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How to optimize current therapy of G1 patients

Predictors of response to IFN-based therapy

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Disclosures

- Consulting, advisory committees or review panel
  - Abbvie, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Janssen, Merck Sharp & Dohme, Roche
- Speaking and teaching
  - Aptalis, Bristol-Myers Squibb, Gilead, Janssen, Merck Sharp & Dohme, Roche

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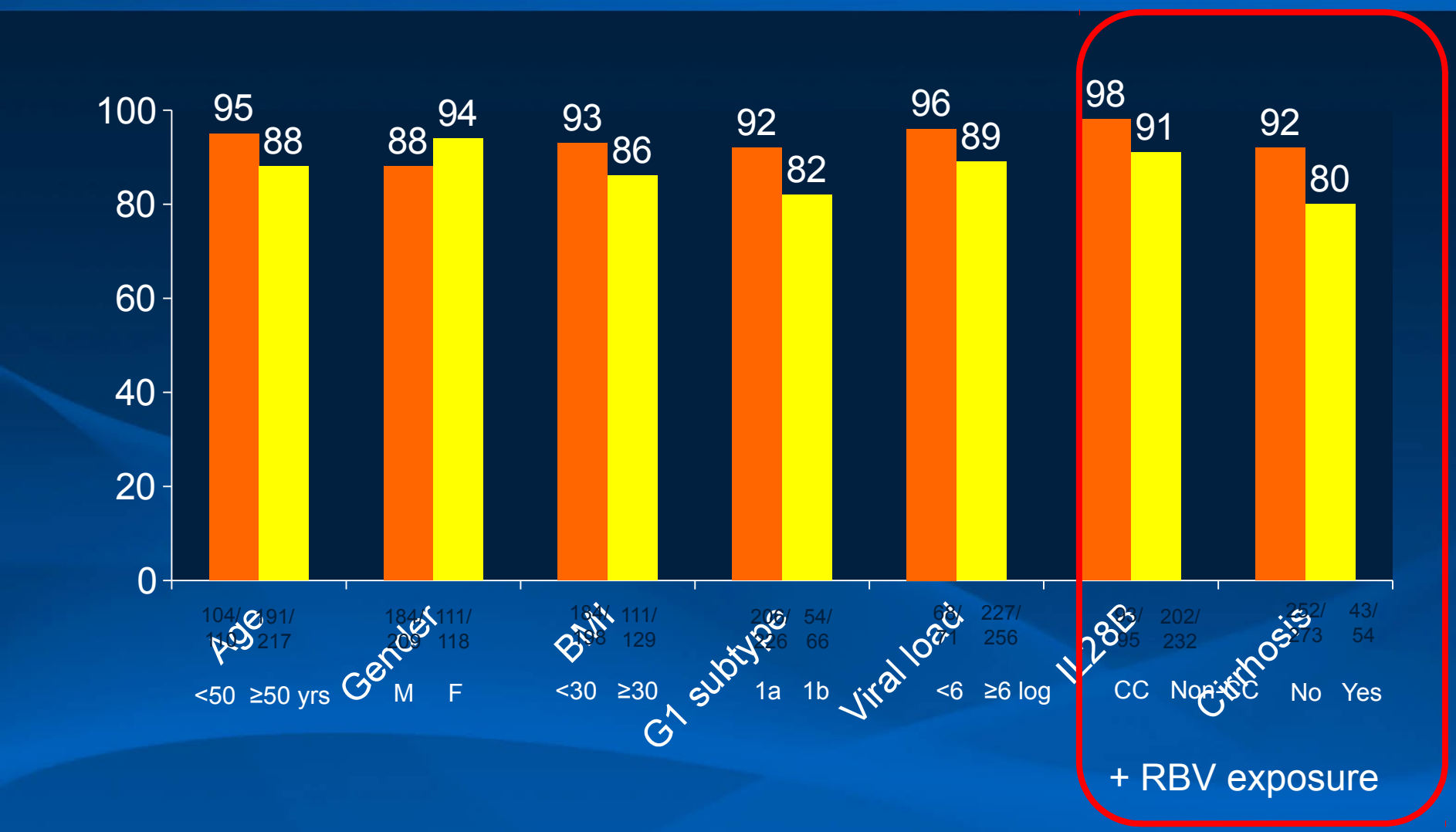
PEG IFN/RBV-based regimen with 2nd wave DAAs

Sofosbuvir	Simeprevir	Daclatasvir
12 weeks fixed duration therapy	Response guided treatment duration	Response guided treatment duration

SOF + PR : NEUTRINO

SVR12 according to traditional predictive factors



Lawitz E et al. NEJM 2013

SOF + PR:NEUTRINO
SVR12 according to fibrosis stage

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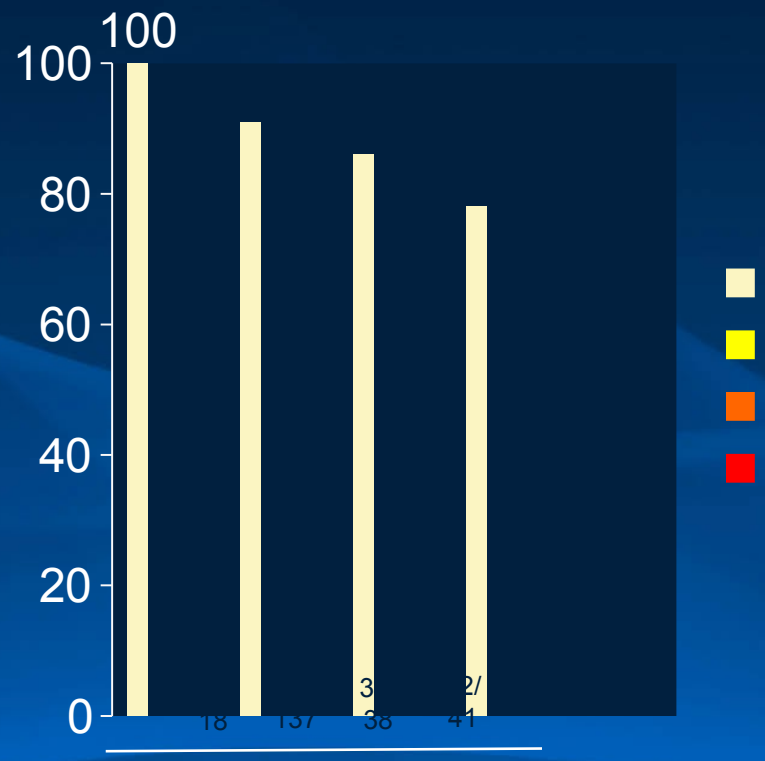
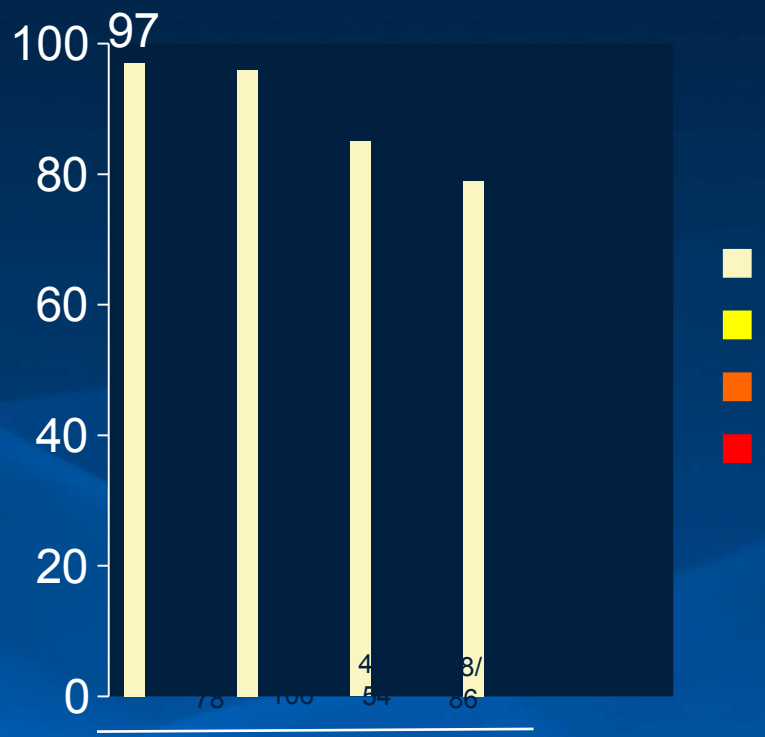
SVR12 rates by biopsy fibrosis stage (n=232)



SVR12 rates by Fibrotest stage (n=323)



Patel K et al. AASLD 2013

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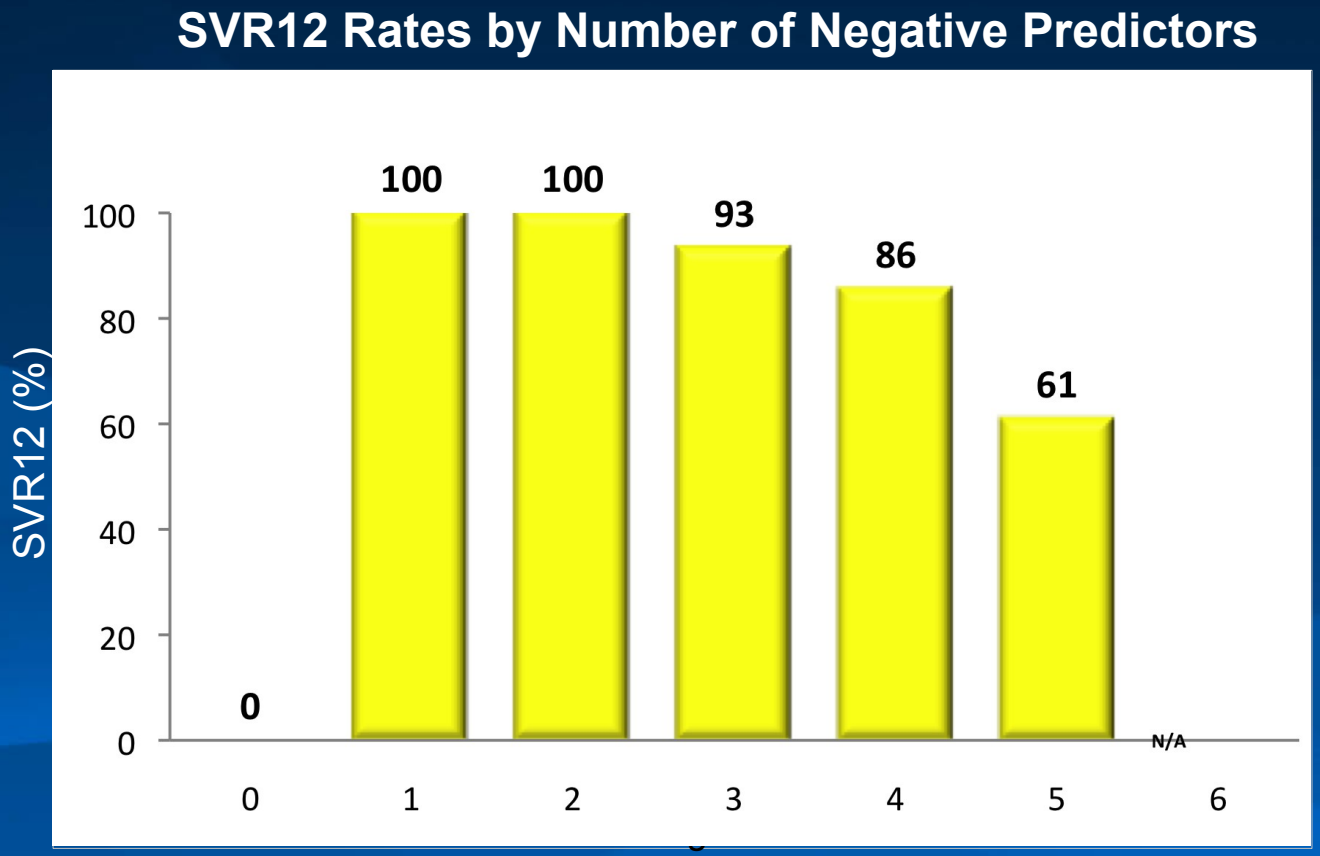
SVR rates of SOF + PR among patients with multiple negative predictive factors (ATOMIC, NEUTRINO)

339 GT1 patients included in SOF-based triple therapy studies
Negative predictors: cirrhosis, *IL28B* non-CC, HCV RNA ≥ 800,000 IU/mL, body weight ≥ 75kg, male gender



Foster G, EASL, 2014

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SOF + PR: in summary

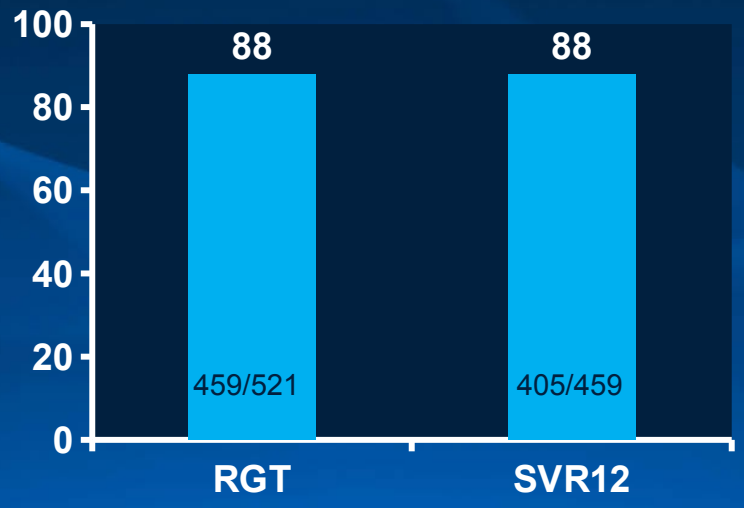
- IL28B non CC and cirrhosis are independent predictors of relapse.
- SVR rates are lower in patients with more than 3 negative predictors.
- Early viral kinetics ?
- No data in treatment experienced patients

SMV + PR: pooled QUEST 1 and 2
Response-guided treatment duration and SVR12

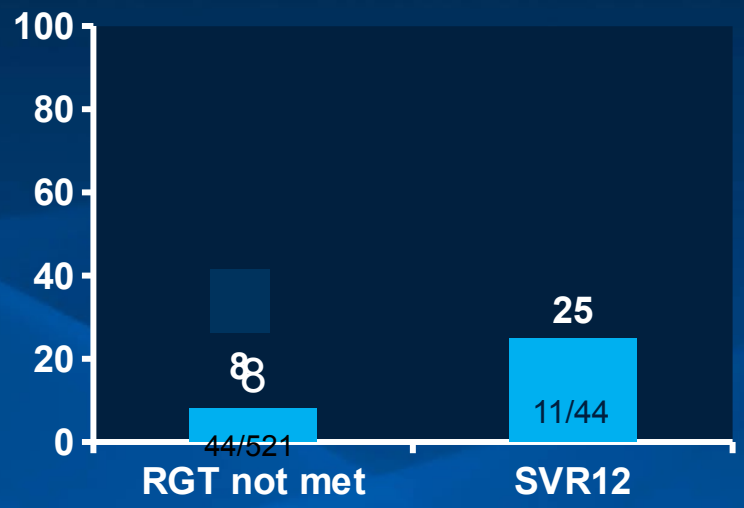
Patients treated with SMV + PR

Met RGT criteria

Eligible for 24 weeks of treatment



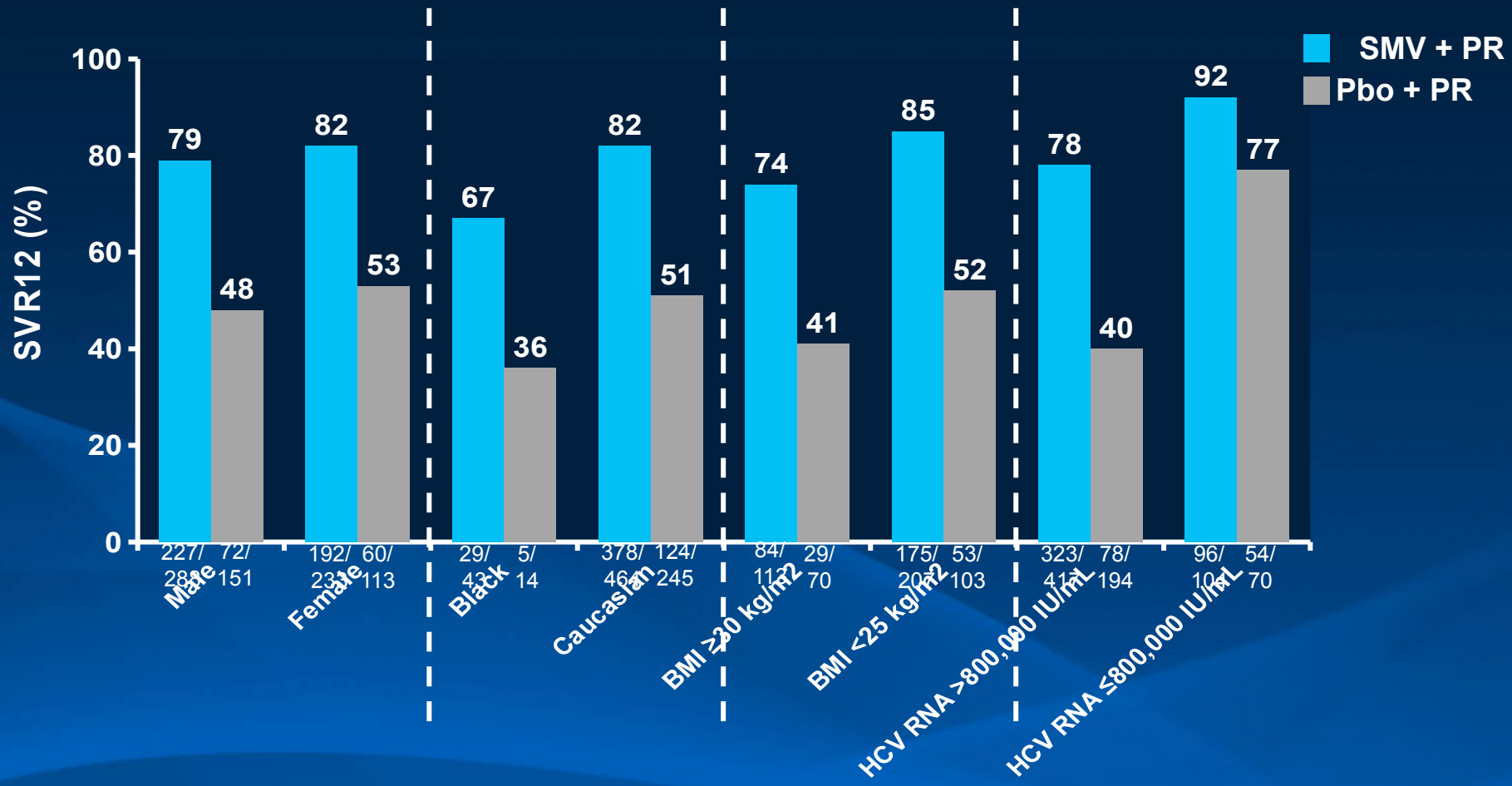
Did not meet RGT criteria



RGT (response guided therapy) – patients were eligible to stop treatment at Week 24 if HCV RNA <25 IU/mL detectable or undetectable at Week 4 and <25 IU/mL undetectable at Week 12

Jacobson I, et al. AASLD 2013

SMV + PR: pooled QUEST 1 and 2
SVR12 by demographic and baseline disease characteristics



Jacobson I, et al. AASLD 2013

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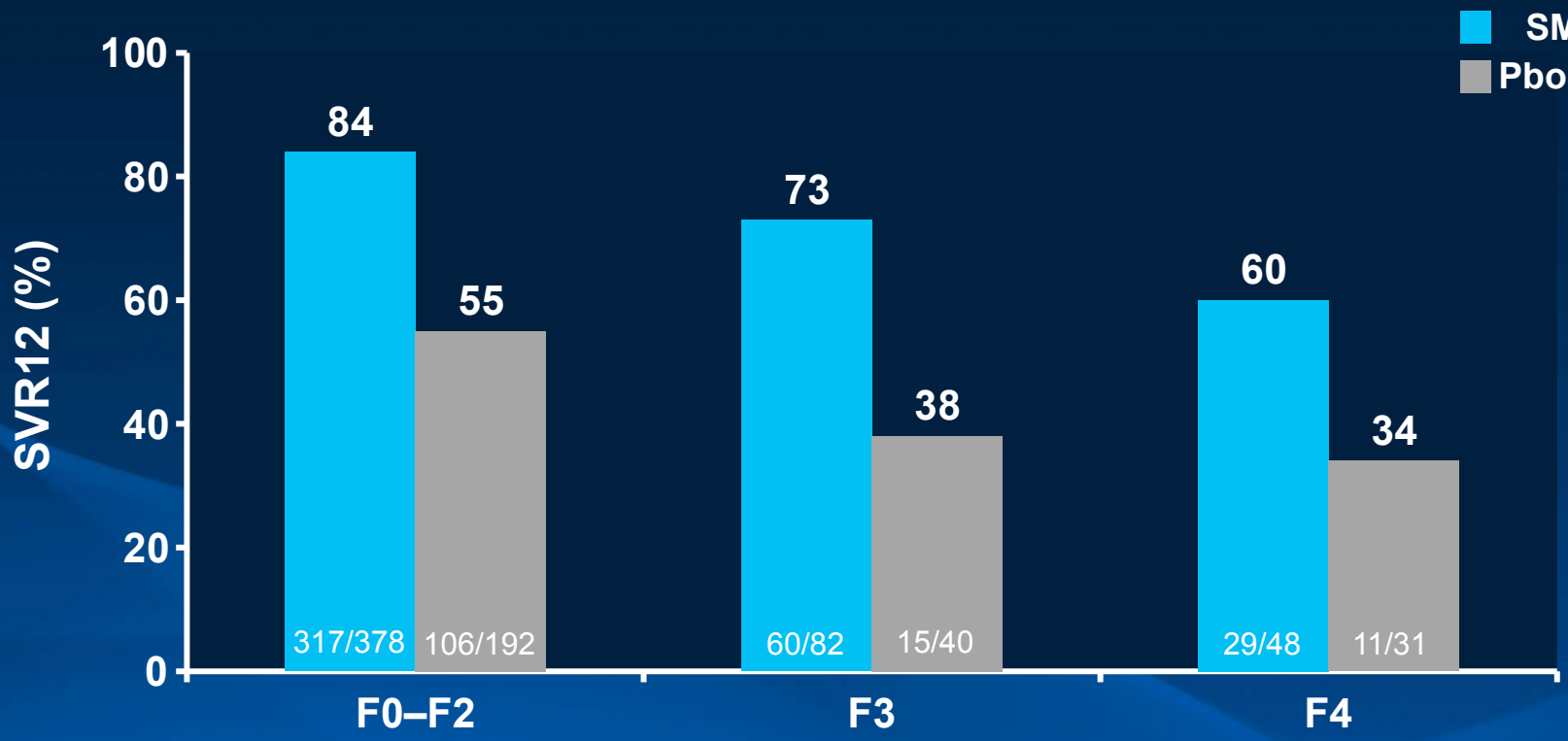
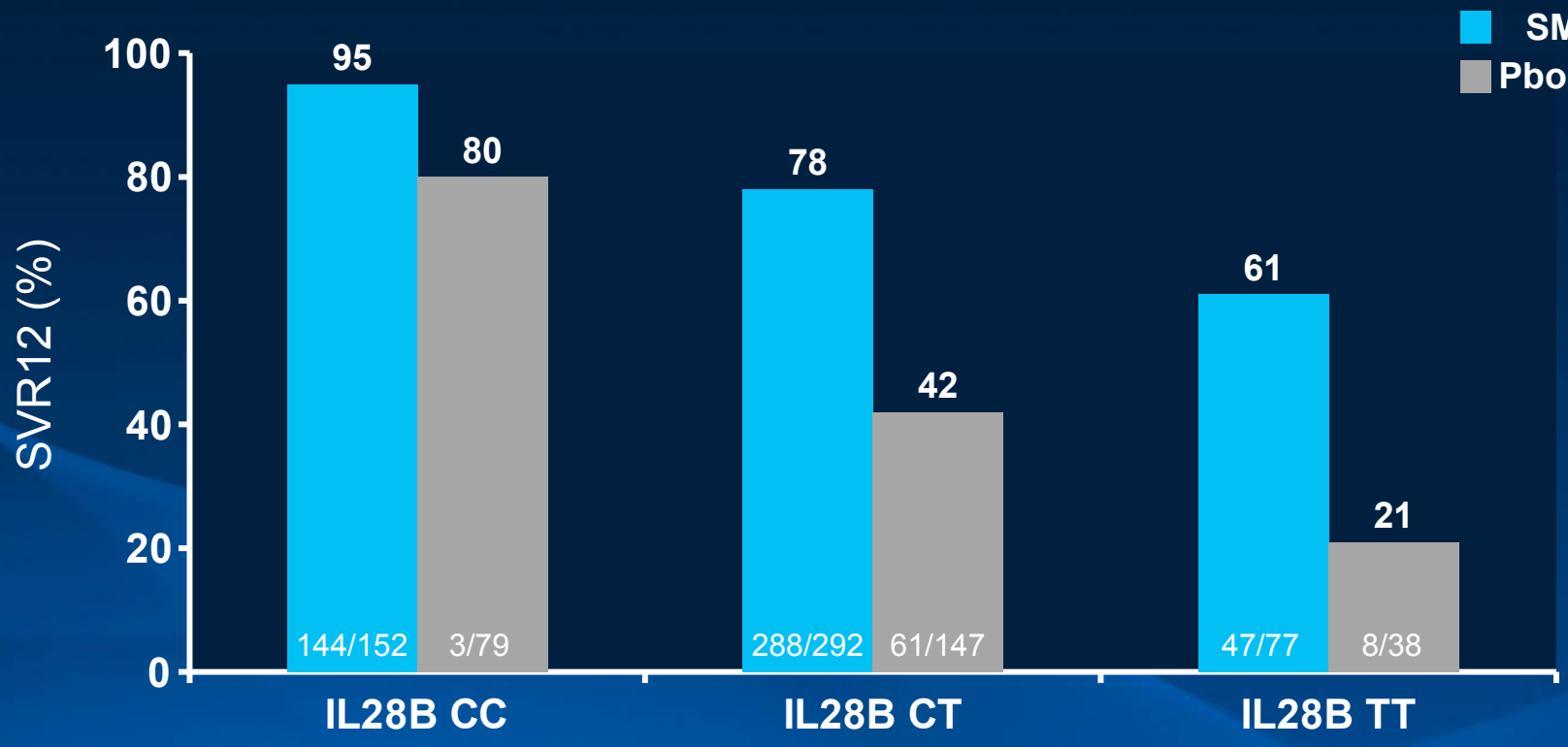
SMV + PR: pooled QUEST 1 and 2 SVR by fibrosis stage



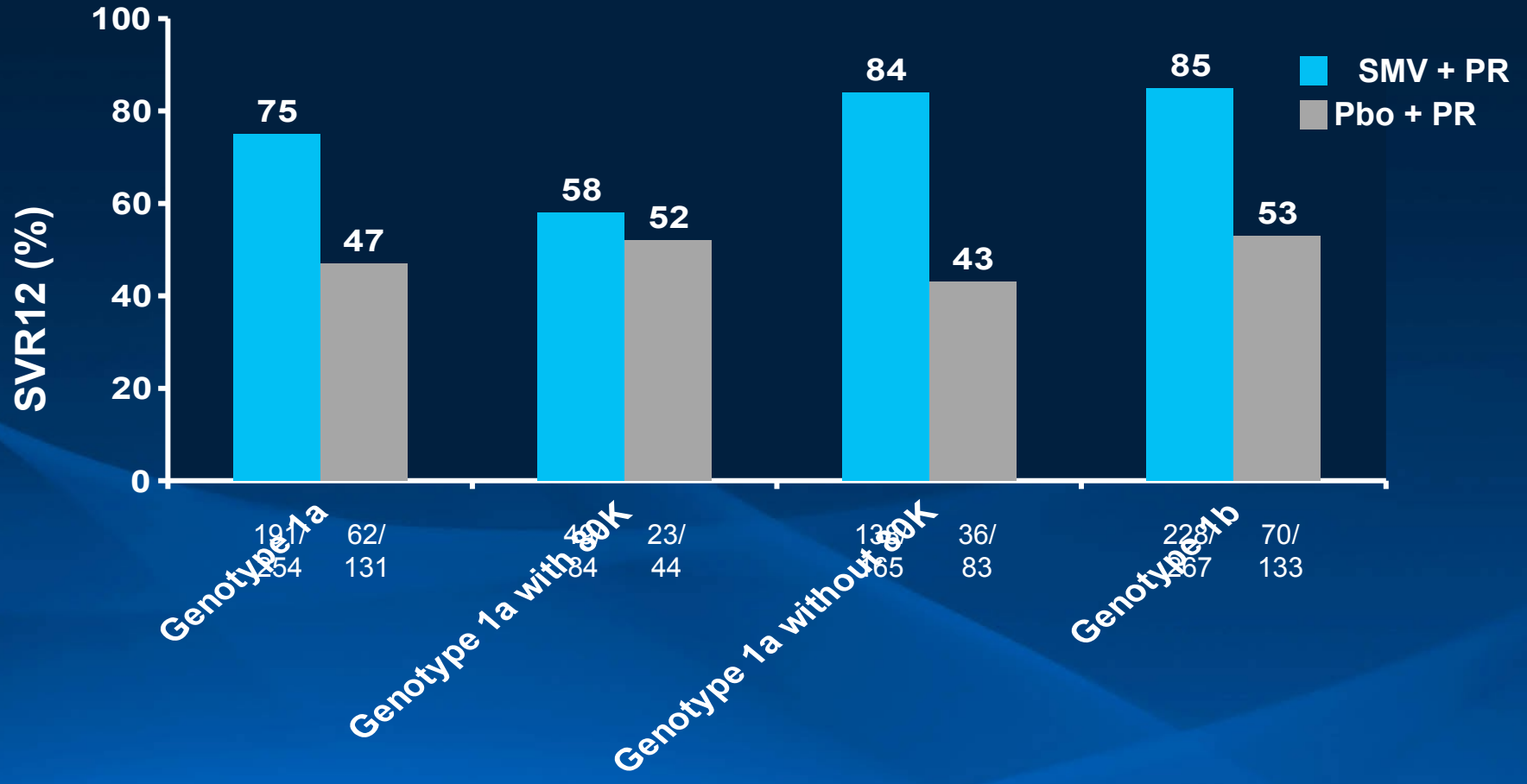
Jacobson I, et al. AASLD 2013

SMV + PR: pooled QUEST 1 and 2 SVR12 by *IL28B* subgroup



Jacobson I, et al. AASLD 2013

SMV + PR: pooled QUEST 1 and 2 – SVR12 by HCV genotype and Q80K polymorphism



Jacobson I, et al. AASLD 2013

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Overall prevalence of Q80K and across different regions *(Phase IIb/III SMV studies)*

n/N (%)	All HCV genotype 1	HCV genotype 1a	HCV genotype 1b
Overall	274/2007 (13.7)	269/911 (29.5)	5/1096 (0.5)
Europe	76/1254 (6.1)	73/377 (19.4)	3/877 (0.3)
North America	185/538 (34.4)	185/385 (48.1)	0/153 (0)
South America	2/60 (3.3)	2/22 (9.1)	0/38 (0)

Includes 15 patients with non-1a/b genotype

Jacobson I, et al. AASLD 2013
Lenz O, et al. AASLD 2013.

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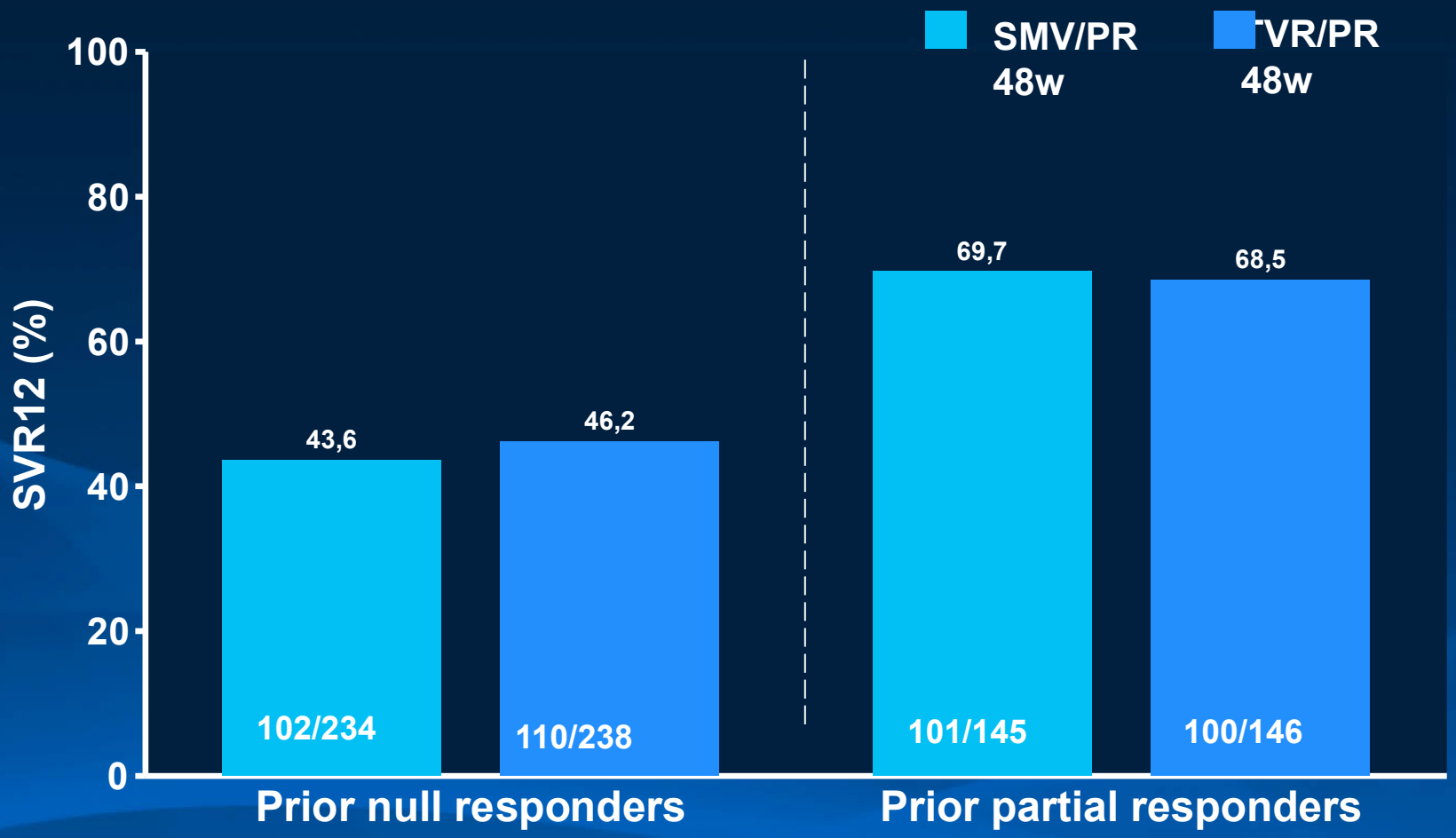
SMV+PR: ATTAIN
SVR12 by prior treatment response



Reddy KR, et al. APASL 2014

DCV + PR: COMMAND-1
Response-guided treatment duration and SVR12

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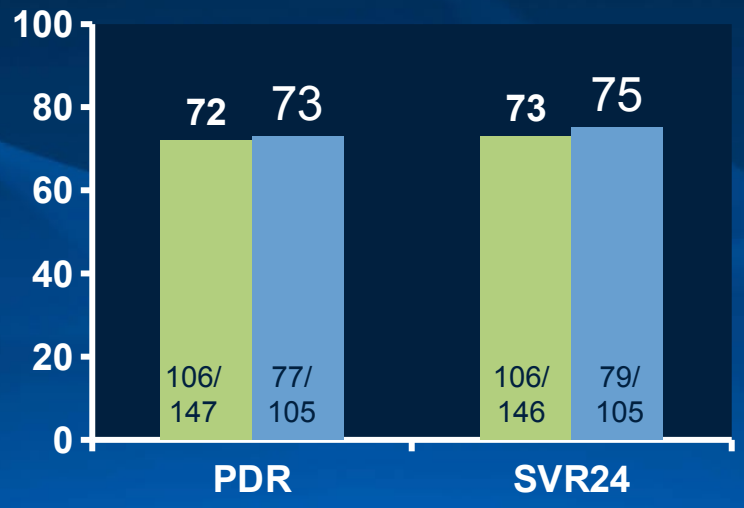
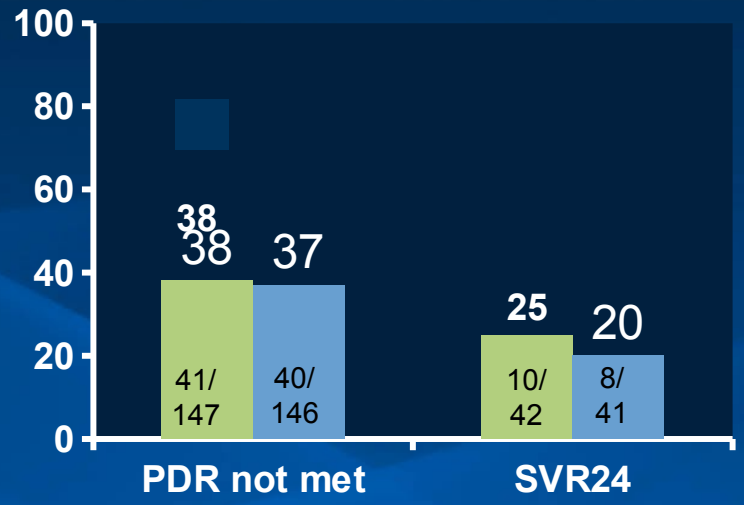
Patients treated with DCV + PR

Met PDR criteria

Eligible for 24 weeks of treatment

Did not meet PDR criteria





PDR (protocol defined response) – patients were eligible to stop treatment at Week 24 if HCV-RNA <lower limit of quantitation (LLOQ) at Week 4 and undetectable at Week 10

Hezode C, et al. Gut 2014

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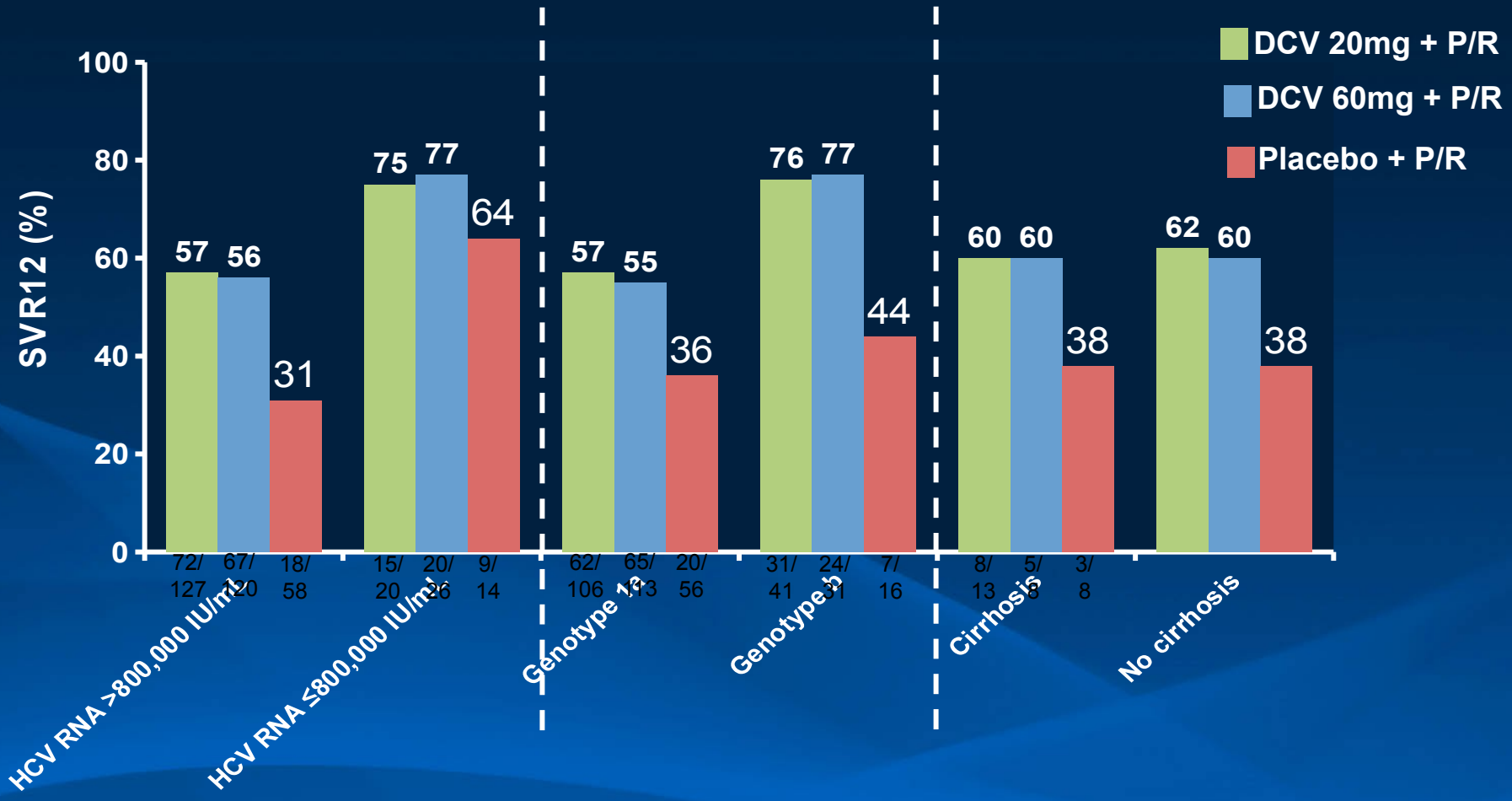
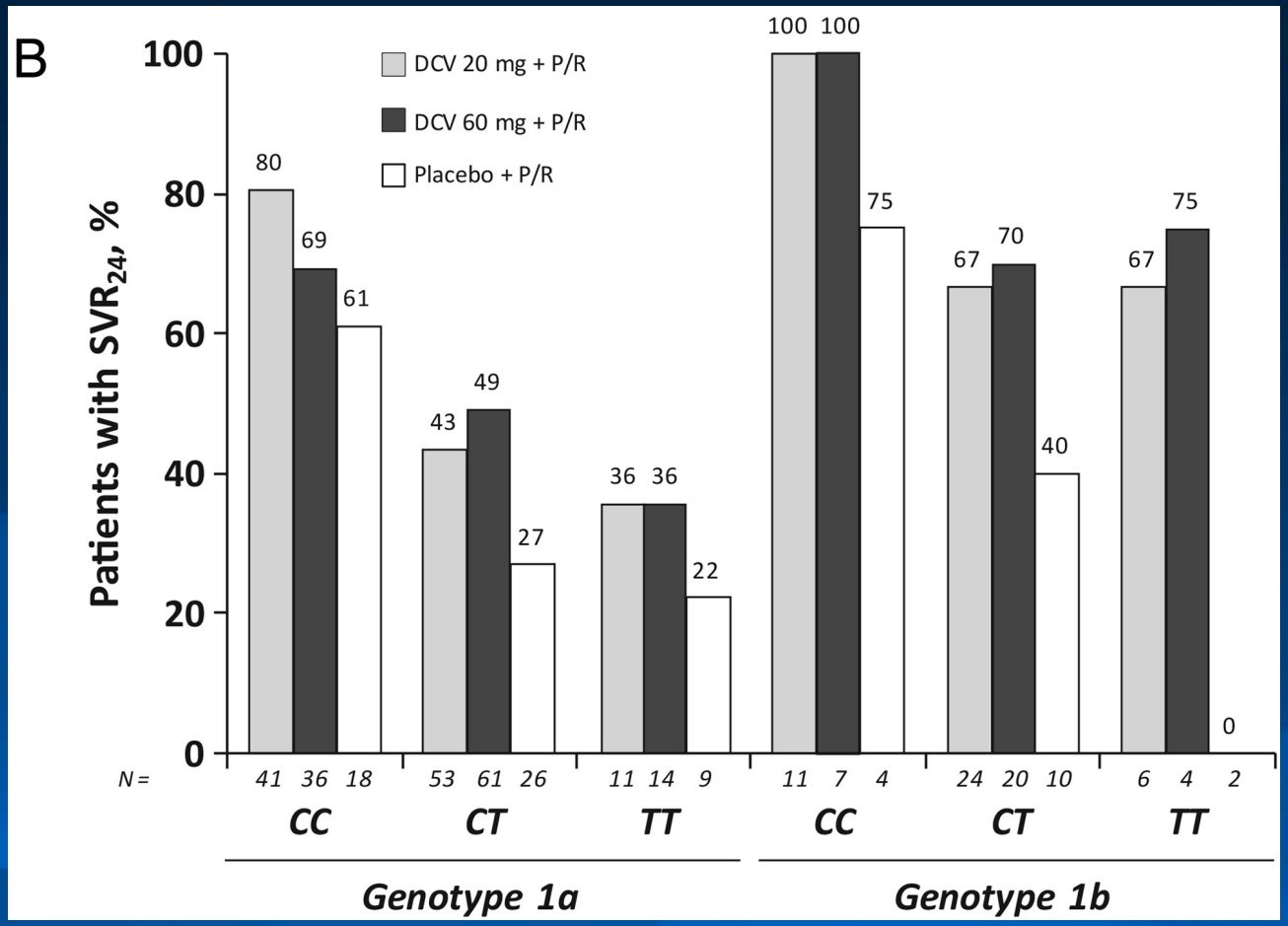
DCV + PR: COMMAND-1
SVR24 by baseline disease characteristics



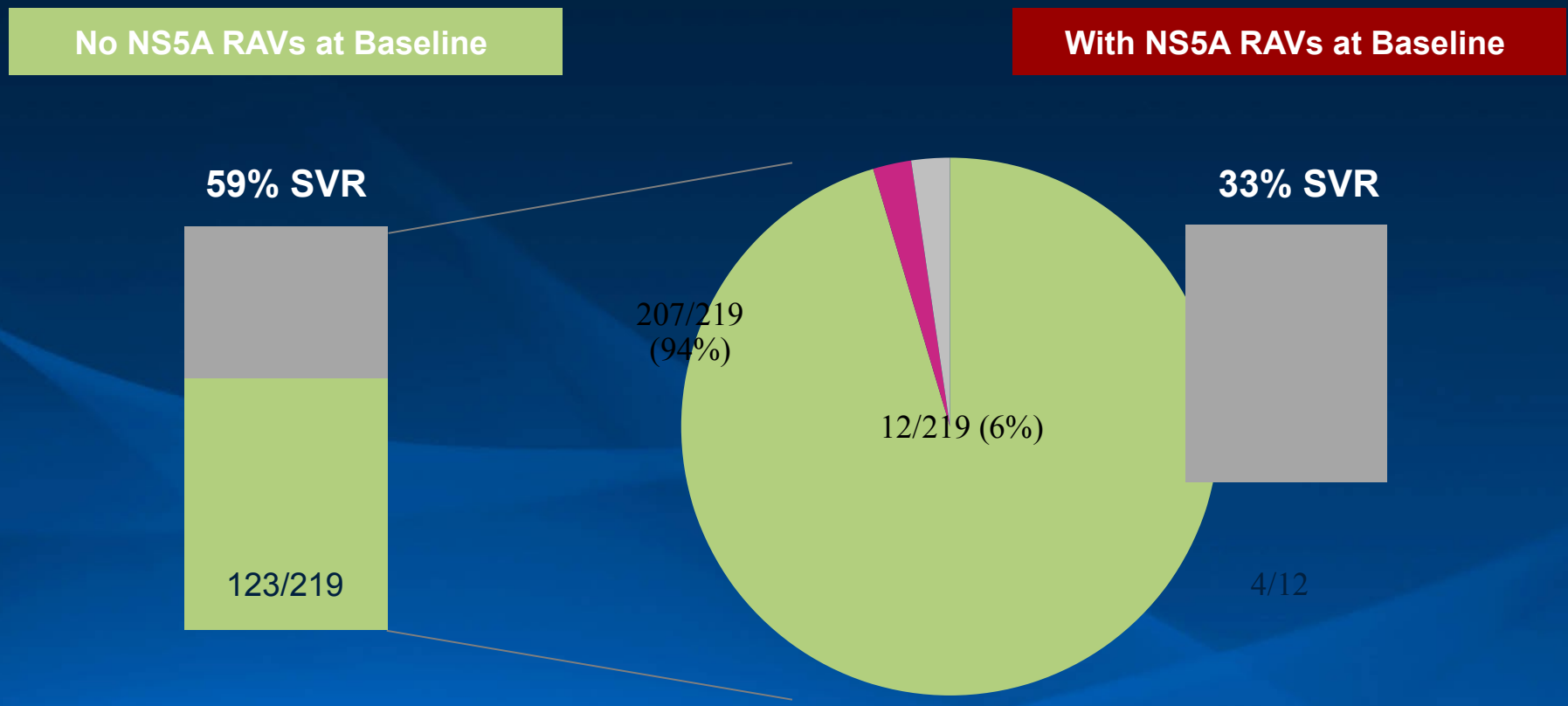
Hezode C, et al. Gut 2014

DCV + PR: COMMAND-1
SVR24 by *IL28B* subgroup



Hezode C, et al. Gut 2014

DCV + PR: COMMAND-1
NS5A RAVs at baseline in genotype 1a patient



Hezode C, et al. Gut 2014

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Conclusion

- Triple therapy with sofosbuvir is a highly potent PEG-IFN/RBV-based regimen for HCV-1 patients; cirrhosis and IFNL3 genotype are still predictors of response.
- PEG-IFN/RBV-based regimens with simeprevir or daclatasvir are less effective in HCV-1 patients
  - efficacy is significantly reduced in HCV-1a patients, especially in the presence of the Q80K mutation when simeprevir is used.
  - these regimens should be mainly initiated in HCV-1b patients with favourable predictors of response to IFN.