Interferon-based therapies with second generation antivirals in 2015

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Disclosures

- None to disclose

Why is this topic important in 2015?

- All oral (interferon-free) therapies may not be available in some areas of the world
- Due to cost constraints, a case has been proposed for highly effective IFN-based therapies in certain situations (e.g. GT-1, low viral load, *IL28b* CC)

Comparison

IFN-based

- Gt-1 SVR rates: ~85%
- *IL28b* dependent
- Lower SVR in Tx-experienced and other populations (HIV, etc)
- Markedly lower SVR in cirrhosis
- Requires RBV
- High toxicity and intolerability

IFN-free

- Gt-1 SVR rates: ~ 97%
- *IL28b* independent
- Similar SVR in Tx-experienced and other populations (HIV, etc)
- Minimally lower SVR in cirrhosis
- RBV may be optional
- Low toxicity and good tolerability

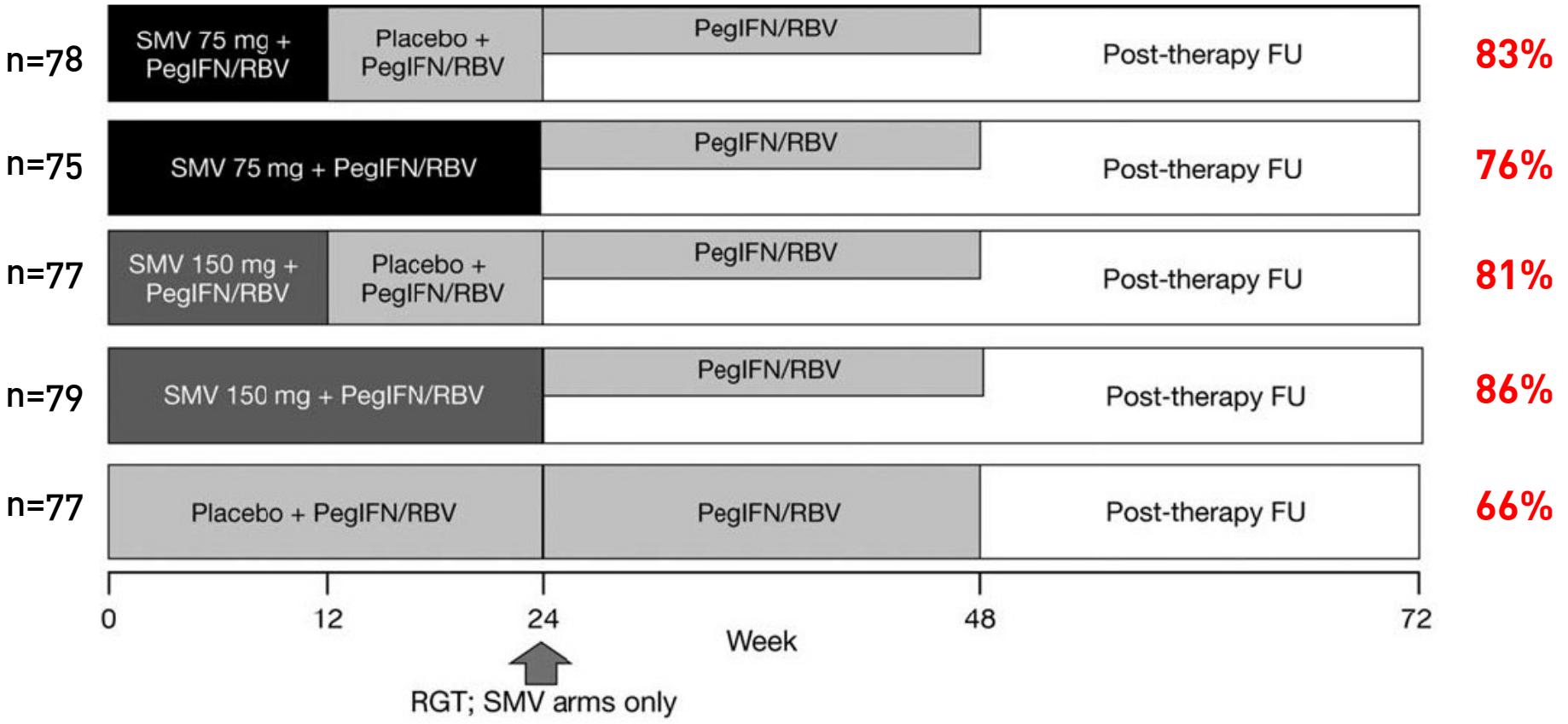
Outline

- PEG/RBV backbone + DAA
  - Protease inhibitors (Simeprevir)
  - NS5A inhibitors (Daclatasvir)
  - NS5B nuc inhibitors (Sofosbuvir)
  - QUAD therapy
  - Real life HCV TARGET data
- Will not discuss first generation protease inhibitors: telaprevir or boceprevir

Simeprevir + P/R

PILLAR trial

Phase IIb, double-blind, placebo-controlled trial of the efficacy and safety of two different simeprevir (SMV) doses administered once-daily (QD) with pegylated interferon (Peg-IFN)-α-2a and ribavirin (RBV) in treatment-naive patients with HCV genotype 1 infection



Fried, et al*: HEPATOLOGY* 2013;58:1918-1929

Safety and Efficacy of Simeprevir QD + PR in GT1 Treatment-Naive Pts

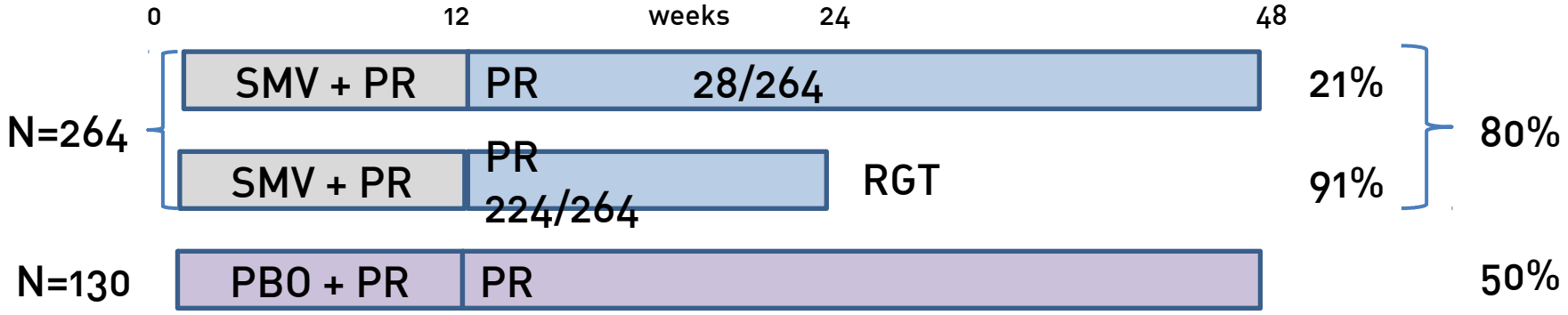
Safety Outcome, %	All SMV Arms (n = 309)	Placebo + PR 48W (n = 77)
Study tx permanently discontinued for AE	3.6	5.2
Grade 3/4 AE	32.0	35.1
Serious AE	6.5	13.0
Most frequent AEs in TMC435-treated pts		
• Fatigue	42.4	48.1
• Flu-like illness	31.7	37.7
• Pruritus	31.1	45.5
• Headache	46.0	51.9
Other AEs of interest		
• Rash	21.0	23.4
• Anemia	20.4	20.8
• Neutropenia	24.3	20.8

Fried MW, et al. AASLD 2011. Abstract LB-5

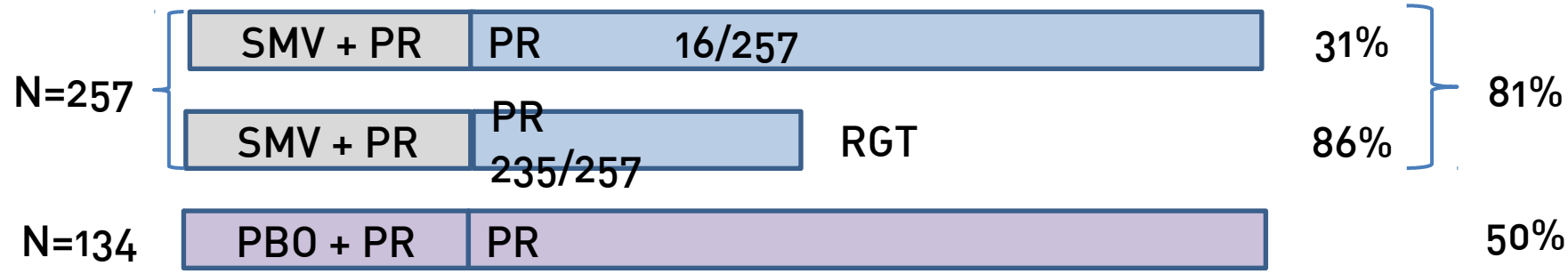
QUEST 1 and 2 trials

QUEST 1: multicenter, phase III, genotype 1, treatment-naïve

SVR



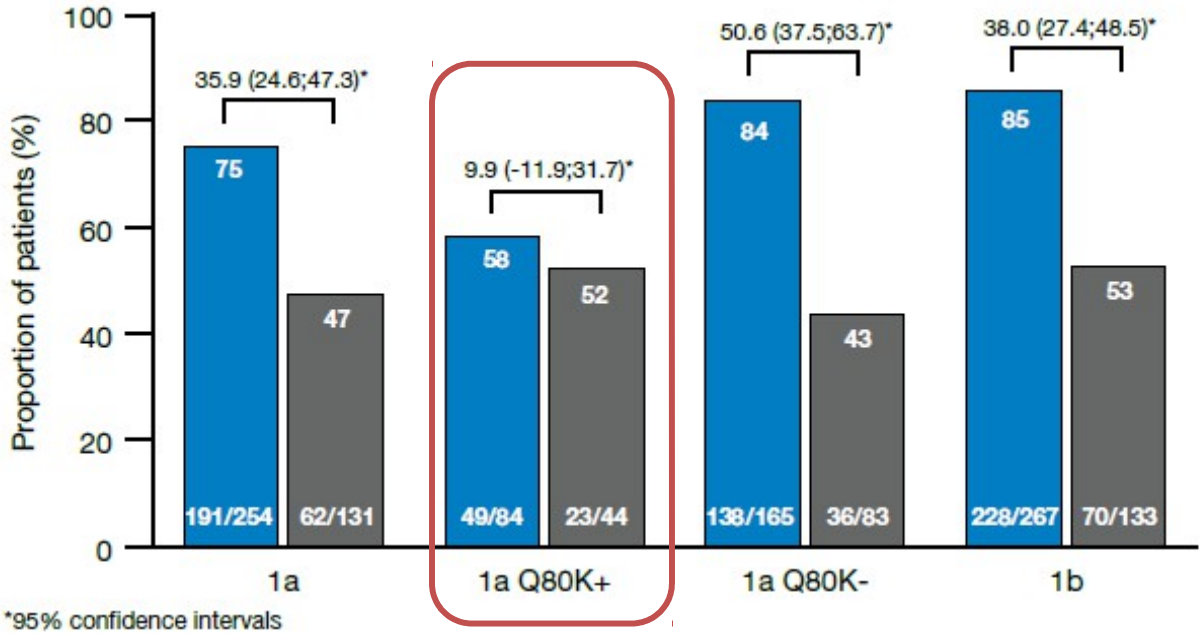
QUEST 2: multicenter, phase III, genotype 1, treatment-naïve
(Peg-α2a vs Peg-α2b)



Lancet, June 4, 2014

Simeprevir plus PR for treatment-naïve patients with genotype 1 infection

- **Quest 1 and 2 trials**: GT 1, treatment naïve patients (n=785)



SMV+PEG/RBV
Placebo+PEG/RBV

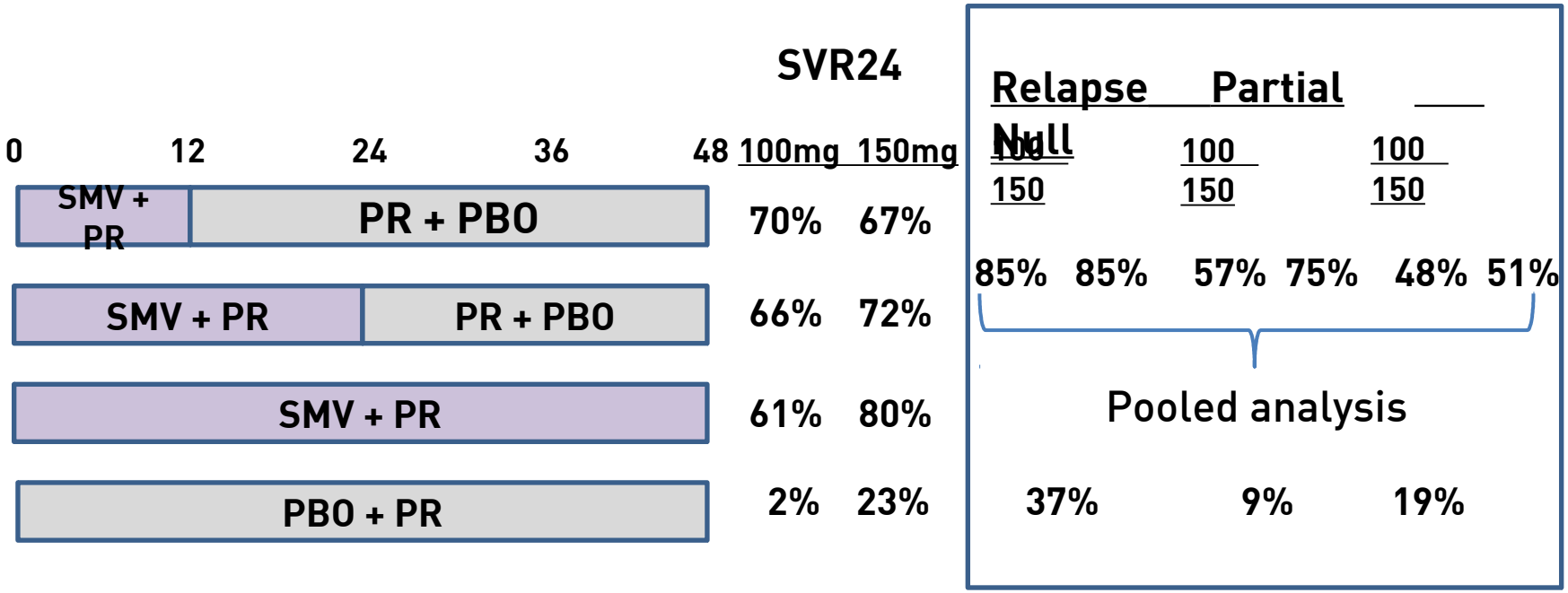
- Q80K prevalence in 1500 clinical specimens sent to an US commercial lab‡
  - **GT 1a, 32.5%**
  - GT 1b, 0.1%

Jacobson IM et al. The Liver Meeting 2013; Abstract 1122; FDA AVDAC 10.24.2013*; Choe SS et al The Liver Meeting Abstract 1500‡

ASPIRE:
SMV+PR in treatment-experienced HCV geno-1

ASPIRE: Phase IIb, multicenter trial of SMV+PR for 462 HCV genotype 1 pts who failed P/R

- 2 doses of SMV were tested: 100 mg and 150 mg once daily **SVR24**

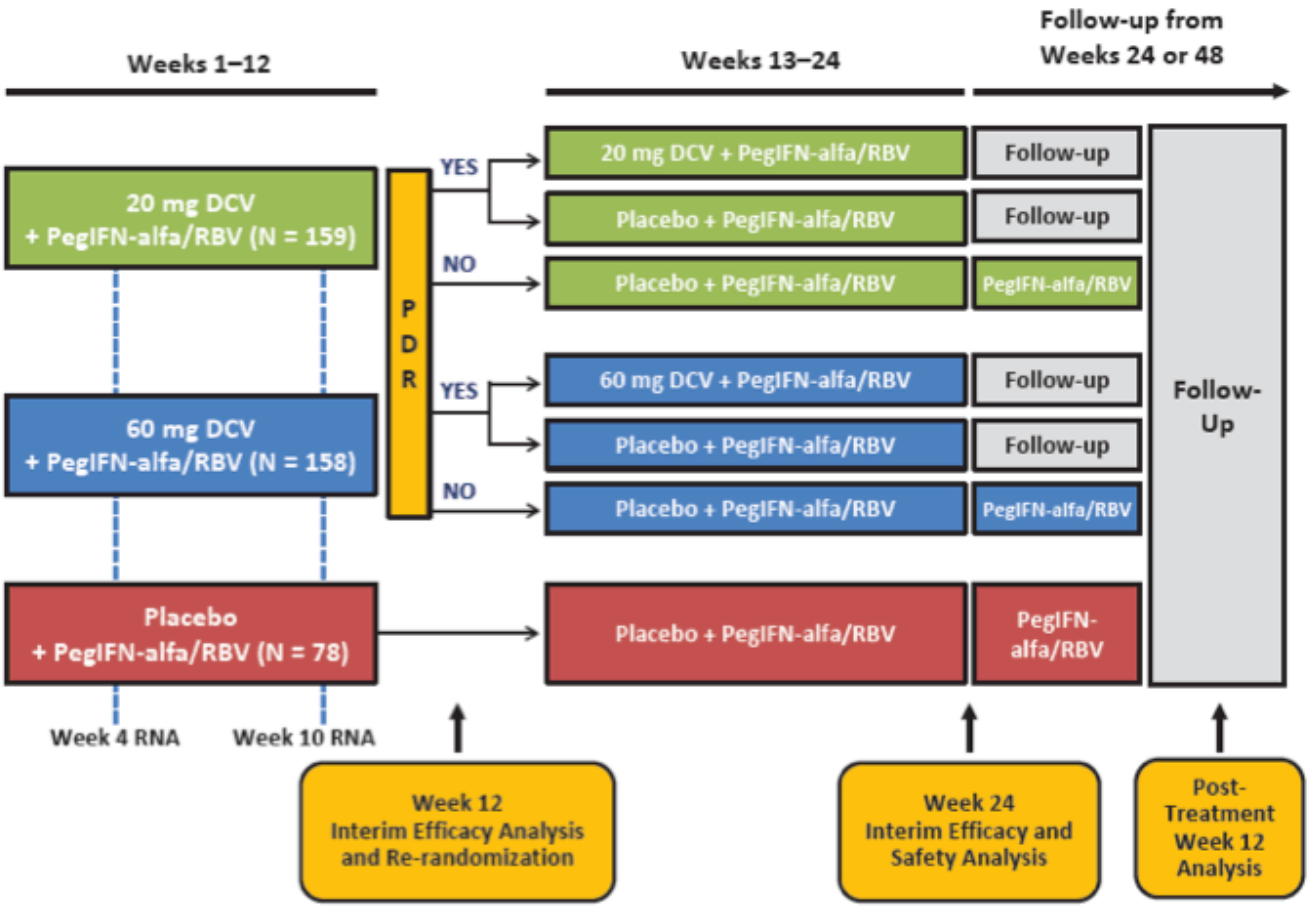


Zeuzem: *Gastroenterology* 2014;146:430–441

Daclatasvir + P/R

COMMAND-1: DCV + P/R

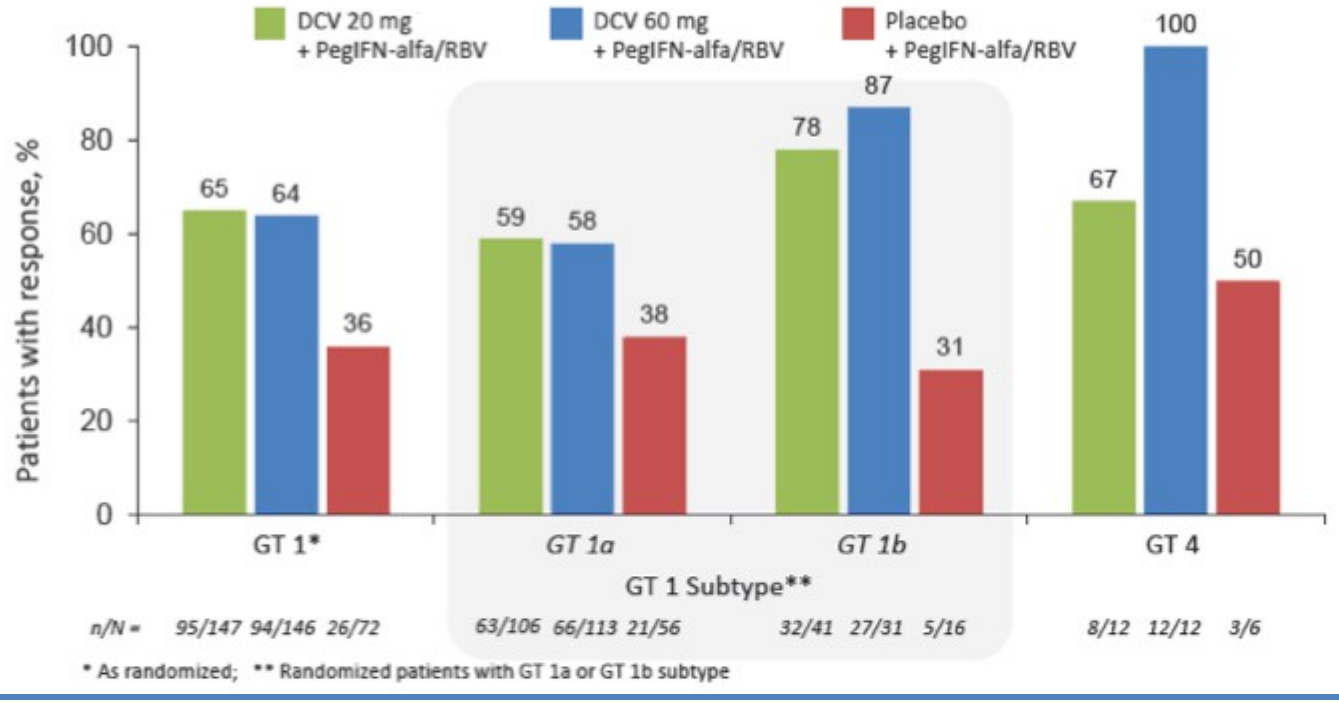
Figure 1. COMMAND-1 Study Design



PDR, protocol-defined response: HCV RNA < LLOQ (25 IU/mL) at week 4 and undetectable (< 10 IU/mL) at week 10.

COMMAND-1: Results

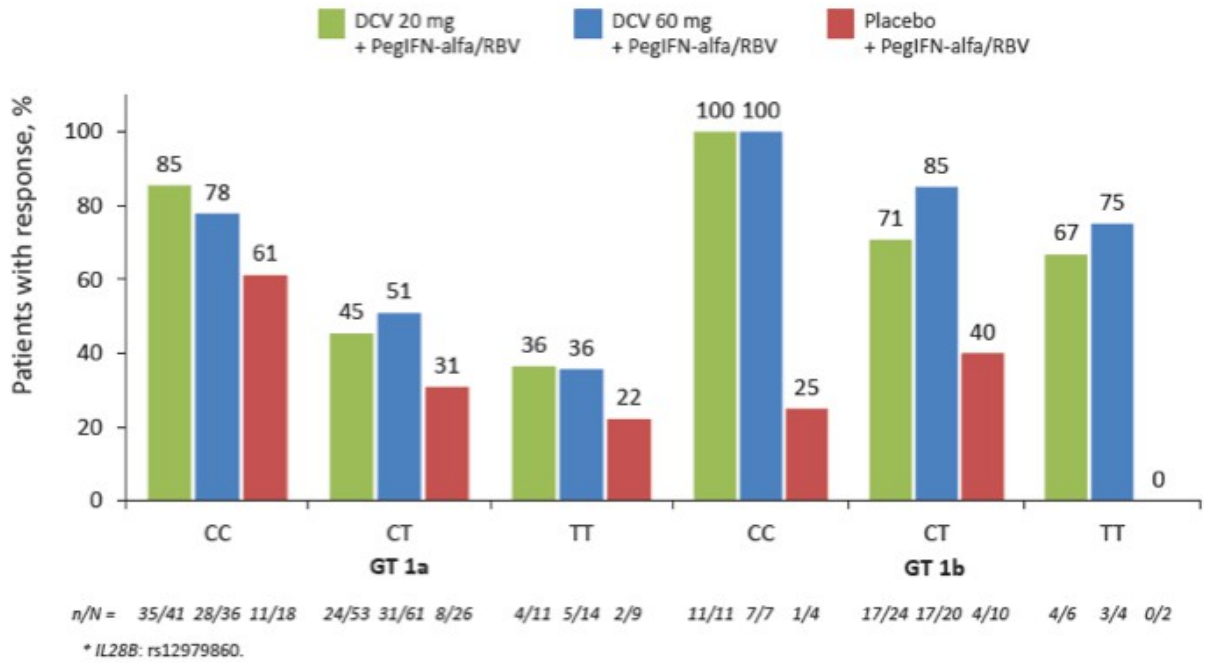
Figure 2. Virologic Response (SVR_{12}) by Genotype



* As randomized; ** Randomized patients with GT 1a or GT 1b subtype

COMMAND-1

Figure 4. SVR_{12} in Genotype 1 Patients by *IL28B Genotype**

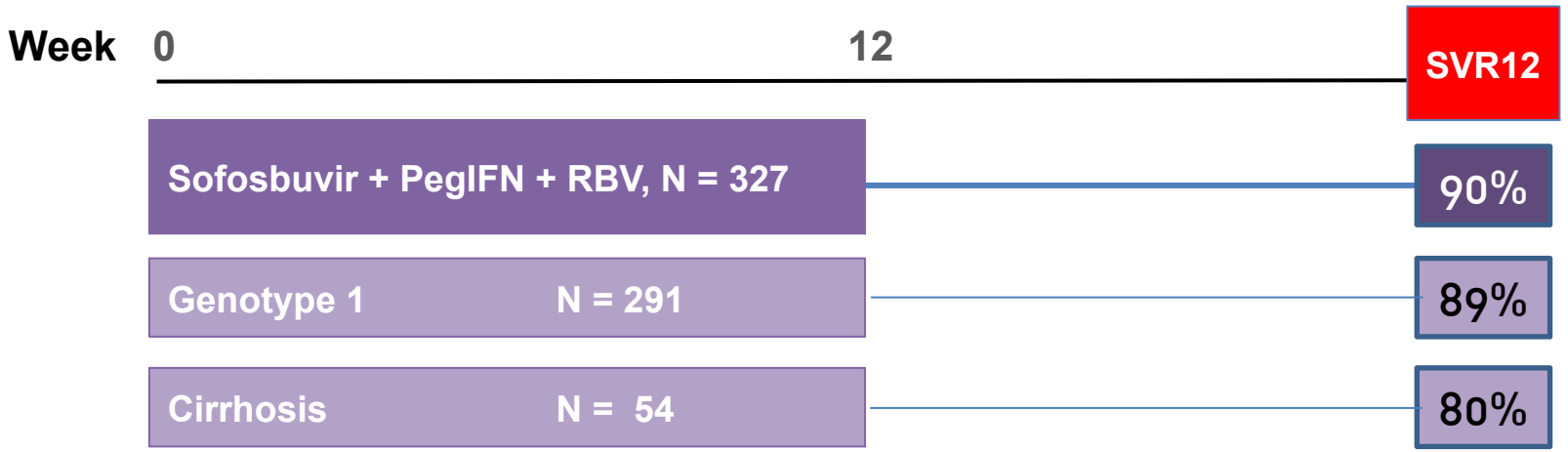


* *IL28B*: rs12979860.

- Both GT 1a and 1b patients treated with DCV + pegIFN-alfa/RBV had higher SVR_{12} rates than pegIFN-alfa/RBV control for all *IL28B* genotypes (CC, CT, or TT)
- For both GT 1a and 1b patients, SVR_{12} was generally higher among those with *IL28B* genotype CC compared with CT or TT
- For patients receiving DCV
  - GT 1b patients had higher SVR_{12} rates than GT 1a patients across all *IL28B* genotypes
  - GT 1a patients with the *IL28B* genotype CC achieved SVR_{12} rates comparable to GT 1b patients with *IL28B* genotypes CT or TT

Sofosbuvir + P/R

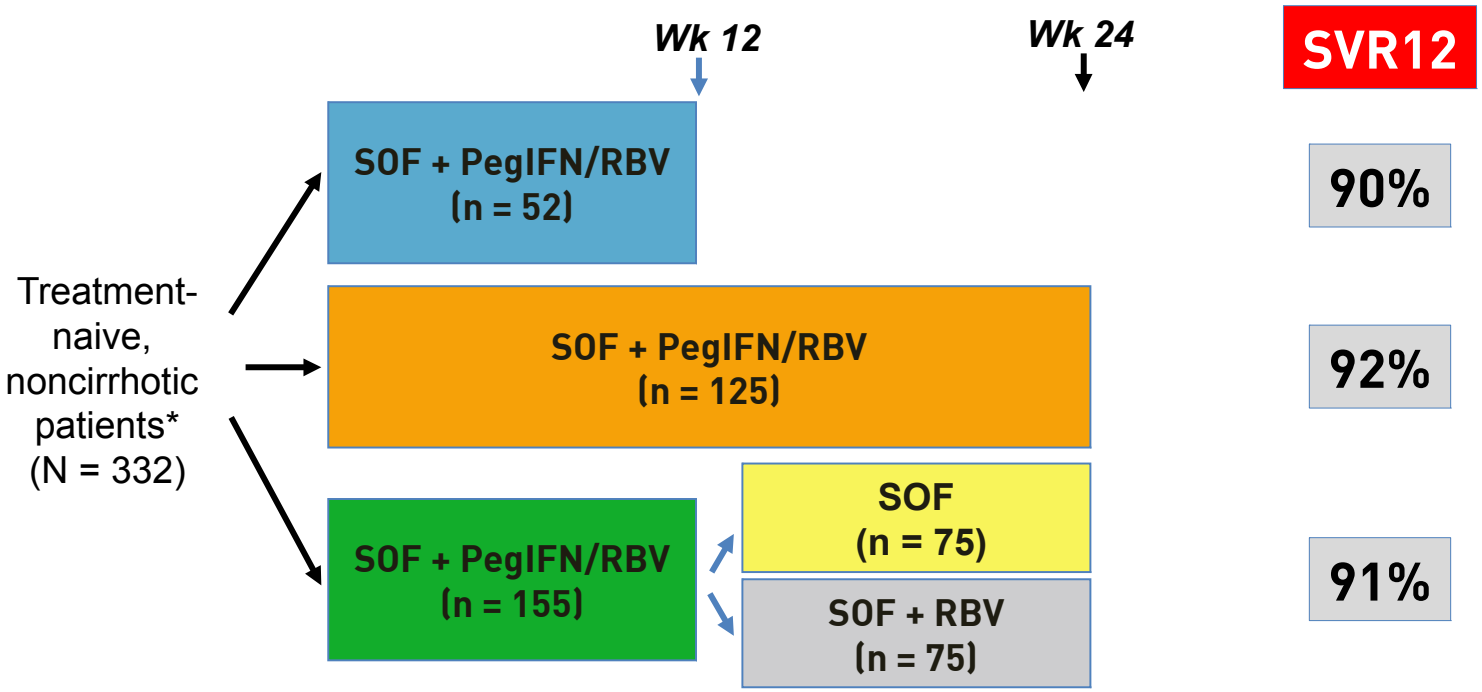
NEUTRINO: Sofosbuvir + PEG + RBV:



- Open label
  - Sofosbuvir 400 mg QD + PegIFN-2a 180 µg/week + RBV 1000–1200 mg/day for 12 weeks (no response-guided therapy)
- Treatment-naive, genotype 1, 4, 5, and 6 HCV-infected patients
  - 89% of patients had genotype 1 HCV
  - 17% of patients with cirrhosis

Lawitz E, et al. N Engl J Med. 2013;368:1878-1887.

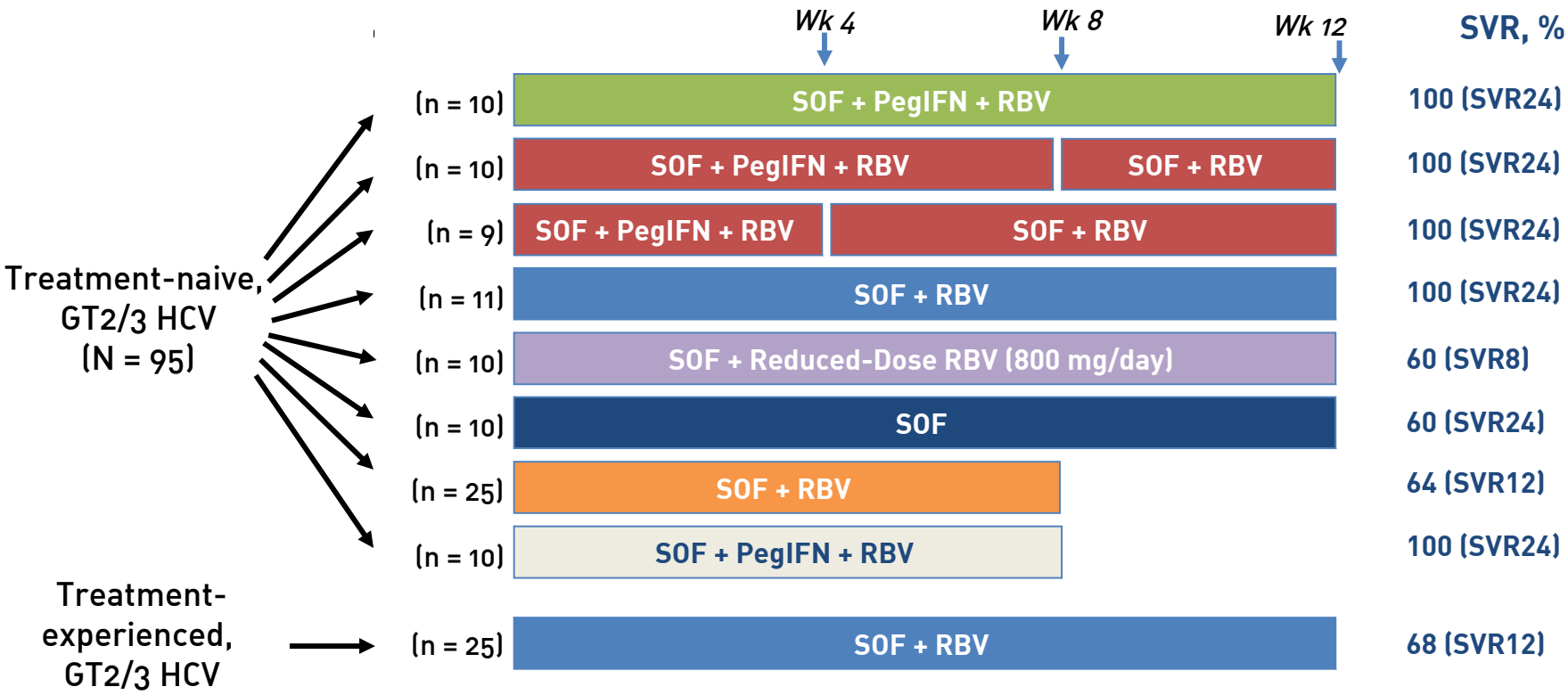
ATOMIC: Sofosbuvir Plus PR in Treatment-Naive Genotype 1 Patients



*All infected with GT1 HCV, except for 11 patients with GT4 HCV and 5 with GT6 HCV in 24-wk arm of SOF + pegIFN/RBV.

Hassanein T, et al. AASLD 2012. Abstract 230.

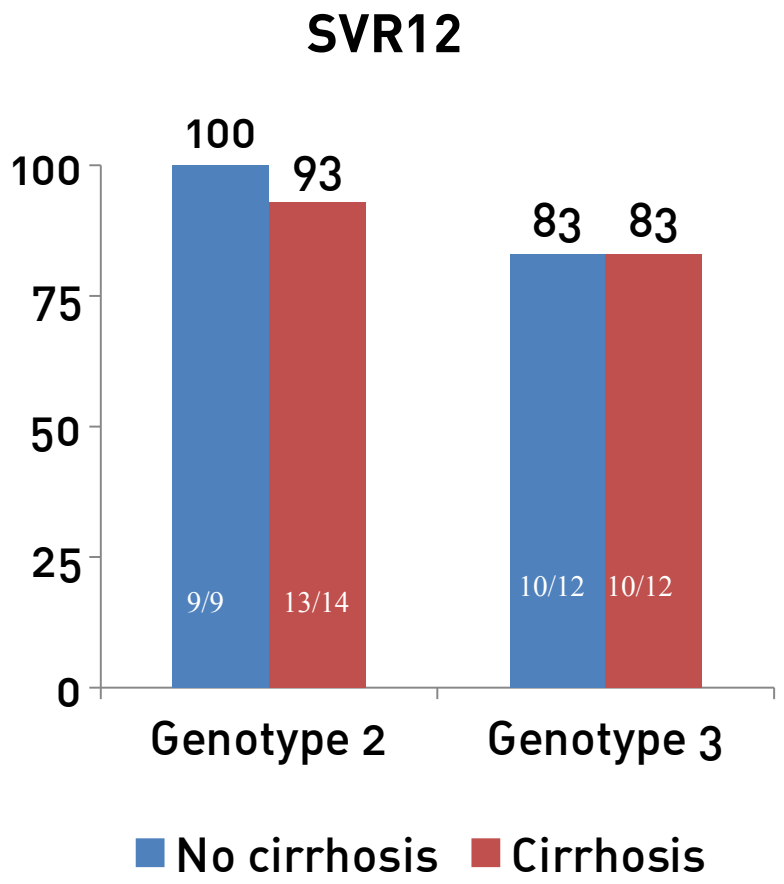
ELECTRON: Sofosbuvir in Patients With GT2/3 HCV



Gane EJ, et al. AASLD 2012. Abstract 229. Reproduced with permission.

LONESTAR-2: Sofosbuvir plus PegIFN/RBV for 12 weeks in treatment experienced patients with Genotype 2 or 3:

- 47 patients with GT 2 (n=23) or GT 3 (n=24)
  - Cirrhosis, n=26 (55%)
  - Prior relapse, 85%
- Single arm, open label SOF 400 mg QD + PegIFN/RBV for 12 weeks
- Non-SVR patients
  - GT 2: Discontinued with quantifiable HCV RNA, n=1
  - GT 3: Lost to follow-up (n=2) Relapse, n=2
- AEs were consistent with PegIFN/RBV



Lawitz E et al. The Liver Meeting 2013; Abstract LB-4

Real world experience: HCV TARGET

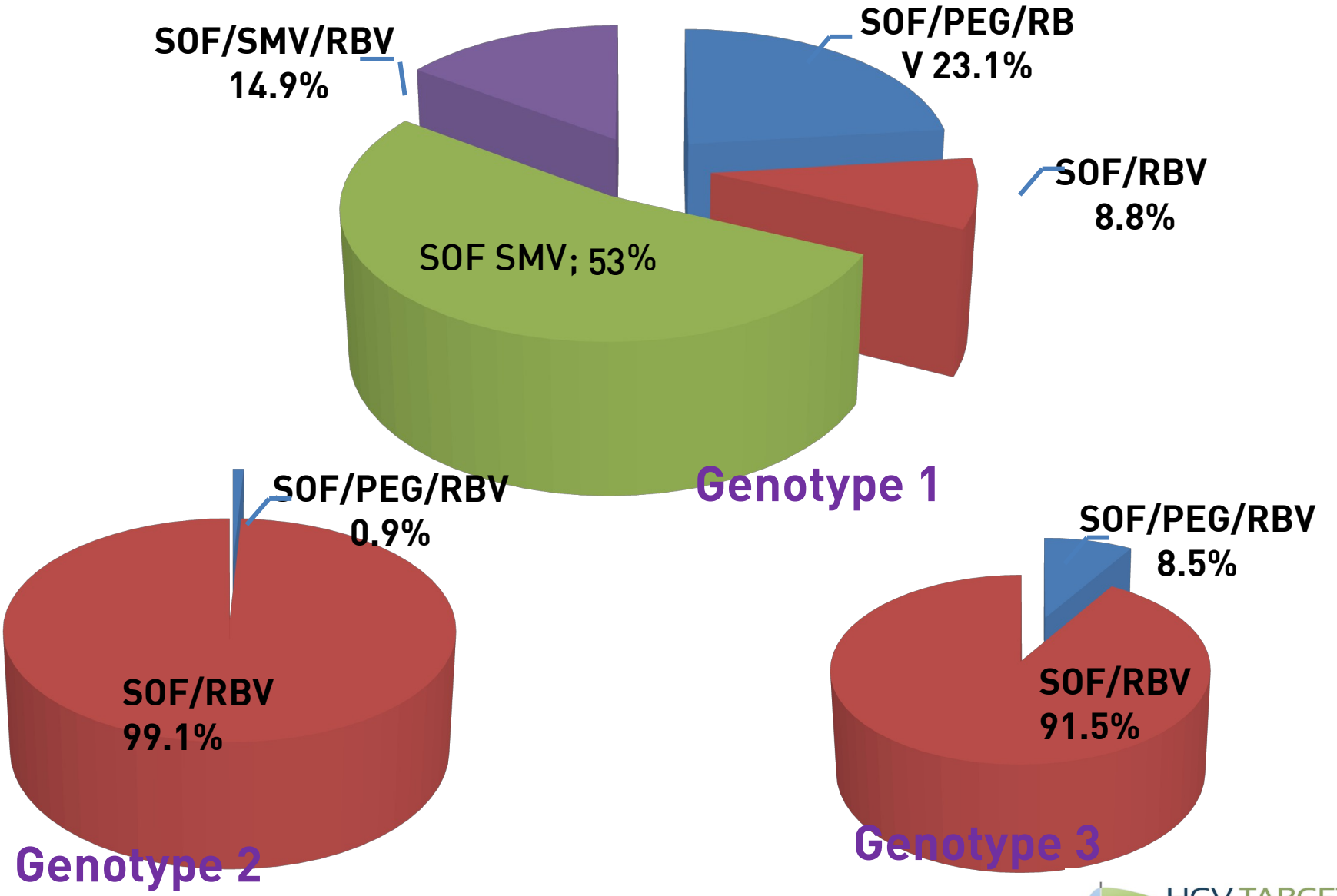
Demographics

	SOF PEG RBV	SOF RBV	SOF SMV	SOF SMV RBV	Total*
n(%)	N=384	N=667	N=784	N=228	N=2063
MALE	253(66.2)	422 (63.6)	478 (62.0)	147 (65.3)	1300 (63.7)
MEAN Age, y (range)	53.9 (23 - 79)	56.9 (21 - 82)	59.5 (20 - 83)	58.8 (29 - 80)	57.6 (20 - 83)
Age 65+	31 (8.1)	131 (19.7)	190 (24.6)	40 (17.8)	392 (19.2)
CAUCASIAN	270 (70.3)	539 (80.8)	584 (74.5)	177 (77.6)	1570 (76.1)
BLACK	68 (17.8)	37 (5.6)	96 (12.5)	33 (14.7)	234 (11.5)
TREATMENT STATUS					
NAIVE	211 (54.9)	371 (55.6)	318 (40.6)	82 (36.0)	982 (47.6)
EXPERIENCED	172 (44.8)	296 (44.4)	465 (59.3)	144 (63.2)	1077 (52.2)
PI FAILURE	47 (27.3)	25 (8.4)	76 (24.8)	45 (31.3)	193 (17.9)
CIRRHOSIS	120 (31.3)	302 (45.3)	440 (56.1)	137 (60.1)	999 (48.4)
Hx Decompensation	12 (11.4)	136 (49.5)	167 (44.8)	60 (50.8)	375 (43.1)
MELD >10	18 (17.1)	120 (43.6)	122 (32.7)	34 (28.8)	294 (33.8)
LIVER CANCER	25 (6.5)	66 (9.9)	88 (11.2)	32 (14.0)	211 (10.2)
LIVER TRANSPLANT	27 (7.0)	57 (8.5)	111 (14.2)	32 (14.0)	227 (11.0)
HIV	14 (3.6)	18 (2.7)	8 (1.0)	7 (3.1)	47 (2.3)

78% (253/323) of G1, non-cirrhotic, naïve had a baseline HCV RNA ←6 million IU/mL

*Total, patients who started therapy

Distribution of HCV Regimens

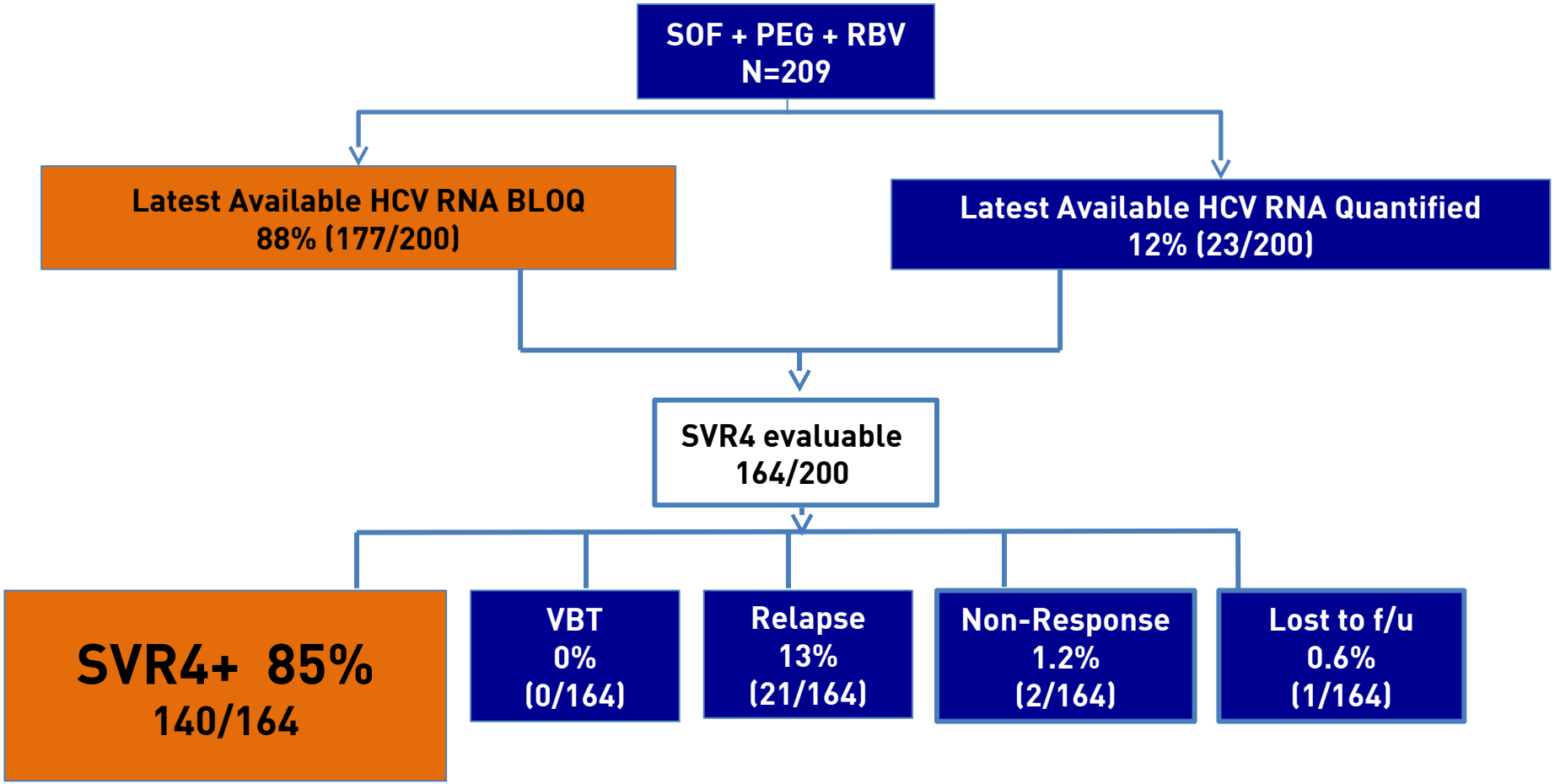


N=1994

HCV-TARGET

SOF Containing Regimen

HCV RNA Outcomes for SOF + PEG+RBV: Genotype 1



Cohort of patients with treatment start on or before 4/15/14

BLOQ=Below Level of Quantitation
VBT= Viral Breakthrough

SVR4+
No cirrhosis: 90% (114/127)
Cirrhosis: 70% (26/37)

Adverse Events (→10%) By Regimen
Impact of PEG and RBV

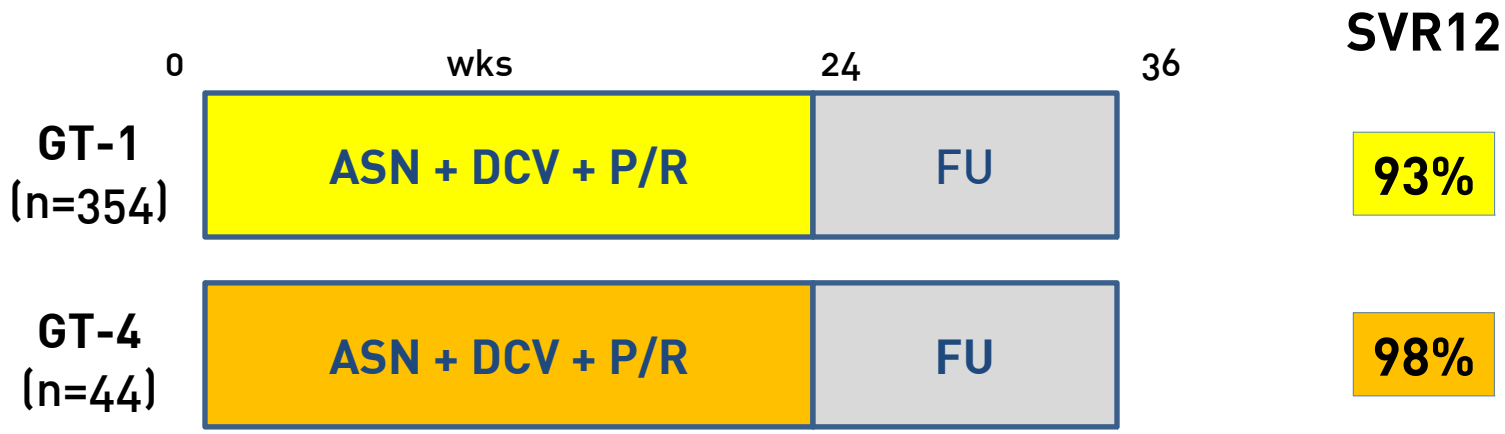
Preferred Term, n(%)	SOF PEG RBV (N=343)	SOF RBV (N=462)	SOF SMV (N=683)	SOF SMV RBV (N=196)	Total* (N=1684)
ANY AE	**306 (89)**	**389 (84)**	**516 (76)**	**173 (88)**	**1384 (82)**
Fatigue	144 (42)	177 (38)	168 (25)	74 (38)	563 (33)
Headache	55 (16)	74 (16)	108 (16)	46 (23)	283 (17)
Nausea	75 (22)	77 (17)	81 (12)	34 (17)	267 (16)
Anemia	95 (28)	98 (21)	7 (1)	58 (30)	258 (15)
Flu like Sx	93 (27)	58 (13)	72 (11)	24 (12)	247 (15)
Insomnia	54 (16)	66 (14)	58 (9)	35 (18)	213 (13)
Rash	62 (18)	50 (11)	57 (8)	28 (14)	197 (12)
Pruritus	34 (9)	39 (8)	56 (8)	28 (14)	157 (9)
Infections (ANY)	29 (9)	40 (9)	56 (8)	20 (10)	145 (9)
Dyspnea	54 (16)	43 (9)	28 (4)	12 (6)	137 (8)
Irritability	55 (16)	32 (7)	19 (3)	15 (8)	121 (7)
Depression	33 (10)	27 (6)	16 (2)	13 (7)	89 (5)

*Tot

hens

Quad Therapy

HALLMARK QUAD: ASN + DCV + P/R: Prior partial or null P/R responders



Subgroups:	Cirrhosis	Partial	GT-1a	GT-1b	*IL28b* TT	Null
GT-1	90%	87%	99%	94%	94%	92%
GT-4	95%	NA	NA	100%	97%	100%

Jensen, et al: *J Hepatol* 2014 (in press)

Is there any role for IFN-based therapies for HCV in the future?

- Not much, but *potentially* if:
  - High SVR rates achieved ↑90%
  - Treatment duration could be ↓12 weeks
  - Lower dose PEG possible (?)
  - Minimize or eliminate RBV
  - Significantly lower cost/SVR

The End