Current Management of HCV: The Path to Interferon Freedom

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Disclosures

Dr. Rob Myers

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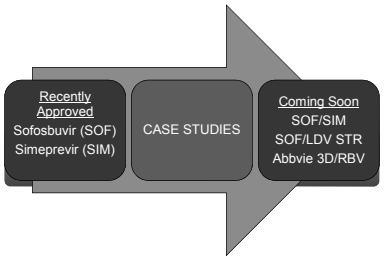
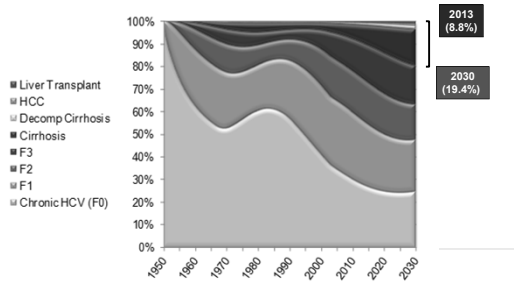
Dr. Kris Kowdley

Objectives



We must maximize utilization of these therapies to truly reduce HCV disease burden in Canada!

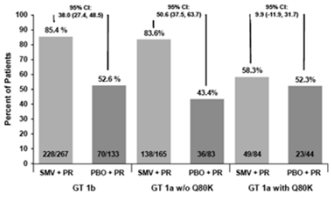
If we don't increase treatment utilization, the burden of disease will continue to rise



Myers et al., CJGH 2014.

Simeprevir plus PEG/RBV for treatment-naïve patients with HCV genotype 1 (QUEST 1 & 2)

- Simeprevir: OD HCV protease inhibitor with minimal toxicity
- Simeprevir 150 mg OD or placebo for 12 wks + PEG/RBV for 24/48 wks (RGT)
- 88% had HCV RNA <25 IU/mL at W4 (stop after 24 wks): **SVR 88%**
- Discontinuation due to AEs, 3%: hyperbilirubinemia/phototoxicity (no anemia)

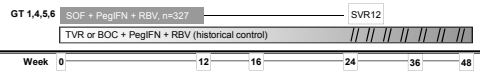


- Q80K prevalence in 1,500 clinical specimens sent to a US commercial lab
  - G1a = 33%
  - G1b = 0.1%

Jacobson, et al. AASLD Abstract #1122; Choe, et al. AASLD #1500.

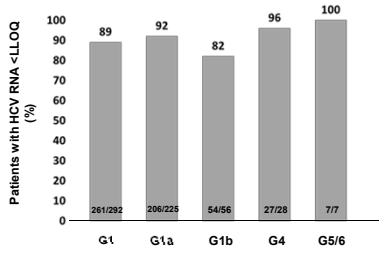
Sofosbuvir plus PEG/RBV x 12 weeks for treatment-naïve patients with HCV genotypes 1, 4, 5, 6 (NEUTRINO)

- Sofosbuvir (GS-797)
  - OD nucleotide polymerase inhibitor with minimal toxicity
  - Pan-genotypic
  - High barrier to resistance
  - No food effect
  - Limited DDIs
- Combined with PEG/RBV, all for 12 wks (no RGT)
- Efficacy compared with a historical control group (PEG/RBV/TPV or BOC), estimated SVR ~60%



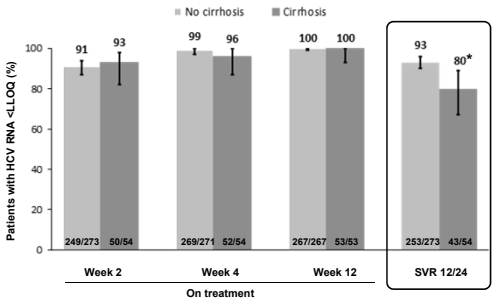
Lowitz. NEJM 2013.

Sofosbuvir plus PEG/RBV x 12 weeks for treatment-naïve patients with HCV genotypes 1, 4, 5, 6 (NEUTRINO)



Lawitz. NEJM 2013.

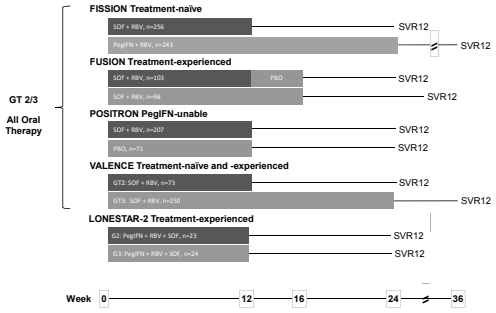
Sofosbuvir plus PEG/RBV x 12 weeks for treatment-naïve patients with HCV genotypes 1, 4, 5, 6 (NEUTRINO)



Lawitz. NEJM 2013.

<2% discontinuation due to AEs

Clinical Trials of Sofosbuvir for HCV G2 and G3

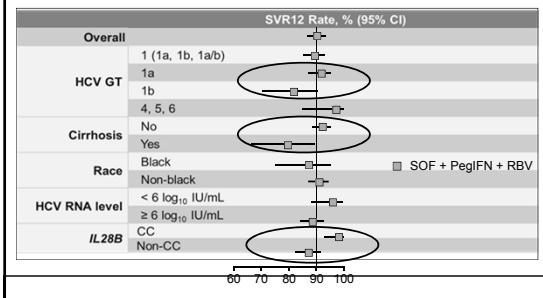


Clinical Trials of Sofosbuvir for HCV G2 and G3

Study	Population (n)	Rx	SVR G2	SVR G3
FISSION	GT 2 & 3 (n=499) Treatment-naïve	SOF/RBV x 12 w PEG/RBV x 24 w	97% 78%	56% 63%
FUSION	GT 2 & 3 (n=201) Treatment-experienced	SOF/RBV x 12 w SOF/RBV x 16 w	82% 89%	30% 62%
POSITRON	GT 2 & 3 (n=278) IFN unable, intolerant, unwilling	SOF/RBV x 12 w Placebo x 12 w	93% 0%	61% 0%
VALENCE	GT 2 & 3 (n=323) Treatment-naïve & treatment-experienced	SOF/RBV x 12 w (G2) SOF/RBV x 24 w (G3)	93% ---	--- 85%
LONESTAR-2	GT 2 & 3 (n=47) Treatment-experienced	SOF/PEG/RBV x 12 w	96%	83%

Are There Any Predictors of Treatment Response (or Failure)?

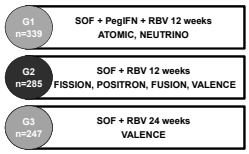
NEUTRINO: SVR by Pre-specified Subgroups



Lowitz. NEJM 2013.

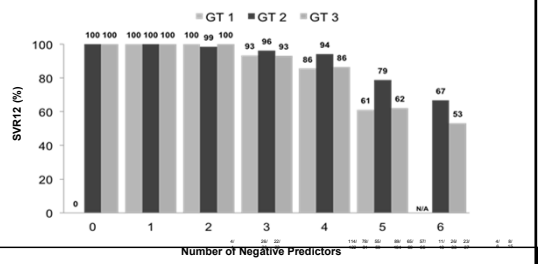
Effect of Negative Predictors on SVR Rates Across Sofosbuvir Trials

- Retrospective multivariate analysis of phase 2 and 3 SOF studies
- 6 negative predictors associated with relapse:
  - Prior treatment failure, cirrhosis, IL28B non-CC, HCV RNA ≥800,000 IU/mL, weight ≥75 kg, male gender
- 89% of patients in the phase 3 program had up to 4 negative predictors



Foster. EASL 2014, Abstract O66.

Effect of Negative Predictors on SVR Rates Across Sofosbuvir Trials



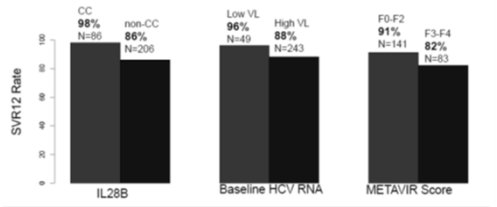
Foster. EASL 2014, Abstract O66.

What About Retreatment of Patients Who Failed Prior Therapy?

Case #1

- 64 year old man
- Relapsed after 48 weeks PEG/IFN
- Genotype 1a
- METAVIR Stage 3
- Treatment options?

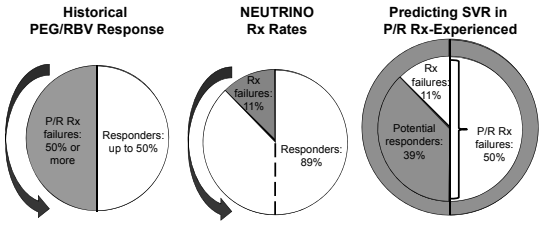
FDA Exploratory Analysis: Predicted Efficacy of SOF + PEG/RBV in Treatment-Experienced G1



Non-CC/High baseline HCV viral load/F3-F4
71% (37/52)
95% CI: (57%, 83%)

Sofosbuvir FDA Hearing. October 25, 2013.

FDA Exploratory Analysis: Predicted Efficacy of SOF + PEG/RBV in Treatment-Experienced G1



Patients who would have failed P/R therapy likely contributed to increased SVR rates with SOF therapy

Predicted SVR in GT1 P/R Rx-experienced population: 78% (39/50)

Sofosbuvir FDA Hearing. October 25, 2013.

Case #2

- 66 year old woman
- Relapsed after BOC/PEG/Riba
- Stage 4
- Genotype 1a
- Platelets 108K
- Treatment options?

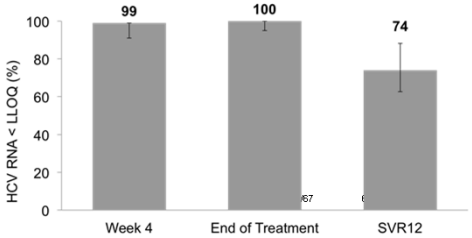
Retreatment of HCV G1 DAA Treatment-Experienced Patients (Interim Analysis)

- Non-cirrhotic G1 patients who failed prior DAA + PEG/RBV with a protease inhibitor (GS-9256) ± one or two additional DAAs (tegobuvir [NS5b NNI] or ledipasvir [NS5a])
- Retreated with PEG/RBV/SOF x 12 weeks

Mean age, y (range)	55 (21–72)
Male, n (%)	60 (75)
Black, n (%)	11 (14)
Mean BMI, kg/m² (range)	28 (21–43)
IL28B non-CC, n (%)	67 (84)
G1a, n (%)	68 (85)
Mean baseline HCV RNA, log_{10} IU/mL (range)	6.6 (5.0–7.3)
Mean duration of prior therapy, weeks (range) 66/67	25 (12–60)
Prior relapsers/non-responders	48%/45%
Courses of prior therapy, n (%)	
1	44 (55)
≥2	36 (45)
Patients with ≥1 resistance-associated variant, n(%)	72 (90)

Pol. EASL 2014, Abstract O55.

Retreatment of HCV G1 DAA Treatment-Experienced Patients (Interim Analysis)



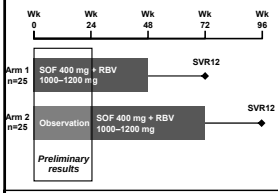
- No clear impact of prior treatment failure on response
- High SVR rates achieved despite presence of RAVs
  - Virologic failure only due to relapse

Pol. EASL 2014, Abstract O55.

Is Sofosbuvir Safe in Patients with (Decompensated) Cirrhosis?

SOF + RBV in Patients with Cirrhosis & Portal HTN ± Decompensation: W24 Interim Results

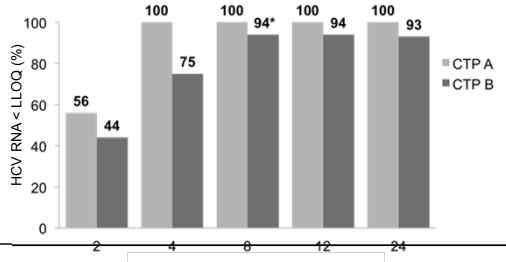
- Randomized, open-label, safety and efficacy study of SOF+RBV x 48 weeks compared to observation for 6 months in patients with cirrhosis and portal HTN (CTP 5-9)



	SOF + RBV n=25	Observation n=25
Male, n (%)	18 (72)	20 (80)
Median age, y (range)	56 (43–69)	55 (44–69)
BMI ≥30 kg/m², n (%)	8 (32)	7 (28)
Mean HCV RNA, log_{10} IU/mL (range)	6.1 (4.4–7.0)	6.1 (3.8–6.9)
GT, n (%)		
1a	10 (40)	9 (36)
1b	9 (36)	6 (24)
2	2 (8)	1 (4)
3	2 (8)	8 (32)
4	2 (8)	1 (4)
IL28B non-CC, n (%)	22 (88)	18 (72)
Prior HCV treatment, n (%)	17 (68)	23 (92)
Mean HVPG mmHg, n (range)	16.9 (9–29)	16.2 (7–27)
HVPG >12 mmHg, n (%)	19 (76)	20 (80)

Afdhal. EASL 2014, Abstract O58.

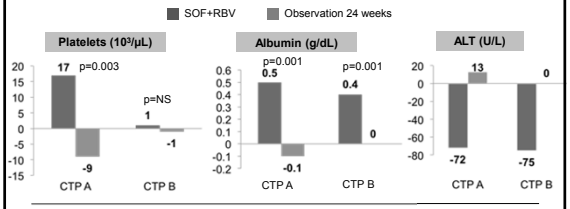
SOF + RBV in Patients with Cirrhosis & Portal HTN ± Decompensation: Virologic Response



*1 patient was a non-responder at Week 8.

Afdhal. EASL 2014, Abstract O58.

SOF + RBV in Patients with Cirrhosis & Portal HTN ± Decompensation: Lab and Clinical Changes



	Ascites		Hepatic Encephalopathy	
Patients, n	SOF + RBV n=25	Observation n=25	SOF + RBV n=25	Observation n=25
Baseline	6	9	5	2
Week 12	5	8	3	3
Week 24	0	7	0	4

Afdhal. EASL 2014, Abstract O58.

SOF + RBV in Patients with Cirrhosis & Portal HTN ± Decompensation: Conclusions

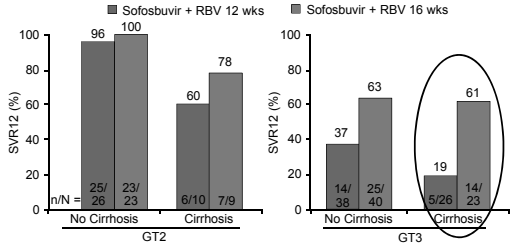
- SOF+RBV for up to 24 weeks resulted in:
  - High rates of virologic suppression irrespective of severity of liver disease
  - Decreased necroinflammation with ALT normalization
  - Improvements in platelet count, albumin, ascites and hepatic encephalopathy
  - Low rates of treatment D/C due to AEs
  - No patients with worsening or new hepatic decompensation

Afdhal. EASL 2014, Abstract O58.

Case #3

- 47 year old man
- Genotype 3a
- Prior relapse after 24 weeks PEG/Riba
- Cirrhosis
- Treatment options?

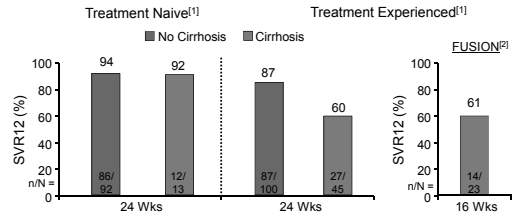
FUSION: SVR by GT and Cirrhosis in Treatment-Experienced Patients



- 12 weeks sufficient for GT2
- 16 weeks better than 12 weeks for GT3… so what about 24 weeks?

Jacobson IM, et al. N Engl J Med. 2013;368:1867-1877.

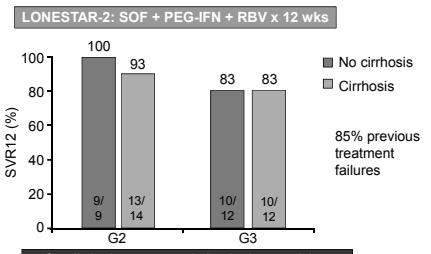
VALENCE: Efficacy of 24-Week SOF + RBV in HCV G3



- 24 weeks better for treatment-naive patients
- Not ideal for cirrhotic treatment failures

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?



- Small single-center study but looks promising. . .
- IFN is not dead yet!

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

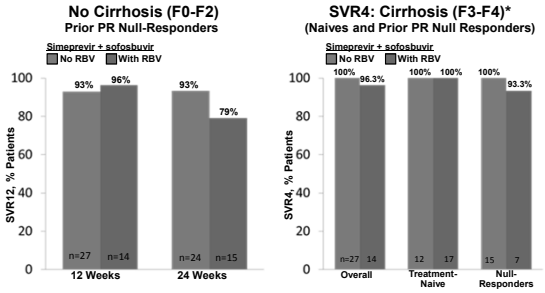
Rationale for IFN-Free Direct-Acting Antiviral Therapy for HCV

- Drawbacks of INF-based Therapy
  - Challenging tolerability
  - High percentage of patients are ineligible for IFN
  - Long duration of therapy
  - Low SVR rates compared to modern all-oral regimens
    - PR: ~40-50% in treatment-naïve patients
    - Triple therapy PR + Boceprevir or telaprevir: ~70%
  - Many patient-specific and virus-specific factors affecting eligibility or treatment response (Race, IL28B, cirrhosis, prior treatment, etc)
  - Development of resistance
  - Requires injection

The Next Wave

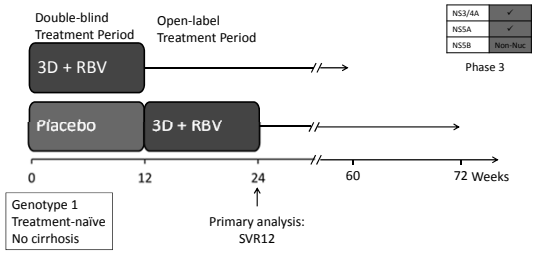
IFN-Free

COSMOS: Simeprevir + Sofosbuvir ± RBV: GT1



Sulkowski M, et al. EASL International Liver Congress, 2014. Abstract O7.
Jacobson IM, et al. Hepatology. 2013;58(suppl 1):73A. Abstract LB-3.

SAPPHIRE-I: ABT-450 + Ombitasvir + Dasabuvir + RBV (3D + RBV)



NS3/4A	✓
NS5A	✓
NS5B	Non-Nuc

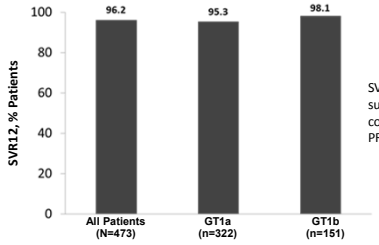
Phase 3

3D: Co-formulated ABT-450/ritonavir/ombitasvir, 150 mg/ 100 mg/ 25 mg + dasabuvir, 250 mg
RBV: 1000-1200 mg daily, weight-based

Feld JJ, et al. EASL International Liver Congress, 2014. Abstract O60.

SAPPHIRE-I: ABT-450 + Ombitasvir + Dasabuvir + RBV (3D + RBV)

NS3/4A	✓
NS5A	✓
NS5B	Non-Nuc



SVR12 non-inferior and superior to a historical control of telaprevir + PR (78%)

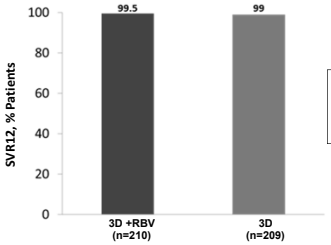
Feld JJ, et al. EASL International Liver Congress, 2014. Abstract O60.

PEARL-III: ABT-450/r + Ombitasvir + Dasabuvir (3D)

± RBV

NS3/4A	✓
NS5A	✓
NS5B	Non-Nuc

Phase 3



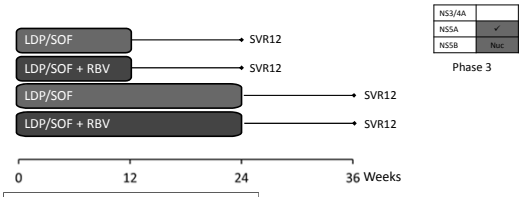
Genotype 1b
Treatment-naïve
No cirrhosis
3D + RBV versus 3D alone

3D: Co-formulated ABT-450/ritonavir/ombitasvir, 150 mg/ 100 mg/ 25 mg + dasabuvir, 250 mg
RBV: 1000-1200 mg daily, weight-based

Ferenci P, et al. EASL International Liver Congress, 2014. Abstract P1299.

ION-1: Ledipasvir + Sofosbuvir

12 Weeks Versus 24 Weeks and ± RBV



NS3/4A	
NS5A	✓
NS5B	Nuc

Phase 3

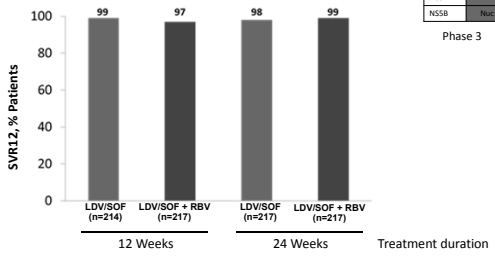
Genotype 1
Treatment-naïve
Targeted 20% with cirrhosis (actual 15-17%)
Platelet count ≥50,000, no neutrophil minimum

LDP/SOF: Ledipasvir/Sofosbuvir fixed-dose combination tablet (90 mg/400 mg daily)

Mangia A, et al. EASL International Liver Congress, 2014. Abstract O164.

ION-1: Ledipasvir + Sofosbuvir

12 Weeks Versus 24 Weeks and ± RBV



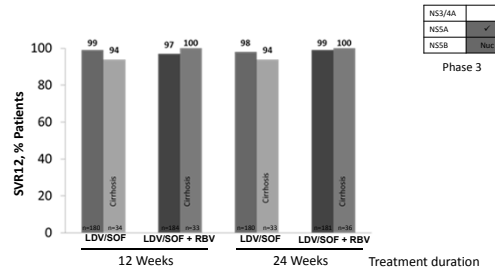
NS3/4A	
NS5A	✓
NS5B	Nuc

Phase 3

Mangia A, et al. EASL International Liver Congress, 2014. Abstract O164.

ION-1: Ledipasvir + Sofosbuvir

12 Weeks Versus 24 Weeks and ± RBV



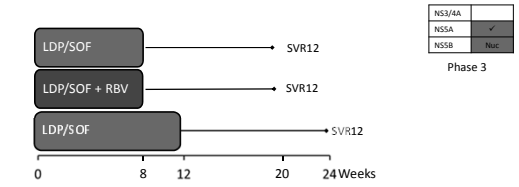
NS3/4A	
NS5A	✓
NS5B	Nuc

Phase 3

Mangia A, et al. EASL International Liver Congress, 2014. Abstract O164.

ION-3: Sofosbuvir + Ledipasvir

8 Weeks Vs 12 Weeks



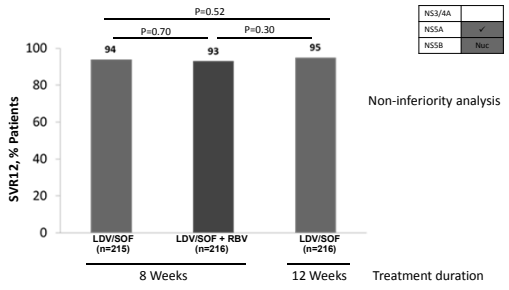
Genotype 1
Treatment-naïve
Non-cirrhotic

LDP/SOF: Ledipasvir/Sofosbuvir fixed-dose combination tablet (90 mg/400 mg daily)

Kowdley KV, et al. EASL International Liver Congress, 2014. Abstract O56.

ION-3: Sofosbuvir + Ledipasvir

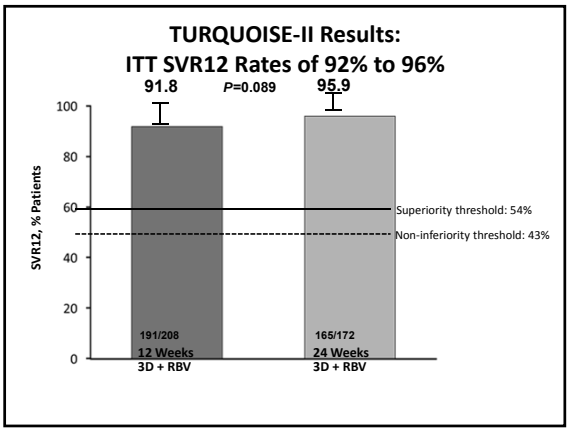
8 Weeks Vs 12 Weeks



Kowdley KV, et al. EASL International Liver Congress, 2014. Abstract O56.

TURQUOISE-II: Eligibility Criteria

- Treatment-naïve and pegIFN/RBV-experienced genotype 1 HCV infected patients, with no prior therapy with direct acting antiviral agents
- Compensated (Child-Pugh A) cirrhosis at screening
- Cirrhosis documented using liver biopsy, or FibroScan (≥14.6 kPa) within 6 months of or during screening
- Platelet count ≥60,000 cells/mL
- Serum albumin ≥2.8 g/dL
- Total bilirubin <3 mg/dL
- INR ≤2.3
- AFP ≤100 ng/mL
- Patients with radiographic ascites and patients with varices were allowed



Summary

- Sofosbuvir is a true "game changer"
- High SVR Rates, no resistance are the norm
- Other all-oral regimens coming soon
- Real world results likely resemble Phase 3
- Expect SVR rates >90%, few AEs
- Who should be treated? Or not treated?