The Beginning of the End for HCV in HIV : Or the End of the Beginning ?

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Change in Causes of Death in Patients with HIV

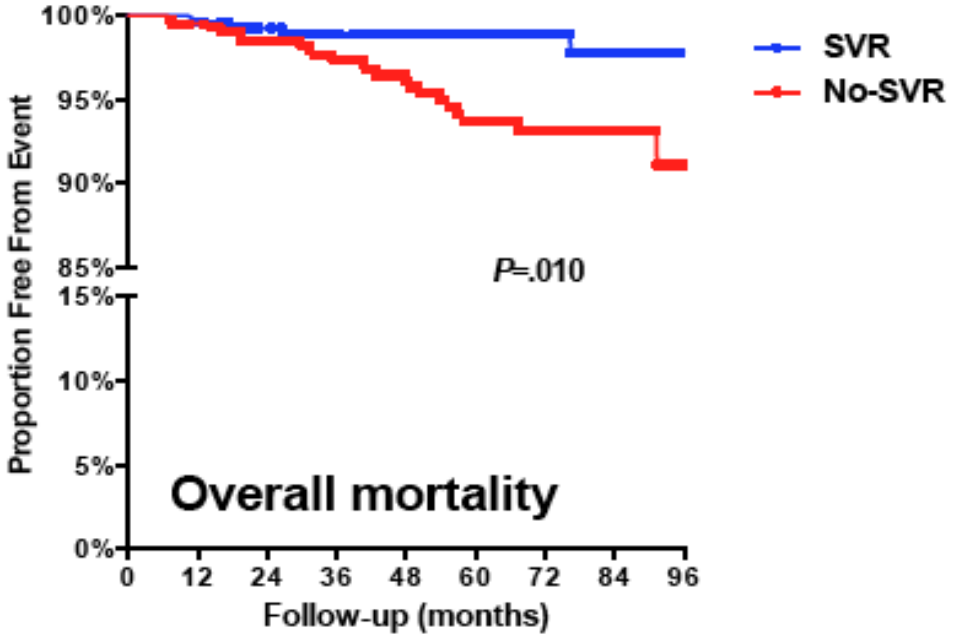
- Swiss HIV Cohort Study (SHCS)
  - 446 deaths between 2005 and 2009
  - Causes of death
    - #1 Non-AIDS defining cancers (n=85, 19.1%) including HCC (n=13, 2.8%)
    - #2 AIDS (n=73, 16.4%)
    - #3 Liver Diseases (n=67, 15%)

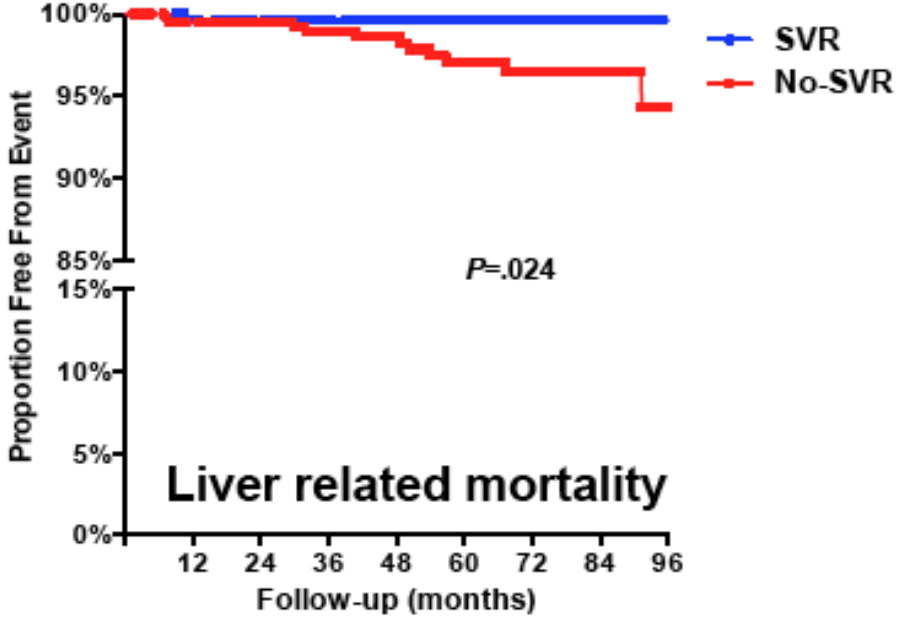
When deaths due to HCC are included among liver-related Deaths (instead of non-AIDS defining cancers)

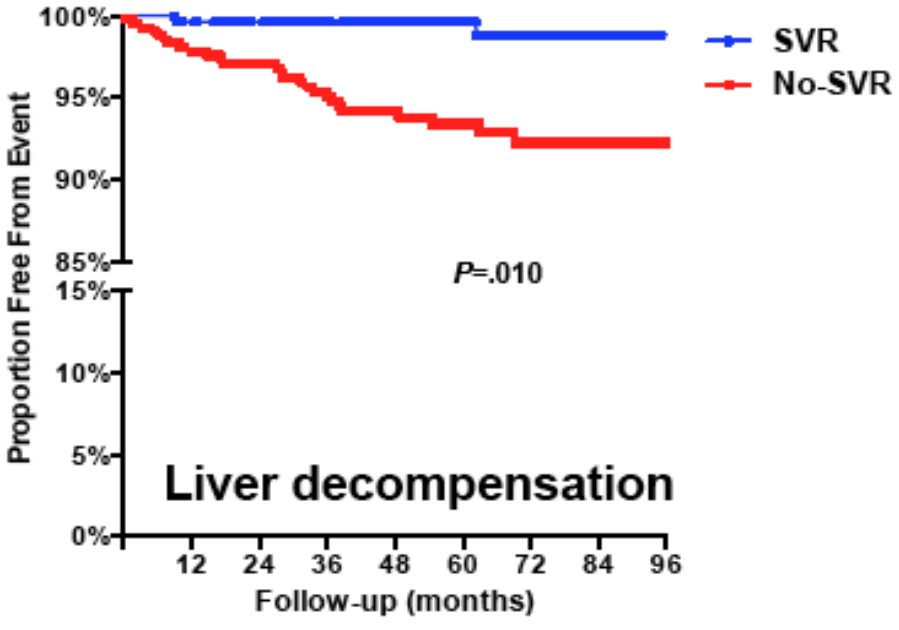
Liver Diseases = #1 Cause of Death (17.9%)

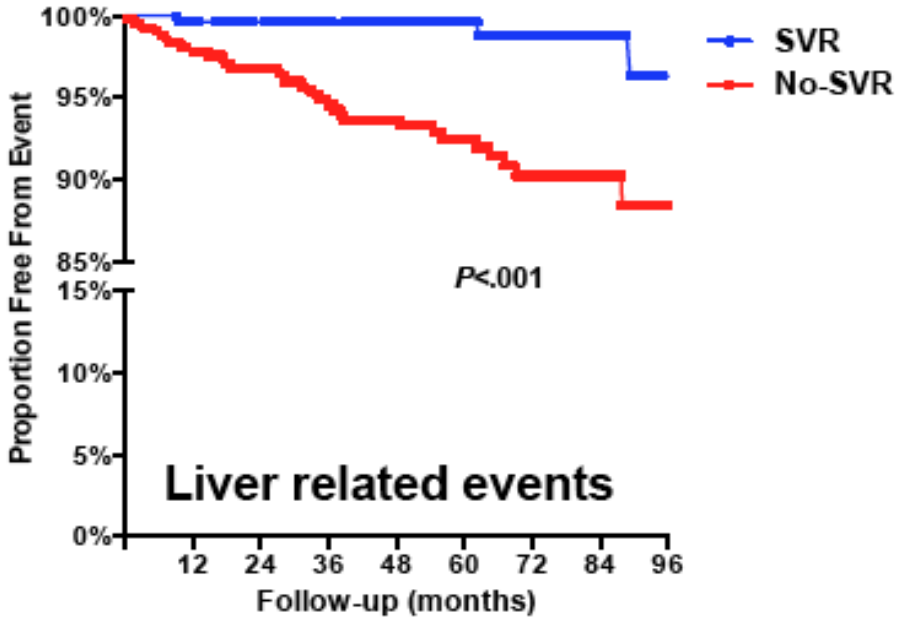
Ruppik M. et al. Changing patterns of causes of death in the SHCS 2005-2009. CROI 2011. Poster # 789. Available at: http://www.retroconference.org/2011/PDFs/789.pdf.

Kaplan Meier Estimates of Events





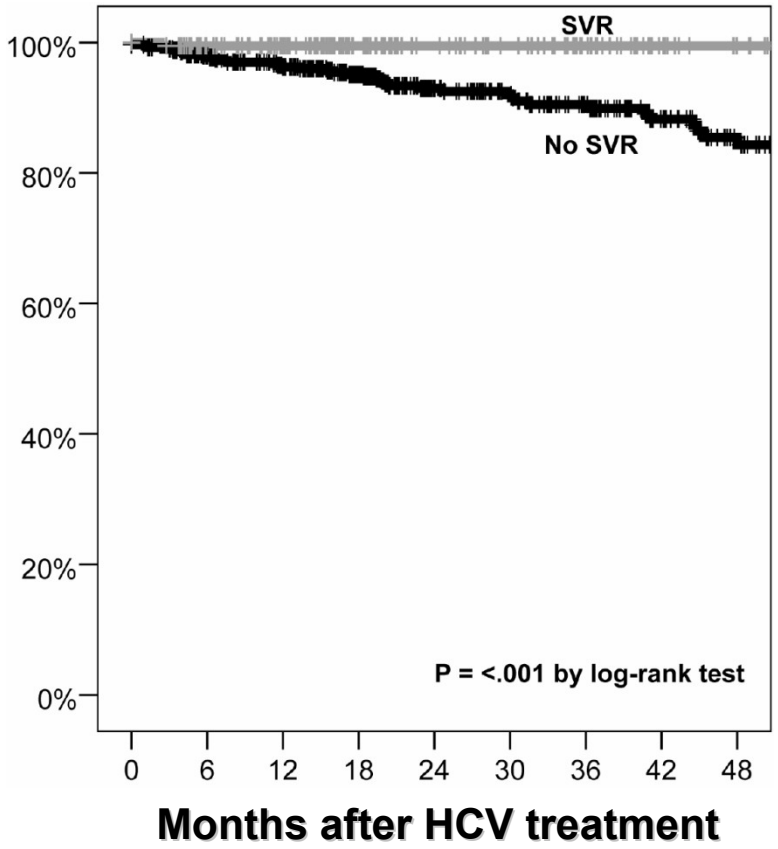




HCV Infection Can Be Cured in HIV + patients and extends life

- Testing and counseling
- Treatment of chronic infection
  - Sustained virologic response is possible[1]
  - Sustained virologic response is durable[2]
  - Sustained virologic response prevents death[3]

Survival after HCV treatment for 493 with no SVR and 218 with SVR

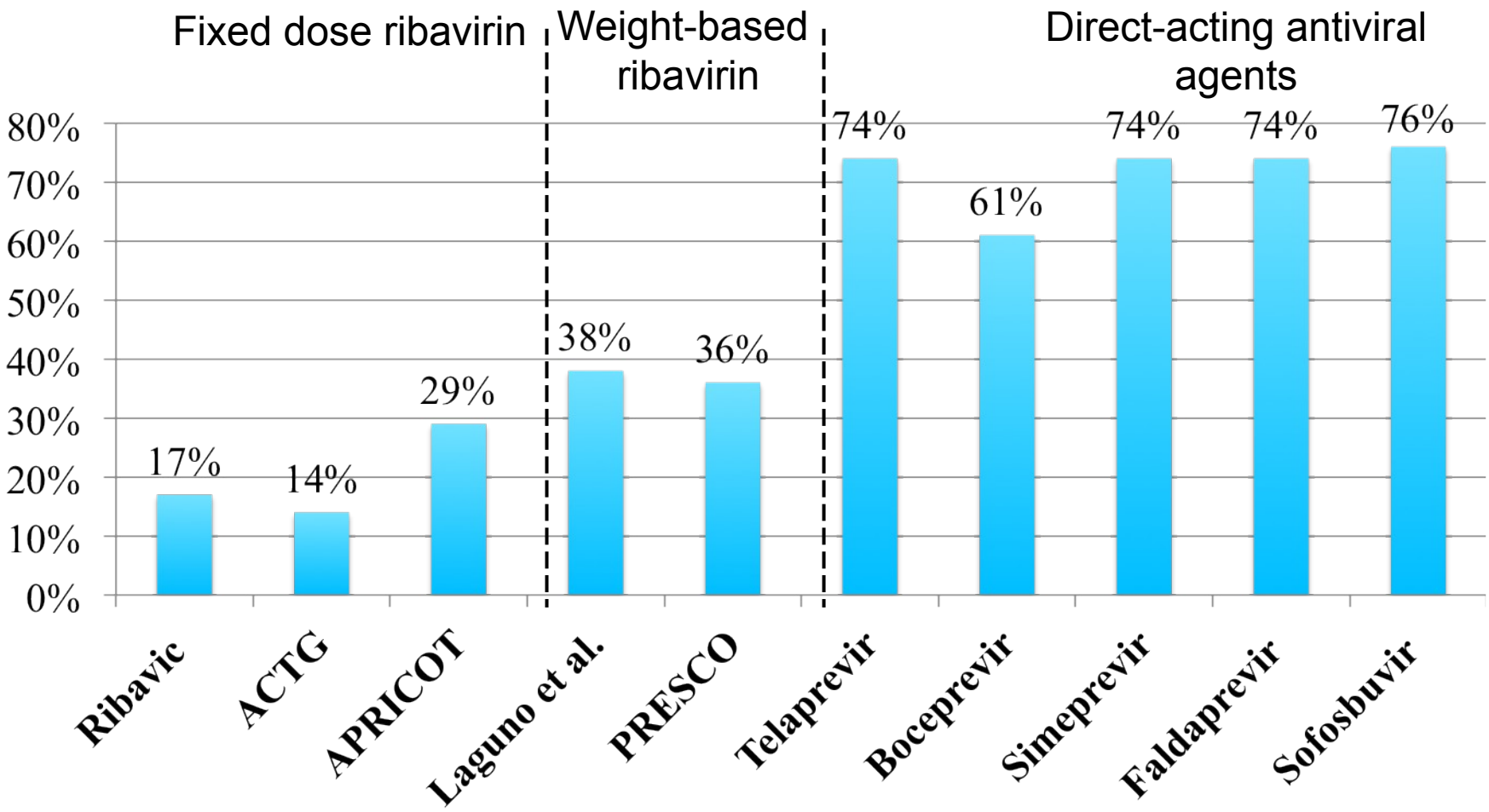


1. Torriani FJ, et al. New Engl J Med. 2004;351:438-450. 2. Soriano V, et al. Antivir Ther. 2004;9:987-992.
3. Berenguer J, et al. Hepatology. 2009;50:407-413.

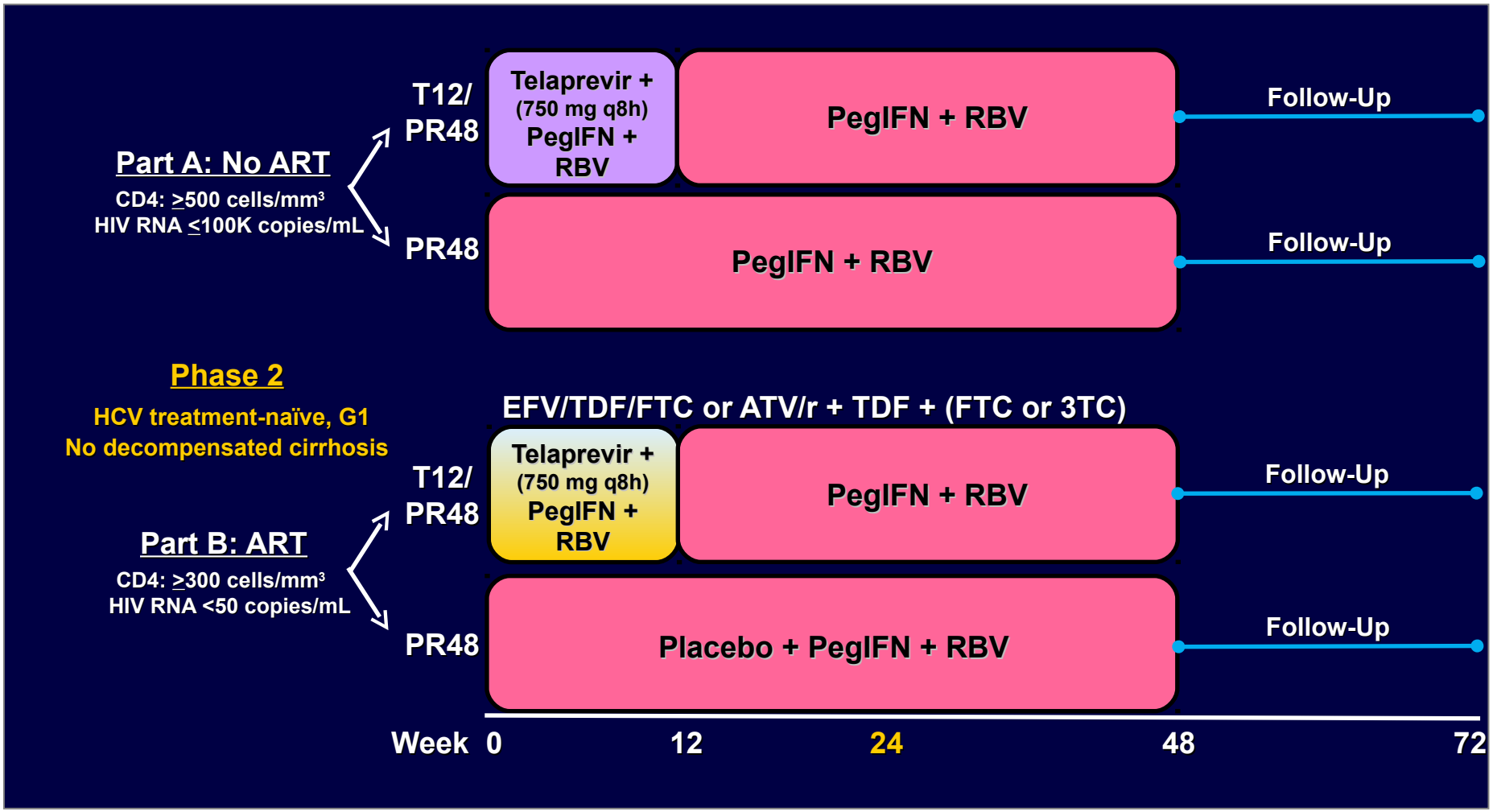
Summary of Results: Coinfection Trials pre DAA

Study	N	Treatment	SVR (%)		
			All	GT 1	GT non-1
RIBAVIC	412	PEG IFN α-2b + RBV 800	27	17*	44
		IFN α-2b + RBV 800	20	6	43
ACTG	133	PEG IFN α 2a + RBV 600	27	14	73
		IFN α -2a + RBV 600	12	6	33
APRICOT	860	PEG IFN α 2a + RBV 800	40	29	62
		IFN α -2a + RBV 800	12	7	20
LAGUNO	93	PEG IFN α-2b + W/B RBV	44	38	53
		IFN α-2b + W/B RBV	21	7	47
PRESCO	389	PEG IFN α-2a + W/B RBV G1 48 w 31 72w 52 G2 24 w 67 48w 82	50	36	72

Progression of SVR in HCV treatment in HIV

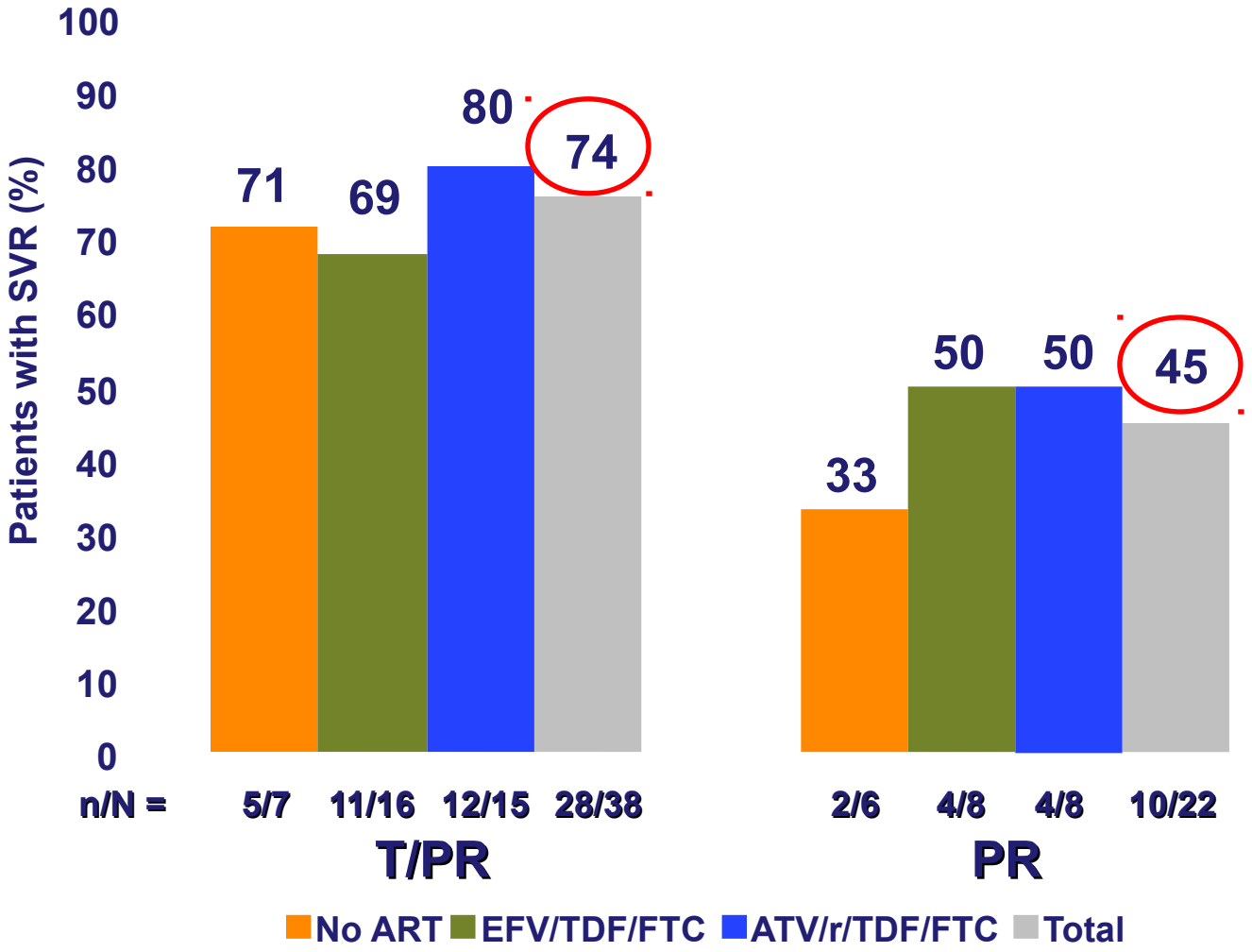


Telaprevir-Based HCV Therapy in HCV/HIV Coinfection (SVR 12)



Dieterich CROI 2012

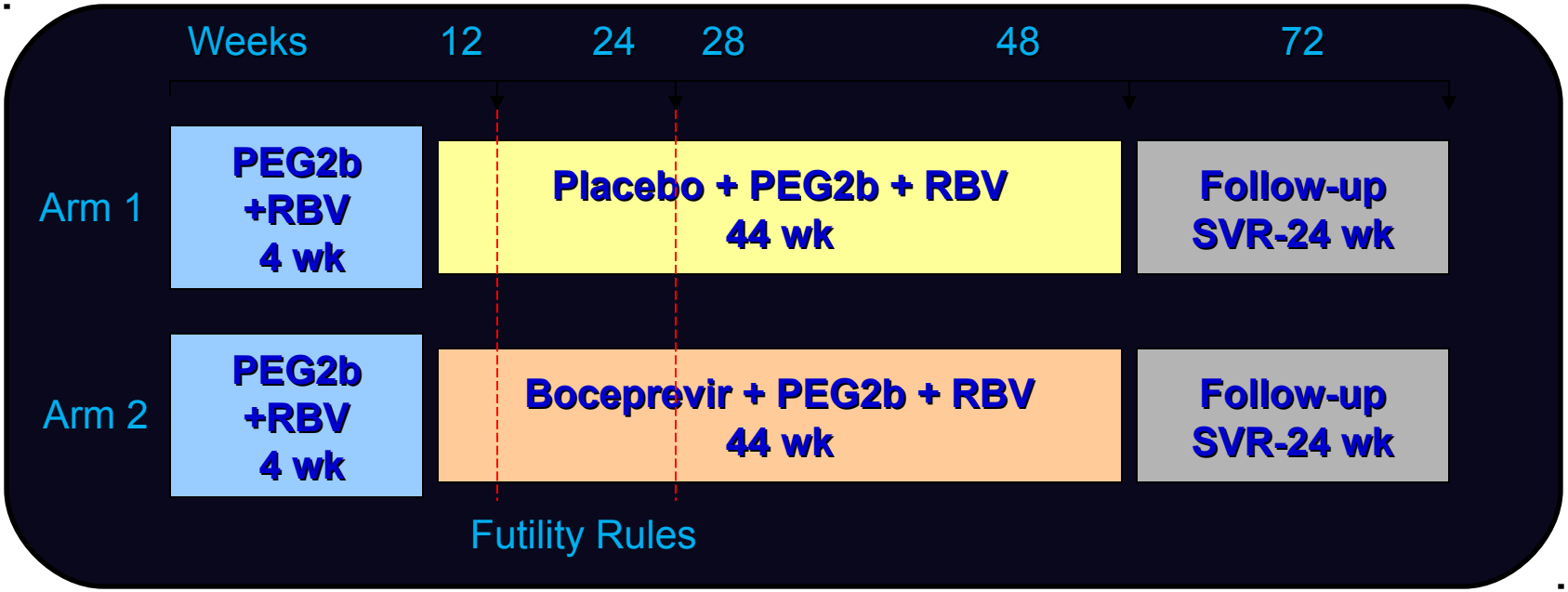
SVR Rates 12 Weeks Post-Treatment (SVR12*)



*Patient was defined as SVR12 if HCV RNA was < LLOQ in the visit window

Dieterich CROI 2012

Boceprevir Study Design



- Two-arm study, double-blinded for BOC, open-label for PEG2b/RBV
  - 2:1 randomization (experimental: control)
  - Boceprevir dose 800 mg TID
- 4-week lead-in with PEG2b/RBV for all patients
  - PEG-2b 1.5 µg/kg QW; RBV 600-1400 mg/day divided BID
- Control arm patients with HCV-RNA ≥ LLOQ at TW 24 were offered open-label PEG2b/RBV+BOC via a crossover arm

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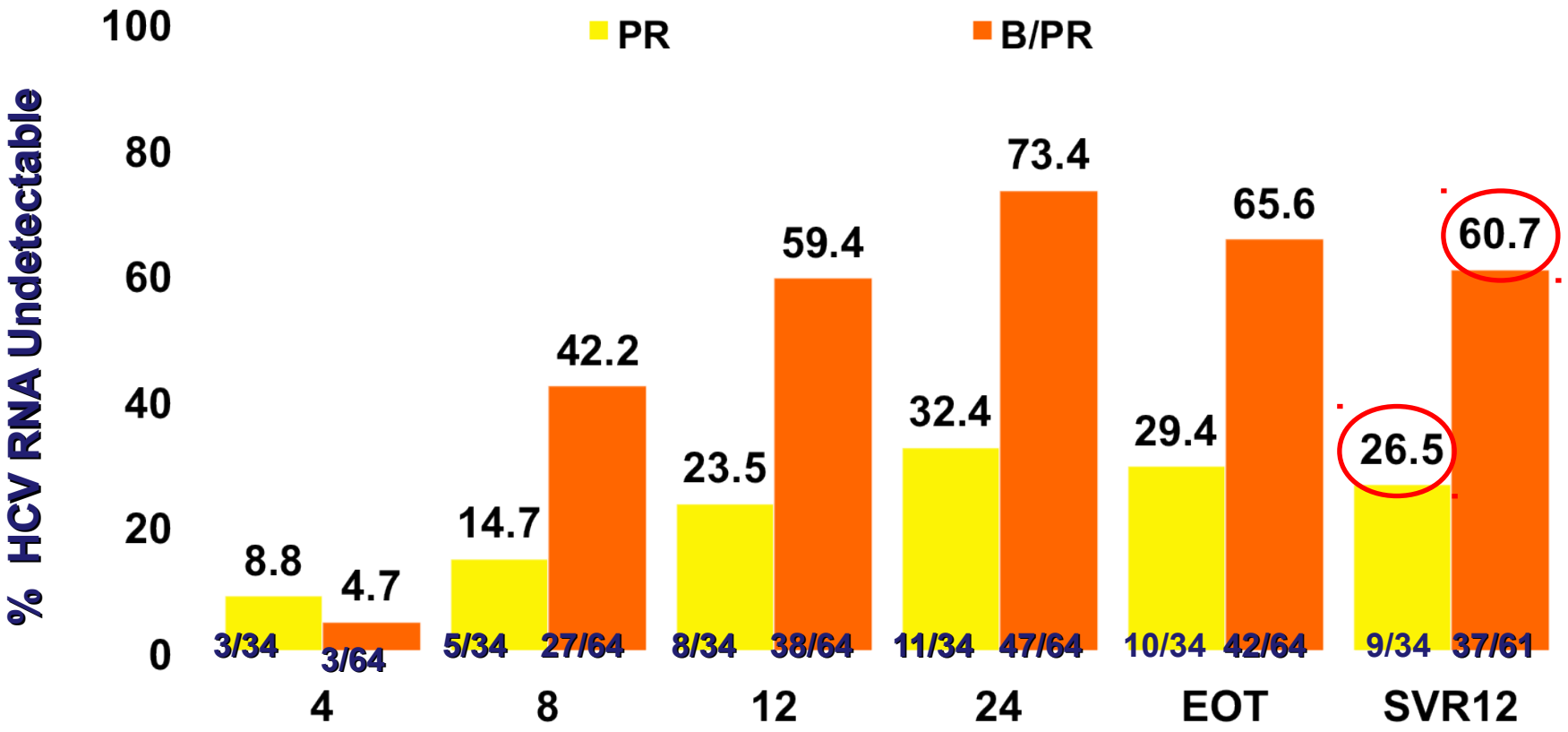
Virologic Response Over Time†



† Three patients undetectable at FW4 have not yet reached FW12 and were not included in SVR12 analysis.

Sulkowski CROI 2012

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A chart summarising the interactions of telaprevir and boceprevir with other drugs has been produced from data in the public domain. Telaprevir and boceprevir will be added as columns to the interaction charts when licensed.

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VERTEX

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On-treatment and Sustained Virologic Responses Rates of Telaprevir-based Hepatitis C Treatment Do Not Differ Between HIV/HCV Co-infected and HCV Mono-infected Patients

Martel-Laferrière V, Brinkley S, Bichoupan K, Posner S, Stivala A, Perumalswami P, Schiano T, Sulkowski M, Dieterich DT, Branch AD

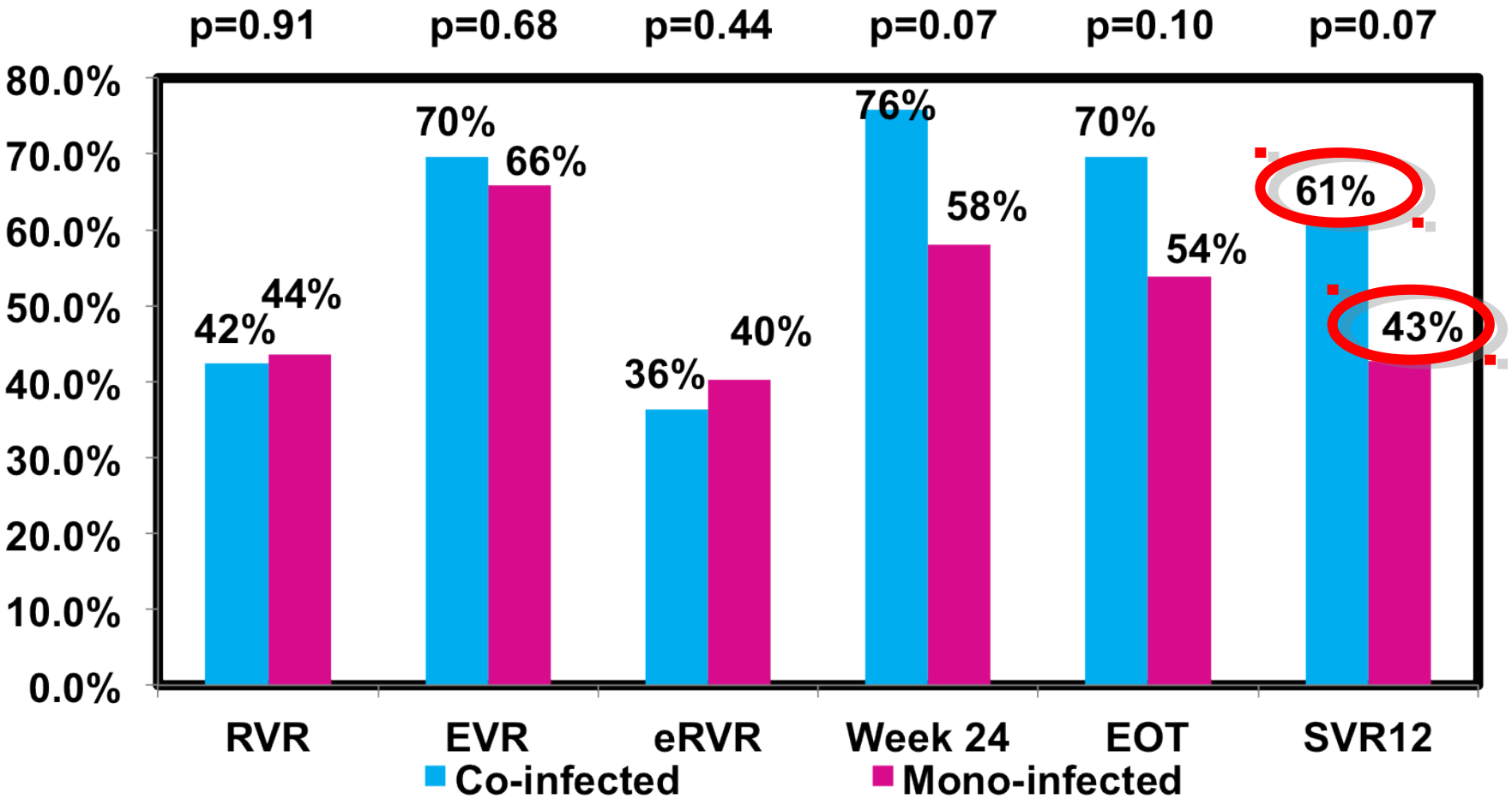
Mount Sinai

JOHNS HOPKINS MEDICINE

Baseline Characteristics

	Co-infected (N = 33)	Mono-infected (N = 117)	P-value
Median age (IQR)	57 (52-59)	56 (51-61)	0.82*
Male (% of total)	26 (78.8%)	79 (67.5%)	0.21§
Race (% of total) White Black Other	 16 (48.5%) 14 (42.4%) 3 (9.1%)	 65 (55.6%) 19 (16.2%) 34 (28.2%)	<0.01§
Prior treatment response (% of total) Naive Relapser Non responder/Intolerant	 3 (9.1%) 5 (15.2%) 25 (75.8%)	 36 (30.8%) 23 (19.7%) 58 (49.6%)	0.02§
Bridging fibrosis/cirrhosis (% of total)	16 (48.5%)	40/113 (35.4%)	0.17§
Baseline HCV viral load $\log_{10}$ IU/mL (IQR)	6.46 (5.92-7.00)	6.46 (5.91-6.73)	0.42†

Virologic Responses

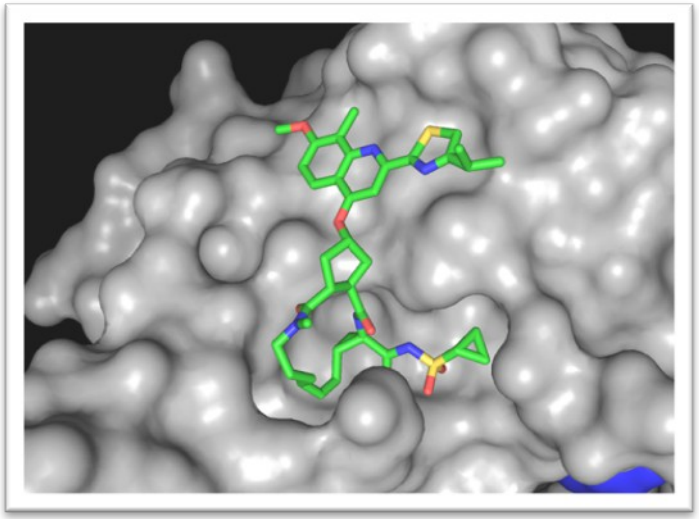


Trend for better virologic responses in co-infected patient is potentially explained by a selection bias

HIV co-infection did not increase rates of discontinuation or severe anemia

	HIV/HCV co-infected patients	HCV mono-infected patients	p-value
Discontinuation due to side effects (%)	6 (18.2%)	16 (13.7%)	0.58
Hospitalization (%)	9 (27.2%)	21 (17.9%)	0.42
Emergency room visits (%)	6 (18.2%)	16 (13.7%)	0.52
Anemia (%)	29 (87.8%)	107 (91.5%)	0.53
Severe anemia (%)	15 (45.5%)	68 (58.1%)	0.20
Rash (% of total)	5 (15.2%)	40 (34.2%)	0.04
Rectal symptoms (%)	4 (12.1%)	51 (43.6%)	<0.01

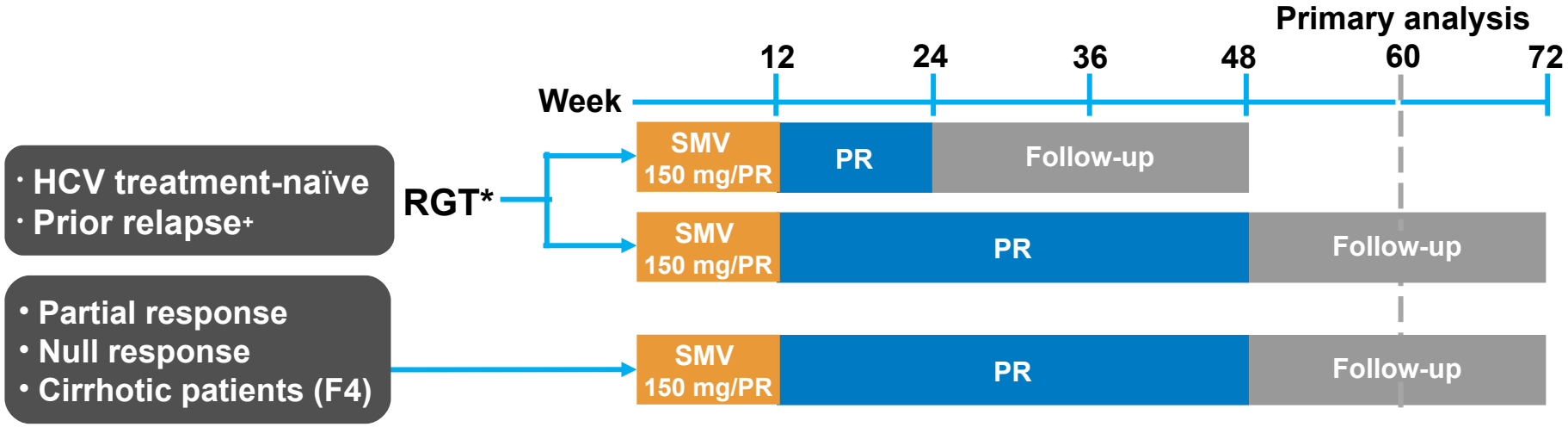
Simeprevir (TMC435) in combination with peginterferon/ribavirin in patients co-infected with HCV genotype-1 and HIV-1: Primary analysis of the C212 study



- **Investigational, one-pill, once-daily, oral HCV NS3/4A protease inhibitor**
- **Multigenotypic: antiviral activity in patients infected with HCV G1, 2, 4, 5 and 6[1–4]**
- **SMV is being investigated in both PR and IFN-free combinations**
- **Phase III trials of SMV + PR in G1 HCV mono-infected treatment-naïve patients and relapsers to IFN-based treatment showed SVR12 rates of approximately 80%[5-7]**
- **Safe and well tolerated (~3,800 patients treated to-date)**

[1]Reesink HW et al. Gastroenterology 2010;138:913–921;[2]Moreno C et al. J Hepatology 2012;56:1247–1253;
[3]Fried MW et al .Hepatology 2013: epub; [4]Zeuzem S et al. Poster LB-2998 presented at EASL 2011;
[5]Manns M et al. Oral presentation at EASL 2013; [6]Jacobson I et al. Poster 1425 presented at EASL 2013;
[7]Lawitz et al. Oral presentation at DDW 2013

C212 study design: Phase III, open-label, single-arm, international trial



Primary endpoints: SVR12, safety and tolerability

Secondary endpoints: virologic response at other time points, meeting RGT criteria* for shortened treatment to 24 weeks, on-treatment failure and relapse rates

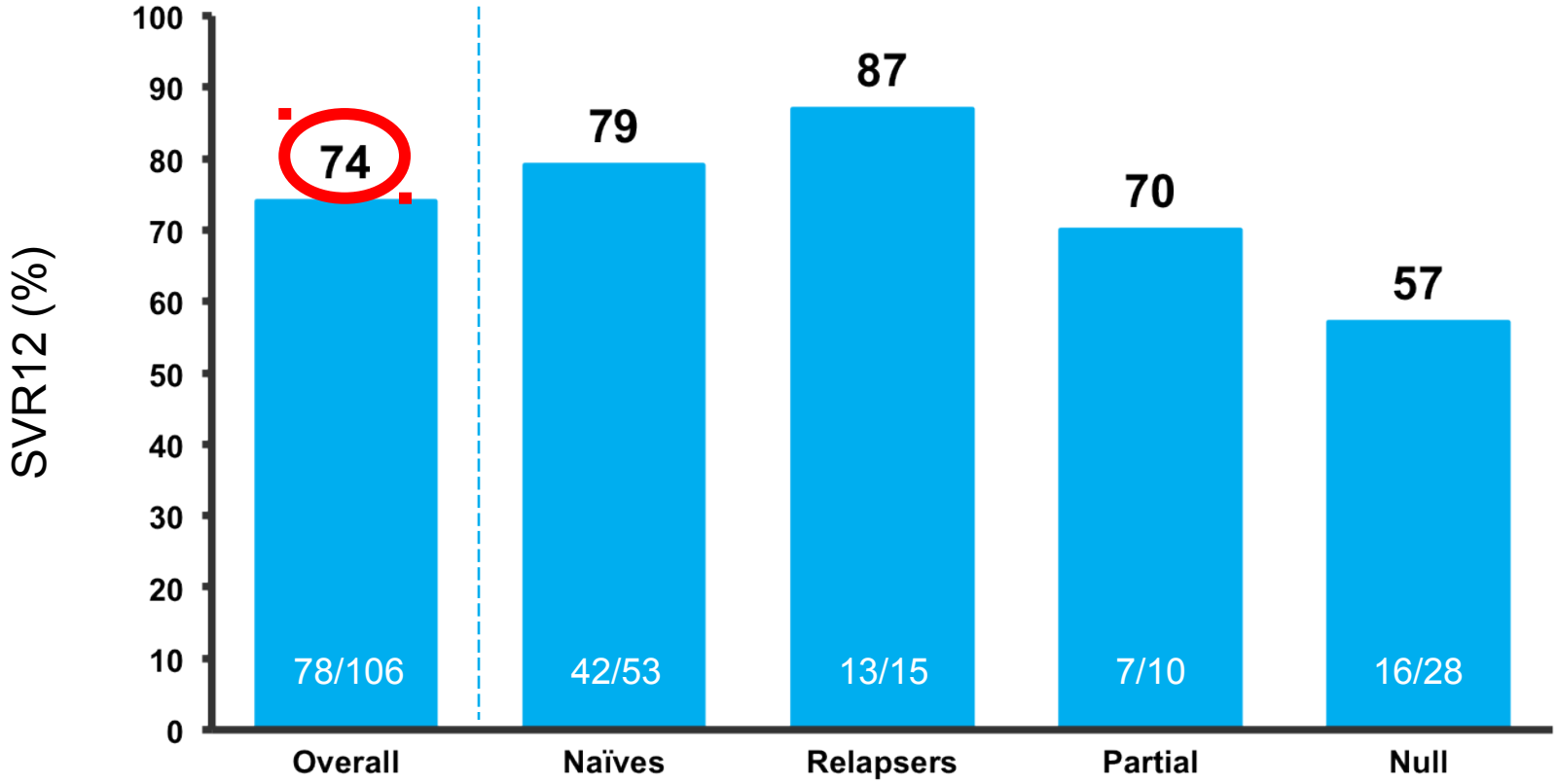
Primary analysis:

All patients included in the analysis (N=106) had completed 24 weeks of treatment, or had reached the time point of the primary efficacy endpoint SVR12 (Week 60), or discontinued prior to that point (for those on 48 weeks of treatment)

PR, peginterferon-α2a + ribavirin;
RGT, response-guided treatment;
SMV, simeprevir; SVR12, sustained virologic response 12 weeks' after end of treatment

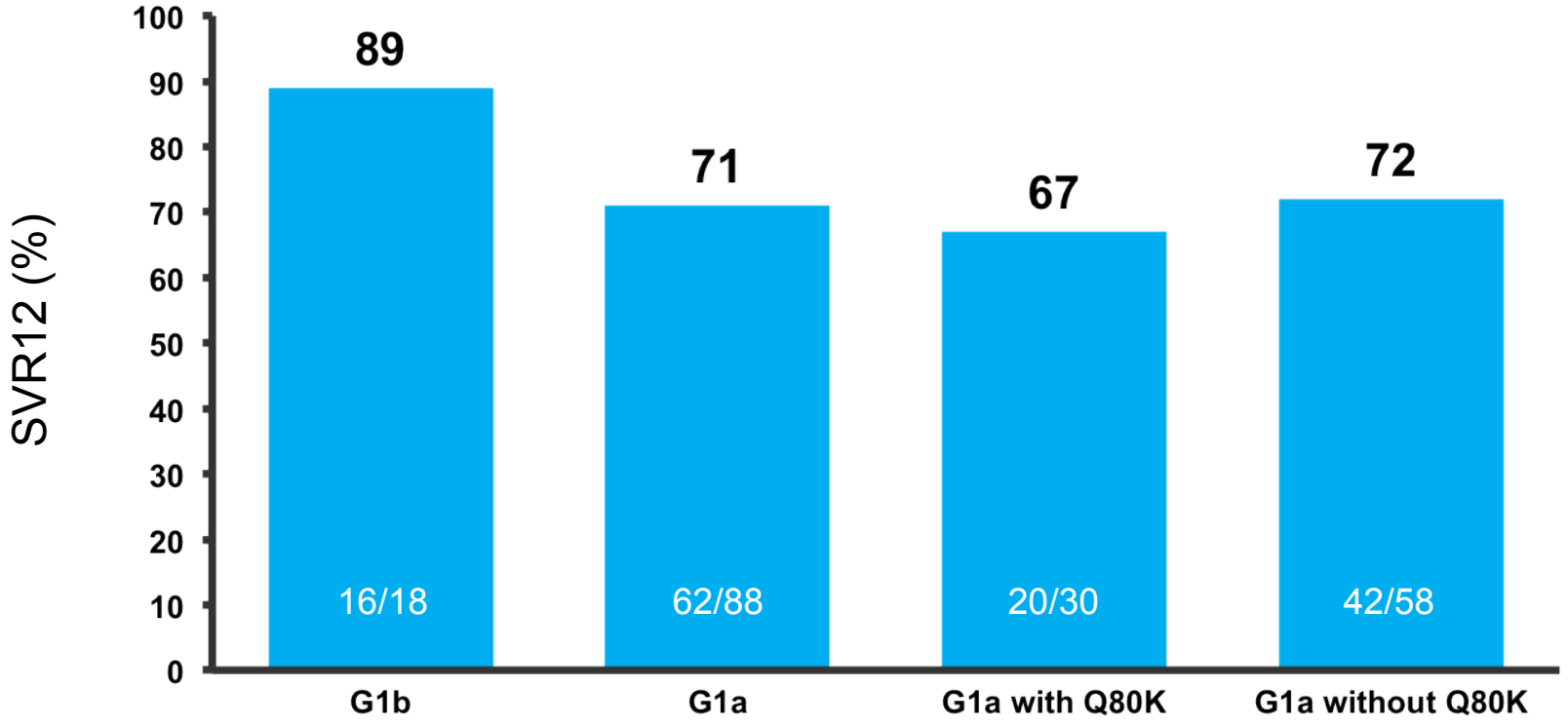
+After PR treatment;
*RGT criteria: HCV RNA <25 IU/mL (detectable or undetectable) at Week 4 and undetectable at Week 12 (measured using Roche COBAS TaqMan HCV/HPS assay, v.2)

C212: SVR12 – Primary endpoint



SVR12, sustained virologic response 12 weeks' after end of treatment

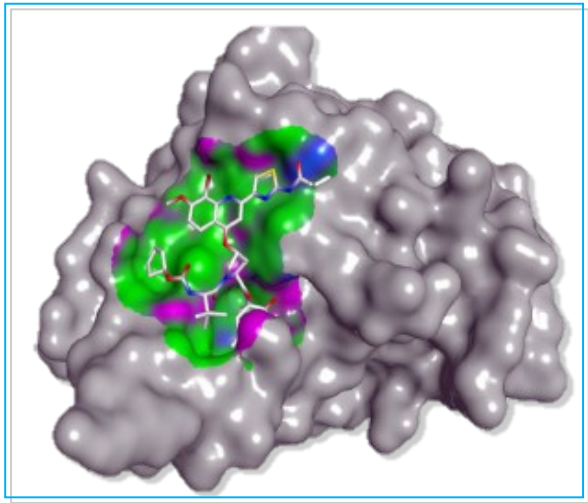
C212: SVR12 by HCV-1 G1 subtype and baseline NS3 Q80K polymorphism



G, genotype; SVR12, sustained virologic response 12 weeks' after end of treatment

STARTVerso 4 Phase III trial of faldaprevir once-daily plus peg interferon α-2a and ribavirin (PR) in patients with HIV and HCV genotype-1 co-infection

- Faldaprevir (FDV) is a potent inhibitor of HCV NS3/4A, with activity against HCV genotypes (GT) 1, 4, 5 and 6 *in vitro*[1]
- Three Phase III trials of FDV + pegylated interferon α-2a and ribavirin (PR) in HCV GT-1 are complete
  - In STARTVerso1, FDV + PR resulted in SVR rates of 79%–80% in treatment-naïve patients with chronic HCV GT-1 infection[2]

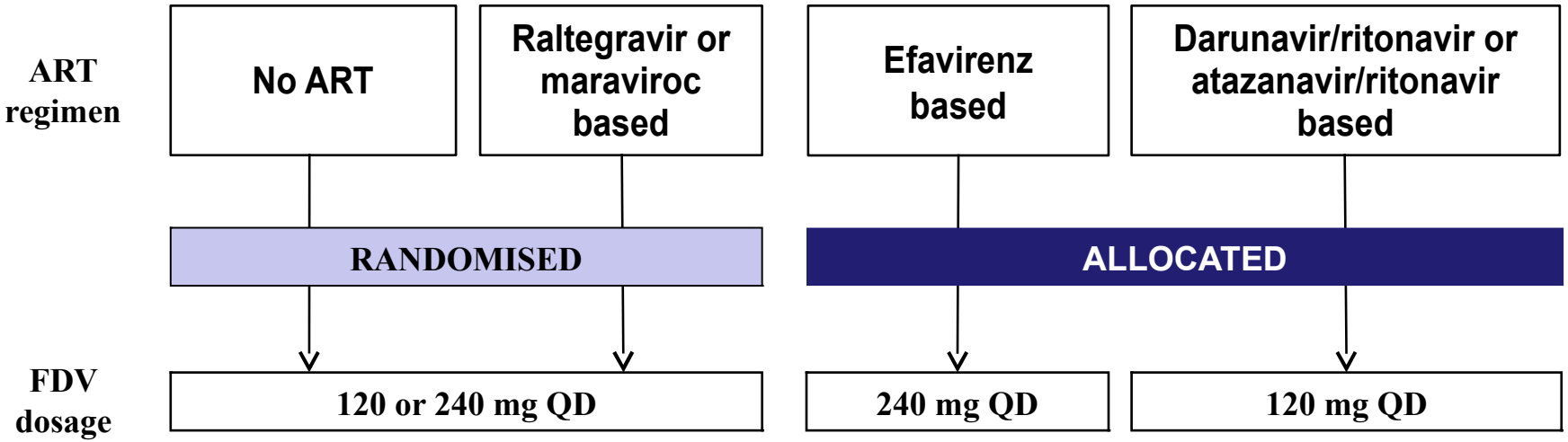


- FDV is also being investigated in Phase III interferon-free trials
- STARTVerso4 is an ongoing Phase III trial evaluating the safety and efficacy of FDV + PR in patients co-infected with HCV and HIV

1. White PW, *et al*. *Antimicrob Agents Chemother* 2010;54:4611–4618; 2. Ferenci P, *et al*. EASL 2013, Abstract 1416.

Study design rationale

FDV with antiretroviral therapy (ART)	Change in FDV AUC[1]
FDV with darunavir/ritonavir	**130% ↑**
FDV with efavirenz	**35% ↓**

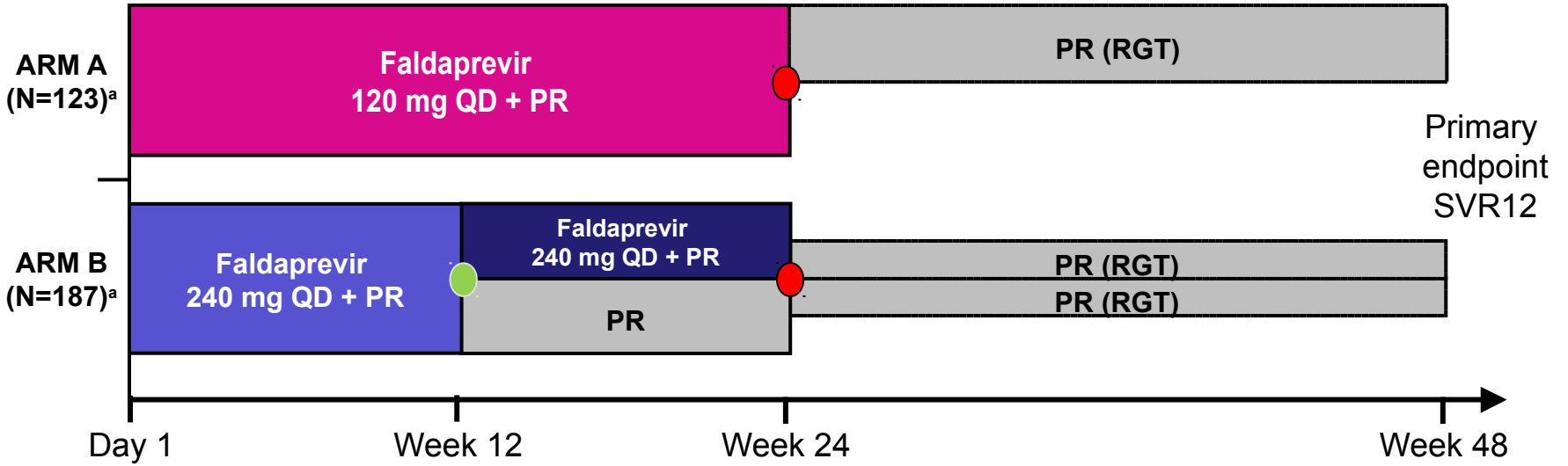


ART, antiretroviral therapy; AUC, area under the curve; FDV, faldaprevir; QD, once daily.

1. Sabo J, *et al.* CROI 2013, Abstract 35.

Study design

Multicenter, open-label, sponsor-blinded, Phase III study in patients co-infected with HCV GT-1 and HIV-1

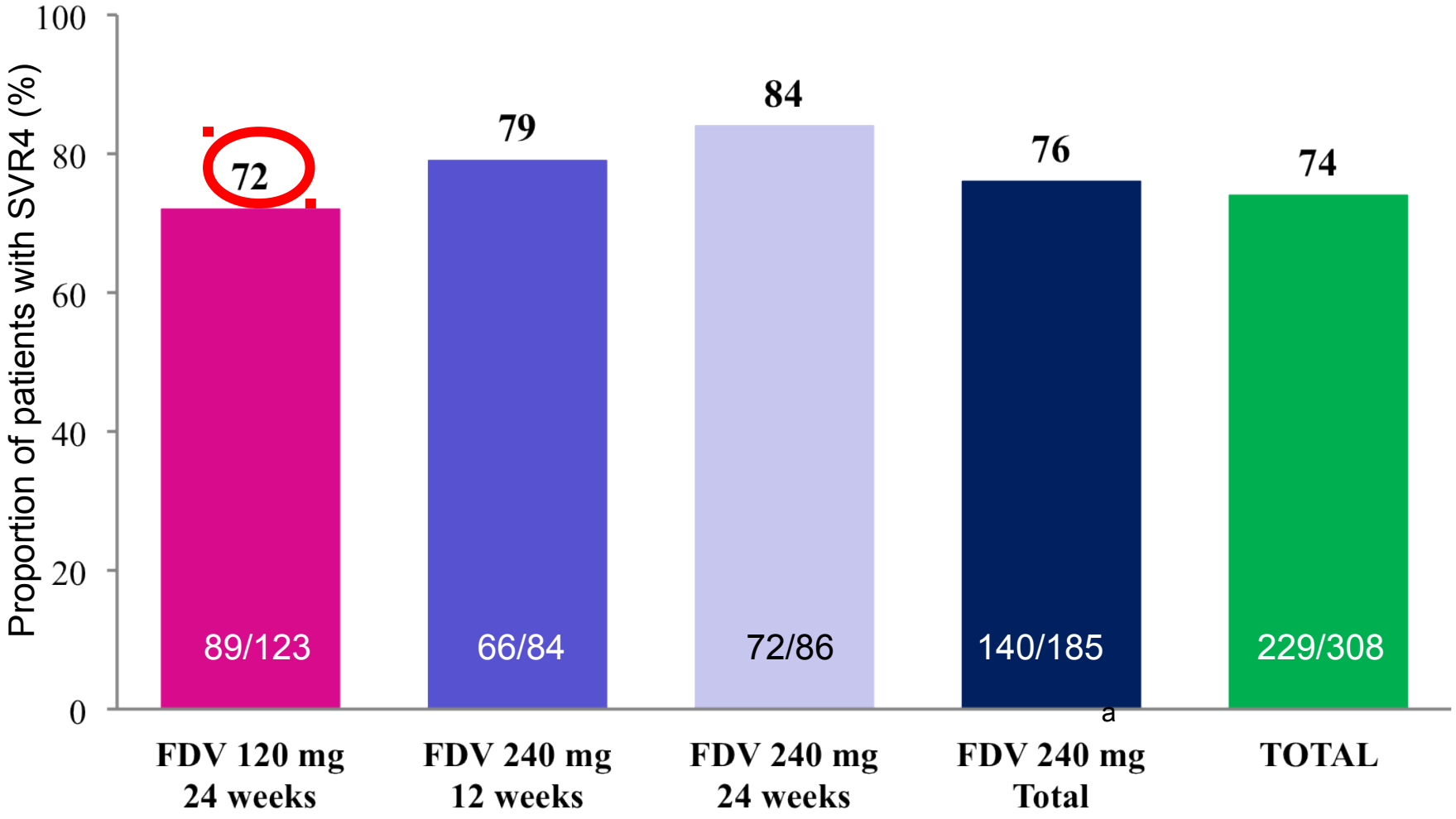


Week 12, FDV 240 mg treatment duration: randomisation (1:1) to 12 or 24 weeks

Week 24, response-guided therapy (RGT)
Patients with ETS randomised 1:1 to stop treatment or continue PR to week 48
Patients who did not achieve ETS continue PR to week 48
ETS = early treatment success (HCV RNA <25 IU/mL at week 4 and undetectable at week 8)

aNumber randomised.
ART, antiretroviral therapy; FDV, faldaprevir; PR, pegylated interferon α-2a and ribavirin; QD, once daily; SVR12, sustained virological response (HCV RNA <25 IU/mL, not detected) 12 weeks after the planned end of treatment.

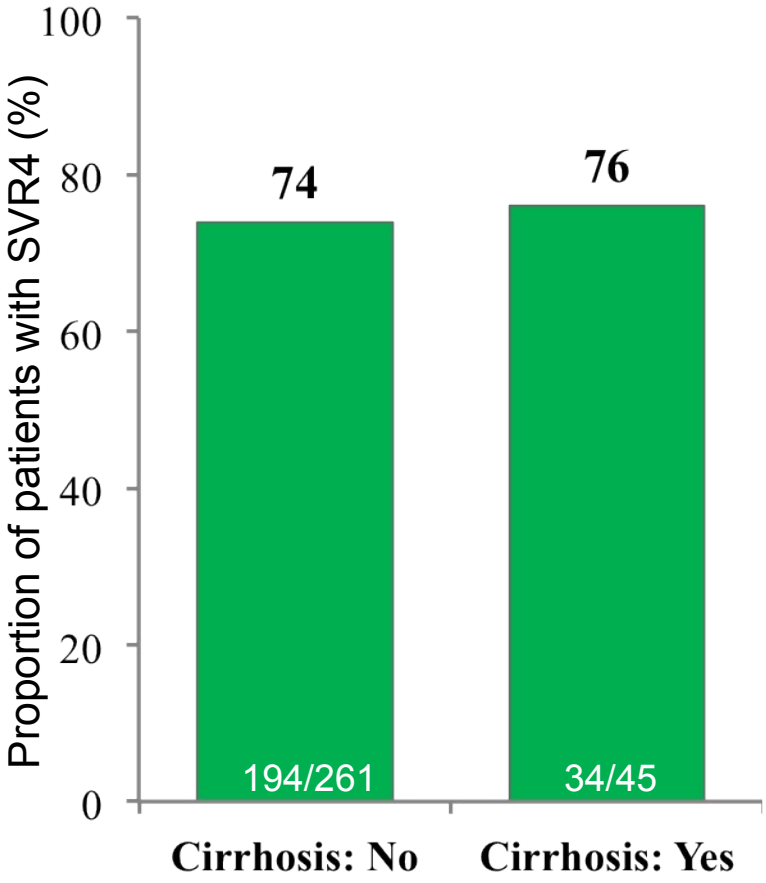
SVR4 overall population

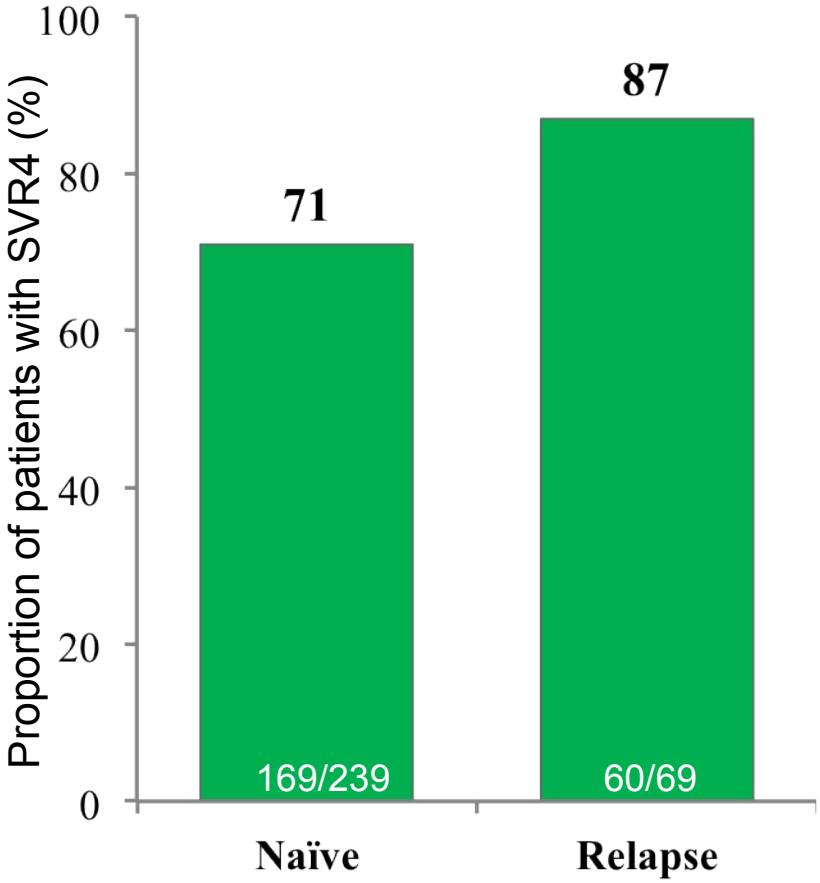


[a]Includes additional patients from 240 mg treatment group who discontinued prior to week 12.

SVR4 by cirrhosis and previous PR treatment

Total population





Daclatasvir (BMS-052)

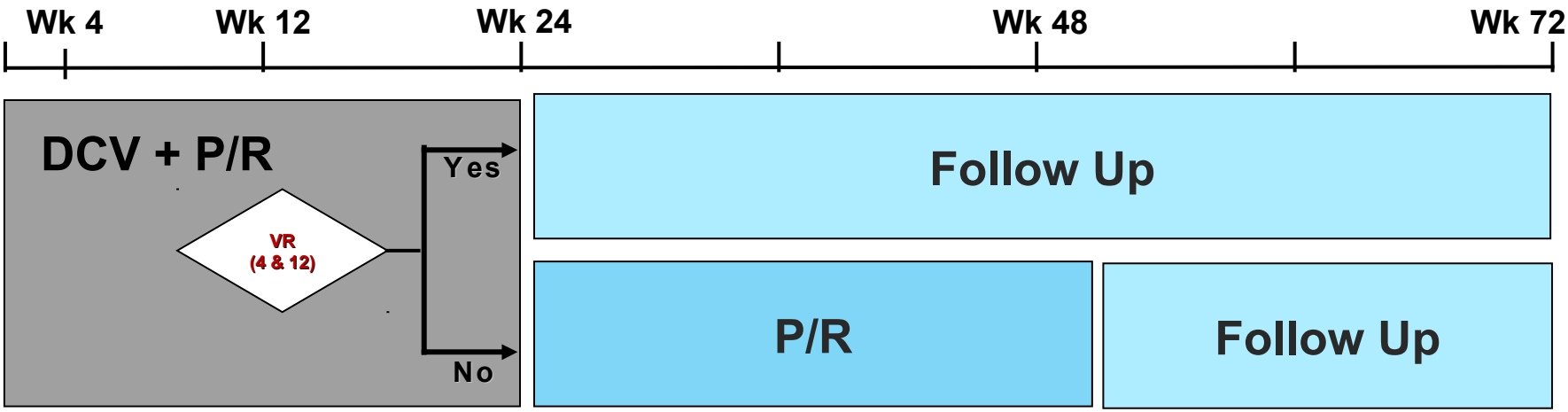
- NS5a inhibitor currently under investigation as part of a QD (60 mg) STR regimen
- Dosing recommendations from ongoing clinical trials (specific data not public):
  - PI regimens: dose reduction → 30 mg QD
    - ATZ/r
  - NNRTIs: increase dose → 90 mg QD
    - Efavirenz
  - NRTIs: no dose adjustment → 60 mg QD
    - TDF
- Birth Control: Oral contraceptive efficacy is likely to be maintained when combined with estrogen/progestin-containing OCP
- Hepatic impairment: dosing adjustments are not anticipated

http://clinicaltrials.gov. Accessed June 25, 2012

Bifano M, et al. AASLD 2011, abstracts 1340 and 1362

Bifano M, et al. CROI 2012, abstract 618

COMMAND-HIV (AI444-043) BMS790052: Study Design & Duration



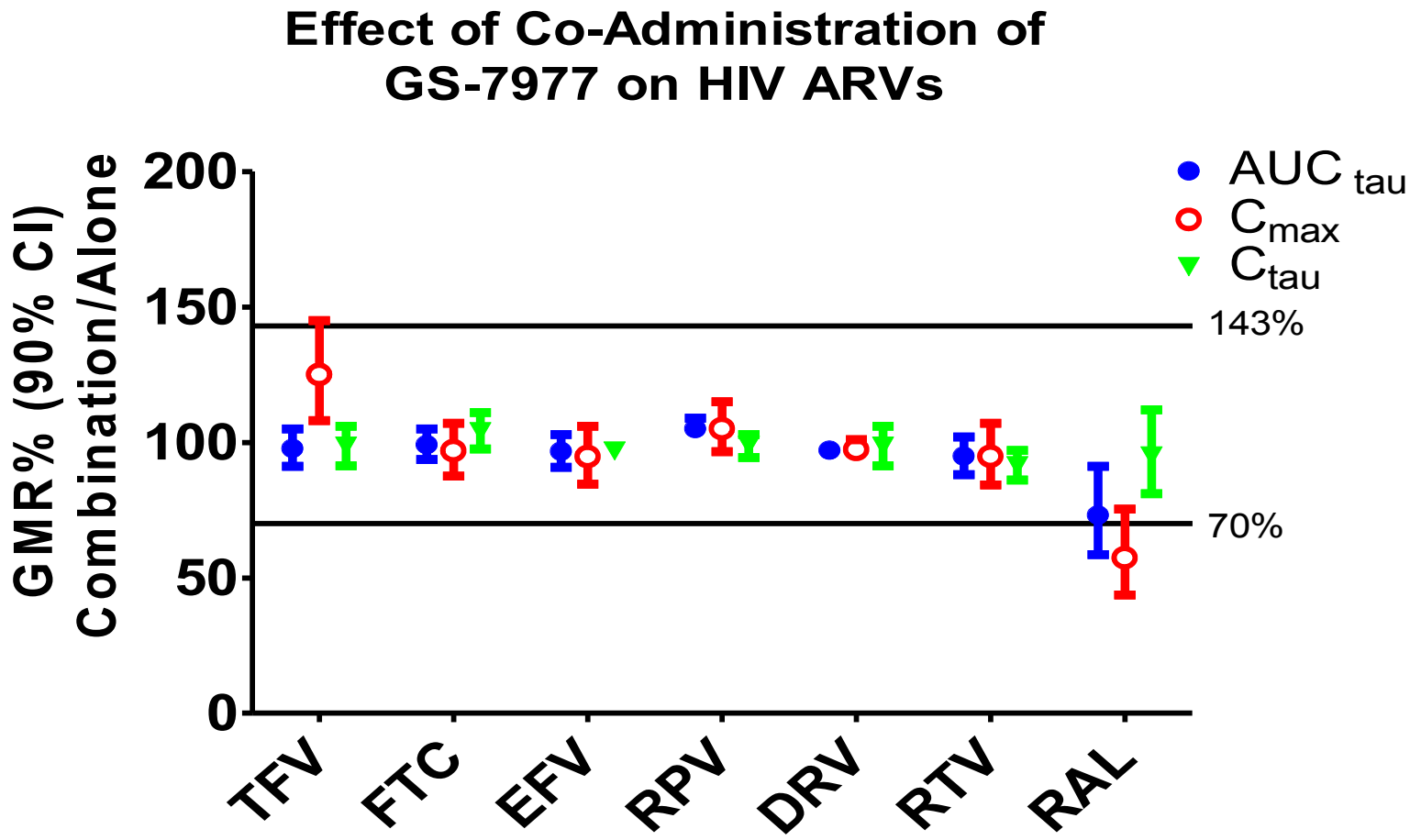
Response Guided Treatment (RGT)

- **Subjects who achieve Virologic Response (VR) at Wks 4 and 12 will complete 24 weeks of triple therapy**
  - **48 weeks follow up after treatment**
- **Subjects not achieving VR at Wks 4 and 12 will receive 48 weeks total duration of therapy (additional 24 weeks P/R)**
  - **24 weeks follow up after treatment**

Therefore, the maximum duration of study for any subject completing treatment will be 72w

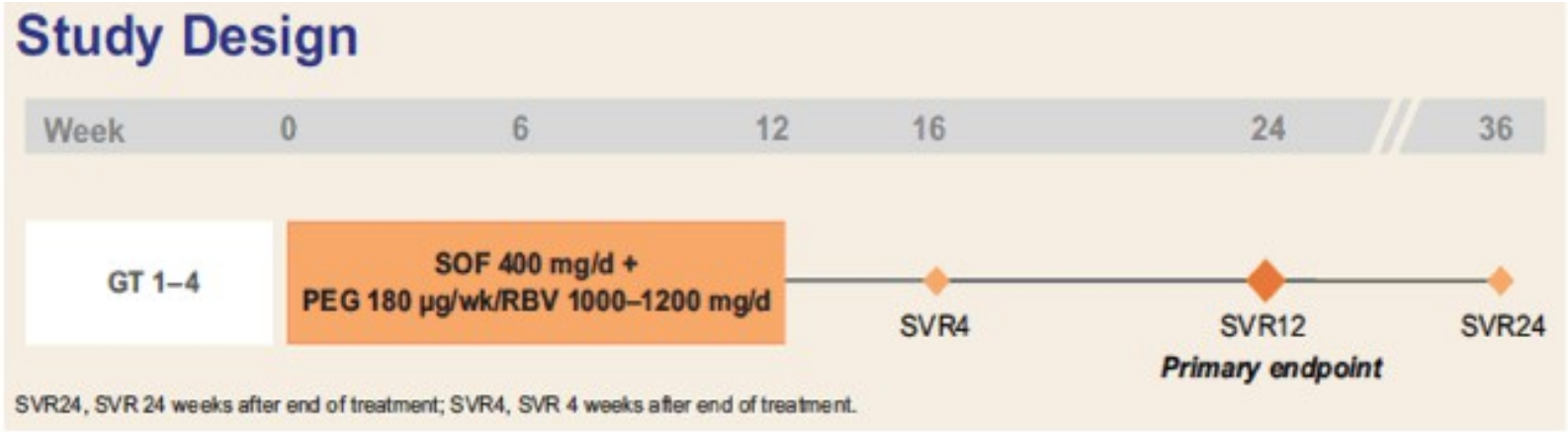
http://clinicaltrials.gov/ct2/show/NCT01471574

Drug Interactions with GS-7977 and HIV Antiretrovirals in Healthy Volunteers



Kirby B, et al. AASLD 2012; Boston. #1877.

Sofosbuvir and Peginterferon Alfa-2a/Ribavirin for Treatment-Naïve Genotype 1-4 HCV-Infected Patients Who Are Coinfected With HIV

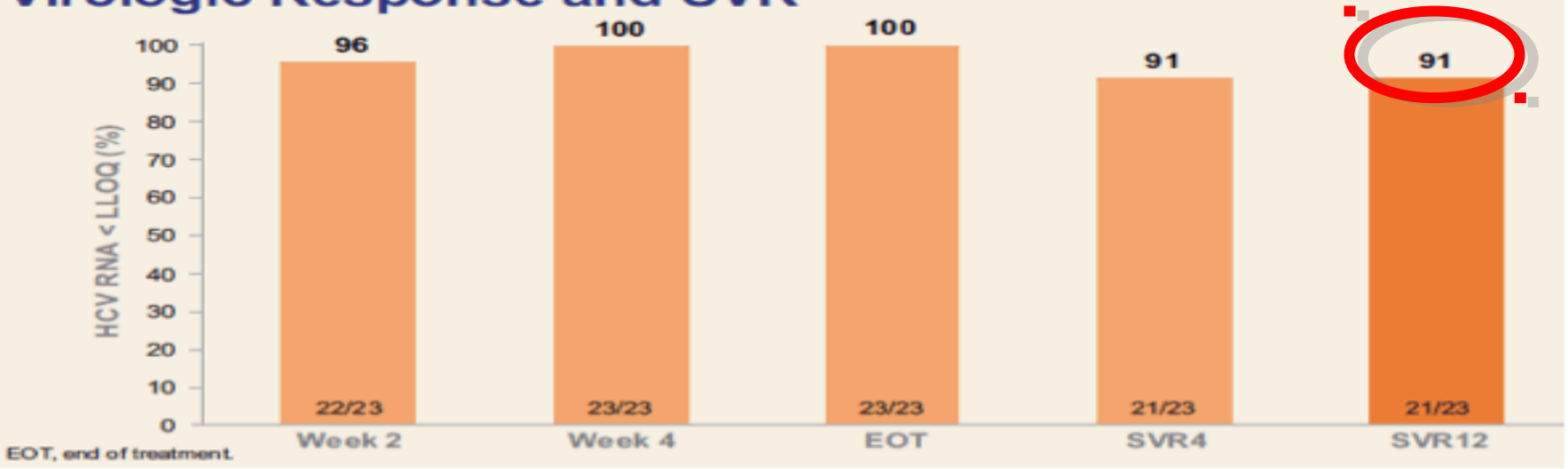


Results

Maribel Rodriguez-Torres,1 Jose Rodriguez-Orengo,2 Anuj Gaggar,3 Gong Shen,3 Bill Symonds,3 John McHutchison,3 Milagros Gonzalez1 IDWeek 2013, October 2-6, 2013, San Francisco, CA

Efficacy

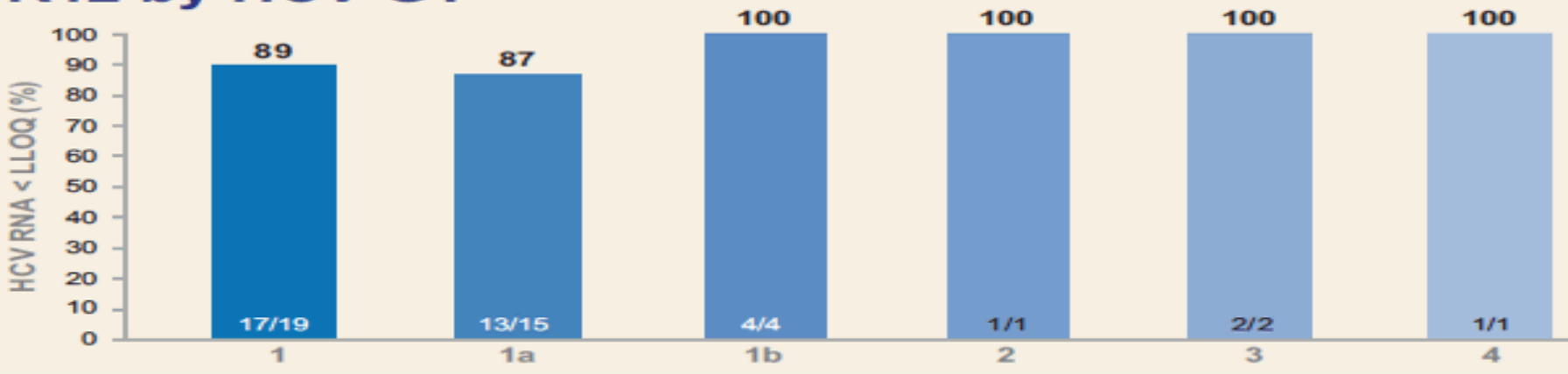
Virologic Response and SVR



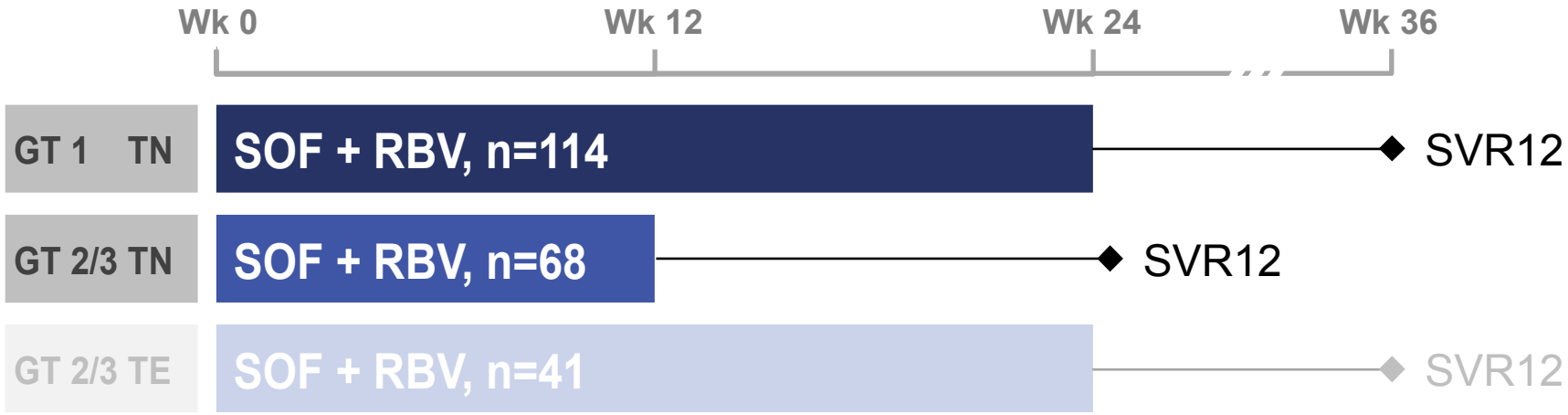
EOT, end of treatment

- No on-treatment HCV virologic breakthrough
- 2 patients did not achieve SVR12:
  - Patient 1: white Latino man aged 41 years with HCV GT 1a and IL28B TT GT, who discontinued treatment after 6 weeks due to withdrawal of consent
  - Patient 2: white Latino man aged 53 years with HCV GT 1a and IL28B CT GT, who completed study treatment and subsequently relapsed

SVR12 by HCV GT

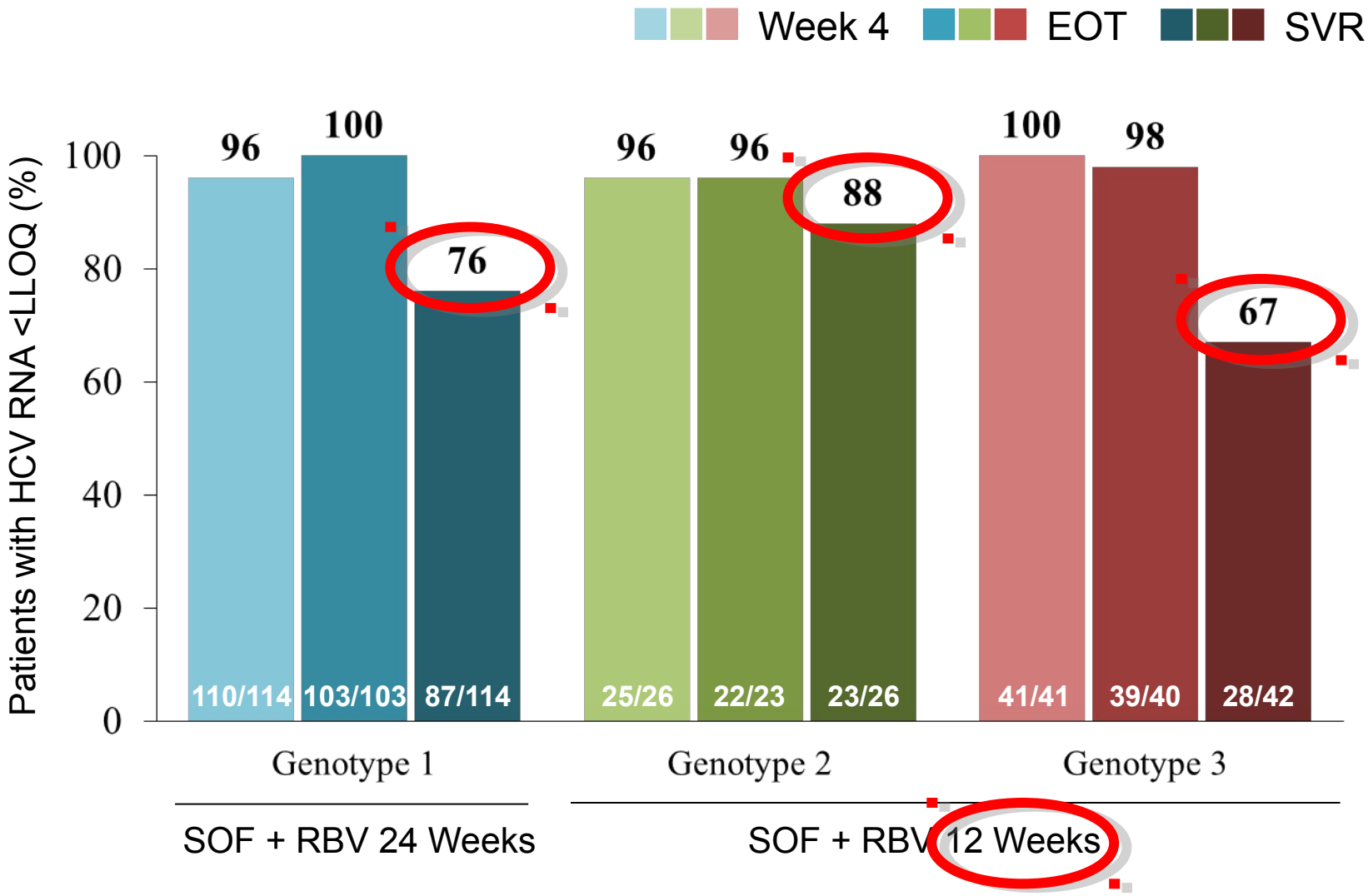


PHOTON Study Design



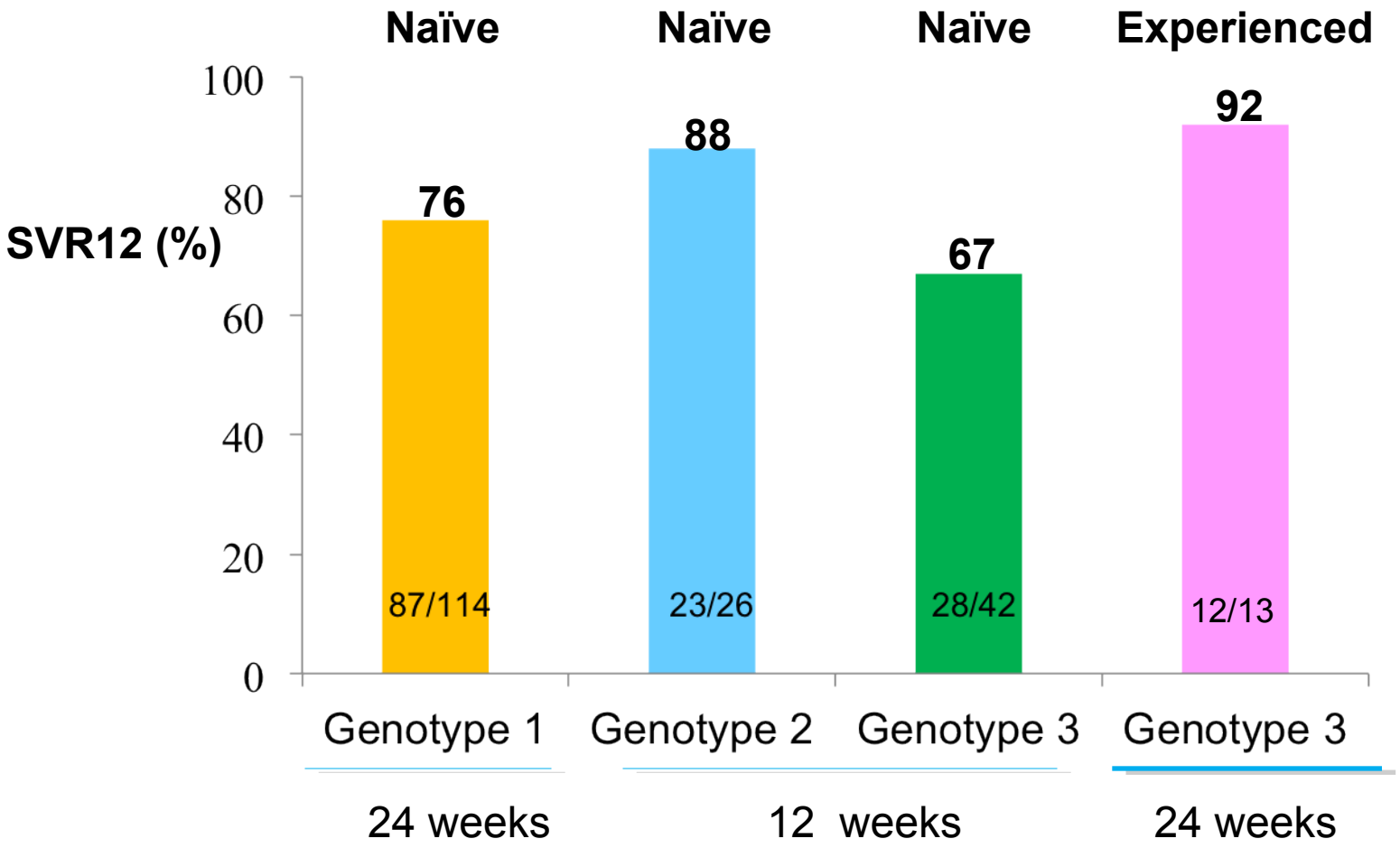
- Broad inclusion criteria
  - Cirrhosis permitted with no platelet cutoff
  - Hemoglobin: ≥12 mg/dL (males); ≥11 mg/dL (females)
- Wide range of ART regimens allowed
  - Undetectable HIV RNA for >8 weeks on stable ART regimen
- Baseline CD4 count
  - ART treated: CD4 T-cell count >200 cells/mm^3 and HIV RNA < 50 c/mL
  - ART untreated: CD4 T-cell count >500 cells/mm^3

On-treatment and Sustained Virologic Response



SOF + RBV in HIV-Coinfected Patients

PHOTON: G1, Treatment Naïve, 7% Cirrhotic



Discontinuation for AEs, n=6

SOFOSBUVIR LABEL

----------INDICATIONS AND USAGE----------

SOVALDI is a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor indicated for the treatment of chronic hepatitis C (CHC) infection as a component of a combination antiviral treatment regimen. (1)

- SOVALDI efficacy has been established in subjects with HCV genotype 1, 2, 3 or 4 infection, including those with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation) and those with HCV/HIV-1 co-infection. (1)

----------DOSAGE AND ADMINISTRATION----------

- One 400 mg tablet taken once daily with or without food. (2.1)
- Should be used in combination with ribavirin or in combination with pegylated interferon and ribavirin for the treatment of CHC. Recommended combination therapy: (2.1)

HCV Mono-infected and HCV/HIV-1 Co-infected	Treatment	Duration
Genotype 1 or 4	SOVALDI + peg-interferon alfa + ribavirin	12 weeks
Genotype 2	SOVALDI + ribavirin	12 weeks
Genotype 3	SOVALDI + ribavirin	24 weeks

- SOVALDI in combination with ribavirin for 24 weeks can be considered for CHC patients with genotype 1 infection who are interferon ineligible. (2.1)
- Should be used in combination with ribavirin for treatment of CHC in patients with hepatocellular carcinoma awaiting liver transplantation for up to 48 weeks or until liver transplantation, whichever occurs first. (2.1)
- A dose recommendation cannot be made for patients with severe renal impairment or end stage renal disease. (2.4, 8.6)

SOFOSBUVIR LABEL

----------DRUG INTERACTIONS----------

Drugs that are potent intestinal P-gp inducers (e.g., rifampin, St. John's wort) may alter the concentrations of sofosbuvir. Consult the full prescribing information prior to use for potential drug-drug interactions. (5.2, 7, 12.3)

----------USE IN SPECIFIC POPULATIONS----------

- Patients with HCV/HIV-1 co-infection: Safety and efficacy have been studied. (8.8, 14.4)
- Patients with hepatocellular carcinoma awaiting liver transplantation: Safety and efficacy have been studied. (8.9)

DAA's in HIV

- TVR and BOC doing phase III trials for label
- Simeprevir (TMC 435) SVR 12

- Faldaprevir (BI1335) SVR 12

- Daclatasvir accrued rapidly
  -Fewer DDI issues
  combined with Peg RBV
  New study with SOF in HIV

  - SOF with and without ribavirin is promising
  - Sofosbuvir/ledipasvir FDC combination trial to open soon (ION4)
  - SVR 12 's and adverse events are virtually identical to HCV monoinfected patients