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Retreatment with an interferon-free combination of simeprevir-sofosbuvir in patients who had previously failed on HCV NS5A inhibitor–based regimens

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Background

- In HCV patients, failure to DAAs is commonly associated with the emergence of RAVs
- While NS3 RAVs are generally overgrown by wild-type virus over time, NS5A RAVs have been seen to persist
- Recently, it has been shown that 71% of patients who failed prior LDV/SOF-containing regimens achieved SVR12 when retreated with LDV/SOF for 24 weeks*
- The presence of baseline NS5A RAV(s) was associated with virologic failure

* Lawitz E et al, EASL 2015

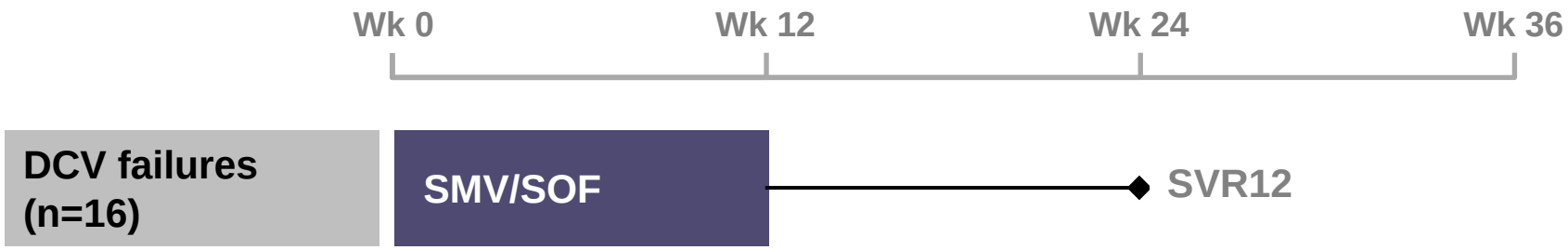
Background and Study Objectives

- SMV/SOF is an approved interferon- and ribavirin-free treatment for patients with HCV genotype 1 or 4 infection

- Objective of this pilot study was to evaluate the efficacy and safety of SMV/SOF for 12 weeks without RBV as a retreatment strategy for patients who had failed prior DCV/PR (n=13) or DCV/ASV/PR (n=3) regimens in phase 2 and 3 studies

- All patients were managed in the department of Hepatology of Henri Mondor Hospital and included in the HEPATHER cohort from ANRS

Study Design



Endpoints

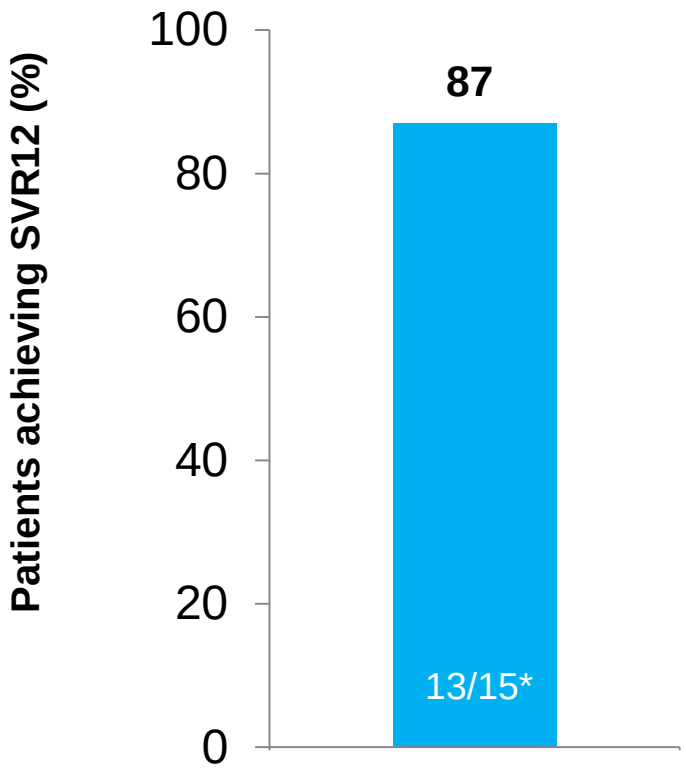
- SVR12 was primary efficacy endpoint
  - HCV RNA <LLOQ at post-treatment Week 12
    - HCV RNA analyzed by Abbott Real*Time* Assay with LLOQ of 12 IU/mL
- HCV resistance was assessed at retreatment baseline by means of population sequencing home made methods targeting the NS3 and NS5A coding regions
- Safety
  - Serious AEs and discontinuations
  - Laboratory abnormalities

Demographics and Baseline Characteristics

	SMV/SOF 12 Weeks N=16
Mean age, y (range)	54 (43–73)
Male, n (%)	13 (81)
Genotype 1a, n (%)	11 (69)
Genotype 1b, n (%)	3 (23)
Genotype 4, n (%)	2 (13)
Median HCV RNA, 10^6 IU/mL	1.38
HCV RNA >800,000 IU/mL, n (%)	14 (88)
Severe fibrosis (FS 9.6 – 12.5 kPa), n (%)	7 (44)
Cirrhosis (FS >12.5 kPa), n (%)	9 (56)
Median time between DCV-based regimen and SMV/SOF, m (range)	32 (16-53)
Presence of NS5A RAVs	13 (81)
Presence of NS3 RAVs	8 (57)*
Prior HCV treatment, n (%)	
DCV/PR	13 (81)
DCV/ASV/PR	3 (19)

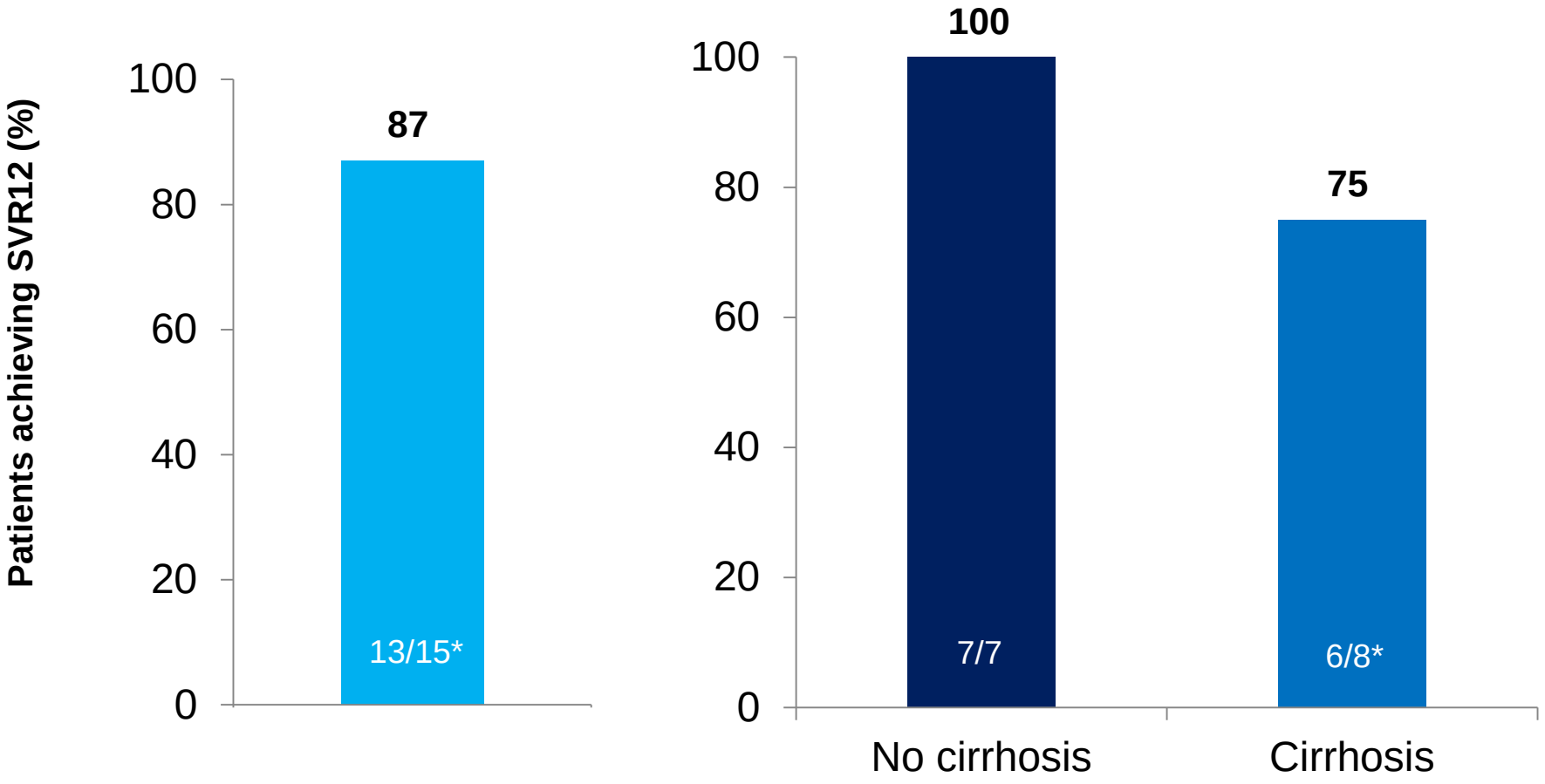
*Available in 14 patients

Retreatment of NS5A failures with 12 weeks SMV+SOF
Overall population



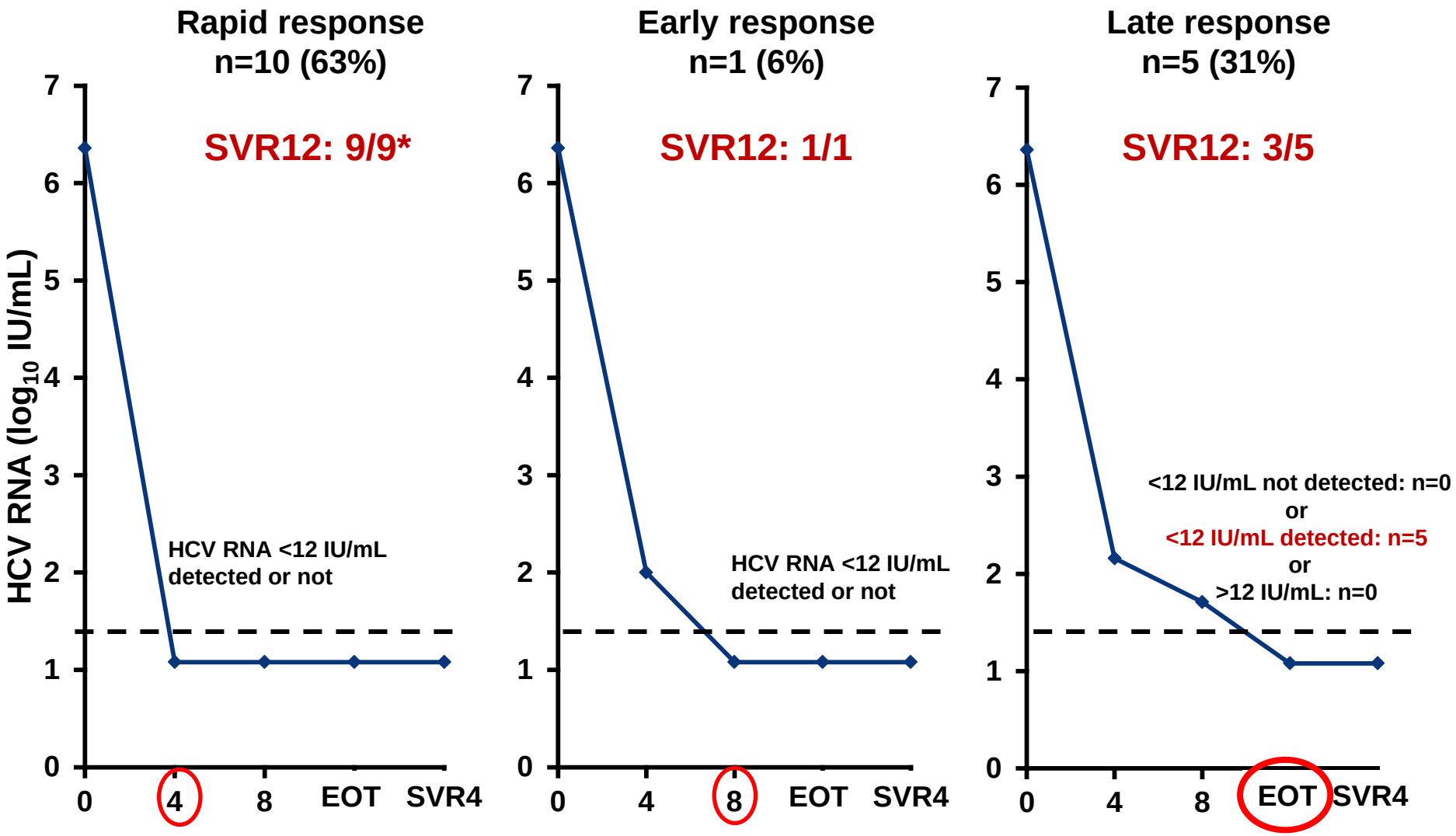
*1 patient does not reach week12 follow-up visit

Retreatment of NS5A failures with 12 weeks SMV+SOF
According to fibrosis stage



*1 patient does not reach week12 follow-up visit

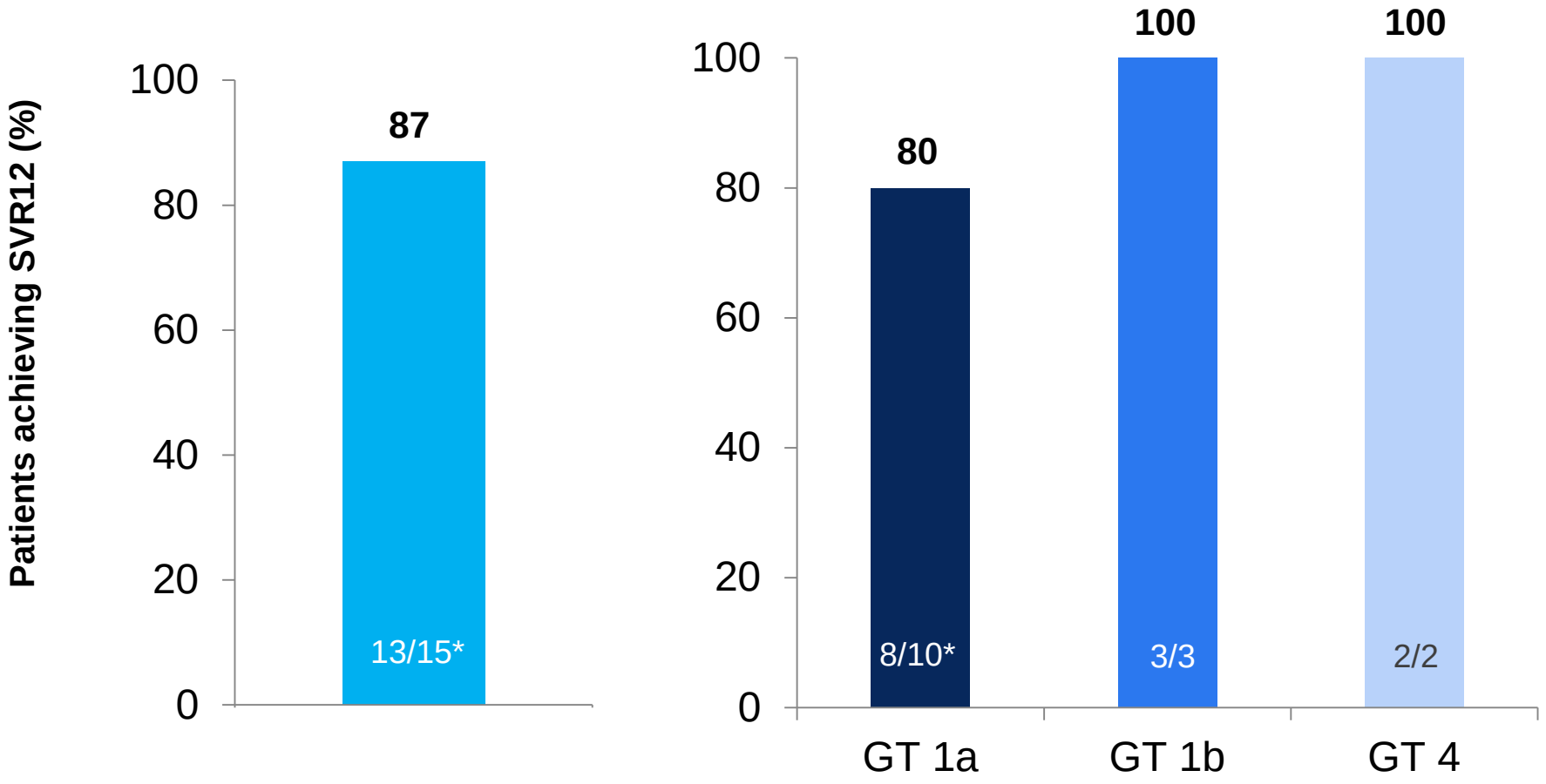
Retreatment of NS5A failures with 12 weeks SMV+SOF according to the on-treatment response



*1 patient does not reach week12 follow-up visit

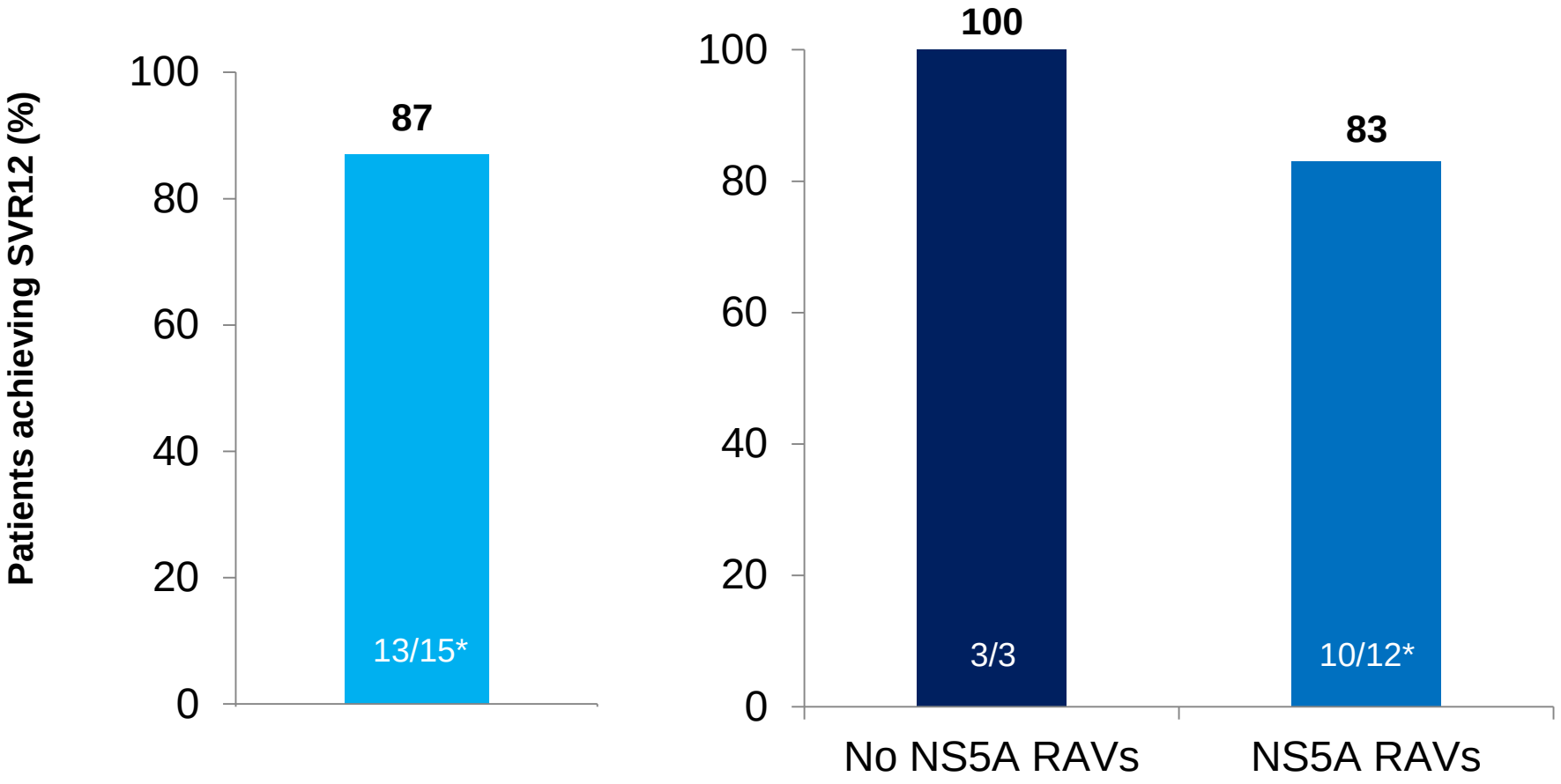
Abbott RealTime HCV assay was used

Retreatment of NS5A failures with 12 weeks SMV+SOF according to the genotype



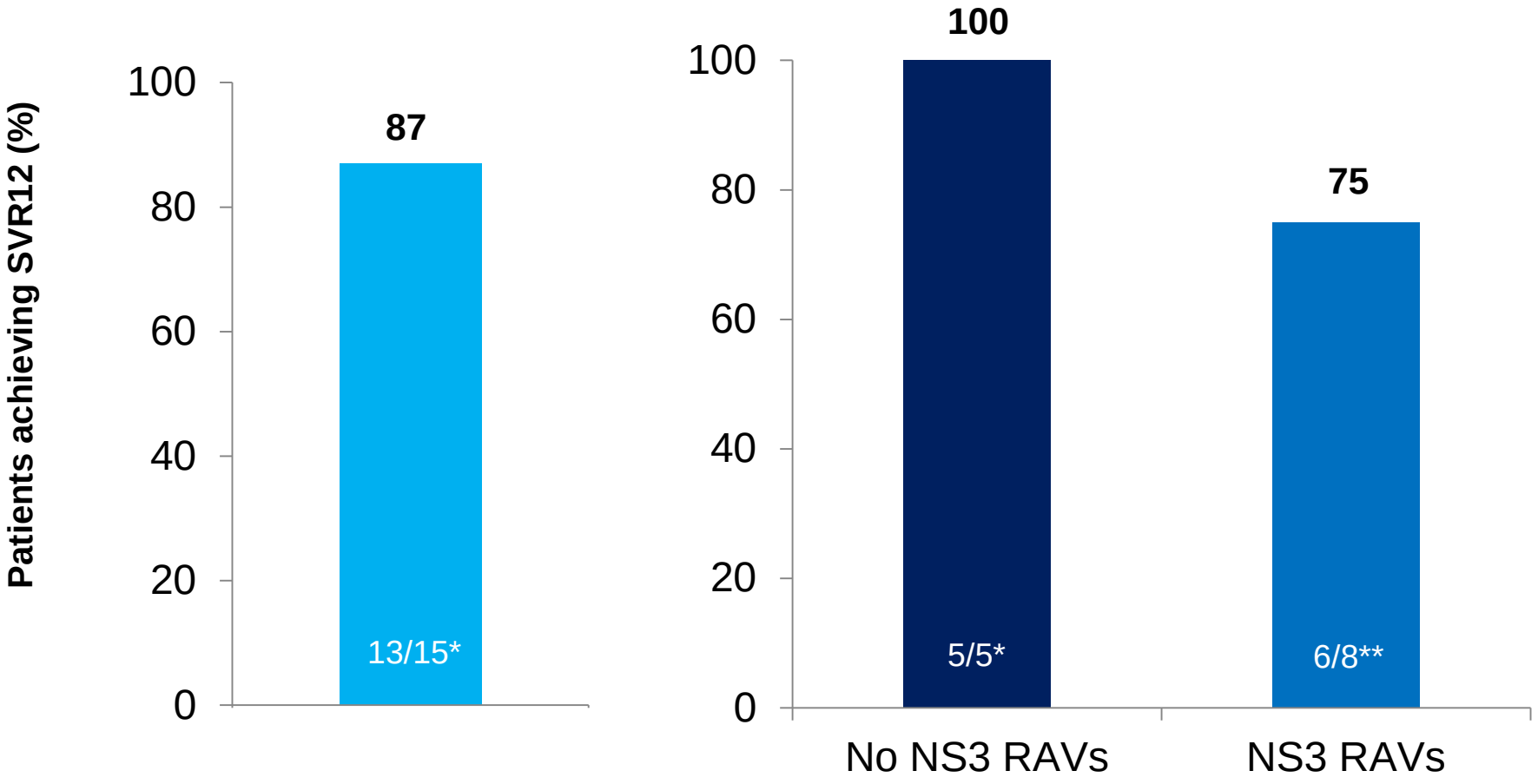
*1 patient does not reach week12 follow-up visit

Retreatment of NS5A failures with 12 weeks SMV+SOF according to the presence of NS5A RAVs at baseline



*1 patient does not reach week12 follow-up visit

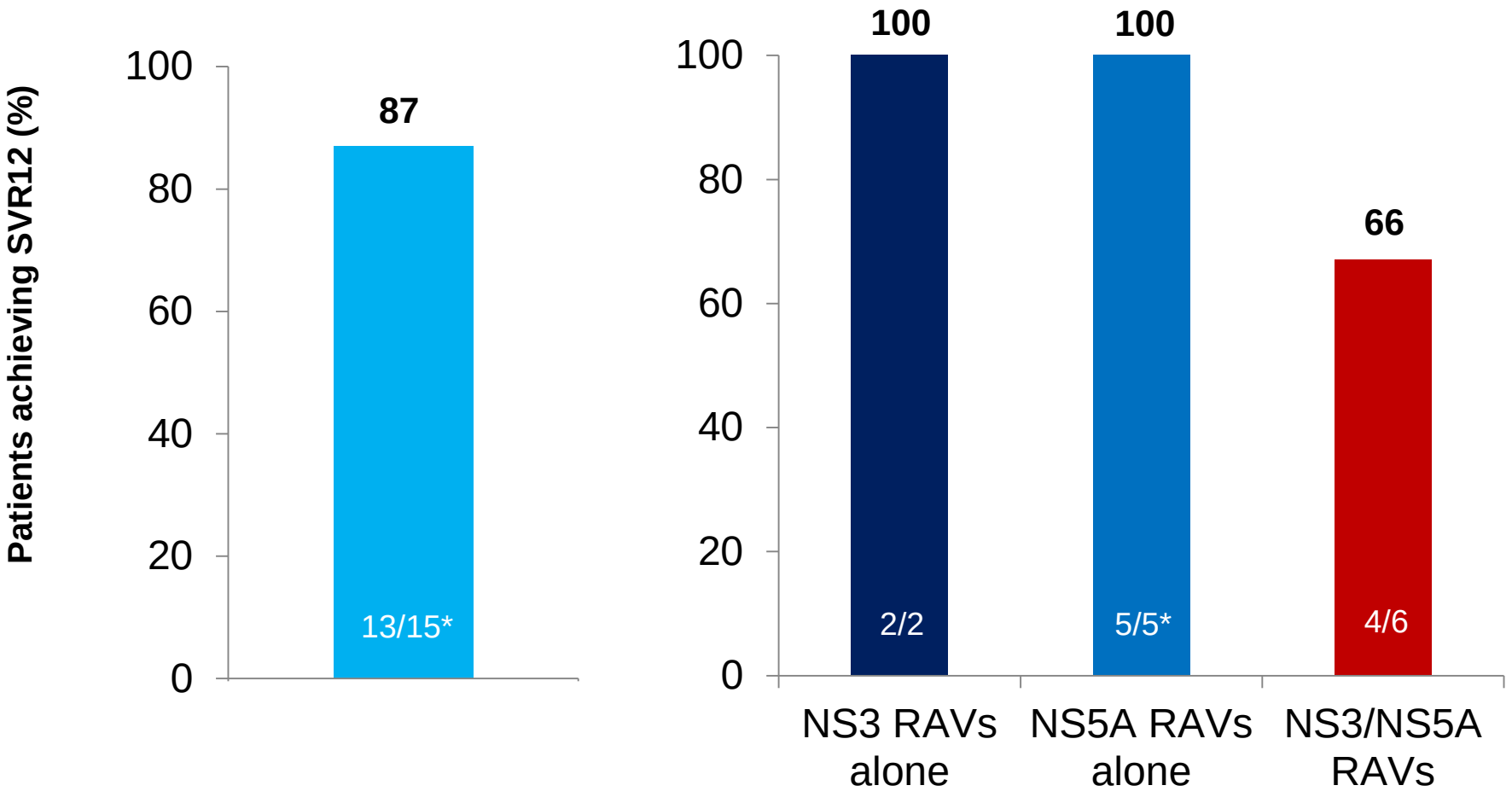
Retreatment of NS5A failures with 12 weeks SMV+SOF according to the presence of NS3 RAVs at baseline



*1 patient does not reach week12 follow-up visit

** NS3 RAVs data not available in 2 patients

Retreatment of NS5A failures with 12 weeks SMV+SOF according to the presence of NS5A/NS3 RAVs at baseline



*1 patient does not reach week12 follow-up visit

NS3 RAVs not available in 2 patients, one with NS5A RAV and one without NS5A RAV

Treatment failure cases (n=2)

Patient	Patient 1	Patient 2
Gender	Female	Male
Age	47	48
Genotype	1a	1a
Cirrhosis	Yes (FS=32.8 kPa)	Yes (FS=14.9 kPa)
Albumin	32	43.5
Platelets	76,000	236,000
Prior treatment	DCV/PR	DCV/ASV/PR
On-treatment response	Slow	Slow
Baseline HCV RNA IU/mL	2,084,631	3,629,157
Baseline NS3 RAVs	R155K	Q80K, V170I
Baseline NS5A RAVs	M28T	L31M

Safety and tolerability

No serious adverse events have been observed

No premature discontinuations have been reported

No grade 3/4 laboratory abnormalities have been observed

Conclusions

- The combination of simeprevir and sofosbuvir was highly effective in this NS5A inhibitor-exposed population
- However, two patients, including one with advanced liver disease and one previously exposed to a PI, failed to achieve SVR
- Our results support the concept of retreating prior NS5A failures with a sofosbuvir plus PI-based regimen
- However, the most difficult to cure patients could benefit from treatment extension beyond 12 weeks and/or the addition of RBV