HCV Clinical Trials Perspective

What Controls Will Be Needed For Future Trials?

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The Long-Awaited New Era:
Protease Inhibitors for HCV Genotype 1

SVR >70%
Genotype 1

Response-guided therapy (RGT)

Increased side effects

Resistance

Drug-drug interactions

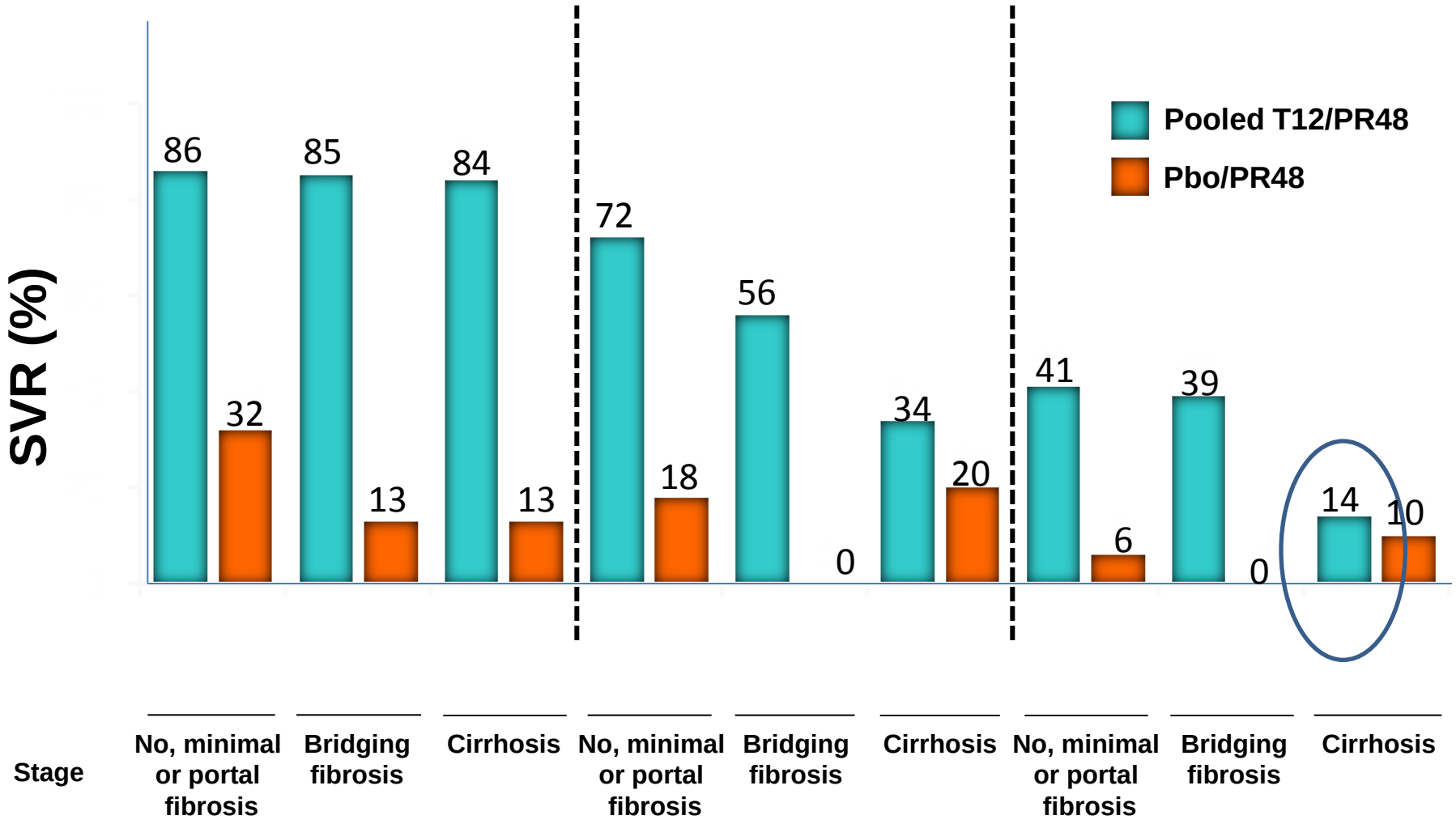
April 27-28, 2011: FDA Advisory Panel voted 18-0 for approval of boceprevir and telaprevir
Both drugs approved by FDA May 2011

The Recent Therapeutic Revolution Is NOT "The End of History"

- Still room for improved SVR rates
- Even 24 weeks may be longer than we really need
- Higher rates of failure in nonresponders
  - Highest in cirrhotic null responders
- Over half of patients who fail are left with resistant variants
- Significant toxicity issues
  - Universal desire to eliminate interferon (alpha)

Some Data From Phase 3 Have Led to Clinical Introspection

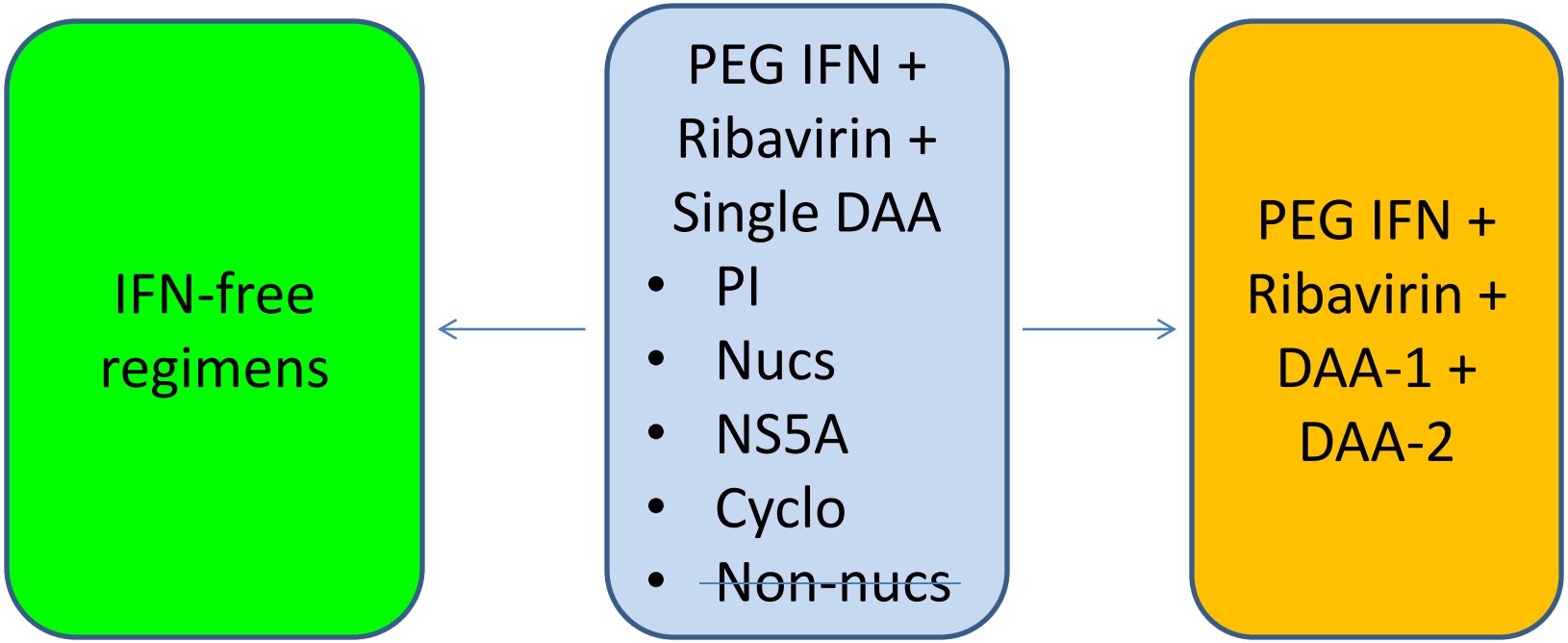
SVR by Fibrosis Stage and Prior Response in REALIZE



Zeuzem S et al.EASL:2011, Oral Presentation 5.

The “Warehouse” Won’t Be Empty Anytime Soon

Various Paradigms Being Developed Simultaneously



- *Some trials involve more than one of these designs*
- *PEG lambda not to be overlooked*
- *Host factor inhibitors (e.g. cyclophilin antagonists) may be equivalent to good DAAs*

Targets for New Hepatitis C Drugs

Protease inhibitors

Linear	Telaprevir Boceprevir ACH-1625 GS-9451
Macrocyclic	Danoprevir (RG7227) TMC 435350 BI-201335 BMS-650032 Vaniprevir MK5172

Clemizole

BMS-790052
GS-5885
ABT-267

Polymerase inhibitors

Active site (nucleosides)	Meracitabine IDX184 PSI-7977
Non-nucleosides	ABT-333 ABT-072 GS 9190 ANA598 VX-222 Filibuvir BI-207127

Cyclophilin

Alisporivir
SCY-635

Not all-inclusive

The need for PR/PI controls in phase 3 trials will be influenced by the results of novel treatment regimens that are already being studied; some with results known, many more pending

The Study That "Stole the Show": EASL 2011

NS5A + Protease Inhibitor + Peg IFN/RBV in Null Responders

BMS-790052 (60 mg QD) + BMS-650032 (600 mg BID) (n=11)	**Follow-up**
BMS-790052 + BMS-650032 + PEG IFN/RBV (n=10)	**Follow-up**

24-week treatment

Post treatment: Week 24: SVR24

- SVR
  - Dual: 36% (4/11, including 2/2 G1b, 2/9 G1a)
  - Quad: 100% (10/10)
- Proof of concept for curability of HCV without IFN
- Major potential for quad therapy in null responders (and others)

Lok A, et al. EASL 2011, Berlin, O1356; 2. McPhee F, et al. EASL 2011, Berlin, P1223

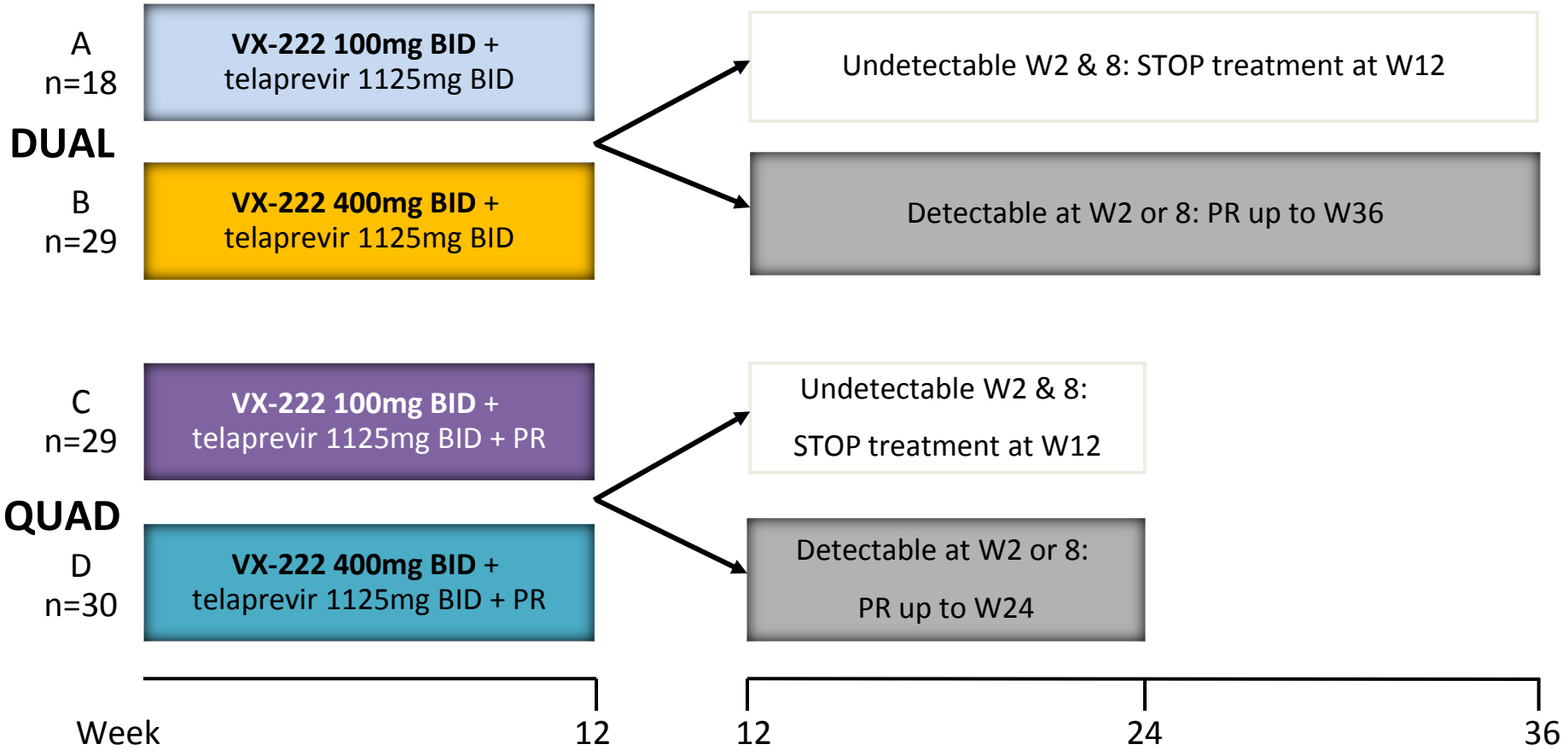
More Proof of Concept for Curability Without Interferon

- 10 Japanese patients treated with BMS 790052 + BMS 650032 for 24 weeks
- Null responders to PR therapy
- All genotype 1b
- 9 had SVR-12 (1 d/c'ed after 2 weeks)

Chayama et al, AASLD 2011

Telaprevir (PI) + VX-222 (non-nuc): ZENITH

- **ZENITH: Phase II study of telaprevir (T) plus VX-222, with or without Peg-IFN/RBV, for 12 weeks in treatment-naïve HCV genotype-1 patients**

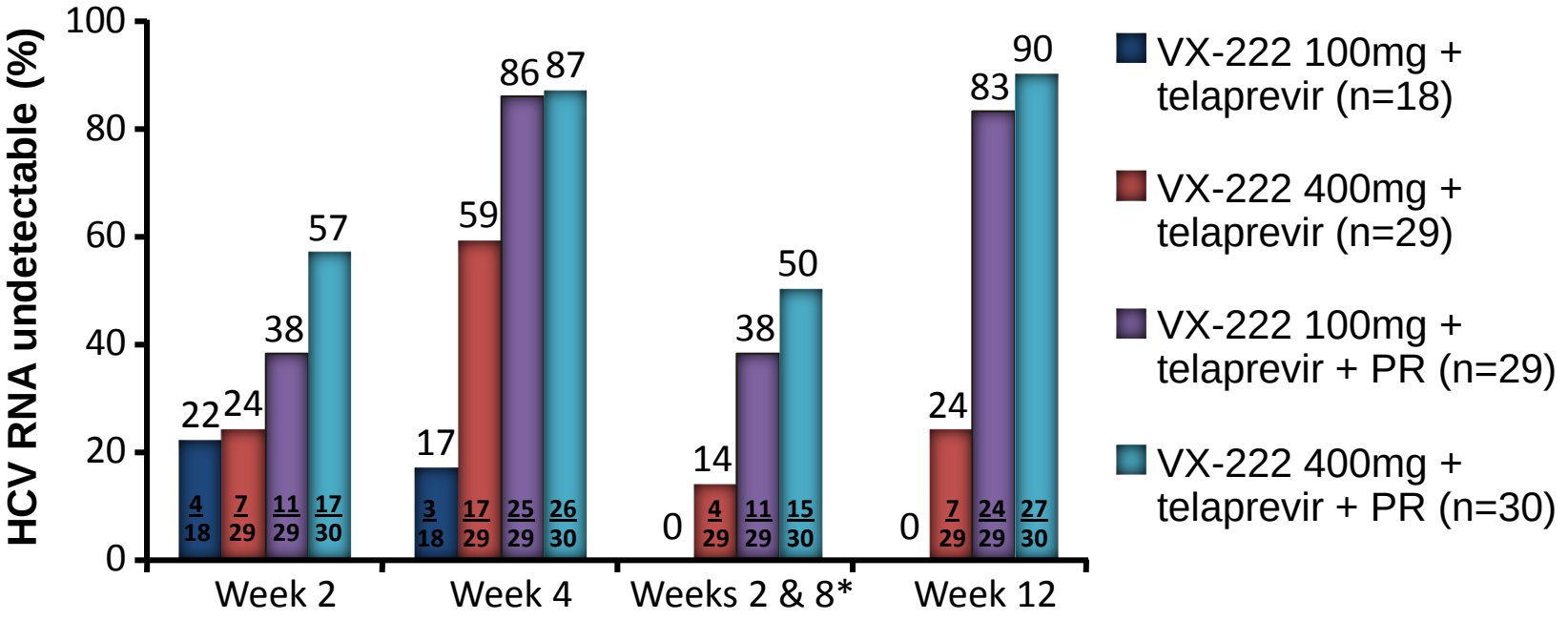


PR: peginterferon alfa-2a (180 µg/wk) + ribavirin (1000–1200 mg/day)

Di Bisceglie AM, et al. J Hepatol 2011;54(Suppl. 1):S540

Telaprevir (PI) + VX-222 (non-nuc): ZENITH

- No virologic breakthrough in quad-therapy arms
- Virologic breakthrough common in VX-222/TVR dual-therapy arms (17% to 31%)
- Both dual regimens stopped early per protocol



*Indicates patients eligible to stop treatment at Week 12

SVR-12 data at AASLD 2011

Di Bisceglie AM, et al. J Hepatol 2011;54(Suppl. 1):S540

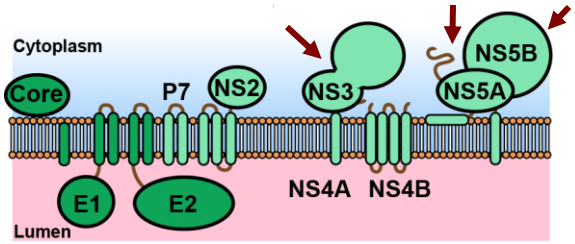
INFORM-3 Study

Treatment Naïve G1 Patients

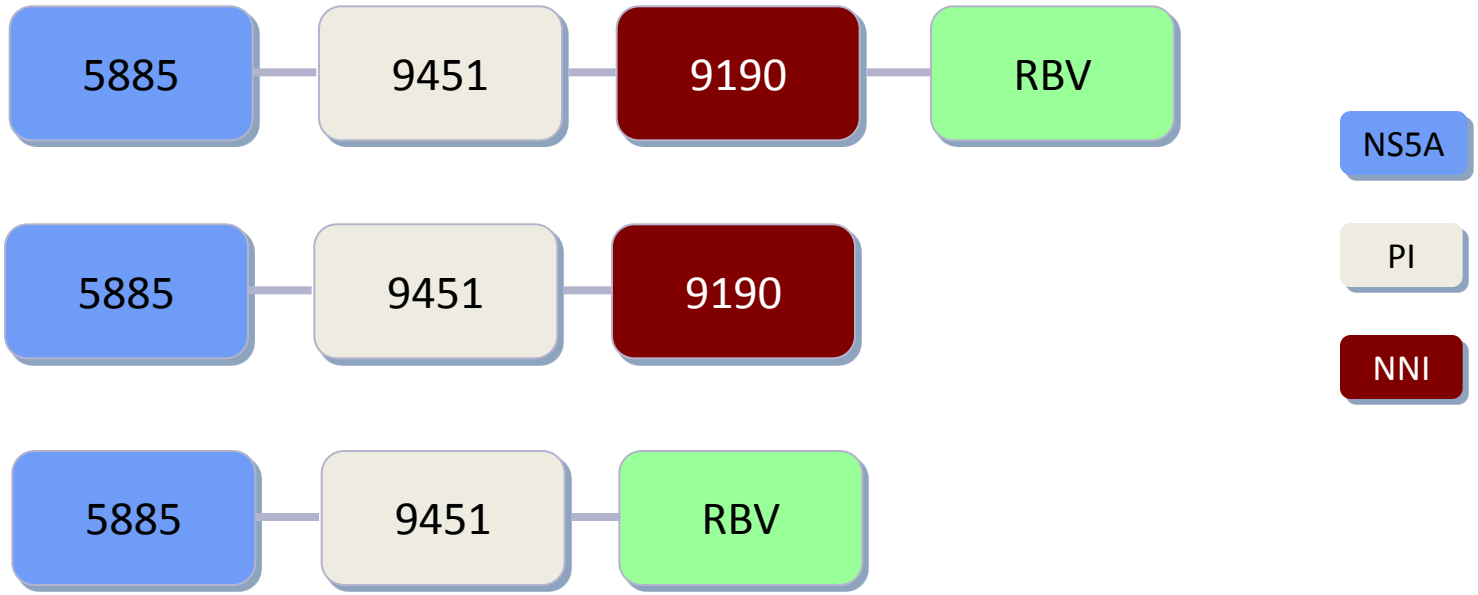
Danoprevir (ritonavir boosted)
+ Meracitabine + Ribavirin

Danoprevir (ritonavir boosted)
+ Meracitabine + Placebo

GS-US-248-0131 and 248-0132 Treatment Regimens

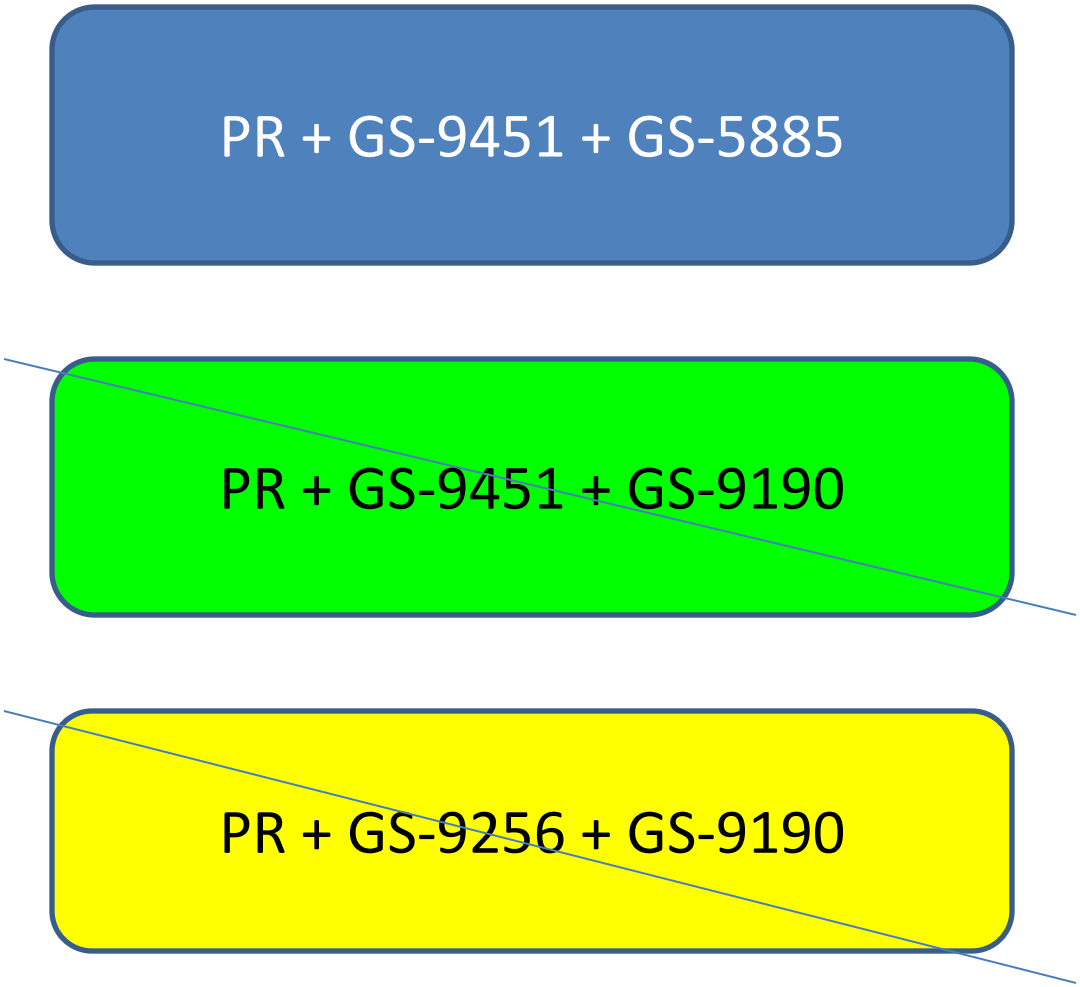


- Evaluation of the contribution of the individual antiviral components



Courtesy of Dr John McHutchison

Quad Therapy for Null Responders



PEG IFN Lambda + DAAs

PEG lambda + BMS 790052 + RBV

PEG lambda + BMS 650032 + RBV

PEG lambda + RBV

PEG lambda + 790052 + 650032 +RBV 24 weeks

PEG lambda + 790052 + 650032 + RBV 16 weeks

PEG lambda + 750052 +650032 24 weeks

PEG lambda + 790052 + 650032 + RBV 16 weeks

PROTON HCV GT2/GT3 - Antiviral Responses

- **24/25 enrolled subjects completed therapy**
  - **One subject lost to follow-up after day 1**
- **Consistent HCV RNA reduction: 24/24 RVR & cEVR(EOT)**
  - **No difference in viral kinetics: GT 2 v GT 3; IL28B CC v T allele**
- **No virologic breakthrough & no relapse through 12 weeks post-therapy**
- **SVR12 in 24/24 subjects with evaluable data**

	Week 2	Week 4 ***RVR***	Week 12 cEVR/***EOT***	***SVR12***
n (evaluable)	**24**	**24**	**24**	**24**
HCV RNA < LOD	21	24	24	24
% Response	88%	100%	100%	100%
Lost to follow-up	1	1	1	1
% Response (ITT)	84%	96%	96%	96%

Lalezeri J et al, J Hepatol 2011;54:S28

PROTON:

Treatment-naïve HCV GT1[1]

	RVR	*cEVR*	*EOT*	Relapse	SVR12
HCV GT1 PSI-7977 200mg QD PEG/RBV n=48	**98%**	**100%**			
HCV GT1 PSI-7977 400mg QD PEG/RBV n=47	**98%**	**92%**			
HCV GT1 Placebo PEG/RBV n=26	**19%**	**62%**			

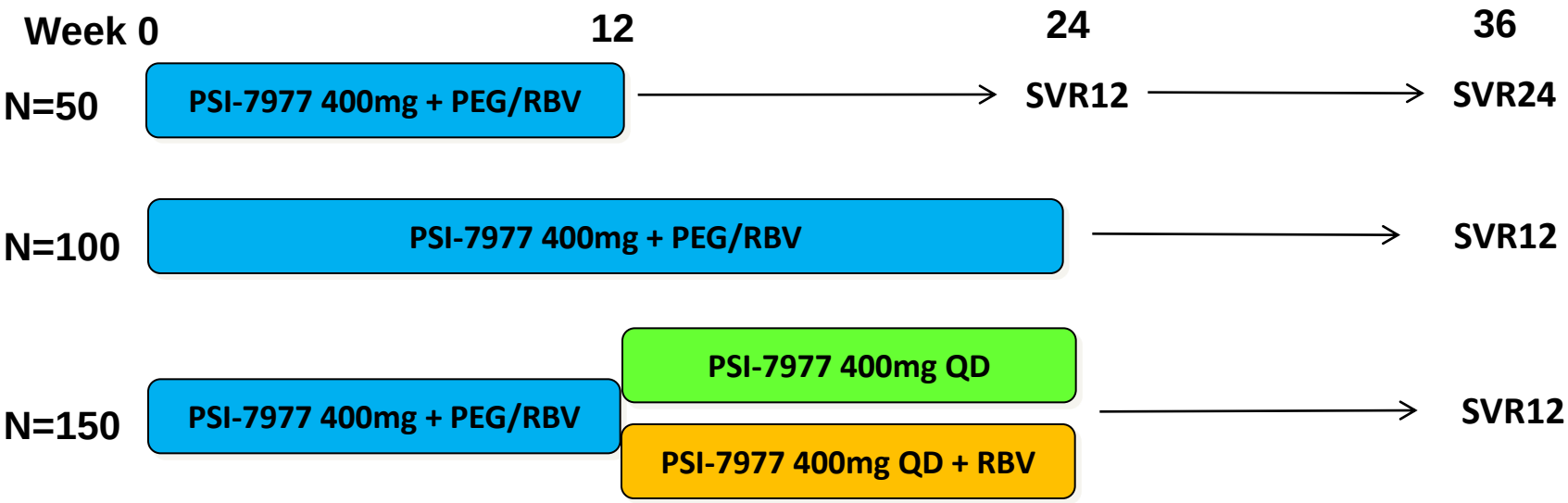
GT1 Portion of Trial Ongoing

Results at AASLD 2011

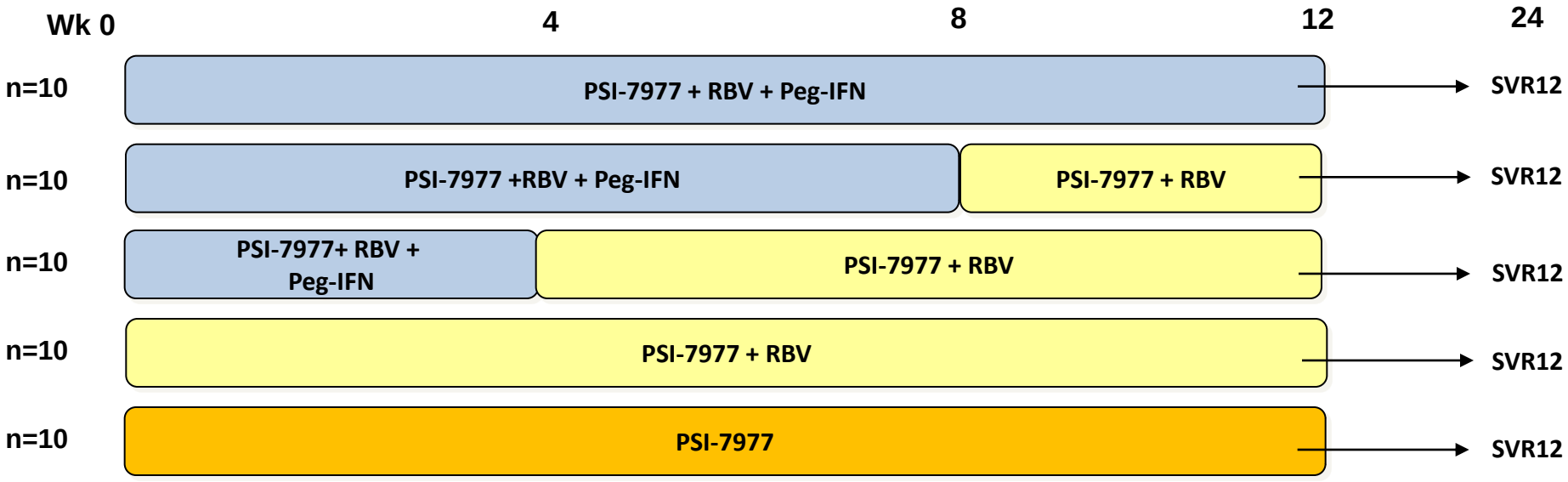
Response was independent of IL28B genotype

Nelson D et al, EASL LB#1372, 2011

ATOMIC Study

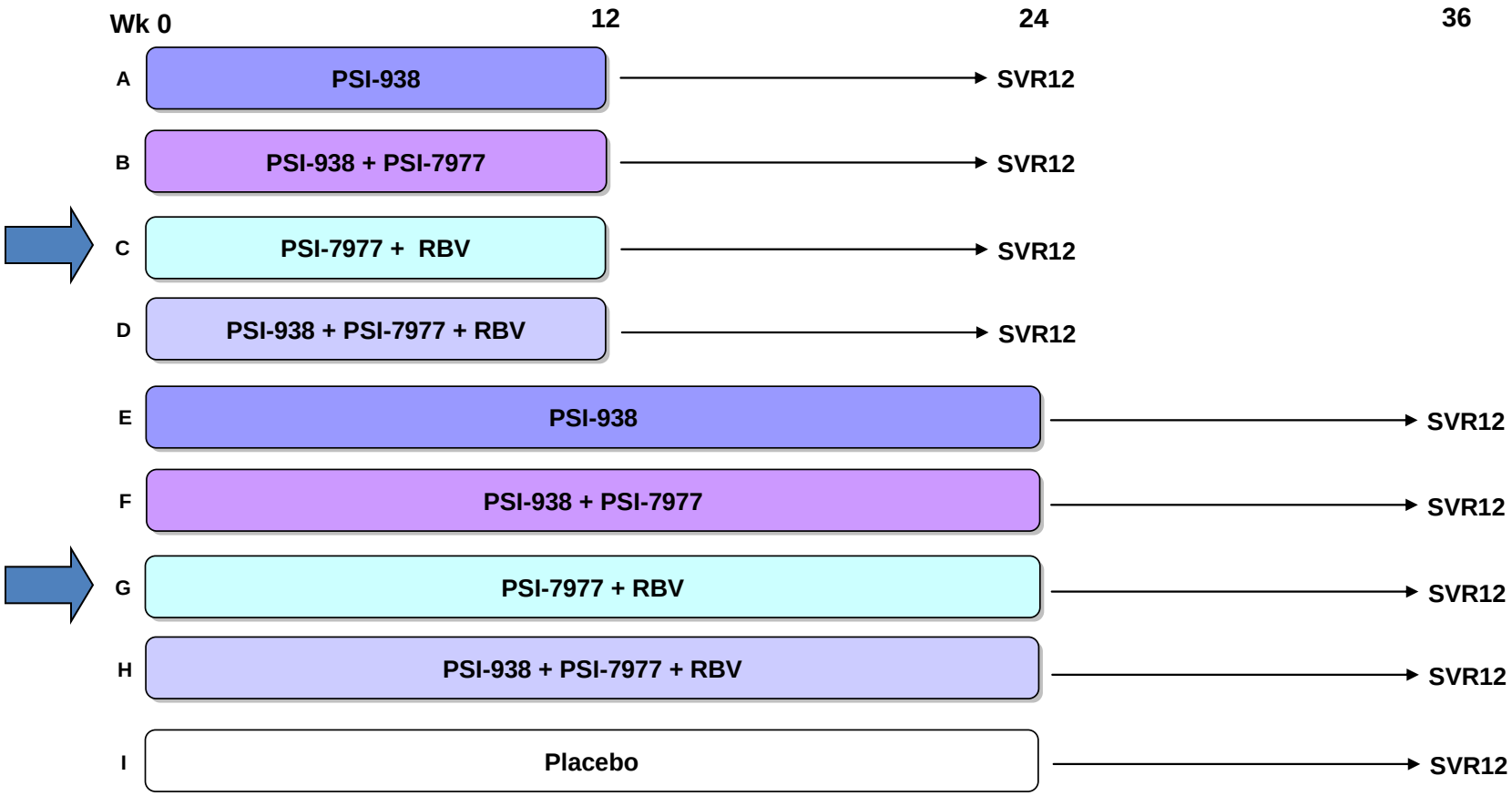


ELECTRON Study



Other arms added

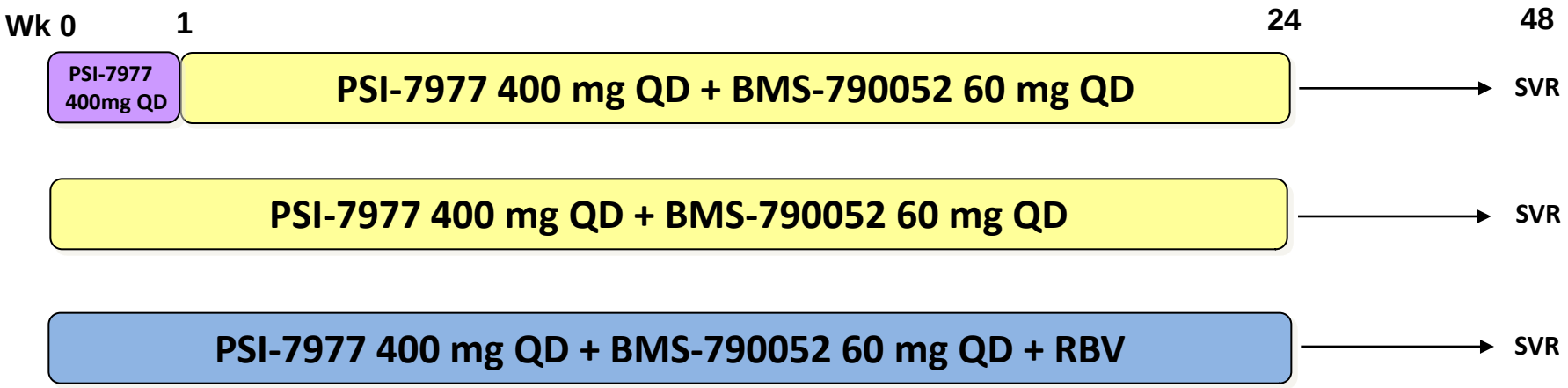
PSI-7977 & PSI-938 QUANTUM



- International, interferon-free combination trial
- All HCV genotypes (N=450)
- Cirrhotic and non-cirrhotic patients
- Primary endpoint : SVR

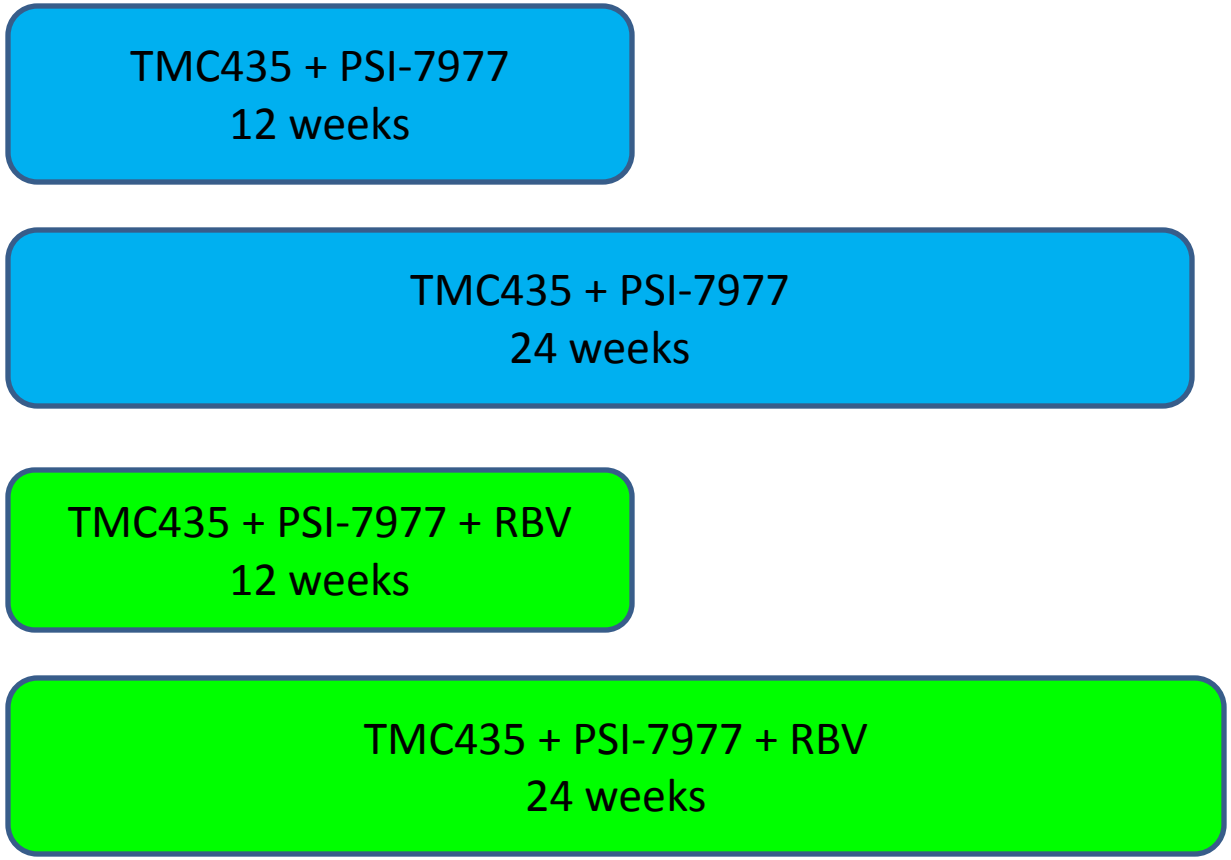
Courtesy of Dr Michelle Berrey

PSI-7977 (Nuc) + BMS-790052 (NS5A)



- 84 Treatment-naïve patients with HCV GT1, GT2/GT3
  - 42 GT1; 42 GT2/3

TMC435 + PSI-7977 ± RBV in Null Responders



What We May Have Learned When Phase 2 Studies Are Done

- Quad regimens (PR + 2 DAAs) are highly effective in nonresponders, including nulls
- Quad regimens may shorten treatment duration to 12 weeks in some subgroups of patients
- 12 weeks of triple therapy may be sufficient in certain subgroups of patients (e.g. CC patients with RVR)
- DAA combination regimens associated with high rates of SVR and low toxicity
- PR + pangenotypic DAA associated with very high SVR and shorter duration of therapy

How might these findings affect the need for, and nature of, control groups in phase 3?

Populations in Which Peg IFN+RBV+PI Controls are Irrelevant

- Interferon incapable or intolerant patients
- Protease inhibitor failures
- Null responders to PR (relevance is “relative”)

Interferon Incapable Patients

A priori

- Anemia
- Thrombocytopenia
- Leukopenia
- Severe psychiatric disease
- Neuropathy
- Seizures
- Cardiac disease
- Pulmonary disease
- Renal disease
- Autoimmune diseases
- Hearing deficits
- Major ophthalmologic issues

Events on previous treatment (overlaps with other column)

- Cytopenias
- Psychiatric disease
- Neuropathy
- Seizures
- Flare or appearance of autoimmune disease
- Symptomatic retinopathy, optic neuritis

IFN Incapable Patients

- What would SVR have to be with DAA regimens?
  - Anything above negligible
  - 25%
  - 50%
  - More?
- Potentially dependent on:
  - Duration of therapy
  - Cost
  - Toxicity

Interferon-incapable studies are being initiated

(Thank heaven and everyone else)

Null Responders

Will controls in phase 3 be

a. Necessary
b. Appropriate

….if phase 2 studies show high SVR rates with quadruple regimens or DAA combinations?

Factors Favoring or not Favoring PR-based Controls in Advanced Trials

Favoring

- Drug with promising efficacy and safety when combined with PR in phase 2 (& ready for phase 3)
- Quad regimens based on PR in populations with already high SVR rates with triple therapy (naives, relapsers) – including studies evaluating further truncation of therapy
- Modest SVR rates/significant rates of resistance/safety issues with DAA combo regimens

Not Favoring

- Populations for which controls are not feasible or inappropriate
- Quad regimens for populations with low SVR rates (e.g. null responders) if phase 2 data overwhelmingly suggest superiority and no extra safety signals
- Safe DAA combination regimens with high SVR rates in phase 2 studies in any population

Important Issues

- Role of IL28B in non-IFN regimens
- Impact of G1 subtype: different regimens for 1a versus 1b, esp re: need for RBV
- Role of pangenotypic protease inhibitors
- Lag in cirrhosis studies at present
- Other needy populations: decompensated cirrhotics, transplant patients, renal disease, HIV-HCV coinfected