Evolution of HCV Therapy in the Era of Direct Acting Antivirals

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HEPATITIS C TREATMENT EXPANSION INITIATIVE
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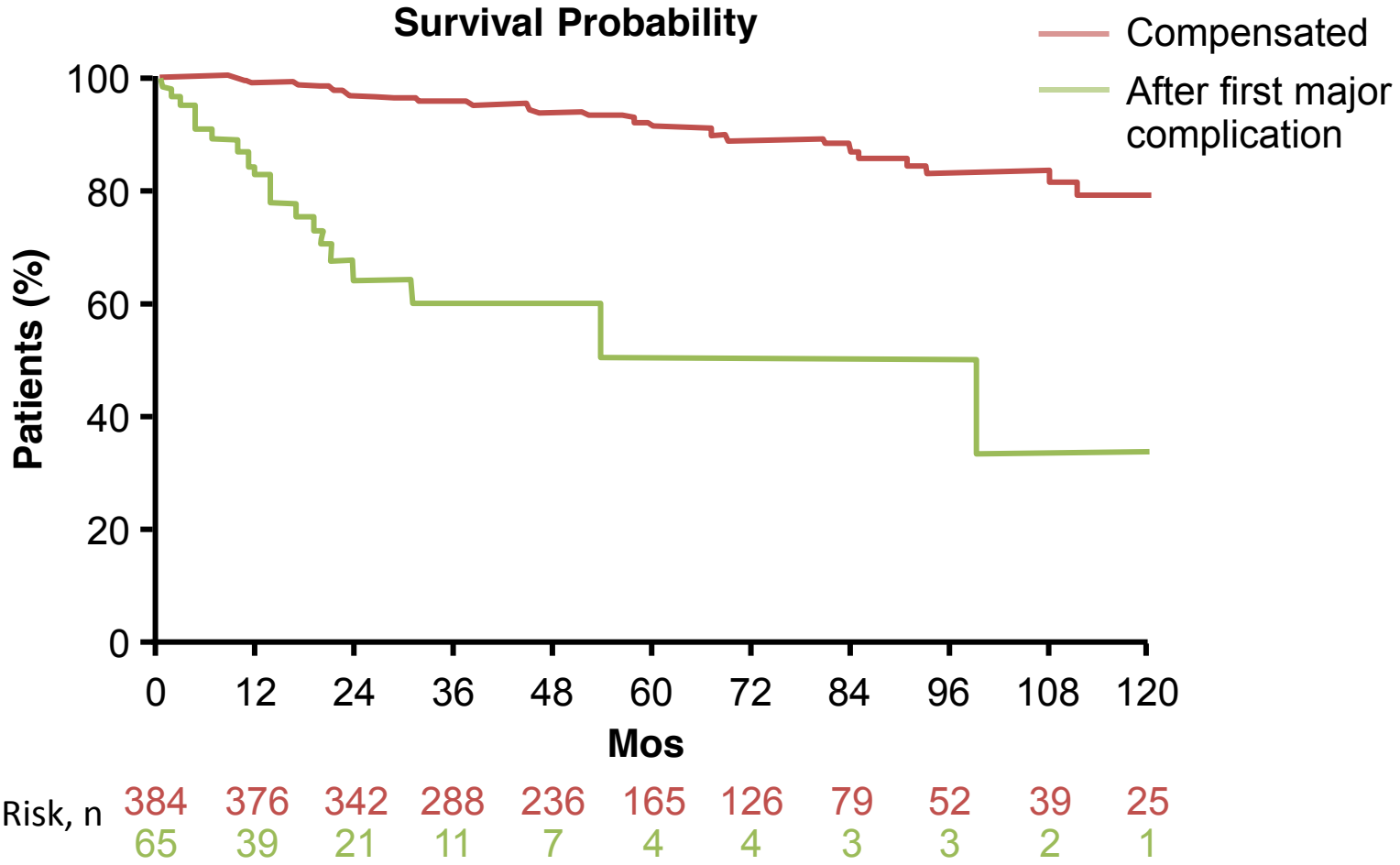
Our Challenge

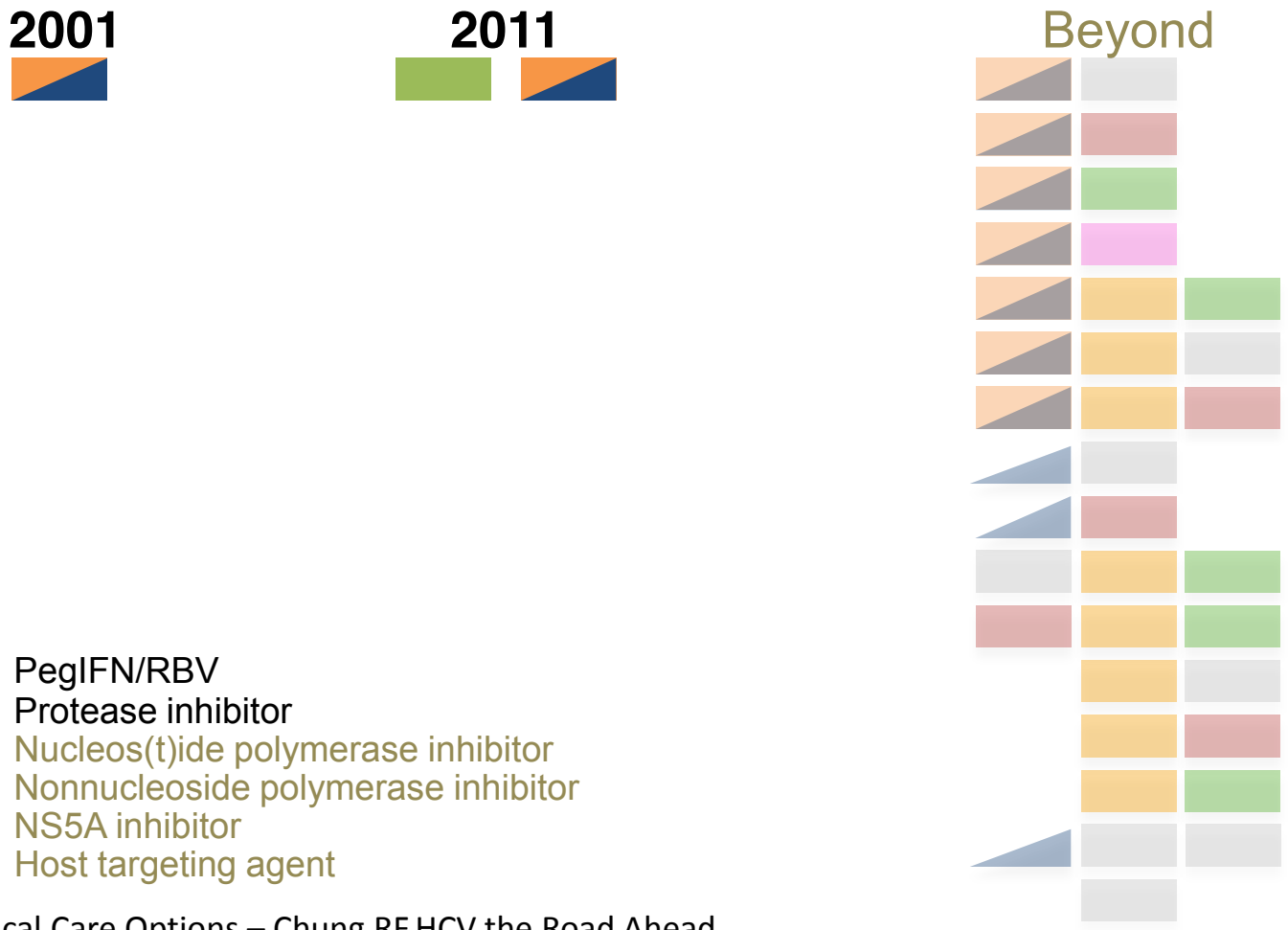
Adapted from Kim, Arthur, HIV/HCV Coinfection Update, Mass Gen Hosp. 2012

The Need to Cure Cirrhosis: Survival in Patients With HCV and Cirrhosis



Fattovich G, et al. Gastroenterology. 1997;112:463-472.

Evolution of HCV Therapy: Where Are We in 2012?

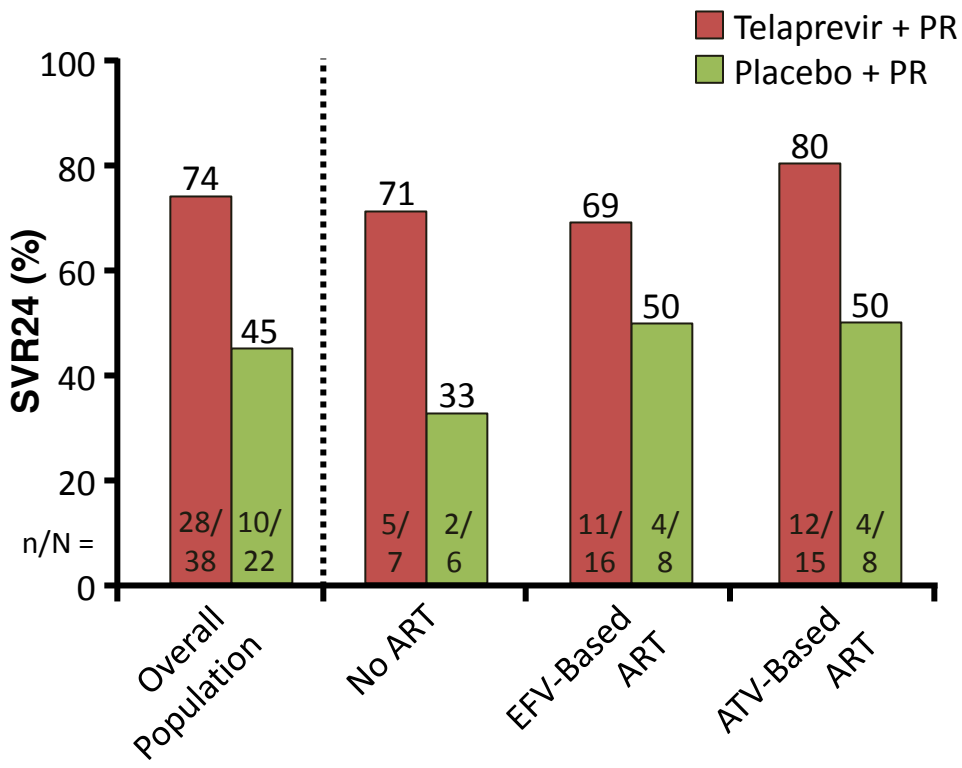


From Clinical Care Options – Chung RF,HCV the Road Ahead

CURRENT THERAPIES

Study 110: SVR24 With TVR + PegIFN/RBV in HCV GT1/HIV-Coinfected Patients

- Higher SVR24 rate with TVR-based therapy

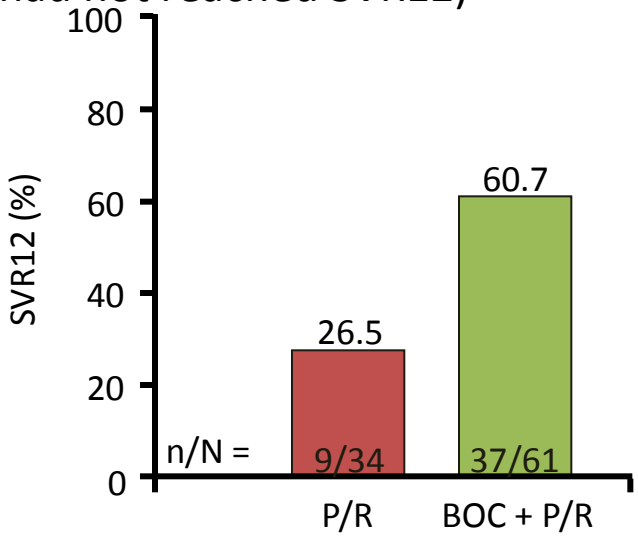


Sulkowski MS, et al. AASLD 2012. Abstract 54

- No significant drug–drug interactions with TVR and ART
  - TVR plasma levels similar in patients with or without ART
  - EFV and ATV/RTV plasma levels similar in patients with or without TVR
- No HIV breakthroughs in patients using ART during HCV treatment
- Safety and tolerability similar to treatment in patients with HCV monoinfection

Higher SVR12 Rates With BOC + P/R vs P/R Alone in HIV/HCV Coinfection

- Interim data reported (3 pts in BOC arm had not reached SVR12)



- HIV-1 RNA breakthrough observed in 7 pts
  - BOC plus P/R: n = 3 (all receiving boosted PIs)
  - Placebo plus P/R: n = 4

SVR12 by ARV Regimen, %	BOC + PegIFN/RBV (n = 61)	PegIFN/ RBV (n = 34)
ATV/RTV	67	62
LPV/RTV	67	0
DRV/RTV	67	0
Other RTV-boosted PI*	57	0
Raltegravir	43	33
Other†	0	0

*SQV, FPV, TPV.
†MVC, EFV.

Sulkowski MS, et al. CROI 2012. Abstract 47

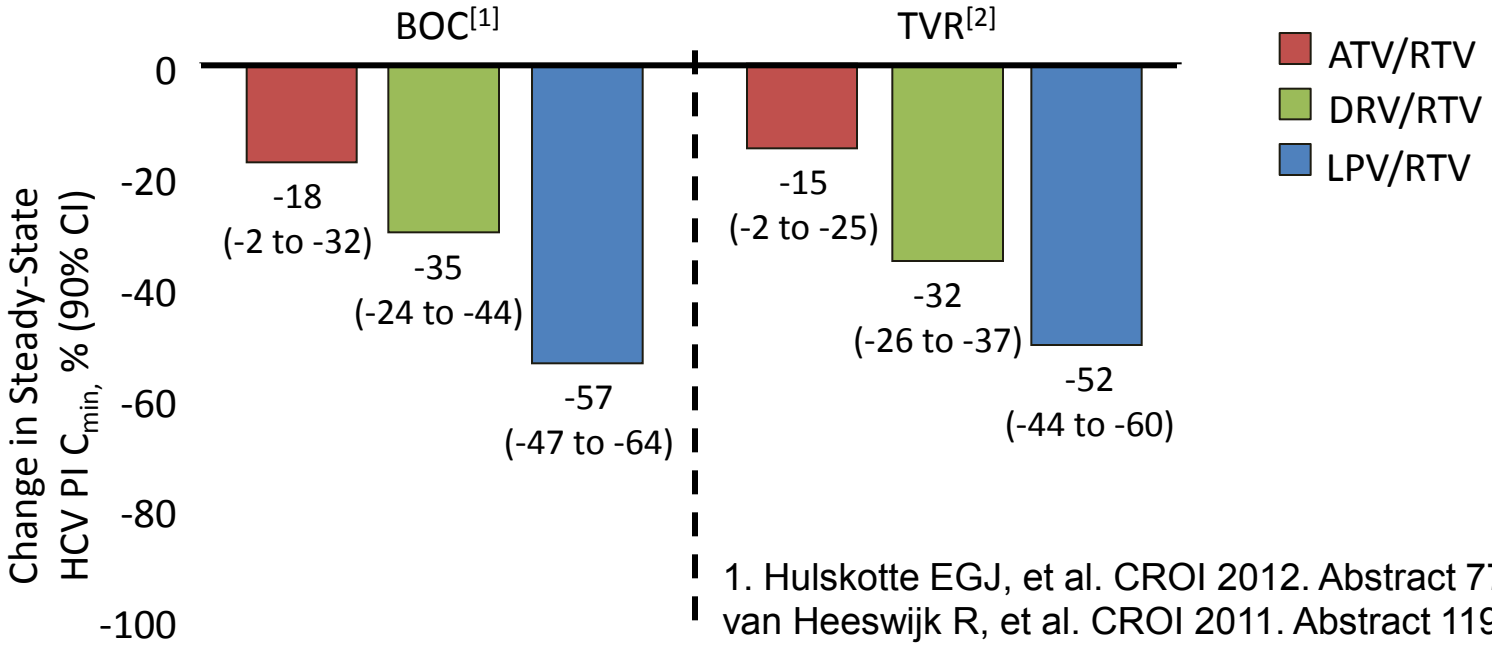
Adverse Events of BOC + P/R vs P/R Alone in HIV/HCV Coinfection

- Overall and serious AE rates similar between arms
  - Anemia, pyrexia, asthenia, decrease appetite, diarrhea, dysgeusia, vomiting, neutropenia more common among BOC recipients
    - Most cases of anemia and neutropenia mild (WHO grade 1/2)
  - Flu-like illness more common among placebo recipients
- More patients discontinued study because of toxicity in BOC vs placebo arm
  - BOC plus pegIFN/RBV: 20%
  - Placebo plus pegIFN/RBV: 9%

Sulkowski MS, et al. CROI 2012. Abstract 47.

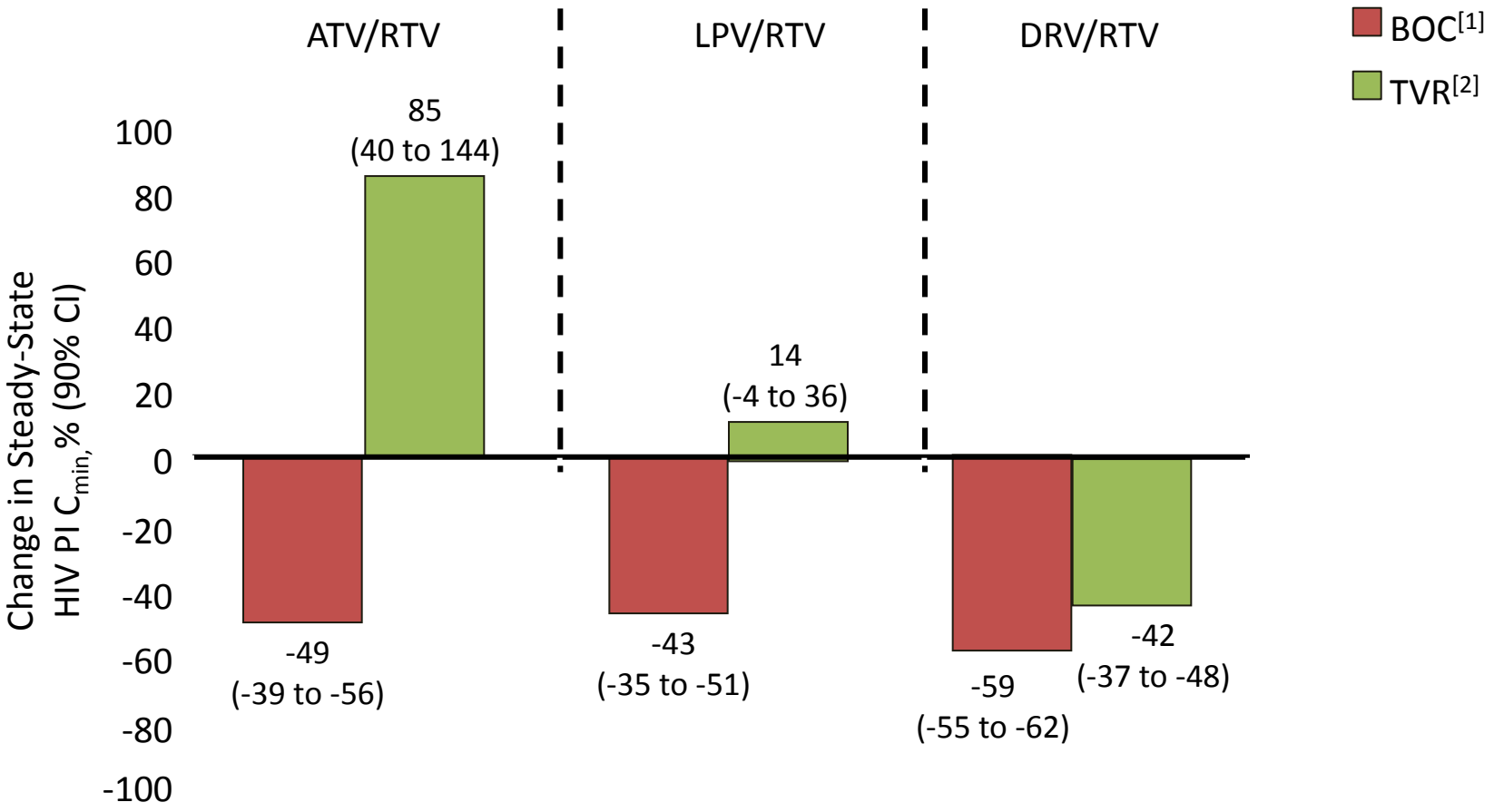
Pharmacokinetic Effects of RTV-Boosted HIV PIs on BOC and TVR

- Similar reductions in BOC and TVR exposures observed with coadministration of ATV/RTV, DRV/RTV, and LPV/RTV
- Prescribing information for TVR does not recommend coadministering TVR with DRV/RTV, FPV/RTV, or LPV/RTV; prescribing information for BOC does not recommend coadministering BOC with any HIV PI



1. Hulskotte EGJ, et al. CROI 2012. Abstract 771LB. 2. van Heeswijk R, et al. CROI 2011. Abstract 119.

Pharmacokinetic Effects of BOC and TVR on RTV-Boosted HIV PIs



1. Hulskotte EGJ, et al. CROI 2012. Abstract 771LB. 2. van Heeswijk R, et al. CROI 2011. Abstract 119.

BOC Plus PegIFN alfa-2b/RBV: Adverse Events

- Higher rates of anemia, neutropenia, and dysgeusia in BOC arms vs control

Adverse Event, %	PR48 (n = 467)	BOC + PR RGT/48* (n = 1225)
Anemia*	30	50
Neutropenia	19	25
Dysgeusia	16	35

*Anemia was managed with RBV reduction and/or epoetin alfa (43% of BOC + PR and 24% of PR).

Boceprevir [US package insert]. July 2012.

TVR Plus PegIFN alfa-2a/RBV: Adverse Events

- Higher rates of rash, anemia, and anorectal signs and symptoms in TVR arms vs control

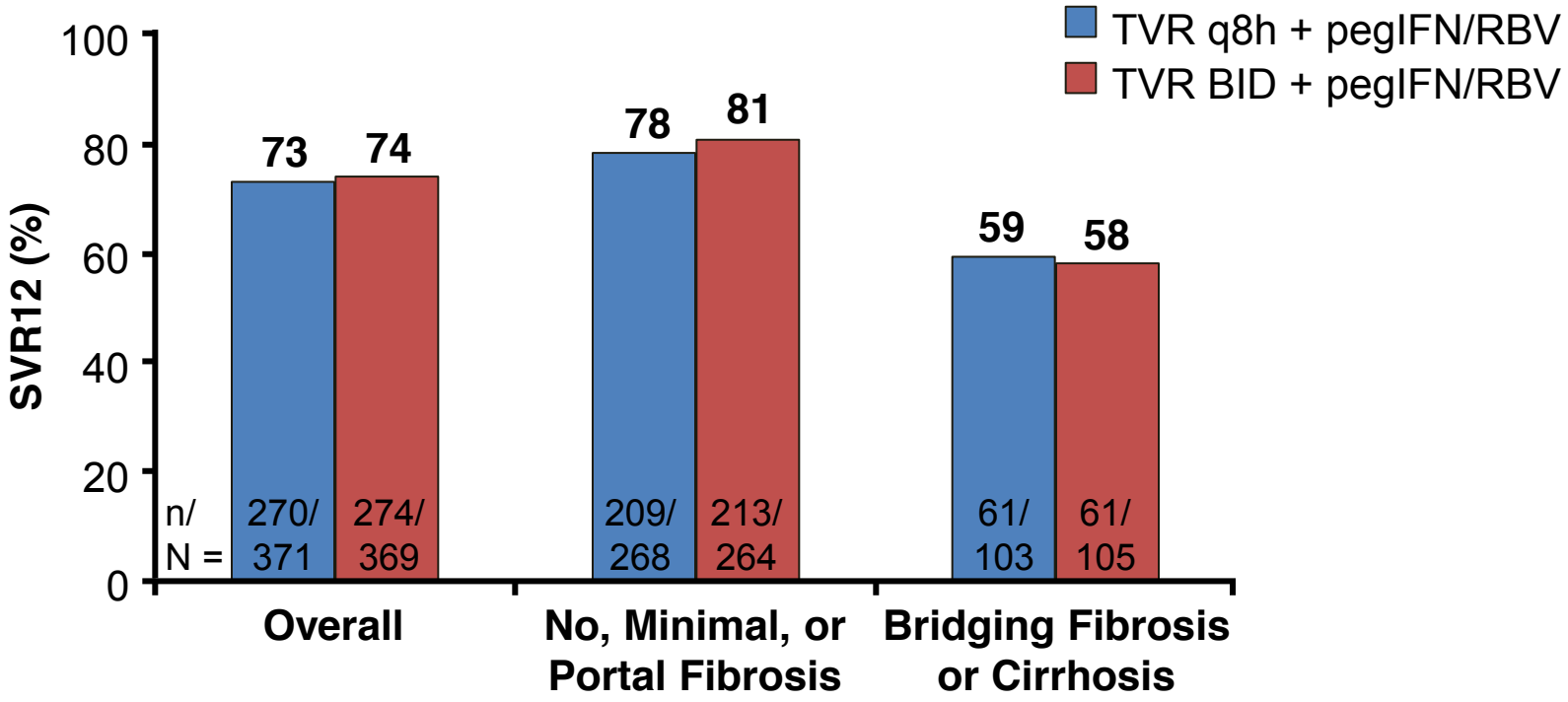
Adverse Event, %	PR48 (n = 493)	TVR + PR RGT/48*† (n = 1797)
Rash	34	56
Anemia‡	17	36
Anorectal events	7	29

*Pooled results from TVR arms.
†Anemia was managed with RBV dose modification; epoetin alfa was not permitted.

- In most subjects, rash was mild to moderate
  - Severe rash in 4%; discontinuation due to rash in 6% of subjects

Telaprevir [US package insert]. October 2012.

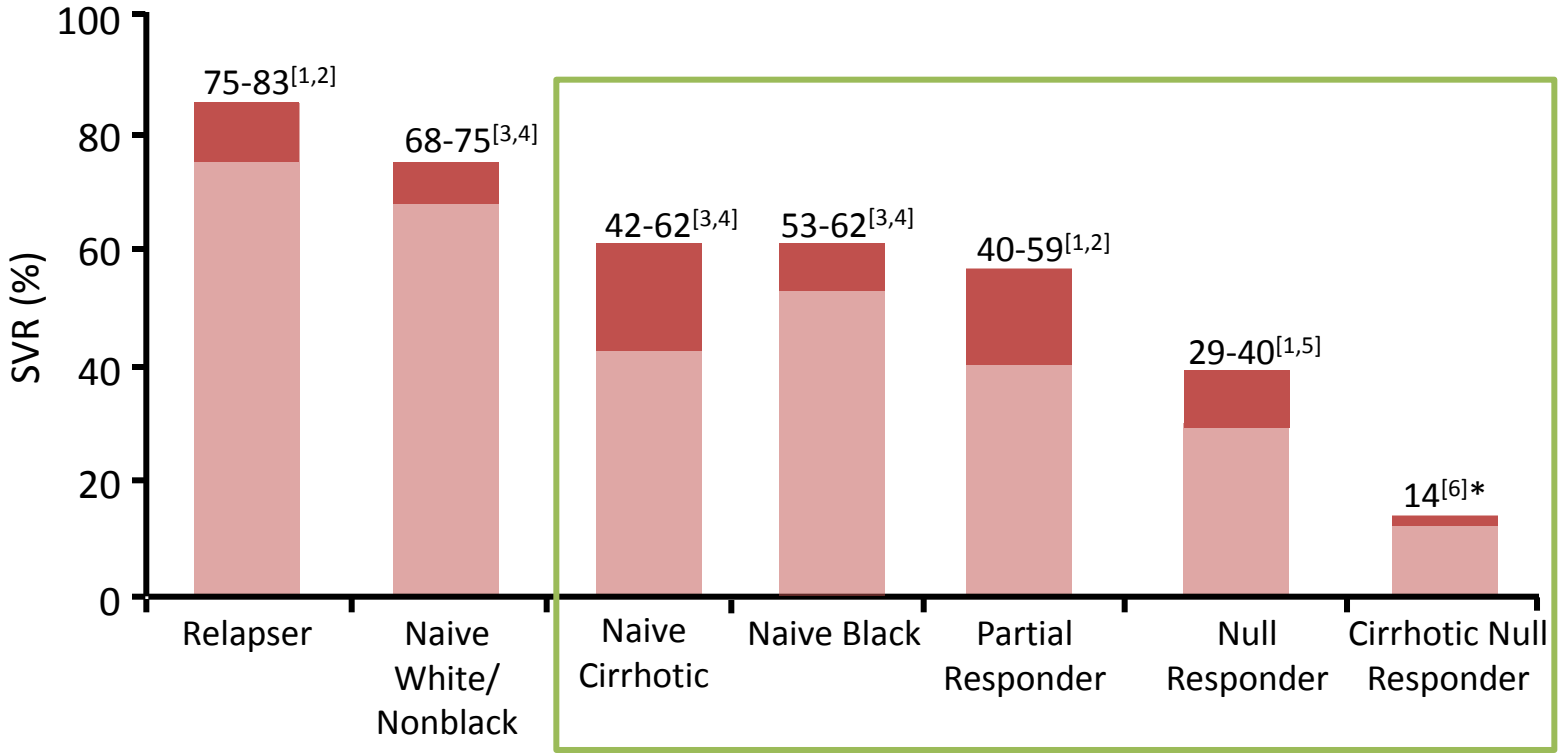
Improved Dosing With Current Therapy: TVR BID Noninferior to TID in Tx-Naive GT1



- Adverse events similar between treatment arms
- No differences in efficacy with 2 strategies in patients with more advanced disease

Buti M, et al. AASLD 2012. Abstract LB-8.

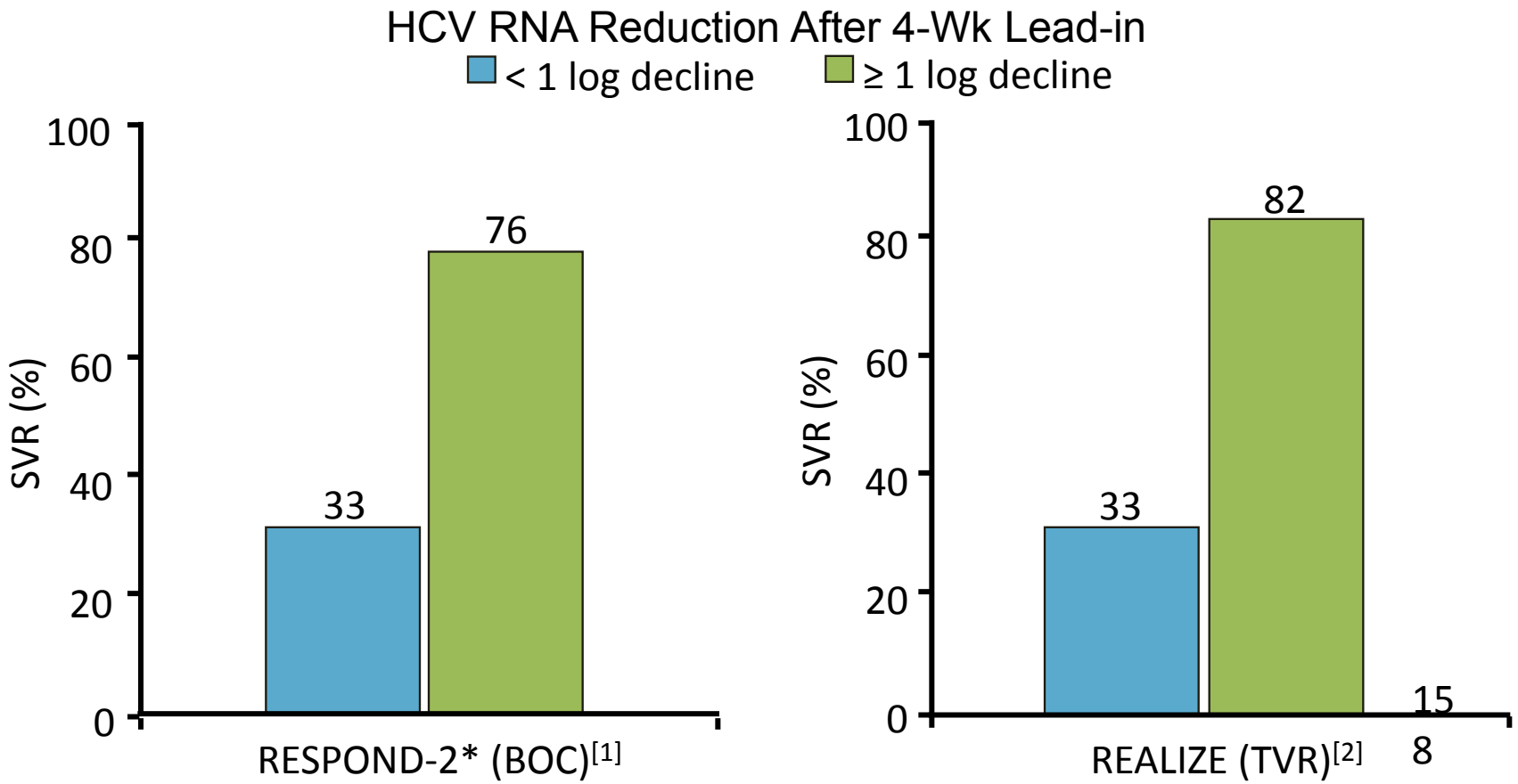
Limited Efficacy With Telaprevir and Boceprevir in Some Patient Groups



*Pooled TVR arms of REALIZE trial.

1. Zeuzem S, et al. N Engl J Med. 2011;364:2417-2428. 2. Bacon BR, et al. N Engl J Med. 2011;364:1207-1217. 3. Jacobson IM, et al. N Engl J Med. 2011;364:2405-2416. 4. Poordad F, et al. N Engl J Med. 2011;364:1195-1206. 5. Bronowicki J, et al. EASL 2012. Abstract 11. 6. Zeuzem S, et al. EASL 2011. Abstract 5.

Likelihood of SVR With Current Therapies Related to IFN Responsiveness



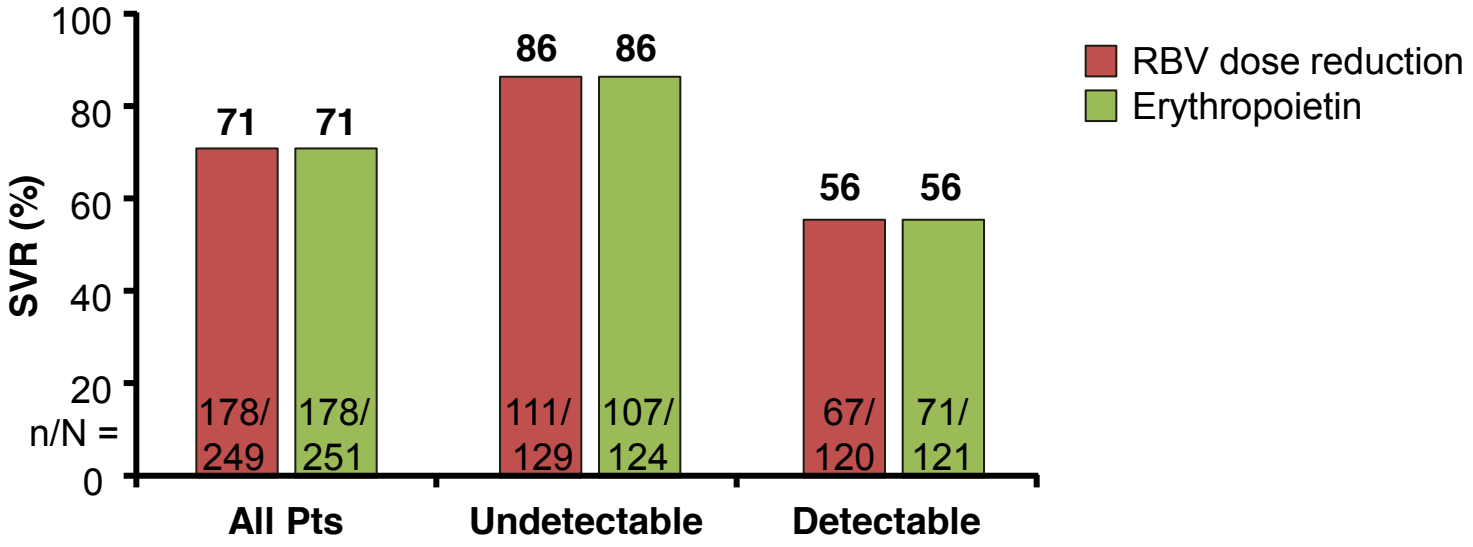
*Pooled data from RGT and arm 3.

1. Vierling JM, et al. EASL 2011. Abstract 481. 2. Foster G, et al. EASL 2011. Abstract 6.

ANEMIA AND RIBAVIRIN DOSE

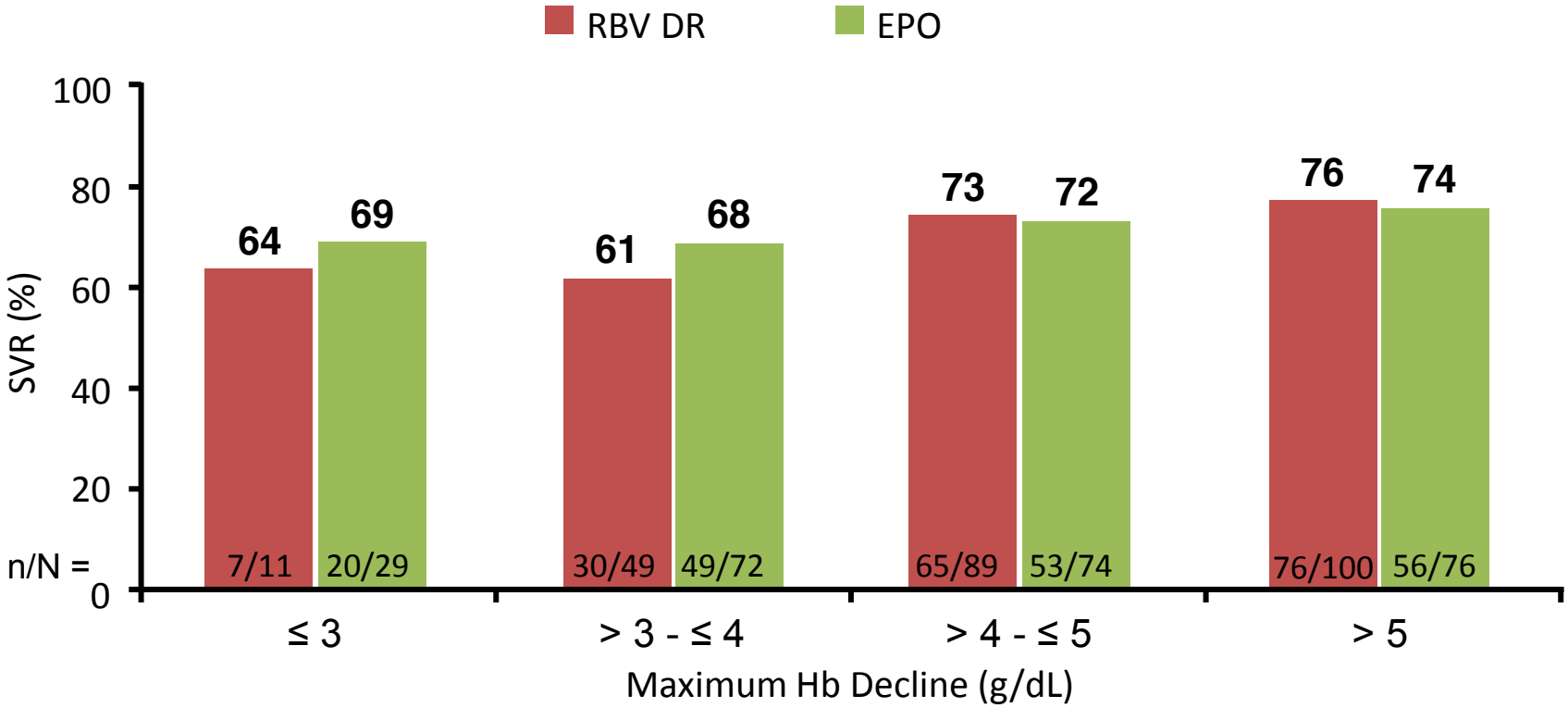
SVR Rates With RBV Dose Reduction or Erythropoietin for Anemia Management

- Similar SVR rates (71%) with both strategies[1,2]
  - Similar SVR rates regardless of timing of anemia management, number of RBV dose reductions, or lowest RBV dose received
  - Lower SVR rates if < 50% of per protocol total RBV dose received
- Higher SVR rate if anemia management initiated with undetectable HCV RNA[2]



1. Poordad F, et al. EASL 2012. Abstract 1419. 2 Poordad F, et al. AASLD 2012. Abstract 154..

No Association Between Degree of Hb Decline and SVR in Pts Developing Anemia



Poordad F, et al. EASL 2012. Abstract 1419.

INVESTIGATIONAL AGENTS

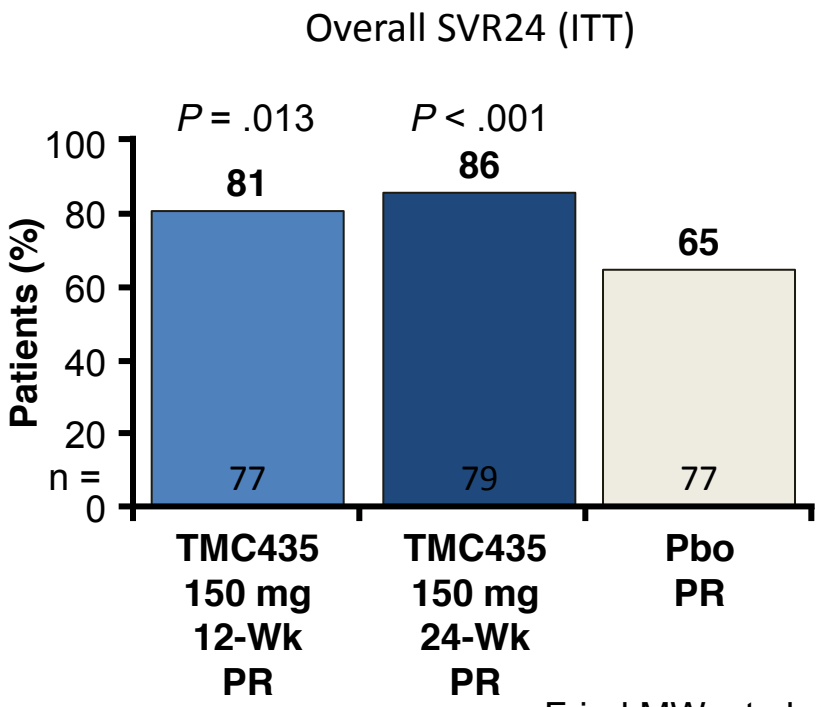
HCV DAA Agents in Late Stage Development

NS3/4A Pis	NS5A replication complex inh	Nucleotide NS5B poly inh	Non-nuc NS5B Pol inh
ABT-450/r	ABT-267	Sofosbuvir	ABT-333
Asunaprevir	Daclatasvir	Mericitabine	
Faldaprevir	GS5885		
Simeprevir			

DAAS WITH INTERFERON AND RIBAVIRIN

Safety and Efficacy of Simeprevir **QD** + PegIFN/RBV in GT1 Treatment-Naive Pts

- Addition of simeprevir (TMC435) to pegIFN/RBV significantly improved SVR rates vs pegIFN/RBV alone at Wk 24

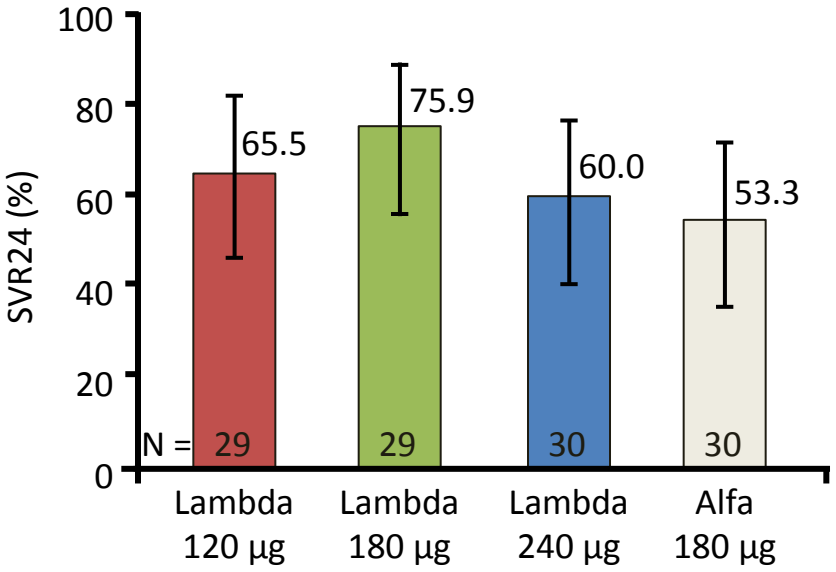


Safety Outcome, %	All TMC435 Arms (n = 309)	Placebo + PR 48W (n = 77)
Study tx permanently discontinued for AE	3.6	5.2
Grade 3/4 AE	32.0	35.1
Serious AE	6.5	13.0
▪ Fatigue	42.4	48.1
▪ Flu-like illness	31.7	37.7
▪ Pruritus	31.1	45.5
▪ Headache	46.0	51.9
Other AEs of interest		
▪ Rash	21.0	23.4
▪ Anemia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

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

Safety and Efficacy of PegIFN lambda-1a vs PegIFN alfa-2a in GT 2/3 Tx-Naive Pts

- EMERGE study: each group received pegIFN + RBV for 24 wks

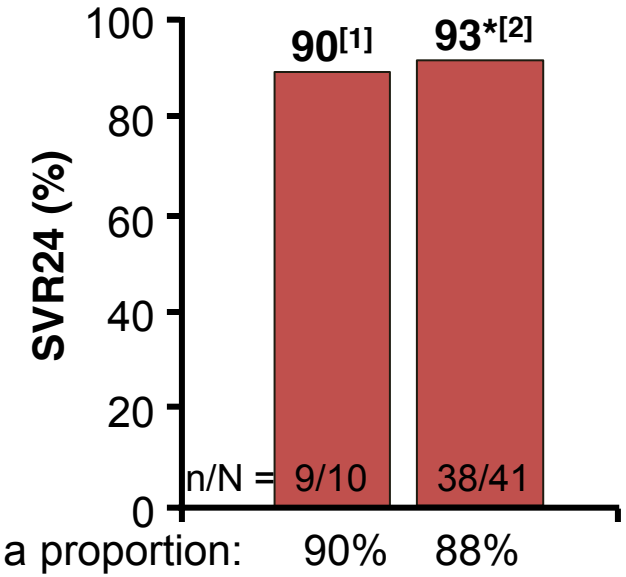


Hematologic Adverse Event, %	Lambda 180 µg (n = 29)	Alfa 180 µg (n = 30)
Hemoglobin low < 10 g/dL *or* Δ > 3.4 g/dL	6.9	44.8
RBV dose reduction (hemoglobin associated)	0	23.3
Neutrophils low < 750 cells/mm^3	0	27.6
Platelets low < 100,000 cells/mm^3	0	24.1
PegIFN dose reduction (hematologic abnormality)	0	23.3

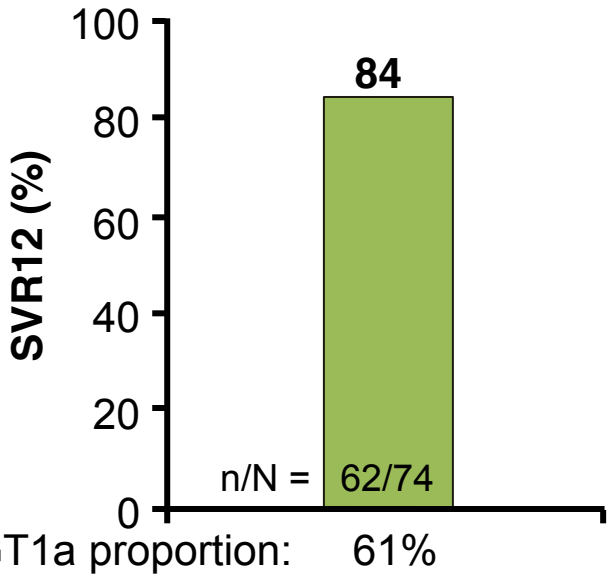
Zeuzem S, et al. EASL 2012. Abstract 10.

2 DAAs + PegIFN/RBV in GT1 Previous Null Responders

Daclatasvir (NS5A) + Asunaprevir (PI) + PegIFN/RBV x 24 Wks



Danoprevir/RTV (PI) + Mericitabine (Nuc) + PegIFN/RBV x 24 Wks[3]



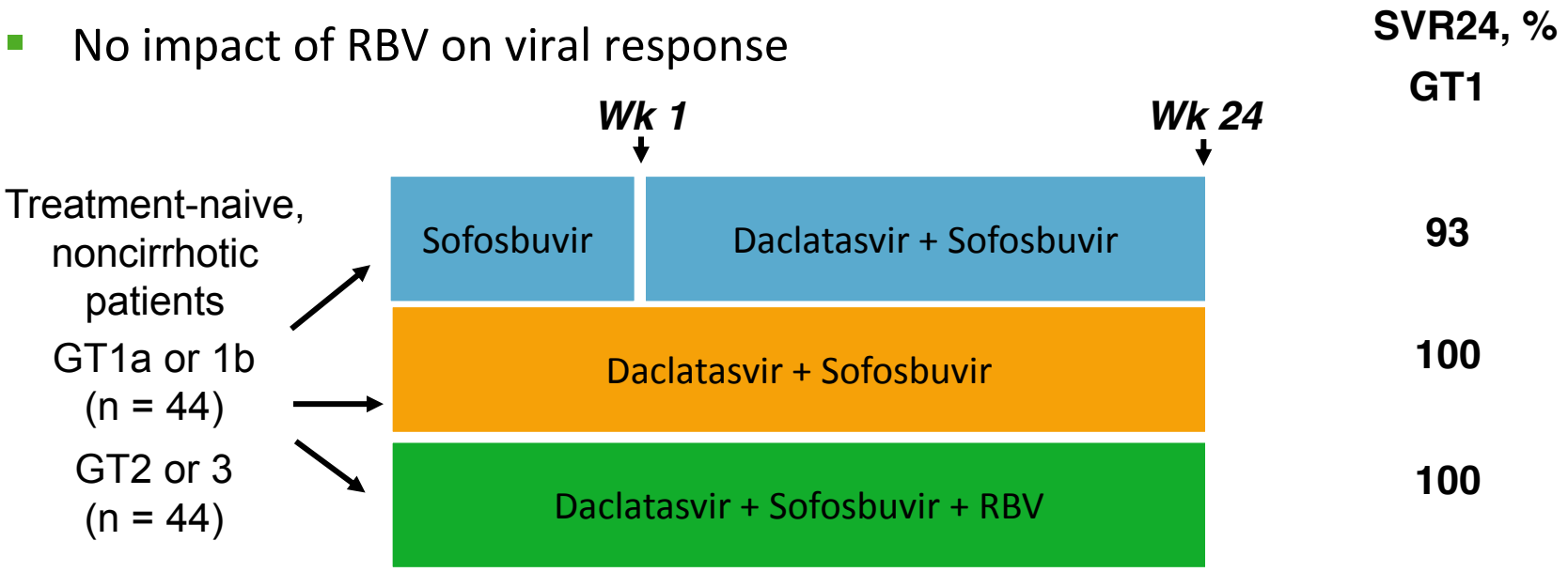
*Asunaprevir QD and BID combined.

1. Lok A, et al. N Engl J Med. 2012;366:216-224. 2. Lok A, et al. AASLD 2012. Abstract 79.
3. Feld JJ, et al. AASLD 2012. Abstract 81 .

INTERFERON SPARING REGIMENS

Daclatasvir Plus Sofosbuvir in GT1 Treatment-Naive Patients

- Pts with poor prognostic indicators: GT1a (73%), male (52%), black (20%), *IL28B* CT/TT (64%); advanced liver disease: 14%
- Mean HCV RNA: 6.6 logs
- No impact of RBV on viral response

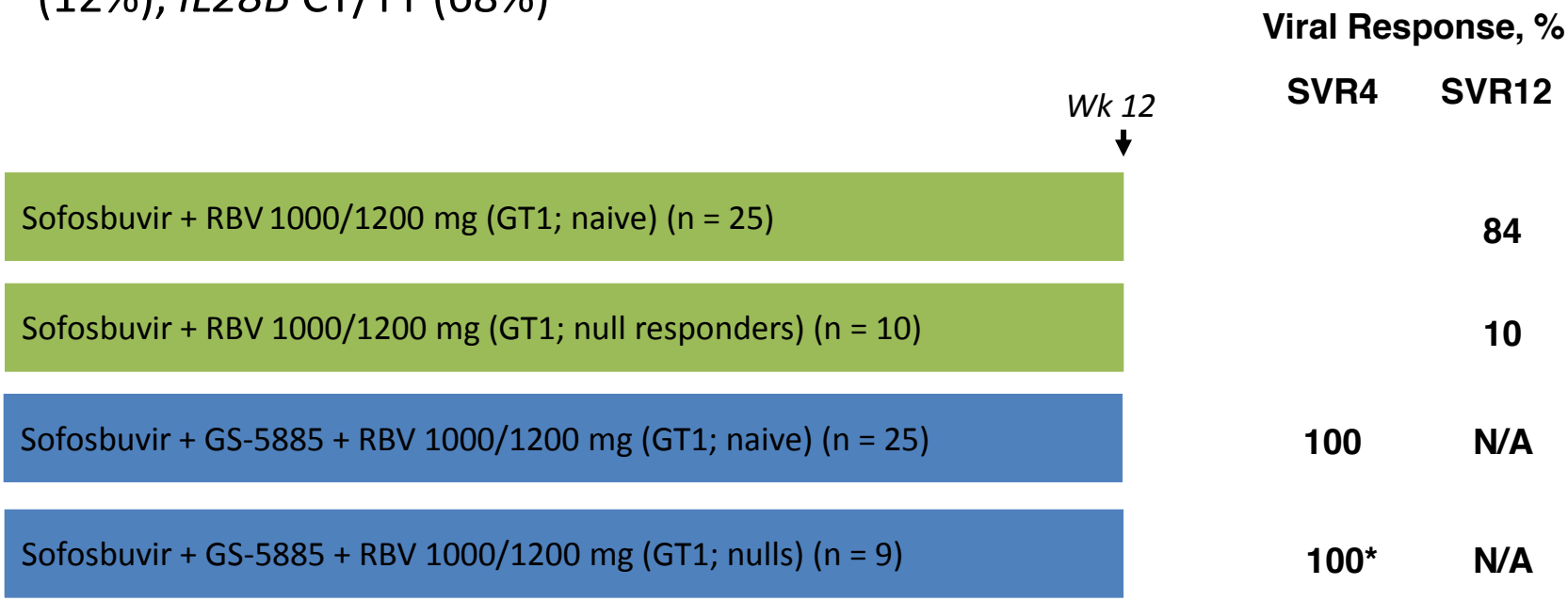


Sofosbuvir dosed 400 mg QD. Daclatasvir dosed 60 mg QD. RBV dosed by body weight for GT1 patients (1000-1200 mg/day); 800 mg/day for GT2/3 patients.

Sulkowski M, et al. AASLD 2012. Abstract LB-2.

ELECTRON: Sofosbuvir ± GS-5885 + RBV in Naive and Previous Null Responders

- Pts with poor prognostic indicators: GT1a (86%), male (54%), nonwhite (12%), *IL28B* CT/TT (68%)

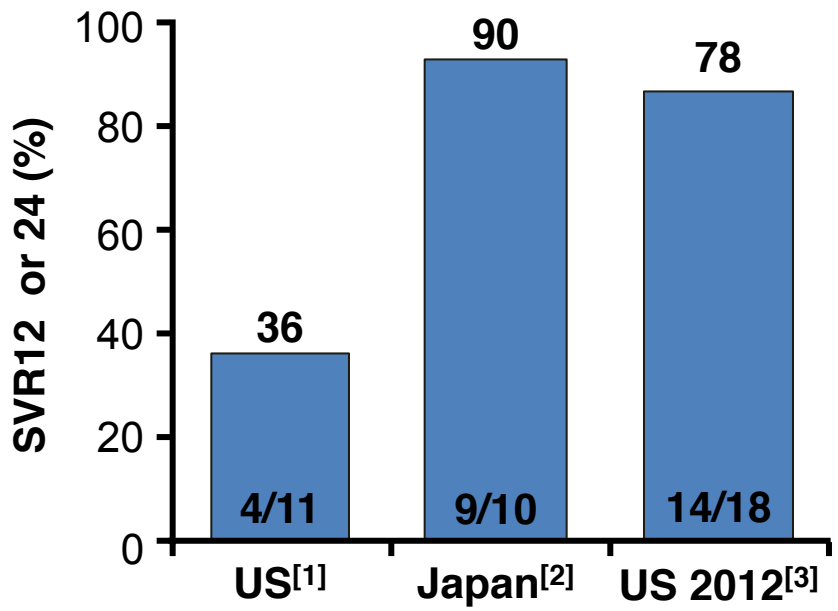


*Data reported for 3 pts only. Data collection ongoing.

Gane EJ, et al. AASLD 2012. Abstract 229.

IFN-Free Therapy in Previous Null Responders

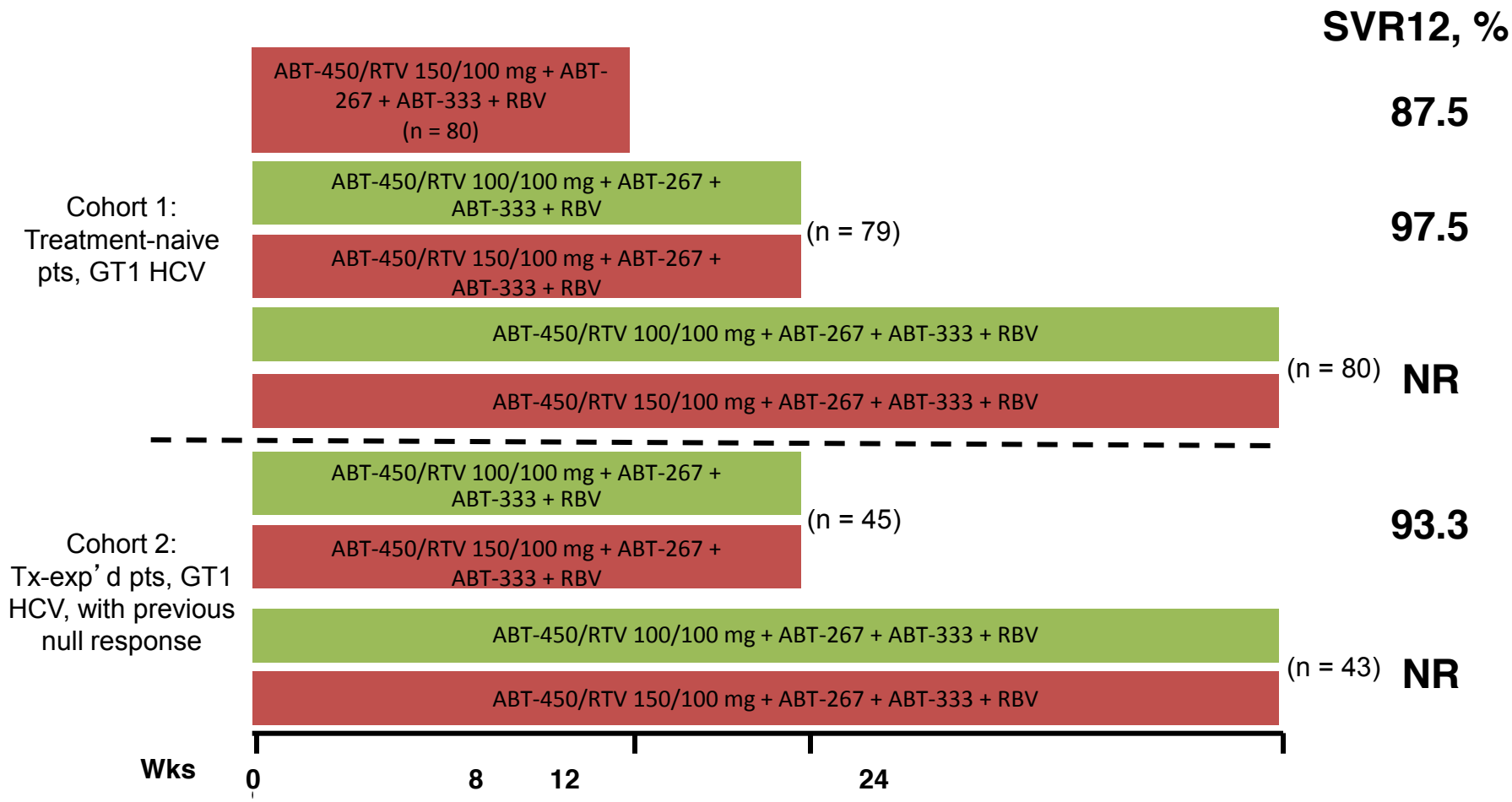
Daclatasvir (NS5A) + Asunaprevir (PI) x 24 Wks (IFN Free)



US Study
9/11 GT1a
Japanese Study
10/10 GT1b
US 2012
GT1b only

1. Lok A, et al. N Engl J Med. 2012;366:216-224. 2. Chayama K, et al. AASLD 2011. Abstract LB-4.
3. Lok A, et al. AASLD 2012. Abstract 79.

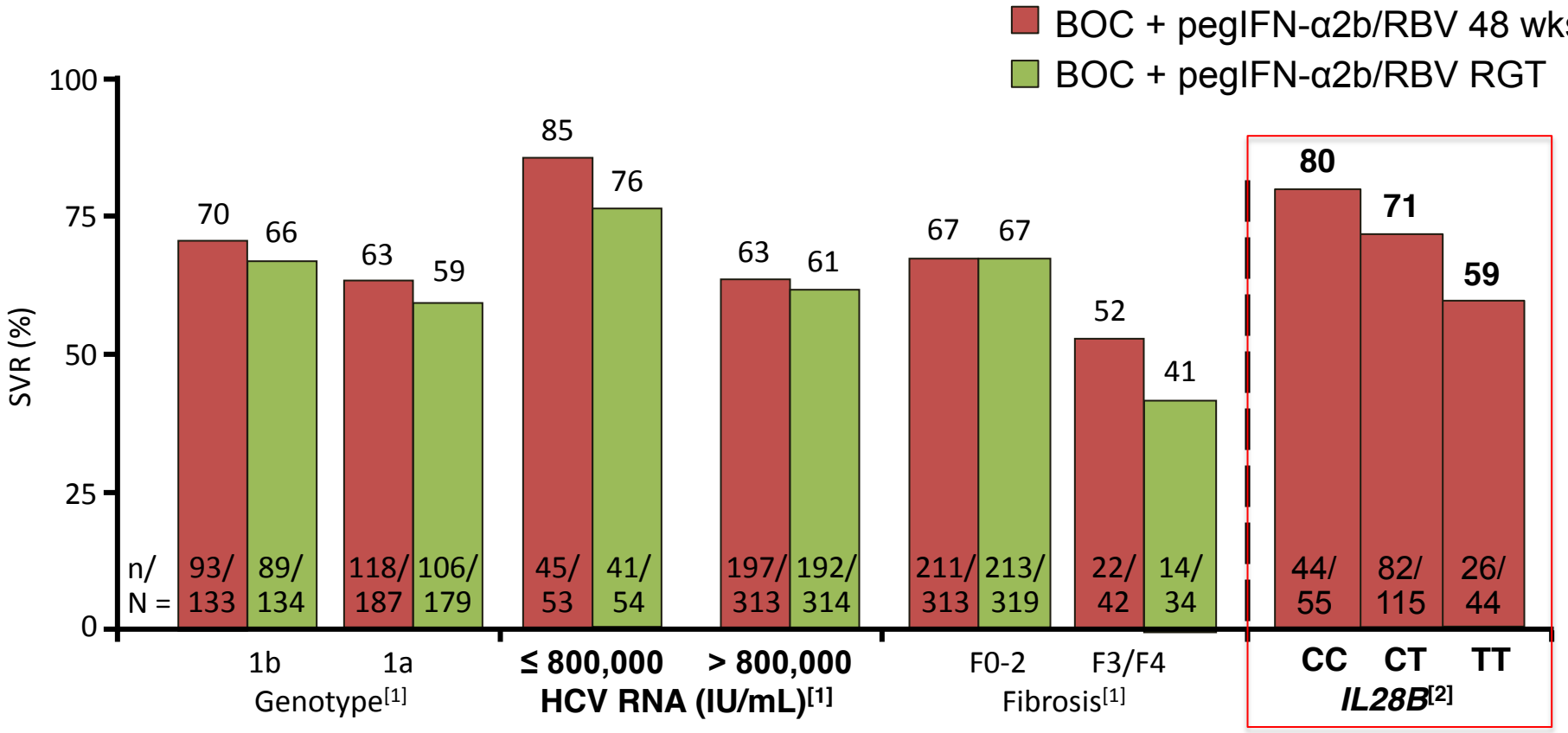
IFN-Free Regimens With ABT-450/RTV, ABT-267, ABT-333, and RBV



Kowdley K, et al. AASLD 2012. Abstract LB-1.

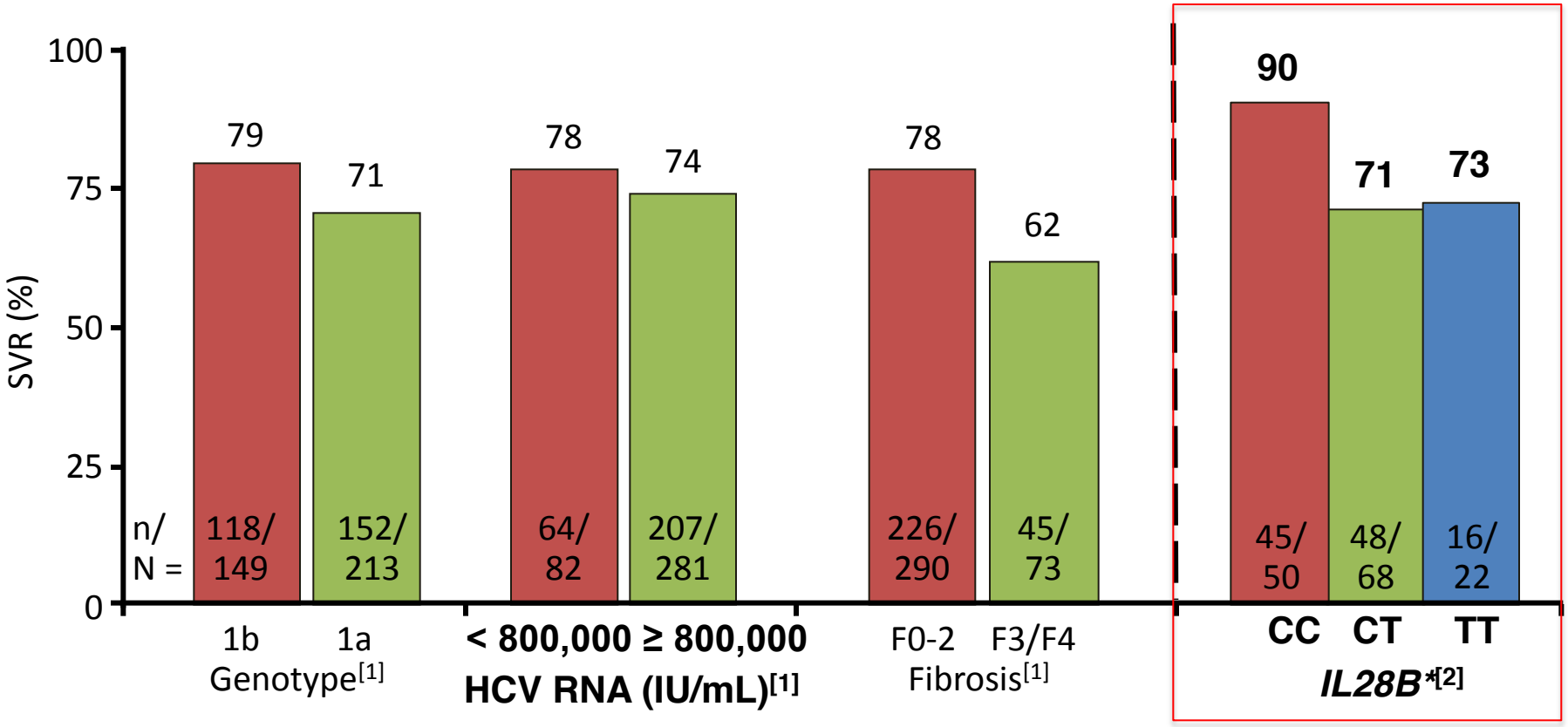
INFLUENCE OF IL28B GENOTYPE

SPRINT-2: Influence of Baseline Patient and Virus Factors on SVR With BOC



1. Poordad F, et al. N Engl J Med. 2011;364:1195-1206.
2. Poordad F, et al. Gastroenterology. 2012;143:608-618.

ADVANCE: Influence of Baseline Patient and Virus Factors on SVR With TVR

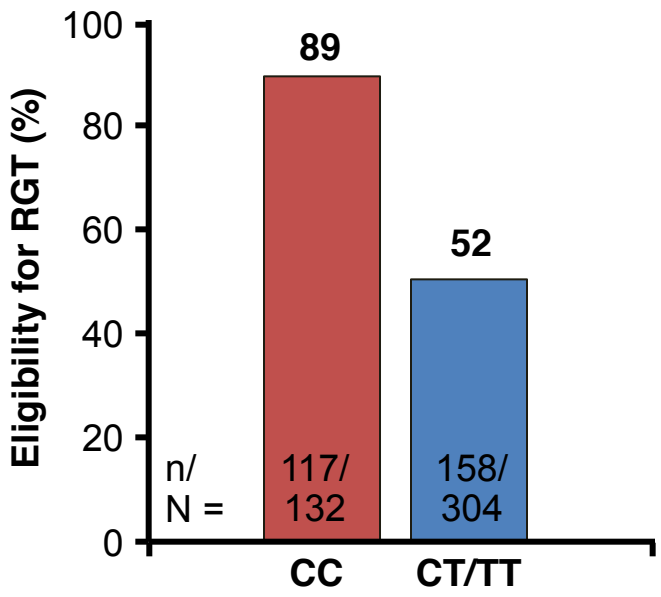


**IL28B* testing was in whites only.

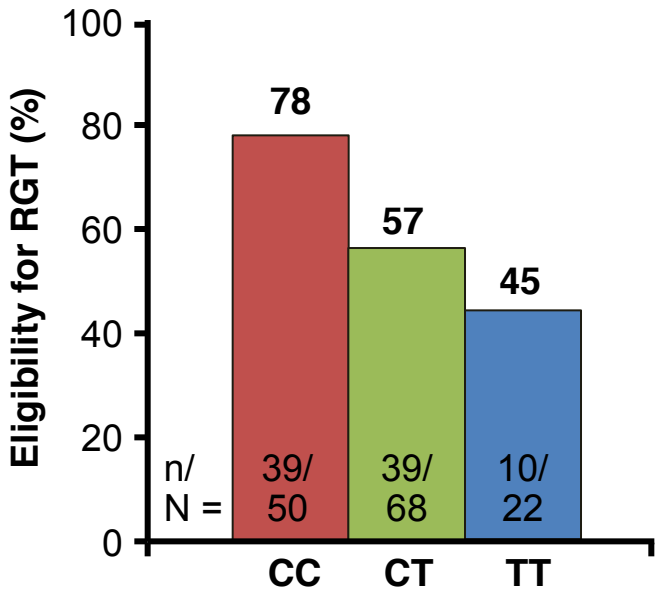
1. Jacobson IM, et al. N Engl J Med. 2011;364:2405-2416. 2. Jacobson IM, et al. EASL 2011. Abstract 1369.

IL28B Genotype Predicts Likelihood of Eligibility for Shortened Therapy

SPRINT-2: BOC +
PegIFN-α2b/RBV [1]



ADVANCE: T12 +
PegIFN-α2a/RBV *[2]



**IL28B* testing in ADVANCE was in whites only.

1. Poordad F, et al. Gastroenterology. 2012;143:608-618. 2. Jacobson IM, et al. EASL 2011. Abstract 1369.

Summary

- HCV therapy for monoinfected and HIV-coinfected patients has revolutionized therapy
- Data regarding drug efficacy, toxicity and drug-drug interactions is helping to refine the role of the HCV PIs in treatment of coinfected patients
- New regimens including RBV and IFN sparing regimens create new questions about timing of treatment