VII CURSO
AVANCES EN INFECCIÓN VIH Y HEPATITIS VIRALES

REGIMENES TERAPÊUTICOS DE LA HEPATITIS C, INTERFERÓN FREE

A Coruña
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Problems associated with current triple therapy

- Phase III clinical trials have shown that ≅ 25-35% of G1 treatment-naïve patients and 50-60% patients who failed a previous treatment do not achieve SVR.

- New regimens are needed to cure these patients
  - Better tolerability
  - Reduced adverse events
  - Lower number of pills and dosages
  - With efficacy in difficult-to-treat populations

Difficulties with new drug development

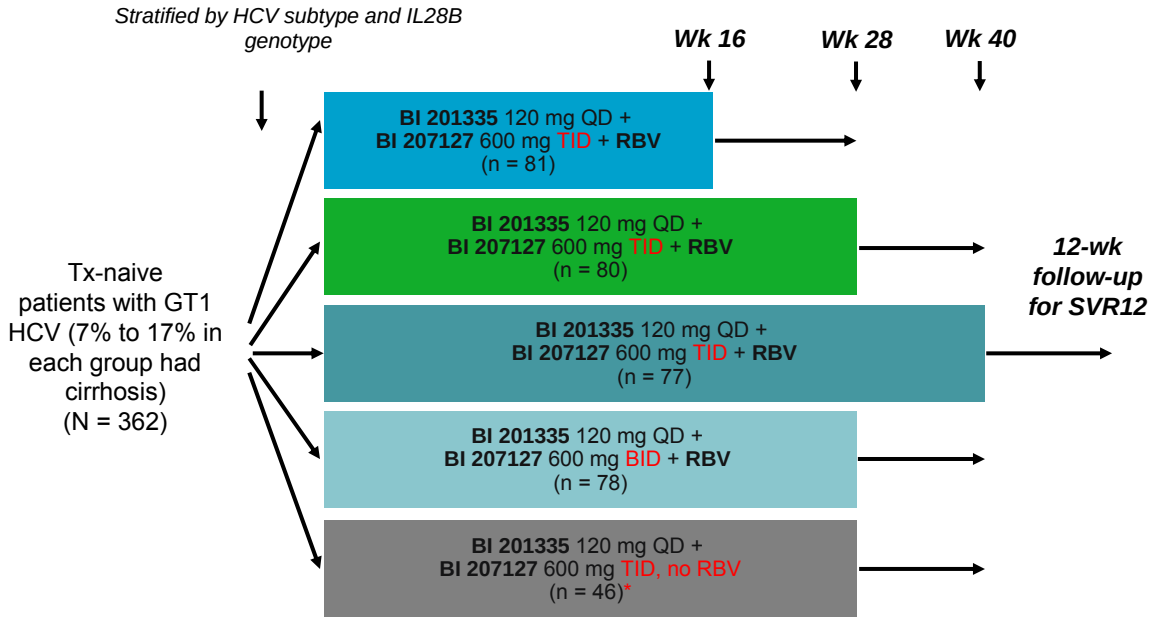
- 2ª generation PIs may have cross-resistance with mutations observed in TPV or BOC.
- Diminished efficacy of the first generation PIs and other drugs in:

  HIV, Genotype 1a, Blacks, IL28B non-CC, Cirrhotics
- Side effects of ribavirin are attenuated when taken without IFN but still remain a problem. Ribavirin is needed as part of some oral regimens.
- Late viral relapse reported
- Convenience
- Unexpected side effects → suspension of some drugs in development
- Costs

IFN-free clinical trials

SOUND C2	- Faldaprevir + BI 207127 ± RBV
	- Daclatasvir + Sofosbuvir ± RBV
ELECTRON	- Sofosbuvir ± RBV
	- Sofosbuvir + GS 5885 + RBV
NIH SPARE	- Sofosbuvir + RBV
CO-PILOT	- ABT-450/r + ABT-333 + RBV
PILOT	- ABT-450/r + ABT-072 + RBV
AVIATOR	- ABT-450/r + ABT-267 + ABT-333 + RBV
	- Daclatasvir + Asunaprevir + BMS 791325
	- Daclatasvir + Asunaprevir

SOUND-C2: BI 201335 (Faldaprevir) + BI 207127(NNI) ± RBV inTx-Naive GT1 Patients – phase 2b

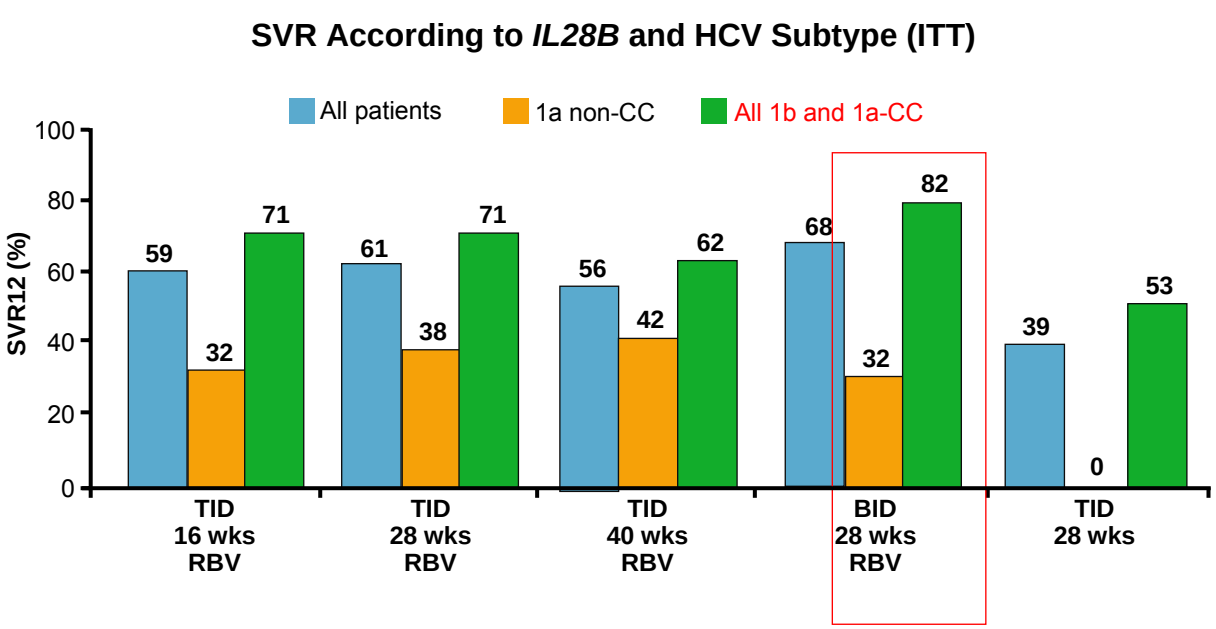


Weight-based RBV dosing (1000-1200 mg/day).

Zeuzem S, et al. EASL 2012. Abstract 101.

*Randomization to this arm stopped early due to FDA concerns regarding lack of RBV.

SOUND-C2: Efficacy According to Study Arm, HCV Subgenotype, and *IL28B*



Zeuzem S, et al. EASL 2012. Abstract 101.

SOUND C-2

Ribavirin was necessary to achieve high SVR rates

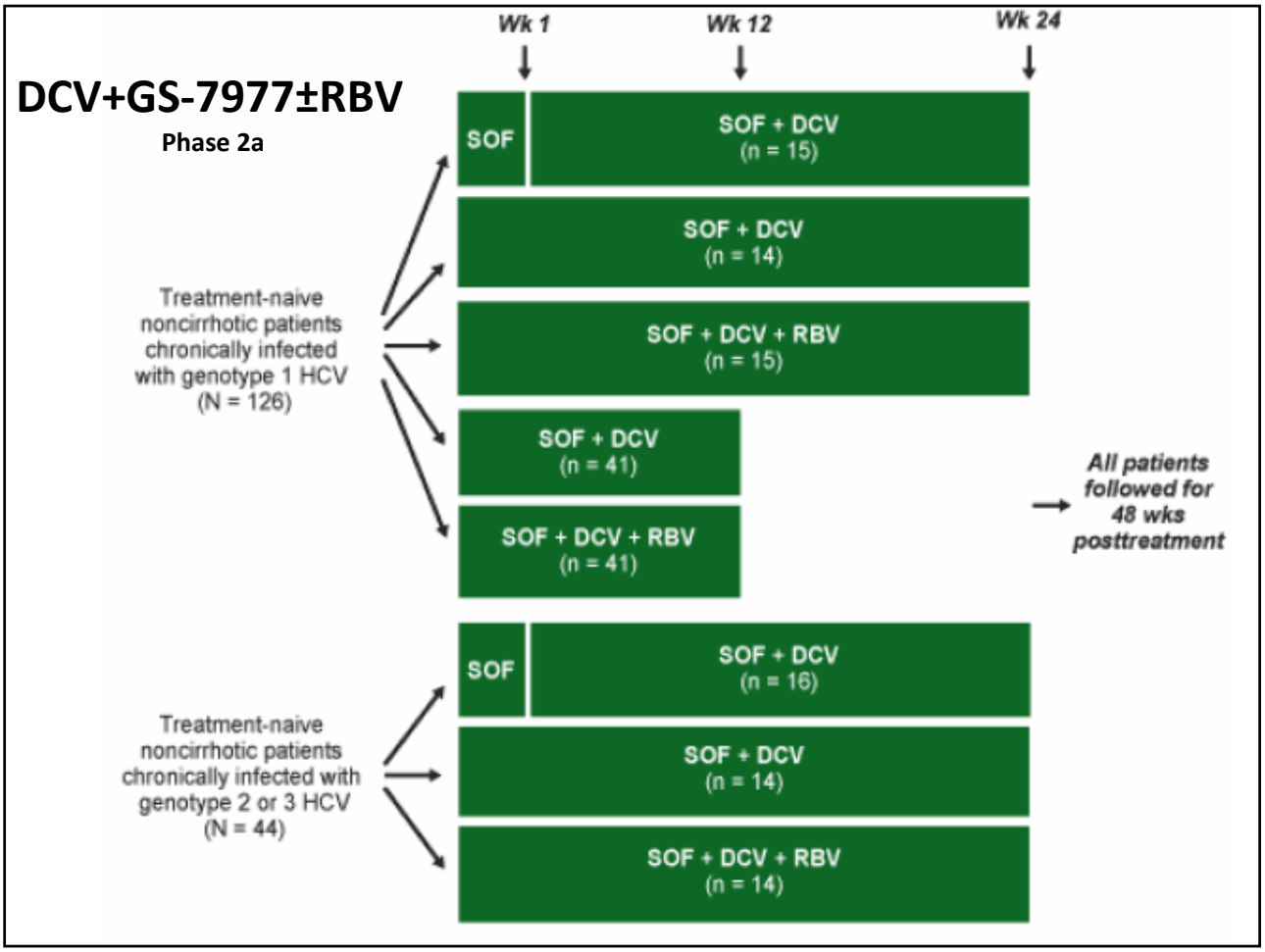
One relapse after SVR12

Combination relatively well tolerated particularly in arm with BI 207127 BID

Adverse events (most frequent): GI, skin reactions, hiperbilirubinemia

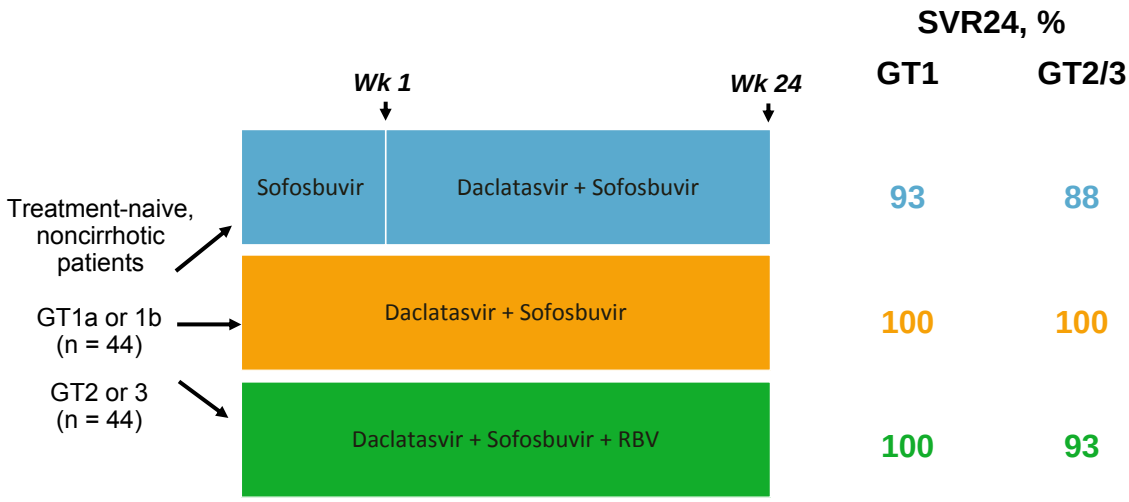
Other outcomes:

Pts with compensated cirrhosis
SVR12 – 43 to 50% in genotype 1a
57 to 80% in genotype 1b


DCV+GS-7977±RBV
Phase 2a
Wk 1
Wk 12
Wk 24
SOF
SOF + DCV
(n = 15)
SOF + DCV
(n = 14)
SOF + DCV + RBV
(n = 15)
SOF + DCV
(n = 41)
SOF + DCV + RBV
(n = 41)
Treatment-naive noncirrhotic patients chronically infected with genotype 1 HCV
(N = 126)
All patients followed for 48 wks posttreatment
SOF
SOF + DCV
(n = 16)
SOF + DCV
(n = 14)
SOF + DCV + RBV
(n = 14)
Treatment-naive noncirrhotic patients chronically infected with genotype 2 or 3 HCV
(N = 44)

Daclatasvir Plus Sofosbuvir ± RBV in Treatment-Naive GT1 or 2/3 Patients

- No impact of RBV on viral response



Sobosbuvir dosed 400 mg QD. Daclatasvir dosed 60 mg QD. RBV dosed by body weight for GT1 patients (1000-1200 mg/day); 800 mg/day for GT2/3 patients.

Sulkowski MS, et al. AASLD 2012. Abstract LB-2.

Daclatasvir (NS5A) + Sofosbuvir (GS-7977) ± RBV

High sustained virologic response rates in non-cirrhotics treatment-naive pts.

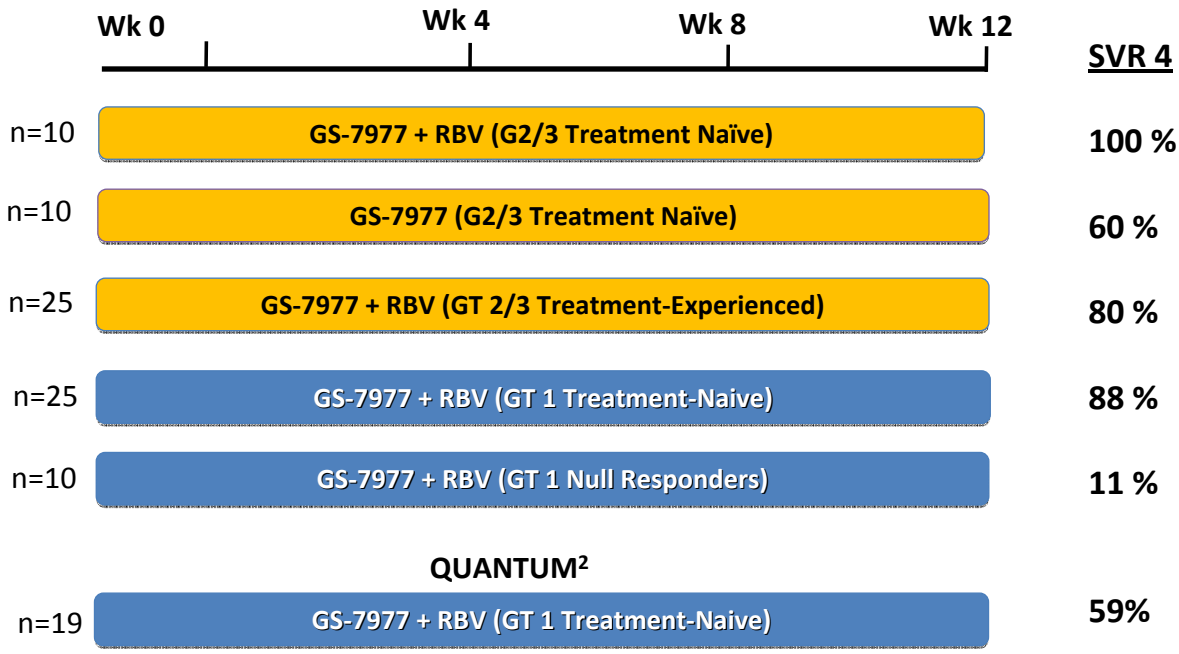
Ribavirin didn't influence the response

Low discontinuation

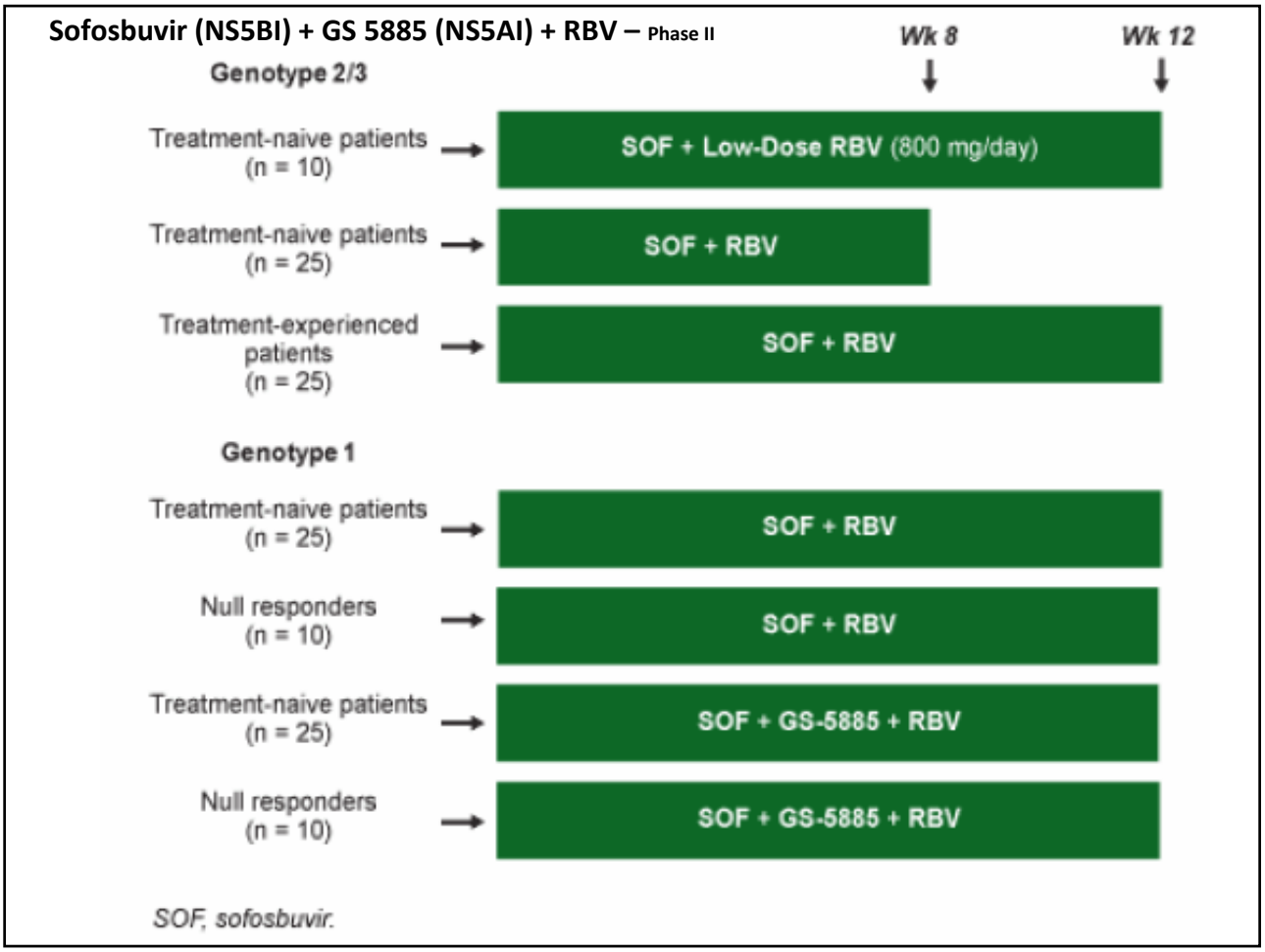
AEs: fatigue, headache, nausea

No difference across all arms between gen 1a or 1b and between CC or non-CC

Electron[1] : IFN-free arms
Impact of Ribavirin and IFN-responsiveness



1. Gane E, et al. AASLD 2011 and EASL2012; 2. Gilead press release April 2012


Sofosbuvir (NS5BI) + GS 5885 (NS5AI) + RBV – Phase II
Wk 8
Wk 12
Genotype 2/3
Treatment-naive patients (n = 10)
SOF + Low-Dose RBV (800 mg/day)
Treatment-naive patients (n = 25)
SOF + RBV
Treatment-experienced patients (n = 25)
SOF + RBV
Genotype 1
Treatment-naive patients (n = 25)
SOF + RBV
Null responders (n = 10)
SOF + RBV
Treatment-naive patients (n = 25)
SOF + GS-5885 + RBV
Null responders (n = 10)
SOF + GS-5885 + RBV
SOF, sofosbuvir.

Sofosbuvir (NS5BI) + GS 5885 (NS5AI) + RBV

HCV RNA < 15 UI/mL	SOF + RBV		SOF + GS-5885 + RBV	
	Treatment-naïve (n = 25)	Null responder (n = 10)	Treatment naïve (n 25)	Null responder (n 9)
Week 1	8/25 (32)	1/10 (10)	11/25 (44)	0/9 (0)
Week 2	17/25 (68)	7/10 (70)	22/25 (88)	4/9 (44)
Week 4	25/25 (100)	10/10 (100)	25/25 (100)	8/9 (89)
EOT	25/25 (100)	10/10 (100)	25/25 (100)	9/9 (100)
SVR4	22/25 (88)	1/10 (10)	25/25 (100)	9/9 (100)
SVR12	21/25 (84)	1/10 (10)	--	--

Gane et al. AASLD 2012 Press Release, 7 January 2013, gilead.com,

Sofosbuvir (NS5BI) + GS 5885 (NS5AI) + RBV – Phase II

Safety Outcome, %	*Genotype 1 Treatment-Naive Patients*		*Genotype 1 Previous Null Responders*	
	SOF + RBV (n = 25)	*SOF + GS-5885 + RBV (n = 25)*	*SOF + RBV (n = 10)*	*SOF + GS-5885 + RBV (n = 9)*
Serious adverse events	4	8	0	0
Adverse event leading to treatment discontinuation	0	4*	0	0
Adverse events ≥ grade 2	40	48	30	22
• Anemia	0	20	10	0
• Headache	4	4	0	0
• Depression	0	8	10	0
• Ligament sprain	4	0	10	0

*Not considered treatment related.

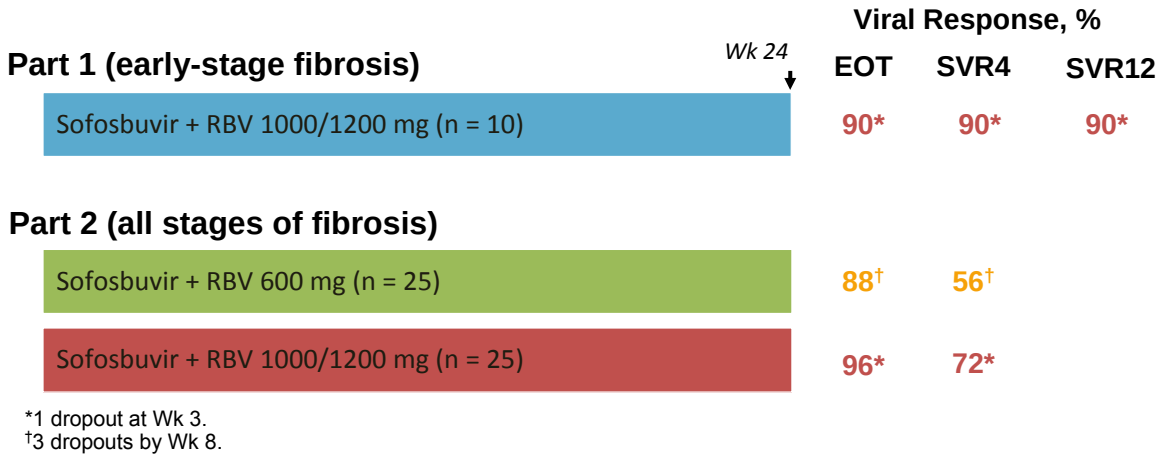
Sofosbuvir (NS5BI) + RBV – Phase II

Outcomes in Genotypes 2 and 3

- Among treatment-naive genotype 2/3 patients receiving sofosbuvir plus RBV, SVR rates lower than previously reported when treatment shortened to 8 weeks or when low-dose RBV used
  - SVR8 of 60% with low-dose RBV regimen
  - SVR12 of 64% with 8-week regimen
- Among treatment-experienced genotype 2/3 patients receiving sofosbuvir plus RBV, SVR rates lower than previously reported for treatment-naive genotype 2/3 patients receiving 12 weeks of therapy
  - SVR12 of 68% with 12-week regimen

NIH SPARE: Interim Data on Sofosbuvir and RBV in Difficult-to-Treat GT1 Patients – Phase II

- Patients with poor prognostic indicators: GT1a (70%), male (63%), black (83%), *IL28B* CT/TT (80%), advanced liver disease (22%)
- Median BMI: 28; median HCV RNA: 6.4 logs



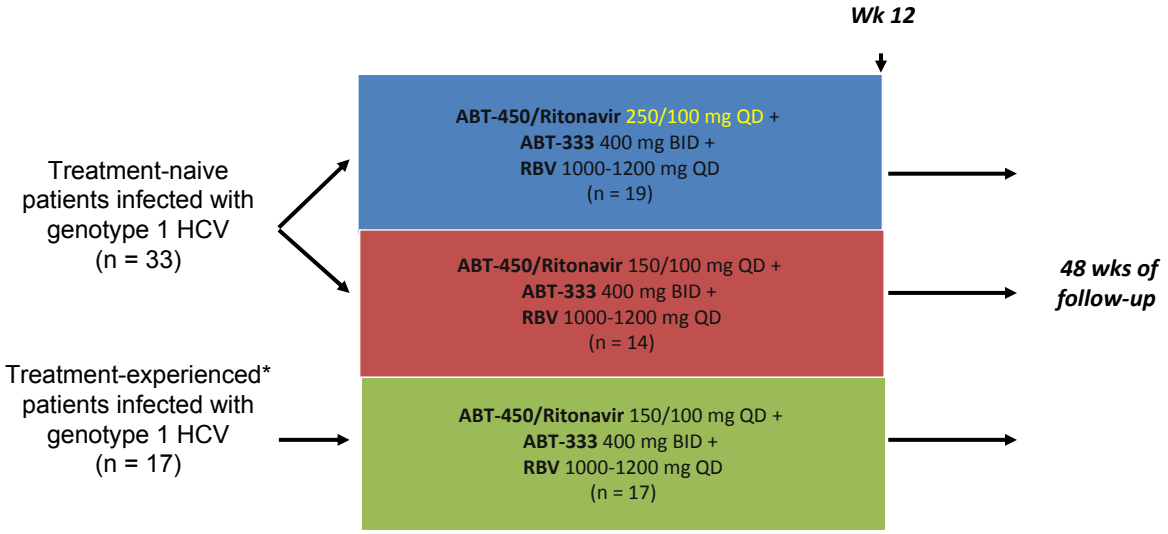
*1 dropout at Wk 3.
†3 dropouts by Wk 8.

Trend to relapse: high VL, advanced fibrosis, low dose ribavirin

Osinusi A, et al. AASLD 2012. Abstract LB-4.

Co-Pilot: 12-Wk ABT-450/r (PI) + ABT-333 (NNI) + RBV in Tx-Naive and Tx–Experienced GT1 Patients

Interim analysis of nonrandomized, prospective, open-label phase II trial

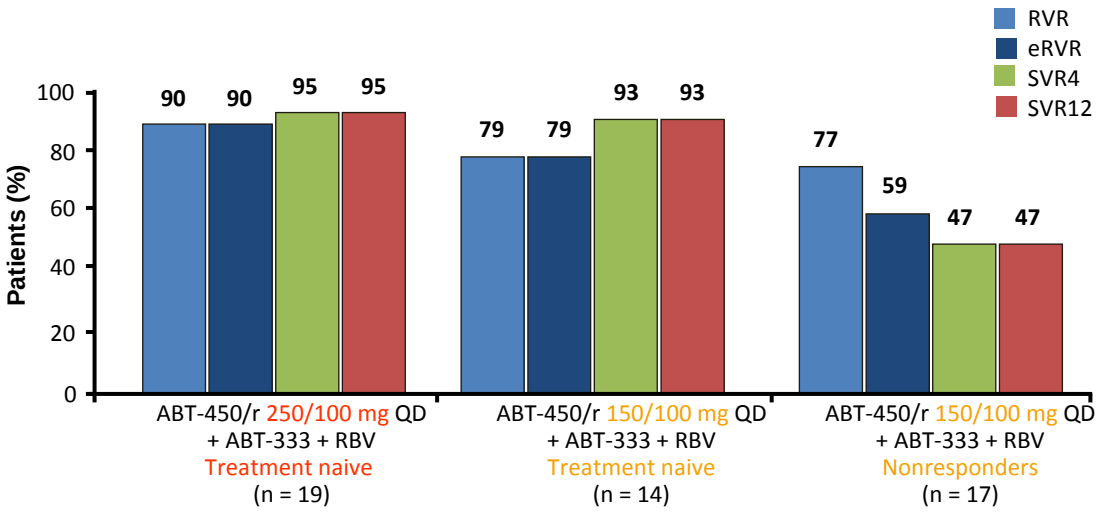


*Previous null response (< 2 $\log_{10}$ decrease in HCV RNA by Wk 12) or partial response (HCV RNA above limit of detection during treatment)

Poordad F, et al. EASL 2012. Abstract 1399.

Co-Pilot: Virologic Outcomes

- SVR12 in 94% of treatment-naive and 47% of treatment-experienced patients
  - Responses independent of *IL28B* genotype



Poordad F, et al. EASL 2012. Abstract 1399.

Co-Pilot: Safety Outcomes

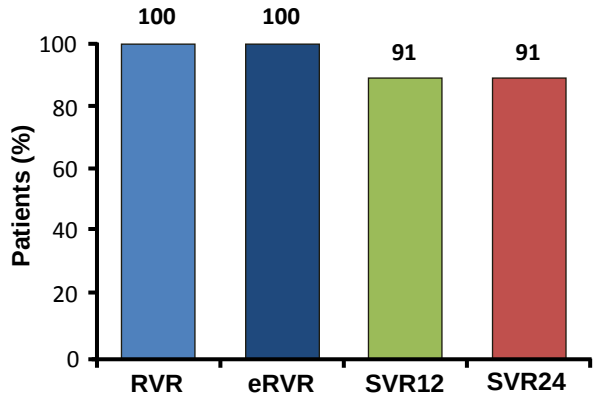
- **Most notable laboratory abnormalities: increased bilirubin and creatinine**
  - Hyperbilirubinemia consistent with known effect of ABT-450 on OATP1B1 bilirubin transporter
  - Both cases of increased creatinine resolved without ABT-450 or ABT-333 dose adjustment

Laboratory Abnormalities of Interest, %	Tx Naive, ABT-450/r 250/100 mg + ABT-333 + RBV (n = 19)	Tx Naive, ABT-450/r 150/100 mg + ABT-333 + RBV (n = 14)	Tx Experienced, ABT-450/r 150/100 mg + ABT-333 + RBV (n = 17)
Total bilirubin ≥ 2 x ULN	15.8	21.4	0
Creatinine ≥ 1.5 ULN*	10.5	0	0
CrCl < 50 mL/min*	10.5	0	0
ALT ≥ 5 x ULN	5.3	0	0

Poordad F, et al. EASL 2012. Abstract 1399.

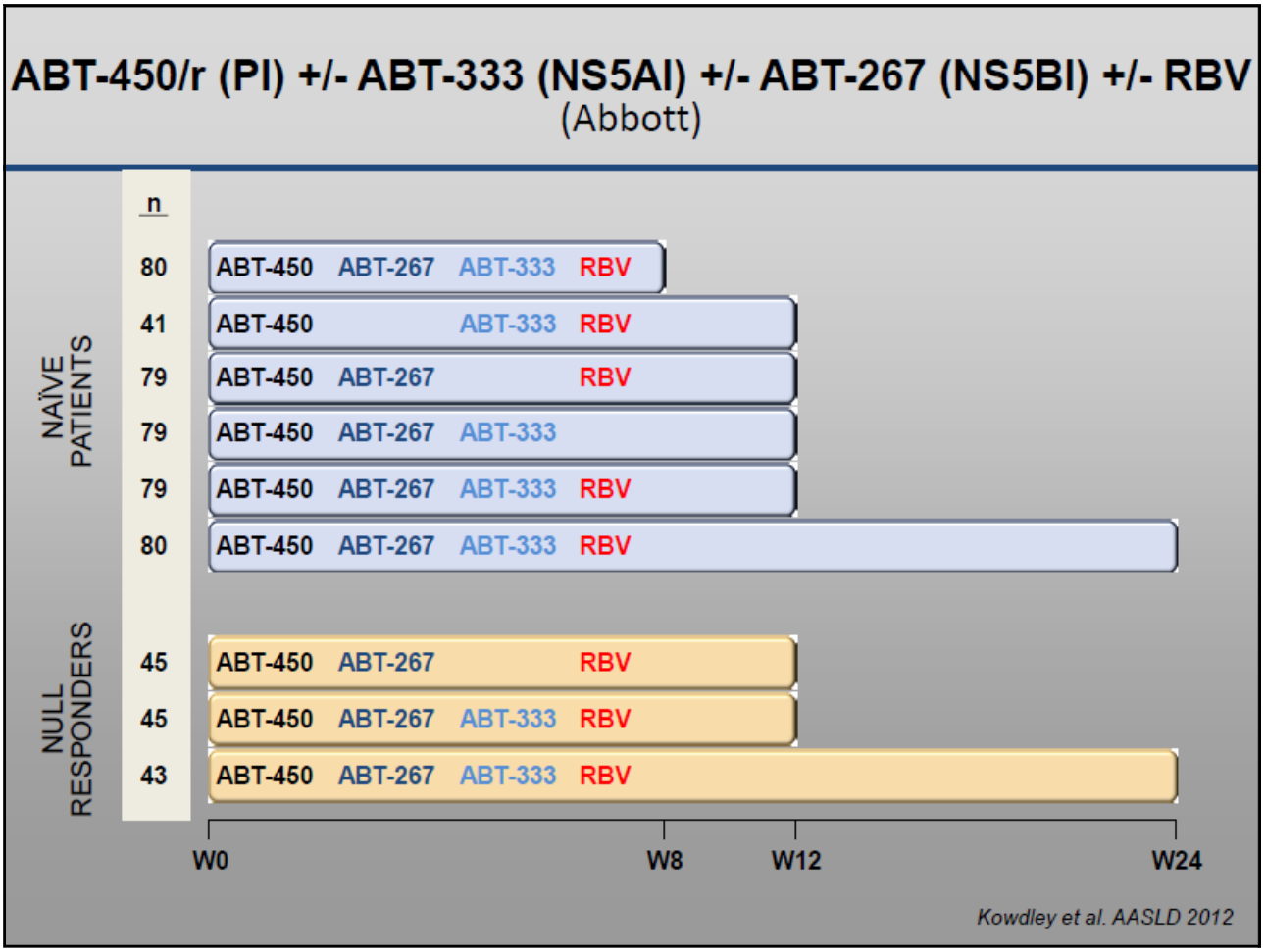
Pilot: ABT-450/r + ABT-072 (NNI) + RBV in Treatment-Naive GT1 HCV, IL28B CC Pts

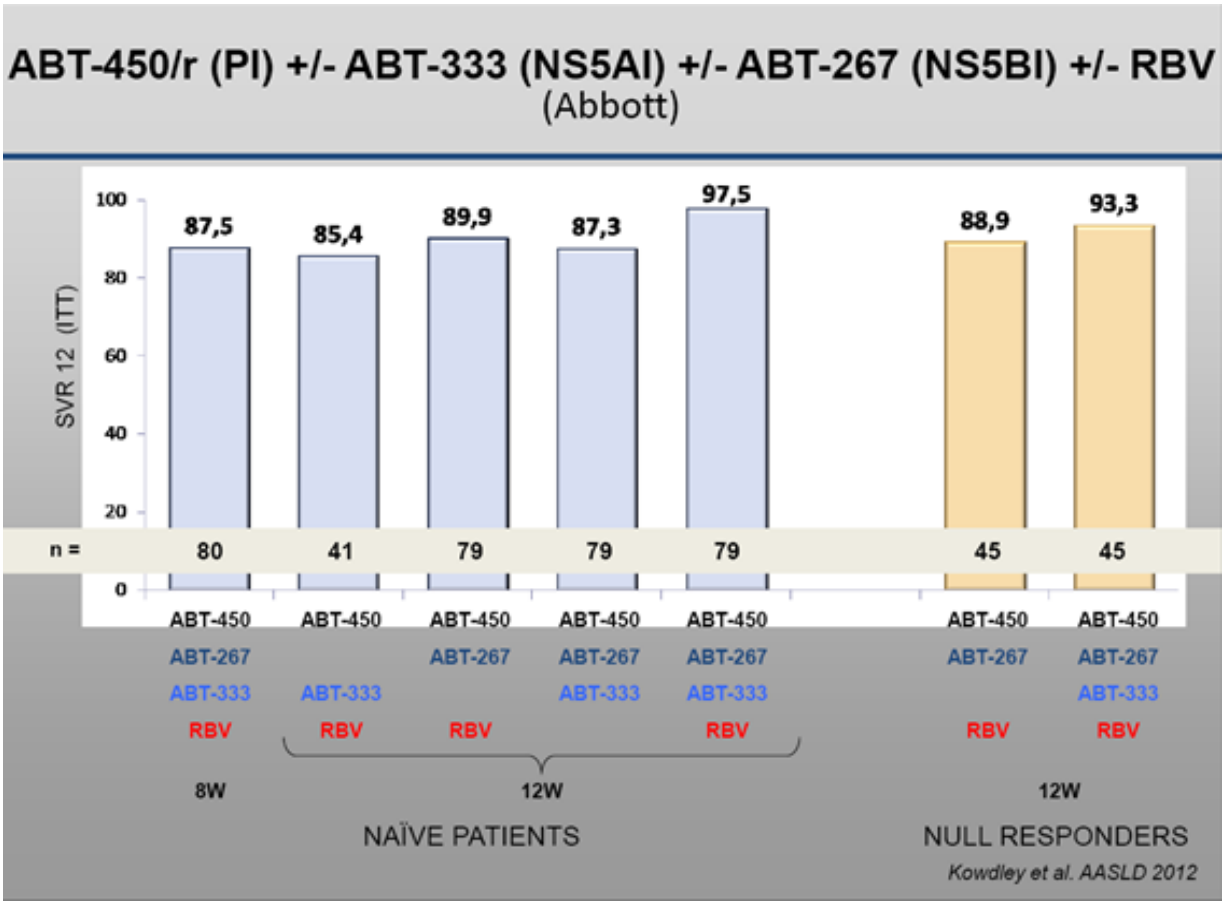
- Single-arm, open-label, pilot study: ABT-450/r 150/100 mg QD + ABT-072 400 mg QD + weight-based RBV 1000-1200 mg/day for 12 wks



- 100% of pts achieved primary endpoint of eRVR; 91% went on to SVR12 and SVR24
- 2 relapses posttherapy
  - 1 at posttreatment Wk 12; resistance variant observed only in protease
    - D168V variant observed in 36% of clones sequenced
  - 1 late relapse at posttreatment Wk 36; resistance variant observed only in polymerase
    - Y448H variant observed in 99% of clones sequenced

Lawitz E, et al. EASL 2012. Abstract 13.


ABT-450/r (PI) +/- ABT-333 (NS5AI) +/- ABT-267 (NS5BI) +/- RBV
(Abbott)
n
NAÏVE PATIENTS
80 ABT-450 ABT-267 ABT-333 RBV
41 ABT-450 ABT-333 RBV
79 ABT-450 ABT-267 RBV
79 ABT-450 ABT-267 ABT-333
79 ABT-450 ABT-267 ABT-333 RBV
80 ABT-450 ABT-267 ABT-333 RBV
NULL RESPONDERS
45 ABT-450 ABT-267 RBV
45 ABT-450 ABT-267 ABT-333 RBV
43 ABT-450 ABT-267 ABT-333 RBV
W0
W8
W12
W24
Kowdley et al. AASLD 2012


ABT-450/r (PI) +/- ABT-333 (NS5AI) +/- ABT-267 (NS5BI) +/- RBV
(Abbott)
SVR 12 (ITT)
100
80
60
40
20
0
87,5
85,4
89,9
87,3
97,5
88,9
93,3
n =
80
41
79
79
79
45
45
ABT-450
ABT-267
ABT-333
RBV
ABT-450
ABT-333
RBV
ABT-450
ABT-267
RBV
ABT-450
ABT-267
ABT-333
RBV
ABT-450
ABT-267
ABT-333
RBV
ABT-450
ABT-267
ABT-333
RBV
8W
12W
12W
NAÏVE PATIENTS
NULL RESPONDERS
Kowdley et al. AASLD 2012

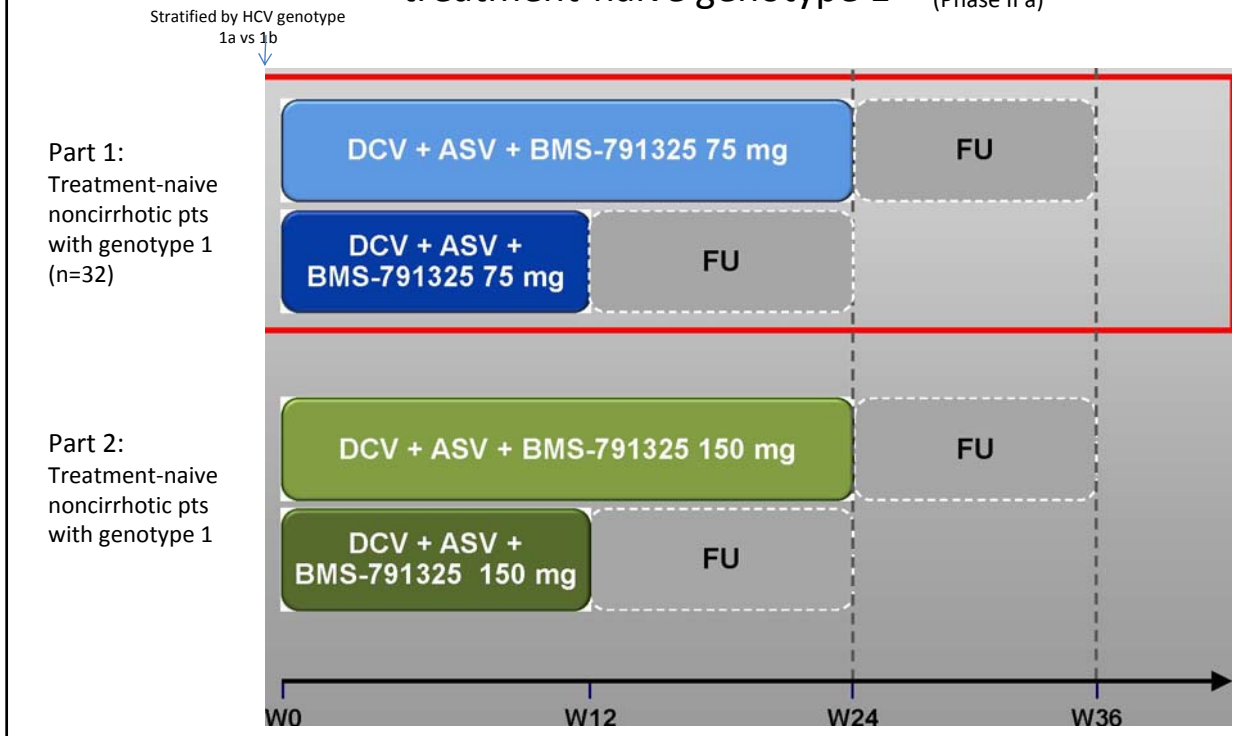
AVIATOR: Results by HCV-1 subgenotype

SVR12, %	Treatment-Naive Patients					Null Responders	
	ABT-450/ Ritonavir + ABT-267 + ABT-333 + RBV for 8 wks (n = 80)	ABT-450/ Ritonavir + ABT-333 + RBV for 12 wks (n = 41)	ABT-450/ Ritonavir + ABT-267 + RBV for 12 wks (n = 79)	ABT-450/ Ritonavir + ABT-267 + ABT-333 for 12 wks (n = 79)	ABT-450/ Ritonavir + ABT-267 + ABT-333 + RBV for 12 wks (n = 79)	ABT-450/ Ritonavir + ABT-267 + RBV for 12 wks (n = 45)	ABT-450/ Ritonavir + ABT-267 + ABT-333 + RBV for 12 wks (n = 45)
ITT analysis	87.5	85.4	89.9	87.3	97.5	88.9	93.3
• Genotype 1a	84	79	85	83	96	81	89
• Genotype 1b	96	100	100	96	100	100	100
Observed-data analysis	88.6	87.5	92.2	92.0	98.7	88.9	93.3
• Genotype 1a	86	82	88	88	98	81	89
• Genotype 1b	96	100	100	100	100	100	100

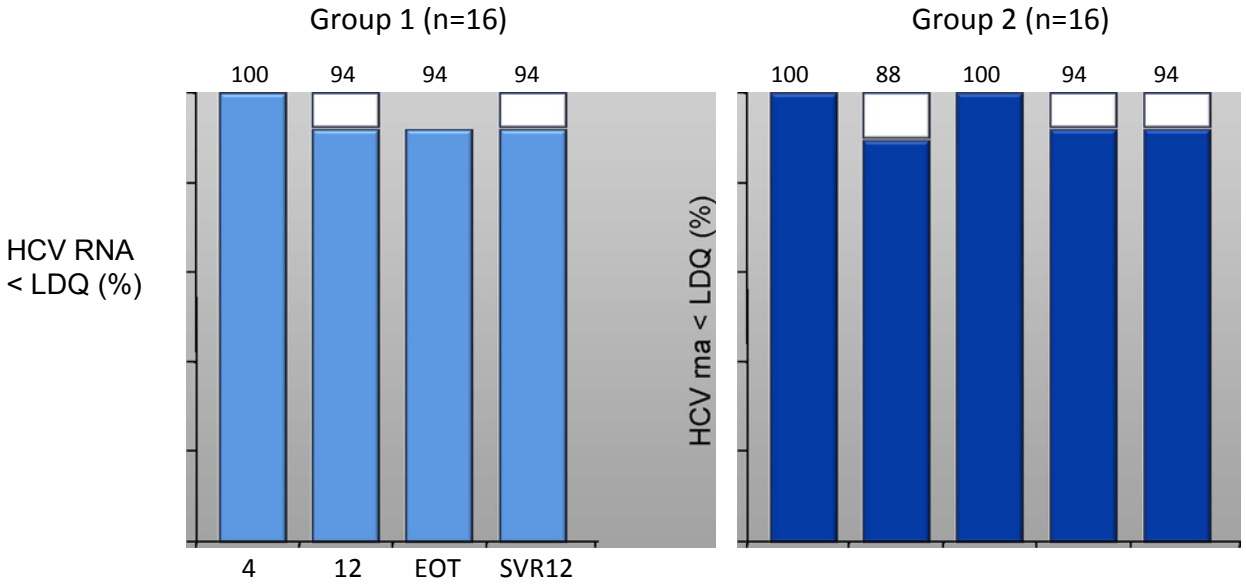
AVIATOR: Results by IL28B genotype

SVR12 According to IL28B Genotype (ITT Analysis), %	Treatment-Naive Patients					Null Responders	
	ABT-450/ Ritonavir + ABT-267 + ABT-333 + RBV for 8 wks (n = 80)	ABT-450/ Ritonavir + ABT-333 + RBV for 12 wks (n = 41)	ABT-450/ Ritonavir + ABT-267 + RBV for 12 wks (n = 79)	ABT-450/ Ritonavir + ABT-267 + ABT-333 for 12 wks (n = 79)	ABT-450/ Ritonavir + ABT-267 + ABT-333 + RBV for 12 wks (n = 79)	ABT-450/ Ritonavir + ABT-267 + RBV for 12 wks (n = 45)	ABT-450/ Ritonavir + ABT-267 + ABT-333 + RBV for 12 wks (n = 45)
CC	96	86	100	87	100	100	100
Non-CC	85	85	86	88	97	89	93

Daclatasvir (NS5AI), Asunaprevir (PI), and BMS-791325 (NNI) in treatment-naïve genotype 1 (Phase II a)



Daclatasvir (NS5AI), Asunaprevir (PI), and BMS-791325 (NNI) in treatment-naïve genotype 1 pts



Conclusions:

SVR12 – 94% with 12 or 24 weeks of treatment

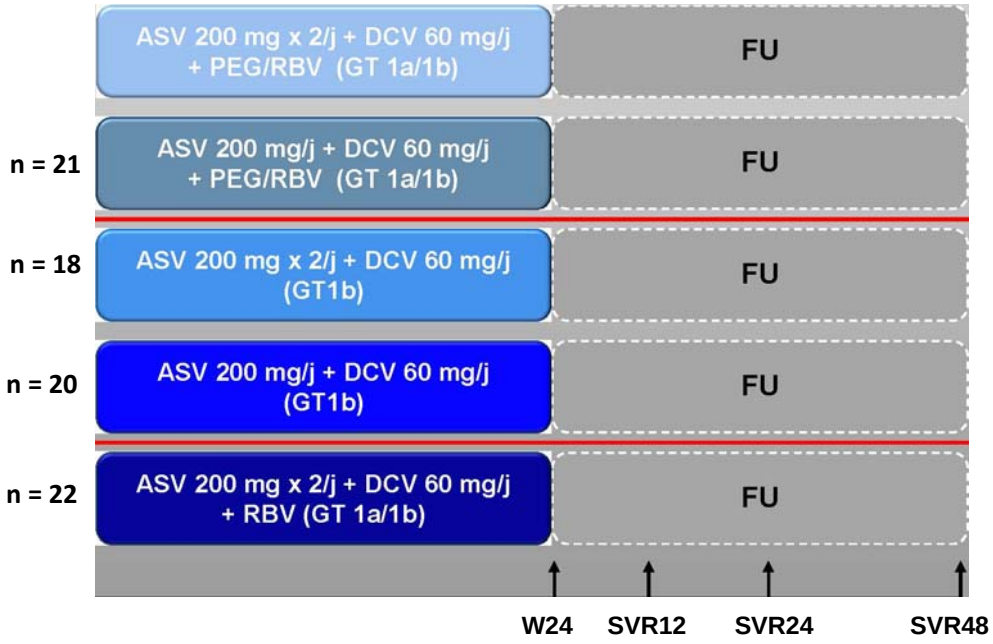
High rates of response in difficult-to-treat populations, including genotype 1a and IL28B non-CC

Part 2 – results not available

Everson GT, et al. AASLD 2012, LB3

Asunaprevir (PI) + Daclatasvir (NS5AI)

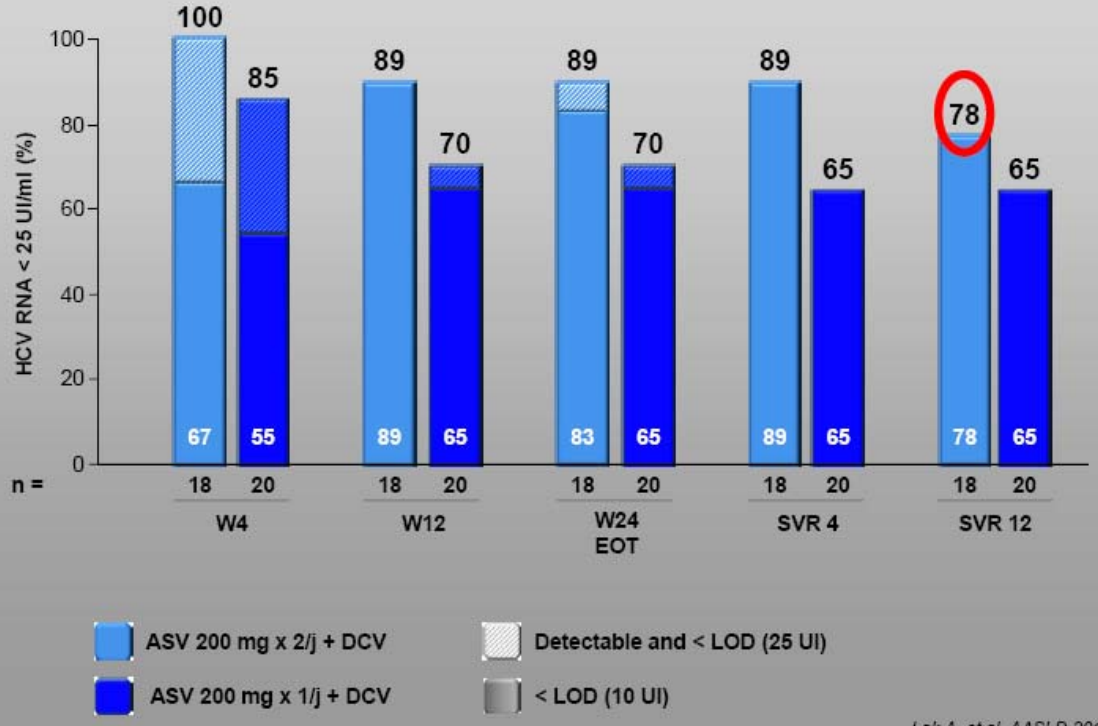
A1 and A2: G1b Null responders, without cirrhosis



Lok A, et al. AASLD 2012, A79

Asunaprevir (PI) + daclastavir (NS5AI)

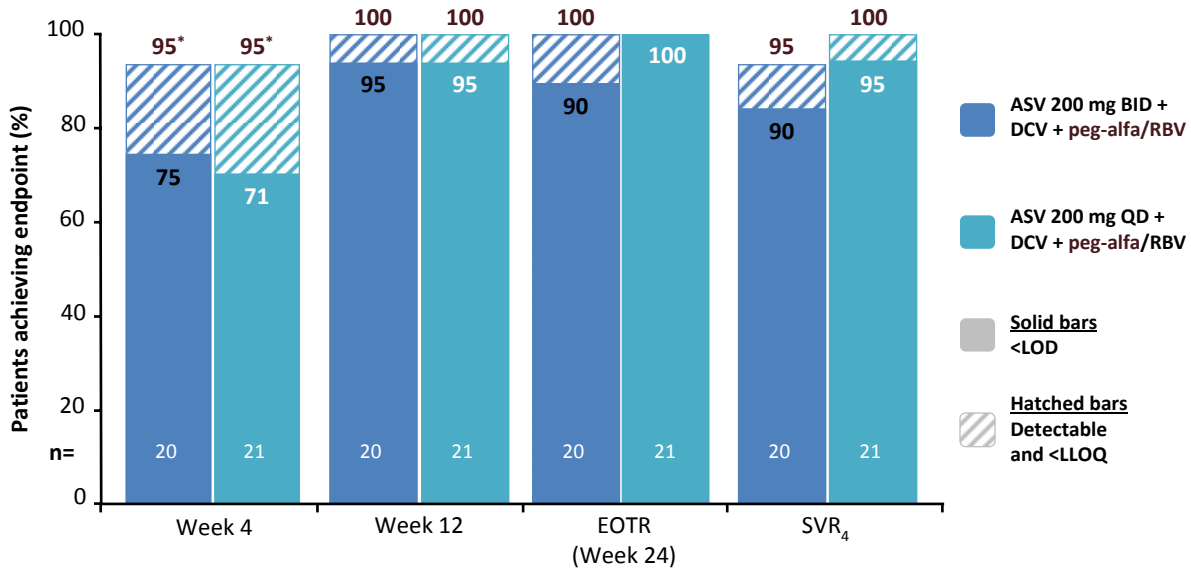
(BMS)



Lok A, et al. AASLD 2012, A79

Quad therapy with DCV + ASV + PR

Virological response rates



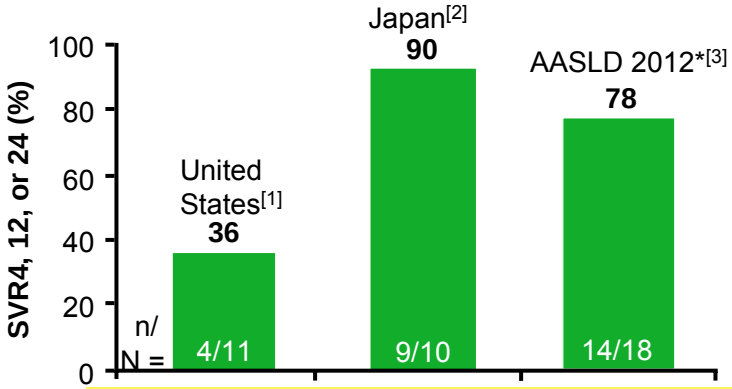
*1 patient with missing HCV-RNA measurement

1. ASV=asunaprevir; DCV=daclatasvir; EOTR=end-of-treatment response; LOD=lower limit of detection (~10 IU/mL); LLOQ=lower limit of quantitation (25 IU/mL); peg-alfa=pegylated interferon alfa-2a; RBV=ribavirin; SVR=sustained virological response

Adapted from Lok A, et al. EASL 2012. LB-1415.

Previous Null Responders: IFN Free

Daclatasvir (NS5A) +
Asunaprevir (PI) x 24 wks



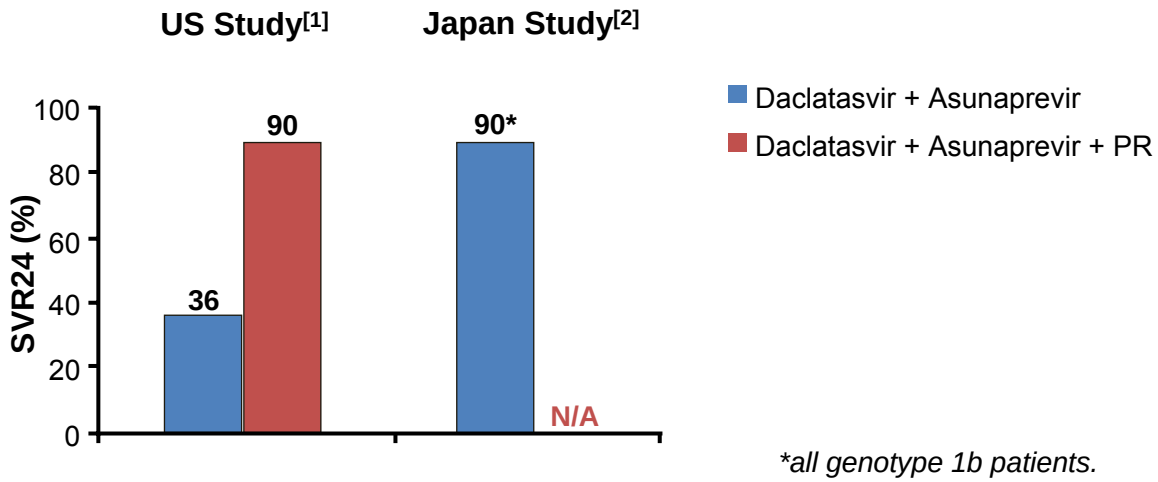
- **First IFN-free SVRs in null responders**
- **Likely adequate for GT1b but not for GT1a**
- **No data in cirrhotics**

*Includes only asunaprevir BID dosing arm.

1. Lok AS, et al. N Engl J Med. 2012;366:216-224. 2. Chayama K, et al. AASLD 2011. Abstract LB-4.
3. Lok AS, et al. AASLD 2012. Abstract 79.

Combination Therapy for Null Responders

- Daclatasvir (BMS-790052) QD (NS5A inhibitor) + asunaprevir (BMS-650032) BID (NS3 protease inhibitor) ± pegIFN/RBV for 24 wks



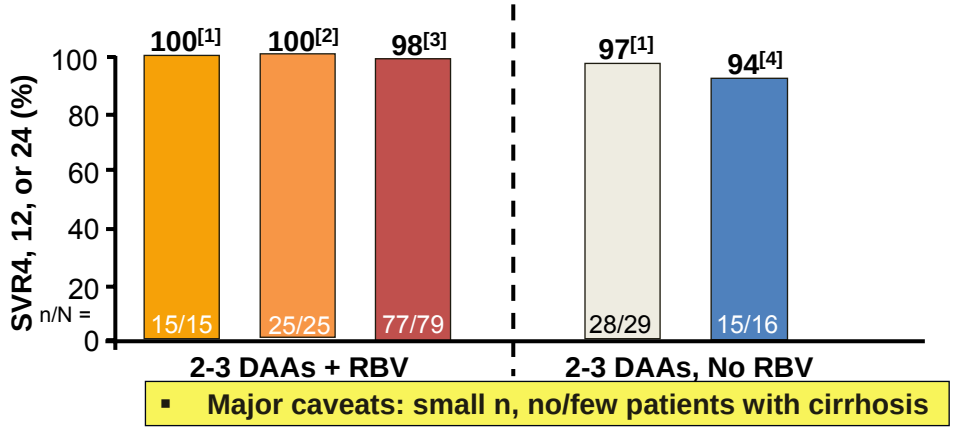
**all genotype 1b patients.*

1. Lok A, et al. EASL 2011. Abstract 1356.
2. Chayama K, et al. AASLD 2011. Abstract LB-4.

Adapted from CCO

Potent IFN-Free DAA Regimens in Treatment-Naive Genotype 1

- Sofosbuvir (Nuc) + daclatasvir (NS5A) + RBV x 24 wks
- Sofosbuvir (Nuc) + GS-5885 (NS5A) + RBV x 12 wks
- ABT-450/r (PI) + ABT-333 (NNI) + ABT-267 (NS5A) + RBV x 12 wks
- Sofosbuvir (Nuc) + daclatasvir (NS5A) x 24 wks
- Daclatasvir (NS5A) + asunaprevir (PI) + BMS 791325 (NNI) x 12 wks

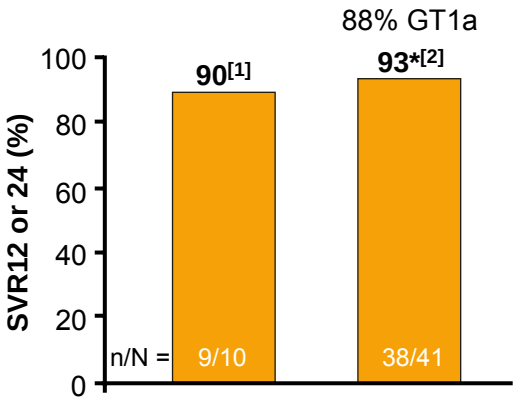


- **Major caveats: small n, no/few patients with cirrhosis**

1. Sulkowski M, et al. AASLD 2012. Abstract LB-2. 2. Gane E, et al. AASLD 2012. Abstract 229.3. Kowdley KV, et al. AASLD 2012. Abstract LB-1. 4. Everson G, et al. AASLD 2012. Abstract LB-3.

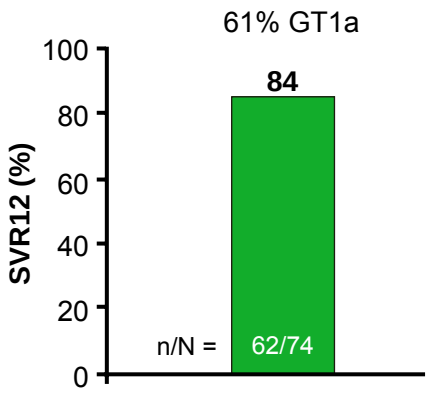
Previous Null Responders: Quad Therapy

Daclatasvir (NS5A) + **Asunaprevir** (PI) + **PegIFN/RBV** x 24 wks (Quad)



*Asunaprevir QD and BID combined.

Danoprevir/r (PI) + **Mericitabine** (Nuc) + **PegIFN/RBV** x 24 wks (Quad)[3]

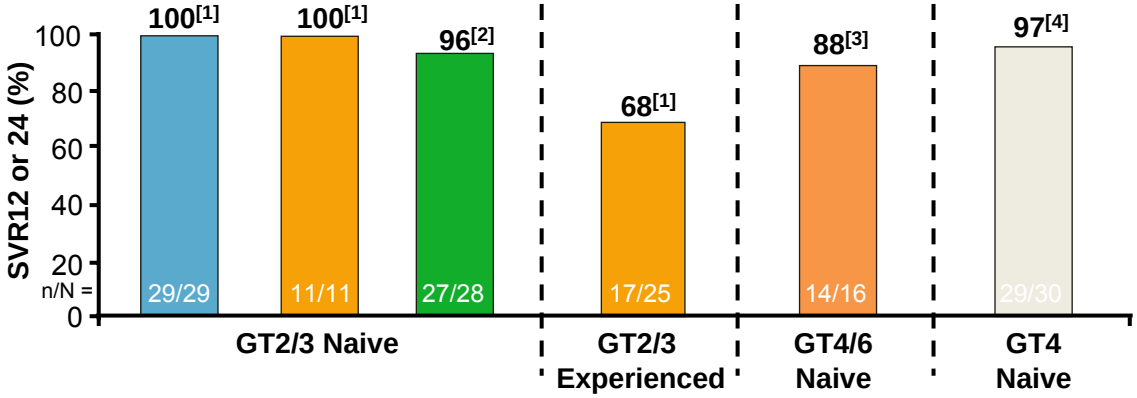


- **Quad therapy may be a good option for null responders**
- **Well tolerated BUT cirrhotics excluded**

1. Lok AS, et al. N Engl J Med. 2012;366:216-224. 2. Lok AS, et al. AASLD 2012. Abstract 79.
3. Feld JJ, et al. AASLD 2012. Abstract 81.

Non-GT1: Options Increasing

- Sofosbuvir (Nuc) + RBV x 12 wks + pegIFN x 4-12 wks
- Sofosbuvir (Nuc) + RBV x 12 wks
- Sofosbuvir (Nuc) + Daclatasvir (NS5A) ± RBV x 24 wks
- Sofosbuvir (Nuc) + RBV + pegIFN x 24 wks
- Danoprevir (PI)/ritonavir + pegIFN + RBV x 12-24 wks



- Major caveat: no patients with cirrhosis included

1. Gane EJ, et al. AASLD 2012. Abstract 229. 2. Sulkowski M, et al. AASLD 2012. Abstract LB-2.
3. Hassanein T, et al. AASLD 2012. Abstract 230. 4. Hezode C, et al. AASLD 2012. Abstract 760.

CONCLUSIONS

✓Several IFN-free ongoing trials with promising results

✓Combinations with good efficacy in GT1 patients

✓Some of the new drugs are also active against HCV G2 and G3

✓Some trials proved that we can make combinations to improve results in difficult-to-treat patients:
HIV/HCV, blacks, G1a, cirrhotics, null responders

✓The majority of the new drugs can be administered once or twice daily

✓RBV must be used in some associations but, in many trials, the drug has no effect on SVR