2nd wave IFN-based triple therapy for HCV genotype 1: Simeprevir, Faldaprevir and Sofosbuvir.

Paris Hepatitis Conference

Pr Tarik Asselah

14 janvier 2014

MD, PhD
Service d'Hépatologie & INSERM U773
University Paris Diderot
Hôpital Beaujon, Clichy
tarik.asselah@bjn.aphp.fr

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2nd wave IFN-based triple therapy for HCV genotype 1: Simeprevir, Faldaprevir and Sofosbuvir.

- **Introduction**
- New IFN-based triple therapy for HCV genotype 1

  Protease inhibitors

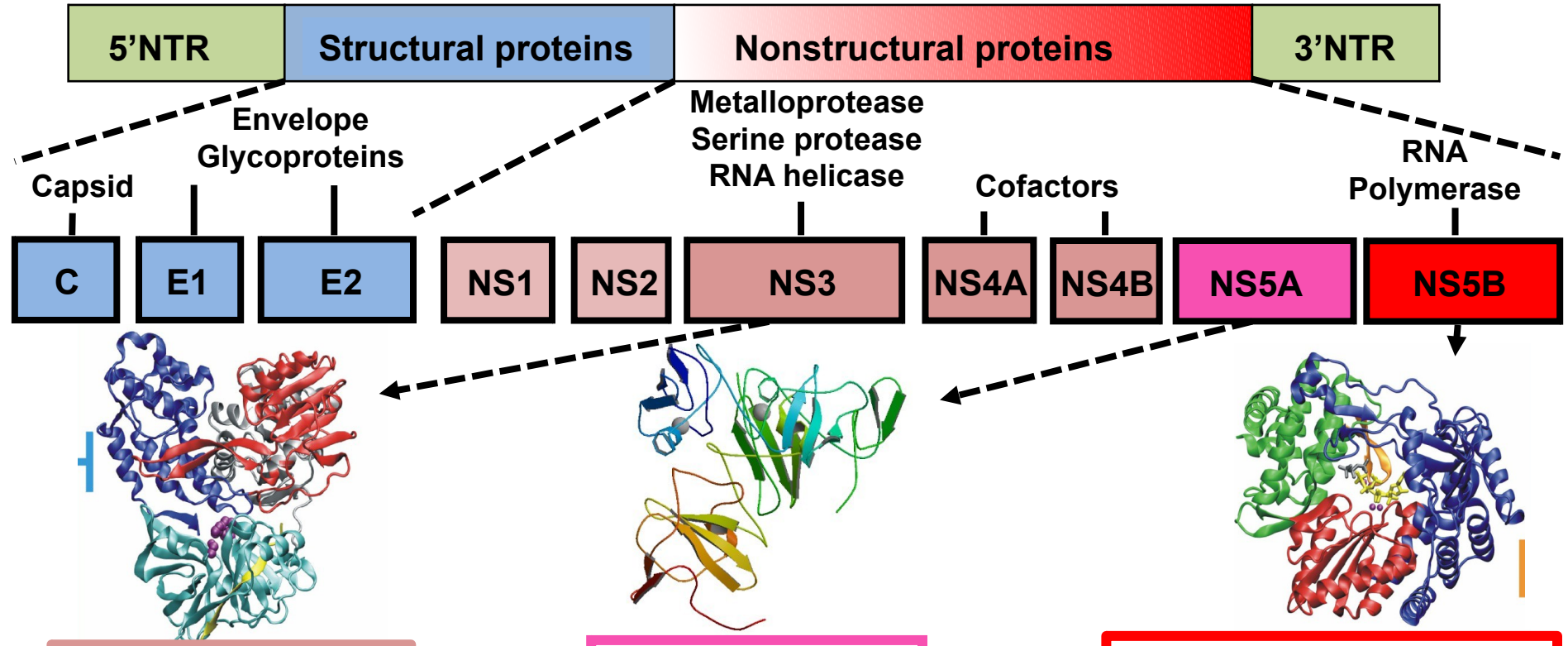
  - Simeprevir (Quest-2, Promise)
  - Faldaprevir (StartVerso 1, StartVerso 3)
  - Other PI : MK5172, Asunaprevir, etc….

  Polymerase inhibitor

  - Sofosbuvir (Neutrino)

- Summary and Conclusion

Direct-acting antivirals



Protease Inhibitors

Telaprevir
Boceprevir
Simeprevir
Faldaprevir
Asunaprevir
ABT-450
MK-5172
Sovaprevir
ACH-2684

NS5A Inhibitors

Daclatasvir
Ledipasvir
ABT-267
GS-5816
ACH-3102
PPI-668
GSK-2336805
Samatasvir
MK-8742

Polymerase Inhibitors

Nucs	Non-Nucs
Sofosbuvir	ABT-333
VX-135	Deleobuvir
IDX-20963	BMS-791325
ACH-3422	PPI-383
	GS-9669
	TMC-647055

Schinazi R, Halfon P, Marcellin P, Asselah T. Liver International 2014

Investigational HCV Regimens in Phase III Trials in 2014

Triple Therapy: 1 DAA + PegIFN alfa/RBV

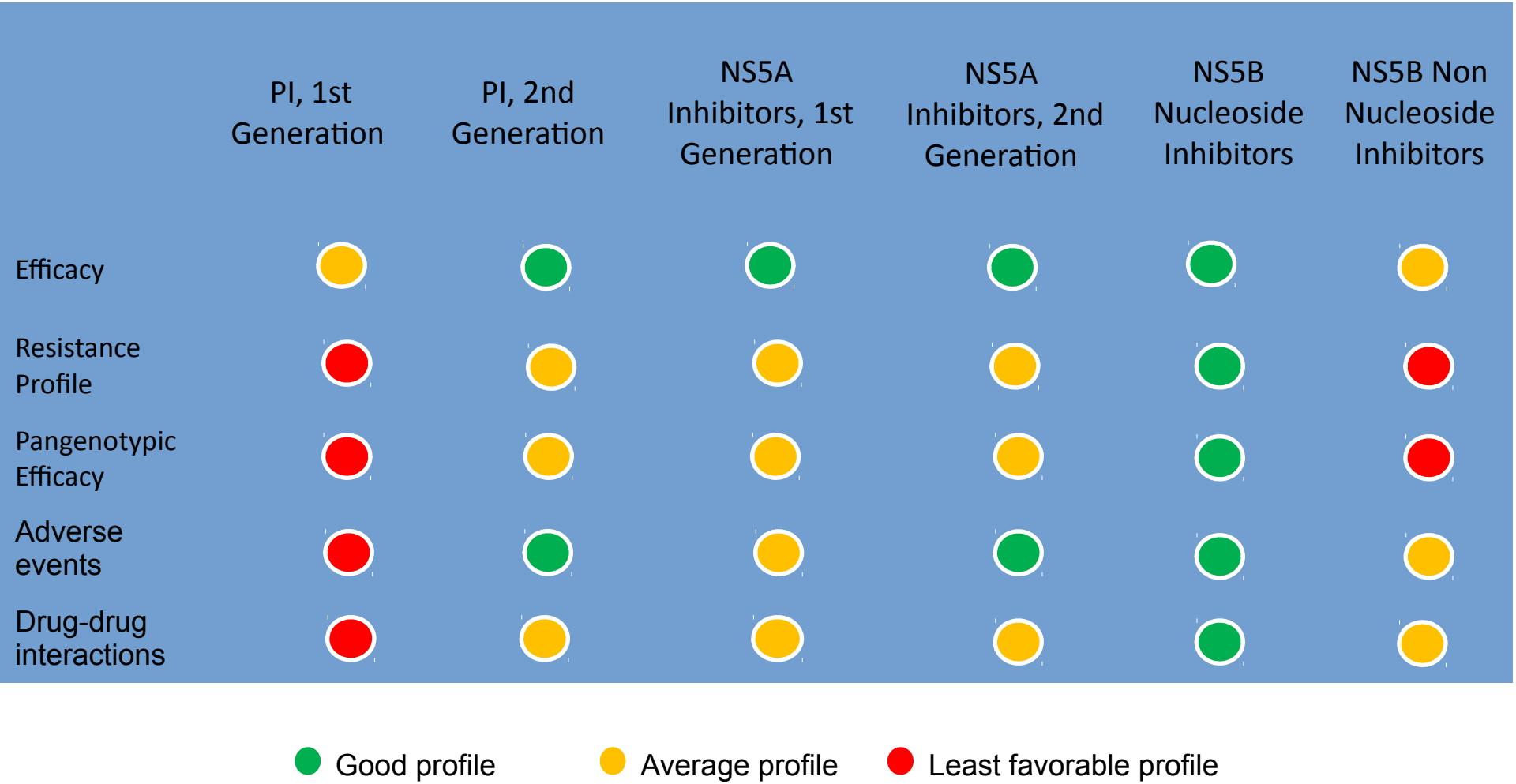
- Simeprevir (PI)
- Faldaprevir (PI)
- Sofosbuvir (NI)
- Daclatasvir (NS5A)
- MK 5172 (PI)
- Danoprevir (PI)
- Alisporivir (CYP)

IFN-Free Regimens

- Sofosbuvir + RBV
- Sofosbuvir + GS-5885 (FDC) ± RBV
- Daclatasvir + asunaprevir
- ABT-450/RTV + ABT-267 ± ABT-333 ± RBV
- Faldaprevir + BI207127 + RBV
- MK 5172 + MK 8742

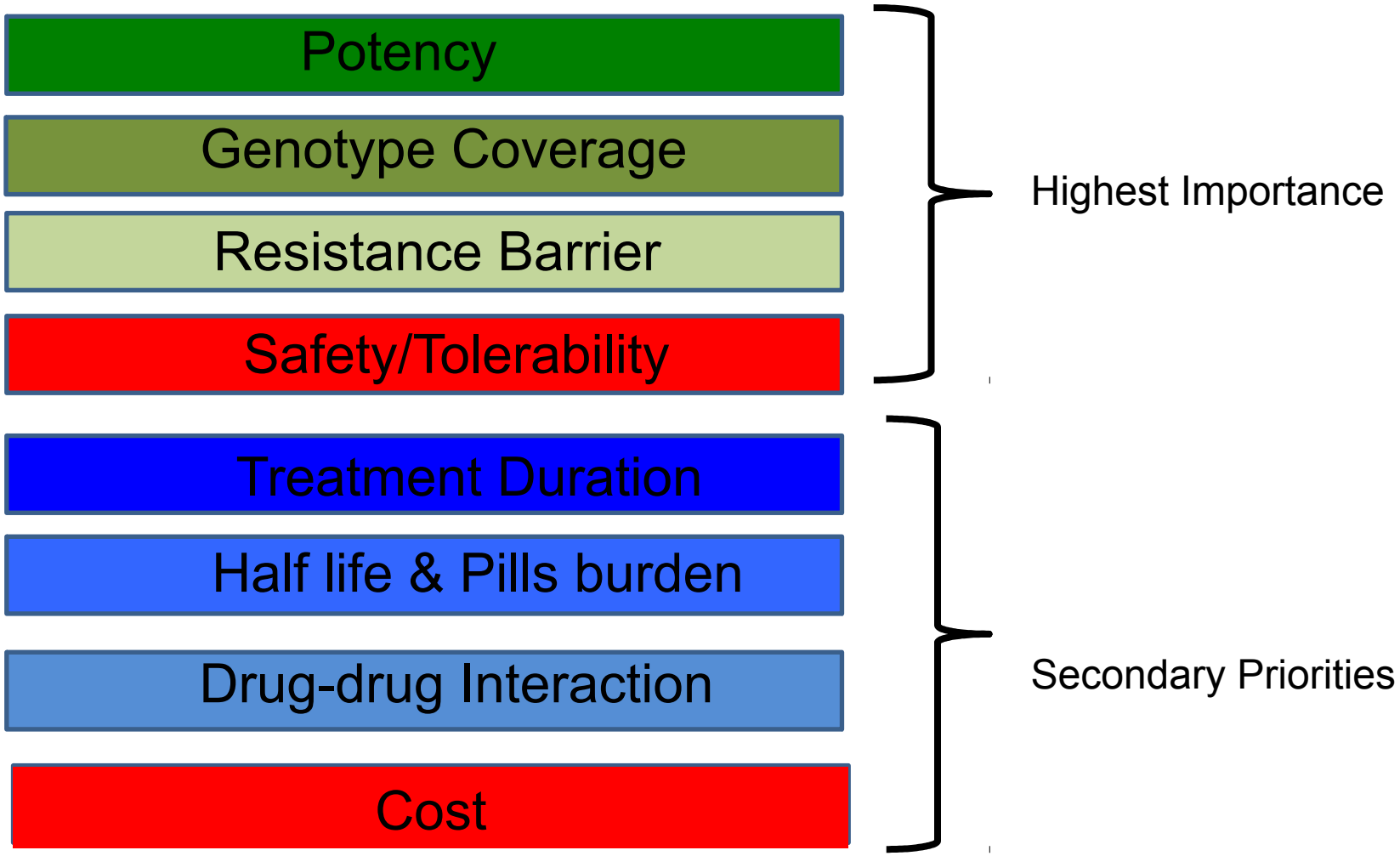
Asselah and Marcellin P,. Liver International 2014

General Characteristics of Direct-Acting Antivirals



Schinazi R, Halfon P, Marcellin P, Asselah T. Liver International 2013

Priorities for Direct-Acting Antivirals



Schinazi R, Halfon P, Marcellin P, Asselah T. Liver International 2013

2nd wave IFN-based triple therapy for HCV genotype 1: Simeprevir, Faldaprevir and Sofosbuvir.

- Introduction
- **New IFN-based triple therapy for HCV genotype 1**

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- Faldaprevir (StartVerso 1, StartVerso 3)

- Other PI : MK5172, Asunaprevir, etc….

Polymerase inhibitor

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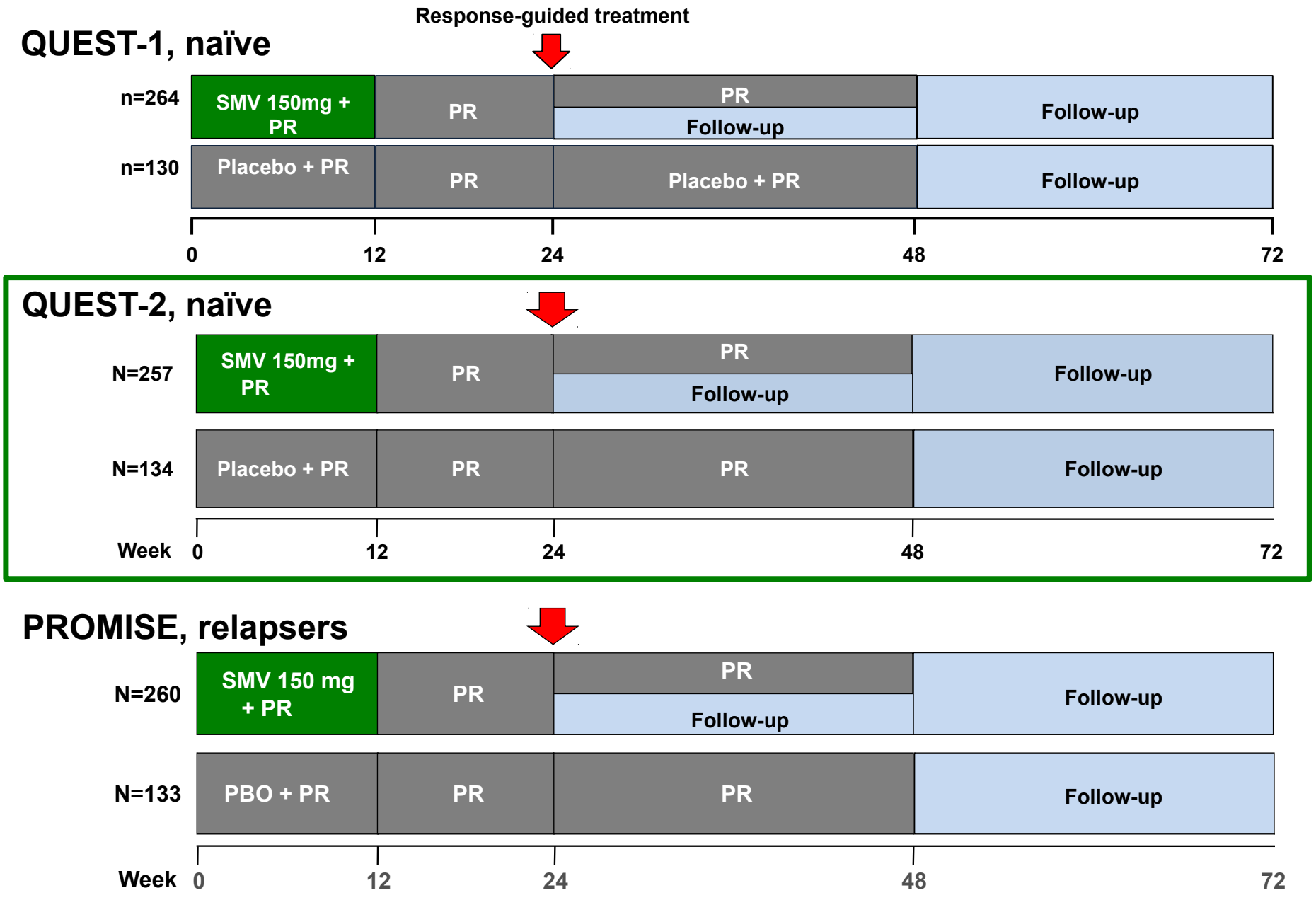
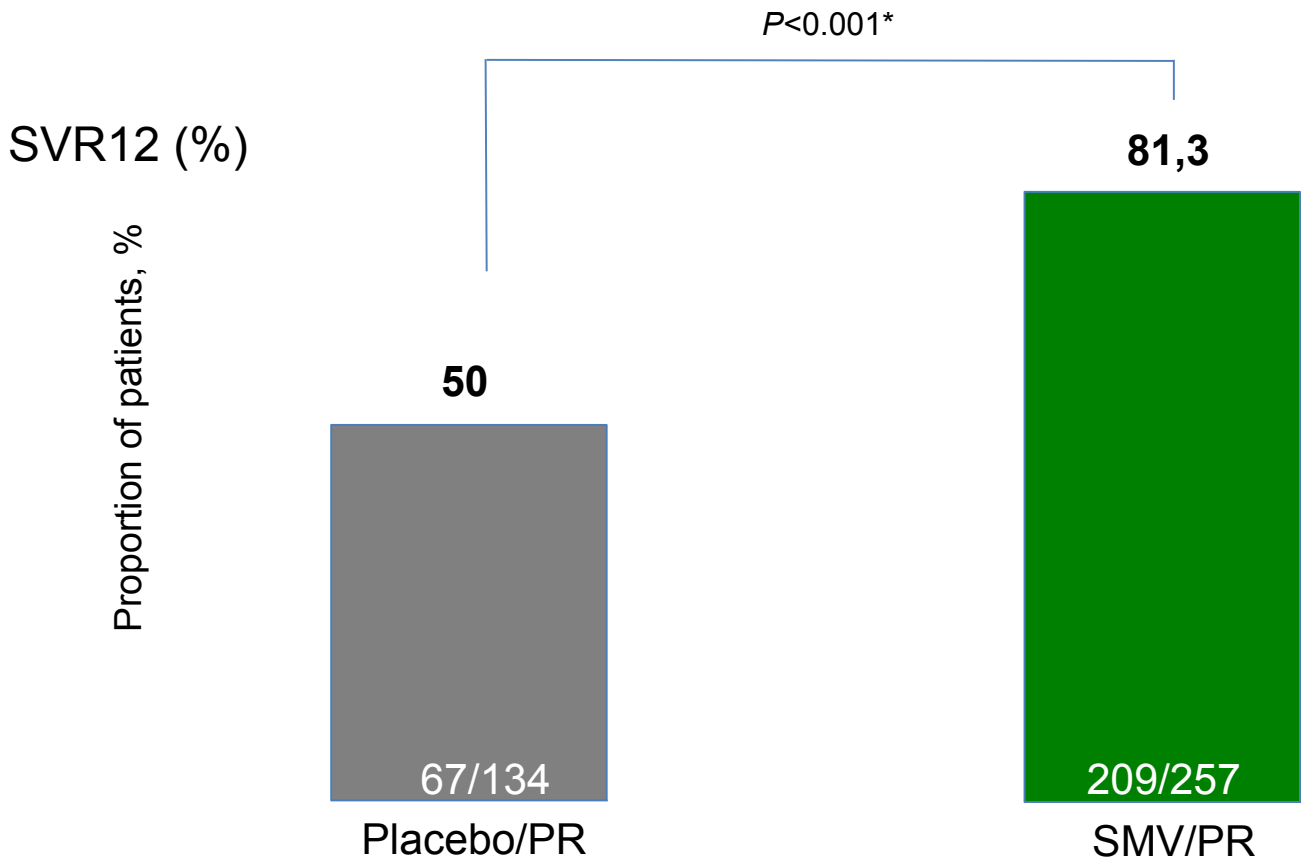
- Summary and Conclusion

Simeprevir (SMV) (PI): G1, phase III trial design



Simeprevir (SMV) (PI): G1 naïve, phase III (QUEST-2)

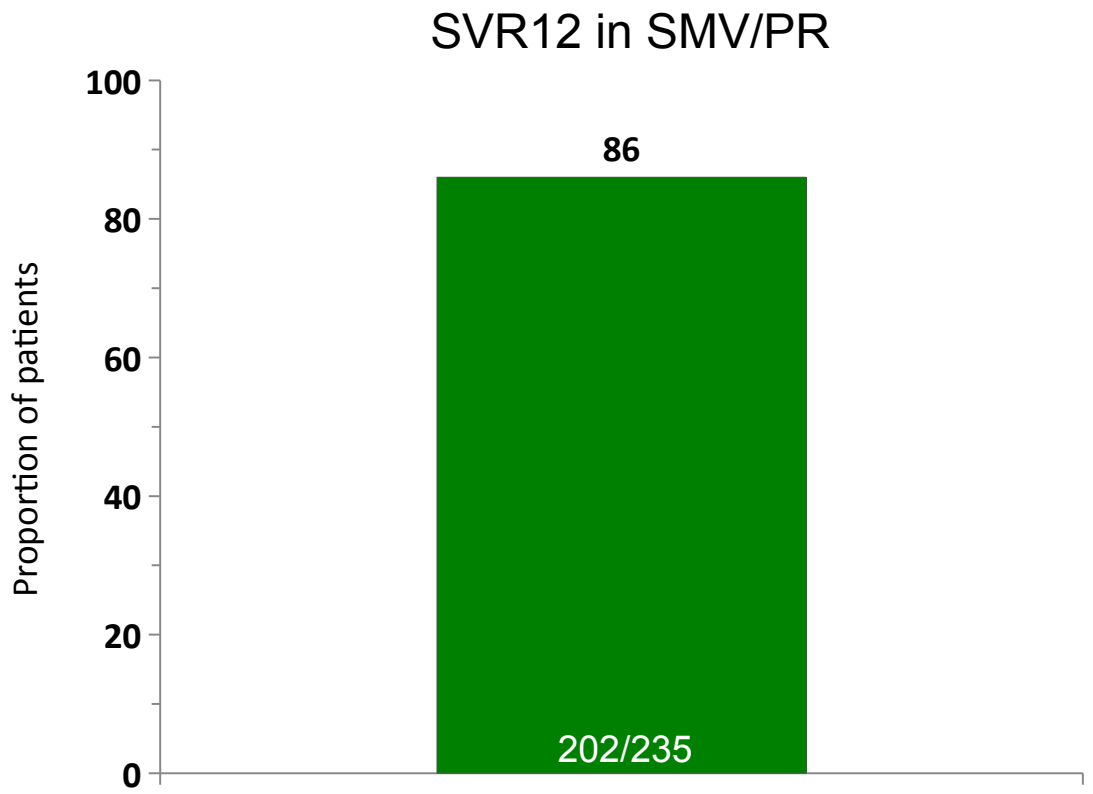


*Based on the Cochran-Mantel-Haensze test controlling for type of PegIFN/ribavirin and stratification factors

Manns et al. EASL 2013, Abstract 1413.

QUEST-2: Response-guided Treatment (RGT) allows shortened treatment duration with high SVR12

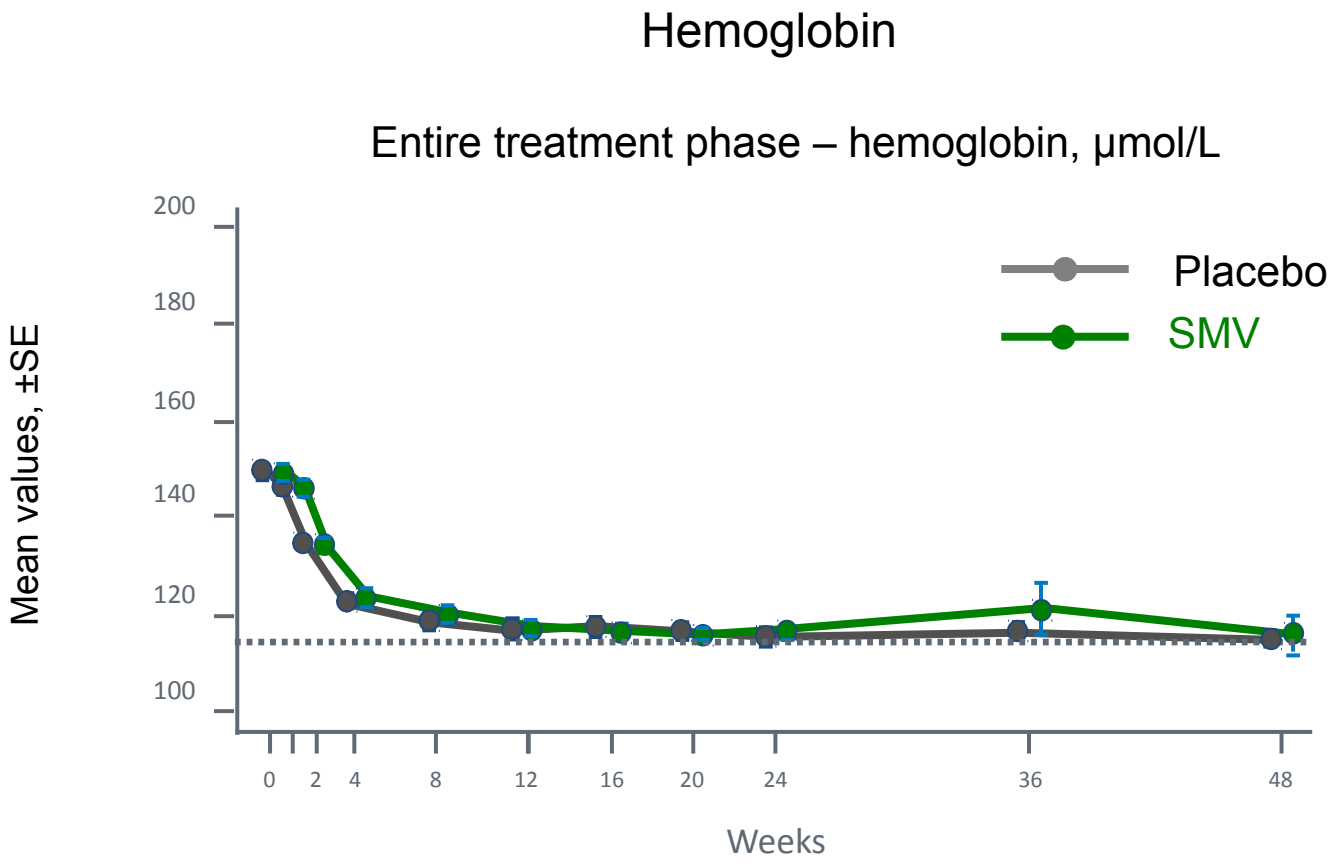
91.4% (235/257) of patients met RGT criteria and were eligible for 24 weeks of treatment



- 8.6% (22/257) of patients did not meet RGT criteria – among them, 31.8% (7/22) achieved SVR12

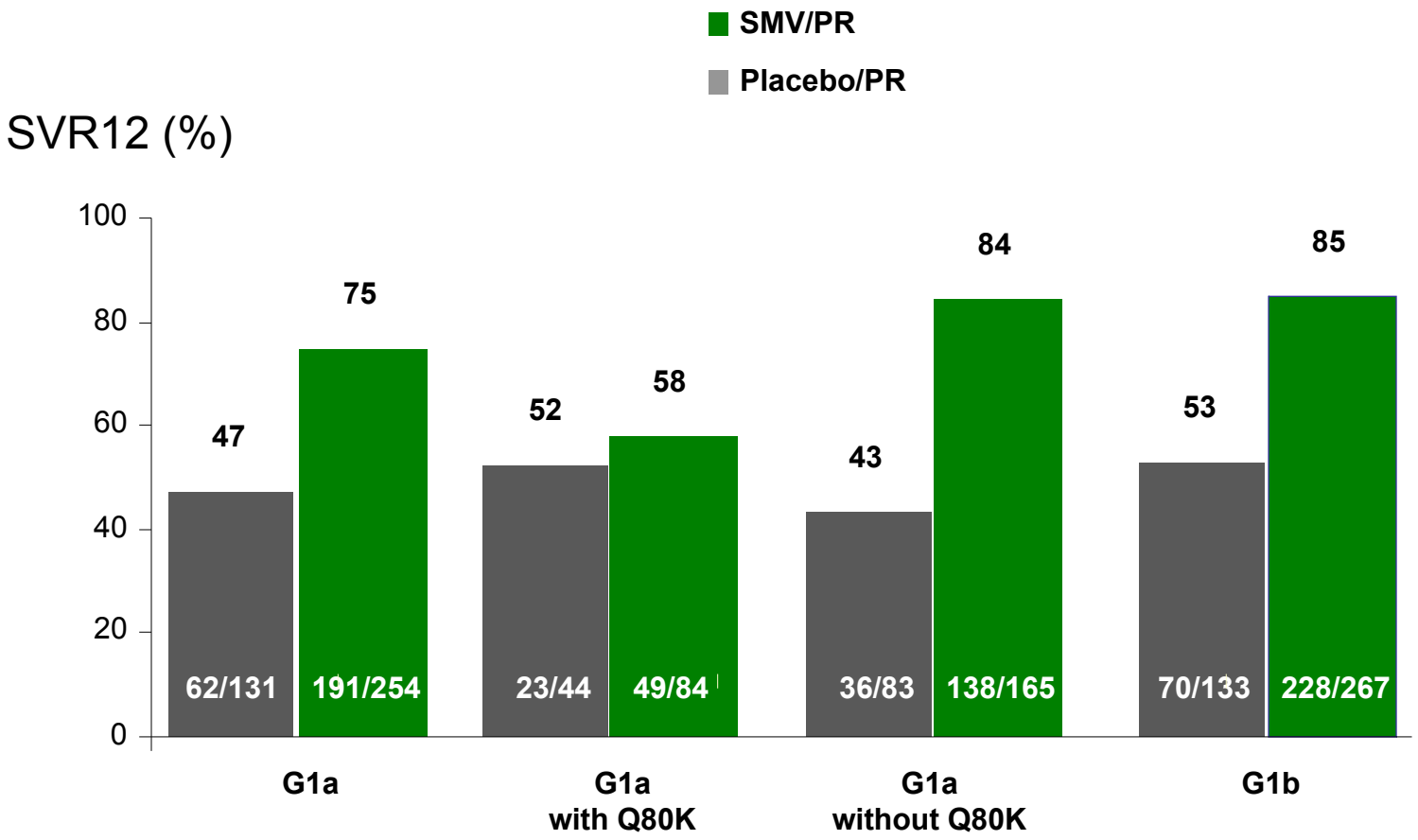
RGT, response-guided therapy; RGT criteria: HCV RNA < 25 IU/mL detectable or undetectable at Week 4 and <25 IU/mL undetectable at Week 12

Quest-2: Changes in haemoglobin



Manns et al. EASL 2013, Abstract 1413.

Simeprevir (SMV) (PI): G1 relapsers (Promise)



Lawitz et al. DDW 2013, Abstract 869b.

Simeprevir: adverse events (phase III trials)

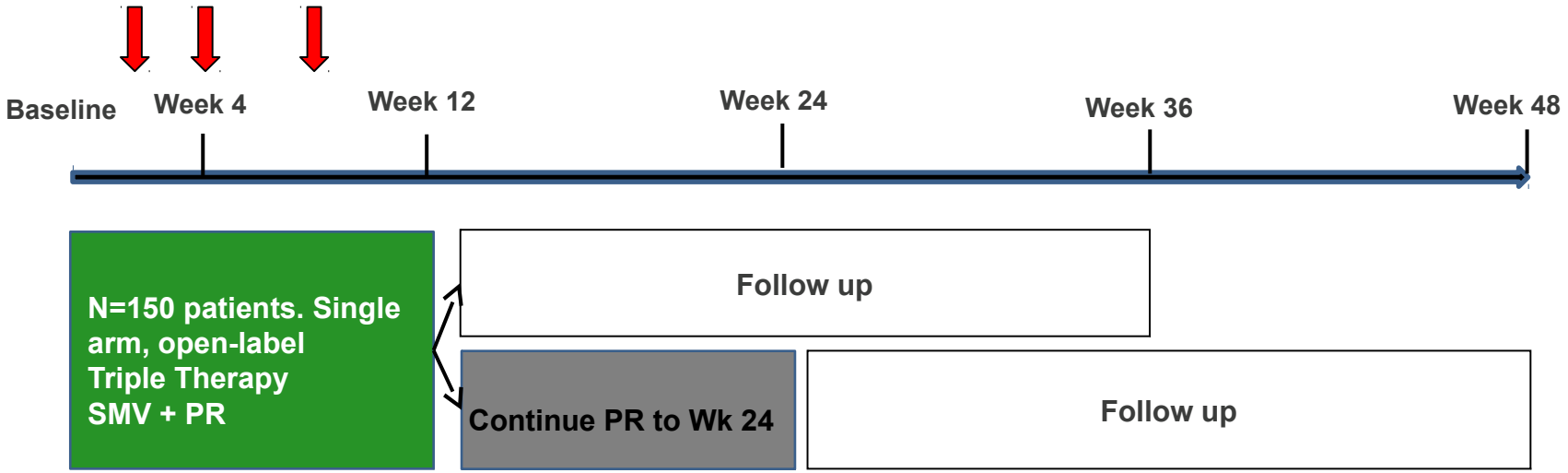
	QUEST-1		QUEST-2		PROMISE	
	Placebo + PR, % (N = 130)	SMV + PR, % (N = 264)	Placebo + PR, % (N = 134)	SMV + PR, % (N = 257)	Placebo + PR, % (N = 130)	SMV + PR, % (N = 264)
Serious AEs	4	3	2	2	4	3
Discontinuation due to AEs	3	3	1	2	3	3
Fatigue	38	40	39	35		
Pruritus	11	21	15	19	28	28
Rash (any type)	25	27	11	24	23	23
Anaemia	11	16	14	16	20	17

Jacobson et al. DDW 2013, Abstract 1674582.
Manns et al. EASL 2013, Abstract 1413.
Lawitz et al. DDW 2013, Abstract 869b.

Simeprevir (PI): 12 weeks phase III trial (G1 naïve)

Ongoing trial

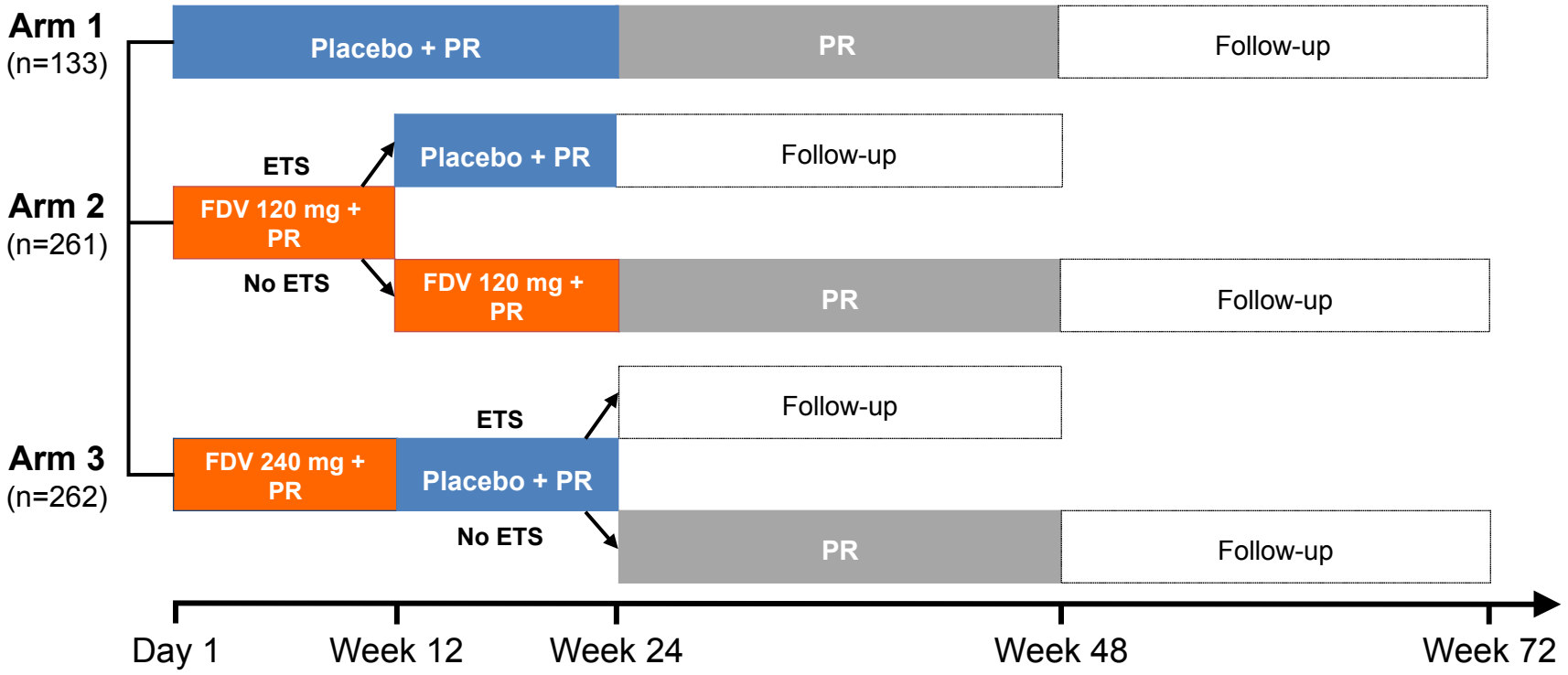
Response-guided therapy of 12 or 24 weeks guided by HCV-RNA measurements at treatment weeks 2, 4, and 8.



PR: PegIFNα-2a 180 ug/wk + RBV 1000-1200mg/day

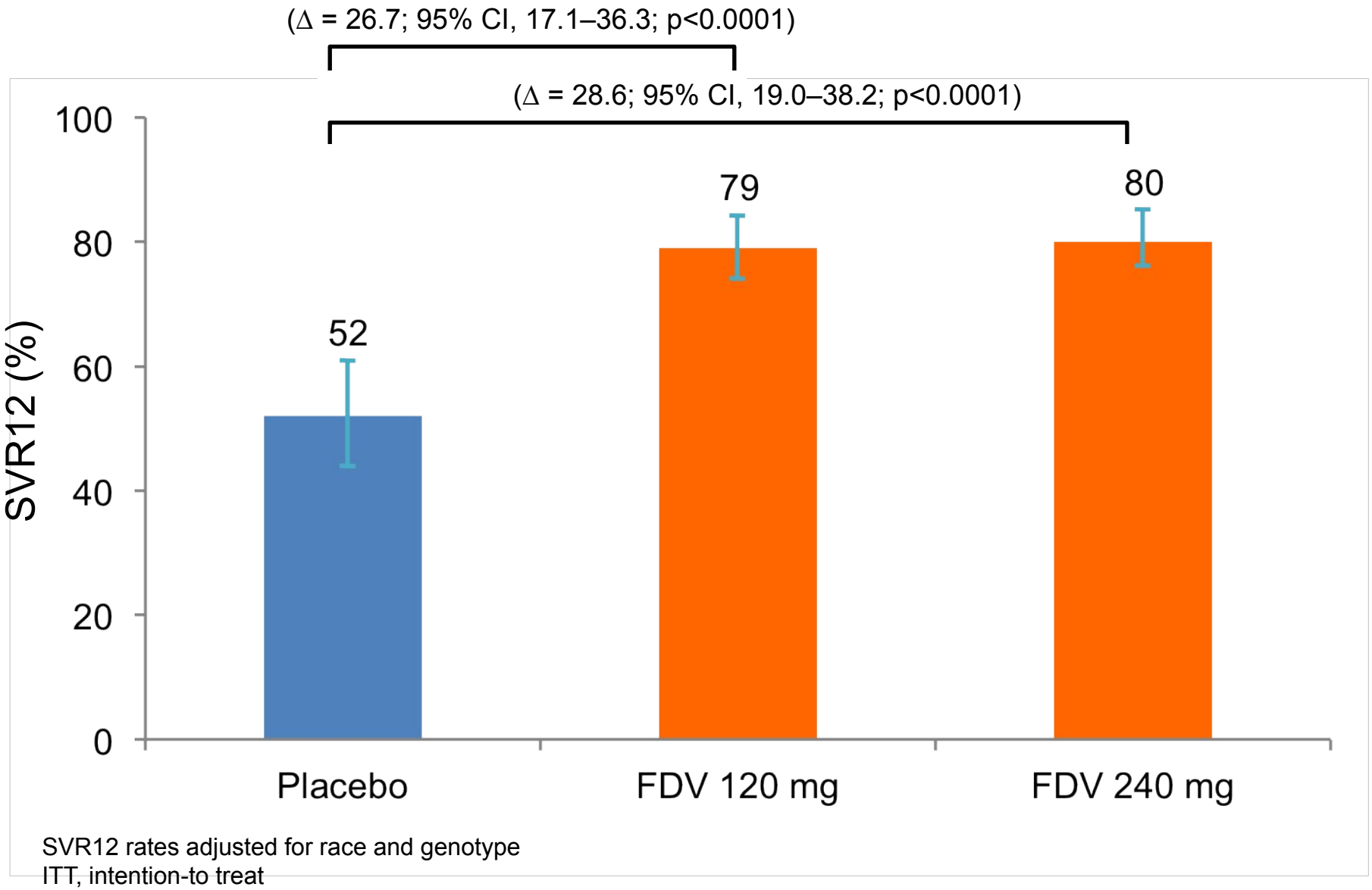
Clinicaltrials.gov: NCT01846832

Faldaprevir (FDV) (PI): phase III trial, G1 naïve (StartVerso1)



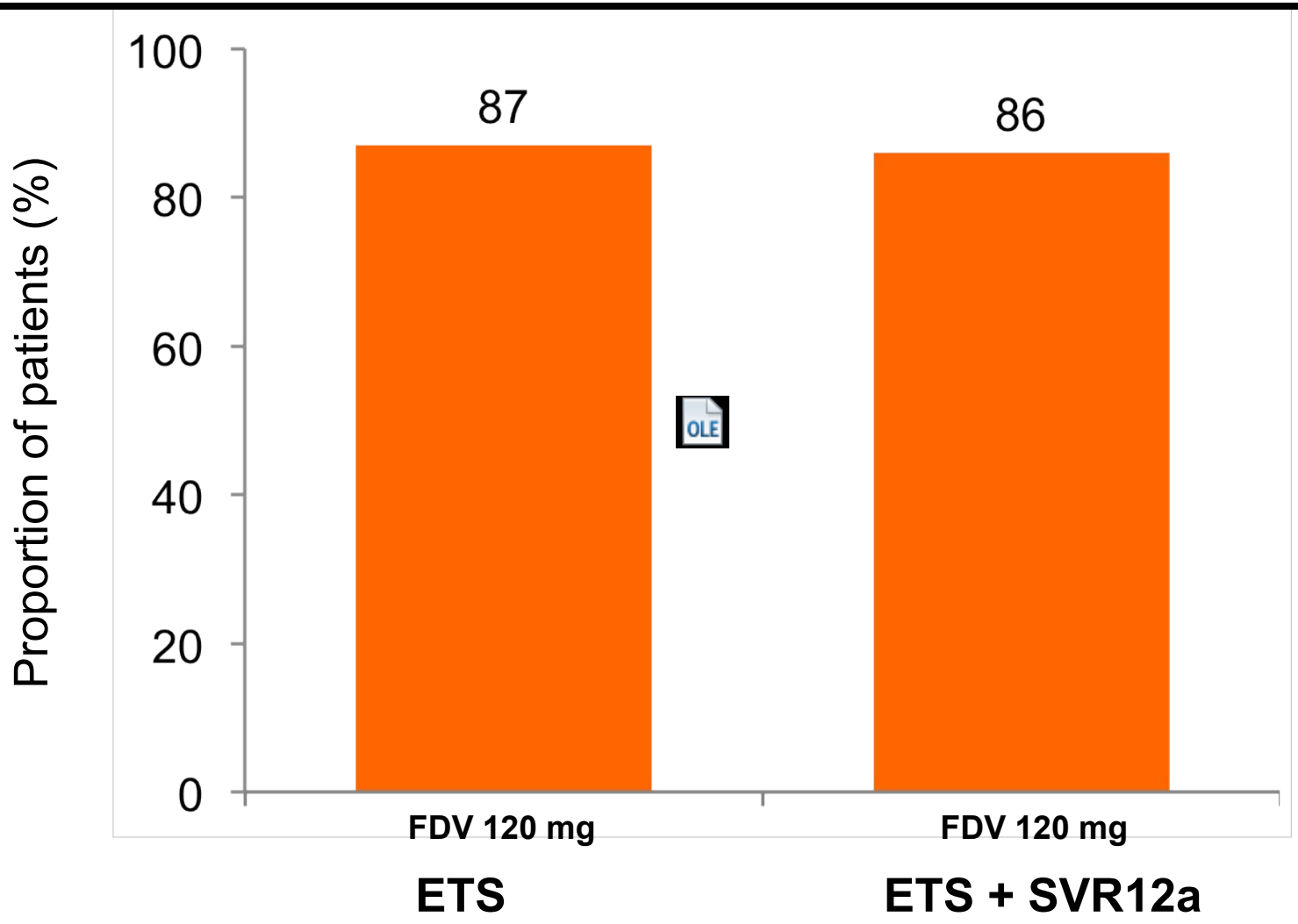
Ferenci et al. EASL 2013, abstract LB 1416.

Faldaprevir (FDV) (PI): G1 naïve, results (StartVerso1)



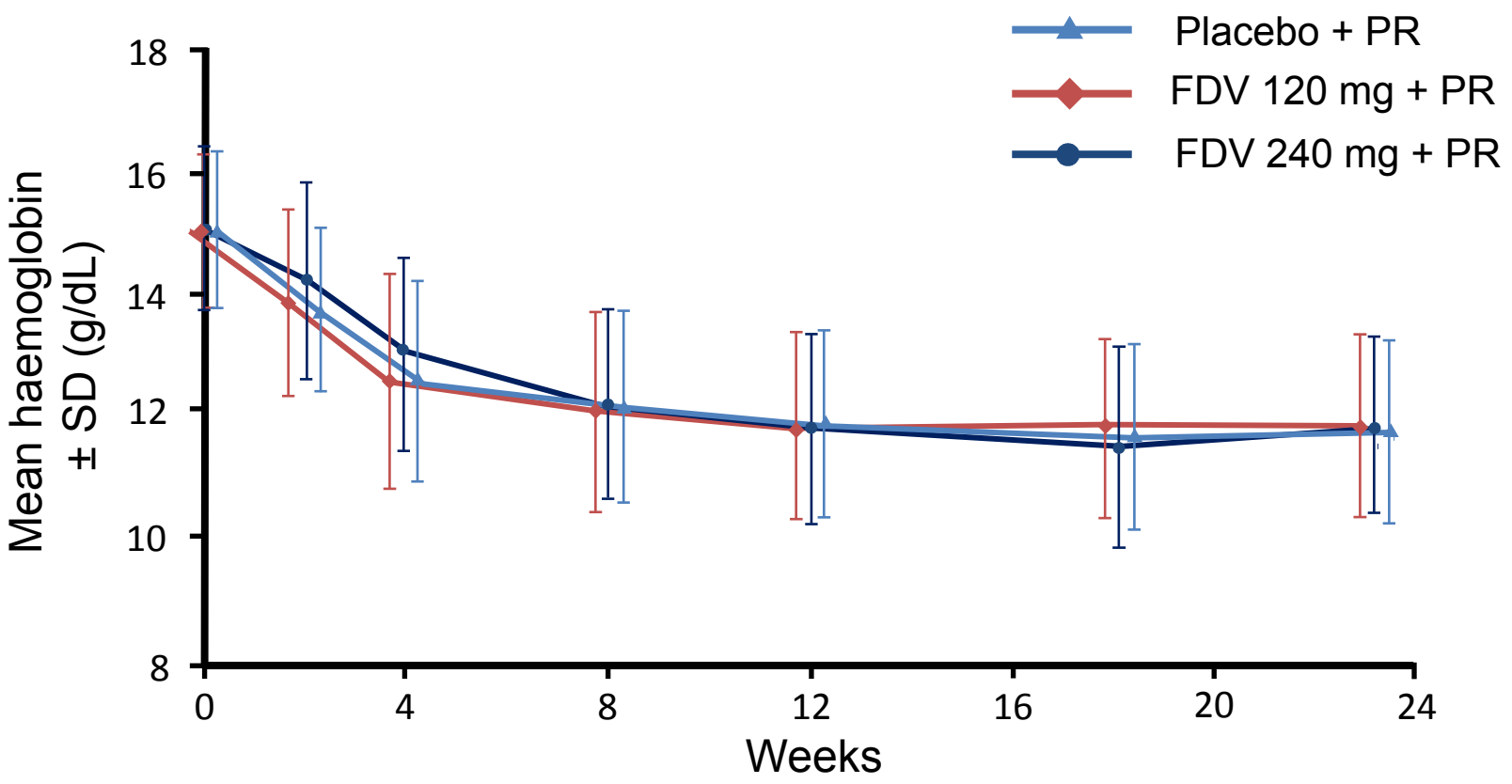
SVR12 rates adjusted for race and genotype
ITT, intention-to treat

Faldaprevir (FDV): Early treatment success (ETS) allows shortened treatment duration with high SVR12



ETS, early treatment success: HCV RNA <25 IU/mL (detected or undetected) at Week 4 and <25 IU/mL (undetected) at Week 8. aDenominator = patients with ETS

Changes in haemoglobin



Faldaprevir: adverse events (phase III trial results)

	Placebo + PR N=264	FDV 120 mg + PR N=521	FDV 240 mg + PR N=524
AEs leading to discontinuation of all medication, n (%)	10 (4)	27 (5)	40 (8)
AEs leading to discontinuation of FDV or placebo only, n (%)	1 (<1)	6 (1)	14 (3)
Serious AEs, n (%)	16 (6)	39 (7)	43 (8)
AEs of at least moderate intensity (any)a, n (%)	156 (59)	302 (58)	332 (63)
Rash	11 (4)	39 (7)	50 (10)
Photosensitivity	0 (0)	0 (0)	3 (1)
GI	19 (7)	58 (11)	96 (18)
Anemia	38 (14)	73 (14)	70 (13)
Bilirubin associated	2 (1)	18 (3)	47 (9)

One patient with cirrhosis at baseline developed acute-on-chronic liver failure after 16 days of FDV (24 0mg) and PR, discontinued all treatment and died 12 days later. The event was considered not related to FDV but to pegylated interferon by investigator.
aDAIDS Grade 2 to 4; protocol-defined AEs of special interest.
DAIDS, Division of AIDS table for grading the severity of adult and pediatric adverse events; DC, discontinuation; GI, gastrointestinal.

Faldaprevir (PI): phase III trial design, G1 experienced (StartVerso3)

Prior relapse

Relapser: Rebound from HCV RNA undetectable at end of 48 week treatmenta but detectable within 24 weeks of follow-up

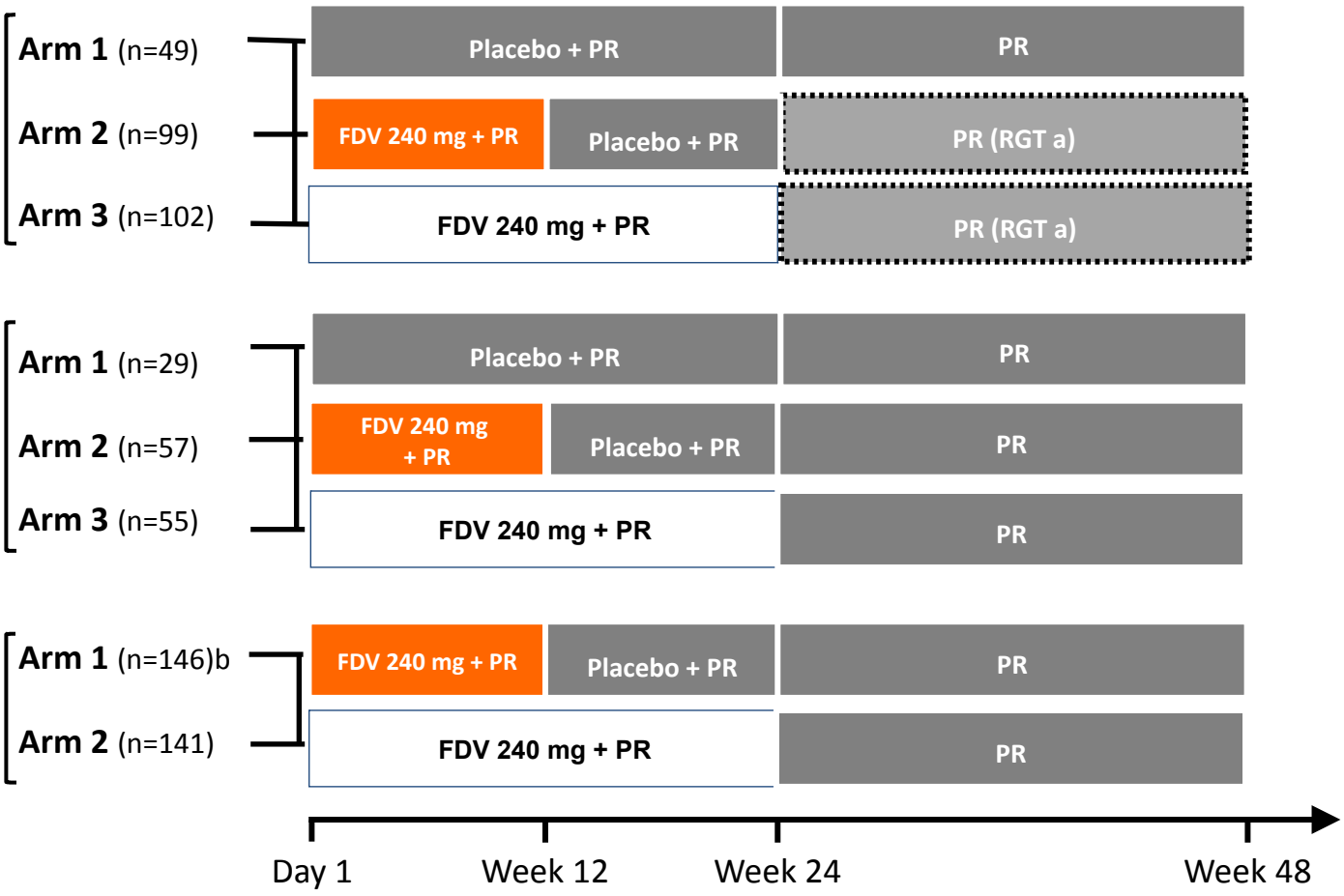
Prior partial response

Partial responder: HCV RNA drop by ≥2 log10 from baseline to week 12, but never undetectable

Breakthrough: HCV RNA undetectable during treatment, but rebound to detected during ongoing treatment

Prior null response

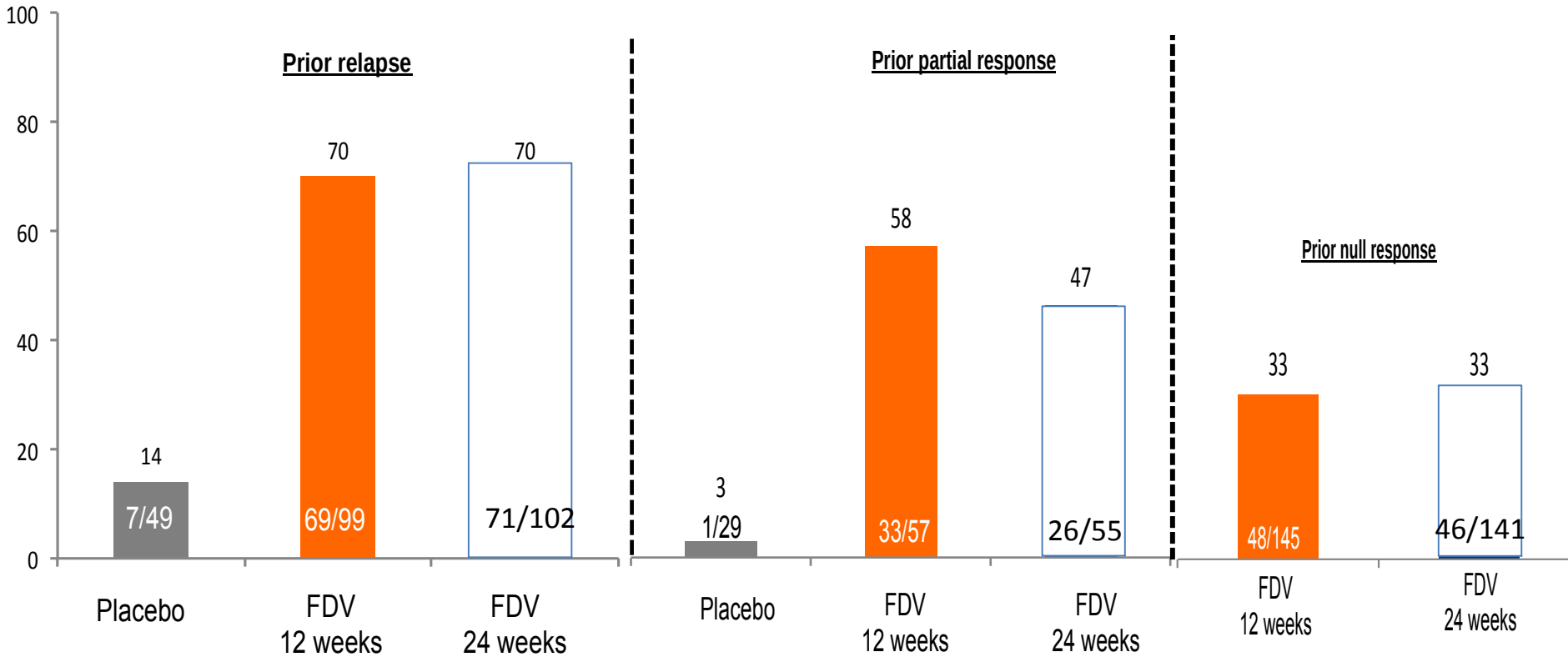
Null responder: Absence of HCV RNA drop by ≥2 log10 from baseline to week 12



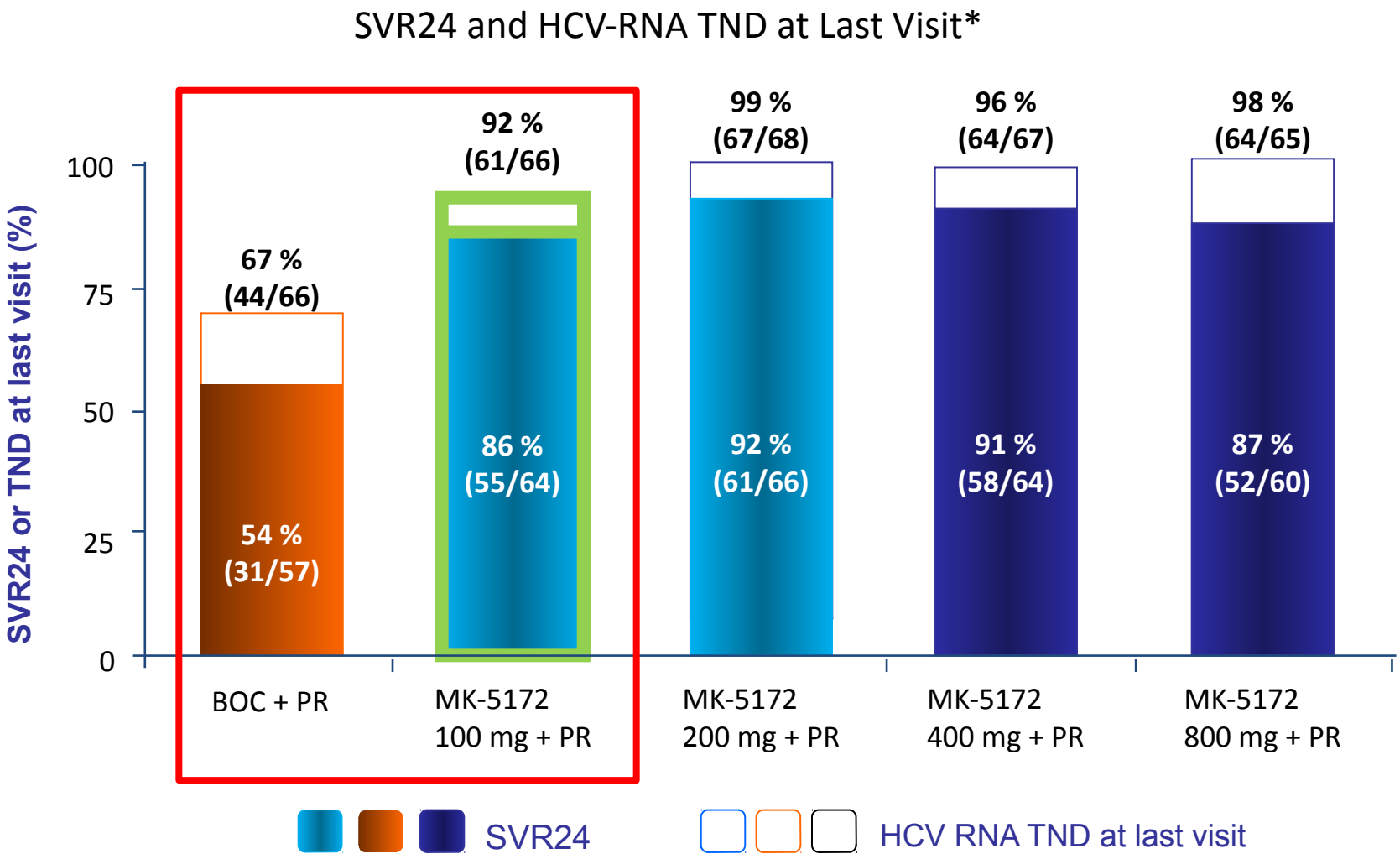
aStopping rule for RGT criteria: all relapsers, who did not achieve ETS (HCV RNA <25 IU/mL (detected or undetected) at week 4 and <25 IU/mL (undetected) at week 8, had extended PR treatment to week 48; bN=146 patients randomized, but N=145 patients treated. PR, pegylated interferon α-2a/ribavirin; QD, once daily; RGT, response-guided therapy.

Jacobson et al. AASLD 2013, abstract 1100.

Faldaprevir (FDV) (PI): SVR12, G1 experienced (StartVerso3)

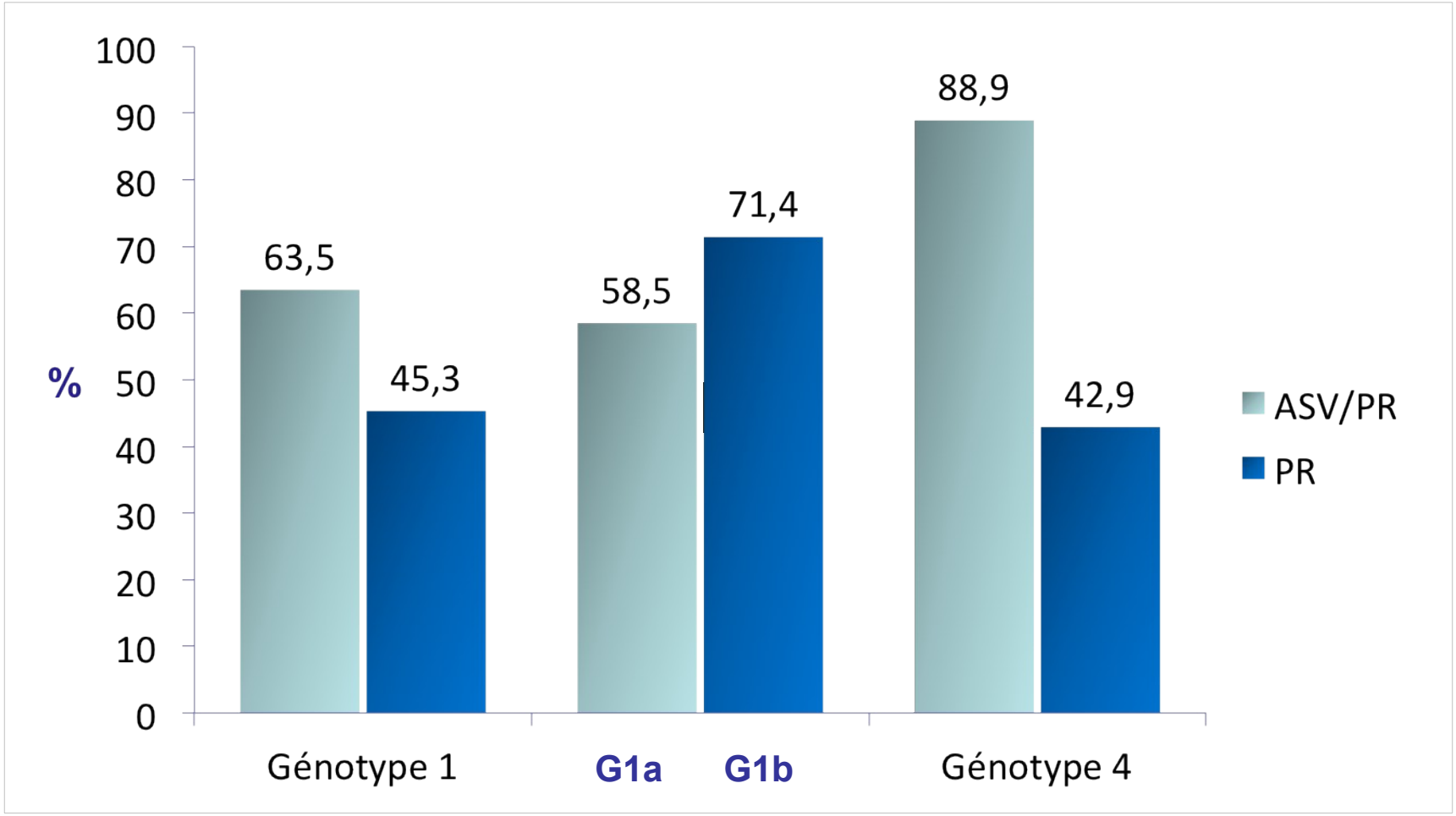


MK-5172 (PI) plus PEG-IFN/RBV: G1 naïve non-cirrhotic



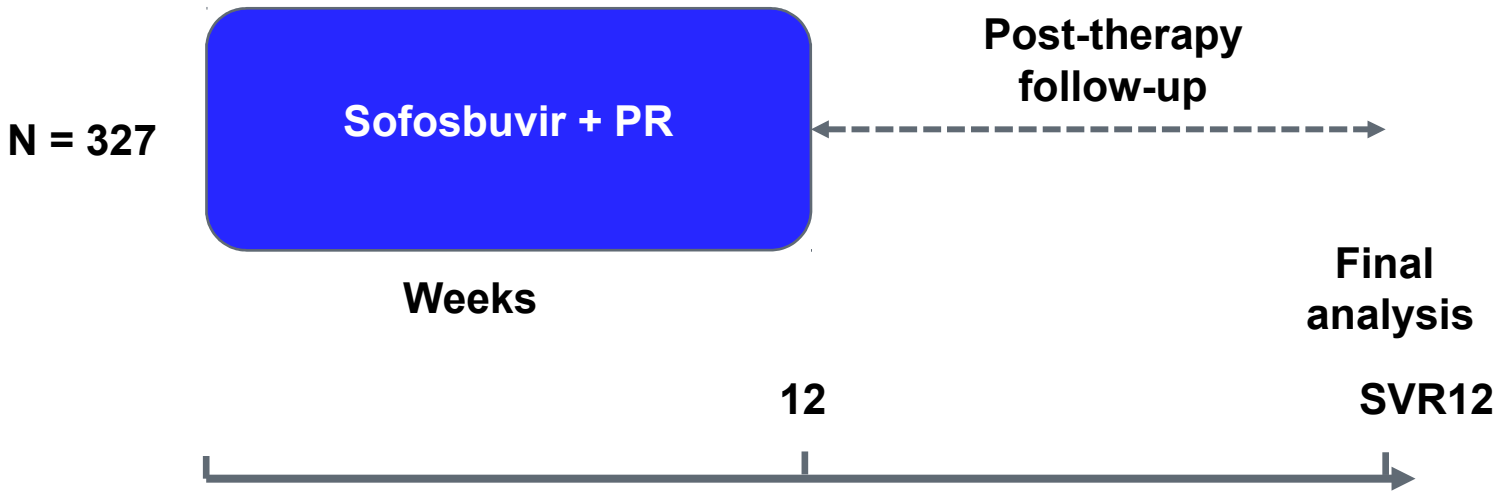
Manns et al. EASL 2013, Abs. 66

Asunaprevir (PI) plus PEG-IFN/RBV: G1 naive



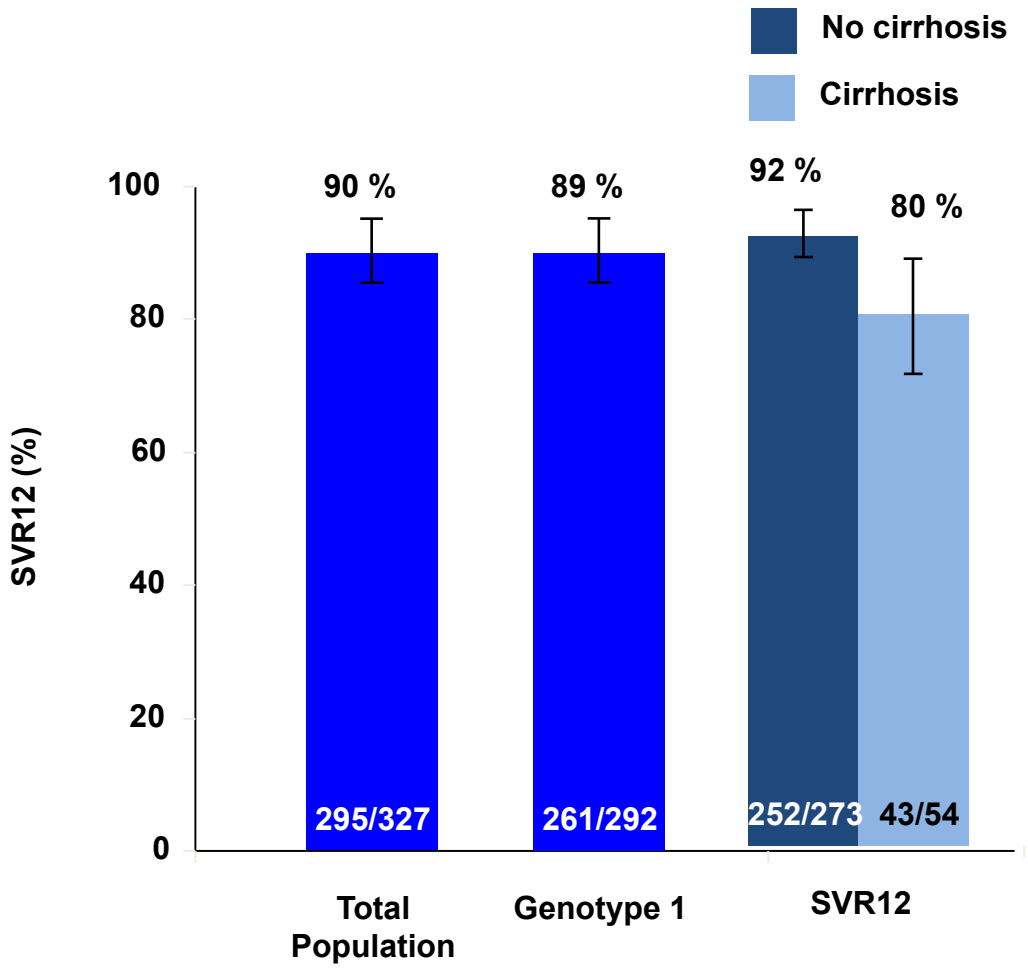
Bronowicki et al. EASL 2013, Abs. 1420

Sofosbuvir (NI): phase III trial design; G1 naïve (Neutrino)



Lawitz et al. *N Engl J Med*. 2013; 368(20):1878-87

Sofosbuvir (NI): SVR12, G1 naïve, phase III trial (Neutrino)



Lawitz et al. *N Engl J Med*. 2013; 368(20):1878-87

Sofosbuvir : side effects (Neutrino)

	Sofosbuvir + PR, % (N = 327)
SAEs	1
Discontinuations due to AEs	2
Fatigue	59
Anaemia	21
Rash (any)	18
Pruritus	17
Neutropenia	17

Lawitz et al. *N Engl J Med*. 2013; 368(20):1878-87

2nd wave IFN-based triple therapy for HCV genotype 1: Simeprevir, Faldaprevir and Sofosbuvir.

- Introduction
- New IFN-based triple therapy for HCV genotype 1

  Protease inhibitors

  - Simeprevir (Quest-2, Promise)
  - Faldaprevir (StartVerso 1, StartVerso 3)
  - Other PI : MK5172, Asunaprevir, etc.…

  Polymerase inhibitor

  - Sofosbuvir (Neutrino)

- **Summary and Conclusion**

Summary: 2nd wave IFN-based triple therapy for HCV G1

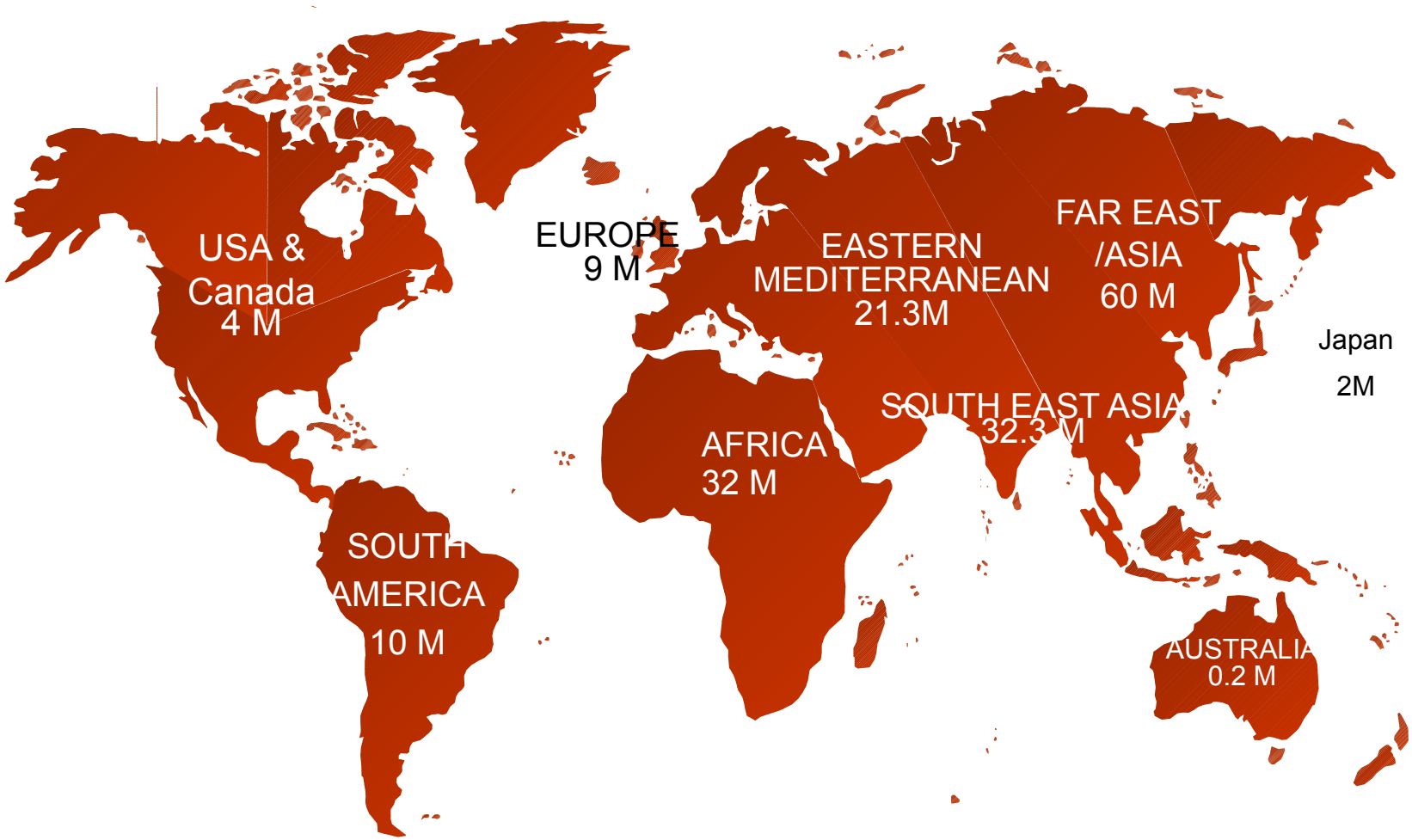
DAA + PEG-IFN + RBV	N	SVR12 DAA+PR vs. PR
Simeprevir QUEST-21	391 (7% F4)	81% vs. 50%
Faldaprevir StartVerso12 (120 vs. 240 mg)	652 (17% ≥ F3)	79-80% vs. 52%
Sofosbuvir3	292 (17% F4)	89 % vs no control arm

1Manns MP et al. Late breaker p1413 EASL 2013
2Ferenci P et al. Late breaker p. 1416, EASL 2013
3Lawitz E, et al. N Engl J Med 2013;368:1878-87.

Summary: 2nd wave IFN-based triple therapy for HCV G1

- The available data on second-generation IFN-based regimens is very promising due to:
  - Higher proportion of patients candidates for short treatment duration
  - Better safety profile when compared with first-generation PIs
  - Less pill burden
- However, a proportion of patients remain difficult to cure and more studies are needed in these populations. These include
  - Cirrhotic patients
  - Previous null responders
  - Failure to triple therapy
  - Patients infected with genotype 4
- Finally we need to explore cost effectiveness of DAA treatment strategies

HCV worldwide: Limited access to new treatment options in countries with the highest HCV prevalence

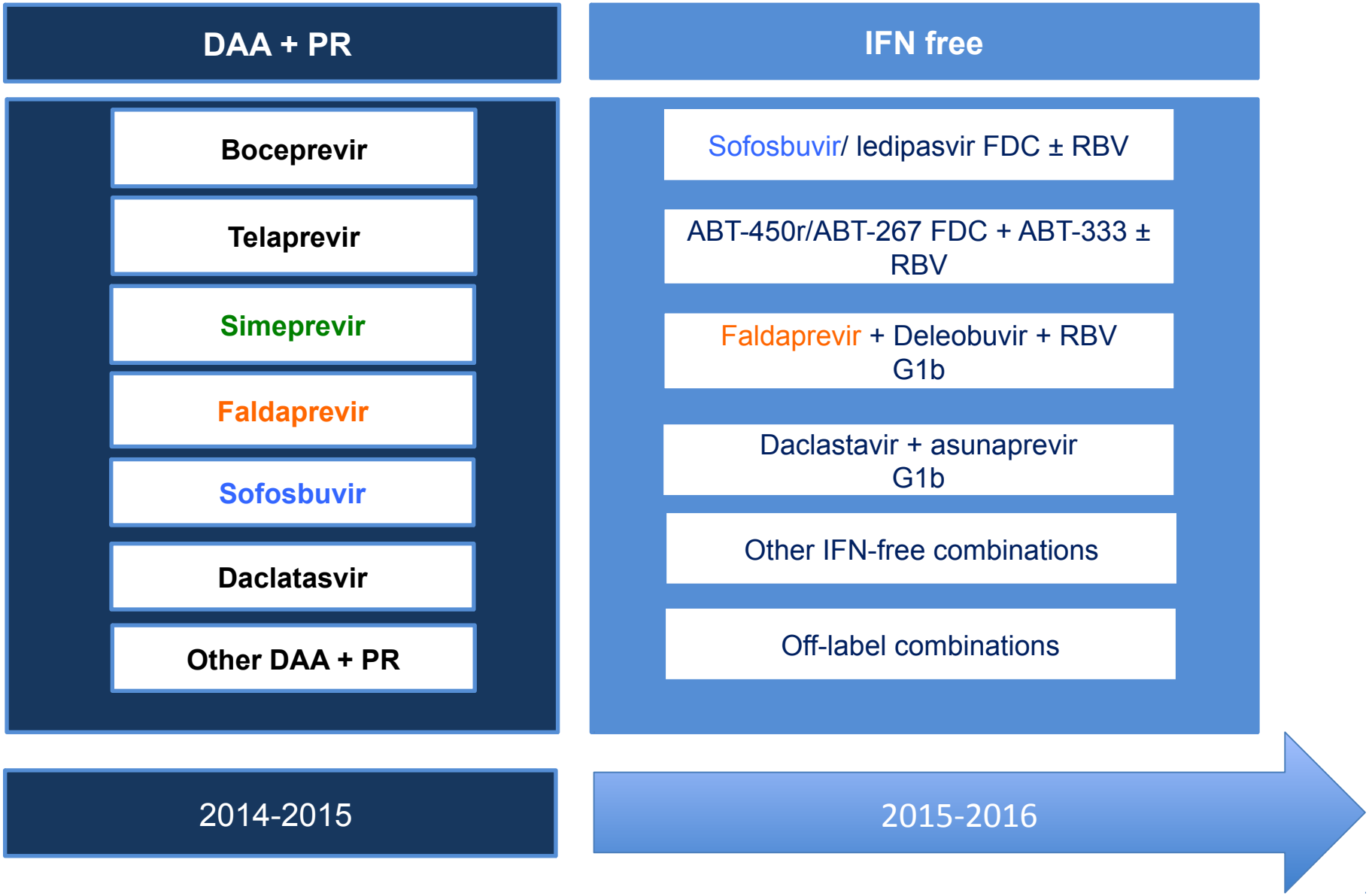


Majority of the World
No treatment or
Dual | PegIFN/RBV

170 Millions worldwide

WHO, 1999

Conclusion & Perspectives



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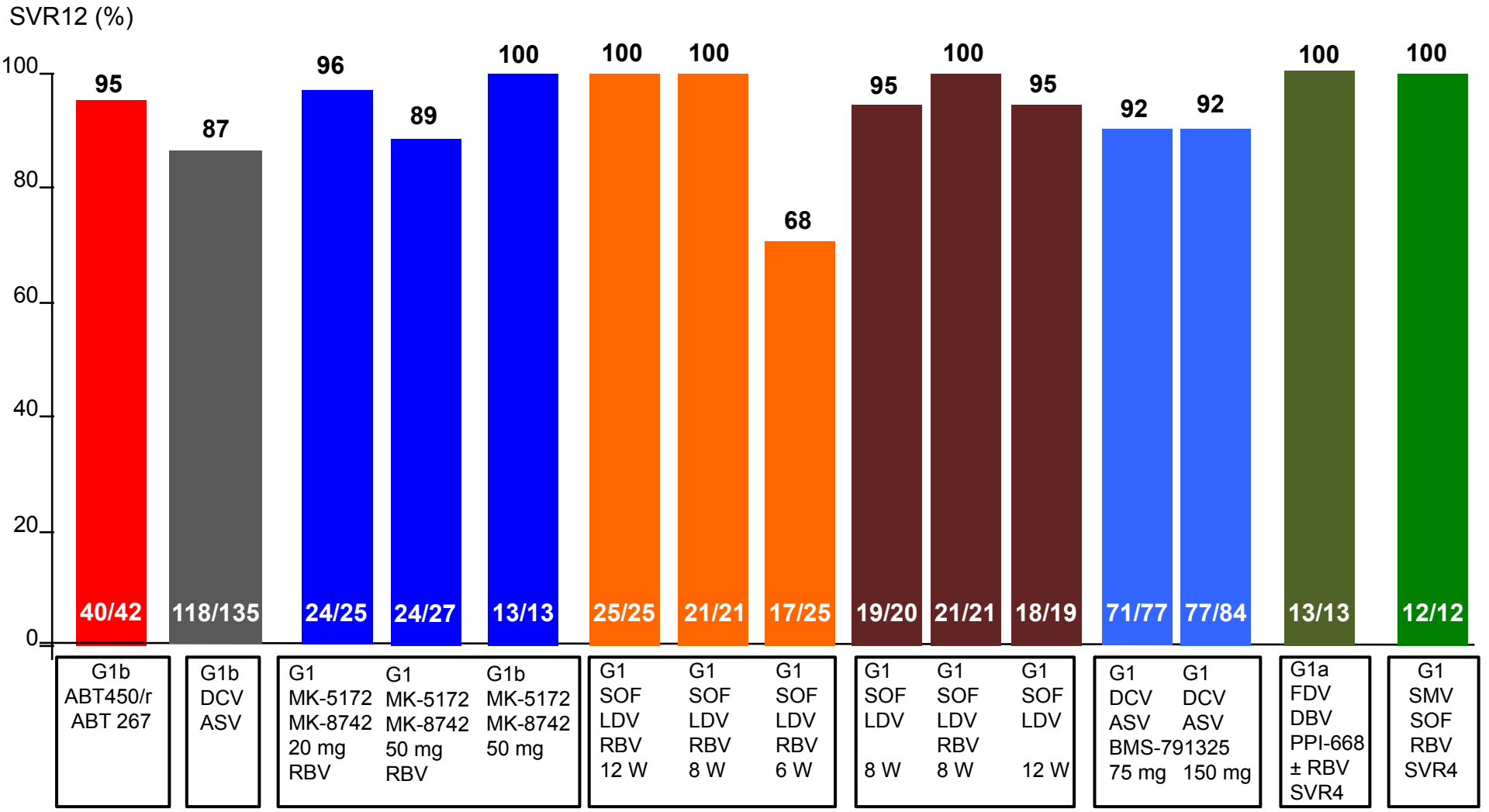
Perspectives 1 (G1 naïves)



Pearl-1, ABT450/r + ABT 267; Lawitz et al. AASLD 2013, A75.

Daclatasvir (DCV) + asunaprevir (ASV); Chayama et al. AASLD 2013, A211.

C-Worthy , MK-5172/MK-8742 ± RBV; Lawitz et al. AASLD 2013, A76.

Electron, SOF/ledipasvir (LDV) ± RBV; Gane et al. AASLD 2013, A73

Lonestar : sofosbuvir (SOF)/ledipasvir (LDV) ± RBV; Lawitz et al. AASLD 2013, A215/1844.

Daclatasvir (DCV) + asunaprevir (ASV) + BMS-791325; Everson et al. AASLD 2013, ALB1.

Faldaprevir (FDV), deleobuvir (DBV) +PPI-668; Lalezari et al. AASLD 2013 ALB20.

Cosmos : sofosbuvir (SOF)/simeprevir (SMV) ± RBV; Jacobson et al. AASLD 2013, ALB3.

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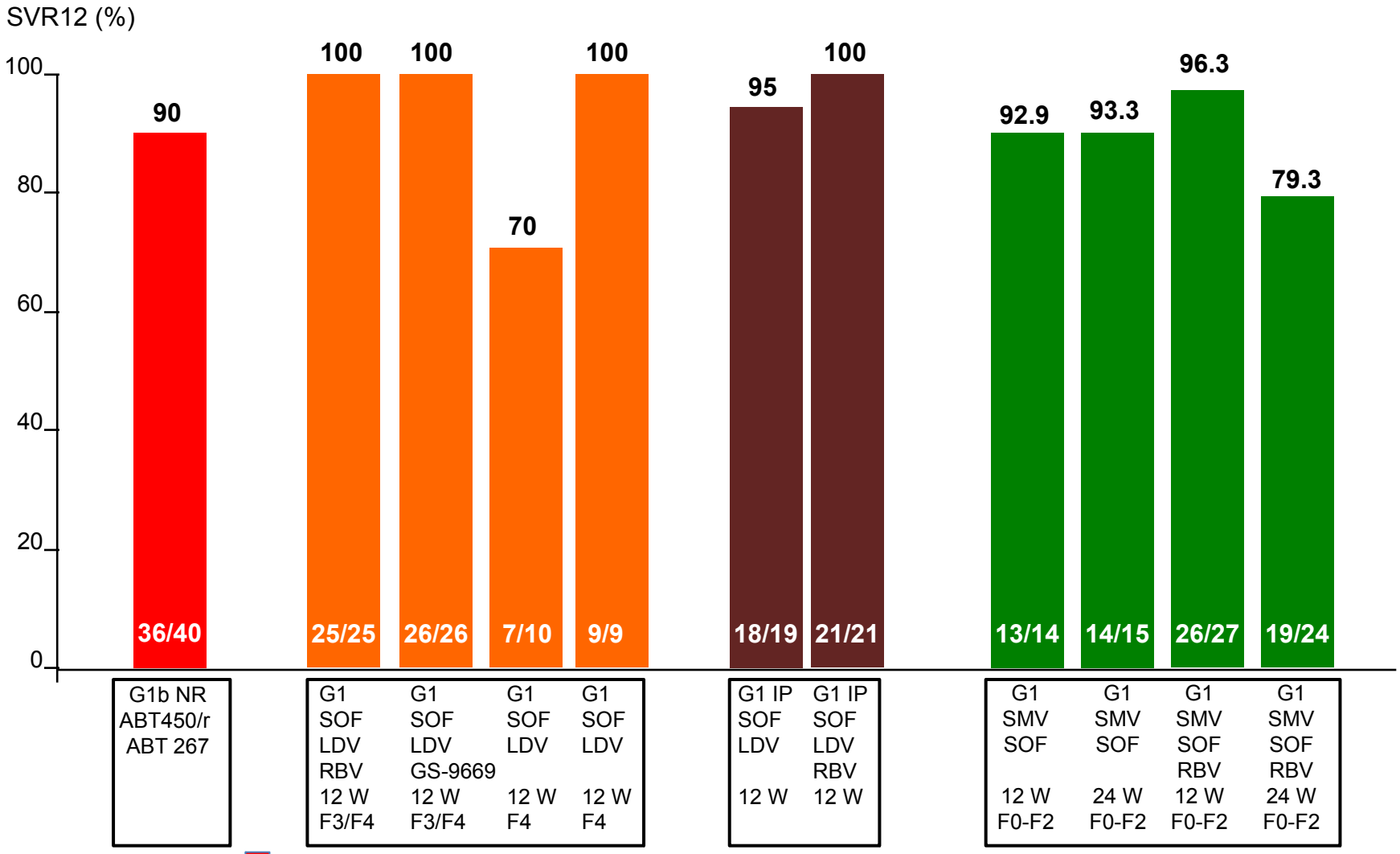
Perspectives 2 (G1 experienced)



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And the Winner is……..

The Patient.