HCV
Where are we now?
(Will we still need you?)

Graham R Foster

Professor of Hepatology

QMUL

HCV – The Future

- I have received consultancy fees from:-

- Roche, Gilead, AbbVie, BI, BMS, Idenix, Regulus, Novartis, Chughai, Merck, Janssen

HCV The Future

- Todays drugs
- What is emerging
- Assessing fibrosis – what do we need?

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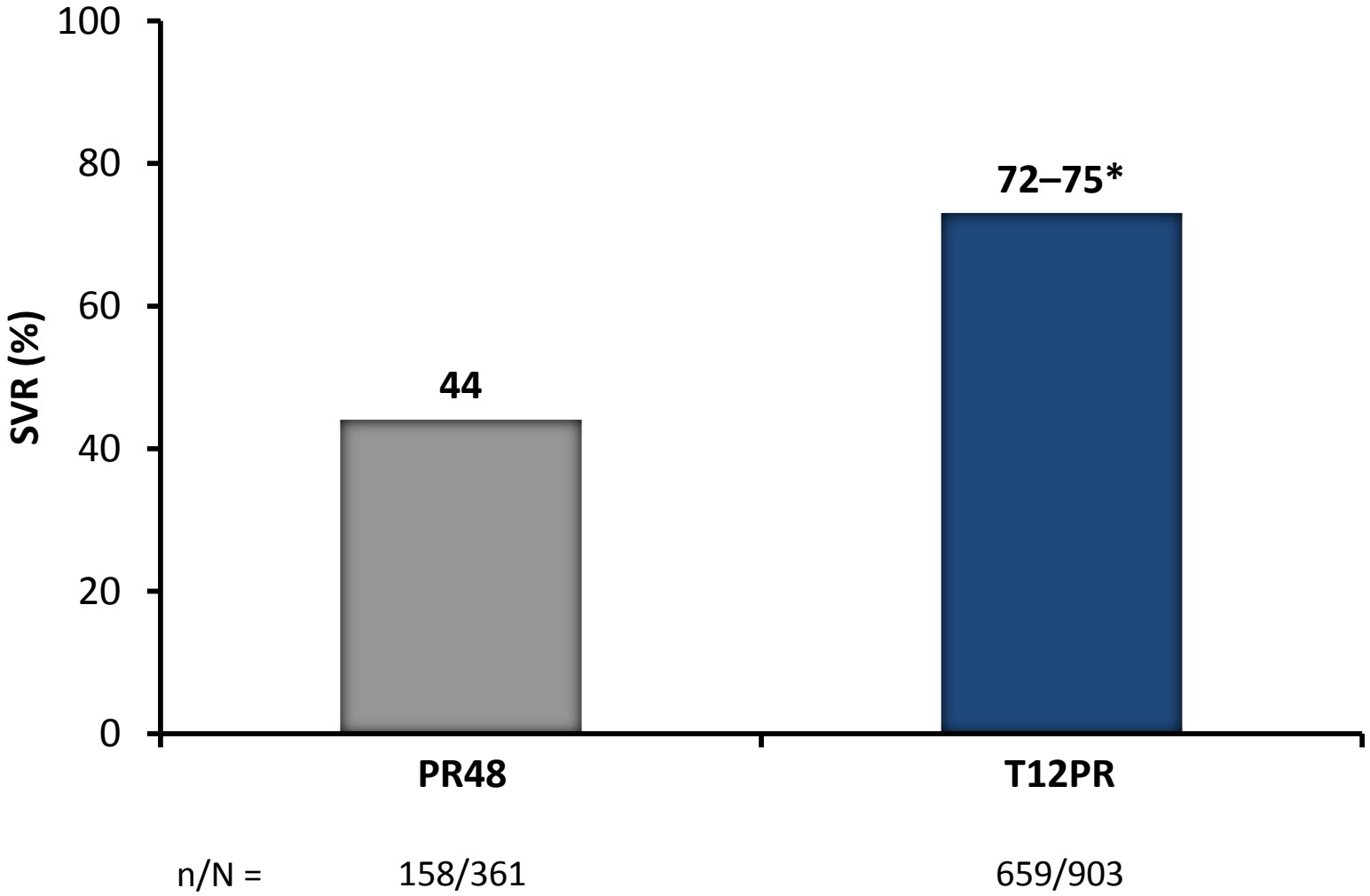
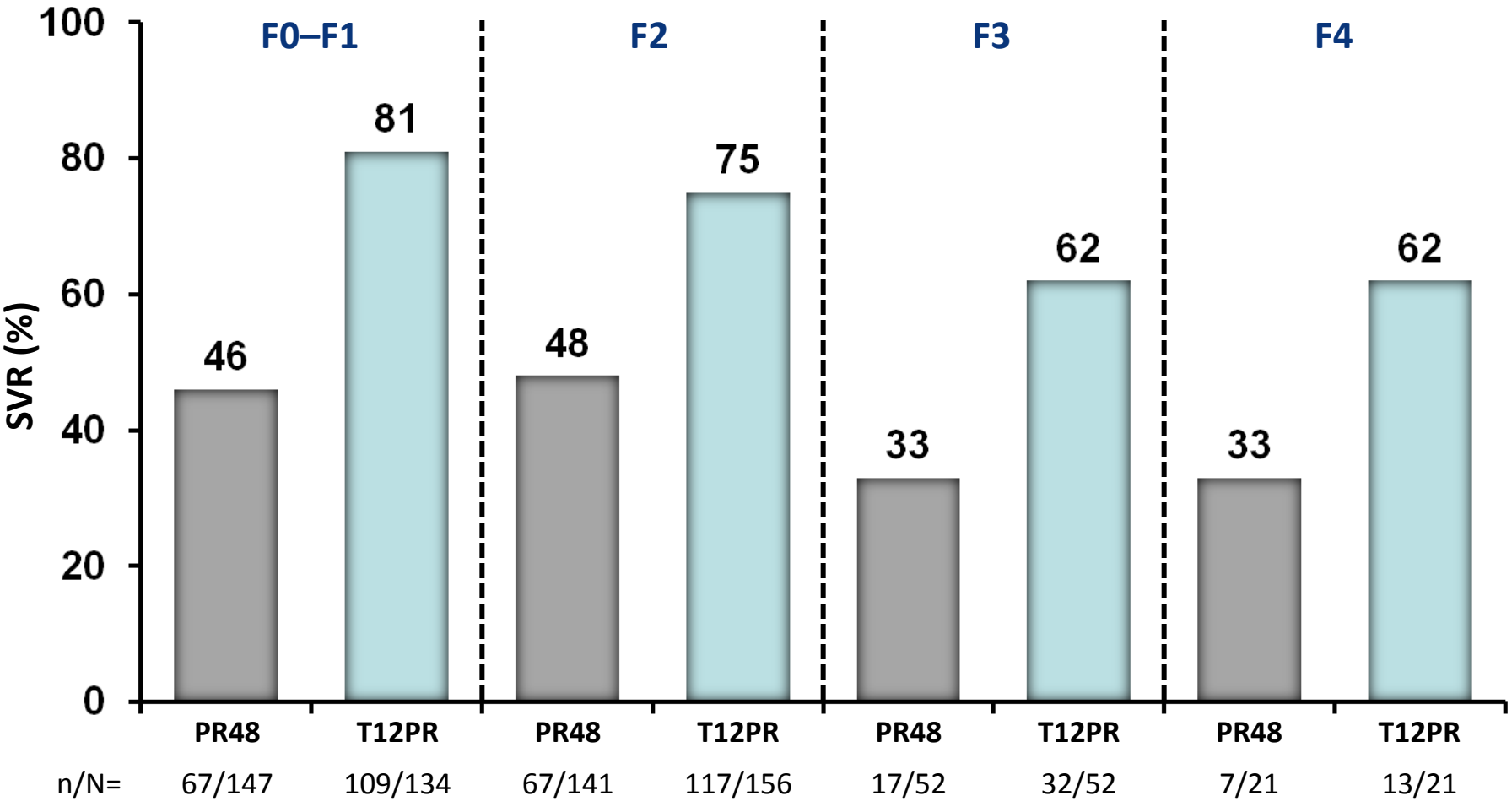
Genotype 1 – Good Drugs on the market PegIFN/Ribavirin and Protease inhibitors



*p<0.001 vs PR48 in ADVANCE (75% versus 44%)

Sherman KE, et al. Hepatology 2010;52(Suppl.):401A
Jacobson IM, et al. N Engl J Med 2011;364:2405-16; Sherman KE, et al. CROI 2011. Abstract 957

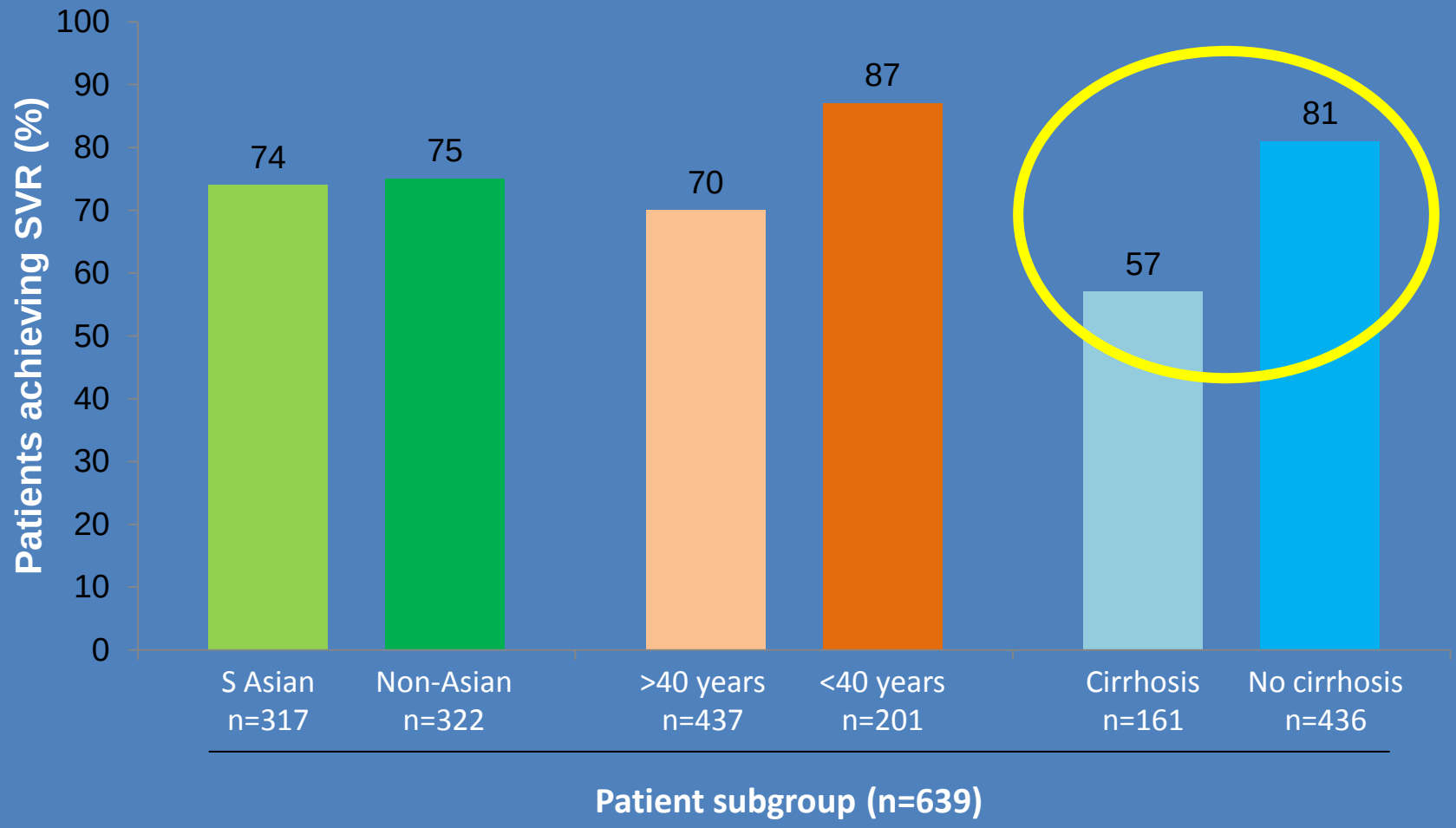
Telaprevir SVR rates by fibrosis stage in treatment-naïve patients



SVR, considered virologic cure, was defined as HCV RNA undetectable 24 weeks after last planned dose

Marcellin P, et al. J Hepatol 2011;54(Suppl 1):S183

Response of HCV G3 patient subgroups to PegIFN/RBV



Data are from an audit of 639 patients tretated with PegIFN/RBV; Shoeb D, et al. *Eur J Gastroenterol Hepatol* 2011;**23**:747–753

Current Drugs - not perfect

- For G1 – reasonable efficacy, high side effects
- For G2/3 – good efficacy, moderate side effects

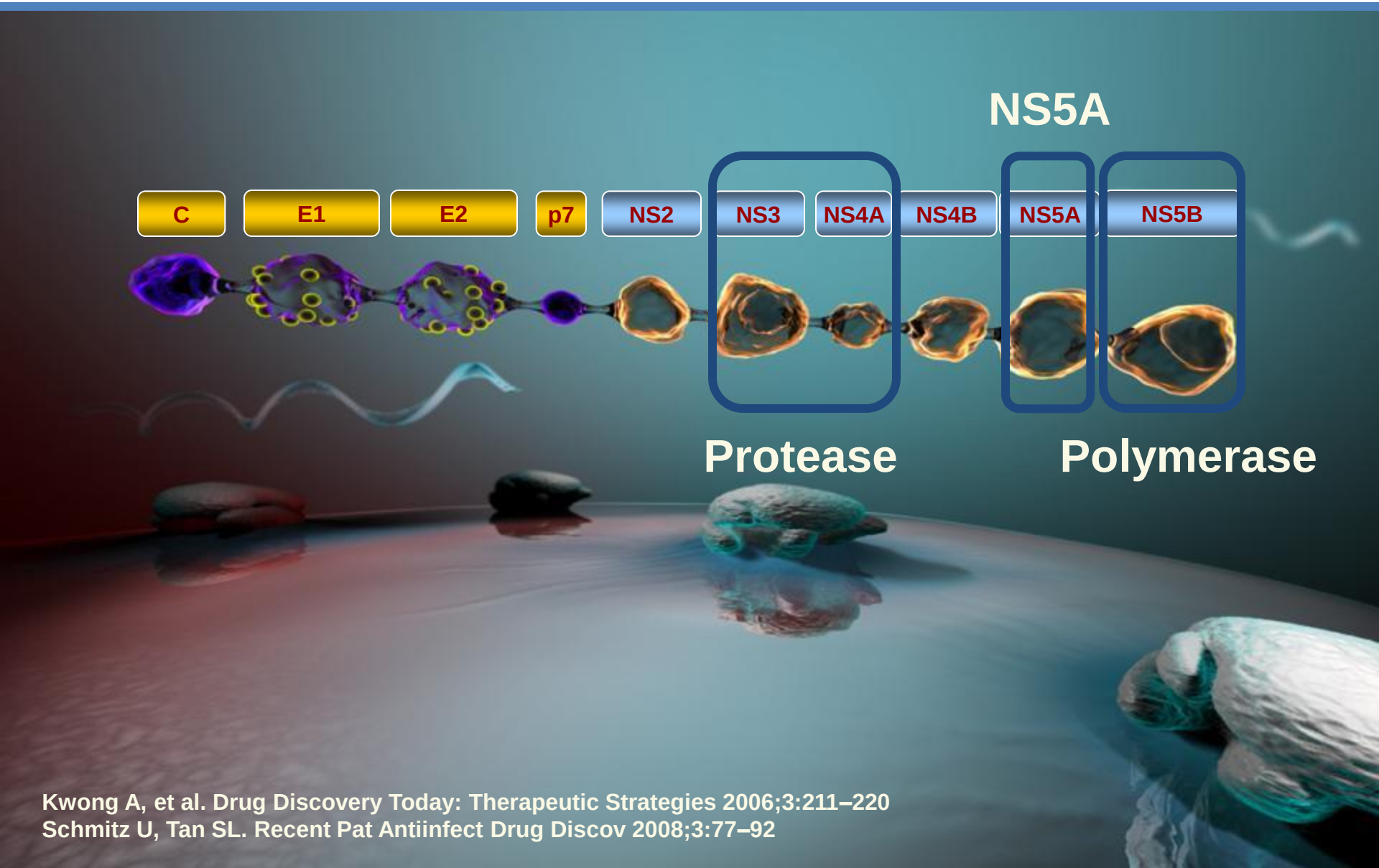
- In cirrhosis efficacy falls, side effects rise

WE NEED TO KNOW WHO HAS CIRRHOSIS

HCV The Future

- Todays drugs
- What is emerging
- Assessing fibrosis – what do we need?

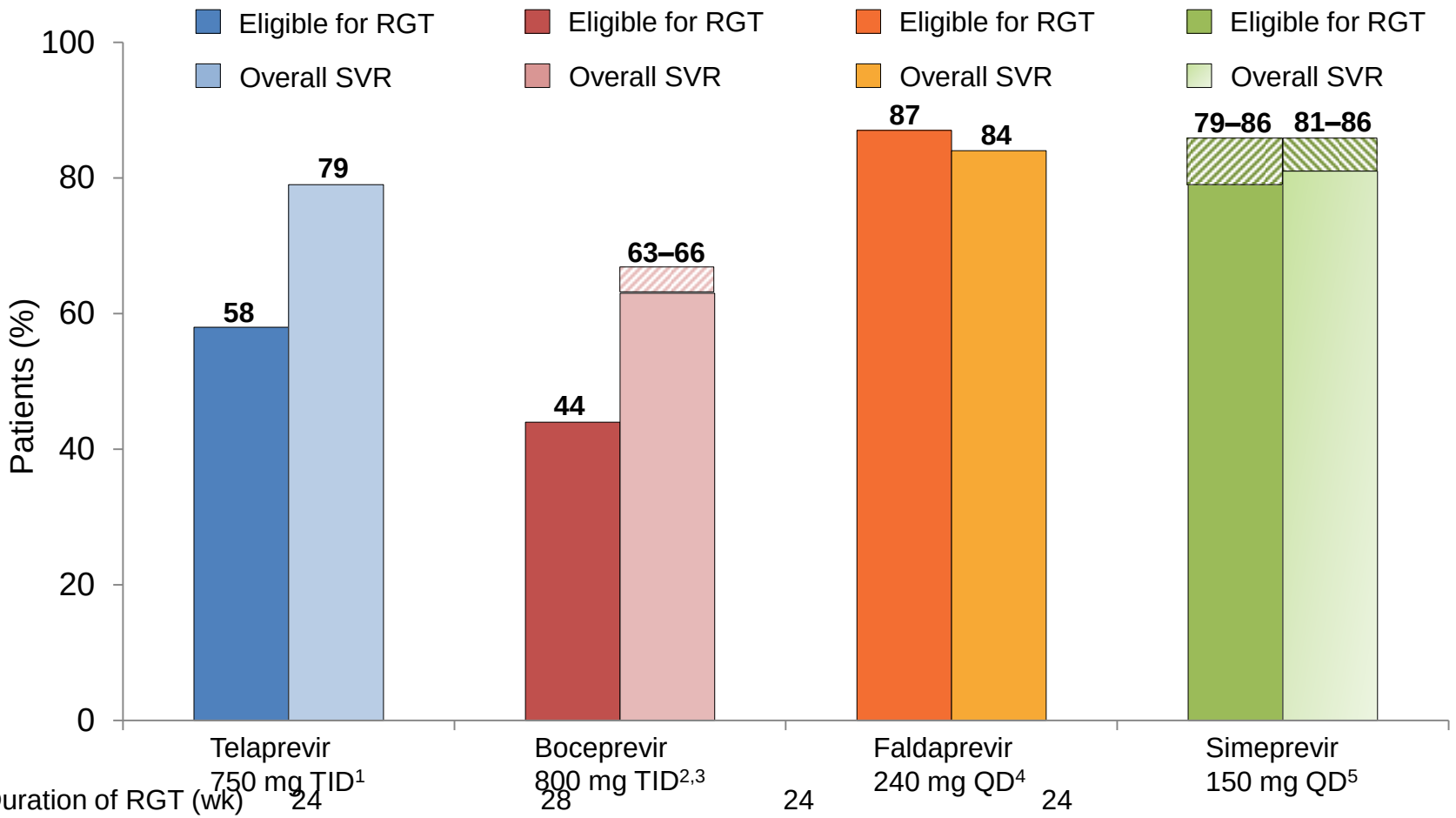
Specific targets for HCV treatment: protease, polymerase and NS5A inhibition



Kwong A, et al. Drug Discovery Today: Therapeutic Strategies 2006;3:211–220
Schmitz U, Tan SL. Recent Pat Antiinfect Drug Discov 2008;3:77–92

New Protease Inhibitors

New Protease Inhibitors (With Peg + Riba)



Results are for separate trials for each compound, not head-to-head studies, in treatment-naïve patients also receiving PegIFN/RBV
Hatched regions indicate ranges of results

QD, once daily; RGT, response-guided therapy; SVR, sustained virological response; TID, three times daily

1. Incivo EU SmPC 2011; 2. Victrelis EU SmPC 2011;
3. Poordad F, et al. N Engl J Med 2011;364:1195–1206;
4. Sulkowski MS, et al. Manuscript in preparation;
5. Fried M, et al. AASLD 2011. Abstract LB-5

New protease inhibitors

Restricted to the US viral strains

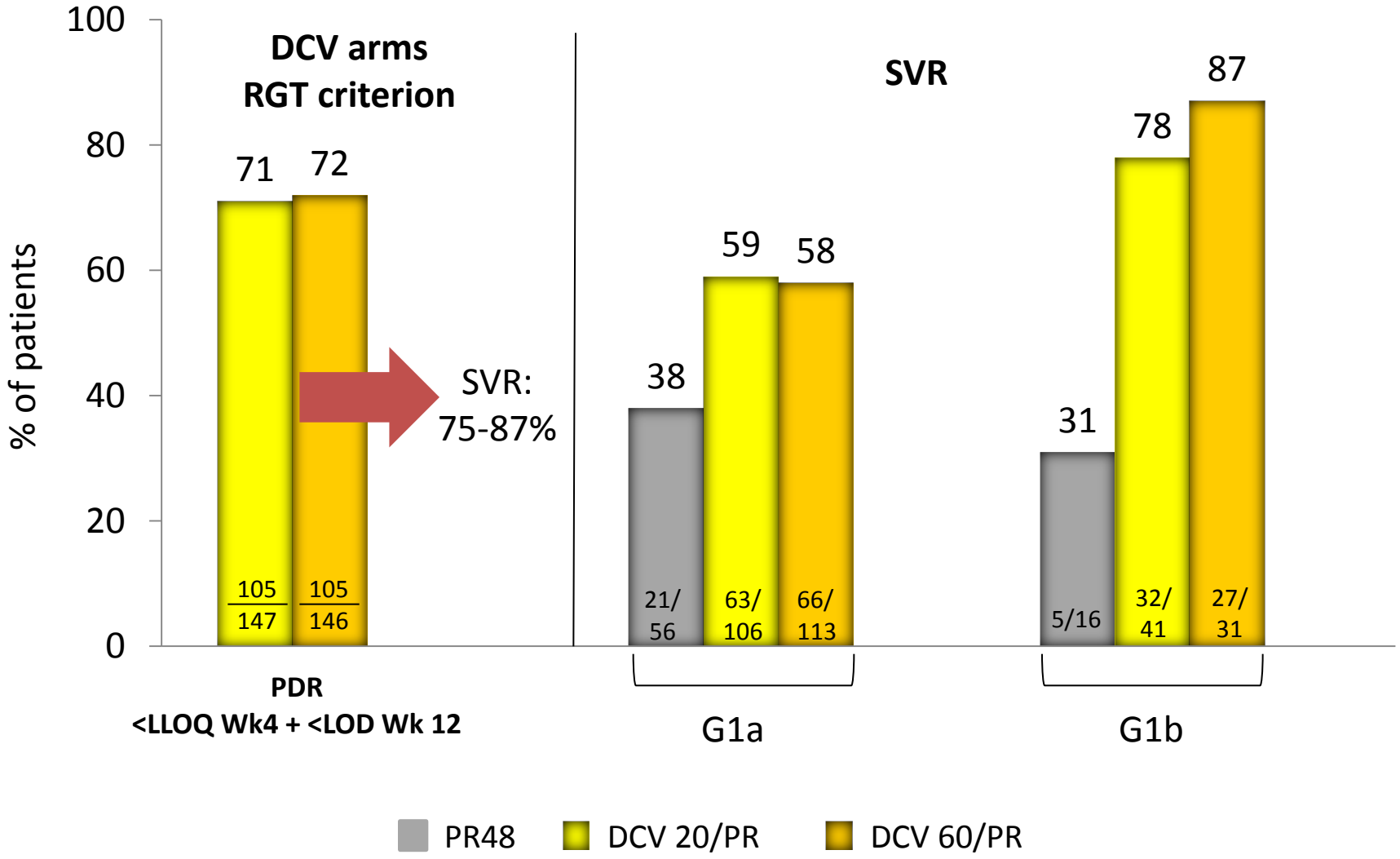
Early data in HIV encouraging

Fewer DDIs

(Not as good as they pretend they are)

NS5A Inhibitors

Daclatasvir + PR



PDR: protocol defined response

Hézode et al, AASLD 2012 (SVR 12 analysis), abstract 755; TVR EU SmPC

NS5A Inhibitors

Quirky

Large variation in efficacy

Good to work with

NS5B – Non Nucleotides

NS5B – Non Nucleotides

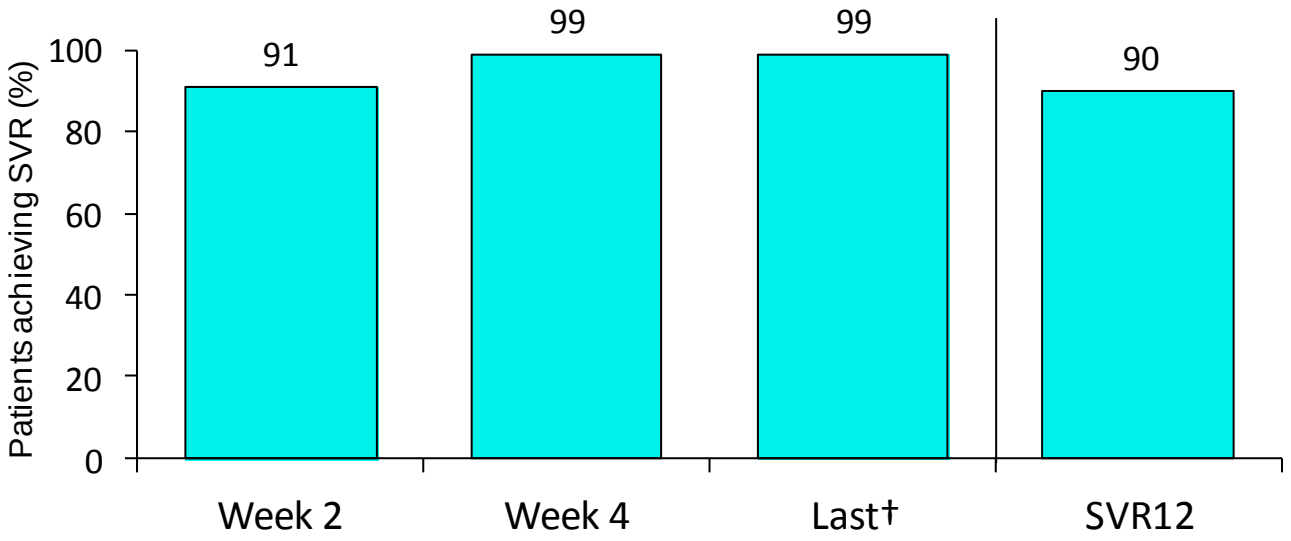
Very unpredictable

Generally G1 specific

Nucleotides

Sofosbuvir with PEG-IFN + RBV

- NEUTRINO Phase III trial
  - Sofosbuvir plus PEG-IFN + RBV* for 12 weeks
  - Treatment naïve, GT1 (89%), 4, 5 or 6 (N=327)
    - 17% had compensated cirrhosis
  - Primary endpoint: SVR12



*Dose administered according to body weight
†Last observed measurement

Lawitz et al. N Eng J Med 2013;368:1878–87

Nucleotides

Fast
Effective
Cures all strains
Side effect free

(Too good to be true)

What about interferon free?

- Interferon is horrid - can we go to interferon free?

Playing Tag (I)

+

BI

+

BMS

Protease Inhibitor + Non – Nuc/NS5A

PI +

BI 201335 + BI207127 ± R (SOUND-C2)	SVR12 (with RBV): Daclatasvir + Asunaprevir (AI-447-017)
• **Non cirrhotics TN**	• **G1b Null R and IFN ineligible/intolerant**
• 16-40 week	• **non cirrhotic**, japanese

• SVR12 (with RBV):
  • G1a: 38-47%
  • G1b: 63-83%
	• 24W
	• SVR24:
	  • 91% in Null R (N=21)
	  • 64% in IFN inel/intol (N=22)

Sulkowski M, et al. EASL 2012: Abstract 1422: http://www.natap.org/2012/EASL/EASL_24.htm
Suzuki et al. EASL 2012;:http://www.natap.org/2012/EASL/EASL_27.htm

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Two drugs

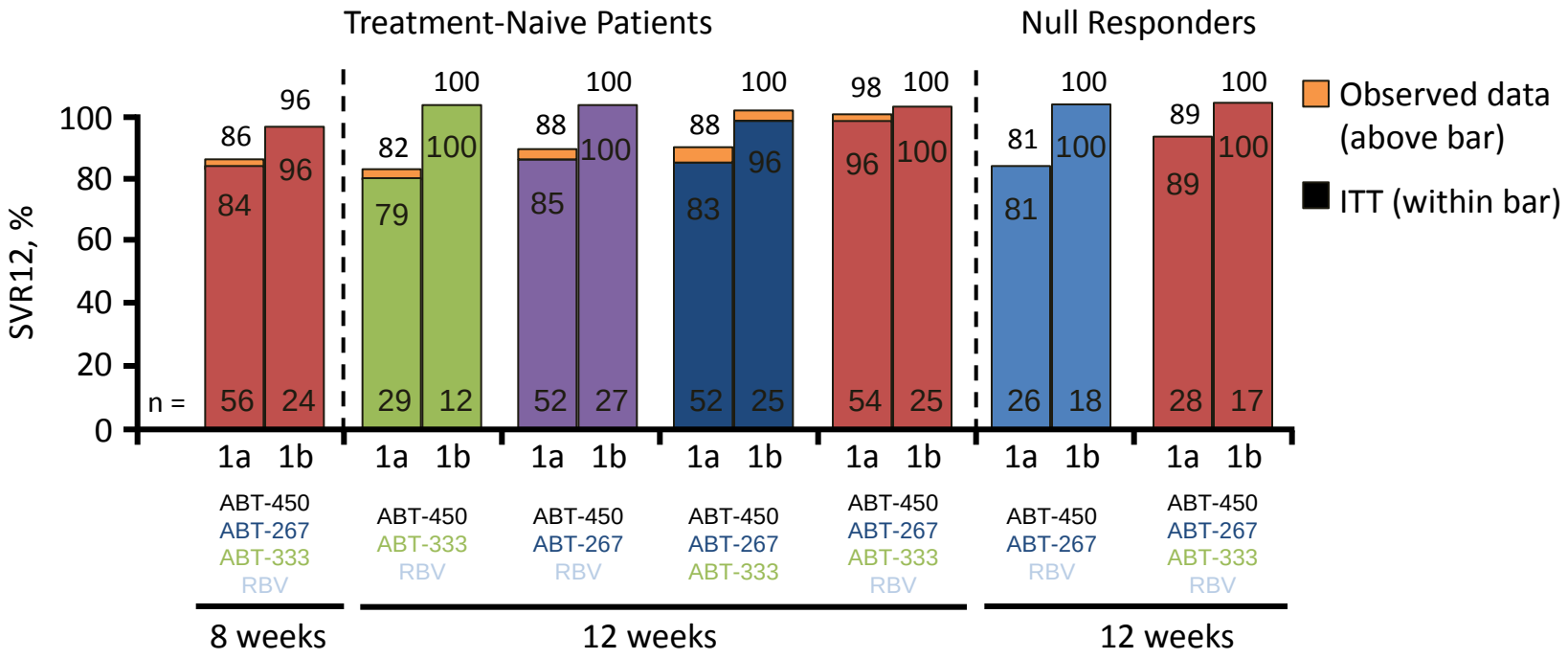
- Great for G1b
- Lots of combinations emerging
- May be very cost effective

Two drugs (PI + X) is good

- But not good enough – send in the boys!

AVIATOR: SVR12 Rates With ABT-450/RTV, ABT-267, ABT-333, and RBV

- SVR12 rates higher in pts with HCV GT1b, but also high in pts with HCV GT1a
  - 12-wk regimen with all 3 DAAs + RBV produced highest SVR12 rates
- No drug-related SAEs reported; 2 pts discontinued tx due to drug-related AEs



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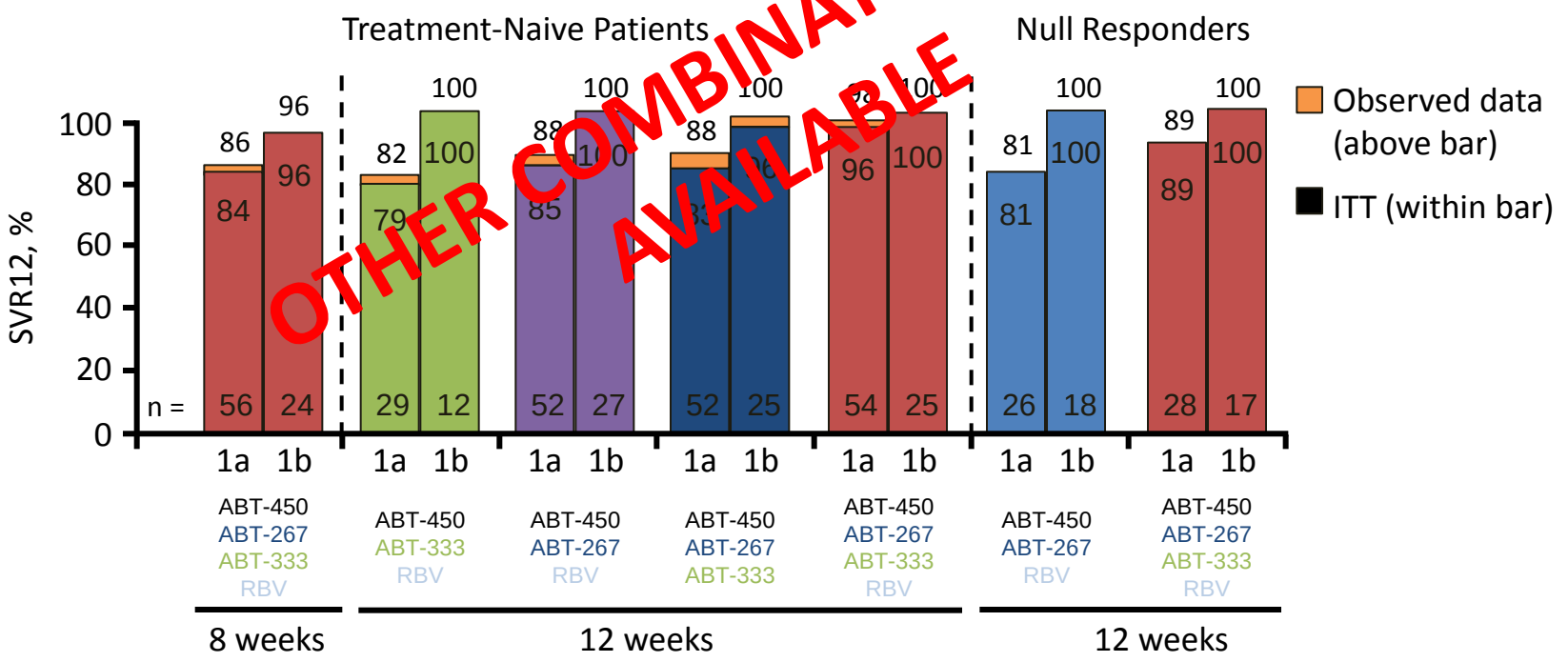


Kowdley K, et al. AASLD 2012. Abstract LB-1.

What about the alternatives?

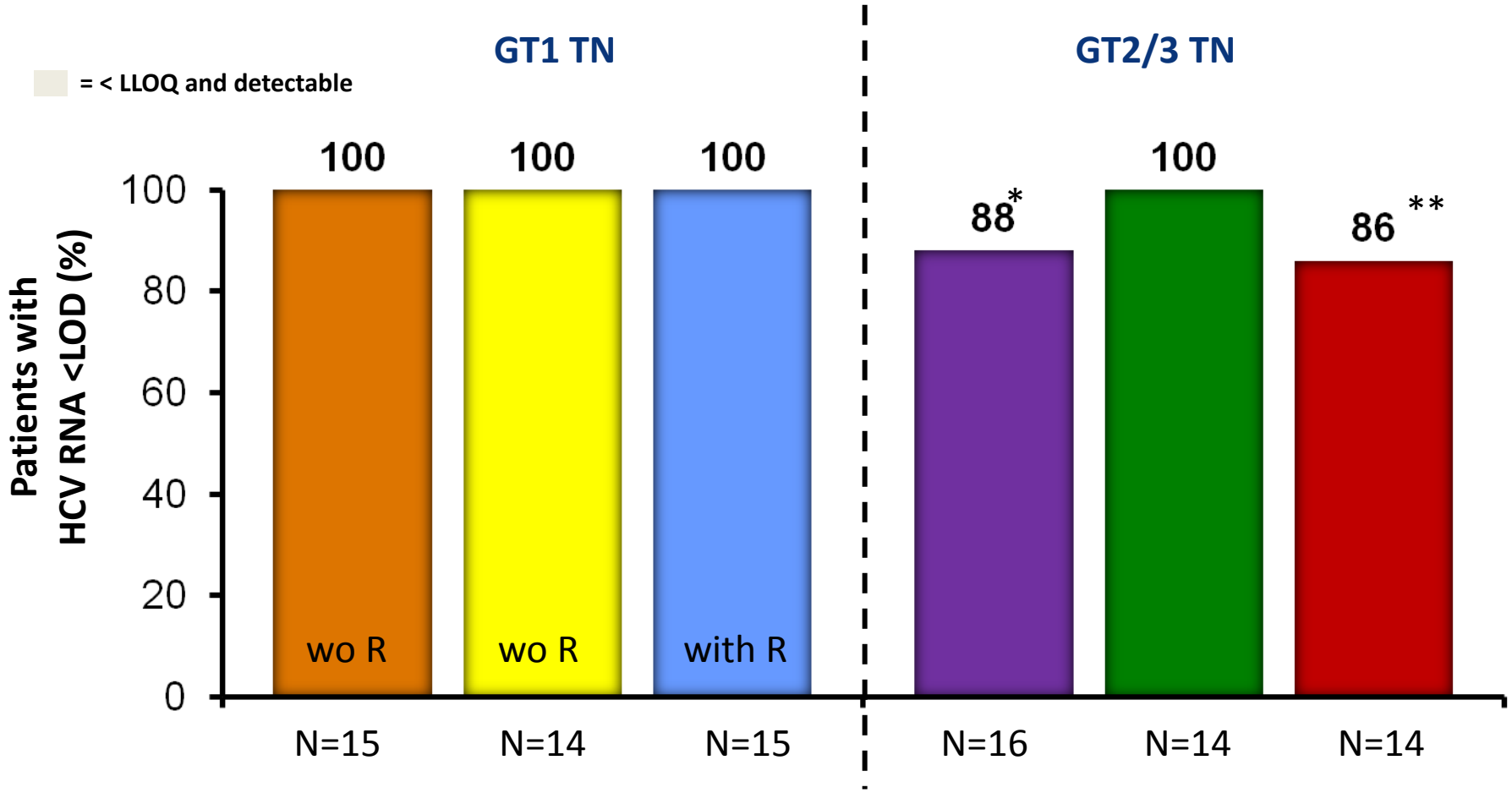
Sofosbuvir + Ribavirin 24 weeks

Cures 68% of tough patients

(Kottilil – JAMA 2013)

Does Superman need a friend

GS-7977+DCV for 24 weeks)



*1 patient required addition of peg-IFN/RBV, 1 patient with relapse at Week4
**2 patients lost to follow-up (following Week 12 and 24 visits)

Sulkowski M, et al. AASLD 2012, LB-2

Sofosbuvir +

- Sofosbuvir + ‘anything potent’ looks wonderful

- Sofosbuvir + Ledipasvir (NS5A) = ~100%
- Sofosbuvir + Simeprevir (NS3) = ~100%

G2
-Current Therapy

- Interferon therapy for G2 is over
- FISSION trial – SVR >90% for Sofos+Ribavirin

  (Lawitz NEJM 2013)
- PHOTON trial (HIV co-infected) – SVR 81%

Genotype 3

G3 (NAÏVE) IFN Intolerant		G3 12 WEEKS		G3 16 WEEKS	
Non Cirrhosis	Cirrhosis	Non Cirrhosis	Cirrhosis	Non Cirrhosis	Cirrhosis
68%	21%	37%	19%	63%	61%

Jacobson NEJM 2013

IFN Intolerant and IFN treated G3

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Jacobson NEJM 2013

Genotype 3

- PHOTON trial (G3 + HIV)
- Sofosbuvir + Ribavirin – SVR = 67% (N=42)

- Breaking news suggests 24 weeks of Sofosbuvir+ Ribavirin may cure G3

Nucleotide struggles with G3

We are nearly there...

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Genotype 1

- Powerful drugs with Peg+ Riba (PIs, Nucs)

- Multiple PI drug regimes without Peg

  G1b = PI + 1, G1a = PI + 2 (Abbott, Nuc+NS5A)

- Sofosbuvir + AN Other – almost perfect!

We are nearly there....

Genotype 2

- Nuc + Ribavirin – Game over

Genotype 3

- Struggling
- We need a partner for the nuc

HCV The Future

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HCV What do we need?

- We NEED to know who has cirrhosis (treatment regimes may be extended or different in cirrhosis)

- Fibroscan etc may be OK

  (but may not work well for some Genotypes)
- Biopsy to exclude cirrhosis may be needed in ‘odd Fibroscans’

HCV What might we need?

- Sofosbuvir costs Euro 54,000
- We may only be allowed to treat F3/4
- Biopsy driven algorithms may return

HCV The Future

- Cure for all with simple regimes
- In the future we will ALL be redundant
- For now – we will need some biopsies to guide therapy in patients where non-invasive tests don’t work

New Therapies for HCV

- The superheroes are in play
- The optimal combinations are emerging
- The costs remain to be seen
- There will be some casualties on the way

The Future

- Oral combination therapy for everyone is very close

- It will be here in 5 years

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- Oral combination therapy for everyone is very close

- It will be here in 5 years

- For NOW
- Sick patients need Peg+Riba+/-PI
- Mild patients should wait