

# **Clinical Efficacy of HCV NS5A Inhibitors**

**Anna S. Lok, MD**

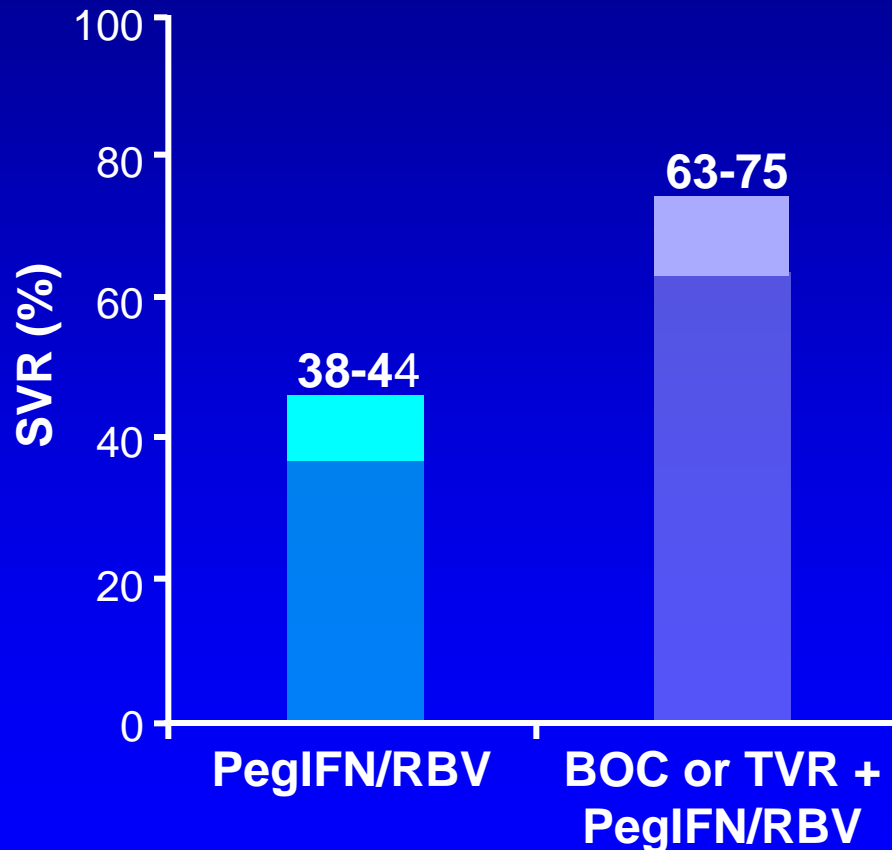
**Alice Lohrman Andrews**

**Research Professor in Hepatology**

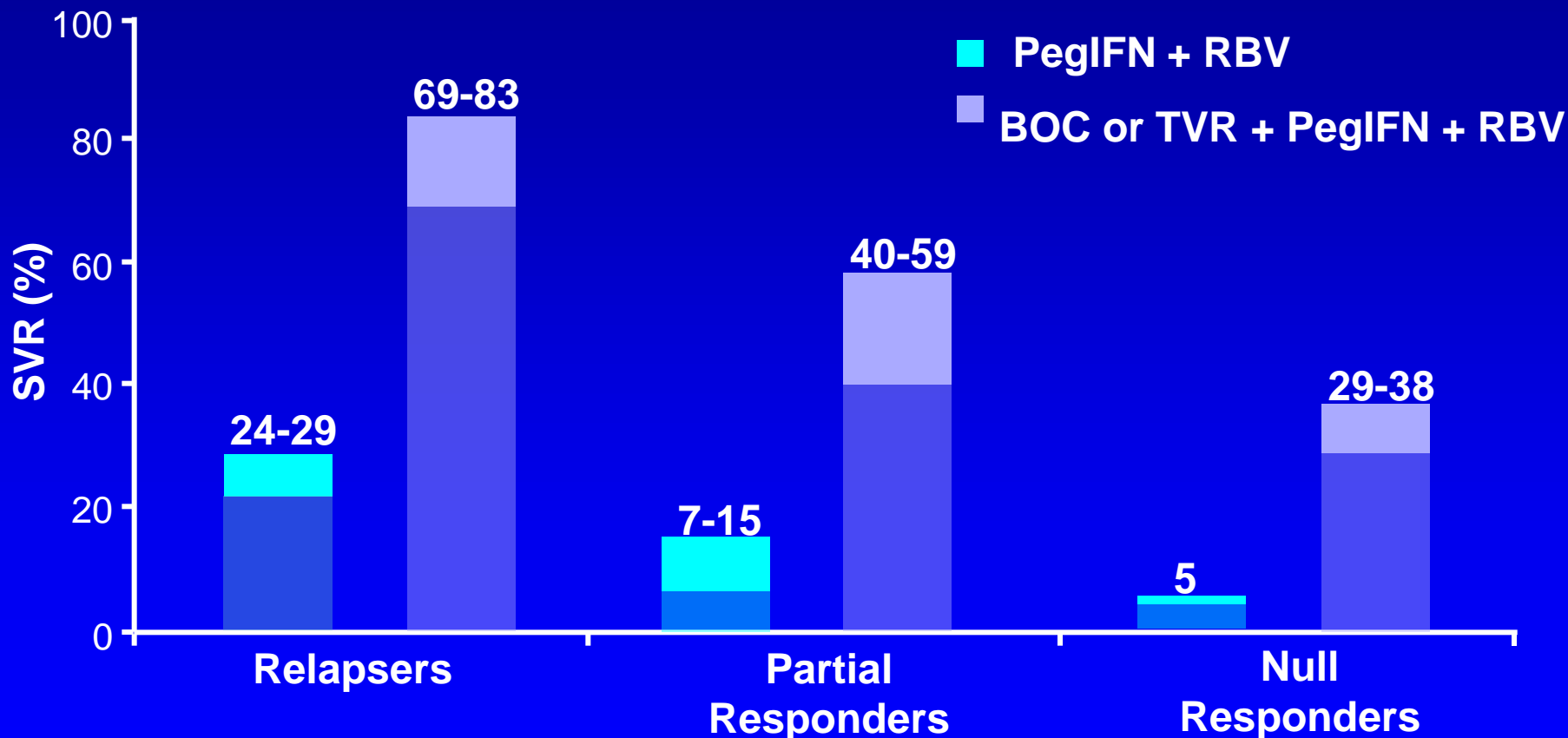
**University of Michigan**

**Ann Arbor, MI, USA**

# SVR Rates With Boceprevir or Telaprevir in Genotype 1 Treatment-Naive Patients



# SVR Rates With BOC or TVR in GT1 Treatment-Experienced Patients

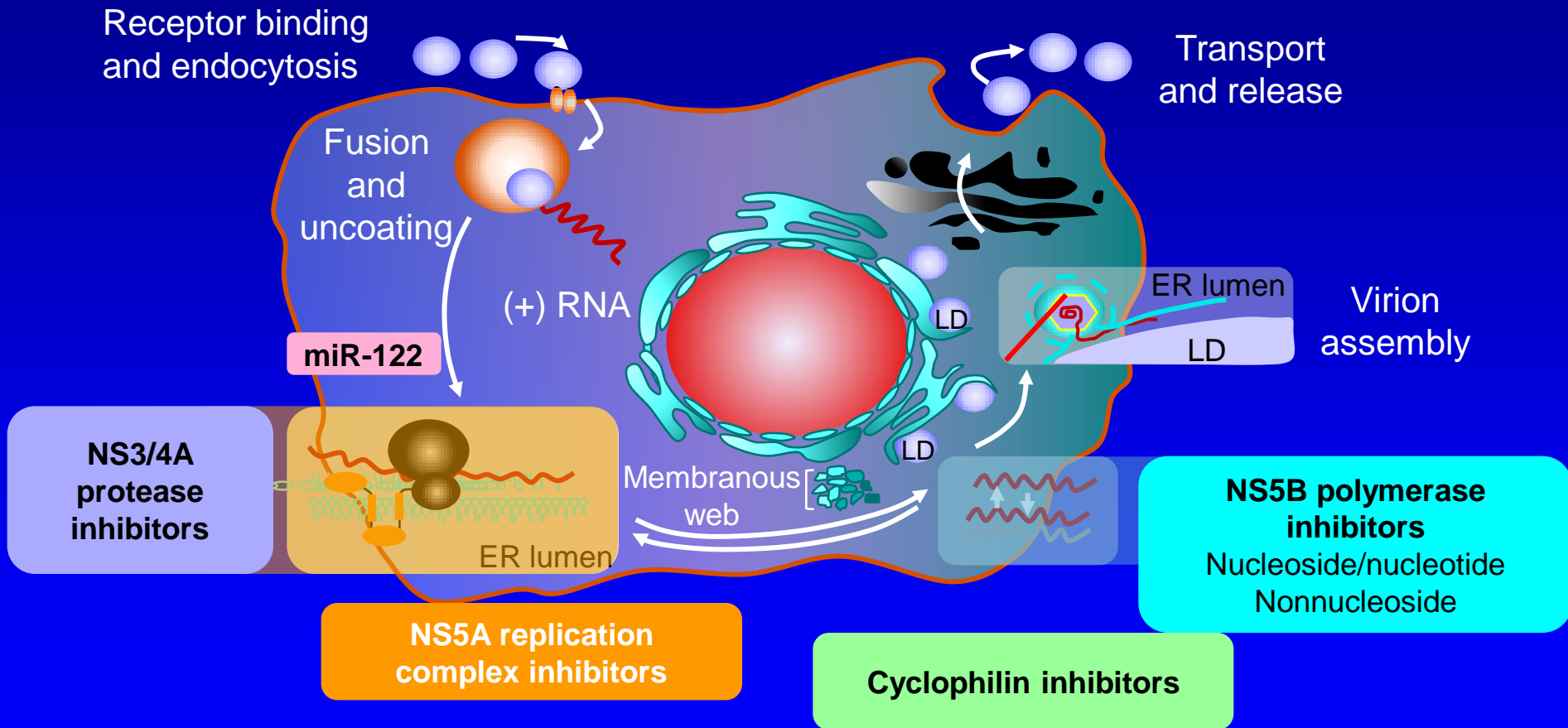


# Limitations of TVR/BOC + PR

---

- Peginterferon and ribavirin still required
- Complicated dose regimen
  - High pill burden
  - Q8 hr dosing
  - Complex algorithms to guide duration of treatment
- Additional side effects
- Drug-drug interactions
- Genotype specific
- Low efficacy in some patient populations: null responders, cirrhotics, Blacks

# HCV Life Cycle and Direct-Acting Antiviral (DAA) Targets



# NS5A as a Target for DAA

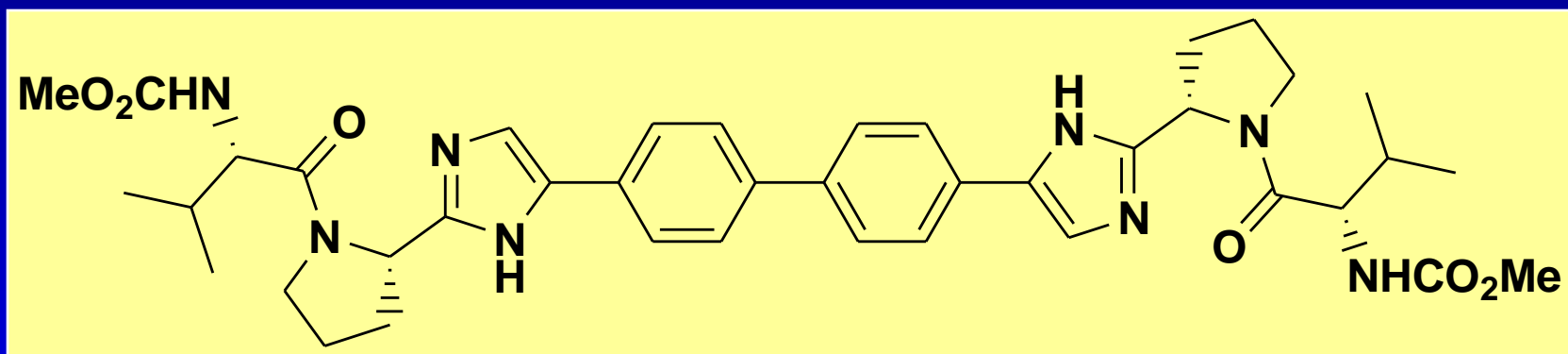
---

- **HCV NS5A protein is unique, with no known human or viral homologs other than NS5A of GBV-B**
- **Multiple functions in HCV life cycle**
- **3 domains**
  - **I - dimeric structure, essential for HCV RNA replication**
  - **II - antagonize innate immune responses, binding to cyclophilin A**
  - **III - assembly of infectious viral particles**

# Clinical Trials of HCV NS5A Inhibitors

Company	Drug	Trial phase	Genotype tested	Patient population	Trial design
BMS	Daclatasvir (DCV, BMS-790052)	II/III	1, 2, 3, 4	Naïve and non responders	<ul style="list-style-type: none"> <li>• Dual therapy with NS3/4A or NS5B inhibitor</li> <li>• Triple therapy with PEG/RBV or λIFN/RBV or DAA/RBV</li> <li>• Quad therapy with NS3/4A + PEG/RBV</li> </ul>
Gilead	GS-5885	I/II	1	Naive	<ul style="list-style-type: none"> <li>• Monotherapy</li> <li>• Quad therapy with GS-9451 + PEG/RBV</li> </ul>
GSK	GSK2336805	I/II	1 or 4	Naive	<ul style="list-style-type: none"> <li>• Monotherapy</li> <li>• Triple therapy with PEG/RBV</li> </ul>
Presidio	PPI-668	I	1	Naive	<ul style="list-style-type: none"> <li>• Monotherapy</li> </ul>

# DACLATASVIR (DCV, BMS-790052)



- First-in-class, highly selective HCV NS5A replication complex inhibitor with picomolar in vitro potency and broad genotypic coverage

# BMS-790052: in vitro Antiviral Activity

Assay	EC <sub>50</sub> (pM)
HCV replicon, G1a	50
HCV replicon, G1b	9
HCV replicon, G2a	71-103
Infectious HCV, G2a, JFH	28
HCV replicon, G3a	146
HCV replicon, G4a	12
HCV replicon, G5a	33

IC<sub>50</sub> in Huh-7 cells 17 ± 1 uM

# Resistance Profile of BMS-790052

Replicon	Genotype 1a		Genotype 1b	
	Replication level (%)	Fold resistance	Replication level (%)	Fold resistance
WT	100	1	100	1
M28A	27	4591	-	-
M28T	31	682	-	-
Q30E	150	25,205	-	-
Q30H	75	1,477	-	-
Q30R	41	1,277	-	-
L31M	55	341	99	3
L31V	117	3,386	158	28
H58D	92	500	-	-
Y93C	11	1,864	-	-
Y93H	18	5,432	27	24
Y93N	13	47,477	-	-

Combination of mutations markedly increase resistance

Resistance variants sensitive to IFN, HCV protease and polymerase inhibitors

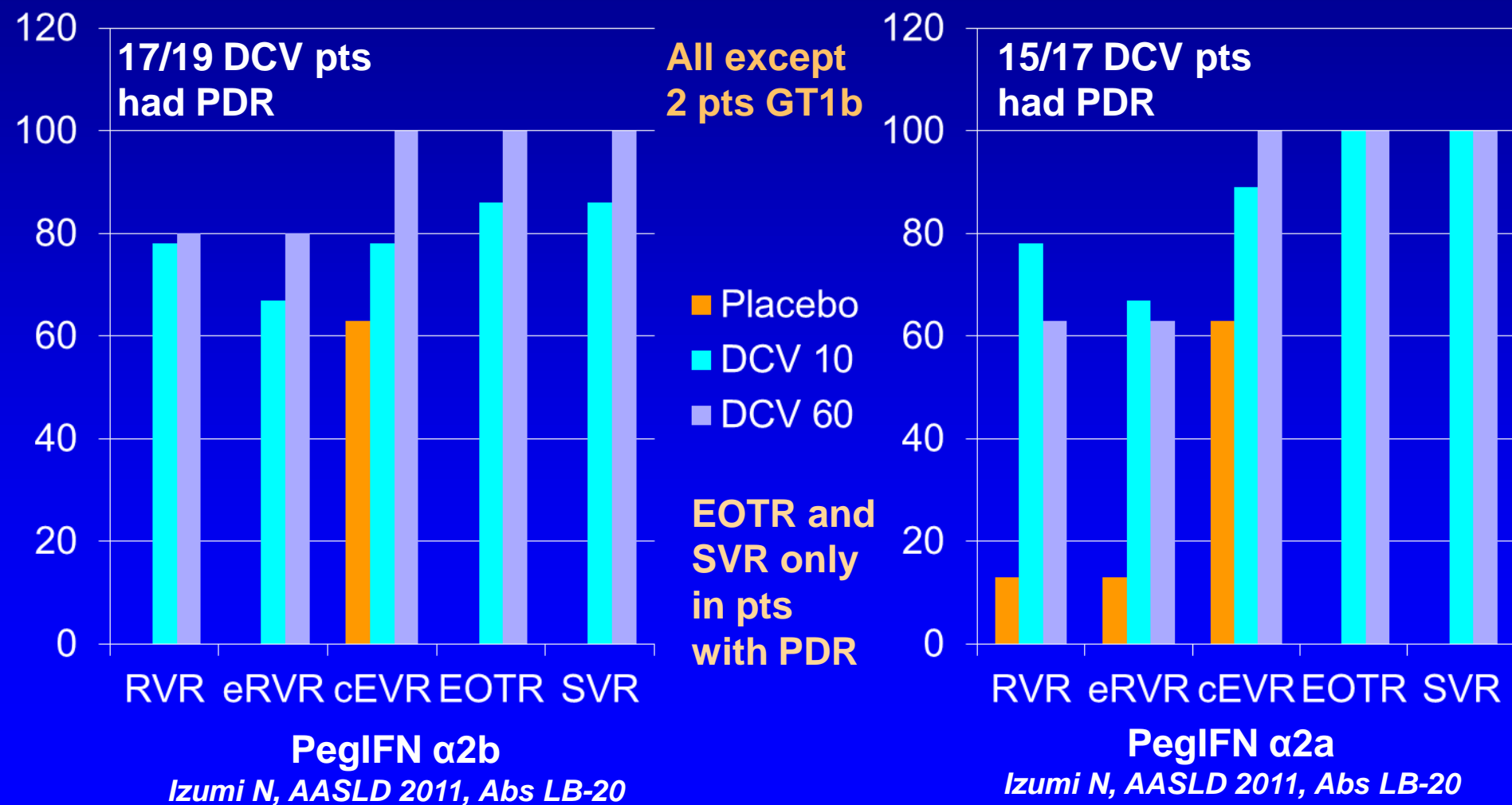
# BMS-790052: Pharmacokinetics

---

- **Daily dosing,  $t_{1/2}$  12-15 hrs**
- **Substrate of CYP3A4 and P-glycoprotein**
  - Interactions with HIV drugs (not tenofovir)
- **No interaction with**
  - Asunaprevir (ASV, BMS-650032)
  - Combined oral contraceptive
- **Severe hepatic impairment**
  - Dose adjustment not required in cirrhotics (including Child C)

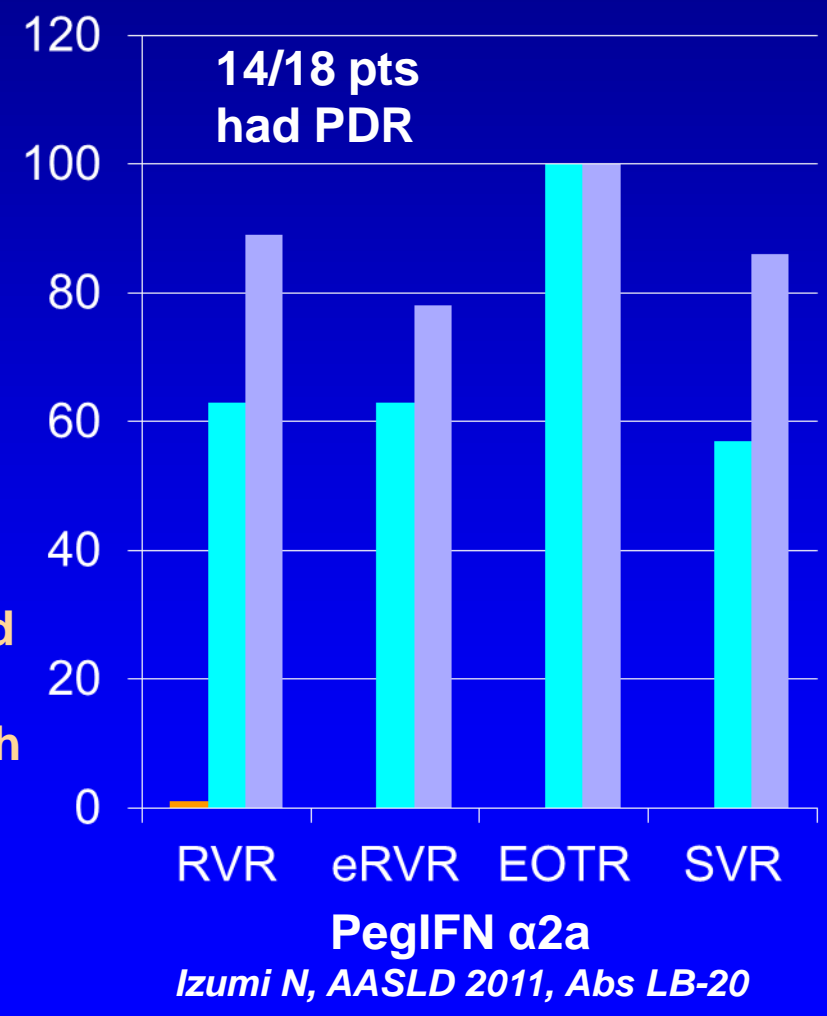
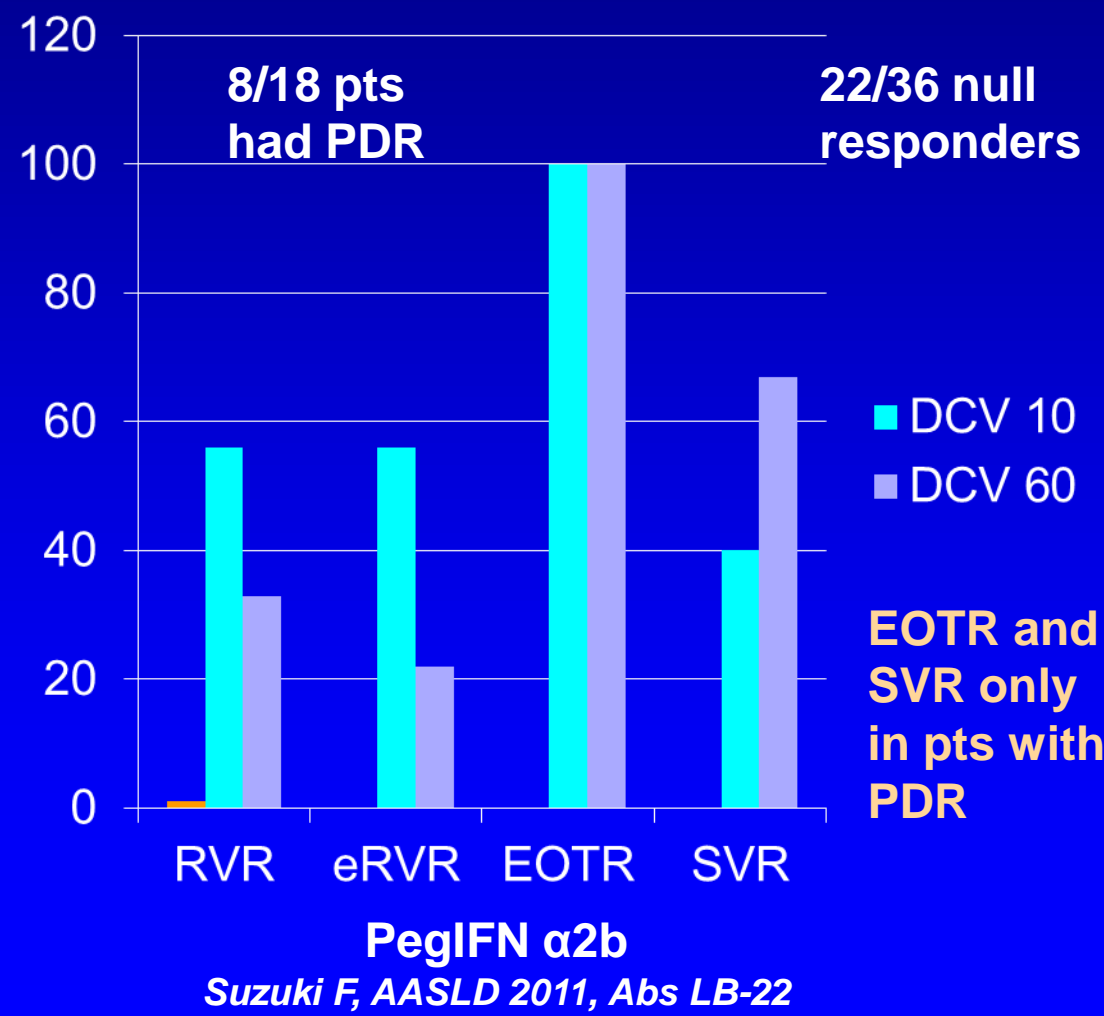


# Daclatasvir + PEG/RBV in Japanese GT1, Treatment-Naïve Patients





# Daclatasvir + PEG/RBV in Japanese GT1b, Partial/Null Responders



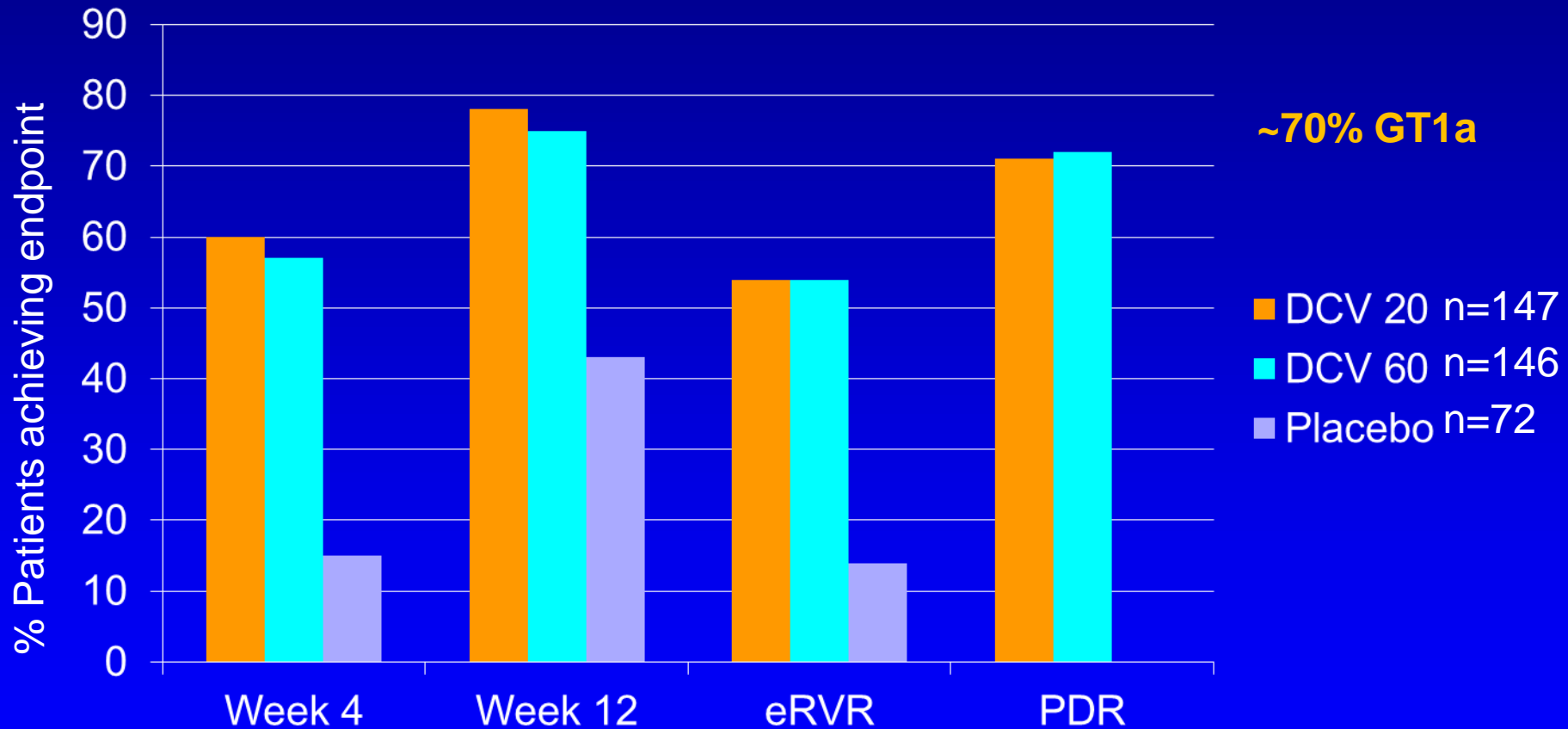
# Daclatasvir + PEG/RBV in Japanese GT1b Treatment-naïve and Nonresponder Patients Virologic Failure at 24 Weeks

Virologic Failure	Treatment-naïve			Nonresponders	
	Placebo (n=16)	DCV 10 mg (n=18)	DCV 60 mg (n=18)	DCV 10 mg (n=17)	DCV 60 mg (n=18)
<b>All failures</b>	<b>3</b>	<b>4</b>	<b>1</b>	<b>11</b>	<b>7</b>
<b>Virologic breakthrough</b>	<b>1</b>	<b>2</b>	<b>0</b>	<b>5</b>	<b>5</b>
<b>Post-treatment relapse</b>	<b>2</b>	<b>1</b>	<b>1</b>	<b>6</b>	<b>2</b>



# Daclatasvir + PEG/RBV

## Virologic Responses in GT1 Patients



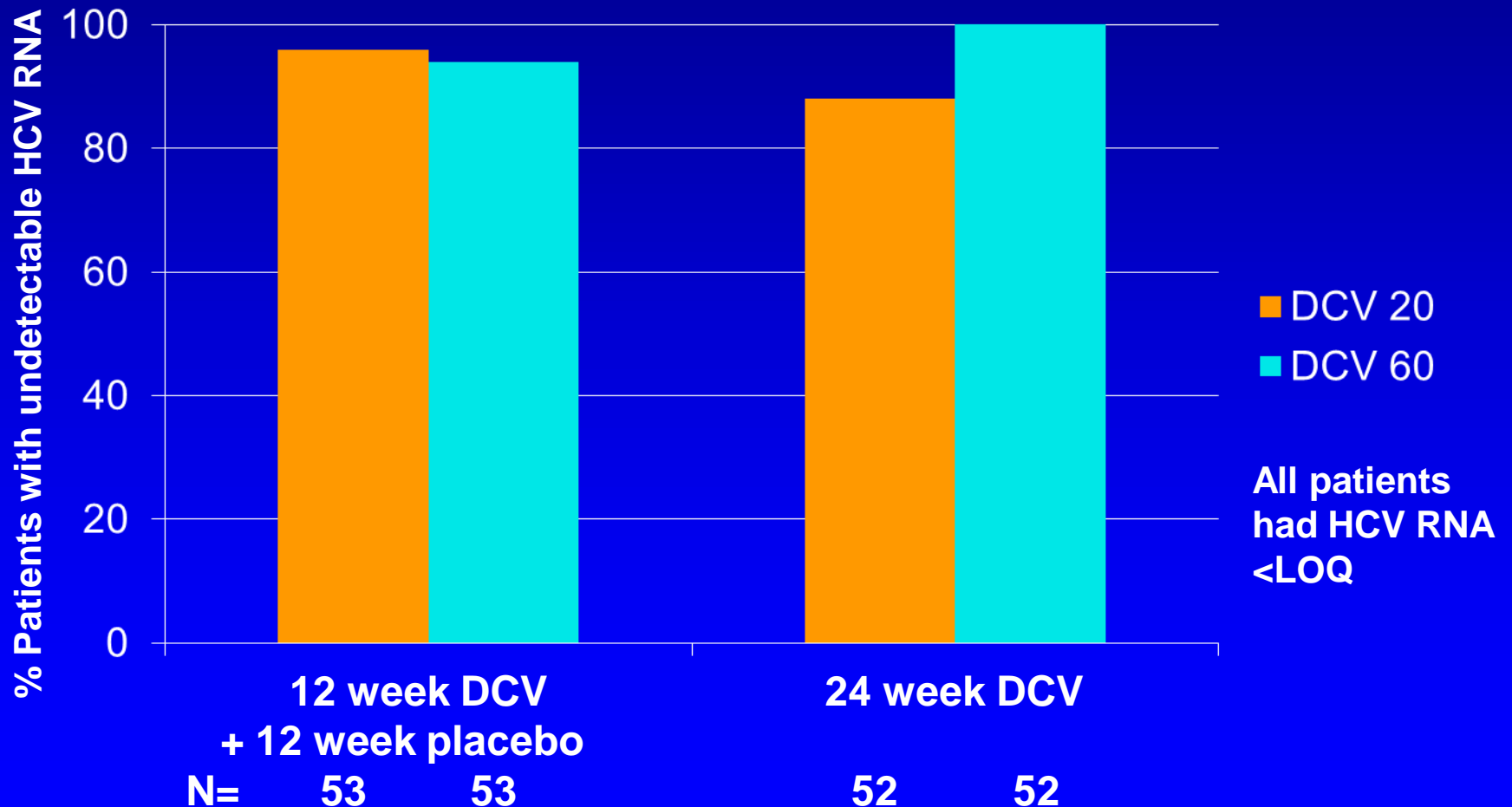
Week 4 & 12 responses: HCV RNA <LOQ

LOQ = 25 IU/mL; LOD = 10 IU/mL

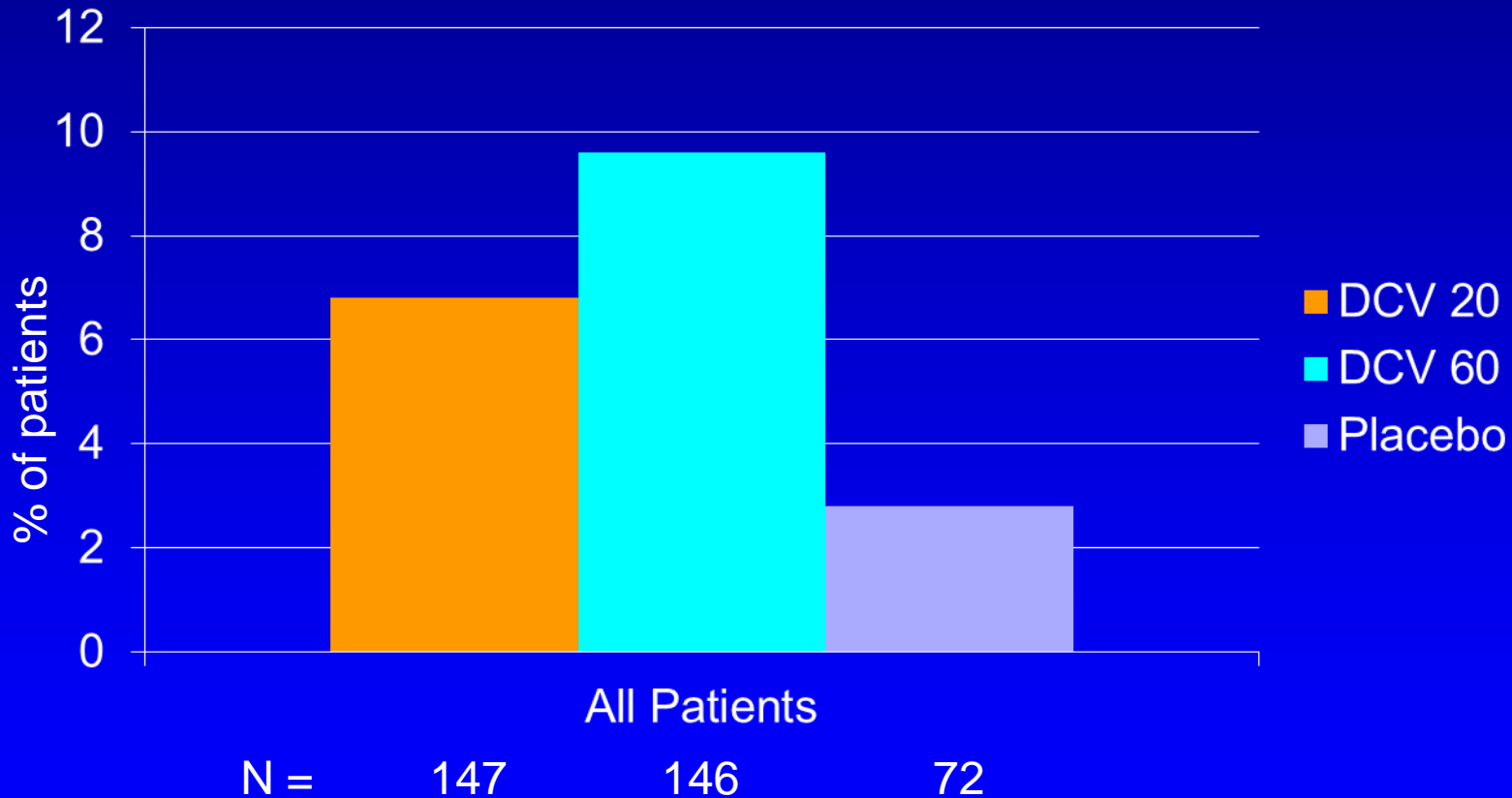
eRVR: HCV RNA undetectable at Week 4 & 12

PDR: HCV RNA <LOQ at Week 4 and undetectable at Week 10

# End of Treatment (Week 24) Responses in GT1 Patients with PDR

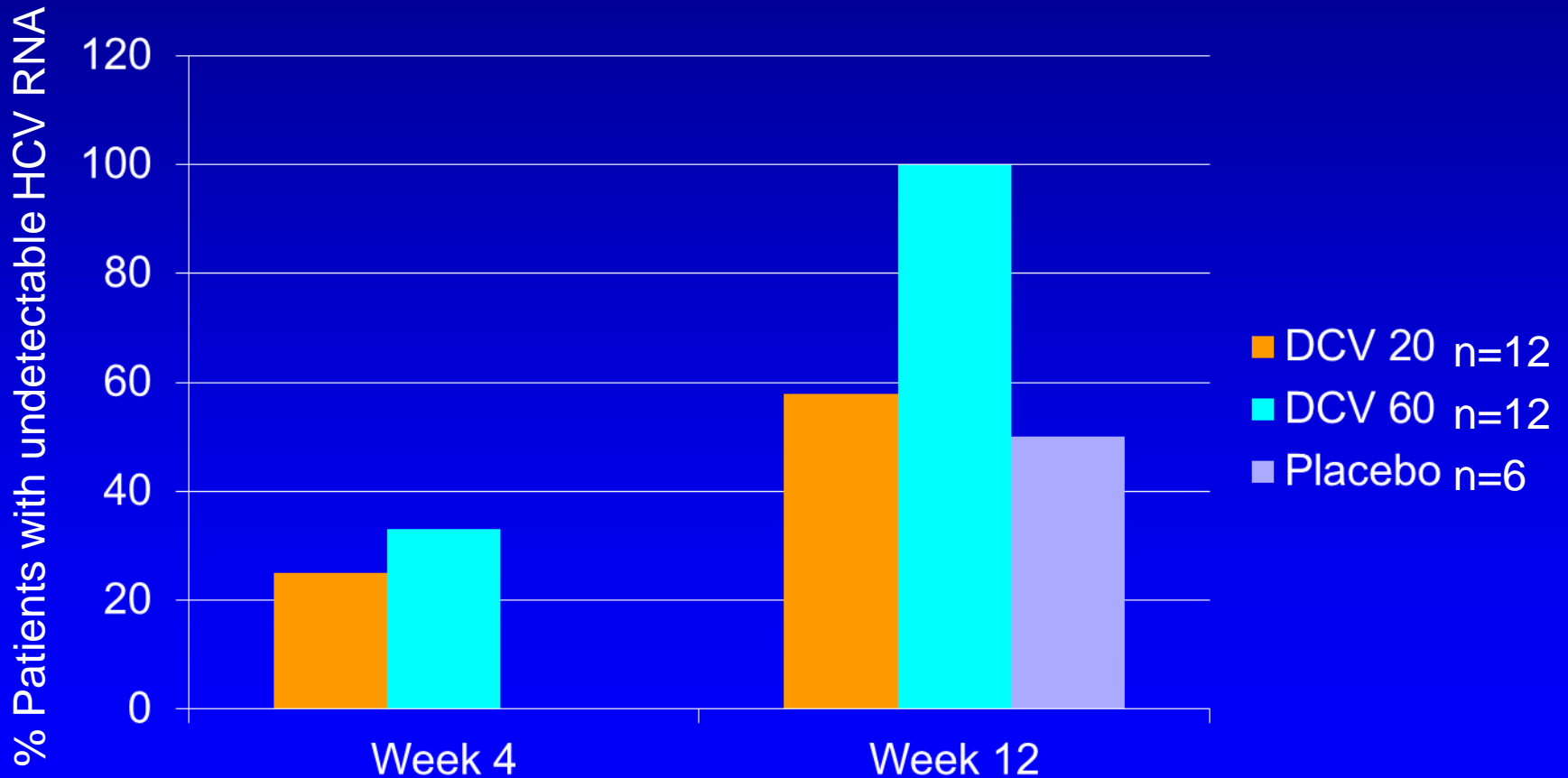


# Daclatasvir + PEG/RBV in GT1 Patients Viral Breakthrough Through Week 24



Viral breakthrough = HCV RNA >1 log<sub>10</sub> IU/mL above nadir or ≥LOQ after undetectable

# Daclatsvir + PEG/RBV in GT4 Patients Virologic Response Through Week 12



# Daclatasvir + PEG/RBV: Adverse Events

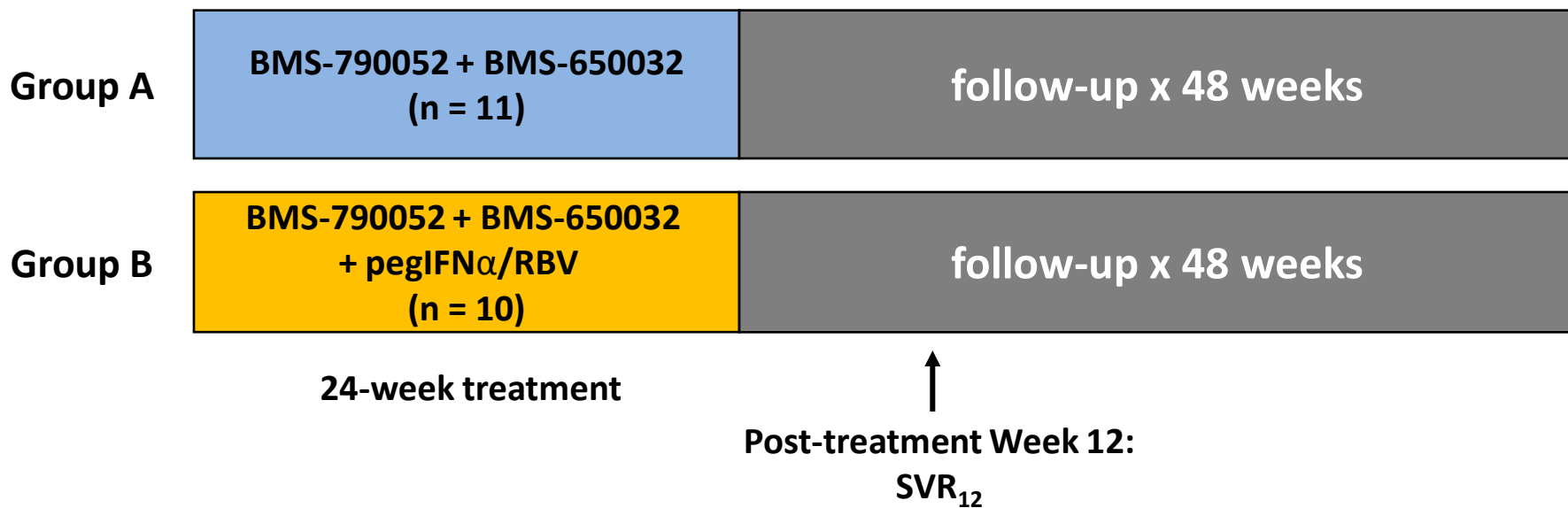
	DCV 20 mg N=159	DCV 60 mg N=158	Placebo N=78
Anemia	6	6	5
Neutropenia	25	27	24
Thrombocytopenia	1	3	3
Gr 3/4 elevated ALT	0	4	1
Gr 3/4 elevated bilirubin	1	0	1
<b>Nausea</b>	<b>35</b>	<b>33</b>	<b>23</b>
Headache	42	41	44
Rash	33	25	31
<b>Dry skin</b>	<b>29</b>	<b>25</b>	<b>19</b>
Fatigue	55	53	59
Diarrhea	22	23	15

# Daclatasvir + PEG/RBV

---

- **GT1a/b treatment-naïve patients**
  - eRVR in 54-80% patients
  - cEVR in 75-100% patients
  - Overall SVR data not available, phase III trial planned
- **GT1b partial/null responders**
  - eRVR in 22-78% patients
  - cEVR in 56-89% patients
  - High rate of treatment failure, another DAA needed
- **GT4 treatment-naïve patients**
  - Week 12 <LOD 58-100% patients
  - 60 mg dose preferred?

# Daclatasvir (DCV) + Asunaprevir(ASV) with or without PEG/RBV in GT1, Null Responders



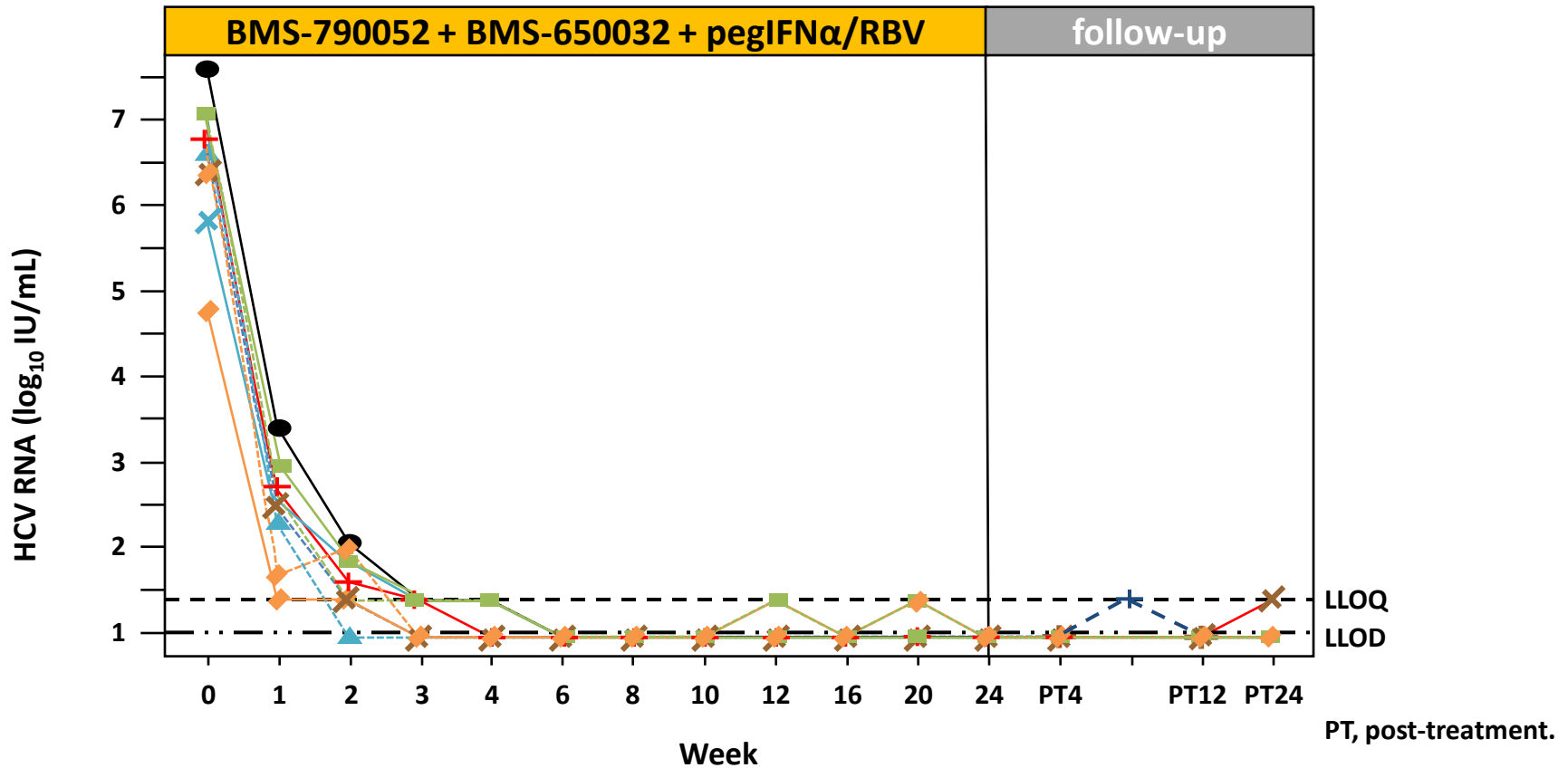
- DCV: BMS-790052 (NS5A replication complex inhibitor) 60 mg PO QD
- ASV: BMS-650032 (NS3 protease inhibitor) 600 mg PO BID
- PegIFN $\alpha$ -2a 180  $\mu$ g SC once weekly
- RBV 1000-1200 mg daily according to body weight

# Patients

---

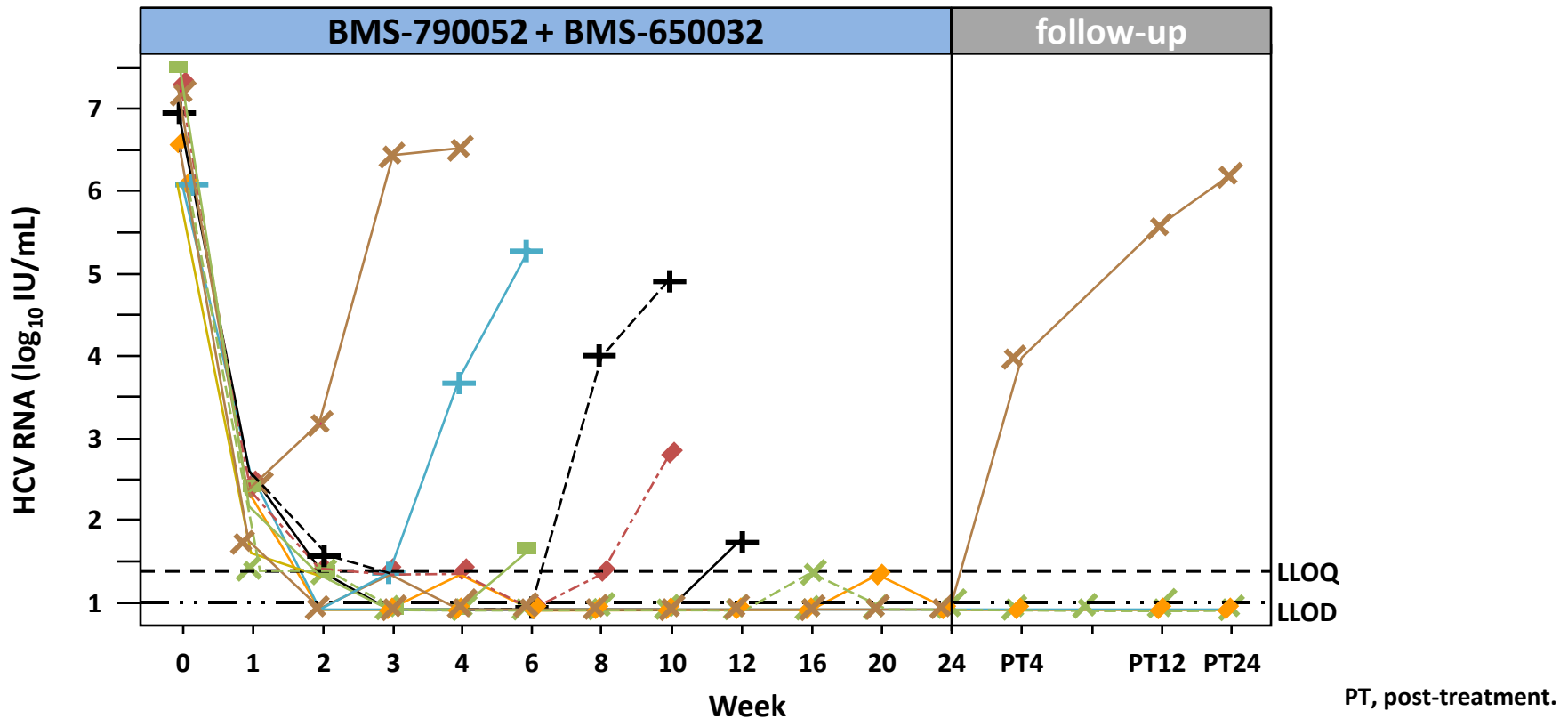
- **18/21 patients GT1a**
- **19/21 with IL28B CT/TT**
- **Absence of cirrhosis**

# HCV RNA by Patient: Group B (Quadruple Therapy)



- 10/10 patients undetectable by week 6 of therapy with no viral breakthrough
- 10/10 patients achieved SVR<sub>12</sub> and 9/10 achieved SVR<sub>24</sub> (1 <LOQ at FU Week 24, <LOD on retest)

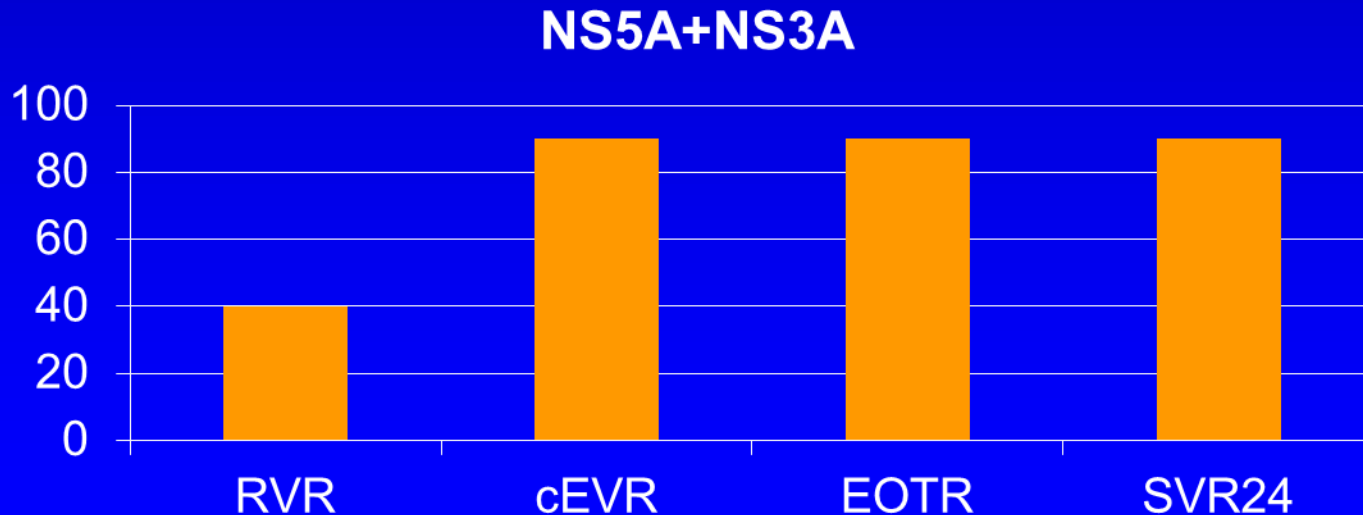
# HCV RNA by Patient: Group A (2 DAAs only)



- Five patients UD HCV RNA end of treatment, 4 SVR (2/9 GT1a and 2/2 GT1b)
- Six patients (all GT1a) experienced viral breakthrough on therapy
  - All 6 had resistance associated variants to both NS3 and NS5A inhibitors

# Dual Oral Therapy: Daclatasvir + Asunaprevir in Japanese GT1b Null Responders

- 2 DAAs x 24 weeks
- 10 patients, 9/10 EOTR and also SVR<sub>24</sub>
  - 1 discontinued treatment at Week 2, HCV RNA undetectable after 24 weeks follow-up



# On-Treatment Adverse Events Occurring in $\geq 3$ Patients

---

Events	Daclatasvir (DCV) + Asunaprevir (ASV) (n=10)
Diarrhea	7
Headache	4
ALT increase	3
AST increase	3

Diarrhea and AST/ALT increase attributed to ASV, improved with reduction in dose of ASV from 600 mg bid to 200 mg bid

# Daclatasvir + Asunaprevir for GT1 Null Responders

---

- **Dual therapy - 2DAAs only**
  - **SVR achieved in**
    - 9/10 Japanese GT1b patients
    - 4/11 American patients (2/2 GT1b and 2/9 GT1a)
  - **High rate of dual drug resistance in GT1a patients**
- **Quadruple therapy with 2DAA + PEG/RBV prevented emergence of drug resistance resulting in SVR12 in 10/10 patients (9 GT1a)**

# Gilead: GS-5885

---

- **GT1, 3 day monotherapy**
  - **G1a: 1, 3, 10, 30, or 90 mg**
  - **G1b: 10 mg**
- **HCV RNA decline -2.3 to -3.3 log**
- **Resistance variants on Day 4 or 14**
  - **3/10 at 1 mg dose**
  - **All patients at doses  $\geq 3$  mg**
  - **Mutations at positions 28, 30, 31 and 93**

# GSK: GSK2336805

---

- **EC50 in replicon system**
  - GT1a, 1b, 2a: 44 pM, 8 pM, 54 pM
- **Phase 1 ascending single dose (1-120 mg) in GT1 patients**
  - HCV RNA, mean change at nadir  $-3.0 \log_{10}$  IU/mL at 60 and 120 mg doses

# Presidio: PPI-461

---

- **Activity against GT1-6**
- **Phase 1 study**
  - **GT1**
  - **3 day monotherapy: 50, 100 or 200 mg qd**
  - **Mean maximal HCV RNA decrease -2.65, -3.65, and -3.62 log<sub>10</sub> IU/mL**
  - **Resistance substitutions M28T, Q30R, L31M and Y93H/C in 17/18 treated patients**

# Merck: MK-4882

---

- **Antiviral activity**
  - In vitro: EC50 pM against GT1a and 1b, nM against GT2-4
  - In chimps: 7 day 3 log decline in HCV RNA
- **Once daily dosing**
- **Resistance selections against GT1a and 1b in replicon cell lines: mutations at aa 30, 31, and 93**

# Achillion: 2<sup>nd</sup> Generation NS5A Inhibitors

---

- **1<sup>st</sup> gen NS5A inhibitors**
  - **Less potent antiviral activity against GT1a and GT2**
- **2<sup>nd</sup> generation NS5A inhibitors**
  - **Antiviral activity against GT1a and GT2 similar or slightly less than GT1b**
  - **Significantly lower EC50 against NS5A resistance variants with mutations at loci 28, 30, 31, and 93 compared to 1<sup>st</sup> generation NS5A inhibitors**

# HCV NS5A Inhibitors

---

- **Potent but low barrier to resistance**
  - 2<sup>nd</sup> generation NS5A, higher barrier?
  - Efficacy in GT-non-1?
- **Excellent safety profile**
- **Clinical utility**
  - **IFN-free regimen – in combination with other DAA(s) with high barrier to resistance**
    - Dual therapy for IFN-naïve / IFN-experienced patients (GT1b only?)
    - Triple therapy with RBV (other genotypes)?
  - **PEG/RBV based regimen**
    - Triple therapy for IFN-naïve patients (GT1b only?)
    - Quadruple therapy for null responders (other genotypes)