





Now what?



SERVIZO
GALEGO
de SAÚDE

**Complexo Hospitalario
Universitario A Coruña**
A Coruña

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QUESTIONS

- Risks:
 - Fibrosis progression → Cirrhosis descompensations → Death
 - Hepatocellular carcinoma development
- Probability of SVR?
- Toxicity?
- Resistances?
- Future?





MINISTERIO
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agencia española de
medicamentos y
productos sanitarios

DEPARTAMENTO DE
MEDICAMENTOS
DE USO HUMANO

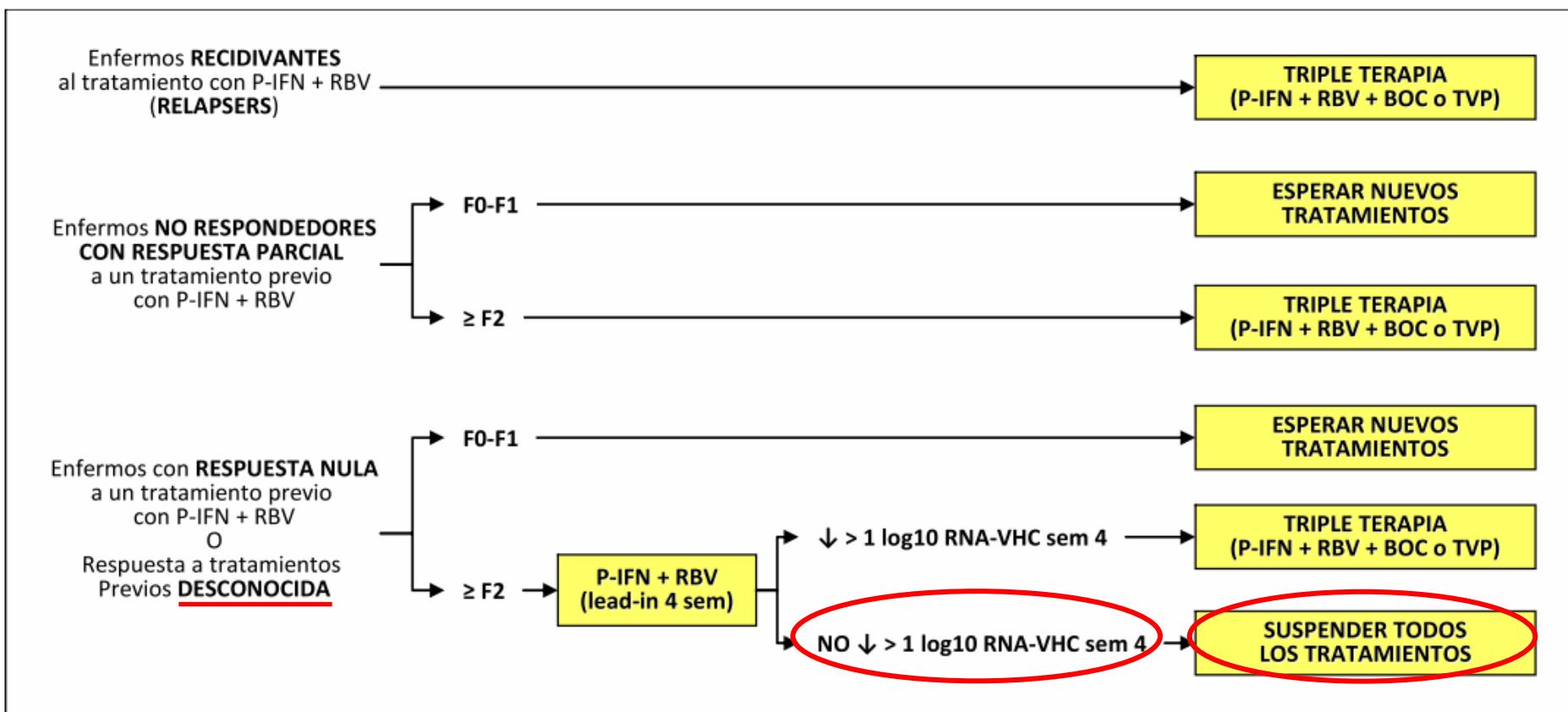
**INFORME DE UTILIDAD TERAPÉUTICA
UT/V1/28022012**

Criterios y recomendaciones generales para el tratamiento con boceprevir y telaprevir de la hepatitis crónica C (VHC) en pacientes monoinfectados



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Criterios y recomendaciones generales para el tratamiento con boceprevir y telaprevir de la hepatitis crónica C (VHC) en pacientes monoinfectados



ALGORITMO DE TRATAMIENTO EN PACIENTES PREVIAMENTE TRATADOS. P-IFN = interferón pegilado; RBV = Ribavirina; BOC = boceprevir; TVP = telaprevir; RVR = respuesta viral rápida; Cv = carga viral.



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Risk factors for fibrosis progression

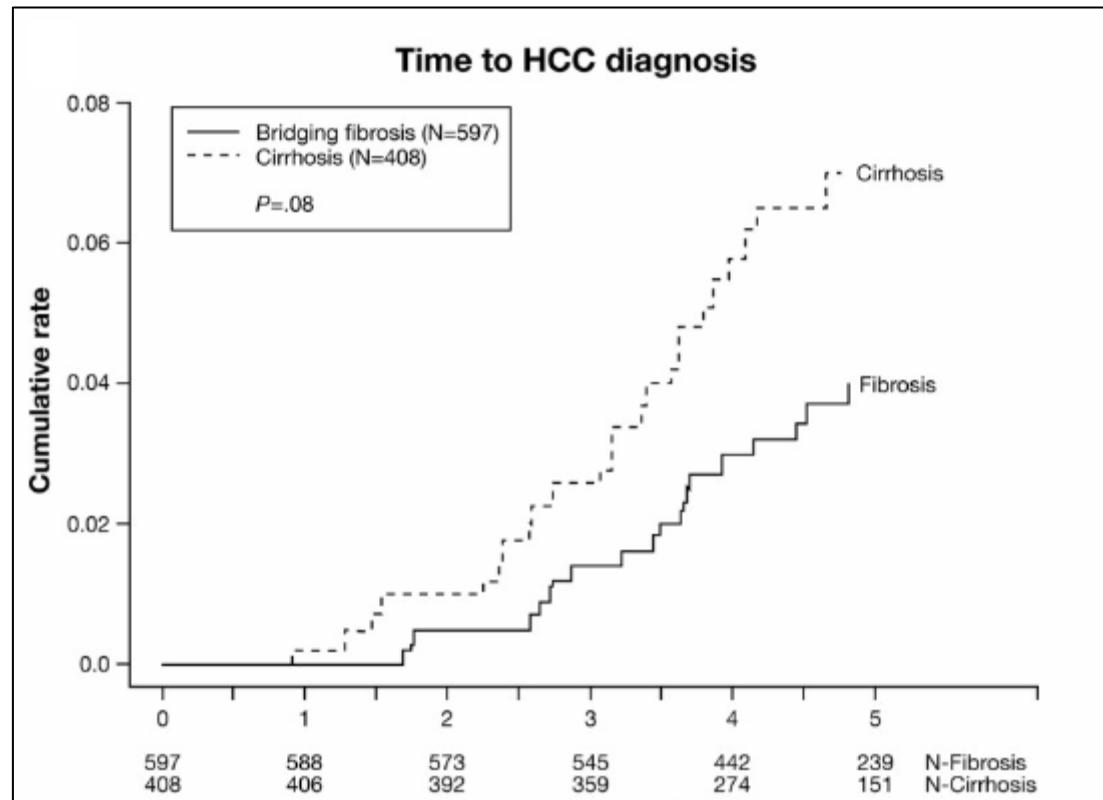
- Male sex.
- HBV and/or HIV coinfection.
- Immunosuppression.
- Alcohol consumption.
- Duration of infection.
- Acquisition of infection at >40 y.
- Insulin resistance.
- Non response to antiviral therapy.

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Median of fibrosis
progression per year → 0.133 fibrosis unit
(0.125-0.143)

Hepatocellular carcinoma development



Hepatocellular carcinoma development

- Male sex, black race.
- HBV and/or HIV coinfection/exposure.
- 1b vs 1a.
- Alcohol consumption, hepatic iron store, smoking.
- Duration of infection.
- Acquisition of infection at >40 y.
- Insulin resistance, obesity.
- Cirrhosis descompensation (esophageal varices).
- Lower platelet count.
- Biomarkers (sTNF-R2, sICAM-1, sCD30).

Hepatocellular carcinoma development

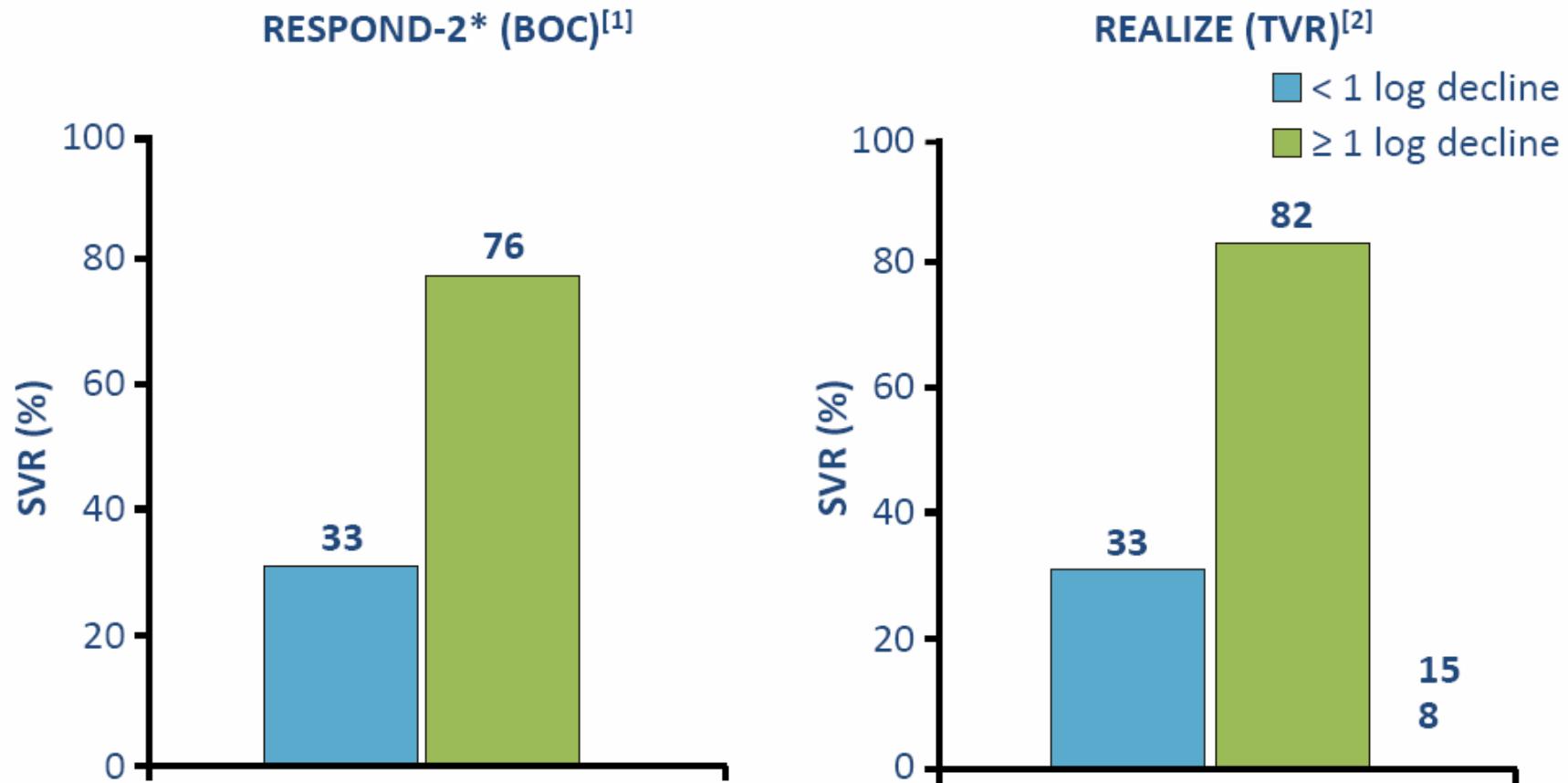
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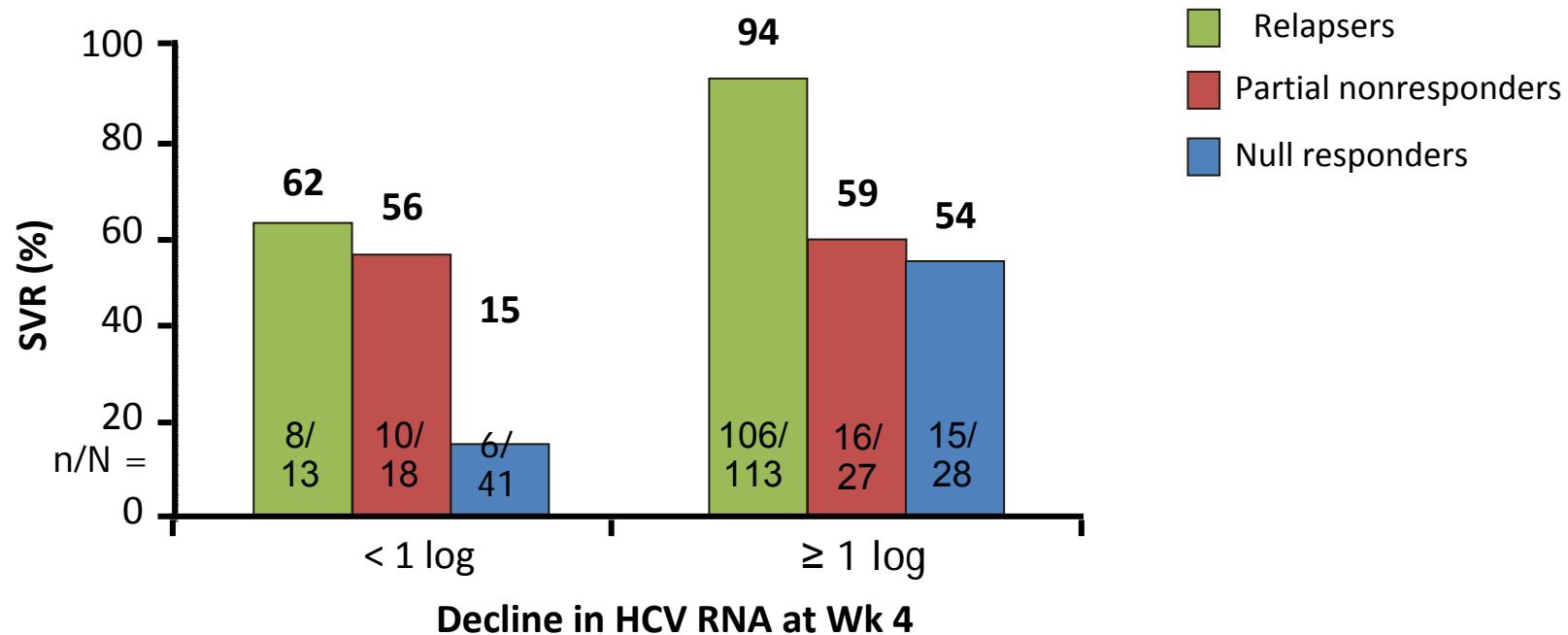
Predictive value of response to lead-in in treatment-experienced patients.



*Pooled data from RGT and fixed dose arms.

1. Bacon BR, et al. N Engl J Med. 2011;364:1207-1217. 2. Foster G, et al. EASL 2011. Abstract 6.

REALIZE: Lead-in vs previous response category as predictor of response to TVR



PREDICTORS OF RESPONSE

KNOWN

- Advanced fibrosis.
- Previous response.
- High viral load.
- Insulin resistance.
- Hepatic steatosis.
- Sex, race.
- Older age.

UNKNOWN

- IL28B?
- Previous response.
- Subtype.

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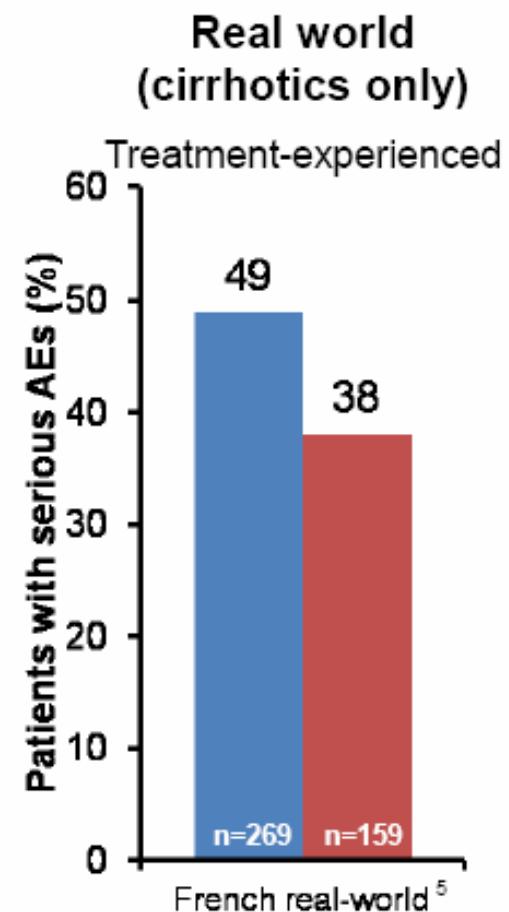
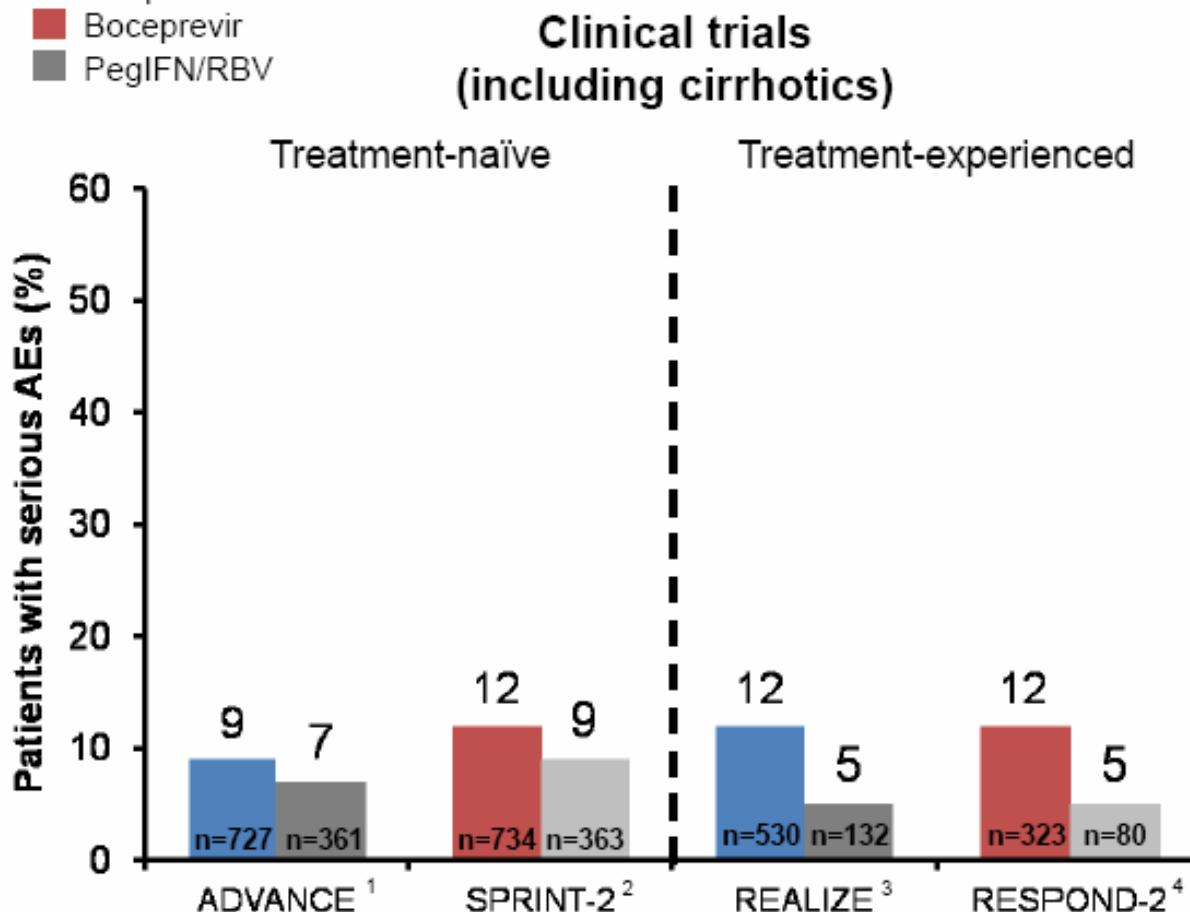


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Clinical Trials vs Real World

- Telaprevir
- Boceprevir
- PegIFN/RBV



Triple therapy: Increased rates of SAEs observed in CUPIC at week 16

Patients, n (% patients with at least one event)	Telaprevir n=292	Boceprevir n=205
Serious adverse events (SAEs)*	132 (45.2%)	67 (32.7%)
Premature discontinuation	66 (22.6%)	54 (26.3%)
Due to SAEs	43 (14.7%)	15 (7.3%)
Death	5 (2.6%)	1 (0.5%)
Infection (Grade 3/4)	19 (6.5%)	5 (2.4%)
Hepatic decompensation (Grade 3/4)	6 (2.0%)	6 (2.9%)
Asthenia (Grade 3/4)	16 (5.5%)	12 (5.8%)
Rash		
Grade 3/SCAR	14 (4.8%)	0
Renal failure	5 (1.7%)	0



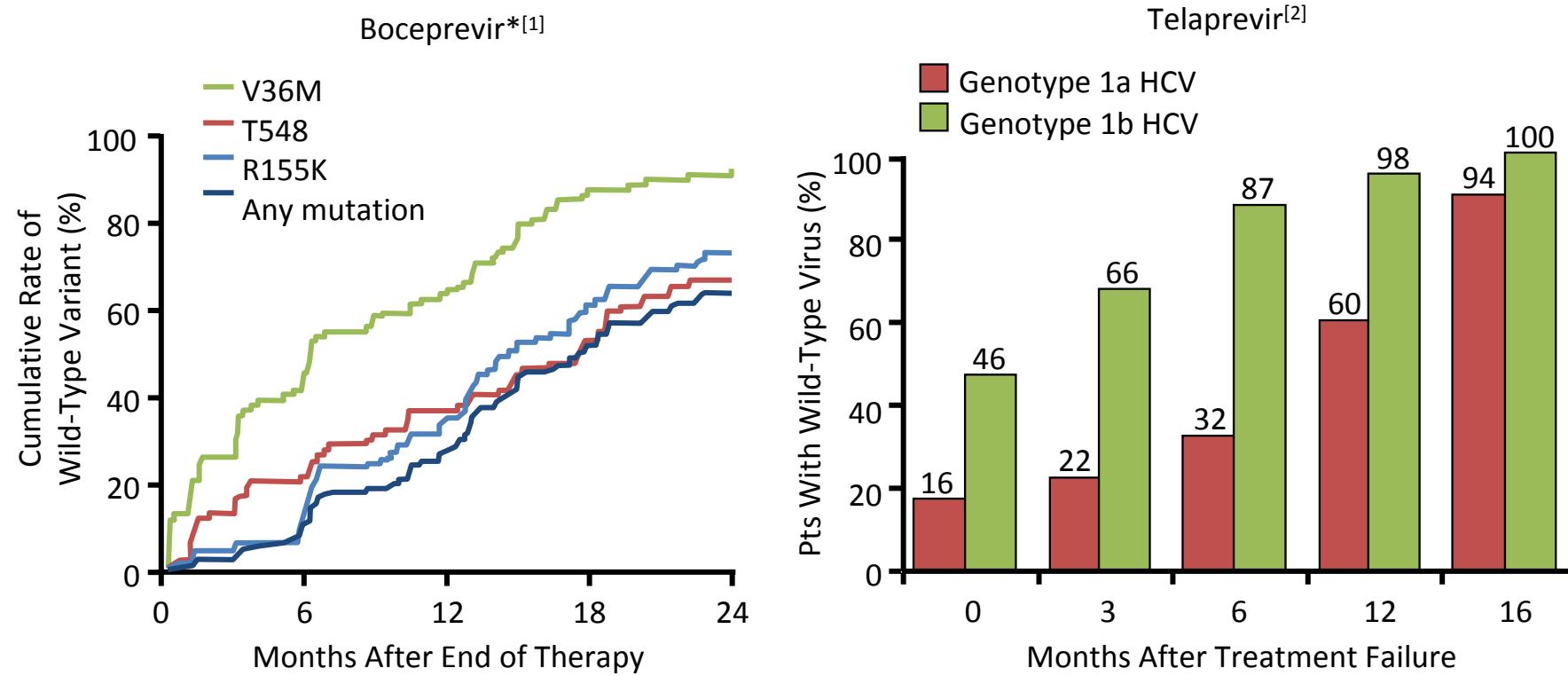
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RESISTANCES. STOPPING RULES

BOC		
Time Point	Criteria	Action
Wk 12	HCV RNA \geq 100 IU/mL	Discontinue all therapy
Wk 24	HCV RNA detectable	Discontinue all therapy
TVR		
Time Point	Criteria	Action
Wk 4 or 12	HCV RNA $>$ 1000 IU/mL	Discontinue all therapy
Wk 24	HCV RNA detectable	Discontinue pegIFN/RBV

Loss of Detectable Resistance in Patients Stopping BOC or TVR + PegIFN/RBV



*Data from phase II studies.

1. Vierling JM, et al. EASL 2010. Abstract 2016. 2. Sullivan J, et al. EASL 2011. Abstract 8.

RESISTANCES. BOCEPREVIR

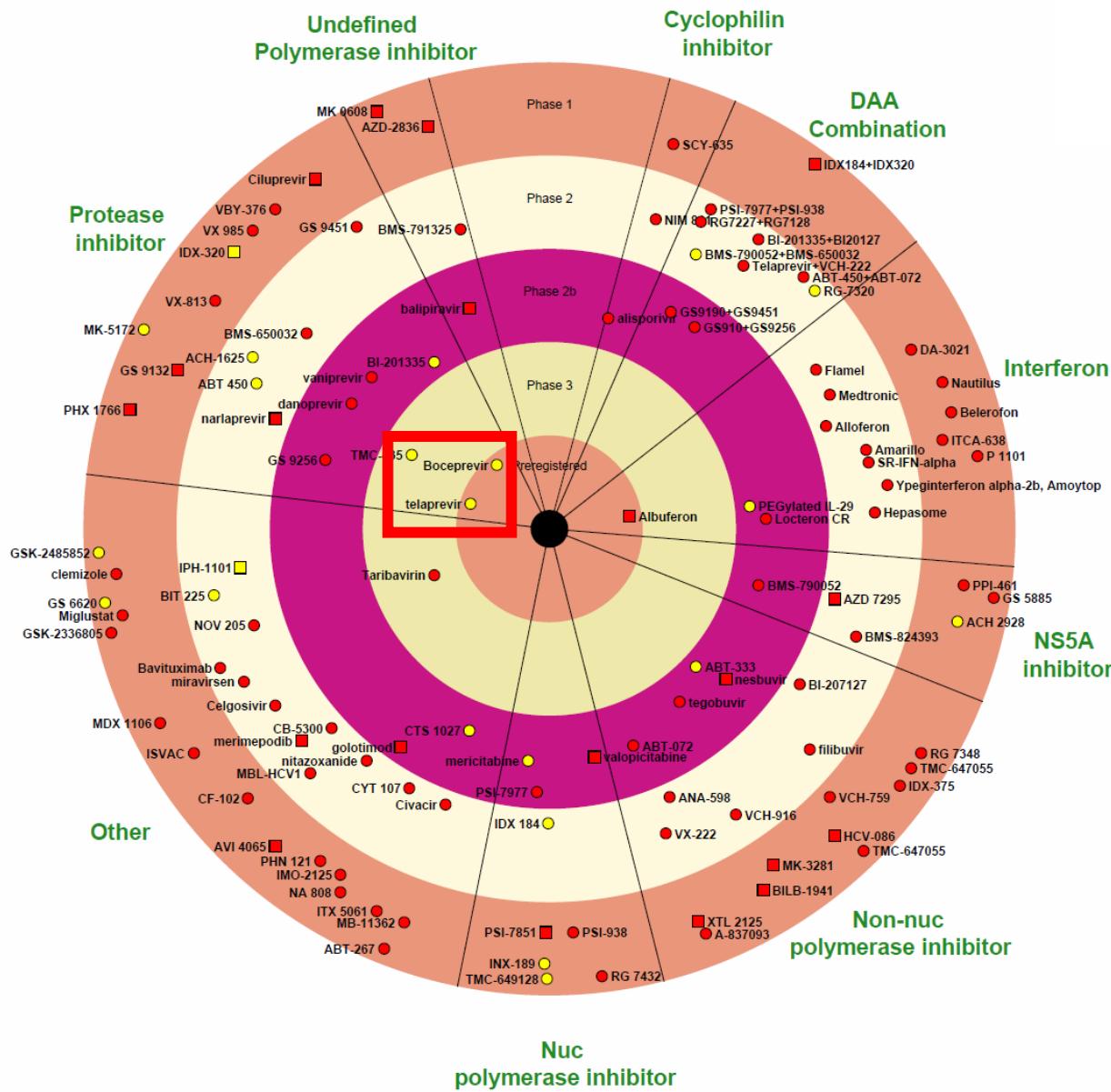
- Boceprevir resistance-associated variants:
- $\geq 1 \log_{10}$ decline:
 - BOC RGT: 4% (10/232)
 - BOC/PR48: 6% (13/231)
- $< 1 \log_{10}$ decline:
 - BOC RGT: 52% (49/95)
 - BOC/PR48: 40% (38/94)



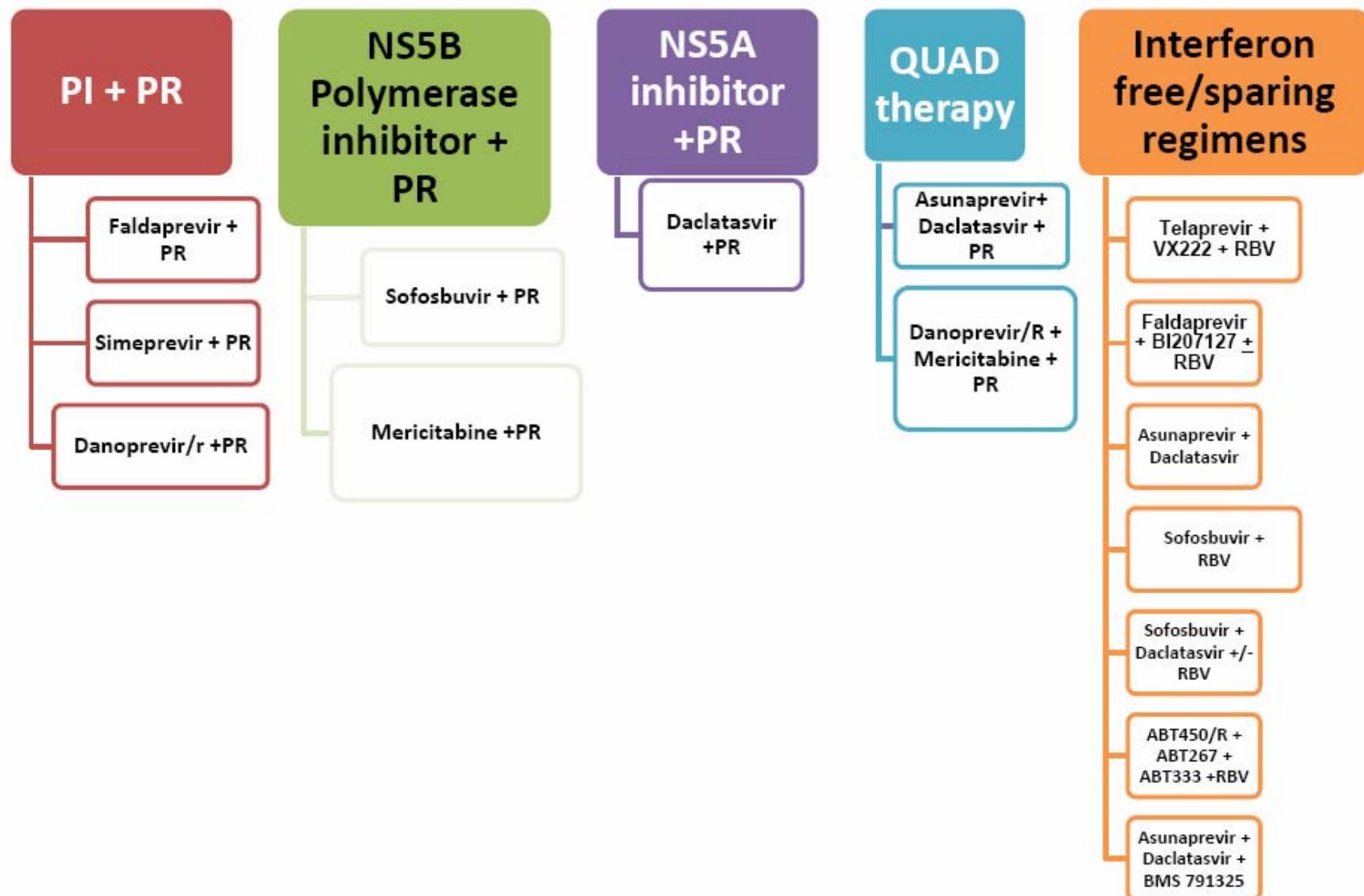
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Hepatitis C pipeline



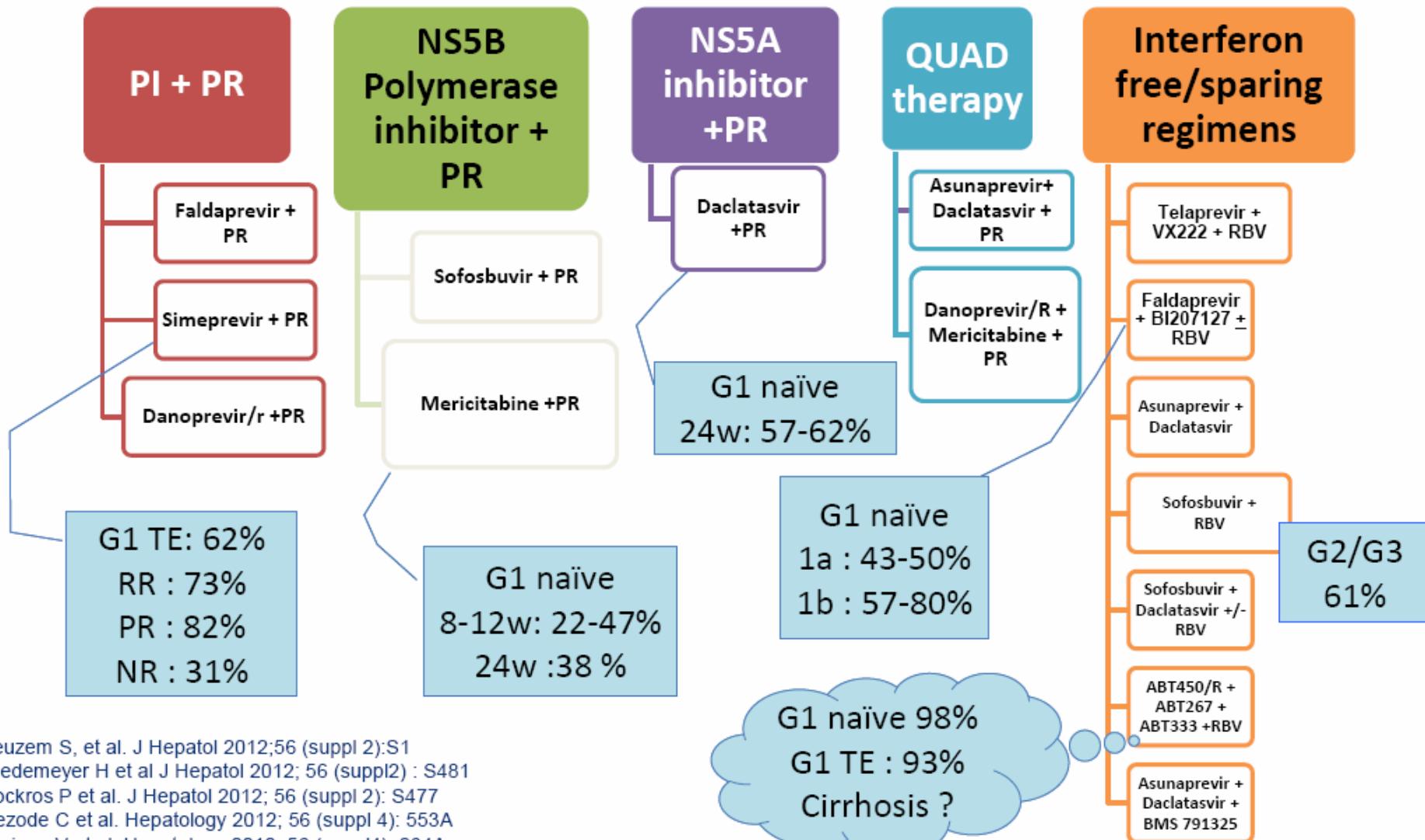
HCV treatment: beyond first generation PIs



PI: protease inhibitor; PR: peginterferon + ribavirin;

HCV treatment: beyond first generation PIs

SVR in cirrhotic

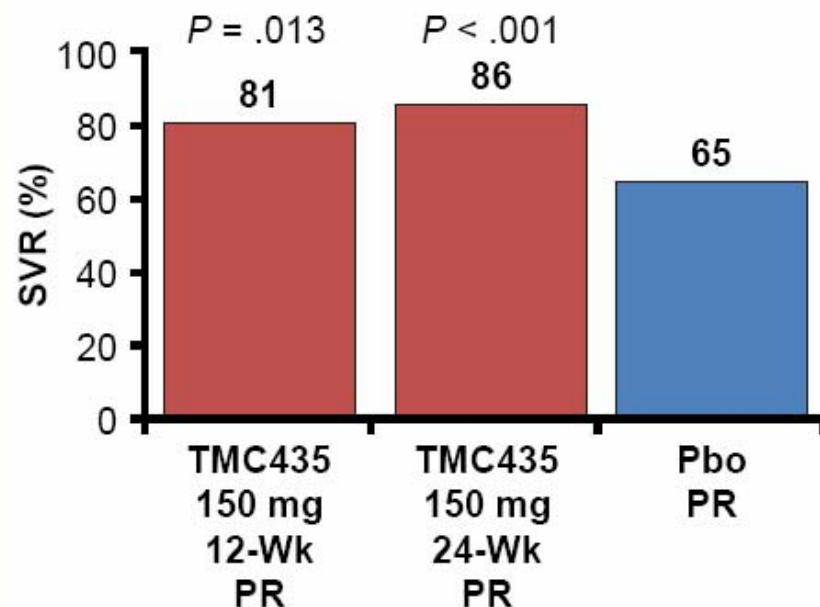


Zeuzem S, et al. J Hepatol 2012;56 (suppl 2):S1
 Wedemeyer H et al J Hepatol 2012; 56 (suppl2) : S481
 Pockros P et al. J Hepatol 2012; 56 (suppl 2): S477
 Hezode C et al. Hepatology 2012; 56 (suppl 4): 553A
 Soriano V et al. Hepatology 2012; 56 (suppl4): 234A
 Gilead Press release Nov 27th 2012

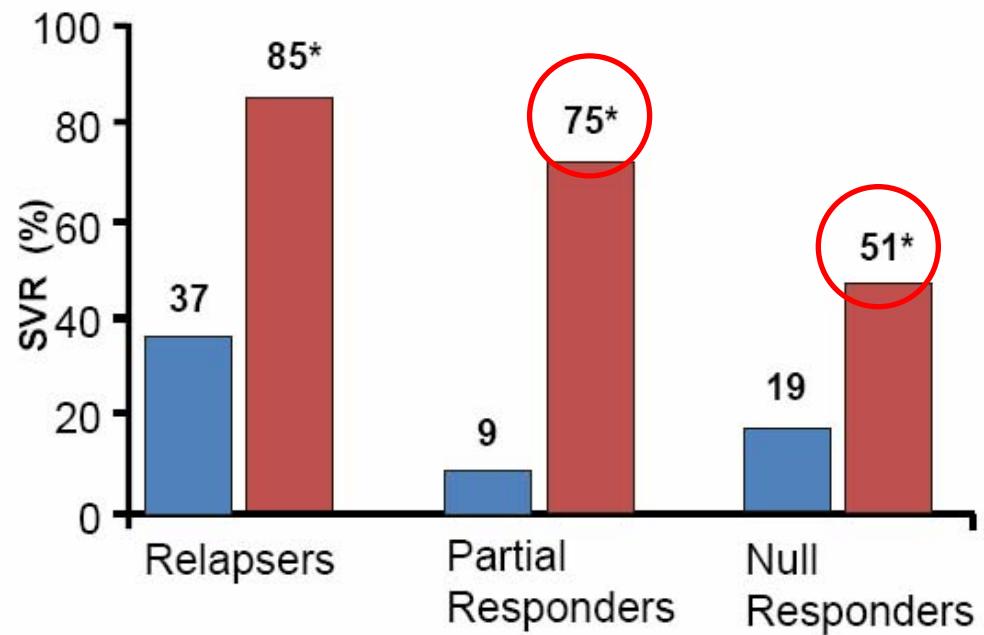
PI: protease inhibitor; PR: peginterferon + ribavirin

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

Treatment naive, G1

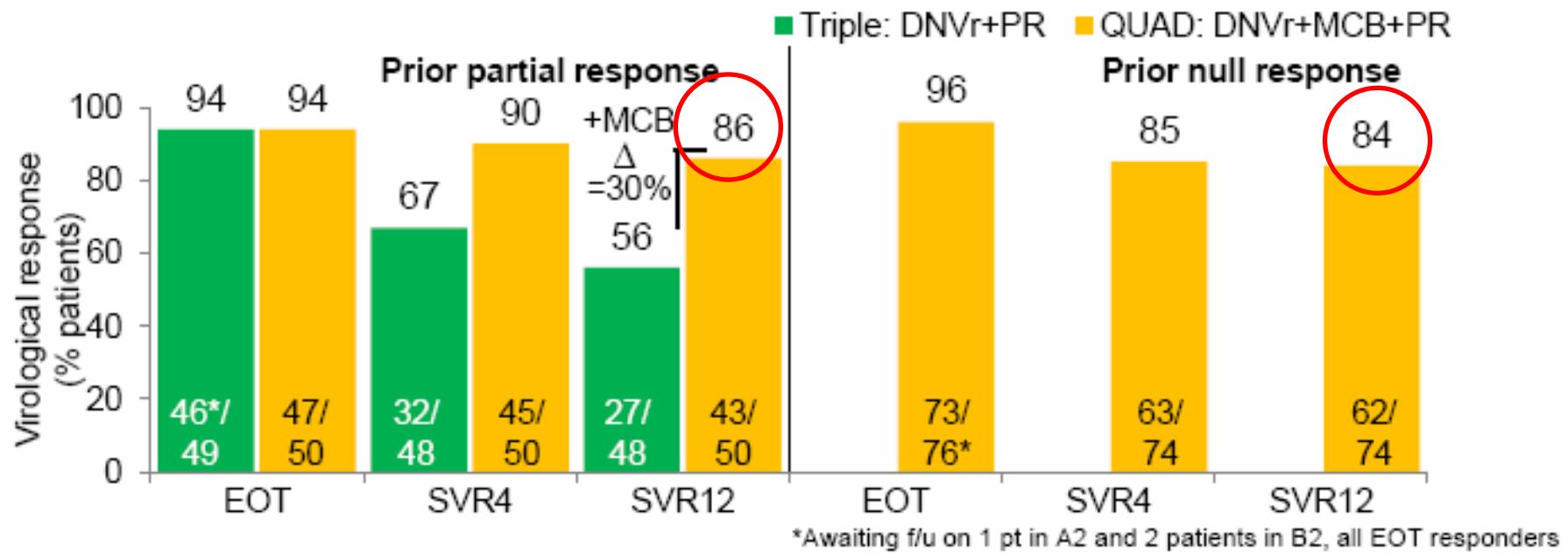


Treatment experienced, G1

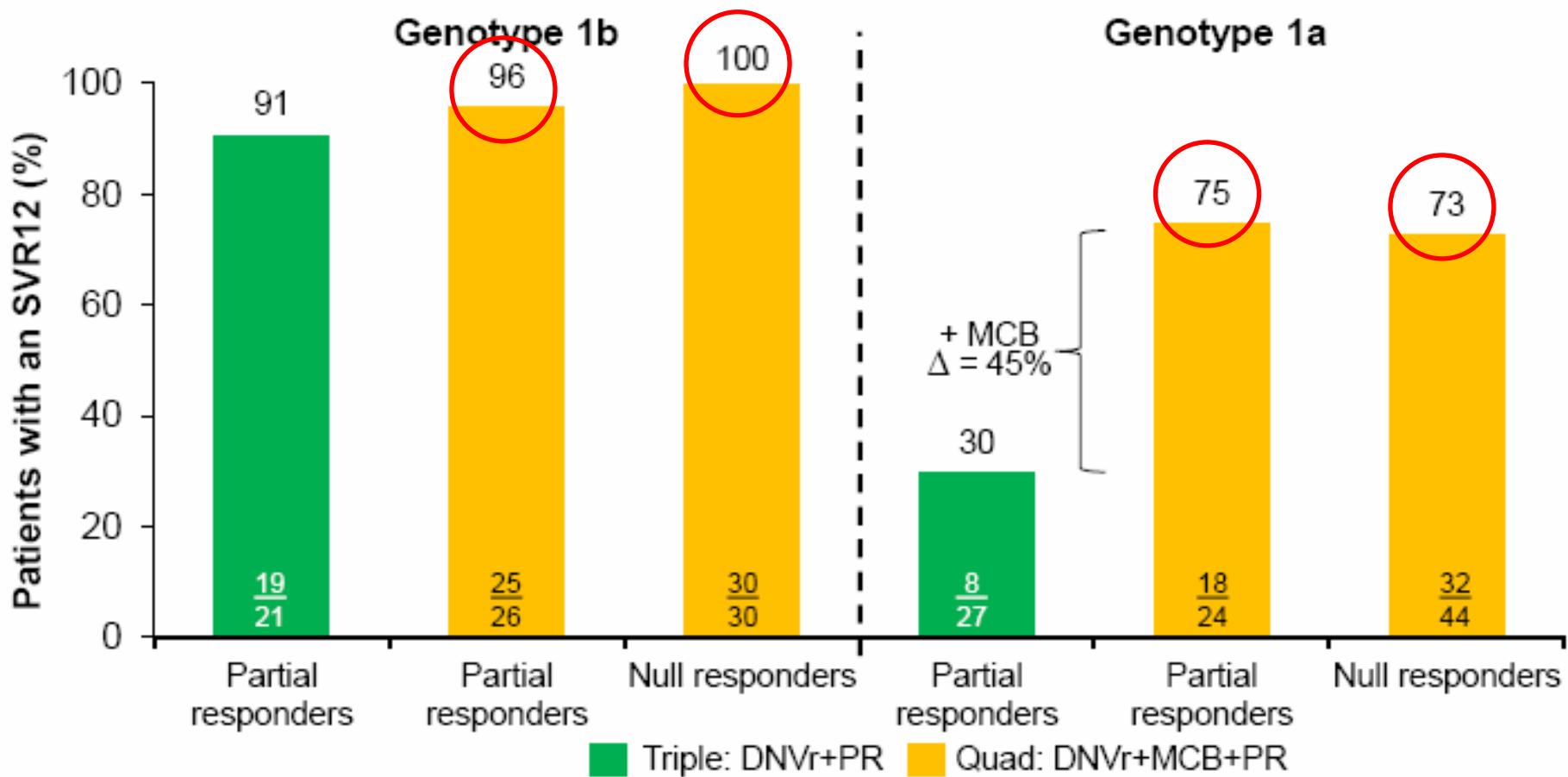


DNVr, MCB, RBV + PEG-IFN in G1-infected partial and null responders: Results from the MATTERHORN study

Efficacy of DNVr +PR and QUAD for 24 weeks



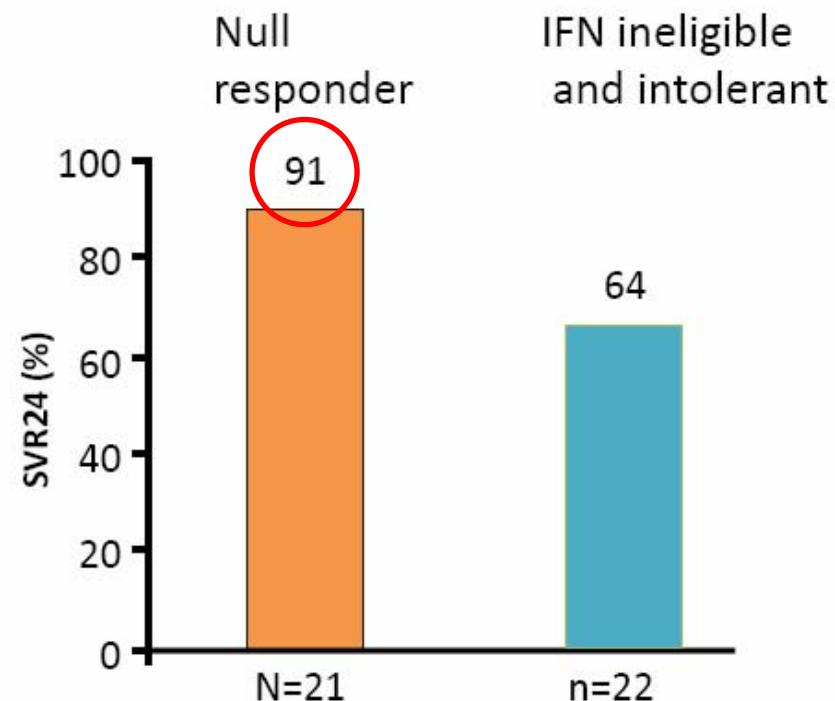
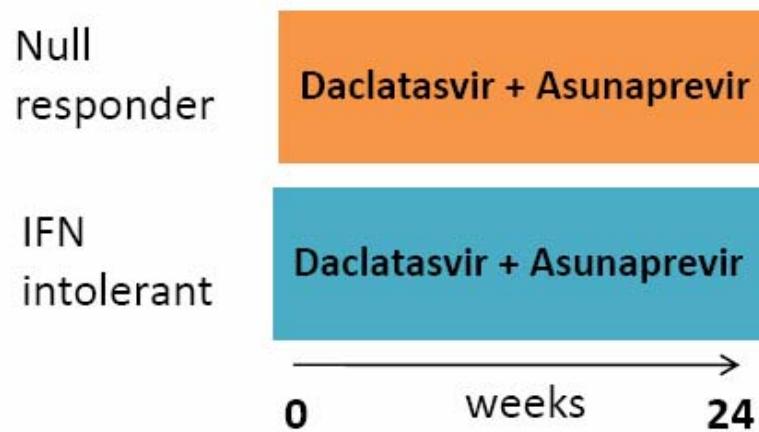
SVR12 by subtype: Addition of MCB improves SVR12 in G1a by 45%



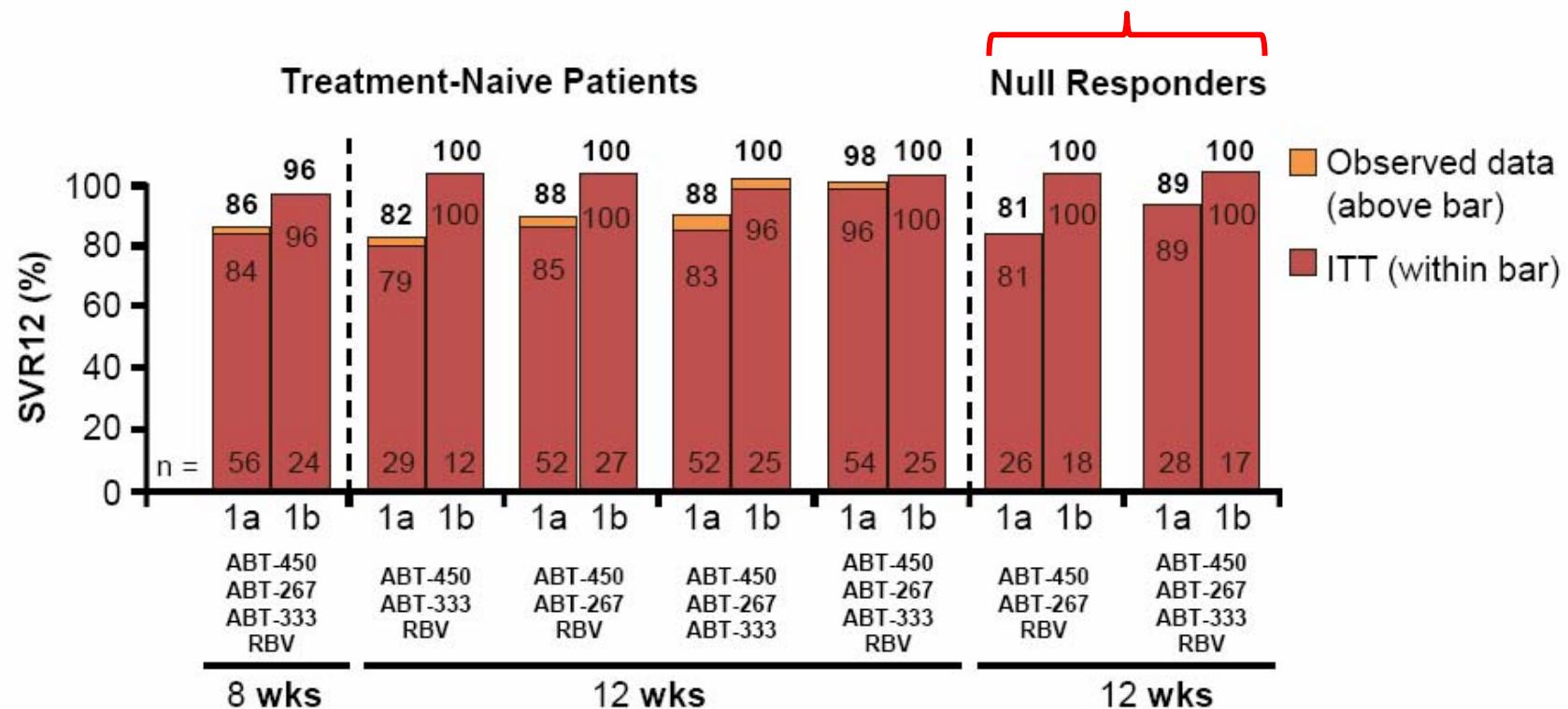
- Triple therapy effective in G1b partials, much less so in G1a
- Mericitabine helps to prevent relapse
- Very high SVR rates to QUAD in nulls, higher in G1b

Asunaprevir (PI) + Daclatasvir (NS5A)

Pts: Gen1b, non-cirrhotic



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

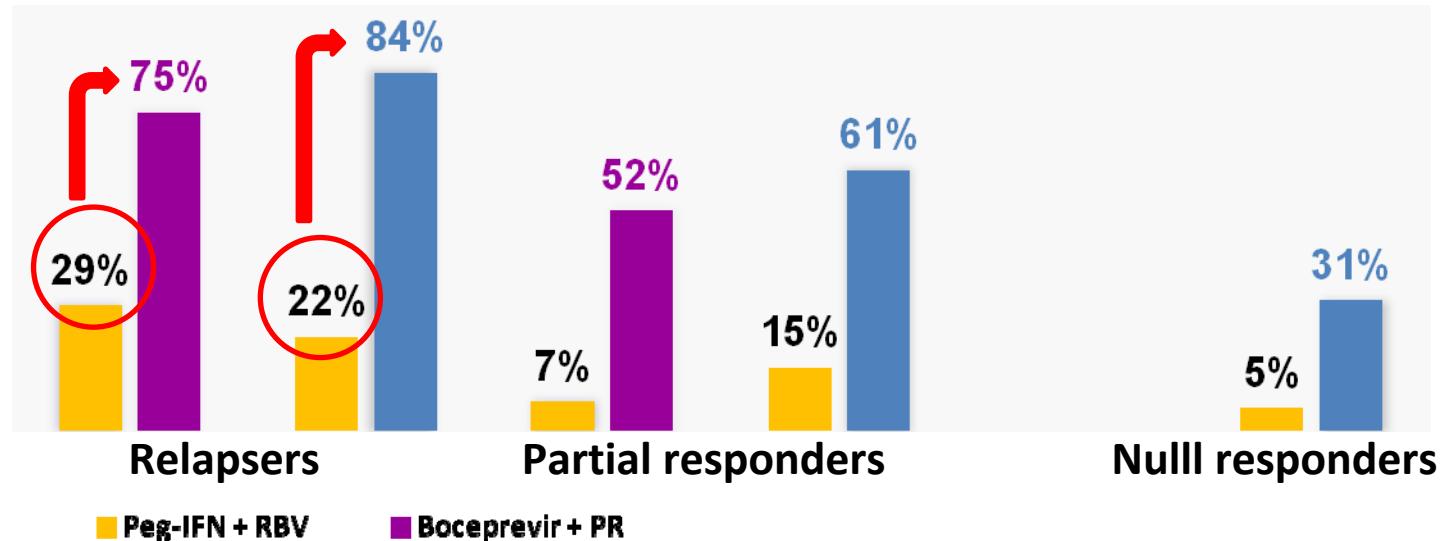


Focus on the bottom line

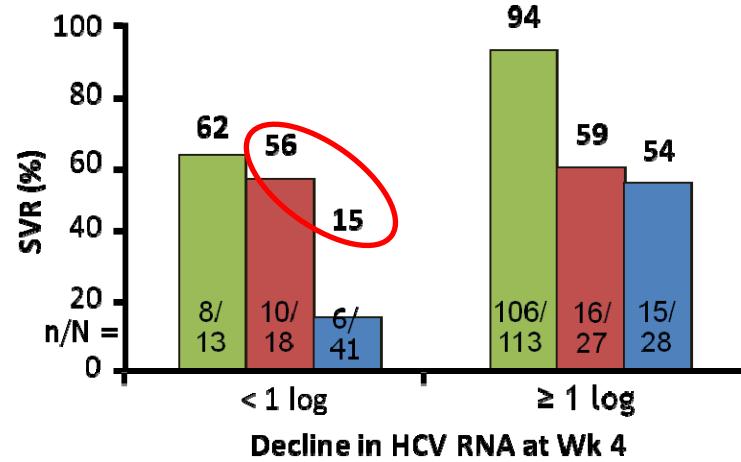
- The probability of achieving an SVR is low.
- First generation PIs in real clinical practice are associated with frequent SAEs.
- New DAAs combination increases SVR in cirrhotic patients, probably with better tolerance.
- IFN-free DAAs regimen demonstrates significant potency in cirrhotic patients.

2011

% of patients achieving SVR



2013



Null Responders

