Neues vom International Liver Congress (EASL 2011)

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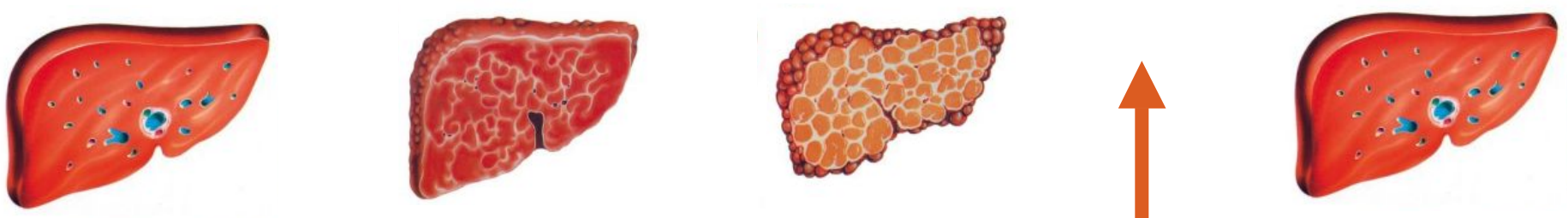
AK AIDS 01.06.2011

Natural History of Hepatitis C

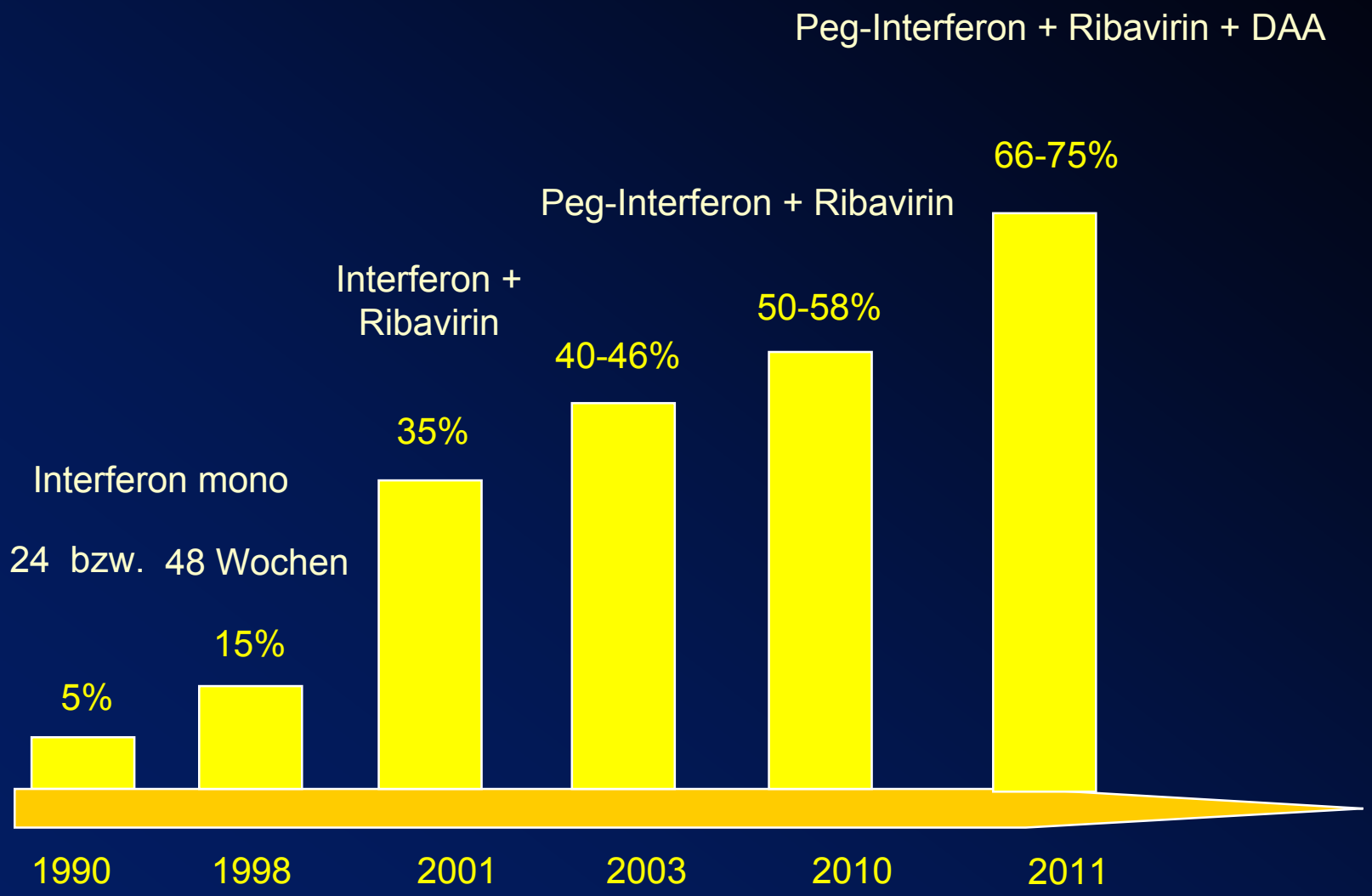
6 Months → 10 - 20 years → 1 year

acute Hep C	chronic Hep C	cirrhosis Hep C	HCV re-infection



50-70% | 10-20% | **Decompensation 6%**
HCC 5%
Liver transplantation? | >90%

Development of treatment options in CHC: SVR rates improving in Genotyp 1

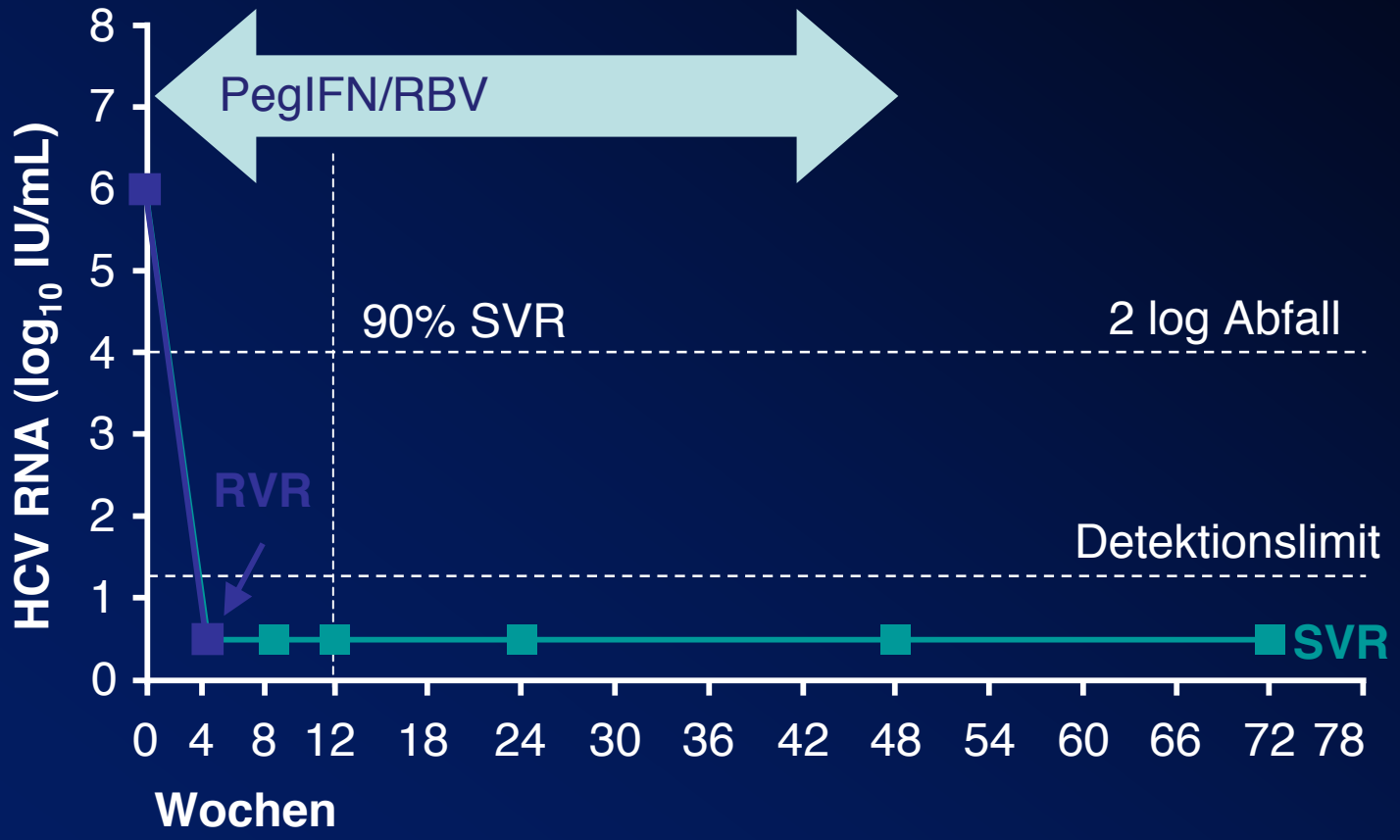


Predictive factors for treatment success in CHC

- on treatment virologic response (RVR, cEVR)
- IL28B Genotyp
- younger age (<40 yrs)
- low fibrosis stage
- low HCV RNA levels at baseline
- BMI (<30)
- gender (f>m)
- no steatosis
- no diabetes mellitus
- no HIV or HBV coinfection
- etc.....

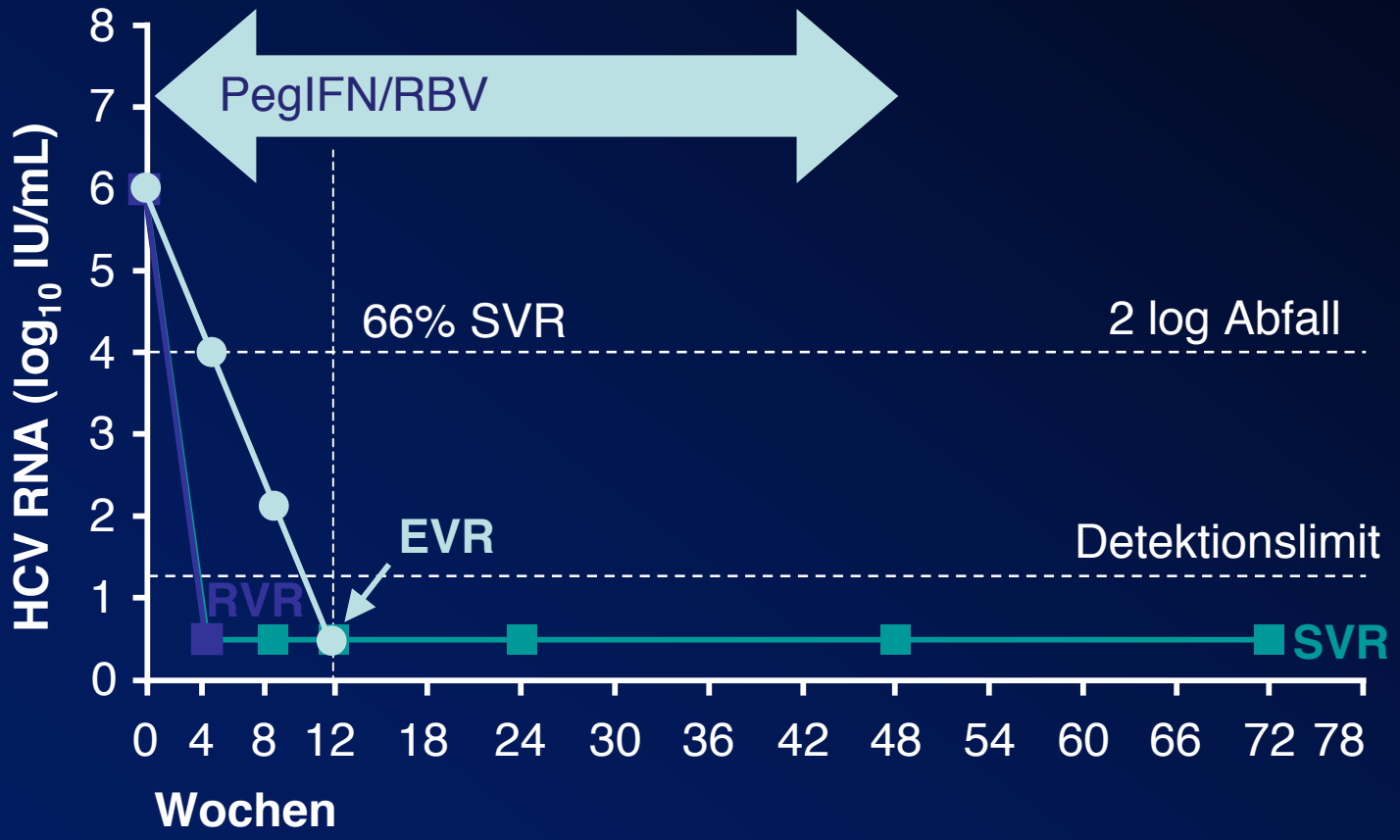
Kau et al., J hepatol 2009

RVR: HCV RNA not detectable at week 4



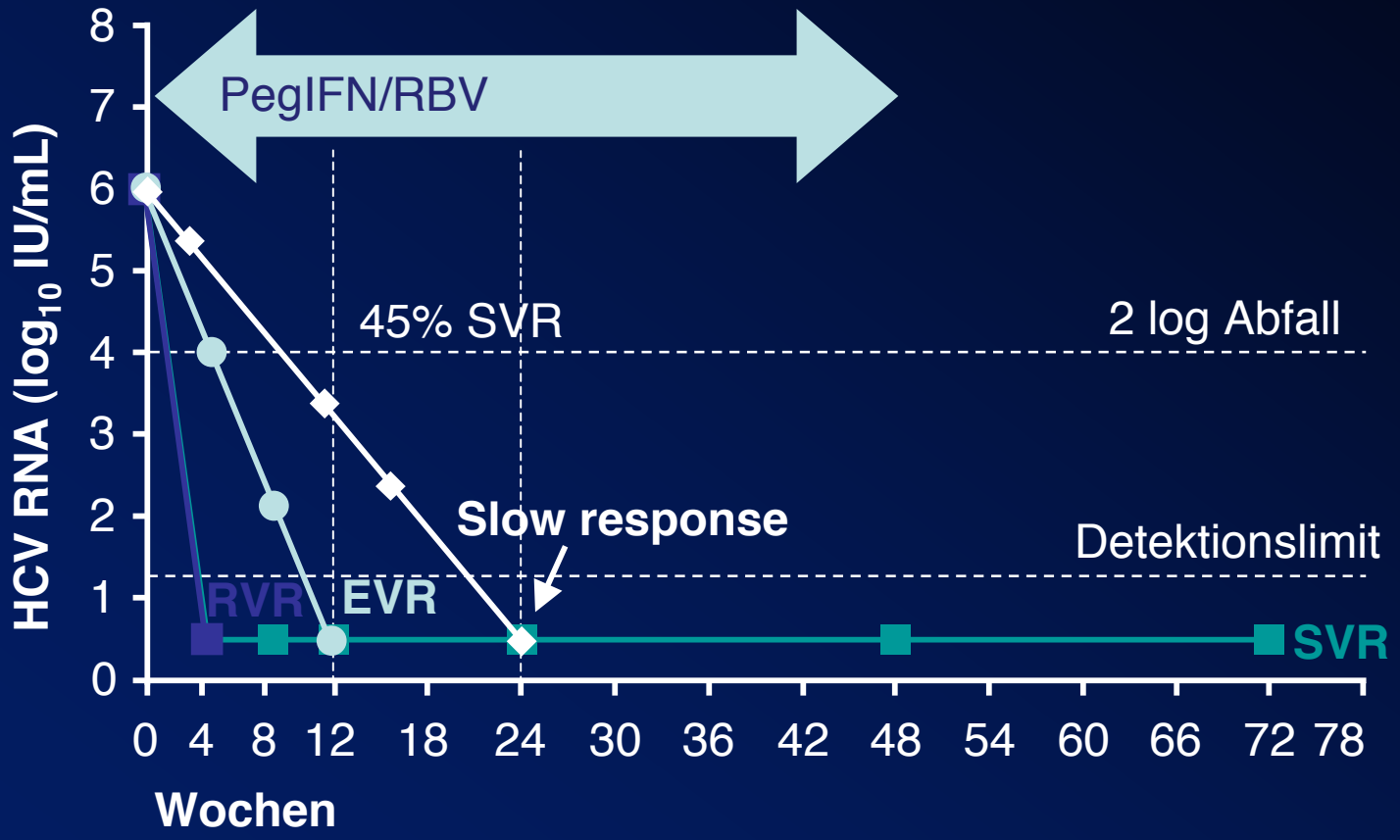
RVR: rapid virologic response

EVR: HCV RNA ↓ ≥ 2 logs or not detectable at week 12

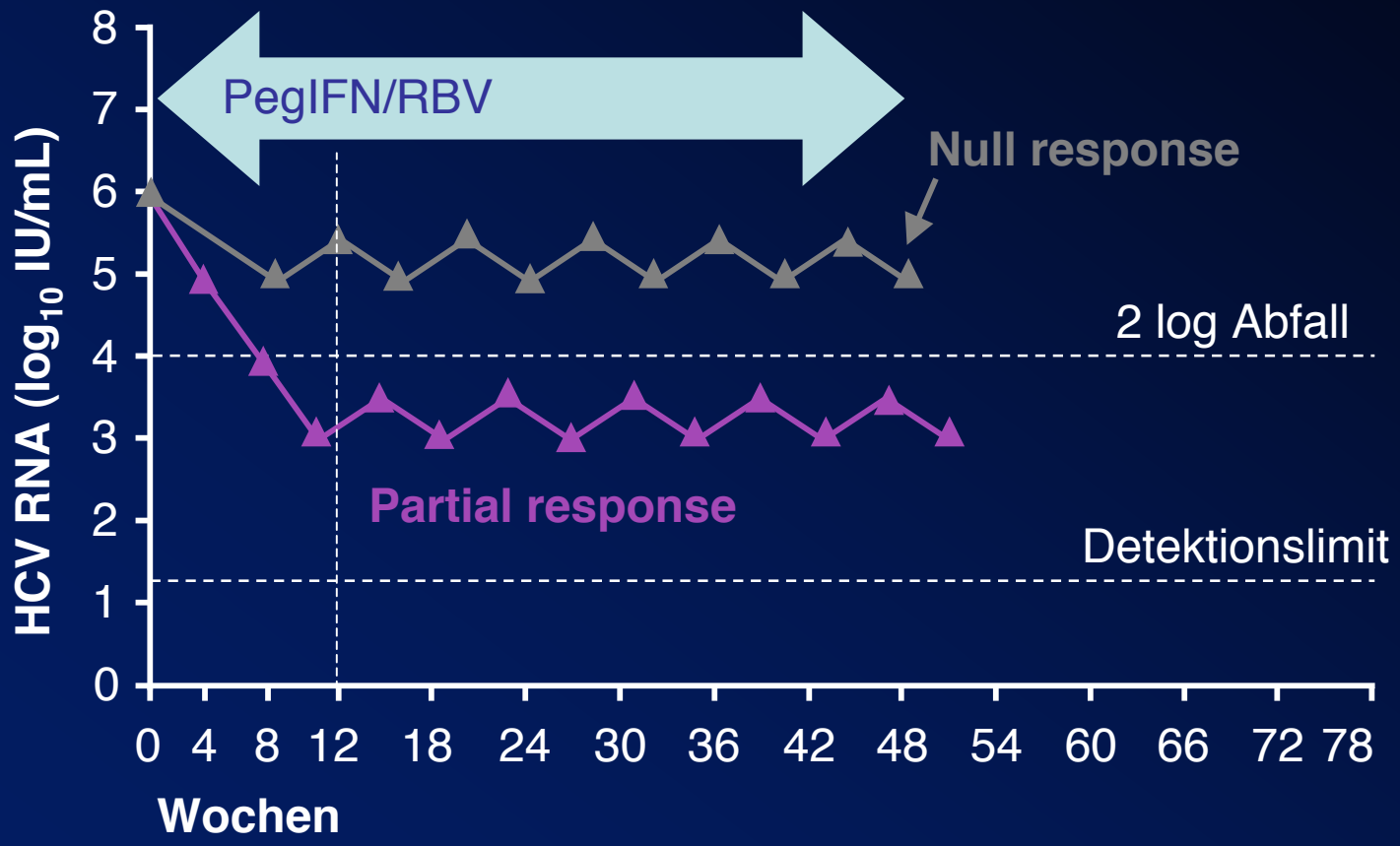


EVR: early virologic response

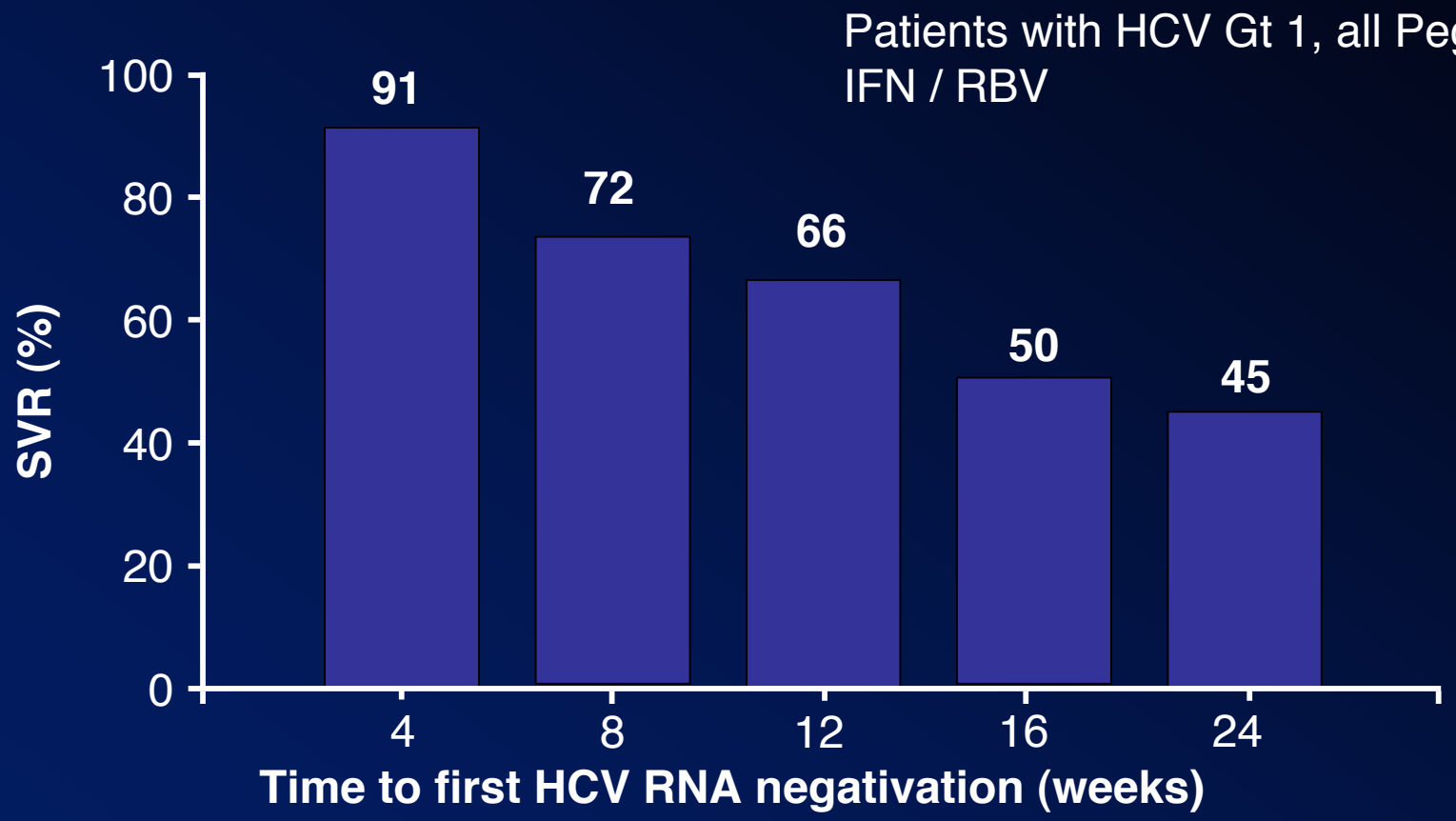
Slow Virologic Response: HCV RNA not detectable at week 24



Null Response / partial response: HCV RNA positive at week 24



Prediction of SVR according to on treatment virologic response

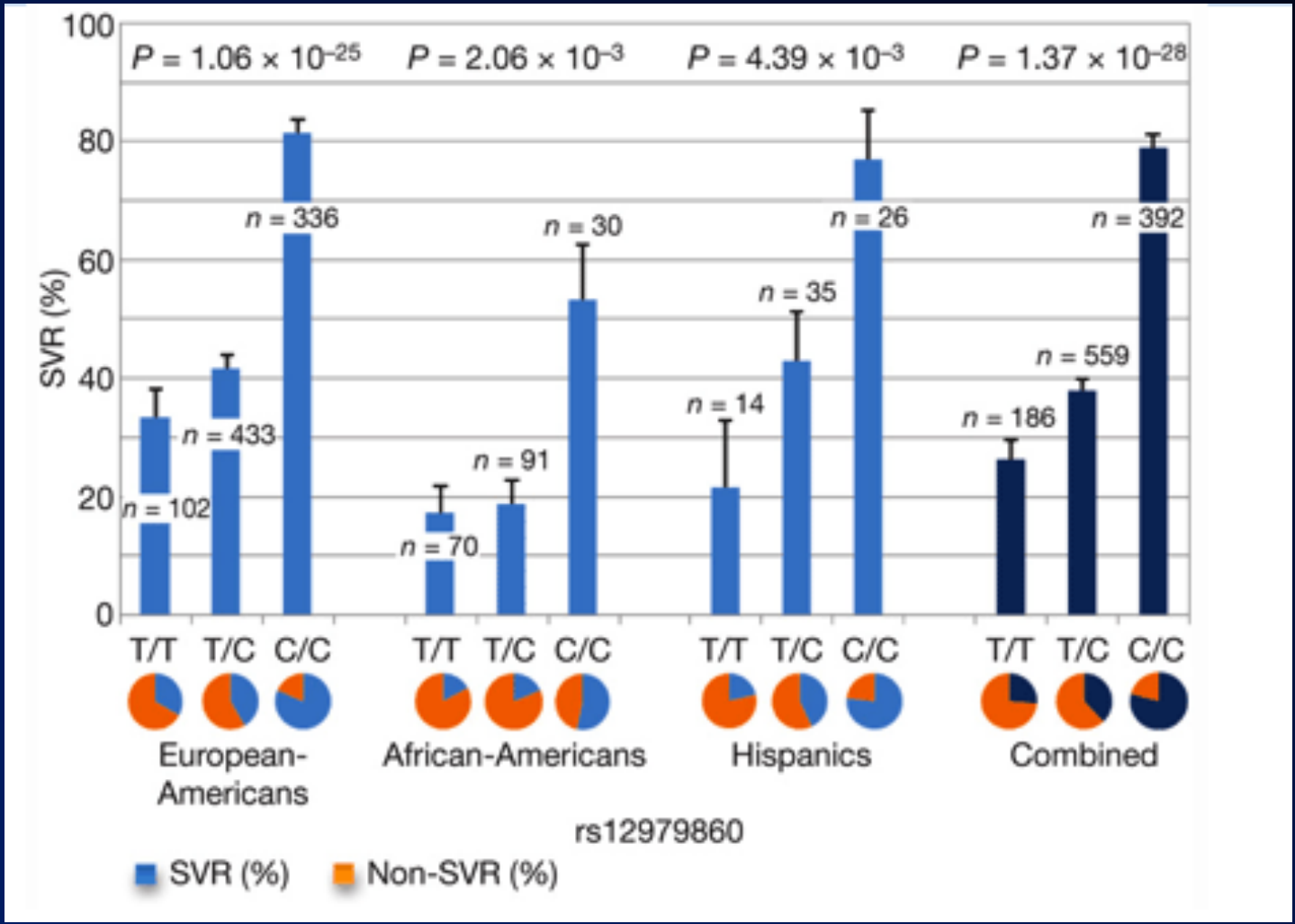


Ferenci P, et al. J Hepatology. 2005;43:453-471.
Tang KH et al. Alim Pharm & Toxicol 2008; 27: 810-819

Predictive factors for treatment success in CHC

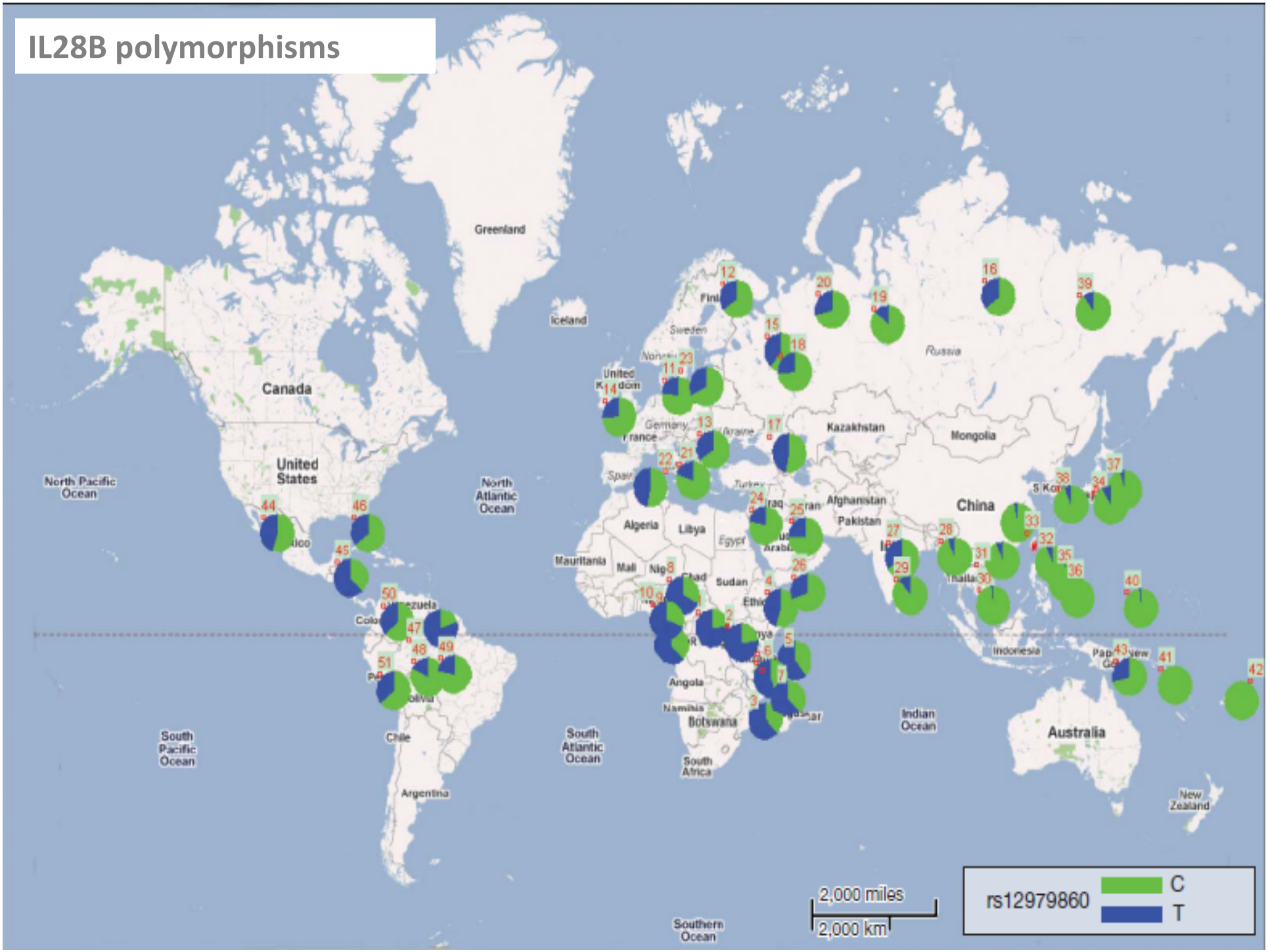
- on treatment virologic response (RVR, cEVR)
- IL28B Genotyp (new)
- younger age (<40 yrs)
- low fibrosis stage
- low HCV RNA levels at baseline
- BMI (<30)
- gender (f>m)
- no steatosis
- no diabetes mellitus
- etc.....

SVR rates according to IL28B-Polymorphism



Ge et al. Nature 2009; 461: 399-401.

IL28B polymorphisms

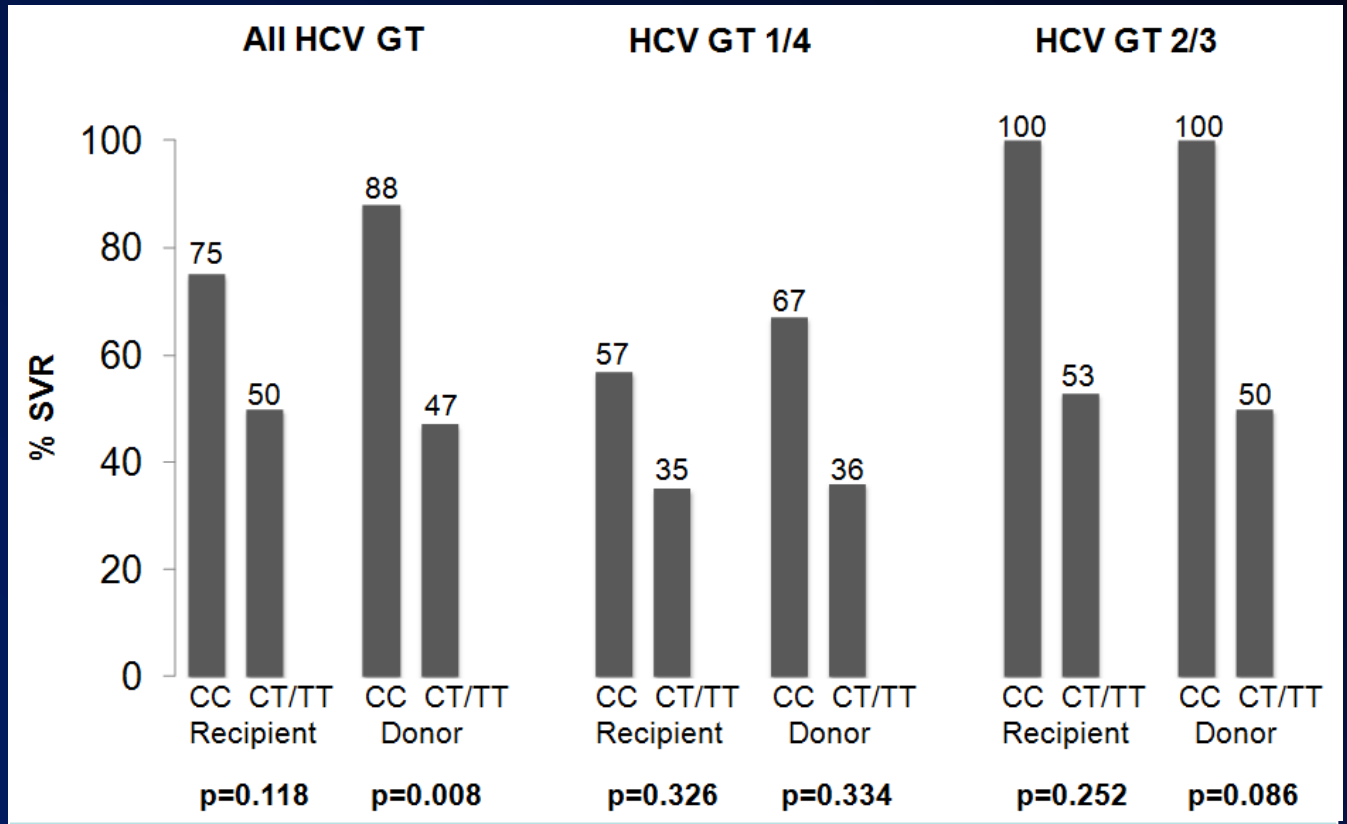


Predictive role of *IL28B* genotypes in many different patient populations

- HCV genotype 1
- HCV genotype 2 and 4
- HIV / HCV coinfected patients
- Liver transplant recipients
- HBV HBeAg positives (Seroconversion rates)
- ...

Reviewed in Lange and Zeuzem, J Hepatol 2011

IL28B genotypes of recipients AND donors predict SVR post OLT



Lange et al., EASL 2011

First generation of direct acting antivirals (DAA) on the market soon.....

Phase III studies

- Therapy naive pts.
  - Boceprevir* (SPRINT-2)
  - Telaprevir (ADVANCE, ILLUMINATE)

- Therapy experienced (Relapser, partial responder, nullresponder)
  - Boceprevir* (RESPOND-2, no nullresponder)
  - Telaprevir (REALIZE)

*Boceprevir approved by FDA on may 13th 2011
**Telaprevir approved by FDA on may 23rd 2011

AASLD 2010, APASL 2011, EASL 2011, Bacon et al., NEJM 2011, Poordad et al., NEJM 2011

How does the new therapy look like?

Telaprevir (Incivek)

6 pills / day
(2-2-2)

Boceprevir (Victrelis)

12 pills / day
(4-4-4)

plus

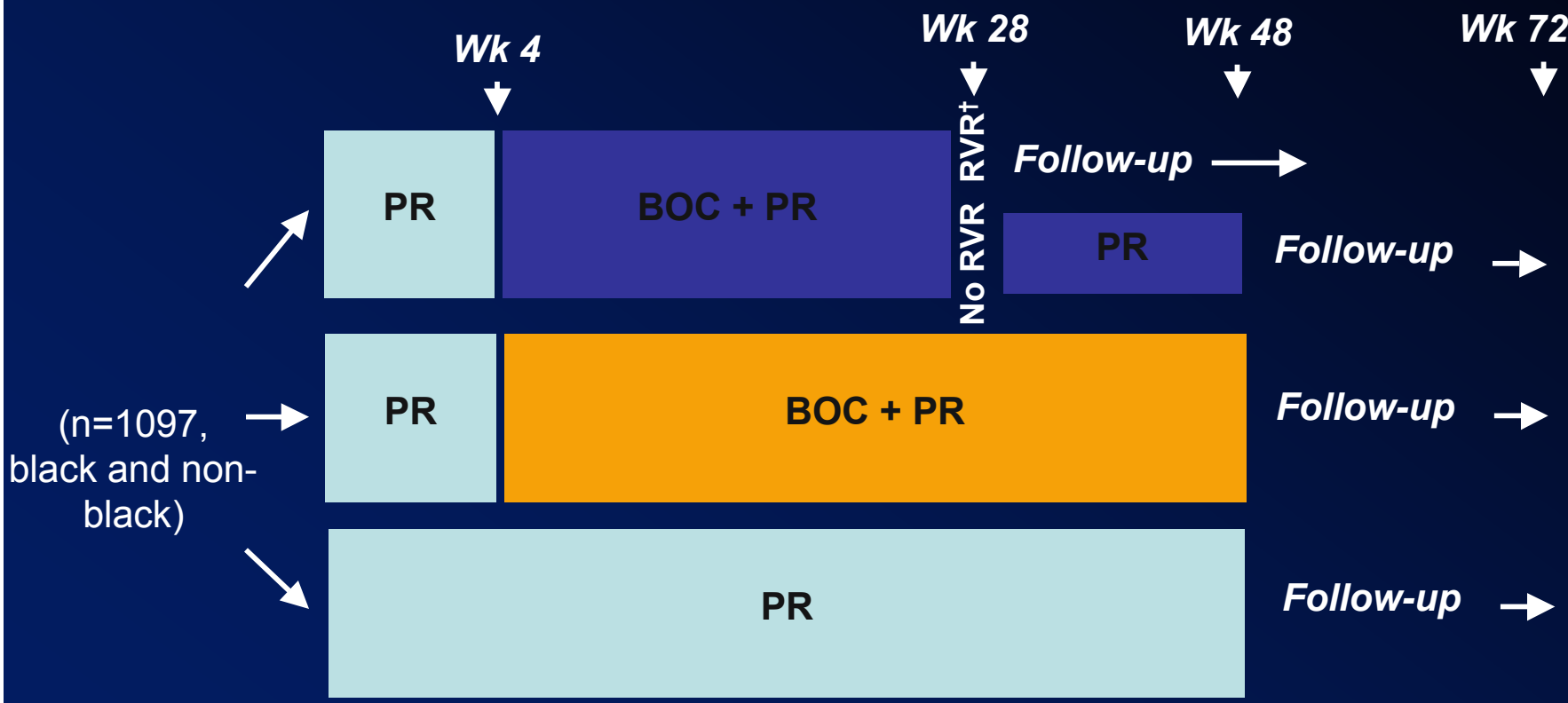
Peg-IFN 1/ week

Ribavirin 4-6 pills / day (1-0-1)

Key data on phase III trials in treatment naive patients with HCV genotype 1

- Boceprevir (SPRINT-2)
- Telaprevir (ADVANCE, ILLUMINATE)

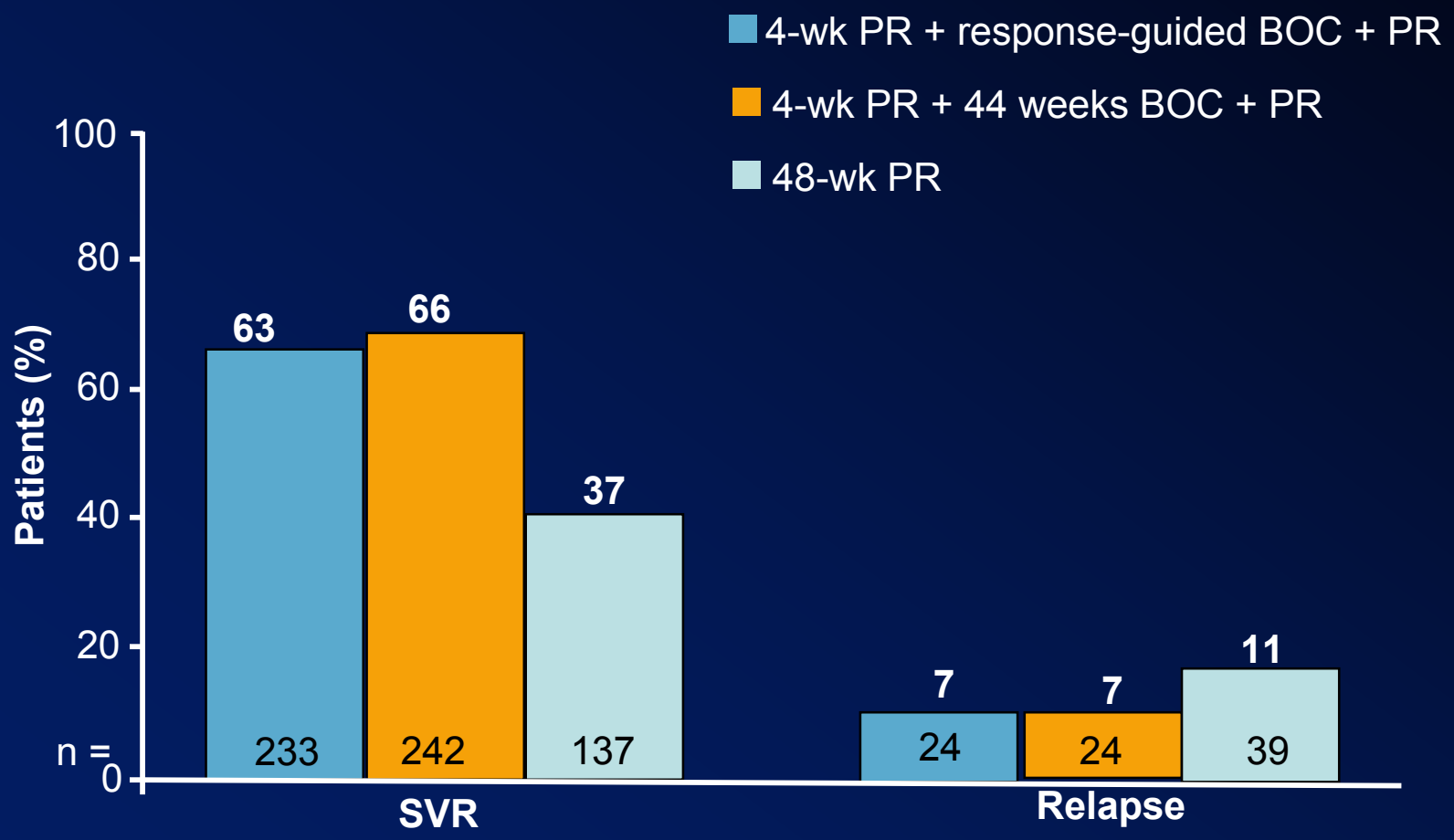
SPRINT-2: Boceprevir + PegIFN/RBV in GT1: therapy naive



†Undetectable HCV RNA at Wk 4 of BOC treatment (ie, at Wk 8) and at all subsequent assays.

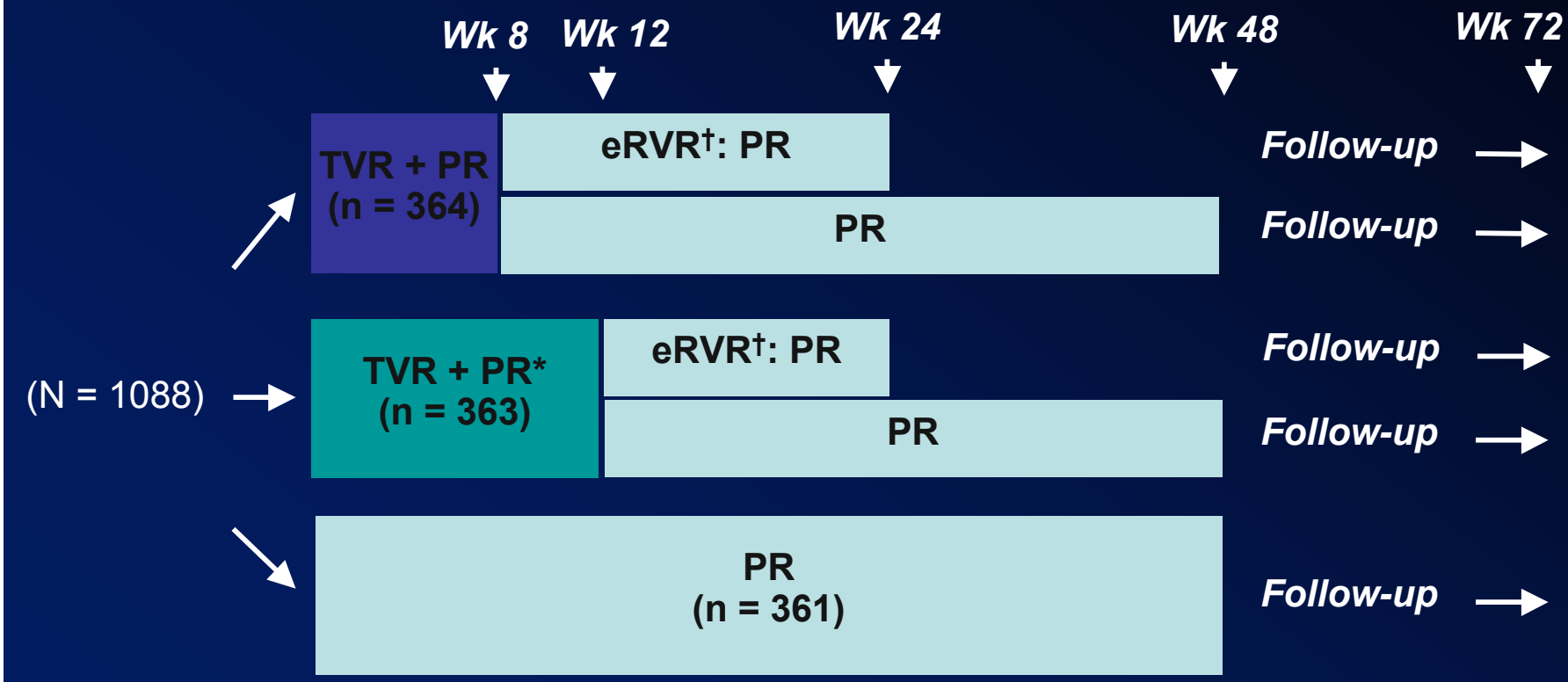
Poordad F, et al. NEJM 2011

SPRINT-2: Overall virologic response rates with Boceprevir / PEG / Riba



Poordad F, et al. NEJM 2011

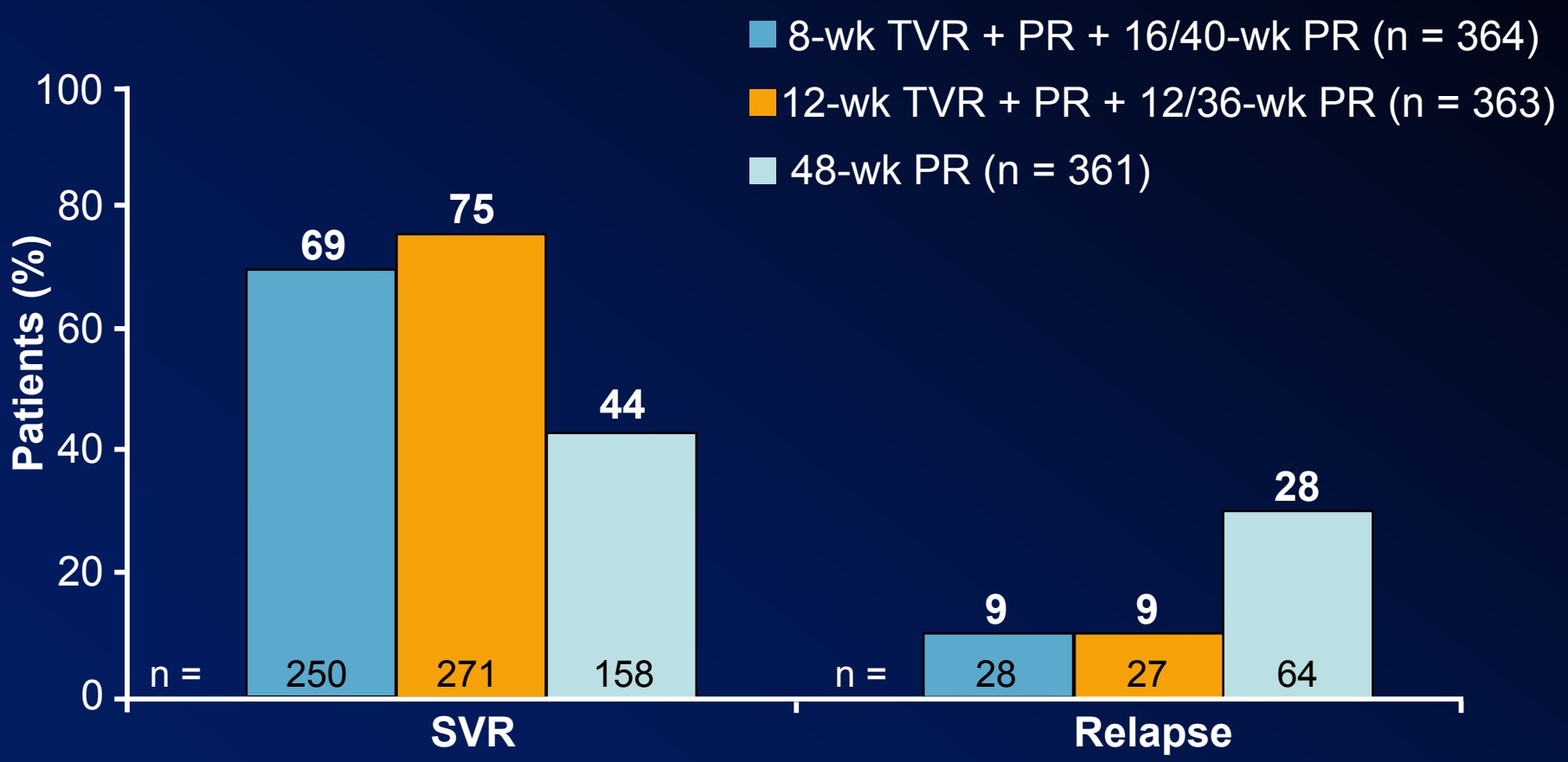
ADVANCE: Telaprevir + PegIFN/RBV in GT1: therapy naive pts.



†eRVR: extended rapid virologic response = undetectable HCV RNA at Wks 4 and 12.

Jacobson IM, et al. AASLD 2010.

ADVANCE: Overall virologic response rates with Telaprevir / PEG / Riba



Jacobson IM, et al. AASLD 2010.

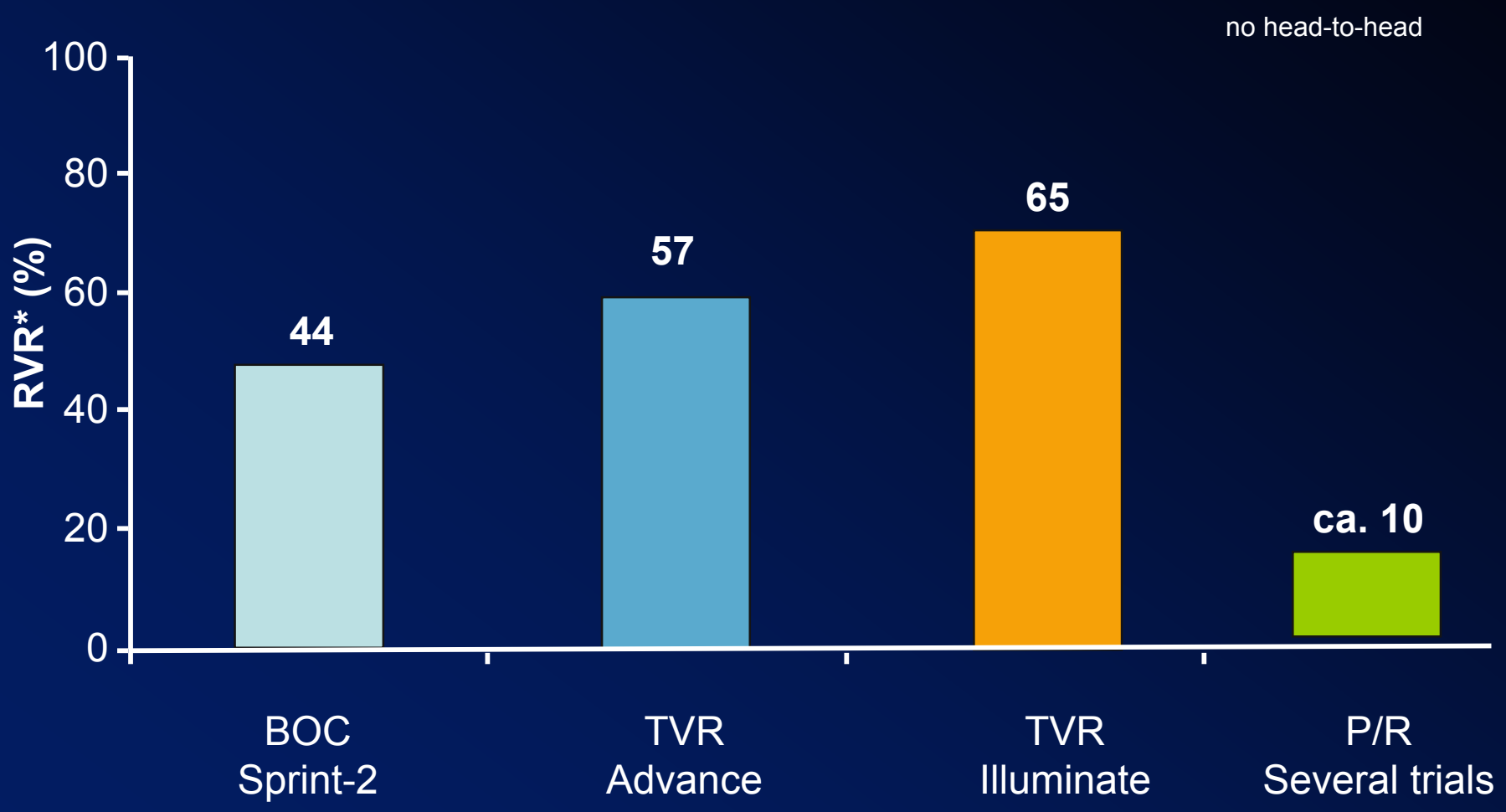
Meilensteine durch DAA Therapie

- höhere SVR Raten im Vergleich zu SOC
- Möglichkeit der Therapieverkürzung (response-guided therapy)

DAA, direct acting antivirals

RVR notwendig für „response-guided therapy“ bei DAA Therapie

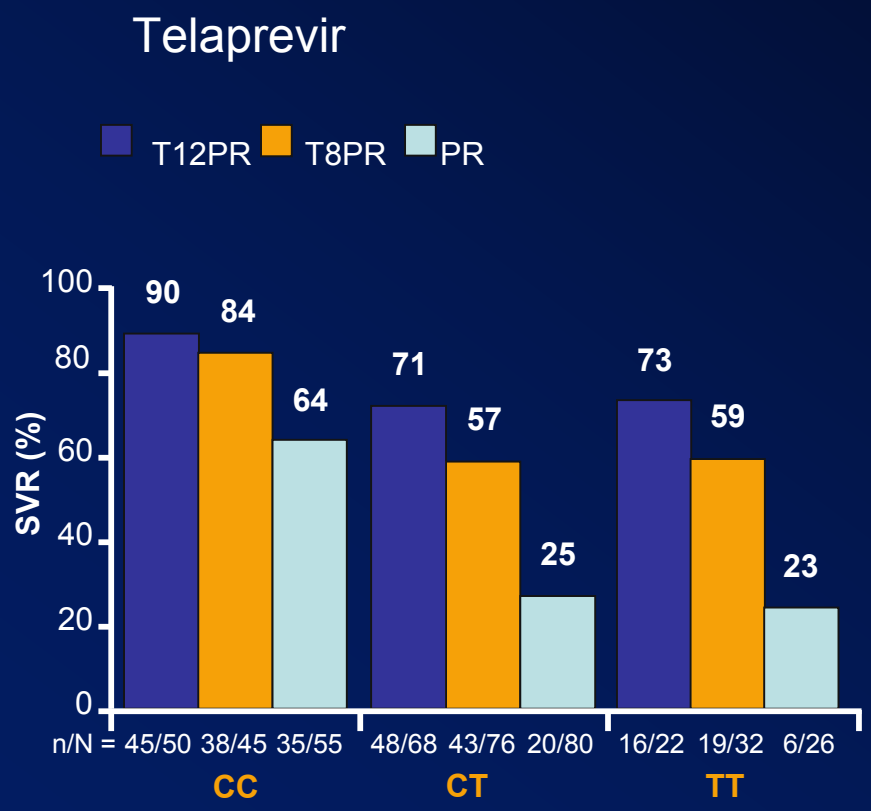
Proportion of patients with RVR in current phase III trials (BOC or TVR plus P/R)

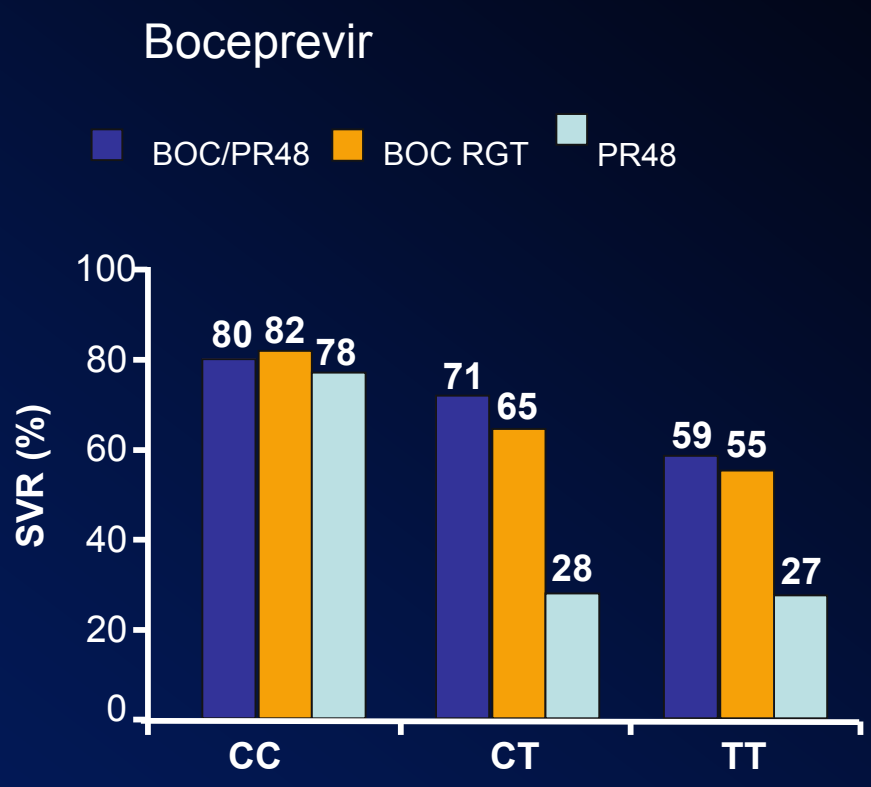


*in BOC HCV RNA neg at week 4 of BOC treatment (i.e. week 8), in TVR HCV RNA neg at week 4

IL28B und Prädiktion des virologischen Ansprechens bei DAA Therapie

SVR rates in *IL28B* genotyped patients in ADVANCE and SPRINT-2 studies





Jacobson I, et al. EASL 2011; Poordad F et al., EASL 2011.

Kommentar zu *IL28B* Genotypisierung und DAA Therapie

- Der Nutzen von DAAs bei CC Patienten ist weniger klar
- CC Patienten könnten übertherapiert sein mit DAAs
- Kosten / Nutzen Argumente bei CC Patienten und DAA Verschreibung
- IL28B Genotypisierung braucht die Einverstandnis des Patienten

Telaprevir

375mg Kapseln (2-2-2 / Tag alle 7-9 Std.)

Boceprevir

200mg Kapseln (4-4-4 /Tag alle 7-9 Std.)

Telaprevir (Incivek): Richtlinien

Treatment-Naïve and Prior Relapse Patients			
HCV-RNA[a]	**Triple Therapy** INCIVEK, peginterferon alfa and ribavirin	**Dual Therapy** peginterferon alfa and ribavirin	**Total Treatment Duration**
Undetectable at Weeks 4 and 12	First 12 weeks	Additional 12 weeks	24 weeks
Detectable (1000 IU/mL or less) at Weeks 4 and/or 12	First 12 weeks	Additional 36 weeks	48 weeks
Prior Partial and Null Responder Patients			
	Triple Therapy INCIVEK, peginterferon alfa and ribavirin	**Dual Therapy** peginterferon alfa and ribavirin	**Total Treatment Duration**
All Patients	First 12 weeks	Additional 36 weeks	48 weeks

Telaprevir (Incivek) stopping rules

Wenn HCV RNA >1000IU/mL zu TW 4 oder 12: Abbruch TPR

Wenn HCV RNA nachweisbar zu TW 24: Abbruch PR

Telaprevir: Kontraindizierte Begleitmedikation

Substrat und Inhibitor von CYP3A

Drug Class	Drugs within Class that are Contraindicated with INCIVEK	Clinical Comments
Alpha 1-adrenoreceptor antagonist	Alfuzosin	Potential for hypotension or cardiac arrhythmia
Antimycobacterials	Rifampin	Rifampin significantly reduces telaprevir plasma concentrations.
Ergot derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Potential for acute ergot toxicity characterized by peripheral vasospasm or ischemia
GI Motility Agent	Cisapride	Potential for cardiac arrhythmias
Herbal products	St. John's wort (*Hypericum perforatum*)	Plasma concentrations of telaprevir can be reduced by concomitant use of the herbal preparation St. John's wort.
HMG CoA reductase inhibitors	Atorvastatin, lovastatin, simvastatin	Potential for myopathy including rhabdomyolysis
Neuroleptic	Pimozide	Potential for serious and/or life-threatening adverse reactions such as cardiac arrhythmias secondary to increases in plasma concentrations of antiarrhythmics
PDE5 inhibitor	Sildenafil (Revatio®) or tadalafil (Adcirca®) [for treatment of pulmonary arterial hypertension][a]	Potential for PDE5 inhibitor-associated adverse events, including visual abnormalities, hypotension, prolonged erection, and syncope
Sedatives/hypnotics	Orally administered midazolam[b], triazolam	Prolonged or increased sedation or respiratory depression

Boceprevir (Victrelis): Richtlinien

	ASSESSMENT* (HCV-RNA Results†)		RECOMMENDATION
	At Treatment	At Treatment	
	Week 8	Week 24	
Previously Untreated Patients	Undetectable	Undetectable	Complete three-medicine regimen at TW28.
	Detectable	Undetectable	1. Continue all three medicines and finish through TW36; and then 2. Administer peginterferon alfa and ribavirin and finish through TW48.
Previous Partial Responders or Relapsers	Undetectable	Undetectable	Complete three-medicine regimen at TW36.
	Detectable	Undetectable	1. Continue all three medicines and finish through TW36; and then 2. Administer peginterferon alfa and ribavirin and finish through TW48.

Package insert Mai 2011

Boceprevir (Victrelis) stopping rules

Wenn HCV RNA >/= 100IU/mL zu TW 12: Abbruch BPR

Wenn HCV RNA nachweisbar zu TW 24: Abbruch BPR

Boceprevir: kontraindizierte Begleitmedikation

Substrat und Inhibitor von CYP3A4/5

Drug Class	Drugs Within Class that are Contraindicated With VICTRELIS	Clinical Comments
Alpha 1-Adrenoreceptor antagonist	Alfuzosin	Increased alfuzosin concentrations can result in hypotension.
Anticonvulsants	Carbamazepine, phenobarbital, phenytoin	May lead to loss of virologic response to VICTRELIS
Antimycobacterial	Rifampin	May lead to loss of virologic response to VICTRELIS.
Ergot Derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Potential for acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
GI Motility Agent	Cisapride	Potential for cardiac arrhythmias.
Herbal Products	St. John's Wort (hypericum perforatum)	May lead to loss of virologic response to VICTRELIS.
HMG-CoA Reductase Inhibitors	Lovastatin, simvastatin	Potential for myopathy, including rhabdomyolysis.
Oral Contraceptives	Drosperinone	Potential for hyperkalemia.
PDE5 enzyme Inhibitor	REVATIO® (sildenafil) or ADCIRCA® (tadalafil) when used for the treatment of pulmonary arterial hypertension*	Potential for PDE5 inhibitor-associated adverse events, including visual abnormalities, hypotension, prolonged erection, and syncope.
Neuroleptic	Pimozide	Potential for cardiac arrhythmias.
Sedative/Hypnotics	Triazolam; orally administered midazolam†	Prolonged or increased sedation or respiratory depression.

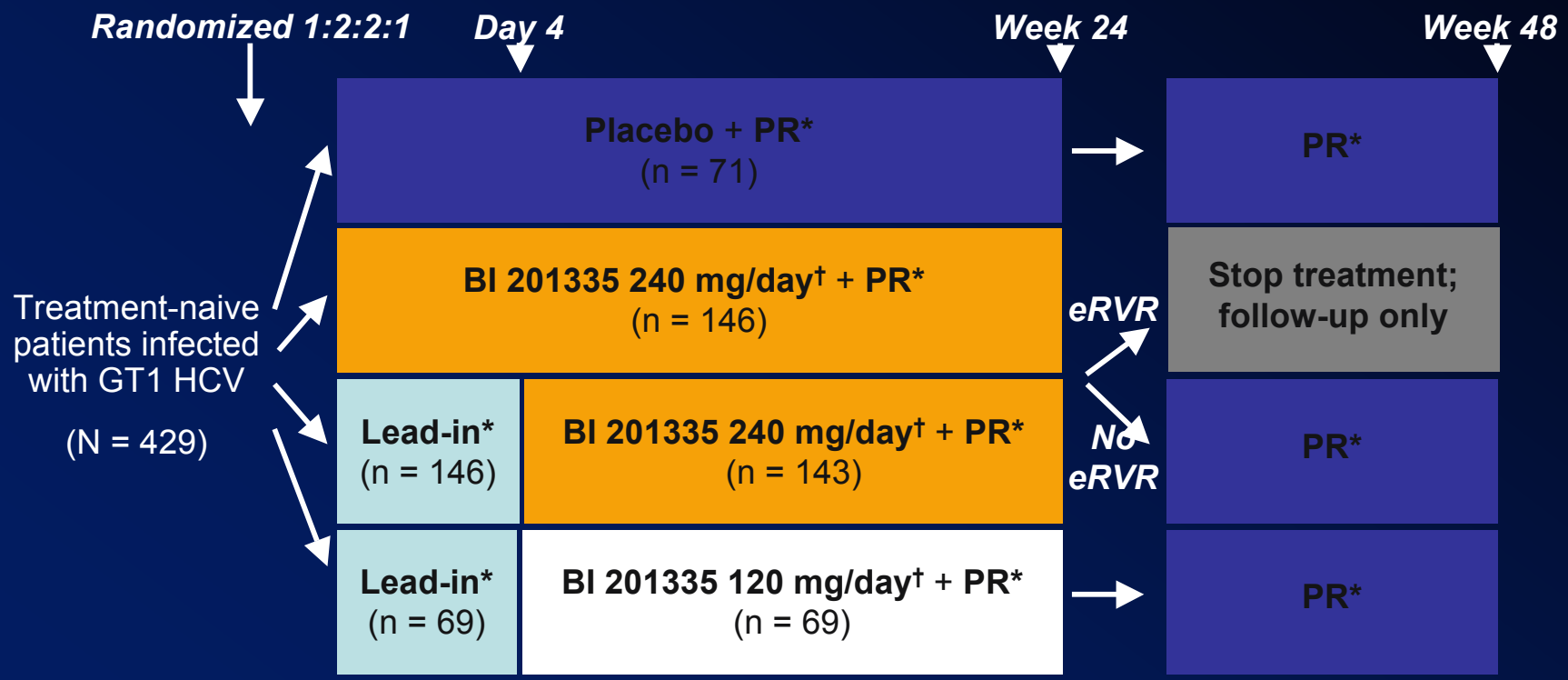
DAAs in klinischer Entwicklung (Auswahl)

	Phase I	Phase II	Phase III
Protease Inhibitors	**ABT-450** **ACH-1625** **GS 9451** **MK-5172** **VX-985**	**BMS-650032** **CTS-1027** **Danoprevir** **GS 9256** **IDX320** **Vaniprevir**	**BI 201335** **Boceprevir** **Telaprevir** **TMC435**
Nonnucleoside polymerase inhibitors	**BI 207127** **IDX375**	**ABT-333** **ABT-072** **ANA598** **BMS-791325** **Filibuvir** **Tegobuvir** **VX-759** **VX-222**	
Nucleoside polymerase inhibitors		**IDX184** **PSI-7977** **RG7128**	
NS5A inhibitors	**A-831** **PPI-461**	**BMS-790052** **BMS-824393** **CF102**	

nach CCO

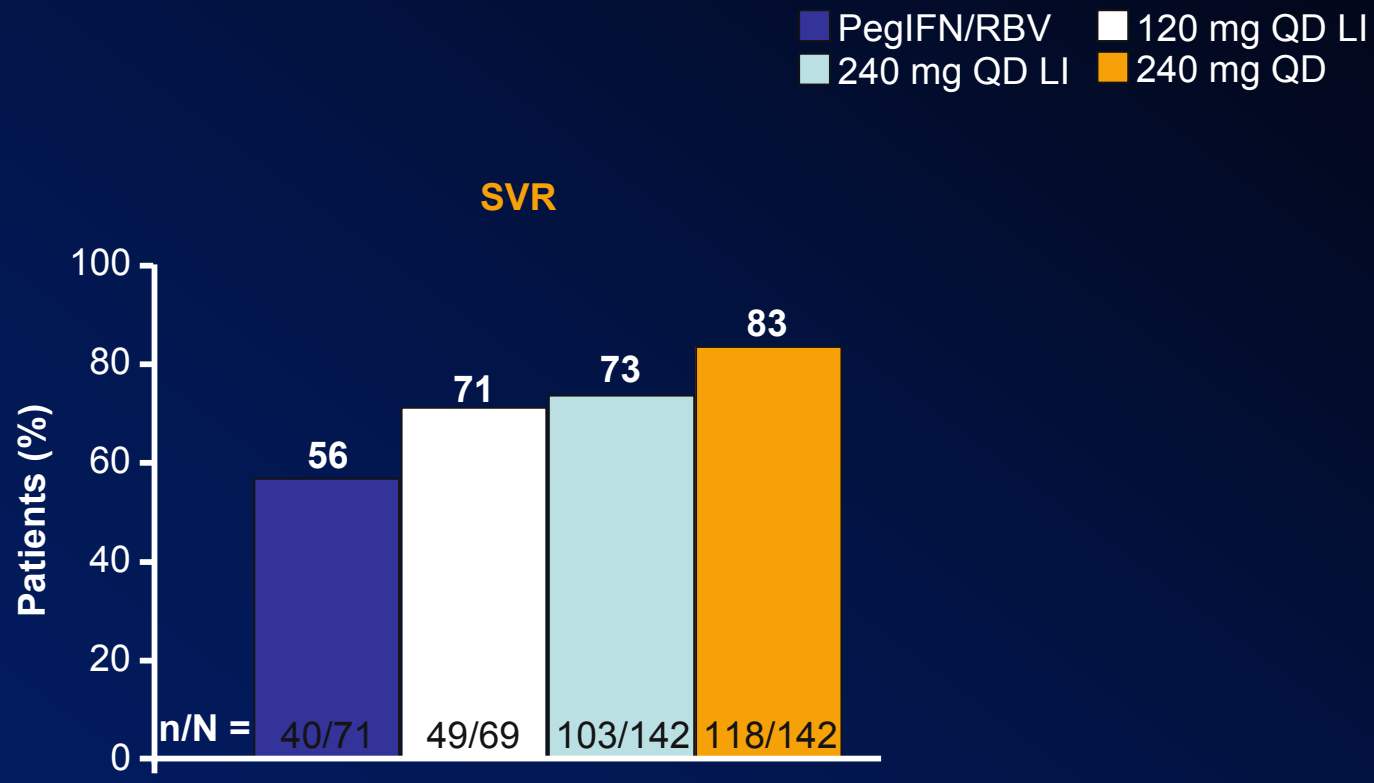
Neue PIs mit PR

SILEN-C1: BI 201335 + PegIFN/RBV in GT1 Treatment-Naive Patients



Sulkowski M, et al. EASL 2011.

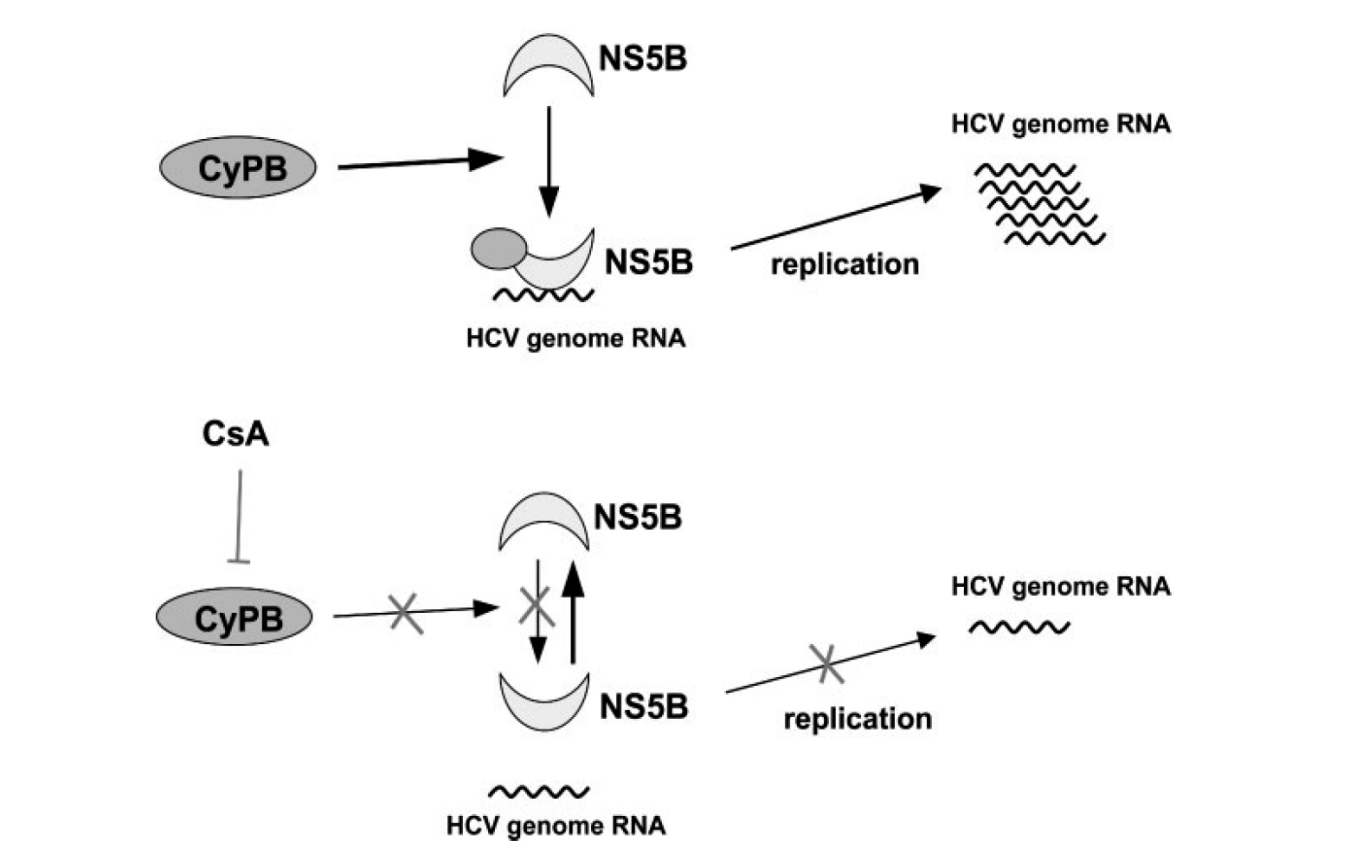
SILEN-C1: BI 201335 + PegIFN/RBV in GT1 Treatment-Naive Patients



Sulkowski M, et al. EASL 2011.

Nicht immunsuppressiv wirkende Cyclophilin Inhibitoren: Alisporivir (Debio-025)

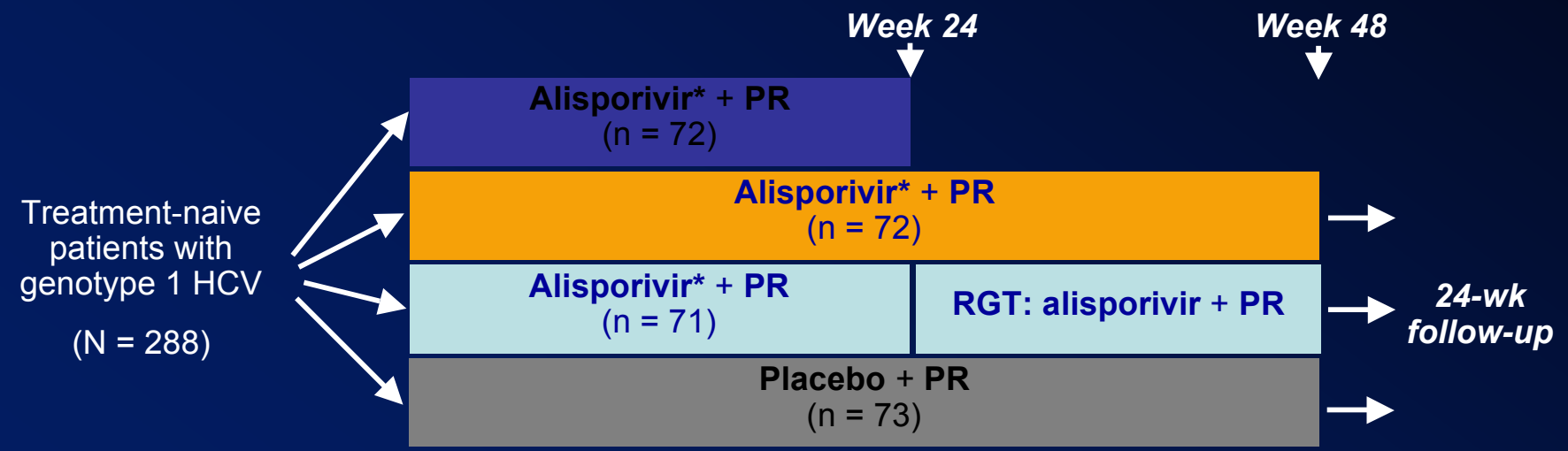
Cyclophilin reguliert die Aktivität der HCV NS5B-Polymerase



Watashi K, Shimotohno K. Rev Med. Virol 2007

ESSENTIAL: Alisporivir + PegIFN/RBV in GT1 Treatment-Naive Patients

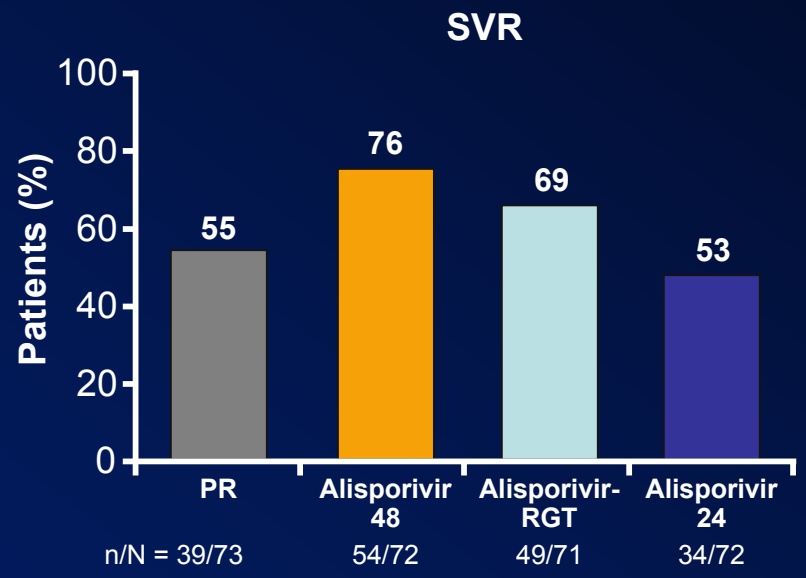
- **Alisporivir: oral inhibitor of cyclophilin that acts as host-targeted antiviral**
- **Placebo-controlled, double-blind phase IIb trial**



*Alisporivir dosed at 600 mg BID for first wk, then 600 mg QD thereafter.

Flisiak R, et al. EASL 2011. Abstract 4.

ESSENTIAL: Alisporivir + PegIFN/RBV in GT1 Treatment-Naive Patients

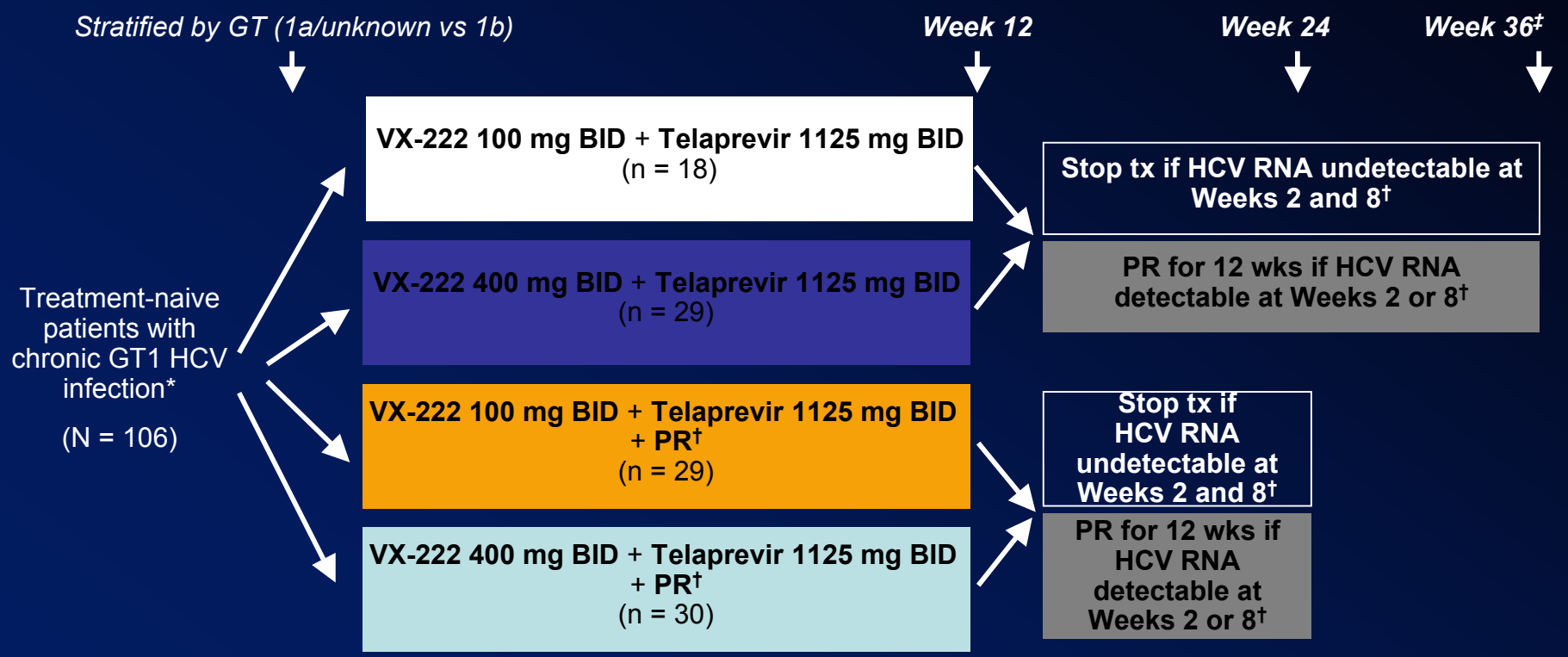


IL28B kein Einfluss auf SVR

Flisiak R, et al. EASL 2011.

DAA Kombination (Pol-Inh. plus PI) mit PR

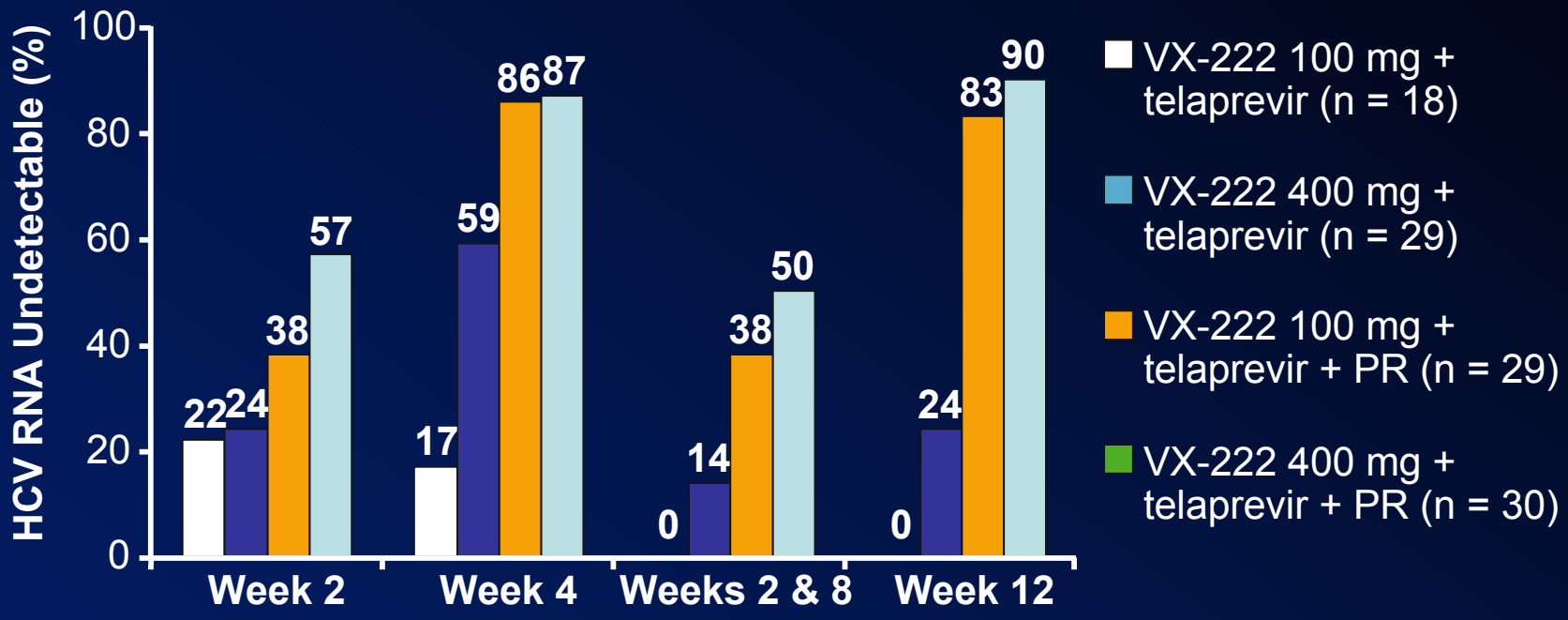
ZENITH Week 12 Interim Analysis: VX-222 + Telaprevir ± PegIFN/RBV in GT1 Tx Naive



*A fifth arm assessing VX-222 400 mg QD + telaprevir 1125 mg BID + RBV currently accruing.
†PegIFN 180 µg/wk + weight-based RBV 1000-1200 mg/day.

Di Bisceglie A, et al. EASL 2011. Abstract 1363.

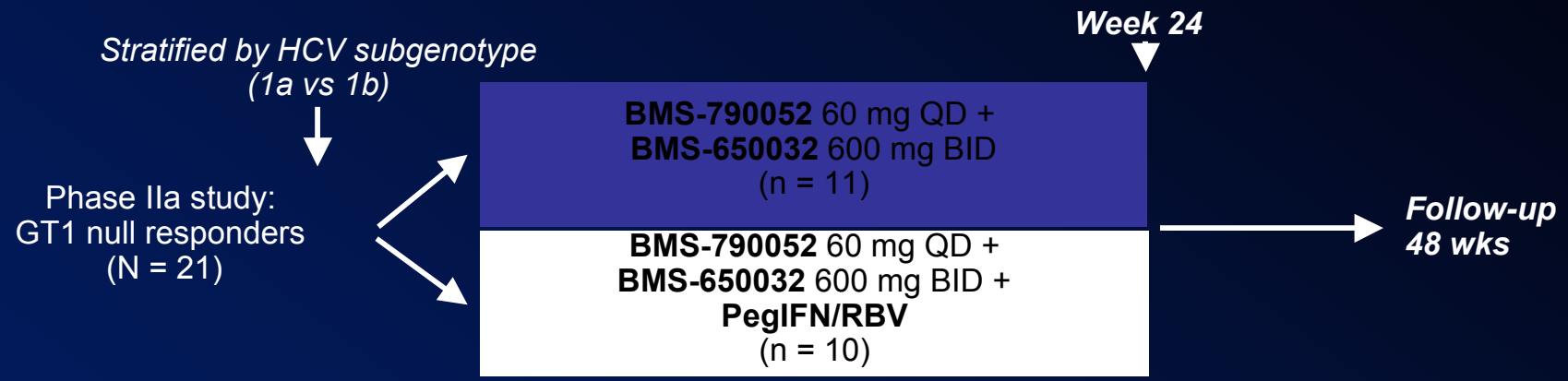
ZENITH Week 12 Interim Analysis: VX-222 + Telaprevir ± PegIFN/RBV in GT1 Tx Naive



Di Bisceglie A, et al. EASL 2011. Abstract 1363.

DAA Kombination (NS5A-Inh. Plus PI) und PR

BMS-790052 + BMS-650032 ± PegIFN / RBV for 24 Wks in GT1 Null Responders



Undetectable HCV RNA, % (n)	BMS-790052 + BMS-650032 (n = 11)	BMS-790052 + BMS-650032 + PR (n = 10)
RVR	**64 (7)**	**60 (6)**
SVR12	**36 (4)**	**100 (10)**
SVR24	**36 (4)**	**90† (9)**

- **In dual therapy arm, 2/2 GT1b vs 2/9 GT1a patients reached SVR12 and SVR24**
- **No viral breakthrough with quadruple therapy**
- **BMS-790052 and BMS-650032 alone or with pegIFN/RBV generally well tolerated**

Lok A, et al. EASL 2011. Abstract 1350.

Zusammenfassung

- Erste Generation DAA wahrscheinlich in 4Q2011 erhältlich
- Problem bei null respondern (mit Telaprevir 30% SVR)
- Strikte Richtlinien zu HCV RNA Messungen und Stopping rules
- Pill burden
- Neue DAAs in phase III (BI 201335, TMC435)
- DAA Kombinationen wahrscheinlich auch mit PR
- Pol.-Inh.
- NS5A-Inh.
- CNI

Telaprevir und ART

HIV-ANTIVIRAL AGENTS: HIV-PROTEASE INHIBITORS (PIs)		
atazanavir/ritonavir*	↓ telaprevir ↑ atazanavir	Nicht empfohlen
darunavir/ritonavir*	↓ telaprevir ↓darunavir	
fosamprenavir/ritonavir*	↓ telaprevir ↓fosamprenavir	Nicht empfohlen
lopinavir/ritonavir*	↓ telaprevir ↔ lopinavir	Nicht empfohlen
HIV-ANTIVIRAL AGENTS: REVERSE TRANSCRIPTASE INHIBITORS		
efavirenz*	↓ telaprevir ↓ efavirenz	
tenofovir disoproxil fumarate*	↔ telaprevir ↑ tenofovir	

Boceprevir und ART

HIV Non-Nucleoside Reverse Transcriptase Inhibitors: efavirenz	↓ boceprevir*	Plasma trough concentrations of boceprevir were decreased when VICTRELIS was coadministered with efavirenz, which may result in loss of therapeutic effect. Avoid combination
HIV Protease Inhibitors: ritonavir	↓ boceprevir* ↑ or ↓ HIV protease inhibitors	Boceprevir concentrations decreased with ritonavir; the effect of ritonavir-boosted HIV protease inhibitors on boceprevir exposure is unknown. The effect of VICTRELIS on HIV protease inhibitor concentrations is unknown.