

Future of Interferon-Free HCV Treatment

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Interferon (IFN)-Free Regimens

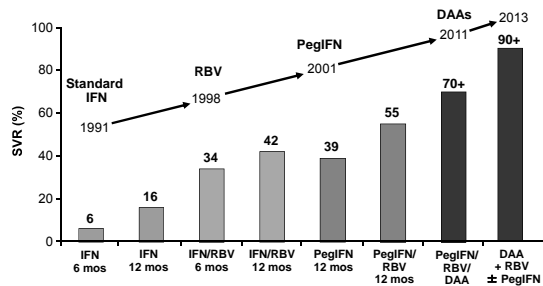
– Current therapies

– IFN-free therapies

- Which DAAs for which patients?
 - The backbones
 - The combinations
 - Will there be a role for IFN?



The Good News



Adapted from the US Food and Drug Administration, Antiviral Drugs Advisory Committee Meeting, April 27-28, 2011, Silver Spring, MD.

CUPIC: Safety of boceprevir and telaprevir in cirrhotic patients with previous treatment failure

Week 16 safety	Telaprevir (n=292)	Boceprevir (n=205)
Serious adverse event (SAE)	132 (45%)*	67 (33%)**
Discontinuation	66 (23%)	54 (26%)
due to SAE	43 (15%)	15 (7.3%)
Death	5 (1.7%)	1 (0.5%)
Infection (grade 3/4)	19 (6.5%)	5 (2.4%)
Hepatic decompensation	6 (2.0%)	6 (2.9%)
Asthenia	16 (5.5%)	12 (5.8%)
Rash/SCAR	14 (4.8%)/0	0/0
Renal failure (eGFR<50)	5 (1.7%)	0

Hezode. J Hepatol 2013.

* 334 SAEs in 132 patients
**159 SAEs in 67 patients

The Downsides of the PIs



Treatment is more effective, but much more difficult

The Downsides of the PIs

Pill burden

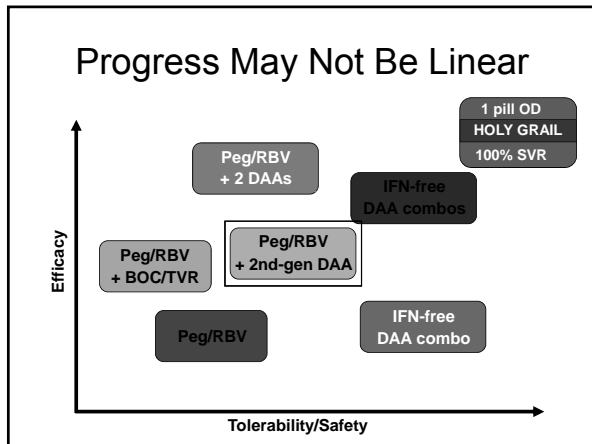
Food requirement

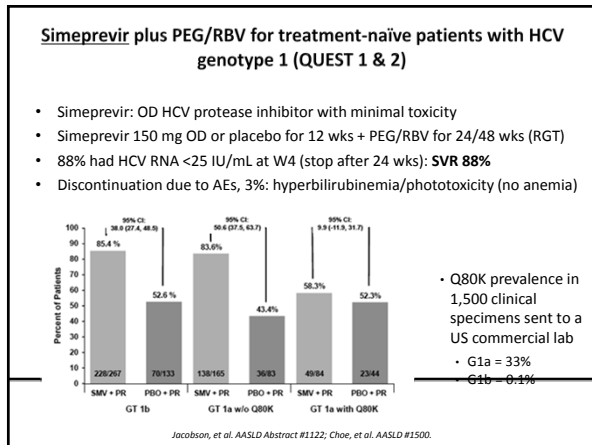
Resistance

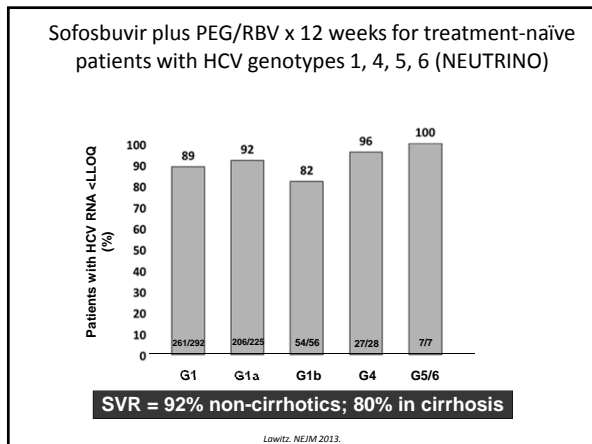
BOC = 12/day TVR = 6/day
RBV = 4-7/day RBV = 4-7/day

Drug-drug interactions

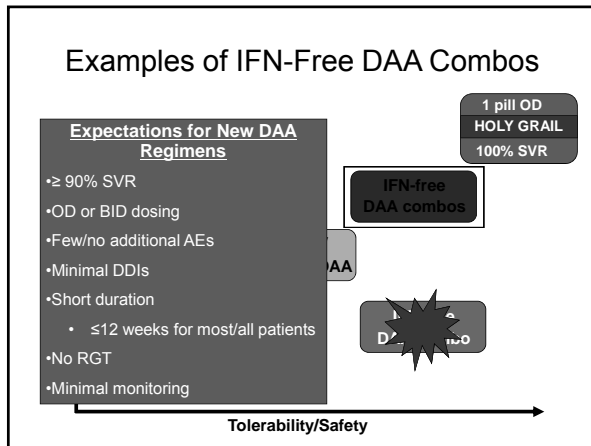
PI CYP3A4 metabolites







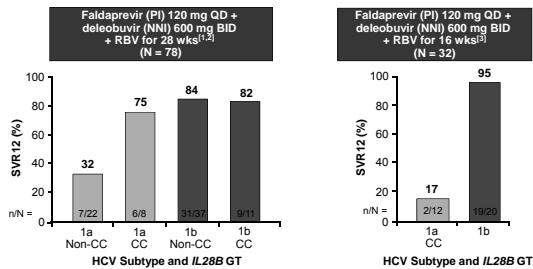
Examples of IFN-Free DAA Combos



Options for DAAs

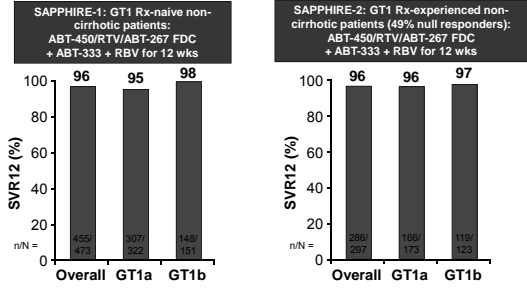
- PI backbone – potent/modest barrier
 - PI + another low-barrier DAA (NNI/NS5A) for G1b
 - PI + 2 low-barrier DAAs for G1a
- Nuc backbone – potent/high barrier
 - Nuc + low-barrier DAA for G1a/b (e.g. NS5A)
 - Nuc + PI
- Include ribavirin?
 - May allow fewer DAAs (2 vs. 3)
 - May allow shorter therapy

PI Backbone + NNI + RBV for GT1b Only



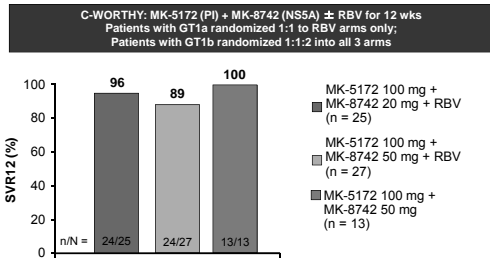
1. Zeuzem S, et al. NEJM. 2013;369:630-639. 2. Zeuzem S, et al. EASL 2012. Abstract 101. 3. Dufour JF, et al. AASLD 2013. Abstract 1102.

PI Backbone + Two Other DAAs (SAPPHIRE-1/2)



Data from Abbvie press release.

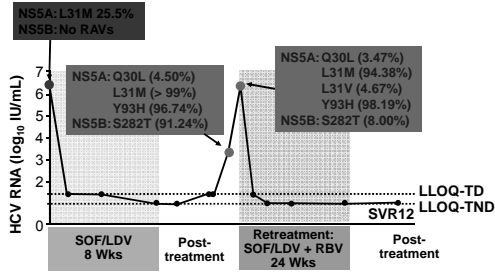
Exception to the Rule: C-WORTHY: PI + NS5A ± RBV in Rx-Naive G1



Lawitz E, et al. AASLD 2013. Abstract 76.

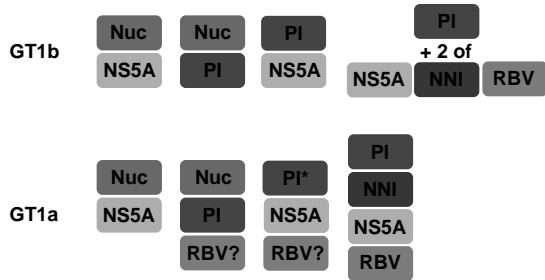
What About a Nucleotide Polymerase Inhibitor (NUC) Backbone?

What About Resistance?



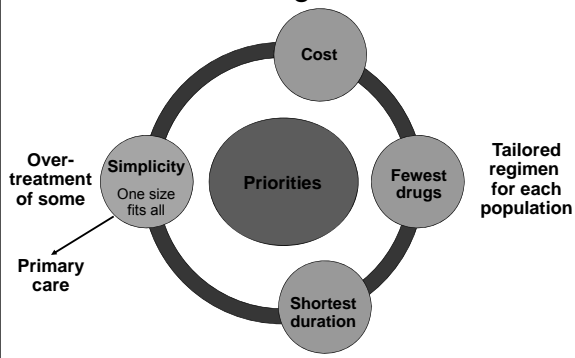
Lawitz E, et al. AASLD 2013. Abstract 215.

Potential 12-Week Options for GT1 HCV With Supportive Efficacy Data



* MK-5172

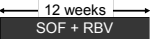
Different Strategies of DAA Rx



What about HCV Genotypes 2 and 3?

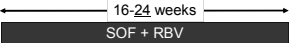
Sofosbuvir + RBV for HCV G2 and 3: Approved Indications

- All G2 patients receive same regimen, regardless of previous treatment history or fibrosis level



12 weeks
SOF + RBV

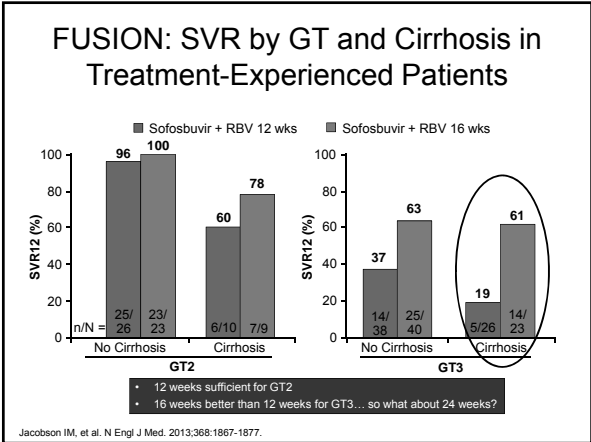
- All GT3 patients receive same regimen, regardless of previous treatment history or fibrosis level



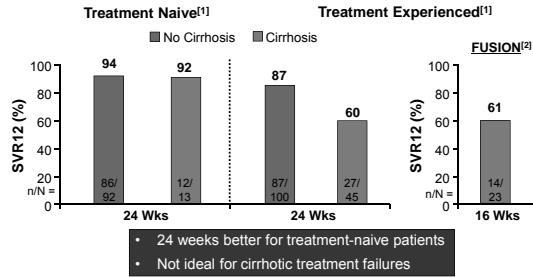
16-24 weeks
SOF + RBV

- If drugs combined with SOF must be permanently discontinued, SOF should also be discontinued

Sofosbuvir Package insert, December 2013.

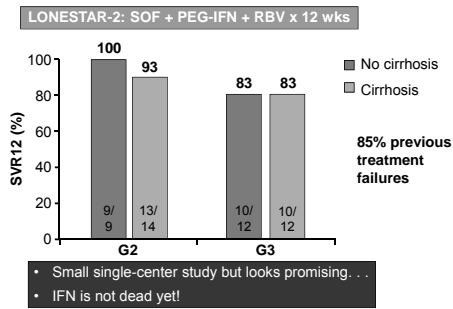


VALENCE: Efficacy of 24-Week SOF + RBV in HCV G3



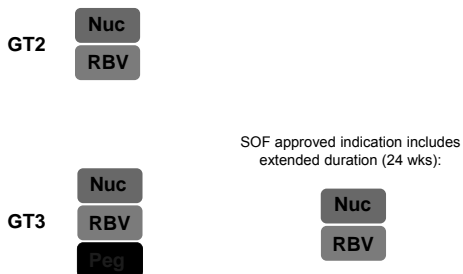
1. Zeuzem S, et al. AASLD 2013. Abstract 1085. 2. Jacobson IM, et al. N Engl J Med. 2013;368:1867-1877.

Do We Still Need IFN for G3?



Lawitz E, et al. AASLD 2013. Abstract LB-4.

Potential 12-Week Options for G2 and G3 With Supportive Efficacy Data



Will There Still Be a Role for IFN?

- Hard to cure
 - G3
 - DAA failures – multi-DAA resistant
 - Prior null responders → Quad?
- Easy to cure
 - *IL28B* CC – high efficacy, short duration → Asia?
 - Mild disease – option of IFN vs. waiting for progression
- Cost containment
 - Fewer or less effective DAAs
 - G2?



Summary: IFN-Free HCV Regimens

- First-generation PIs (BOC/TVR) have a limited lifespan
 - SMV + PEG/RBV x 24 weeks in G1 (issue with Q80K in G1a)
 - SOF + PEG/RBV x 12 weeks in G1 and G4
- IFN will be around for a short while ...
 - IFN-free therapy here for G2/3 and coming soon for G1
- Challenges
 - G1a vs. G1b
 - One size fits all vs. G1b regimens
 - G3 may still need IFN (at least for now in treatment-experienced, F4)
- Will simplify with time and we will have something for everyone
 - Single-tablet, once daily, pan-genotypic, short duration regimen is probably not too far away
