2014 7th PARIS HEPATITIS CONFERENCE

Organised by Pr Patrick Marcellin

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Patients with cirrhosis

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HCV-related cirrhosis:
a condition with a wide heterogeneity of clinical features

COMPENSATED (very early stage)

Recent, often incidentally, diagnosis by histology (F4 Metavir, F5 to 6 Ishak) or LSM: ≥ 12.5 KPa#, usually with no clinically significant portal hypertension*: HVPG ≥ 6, mmHg < 10 mmHg, no esophageal varices, **Child A5, MELD < 10.** A number of patients may be naive to IFN-based therapy

COMPENSATED (more severe stage)

Older diagnosis obtained by histology in the past or clinically based, with moderate to severe portal hypertension§: HVPG ≥ 10/12 mmHg, ±esophageal varices , PLT ≤ 100000 /mm3, lower albumin value, **Child A6, rarely B7.** In the vast majority of cases these patients experienced IFN-based failure treatment.

DECOMPENSATED

Child B7 or more, MELD >15 and/or

waiting for OLT for ESLD

#Castera L. Gastroenterology 2012
**Garcia Tsao G. et al, Hepatology 2010*
§Qamar A. et al, Hepatology 2008

Boccaccio V, Bruno S. Liver International 2014

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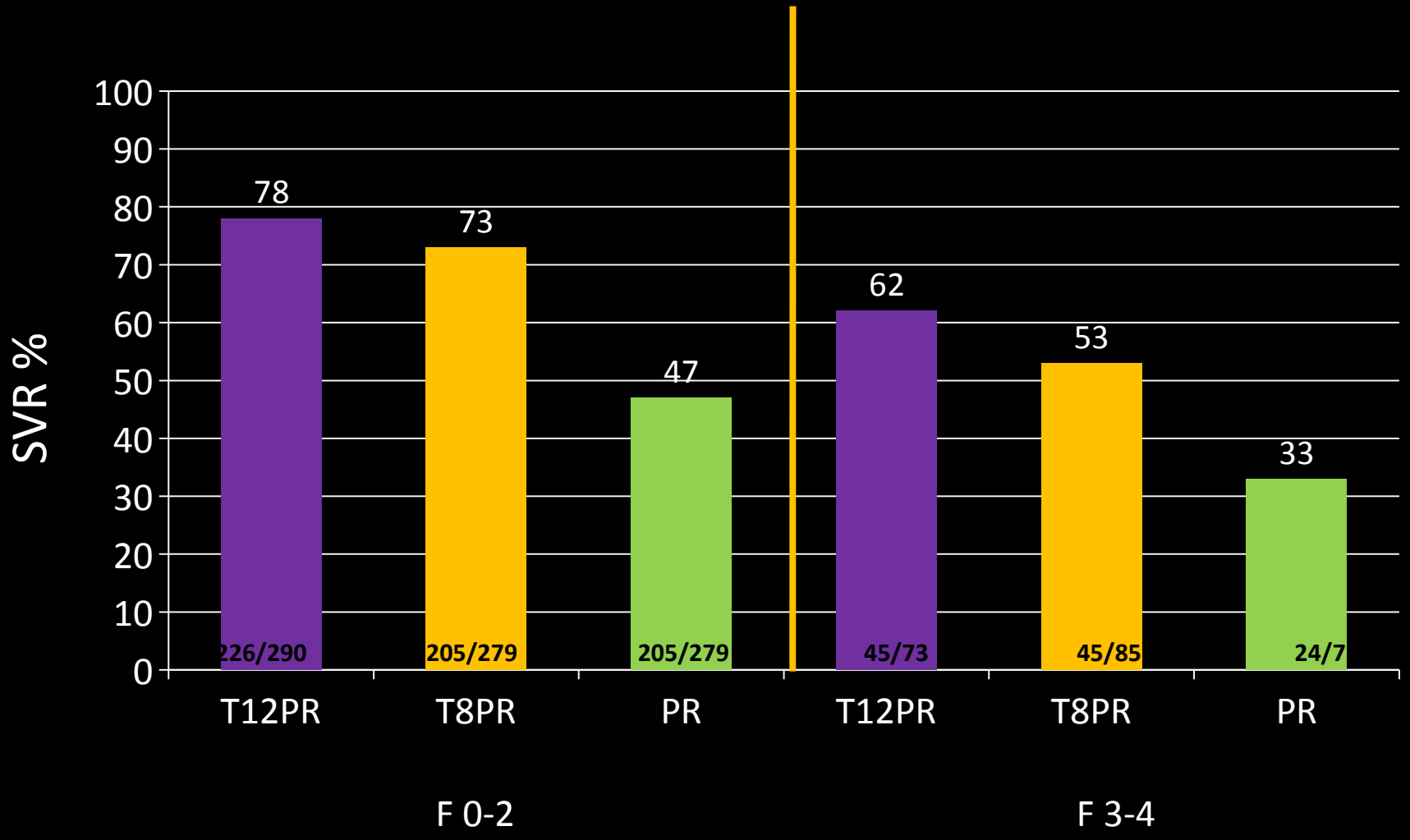
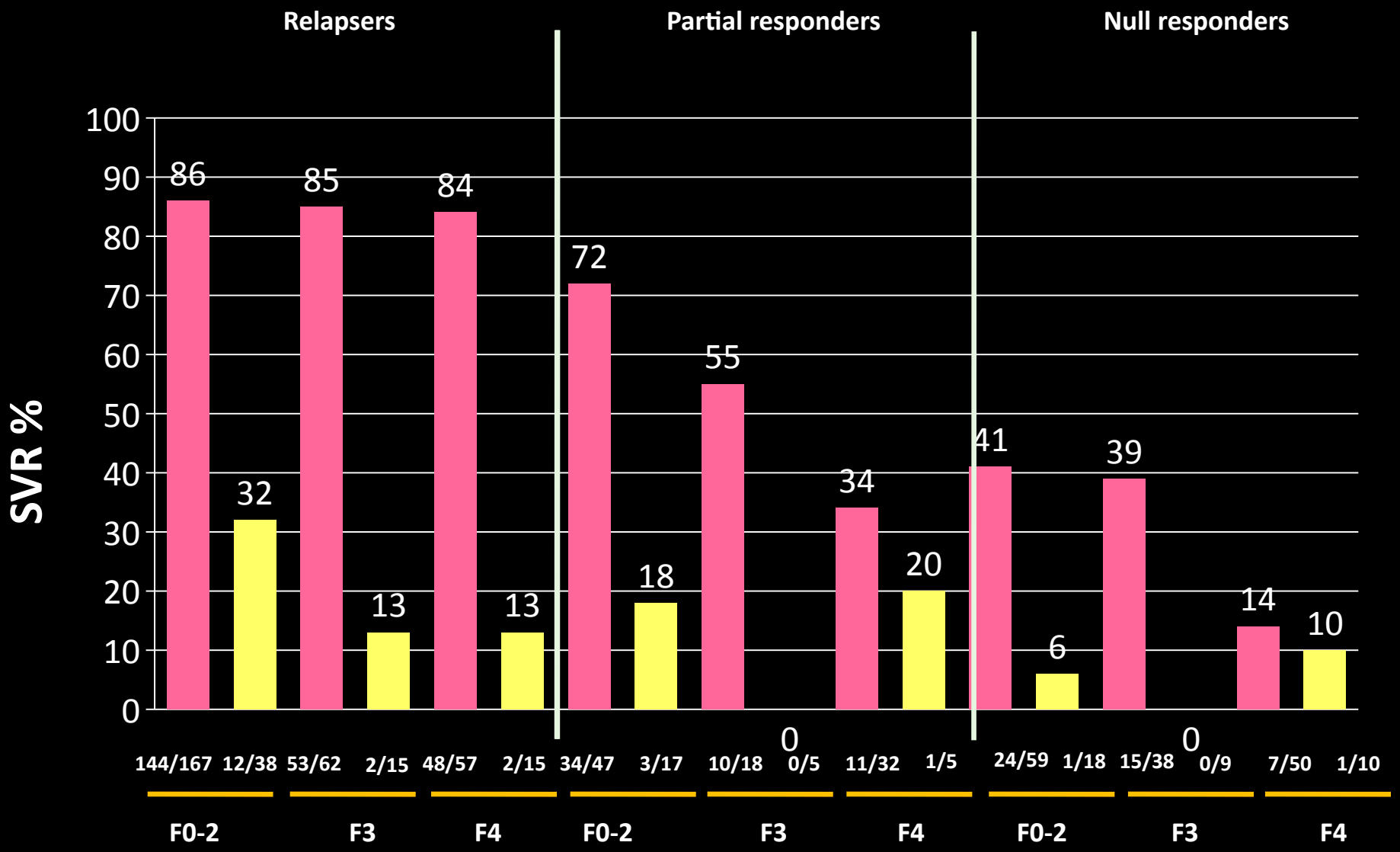
Impact of severe Fibrosis on SVR

Naive genotype 1 patients (ADVANCE)



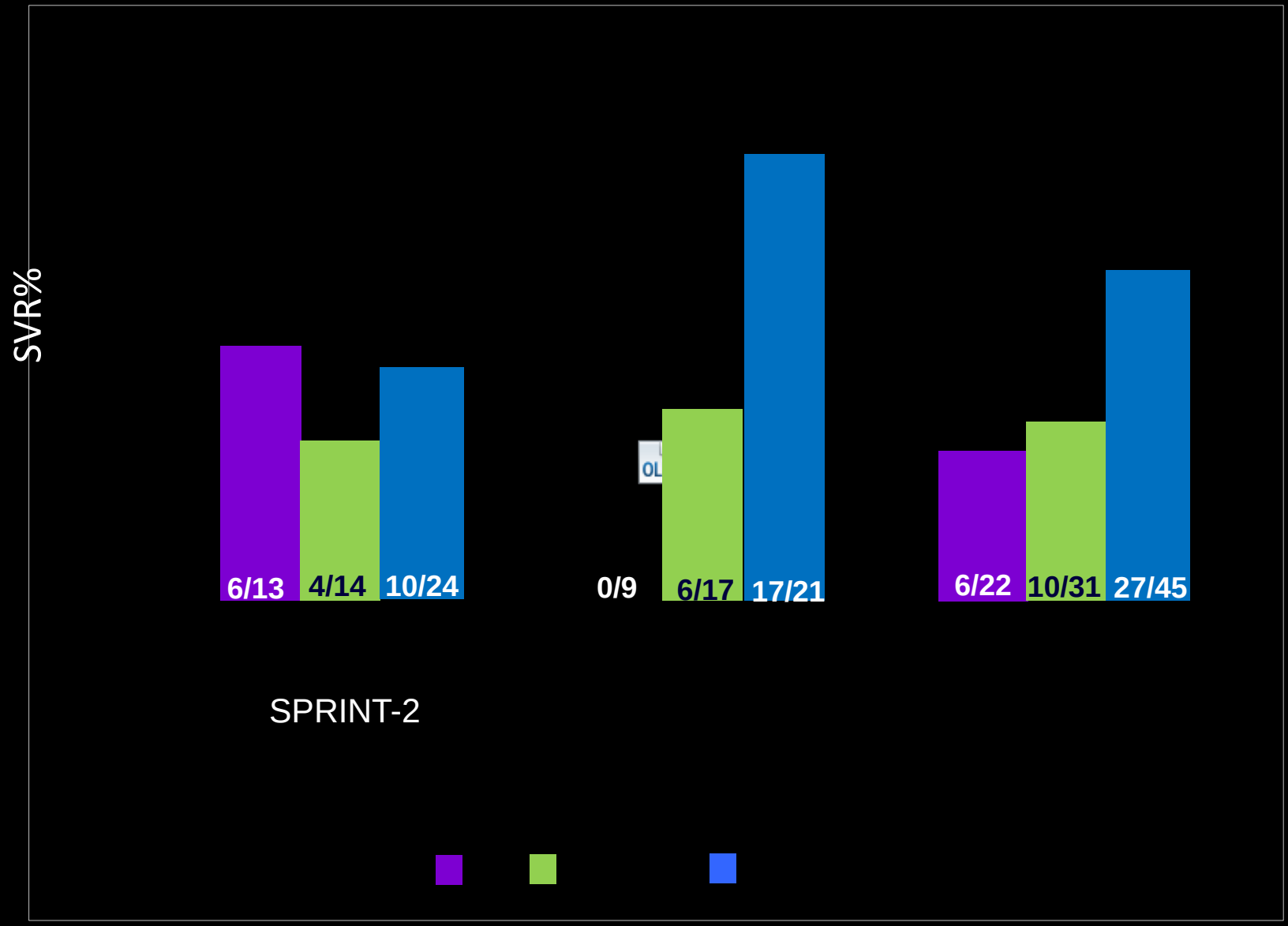
Jacobson IM, et al. Hepatology 2010

SVR according to fibrosis score and historical response in REALIZE study



Zeuzem S, et al. J Hepatol 2011

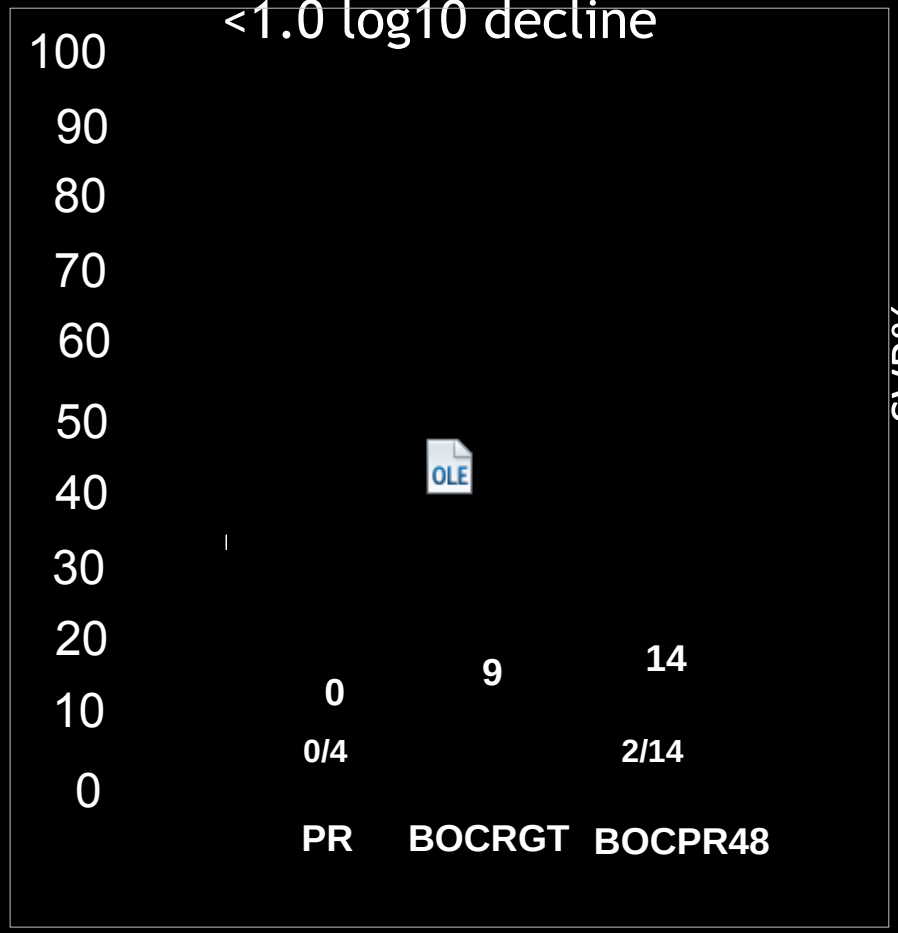
SPRINT-2 and RESPOND-2: Overall SVR by F4

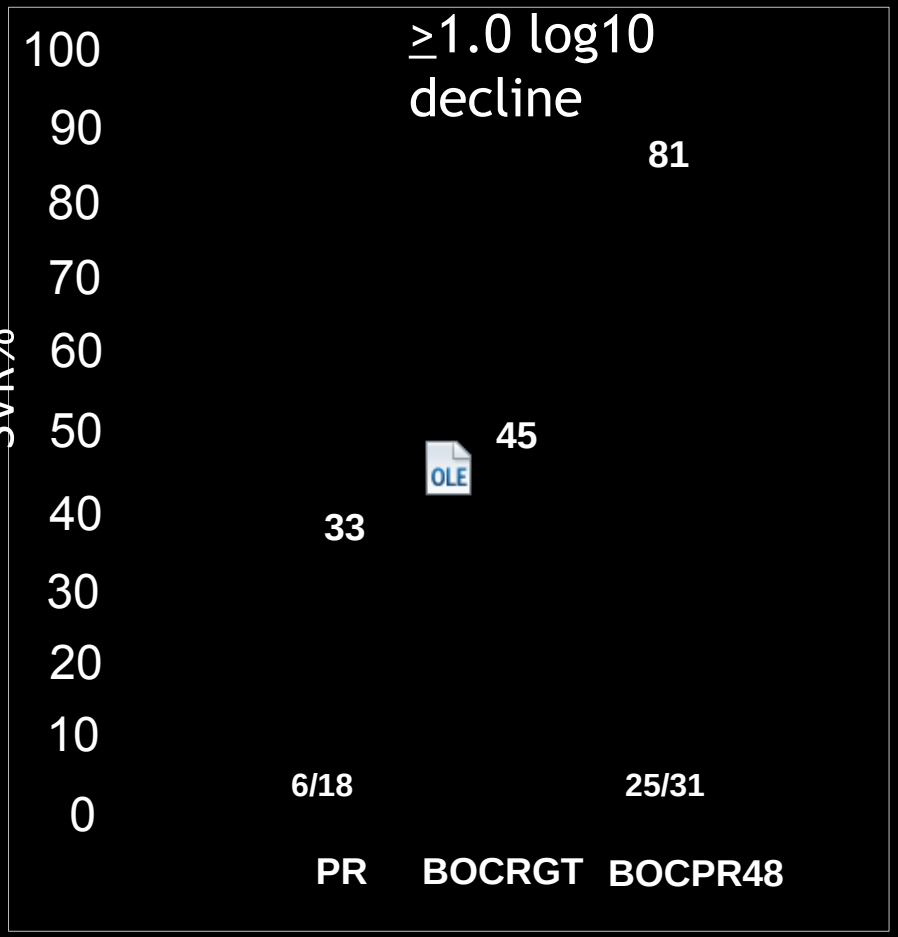


Bruno S, et al. J Hepatol 2013

COMBINED STUDIES (SPRINT-2 and RESPOND-2):

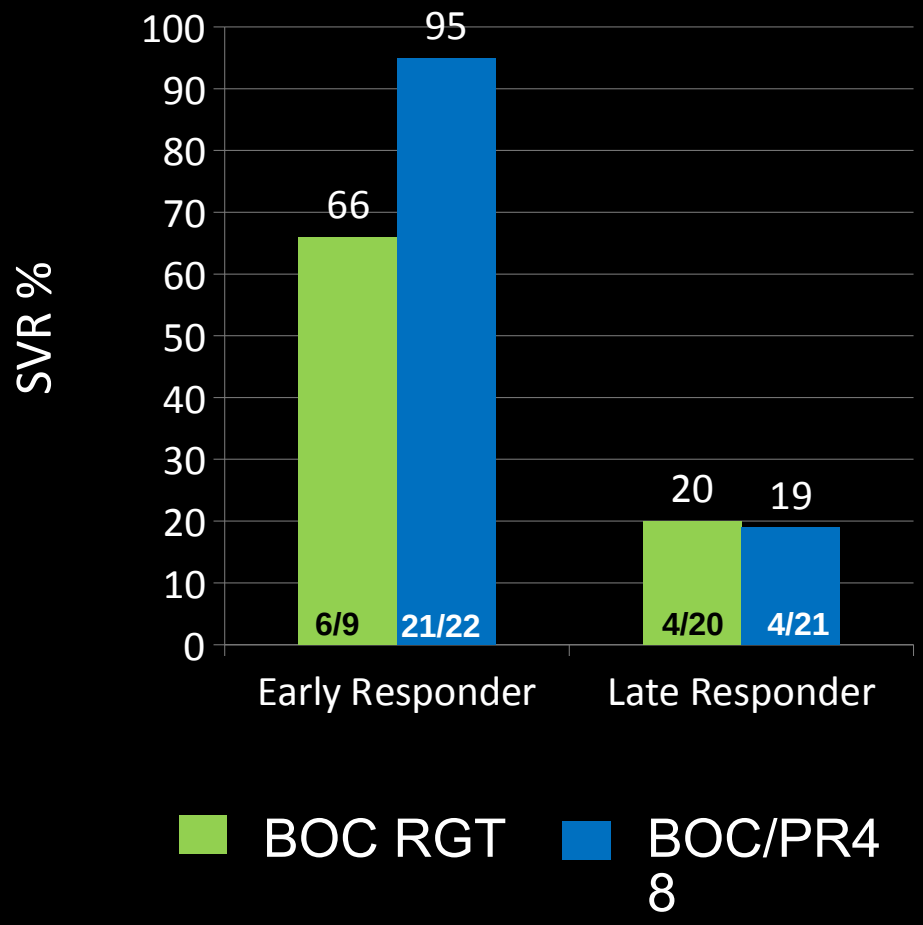
SVR by Week 4 Lead-in Response in F4





Bruno S, et al. J Hepatol 2013

COMBINED STUDIES (SPRINT-2 and RESPOND-2) SVR by Early (TW8 HCV-RNA neg) and Late (TW8 HCV-RNA pos) Responders in F4



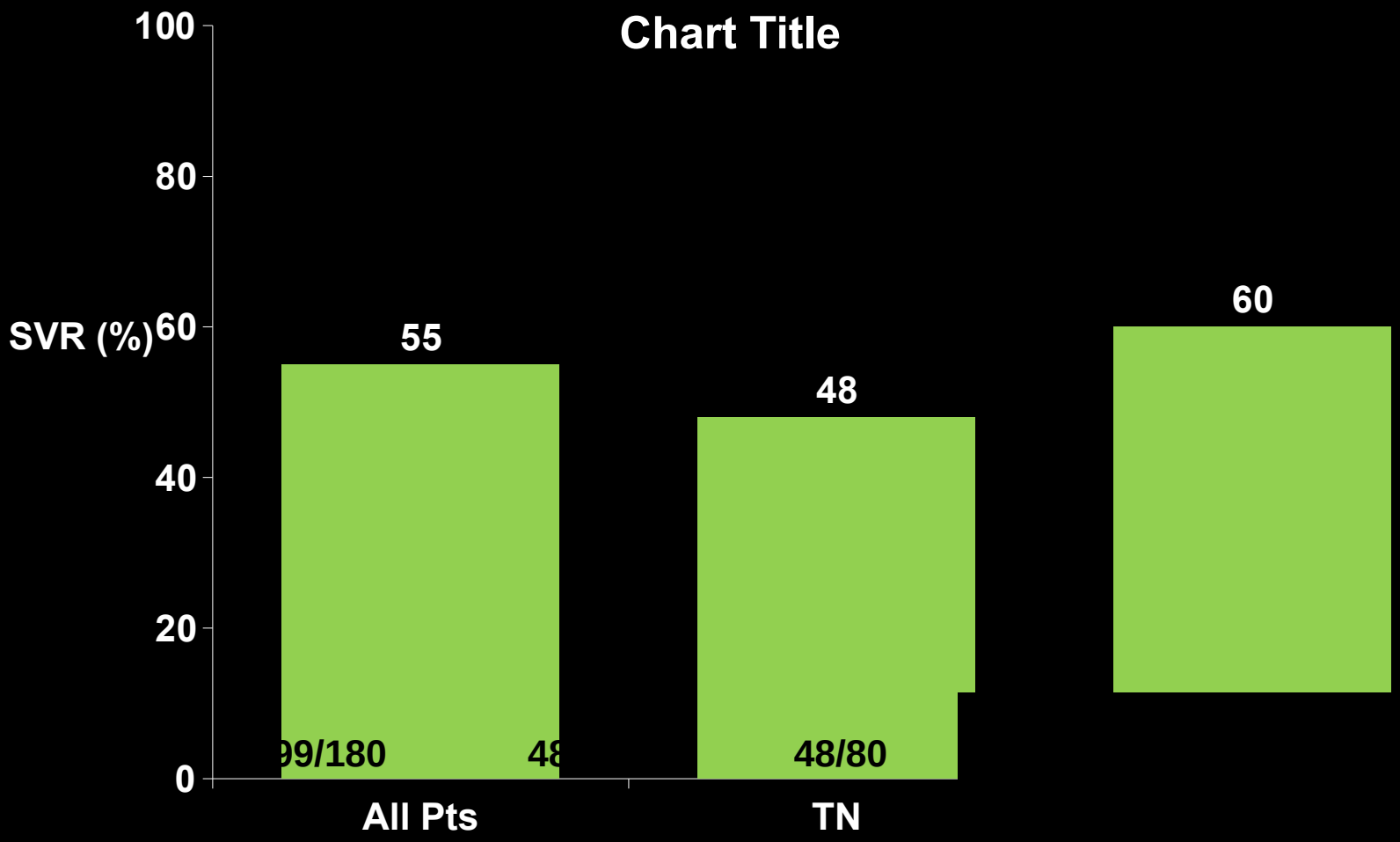
Bruno S, et al. J Hepatol 2013

Meta-Analysis of Cirrhotic Patients in Boceprevir Trials

- Sources of data
  - SPRINT-2
  - RESPOND-2
  - PEGASYS study
  - EPO study
  - Interim data from PROVIDE
- Total of 212 F4 patients (180 on BOC/PR, 32 on PR)
  - Dx by central reading of liver biopsies
- Aims
  - to consolidate results from SPRINT2/RESPOND2 in a larger population of patients
  - to provide predictors of SVR by multiple logistic regression analysis
  - to evaluate risk of severe AE's
  - to develop newer reliable futility which will enable sparing cost and risk of therapy
  - to assess whether short treatment duration (i.e. 36 weeks) might be used in a subset of patients

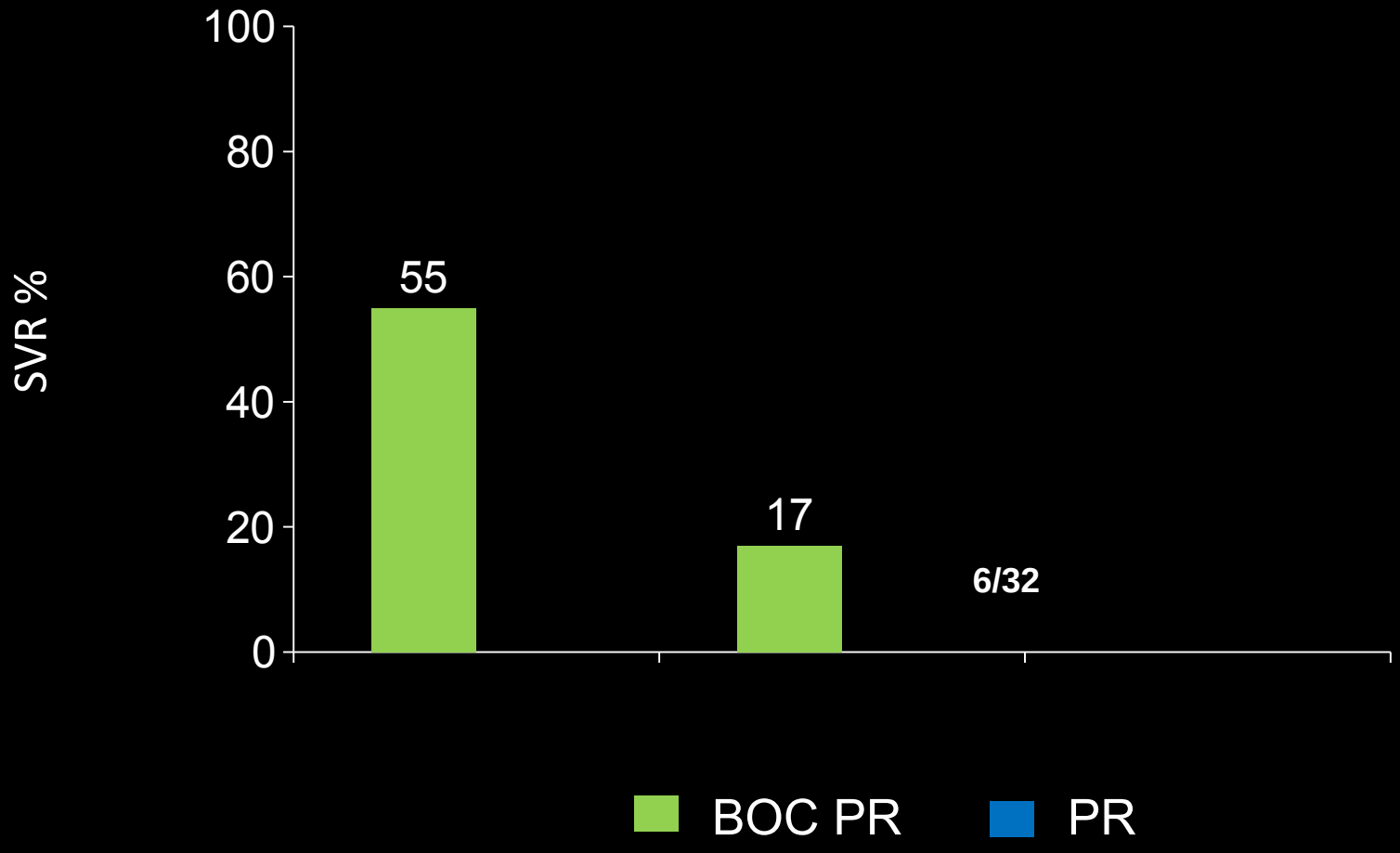
Vierling JM, Bruno S, et al. J Hepatol accepted

Overall SVR by BOC/PR in F4 Patient Subgroups



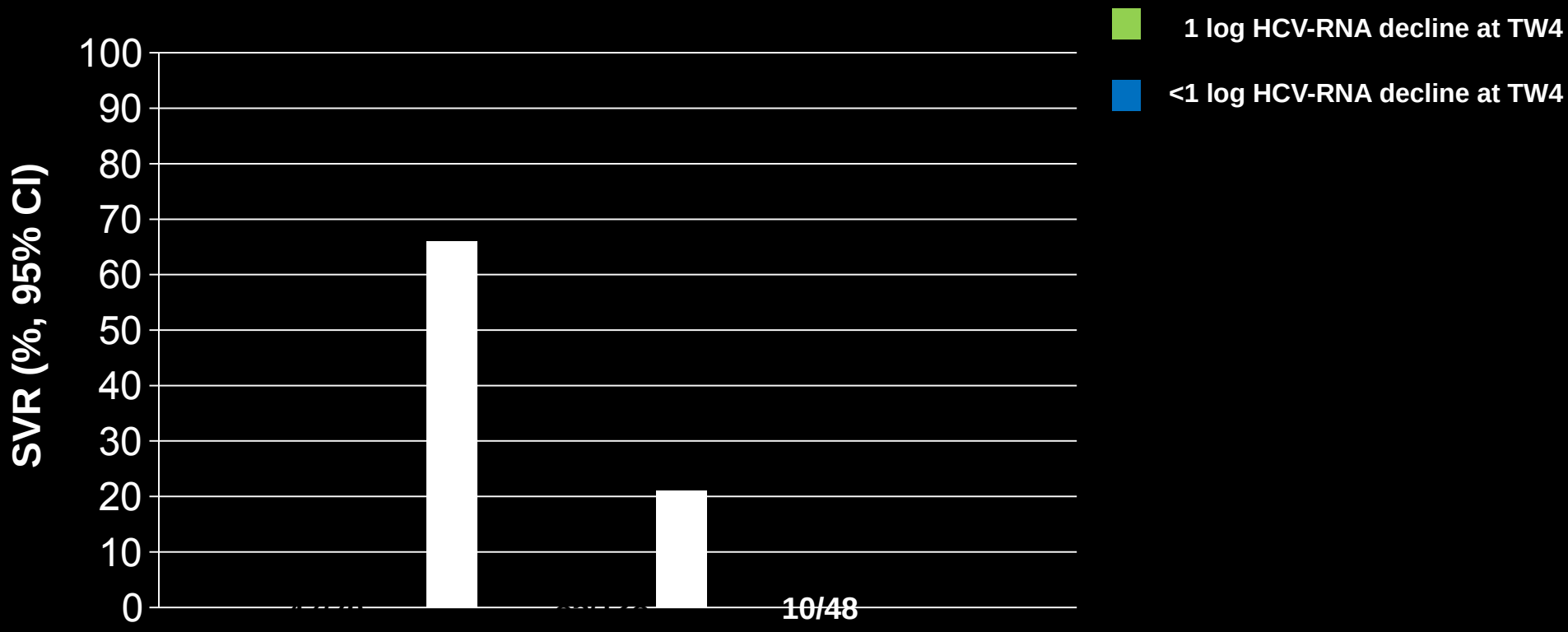
Vierling JM, Bruno S, et al. J Hepatol accepted

Overall SVR by F4



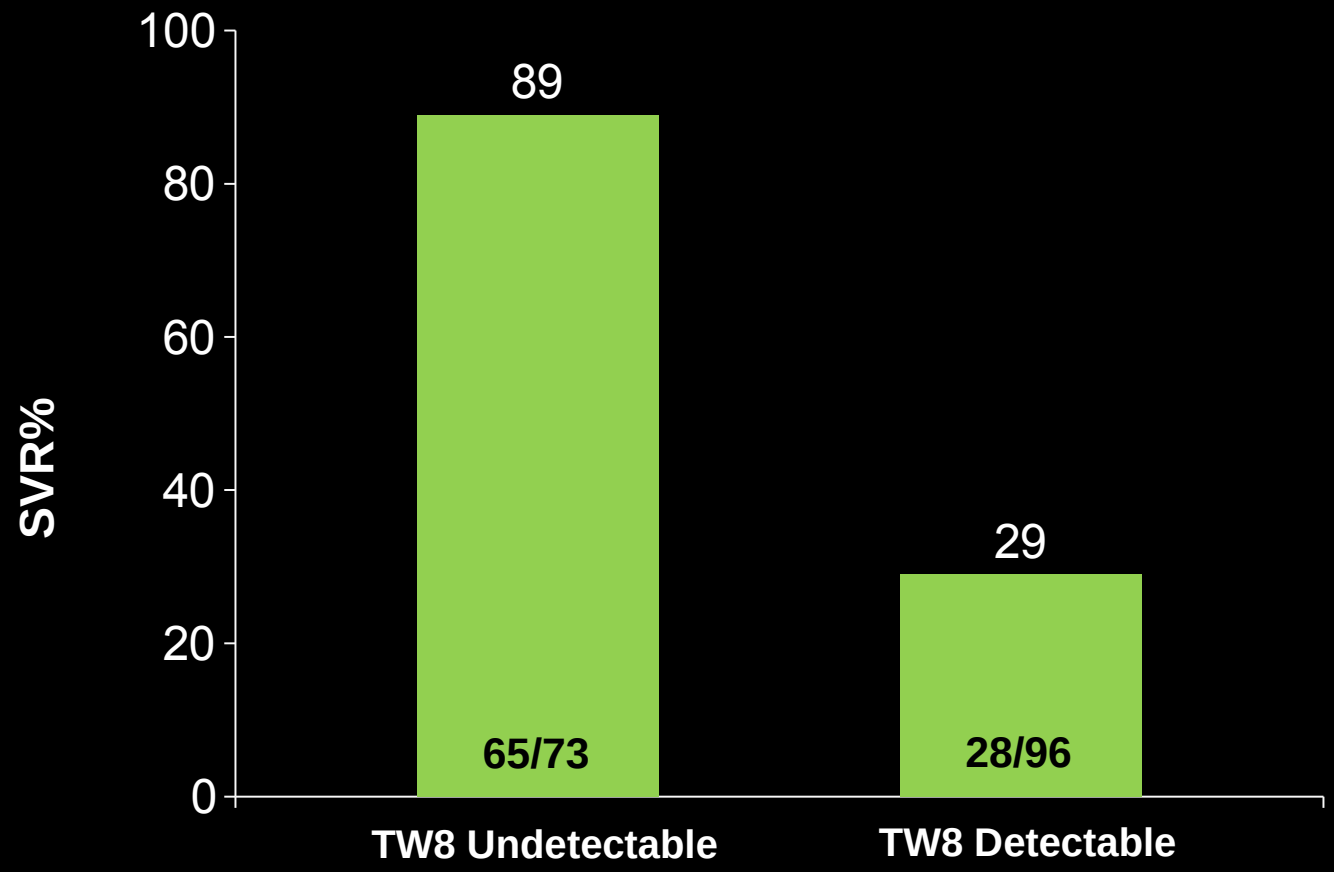
Vierling JM, Bruno S, et al. J Hepatol accepted

SVR according to treatment week 4 virologic response in F4



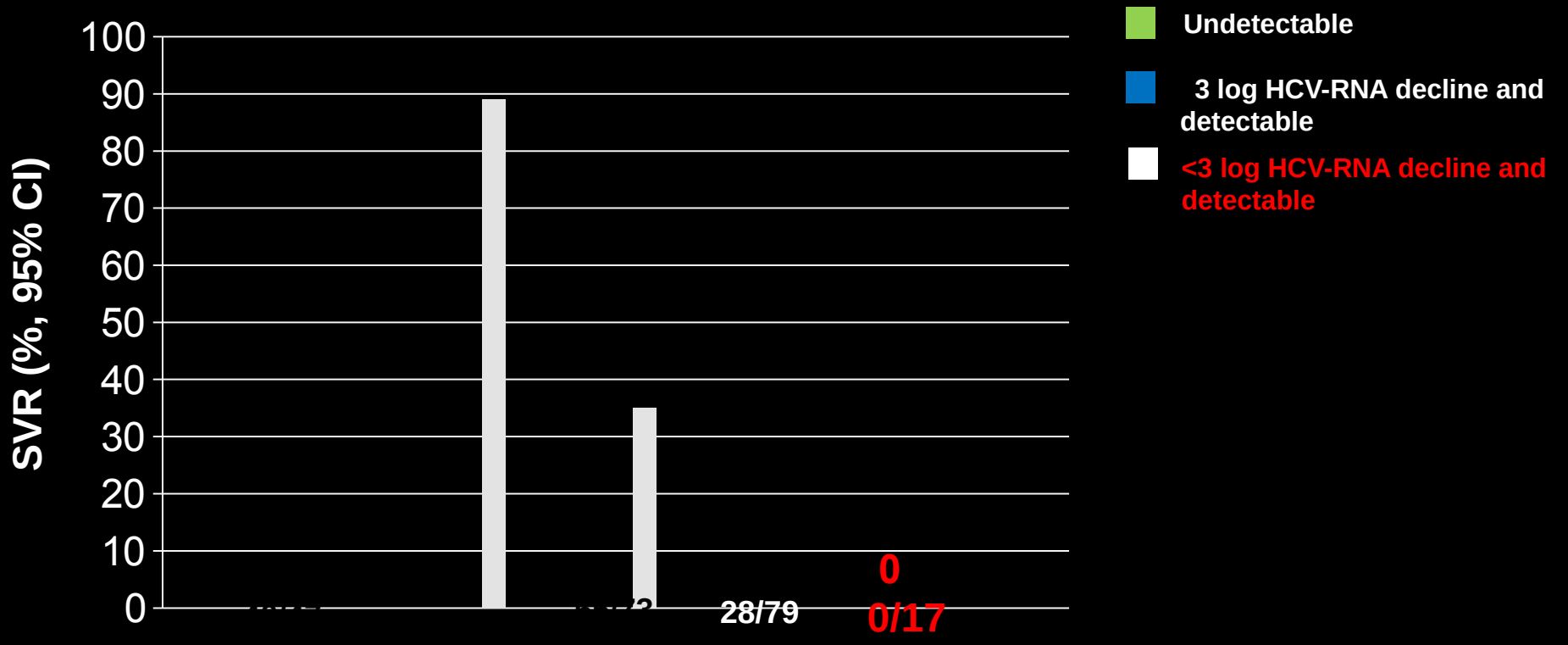
Vierling JM, Bruno S, et al. J Hepatol accepted

Response to BOC/PR in F4 Patients: SVR by TW8 HCV-RNA detectability



Vierling JM, Bruno S, et al. J Hepatol accepted

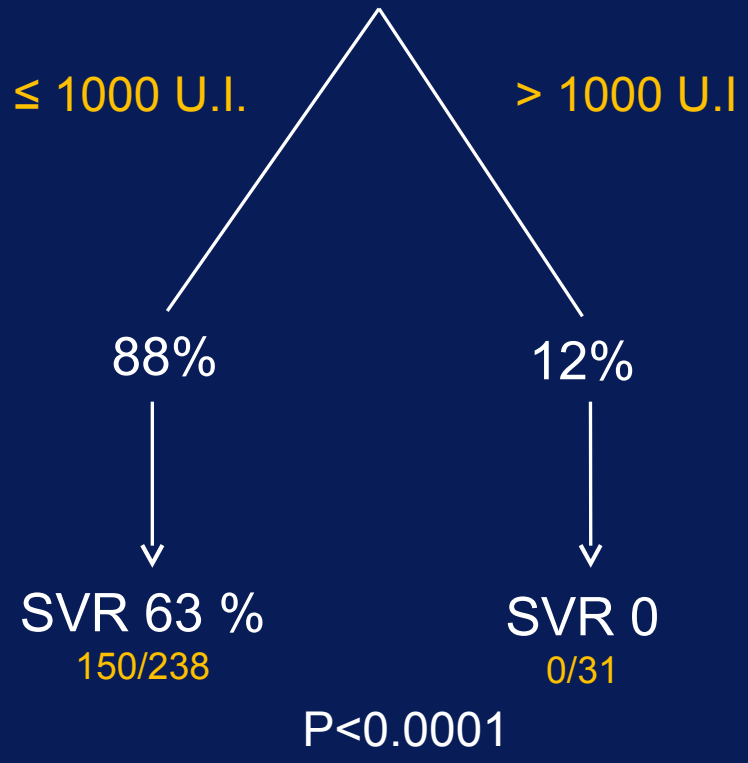
SVR according to treatment week 8 virologic response* in F4



*Treatment-naïve and previous treatment failures combined

Vierling JM, Bruno S, et al. J Hepatol accepted

The importance of TW 8 HCV-RNA decline in patients with advanced fibrosis/cirrhosis during BOC-therapy.



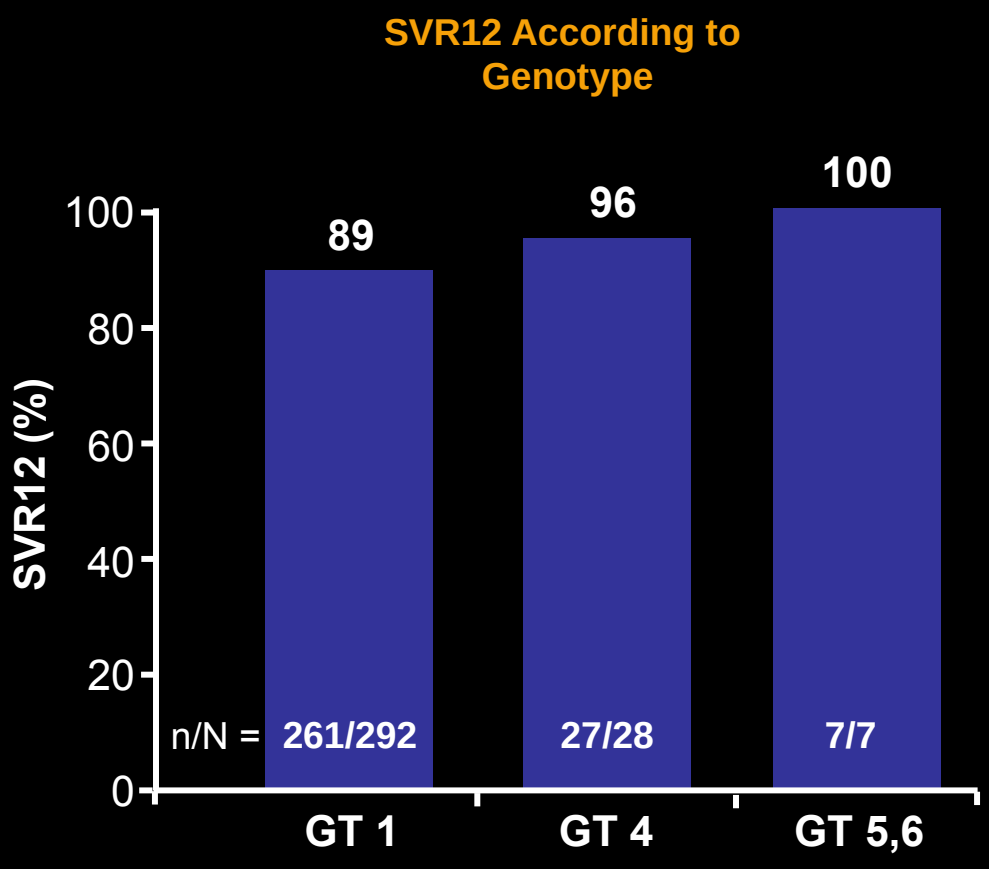
Data on file

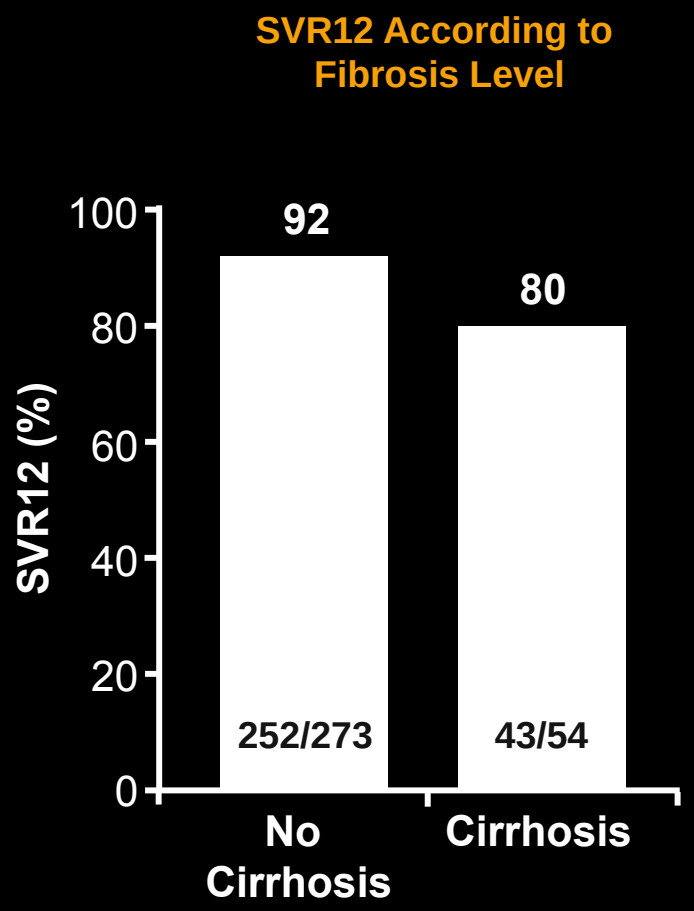
Three Cirrhotic Patients With Potential Hepatic Decompensation or Sepsis

Patient ID (Study)	Baseline Data	Event	Treatment regimen (weeks of treatment)	Outcome
016301 (PROVIDE)	Male, 64 y; F4. hx of ascites Platelets 108K Albumin 3.7 g/L	**Decompensated cirrhosis with ascites and encephalopathy (confusion)**	BOC/P/R (TW 6)	Discontinued treatment; events resolved
012072 (RESPOND-2)	Female, 51 y; F4 Platelets 170K Albumin 3.5 g/L	**Bleeding esophageal varices and portal hypertension**	P/R (TW2)	Discontinued treatment; events resolved
000603 (PEG2a study)	Male, 48 y; F4 Diabetic, IVDU Platelets 135K Albumin 3.8 g/L	**Multi-organ failure with total bilirubin peak 17.4 mg/dL** (*Staph.* pneumonia, resulting in multi-organ failure)	BOC/P/R (TW12)	Died of multi-organ failure

Vierling JM Bruno S, et al. J Hepatol, accepted

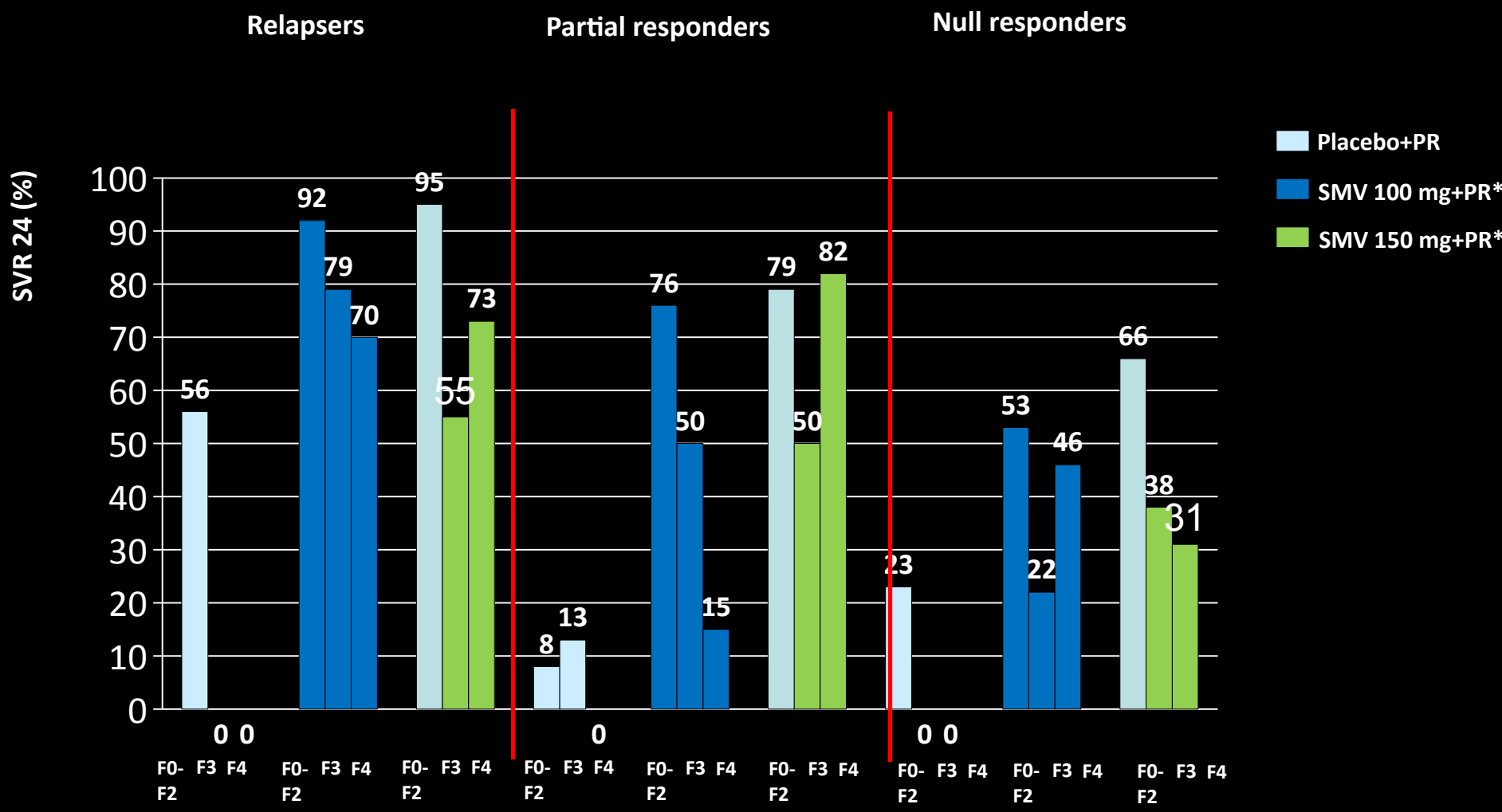
NEUTRINO: SVR12 by Sofosbuvir + P/R (12 weeks) According to Genotype and Fibrosis Level





Lawitz E, et al. NEJM 2013

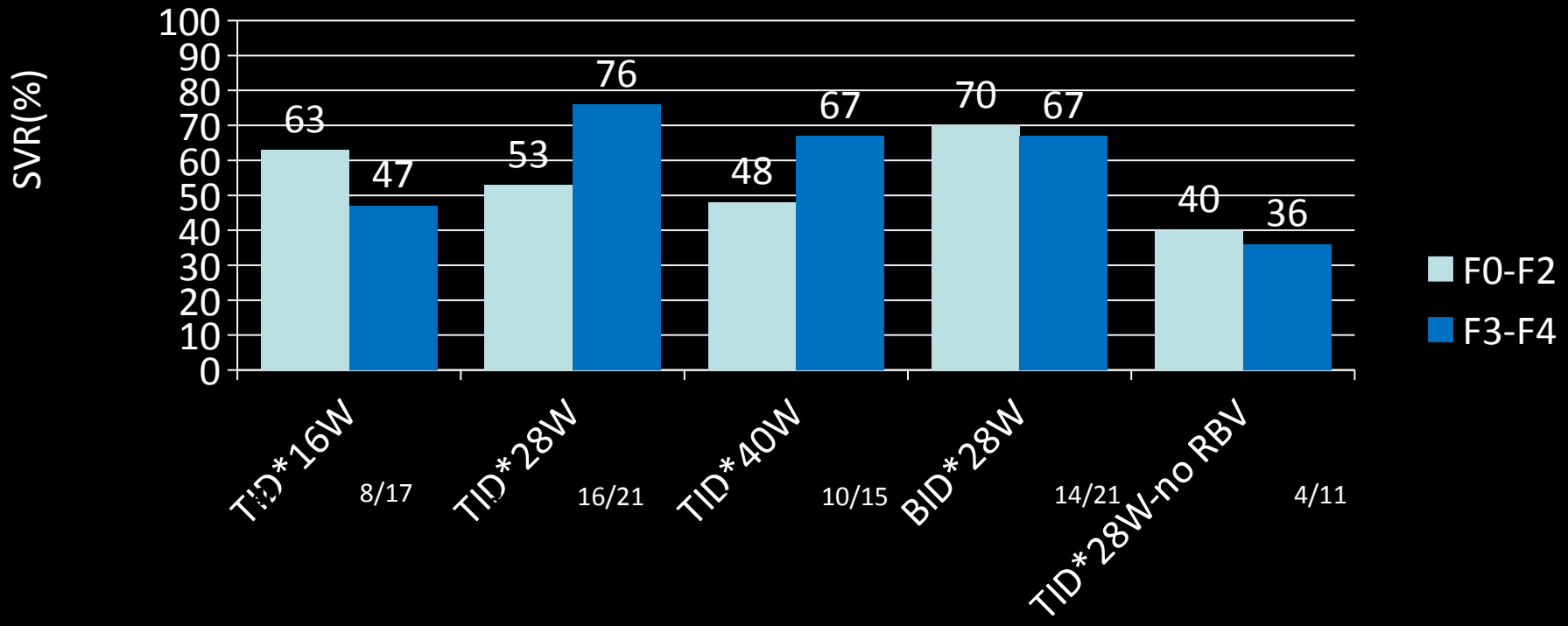
Simeprevir plus PegIFN and Ribavirin in treatment- experienced patients with HCV Genotype-1 infection (the ASPIRE trial)



*duration groups pooled

Zeuzem S, et al. Gastroenterology 2013

SVR by fibrosis stage in G1 naïve patients treated with Faldaprevir, BI207127 and Ribavirin (The SOUND-C2 Study)



* BI207127 600 mg BID or TID

Zeuzem S, et al. NEJM 2013

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Older diagnosis obtained by histology in the past or clinically based, with moderate to severe portal hypertension§: HVPG ≥ 10/12 mmHg, ±esophageal varices , PLT ≤ 100000 /mm3, lower albumin value, **Child A6, rarely B7.** In the vast majority of cases these patients experienced IFN-based failure treatment.

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Boccaccio V, Bruno S. Liver International 2014

CUPIC SVR12 rates and safety (ANRS CO20-CUPIC) - EASL 2013

Undetectable HCV RNA (ITT) n (%)	BOC n = 190	TVR n = 295
Week 12	118(62)	239(81)
Week 24	128(67)	200(68)
Week 48 (EOT)	108(57)	165(56)
SVR12 (Total)	79(41)	118(40)
SVR12 in relapsers	43/85(51)	61/116(53)
SVR12 in partial responders	32/80(40)	43/135(32)
SVR12 in null responders	1/9(11)	8/28(29)
SAE	51.0%	54.2%
Death	1.6%	2.4%
Infections	4.2%	9.1%
Hepatic decompensation	4.7%	5.1%
Anemia <8g/dl or blood tx	10%/13.7%	12.9%/18%

Fontaine H, et al. EASL 2013

Multivariate analysis: baseline predictors of severe complications*

Predictors	OR	95%CI	p-value
Prothrombin Time (per unit decrease)	1.03	1.01-1.06	0.038
Age (per year increase)	1.05	1.01-1.11	0.025
Platelet count ≤100,000/ mm3	3.19	1.32-7.73	0.0098
Albumin level <35 g/L	4.95	2.04-12.01	0.0004

*** Death, severe infection and hepatic decompensation, n=32**

Hézode C, et al. J Hepatol 2013

CUPIC: Risk of Occurrence of Death or Severe Complications

Factors	Platelets count >100,000/mm3	Platelets count ≤100,000/mm3
Albumin 35 g/L	**3.4 % (10/298)**	4.3 % (3/69)
Albumin <35 g/L	7.1 % (2/28)	**44.1 % (15/34)**

Hezode C, et al. J Hepatol 2013

Safety and efficacy of triple therapy with boceprevir in treatment-experienced patients with advanced fibrosis and cirrhosis: the Italian Spanish NPP Study

- **Primary objective**

  SVR24

  Overall safety

  - **Interim analysis**

  SVR12

  Safety and tolerability

Baseline patient characteristics

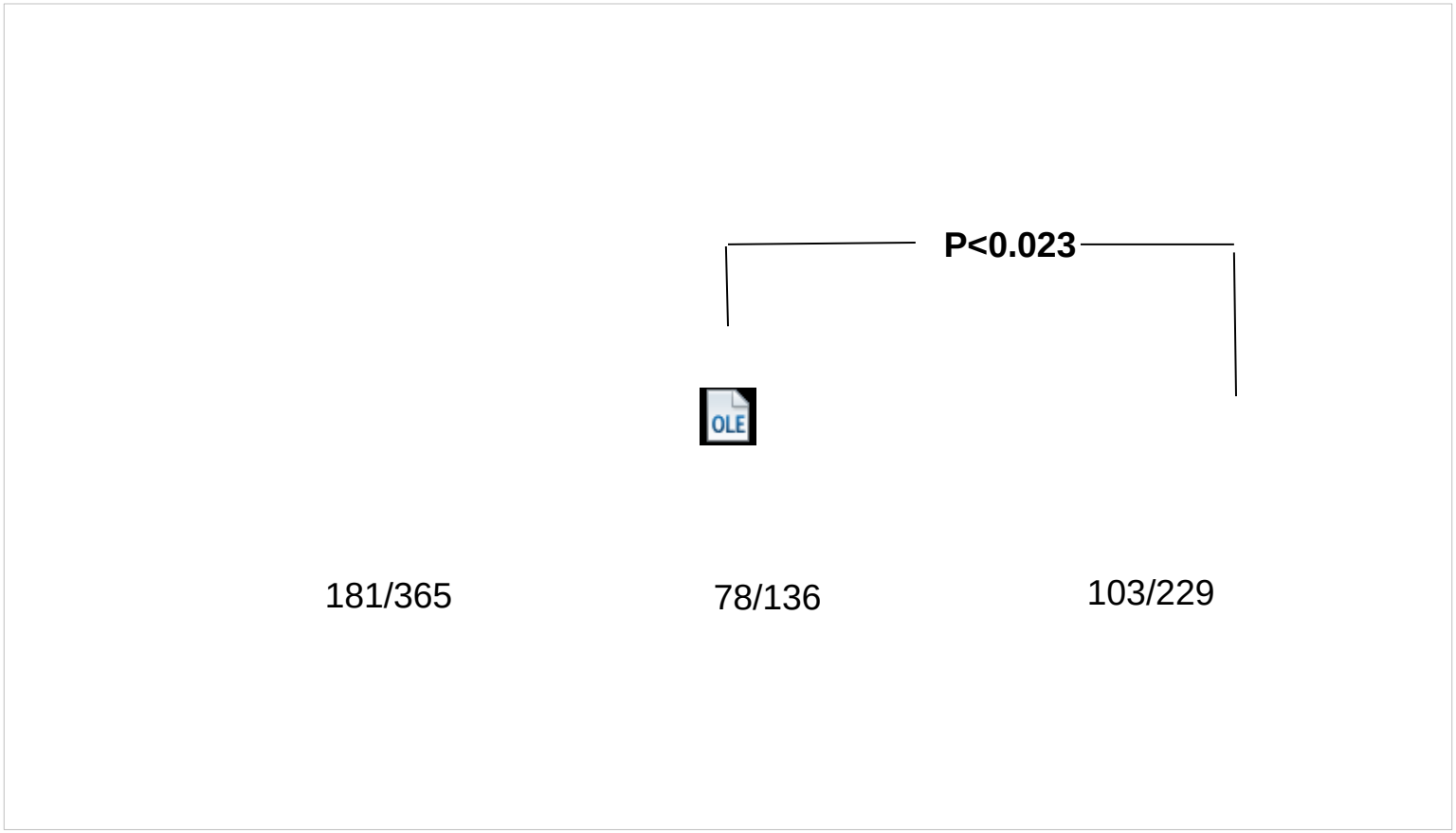
Characteristics	N = 402, n (%)
Male	221 (54.9)
Mean age, years (range)	55 (22 to 75)
HCV genotype 1 subtype	
1a	84 (20.9)
1b	316 (78.6)
Unclassified	2 (0.5)
HCV-RNA ≥ 800.000 IU/mL	280 (69.6)
Prior Relapse	137 (34.1)
Prior Partial response	95 (23.6)
Prior Null response	168 (41.8)
Not defined	2 (0.5)
METAVIR score	
F3	147 (36.6)
F4	255 (63.4)
Esophageal varices available in: 195 (76.5%) F4 pts	
No	134 (68.7)
F1	59 (30.3)
F2	1 (0.5)
F3	0 (0.0)
Gastric varices	1 (0.5)

Baseline patient characteristics (2)

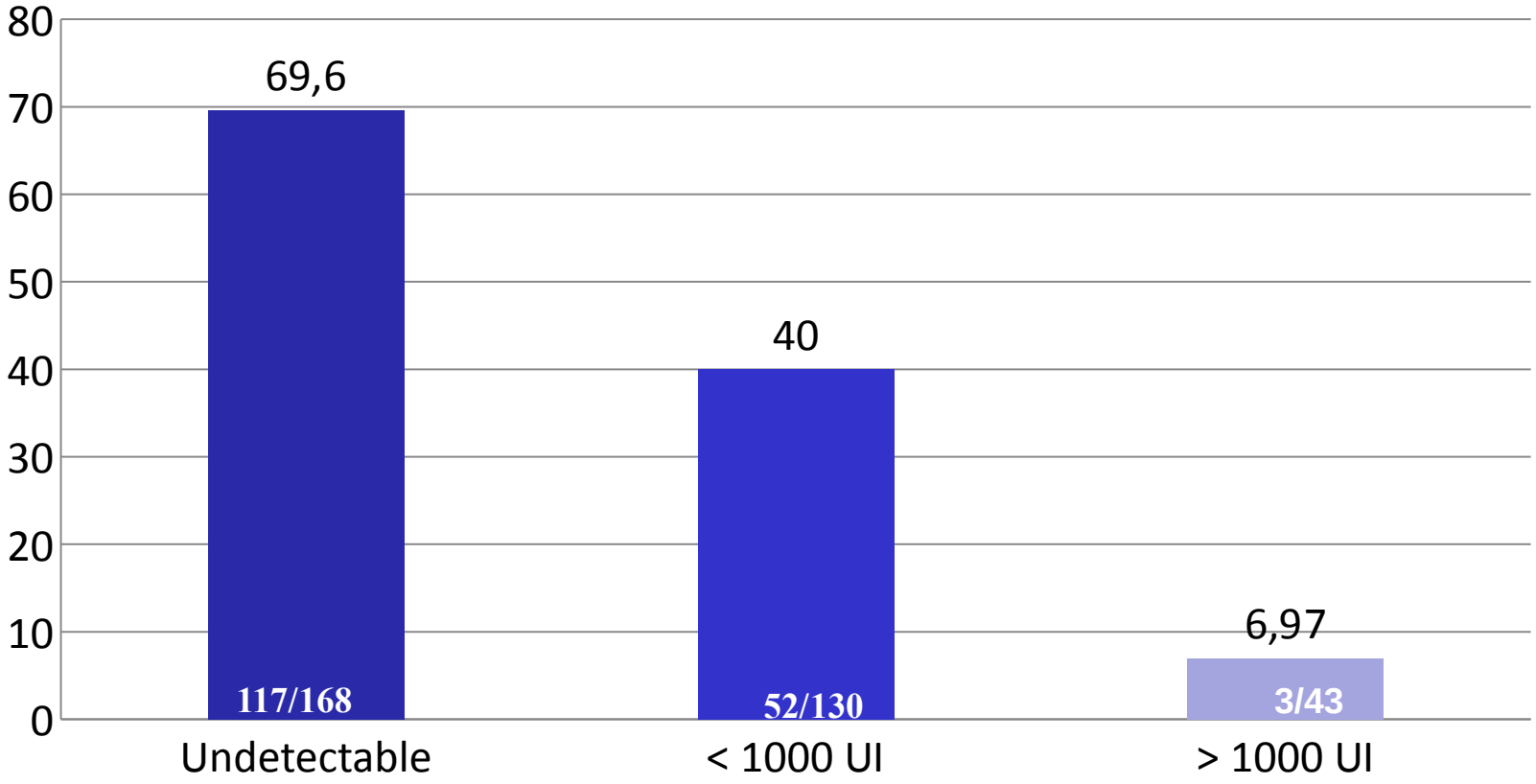
Characteristics	N = 402
Hb level g/dL, mean (range)	15.1 (10.0 – 18.0)
Neutrophils 106/mm3, mean (range)	3.3 (0.8 – 9.8)
Platelet count 109/mm3, mean (range)	166 (45 – 820)
Prothrombin time INR, mean (range)	1.04 (0.84 – 1.90)
Serum albumin g/dL, mean (range)	4.08 (2.98 – 5.30)
Total bilirubin mg/dL , mean (range)	0.89 (0.15 – 3.80)

Characteristics	N = 402 n (%)
PLT < 100.000/mm3	49 (12.2%)
Albumin < 3.5 g/dl	22 (6.3%)
Combined PLT < 100.000/mm3 and Albumin < 3.5 g/dl	7 (2.0%)

SVR12 rates by ITT Analysis:
all patients assuming at least 1 dose of BOC included
(N= 365)



Overall SVR12 according to treatment week 8 virologic response



Multivariate logistic regression analysis
Predictors of **Treatment Failure** (NO SVR)
in 369 F3/F4 patients receiving BOC

ITT SVR12 and NNT in patients receiving at least one BOC dose according to at-entry characteristics, fibrosis stage, historical response and TW8 HCVRNA value

	All Patients		Metavir F3		Metavir F4	
Strata	**SVR12 N (%)**	**NNT**	**SVR12 N (%)**	**NNT**	**SVR12 N (%)**	**NNT**
Overall	180/369 (48.8)	2.1	77/139 (55.4)	1.8	103/230 (44.8)	2.2
Prior Relapser	79/130 (60.8)	1.6	29/48 (60.4)	1.7	50/82 (61.0)	1.6
Prior Partial	44/89 (49.4)	2.0	22/38 (57.9)	1.7	22/51 (43.1)	2.3
Prior Null	56/148 (37.8)	2.6	25/52 (48.1)	2.1	31/96 (32.3)	3.1
TW8 HCV-RNA undetectable	117/168 (69.6)	1.4	55/75 (73.3)	1.4	62/93 (66.7)	1.5
TW8 detectable <1000 IU/ml	52/130 (40.0)	2.5	19/42 (45.2)	2.2	33/88 (37.5)	2.7
TW8 detectable >1000 IU/ml	3/43 (7.0)	14.3	0/12 (0.0)	-	3/31 (9.7)	10.3

Safety profile

Adverse event	N (%) at anytime during TW4-TW48
Death	2 (0.5) 1 at TW6 and 1 at TW28
Sepsis, MOF	2 (0.5)
Infections	43 (10.7)
Hepatic decompensation	13 (3.2)
Anemia Grade 2-3 (8,5 < Hb < 10 g/dL) Grade 4 (Hb < 8,5 g/dL)	 139 (34.6) 41 (10.2)
Neutropenia Grade 3 (500 < N < 750) Grade 4 (N < 500)	 91 (22.6) 50 (12.4)
Thrombocytopaenia Grade 3 (25000< PLT< 50000) Grade 4 (PLT< 25000)	 23 (5.7) 2 (0.5)
Cutaneous AE	68 (16.9)
Cardiovascolar AE	7 (1.7)
Gastrointestinal Disorders	64 (15.9)
EPO	159 (39.5)
Transfusion	31 (7.7)

HEP3006: Predictive Model of a Sustained Virological Response (SVR24) in 995 Patients

Factor	Achieved SVR24 (n/N, %)*	P-value
AFP		
<10 µg/L	423/630 (67%)	
≥10 µg/L	146/365 (40%)	<.0001
Fibrosis		
Bridging fibrosis (F3)	332/507 (65%)	
Cirrhosis (F4)	237/488 (49%)	<.0001
Genotype		
1b	446/735 (61%)	
1a/other	123/260 (47%)	0.0002
Prior response		
Any other than null	477/716 (67%)	
Null response	92/279 (33%)	<.0001

Colombo M, et al. submitted

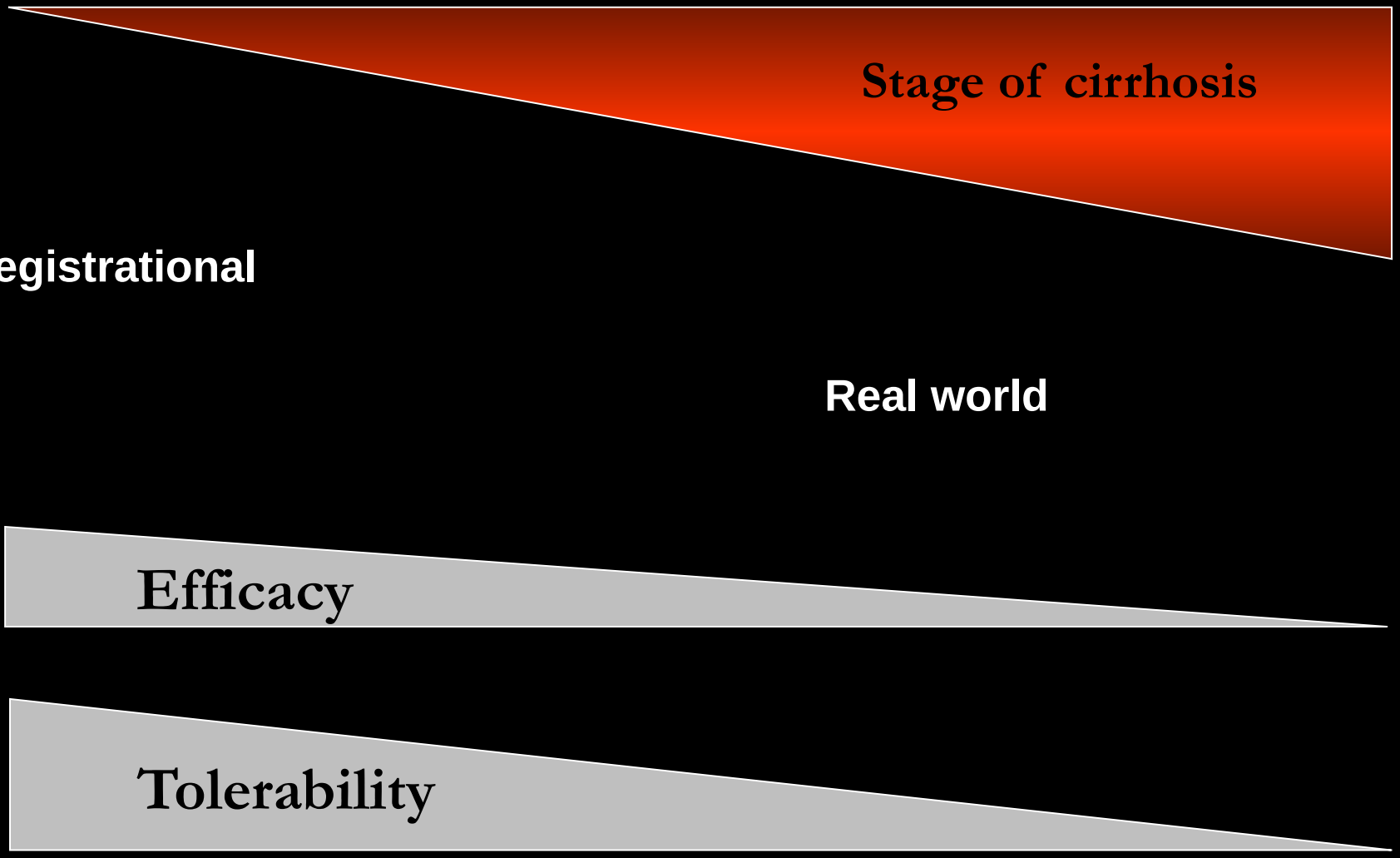
HEP3002 Wk 16: Adverse Events with Fatal Outcome

Patients, n	7 (0.4%)
M/F	5/2
Metavir F3/F4	1/6
Rate of death after TVR d/c, wk	2-30 (4)
Infection, n	4
Hepatic failure, n	2
Variceal bleeding, n	1

Colombo M, et al. Gut in press

First generation DAA,s in cirrhotic patients:

More severe the stage, lower the efficacy and the tolerability



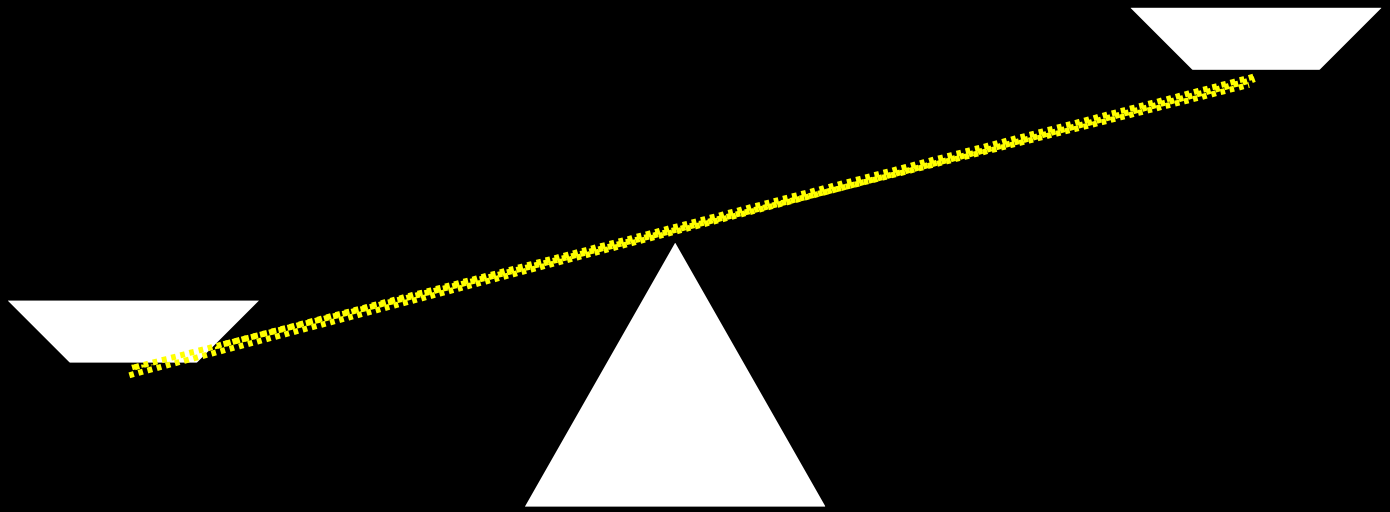
Treating vs Deferring Therapy in patients with “early” stage compensated cirrhosis

Treat

- Overall SVR rates acceptable
- Safety prof le manageable
- Still many patients already “warehoused” awaiting DAAs
- Emerging futility rule permitting to early identify the likelihood of response enhances the assessment of Risk-Cost/Benef t

Defer

- Short-term prognosis still favorable



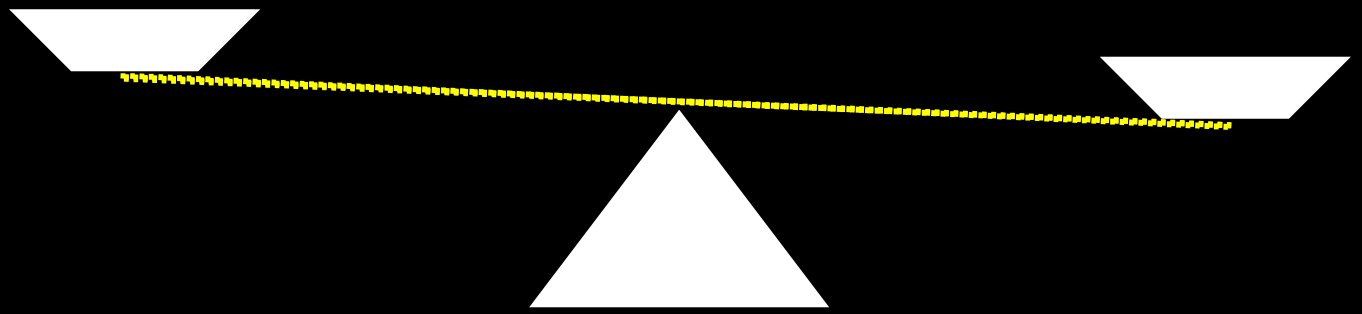
Treating vs Deferring Therapy in compensated Cirrhotic patients with moderate to severe portal hypertension

Treat

- Short-term prognosis worrying
- Overall SVR rates acceptable in a subset of patients
- Will the cost of “around-the-corner” 2nd generation treatment be affordable by Health Care Systems?
- Baseline characteristics of single individual and emerging early futility rule might enhance the assessment of Risk-Cost/Benef t

Defer

- Safety prof le concerns
- Risk vs benef t questionable in Nulls
- Potential for better treatment, with higher response rates fewer adverse events, shorter duration soon available either by EAP program or by compassionate use



Lesson from IFN-based tx + first generation DAA's studies: the importance of futility rules

- Futility rules for HCV treatments define thresholds for virologic response without which SVR is very unlikely to occur
- Stopping treatment for futility limits adverse events, cost, and the risk of resistance
- *"The earlier is the futility the higher is the benefit"*

Thank you for your attention!

The opinions expressed here represent the opinion of the author. All products mentioned in the presentation should be applied according to the Product Labels.

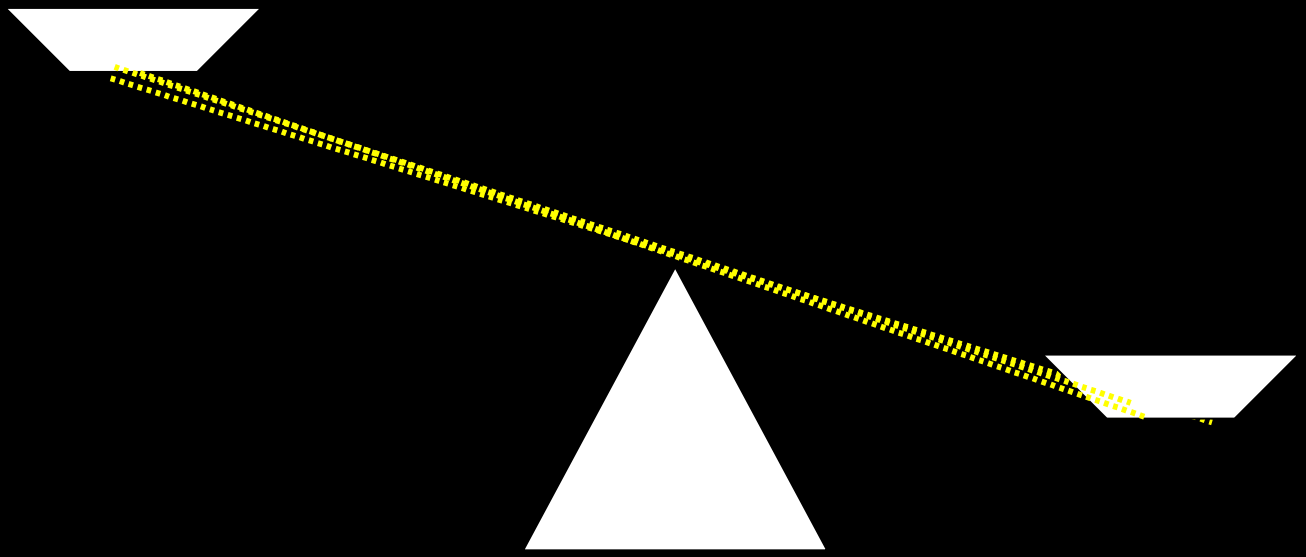
Treating vs Deferring Therapy in decompensated or waited for OLT Cirrhotic patients

Treat

- Short-term prognosis extremely poor

Defer

- SVR rates unknown, risk vs benef t questionable
- Better treatment options, with higher response rates, fewer adverse events, shorter duration soon available by compassionate use



Triple therapy for HCV infection in patients with compensated liver cirrhosis: lessons learned from the first real-world experience

- n=48 cirrhotic pts, 31% naïve, platelets 144/nl
- 50% anemia <10g/dl, 27<8.5g/dl, dose reduction in 50%
- TVR 33 (69%), BOC 15 (31%)

	Group A Platelets <110/nl and Child-Pugh Score >5 n=7	**Group B** Platelets <110/nl or Child-Pugh Score >5 n=16	**Group C** Platelets ≥110/nl and Child-Pugh Score 5 n=20#
Treatment Failure	100% (n=7/7)	69% (n=11/16)	30% (n=6/14)
SAE	57% (n=4/7)	63% (n=10/16)	25% (n=5/20)
Either SAE or Treatment Failure	100%	94%	50%

- **Almost every patient (96%; n=22/23) with a Child-Pugh Score >5 and/or baseline platelets <110/nl (Group A/B) experienced either a treatment failure and or at least one SAE until EOT**

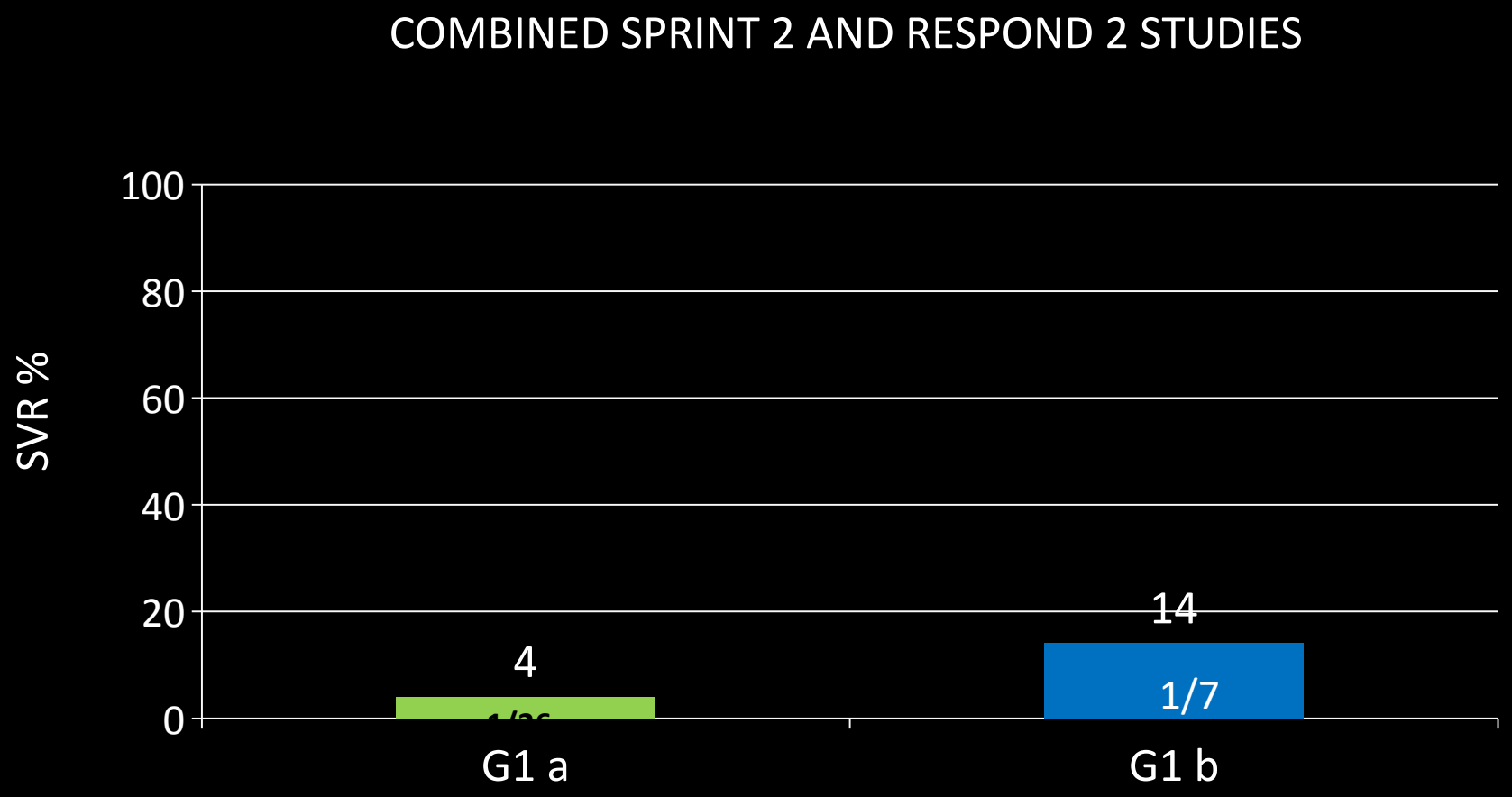
Massoumy B, et al. PLoS One 2013

LAST BUT NOT LEAST

Because F3 and F4 (mainly treatment-naïve) patients treated with BOC with undetectable viral load at treatment week 8 achieved similar SVR rates with durations of treatment between 28 and 40 weeks compared to ≥40 weeks, ***therapy of these subjects might be stopped after week 28 if the regimen is poorly tolerated***

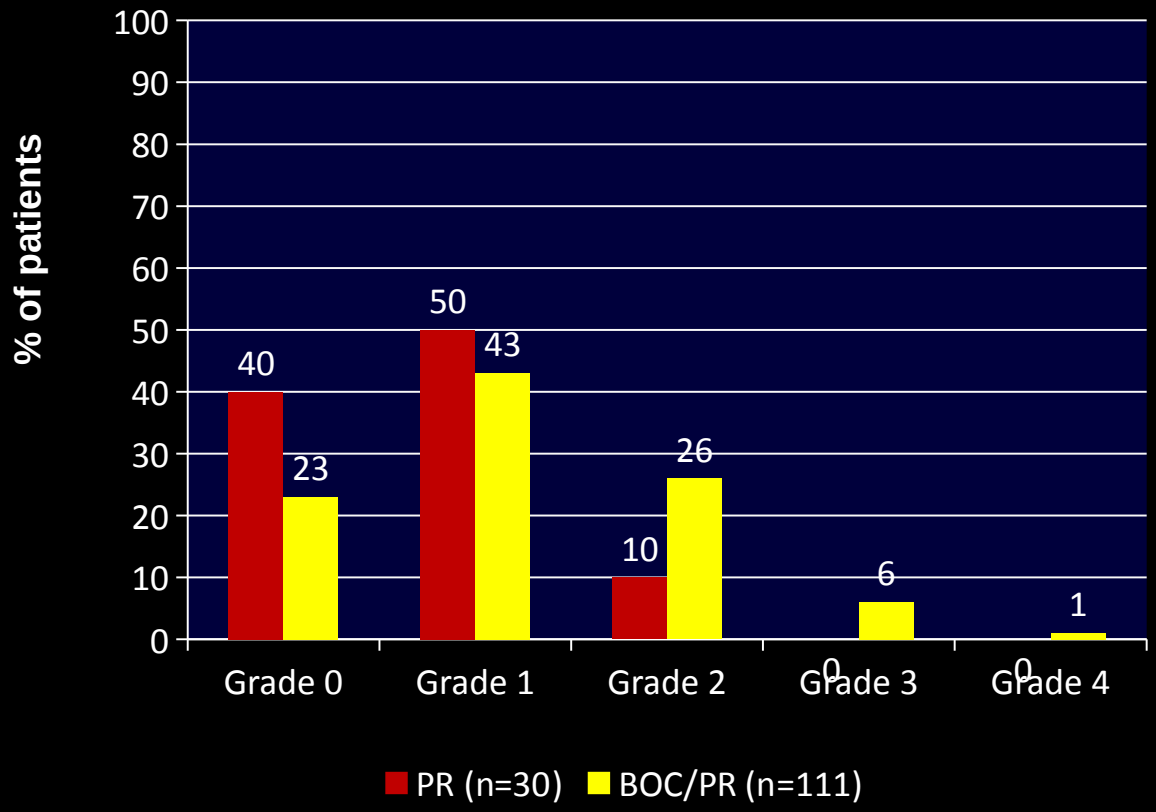
Vierling JM, et al. EASL 2013

SVR rates (%) in *F3-4* PATIENTS POORLY RESPONSIVENESS TO IFN according to GENOTYPE *and baseline HVL (>2.000.000 U.I.)*



Bruno S, et al, J Hepatol 2013

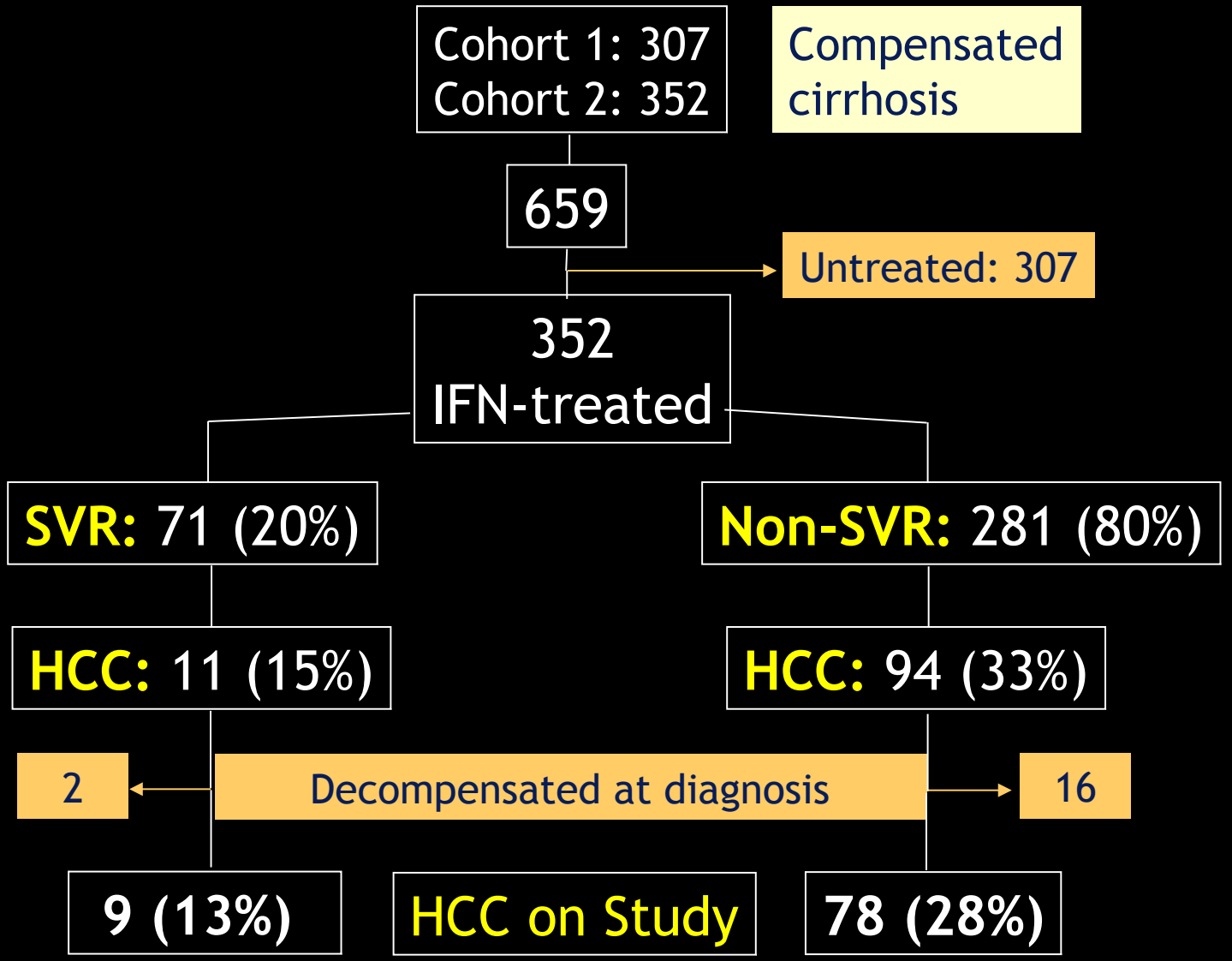
Mean Hb value during treatment in F4



Grade 0 = ≥11.0 g/dL; Grade 1 = 9.5 to <11.0 g/dL; Grade 2 =8.0 to <9.5 g/dL; Grade 3 = 6.5 to <8.0 g/dL; Grade 4= <6.5 g/dL

Bruno S, et al. J Hepatol 2013

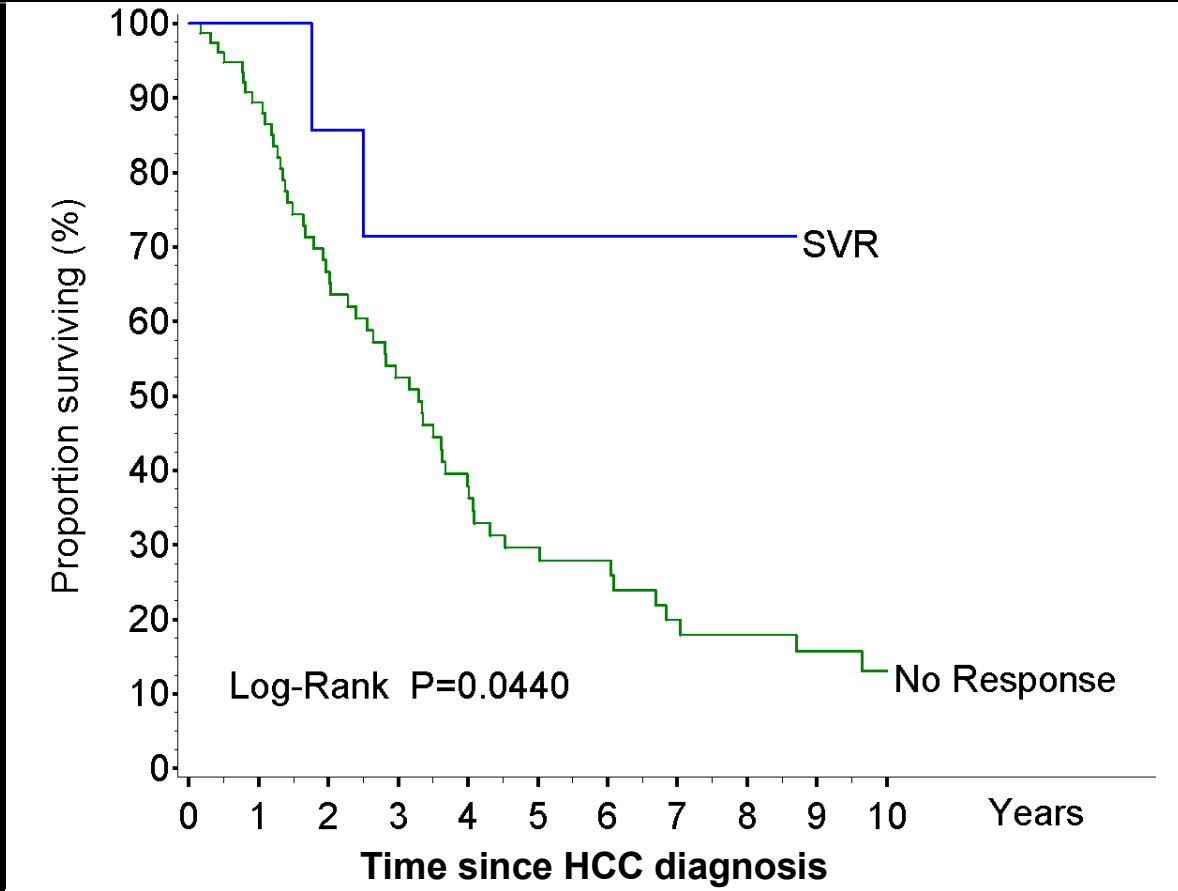
Improved survival in hepatitis C patients developing hepatocellular carcinoma after sustained virologic response to interferon-based therapy



Bruno S, Colombo M et al, EASL 2012

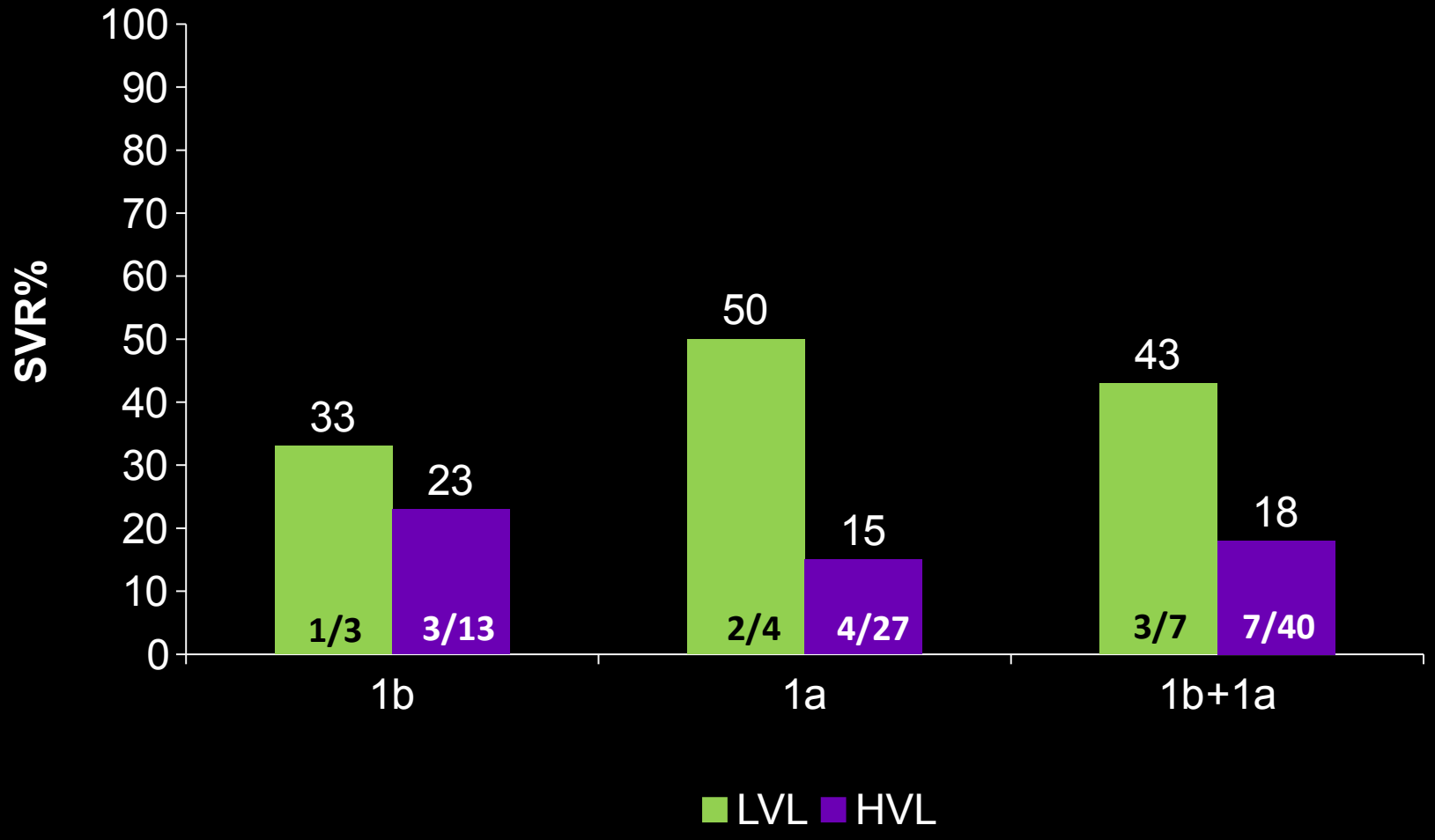
Incidence of Liver-Related Decompensation in patients developing HCC According to prior IFN Virological Response

Mortality in patients developing HCC According to prior IFN Virological Response



Patients at risk						
Non SVR	78	31	16	9	6	2
SVR	9	6	4	2	1	-

SVR poorly responsiveness (TW4, <1log decline) F4 patients according to viral load and genotype



Vierling JM, et al. EASL 2013

LA TERAPIA TRIPLICE DELL'HCV: come ottimizzare il trattamento del paziente pre cirrotico e cirrotico

Milano, 17 dicembre 2013

HEP3002: accesso precoce di TVR in Europa

Prof. Massimo Colombo

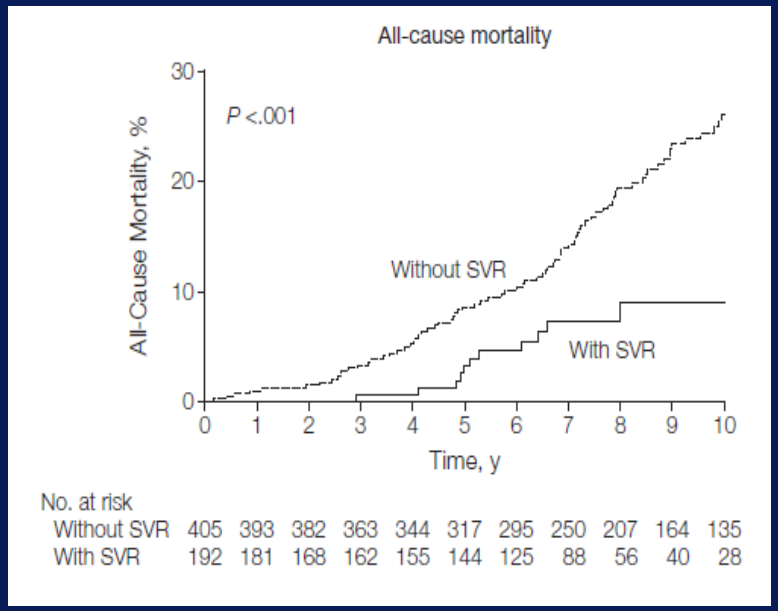
Chairman Department of Liver, Kidney, Lung and Bone Marrow Units and Organ Transplant
Head 1st Division of Gastroenterology
Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico
University of Milan

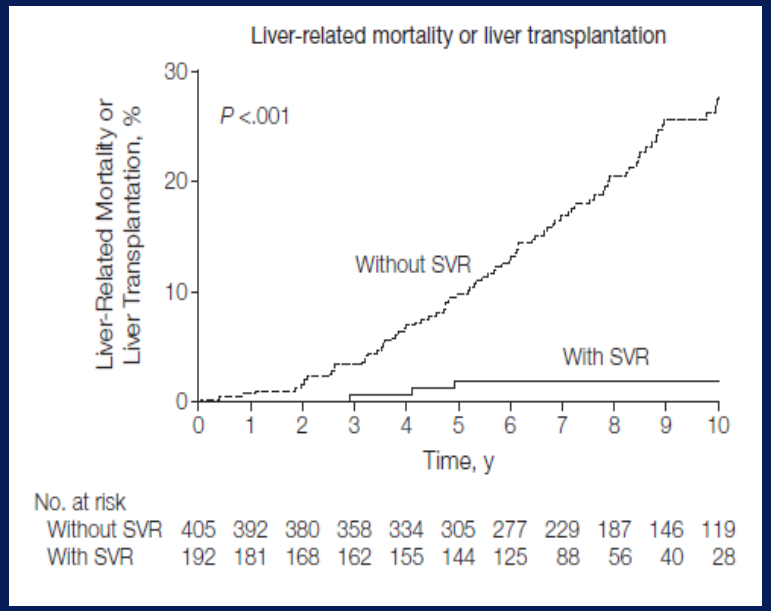
Treatment of HCV-1 in Italy: the Current Situation

- ~ 7000 patients treated each year with a 10% yearly trend to decrease
- ~ ¼ of HCV-1 patients were re-treatments: warehousing for triple therapy
- Yearly expenditure (2011) for dual therapy: 220,000,000 €
- Aging population of naives (48 years) with 25-30% of F3/F4
- At least 20,000 patients with previous P/R failures: usually unclassified, mean age > 55 years and ~ 40% F3/F4

Craxì A, «Trattamento dell'epatite C: dall'efficacia degli studi registrativi alla pratica clinica» Milan 15 May 2013

Survival Outcomes in Patients with Advanced Hepatic Fibrosis Due to HCV





Van der Meer JAMA 2012;308:2584-93

Extrahepatic Clinical Benefits of a SVR in Patients with Chronic Hepatitis C

Clinical Event	Number/Total Patients		Reference
	SVR (+)	SVR (-)	
Diabetes	26/1167 (2.2%)	117/1175 (9.9%)	Arase et al 2009
Malignant lymphoma	0/2161 (0%)	25/1048 (12.6%)	Kawamura et al 2007
Improved Neurocognitive Functions*	8/8 100%	0/6 0%	Byrnes et al 2012

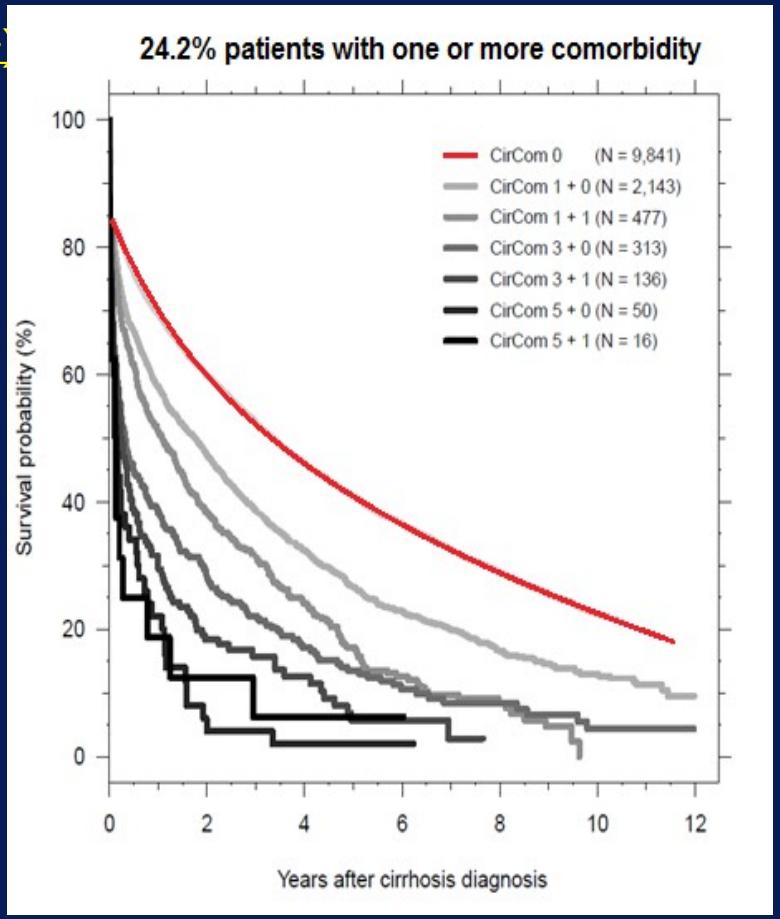
* Improved Brain Metabolism: basal ganglia Cho/Cr and ml/Cr ratios

Development and Validation of a Comorbidity Scoring System for Patients with Cirrhosis

Survival probabilities in the Danish Patient Registry cohort, by CirCom group

CirCom score (validated in 4,656 HCV-RNA+)

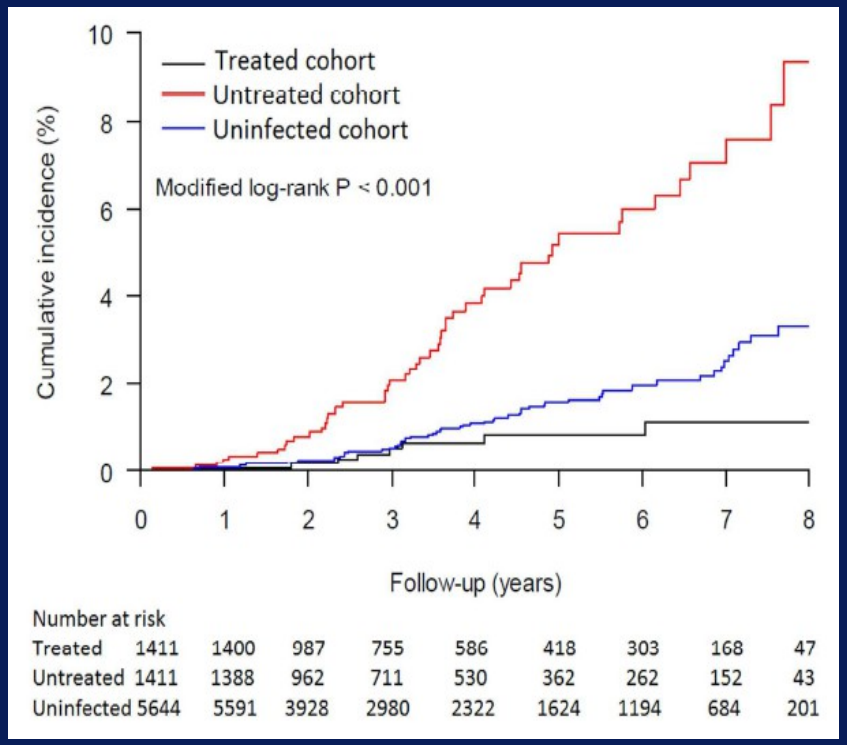
- COPD
- AMI
- PAD
- Epilepsy
- Substance Abuse
- Heart Failure
- Non Meta Cancer
- Meta cancer
- CKD



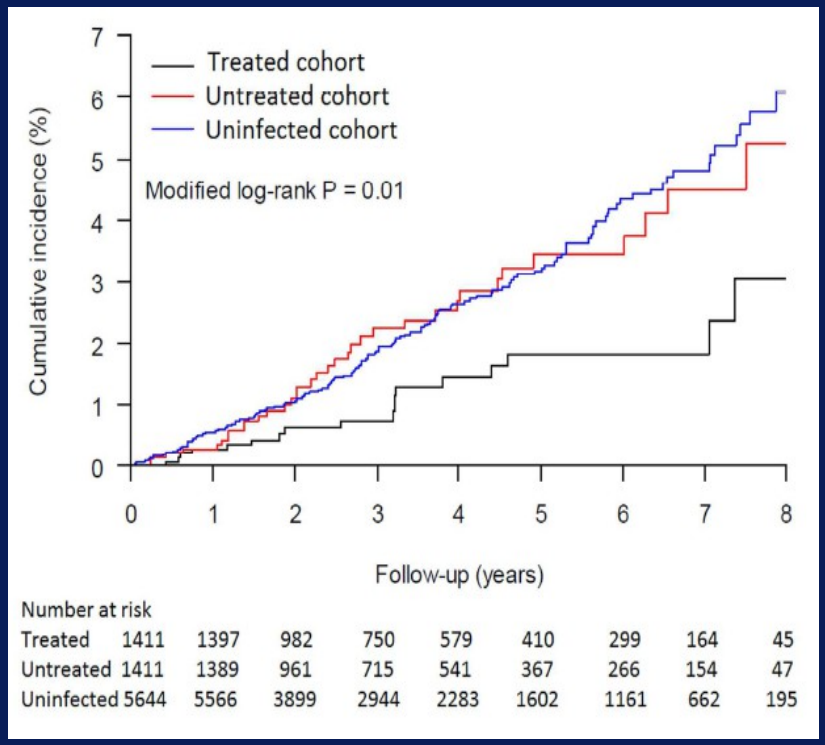
Jepsen et al, Gastroenterology 2013 in press

Antiviral Treatment For HCV Is Associated With Improved Renal And Cardiovascular Outcomes In Diabetic Patients

End-stage renal disease (3 cohorts)



Ischemic stroke (3 cohorts)



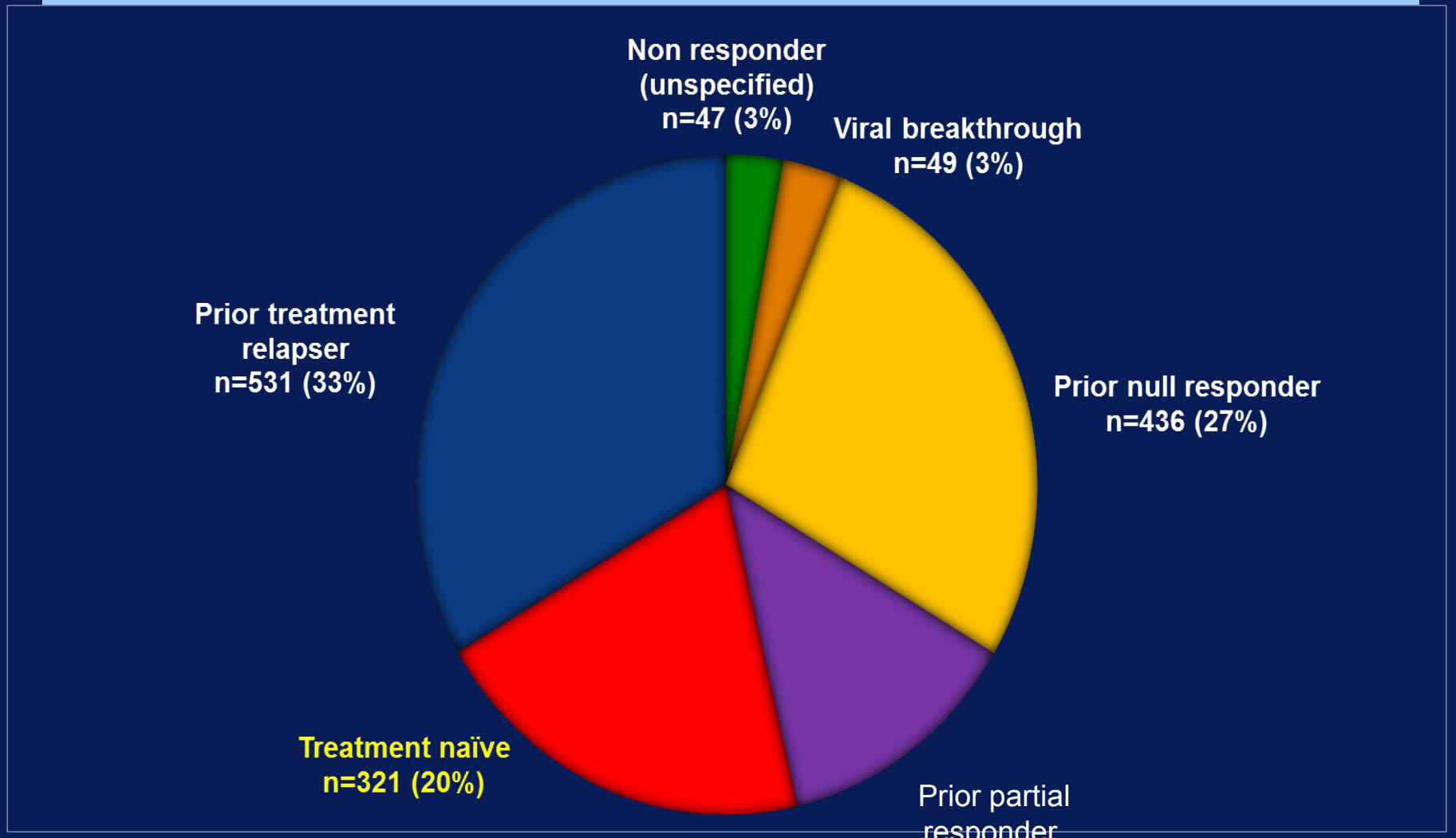
Hsu et al, Hepatology in press

HEP3002: Open Label Early Access Program (EAP) of Telaprevir for Adult Patients with HCV-1

Study Time	Aug 2011- Mar 2013
Patients enrolled	> 2000 in 16 countries in Europe, South America and Australasia
Criteria	Naive and experienced patients, 18-70 yr
	Persistently compensated bridging fibrosis or cirrhosis
	≥ 3.5g albumin
	≥ 90,000 platelets, ≥ 1500 neutrophils, Hb>12g/dl ♀ / 13g/dl ♂

Colombo M, et al. Gut in press

HEP3002 Wk 16: Patient Disposal, Interim Analysis N=1587



Colombo M, et al. Gut in press

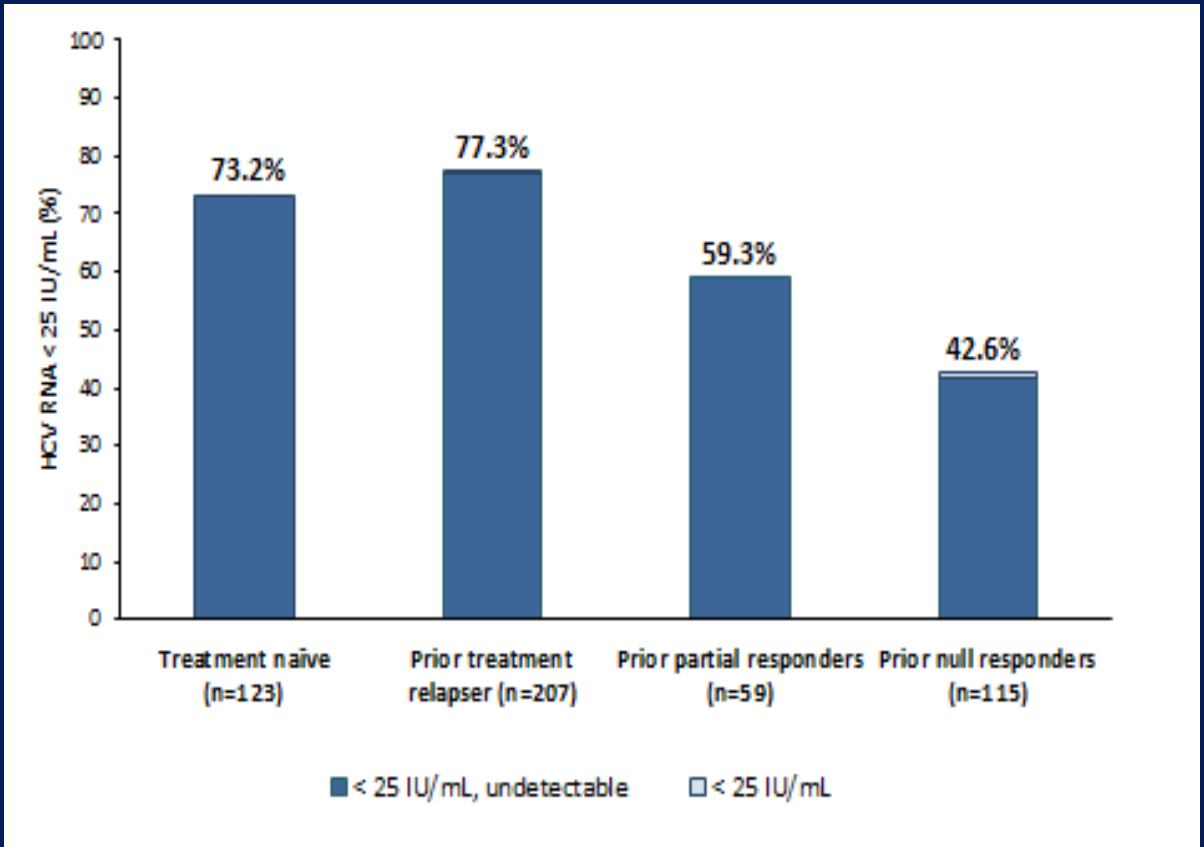
HEP3002 Wk 16: Baseline Patient Demographics

Characteristic	Bridging Fibrosis (N=752)	Cirrhosis (N=835)	Overall (N=1587)
Age yr – mean (range)	52 (22-73)	54 (19-75)	53 (19-75)
Males sex – no. (%)	463 (62)	549 (66)	1012 (64)
Body-mass index	26±3.7	27±4.2	27±4.0
Race or ethnic group – no. (%)			
White	740 (98)	817 (98)	1557 (98)
Black, Asian or other	12 (2)	18 (2)	30 (2)
HCV1 subtype – no. (%)			
1a	168 (22)	189 (23)	357 (22)
1b	562 (75)	609 (73)	1171 (74)
HCV RNA log10 – IU/mL	6.2±0.66	6.1±0.74	6.1±0.71

Colombo M, et al. Gut in press

HEP3002 Interim Analysis at Week 16 of 1587 Patients with F3, F4 HCV

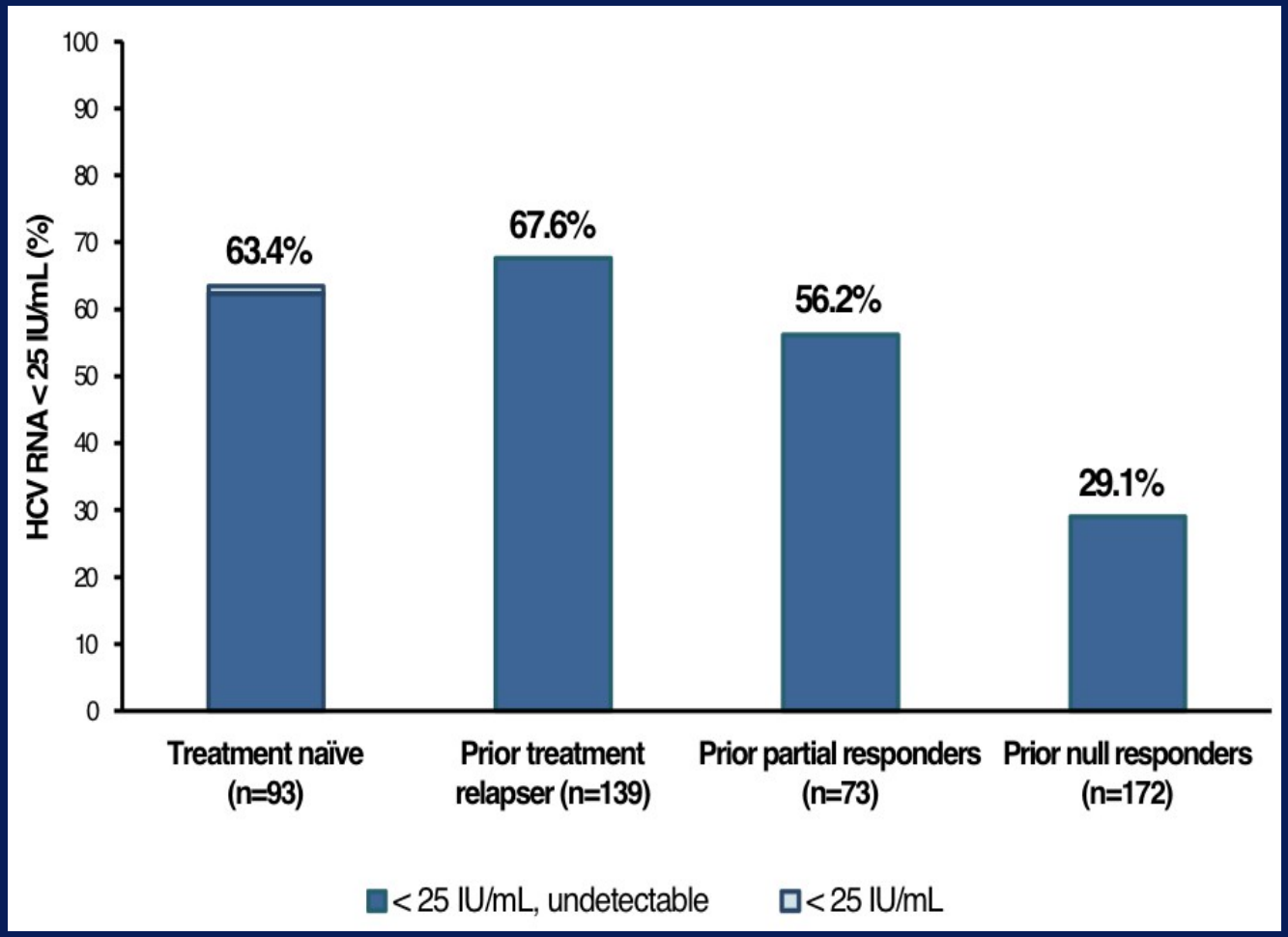
SVR24 for patients with bridging fibrosis (F3) at baseline, by prior treatment



Ferreira et al, AASLD 2013 Washington abs #1873

HEP3002 Interim Analysis at Week 16 of 1587 Patients with F3, F4 HCV

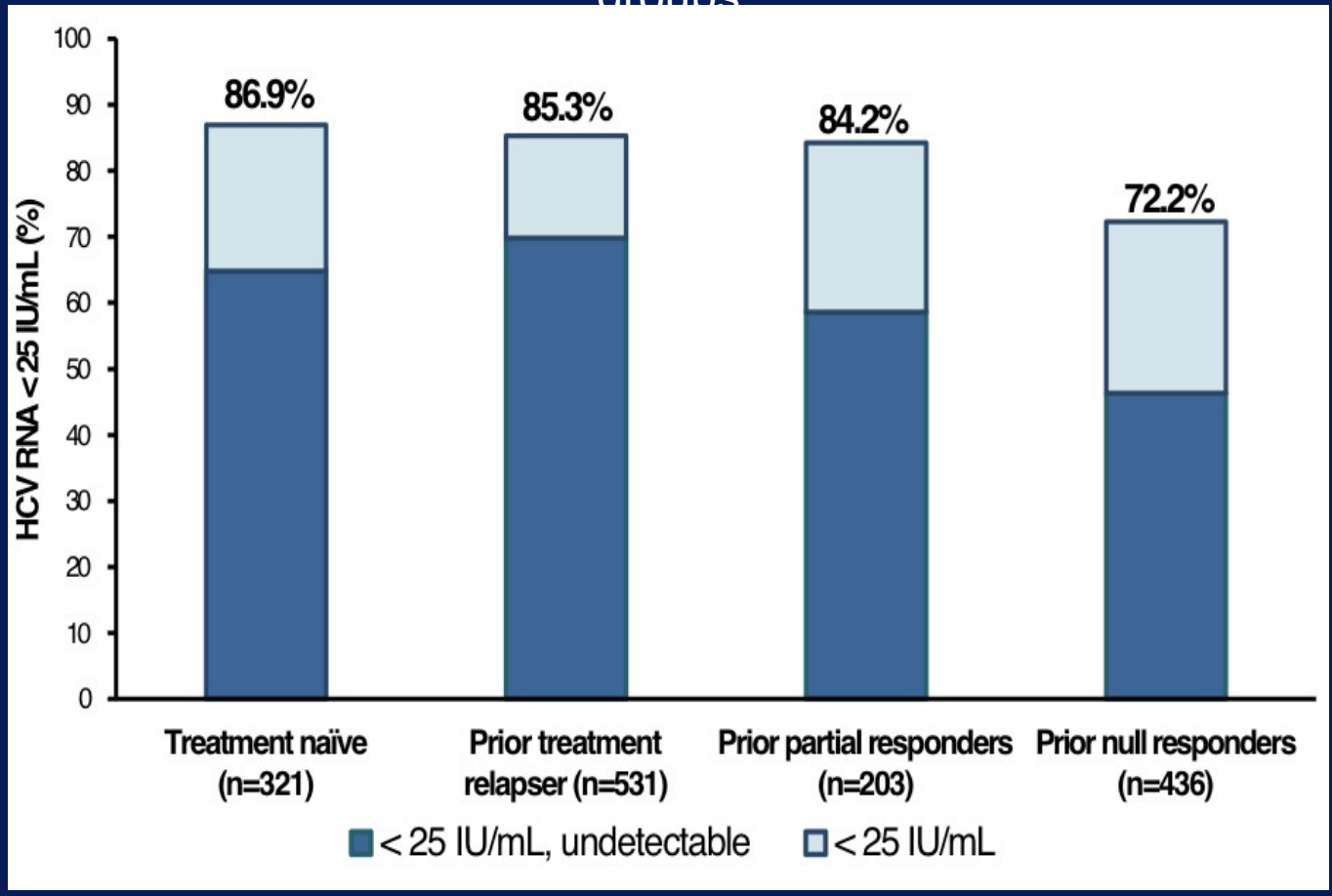
SVR24 for patients with cirrhosis (F4) at baseline, by prior treatment



Ferreira et al, AASLD 2013 Washington abs #1873

Treatment Of HCV Genotype 1 Patients With Severe Fibrosis Or Compensated Cirrhosis: Efficacy Results To Week 16 On 1587 Patients From The International Telaprevir EAP

HCV RNA < 25IU/mL (detectable and undetectable) at Week 4: main sub groups



Ferreira et al, AASLD 2013 Washington abs #1873

HEP3002 Wk 16: Serious Adverse Events

Variable	Bridging Fibrosis (F3) (N=752)	Cirrhosis (F4) (N=835)	Overall (N=1587)
Subjects with one or more serious AE	76 (10%)	110 (13%)	186 (12%)
Anaemia	32 (4%)	43 (5%)	75 (5%)
Rash	12 (2%)	16 (2%)	28 (2%)
Infection	6 (1%)	20 (2%)	26 (2%)
Pyrexia	4 (1%)	8 (1%)	12 (1%)

Colombo M, et al. Gut in press

HEP3002 Wk 16: Reason for Discontinuation

Variable	Bridging Fibrosis (N=752)	Cirrhosis (N=835)	Overall (N=1587)	
Any adverse event	80 (11%)	113 (14%)	193 (12%)	n.s.
Rash	36 (5%)	36 (4%)	72 (5%)	n.s.
Anaemia	14 (2%)	31 (4%)	45 (3%)	P=0.01
Asthenia	6 (1%)	10 (1%)	16 (1%)	n.s.
Abdominal Pain	1 (0%)	8 (1%)	9 (1%)	n.s.
Nausea	7 (1%)	9 (1%)	16 (1%)	n.s.
Pruritus	3 (0%)	10 (1%)	13 (1%)	n.s.
Vomiting	8 (1%)	9 (1%)	17 (1%)	n.s.

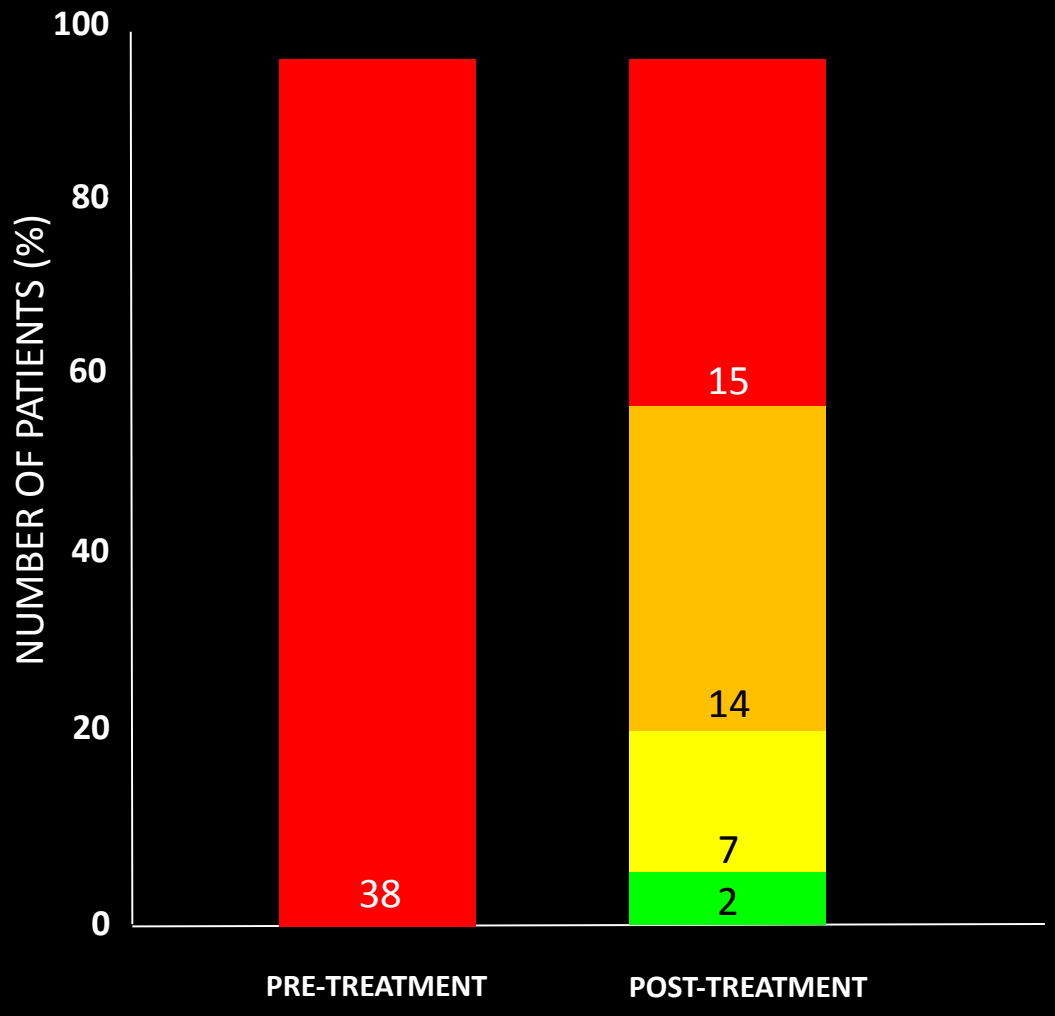
Colombo M, et al. Gut in press

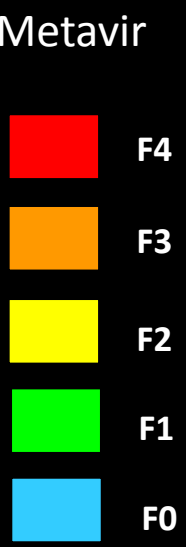
HEP3002 Wk 16: Management of Anaemia by Fibrosis Stage

Characteristic	Bridging Fibrosis (N=752)	Cirrhosis (N=835)	Overall (N=1587)
D/C TVR due to anaemia – no. (%)	14 (2)	31 (4)	45 (3)
Initial RBV dose (mg/kg/day) – mean	14.6	14.3	14.4
RBV dose reductions – no. (%)	270 (36)	356 (43)	630 (40)
EPO use – no. (%)	138 (19)	194 (23)	332 (21)
Blood transfusion – no. (%)	60 (8)	96 (12)	157 (10)
RBV dose reduction + Other intervention (EPO or blood transfusion) – no. (%)	126 (17)	182 (22)	309 (20)

Colombo M, et al. Gut in press

Rates of Cirrhosis Regression According to the METAVIR Scoring System
Post hoc analysis of the MIST study



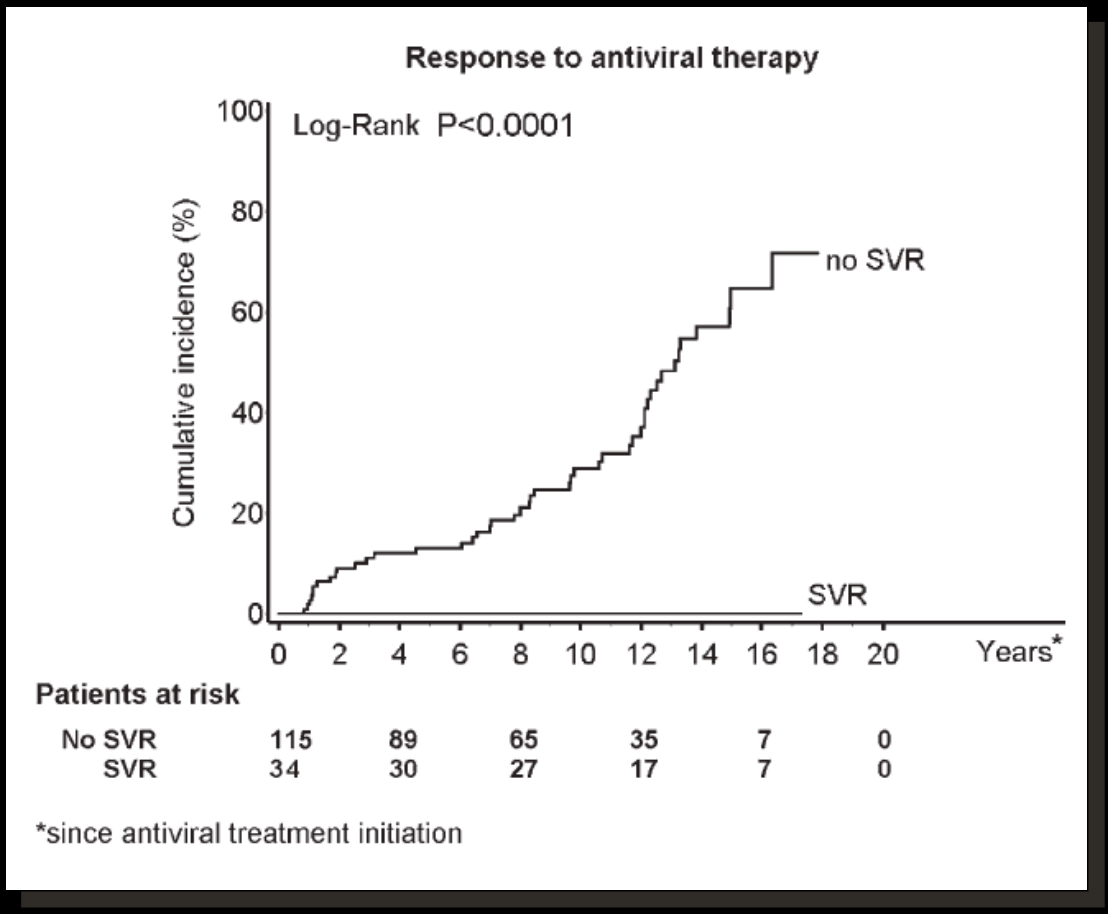


Cirrhosis Regression in
23 (61%) Patients

D'Ambrosio R, et al. Hepatology 2012

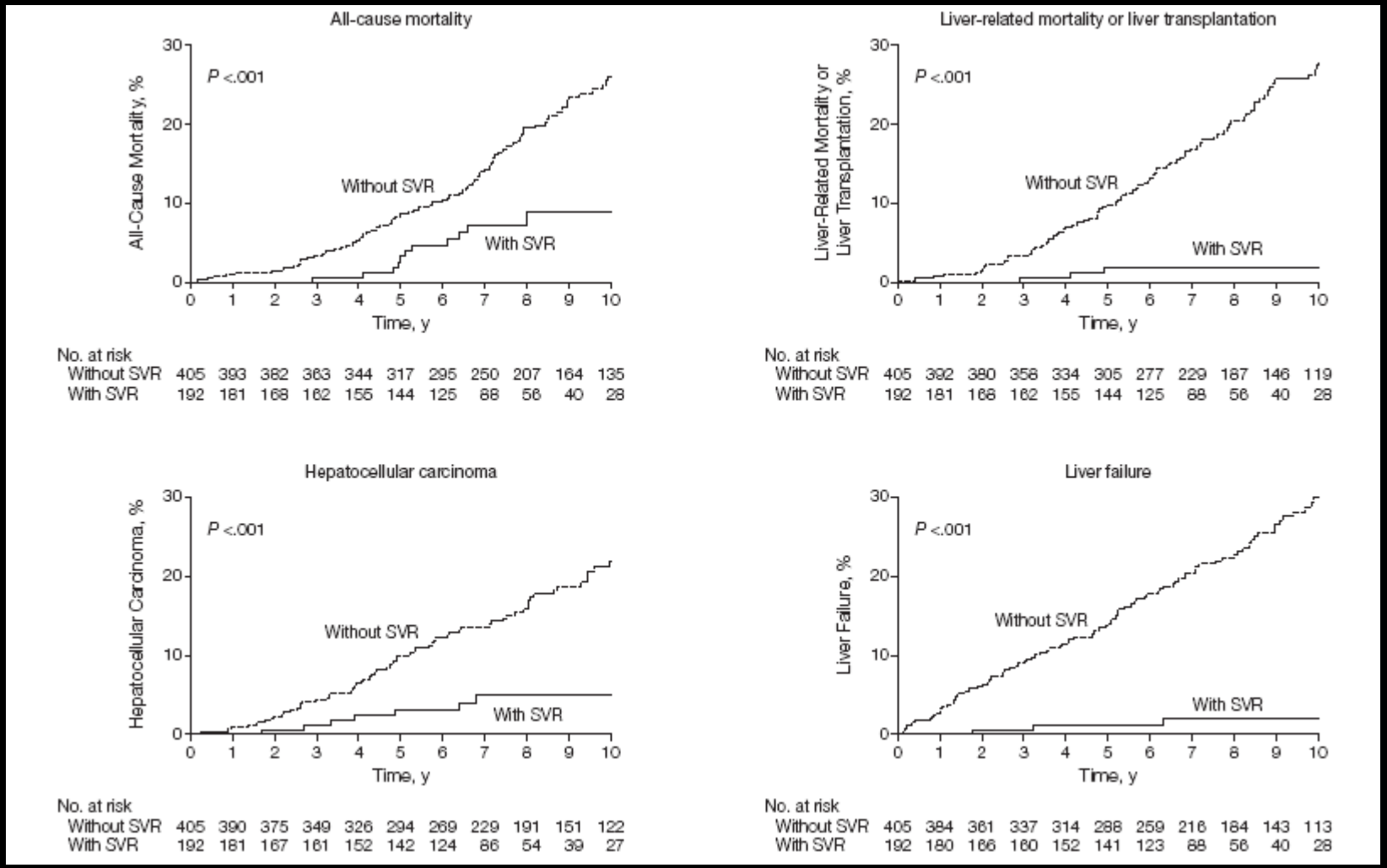
The Impact of SVR on the "de novo" Development of Esophageal Varices: Pre-primary Profilaxis

Cumulative incidence of esophageal varices *in 149 IFN ± RBV-treated patients with compensated HCV-induced (stage 1) cirrhosis according to response to therapy*



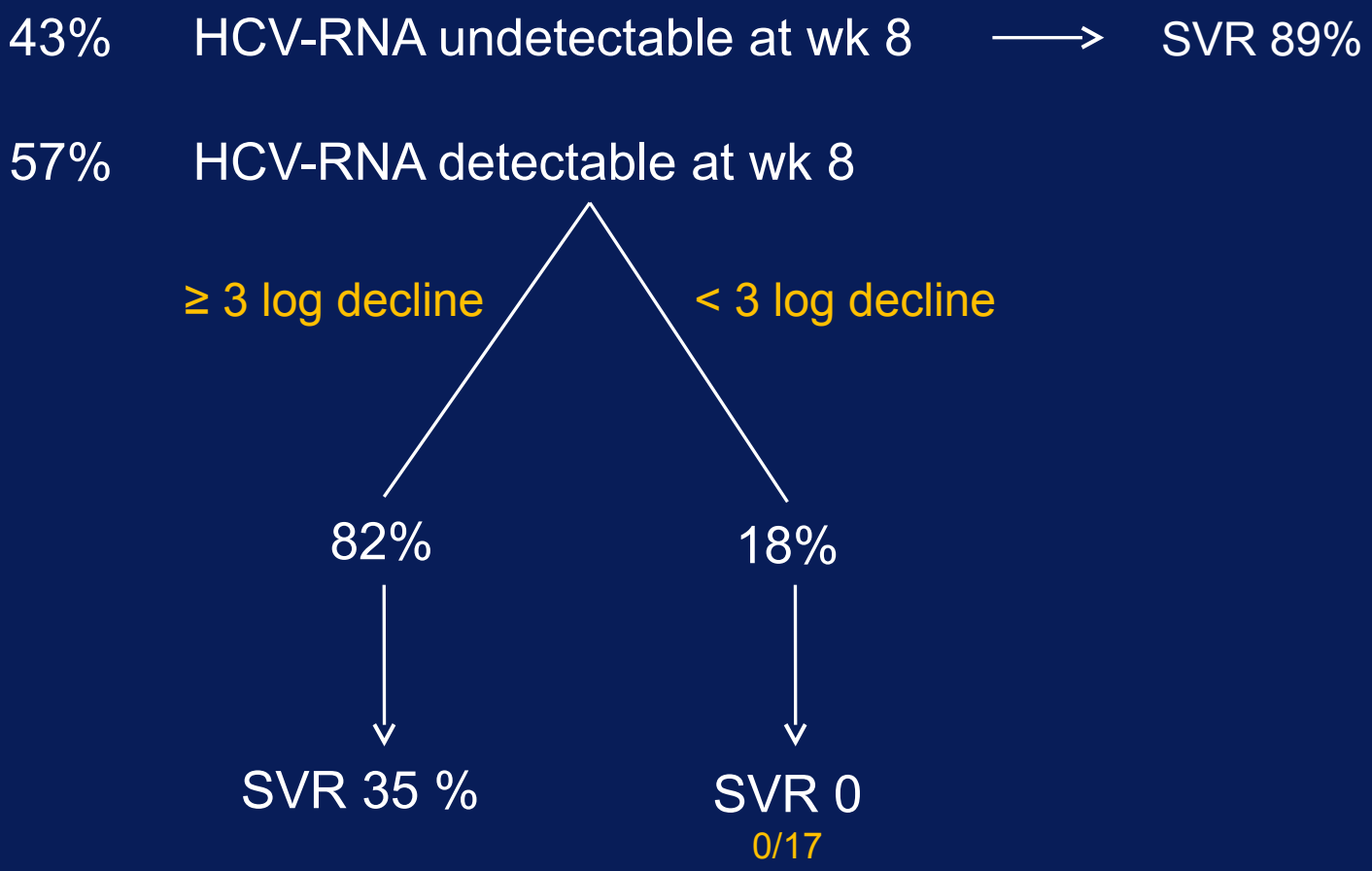
Bruno S, et al. Hepatology 2010

Survival Outcomes in Patients With CHC and Advanced Hepatic Fibrosis With and Without SVR



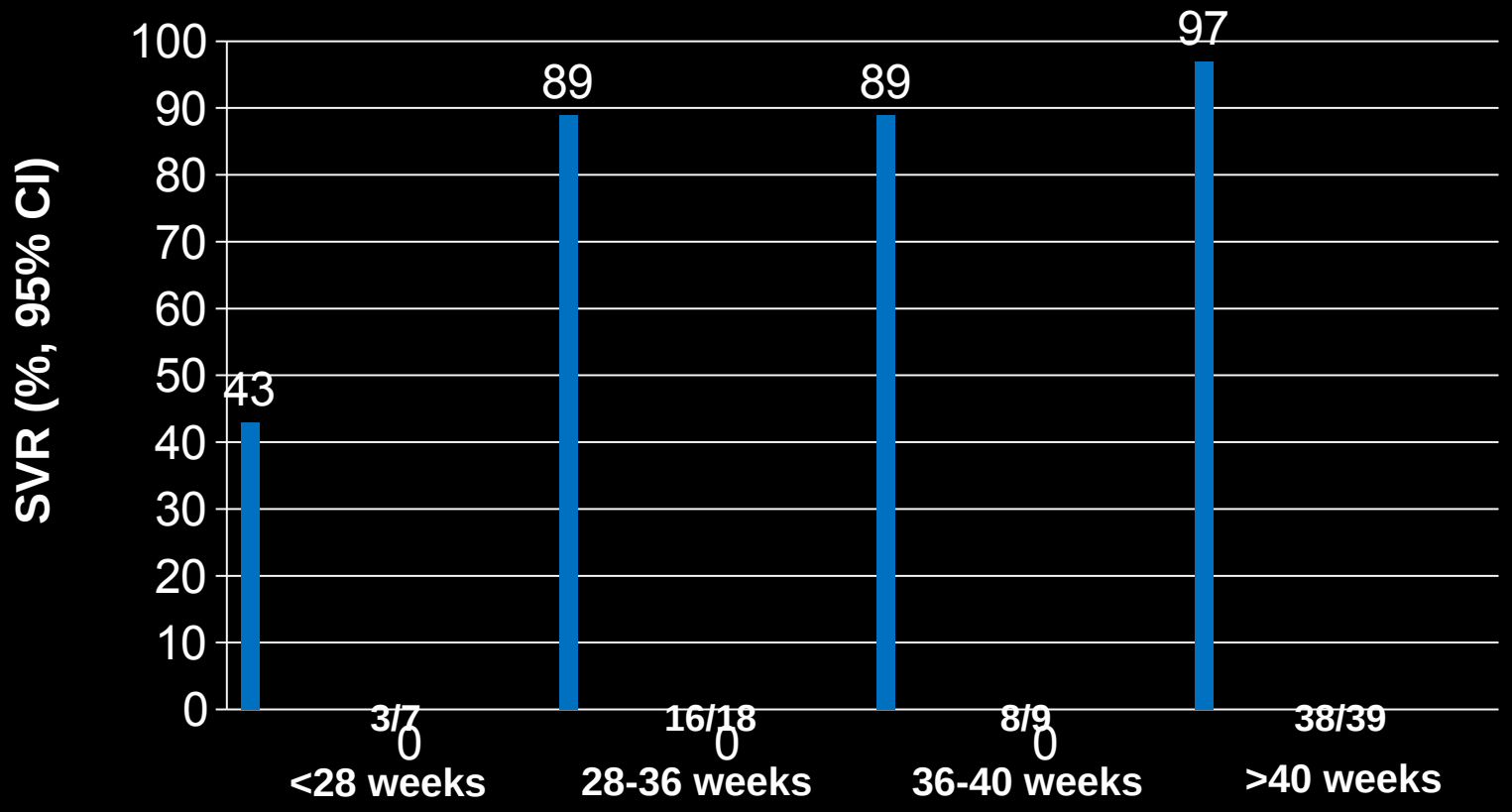
Van der Meer AJ, et al. JAMA 2012

The importance of TW 8 HCV-RNA decline in patients with cirrhosis (F4 Metavir) during BOC-therapy



Vierling JM, Bruno S, et al. J Hepatol accepted

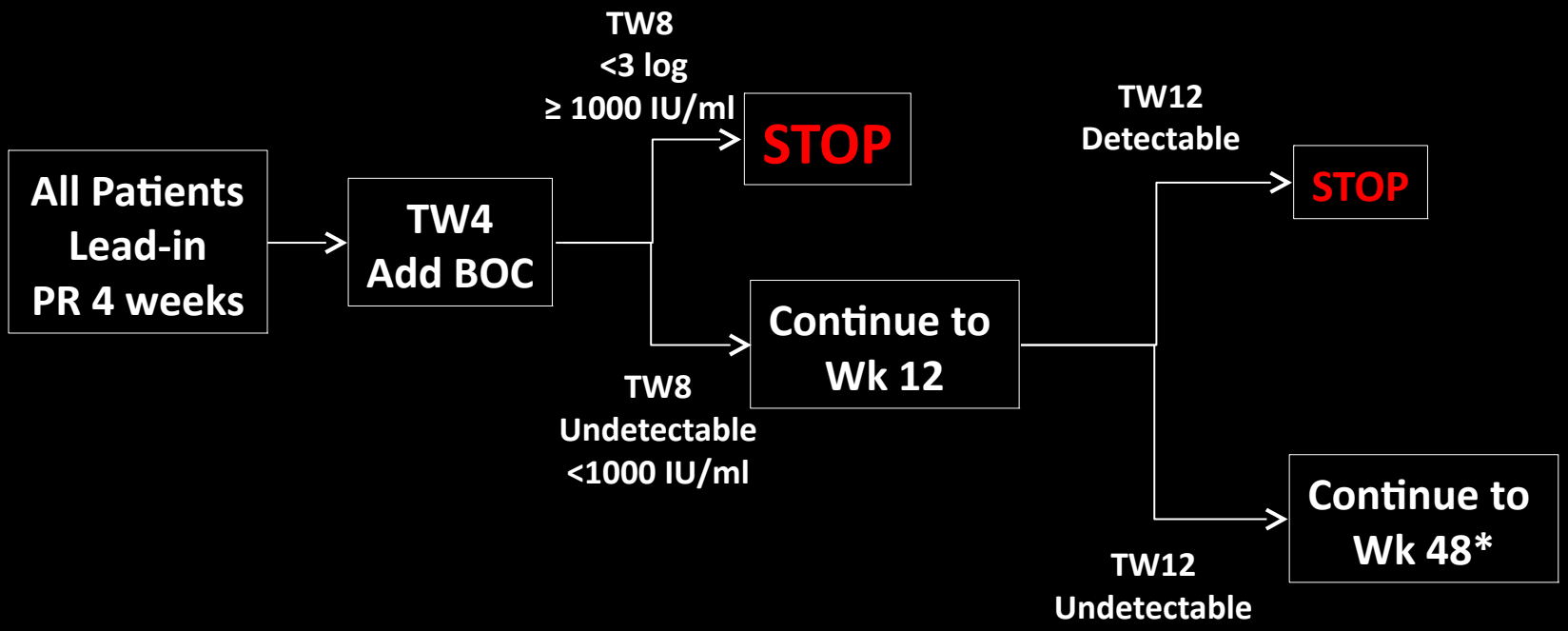
SVR according to treatment duration in F4 patients with undetectable HCV RNA at TW 8*



***Treatment-naïve and previous treatment failures combined**

Vierling JM, Bruno S, et al. J Hepatol accepted

Proposed Treatment Algorithm for Patients with advanced fibrosis/cirrhosis Treated with BOC/PR (naïve and previous treatment failures)



*** Consider stopping based on low chance of SVR in F3 and F4 patients with detectable HCV-RNA and <3 log10 decline in HCV-RNA from baseline (SVR=0/22; 0%; 95% CI [0, 13]).**

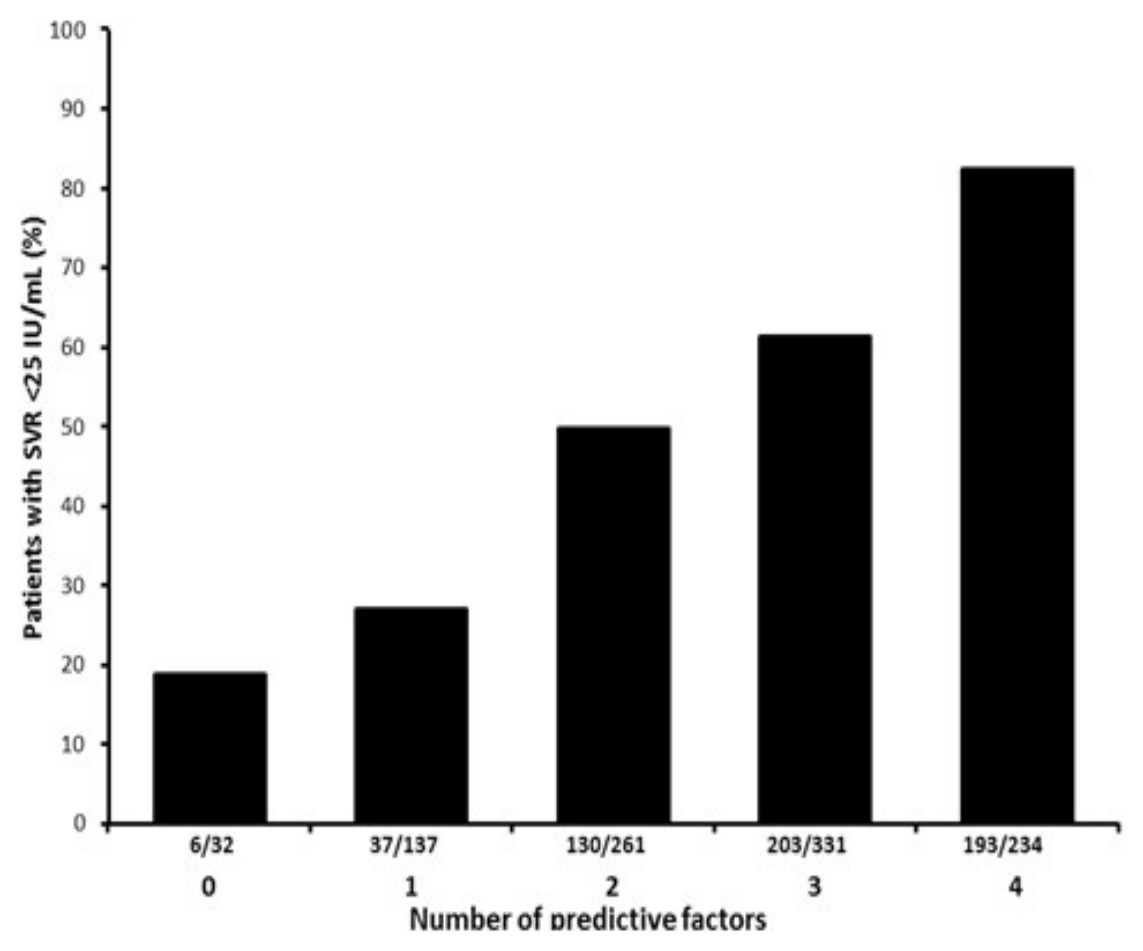
† Consider stopping treatment of treatment-naïve patients after TW28 if undetectable HCV RNA from TW8 through TW24

Prediction of a SVR24 In 932 Patients in the HEP3006

Factor	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
AFP <10 µg/L	3.18 (2.41, 4.19)	<.0001	2.50 (1.87, 3.36)	<.0001
BVL <800,000 IU/mL	1.48 (1.12, 1.96)	0.0057		
Fibrosis (F3 vs. F4)	1.96 (1.51, 2.55)	<.0001	1.51 (1.31, 2.00)	0.0051
Genotype (1b vs. 1a/other)	1.77 (1.31, 2.38)	0.0002	1.63 (1.18, 2.24)	0.0029
Platelets ≥150,000 cells/mm3	1.85 (1.42, 2.42)	<.0001		
Prior response (other vs. null response)	3.99 (2.94, 5.41)	<.0001	3.29 (2.40, 4.52)	<.0001

Colombo M, et al. submitted

HEP3006: SVR Rate by Number of Predictive Factors



Colombo M et al, submitted

CUPIC: SVR12 And The Risk Of Occurrence Of Severe Complications

	Outcomes	Platelets count ≤ 100,000/mm3	Platelets count > 100,000/mm3
Albumin < 35 g/L		N=37	N=31
	Complications, n (%)	19 (51.4%)	5 (16.1%)
	SVR12, n (%)	10 (27.0%)	9 (29.0%)
Albumin 35 g/L		N=74	N=306
	Complications, n (%)	9 (12.2%)	19 (6.2%)
	SVR12, n (%)	27 (36.5%)	168 (54.9%)

Hézode C, et al. J Hepatol 2013;59:434-441

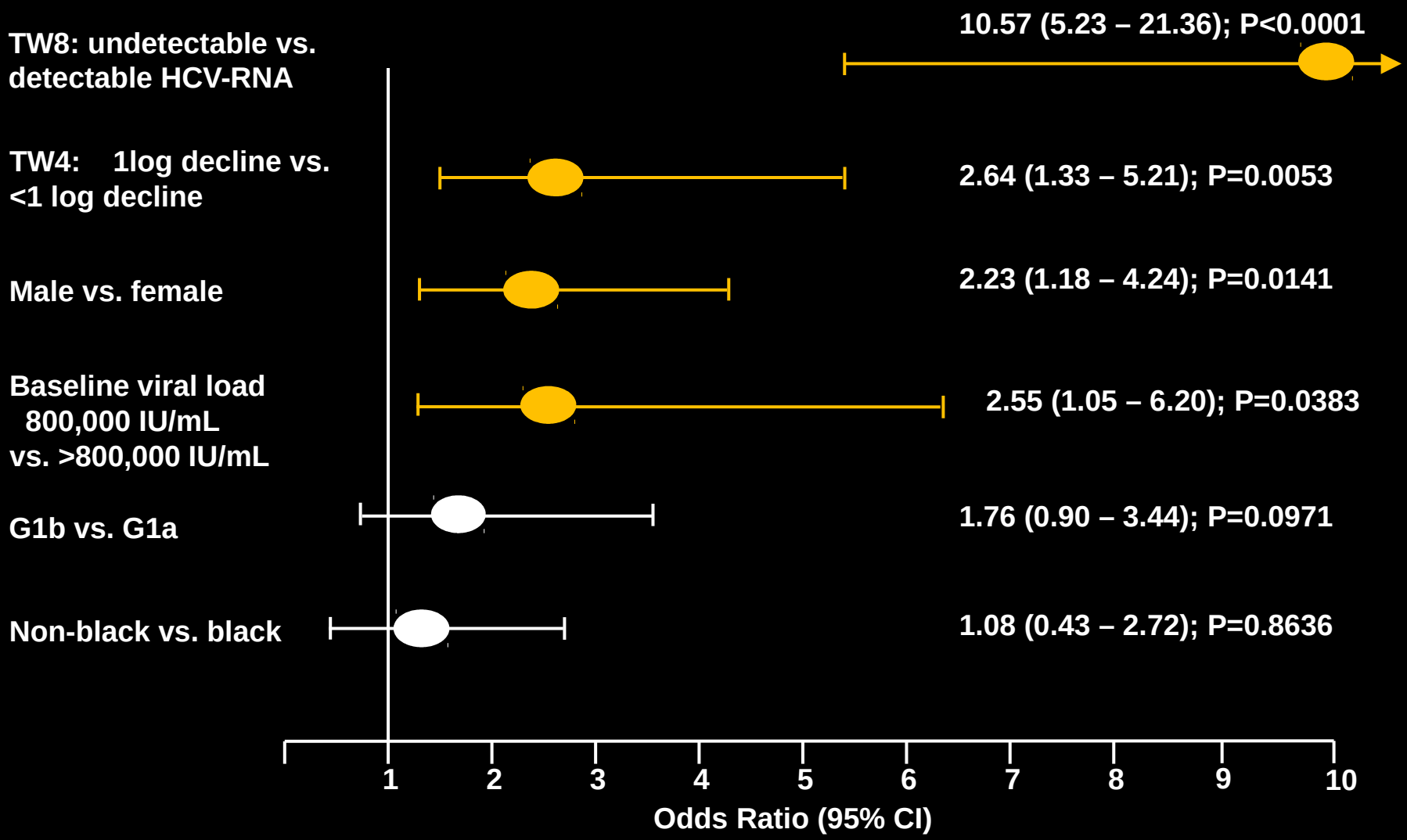
Overall Conclusions

- Clinical trial efficacy is confirmed in real-life patients treated according to the product label. Null responders with advanced fibrosis, however, are poor candidates to triple therapy

- The profile of AE in patients treated according to label recommendations in the real-life setting was consistent with that reported during clinical trials

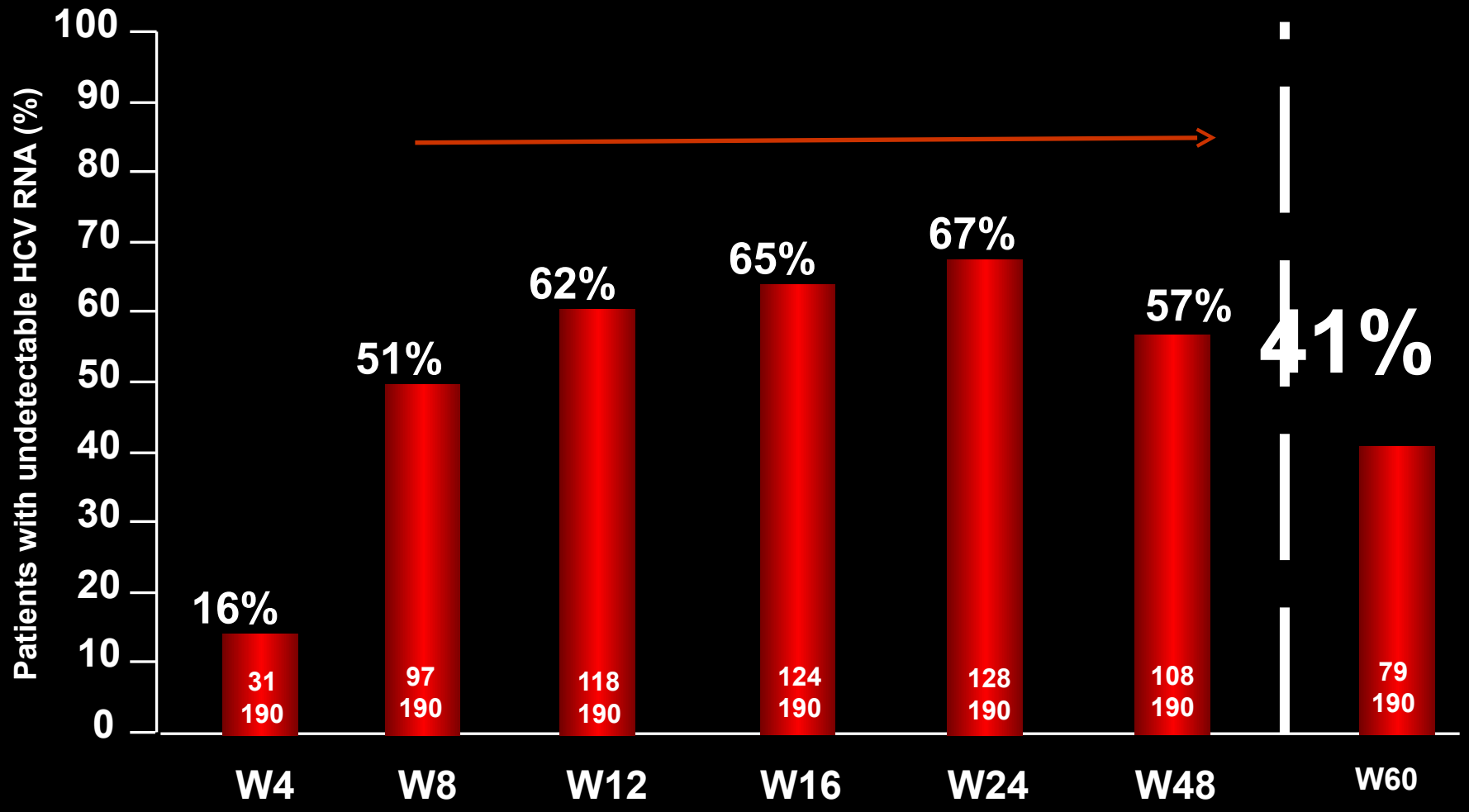
- Safety is challenging in advanced cirrhotic patients with negative prognostic factors.

Multivariate Logistic Regression Analysis
Predictors of SVR in F3/F4 Patients Receiving BOC/PR

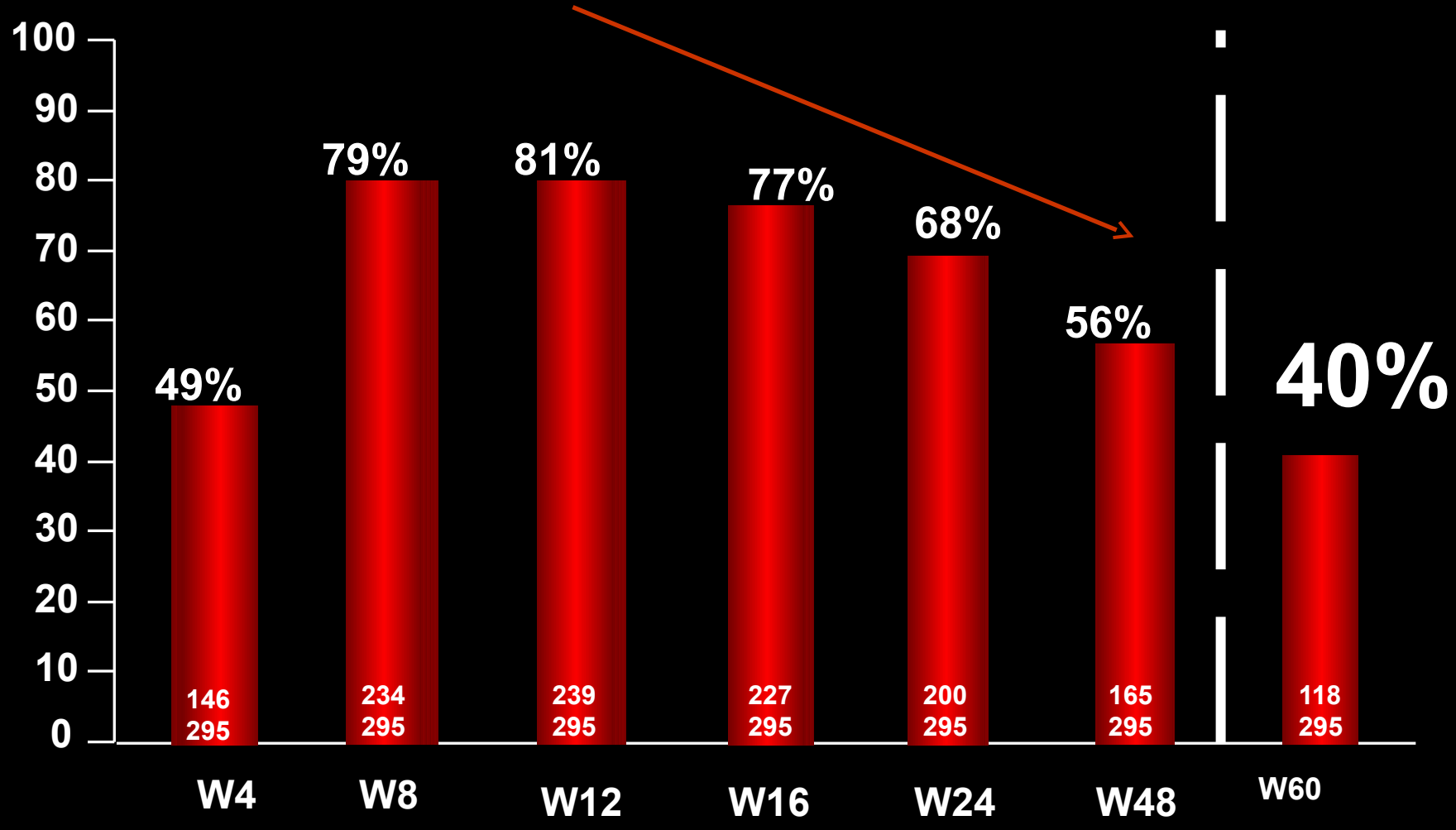


Vierling JM, et al. EASL 2013

Boceprevir: virological response (ITT)



Telaprevir: virological response (ITT)



Multivariate logistic regression analysis
Predictors of **Treatment Failure** (NO SVR)
in 369 F3/F4 patients receiving BOC

Reduced Multivariate Model

Variable	Reference	Multivariate RR (95% CI)
TW8 <1000 IU/mL	Undetectable	**3.71 (2.23-6.17)**
TW8 >1000 IU/mL	Undetectable	**31.8 (8.98-113.)**
Prior null or partial	Prior relapser	**1.73 (1.06-2.85)**
Albumin <3.5	≥3.5	**15.9 (1.87-134.)**
PLT <100,000	≥100,000	**4.46 (1.89-10.5)**

SVR rate according to characteristics associated with SVR at multivariate analysis

Variable	Patients	SVR (%)
TW8 Undetectable	168	117 (69.6)
TW8 <1000 IU/mL	130	52 (40.0)
TW8 >1000 IU/mL	43	3 (7.0)
Prior relapser	130	79 (60.8)
Prior null or partial	237	100 (42.2)
Albumin ≥3.5	301	155 (51.5)
Albumin <3.5	17	1 (5.9)
PLT ≥100,000	329	171 (52.0)
PLT <100,000	40	9 (22.5)