Paris Hepatitis Conference

New Therapeutic Strategies
Second Generation Protease inhibitors

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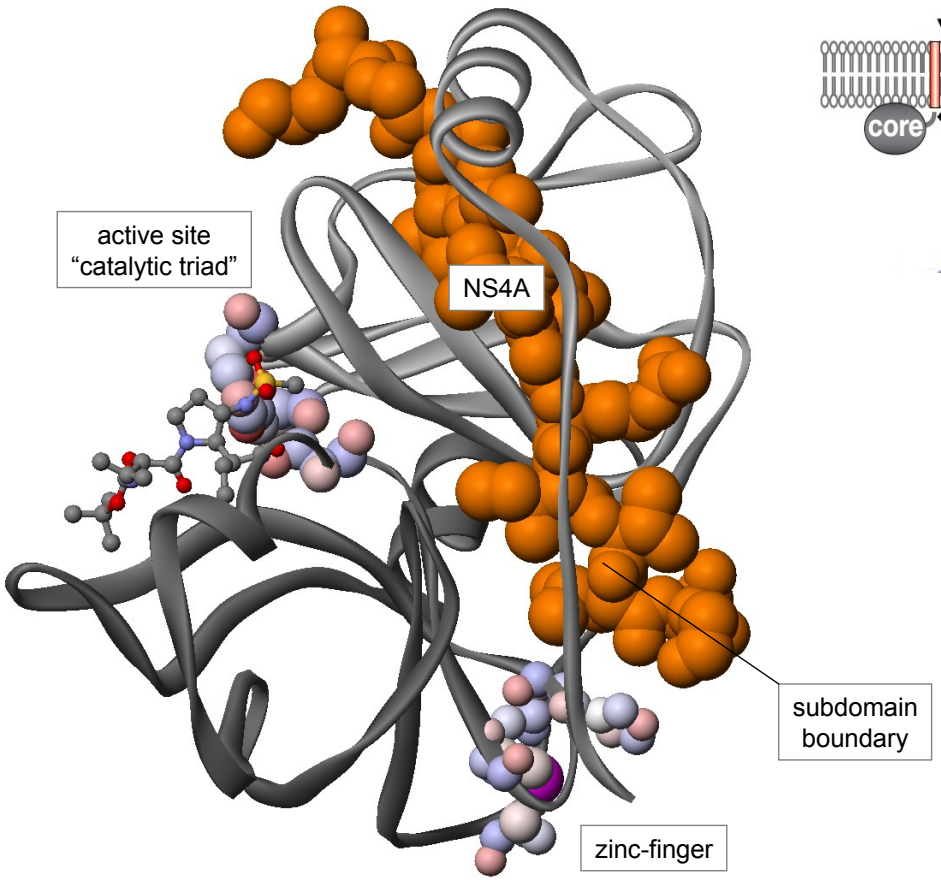
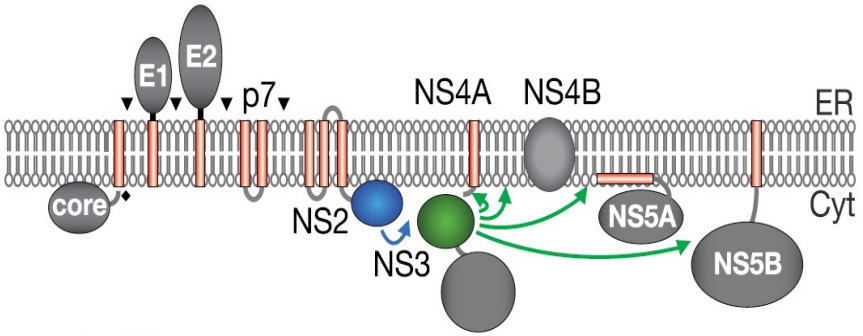
Outline

- HCV protease structure and drug targeting
- First generation PIs
  - Major step forward
  - Major limitations
- PIs in development
  - Second wave
  - Second generation
- Clinical trial data
  - IFN-containing PI regimens
  - IFN-free PI regimens
- Timelines and treatment paradigms

NS3 protease targeting



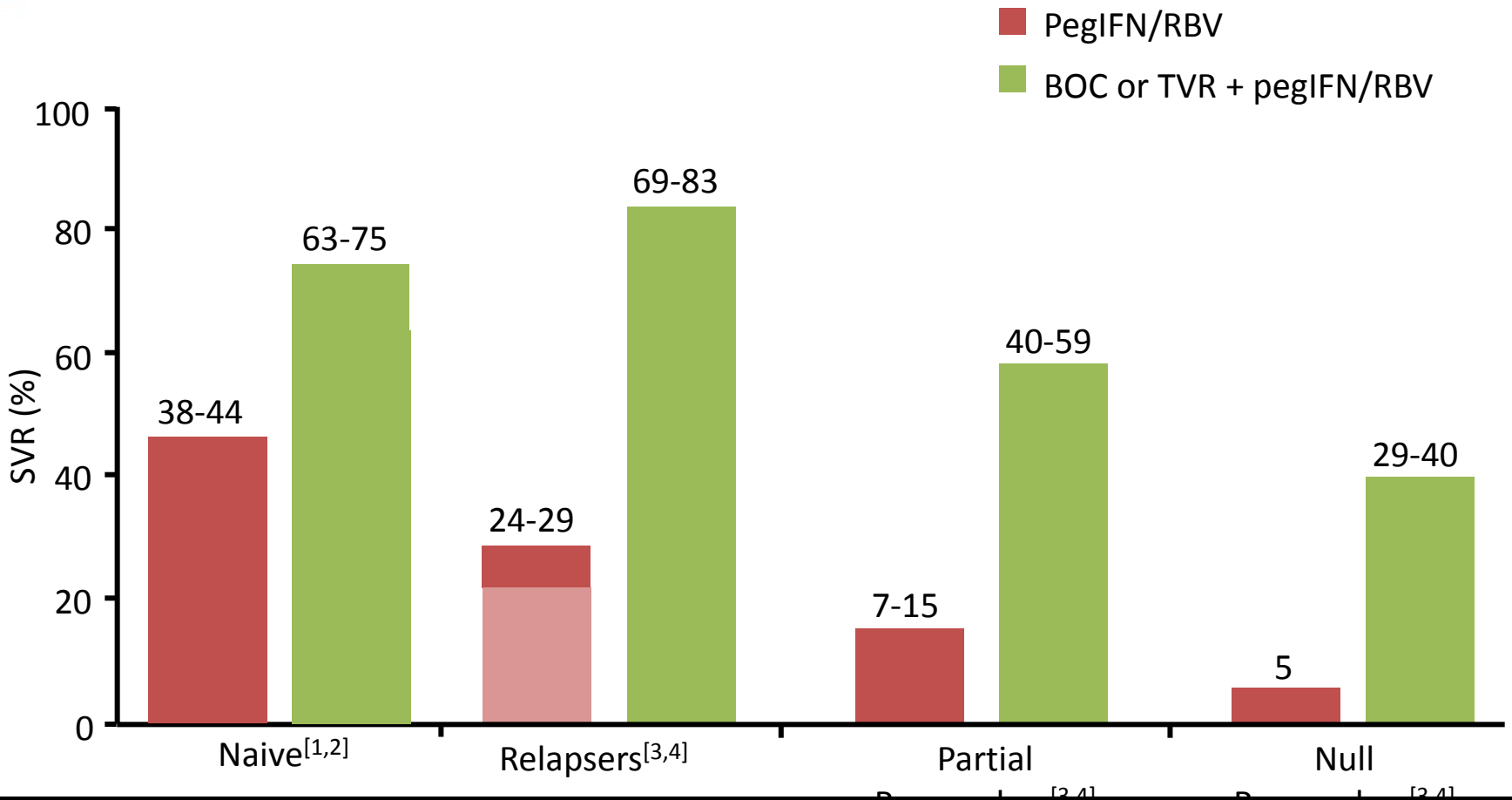


TARGETING

- **Substrate- and product analogs**
- **Tri-peptides**
- **Serine-trap inhibitors**
- **Ketoamides** (boceprevir, telaprevir)
- **Macrocyclic inhibitors**
  (e.g. Simeprevir, Danoprevir, Vaniprevir, etc.)
- **NS4A inhibitors**

Lorenz et al., *Nature* 2006
Kronenberger et al., *Clin Liver Dis* 2008
Welsch et al. *Gut* in press

A Major Step Forward: First Generation PIs



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

Limitations of First Generation PI-Based Therapy

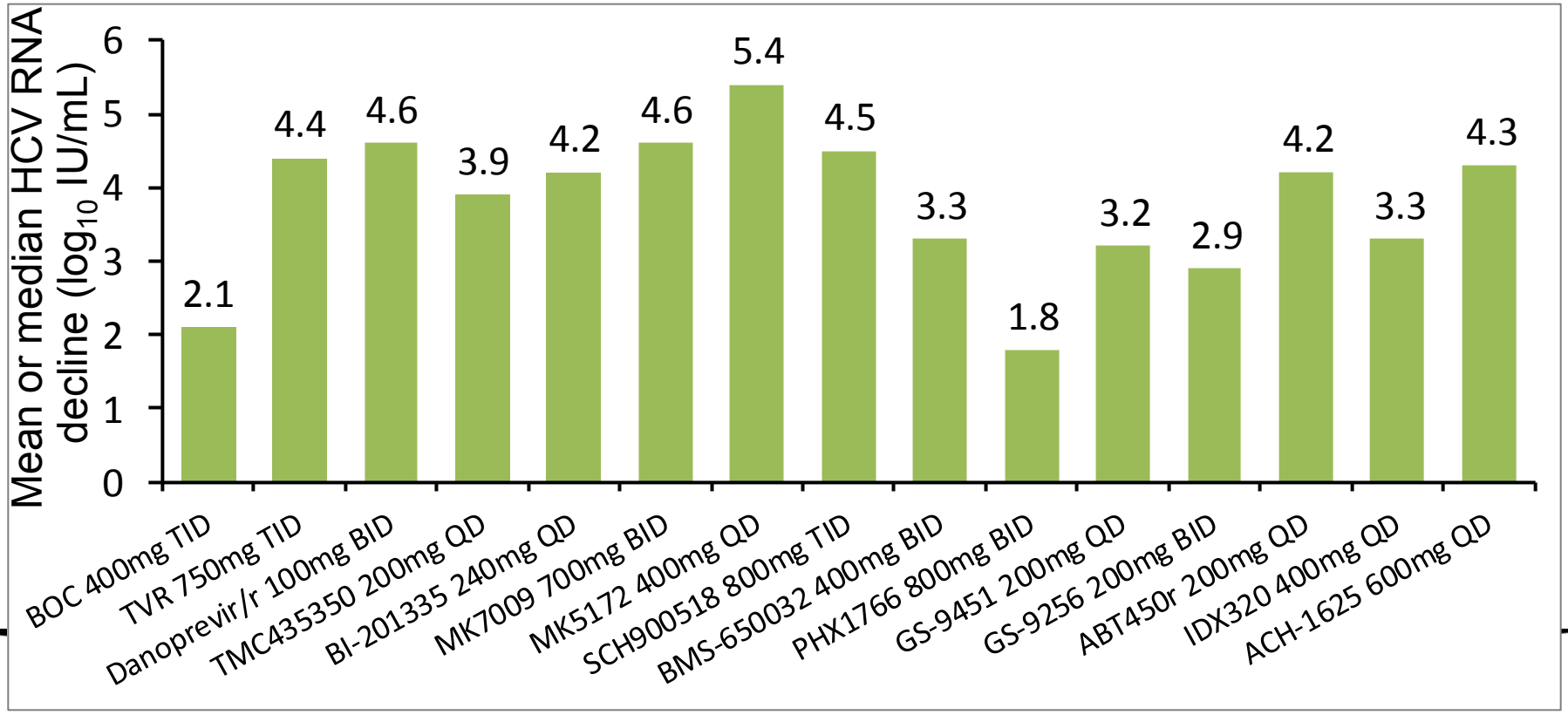
- Efficacy
  - Very dependent on the IFN response
  - Limited to gen 1 (1b>1a)
- Low genetic barrier to resistance
- Tolerability
  - Additional AEs beyond pegIFN/RBV
- Regimens
  - Complicated (lead-in, RGT)/pill burden
  - TID regimens (food required with TVR)
- DDIs
  - Many with both agents to common drugs (CYP3A4)

Protease Inhibitors in Active Phase 2/3 Development

- Second Wave (better dosing, improved tolerability, broader genotype cverage)
  - Asunaprevir (BMS)
  - Faldaprevir (Boehringer)
  - Simeprevir (Janssen/Tibotec)
  - Sovaprevir, (Achillion)
  - Danoprevir/r (Roche)
  - Vaniprevir (Merck)
  - ABT-450/r (Abbott)
  - GS-9451 (Gilead)
- Second generation (pan-genotype, high barrier to resistance)
  - MK-5172 (Merck)
  - ACH-2684 (Achillion)

Antiviral Activity of NS3 Protease-Inhibitors

Protease-Inhibitor Monotherapy Data for 3–14 days in HCV genotype 1 patients (no head-to-head studies)



Adapted from Sarrazin et al., *J Hepatol* 2012 suppl

Expanded genotype activity of next generation HCV protease inhibitors

	1	2	3	4	5	6
Boceprevir	+					
Telaprevir	+	+				
Simeprevir	+	+		+	+	+
Faldaprevir	+			+	+	+
Asunaprevir	+					
MK-5172	+	+	(+)	+	+	+
ACH-2684	+	+	+	+	+	+

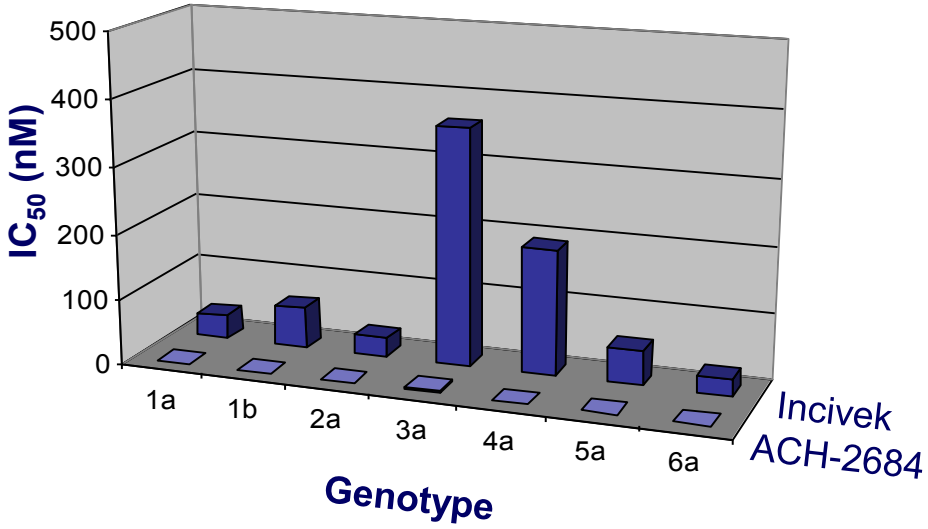
Improved genetic barrier to resistance for next generation protease inhibitors

	V36A /M	T54S/ A	V55A	Q80R/ K	R155K/ T/Q	A156S	A156T /V	D168A/E/G/ H/T/V/Y	V170A/ T
Telaprevir			**						
Boceprevir									
Faldaprevir									
Simeprevir							**		
Asunaprevir*									
GS-9451*									
ABT450*									
MK-5172***							**		
ACH-2684									

mutations associated with resistance in patients
** mutations associated with resistance in vitro
*** no viral break-through during 7 days monotherapy

Adapted from Sarrazin et al., *J Hepatol* 2012 suppl

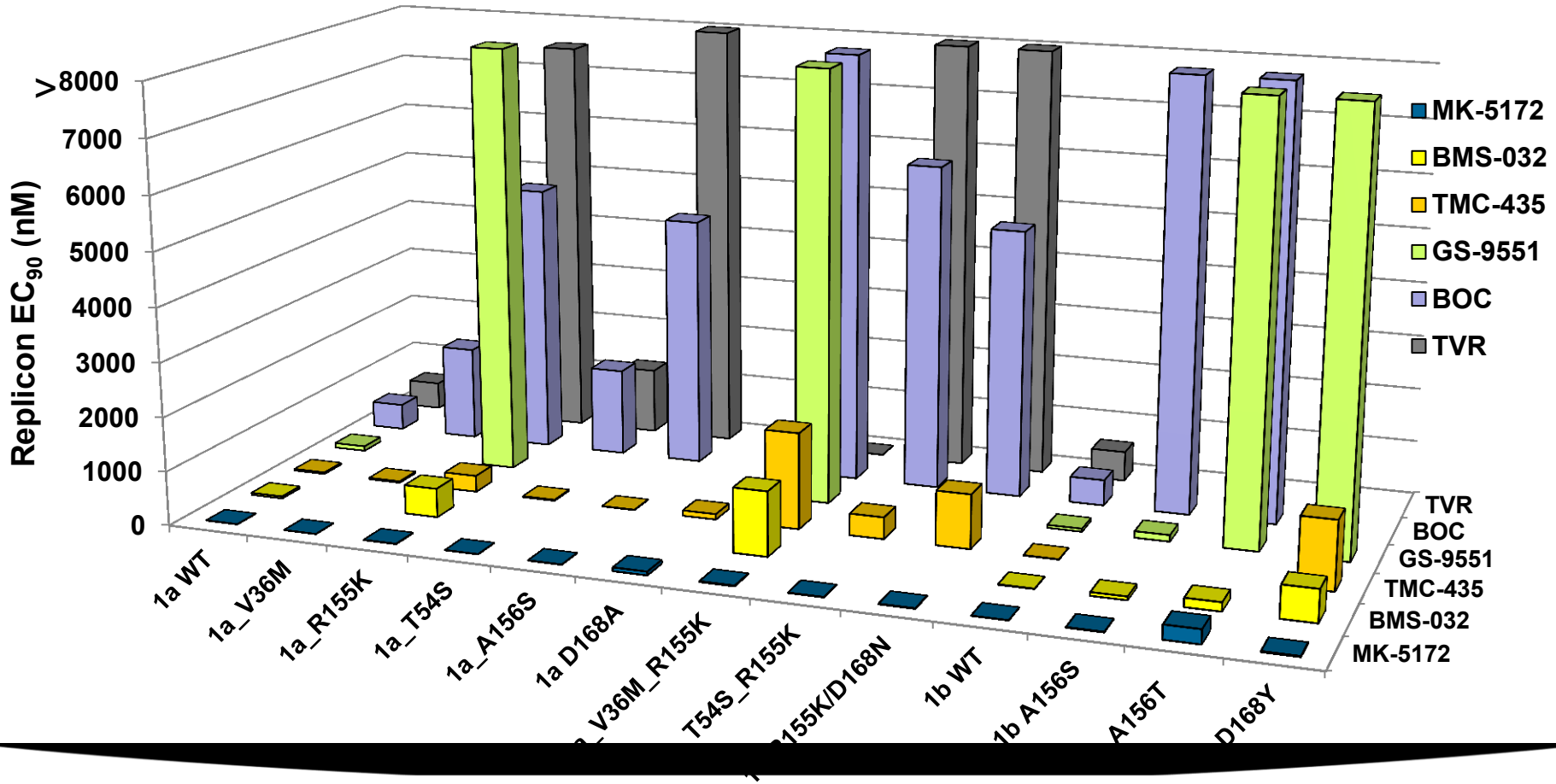
ACH-2684
Potency against GT 1-6 and Activity Against Common 1st-Gen PI Resistant Mutations



Protease Inhibitor	Potency Against Resistant Mutations IC_{50} (nM)					
	R155Q	R155K	A156S	A156T	D168A	D168V
Incivek	370	500	>1000	>1000	33	29
ACH-2684	1.6	2.1	0.21	1.6	2.4	7.5

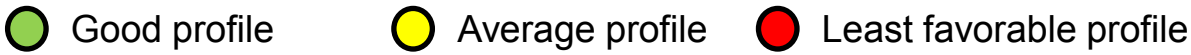
Data on File, Achillion Pharmaceuticals, Inc.

MK-5172 has activities against RAVs elicited by the 1st generation PIs



Summary: Protease Inhibitor Profiles

	DAA		
	NS3[1]	NS3[2]	NS3[3]
Resistance profile			
Pan-genotypic efficacy			
Efficacy			
Adverse events			



[1]: 1st generation
[2]: 2nd wave
[3]: 2nd generation

Investigational HCV Regimens with PIs in Phase III Clinical Trials

Regimens With 1 DAA + PegIFN alfa/RBV

- Faldaprevir (BI 201335)
- Simeprevir (TMC-435)
- Vaniprevir (MK-7009)

Regimens With 2 DAAs + PegIFN alfa/RBV

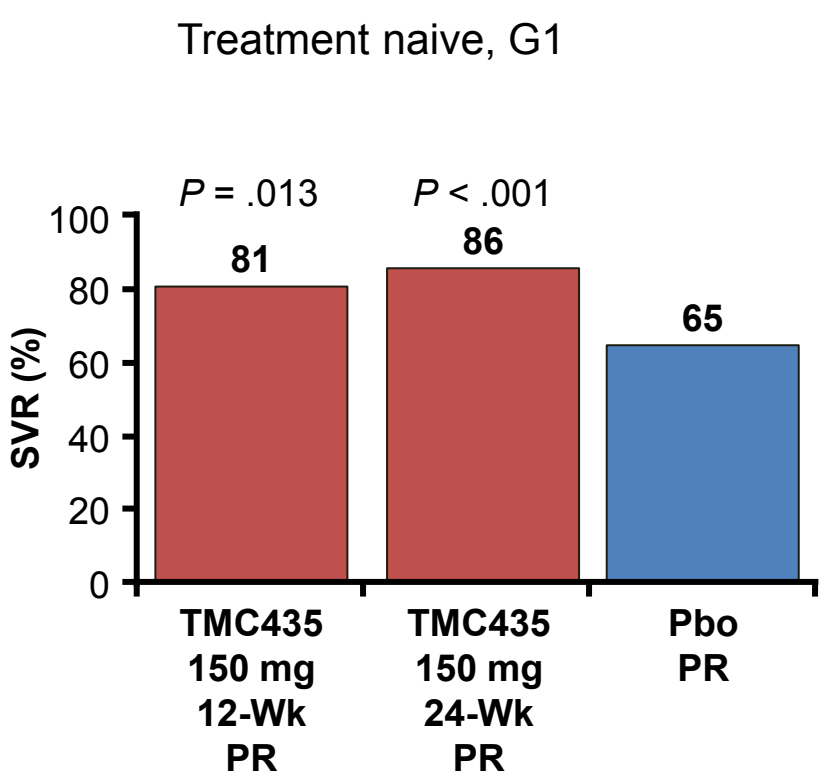
- Daclatasvir + Asunaprevir

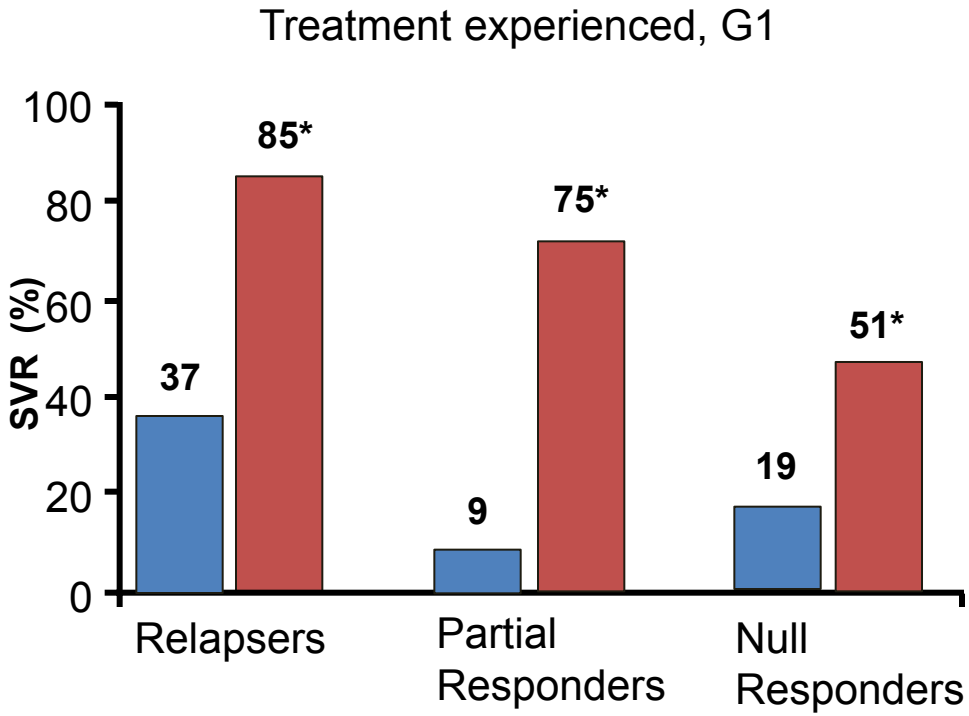
IFN-Free Regimens

- Daclatasvir + asunaprevir
- ABT-450/RTV + ABT-267 ± ABT-333 ± RBV
- Faldaprevir + BI 207127 + RBV

ClinicalTrials.gov.

TMC 435 (PI) + PEG-IFN/RBV in Treatment Naïve and Experienced Patients

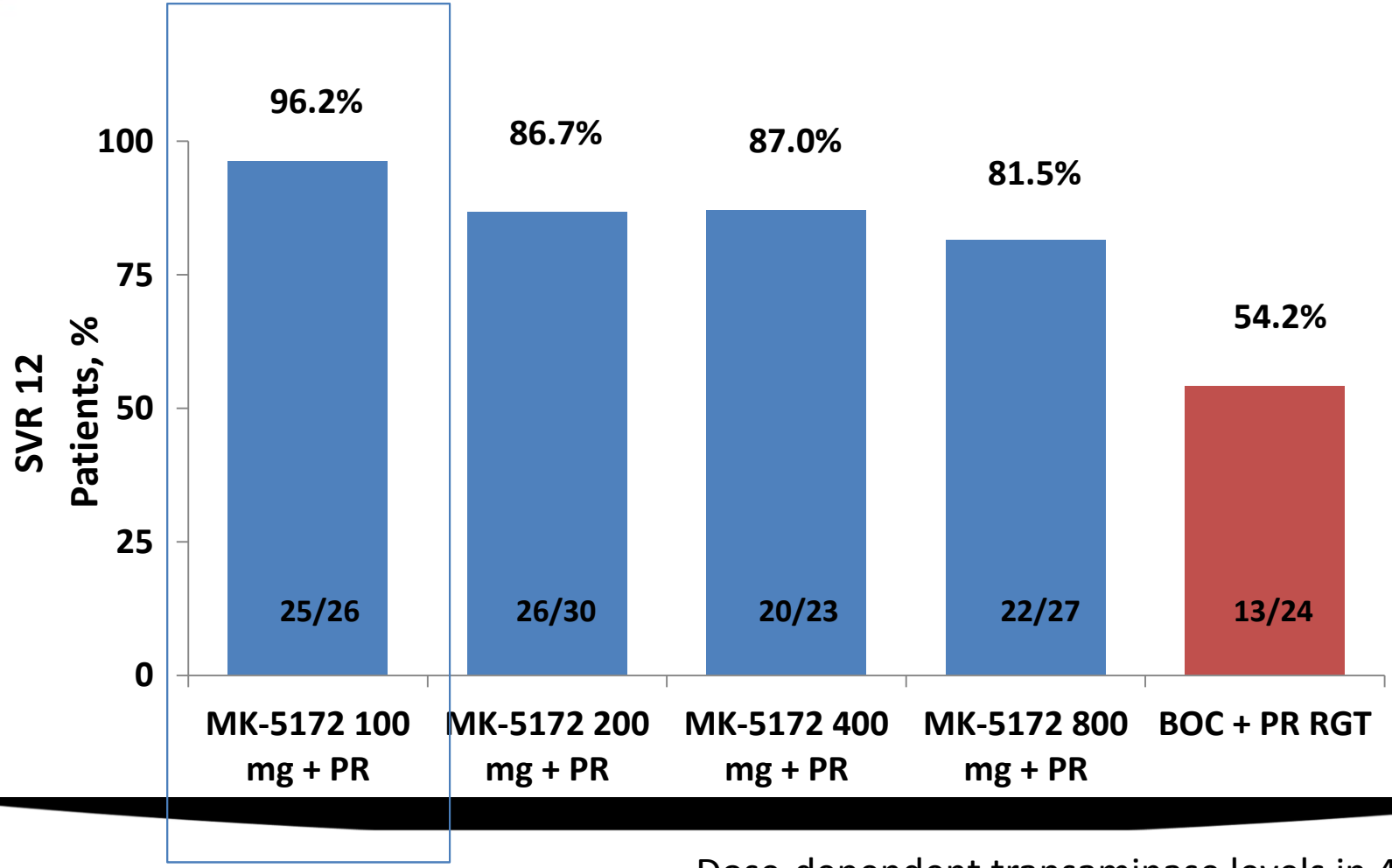




dose

Fried MW, et al. AASLD 2011. Abstract LB-5; Zeuzem S, et al. EASL 2012. Abstract 2;

SVR 12 of MK-5172 for 12 Weeks in Combination With Pegylated Interferon Alfa-2b and Ribavirin for 24 Weeks in HCV Genotype 1 Treatment-Naïve, Noncirrhotic Patients (Vanguard Cohort Analysis)

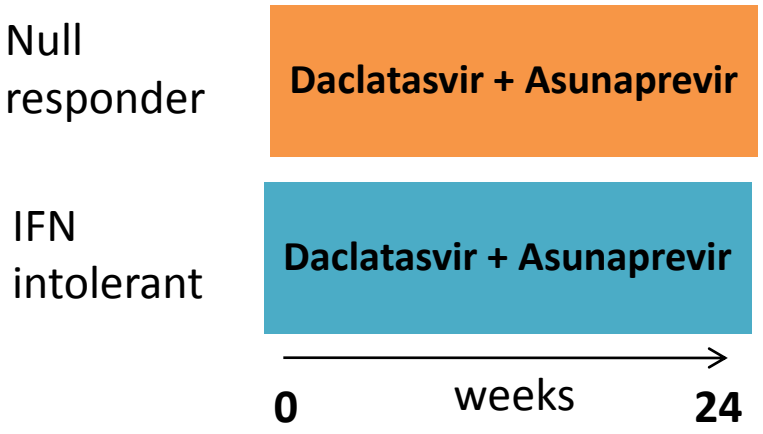


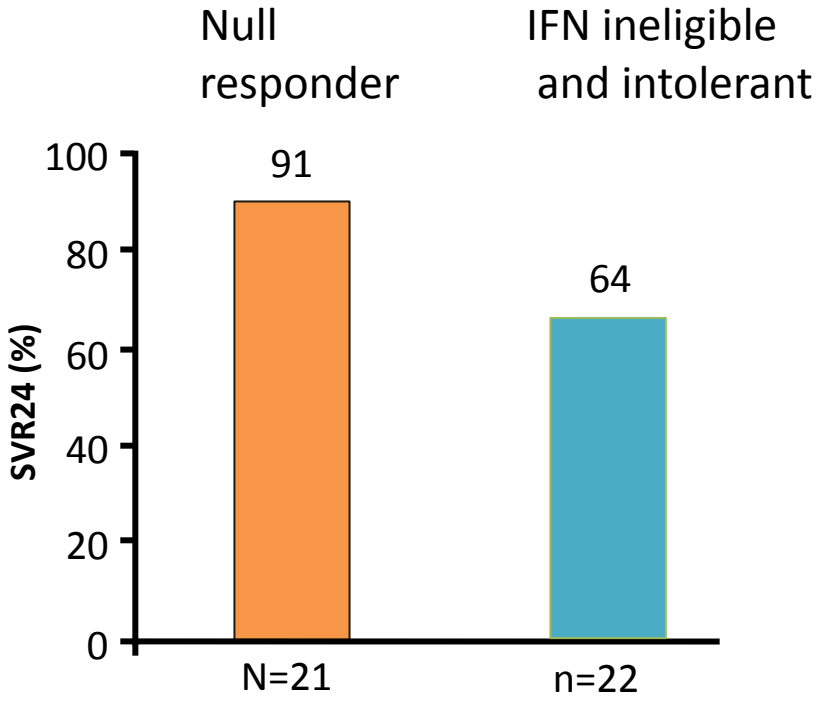
Dose-dependent transaminase levels in 400 mg and 800 mg dosing in the course of therapy

Marcellin, P et al. AASLD 2012 Poster # 766

Asunaprevir (PI) + Daclatasvir (NS5A)

Pts: Gen1b, non-cirrhotic

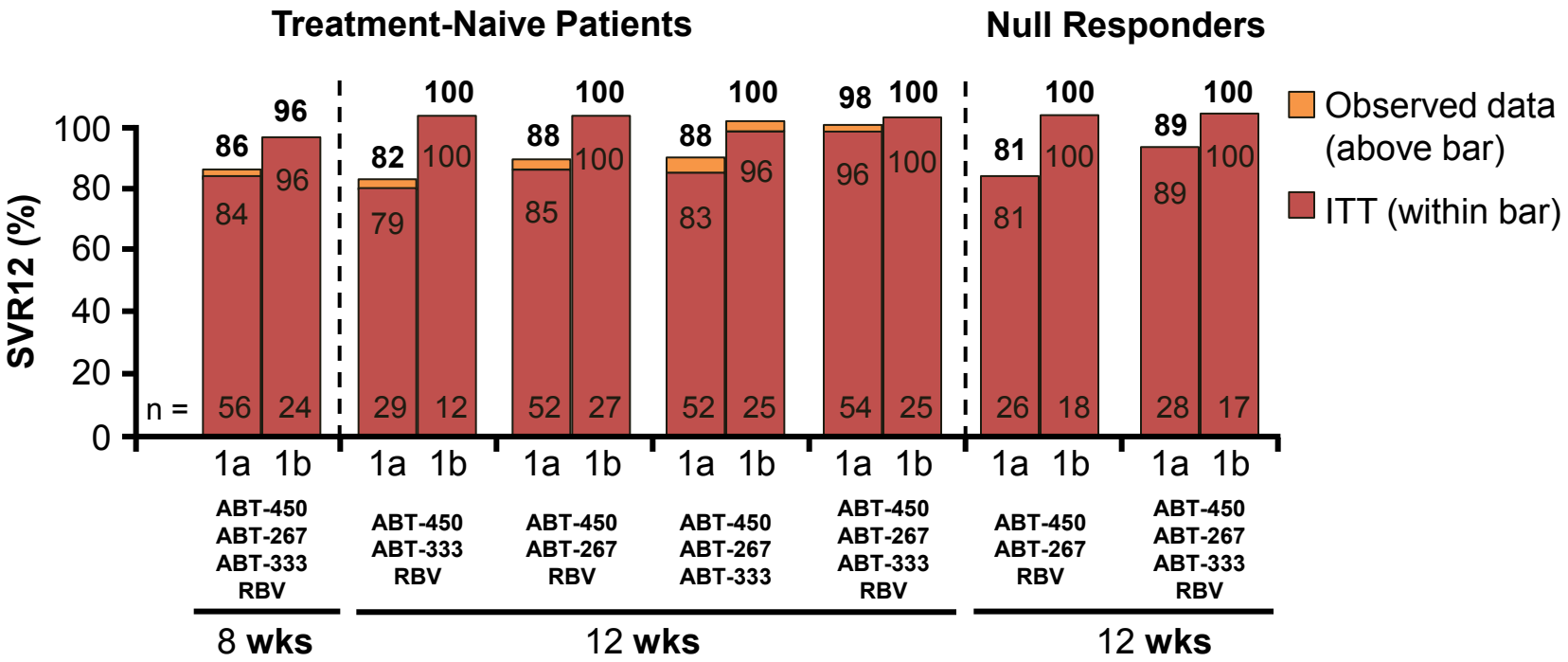




Among pts with breakthrough (7%) or relapse (9%), low plasma concentrations of DAC and ASU

Suzuki F, et al. EASL 2012. Abstract 14

AVIATOR: SVR12 Rates With ABT-450/ RTV, ABT-267, ABT-333, and RBV



ABT-450: Protease/RTV QD

ABT-267: NS5A QD

ABT-333 NNI BID

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

First All Oral HCV Regimens Likely Available In The US in 2014-2015

Options for PI-Based Regimens

Nucleoside-based regimens

- Sofosbuvir + RBV (G2/3, select G1)
- Sofosbuvir + Daclatasvir (off-label)
- **Sofosbuvir + PI (TMC 435, TVR, BOC, etc)** (off-label)
- Sofosbuvir + GS-5885 ± RBV (pan-genotype)

Other regimens

- **Asunaprevir** + Daclatasvir (G1b)
- **ABT-450/r** ± ABT-333 ± ABT-267 ± RBV (G1)
- **Faldaprevir** + BI-207127 + RBV (G1b)

Conclusions: Future therapy options for PI

The second wave of PIs

- Better tolerability, safety profile
- Improved dosing
- Broader genotype coverage for some
- Improved DDI profile

Second generation of PIs

- Higher efficacy
- Pan-genotypic
- High barrier to resistance