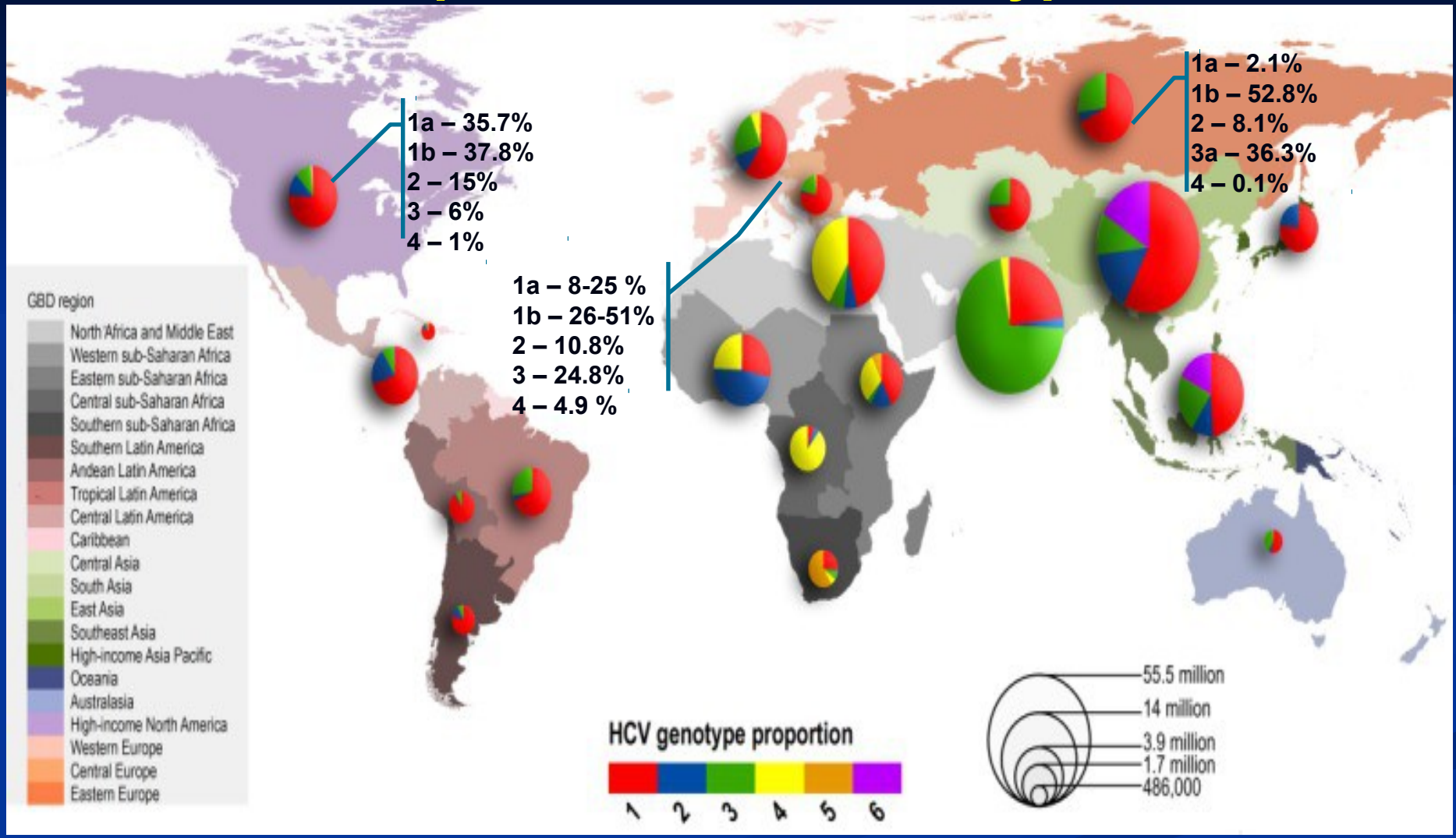
Clinical case

A previously partial response to PEG IFN + RBV in HCV G1b cirrhotic patient

Konstantin Zhdanov

Regional Distribution and Prevalence of Hepatitis C Virus Genotypes



Jane P M et al Hepatology. 2015 Jan; 61(1): 77–87.
Mahaney et. al. Hepatology.,1994Dec;20(6):1405-11.
Chulanov V.P. et al Epidemiology and infection diseases 2012, 3: 4-10
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Characteristics of the patient, medical history

- Male, 47 years old, Caucasian, BMI 31.1 kg/m2
- Anti HCV was detected since 2009
- No history of drug abuse
- No history of alcohol abuse
- No history of blood transfusion
- Generalized weakness and heaviness in the liver
- Obesity II degrees, Cholelithiasis
- Hepatosplenomegaly
- No varices in endoscopy
- No portal hypertension and encephalopathy

Characteristics of the patient (2010)

Genotype	1b
RNA HCV	5.6x105 IU/ml
IL 28B (rs12979860)	CT
ALT	163.9 IU/l
Total Bilirubin	27.93 (mkmol/l)
Albumin	42.5 g/l
Prothrombin Index	100%
Hemoglobin	155 g/l
Neutrophils	3.9 x 109/l
Platelets	179 x 109/l
TSH	1.35 IU/l
Liver Biopsy	A2, F4

Therapy was started with Peg-IFN α2a 180 μg/wk + RBV 1200 mg/d in 2010

	ALT (IU/l)	Hb (g/l)	Neu (x109/l)	Plt (x109/l)	TSH (IU/l)	T. bil (mkmol/l)	HCV RNA (IU/ml)	Fs (kPa)
W4	77.3	130	1.9	170	-	25.11	-	-
W12	70.5	127	1.5	129	1.65	27.30	2.5x102	-
W24	65.2	117	1.4	131	1.11	25.34	2.5x103	-
Stop treatment! Partial response								
FU W24	101	160	2.9	161	-	26.50	4.4x106	19.4

- Flu-like syndrome till week 4
- Weight loss to 10 kg

What it means "difficult to treat patient" in 2010 ?

Host Factors

- Ethnicity (Afro-American)
- Older age
- Male
- F3-F4 (Cirrhosis)!
- Increased BMI
- Insulin Resistance
- Alcohol consumption
- Comorbidities (Co-infection)
- IL28B Genotype CT-TT

Viral Factors

- Genotype 1
- High viral load

Therapy

- Low adherence
- Adverse events
- Insufficiently effective regimen

What to do in 2010 ?

- Retreatment with Peg-IFN and RBV for 72 weeks?
- Wait new drugs (clinical trials)?

What to do in 2013 ?

- Retreatment with TVR/BOC + Peg-IFN + RBV?
- Wait new drugs (clinical trials)?

Retreatment SOF 400 mg QD + RBV 1200 mg 16 weeks (2013)

	ALT (IU/l)	Hb (g/l)	Plt (x109/l)	T. bil (mkmol/l	HCV RNA (IU/ml)	Fs (kPa)
Base Line	86	151	138	25.1	2420000	21.3
W1	44	151	141	26.3	1040	-
W2	97	150	155	25.9	97	-
W4	25	139	172	27.5	<25	-
W12	24	141	180	25.5	0	-
W16	30	150	194	25.7	0	-
FU W4 Relapse	68	144	158	27.0	832000	18.7

There are no significant adverse events

Sofosbuvir Plus Ribavirin for the Treatment of Russian Patients With Chronic HCV Genotype 1 or 3 Infection

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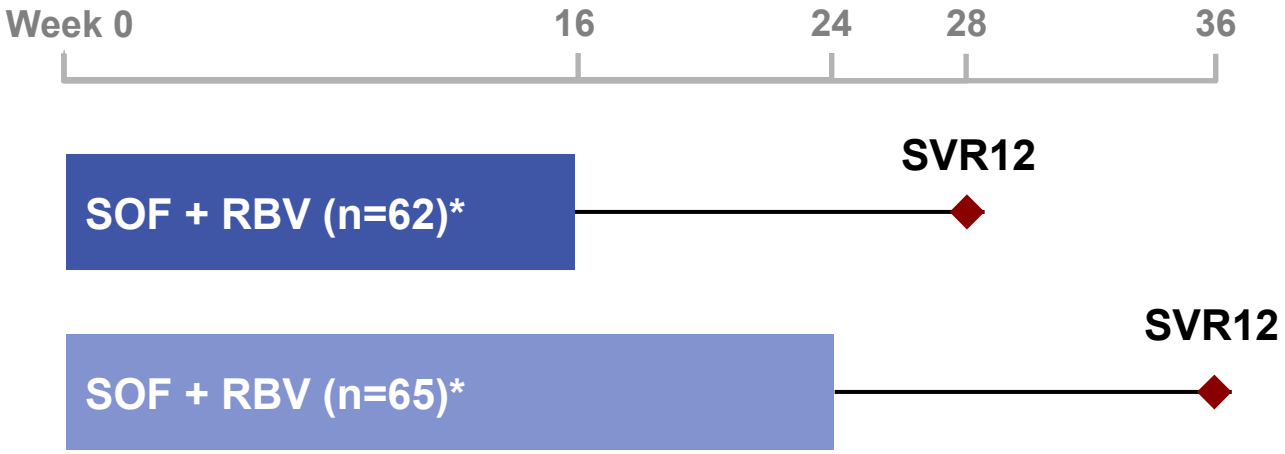
Study Design



- Randomized, 16-center, open-label study conducted in Russia
- Treatment-naïve patients with chronic HCV GT 1 or 3
  - Up to 20% with compensated cirrhosis

Treatment assignment stratified by genotype and presence/absence of cirrhosis

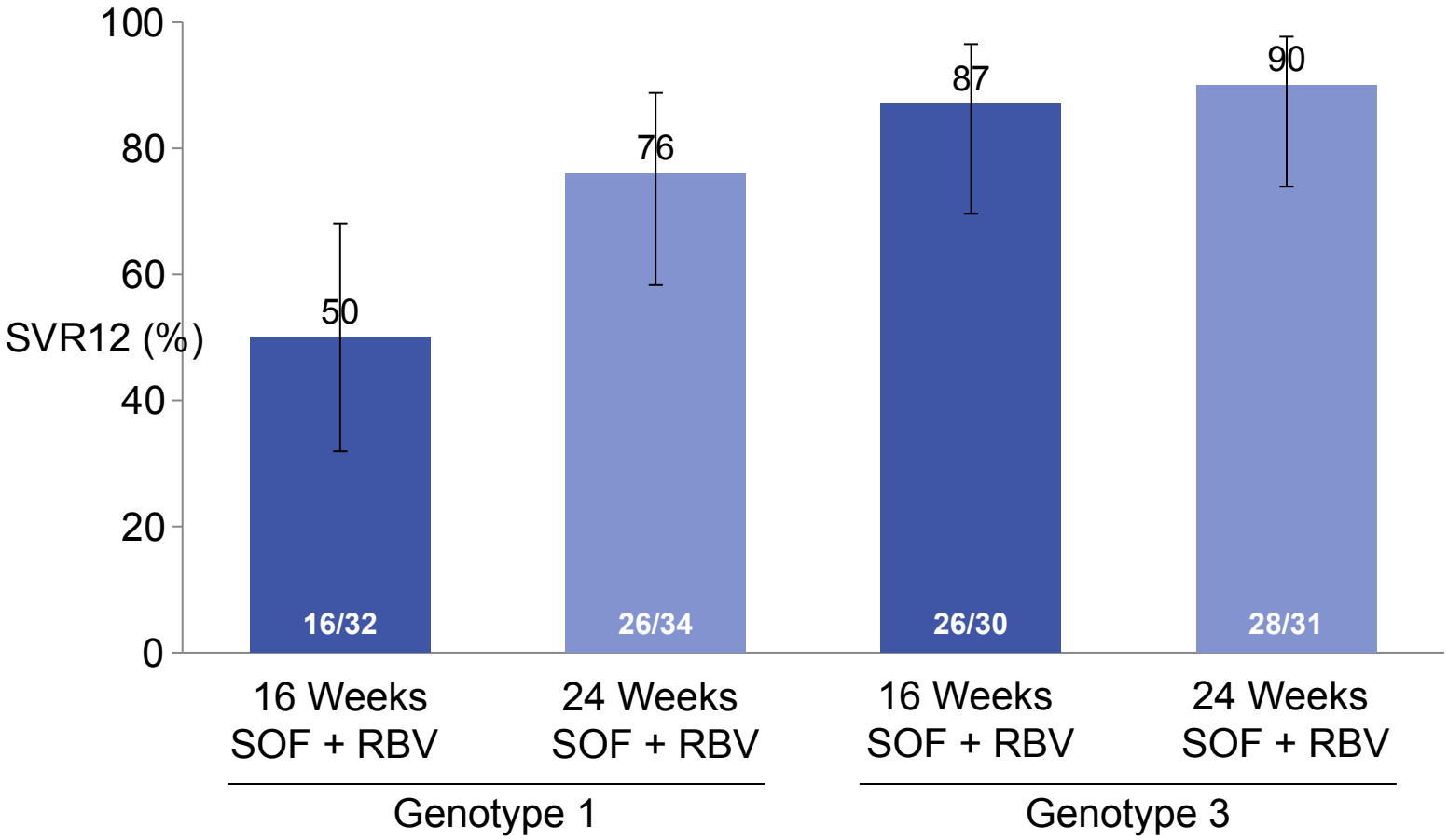
*SOF 400 mg/d; RBV 1000–1200 mg/d.

Demographics and Disease Characteristics

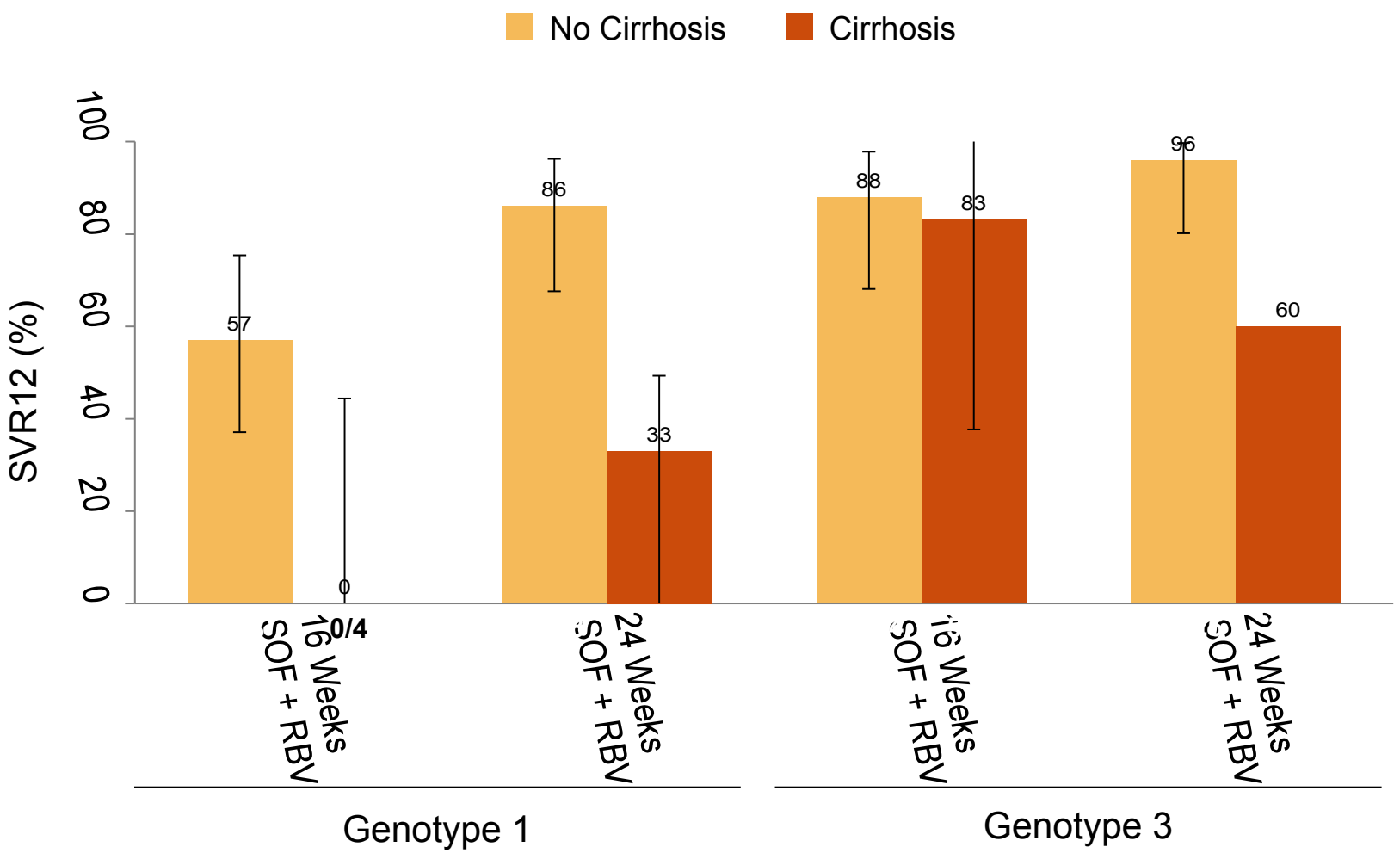
	Genotype 1		Genotype 3	
	16 Weeks SOF + RBV n=32	24 Weeks SOF + RBV n=34	16 Weeks SOF + RBV n=30	24 Weeks SOF + RBV n=31
Mean age, y (range)	41 (19–66)	42 (21–57)	38 (26–61)	40 (26–65)
Male, n (%)	13 (41)	16 (47)	19 (63)	19 (61)
Mean BMI, kg/m2 (range)	27 (19–37)	27 (19–42)	27 (20–42)	26 (20–38)
GT 1b, n (%)	32 (100)	33 (97)	--	--
GT 3a, n (%)	--	--	30 (100)	31 (100)
Mean baseline HCV RNA, log10 IU/mL (range)	6.2 (5.2–7.4)	6.1 (4.7–7.2)	6.2 (4.4–7.3)	6.2 (4.5–7.1)
Cirrhosis, n (%)	4 (13)	6 (18)	6 (20)	5 (16)
IL28B CC, n (%)	10 (31)	6 (18)	12 (40)	15 (48)

BMI, body mass index.

SVR12 in Genotypes 1 and 3

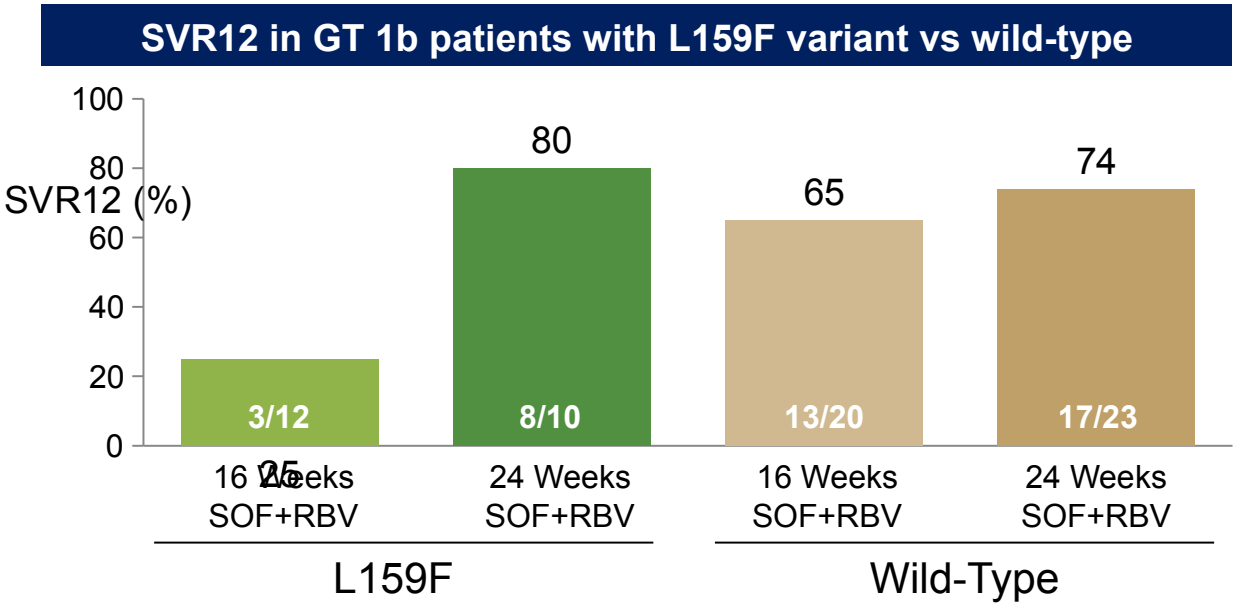


SVR12 by Genotype and Cirrhosis Status



Virology Results

- Baseline RAVs and TEVs
  - No S282T NS5B detected
  - L159F variant detected in 22 of 65 (34%) of patients with HCV GT 1b



RAVs or TEVs at virologic failure

- No S282T detected
- L159F emerged in 2 patients (GT 1b and 3a)
- L320F emerged in 4 patients with GT 1b infection

Safety Summary

	Patients, n (%)	16 Weeks SOF + RBV n=62	24 Weeks SOF + RBV n=65
Adverse Events	Serious AE	1 (2)	1 (2)
	Any AE	28 (45)	45 (69)
	Common AEs (in ≥5% of patients)		
	Headache	5 (8)	10 (15)
	Asthenia	7 (11)	4 (6)
	Viral respiratory tract infection	3 (5)	5 (8)
	Fatigue	2 (3)	4 (6)
	Insomnia	1 (2)	4 (6)
	Alopecia	1 (2)	4 (6)
Laboratory Abnormalities	Hemoglobin <10 g/dL	0	1 (2)
	Platelets <50,000/mm3	0	1 (2)
	Absolute neutrophil count <750/mm3	0	2 (3)
	Total bilirubin >2.5 x ULN	2 (3)	3 (5)

Summary

SOF + RBV resulted in high SVR rates following 16 or 24 weeks of treatment in treatment-naive patients with HCV GT 3

A longer treatment duration of 24 weeks was associated with a higher SVR rate in treatment-naïve patients with HCV GT 1

SOF + RBV provides a simple and well-tolerated treatment option for patients with HCV GT 3 infection and for patients with HCV GT 1 infection who are not eligible for or do not wish to take interferon

In the era of DAAs, what populations are still difficult to cure?

- **No longer challenging**
  - ✓ Genotype 1
  - ✓ Black Race
  - ✓ Hispanic/Latino ethnicity
  - ✓ Null responders
  - ✓ DAA+PR failures
  - ✓ Post OLT
  - ✓ HIV/HCV
- **Remain challenging**
  - ✓ Decompensated cirrhosis
  - ✓ Genotype 3
  - ✓ Renal Disease
  - ✓ DAA failures

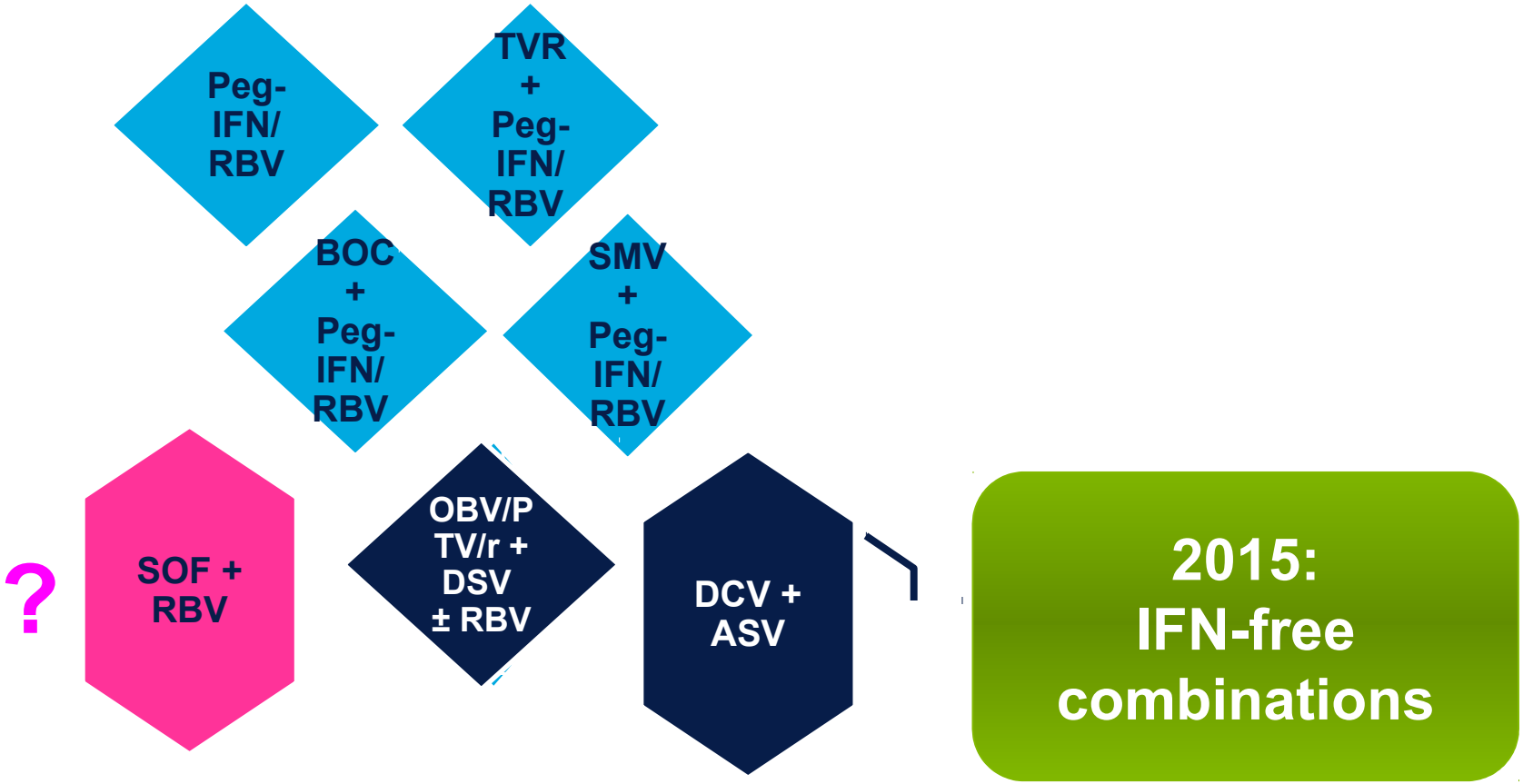
P. Kwo, AASLD 2015

Considerations in patients who failed a DAA-based regimen

- **Was initial therapy sub-optimal (or sub-maximal)?**
  - ✓ **Duration**
  - ✓ **RBV use**
- **What specific medication classes were used**
  - ✓ **What role dose resistance play?**
- **Stage of liver disease/host characteristics**
- **Indication of other problems**
  - ✓ **Adherence?**
  - ✓ **Significant drug interactions?**
  - ✓ **Immunosuppression?**

D. Wyles, AASLD 2015

HCV treatment in Russia



OBV/PTV/r + DSV = ombitasvir/paritaprevir/ritonavir + dasabuvir;
BOC = boceprevir; SMV = simeprevir; TVR = telaprevir.

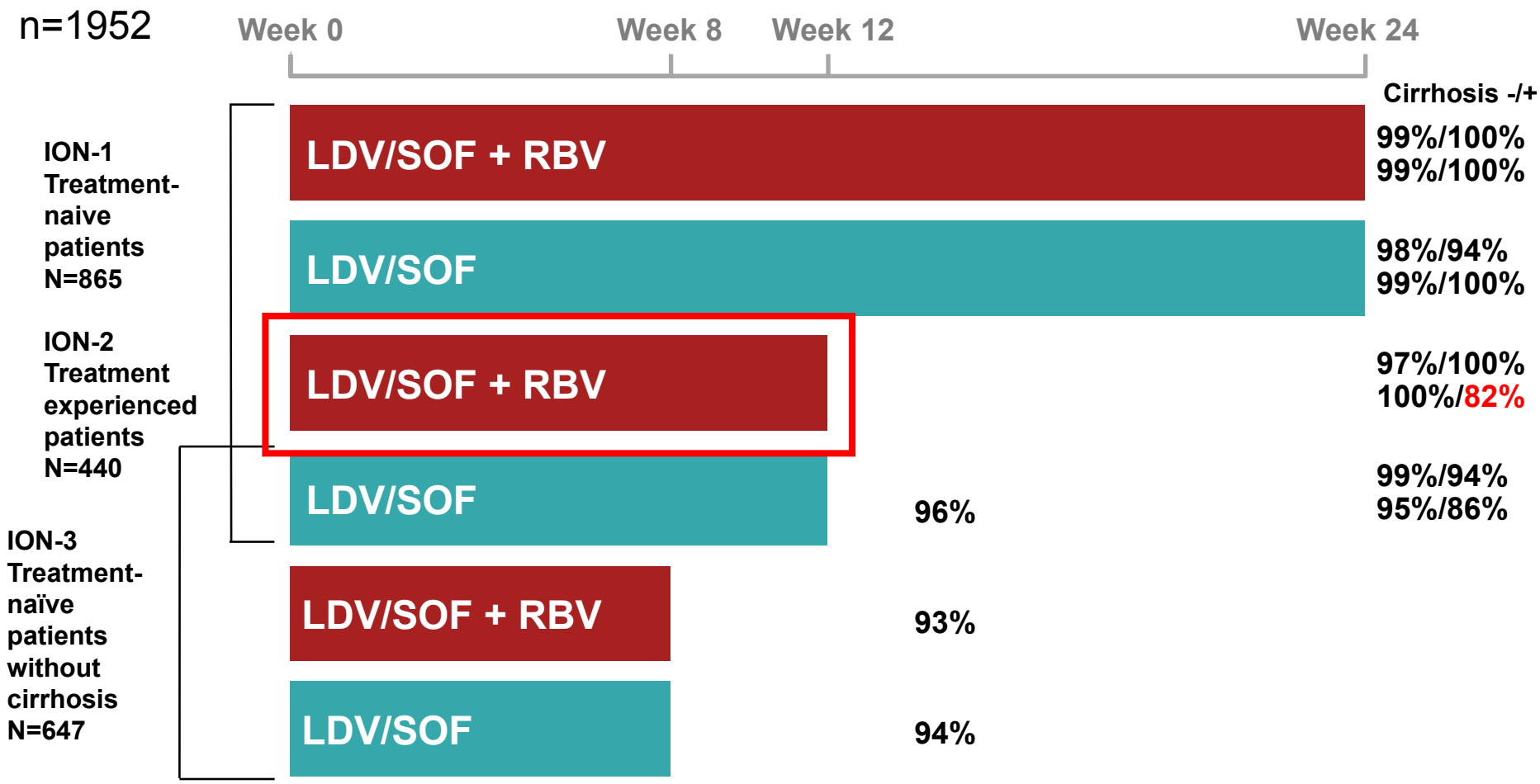
Retreatment LDV 90 mg QD + SOF 400 mg QD + RBV 1200 mg 12 weeks (2015)

("A phase 3b, multicenter, open-label study to evaluate the safety and efficacy of LDV/SOF in adults with chronic HCV-infection")

	ALT (IU/l)	Hb (g/l)	Plt (x109/l)	T. bil (mkmol/l)	HCV RNA (IU/ml)	Fs (kPa)
Base Line	147	155	128	24.5	5150000	20.5
W1	50	154	105	25.6	472	-
W2	26	149	165	26.1	<15	-
W4	23	140	140	25.5	0	-
W8	22	140	205	26.5	0	-
W12	23	139	201	24.9	0	-
SVR4	38	142	160	25.8	0	14.4

There are no significant adverse events

LDV/SOF: Clinical trials phase 3 (ION-1, ION-2, ION-3)



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CONCLUSIONS

- High prevalence of G1b in Russia is associated with easy to cure after IFN-free regimens
- SOF+RBV is sub-optimal both for treatment-naïve and treatment experienced patients with G1, in cirrhotic patients is ineffective
- In the era of DAAs many previously important predictors are no longer challenging
- Previous partial response to Peg-IFN+RBV and relapse to SOF+RBV cirrhotic patient with G1b achieved SVR rate with all-oral IFN-free LDV+SOF+RBV 12 weeks