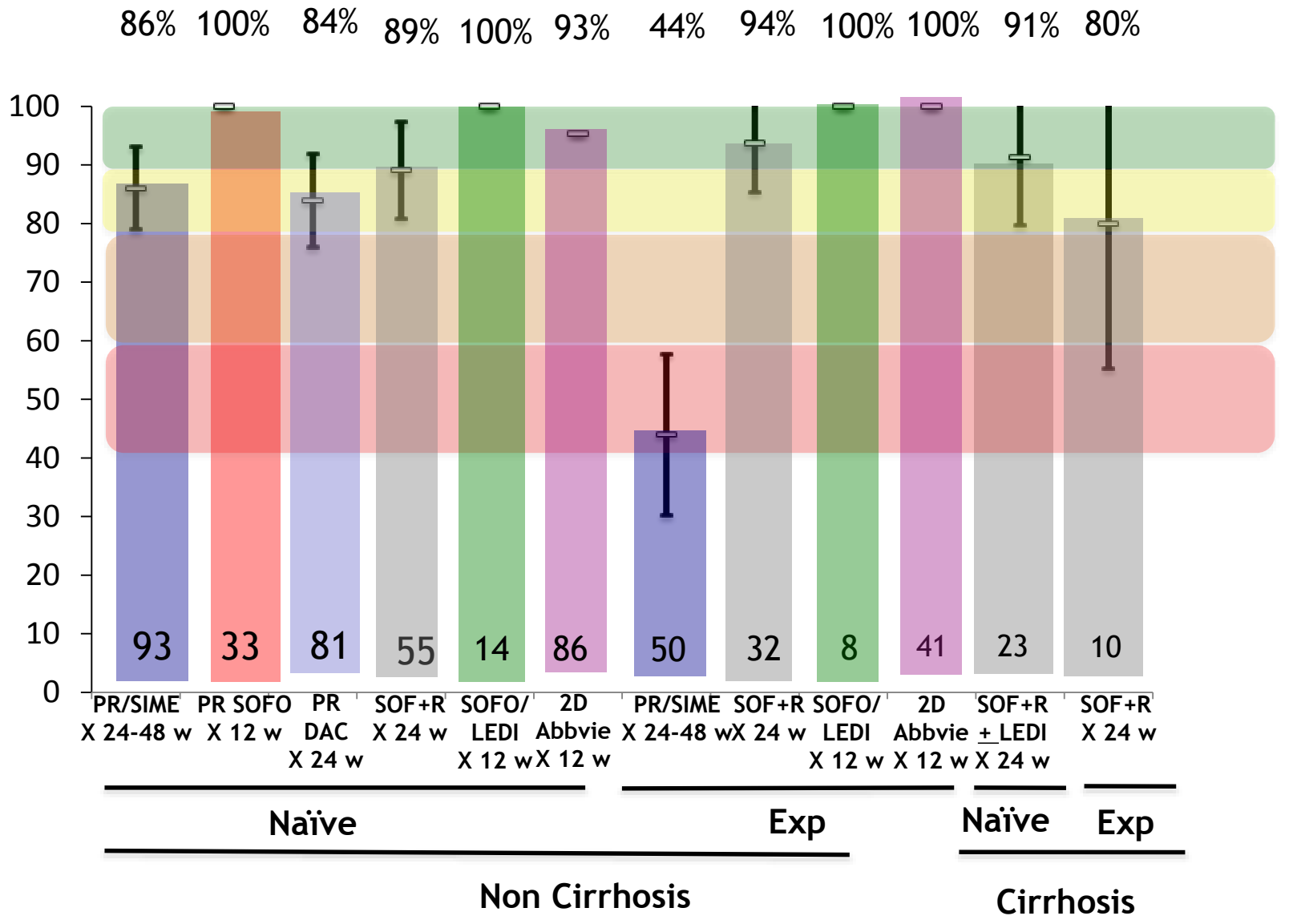
Feld J et al ISVHLD 2015

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

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

SVR12 in Compensated and decompensated cirrhosis

HCV GT	Ref	Treatment Schedule	N with SVR 12 /total (%)		
			CTP Class A	CTP Class B	CTP Class C
1 & 4	Poordad EASL 2015	SOFO + DAC + RBV 12 w	11/12 (92%)	30/32 (94%)	9/16 (56%)
	Bourliere AASLD 2014 Flamm AASLD 2014 Manns EASl 2015	SOFO + LEDI + R 12 w	305/322 (95%)	48/56 (86%)	36/43 (84%)
		SOFO + LEDI + RBV 24 w	188/191 (98%)	48/52 (92%)	32/40 (80%)
	Foster EASL 2015	SOFO + LEDI + RBV 12 w		141 /164 (86%)	
		SOFO + DAC + R 12 w		37/45 (82%)	
	ALL	SOFO + DAC + R12 w	11/12 (92%)	76/93 (82%)	
		SOFO + LEDI+ R 12 w	305/322 (95%)	225/263 (85%)	
		SOFO + LEDI + R 24 w	188/191 (98%)	80/92 (87%)	

IFN-Free Options, Gen 1a

	SOF/LDV	3D	SOF + SIM	SOF + DCV
No cirrhosis	8-12 wk without RBV	12 wk with RBV	12 wk without RBV	12 wk without RBV
Compensated cirrhosis (CPT-A)	12 wk with RBV, or 24 wk without RBV*	24 wk with RBV	12 wk with RBV, or 24 wk without RBV*	12 wk with RBV, or 24 wk without RBV*
Decompensated cirrhosis (CPT-B and CPT-C)	12 wk with RBV, or 24 wk without RBV*	No	No	12 wk with RBV, or 24 wk without RBV*

*Patients with negative predictors of response can be treated 24 weeks with ribavirin (negative predictors: treatment-experienced, platelet <75x10^3/uL)

IFN-Free Options, Gen 1b

	SOF/LDV	3D	SOF + SIM	SOF + DCV
No cirrhosis	8-12 wk without RBV	12 wk without RBV	12 wk without RBV	12 wk without RBV
Compensated cirrhosis (CPT-A)	12 wk with RBV, or 24 wk without RBV*	12 wk with RBV	12 wk with RBV, or 24 wk without RBV*	12 wk with RBV, or 24 wk without RBV*
Decompensated cirrhosis (CPT-B and CPT-C)	12 wk with RBV, or 24 wk without RBV*	No	No	12 wk with RBV, or 24 wk without RBV*

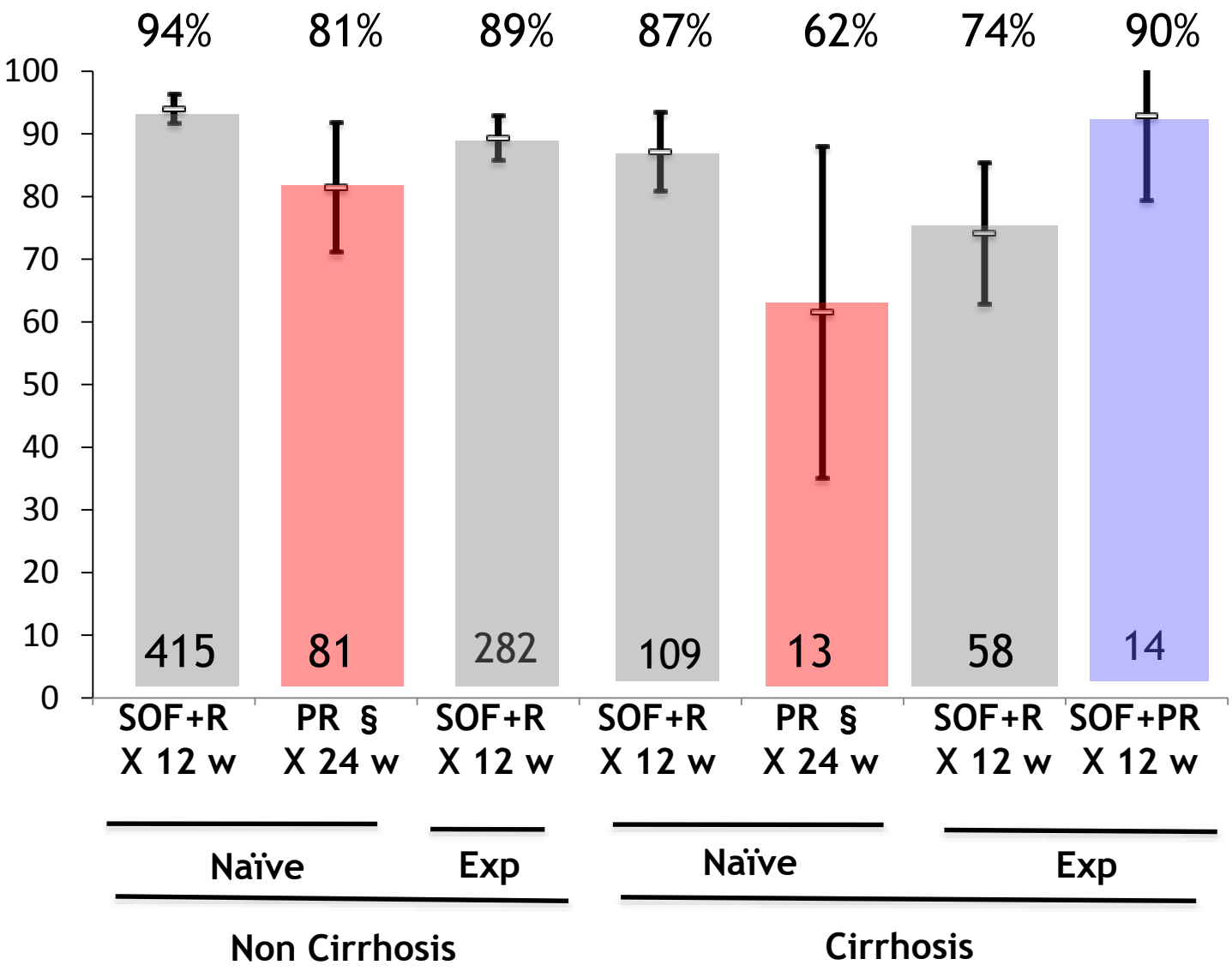
*Patients with negative predictors of response can be treated 24 weeks with ribavirin (negative predictors: treatment-experienced, platelet <75x10^3/uL)

IFN-Free Options, Gen 4

	SOF/LDV	2D	SOF + SIM	SOF + DCV
No cirrhosis	12 wk without RBV	12 wk with RBV	12 wk without RBV	12 wk without RBV
Compensated cirrhosis (CPT-A)	12 wk with RBV, or 24 wk without RBV*	24 wk with RBV	12 wk with RBV, or 24 wk without RBV*	12 wk with RBV, or 24 wk without RBV*
Decompensated cirrhosis (CPT-B and CPT-C)	12 wk with RBV, or 24 wk without RBV*	No	No	12 wk with RBV, or 24 wk without RBV*

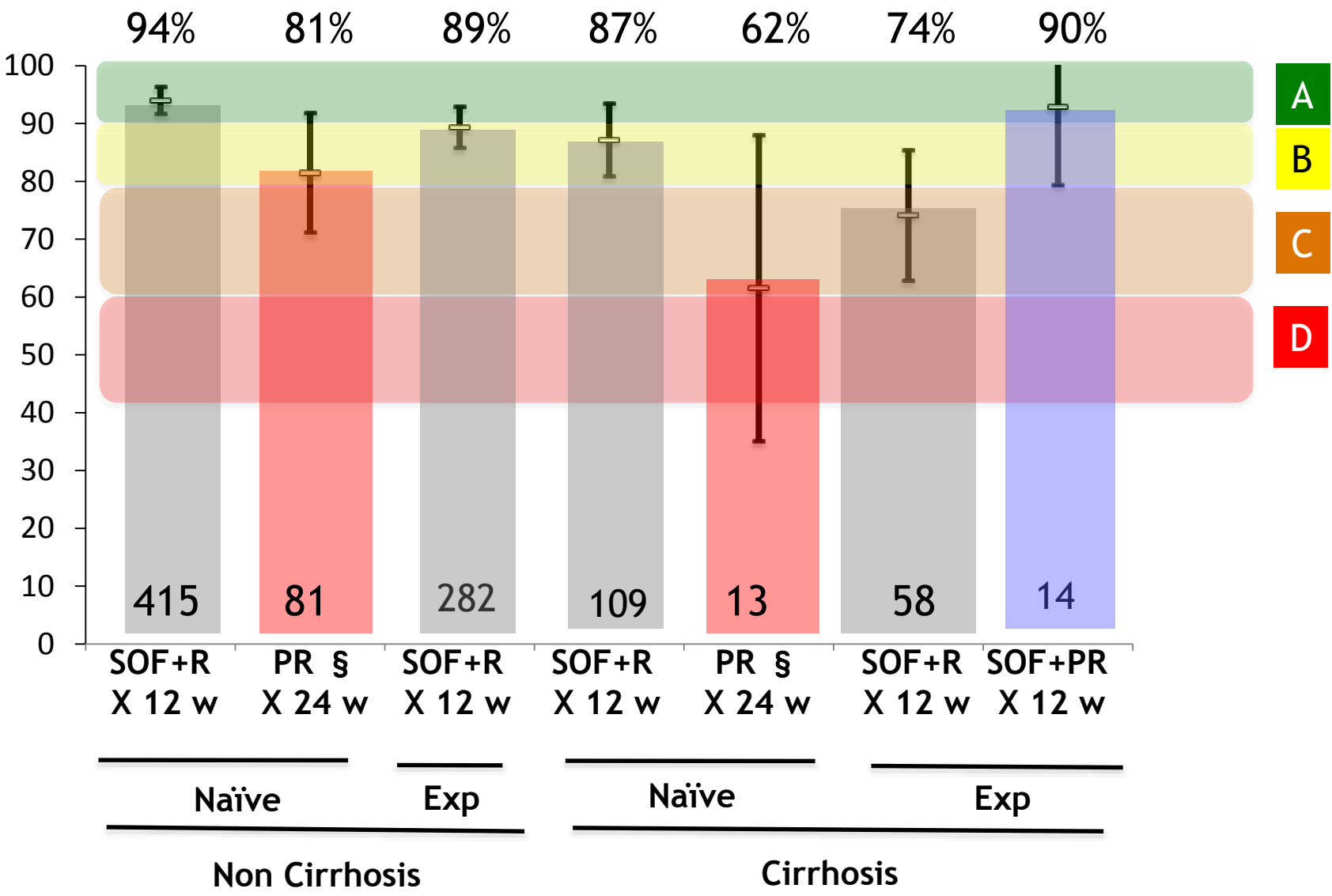
*Patients with negative predictors of response can be treated 24 weeks with ribavirin (negative predictors: treatment-experienced, platelet <75x10^3/uL)

Summary of SVR rates in HCV G2 HIV-



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

Summary of SVR rates in HCV G2 HIV-

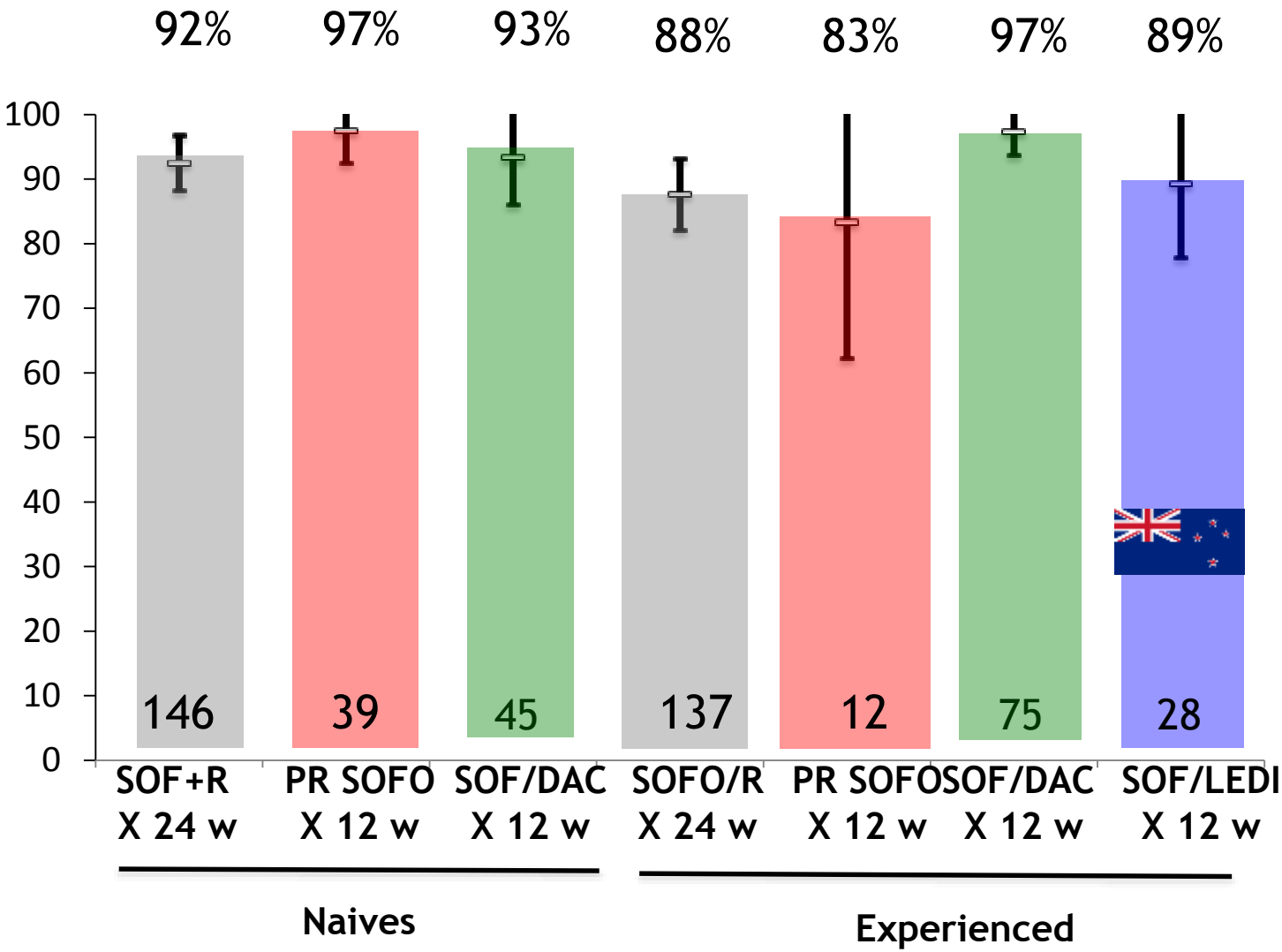


Registrative studies: Fusion, Fission Positron, Valence, Lonestar, cohorts: TRIO, TARGET

IFN-Free Options, Gen 2

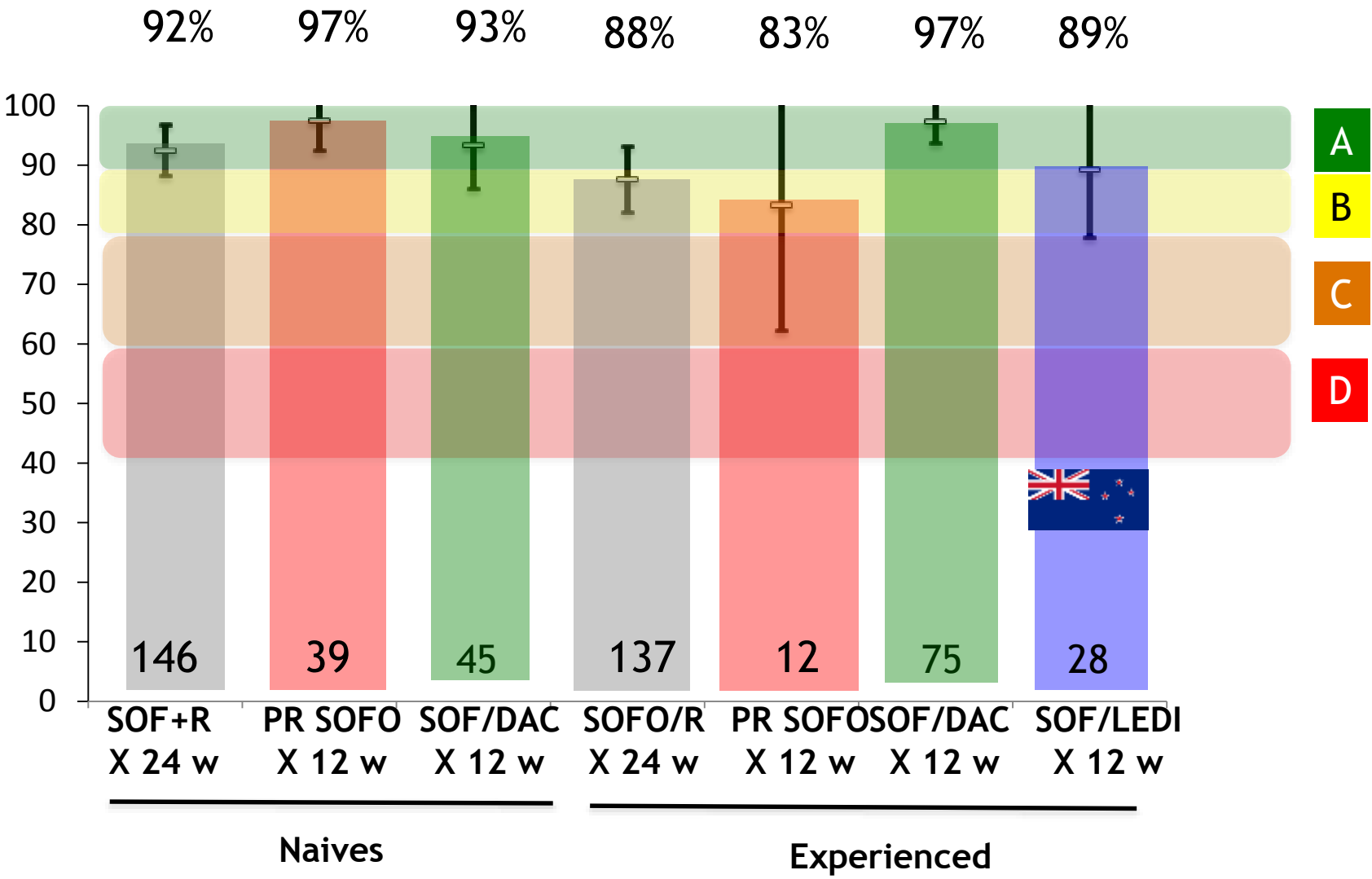
	SOF + RBV	SOF + DCV
No cirrhosis	12 wk	12 wk without RBV
Compensated cirrhosis (CPT-A)	16-20 wk	12 wk without RBV
Decompensated cirrhosis (CPT-B and -C)	16-20 wk	12 wk with RBV

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



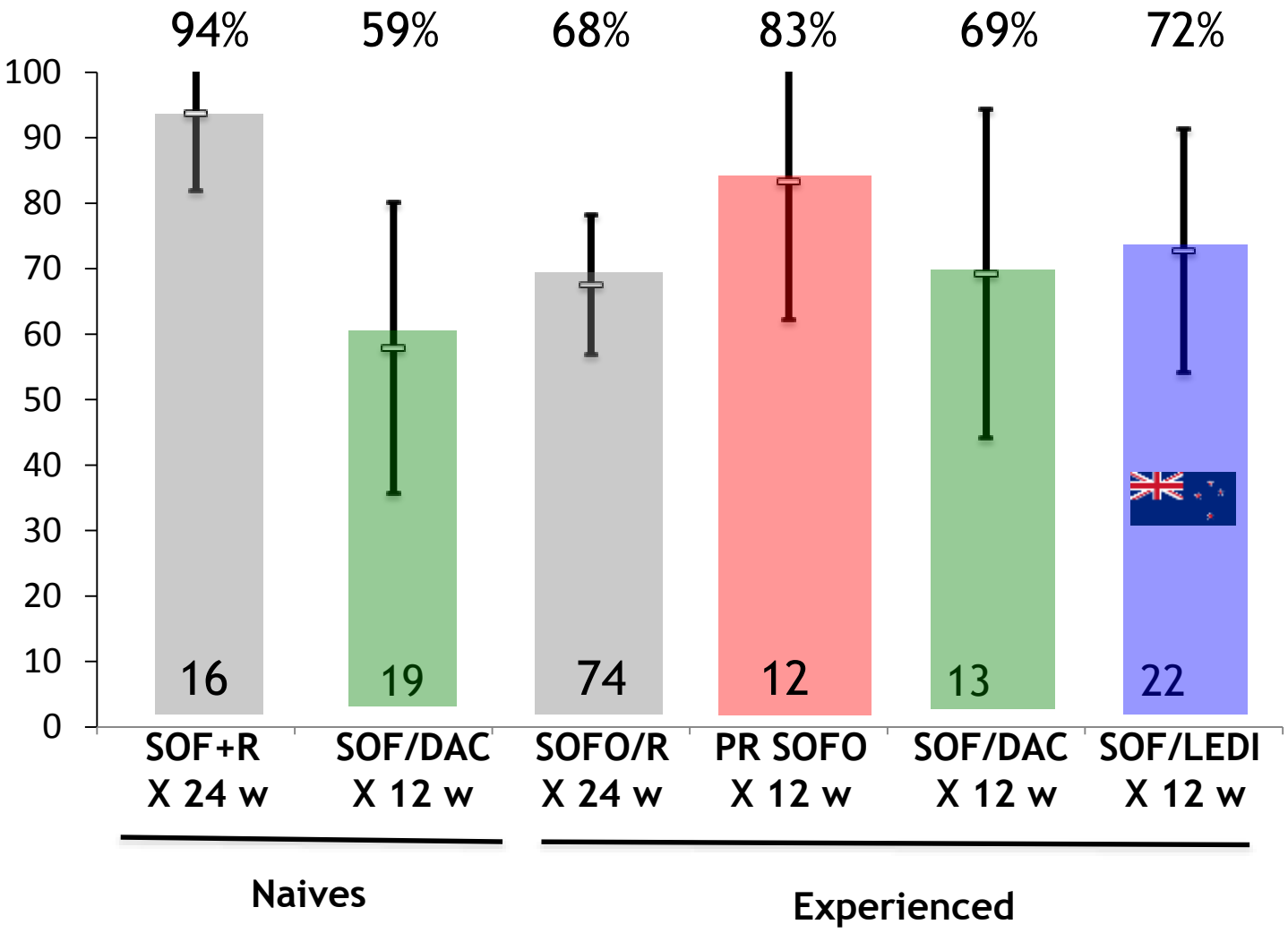
Registrative studies: Fusion, Fission Positron, Valence, Lonestar, Ally 3, Gane et al AASLD 2014

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



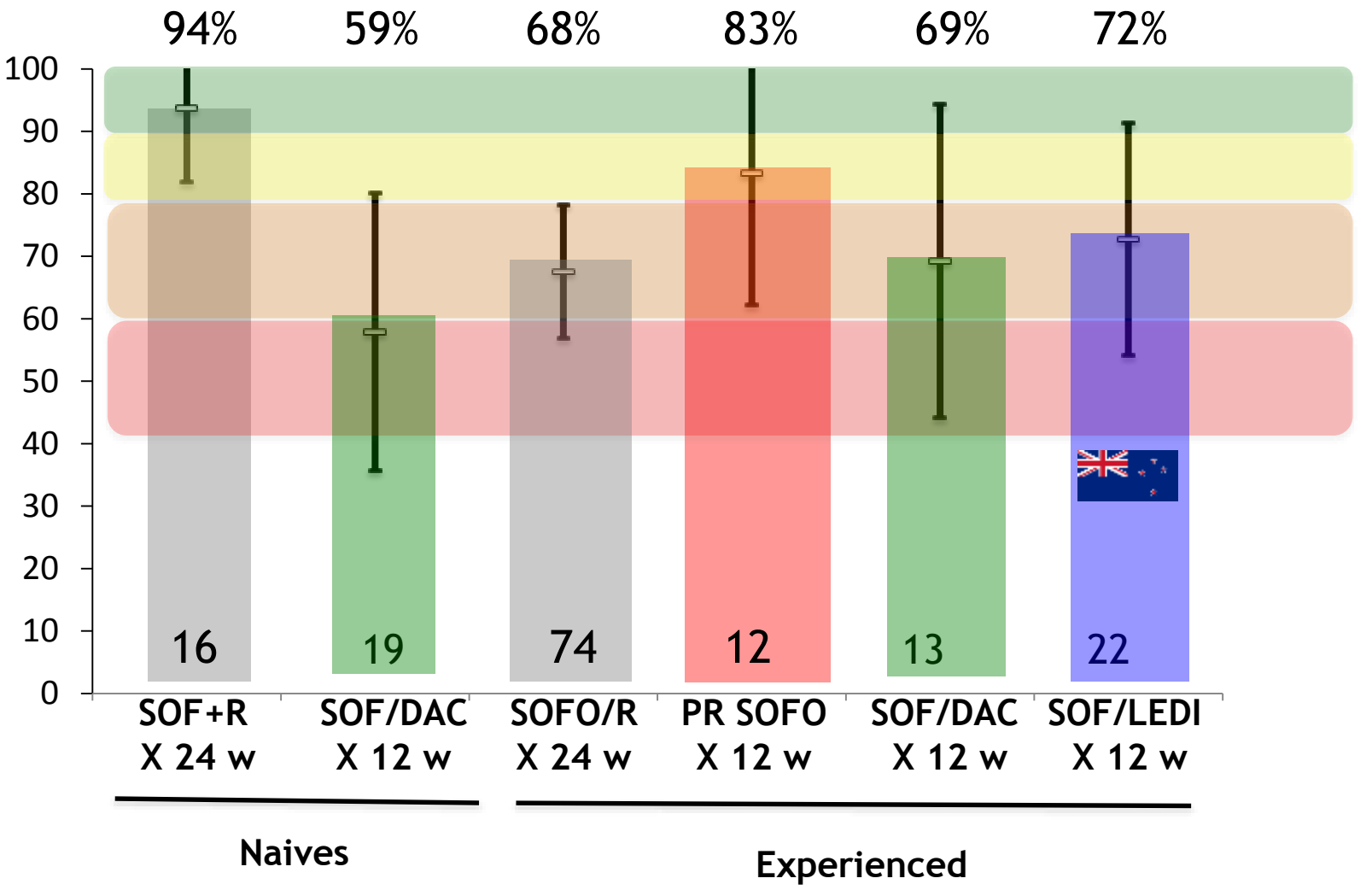
Registrative studies: Fusion, Fission Positron, Valence, Lonestar, Ally 3, Gane et al AASLD 2014

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



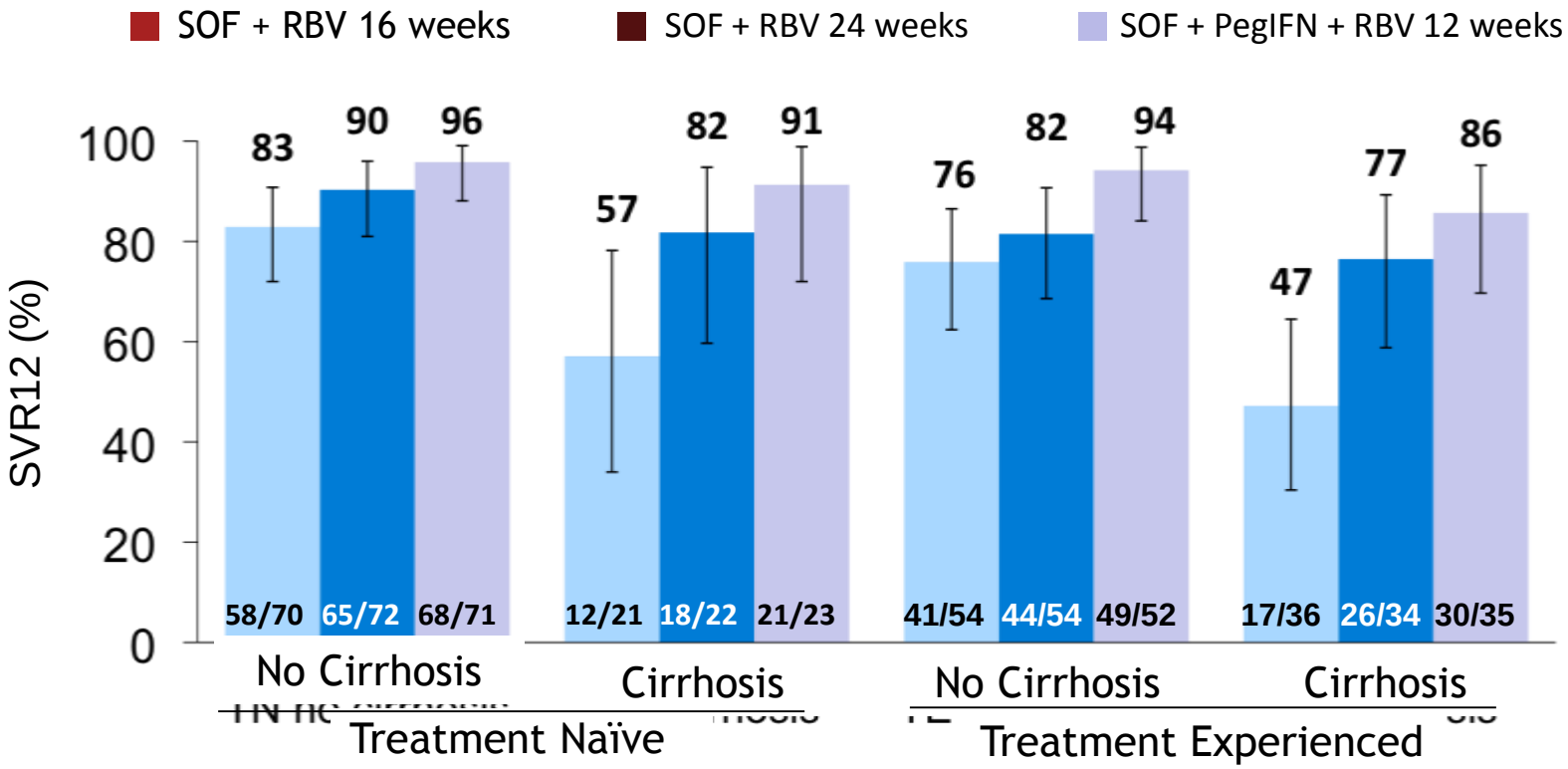
Registrative studies: Fusion, Fission Positron, Valence, Lonestar, Ally 3, Gane et al AASLD 2014

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



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

BOSON: SOF Based Regimens in TN/TE NC/CC GT 3 and TE CC GT 2 Patients



- Higher SVR12 rates with SOF+PegIFN+RBV compared to SOF+RBV for 16 or 24 weeks
  - 86% SVR12 in GT 3 TE with cirrhosis treated with SOF+PegIFN+RBV
  - > 80% in all other subgroups treated with 24 weeks SOF+RBV; consistent with earlier Phase 3 studies

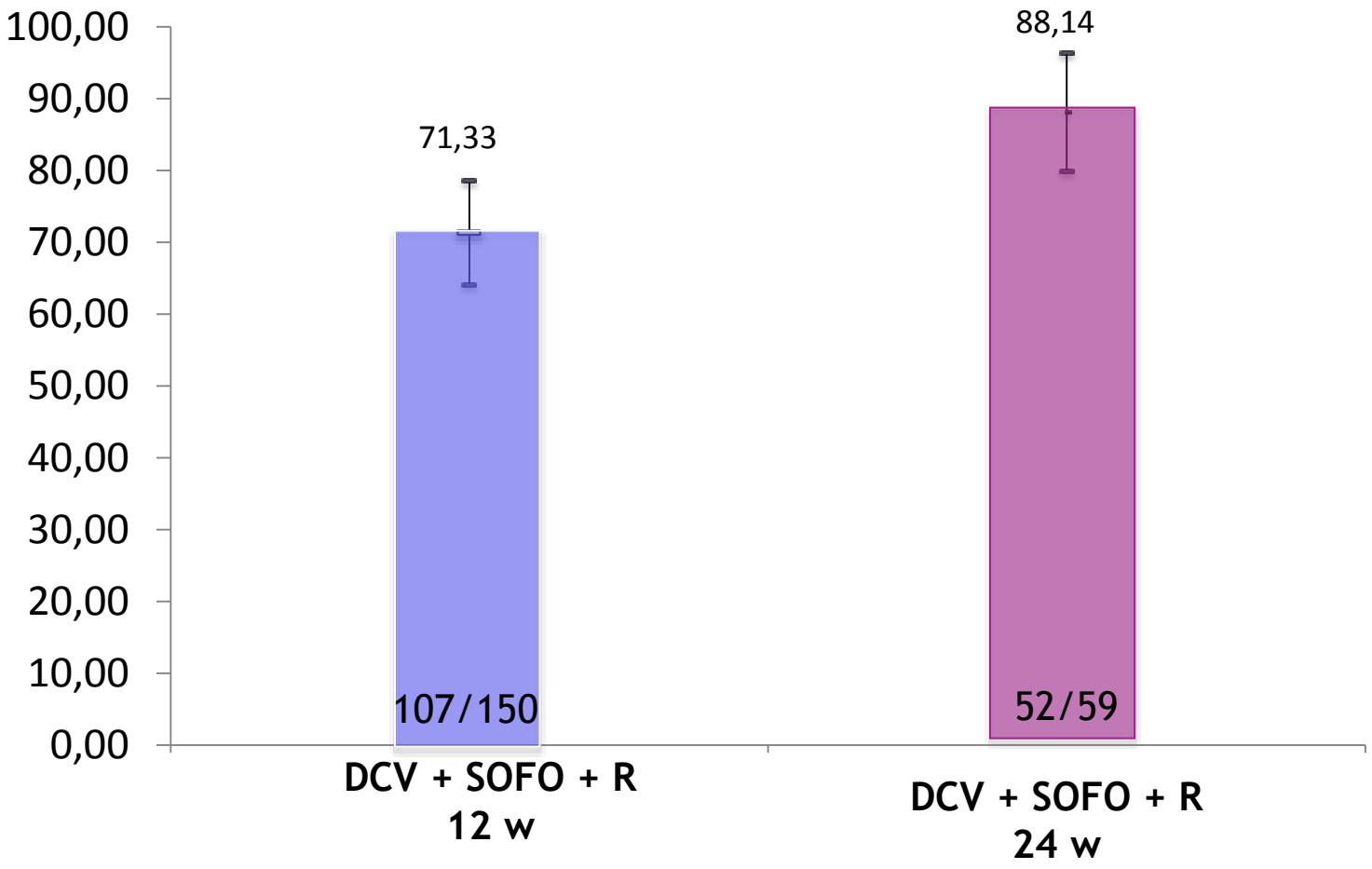
Error bars represent 95% confidence intervals.

Foster, EASL, 2015, L05

SVR12 in Compensated and decompensated cirrhosis

HCV GT	Ref	Treatment Schedule	N with SVR 12 /total (%)		
			CTP Class A	CTP Class B	CTP Class C
3	Foster EASL 2015	SOFO + LEDI + R 12 w		36/59 (61%)	
		SOFO + DAC + R 12 w		80/114 (70%)	

Summary of UK NHS & ANRS compassionate use studies
DCV + SOF in HCV G3
Cirrhotic patients



Foster G et al EASL 2015; Hezode C et al EASL 2015

IFN-Free Options, Gen 3

	SOF + RBV	SOF + DCV
No cirrhosis	24 wk	12 wk without RBV
Compensated cirrhosis (CPT-A)	No	24 wk with RBV
Decompensated cirrhosis (CPT-B and -C)	No	24 wk with RBV

IFN-Free Options, Gen 5-6

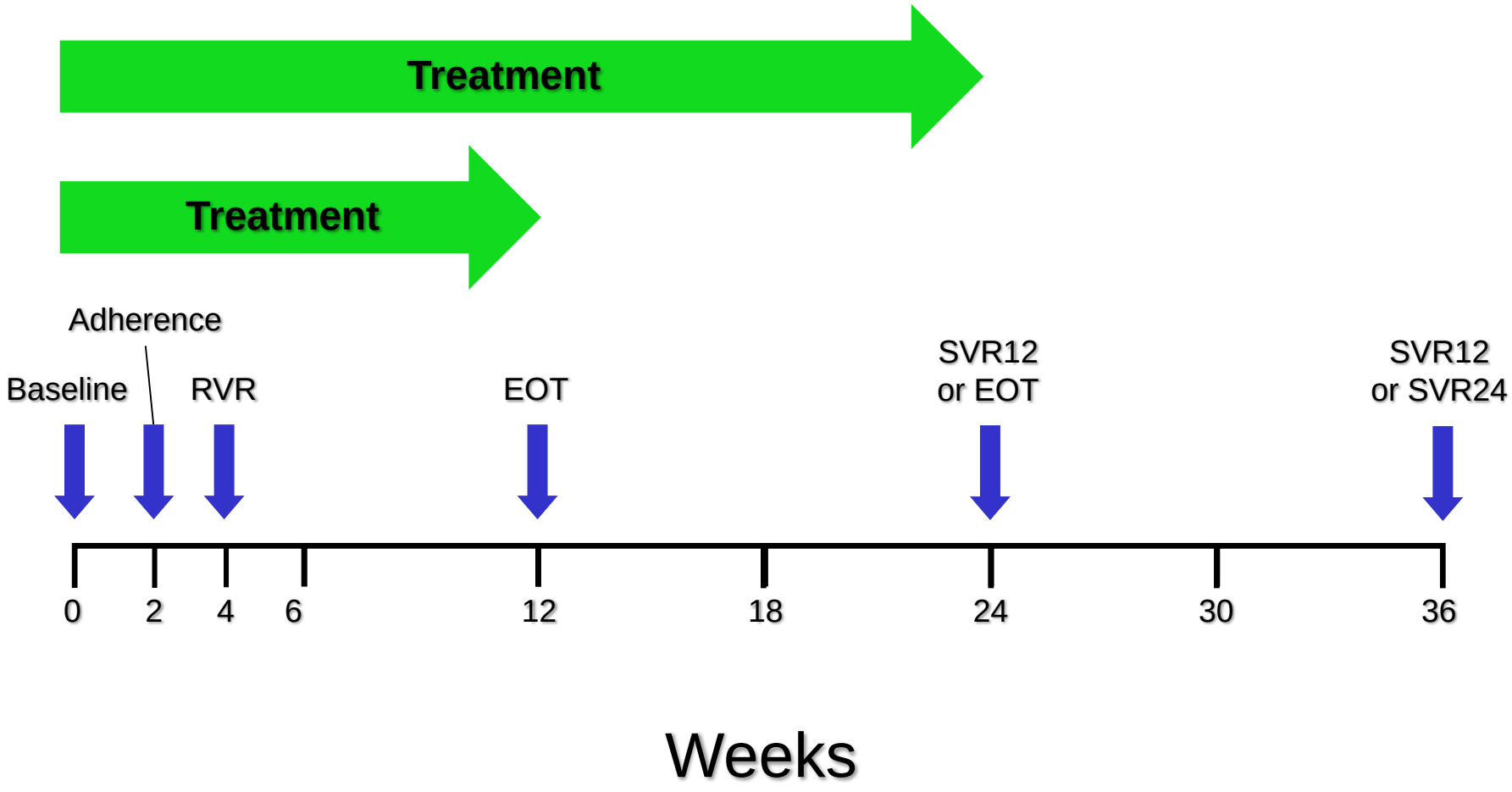
	SOF/LDV	SOF + DCV
No cirrhosis	12 wk without RBV	12 wk without RBV
Compensated cirrhosis (CPT-A)	12 wk with RBV, or 24 wk without RBV*	12 wk with RBV, or 24 wk without RBV*
Decompensated cirrhosis (CPT-B and CPT-C)	12 wk with RBV, or 24 wk without RBV*	12 wk with RBV, or 24 wk without RBV*

*Patients with negative predictors of response can be treated 24 weeks with ribavirin (negative predictors: treatment-experienced, platelet <75x10^3/uL)

Recommendations for Treatment of HCV EASL 2015 vs AASLD 2014: Treatment Options

IFN-free regimens	AASLD	EASL
Sofosbuvir + RBV	2, 3, 4	2, 3
Sofosbuvir/Ledipasvir (± RBV)	1,4,5,6, 3?	1, 4, 5, 6
Ombitasvir/Paritaprevir/Ritonavir + Dasabuvir (± RBV)	1	1
Sofosbuvir + Simeprevir (± RBV)	1,4	1, 4
Sofosbuvir + Daclatasvir (± RBV)	No FDA appr	All
Ombitasvir/Paritaprevir/Ritonavir (± RBV)	4	4
IFN-containing regimens		
PegIFNα + RBV + sofosbuvir	3, 4	All
PegIFNα + RBV + simeprevir	Suboptimal	1, 4

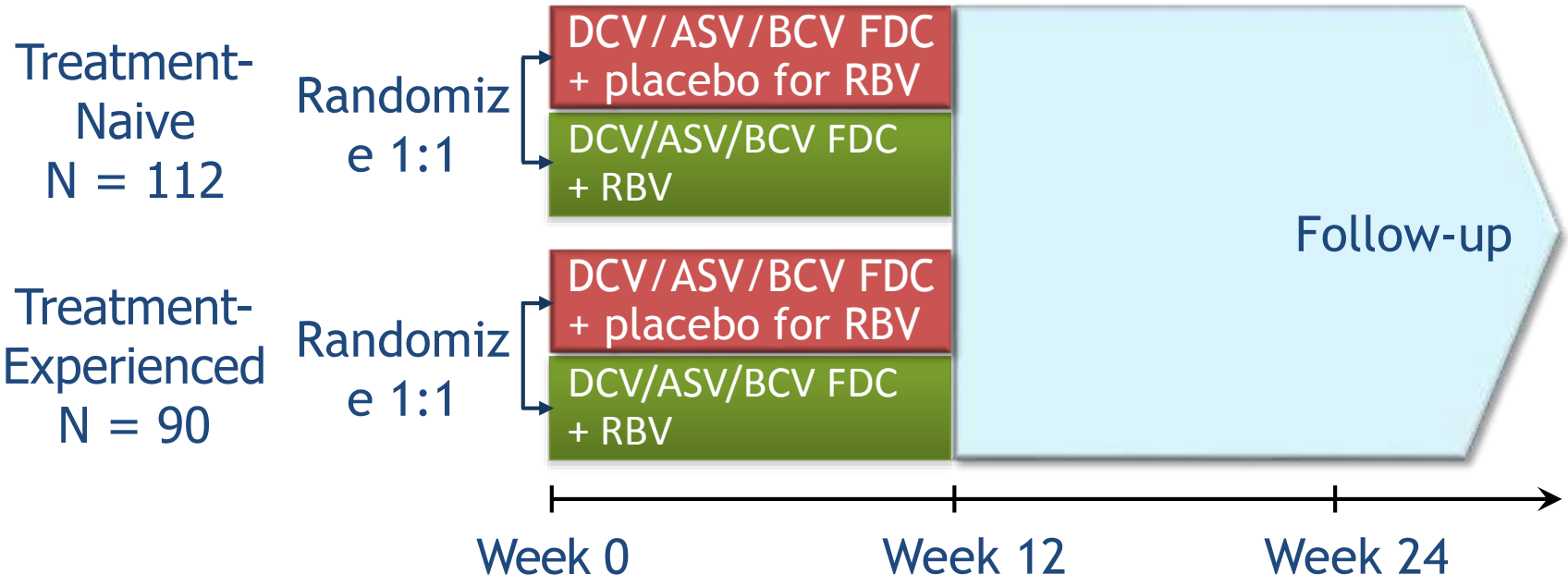
Treatment Monitoring (IFN-Free)



Il trattamento dell'epatite C: stato dell'arte

- Basi virologiche del trattamento
- Strategie di terapia
- Terapia anti HCV : AD 2015
- Terapia anti HCV: il futuro prossimo

UNITY-2: DCV + ASV + BCV Randomized, Double-Blind, Phase 3 Study

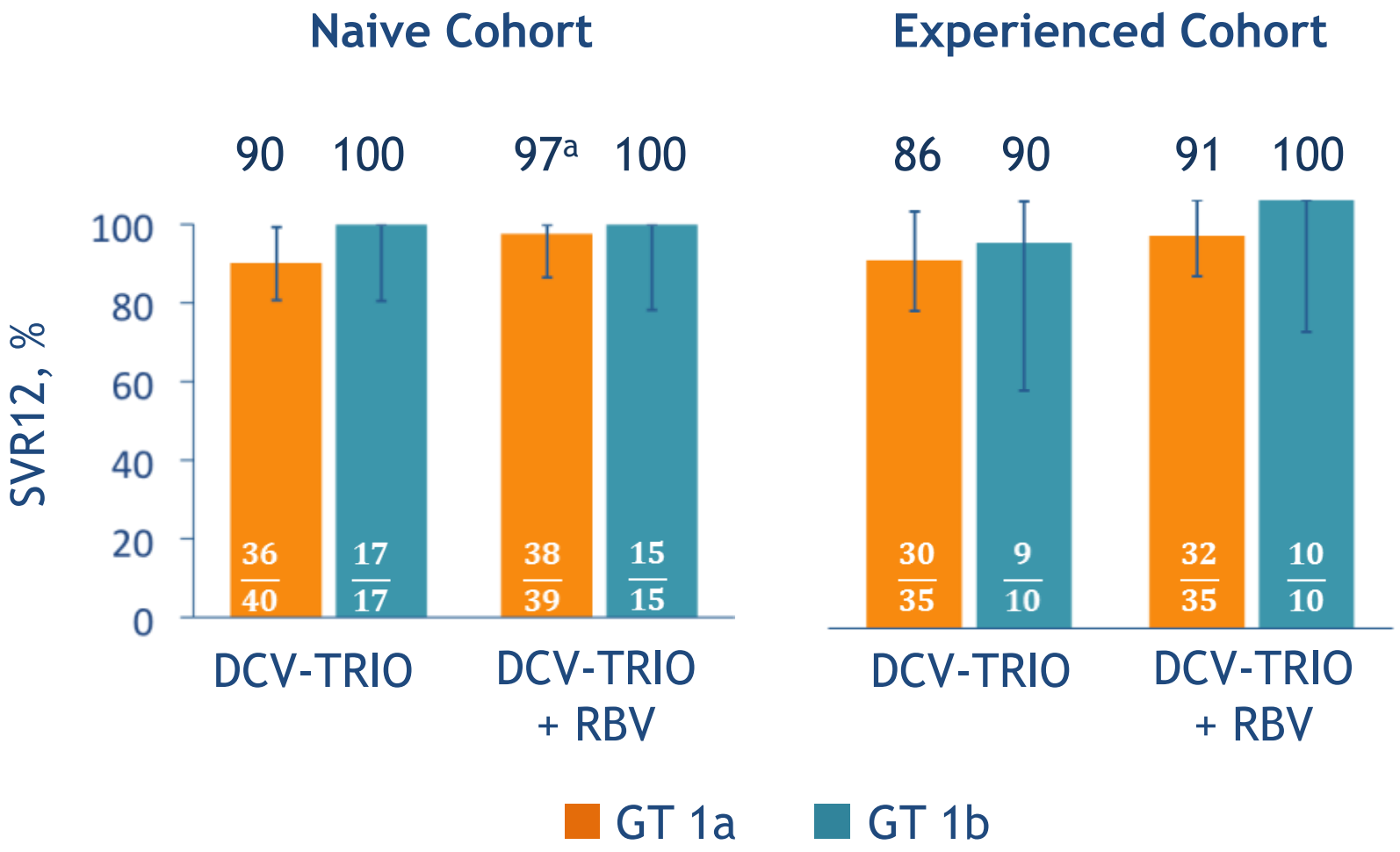


- Primary efficacy assessment: SVR12
  - HCV RNA < LLOQ (25 IU/mL) TD or TND at posttreatment Week 12
- Twice-daily fixed-dose combination (FDC)
  - DCV 30 mg / ASV 200 mg / BCV 75 mg
  - With or without weight-based ribavirin twice-daily

TD, target detected; TND, target not detected

Muir AJ et al. AASLD 2014

UNITY-2: DCV + ASV + BCV SVR12 by GT 1 Subtype



[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 95% confidence intervals.

Muir AJ et al. AASLD 2014

Strategies of DAA based HCV eradication

- Sofosbuvir based
  - Sofosbuvir (high resistance barrier) + RBV
  - Sofosbuvir (high resistance barrier) + 1 DAA ± RBV
- Sofosbuvir free
  - 3 (2) DAAs low resistance barrier

Still challenging

Phase IV

Adjusted for HCV Genotype.

Fine tuning by RBV & Tx duration In PR failures & Cirrhosis

- Sofosbuvir based "pangenotypic"
  - Sofosbuvir + 1/2 DAA Pangenotypic
- Sofosbuvir free "pangenotypic"
  - 2 DAA pangenotypic

One pill (injection?) for all

Strategies of DAA based HCV eradication

- Sofosbuvir based
  - Sofosbuvir (high resistance barrier) + RBV
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Still challenging

Phase IV

Adjusted for HCV Genotype.

Fine tuning by RBV & Tx duration In PR failures & Cirrhosis

- Sofosbuvir based "pangenotypic"
  - Sofosbuvir + 1/2 DAA Pangenotypic
- Sofosbuvir free "pangenotypic"
  - 2 DAA pangenotypic

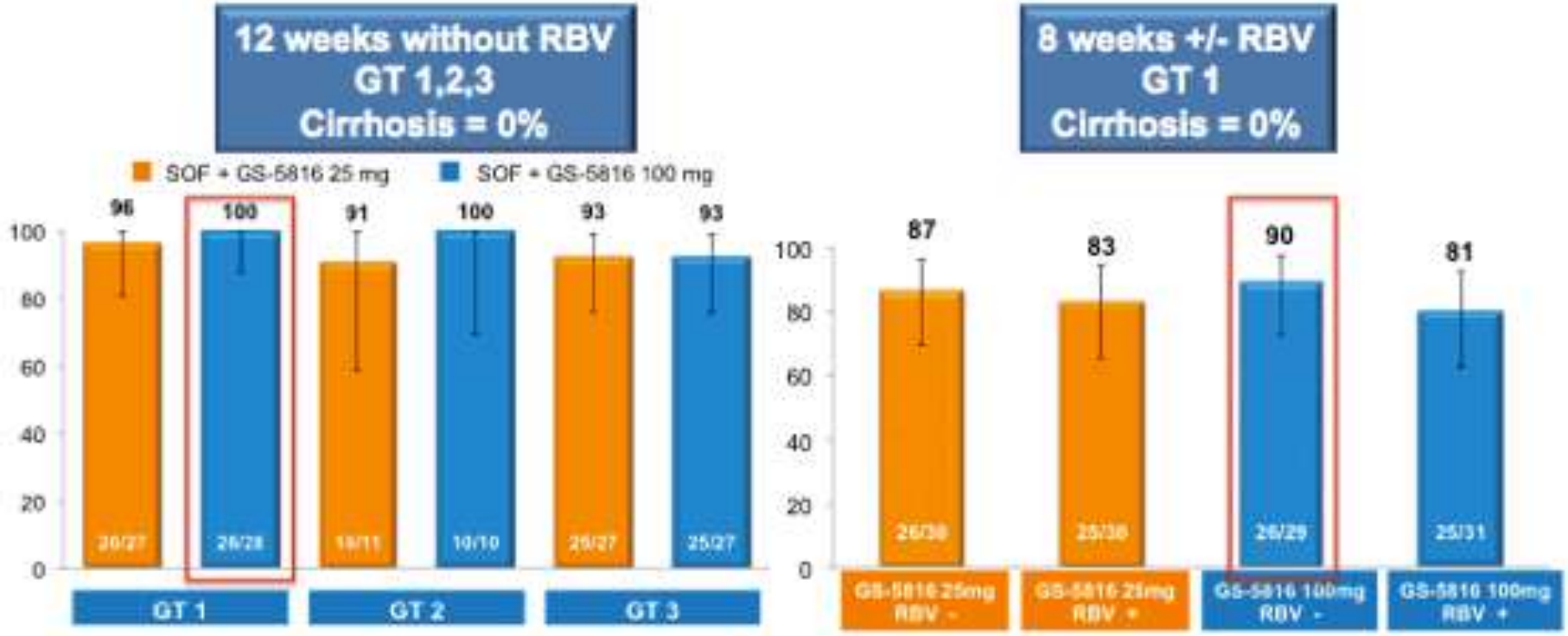
Smoother

Phase II-III

One pill (injection?) for all

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

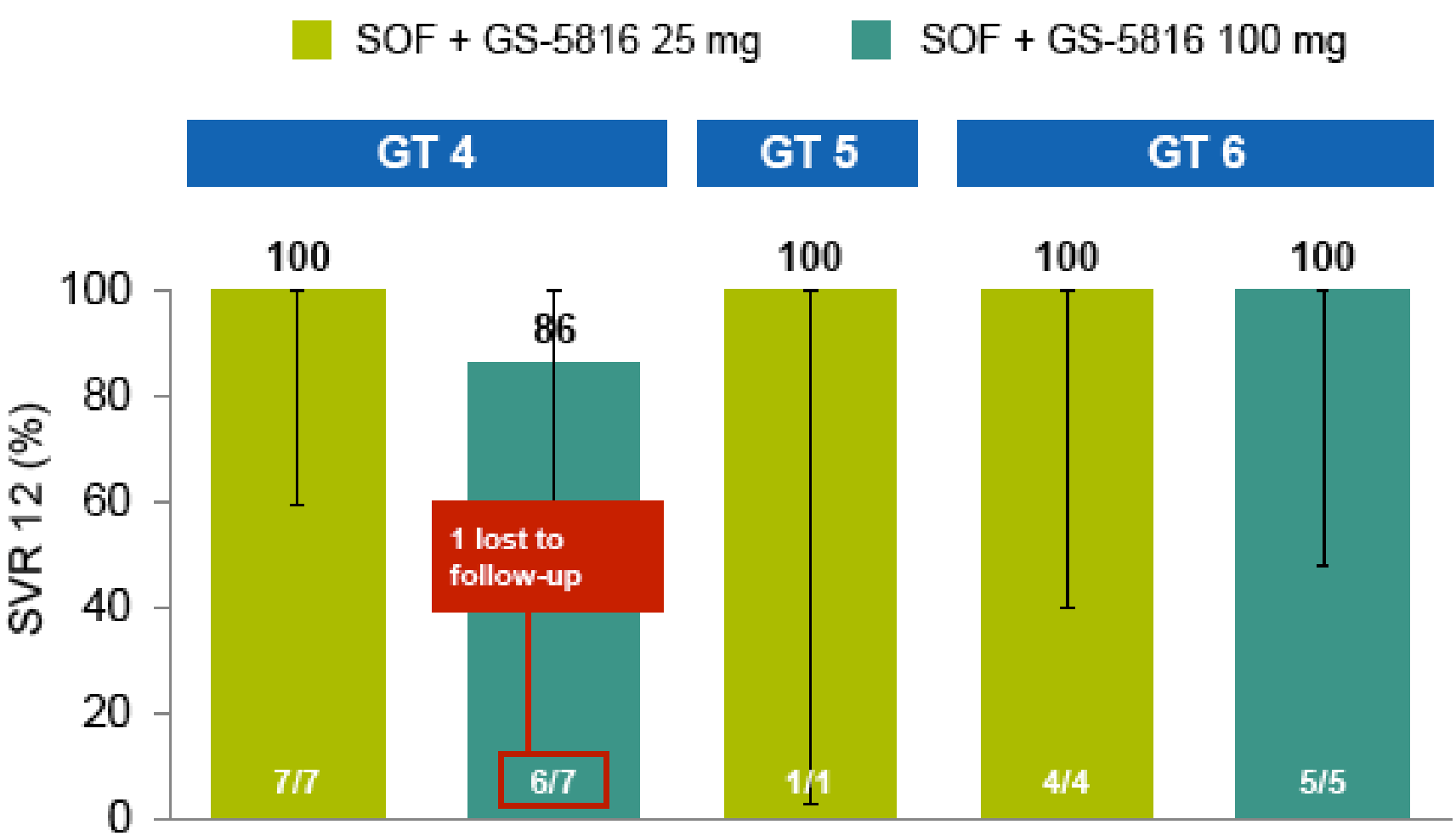


- Higher relapse rates in 8 wks vs 12 wks
- RBV did not mitigate risk of relapse w/ 8 week duration
- Virological failure associated with NS5A RAVs

T.T. Tran, Abst# 80

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

Results: SVR12



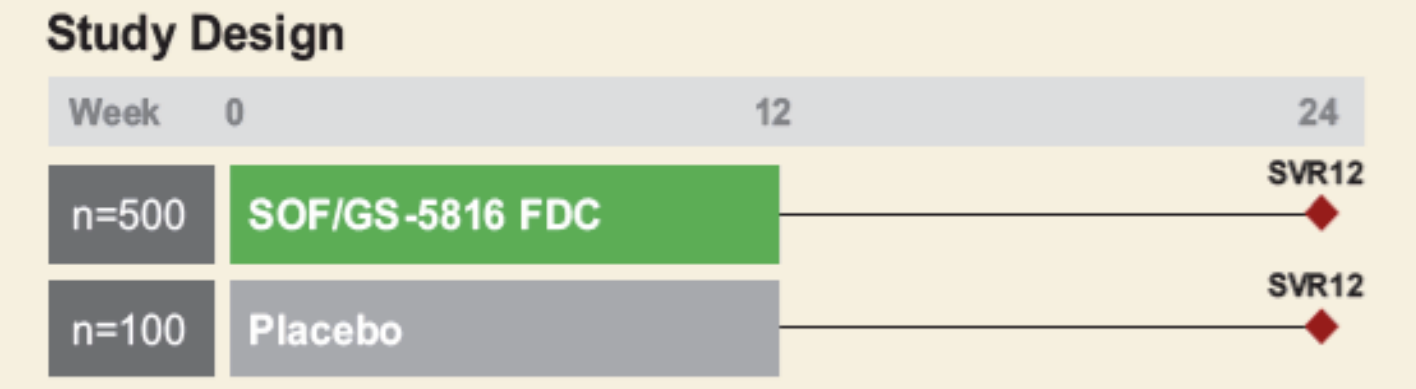
Everson G EASL 2015

SOFOSBUVIR + VELPATASVIR: the Phase III ASTRAL program

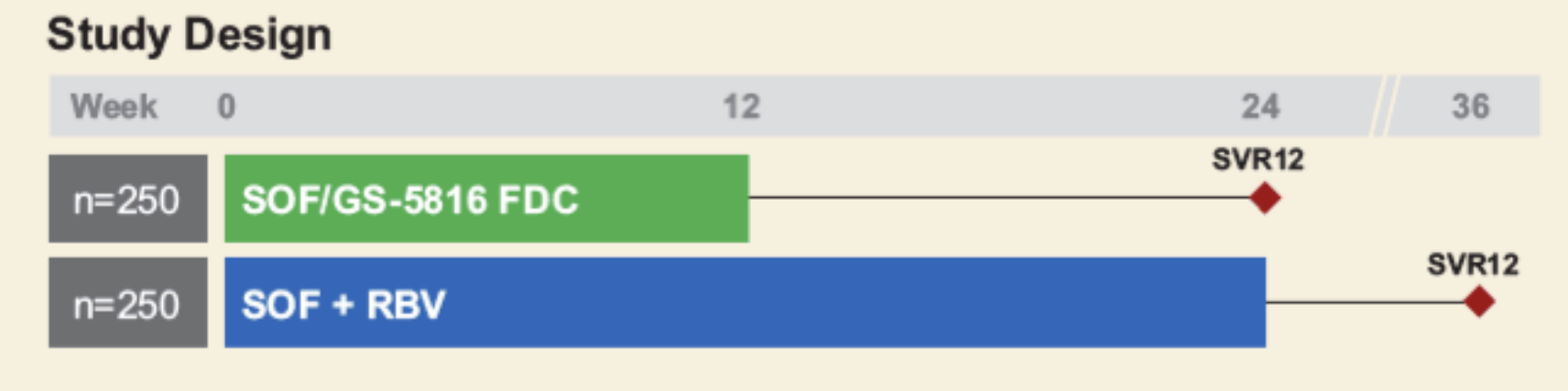
Shared Design Features

- The international Phase 3 ASTRAL program comprises 4 multicenter, randomized clinical studies in HCV patients
  - ASTRAL-1: GT 1, 2, 4, 5, 6
  - ASTRAL-2: GT 2
  - ASTRAL-3: GT 3
  - ASTRAL-4: GT 1–6 and Child-Pugh-Turcotte (CPT) B cirrhosis

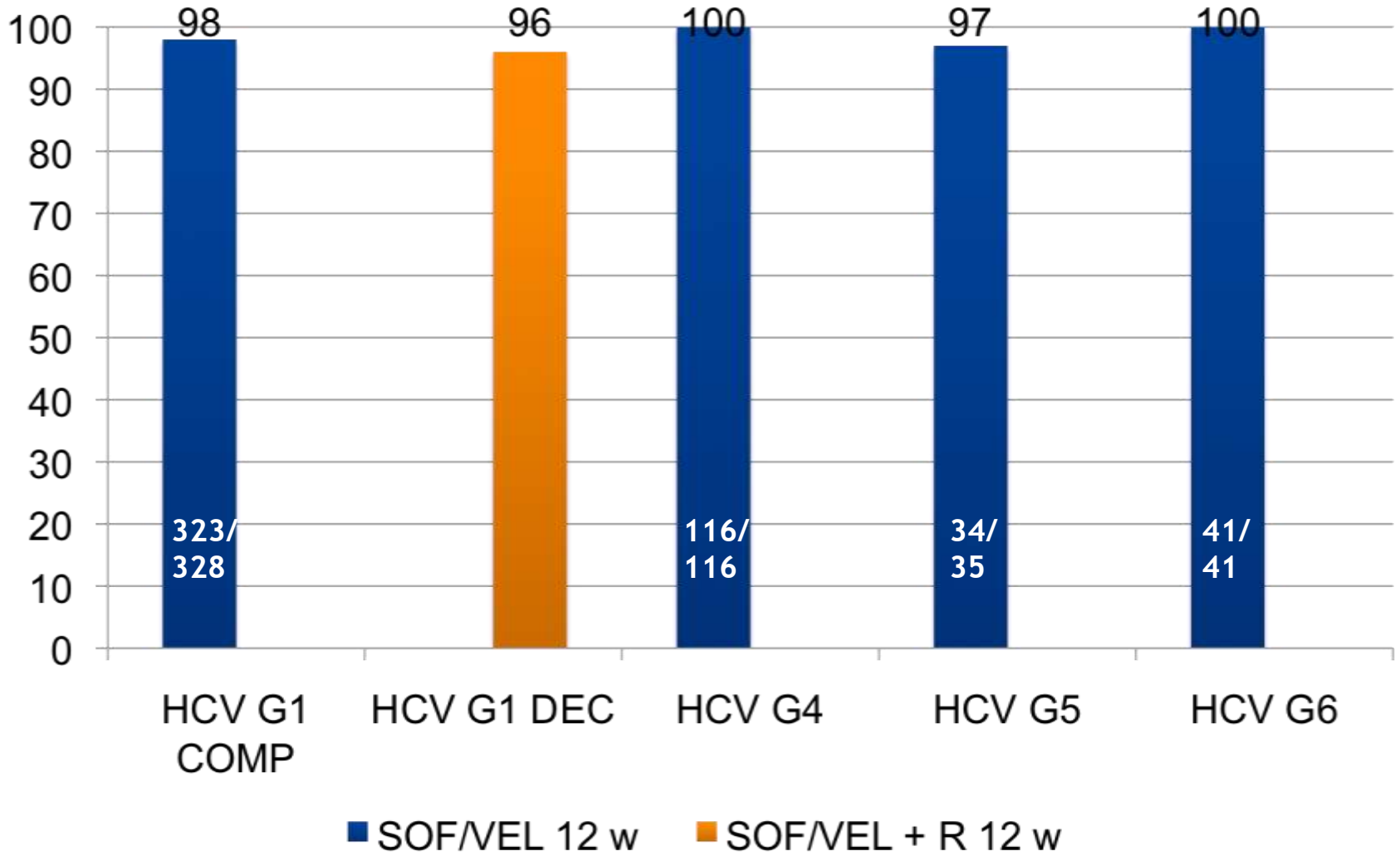
HCV GT 1,2,4, 5 & 6



HCV GT 3

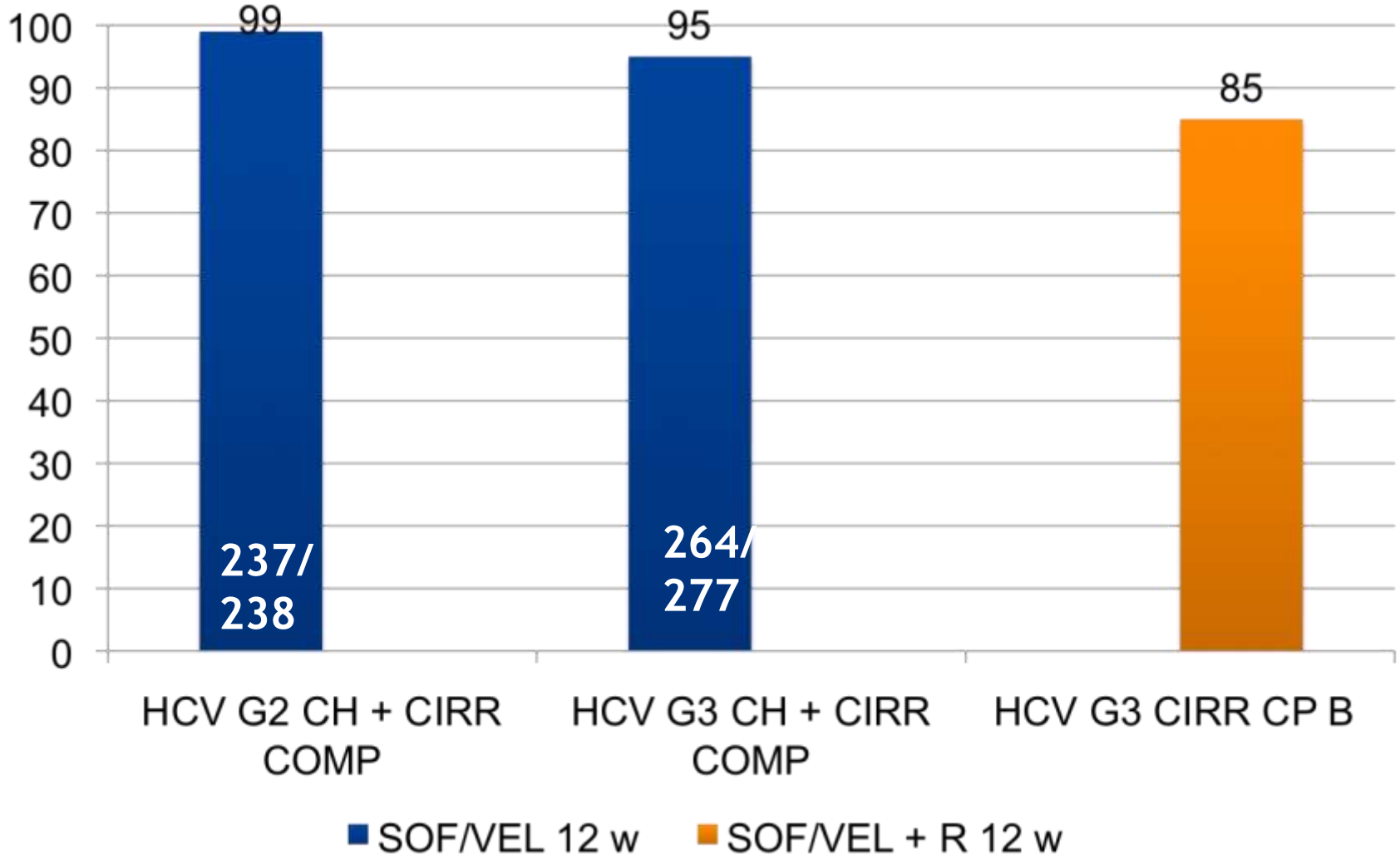


ASTRAL studies :
Sofosbuvir + Velpatasvir FDC in HCV G1, 4, 5, 6 stratified according to liver disease stage



Gilead sciences Inc: http://www.businesswire.com/news/home/20150921005402/en/

ASTRAL studies :
Sofosbuvir + Velpatasvir FDC in HCV G 2 & 3 stratified according to liver disease stage

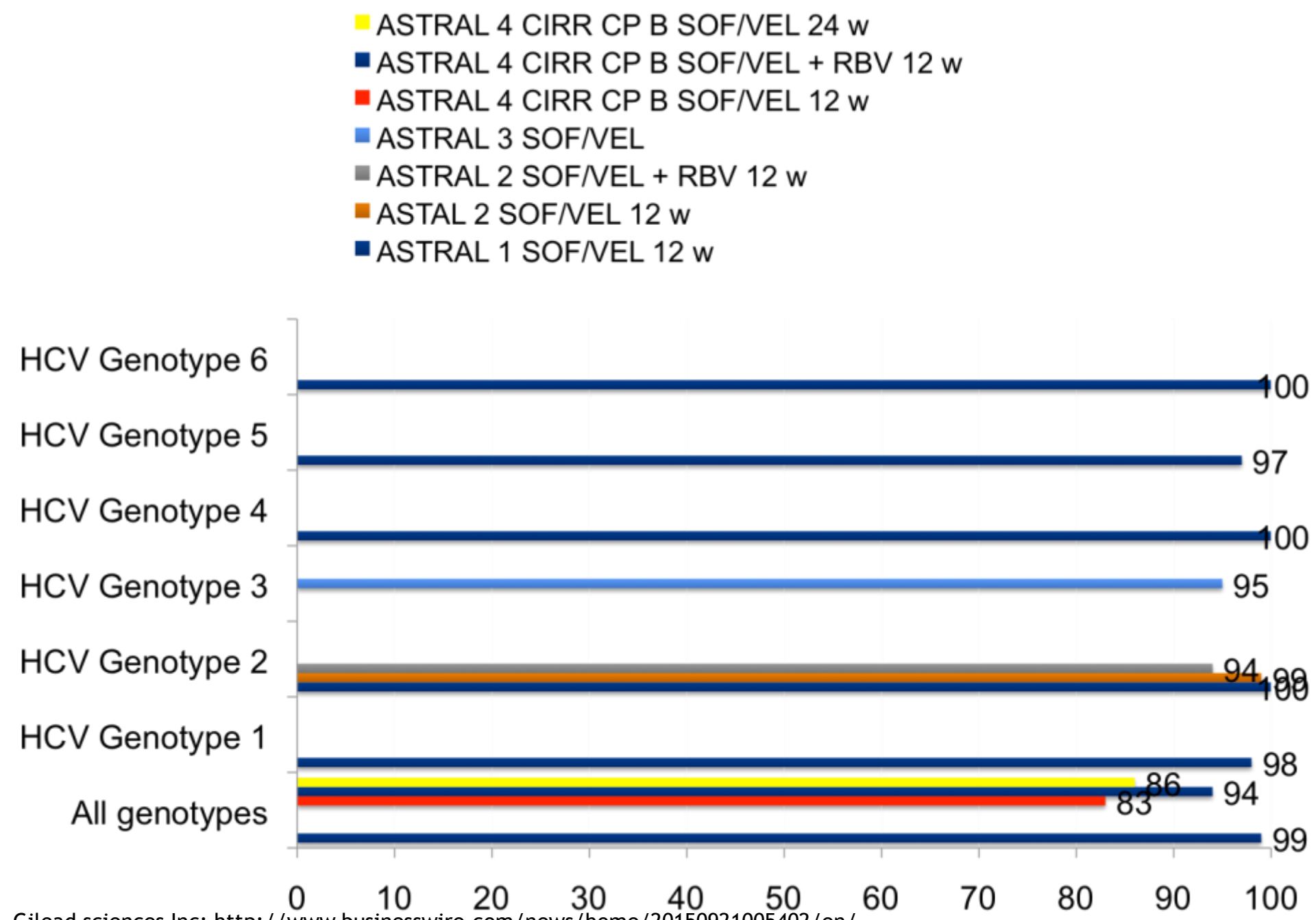


Gilead sciences Inc: http://www.businesswire.com/news/home/20150921005402/en/

ASTRAL STUDIES
VIROLOGICAL FAILURES WITH RELAPSE STRATIFIED ACCORDING TO GENOTYPES & SAFETY

- 1015/1035 SVR (98%)
- 20 failures:
  - 7 lost to follow up
  - 1 reinfection
  - 12 Virological relapse:
    - 2 HCV G1
    - 10 HCV G3
- In CH or compensated cirrhosis adverse events similar to placebo 2/1035 stopped treatment for adverse events
- In 257 pts with decompensated cirrhosis pts 46 had 1 or more SAE (18%) and 9 died (3.5%) in relationship with liver disease

Gilead sciences Inc: http://www.businesswire.com/news/home/20150921005402/en/



Gilead sciences Inc: http://www.businesswire.com/news/home/20150921005402/en/

SOFOSBUVIR/Velpatasvir FDC

- 1 Single Tablet Regimen (STR) x 12 w for HCV G 1,2,4,5,6 with Chronic Hepatitis (CH) or Compensated Cirrhosis (CC)
- 1 STR x 12 w + RBV 1000/1200 for HCV G 1,2,4,5,6 with Decompensated Cirrhosis (DC: Child Pugh class B score $\geq$ 7)
- HCV G3
  - CH & CC
    - 1 STR x 12 w or
    - 1 STR x 12 w + RBV ?
  - DC
    - 1 STR + R x 12 w or
    - 1 STR + R x 24 w i ?

THE C-EDGE TREATMENT-NAIVE STUDY OF A 12-WEEK ORAL REGIMEN OF GRAZOPREVIR (MK-5172) / ELBASVIR (MK-8742) IN PATIENTS WITH CHRONIC HCV GENOTYPE 1, 4, OR 6 INFECTION

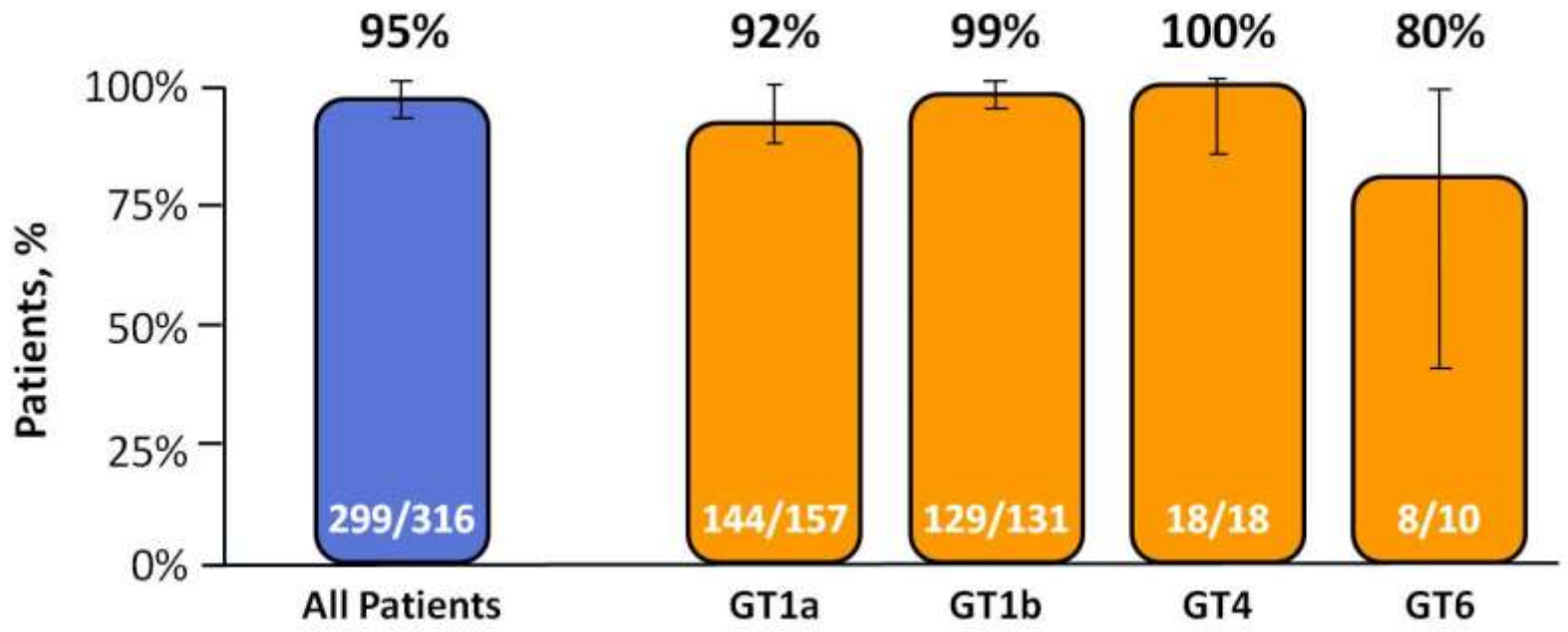
Stefan Zeuzem, Reem Ghalib, K. Rajender Reddy, Paul J. Pockros, Ziv Ben Ari, Yue Zhao, Deborah D. Brown, Shuyan Wan, Mark J. DiNubile, Bach-Yen Nguyen, Michael N. Robertson, Janice Wahl, Eliav Barr, Joan R. Butterton*

**Goethe University Hospital, Frankfurt, Germany*

EASL 2015: Abstract G07 [08:30-08:45, Friday April 24th Hall D]

SVR12 – FULL ANALYSIS SET

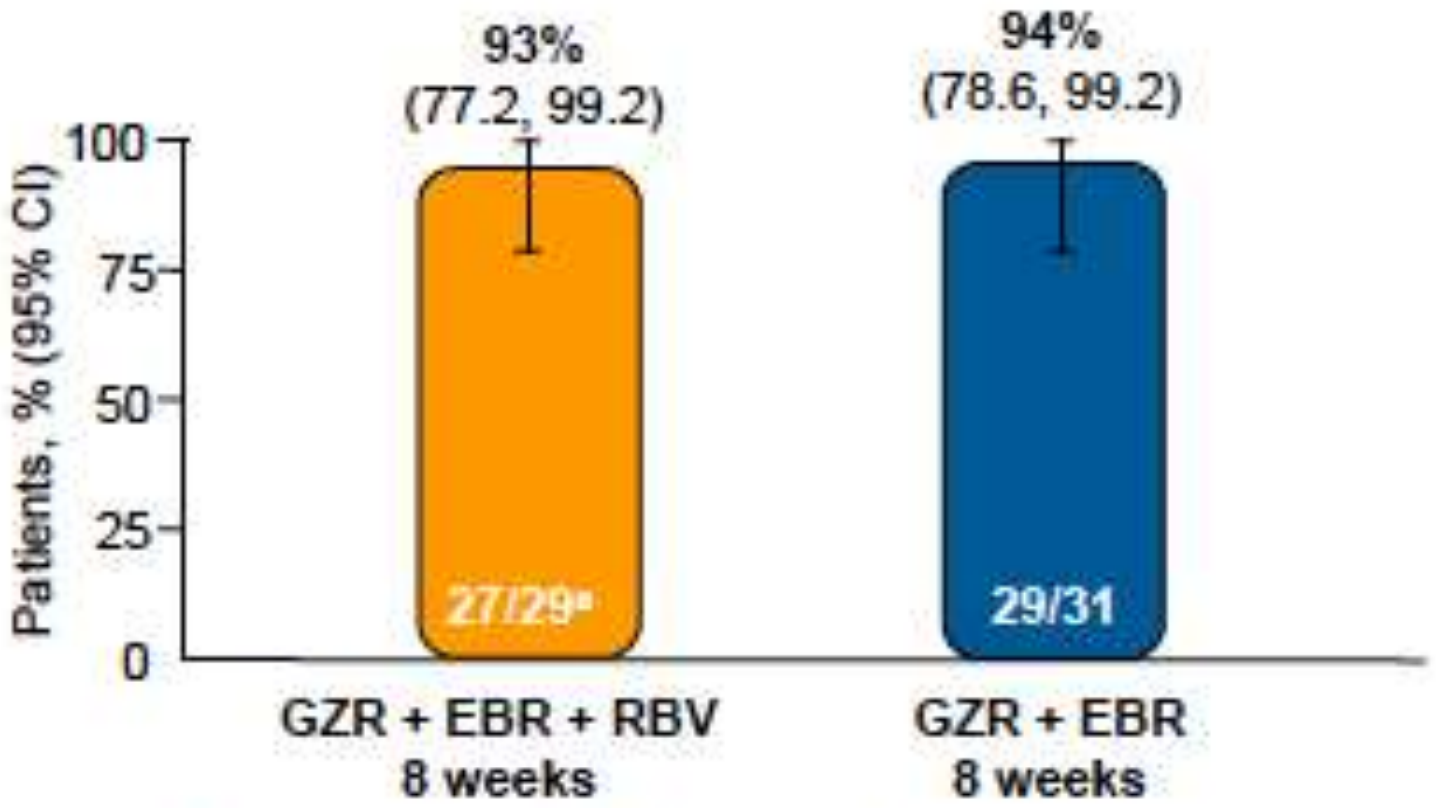
Grazoprevir (100 mg) Elbasvir (50 mg)



Non-virologic failure	4	3	1	0	0
Breakthrough	1	1	0	0	0
Relapse	12	9	1	0	2

C-EDGE TN

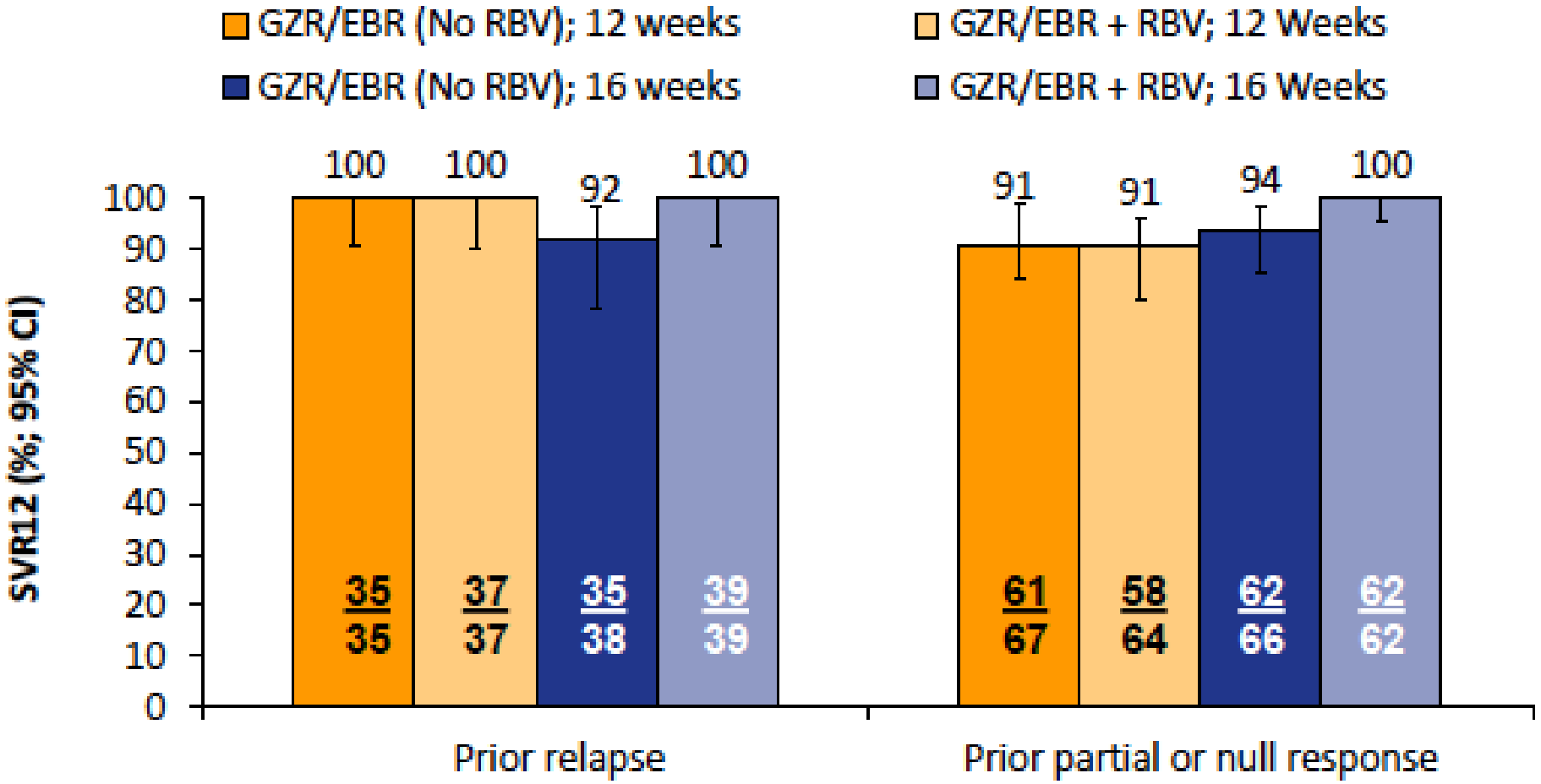
EFFICACY OF AN 8-WEEK REGIMEN OF GRAZOPREVIR PLUS ELBASVIR WITH AND WITHOUT RIBAVIRIN IN TREATMENT-NAIVE, NONCIRRHOTIC HCV GENOTYPE 1B INFECTION



AE = adverse event; CI = confidence interval; EBR = elbasvir; FW = follow-up week; GZR = grazoprevir; RBV = ribavirin; SVR12 = sustained virologic response (HCV RNA <25 IU/mL) at follow-up week 12.
[a]Excludes 1 patient who discontinued early unrelated to AE or virologic failure.
Values are % (95% CI).

Vierling JM et al EASL 2015

EFFICACY AND SAFETY OF GRAZOPREVIR/ELBASVIR +/- RBV FOR 12 OR 16 WEEKS IN PATIENTS WITH HCV G1, G4 OR G6 INFECTION WHO PREVIOUSLY FAILED PEGINTERFERON/RBV: C-EDGE TREATMENT-EXPERIENCED



* Per-protocol population excluded 12 patients [Lost to follow up (2 patients), Withdrew consent (2 patients), No documentation for prior treatment failure classification (2 patients), Prohibited prior medical condition - ascites (1 patient), Non-medication-related non-compliance with study drug (1 patient), Illegal drug user (1 patient), Prohibited medication (1 patient), Non-compliance due to adverse event (1 patient), Death (1 patient)]
95% Confidence Intervals by the Clopper-Pearson (exact) method

Kwo P et al EASL 2015

EFFICACY AND SAFETY OF GRAZOPREVIR AND ELBASVIR IN HEPATITIS C GENOTYPE 1 INFECTED PATIENTS WITH CHILD-PUGH CLASS B CIRRHOSIS (C-SALT)

Ira M. Jacobson, Fred Poordad, Roberto Firpi-Morell, Gregory T. Everson, Elizabeth C. Verna, Sanhita Bhanja, Boan Zhang, Luzelena Caro, Janice Wahl, Michael Robertson, Eliav Barr, Edgar D. Charles

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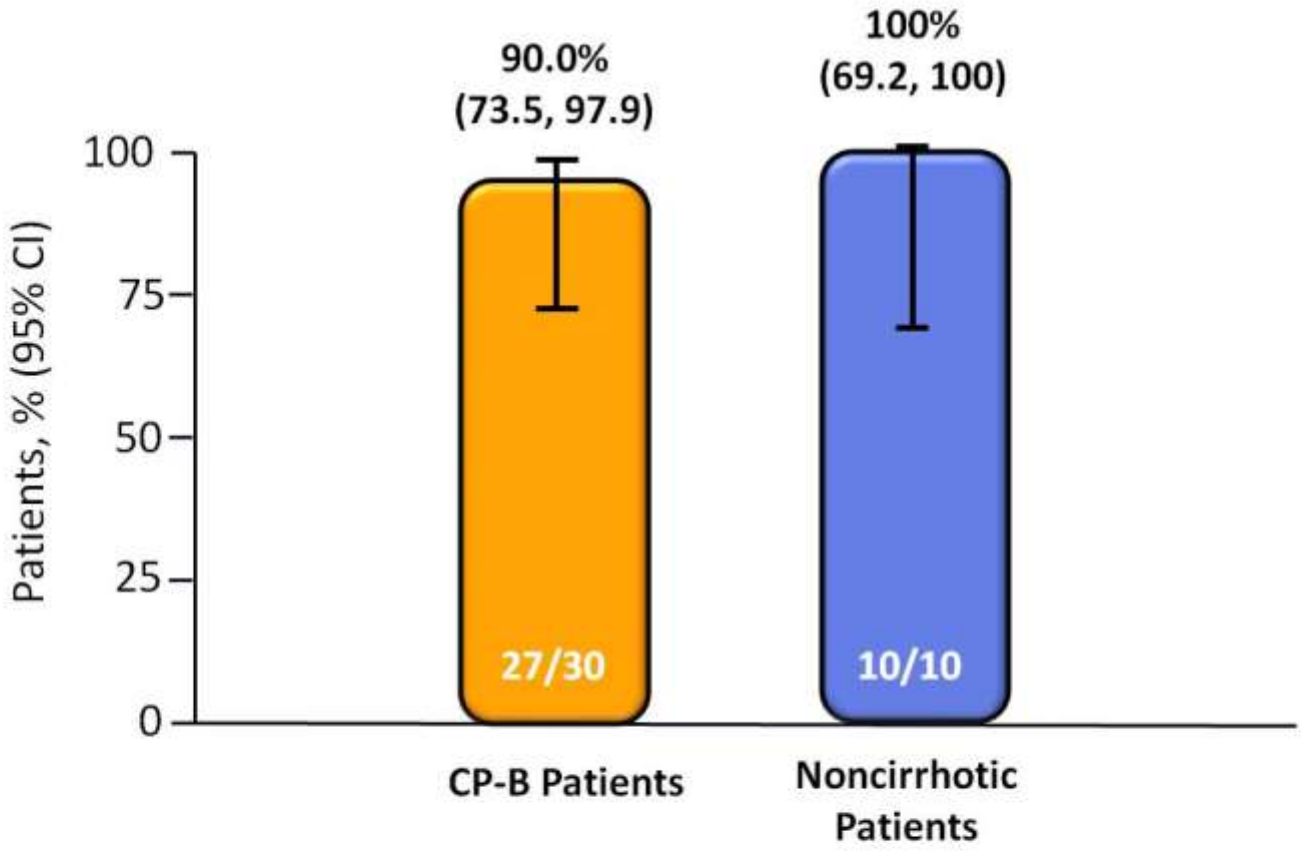
C-SALT

SVR12 (INTENT TO TREAT)

Grazoprevir (50 mg)

Elbasvir (50 mg)



C-SALT

GRAZOPREVIR (GZR)/ELBASVIR (EBR) PLUS RIBAVIRIN (RBV) FOR CHRONIC HEPATITIS C VIRUS GENOTYPE-1 INFECTION AFTER FAILURE OF COMBINATION THERAPY CONTAINING A DIRECT-ACTING ANTIVIRAL AGENT

Xavier Forns, Stuart Gordon, Eli Zuckerman, Eric Lawitz, Jose Luis Calleja, Harald Hofer, Christopher Gilbert, John Palcza, Anita Howe, Mark DiNubile, Michael Robertson, Janice Wahl, Eliav Barr, Maria Buti

MERCK

C-SALVAGE

EASL 2015: Abstract O001 [16:00-16:15, Thursday April 23rd Hall D]

BASELINE CHARACTERISTICS

Grazoprevir (100 mg)
Elbasvir (50 mg)

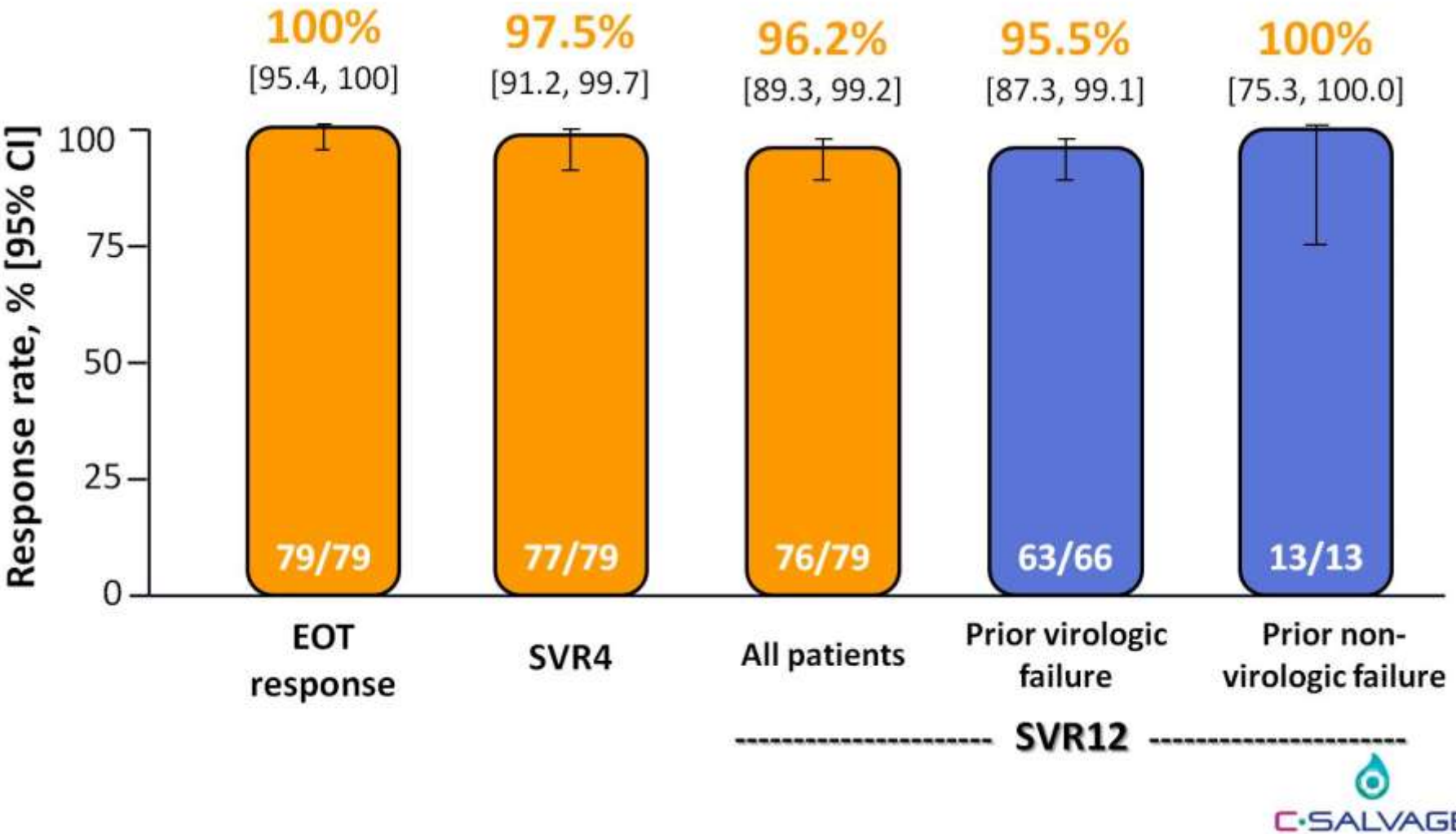
	All treated patients (N = 79)	Evaluable patients*	
		Baseline NS3 RAVs (N = 34)	No baseline NS3 RAVs (N = 44)
Mean (median) age, years	54.4 (55)	53.9 (55.0)	54.6 (56.5)
Male gender, n (%)	46 (58.2)	21 (61.8)	24 (54.5)
HCV genotype, n (%)			
GT1a	30 (38.0)	23 (67.6)	7 (15.9)
GT1b	49 (62.0)	11 (32.4)	37 (84.1)
Cirrhosis, n (%)	34 (43.0)	15 (44.1)	19 (43.2)
Prior DAA experience, n (%)			
Boceprevir	28 (35.4)	10 (29.4)	17 (38.6)
Telaprevir	43 (54.4)	19 (55.9)	24 (54.5)
Simeprevir	8 (10.1)	5 (14.7)	3 (6.8)
Past history of virologic failure	66 (83.5)	32 (94.1)	33 (75.0)

*Evaluable patients included 78/79 treated patients with available baseline NS3 population-sequencing data.
†Reasons for non-virologic failure were adverse events/drug intolerance (n = 12) and short-course therapy in clinical trial (n = 1).

C-SALVAGE

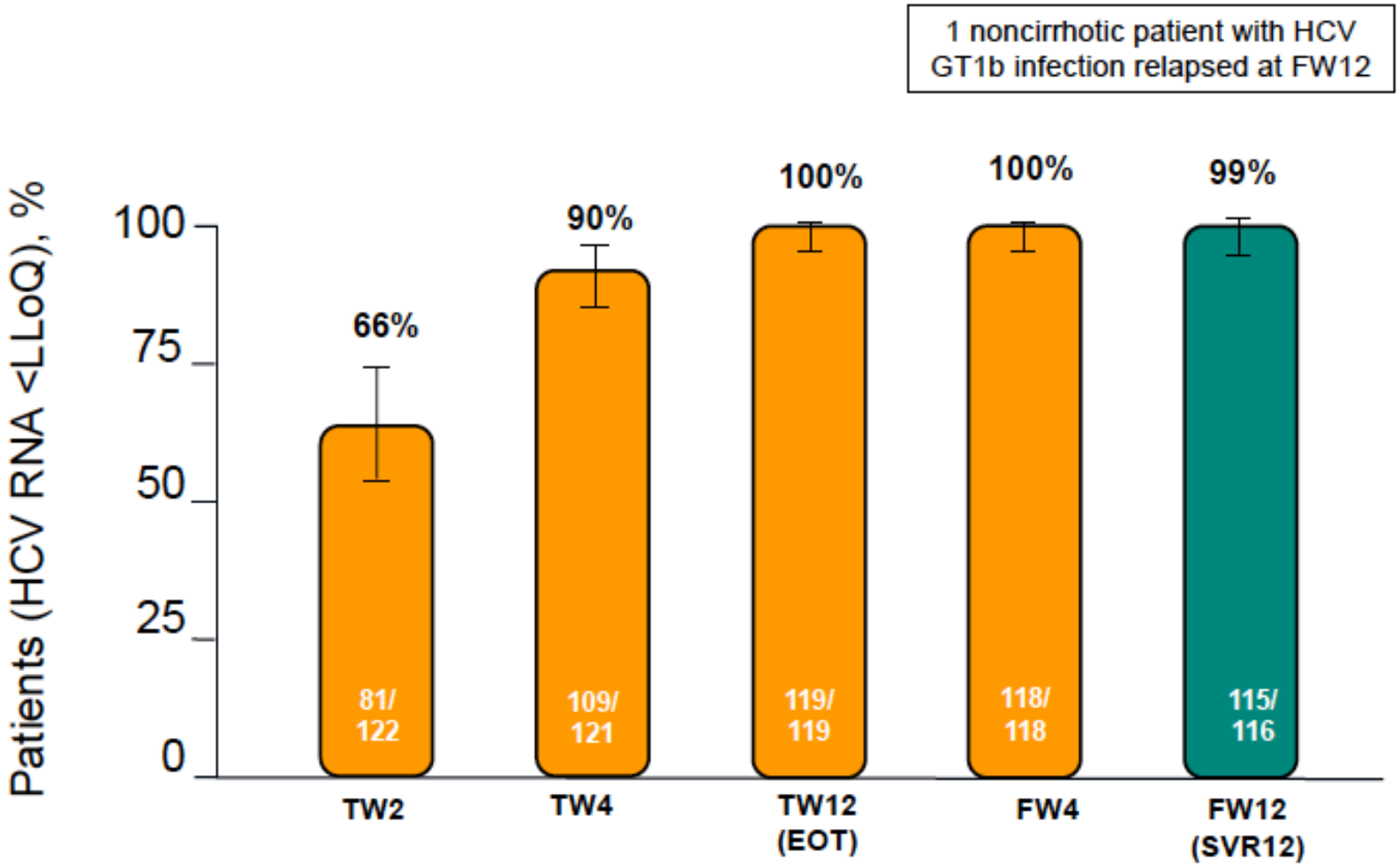
EFFICACY ENDPOINTS OVER TIME (FULL ANALYSIS SET)

Grazoprevir (100 mg)
Elbasvir (50 mg)



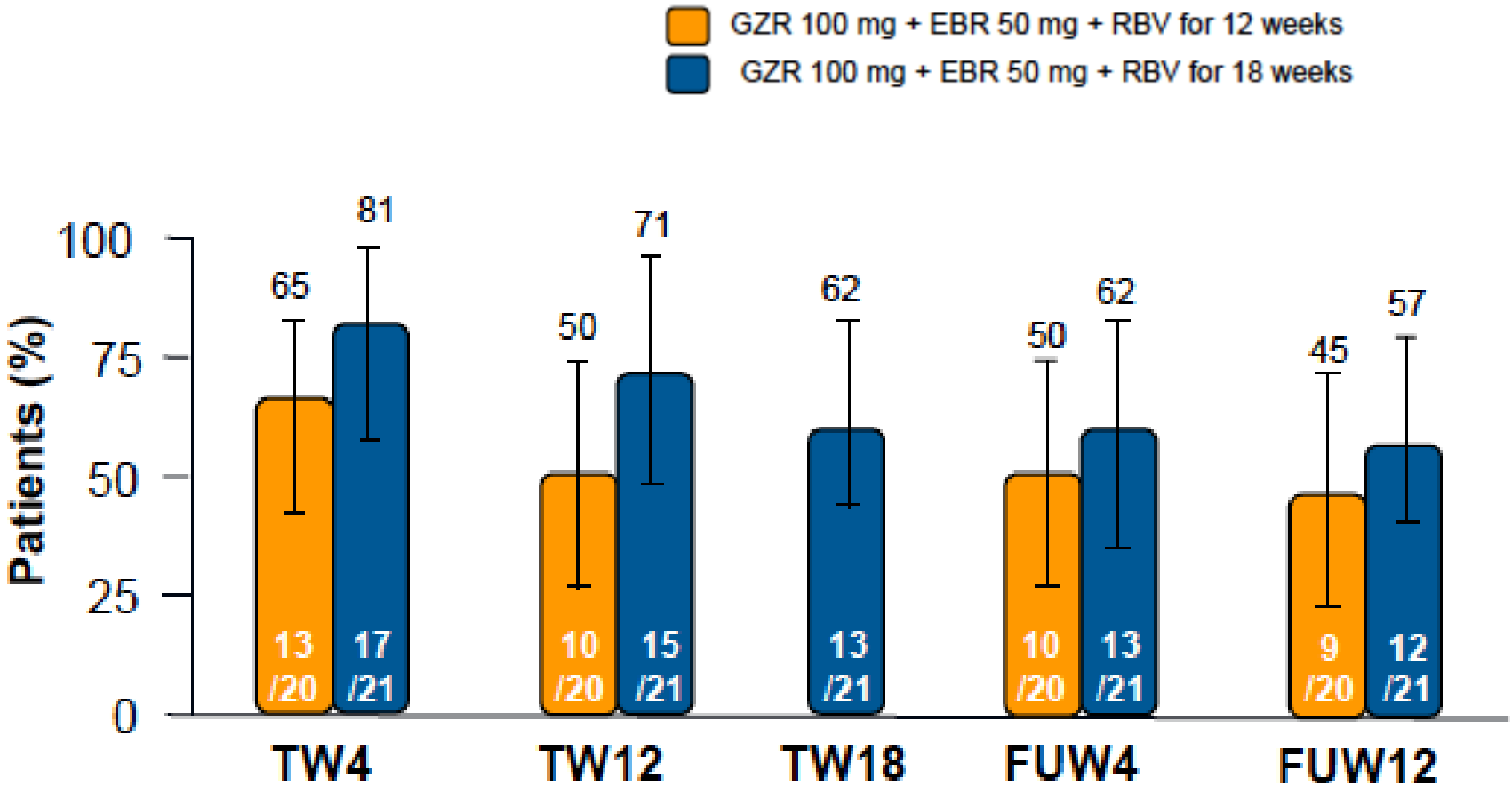
C-SALVAGE

C-SURFER: GRAZOPREVIR PLUS ELBASVIR IN TREATMENT-NAIVE AND TREATMENT-EXPERIENCED PATIENTS WITH HEPATITIS C VIRUS GENOTYPE 1 INFECTION AND CHRONIC KIDNEY DISEASE



Roth D et al. EASL 2015

EFFICACY OF 12 OR 18 WEEKS OF GRAZOPREVIR PLUS ELBASVIR WITH RIBAVIRIN IN TREATMENT-NAIVE, NONCIRROHTIC HCV GENOTYPE 3–INFECTED PATIENTS



EBR = elbasvir; FUW = follow-up week; GZR = grazoprevir; RBV = ribavirin; TW = treatment week.
Efficacy is presented for the intention to treat population, which includes all patients who received ≥1 dose of study medication.
[a]Virologic response defined as HCV RNA <25 IU/mL.

Gane E et al EASL 2015

C-SWIFT: GRAZOPREVIR/ELBASVIR + SOFOSBUVIR IN CIRRHOTIC AND NONCIRRHOTIC, TREATMENT NAIVE PATIENTS WITH HEPATITIS C VIRUS GENOTYPE 1 INFECTION FOR DURATIONS OF 4, 6 OR 8 WEEKS AND GENOTYPE 3 INFECTION FOR DURATIONS OF 8 OR 12 WEEKS

Fred Poordad[*1], Eric Lawitz[1], Julio A. Gutierrez[1], Barbara Evans[2], Anita Howe[2], Hwa-Ping Feng[2], Jerry Jing Li[2], Peggy Hwang[2], Michael Robertson[2], Janice Wahl[2], Eliav Barr[2], Barbara Haber[2]*

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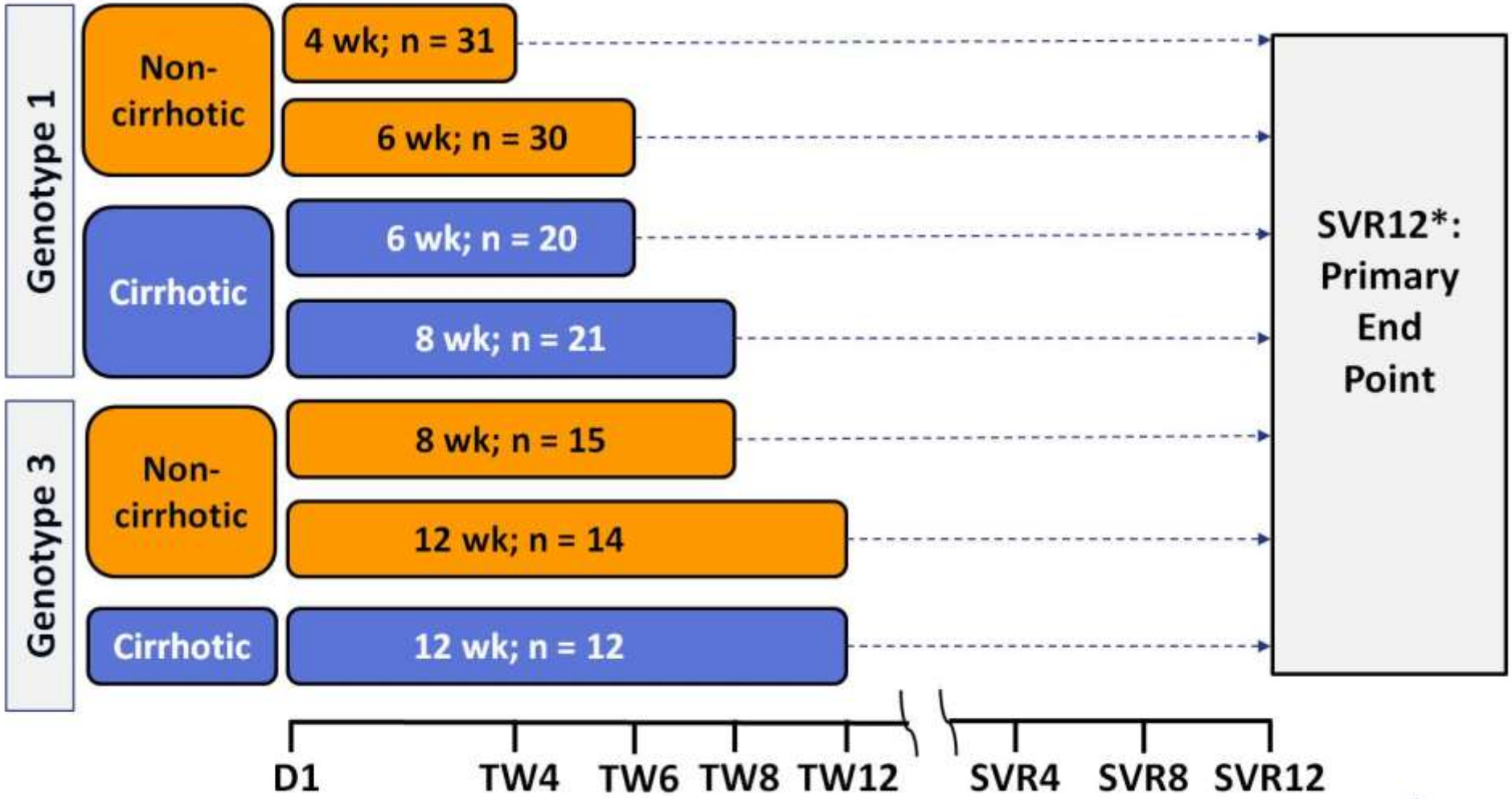
[1]The Texas Liver Institute, University of Texas Health Science Center, San Antonio, Texas [2]Merck & Co., Inc., Kenilworth, NJ USA

C-SWIFT

STUDY DESIGN

All treatment arms:
Grazoprevir 100 mg QD/Elbasvir 50 mg QD FDC + Sofosbuvir 400 mg QD

Grazoprevir (100 mg) Elbasvir (50 mg)

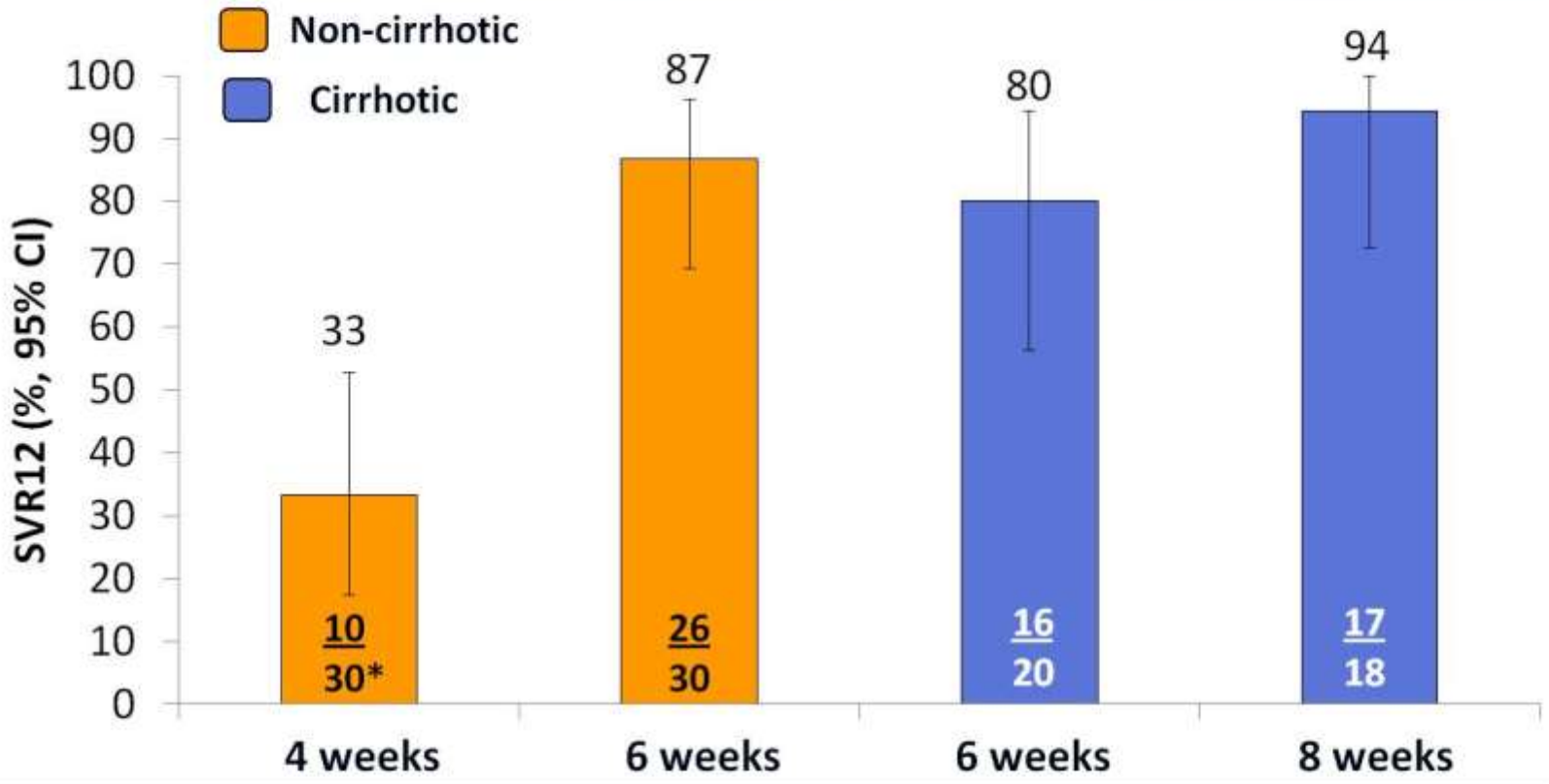


*SVR12 = Primary End Point (HCV RNA < 15 IU/mL), COBAS TaqMan v2.0

C-SWIFT

HCV G1: PRIMARY EFFICACY RESULTS SVR12 MODIFIED INTENT TO TREAT ANALYSIS*

Grazoprevir (100 mg) Elbasvir (50 mg)



Breakthrough	0	0	0	0
Relapse	20	4	4	1
Excluded*	1	0	0	3†

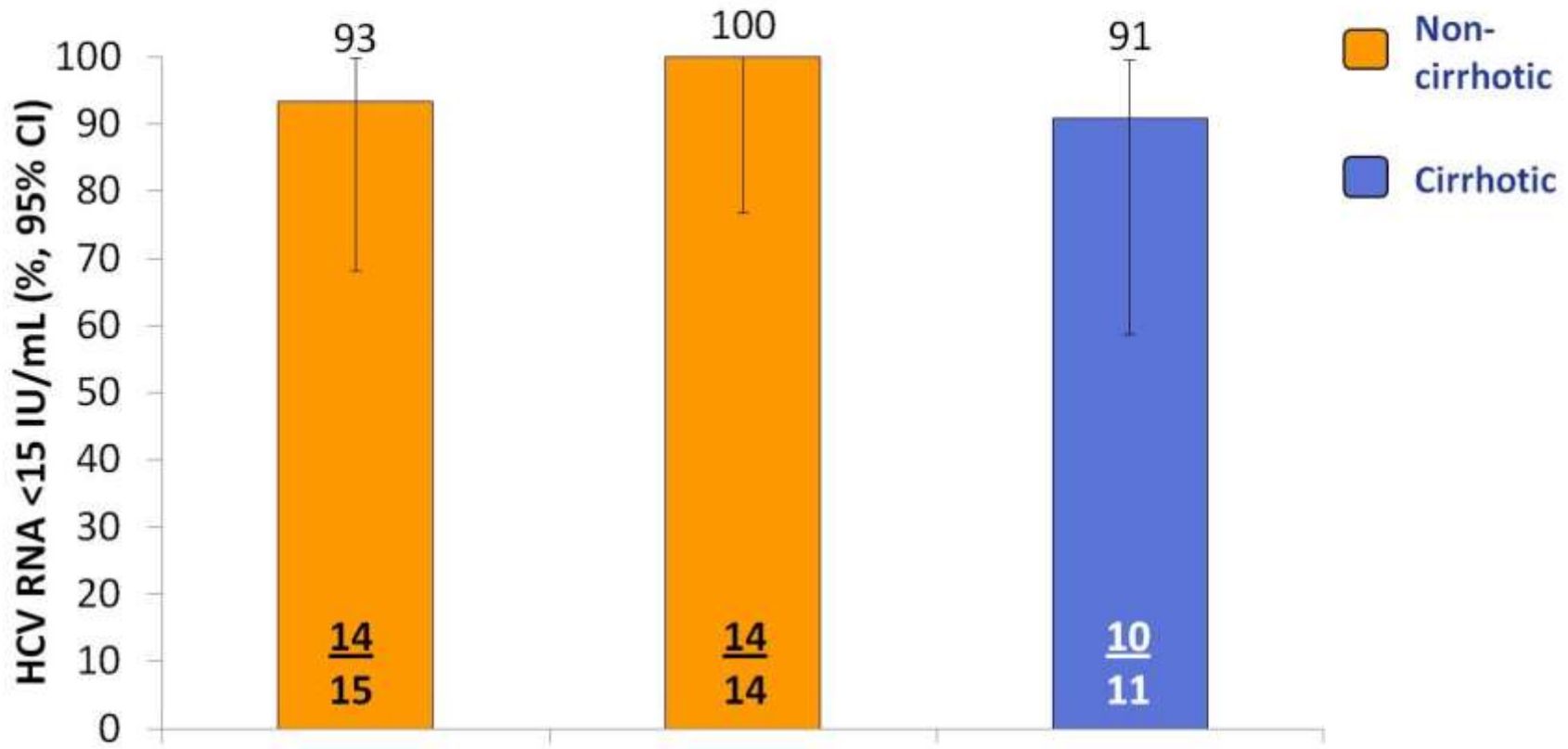
*Excluded patients who discontinued due to reasons other than virologic failure

† One of the 3 patients who discontinued had HCV G2 at discontinuation

C-SWIFT

HCV GENOTYPE 3: PRIMARY EFFICACY:
SVR12, MODIFIED INTENT TO TREAT ANALYSIS*

Grazoprevir (100 mg) Elbasvir (50 mg)

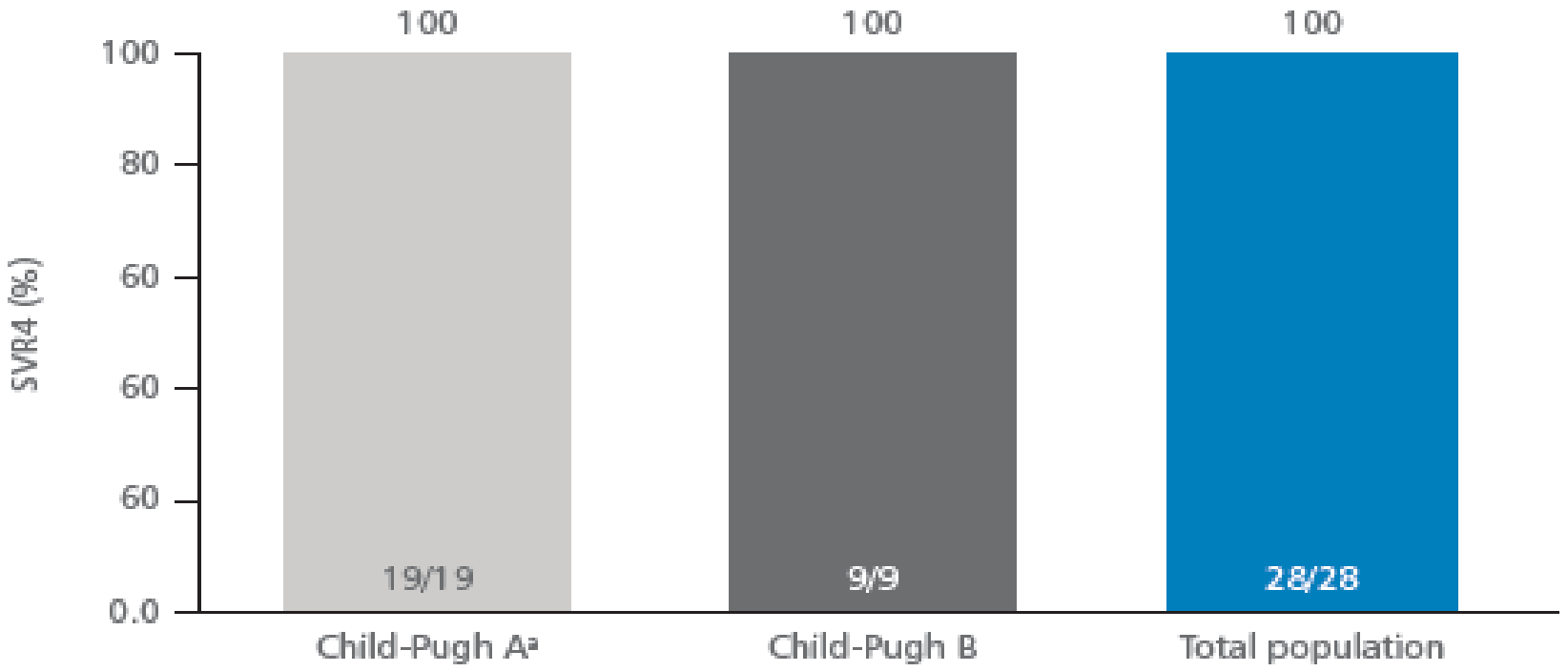


Treatment Duration	8 weeks	12 weeks	12 weeks
Breakthrough	0	0	0
Relapse	1	0	1
Early discon.	0	0	1*

* mITT excluded patients who discontinued early (Early discon.) due to reasons other than virologic failure

C-SWIFT

Simeprevir plus daclatasvir and sofosbuvir in treatment-naïve and treatment-experienced patients with chronic hepatitis C virus genotype 1 or 4 infection and decompensated liver disease: interim results from the Phase II IMPACT study

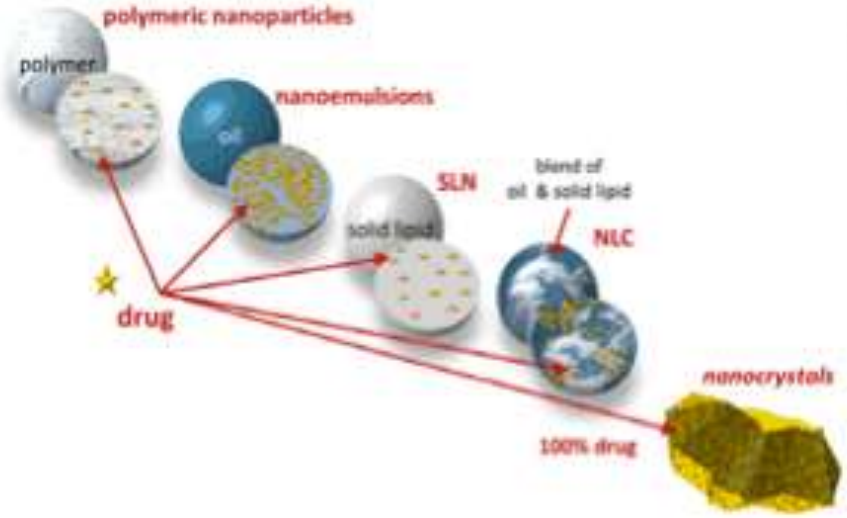


[a]With evidence of portal hypertension.
ITT, intent-to-treat; SVR4, sustained virologic response (HCV RNA < 15 IU/mL undetectable) 4 weeks after end of treatment.

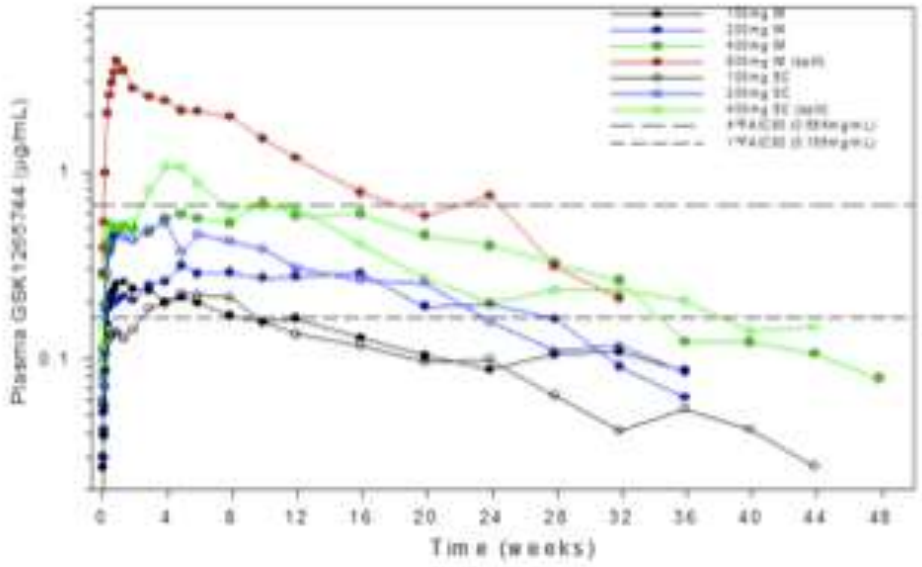
Lawitz E et al EASL 2015

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?
  - Two very successful strategies: tailored treatment → difficult access to treatment (price and complexity)
    - Sofosbuvir based
    - Sofosbuvir free
  - Lower efficacy in HCV G3 with poorer results in cirrhotics PEGIFN experienced --> add (PEGIFN ?) RBV &/or increased duration SOFO + NS5A + RBV x 24 weeks
  - Future perspectives → improvement in efficacy
    - One pill (injection?) for all → Sofosbuvir(Velpatasvir FDC but not Grazoprevir/Elbasvir)
    - No Ribavirin in HCV G2 & 3 & in compensated cirrhosis
    - Shorter treatment duration ?
  - Unmet need failure of NS5A ???