Optimal Treatment with Boceprevir

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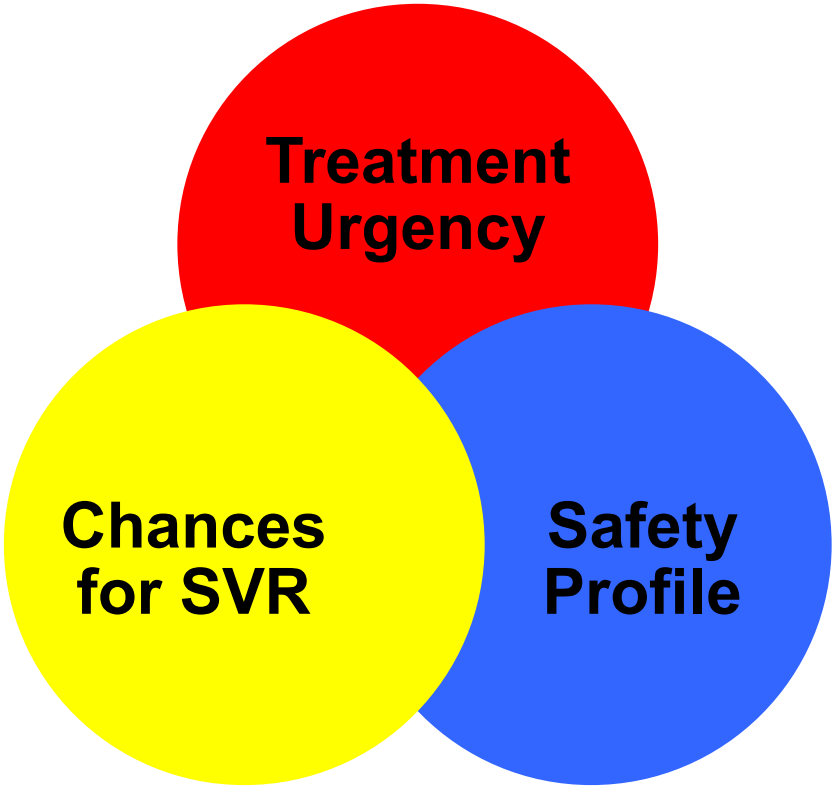
6th Paris Hepatitis Conference, 14th January 2013

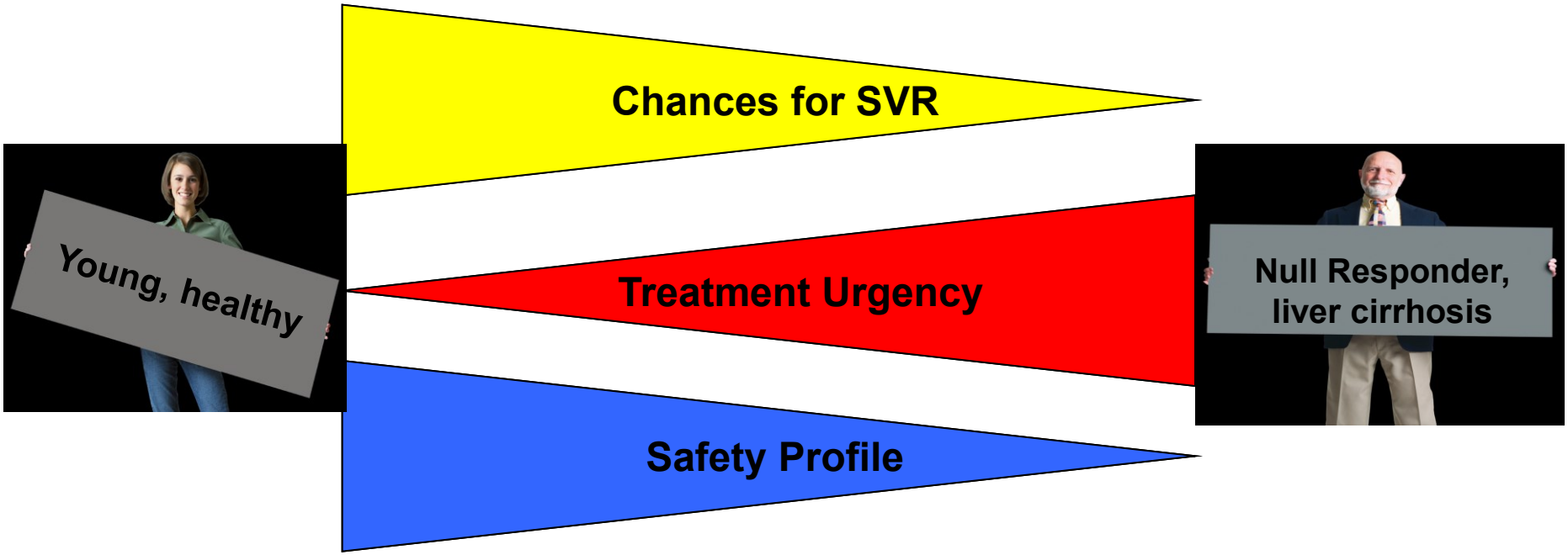
Acknowledgements

Benjamin Maasoumy

Optimal Patient Selection
Defining the Ideal Candidate



Optimal Patient Selection
Defining the ideal Candidate



In the real world there may even occur additional, nonmedical factors that interfere with aim to initiate treatment

i.e. professional drivers, social reasons, poor compliance, patient wish

Optimal Patient Selection
Real Life Safety of Triple Therapy

	CUPIC Week 16	MHH Week 12 (+/- Personalized lead-in)	EAP Week 16
Patient number	497	86	609
SAEs (% of patients affected)	40%	19%	14%
Death - due to Infection	6 (1.2%) 50%	1 (1.2%) 100%	3 (0.5%) 100%
Anemia			
RBV Dose reduction EPO	12% 51%	36% 0%	28% 24%
Blood Transfusion	12%	14%	12%

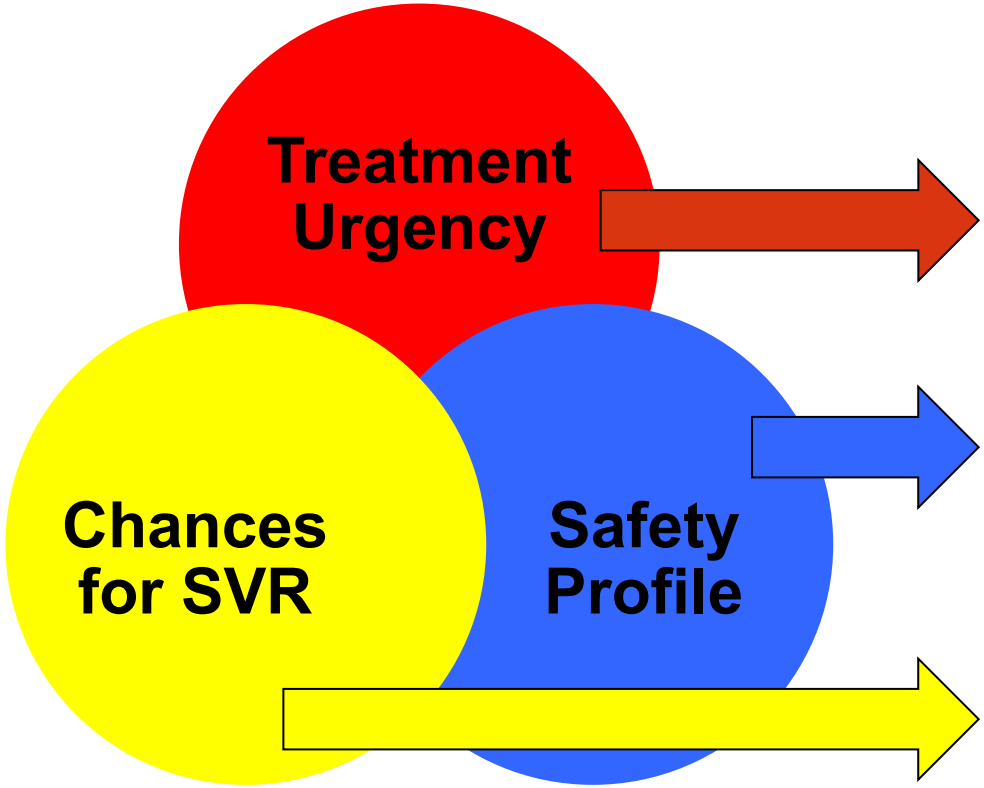
Predictors for SAEs:

CUPIC	MHH
Platelets <100.000/nl	Platelets <110.000/nl (SAE rate 48%)
Albumin <35g/l	Child-Pugh Score >5 (SAE rate 45%)

EAP: Patients with advanced cirrhosis were not included – may explain lower rate of SAEs

Maasoumy et al, AASLD 2012; PLoS One 2013 in press
Colombo et al., AASLD 2012; Hezode et al., AASLD 2012;

Optimal Patient Selection
Defining the ideal Candidate



Ideal Candidate

(F2/)F3 fibrosis
early cirrhosis

No significant
Co-Morbidities

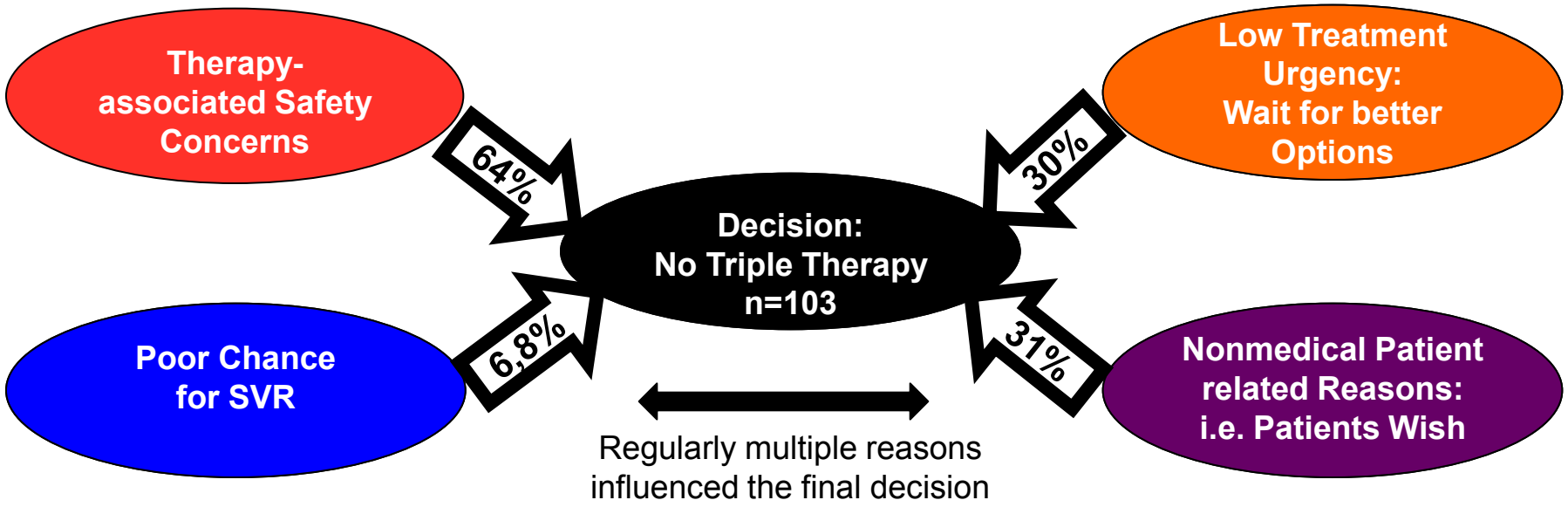
Previous Relapser
Treatment naïve

Things may not be that easy in many cases !

Optimal Patient Selection
Real Life Eligibility for Triple Therapy

208 patients with chronic HCV GT1 infection referred to hepatitis outpatient clinic of Hannover Medical School between June 1st and November 30th 2011 were evaluated for triple therapy
Real Life ≠ Phase-3 trials:

F3/F4: 64%; platelets <90/nl: 16%, treatment-experienced: 60%



Real Life

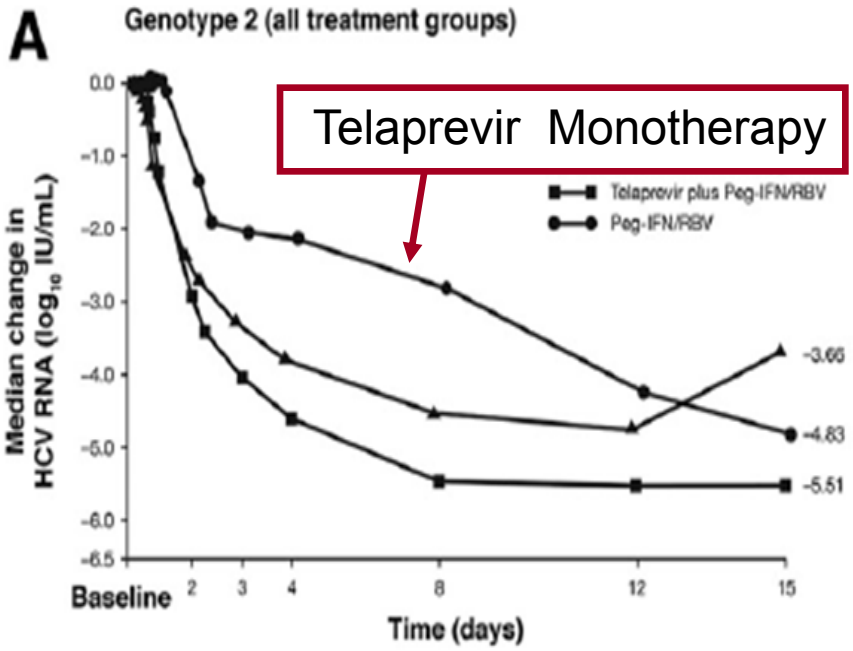
Almost **50%** (n=103) not treated

Optimal Patient Selection
Telaprevir vs. Boceprevir

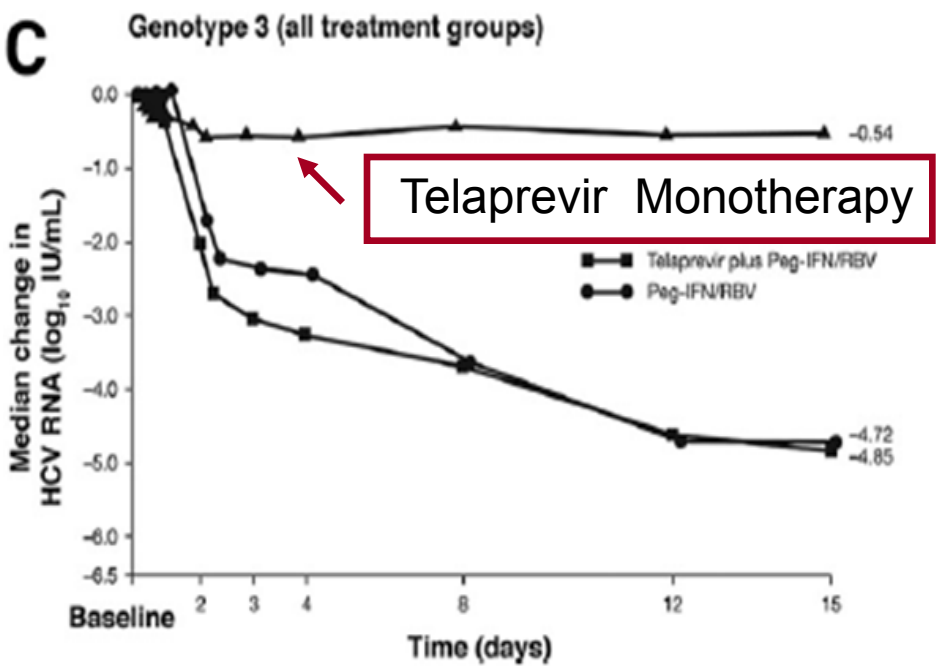
	Telaprevir	Boceprevir
Treatment Duration	RGT possible for Relapsers	
Co-Infections	Some efficacy in GT2	Some efficacy in GT3

Telaprevir has some antiviral efficacy against HCV genotype 2 but not against genotype 3

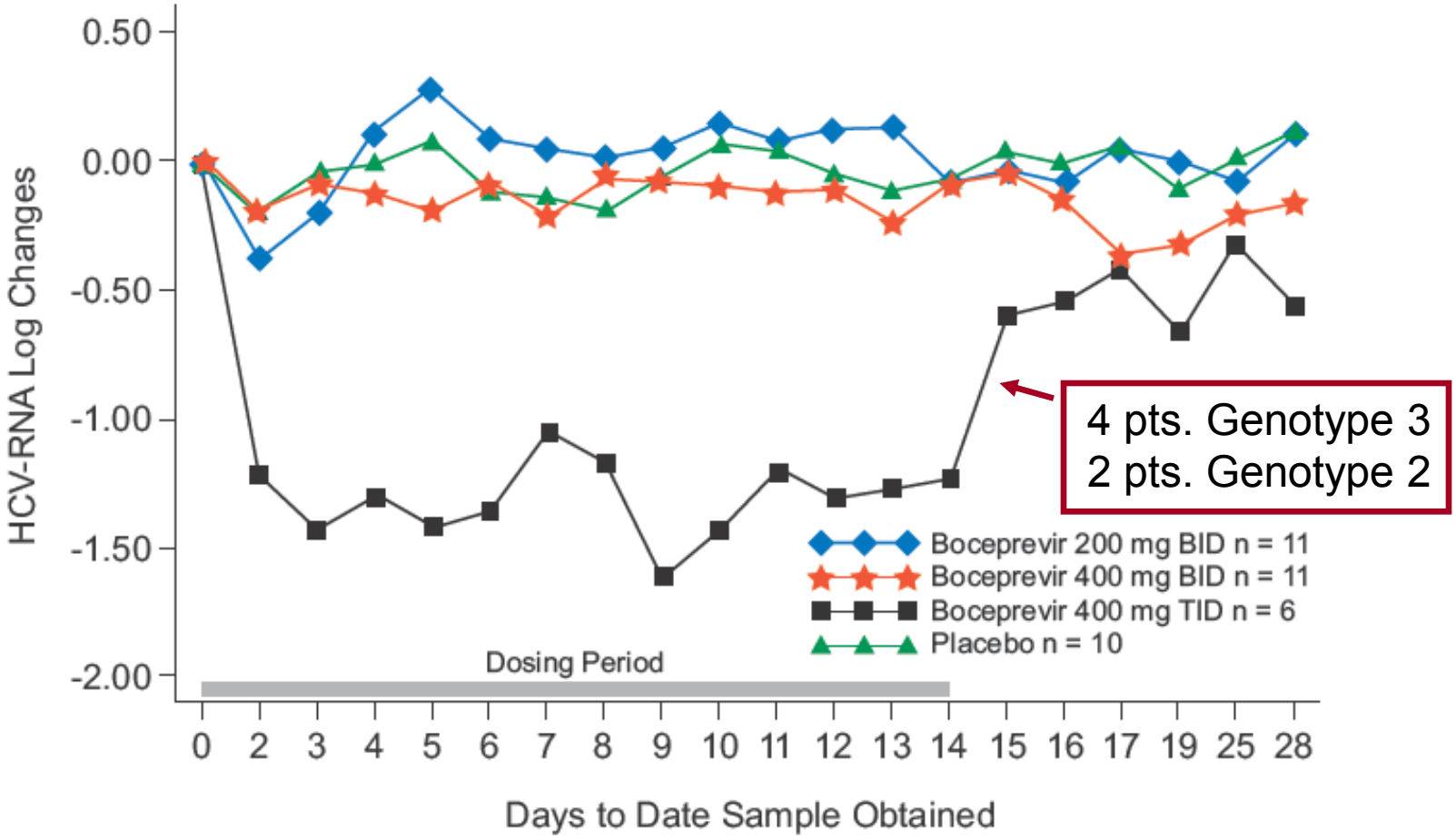
Genotype 2



Genotype 3



Boceprevir has some antiviral efficacy against HCV genotype 2 and genotype 3

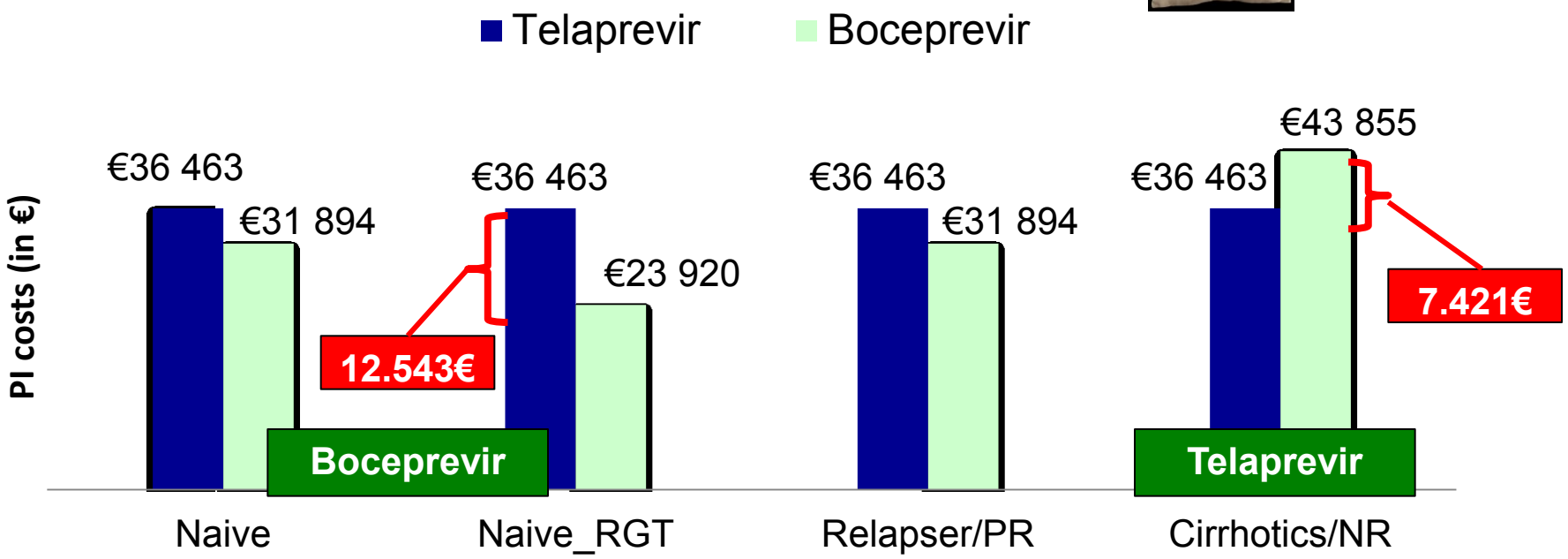


Silva M et al, APASL 2011

Optimal Patient Selection
Telaprevir vs. Boceprevir

	Telaprevir	Boceprevir
Treatment Duration	RGT possible for Relapsers	
Co-Infections	Some efficacy in GT2	Some efficacy in GT3
Lower PI Costs	In Null Responders and Cirrhotics (if treatment is not discontinued)	Naïve patients In cases of treatment discontinuation

PI Treatment costs



Boceprevir PI treatment costs per month lower: 3.987€ vs. 12.154€

Boceprevir cheaper in cases of early treatment failure

Sarrazin et al, Z Gastro 2012

Optimal Patient Selection
Ideal Candidate for Boceprevir

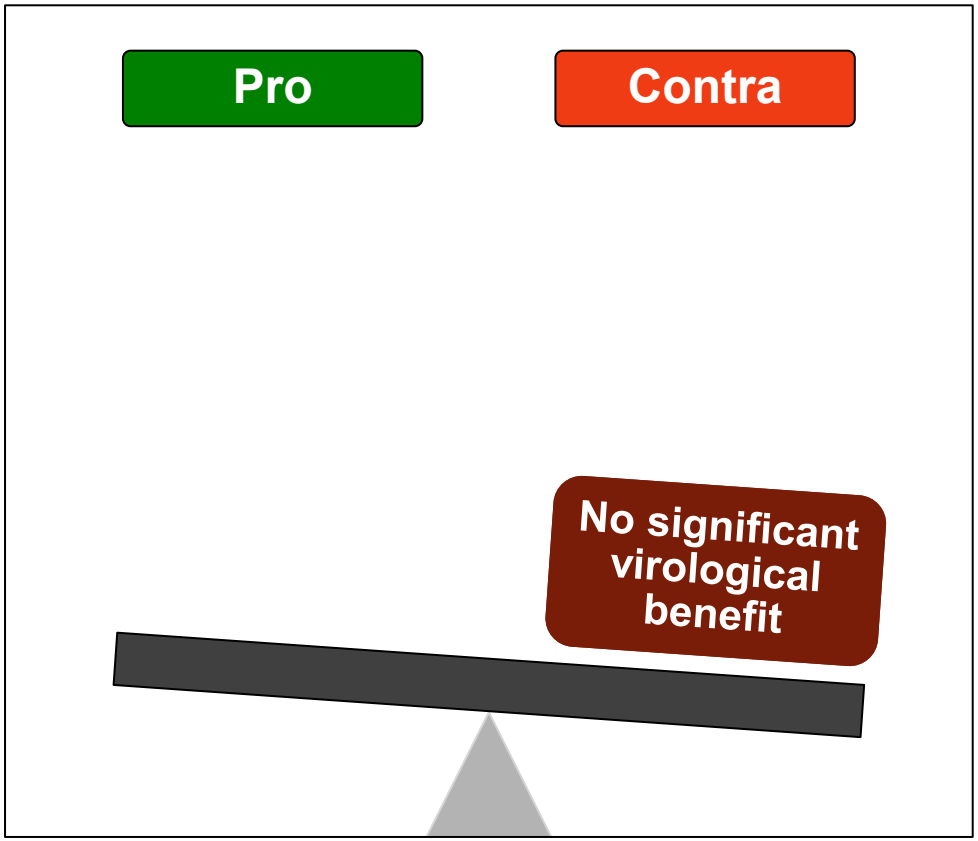
Treatment-naïve

Co-infected with HCV GT3

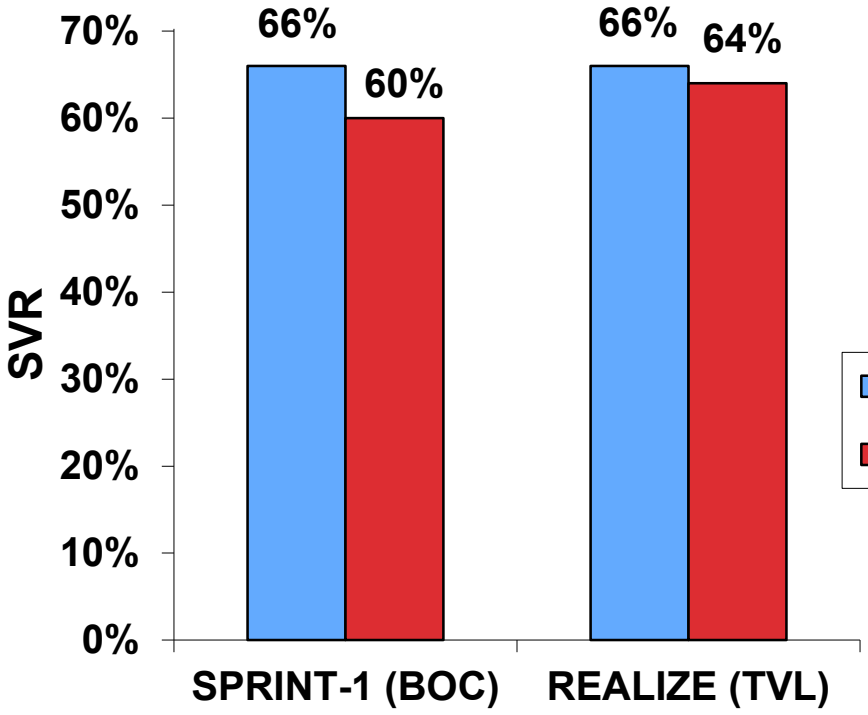
and

Patients that benefit from a Lead-In

Optimal Treatment Design
Lead-In – a controversial debate



Optimal Treatment Design
Lead-In – Virological data

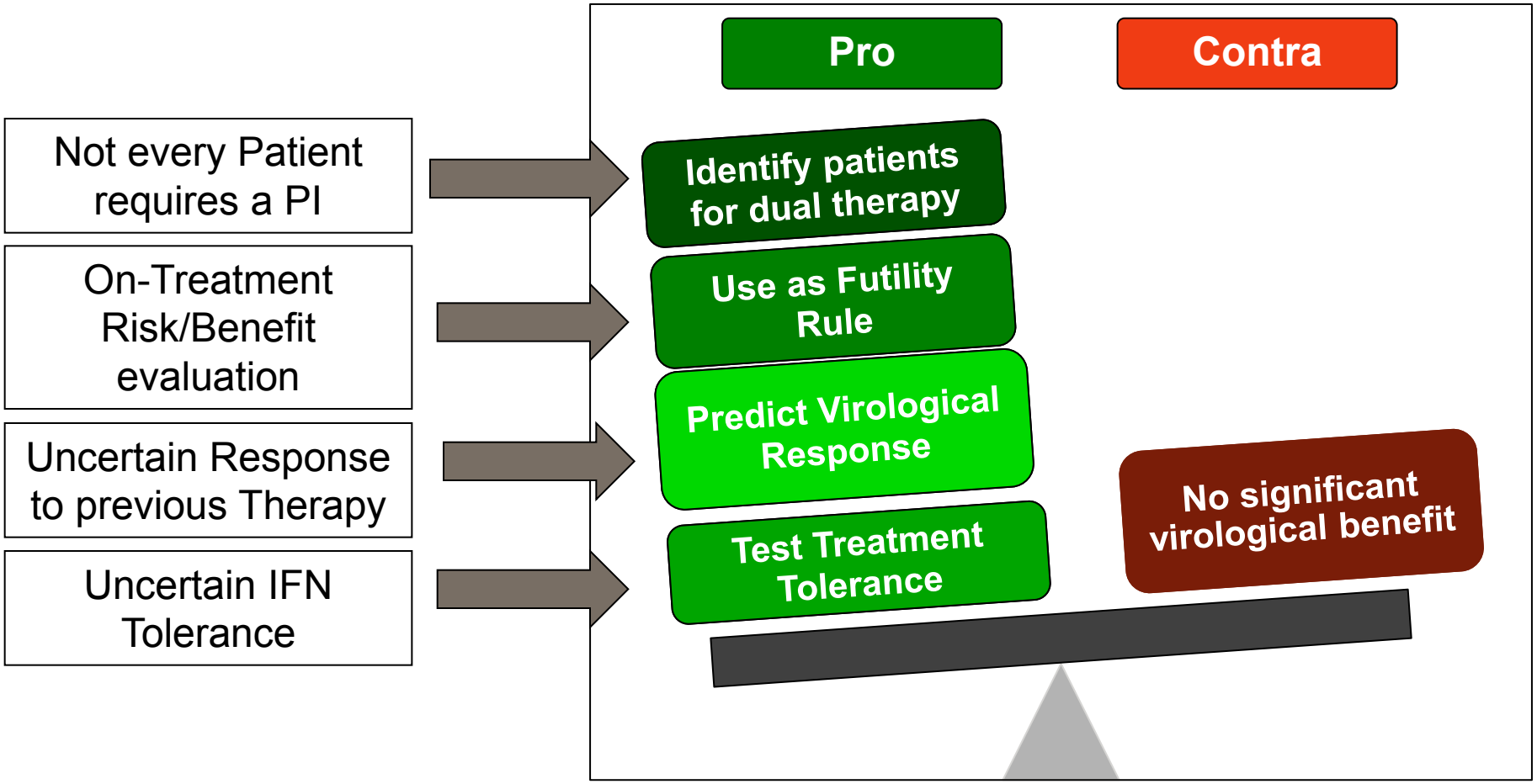


No significant differences

Zeuzem et al., NEJM 2011

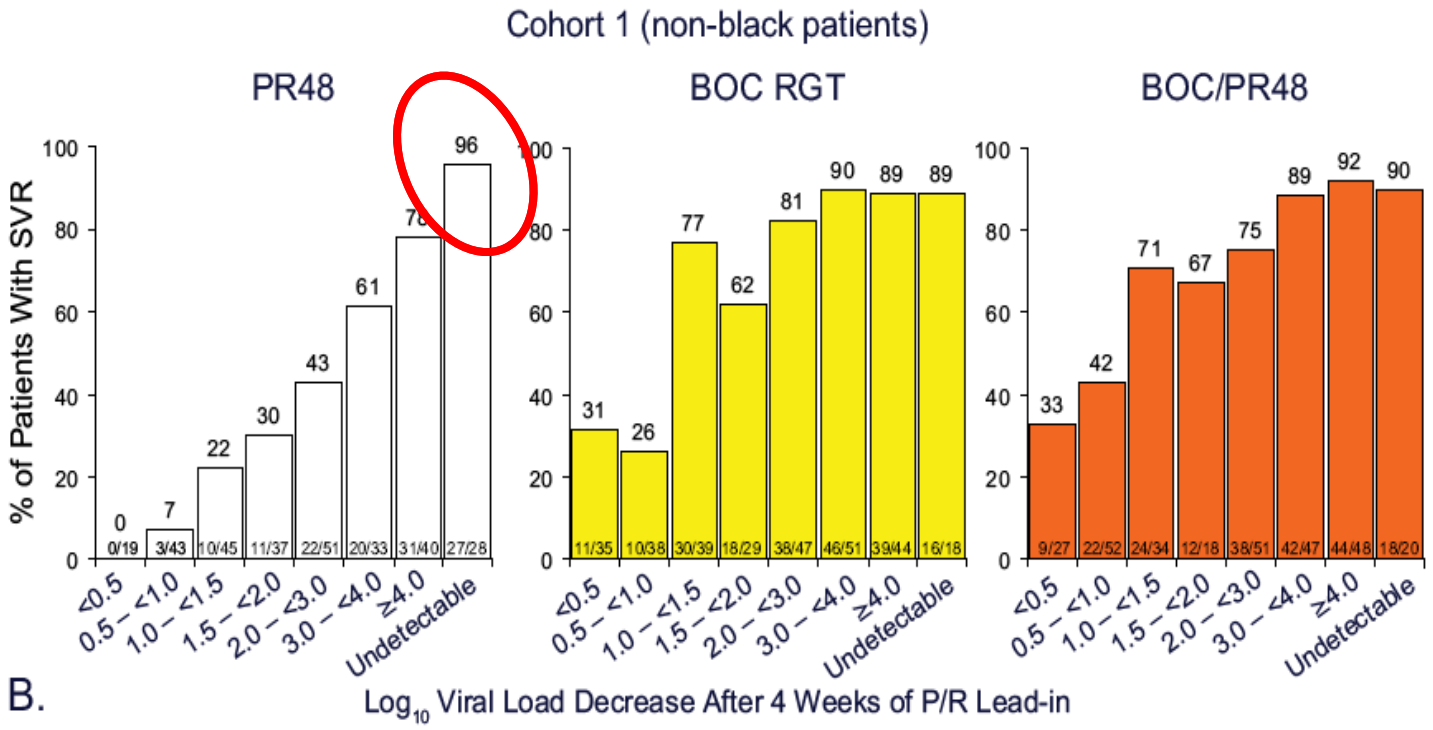
Kwo et al., Lancet 2010

Optimal Treatment Design
Lead-In – a controversial debate



Lead-In as a “test phase”
important tool used to gain additional information

Lead-in in easy to treat patients
Not every patient benefits from a PI

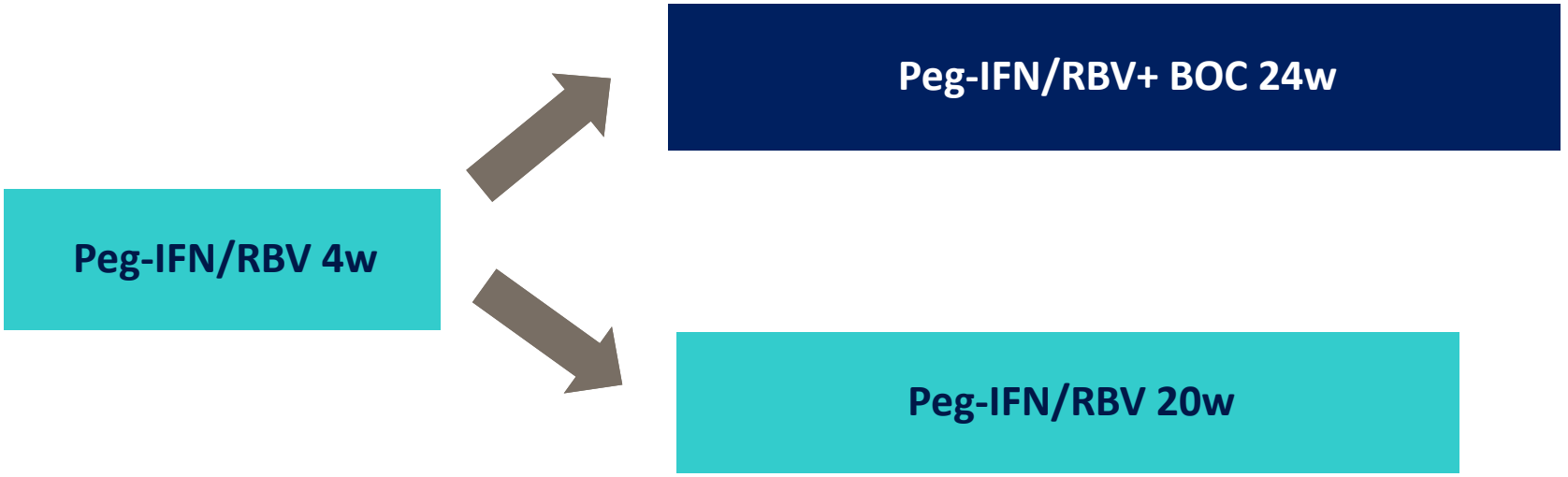


Vierling et al., EASL 2011

Poordad et al., NEJM 2011

P/R = P/R/PI?
A randomized trial - Study Design

179 **treatment-naïve** patients with chronic HCV GT1 infection and a **LVL** (<600,000 IU/ml)



Patients with HCV RNA BLOD (48%) randomized into 2 arms (1:1)

P/R = P/R/PI?
A randomized trial - Results

	P/R/BOC n=41	P/R n=38	p-values
SVR			
- **Overall**	**90%**	**89%**	**0.8**
- IL28B			
CC	96%	96%	0.51
non-CC	79%	77%	0.72
- GT			
1a	81%	85%	ns
1b	96%	92%	ns
Relapse rates	3%	6%	0.52
Dose reductions	32%	29%	ns
Discontinuations	7%	5%	ns

Pearlman et al, AASLD 2012

Optimal Patient Selection
Ideal Candidate for Boceprevir

Treatment-naïve

Co-infected with HCV GT3

Patients that benefit from a Lead-In

“Easy-to-treat” patients

Patients with uncertain virological outcome

Patients with uncertain treatment tolerance

Lead-In also possible for Telparevir

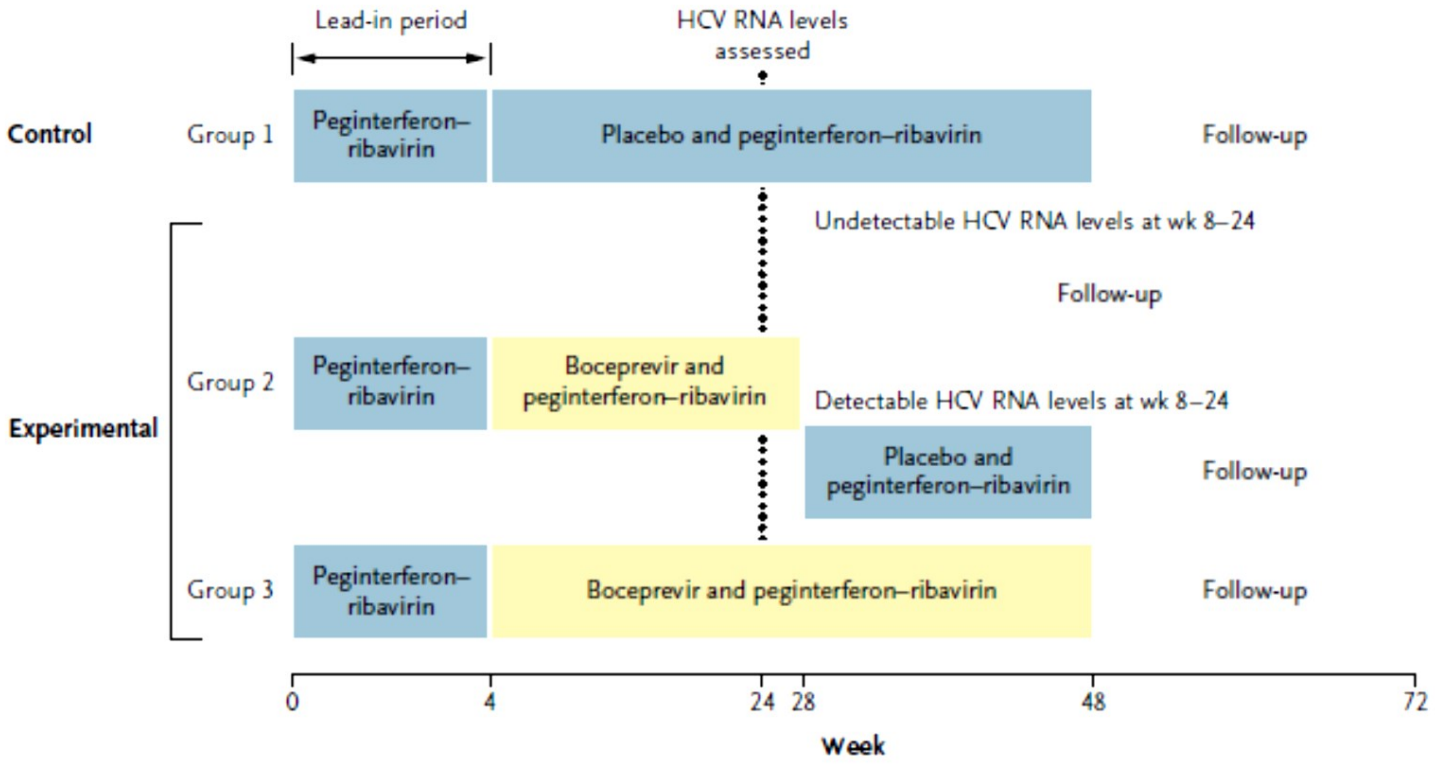
…not well established !

Optimal treatment with boceprevir
Finding the optimal treatment design

- Lead-in?
- RGT vs. fixed duration
- Regimens for treatment-experienced patients
- Stopping criteria

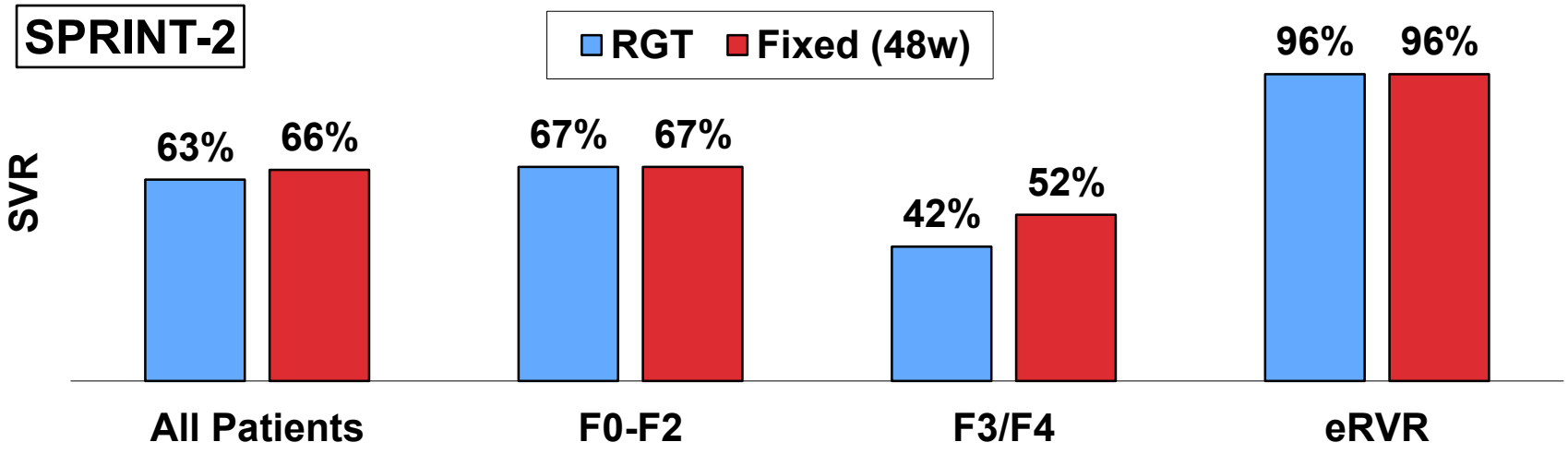
Optimal Treatment Design
Response Guided Treatment

SPRINT-2 study: Phase 3 trial with 1097 treatment-naïve patients.



Poordad et al., NEJM 2011

Optimal Treatment Design
Response Guided Treatment



Decision by FDA and EMA: RGT for treatment-naïve, non-cirrhotic patients

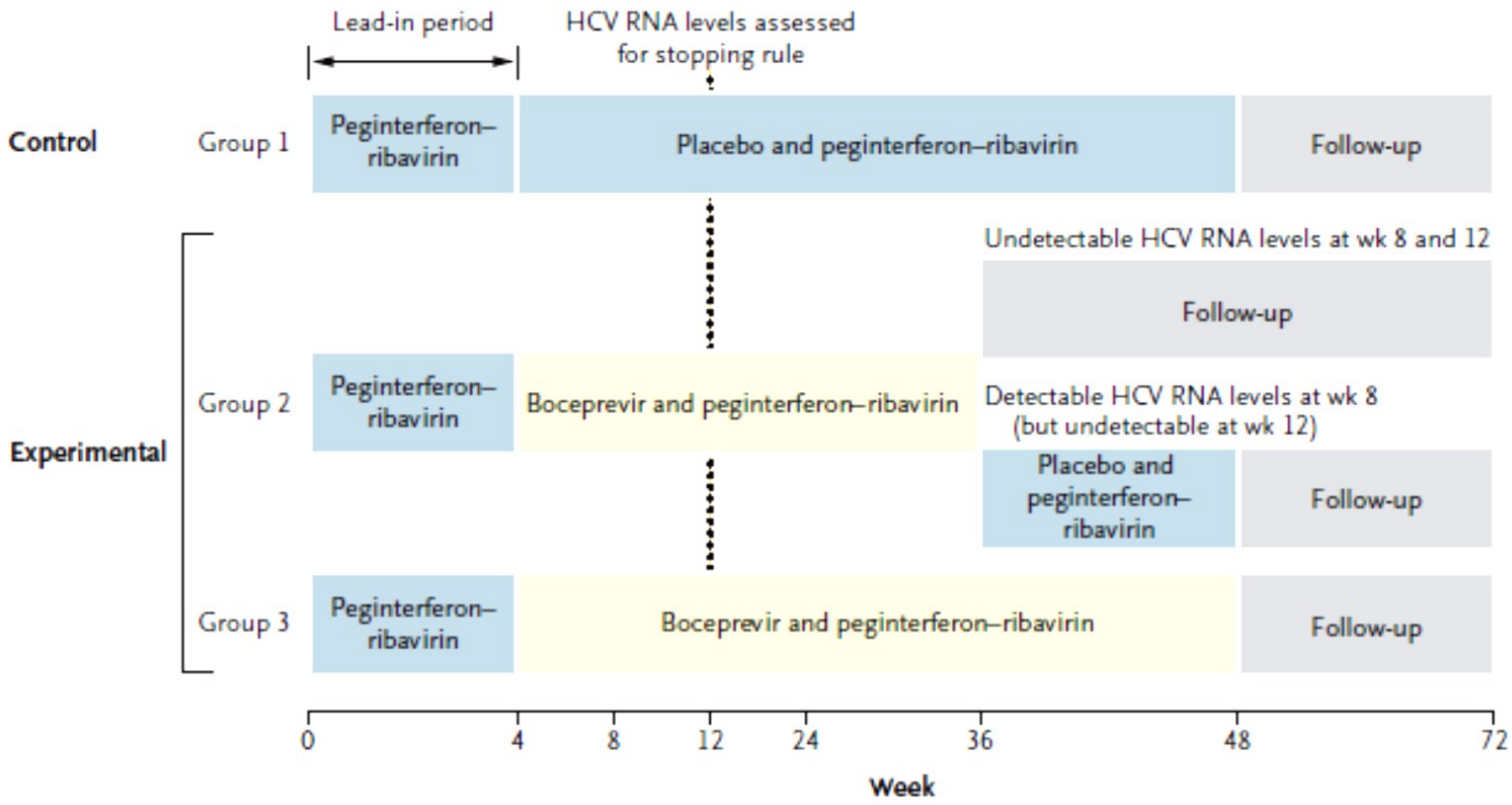
Patients with eRVR
- End treatment after 28 weeks
- Just like in the SPRINT-2 trial

Those without eRVR
- **not directly studied!!!**
- Recommended regimen ≠ SPRINT-2
- Non-eRVR patients considered to be a mixture of PR and NR
  - Treated like non-eRVR patients in RESPOND-2 (4w P/R; 32 w P/R/BOC; 12w P/R)

Poordad et al., NEJM 2011

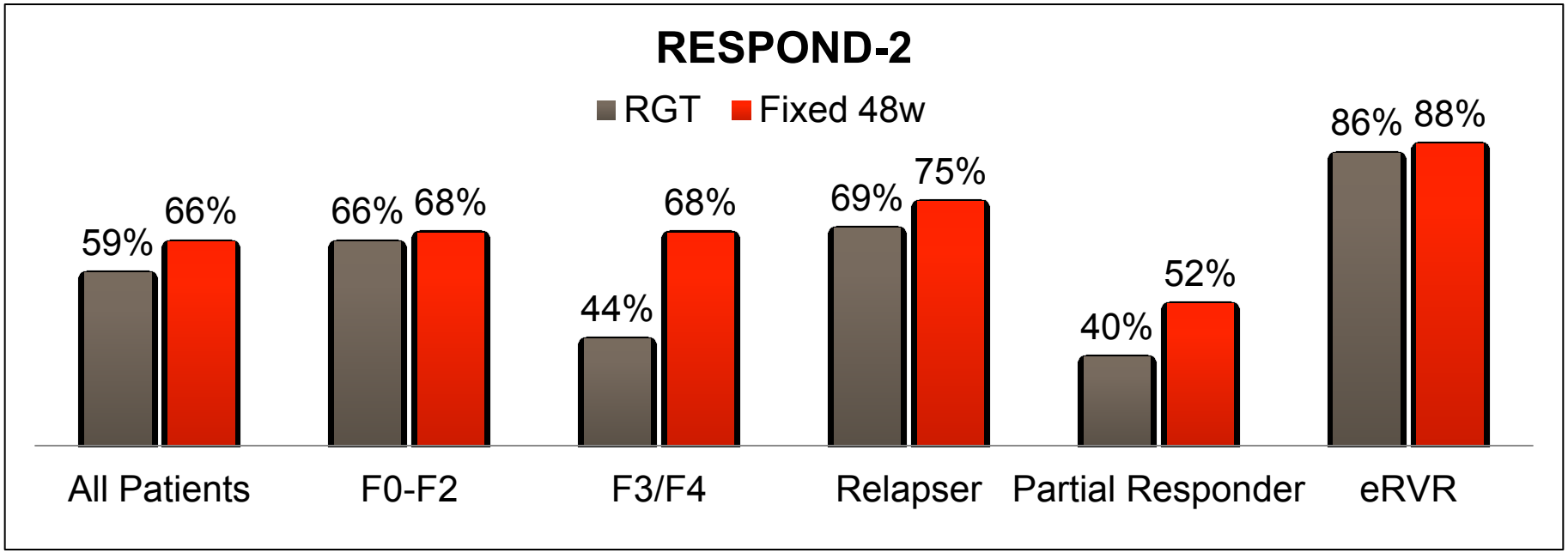
Optimal Treatment Design
Response Guided Treatment

Respond-2 study: Phase 3 trial with 403 IFN partial responders or relapsers. Null responders excluded!!



Bacon et al., NEJM 2011

Optimal Treatment Design
Response Guided Treatment



Decision by:

FDA: no significant difference in non-cirrhotics with eRVR

RGT possible in non-cirrhotic Relapsers and PR

Same regimen like in the RESPOND-2 trial

EMA: no RGT!!! All non-cirrhotic Relapsers and PR should be treated for 48 weeks (4w LI; 32w P/R/BOC; 12w P/R)

Bacon et al., NEJM 2011

Optimal Treatment Design
RGT in Relapsers and PR – the EMA approach

FDA

	Patients with undetectable HCV RNA W8	
	Group 2: RGT	Group 3: fixed
Relapse	*8/71 (11%)	*6/80 (8%)
SVR	64/74 (86%)	74/84 (88%)

*In a few patients without FU24 data SVR12 data were used

EMA Rationale: Patients in both groups were treated the same way until week 36
Thus analysis should exclude those who dropped out before this stage **!!!!!**

EMA

	Patients with undetectable HCV RNA W8	
	Group 2: RGT	Group 3: fixed
Relapse	*7/69 (10%)	*0/71 (0%)
SVR	63/71 (89%)	71/73 (97%)

No RGT due to **seven** Relapses in the RGT arm!

Optimal Treatment Design
Cirrhotics and null responders

Cirrhotics:

-Data on efficacy in cirrhotics are limited

- RESPOND-2: 39 cirrhotic patients; SVR: 35% (RGT) vs. 77% (fixed)
- SPRINT-2: 40 cirrhotic patients; SVR: 31% (RGT) vs. 42% (fixed)

-Overall, less favorable outcome

-*Recommendation:* 4 weeks lead-in and 44 weeks triple therapy if tolerated

- If AEs i.e. anemia is challenging dual therapy (P/R) in the last 12 weeks can be considered

Null Responder:

-not studied in the pivotal trials!

-Indirect analysis by considering those with a poor lead-in response comparable to previous null responders

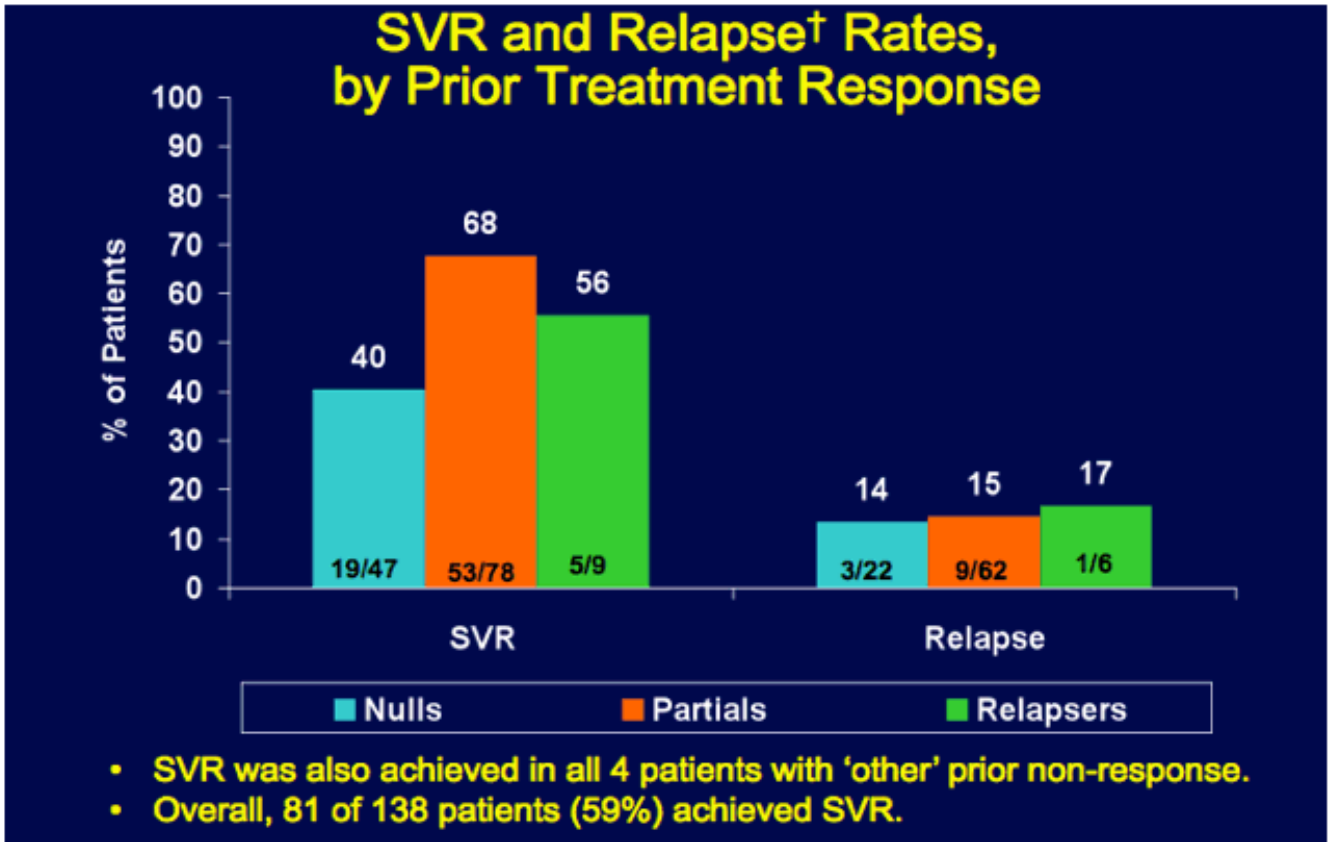
-*Recommendation:* difficult-to treat cohort; 4 weeks lead-in and 44 weeks triple therapy

EMA Victrelis assement report

Bacon et al., NEJM 2011; Poordad et al., NEJM 2011

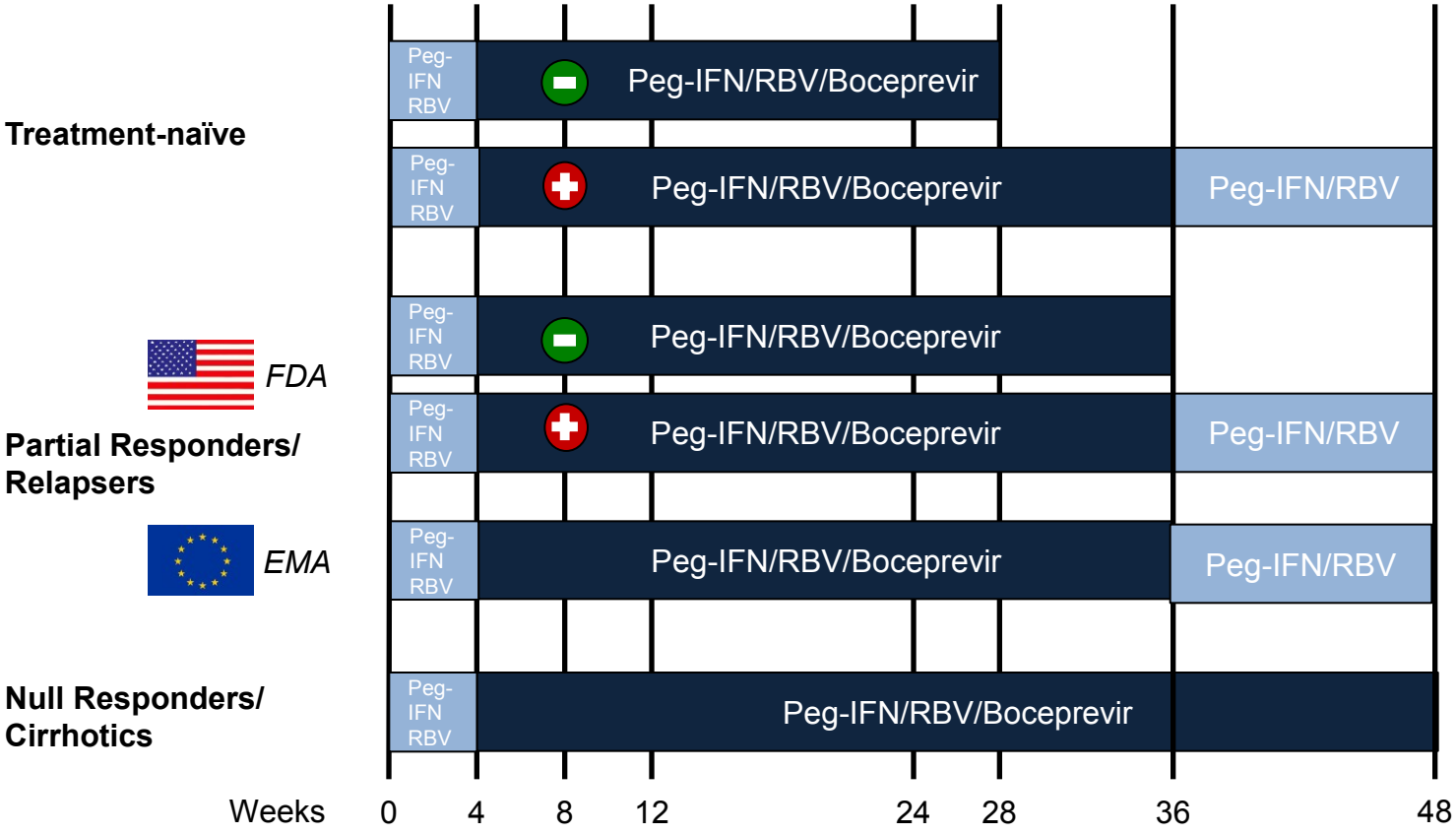
Boceprevir in null-responders
PROVIDE-Study - Efficacy

164 patients treated with P/R/BOC
previously experienced a treatment failure with P/R in a BOC phase 2/3 control arm



Bronowicki et al., EASL 2012

Optimal Treatment Design
Recommended Design



Victrelis Prescribing information EMA
Victrelis Prescribing information FDA

Optimal Treatment Design
RGT - Personalized Approaches

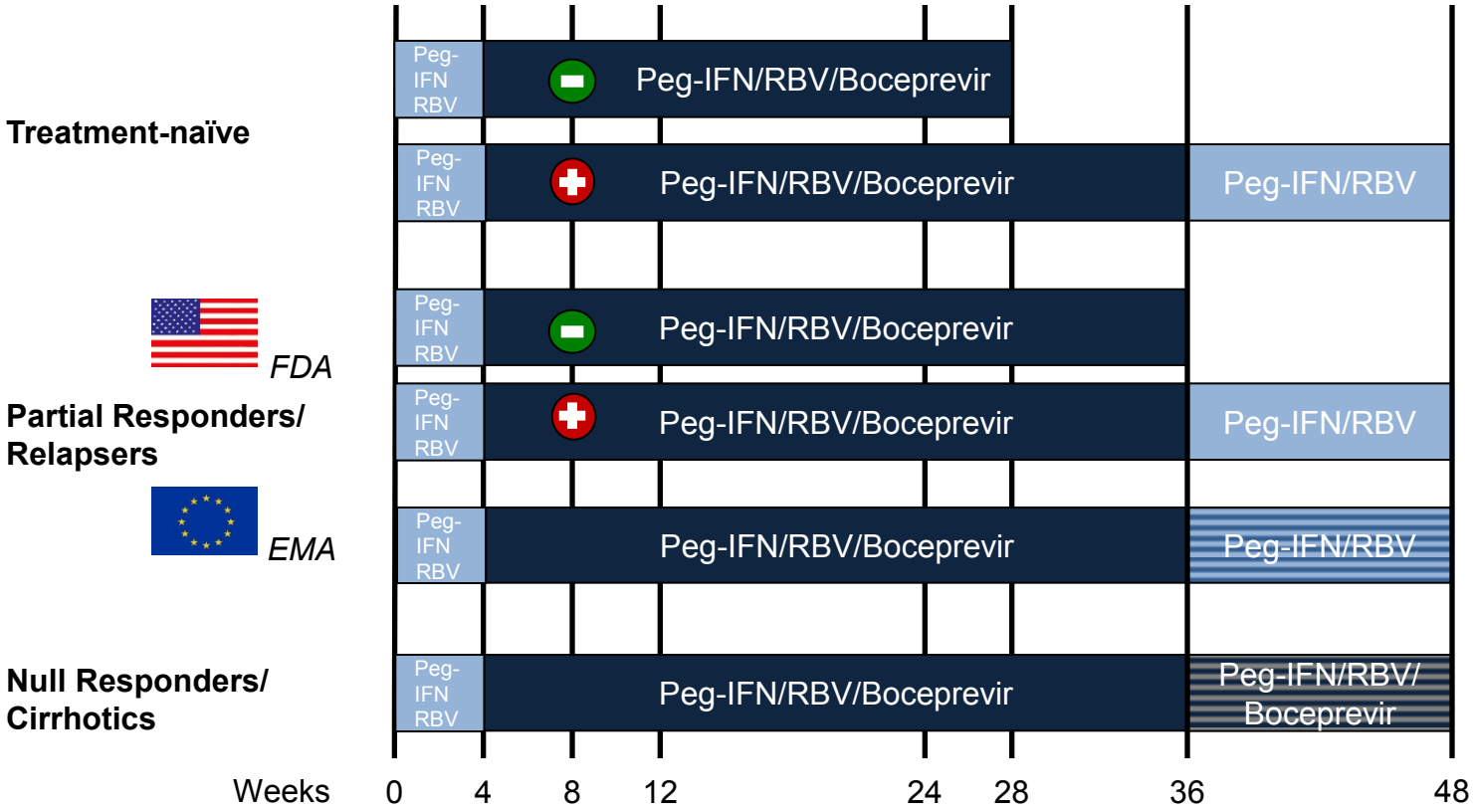
Based on the *risk/benefit* ratio personalized approaches may be applied i.e.

-Dual therapy for treatment-naïve patients with RVR

-PR and relapsers with eRVR: risk of AEs vs. small chance for a relapse (10%)

-Null Responders and cirrhotics with eRVR: Lack of data

Optimal Treatment Design – Some Personalized Approaches



EMA Decision based on seven patients

Lack of data for null responders/cirrhotics
Room for personalized approaches:

*Personalized

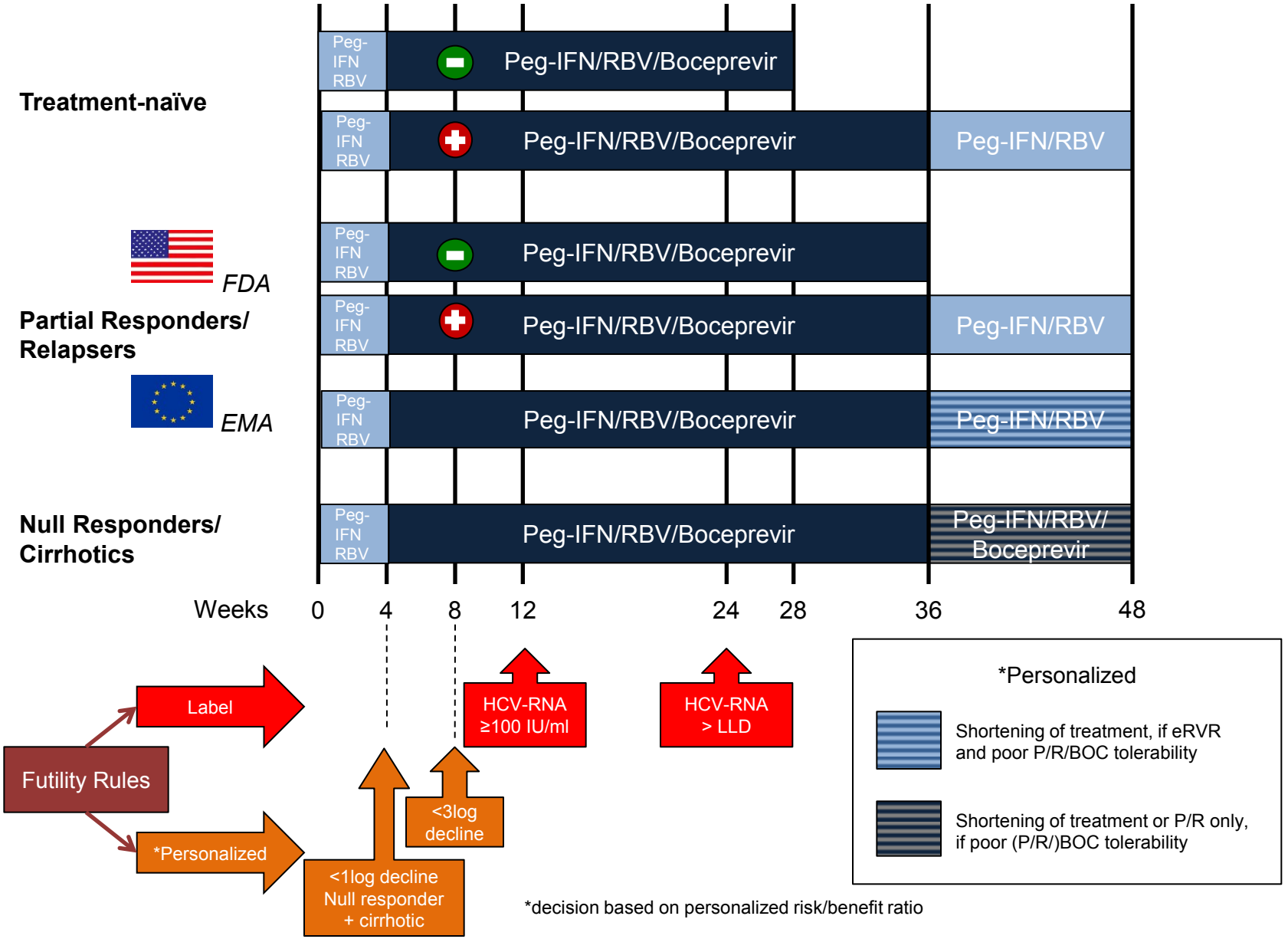
Shortening of treatment, if eRVR and poor P/R/BOC tolerability

Shortening of treatment or P/R only, if poor (P/R/)BOC tolerability

*decision based on personalized risk/benefit ratio

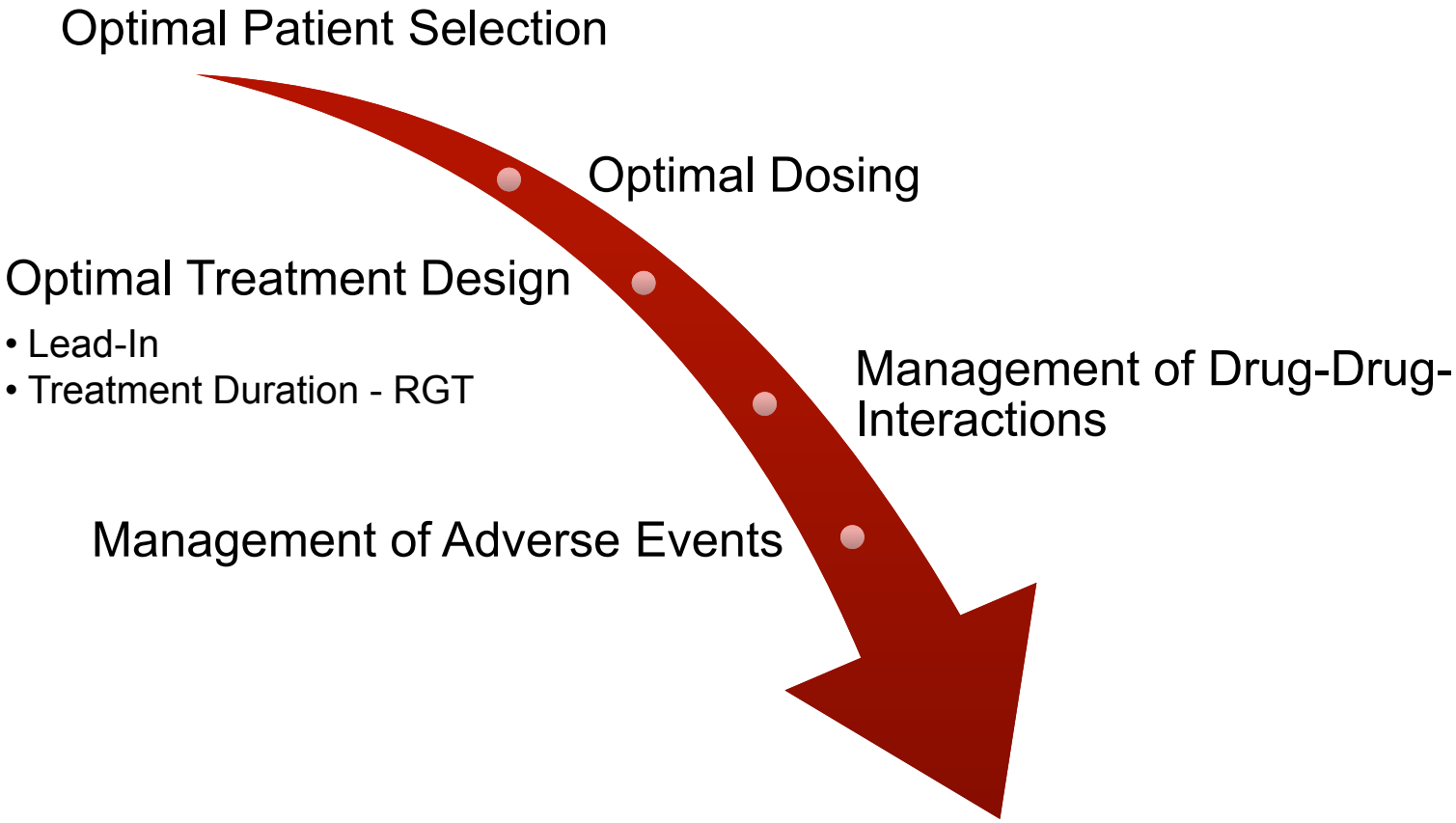
Maasoumy and Manns, Liver International 2013

Optimal Treatment Design – Some Personalized Approaches



Maasoumy and Manns, Liver International 2013

Optimal Treatment for Boceprevir
Every Single Step is essential !!



Thank you for your attention !!