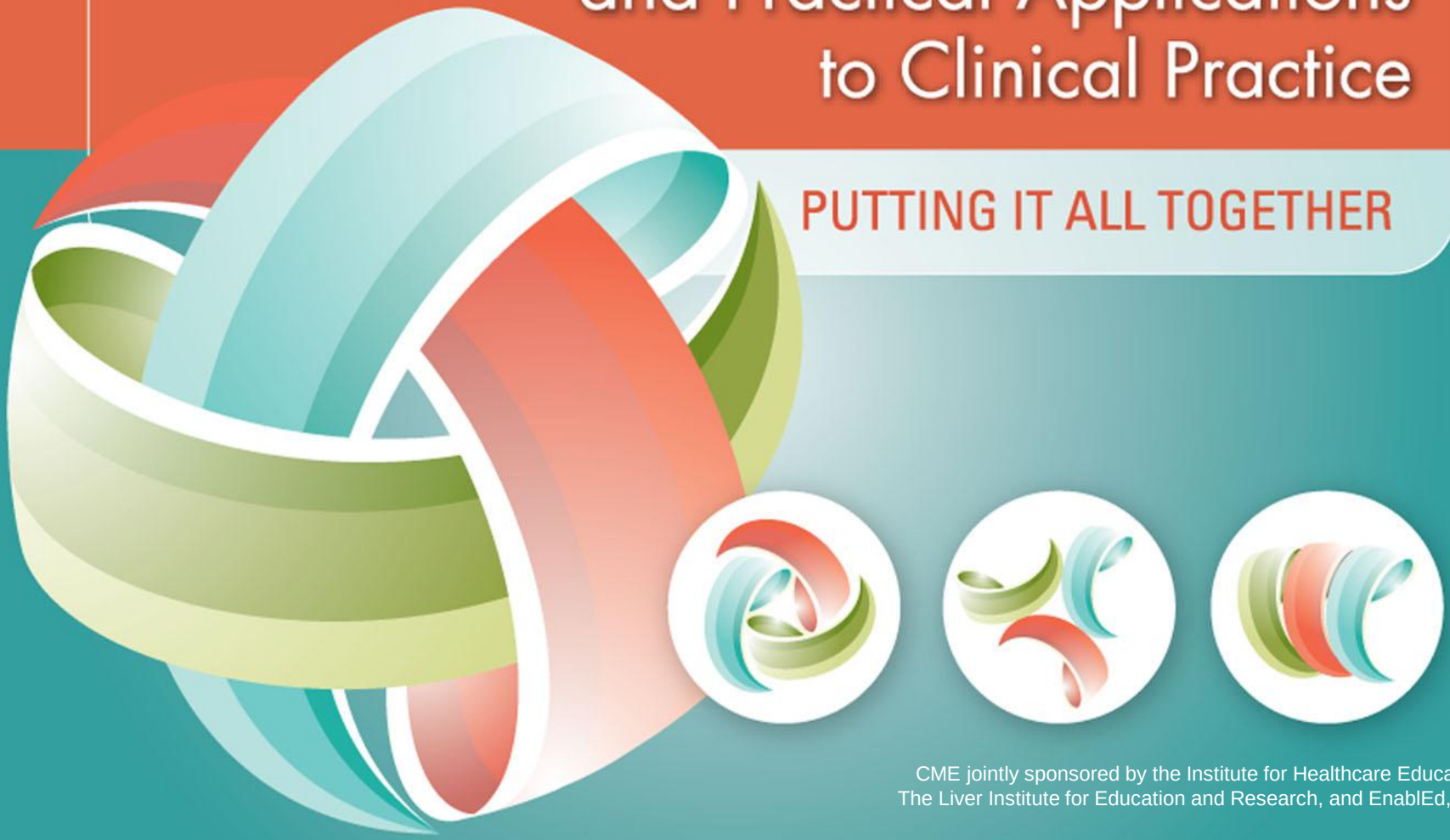
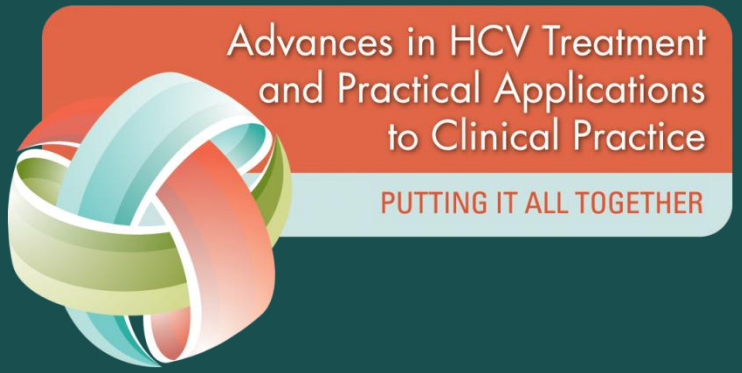
Advances in HCV Treatment and Practical Applications to Clinical Practice

PUTTING IT ALL TOGETHER



CME jointly sponsored by the Institute for Healthcare Education, The Liver Institute for Education and Research, and EnablEd, LLC



CASE:

Future Treatments for HCV Infection

Case: 42-Year-Old Man with HCV Genotype 1, Depression, and Relapsing Intravenous (IV) Drug Use

- 42-year-old man
- HCV genotype 1b, viral load 970,000 IU/μL; treatment-naïve
- Medical history
  - History of IV drug abuse (drug-free for 1 year); multiple relapses in past
  - Severe depression, worse when off IV drugs; 1 hospitalization 4 years ago; no suicidal ideation
  - Hashimoto's thyroiditis
  - No alcohol since his teens
- Unemployed and in halfway house

Case: 42-Year-Old Man with HCV Genotype 1, Depression, and Relapsing Intravenous (IV) Drug Use

- Physical examination normal
- Laboratory results
  - ALT 86 IU/L, AST 54 IU/L
- Liver biopsy 3 years ago: Stage 2, Grade 2
- Impaired renal function and mild anemia
- All else normal

"Doctor, should we start an antiviral therapy?"

ALT = alanine aminotransferase; AST = aspartate aminotransferase.

Whom Not to Treat?

- Relative decision – needs individualization
  - Mild disease F0–F1 fibrosis
  - RVR on lead-in: can you hold the PI?
  - Null responders and relapsers
  - Prior intolerance
  - Psychiatric disease: multidisciplinary team needed
  - Skin disorders: boceprevir preferred
  - HIV coinfection
  - Post-liver transplantation

RVR = rapid virologic response; PI = protease inhibitor.

Ghany MG et al. Hepatology 2009;49:1335-74; Ghany MG et al. Hepatology 2011;54:1433-44.

Whom Not to Treat?

- ABSOLUTE CONTRAINDICATION
  - Prior interferon (IFN) hypersensitivity
  - Concomitant severe cardiac, pulmonary, or other disease
  - Liver failure
  - Renal disease: creatinine clearance <50 mL/min
  - Anemia and hemoglobinopathies
  - Autoimmune disease sensitive to interferons or ribavirin

Ghany MG et al. Hepatology 2009;49:1335-74; PegIntron prescribing information. 2011.

Why Should We Wait? Disadvantages of Current Treatment

Long treatment duration

- At least 24 weeks for HCV genotype 1
- Bad results for non-RVR patients after 48 weeks of treatment

Poor safety profiles

- Several interferon-related adverse events (AEs)
- New PIs: anemia, rash, etc

Low efficacy in certain patients

- Previous null response
- *IL-28B* TT genotype
- Cirrhosis

Ghany MG et al. Hepatology 2009;49:1335-74; Ghany MG et al. Hepatology 2011;54:1433-44.

What Should We Wait For? Future Therapy Options

The second wave of PIs
- Better tolerability, safety profile
- Higher proportion of shorter duration: RGT

The second generation of PIs
- Higher efficiency
- Pangenotypic
- Better tolerability

NUCs
- Interferon-free regimens
- Better tolerability?
- Options for previous PI failure
- High barrier to resistance
- Pangenotypic

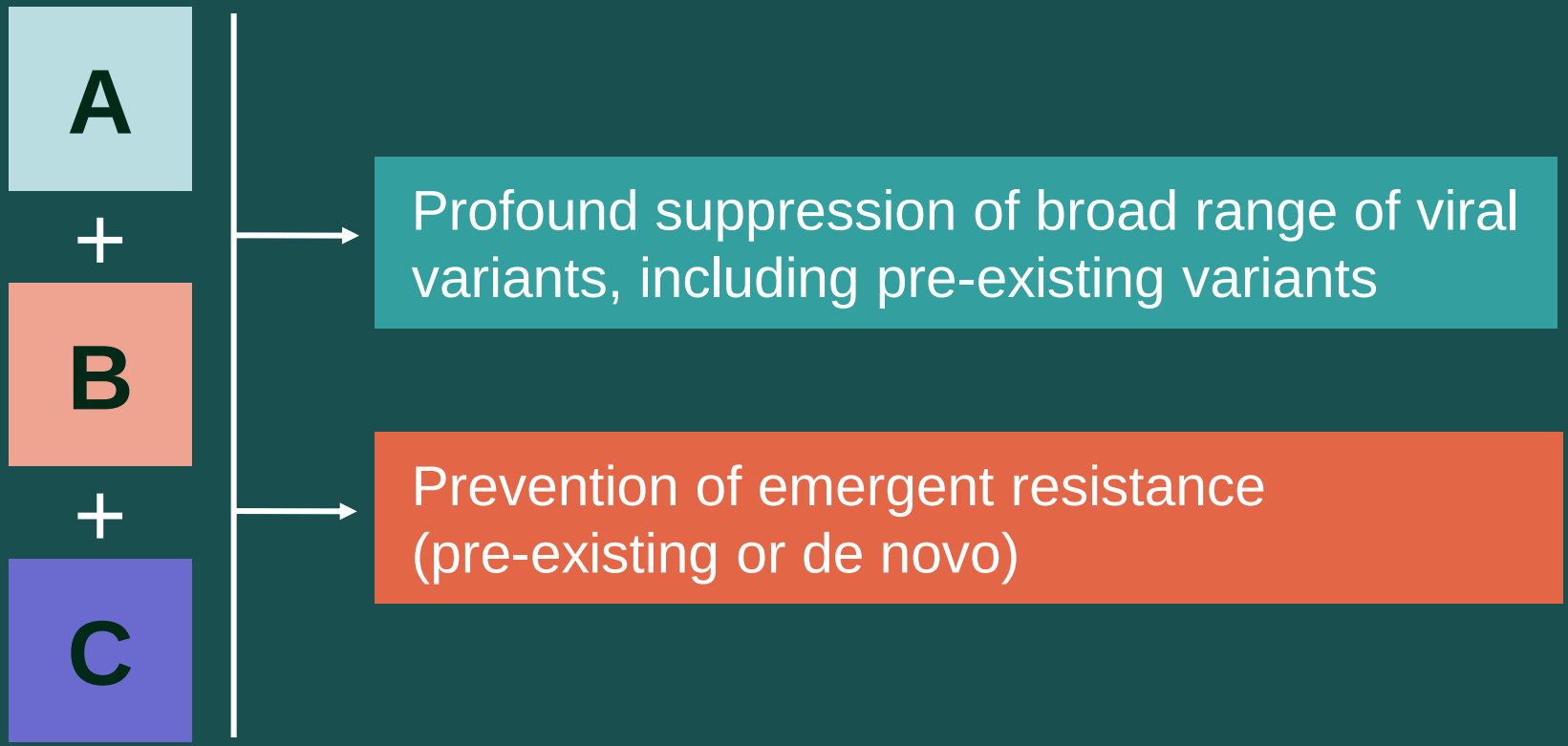
Non-NUCs
- Interferon-free regimens
- Options for previous PI failure ?

Host targeting agents
- Pangenotypic
- Different resistance profile
- Different safety profile

RGT = response-guided therapy; NUCs = nucleoside analogs.

Pawlotsky JM. F1000 Biol Rep 2012;4:5(doi:10.3410/B4-5).

The Goal of Combination Regimens



- Different drugs can contribute variably to each goal. Not all components must be direct-acting antivirals (DAAs).

Key for Waves of New Agents: DAAs and Host-Targeting Antivirals

DAAs

First Wave (1st)

Telaprevir
Boceprevir

Second Wave (2nd)

TMC435
BI 201335
BMS-790052 (daclatasvir)
GS-7977
Other NS5a inhibitors

Third Wave (3rd)

BI 201335/BI 207127
Daclatasvir/BMS-650032 (asunaprevir)
MK-5172 (mericitabine)

Host-targeting antivirals (HTAs)

DEB025 (alisporivir)

Program on clinical hold as of April 19, 2012

SCY635

Keller DM. Medscape News, April 19, 2012.

What's In Our Future? More Triple Therapy

- Single DAA plus IFN backbone plus ribavirin (RBV)
  - Second-generation PIs
  - Nucleoside polymerase inhibitors
  - Nonstructural protein (NS)5A inhibitors
- Considerations
  - RVR > 90%
  - Sustained virologic response (SVR): 80%
  - Tolerability and side effects
  - RGT
  - 12–16 weeks of therapy for *IL-28B* CC genotype

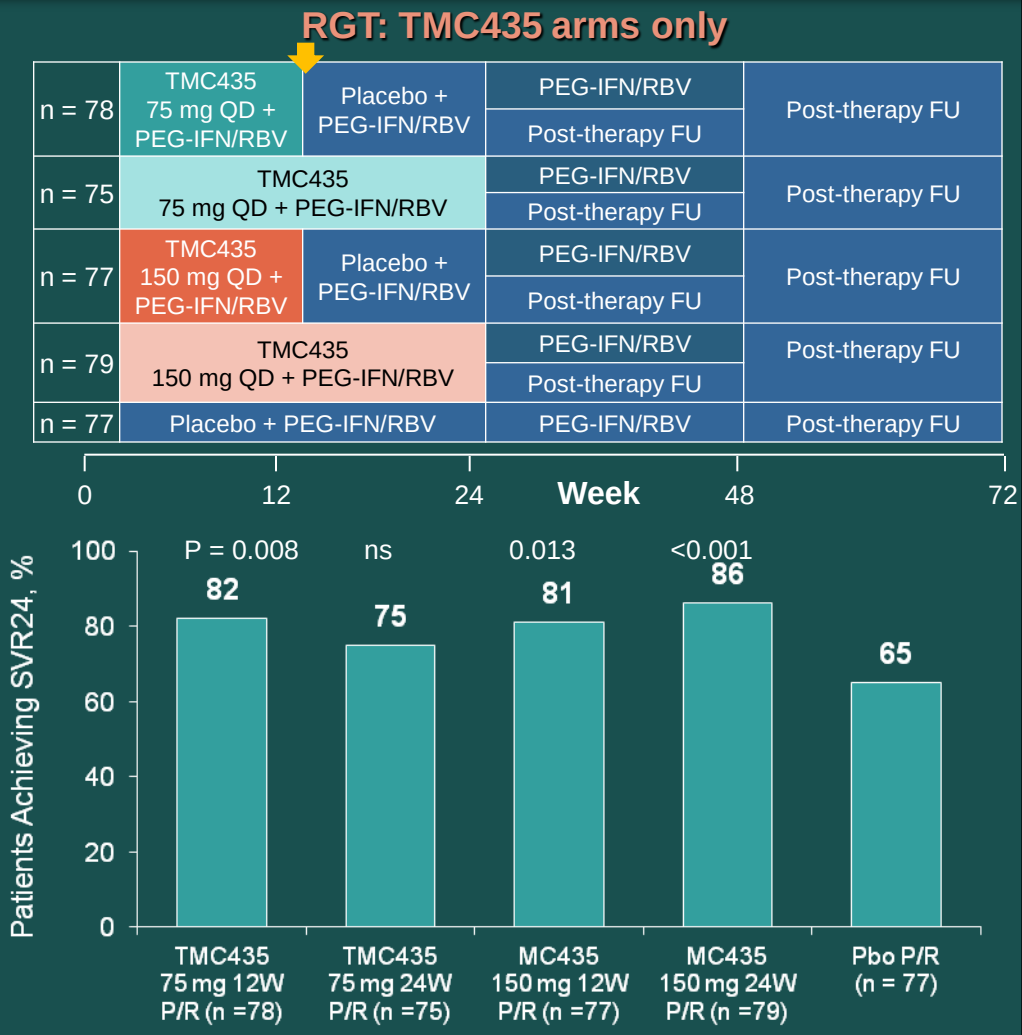
PILLAR: High SVR Rates with TMC435 at 24 Weeks; Attractive Safety Profile

2nd

- High Week 24 SVR rate with TMC435, but Δ remains low due to high placebo (PBO) response[1]

	ADVANCE		SPRINT-2		PILLAR	
	TPV	PBO	BOC	PBO	TMC	PBO
SVR, %	75	44	68	40	86	65
Δ, %	31		28		21	

  - Low proportion of genotype 1a (38%)
  - High SVR rates related to good compliance?
  - Rate of AEs similar to that with placebo
- Breakthrough/relapse associated with emergent 168 and 155 variants
- TMC435 is pangenotypic

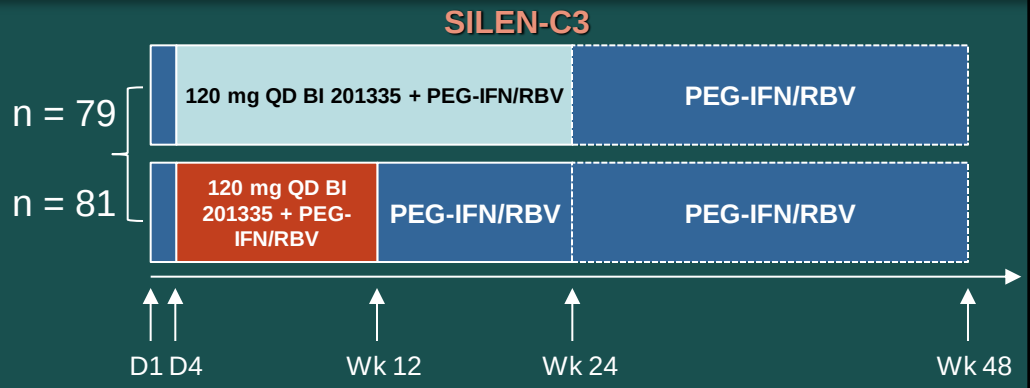


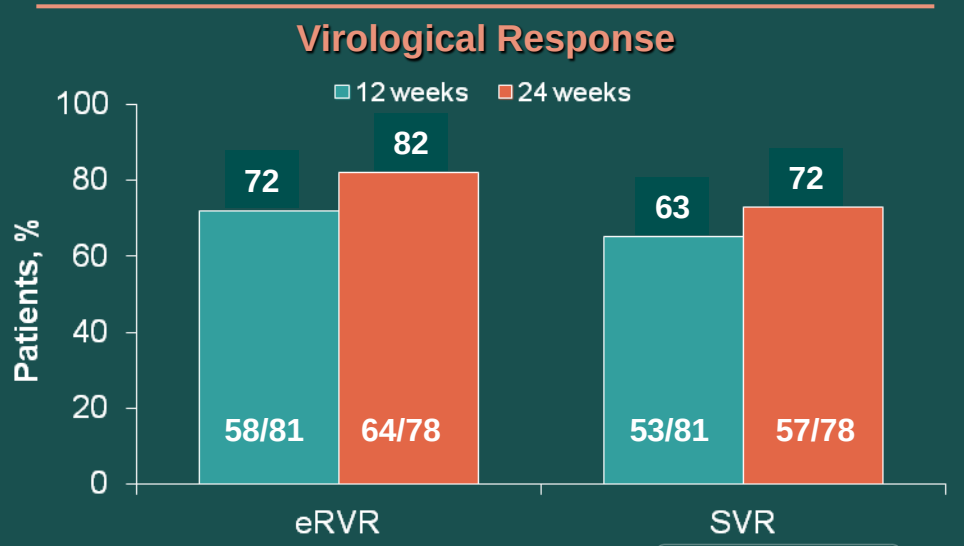
Fried M, et al. AASLD 2011, Abstract LB-5; Lenz O et al. AASLD 2011; Abstract 1329; Jacobson IM, et al. N Engl J Med 2011;364(25):2405-16; Poordad F, et al. N Engl J Med 2011;364(13):1195-206.

PEG-IFN = pegylated interferon; RBV = ribavirin; QD = once daily; FU = follow-up.

SILEN-C3: 69% SVR Rate with BI 201335 in Treatment-Naïve Patients

- Compared 12 vs. 24 wks of treatment
- All patients received PEG-IFN/RBV for ≥24 wks (48 wks if no extended RVR [eRVR])
  - 24-wk treatment similar to SILEN-C1 presented at EASL (71% SVR)
- Vomiting and rash seen after 24 wks; not reduced by shortening BI 201335 therapy
- Rebound in SILEN-C1 most often associated with 155 and 168 variants

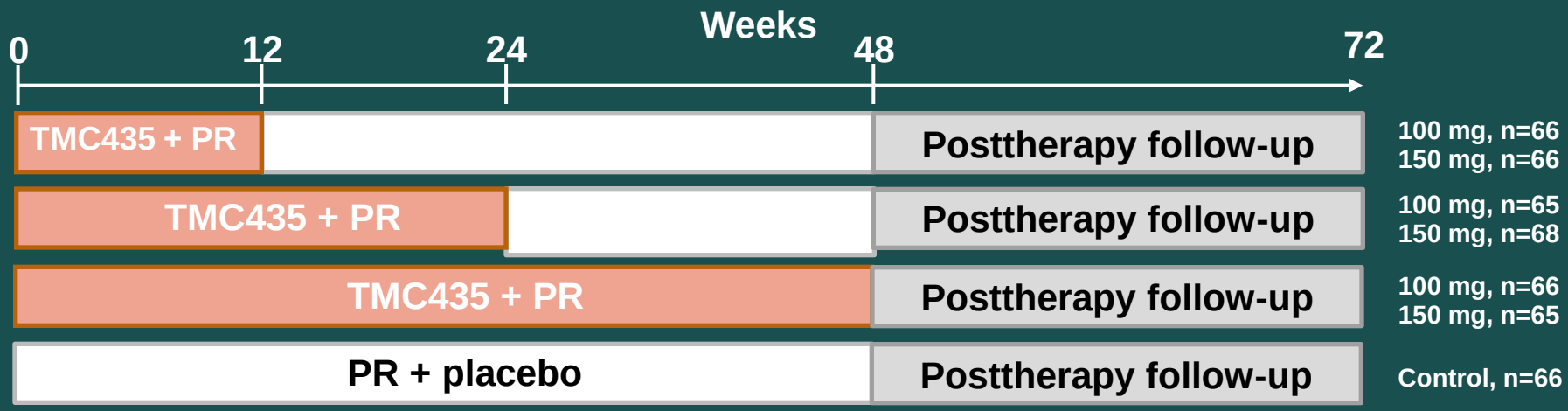




Dieterich D, et al. AASLD 2011, Abstract 36; Kukolj G et al. AASLD 2011, Abstract 1339.

ASPIRE: TMC435 in HCV Genotype 1 Patients Who Have Failed Previous PR Therapy

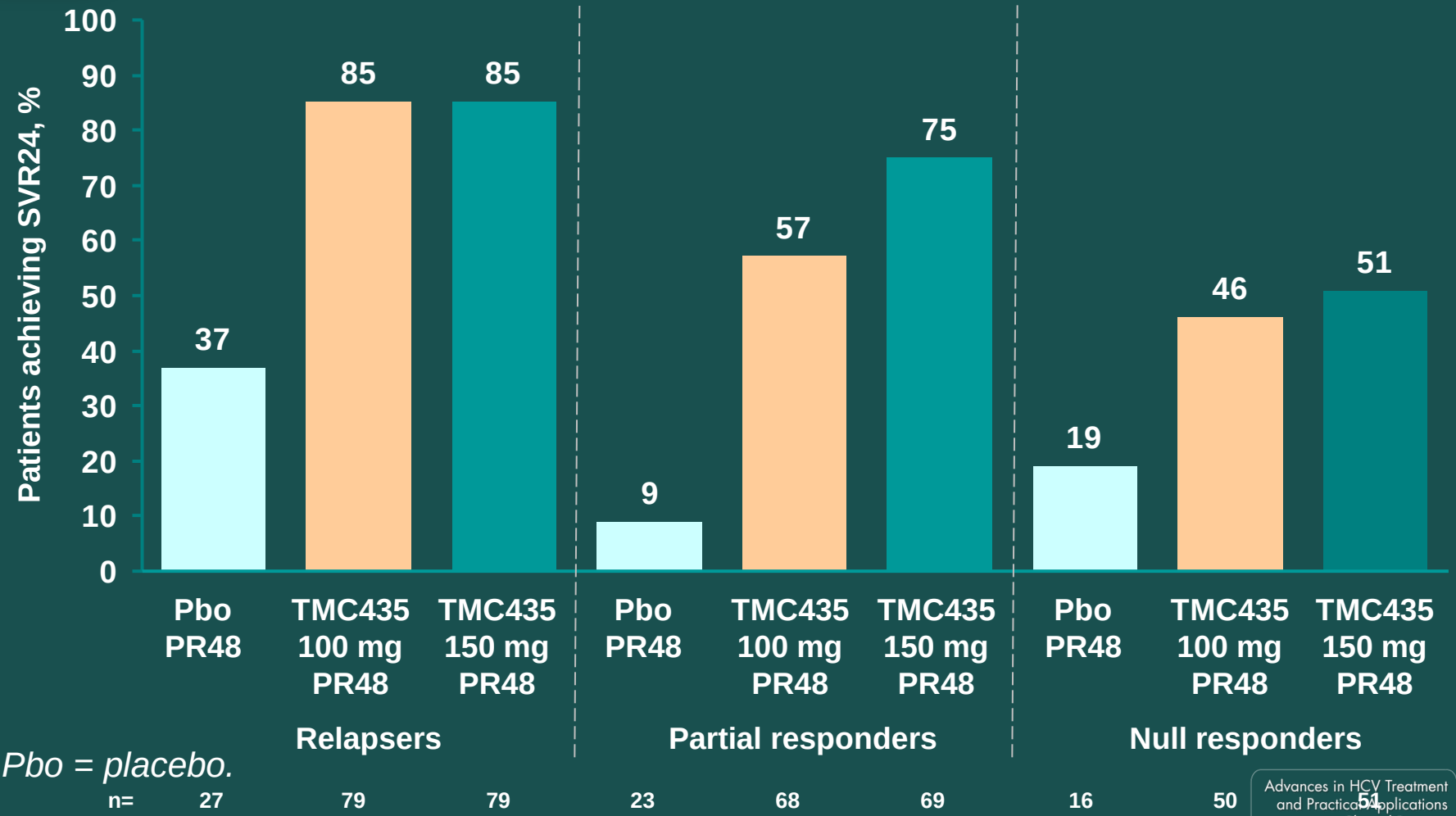
2nd



- TMC435 either 100 or 150 mg/d

Zeuzem S, et al. EASL 2012 Abstract 2.

ASPIRE: Proportion of Patients Achieving SVR24, by Prior Treatment Response



Pbo = placebo.

n=	27	79	79	23	68	69	16	50	51

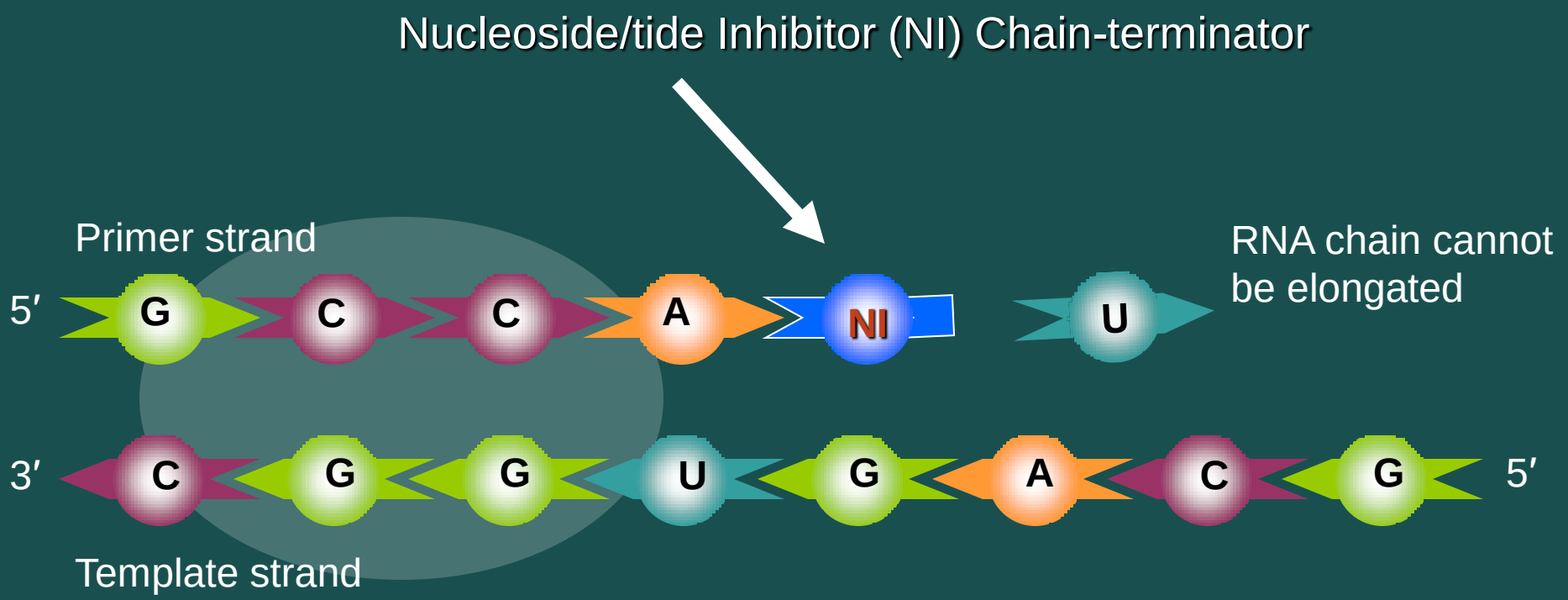
Zeuzem S, et al. EASL 2012 Abstract 2.

Nucleoside Inhibitors

- Advantages of nucleoside inhibitors
  - **N** No evidence of resistance mutations
  - **U** Urinary excretion (not hepatic): less risk of drug interactions
  - **C** Chain terminators: means greater pangenotypic potency
- No resistance: no S282T in treatment-naïve patients in trials to 12 weeks with mericitabine or 4 weeks with PSI-7977
- Urinary excretion: no evidence of hepatic metabolism via CYP enzymes, less risk of dose modification
- Chain terminators: homology of enzyme not required for antiviral activity

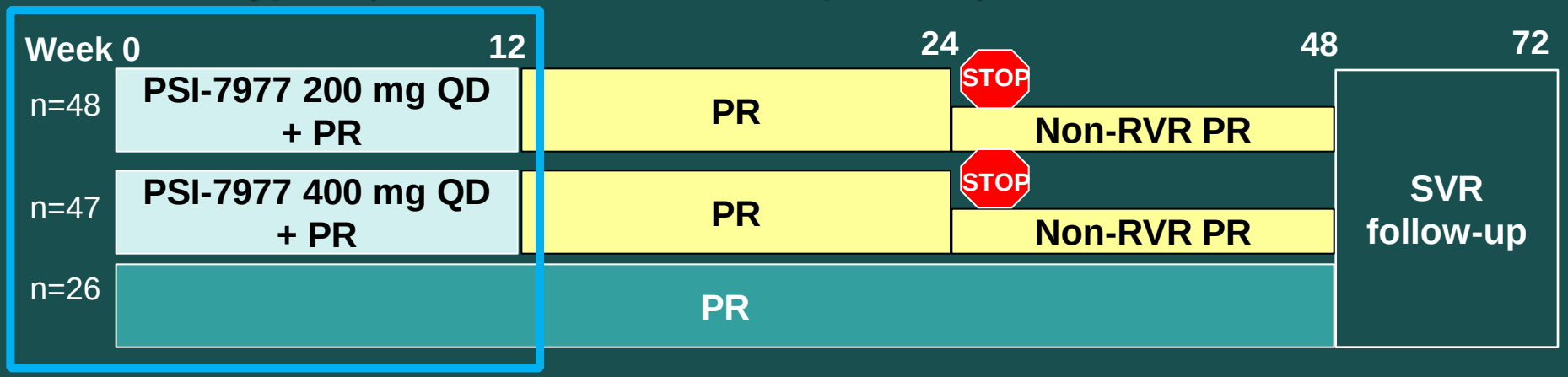
Pawlotsky JM, et al. Antivir Ther 2012 Mar 8. doi: 10.3851/IMP2088;
Gane EJ, et al. AASLD 2011 Abstract 34.

Nucleoside/tide Analog Polymerase Inhibitors are Chain-Terminators



PROTON: Once-Daily PSI-7977 plus PEG-IFN and RBV in Treatment-Naïve Patients

HCV Genotype 1 (N=121 treatment-naïve patients)



HCV Genotype 2/3 (N=25 treatment-naïve patients)

100% SVR

PR = PEG-IFN plus ribavirin.

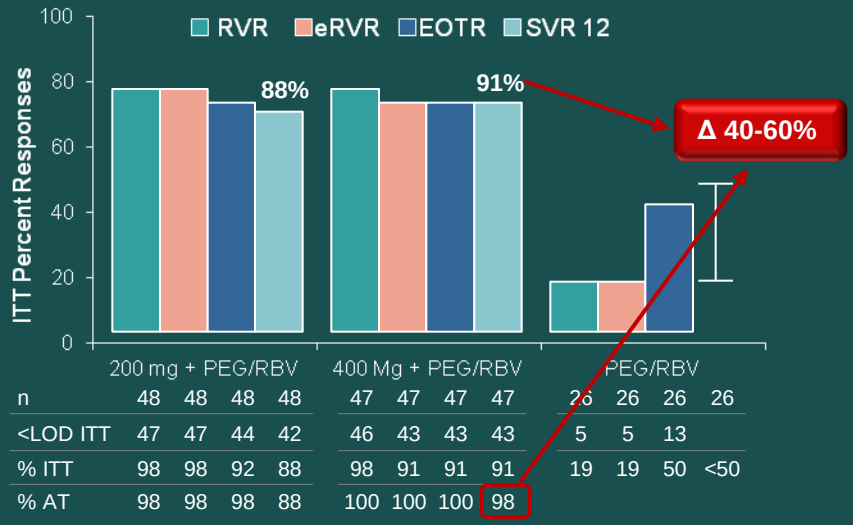
Nelson DR, et al. EASL 2011 Poster LB1372; Lalezari J, et al. EASL 2011 Oral #61.

PSI-7977: PROTON Genotype 1

- SVR at 12 weeks 91% with 400 mg PSI-7977/PR; 88% with 200 mg
  - Insomnia only notable AE; unknown severity/duration
- Data good, but ELECTRON arms required to support IFN-free regimen
  - Uncertain degree of fibrosis and rebounds also raise some questions
- Phase 3 program: 3 IFN-free studies
  - FISSION–12 weeks of tx in G2/G3 (3:1 bias for G3); started 12/2011
  - POSITRON–12 weeks of tx in G2/G3; started 3/2012
  - NEUTRINO–G1 IFN-unable; starting mid-2012. Design to be finalized based on ELECTRON and QUANTUM
- IFN-unable population defined as broad, real-world cohort

Week 12 SVR Rates

PSI-7977 400 mg QD + PR: 91%
Placebo/PR: ~35%–50%



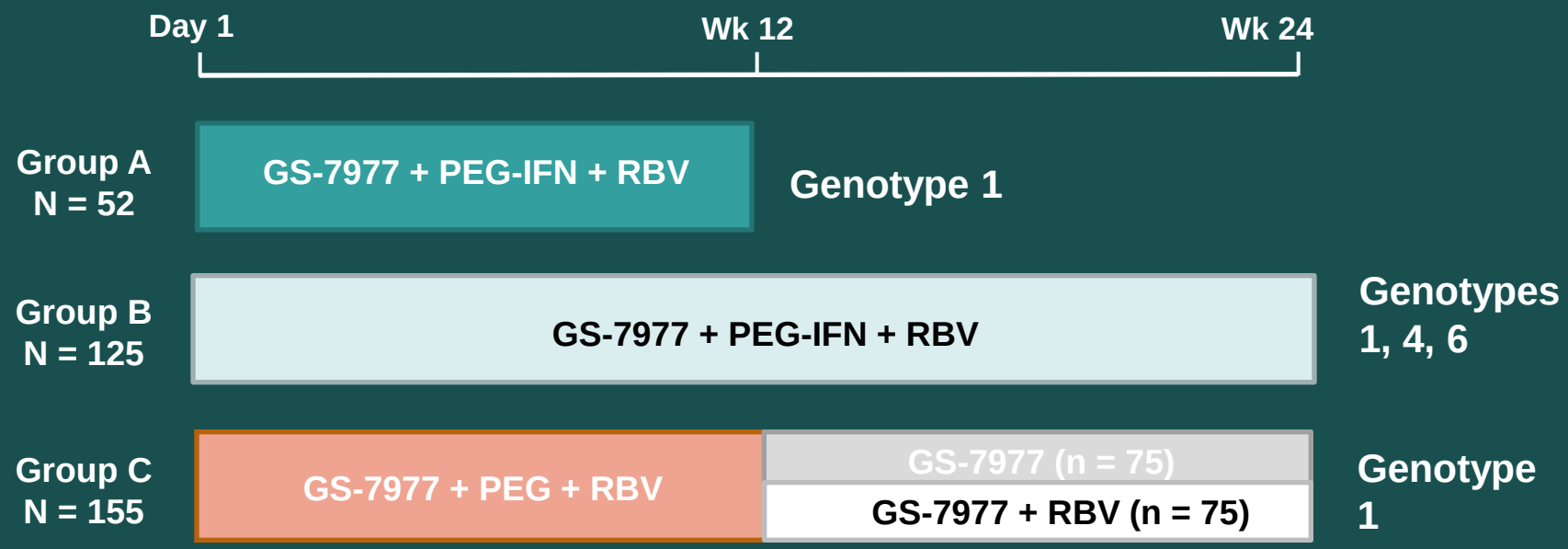
n	48	48	48	48	47	47	47	47	26	26	26	26
<LOD ITT	47	47	44	42	46	43	43	43	5	5	13	
% ITT	98	98	92	88	98	91	91	91	19	19	50	<50
% AT	98	98	98	88	100	100	100	98				

ITT: intent-to-treat cohort; AT: As treated--patients who received >8 wks PSI-7977.

G1 = genotype 1; G2/3 = genotype 2 or 3; LOD = limit of detection.

Gane EJ, et al. AASLD 2011 Abstract 34; Lawitz E, et al. AASLD 2011 Abstract 225; clinicaltrials.gov: NCT01497366, NCT01542788.

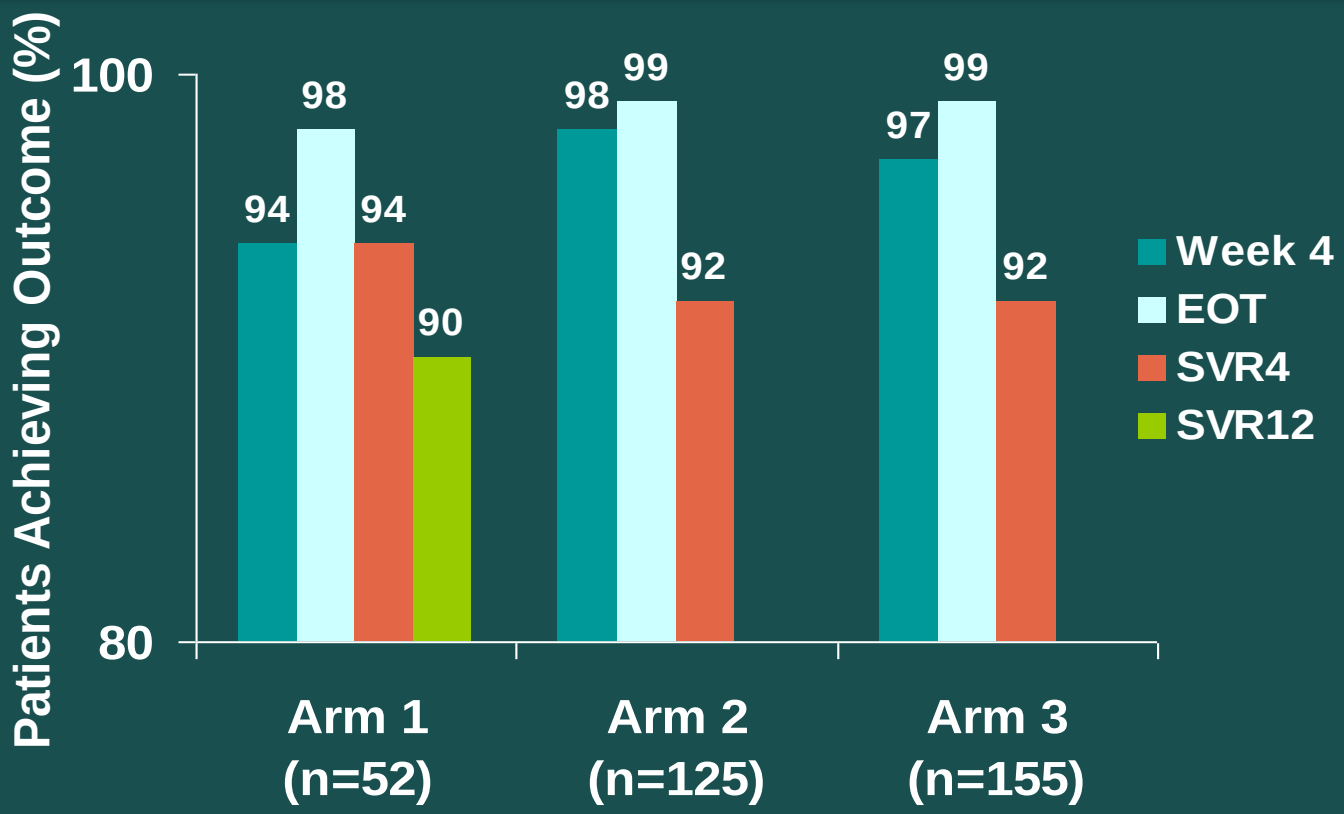
ATOMIC: PR and GS-7977 Therapy in HCV Treatment-Naïve Patients



- HCV genotype 1 randomized 1:2:3 into 1 of 3 open-label arms
- Stratified by:
  - *IL-28B* genotype (CC vs non-CC)
  - HCV RNA at screening (≤ vs. >800,000 IU/mL)

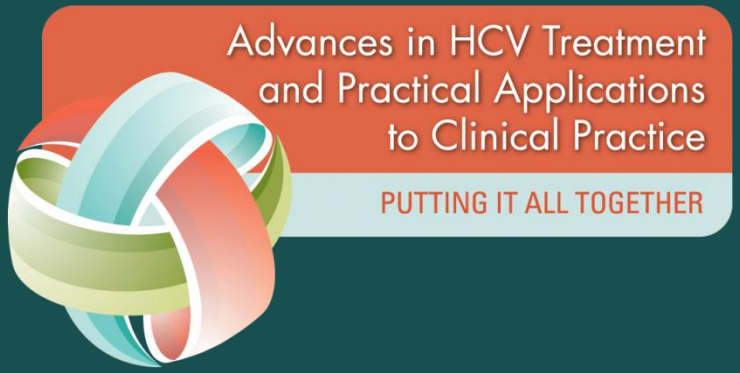
Kowdley KV, et al. EASL 2012 Abstract 1.

ATOMIC: PR and GS-7977 Therapy in HCV Treatment-Naïve Patients



- 12 weeks of GS-7977 + PEG/RBV resulted in an SVR12 rate of 90% in Genotype 1 patients in intent-to-treat analysis

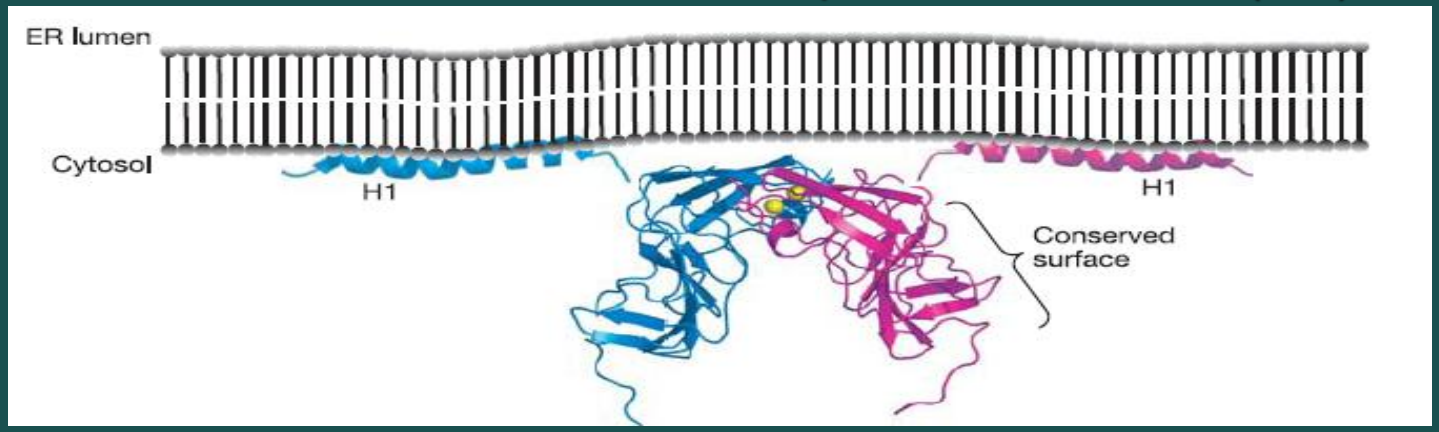
Kowdley KV, et al. EASL 2012 Abstract 1.



NS5A Inhibitors

Characteristics of HCV NS5A – Replication Complex

Structure of NS5A domain I (N-terminal) at 2.5-Å resolution associated with endoplasmic reticulum (ER)



- Large phosphoprotein
- Associates at least as a dimer
- Binds RNA
- Amphipathic helix (H) at amino terminus promotes membrane association
- Essential component of HCV RNA ER-membrane–associated replication complex
- Modulates cellular systems involved in IFN resistance

Tellinghuisen TL, et. al. *Nature.* 2005;435(7040):374-379.
Love RA, et al. *J Virol.* 2009;83(9):4395–4403.

Characteristics of NS5A Inhibitors

- Daclatasvir (BMS-790052)
  - First in class
  - PK profile supports once-daily oral dosing
  - Picomolar in vitro potency against genotypes 1a and 1b
  - Well tolerated in Phase 1 studies
- PPI-461
  - Favorable preclinical profile
  - Plasma half-lives suggest once-daily dosing possible
  - Good oral bioavailability
  - Antiviral activity against all genotypes in replicon assays
  - EC_{50} ≤0.2 nmol/L for genotypes 1a/1b; 0.1–9 nmol/L for other genotypes
  - Variants with high resistance generated (genotype 1a)

PK = pharmacokinetic; EC_{50} = 50% maximum effective concentration .

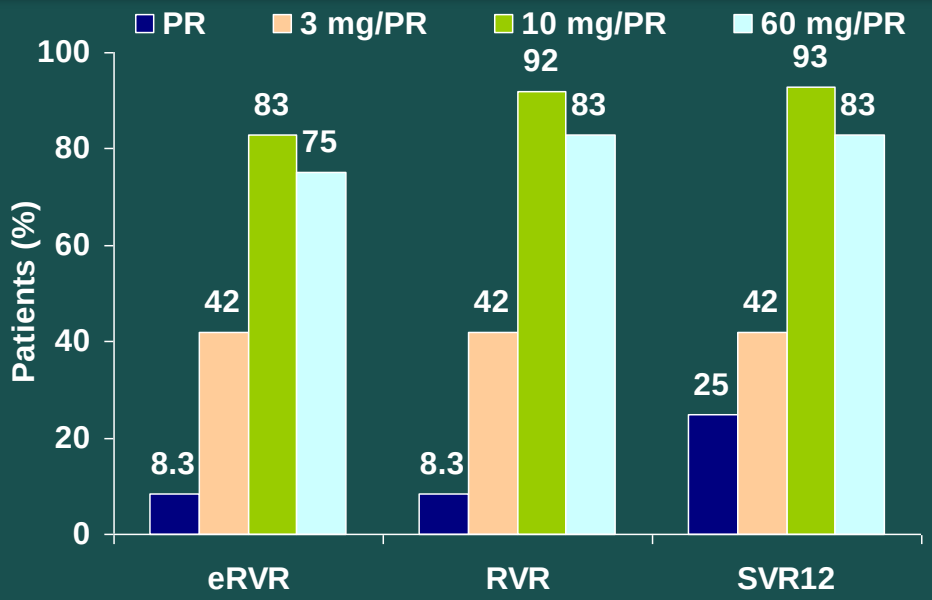
Pol S, et al. EASL 2010 Oral #1189
Colonno R, et al. EASL 2011 Abstract 33.

eRVR with Daclatasvir, an NS5A Inhibitor, in Treatment-Naïve Genotype 1 Patients

- Phase 2a trial with PR
- 48 weeks of triple therapy all arms
- 1:1:1:1 ratio (n=12 each group)

PR
Daclatasvir 3 mg/PR
Daclatasvir 10 mg/PR
Daclatasvir 60 mg/PR

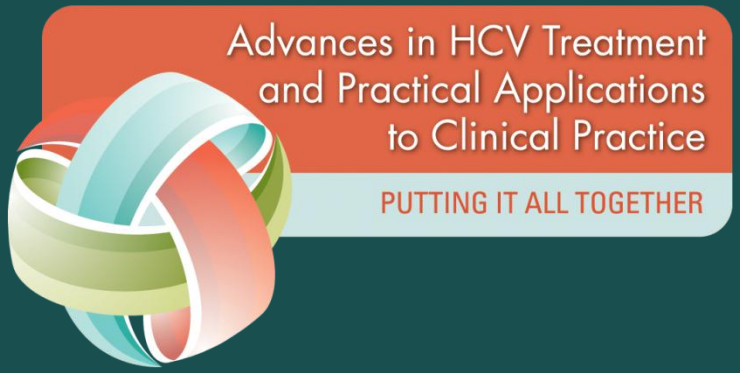
- No effect of *IL-28B* genotype
- AEs/serious AEs comparable across groups
- Discontinuations comparable
- 2 pts (3 and 60 mg) had Hgb <9 g/dL
- EPO use comparable
- 3 breakthroughs, 5 relapses with NS5A



eRVR = undetectable HCV RNA at Weeks 4 and 12
RVR = undetectable HCV RNA at Week 4
cRVR = undetectable HCV RNA at Week 12

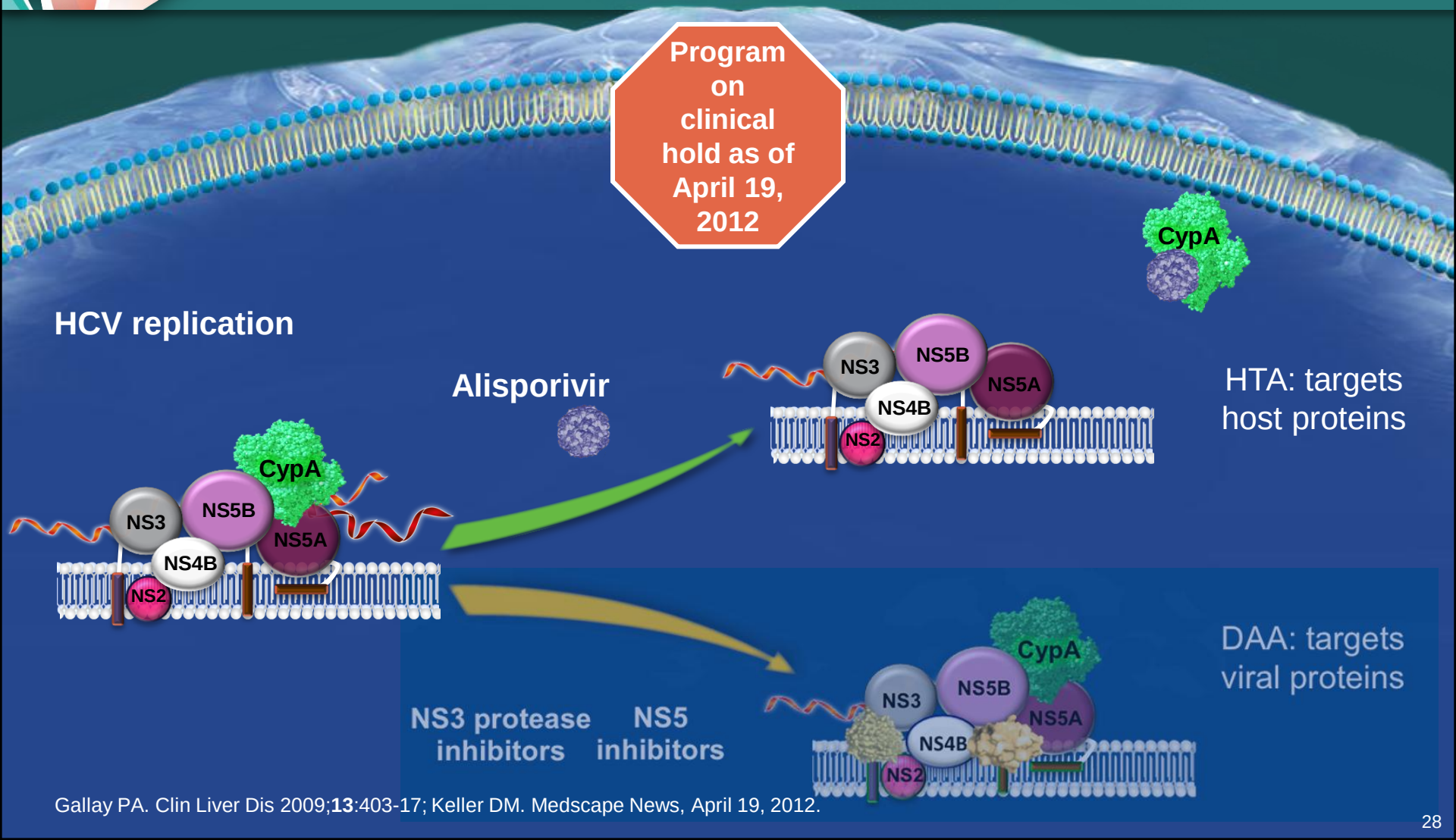
Daclatasvir fulfils early promise from monotherapy studies; very attractive agent for further development with PR or in combination regimens

Pol S, et al. EASL 2011 Poster P1373.



Cyclophilin Inhibitors

Alisporivir (DEB025) Has a Fundamentally Different Mechanism of Action from that of DAAs



Gallay PA. Clin Liver Dis 2009;**13**:403-17; Keller DM. Medscape News, April 19, 2012.

Alisporivir Has a High Barrier to Resistance

Program on clinical hold as of April 19, 2012

- Mutant HCV variants require cyclophilin A for replication
  - For high-level viral resistance to occur with the HTA alisporivir, the virus must acquire mutations that allow it to be less dependent on the essential host factor for replication

In vitro data	Cyclophilin inhibitors	NS3/NS5B inhibitors
Time needed for resistance selection	+++ (3–6 months)	- (2–3 weeks)
Level of resistance	Low (<5-fold)	High (>100-fold)
Number of mutations needed for high-level resistance	Multiple mutations at NS5A and other regions	Single mutation at NS3 or NS5B

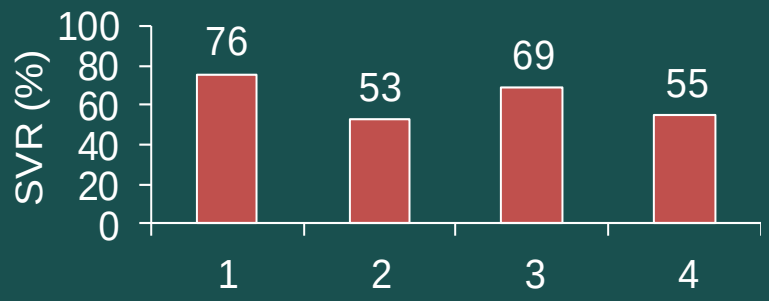
By targeting host factors essential for HCV replication, alisporivir has a lower potential for viral resistance

Coelomont L, et al. PLoS One 2010;**5**:e13687; Lu L, et al. Antiviral Res 2007;**76**:93-7; Lu L, et al. Antimicrob Agents Chemother 2004;**48**:2260-6; Keller DM. Medscape News, April 19, 2012.

Alisporivir + PR in Genotype Treatment-Naïve Patients

Program on clinical hold as of April 19, 2012

- Cyclophilin inhibitor
- Potent pangenotypic activity
- Phase 2b study, 4 arms (N=288):
  1. DEB025 + PR x 48 weeks
  2. DEB025 + PR x 24 weeks
  3. DEB025 + PR RGT by RVR (24 vs. 48 weeks)
  4. PR x 48 weeks
- DEB025 600 mg BID first week, then 600 mg daily
- RVR lower than with PIs
- SVR 100% in *IL-28B* CC patients



Flisiak R, et al. EASL 2011 Oral # 4; Keller DM. Medscape News, April 19, 2012.

- No null responses with DEB025 for 12 wks (n=196)
- Viral breakthrough 4.7% with DEB025 vs. 5.5% for PR
  - 2.8% had full dose of DEB025 at breakthrough
- Hyperbilirubinemia 33% with DEB025 vs 1.4% with PR
  - 4.2% of DEB025 patients had bilirubin ≥5 x ULN, reversible, no ALT elevations
  - 10% of patients had jaundice

- Alisporivir enhances SVR in G1 naïve and might be given as RGT; warrants further development.
- Hyperbilirubinemia and transporter effect are potential issues

ULN = upper limit of normal.

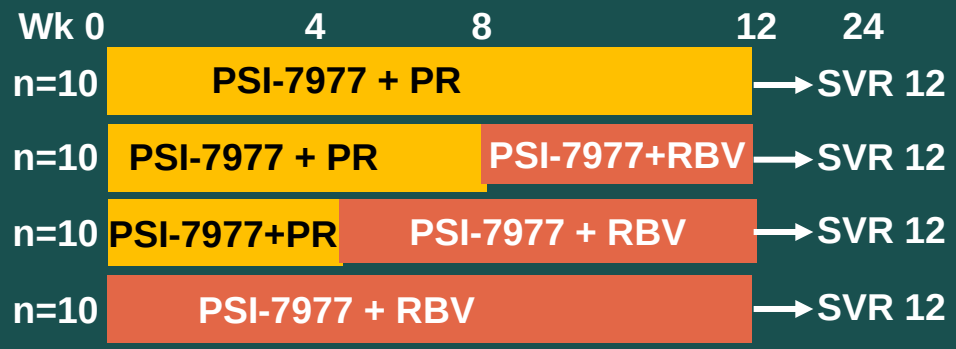
What's In the Future? Interferon-Free?

Polymerase backbone

- Highest resistance barrier
- Pangenomic
  - Second-generation PIs, NS5A inhibitors, nonnucleoside inhibitors, ribavirin
  - Cyclophilin inhibitor?
  - 3- or 4-drug regimens
  - SVR?

PSI-7977 QD + RBV: PEG-IFN Not Required for Complete RVR in Treatment-Naïve G2/G3 Patients

ELECTRON; n=40; G2 (40%); G3 (60%)



- 40%–50% of patients had *IL-28B* CC genotype
- Median HCV RNA: 6.4–6.7 logs
- AEs: Transition from 12 wk IFN to no IFN
  - AE frequency decreased from 72% to 40%
  - Grade 3 hematologic effects absent without IFN (vs. 64% Grade 3 neutropenia in controls)
- ALT normalized in all by Week 3
- Viral decay curves unchanged regardless of duration or presence of IFN
- Other trial: PSI-7977 monotherapy x 12 weeks results in similar suppression, but 4/10 relapse by 4 weeks later

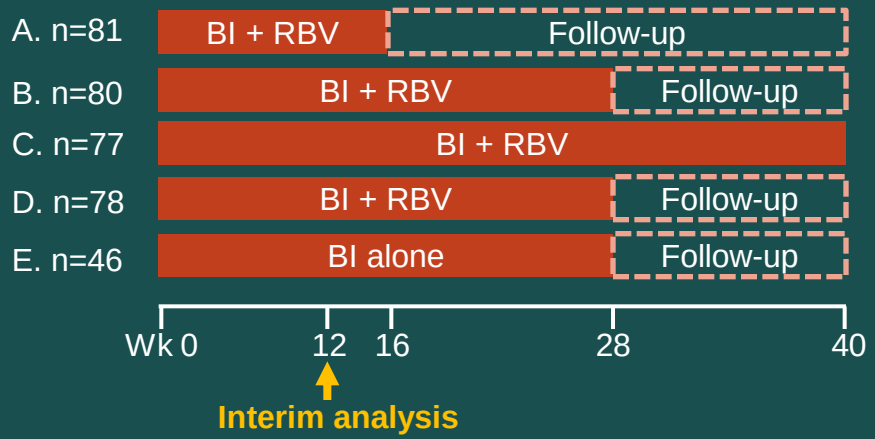
Wk	PSI-7977 RBV 12 wks PEG		PSI-7977 RBV 8 wks PEG		PSI-7977 RBV 4 wks PEG		PSI-7977 RBV No PEG	
	n	% <LOD	n	% <LOD	n	% <LOD	n	% <LOD
0	11	0	10	0	9	0	10	0
4	11/11	100	10/10	100	9/9	100	10/10	100
12	11/11	100	10/10	100	9/9	100	10/10	100
SVR 12	11/11	100	10/10	100	9/9	100	10/10	100

- PSI-7977 + RBV achieves impressive results with or without IFN in a small trial in G2/3 patients (100% SVR)
- Relapse prevented with RBV
- Need to confirm results in larger controlled trials and investigate strategy in G1
- Game changer, if validated
- Could provide paradigm shift in field

Gane EJ, et al. AASLD 2011, San Francisco, #34

IFN-Free Regimens of BI201335/207127 ± RBV in Treatment-Naïve G1 Patients: Week 12 Interim Results of SOUND-C2

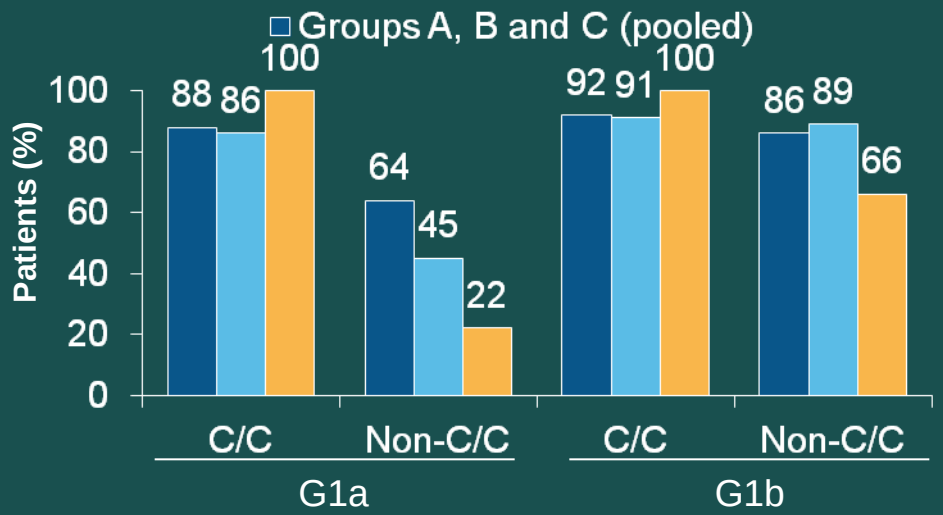
Study Design



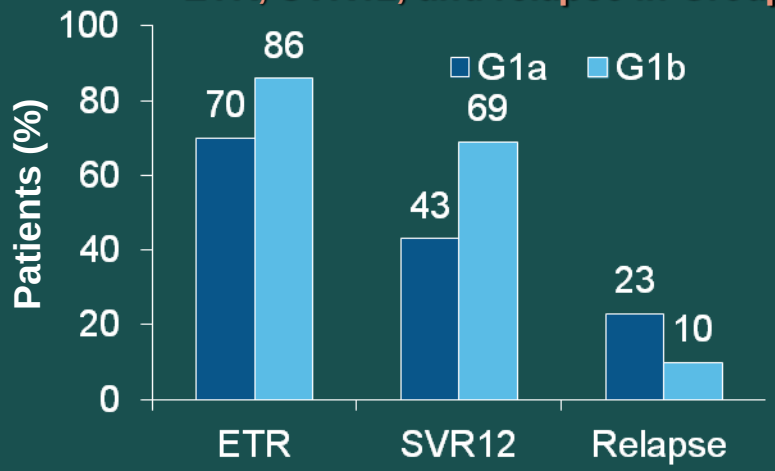
- Patient characteristics
  - 52% male, 98% white, 85% BL HCV RNA ≥800,000 IU/mL, 38% G1a, 10% compensated cirrhosis, 26% *IL-28B* CC
- Most common AEs
  - Asthenia, pruritus, rash, photosensitivity, jaundice, nausea, vomiting, diarrhea

Combination has potent antiviral activity with high chance to achieve SVR in G1b-infected pts

Patients with HCV RNA <LLOQ at Week 12



ETR, SVR12, and relapse in Group A



Zeuzem S, et al. AASLD 2011 Abstract LB-15.

Dual Oral vs. Quad Therapy: Daclatasvir + Asunaprevir ± PR

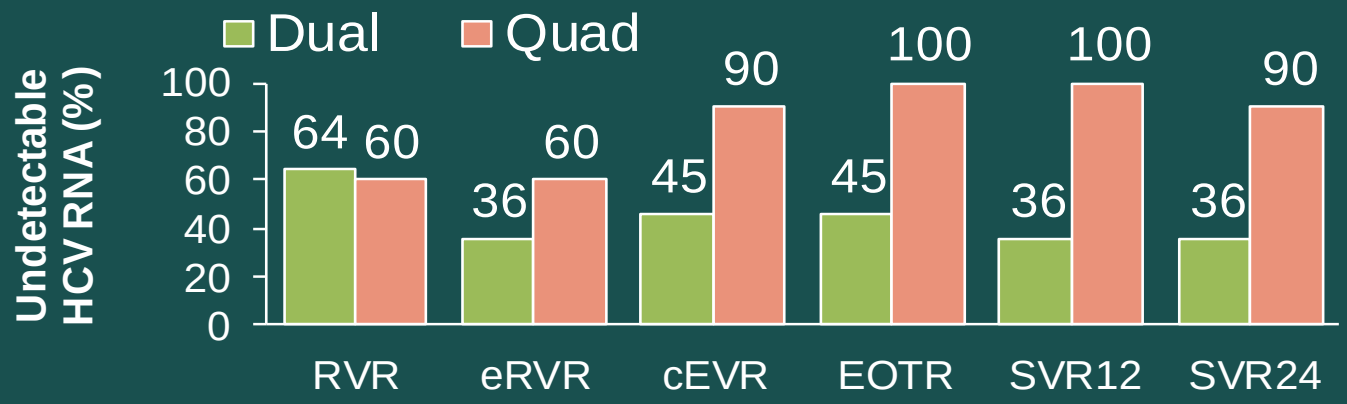
Group A	**Daclatasvir 60 mg QD + Asunaprevir 600 mg BID (n=11)**	Follow-up × 48 weeks
Group B	**Daclatasvir (60 mg QD) + Asunaprevir (600 mg BID) + PR (n=10)**	Follow-up × 48 weeks

24-week treatment

Post treatment: Week 24: SVR24

Phase 2a study (n=21)

- G1 null responders to 12 weeks of PR
- 19 with *IL-28B* genotype CT/TT
  Daclatasvir: NS5A replication complex inhibitor
- Asunaprevir: NS3 PI



Lok AS, et al. N Engl J Med 2012;366(3):216-24; McPhee F, et al. EASL 2011 Poster 1223.

Dual Oral vs. Quad Therapy: Daclatasvir + Asunaprevir ± PR

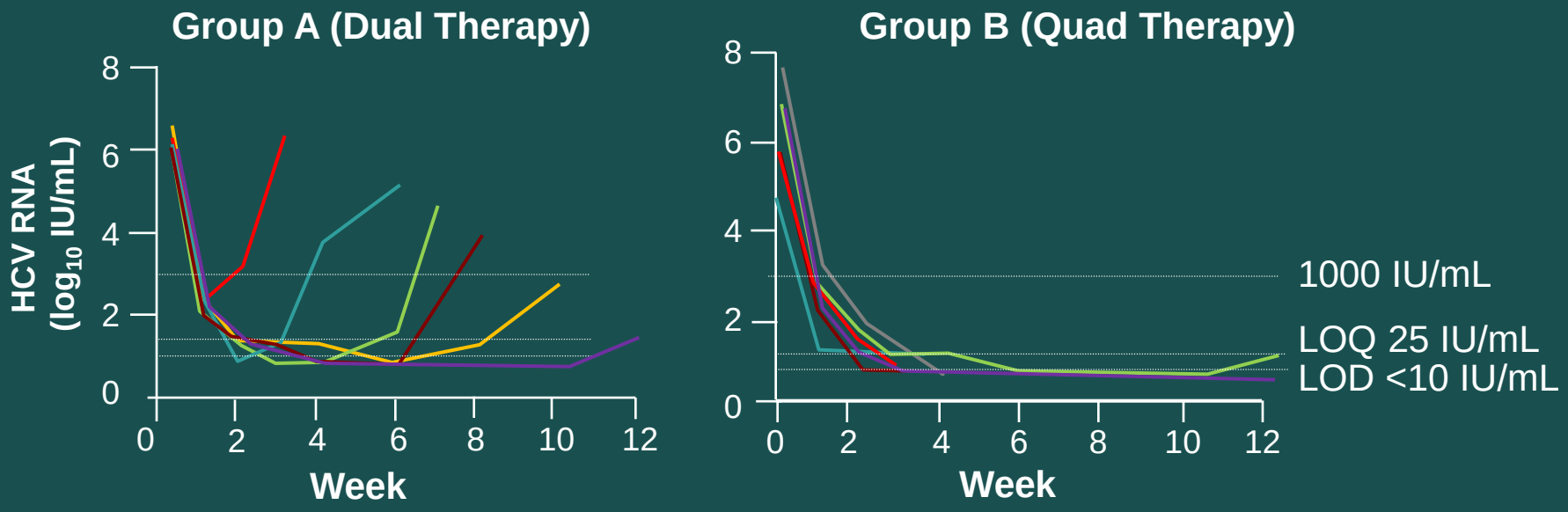
- Dual: 36% with SVR24 (2/9 G1a and 2/2 G1b)
  - 6 pts (all G1a) with viral breakthrough on therapy, 1 relapse 4 weeks after therapy
- Quad therapy: 100% undetectable by Wk 6; 90% with SVR24 (1 pt had HCV RNA <LLOQ but detectable at Wk 24, was undetectable on repeat testing)
  - No viral breakthrough
- Resistance variants
  - NS5A: Q30E/R, L31V/M, and Y93C/N
  - NS3: R155K and D168A/E/T/V/Y
- Safety
  - Dual: Diarrhea 73%, fatigue 55%, headache 45%
  - Quad: Diarrhea 70%, fatigue 70%, headache 50%, nausea 50%
  - ALT elevations >3 × ULN in 6 pts (NS3 related)

- HCV can be cured without IFN
- Quad therapy might yield superior SVR rates (vs triple therapy) after null response
- Combination DAA therapy may be sufficient for SVR in G1b; but G1a will either need additional or host-targeted agents to optimize SVR

Lok AS, et al. N Engl J Med 2012;366(3):216-24; McPhee F, et al. EASL 2011 Oral #327; Zeuzem S, et al. N Engl J Med 2011;364(25):2417-28.

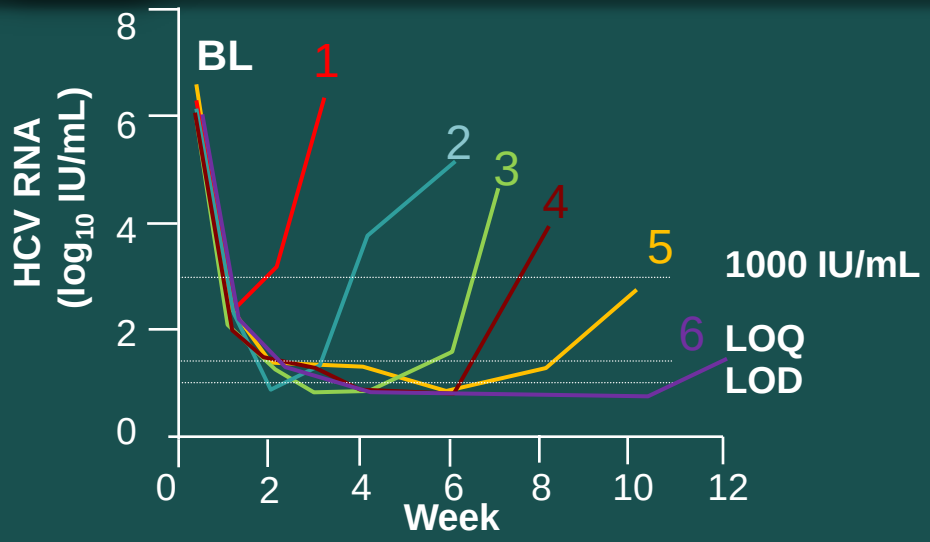
Dual Oral vs. Quad Therapy: Daclatasvir + Asunaprevir ± PR: Virologic Escape

HCV RNA Levels over Time for Individual Patients



McPhee F, et al. EASL 2011 Oral #327.

Dual-Therapy Group: Resistance Variants in Patients with Viral Breakthrough



- Viral breakthrough in 6 of 11 pts: All G1a; no resistance variants detected at baseline
- NS3 protease and NS5A resistance variants detected after viral breakthrough
- Role of emerging variants confirmed by phenotypic analysis
  - NS3:30- to 525-fold resistance
  - NS5A: 3400- to >330,000-fold resistance

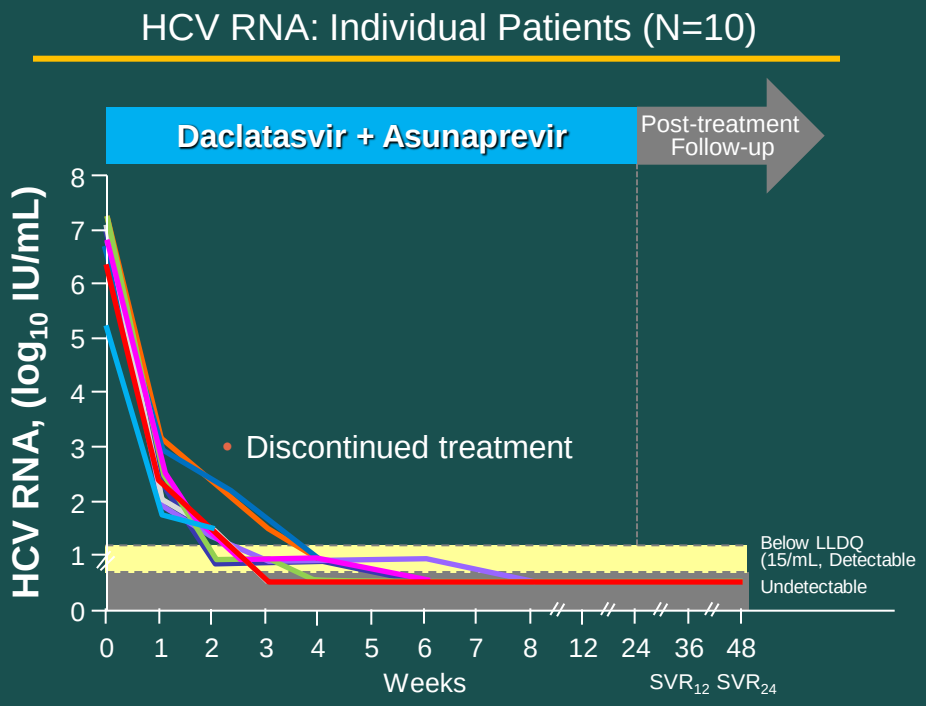
Patient #	1	2	3	4	5	6*
Week tested	2	4	7	8	10	12
NS3 protease variants (%)	D168Y (87) D168A (13)	R155K (100)	D168Y (100)	D168E (100)	R155K (100)	D168V
NS5A variants (%)	Y93N (100)	L31V (100)	Q30R (100) L31M (100)	Q30R (76) L31V (100) Y93C (17)	Q30R (45) L31V (77) H58P (39) Y93C (16) Y93N (13)	Q30R L31V H54Y Y93C

*Clonal analysis not performed on Patient 6

McPhee F, et al. EASL 2011 Oral #327.

Daclatasvir/Asuneprevir: Success in Genotype 1b Prior Null Responders

- Data from small trial: 100% SVR at 24 weeks with daclatasvir/asuneprevir (IFN/RBV-free) in genotype 1b prior null responders
- Phase 3 trial began in 2012
- Quad therapy might be required for G1a
- Hard-to-treat G1a may be a target for PSI-7977/ asuneprevir combo, as an alternative to daclatasvir/ asuneprevir



Lok AS, et al. N Engl J Med 2012;366(3):216-24;
Chayama K, et al. Hepatology 2012;55(3):742-8.

Study AI-444040: Daclatasvir and GS-7977, ± Ribavirin, in Treatment-Naïve HCV Genotype 1–3 Patients

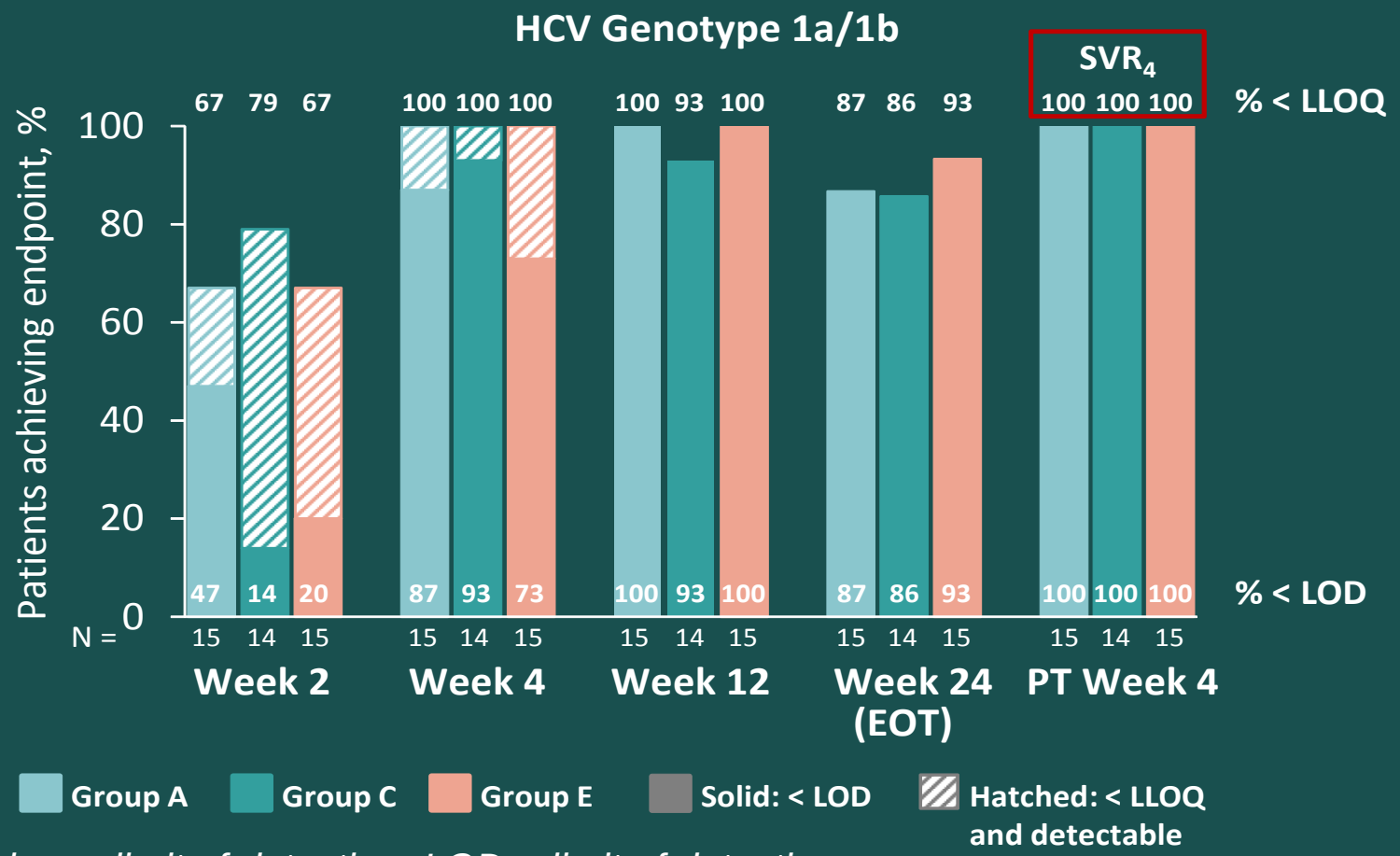
2nd

- Open-label study in patients with HCV genotype 1 (n=44) and genotype 2 or 3 (n=44), no cirrhosis
- Randomized (1:1:1) to receive:
  - GS-7977 (400 mg/d) x 7 days, then DCV (60 mg/d)+ GS-7977 (400 mg/d) for 23 weeks
  - DCV + GS-7977 for 24 weeks
  - DCV + GS-7977 + ribavirin (1000–1200 mg/d for genotype 1; 800 mg/d for genotype 2/3) for 24 weeks
- Primary endpoint: undetectable HCV RNA at 12 weeks after treatment

DCV = daclatasvir.

Sulkowski M, et al. EASL 2012 Abstract 1422.

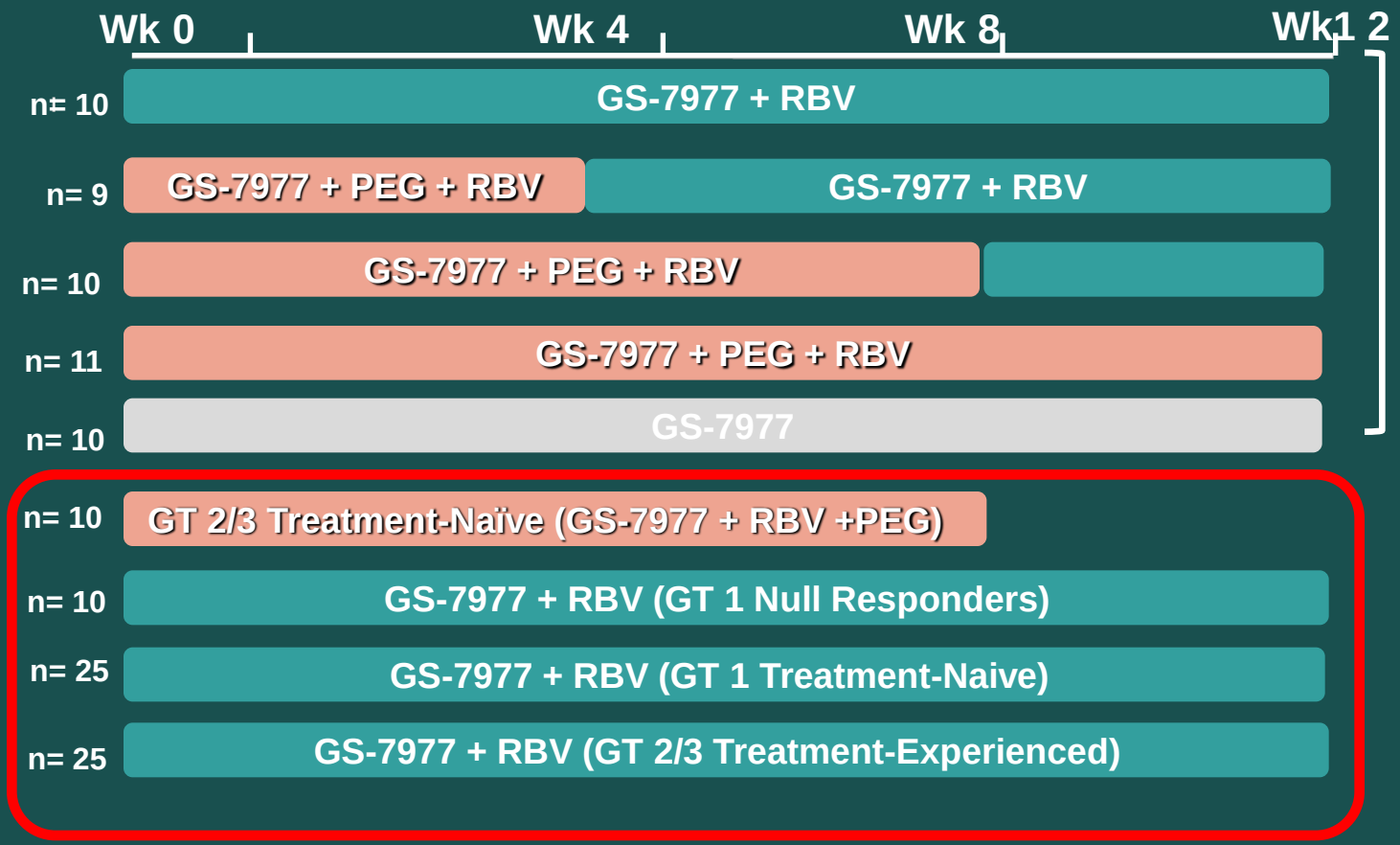
Study AI-444040: Incidence of Undetectable HCV RNA



LLOQ = lower limit of detection; LOD = limit of detection.

Sulkowski M, et al. EASL 2012 Abstract 1422.

ELECTRON: Once-Daily GS-7977 Plus Ribavirin in HCV Genotypes 1–3



Gane EJ, et al. EASL 2012 Abstract 1113.

ELECTRON: Once-Daily GS-7977 Plus Ribavirin in HCV Genotypes 1–3

Patients with HCV RNA <LOD Over Time, n/N (%)

	Genotype 2/3 Treatment-naïve 8 wks (N=10)	Genotype 1 Null Responders 12 wks (N=10)	Genotype 1 Treatment-naïve 12 wks (N=25)	Genotype 2/3 Treatment-experienced 12 wks (N=25)
Week 1	6/10 (60)	1/10 (10)	7/25 (29)	8/25 (32)
Week 2	10/10 (100)	7/10 (70)	17/24 (71)	21/25 (84)
Week 4	10/10 (100)	10/10 (100)	25/25 (100)	25/25 (100)
EOT	10/10 (100)	9/9 (100)	25/25 (100)	21/21 (100)
SVR 4	10/10 (100)	1/9 (11)	22/25 (88)	12/15 (80)
SVR 8	10/10 (100)	1/9 (11)	–	
SVR 12	10/10 (100)	–	–	–

- No virologic breakthrough in any arm, suggesting high barrier to resistance

EOT = end of treatment.

Gane EJ, et al. EASL 2012 Abstract 1113.

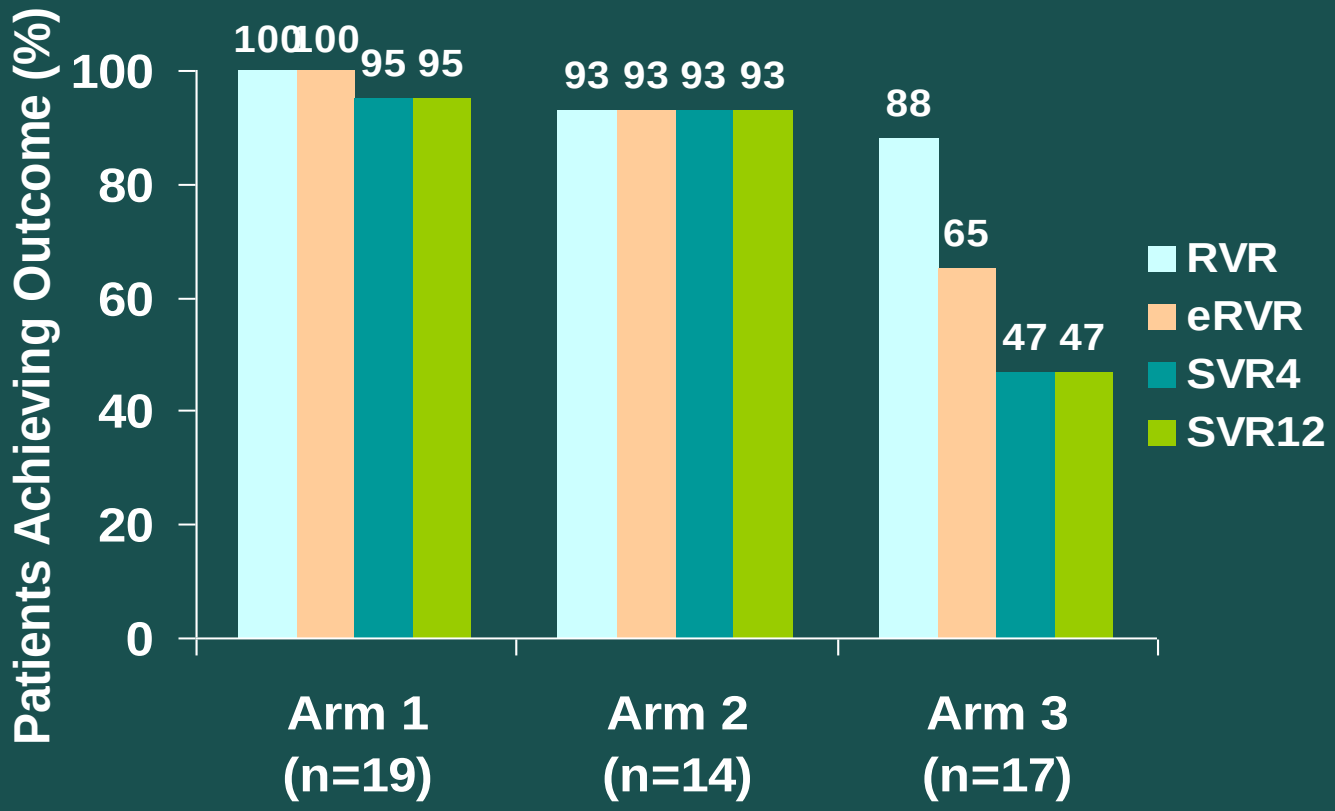
CoPilot: ABT-450/r, ABT-333, and Ribavirin for HCV Genotype 1 Treatment-Naïve and Nonresponder Patients

2nd

- ABT-450: a potent NS3 HCV protease inhibitor (boosted with low-dose ritonavir, ABT-450/r)
- ABT-333: a nonnucleoside NS5B polymerase inhibitor
- Three treatment arms for noncirrhotic patients with HCV genotype 1 infection, all x 12 weeks:
  1. Treatment-naïve: ABT-450 250 mg/ritonavir 100 mg/d, ABT-333 400 mg/d, ribavirin 1000–1200 mg/d (in 2 divided doses)
  2. Treatment-naïve: ABT-450 150 mg/ritonavir 100 mg/d, ABT-333 400 mg/d, ribavirin 1000–1200 mg/d (in 2 divided doses)
  3. Prior PR nonresponders: ABT-450 150 mg/ritonavir 100 mg/d, ABT-333 400 mg/d, ribavirin 1000–1200 mg/d (in 2 divided doses)

Poordad F, et al. EASL 2012 Abstract 1399.

CoPilot: Virologic Results



- ABT-450/r + ABT-333 + RBV for 12 weeks has the potential to produce SVR in a high proportion of subjects, without interferon

Poordad F, et al. EASL 2012 Abstract 1399.

HCV — The Revolution Has Begun

- Antiviral activity in all HCV genotypes
- No selection of resistance
- All-oral combination regimen
- Short treatment duration
- QD (or BID) dosing
- Excellent safety and tolerability

Applicable in difficult-to-treat populations:

- Transplant
- Coinfection
- End-stage renal disease, etc.