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COMPETING INTEREST OF FINANCIAL VALUE ≥ £1,000:	
Speaker Name	**Statement**
Stefan Zeuzem	Acts in a consultancy capacity and and has received speaker fees from Abbott, Actelion, AstraZenica, Bristol-Myers Squibb Pharmaceuticals, Boehringer Ingelheim, Gilead Sciences, Janssen, Merck, Novartis, Presidio, Roche, Vertex
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HCV mono-infection: when to treat and when to wait ?

5th Annual BHIVA Conference for the Management of HIV/Hepatitis Co-Infection
in collaboration with BASL and BVHG
London – October 3, 2012

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MEDIZINISCHE KLINIK 1

1st Generation Protease-Inhibitors

- Telaprevir and Boceprevir are both linear ketoamid HCV-NS3/4A protease inhibitors
- Clinical trials: SOC + PI vs. SOC (PEG-IFN/RBV)

Telaprevir (phase 3)

ADVANCE: tx-naive GT1 pts

ILLUMINATE: response-guided therapy in tx-naive GT1 pts

REALIZE: tx-experienced GT1 patients (relapsers, partial responders, null responders)

Boceprevir (phase 3)

SPRINT-2: tx-naive GT1 patients

RESPOND-2: tx-experienced GT1 patients (relapsers and partial responders)

Treatment-naive Patients

The data

Virologic response rates in treatment naive patients

(no head-to-head data)

	ADVANCE (TVR)		SPRINT-2 (BOC)	
	PR + TVR	PR	PR + BOC	PR
RVR (wk 4)	66-68%	9%	-	-
Wk 8 (LI + 4 wk)	-	-	Not reported	Not reported
eEVR[1]	57-58%	8%	44%	N/A
EoT	81-87%	63%	71-76%	53%
Relapse	9%	28%	9%	22%
SVR (all)	69-75%	44%	63-66%	38%

RVR, rapid virologic response; LI, lead-in; eRVR, extended RVR; EoT, end of treatment; SVR, sustained virologic response

[1] Different definitions of eEVR in ADVANCE and SPRINT-2

Jacobson et al., NEJM 2011
Reddy et al., APASL 2011
Poordad et al., NEJM 2011

SVR rates in treatment naive patients

(no head-to-head data)

SVR	ADVANCE (TVR)		SPRINT-2 (BOC)	
	PR + TVR	PR	PR + BOC	PR
Lead-in < 1 log	-	-	28-38%	4%
Lead-in ≥ 1 log	-	-	79-81%	51%
eRVR[1] achieved	83-89%	97%	96%	93%
eRVR[1] not achieved	50-54%	39%	72-75%	66%
Caucasian, non-black	70-75%	46%	67-68%	40%
African Amer., black	58-62%	25%	42-53%	23%
Stage F0-2	73-78%	47%	67%	38%
Stage F3-4	53-62%	33%	41-52%	38%
IL28B CC	84-90%	64%	80-82%	78%
IL28B CT/TT	57-73%	23-25%	55-71%	27-28%

[1] Different definitions of eEVR in ADVANCE and SPRINT-2

Jacobson et al., AASLD 2010; EASL 2011
Reddy et al., APASL 2011
Poordad et al., NEJM 2011; EASL 2011

Telaprevir and Boceprevir - Safety

(no head-to-head data)

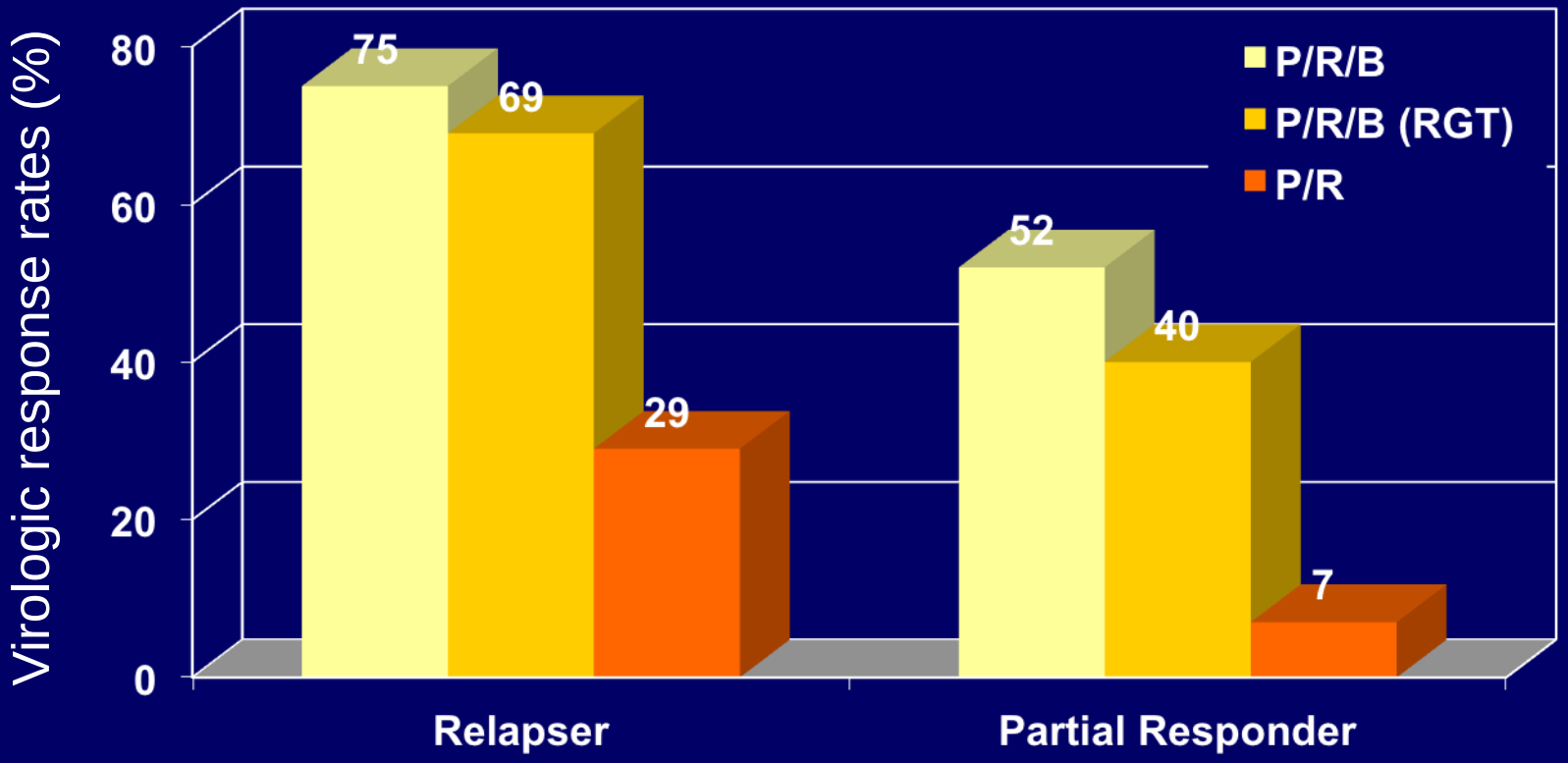
	ADVANCE (TVR)		SPRINT-2 (BOC)	
	TVR12/PR	PR	BOC RGT	PR
Discontinuation due to AEs	10%	7%	12%	16%
Discontinuation due to rash	7%	1%		
Anemia (<10 / < 8.5 g/dL)	36% / 9%	14% / 2%	45% / 5%	26% / 4%
Use of EPO	Not permitted		43%	24%

Jacobson et al., NEJM 2011
Poordad et al., NEJM 2011

Treatment-experienced Patients

The data

RESPOND-2: Phase 3 Trial in Tx-Experienced* HCV-1 Infected Patients

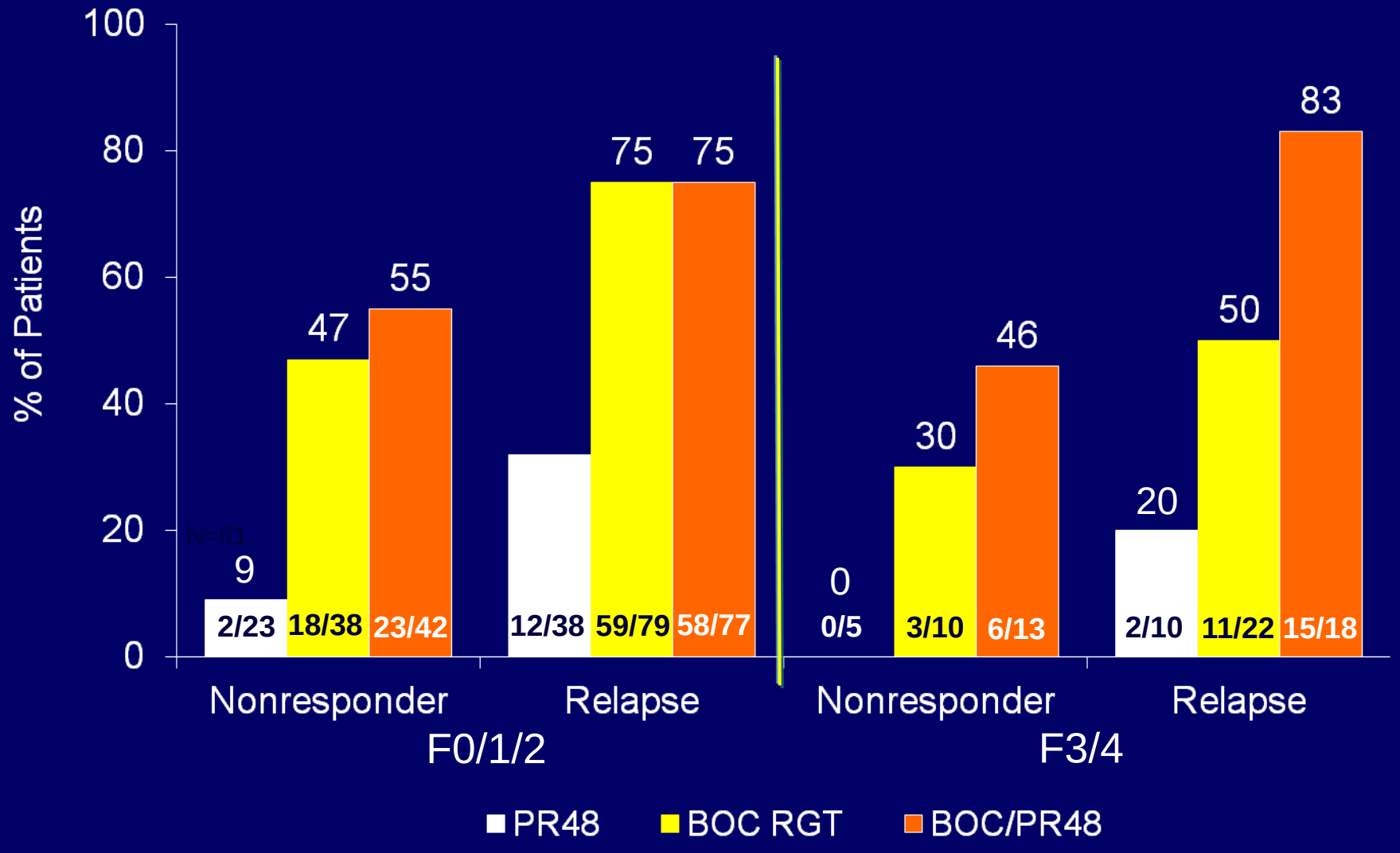


Peginterferon alfa-2b 1.5 µg/kg qw
Ribavirin 600-1400 mg/day
Lead-in phase
Boceprevir 800 mg q8h

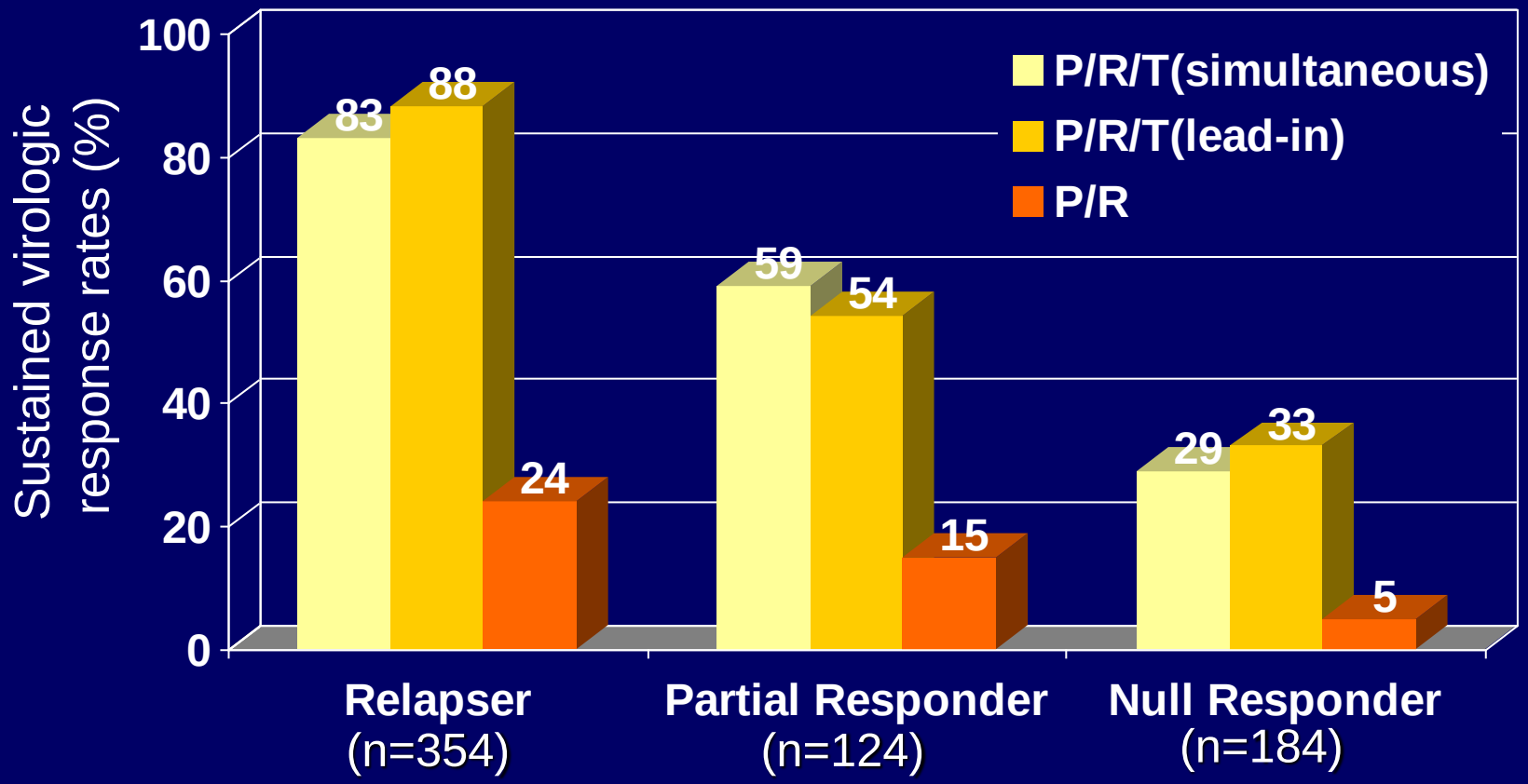
* Only previous partial responders and relapsers enrolled (N=403)

Bacon et al., NEJM 2011

RESPOND-2: SVR by Fibrosis Score and Historical Response



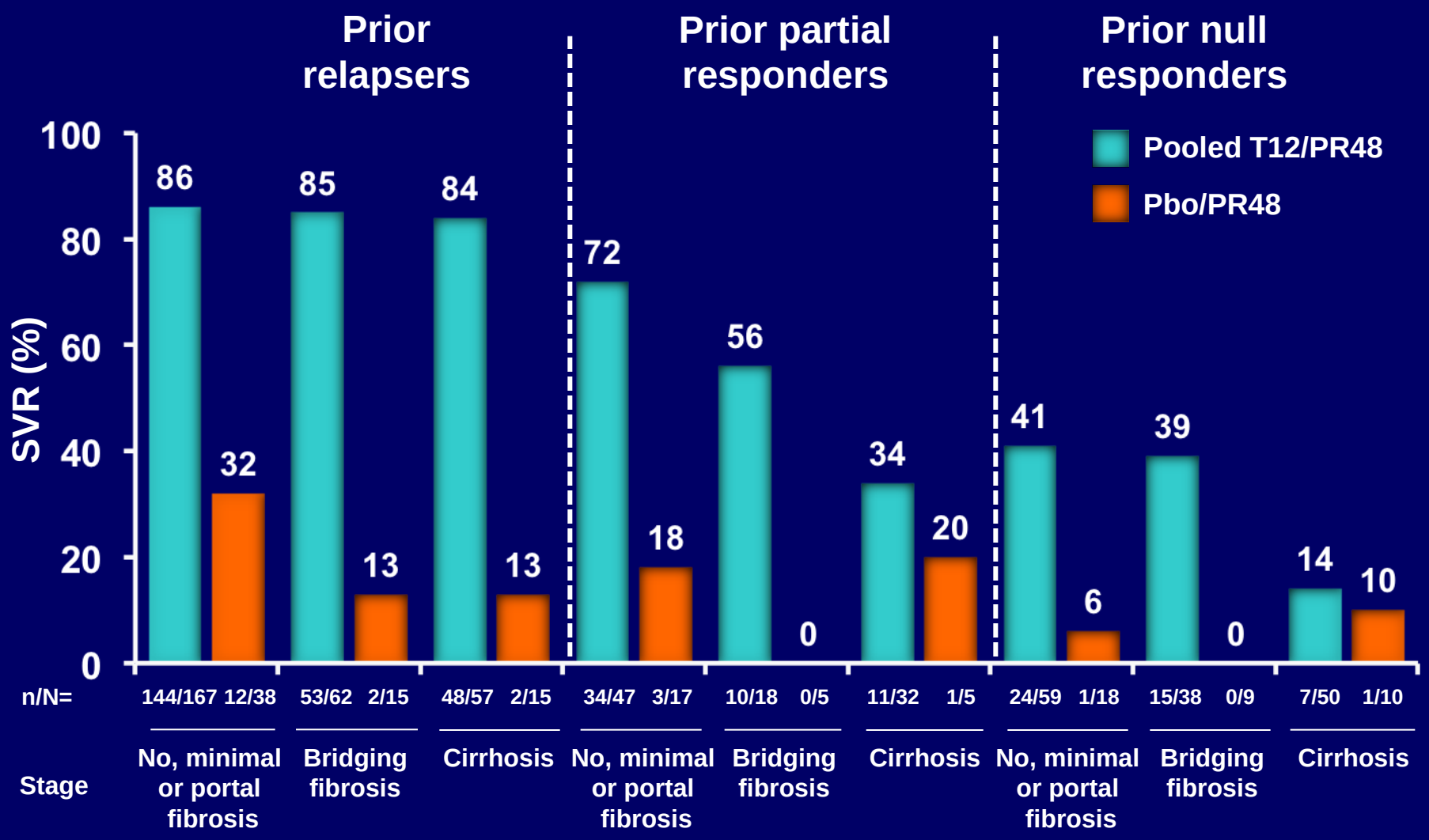
REALIZE: Phase 3 Trial in Tx-Experienced HCV-1 Infected Patients



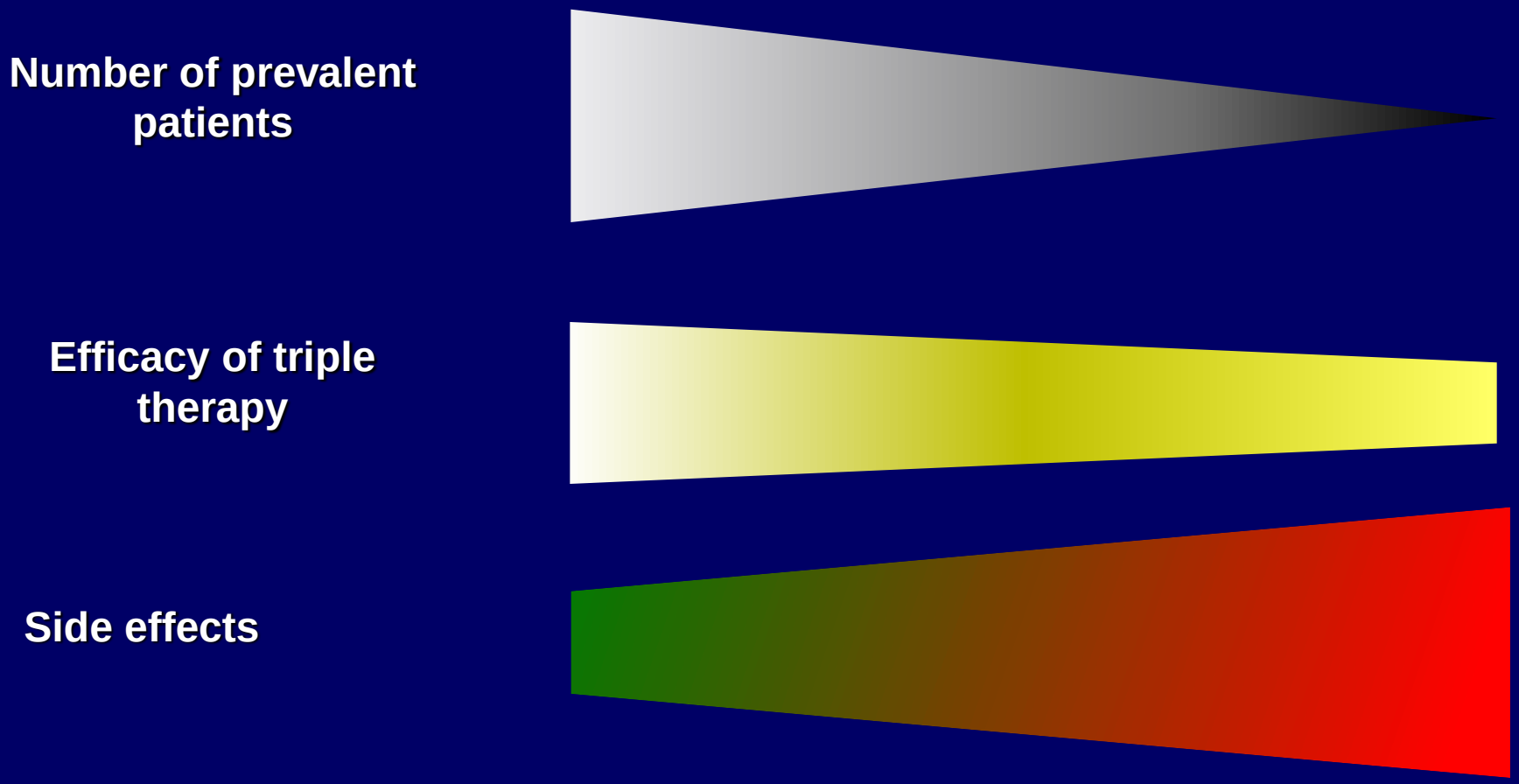
Peginterferon alfa-2a 180 µg qw
Ribavirin 1000-1200 mg/day
Telaprevir 750 mg q8h

Zeuzem et al., NEJM 2011

REALIZE: SVR by Baseline Fibrosis Stage and Prior Response



Cirrhosis spectrum



Telaprevir & Boceprevir

Approved schedules

Telaprevir in Genotype 1 Patients

- 750 mg (two 375-mg tablets) q8hr with food (not low fat; standard fat meal is >20 g, eg, 1/2-cup nuts or 2-oz cheddar cheese)

Treatment Naive and Previous Relapsers

Previous Partial or Null Responders

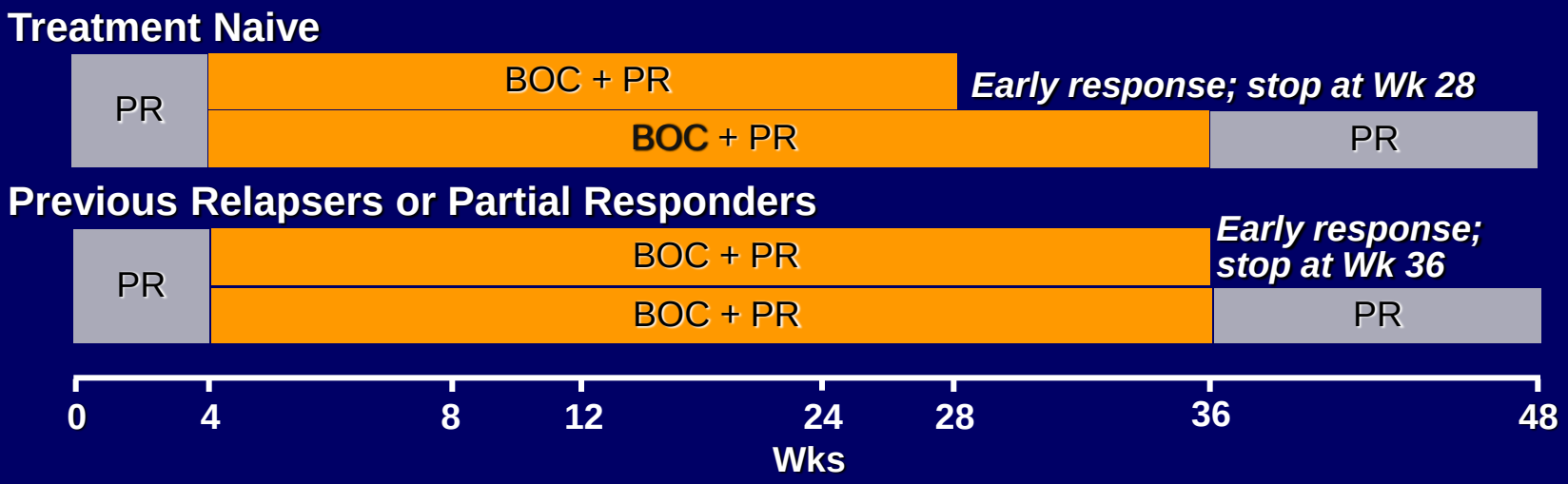
- Treatment-naive patients with compensated cirrhosis and eRVR may benefit from additional 36 wks of pegIFN + RBV (ie, to Wk 48)

Time Point	Criterion	Stopping Rule
Wk 4 or 12	HCV RNA > 1000 IU/mL	Discontinue all therapy
Wk 24	Detectable HCV RNA	Discontinue PR
Any	Discontinuation of PR for any reason	Discontinue TVR

Telaprevir [package insert]. May 2011. EMA. Telaprevir [package insert] 2011.

Boceprevir in Genotype 1 Patients

- 800 mg (four 200-mg capsules) q8hr with meal or light snack



- All cirrhotic patients should receive lead-in followed by PR + BOC for 44 wks
- If considered for treatment, null responders should receive lead-in then PR + BOC for 44 wks
- EMA label recommends fixed-duration therapy for all tx-expd patients: LI + 32 wks triple + 12 wks PR

Time Point	Criterion	Stopping Rule
Wk 12	HCV RNA ≥ 100 IU/mL	Discontinue all therapy
Wk 24	Detectable HCV RNA	Discontinue all therapy
Any	Discontinuation of PR for any reason	Discontinue BOC

Boceprevir [package insert]. May 2011. EMA. Boceprevir [package insert] 2011.

Choice between first generation protease inhibitors in HCV-1

Boceprevir

- Tx duration 24-44 wks
- Total Tx duration in Relapsers always 48 wks
- Main side effects
  - Anemia
  - Dysgeusia
- Approved with LI phase
- 3 x 4 tablets/day with food
- DDI (perhaps less critical ?)

Telaprevir

- Tx duration 12 wks
- Tx duration in Relapsers response-guided (24/48 wks)
- Main side effects
  - Rash (potentially severe)
  - Anemia
- LI phase not required, but possible
- Fatty meal required with intake, 3 x 2 tablets
- DDI

Practical Approach to Treatment

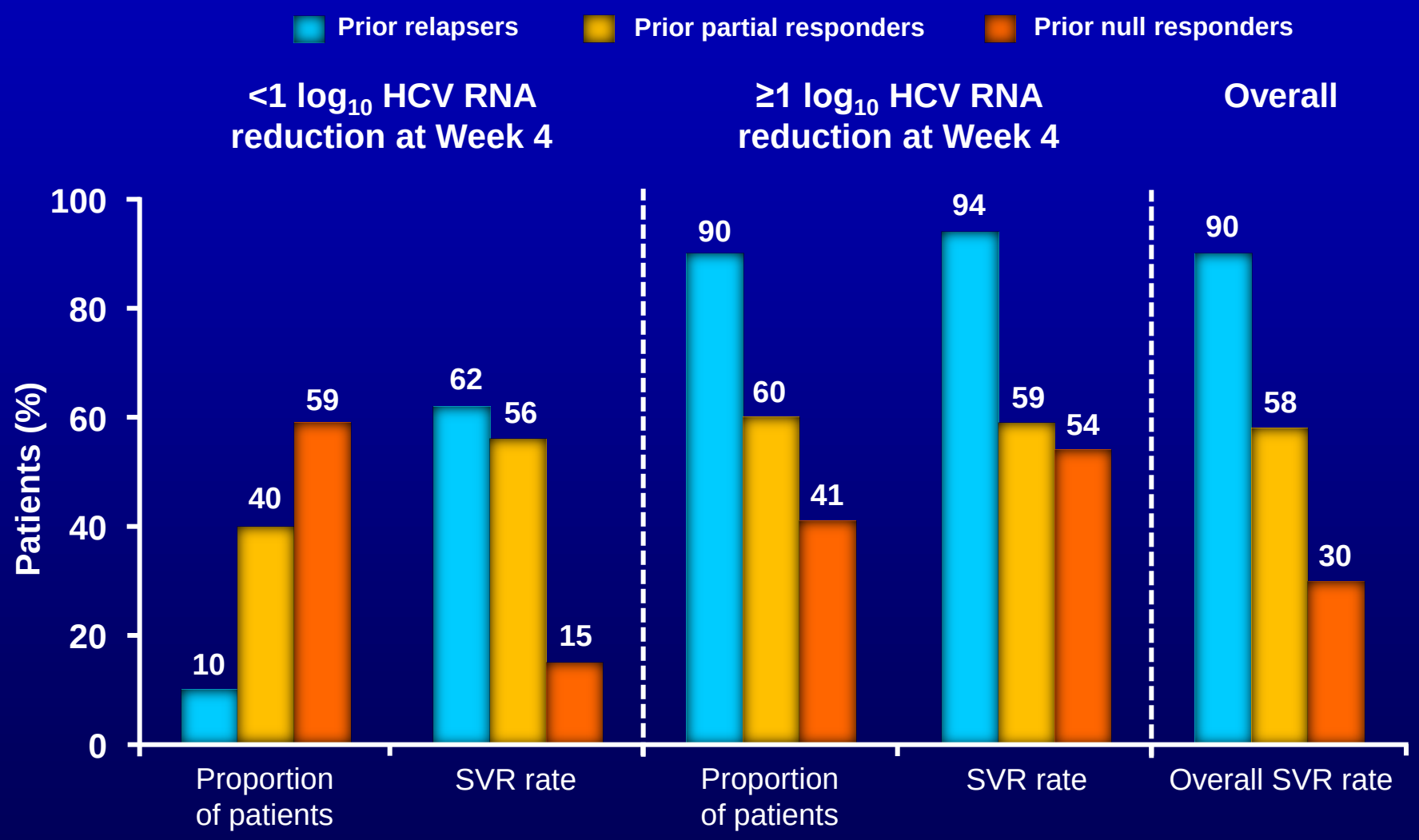
Treatment Indication

- Symptoms, extrahepatic manifestations
- Stage and progression of disease
  (in particular: cirrhosis, portal hypertension ?)
- Chances for SVR
- Concomitant diseases, Drug-drug interactions
- Motivation of the patient
- Contraindication

Virologic Assessment and Previous Treatment

- Genotype, Subtype (HCV-1a, -1b, ...)
- Viral load
- Previous treatment response (if any)
  - Relapser
  - Partial Responder
  - Null Responder
- Tolerability and side effects of previous treatment
- Adherence and persistence to previous treatment

SVR Rates in LI T12/PR48 Arm by HCV RNA Reduction at Week 4 and Prior Response



Foster et al., EASL 2011

Basic laboratory tests

- Full blood count
  - Anemia ?
  - Neutropenia? Thrombocytopenia?
- Liver function
  - Aminotransferases, GGT
  - Synthesis parameters
- Co-Infections (HBV, HIV ?)
- Exclusion of concomitant liver disease (autoimmune hepatitis)
- Thyroid function
- IL28B (tx-naive pts: YES; tx-experienced pts: NO)

Councelling the patients about current and future treatment options

- Previously untreated patients
  - HCV1: Triple therapy,
  - Remaining indication for PEG-IFN/RBV dual therapy (?)
  - HCV2-6: no approved DAAs/HTAs; PEG-IFN/RBV
- Treatment-experienced patients
  - HCV1: Triple therapy
  - HCV2-6: no approved DAAs/HTAs; PEG-IFN/RBV
- Future options (when ?)
  - Quadruple treatment (SVR rates > 90%)
  - IFN-free regimen (SVR rates >80%)

Some considerations concerning a lead-in phase

- Virologic value of LI phase is questionable
  - SPRINT-1: higher SVR rates with lead-in (but small number of patients)
  - REALIZE: Lead-in phase did not affect breakthrough, relapse and SVR rates
- Lead-in may be clinically useful if physician is willing to take decisions at week 4
  - only PEG/RBV, no PI in excellent initial virologic responders (RVR)
  - stop therapy in patients with poor initial virologic response (< 1 log) to avoid treatment failure and selection of resistant variants
- Improve adherence

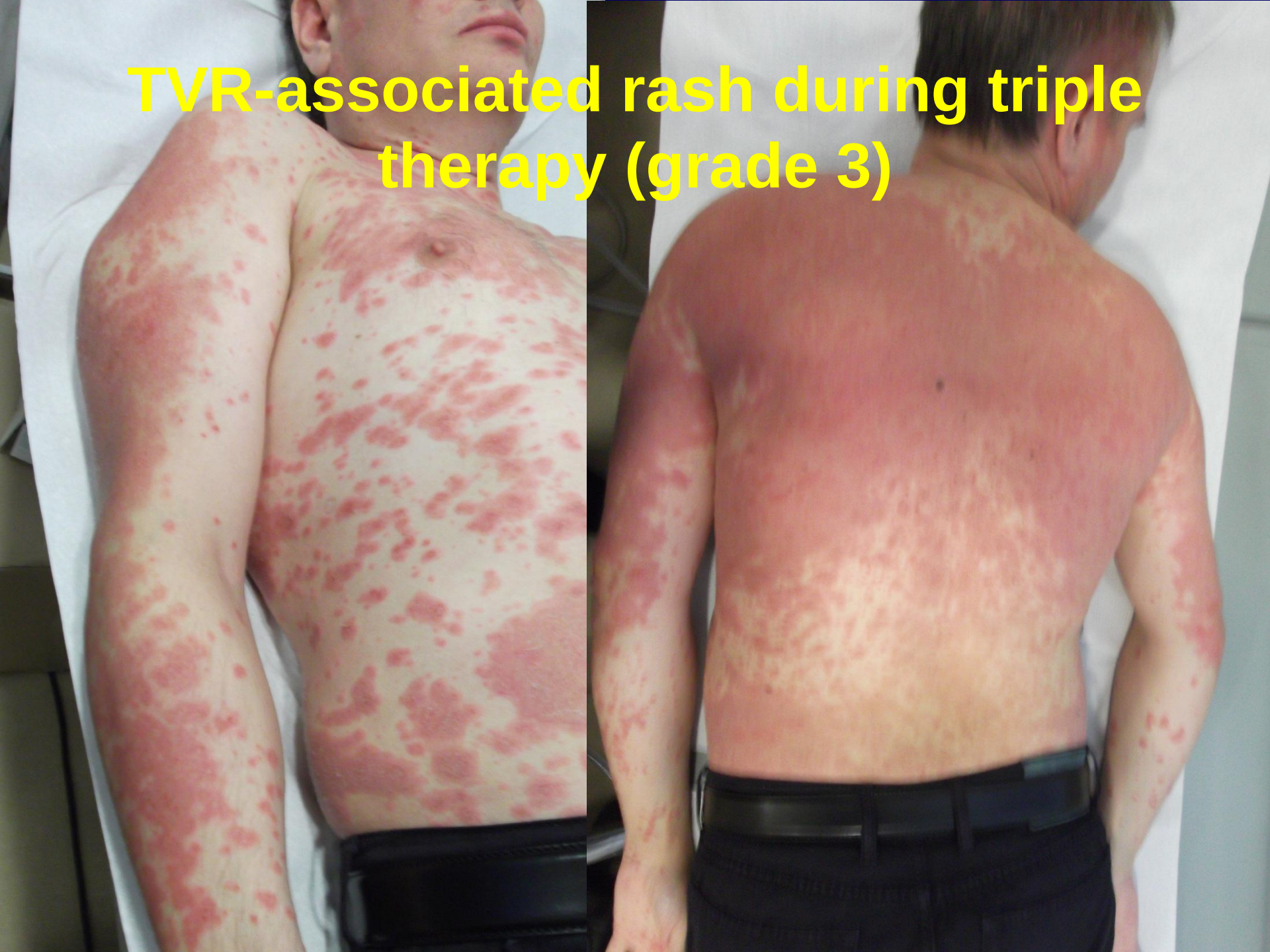
Management of anemia

- Check frequently hemoglobin levels, however, avoid iatrogenic anemia
- Cave: patients with liver cirrhosis
- Never (!!) dose reduce the protease inhibitor
- Use stepwise reduction of RBV
- Start RBV dose reduction early
- Consider the use of erythropoetin (Reimbursement ?) and blood transfusions
- Reduced efficacy of EPO in patients with cirrhosis (no studies)

Rash management plan with TVR

- Rash primarily eczematous and resolves (slowly) upon cessation of therapy
- Explain 9er-rule for estimating BSA
- Preemptive (?) prescription of e.g. Cetirizine and highly potent steroid creme
- Moderate and severe rash with progression are managed by sequentially discontinuing TVR, followed by RBV and, if indicated, Peg-IFN for continued progression
- Potential risk of DRESS and SJS
- Establish collaboration with dermatologist

TVR-associated rash during triple therapy (grade 3)

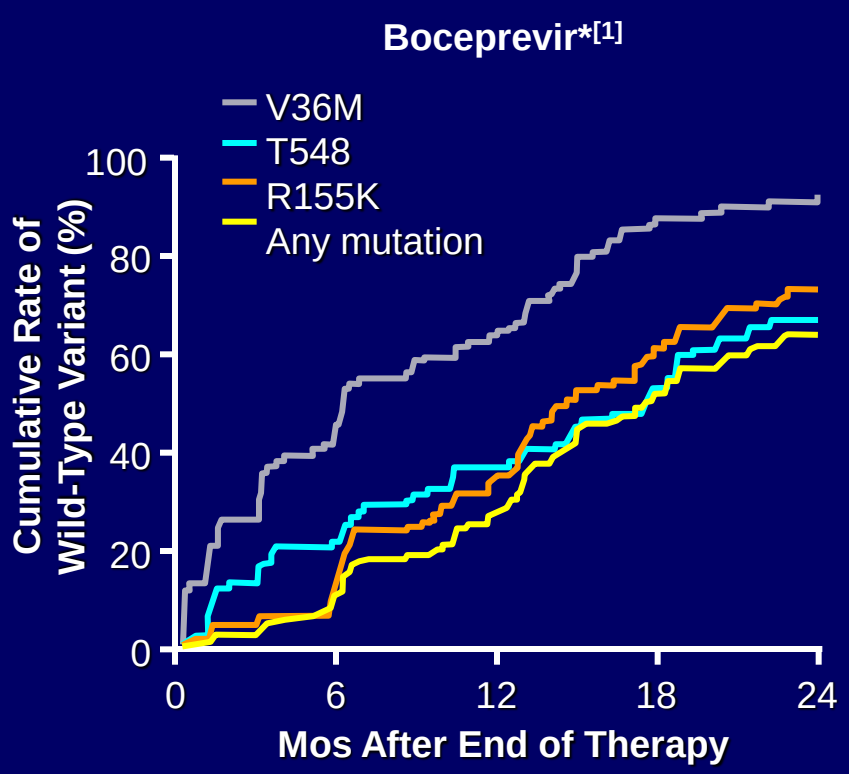


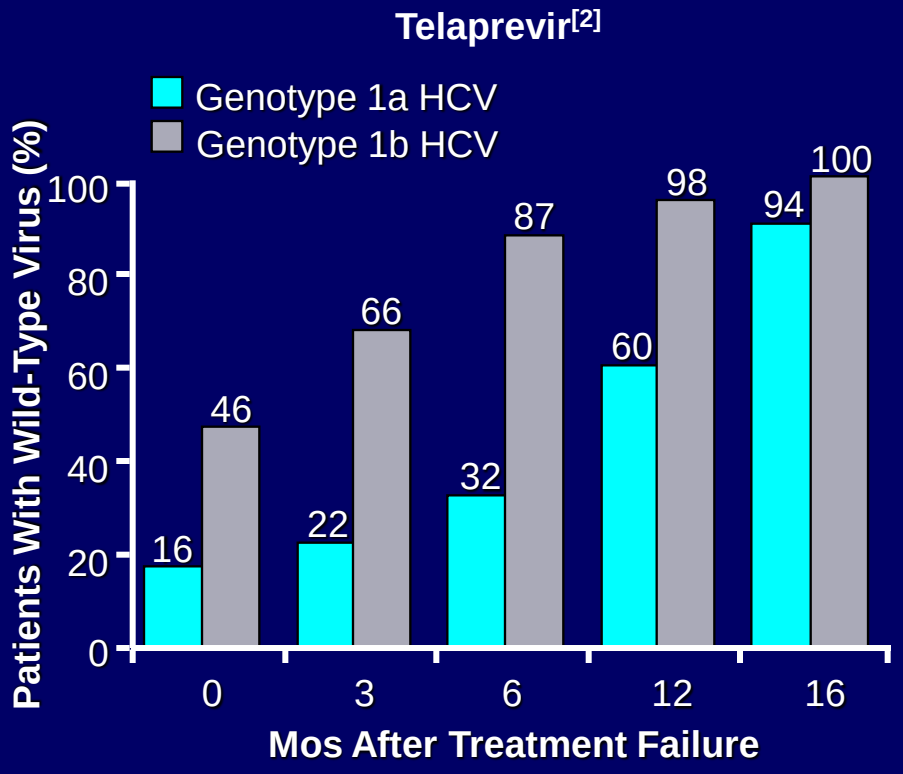
Any role for switching the PI during therapy ?

- No role for switching from one PI to the other in case of emergence of resistant variants
- Switch from TVR to BOC in case of severe rash safety-wise not explored

	TVR	BOC
V36A/M	+	+
T54S/A	+	+
V55A	in vitro	+
R155K/T/Q	+	+
A156S	+	+
A156T/V	+	in vitro
D168A/V/T		
V170A/T	in vitro	+

Loss of Detectable Resistance in Pts 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.

Key messages

- First generation PIs allow for major improvement of SVR rates in GT1-infected patients with hepatitis C
- Treatment schedules are complex and require thorough planning for patient and physician
- Careful consideration of potential DDI
- Optimal management of side effects
- Follow virological (resistance) and clinical (side effects) stopping rules
- Don‘t be afraid of triple therapy, but be carefully prepared !!
- Know about future treatment developments and advice your patients accordingly

Treat now !

- Good efficiency of current treatment options
  - Treatment naive pts and relapsers (HCV-1)
  - All HCV-2,3 infected patients
- Avoid progression of disease
  - In particular in pts with F3/4
  - Reduce the risk to develop HCC
- Side effects of current treatment regimen are manageable
- Approval date and price of new treatment options are unknown
- If the patient has no contraindications and is motivated, treat him now!

Wait !

- Current SVR rates are suboptimal
  - Partial and null-responders
  - Pts with cirrhosis and concomitant disease
- Side effects with Peg-IFN, RBV, and BOC/TVR are hardly acceptable
- In most patients fibrogenesis is slow and incidence of HCC low
- Future treatments will be shorter, more efficacious, safer, more tolerable and more convenient
- IFN-free will be become the new SOC
- Approval in 2-3 yrs, high competition, affordable

No fixed rules !

Optimal councelling of patient required !

Personalized decision !