DEEP
General Assembly/ Scientific Meeting

July 5th 2014 - Athens, Greece

New drugs for HCV treatment

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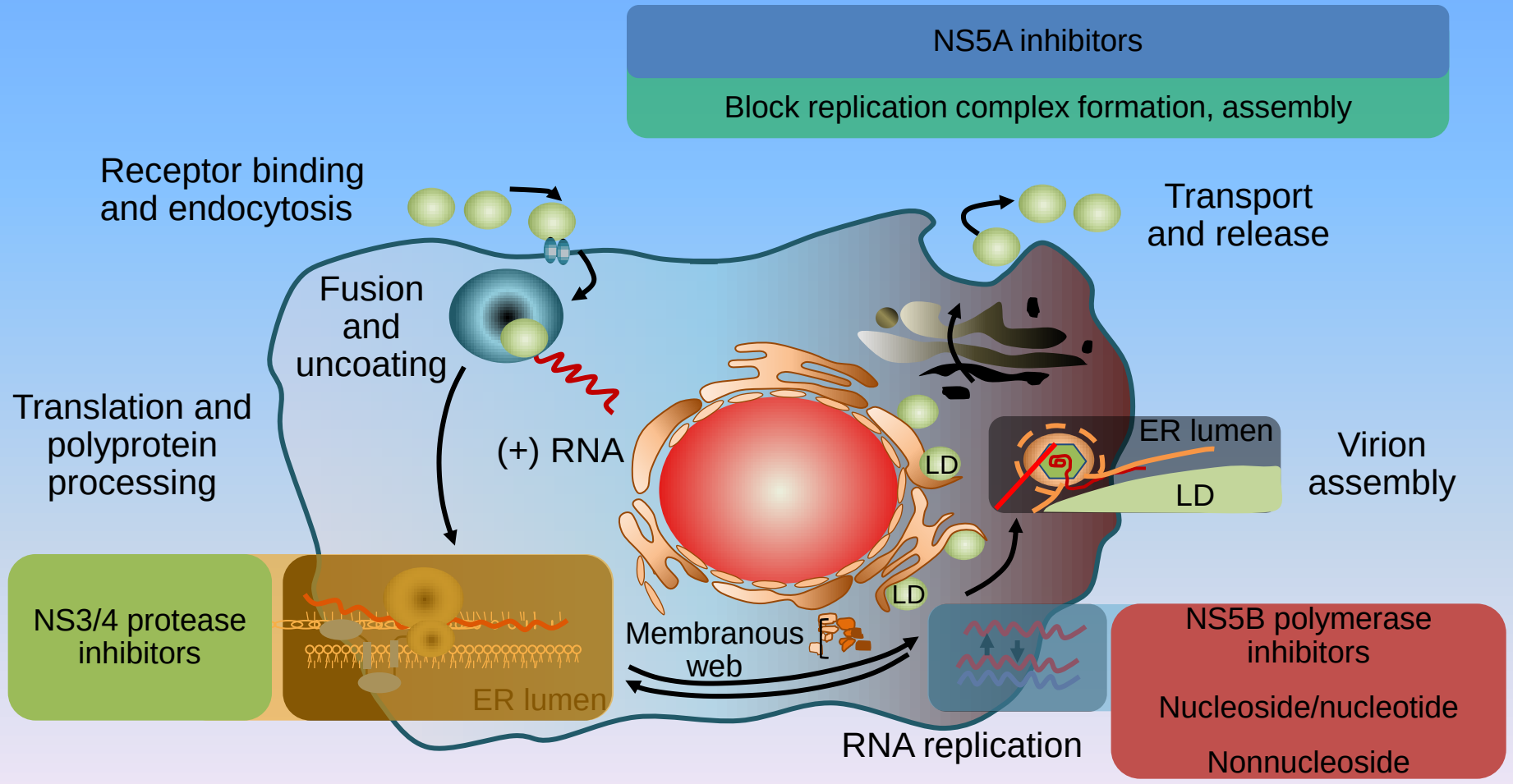
Disclosures

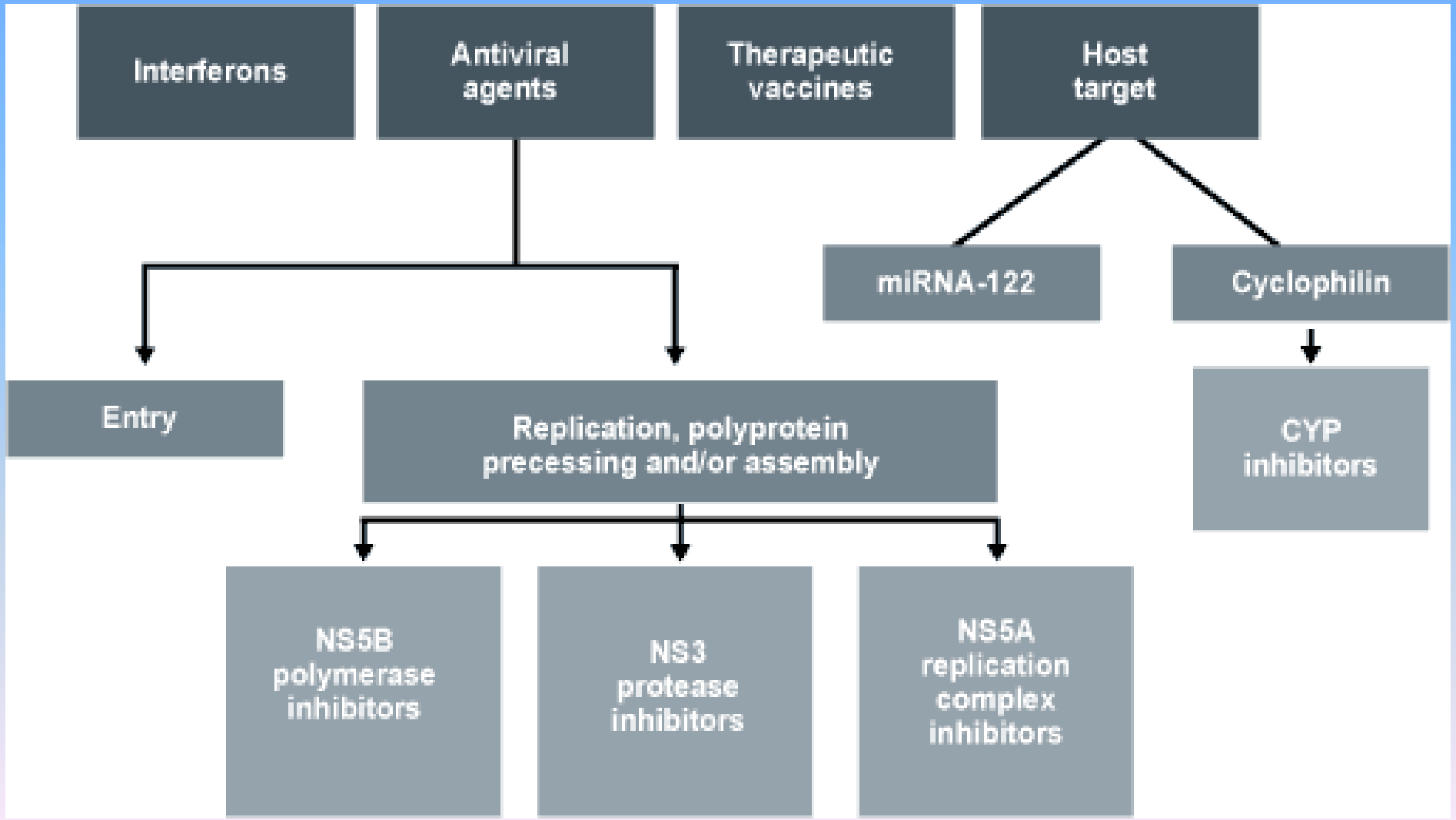
I have received consulting fees from Janssen and Novartis.

HCV Life Cycle and DAA Targets

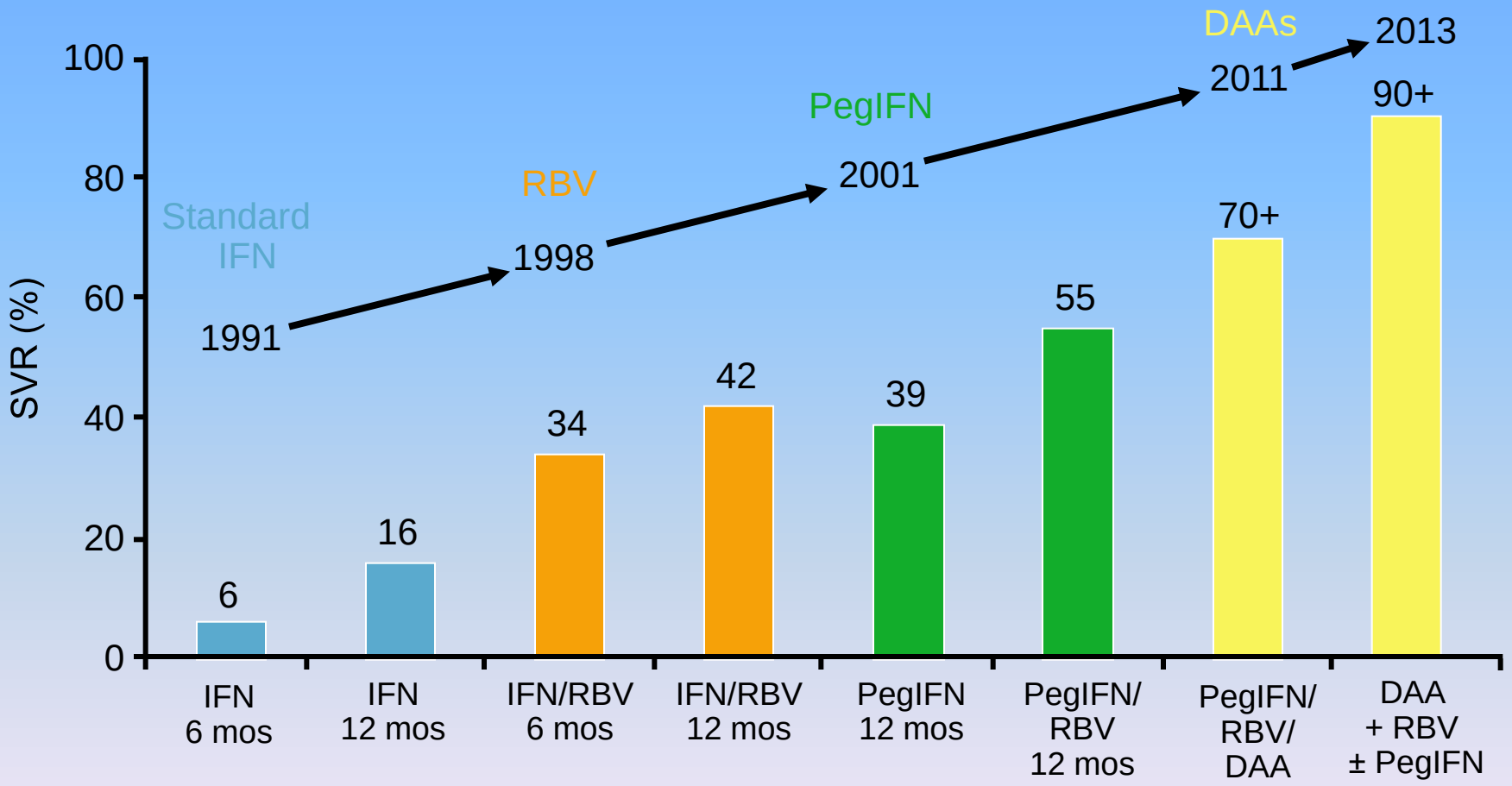


Adapted from Manns MP, et al. Nat Rev Drug Discov. 2007;6:991-1000.

Classes of investigational agents for treatment of chronic HCV infection.



The Good News



Adapted from the US Food and Drug Administration, Antiviral Drugs Advisory Committee Meeting, April 27-28, 2011, Silver Spring, MD.

Summary of Direct-Acting Antivirals

Class	Drug	Dosing
NS3/4A protease inhibitor	ABT-450/RTV	150/100 mg
NS3 protease inhibitor	Asunaprevir	100 mg BID
NS3/4A protease inhibitor	MK-5172	100 mg QD
NS3/4A protease inhibitor	Simeprevir	150 mg QD
NS5B nonnucleoside polymerase inhibitor	Dasabuvir	250 mg BID
NS5B nucleotide polymerase inhibitor	Sofosbuvir	400 mg QD
NS5A inhibitor	Daclatasvir	60 mg QD
NS5A inhibitor	GS-5816	25 or 100 mg QD
NS5A inhibitor	Ledipasvir	90 mg QD
NS5A inhibitor	MK-8742	20 or 50 mg QD
NS5A inhibitor	Ombitasvir	25 mg QD

Not All Direct-Acting Antivirals are Created Equal

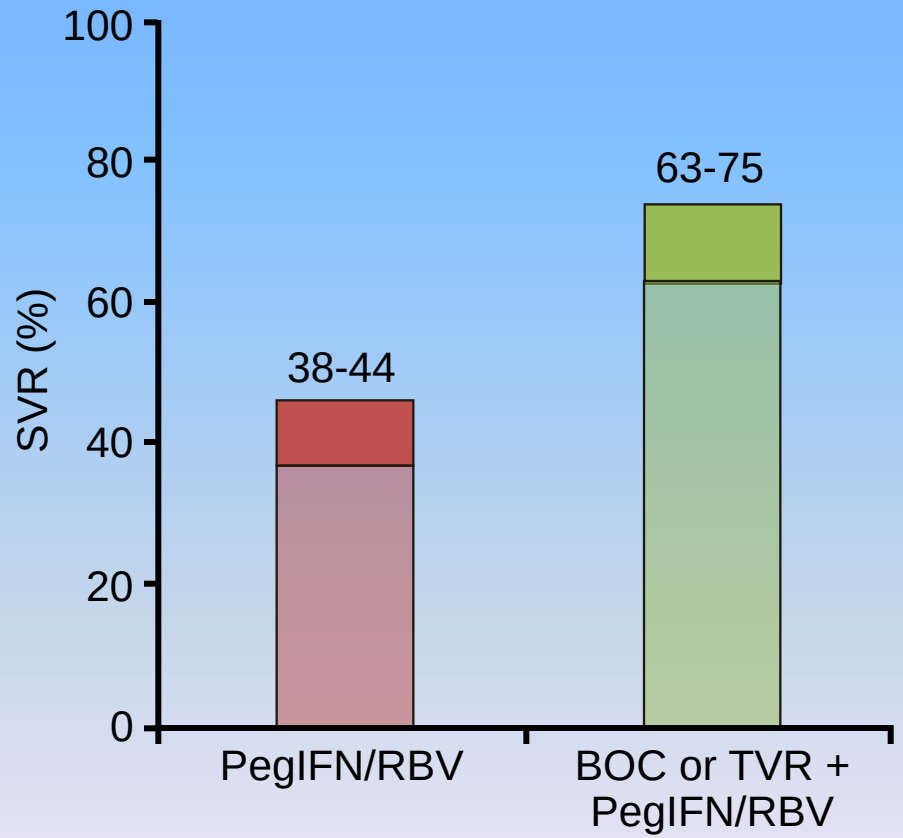
Characteristic	Protease Inhibitor*	Protease Inhibitor**	NS5A Inhibitor	Nuc Polymerase Inhibitor	Non-Nuc Polymerase Inhibitor
Resistance profile					
Pangenotypic efficacy					
Antiviral potency					
Adverse events					

 Good profile  Average profile  Least favorable profile

*First generation. **Second generation.

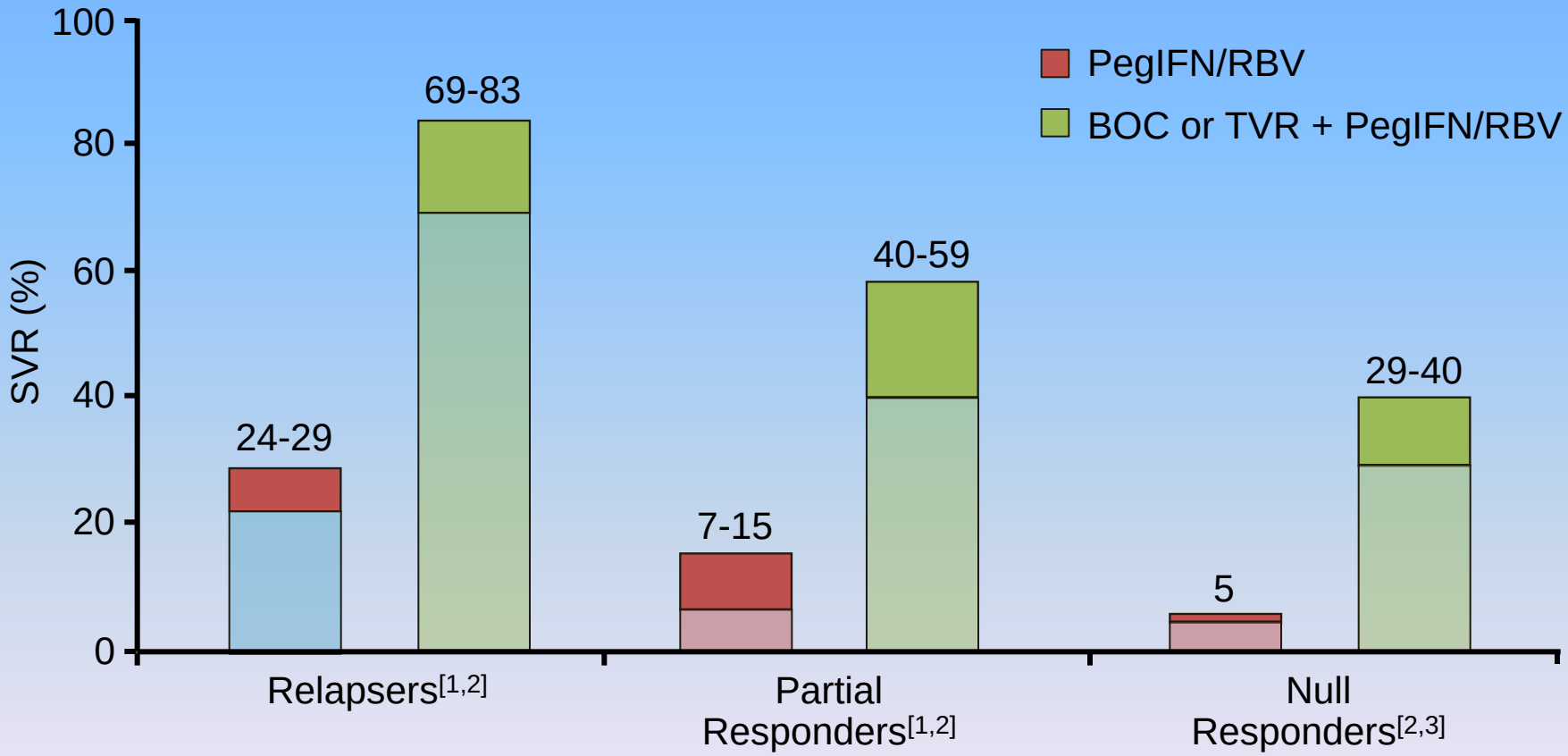
The First DAAs:
Telaprevir and Boceprevir

A Major Advance: GT1 Treatment-Naive Patients



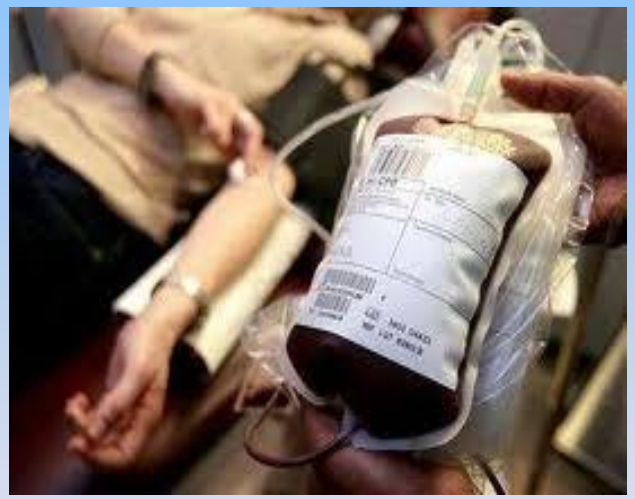
Poordad F, et al. N Engl J Med. 2011;364:1195-1206.
Jacobson IM, et al. N Engl J Med. 2011;364:2405-2416.

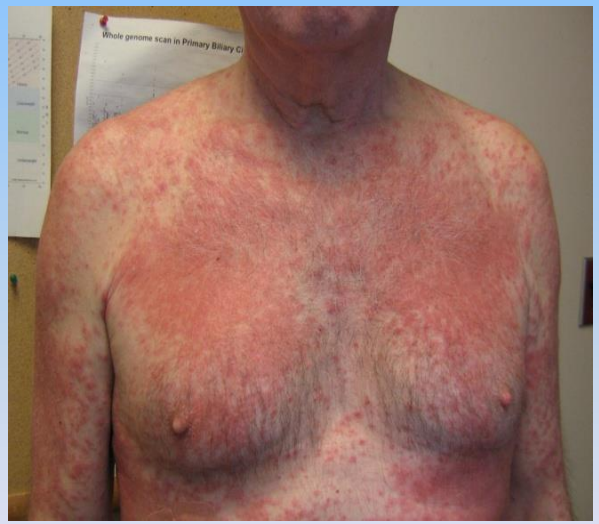
A Major Advance: GT1 Treatment Failures



1. Bacon BR, et al. N Engl J Med. 2011;364:1207-1217. 2. Zeuzem S, et al. N Engl J Med. 2011;364:2417-2428. 3. Bronowicki JP, et al. EASL 2012. Abstract 11.

No Free Lunch





Treatment is more effective but much more difficult

Other Issues With PI-Based Therapy

Pill burden

BOC = 12/day
RBV = 4-7/day

TVR = 6/day
RBV = 4-7/day

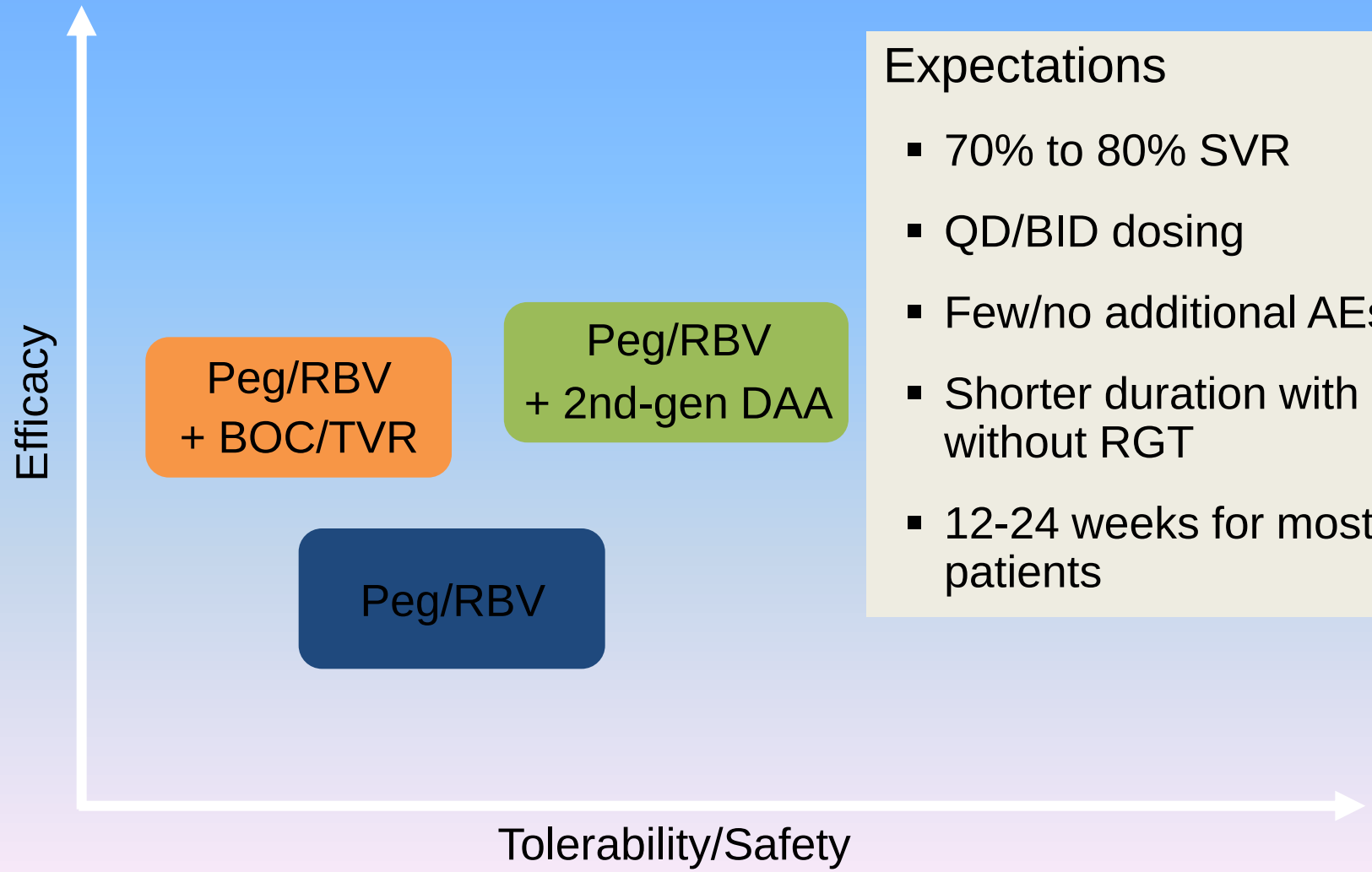
Food requirement

Resistance

Drug-drug interactions

PI — CYP3A4 — metabolites

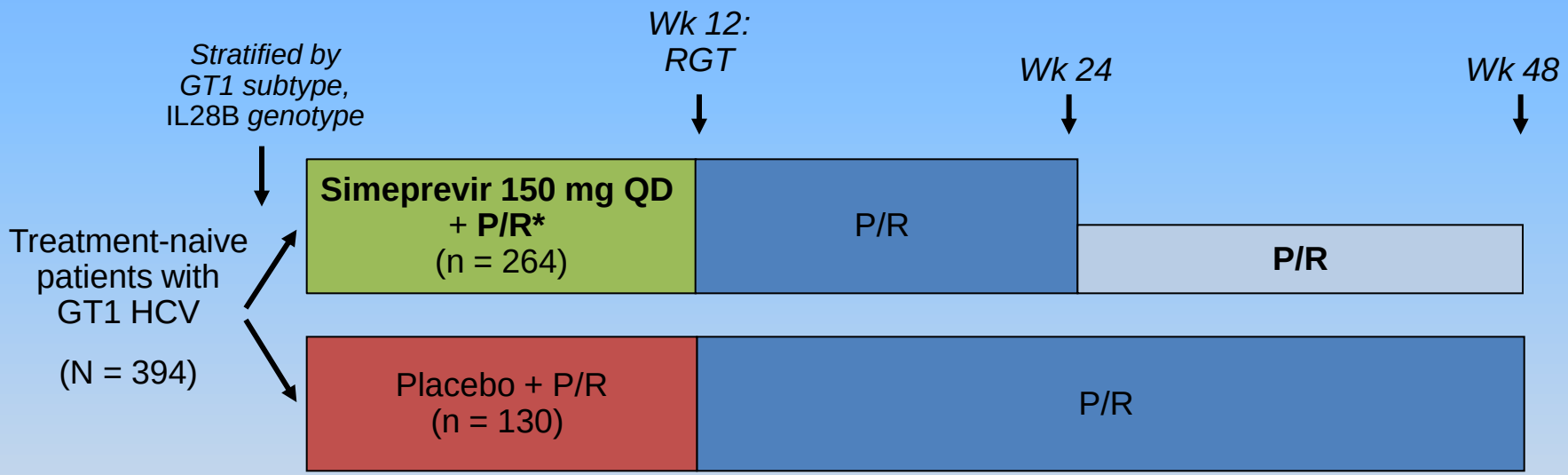
Expectations for New Regimens



Expectations

- 70% to 80% SVR
- QD/BID dosing
- Few/no additional AEs
- Shorter duration with or without RGT
- 12-24 weeks for most/all patients

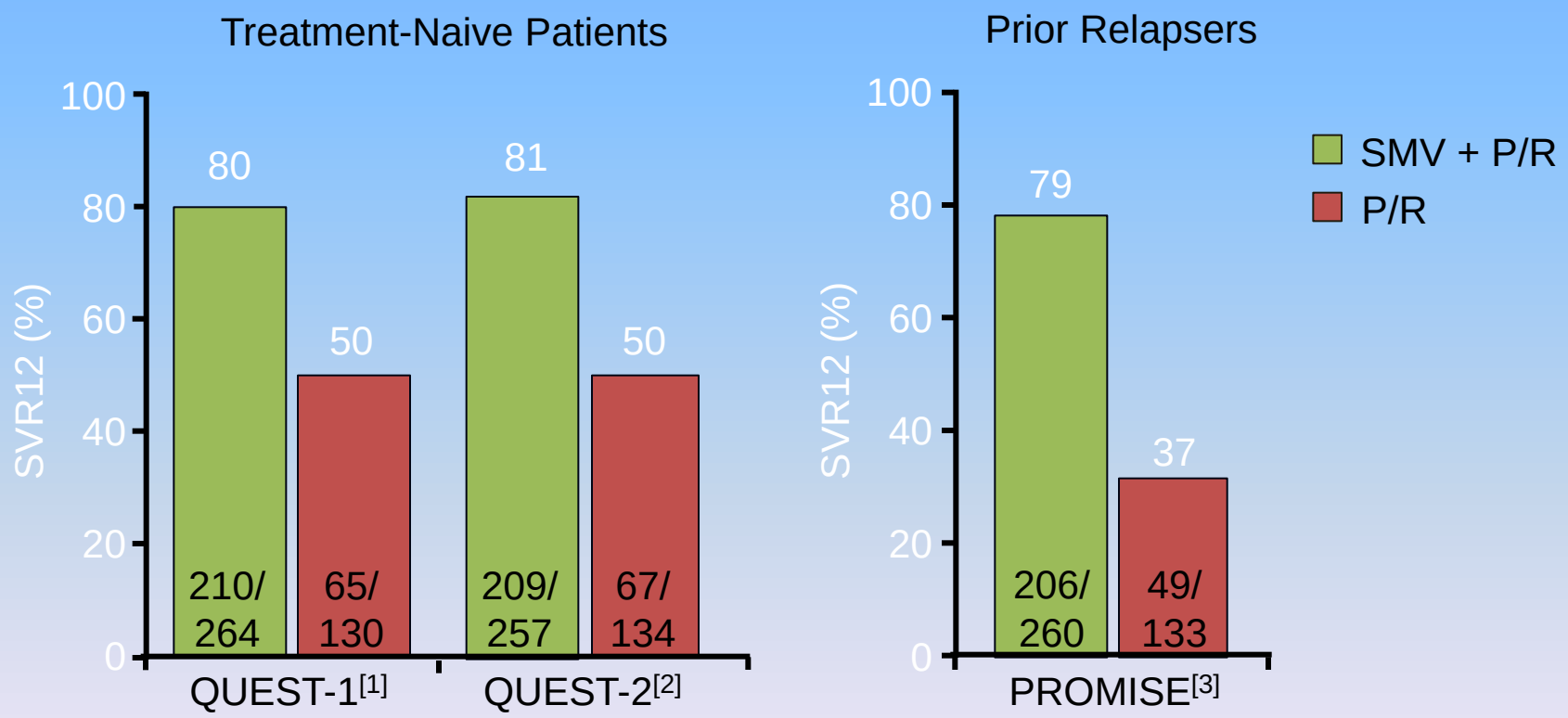
QUEST-1: Simeprevir + P/R RGT in Treatment-Naive GT1 HCV



***Response-guided therapy:** Patients with HCV RNA < 25 IU/mL at Week 4 and HCV RNA undetectable at Week 12 received a total of 24 weeks of therapy. Patients not achieving this on-treatment response received 48 weeks of therapy.

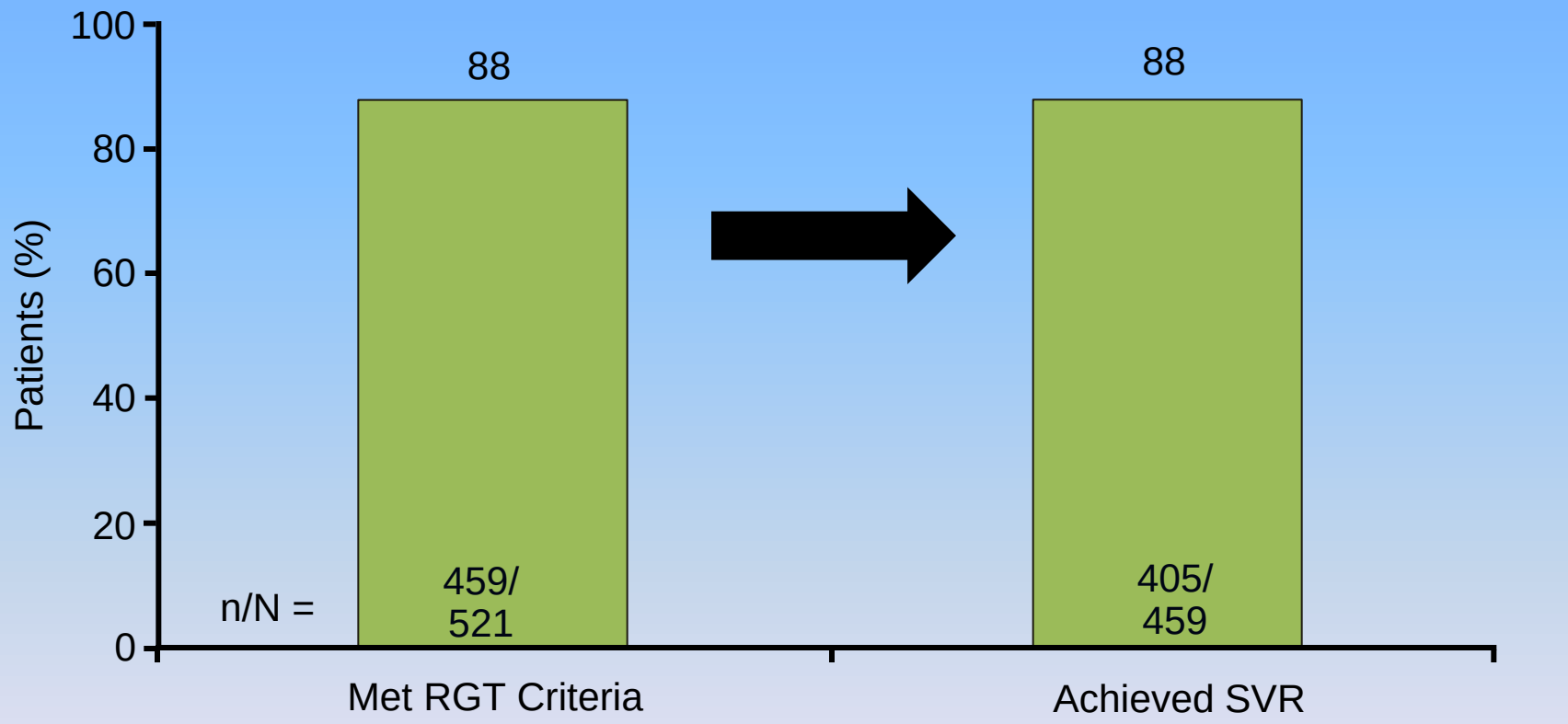
Jacobson I, et al. EASL 2013. Abstract 1425.

QUEST-1, QUEST-2, PROMISE: SMV + P/R in GT1 Treatment-Naive Patients/Relapsers



1. Jacobson I, et al. EASL 2013. Abstract 1425. 2. Manns M, et al. EASL 2013. Abstract 1413.
3. Lawitz E, et al. DDW 2013. Abstract 869b.

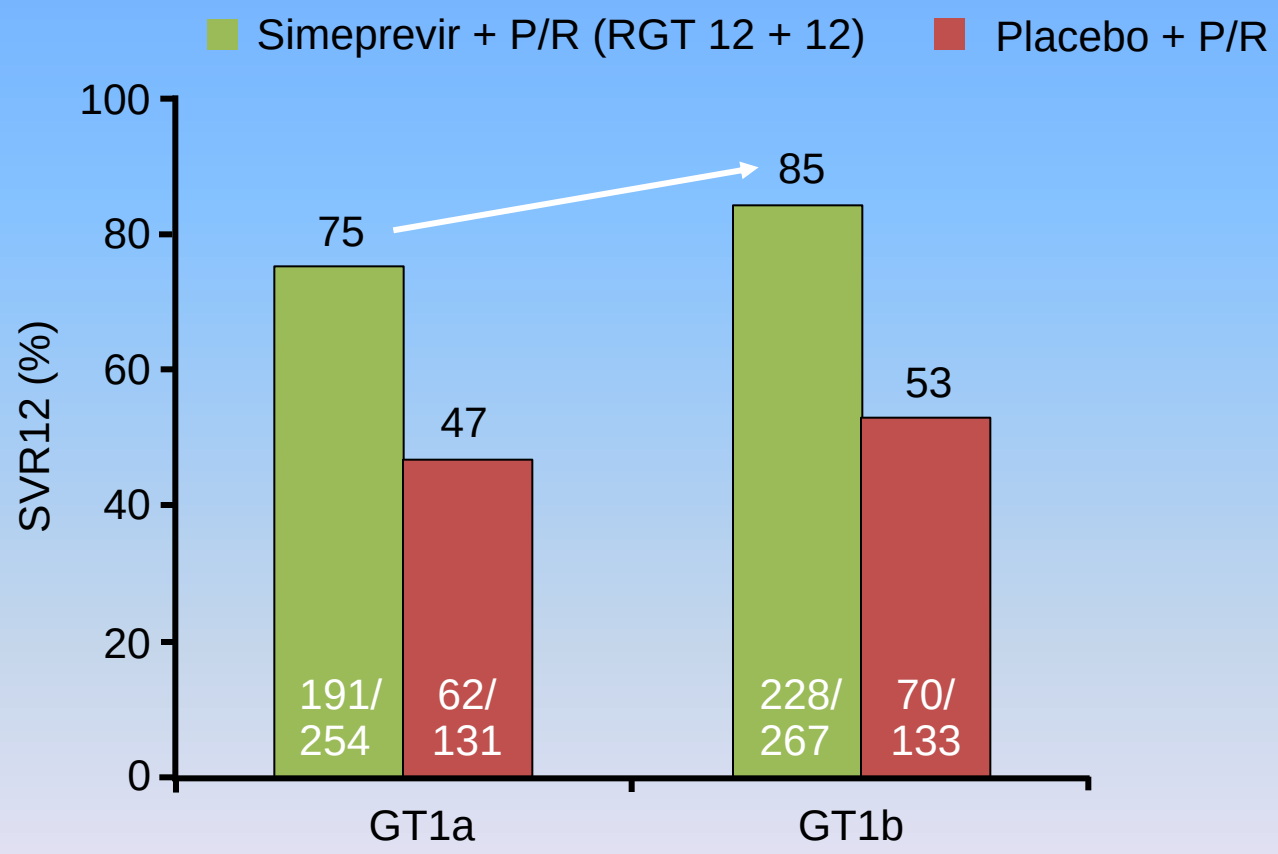
QUEST: 88% Qualified for Shortened Therapy in Simeprevir Phase III Studies



8% did not meet RGT→SVR 25%; therefore, RGT not recommended in US label

Jacobson I, et al. AASLD 2013. Abstract 1122.

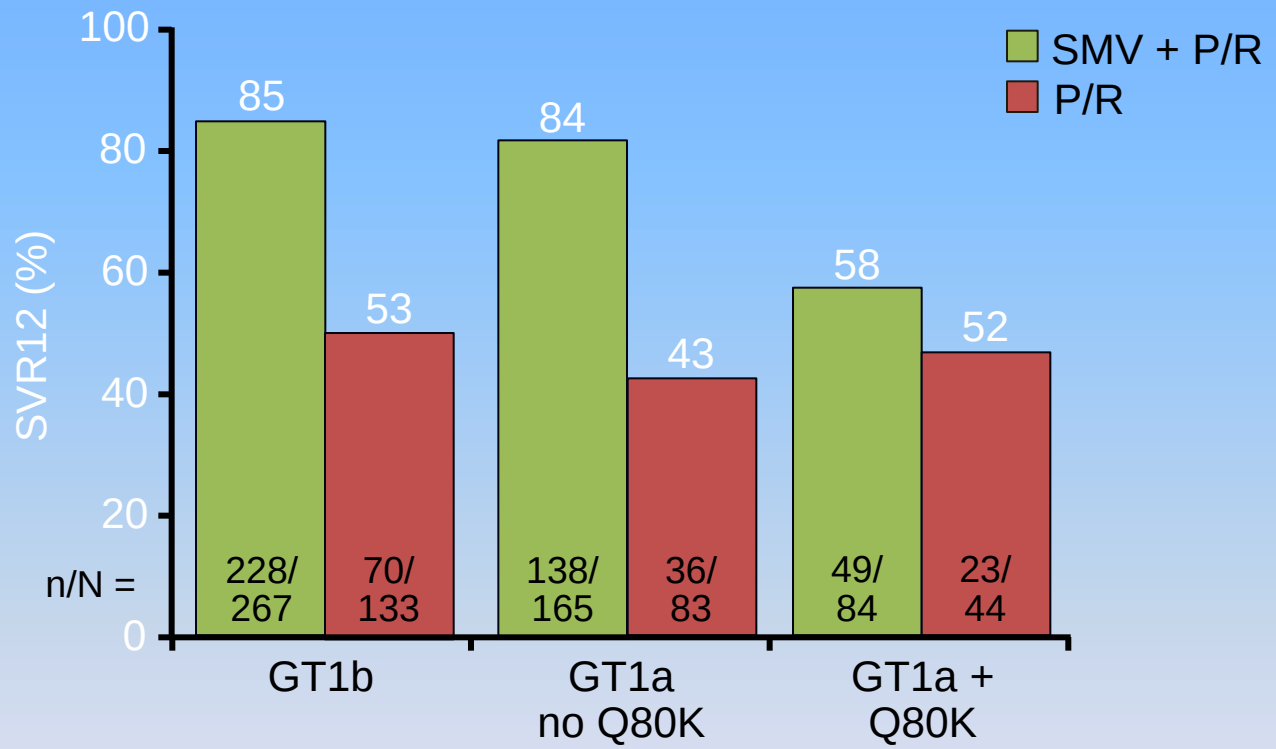
QUEST Studies: Subtype 1a ≠ 1b



Likely relates to presence of Q80K polymorphism in GT1a

Jacobson I, et al. AASLD 2013. Abstract 1122.

QUEST: No Benefit of Simeprevir if Q80K Positive

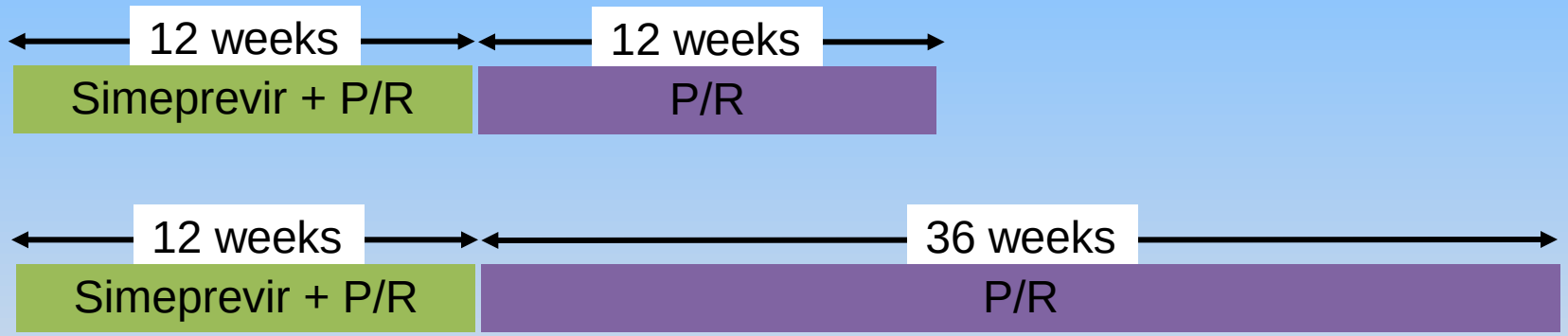


Q80K present in 34% of GT1a patients
No benefit of simeprevir if Q80K positive

Jacobson I, et al. AASLD 2013. Abstract 1122.

Simeprevir + P/R for GT1 HCV: Approved Indications

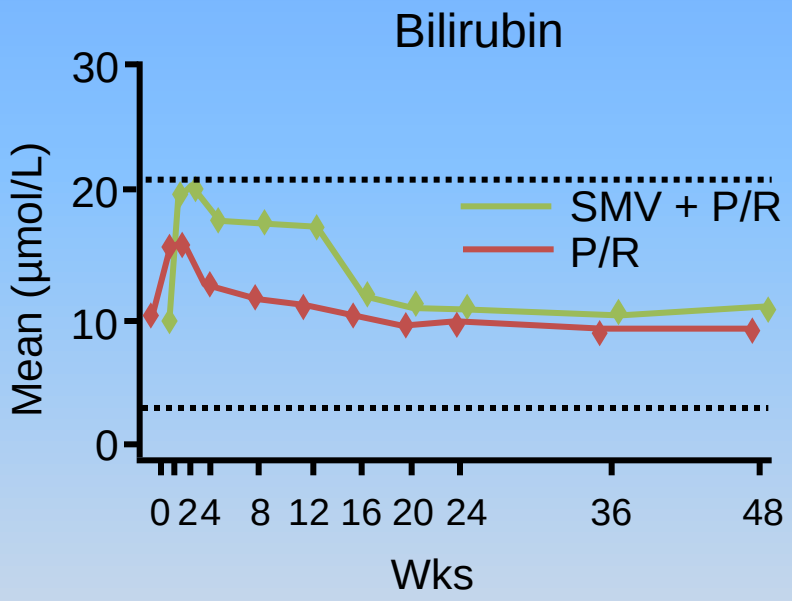
- Simeprevir 150 mg/day with food, administered with P/R
  - Fixed duration (no RGT)
- Treatment-naive patients and relapsers (including cirrhotic patients)
- Previous partial or null responders (including cirrhotic patients)
- Stopping rules

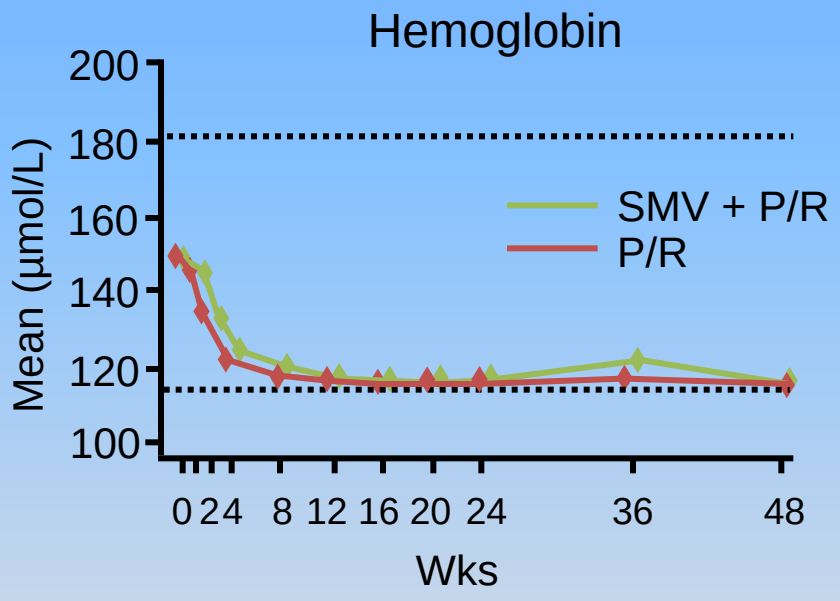


Treatment Wk	HCV RNA (IU/mL)	Action
4	≥ 25	Discontinue simeprevir, pegIFN, and RBV
12	≥ 25	Discontinue pegIFN and RBV (SMV stops at 12 wks)
24	≥ 25	Discontinue pegIFN and RBV

Simeprevir [package insert]. November 2013.

Simeprevir Is Well Tolerated

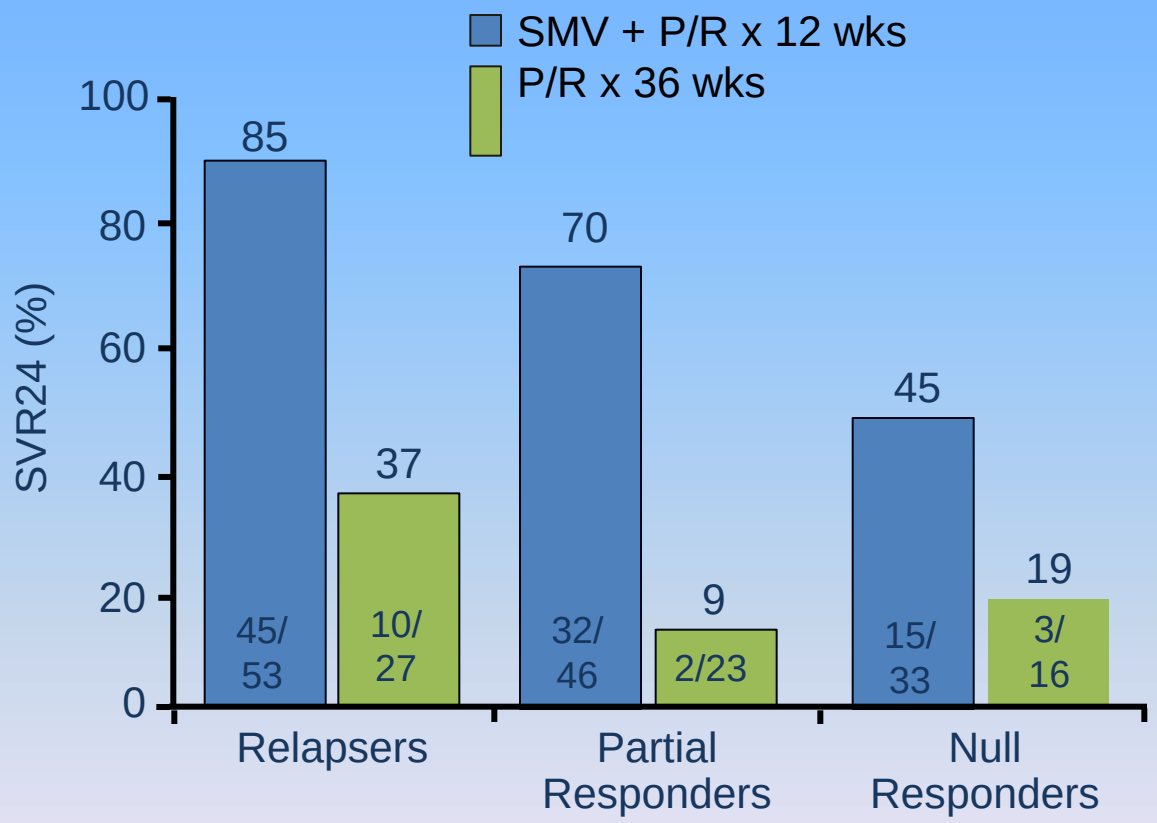




- Mild unconjugated hyperbilirubinemia → transporter
- No anemia signal beyond P/R
- Rash up to 25% (mild)

Manns M, et al. EASL 2013. Abstract 1413.

Extending Beyond Phase III Trials: SMV in Treatment-Experienced Patients

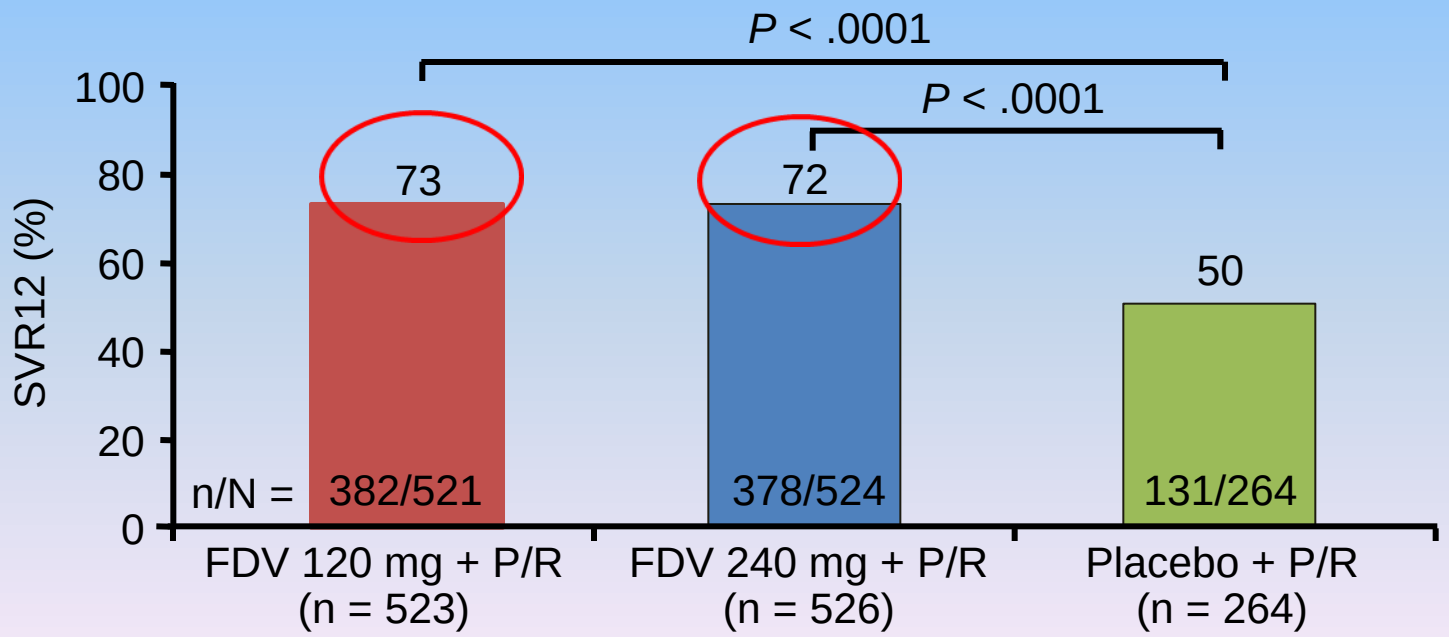


FDA extended indication to partial and null responders

Simeprevir FDA Hearing. October 24, 2013.

STARTVerso 1 and 2: SVR12 With Faldaprevir + P/R in Naive GT1 HCV

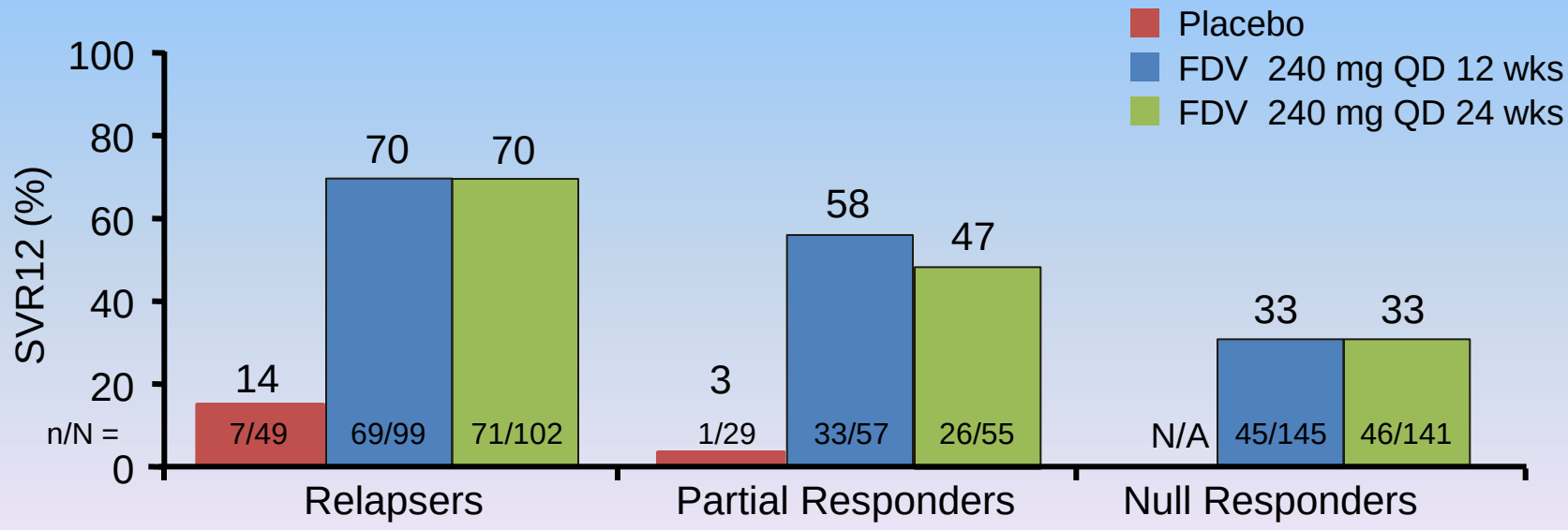
- Significantly higher rates of SVR12 with FDV + P/R vs placebo + P/R
- Patients treated with FDV: 84% achieved ETS, stopped treatment at Wk 24
- Treatment failure more common with subtype 1a; no impact of Q80K on SVR
- Safety profile of FDV 120 mg regimen similar to placebo



Jensen D, et al. AASLD 2013. Abstract 1088.

STARTVerso 3: SVR12 With Faldaprevir + P/R in Treatment-Experienced GT1 HCV

- Relapsers underwent RGT; nonresponders received fixed-duration therapy
  - 87% of relapsers were eligible to stop treatment at 24 Weeks; 75% of those achieved SVR
- Higher virologic failure rates with subtype 1a; no impact of Q80K
- Higher rates of bilirubin with 240 mg dose than with 120 mg dose in naive trials



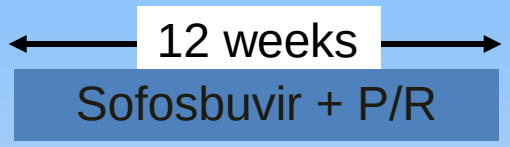
Jacobson I, et al. AASLD 2013. Abstract 1100.

Summary of New PIs + P/R in GT1 HCV: Simeprevir and Faldaprevir

- Pros
  - Once-daily PI
  - Well tolerated with less rash and no anemia
  - > 85% of patients shorten treatment duration to 6 months and most achieve SVR → RGT eliminated in SMV label
- Cons
  - Q80K major issue with SMV (not with FDV): pretreatment testing required in all GT1a patients considered for SMV
  - DDIs still an issue (SMV > FDV)
  - Must be combined with P/R

Sofosbuvir + P/R for GT1 HCV: Approved Indications

- Sofosbuvir 400 mg/day with or without food, administered with P/R
- All GT1 patients receive same regimen, regardless of previous treatment history or fibrosis level
  - Same regimen approved for GT4 HCV

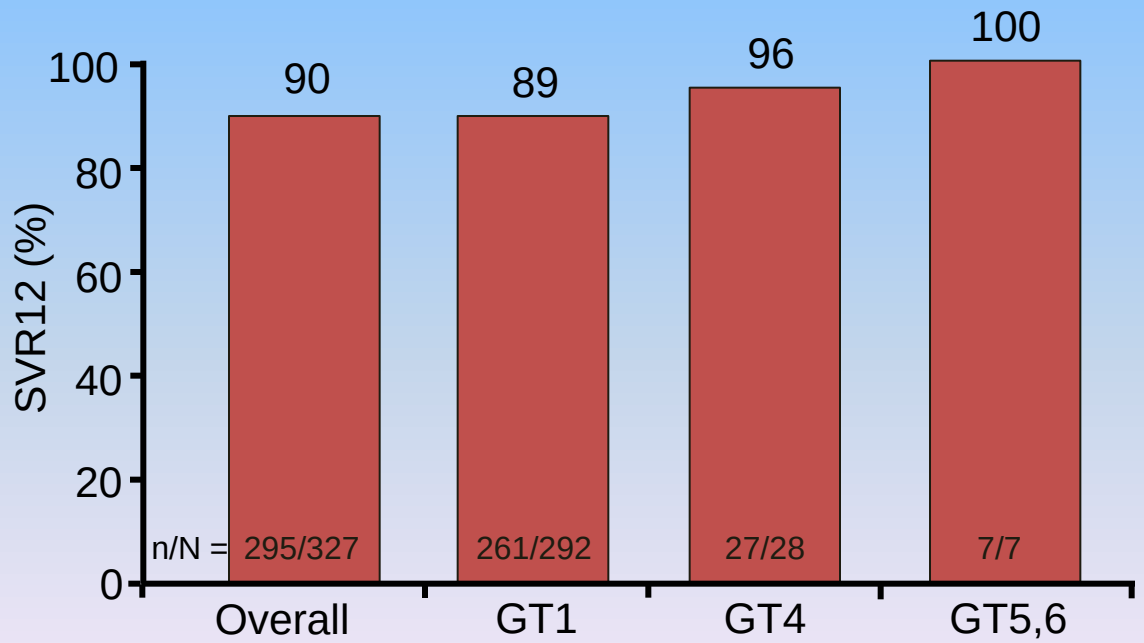


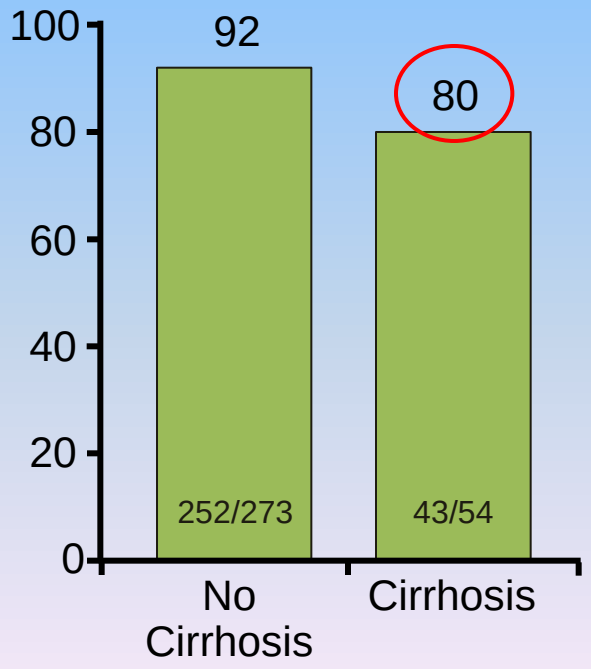
- Additional option for GT1 patients ineligible for IFN therapy
  - Sofosbuvir + ribavirin for 24 weeks
- If drugs combined with sofosbuvir must be permanently discontinued, sofosbuvir should also be discontinued

Sofosbuvir [package insert]. December 2013.

NEUTRINO: Sofosbuvir + P/R for 12 Weeks in Treatment-Naive GT 1/4/5/6 HCV

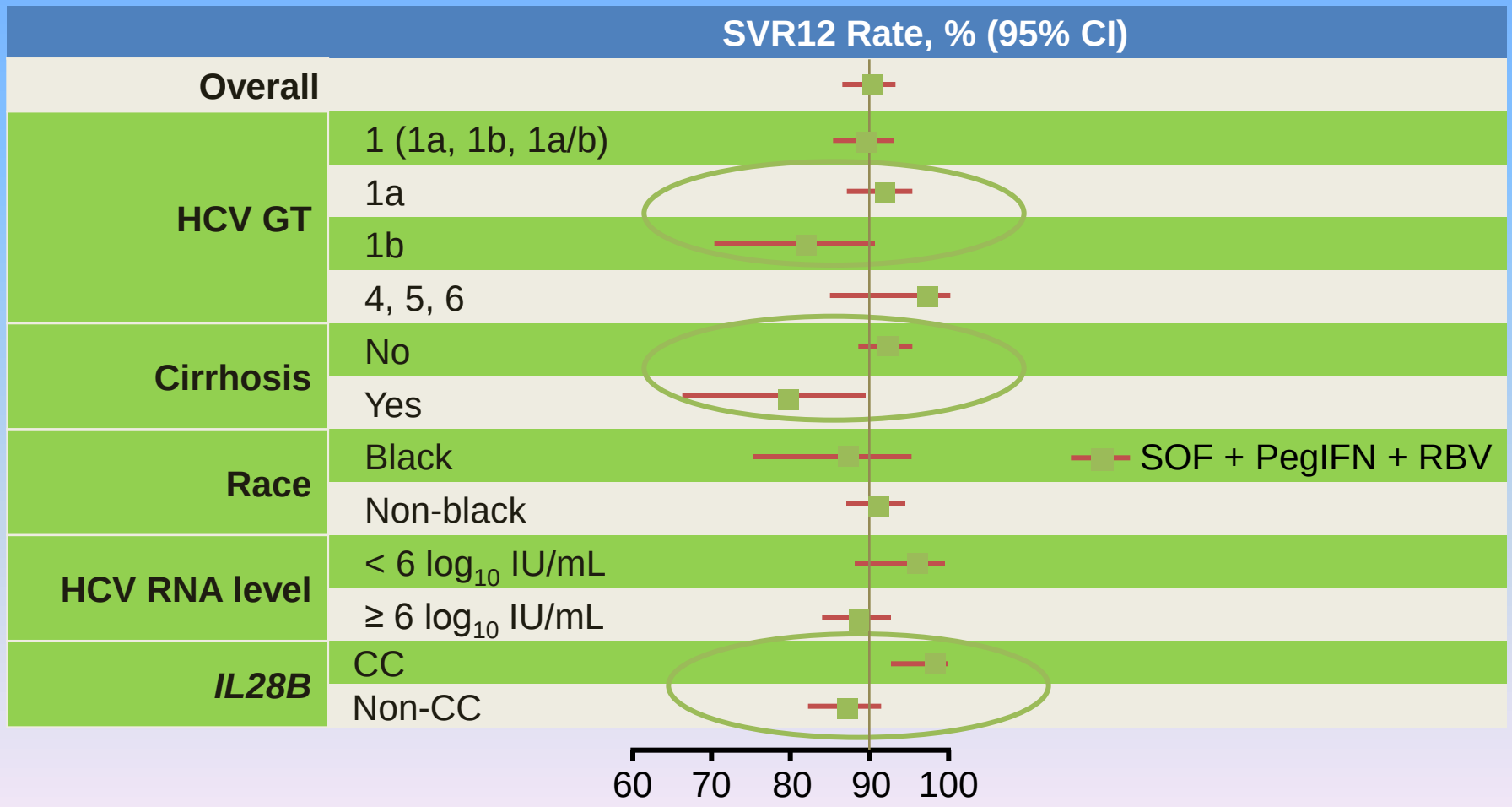
- Open-label, single-arm study of sofosbuvir 400 mg QD + P/R for 12 weeks in treatment-naive patients with GT1/4/5/6 HCV
  - 17% cirrhosis; 89% GT1; 9% GT4; < 1% GT5; 2% GT6





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

NEUTRINO Study: SVR12 by Prespecified Subgroups



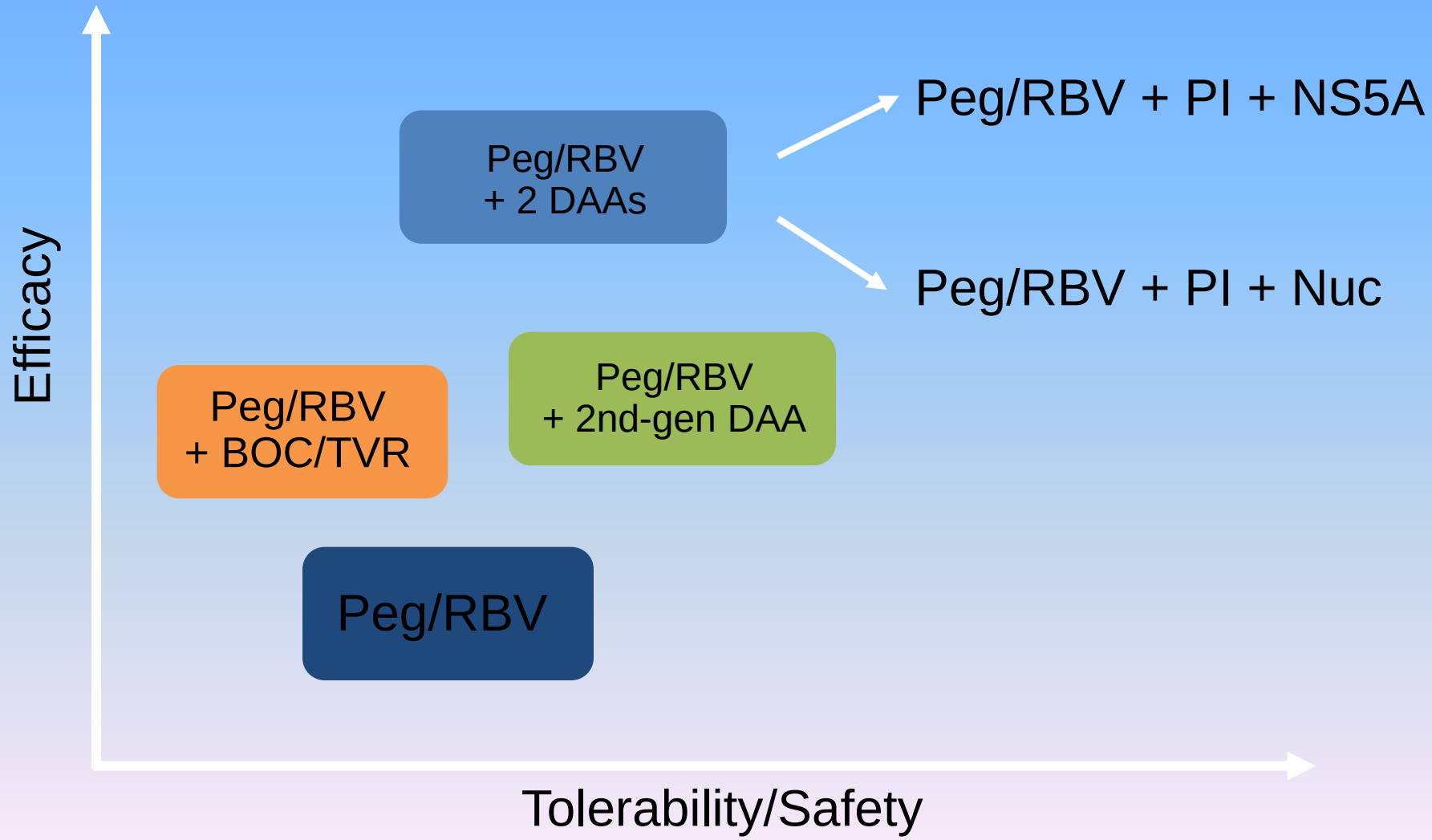
Lawitz E, et al. N Engl J Med. 2013;368:1878-1887.

Summary of Sofosbuvir + P/R in GT1 HCV

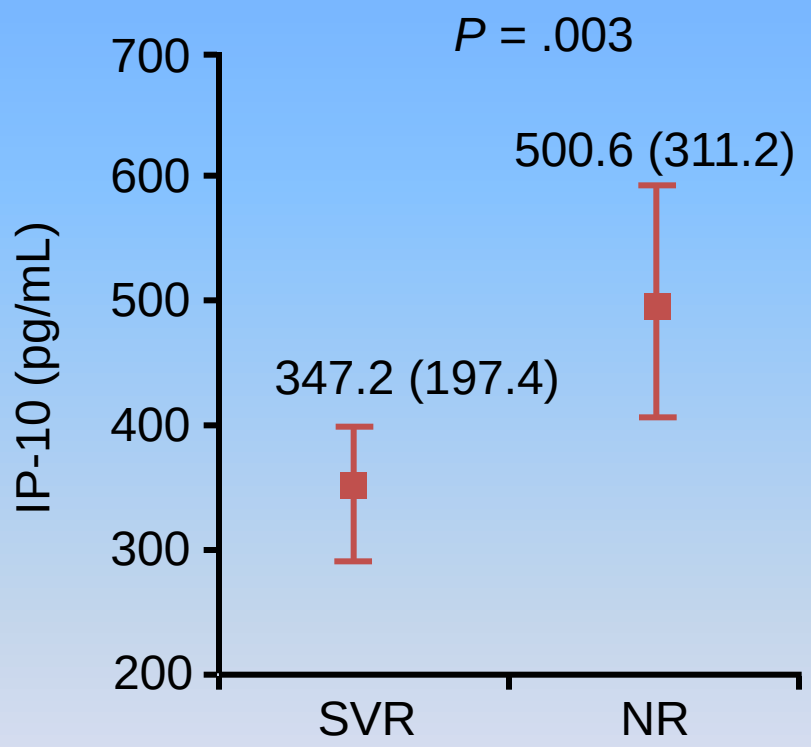
- Pros
  - Once-daily nucleotide polymerase inhibitor
  - Very well tolerated
  - Given for only 12 weeks in all GT1 patients (no RGT)
  - High SVR even in cirrhosis (80%)
  - Same regimen approved for GT4
- Cons
  - No control group for GT1
  - Insufficient data for GT5,6
  - But data are hard to argue with—very promising

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

Options for IFN-Based Quad Therapy



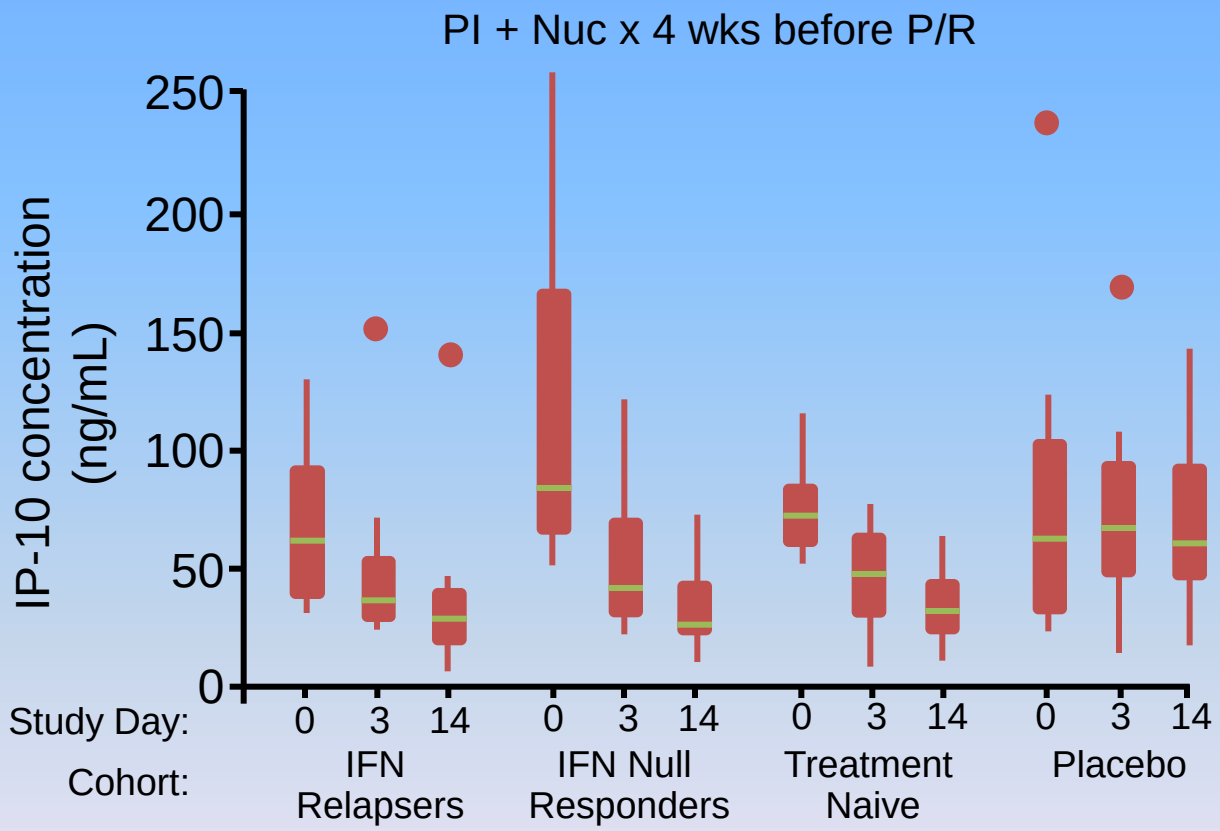
Can DAAs Improve the Interferon Response?



- IP-10 increased in nonresponders at baseline
- Confirmed by multiple groups

Diago M, et al. Gut. 2006;55:374-379.

Converting Nonresponders to Responders

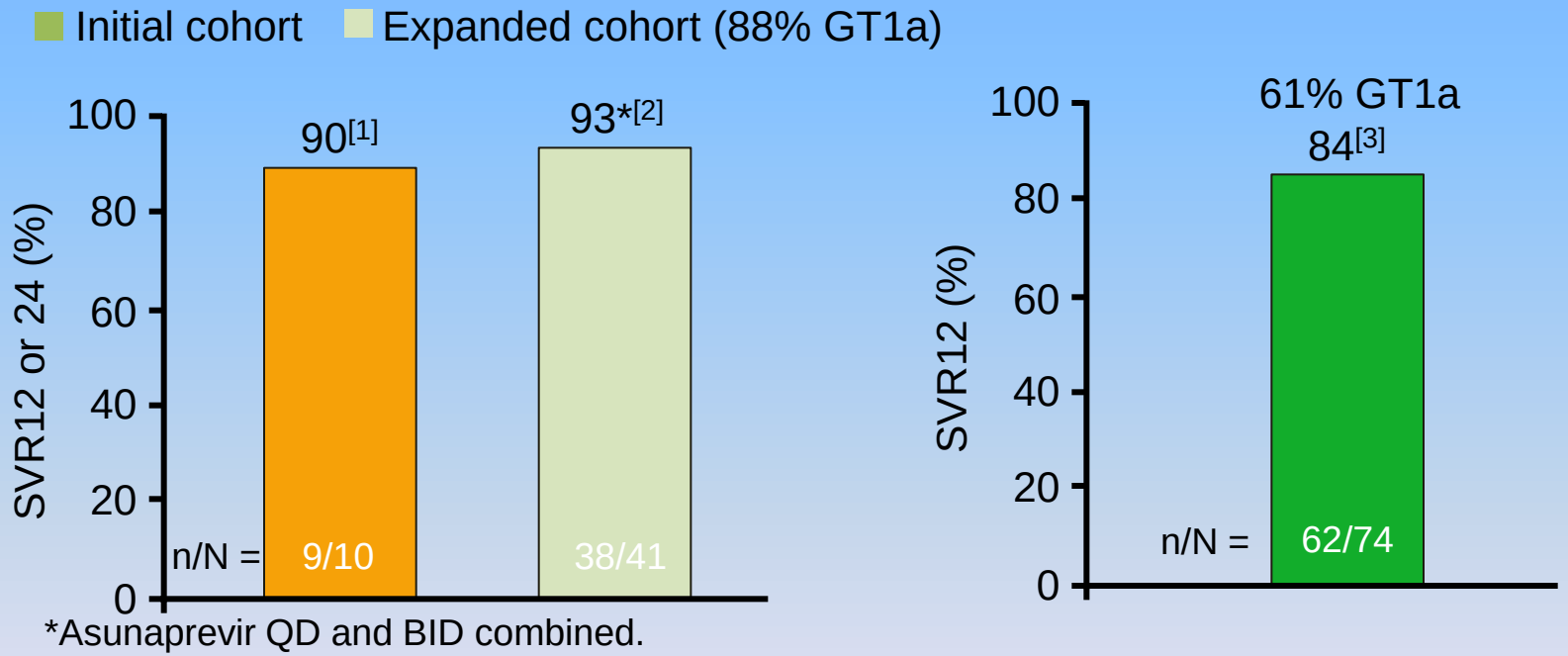


- IP-10 levels decreased during IFN-free therapy
- "Reset" of ISG set-point may improve IFN response

Gane EJ, et al. Lancet. 2010;376:1467-1475.

Previous Null Responders: Quad Therapy

Daclatasvir (NS5A) + Asunaprevir (PI) + P/R x 24 wks (Quad)	Danoprevir/r (PI) + Mericitabine (Nuc) + P/R x 24 wks (Quad)[3]



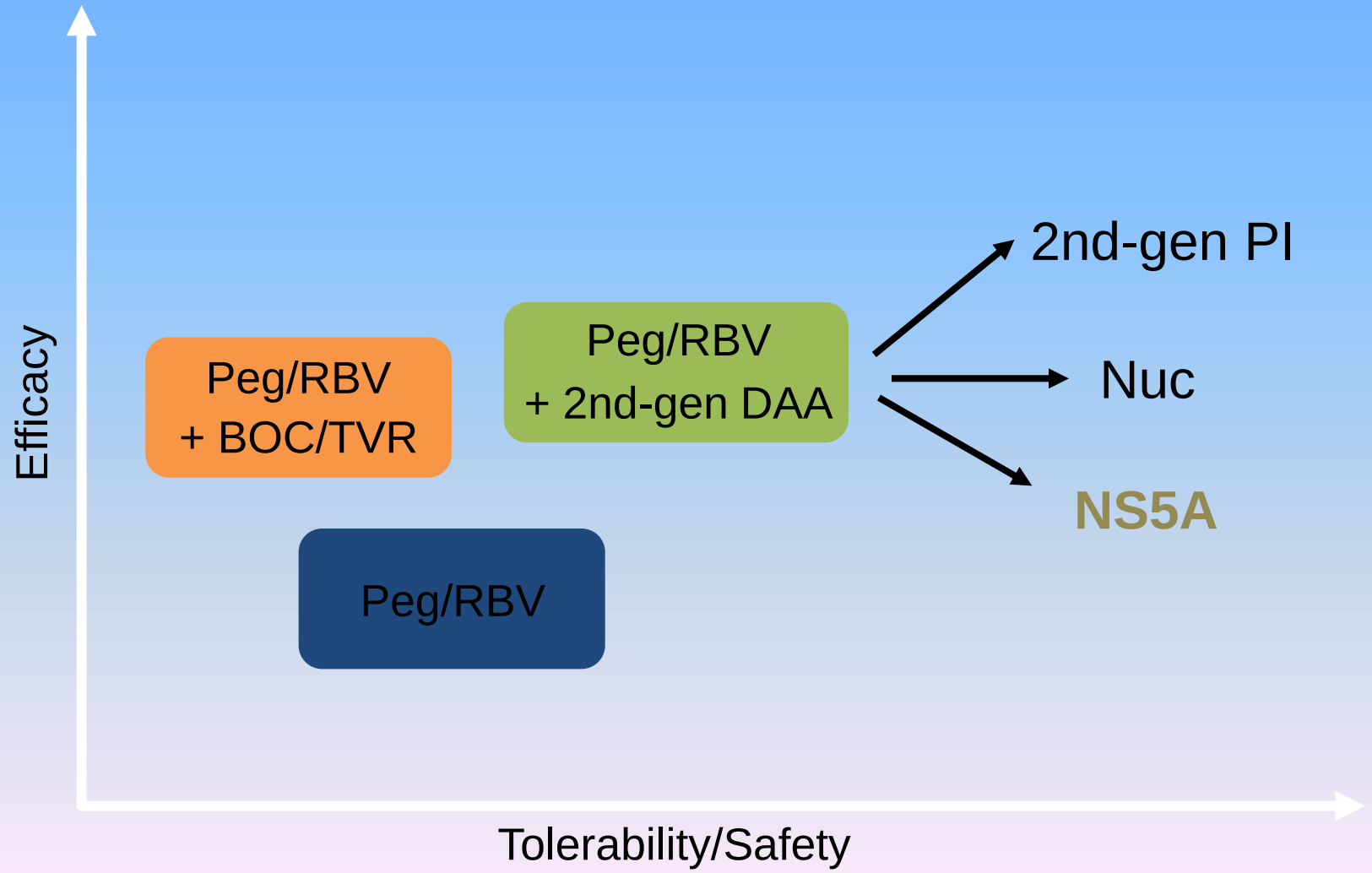
- Quad therapy may be a good option for null responders
- Well tolerated BUT cirrhotic patients excluded; potent IFN-free therapy likely equally effective

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

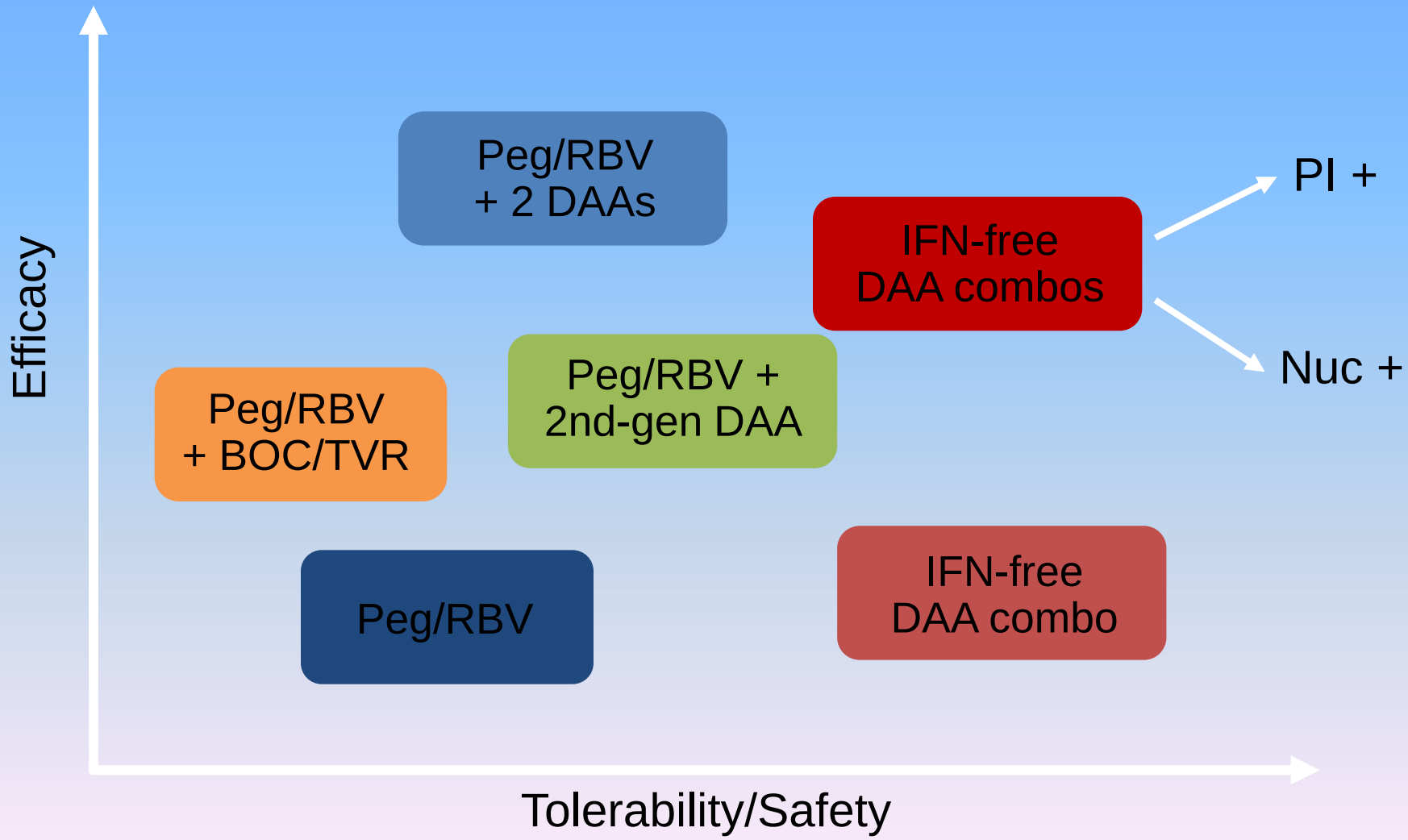
IFN-Free Therapies: Considerations

- How many DAAs?
- Which combinations?
- One size fits all vs tailored therapy?

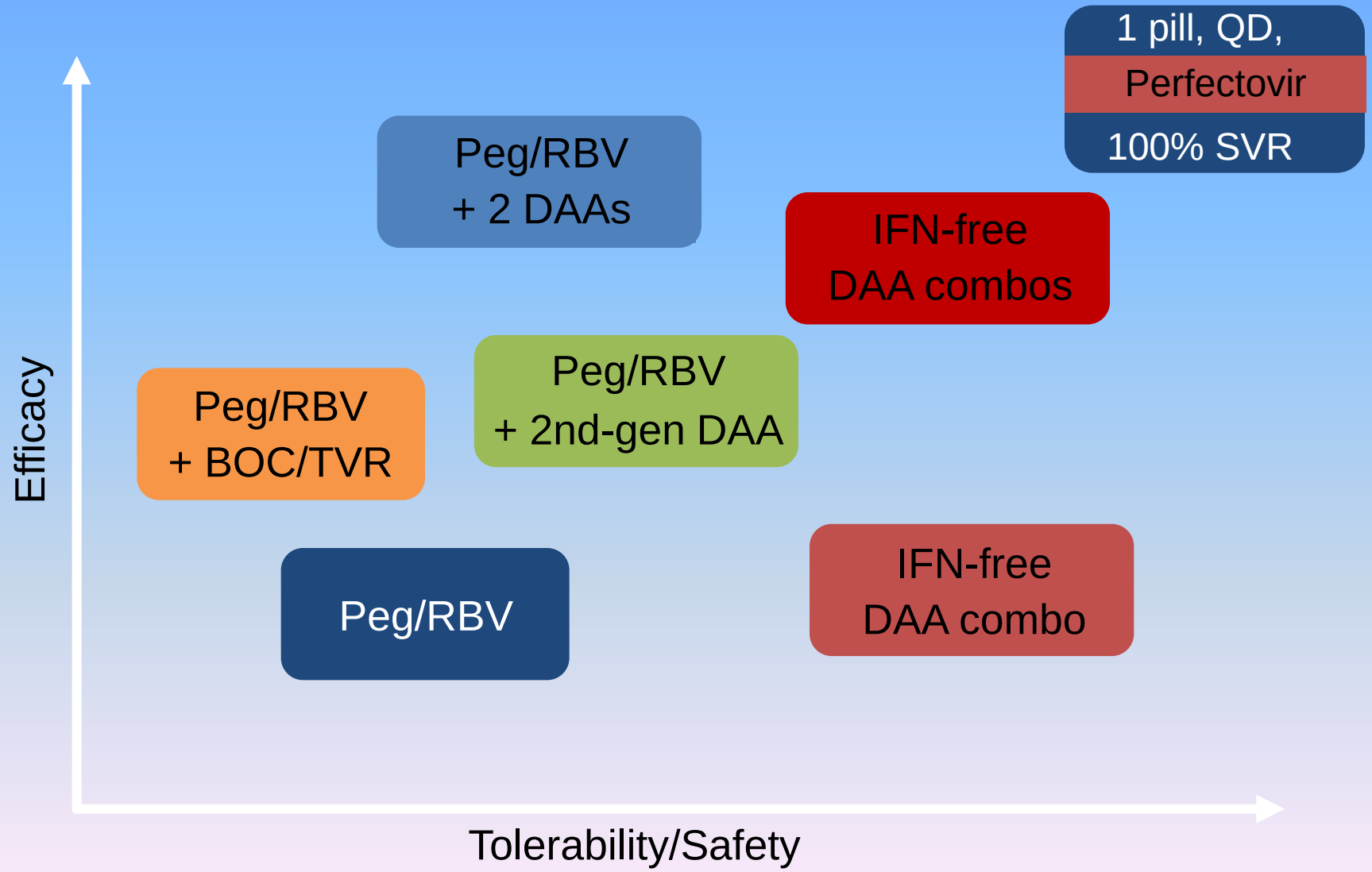
Potential Options



Examples of IFN-Free DAA Combinations



Progress May Not Be Linear



How Many DAAs Do We Need?

Assumptions:
1) Production of new virions = ~10^{12}/day
2) HCV genome length = ~9600 nucleotides
3) Error rate = ~10^{-5}/per nucleotide copied

Therefore, average number of changes/genome = 0.096/replication cycle

# of Nucleotide Changes	Probability	# of Virions/Day	# of All Possible Mutants	% of All Possible Mutants/Day
0	0.91	9.1×10^{11}		
1	0.087	8.7×10^{10}	2.9×10^{4}	100
2	0.0042	4.2×10^{9}	4.1×10^{8}	100
3	0.00013	1.3×10^{8}	1.0×10^{12}	3.4×10^{-5}

If the theory is right: should need 3 DAAs

Rong L, et al. Sci Transl Med. 2011;2:30-32.

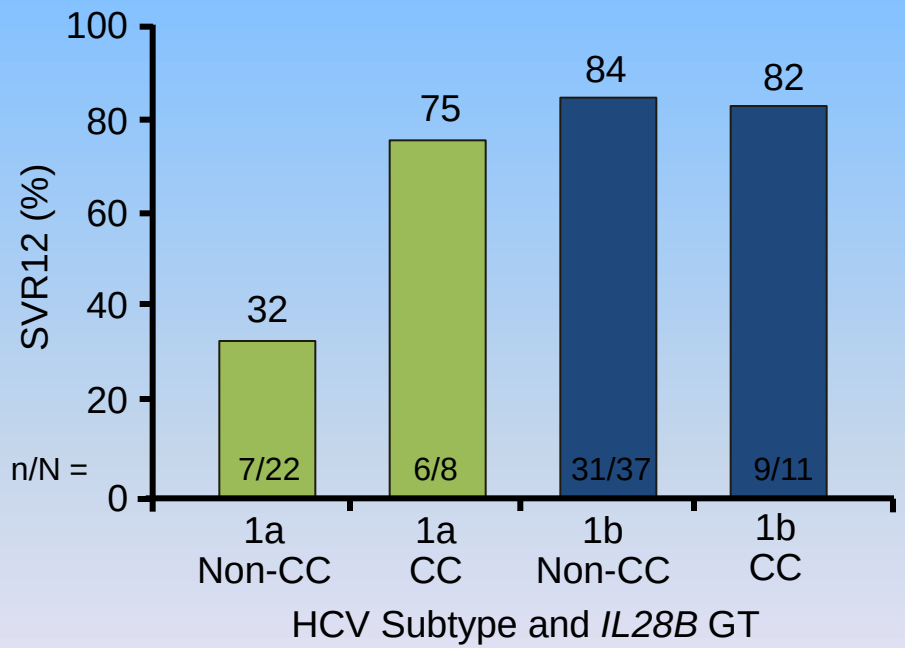
DAA Options

- PI backbone – potent/modest barrier
  - PI + another low-barrier DAA (NNI/NS5A) for GT1b
  - PI + 2 low-barrier DAAs for GT1a
- Nuc backbone – potent/high barrier
  - Nuc + low-barrier DAA for GT1a/b
  - Nuc + PI
- Include ribavirin?
  - May allow fewer DAAs (2 vs 3)
  - May allow shorter therapy

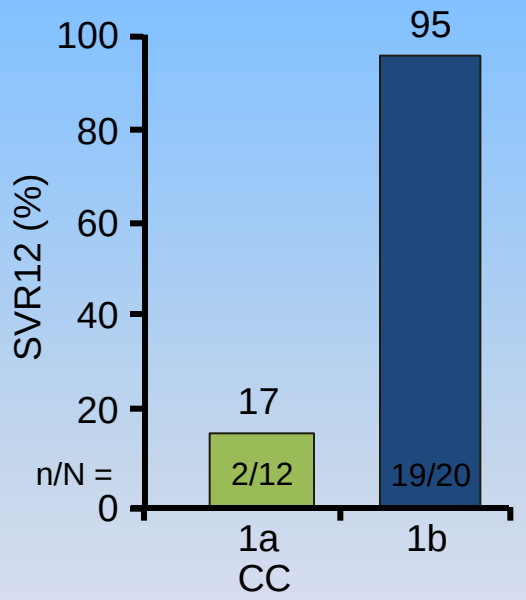
Examples of PI Backbone

Example of PI Backbone + NNI + RBV for GT1b Only

Faldaprevir (PI) 120 mg QD + deleobuvir (NNI) 600 mg BID + RBV for 28 wks[1,2] (N = 78)



Faldaprevir (PI) 120 mg QD + deleobuvir (NNI) 600 mg BID + RBV for 16 wks[3] (N = 32)

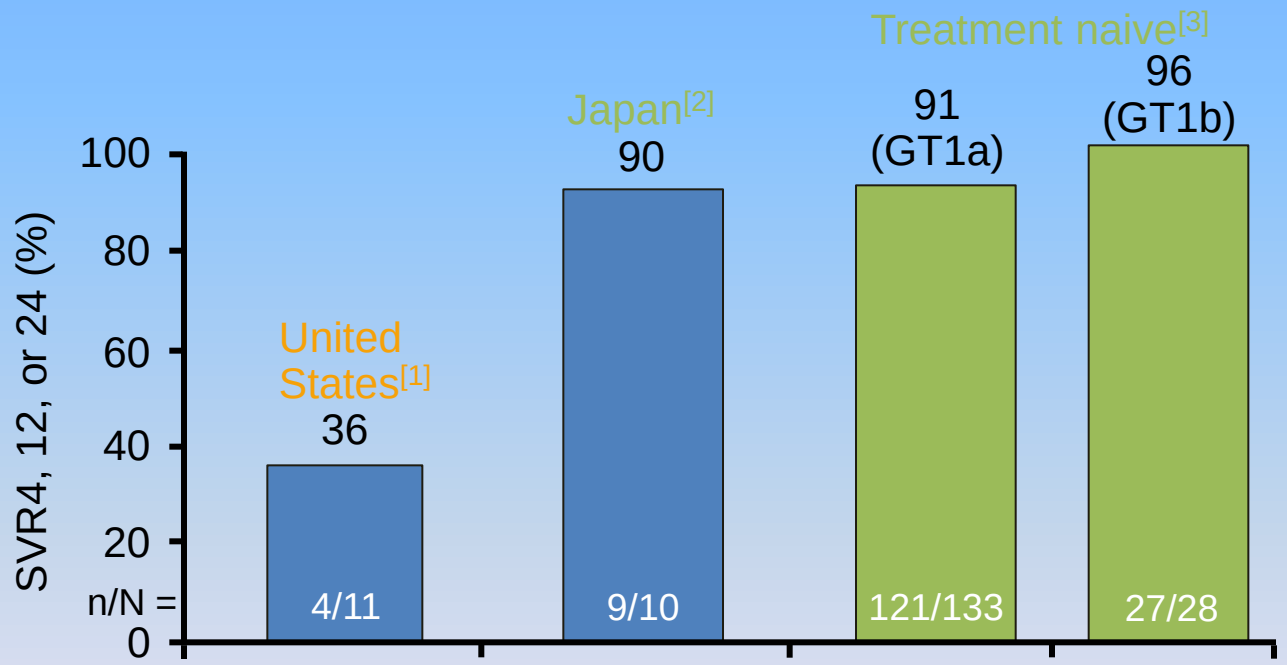


Simple regimen for GT1b only?

1. Zeuzem S, et al. NEJM. 2013;369:630-639. 2. Zeuzem S, et al. EASL 2012. Abstract 101.
3. Dufour JF, et al. AASLD 2013. Abstract 1102.

Example of PI Backbone + NS5A in Prior Null Responders

- Daclatasvir (NS5A) + Asunaprevir (PI) x 24 wks
- Daclatasvir (NS5A) + Asunaprevir (PI) + BMS 791325 (NNI) x 12 wks



US study
9/11 GT1a

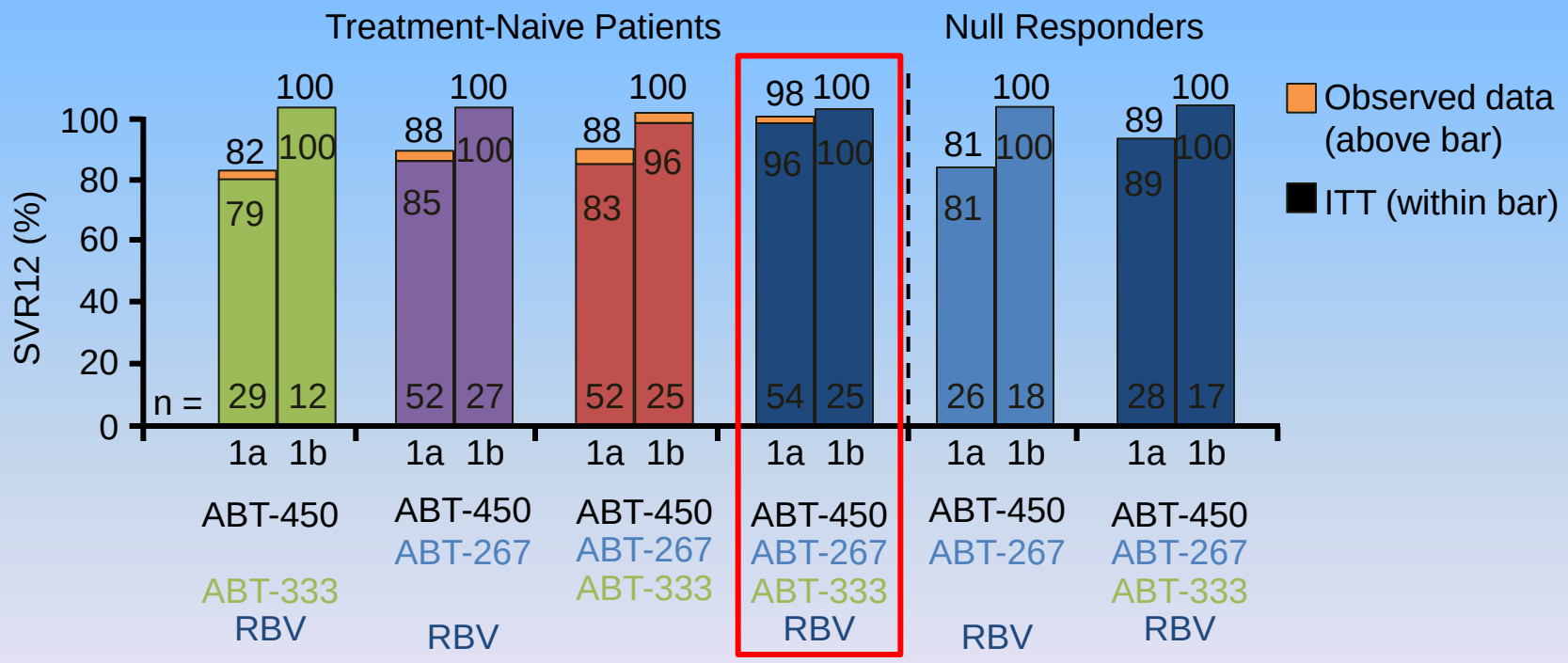
Japanese study
10/10 GT1b

- Likely adequate for GT1b but not for GT1a
- Overcome by addition of third drug: only 12 wks

1. Lok AS, et al. N Engl J Med. 2012;366:216-224. 2. Chayama K, et al. Hepatology. 2012;55:742-748.
3. Everson G, et al. AASLD 2013. Abstract LB-1.

Example of PI Backbone + 2 Other DAAs

ABT-450/RTV (PI) ± ABT-333 (NNI) +
ABT-267 (NS5A) ± RBV x 12 wks

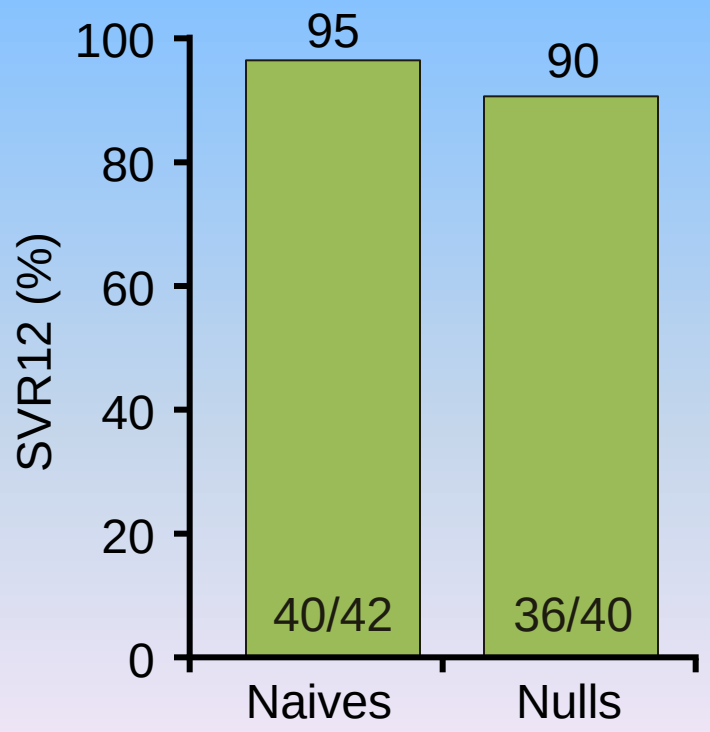


5 drugs (3 pills) but 12 weeks, one size fits all

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

Example of PI Backbone + NS5A in GT1b Trt-Naive Pts and Nulls (PEARL-1)

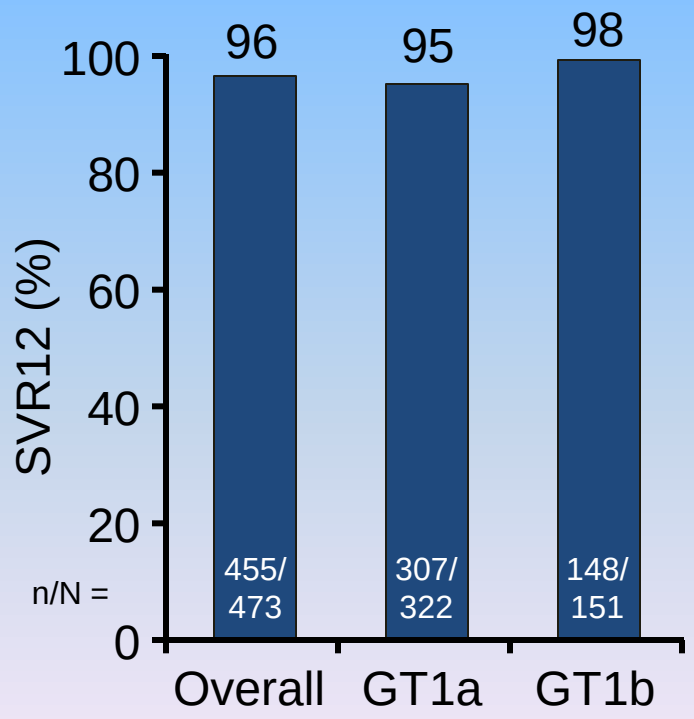
ABT-450/RTV (PI) +
ABT-267 (NS5A) for 16 wks (N = 32)



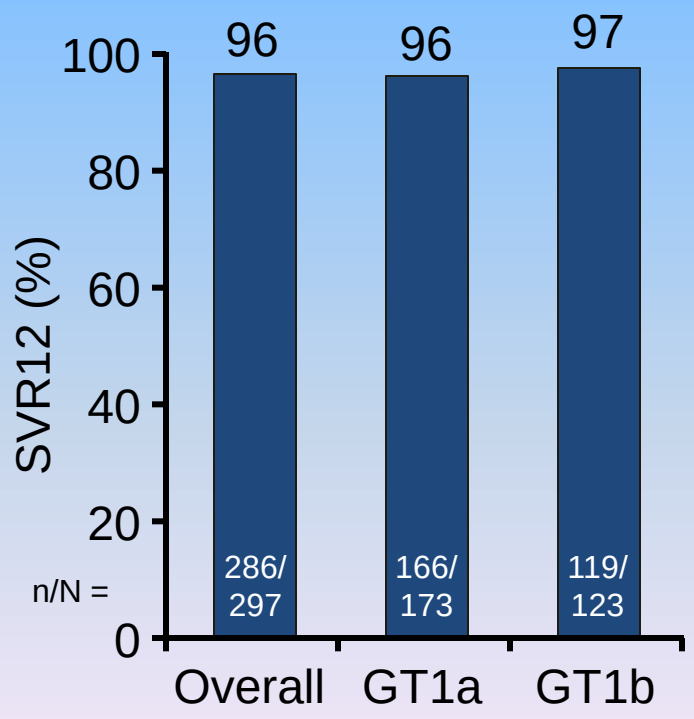
Lawitz E, et al. AASLD 2013. Abstract 75.

SAPPHIRE Phase III Studies: PI Backbone + 2 Other DAAs

SAPPHIRE-1: GT1 treatment-naive noncirrhotic patients:
ABT-450/RTV/ABT-267 FDC
+ ABT-333 + RBV for 12 wks



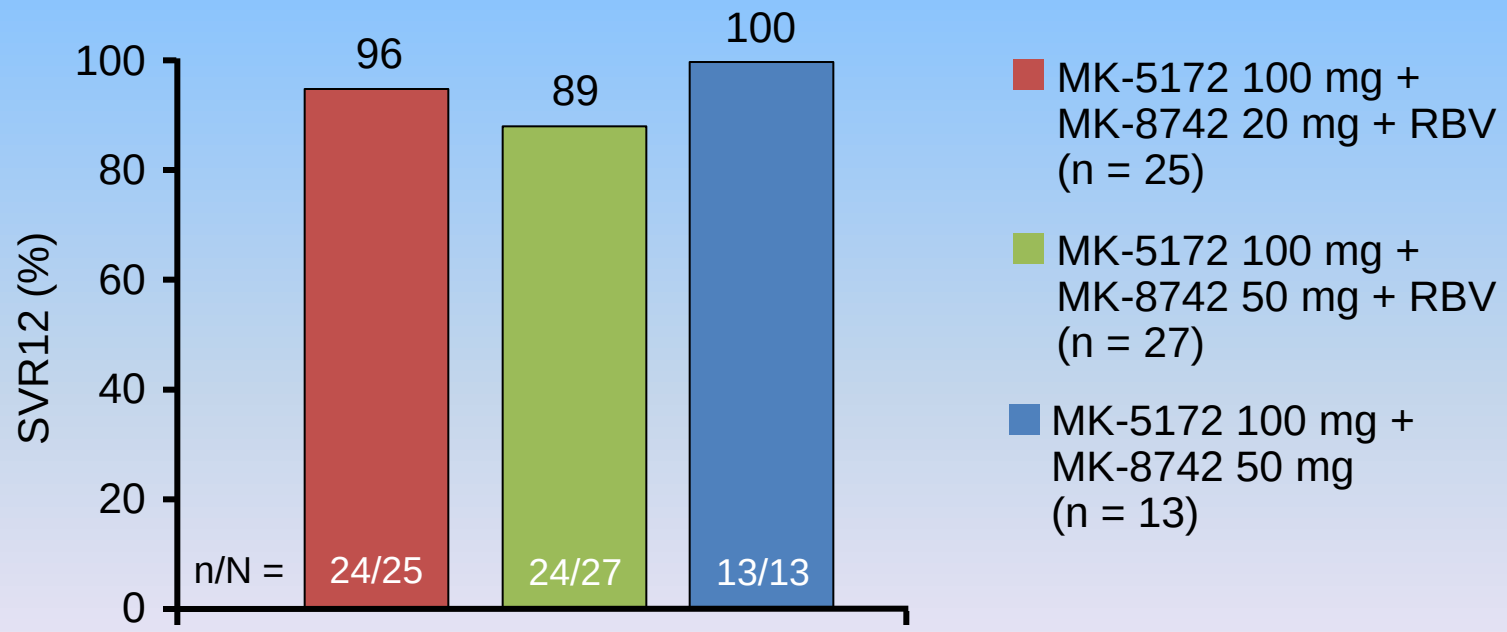
SAPPHIRE-2: GT1 treatment-experienced noncirrhotic patients (49% null responders):
ABT-450/RTV/ABT-267 FDC
+ ABT-333 + RBV for 12 wks



Press release. These data are available in press release format only, have not been peer reviewed, may be incomplete, and we await presentation or publication in a peer-reviewed format before conclusions should be made from these data.

Exception to the Rule: C-WORTHY: PI + NS5A ± RBV in Treatment-Naive GT1 HCV

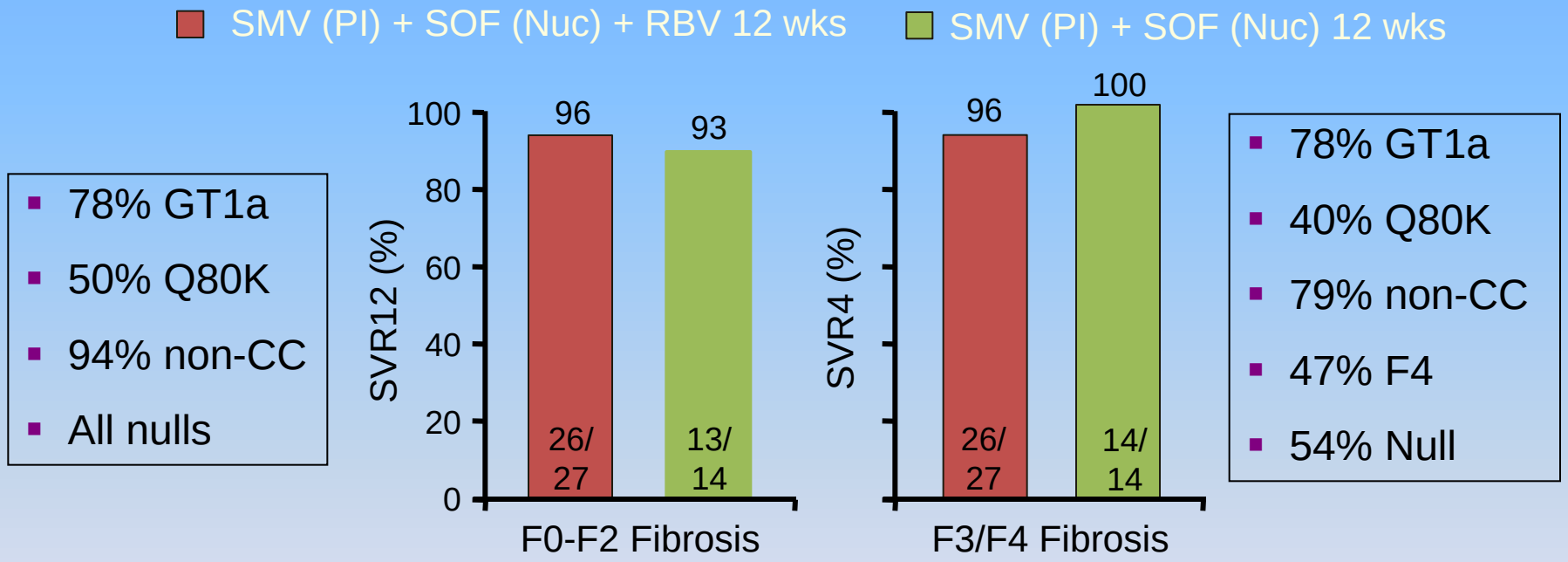
C-WORTHY: MK-5172 (PI) + MK-8742 (NS5A) ± RBV for 12 wks
patients with GT1a randomized 1:1 to RBV arms only;
patients with GT1b randomized 1:1:2 into all 3 arms



Lawitz E, et al. AASLD 2013. Abstract 76.

Examples of Nuc Backbone

Example of Nuc Backbone + PI in Trt-Naive Pts and Nulls (COSMOS)



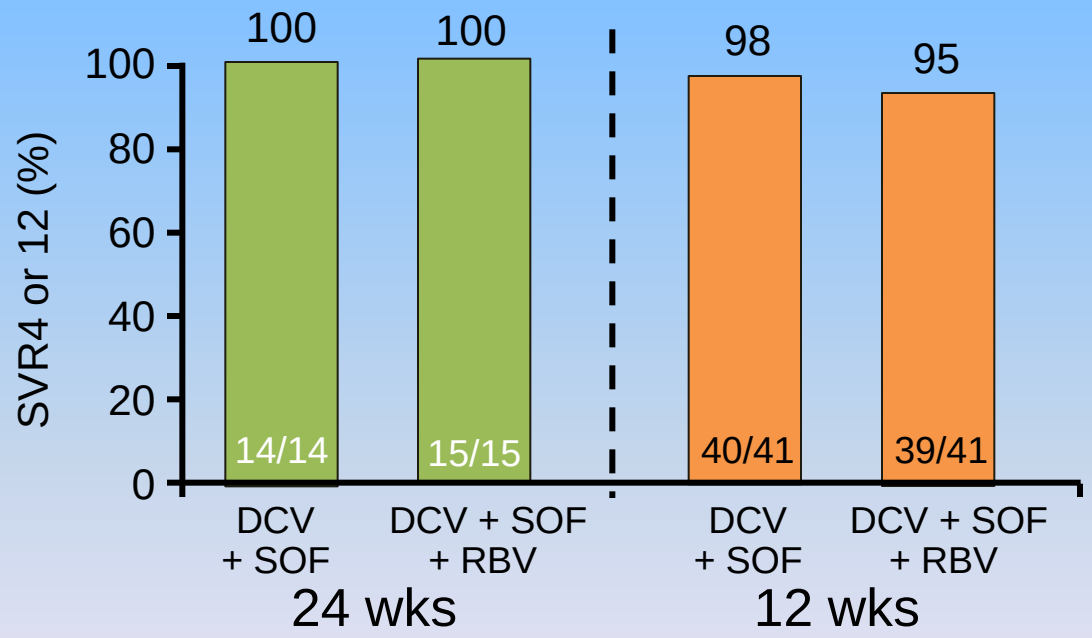
- Major caveats: small n, no plan for phase III trial

Jacobson I, et al. AASLD 2013. Abstract LB-3.

Another Option: Nuc Backbone + NS5A

SOF (Nuc) + daclatasvir (NS5A) ± RBV x 24 wks

SOF (Nuc) + daclatasvir (NS5A) ± RBV x 12 wks

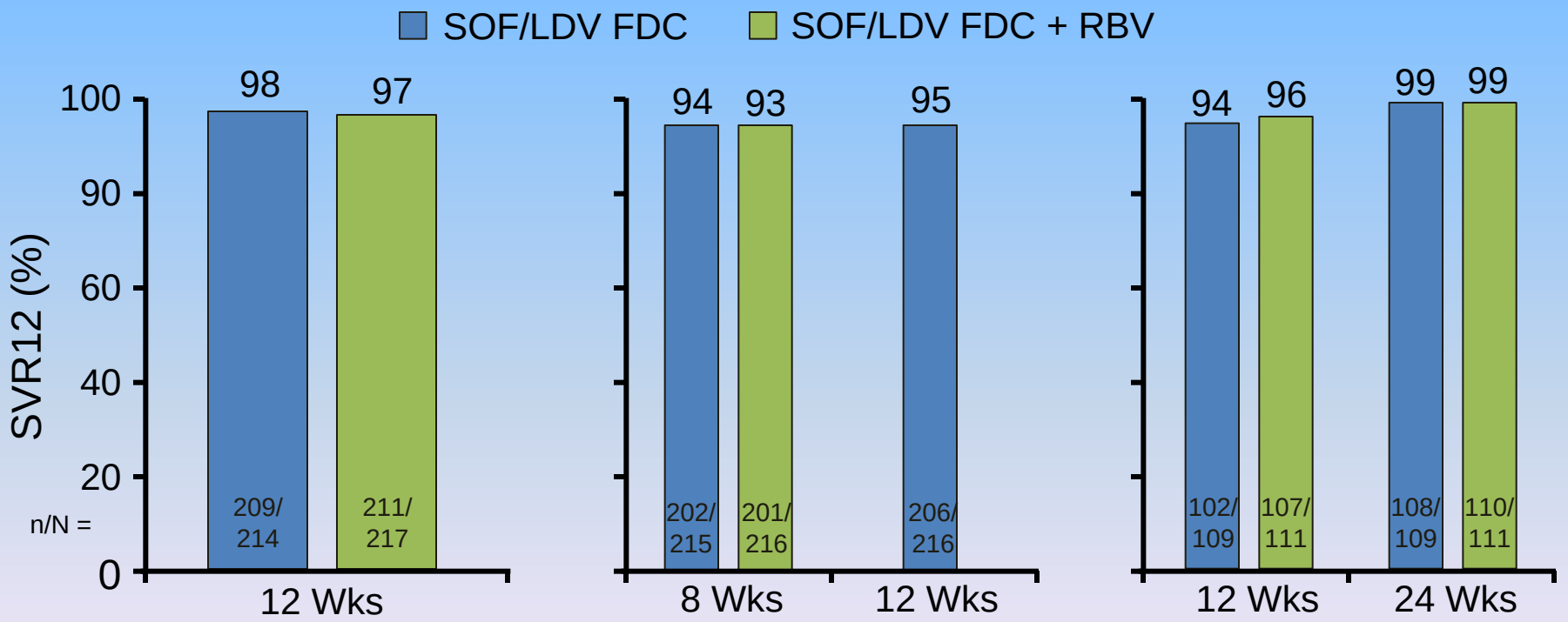


Major caveats: small n, no plan for phase III trial

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

Phase III Studies of Sofosbuvir (Nuc) + Ledipasvir (NS5A) ± RBV in GT1 HCV

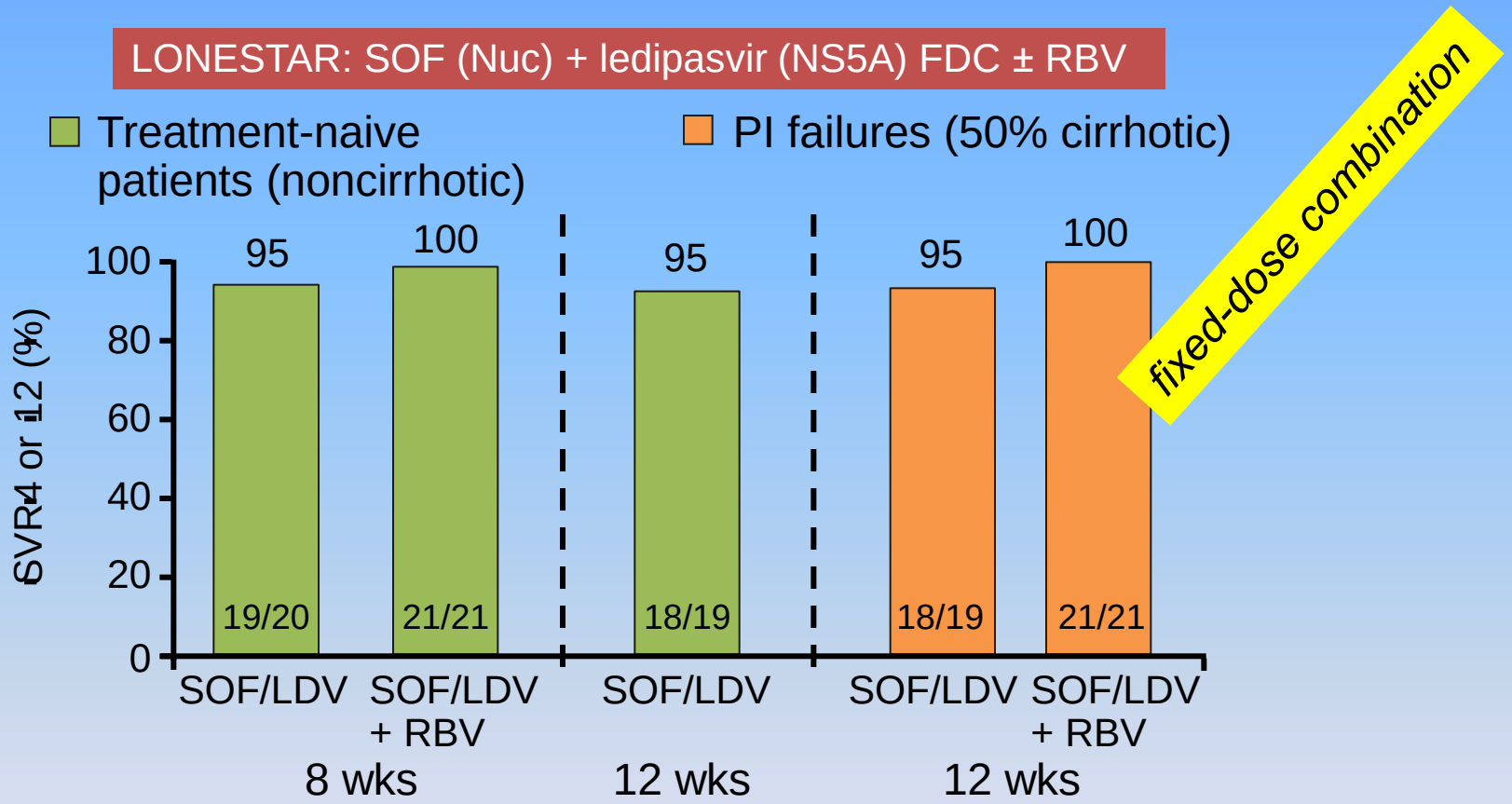
ION-1*: GT1 treatment-naive pts (16% cirrhotic): SOF/LDV FDC ± RBV for 12 wks	ION-3: GT1 treatment-naive pts: SOF/LDV FDC ± RBV for 8 or 12 wks	ION-2: GT1 treatment-experienced pts (20% cirrhotic): SOF/LDV FDC ± RBV for 12 or 24 wks



*24-wk arms not yet reported.

Press release. These data are available in press release format only, have not been peer reviewed, may be incomplete, and we await presentation or publication in a peer-reviewed format before conclusions should be made from these data.

1-Pill Version of Nuc + NS5A



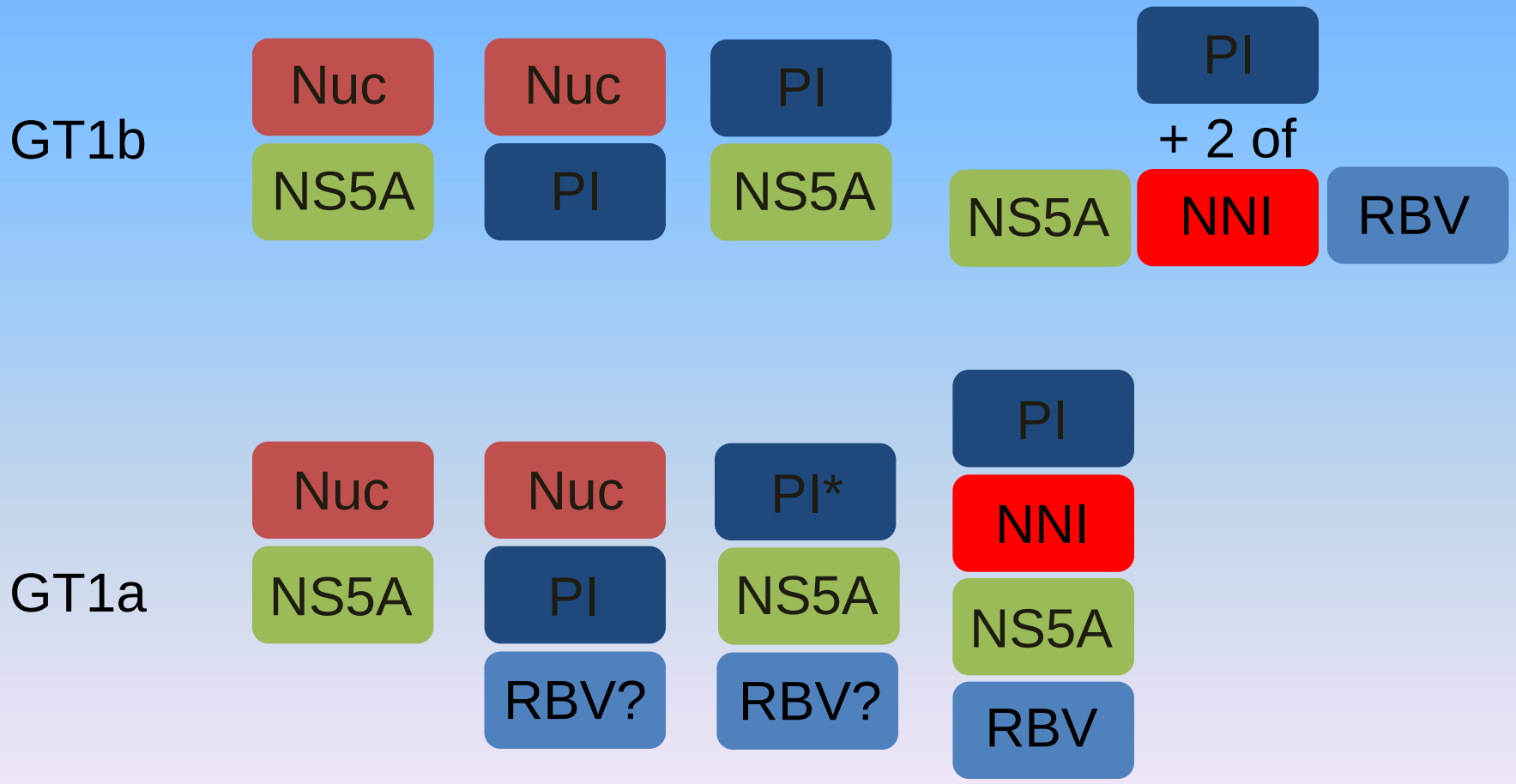
- No breakthrough; 2 relapses, both without RBV
- 1 case of resistance – retreated with SOF/LDV + RBV x 24 weeks → SVR

Lawitz E, et al. AASLD 2013. Abstract 215.

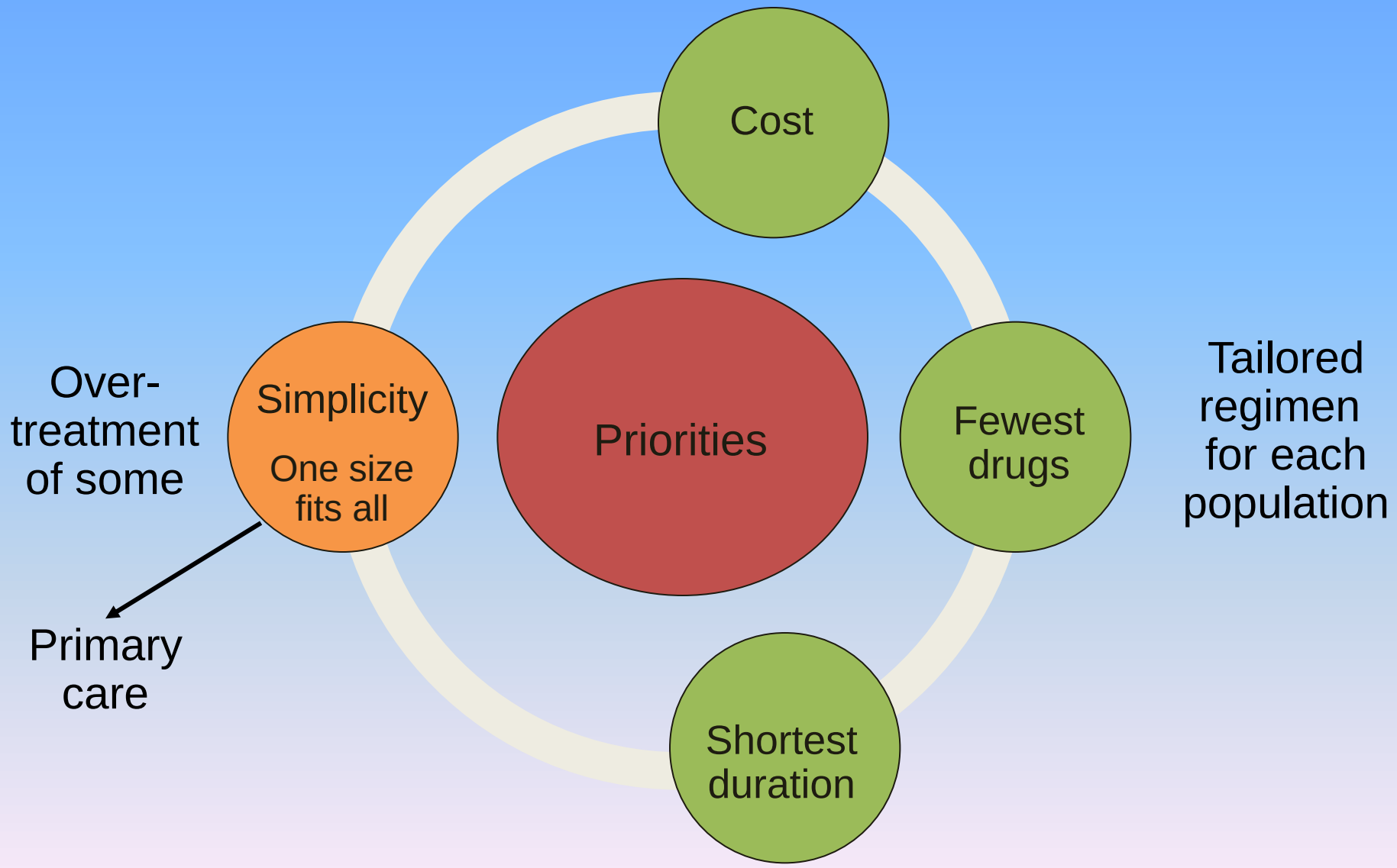
Include ribavirin?

May allow fewer DAAs (2 vs 3)
May allow shorter therapy

Potential 12-Week Options for GT1 HCV With Supportive Efficacy Data



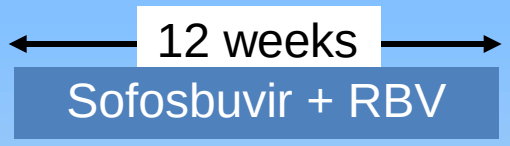
Different Strategies



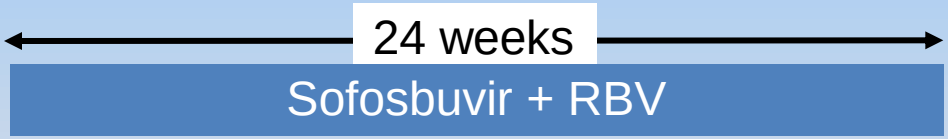
What about GT2 and GT3?

Sofosbuvir + RBV for GT2 and GT3 HCV: Approved Indications

- All GT2 patients receive same regimen, regardless of previous treatment history or fibrosis level



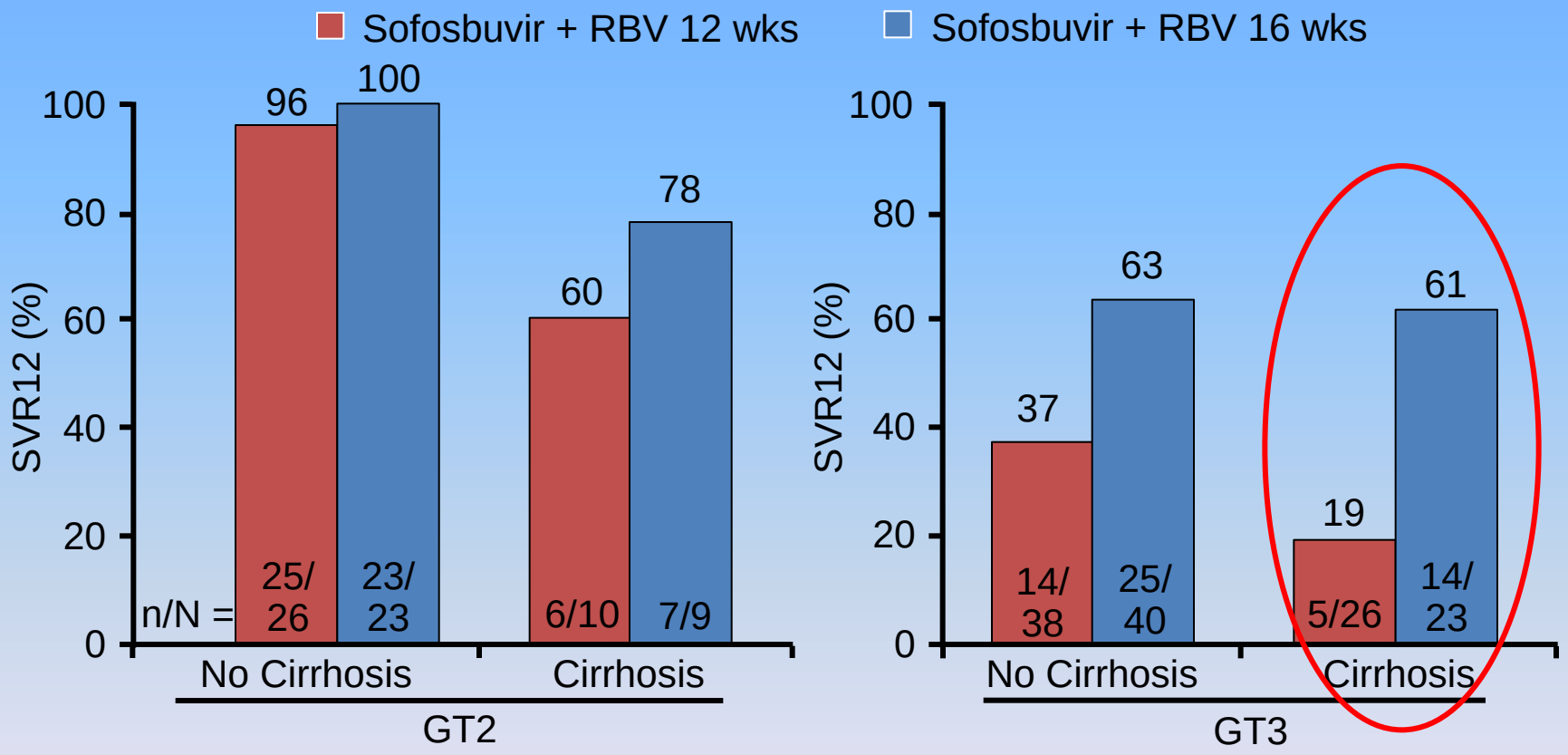
- All GT3 patients receive same regimen, regardless of previous treatment history or fibrosis level



- If drugs combined with sofosbuvir must be permanently discontinued, sofosbuvir should also be discontinued

Sofosbuvir [package insert]. December 2013.

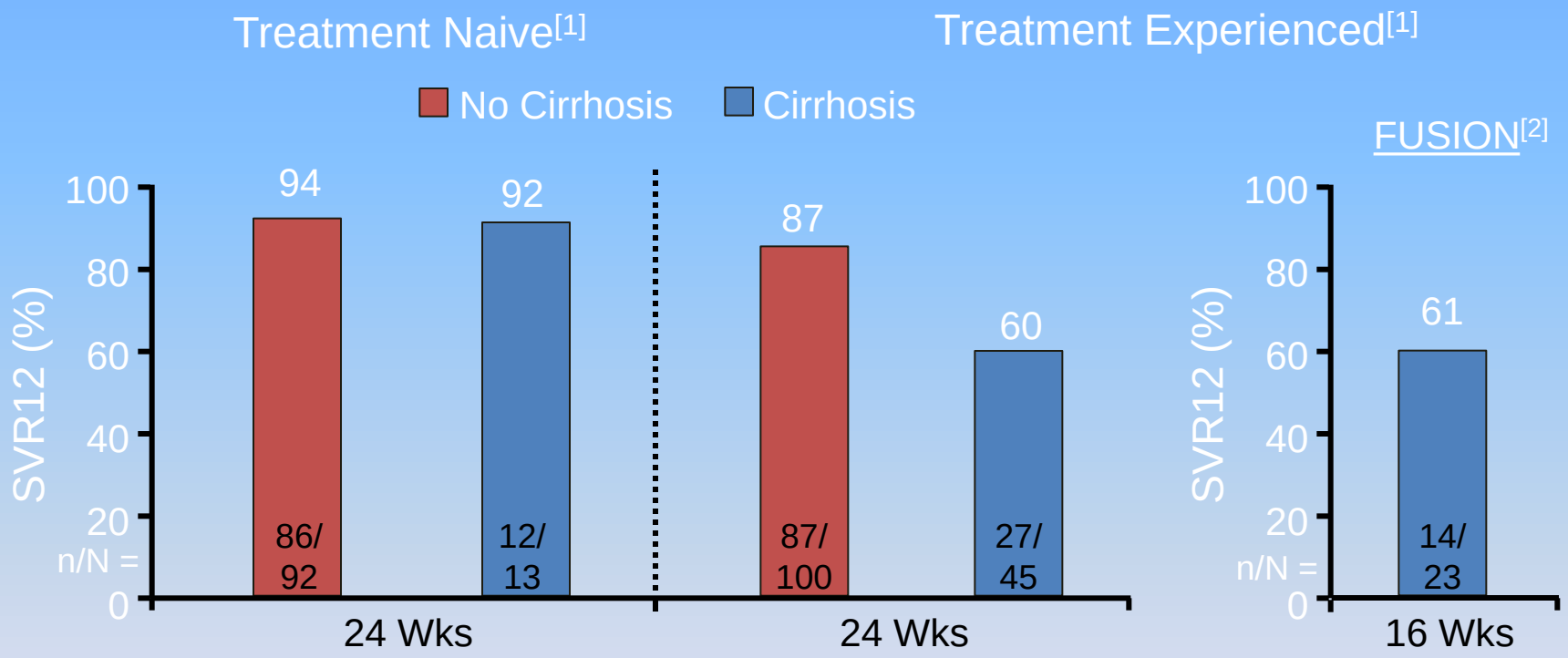
FUSION: SVR by GT and Cirrhosis in Treatment-Experienced Patients



- 12 weeks sufficient for GT2
- 16 weeks better than 12 weeks for GT3… so what about 24 weeks?

Jacobson IM, et al. N Engl J Med. 2013;368:1867-1877.

VALENCE: Efficacy With 24-Week Sofosbuvir Plus Ribavirin in GT3 Patients

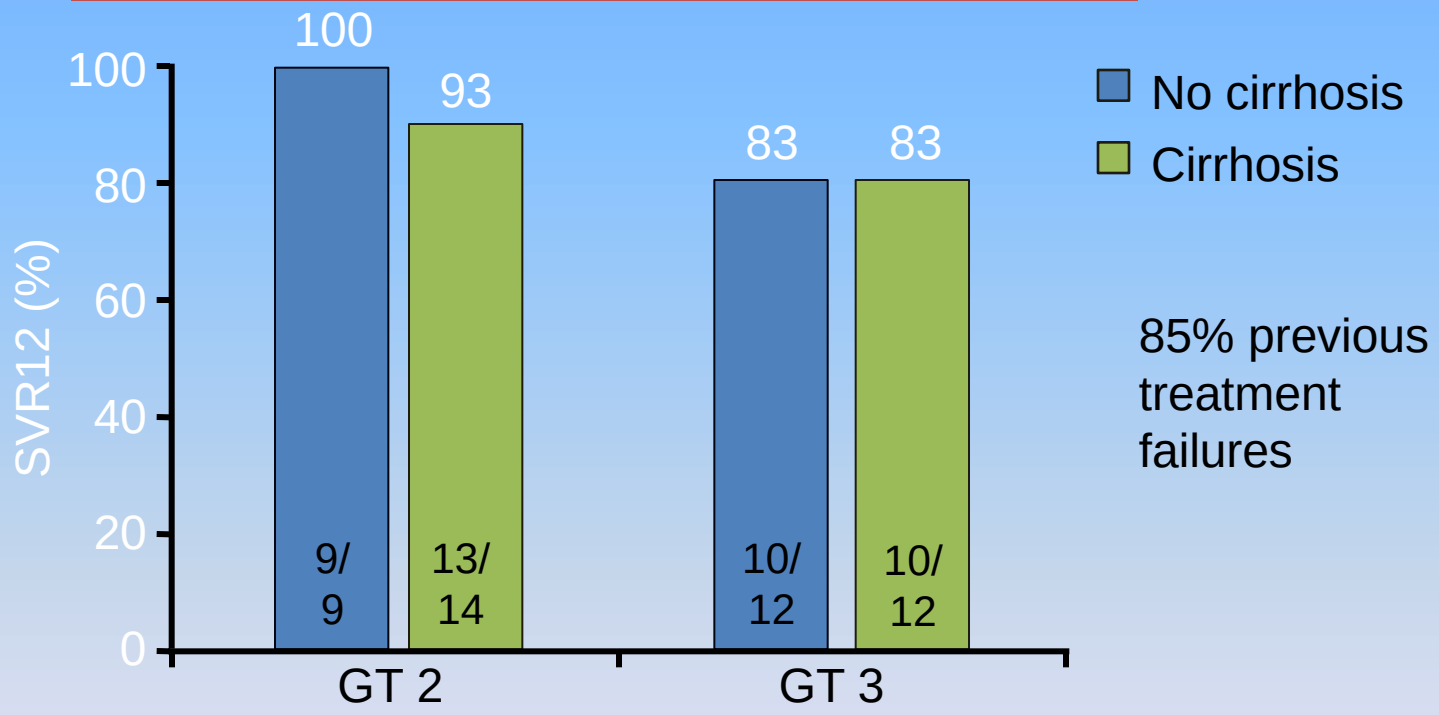


- 24 weeks better for treatment-naive patients
- Not ideal for cirrhotic treatment failures

1. Zeuzem S, et al. AASLD 2013. Abstract 1085. 2. Jacobson IM, et al. N Engl J Med. 2013;368:1867-1877.

Do We Still Need IFN for GT3?

LONESTAR-2: SOF + PegIFN + RBV x 12 wks



- Small single-center study but looks promising. . .
- IFN is not dead yet!

Lawitz E, et al. AASLD 2013. Abstract LB-4.

Potential 12-Week Options for GT2 and GT3 With Supportive Efficacy Data

GT2

- Nuc
- RBV

GT3

- Nuc
- RBV
- Peg

SOF approved indication includes extended duration (24 wks):

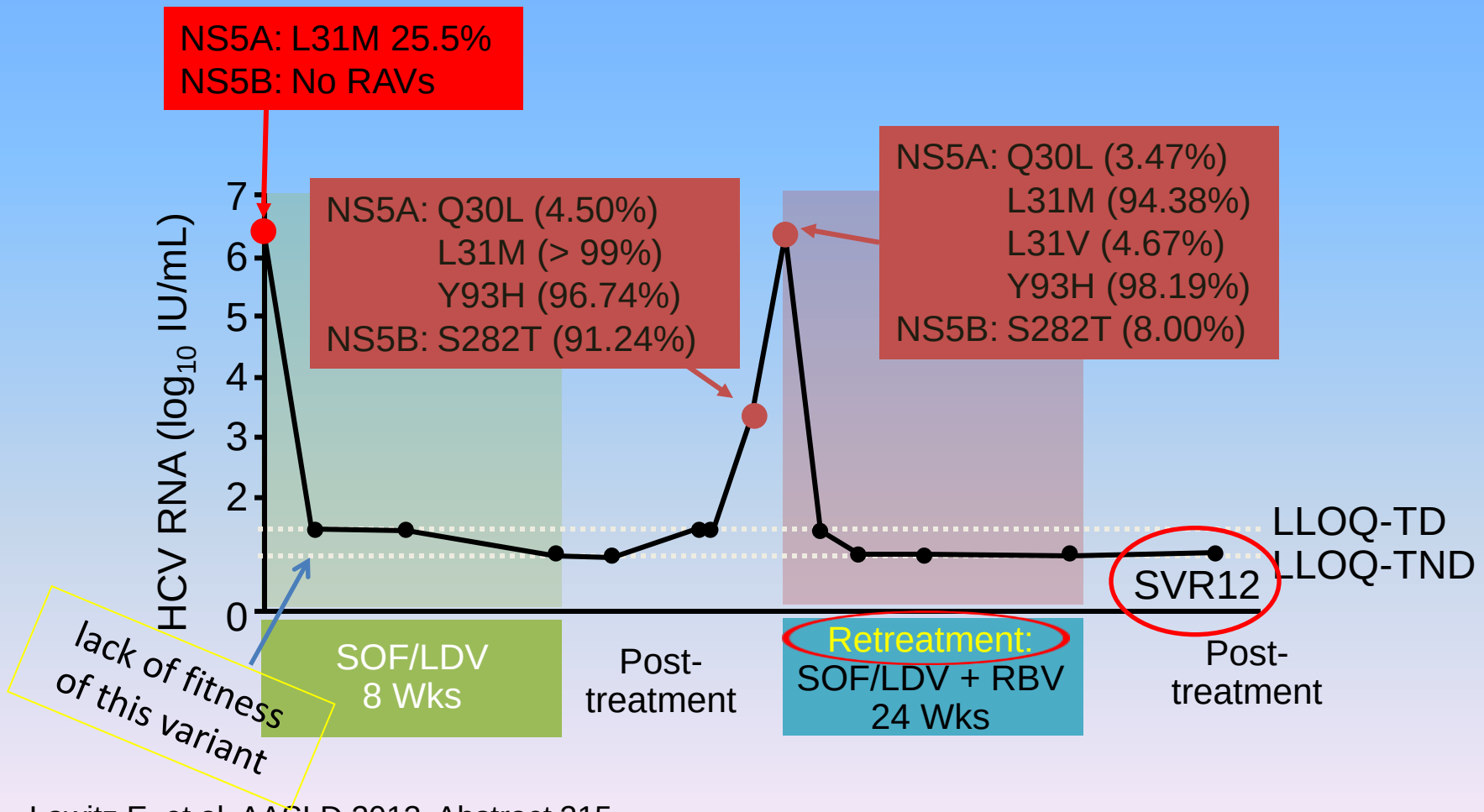
- Nuc
- RBV

Will There Still Be a Role for IFN?

- Hard to cure
  - GT3
  - DAA failures – multi-DAA resistant
  - Prior nonresponders → Quad?
- Easy to cure
  - *IL28B* CC – high efficacy, short duration → Asia?
  - Mild disease – option of IFN vs waiting for progression
- Cost containment
  - Fewer or less effective DAAs
  - GT2?

What About Resistance?

Already at baseline, 25% of quasispecies population resistance to NS5A inhibitor (1pt)



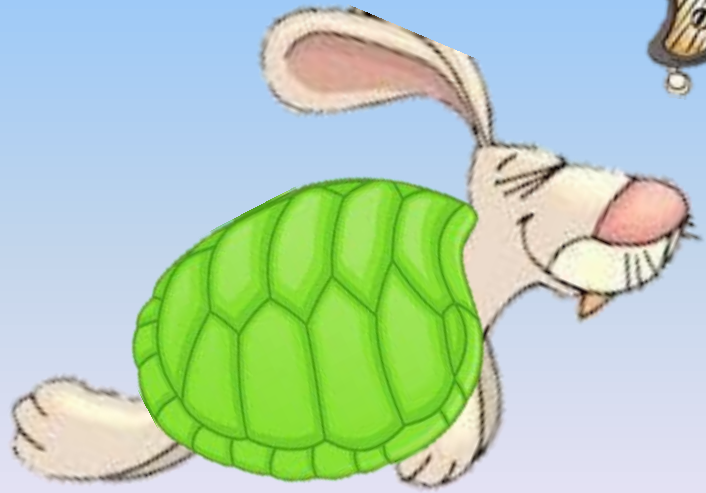
Lawitz E, et al. AASLD 2013. Abstract 215.

Fitness Affects Resistance

Drug A - Nuc

HCV

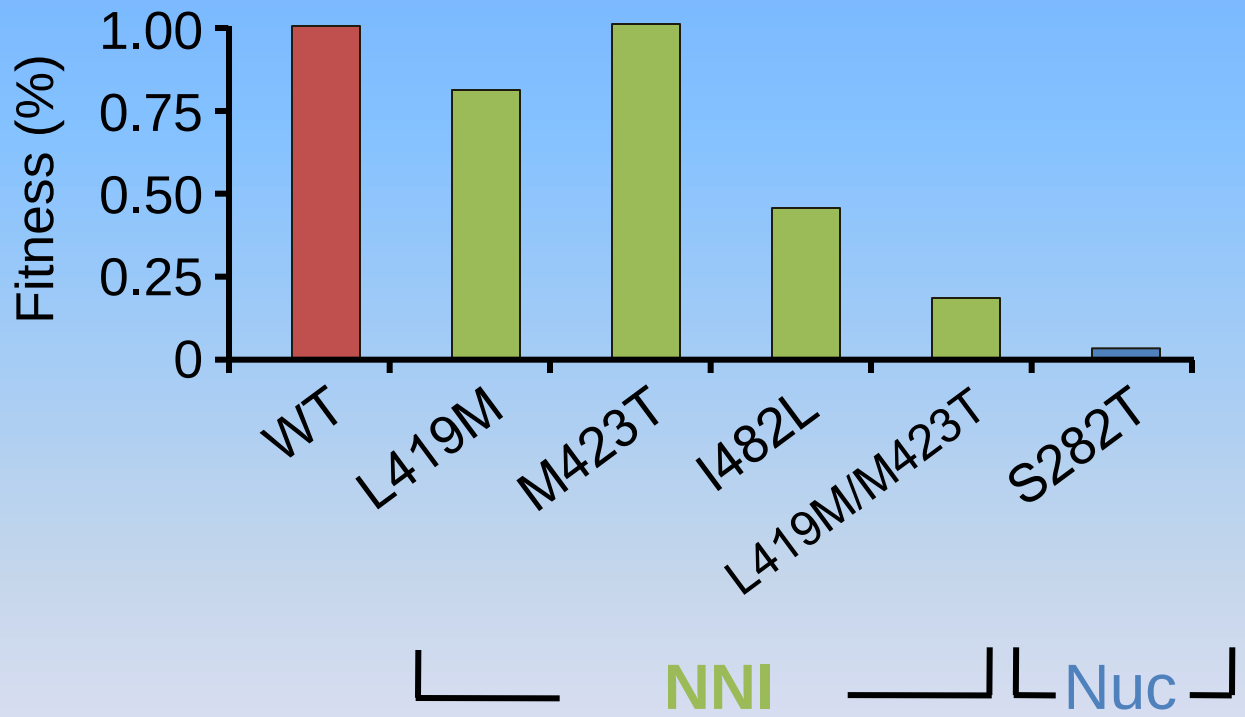
Drug B – PI



Resistant mutant…not so fit
(like *S282T* – resistant but unfit)

Resistant mutant…
(like *R155K* - ? slower but still fit)

Fitness of Polymerase Inhibitor Mutants



Le Pogam S, et al. J Virol. 2006;80:6146-6154.
Le Pogam S, et al. J Infect Dis. 2010;202:1510-1519.

EASL HCV Guidelines 2014: Genotype 1

Genotype	Options for Therapy
Genotype 1*	**PegIFN/ribavirin** + **sofosbuvir**: 12 wks (A1)
	PegIFN/ribavirin + **simeprevir**†: 12 wks, followed by 12 wks of **pegIFN/ribavirin** in previously untreated pts and prior relapsers (A1), or 36 wks of **pegIFN/ribavirin** in previous partial responders and null responders (B1)
	PegIFN/ribavirin + **daclatasvir** (genotype 1b only; B1): 12 wks followed by 12 wks of **pegIFN/ribavirin** alone or a further 12 wks of **pegIFN/ribavirin** + **daclatasvir** (response-guided therapy) (B2)
	Sofosbuvir + **ribavirin**: 24 wks for interferon-intolerant pts only, where no other interferon-free option available (B2)
	Sofosbuvir + **simeprevir**: 12 wks (ribavirin may be added for previous nonresponders & cirrhotics) (B1)
	Sofosbuvir + **daclatasvir**: 12 wks in previously untreated pts; 24 wks in treatment-experienced patients (including TVR/BOC-experienced patients) (ribavirin may be added in previous nonresponders and cirrhotics) (B1)

*In settings where recommended options are not available, treatment with pegIFN/ribavirin + TVR or BOC remains acceptable.

†Not recommended in pts with genotype 1a and detectable Q80K polymorphism.

EASL. J Hepatology. 2014;60:392-420.

EASL HCV Guidelines 2014: Genotype 2-6

Genotype	Options for Therapy
Genotype 2*	**Sofosbuvir** + **ribavirin**: 12 wks (16-20 weeks in cirrhotic patients, especially treatment experienced) (A1)
	PegIFN/ribavirin + **sofosbuvir**: 12 wks for cirrhotic and/or treatment-experienced patients (B1)
Genotype 3*	**Sofosbuvir** + **ribavirin**: 24 wks (unsuitable for treatment-experienced cirrhotics, no specific alternative proposed) (A2)
	PegIFN/ribavirin + **sofosbuvir**: 12 wks (A2)
	Sofosbuvir + **daclatasvir**: 12 wks (24 wks for treatment-experienced patients) (B1)
Genotype 4*	**PegIFN/ribavirin** + **sofosbuvir** 12 weeks (B1)
	PegIFN/ribavirin + **simeprevir**: 12 wks, followed by 12 wks of **pegIFN/ribavirin** in previously untreated patients & prior relapsers (B1), or 36 wks of **pegIFN/ribavirin** in previous partial responders & null responders (B1)
	PegIFN/ribavirin + **daclatasvir**: 12 wks followed by 12 wks of **pegIFN/ribavirin** alone or a further 12 wks of **pegIFN/ribavirin** + **daclatasvir** (response-guided therapy) (B1)
	Sofosbuvir + ribavirin: 24 wks for interferon-intolerant patients (C2)
	Sofosbuvir + simeprevir: 12 wks (ribavirin may be added in previous nonresponders and cirrhotics) (B2)
	Sofosbuvir + daclatasvir: 12 wks in previously untreated patients; 24 wks in treatment-experienced patients (ribavirin may be added in previous nonresponders and cirrhotics) (B2)
Genotype 5/6*	**PegIFN/ribavirin** + **sofosbuvir** 12 wks (B1)
	Sofosbuvir + **ribavirin**: 24 wks for interferon-intolerant patients (C2)

*In settings where recommended options are not available, treatment with pegIFN/ribavirin remains acceptable.

EASL. J Hepatology. 2014;60:392-420.

WHO HCV Guidelines 2014: Recommendations on HCV Treatment

- All adults and children with chronic HCV infection, including people who inject drugs, should be assessed for antiviral treatment (strong recommendation; moderate quality of evidence)
- PegIFN + RBV recommended rather than standard nonpegylated IFN with RBV (strong recommendation; moderate quality of evidence)
- TVR or BOC, in combination with pegIFN/RBV, suggested for GT1 chronic HCV infection rather than pegIFN/RBV alone (conditional recommendation; moderate quality of evidence)
- Sofosbuvir, in combination with RBV with or without pegIFN (depending on HCV genotype), recommended for GT1-4 HCV infection rather than pegIFN/RBV alone (and rather than no treatment for persons who cannot tolerate IFN) (strong recommendation; high quality of evidence)
- Simeprevir, in combination with pegIFN/RBV, recommended for GT1b HCV infection and genotype 1a HCV infection without the Q80K polymorphism, rather than pegIFN/RBV alone (strong recommendation; high quality of evidence)

WHO 2014. Guidelines for the screening, care and treatment of persons with hepatitis C infection.

Sofosbuvir + RBV for Special Populations: Approved Indications

- Sofosbuvir + RBV for treatment of patients with HCC awaiting liver transplantation for up to 48 weeks or until liver transplantation, whichever occurs first
- For HIV/HCV-coinfected patients, sofosbuvir should be administered according to HCV genotype
  - No differences between monoinfected and coinfected patients

Sofosbuvir [package insert]. December 2013.

Summary

- First-generation PIs have now been replaced
  - SMV + P/R x 24 weeks – issue with Q80K in GT1a
  - SOF + P/R x 12 weeks in GT1
- IFN will hang around for a short while. . .
  - IFN-free therapy coming soon for GT1
- Challenges
  - GT1a vs GT1b
  - One size fits all vs GT1b regimens
  - GT3 may still need IFN, at least for now
- Will simplify with time and we will have something for everyone
- The final challenge will be paying for perfectovir!