Optimal Treatment With Telaprevir

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Optimal Treatment With Telaprevir

- Phase 3 trials
- Treatment algorithm with response guided therapy
- Stopping rules
- Management of side effects
- Drug-drug interactions
- Potential for bid dosing of telaprevir
- Special populations
  - Cirrhosis, transplant recipients
  - HIV/HCV coinfection

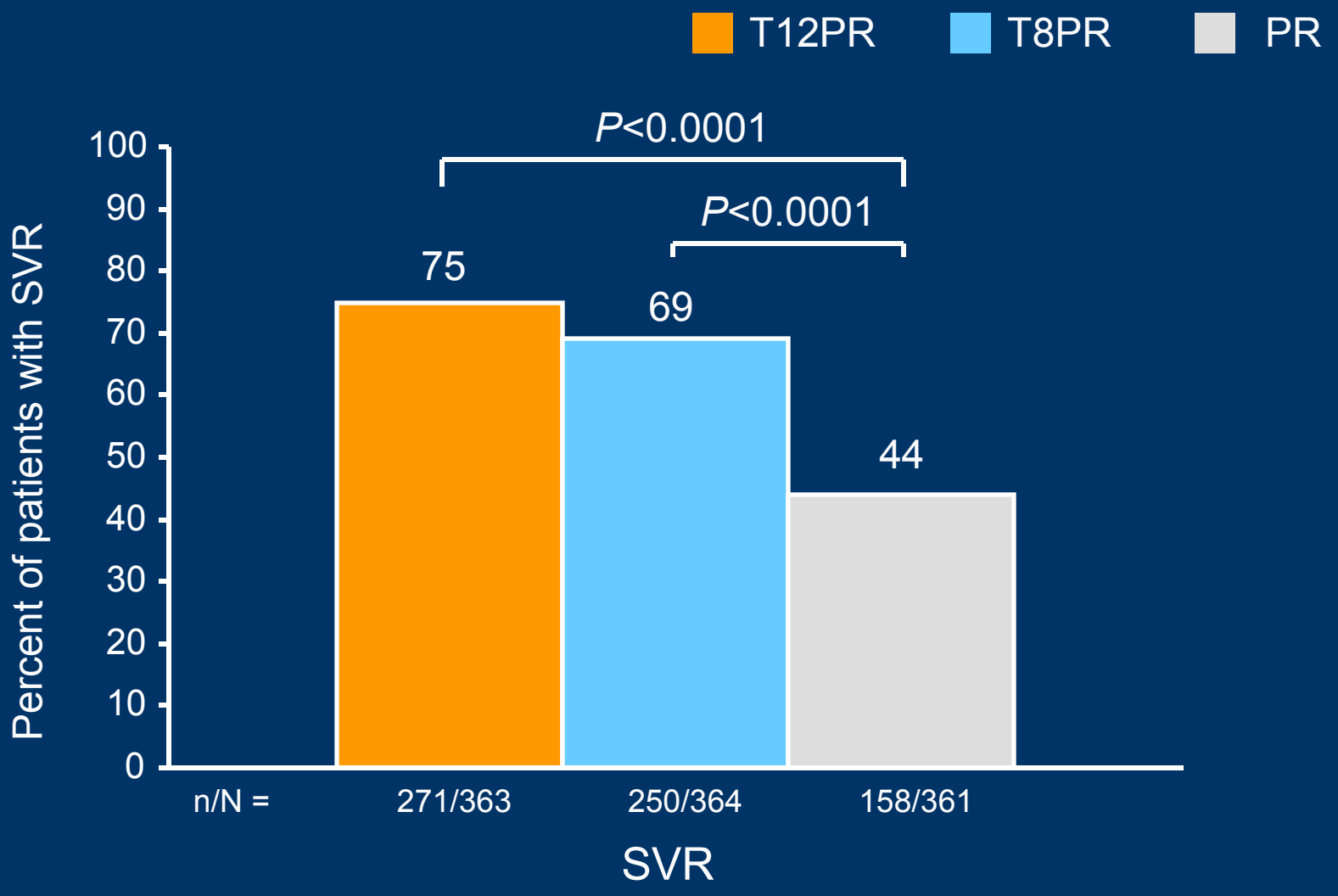
Phase 3 Trials of Telaprevir

ADVANCE
Pivotal
N=1088

ILLUMINATE
Supportive
N=540

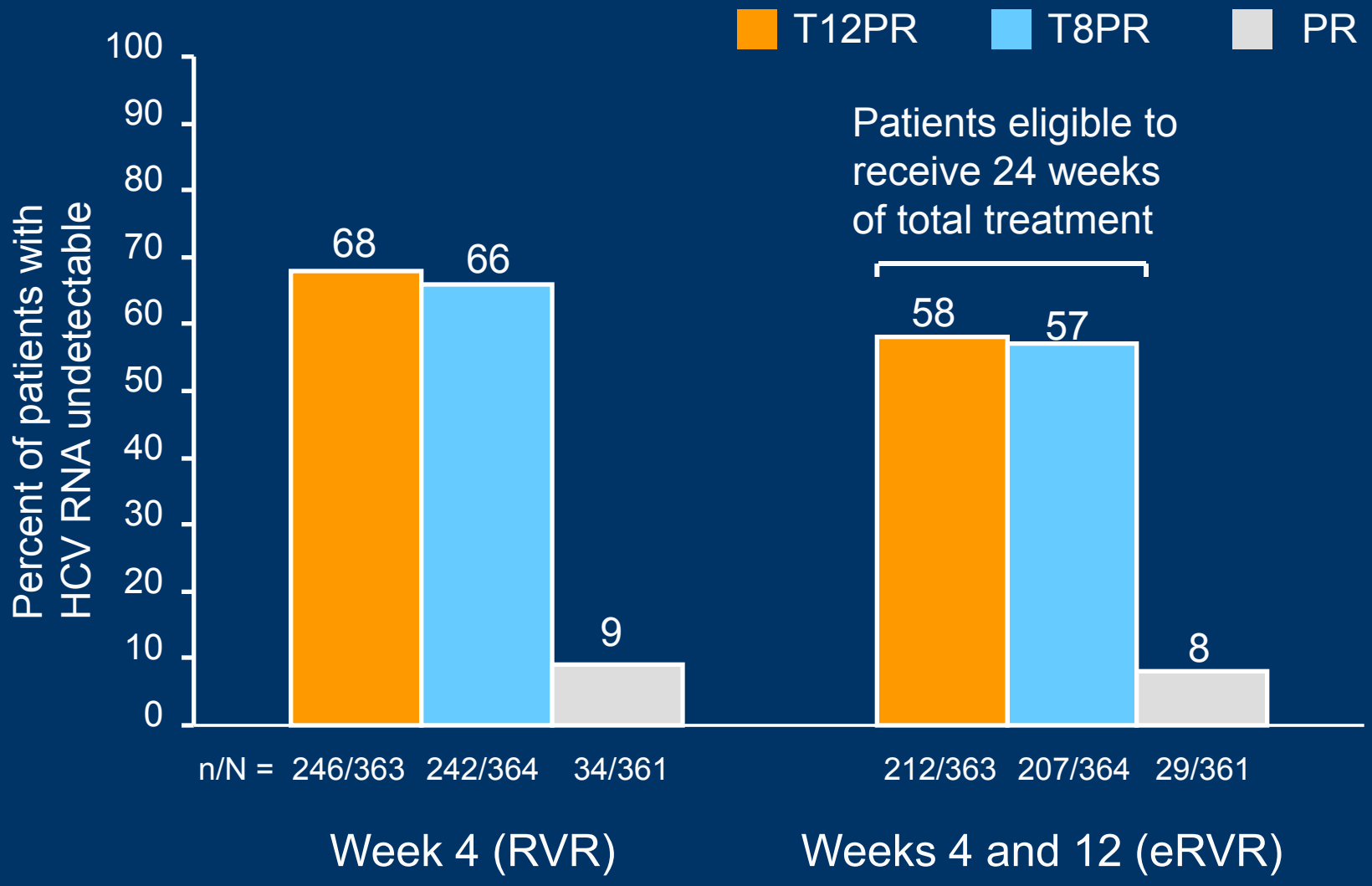
REALIZE
N=662

ADVANCE: SVR Rates



Jacobson IM, et al. N Engl J Med 2011;364:2405-16

ADVANCE: RVR and eRVR Rates



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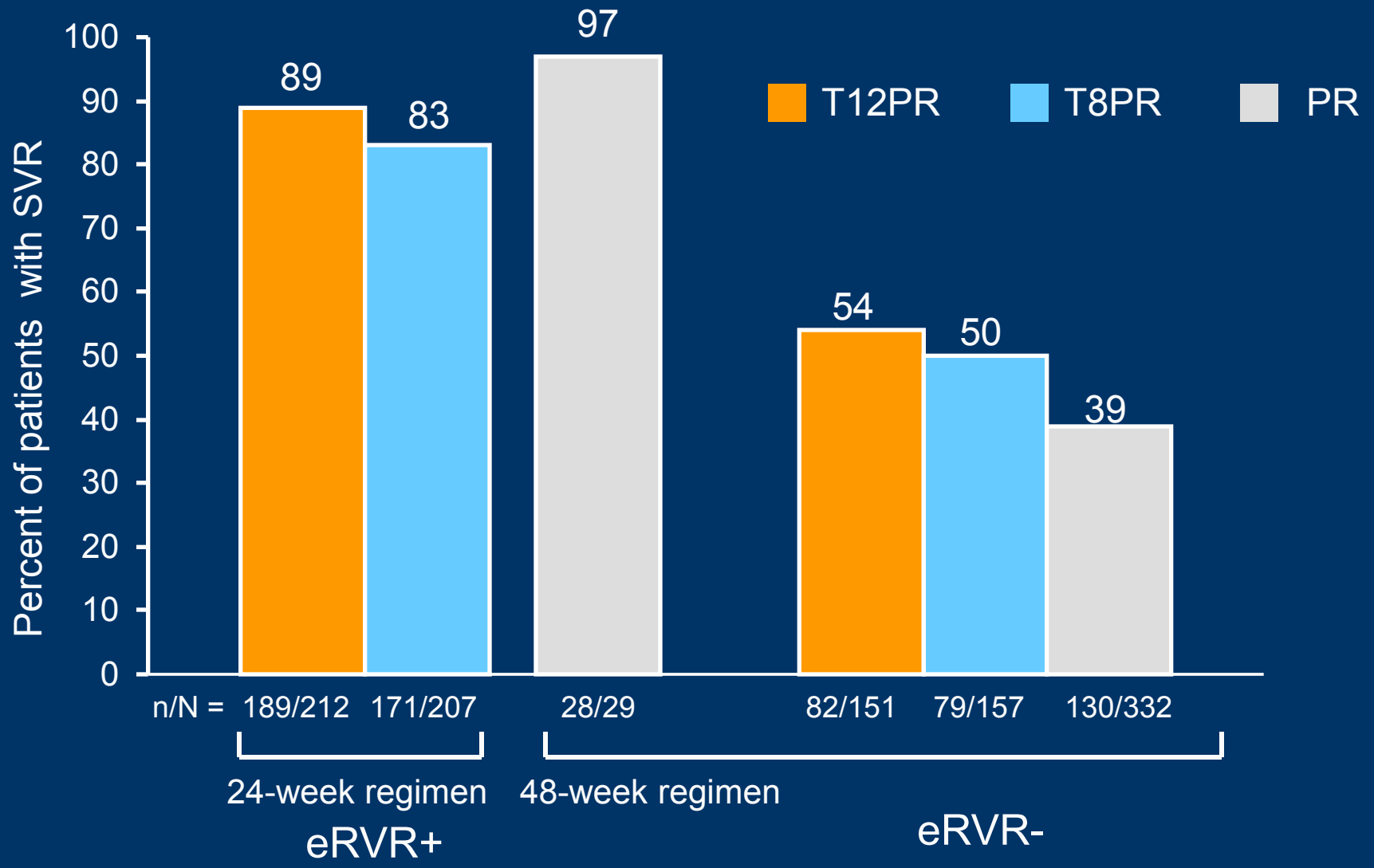
ADVANCE: SVR Rates by eRVR Status



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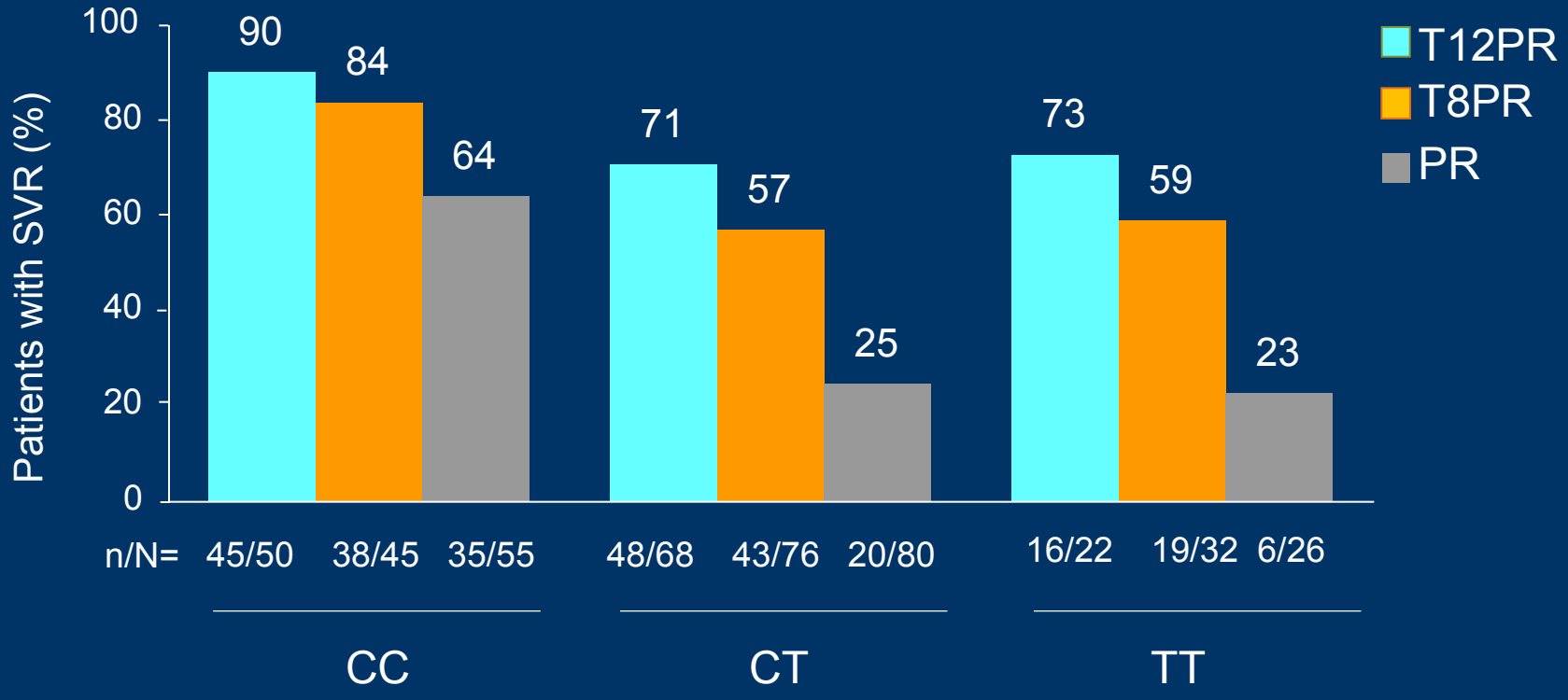
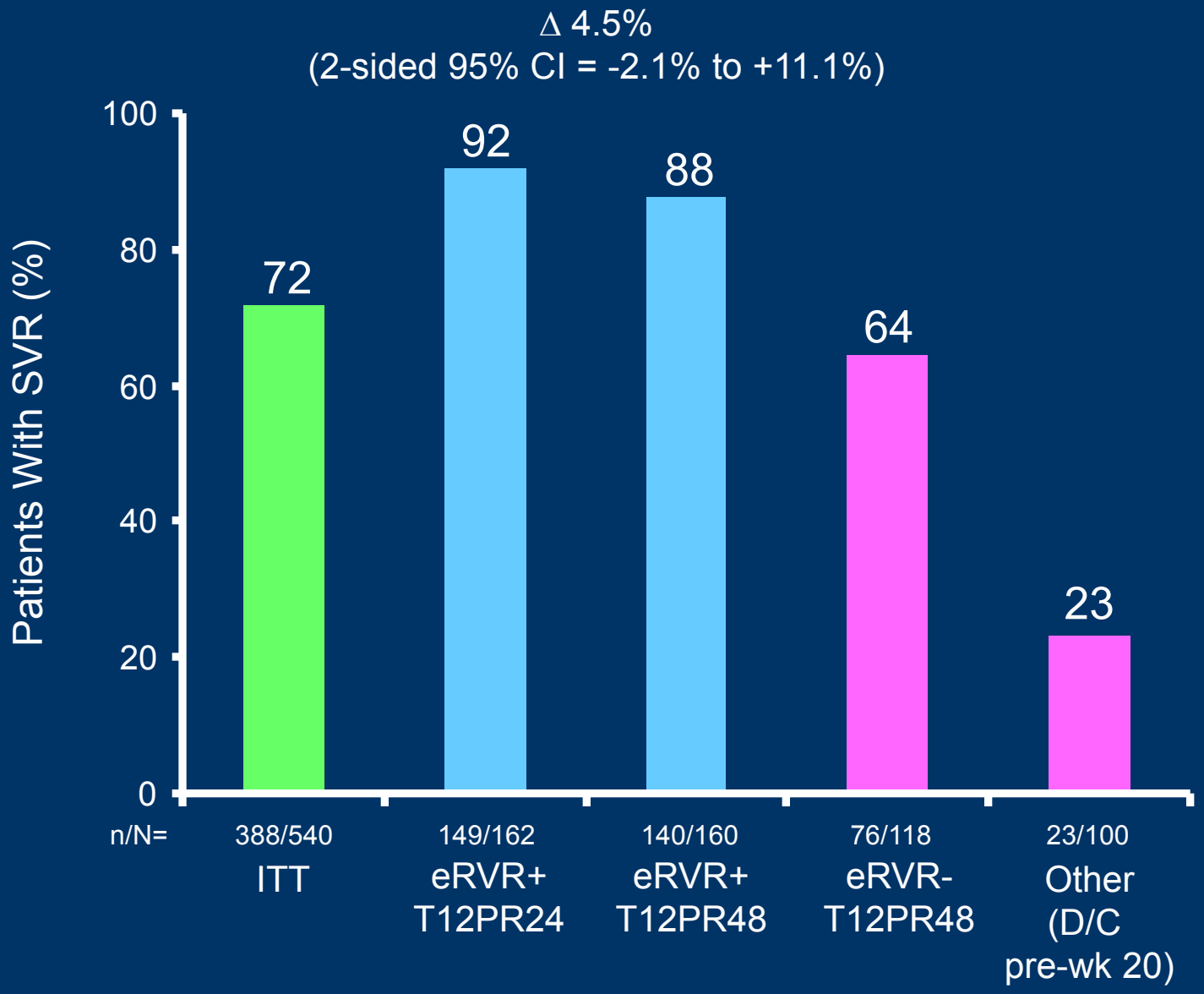
SVR Rates in ADVANCE Patients Genotyped for *IL28B*

U.S. Caucasians



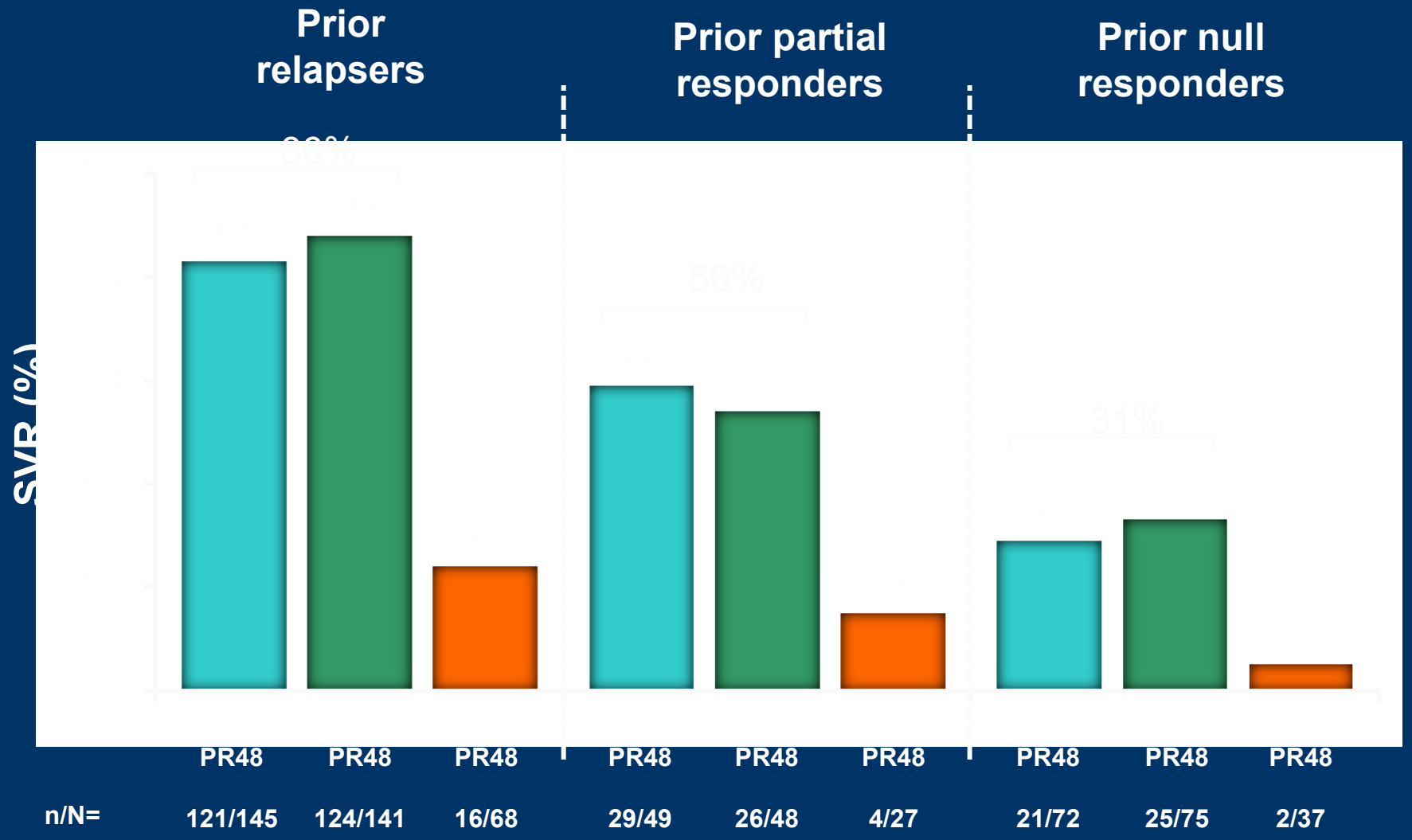
Jacobson IM, et al. Poster presented at: EASL: The International Liver Congress 2011; March 30-April 3, 2011; Berlin, Germany. Poster LB1369.

SVR Rates: ILLUMINATE



Sherman KE, et al. NEJM 365:1014-24, 2011

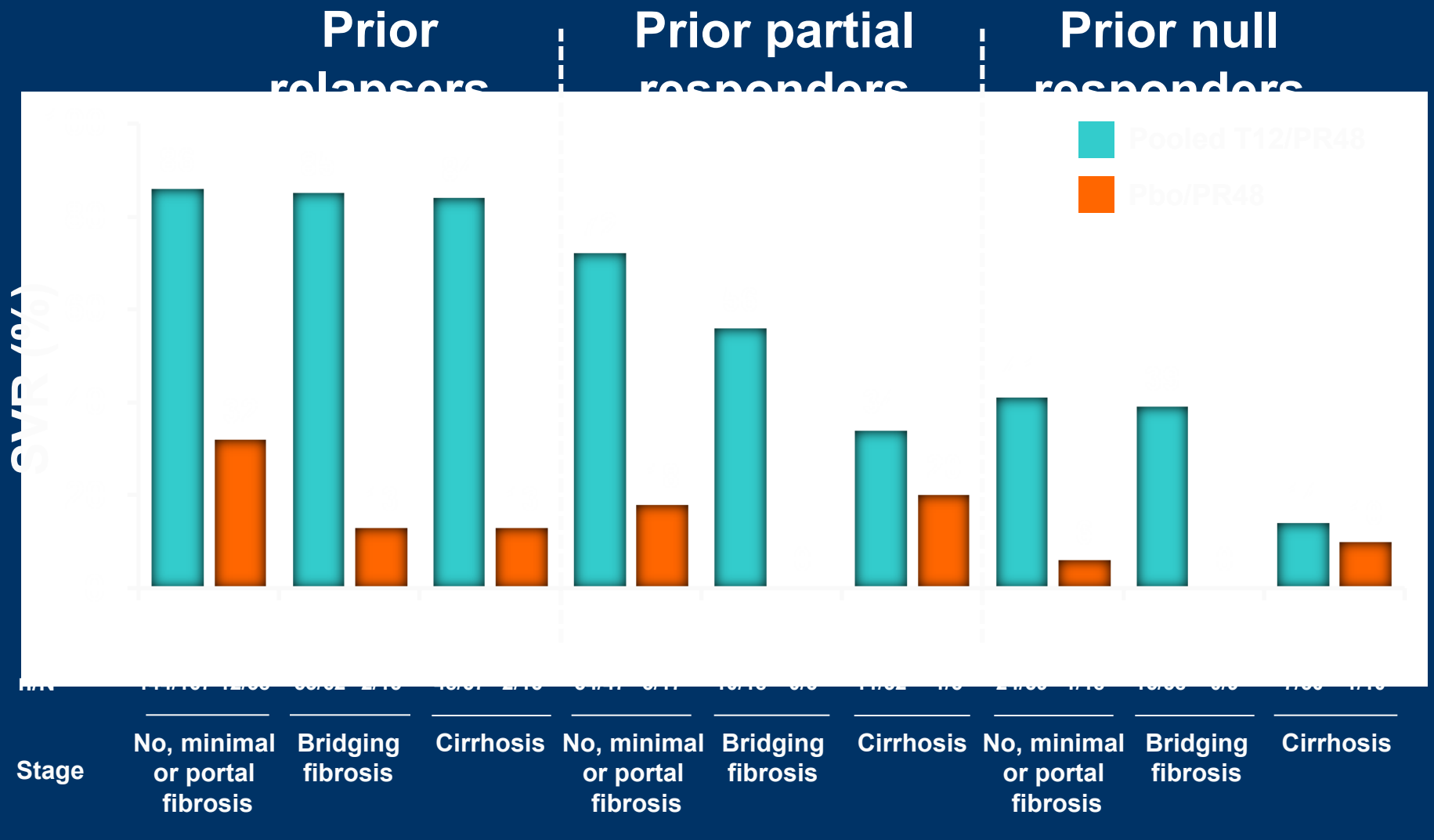
REALIZE: SVR in Prior Relapsers, Prior Partial Responders and Prior Null Responders



Zeuzem S, et al. N Engl J Med 2011;364:2417-27

*p<0.001 vs Pbo/PR48

REALIZE: SVR by Baseline Fibrosis Stage and Prior Response



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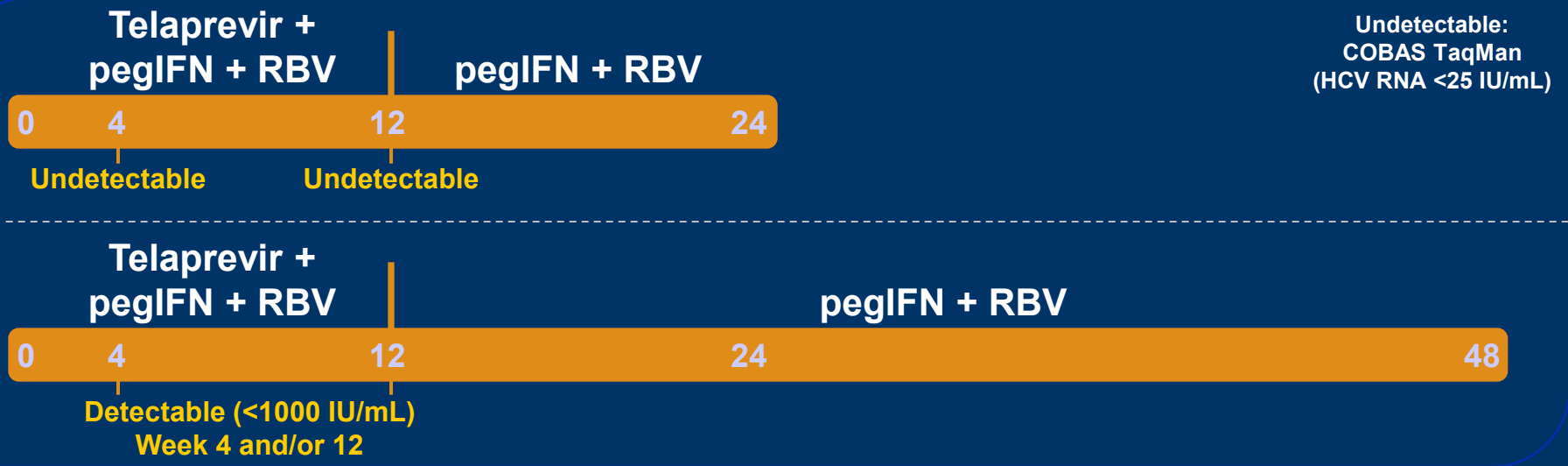
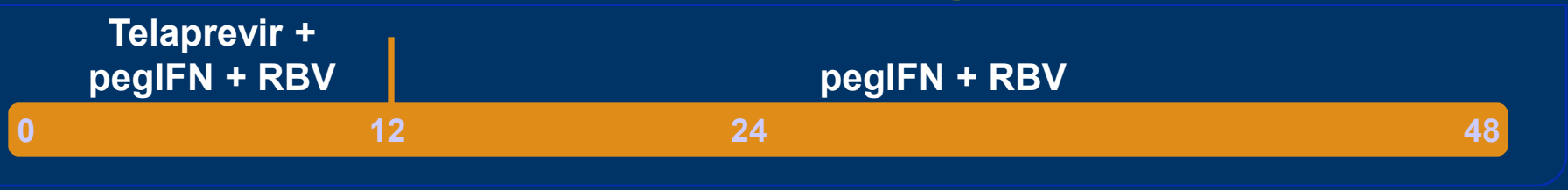
Telaprevir: Recommended Treatment Duration (weeks)

Treatment-Naïve or Prior Relapsers



Prior Partial and Null Responders



Cirrhotics should receive 48 weeks of therapy

Full prescribing information for telaprevir.

Stopping Rules for Telaprevir

Treatment Naïve & Experienced

Week 4	Week 12	Week 24
HCV RNA >1000 IU/ml	HCV RNA >1000 IU/ml	HCV RNA detectable
Stop all therapy	Stop all therapy	Stop all therapy

Telaprevir Package Insert, 2011

Contraindicated Drugs With Telaprevir

- *Interaction with CYP3A4*
  - *May occur via inhibition OR induction*

- Alfuzosin
- Ergot derivatives
- Cisapride
- Lovastatin, simvastatin, atorvastatin
- Sildenafil or tadalafil for PA hypertension
- Oral midazolam, triazolam
- Rifampin
- St. John's wort

Interact by inhibition

Interact by induction

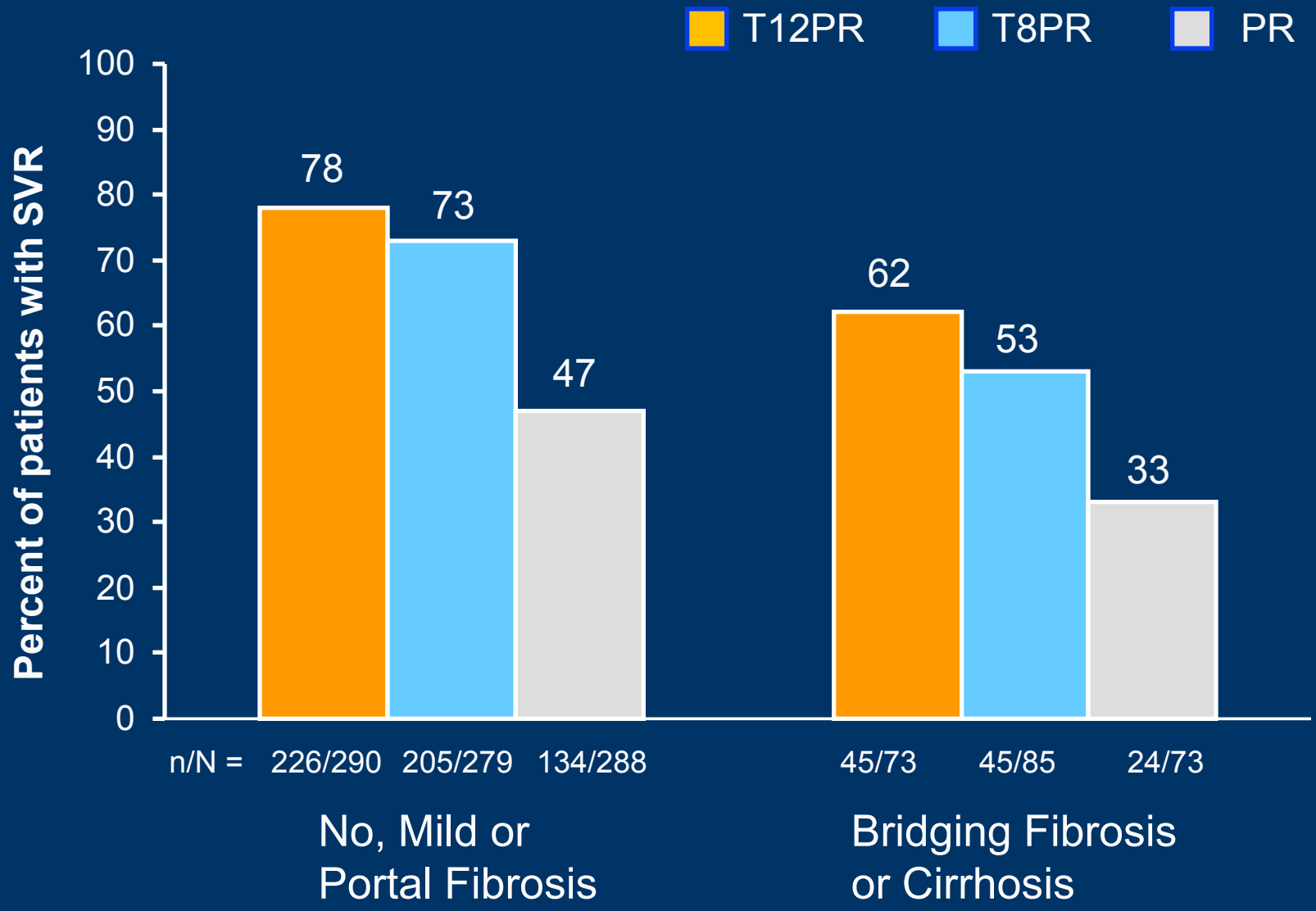
Many other drugs with established or potential drug-drug interactions that require caution, including tacrolimus, cyclosporin, estrogens, antiretrovirals

Telaprevir Package insert

Can Telaprevir be Given Twice Instead of Three Times Daily?

Telaprevir in Cirrhotic Patients

ADVANCE: SVR Rates by Fibrosis Stage



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Telaprevir Safety Data: Cirrhosis vs No Cirrhosis

Treatment Naive

	T12 PR(ADVANCE, ILLUMINATE)		PR (ADVANCE)	
	Cirrhosis N=82	No cirrhosis N=821	Cirrhosis N=21	No cirrhosis N=340
Anemia				
Grade 3	55 (67%)	377 (46%)	5 (24%)	85 (25%)
Grade 4	2 (2%)	11 (1%)	0 (0%)	0 (0%)
Neutropenia				
Grade 3	8 (10%)	72 (9%)	4 (19%)	39 (11%)
Grade 4	2 (2%)	11 (1%)	0 (0%)	10 (3%)
Thrombopenia				
Grade 3	10 (12%)	12 (2%)	0 (0%)	1 (<1%)
Grade 4	1 (1%)	0 (0%)	1 (5%)	0 (0%)

Kaufman R et al, HepDart December 2011

Safety and efficacy of telaprevir or boceprevir in combination with peginterferon alfa/ribavirin in cirrhotics: Week 16 analysis of the French early access program (CUPIC) N=497

	TVR n=292	BOC n=205
SAEs	45%	32.7%
Discontinuation (SAEs)	14.7%	7.3%
Death*	5	1
Infection (G3/4)	6.5%	2.4%
Hepatic decompensation	2%	2.9%
Anemia		
G2: 8.0 – <10.0 g/dL	18.8%	23.4%
G3/4: <8.0 g/dL	11.6%	4.4%
EPO use	53.8%	46.3%
Transfusion	16.1%	6.3%
RBV dose reduction	13%	10.7%
G4: <500/mm^3	2 (0.7%)	3.4%
Thrombopenia		
G3: 25000 – <50000/mm^3	9.6%	4.9%
Undetectable HCV-RNA (PP/ITT)(%)		
W4	58/55	3/2
W8	92/80	42/38
W12	93/79	64/55
W16	92/67	77/58

- N=497 G1 Child A cirrhosis patients reached W16 of therapy
  - History of prior non-response
- Multivariate analysis: Baseline predictors severe complications
  - Plts ≤100,000/mm^3
  - Albumin <3.5 g/L
- Multivariate analysis: Baseline predictors anemia/transfusion
  - Female gender
  - No lead-in
  - Age ≥65 yrs
  - Low Hb

Hezode C, et al. AASLD 2012, Boston. #51

PR + Telaprevir in Cirrhotics at a Transplant Center

- 39 patients, 9 on wait list; all MELD<15
- 80% HCV RNA negative by week 12
- 23% d/c'ed due to AEs
  - 4 with infectious complications
  - 1 decompensation requiring liver transplantation
- Higher MELD and lower platelet count related to complications

Gallegos-Orozco JF et al, AASLD 2012 abstract 53

PI Therapy in Advanced Cirrhotics

- Virologic response frequently attainable
- Higher incidence of side effects, including infection and decompensation
- Prudent to get transplant evaluation before treating a borderline patient
- Possible role for prophylactic antibiotics

PI Therapy in Liver Transplant Recipients: The CRUSH-C Study

- 61 patients
  - 43% with bridging fibrosis/cirrhosis
  - 10% fibrosing cholestatic hepatitis
- Median time to treatment 33 months post-LT
- Most received telaprevir with lead-in
- Mean daily doses before/after initiation of treatment:
  - Cyclosporin 200 mg/50 mg
  - Tacrolimus 1.0 mg/0.06 mg
- HCV RNA<LOD at 4 and 12 wks in 63% and 71%

Burton JR et al, AASLD 2012 abstract 211

PI Therapy in Liver Transplant Recipients: The CRUSH-C Study

- 37% required transfusion
- 86% used growth factors
- Dose reductions in 78%
- 33% had creatinine increase > 0.5 mg/dL
- Hospitalizations for SAEs in 18%
- Rejection in 2 patients
- 2 deaths – sepsis and hepatorenal syndrome

Burton JR et al, AASLD 2012 abstract 211

HIV Coinfection

Points to Remember

- Total daily dose should be 2250 mg in 2 or 3 doses
- Administer telaprevir with 20 gm fat
- Undetectable HCV RNA required at 4,12 weeks to be eligible for shortened therapy (only naives or relapsers)
- Adhere to stopping rules
- Anemia may require RBV dose reduction ± epo
- Stop TVR for severe rash, stop all drugs for severe symptoms with systemic effects
- Caution in cirrhotics, especially advanced cirrhotics
- TVR appears to be effective in HIV coinfected patients with unchanged safety profile