HepAtölye III

Hepatit C Virusu İnfeksiyonunun Tedavisinde Yeni Antiviraller

4-6 Aralık 2015, Radisson Blu Hotel Istanbul Asia, İstanbul

HCV Genotip 2 ve 3 tedavi yaklaşımı

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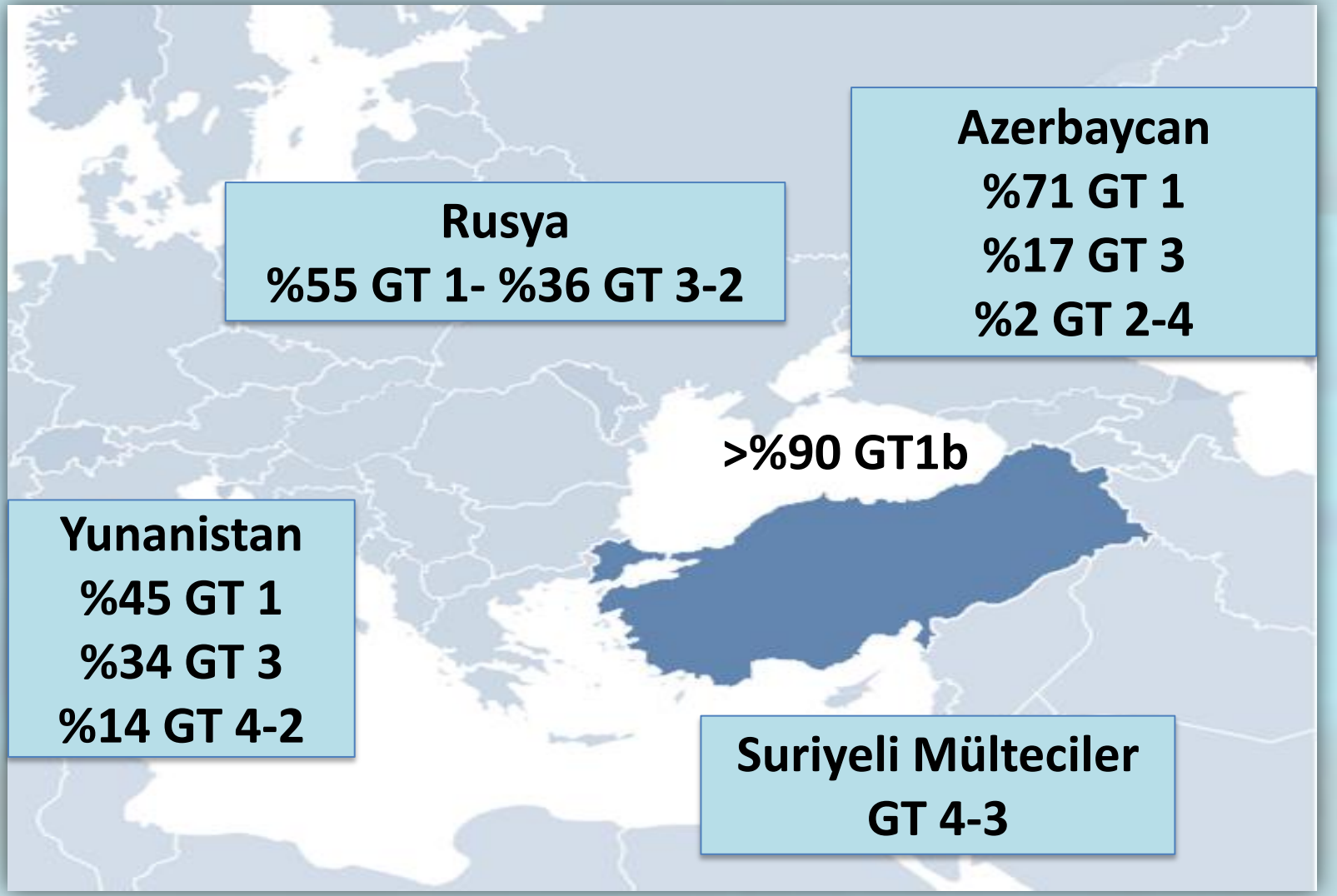
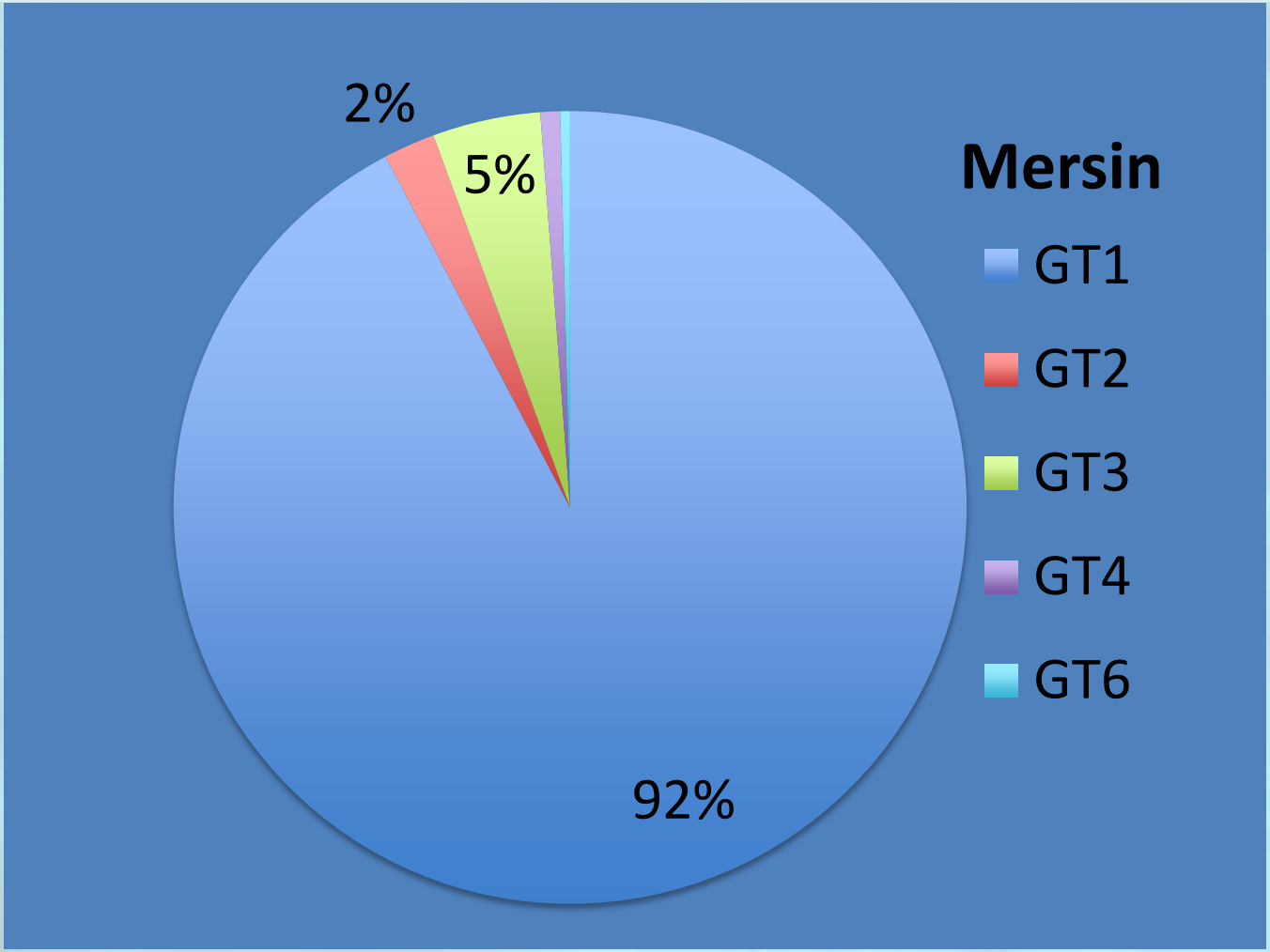
Enfeksiyon Hastalıkları AD

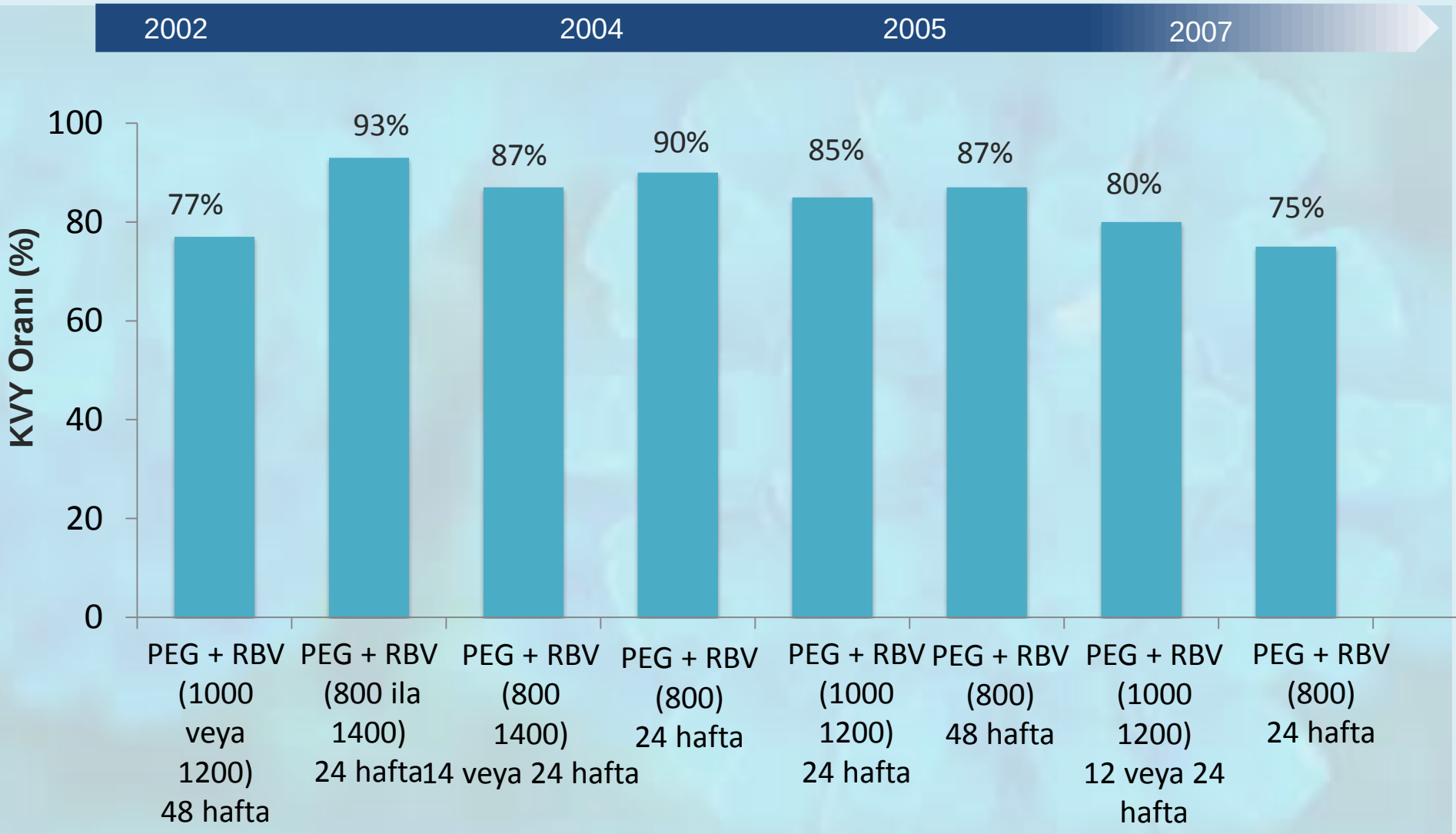
Değişen genotip?



Değişen genotip?



HCV Genotip 2/3
Klasik tedavi etkili miydi?



Başarılı sonuçlar var
Problem nerede?

- **Etkin ama tolere edilme**
  - Ribavirin dozu azaltıldı*
- **Tedavi süresi uzun**
  - Süre kısaltıldı
- **Neden %100 değil**
  - Zor gruplar
  - Tedavi tekrarlanması?

Hedef;

- **Hastanın tedavide kalmasını arttırmak**
- **%100 başarı**

****15mg/kg dozdan kiloya ayarlanmış RBV erken virolojik yanıt ve zor hasta gruplarında tedavi oranlarını arttırmakta**

- **Yüksek viral yük, metabolik sendrom, ileri fibrozis**

*Jacobson IM, et al. Hepatology 2007

**Di Martino V, et al. Hepatology 2011

KLİMİK BÜLTENİ
Türk Klinik Mikrobiyoloji ve İnfeksiyon Hastalıkları Derneği Yayın Organıdır
23
KASIM
2015

NEJM

HCV İnfeksiyonu Tedavisinde Sona Doğru

Tedavi deneyimli ve deneyimsiz HCV genotip 1, 2, 4, 5 ve 6 ile infekte 624 hastada yapılan çift kör, plasebo kontrollü faz III çalışmada, 12 hafta boyunca günde tek doz alınan sofosbuvir ve velpatasvirle kalıcı viral yanıt oranının (%99), plaseboya göre çok yüksek olduğu gösterilmiş (Dr. Mehtap Aydın).

Feld JJ, Jacobson IM, Hézode C, et al. Sofosbuvir and velpatasvir for HCV genotype 1, 2, 4, 5, and 6 infection. N Engl J Med. 16 Kasım 2015.

Table 2. Response during and after Treatment.*

Response	Sofosbuvir–Velpatasvir (N = 624)
HCV RNA <15 IU/ml	
During treatment period — no. (%)	
At wk 2	355 (57)
At wk 4	564 (90)
At 12 wk after treatment period — no./total no. (%)	
Any genotype	618/624 (99)
1a	206/210 (98)
1b	117/118 (99)
2	104/104 (100)
4	116/116 (100)
5	34/35 (97)
6	41/41 (100)
Virologic failure — no. (%)	
During treatment	0
After treatment	2 (<1)
Other reason for classification as failure — no. (%)	
Loss to follow-up	2 (<1)
Withdrawal of consent	1 (<1)
Death	1 (<1)

Table 3. Discontinuations, Adverse Events, and Hematologic Abnormalities.

Event	Placebo (N = 116)	Sofosbuvir–Velpatasvir (N = 624)
	no. of patients (%)	
Discontinuation of treatment owing to an adverse event	2 (2)	1 (<1)
Serious adverse event*	0	15 (2)
Any adverse event	89 (77)	485 (78)
Common adverse events†		
Headache	33 (28)	182 (29)
Fatigue	23 (20)	126 (20)
Nasopharyngitis	12 (10)	79 (13)
Nausea	13 (11)	75 (12)
Insomnia	11 (9)	50 (8)
Diarrhea	8 (7)	48 (8)
Asthenia	9 (8)	41 (7)
Arthralgia	9 (8)	40 (6)
Cough	4 (3)	39 (6)
Back pain	11 (9)	29 (5)
Myalgia	6 (5)	25 (4)
Hematologic event		
Hemoglobin level <10 g/dl	0	2 (<1)
Lymphocyte count 350 to <500 per mm^3	0	3 (<1)
Neutrophil count 500 to <750 per mm^3	0	4 (1)
Platelet count 25,000 to <50,000 per mm^3	0	1 (<1)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sofosbuvir and Velpatasvir for HCV Genotype 2 and 3 Infection

G.R. Foster, N. Afdhal, S.K. Roberts, N. Bräu, E.J. Gane, S. Pianko, E. Lawitz, A. Thompson, M.L. Shiffman, C. Cooper, W.J. Towner, B. Conway, P. Ruane, M. Bourlière, T. Asselah, T. Berg, S. Zeuzem, W. Rosenberg, K. Agarwal, C.A.M. Stedman, H. Mo, H. Dvory-Sobol, L. Han, J. Wang, J. McNally, A. Osinusi, D.M. Brainard, J.G. McHutchison, F. Mazzotta, T.T. Tran, S.C. Gordon, K. Patel, N. Reau, A. Mangia, and M. Sulkowski, for the ASTRAL-2 and ASTRAL-3 Investigators*

ASTRAL-2 ve ASTRAL-3 çalışmaları

17 Kasım 2015

Ön bilgi

- HCV genotip 2 ve 3 rehberlere göre

  "Kolay tedavi edilen genotipler"
- Genotip 3; genotip 2'ye göre
  - Daha hızlı progresyon göstermekte
  - Tedaviye cevabı daha düşük
    - Sirotik hastalarda
    - Cevapsız olan tedavi deneyimlilerde

- GT 2 Sofosbuvir (SOF)–ribavirin (RBV); 12-20 hafta
- GT 3 SOF–RBV; 24 hafta

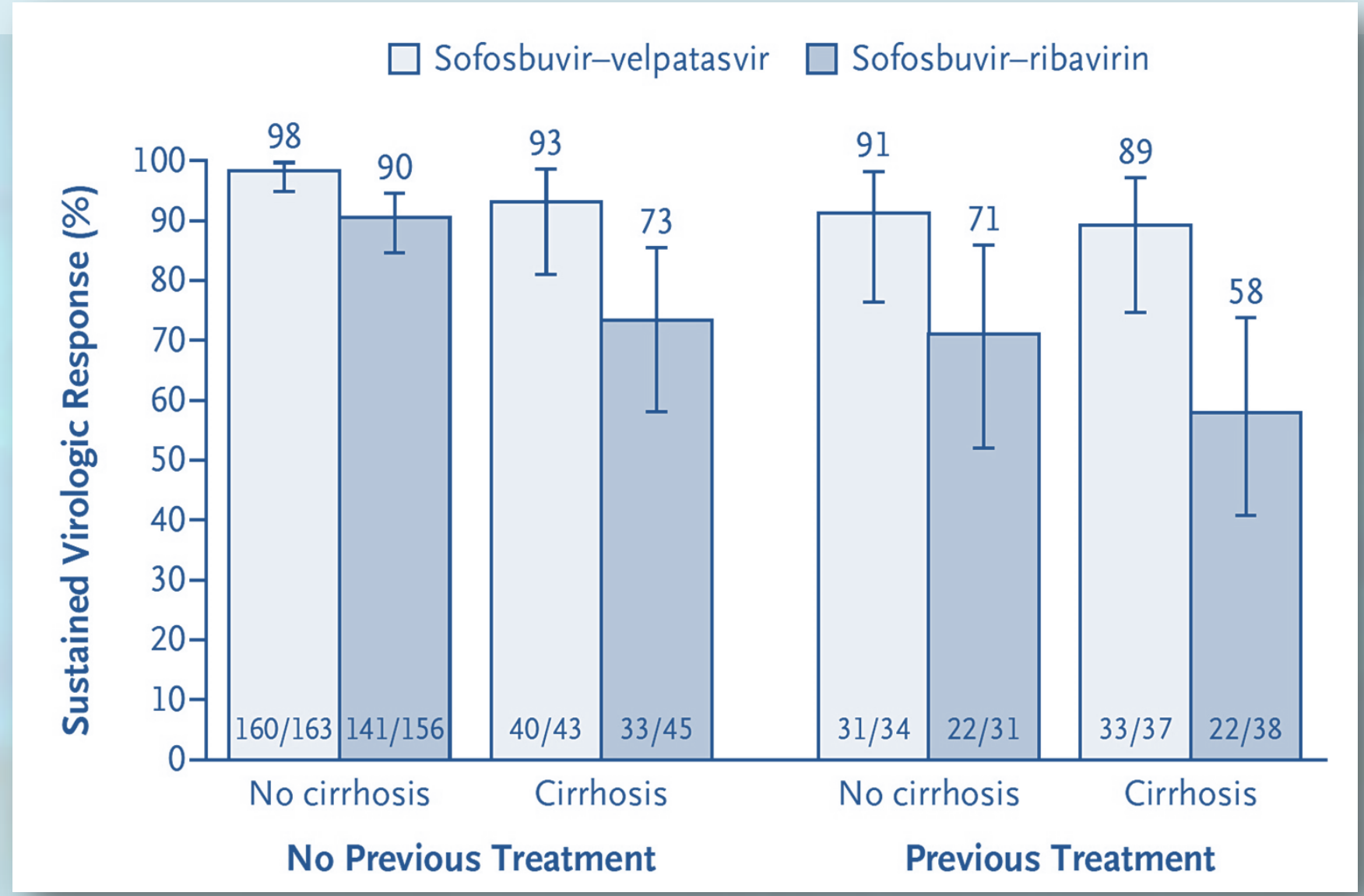
- **Velpatasvir yeni NS5A inhibitörü (GS-5816); tüm GT etkili**
- **Faz 2 çalışmalar; 12 hafta SOF ve Velpatasvir yüksek etkinliğe sahip (GT 2-3)**
- **ASTRAL-2 ve 3: Randomize**
  - **1:1 kontrollü (SOF-RBV)**

Characteristic	HCV Genotype 2		HCV Genotype 3	
	Sofosbuvir–Velpatasvir for 12 Wk (N=134)	Sofosbuvir–Ribavirin for 12 Wk (N=132)	Sofosbuvir–Velpatasvir for 12 Wk (N=277)	Sofosbuvir–Ribavirin for 24 Wk (N=275)
Mean age (range) — yr	57 (26–81)	57 (23–76)	49 (21–76)	50 (19–74)
Male sex — no. (%)	86 (64)	72 (55)	170 (61)	174 (63)
Mean body-mass index (range)†	28 (17–45)	29 (19–61)	26 (17–48)	27 (17–56)
Race — no. (%)‡				
White	124 (93)	111 (84)	250 (90)	239 (87)
Black	6 (4)	12 (9)	3 (1)	1 (<1)
Asian	1 (1)	5 (4)	23 (8)	29 (11)
Other	3 (2)	4 (3)	1 (<1)	6 (2)
HCV RNA				
Mean — $\log_{10}$ IU/ml	6.5±0.78	6.4±0.74	6.2±0.72	6.3±0.71
≥800,000 IU/ml — no. (%)	111 (83)	101 (77)	191 (69)	194 (71)
IL28B genotype — no. (%)				
CC	55 (41)	46 (35)	105 (38)	111 (40)
CT	61 (46)	64 (48)	148 (53)	133 (48)
TT	18 (13)	22 (17)	24 (9)	31 (11)
Compensated cirrhosis — no. (%)	19 (14)	19 (14)	80 (29)	83 (30)
Previous HCV treatment — no. (%)				
No	115 (86)	112 (85)	206 (74)	204 (74)
Yes	19 (14)	20 (15)	71 (26)	71 (26)
Response to previous HCV treatment — no./total no. (%)				
No response	3/19 (16)	3/20 (15)	20/71 (28)	24/71 (34)
Relapse or breakthrough	16/19 (84)	17/20 (85)	51/71 (72)	47/71 (66)

Response	HCV Genotype 2		HCV Genotype 3	
	Sofosbuvir–Velpatasvir for 12 Wk (N=134)	Sofosbuvir–Ribavirin for 12 Wk (N=132)	Sofosbuvir–Velpatasvir for 12 Wk (N=277)	Sofosbuvir–Ribavirin for 24 Wk (N=275)
HCV RNA <15 IU/ml — no. (%)				
During treatment period				
At 2 wk	76 (57)	79 (60)	171 (62)	137 (50)
At 4 wk	120 (90)	119 (90)	253 (91)	240 (87)
After end of treatment				
At 4 wk	133 (99)	127 (96)	268 (97)	225 (82)
At 12 wk*	133 (99)	124 (94)	264 (95)	221 (80)
95% CI at 12 wk	96–100	88–97	92–98	75–85
Virologic failure — no./total no. (%)				
On-treatment failure	0	0	0	1/275 (<1)
Relapse	0	6/132 (5)	11/276 (4)	38/272 (14)

ASTRAL-2; SOF–velpatasvir grubunda %60 NS5A direnci, %10 NS5B direnci olmasına karşın klinik cevap çok yüksek (NS5B L31M varyasyonu %52)

GT 3


Sofosbuvir–velpatasvir
Sofosbuvir–ribavirin
Sustained Virologic Response (%)
100
90
80
70
60
50
40
30
20
10
0
98
90
93
73
91
71
89
58
160/163
141/156
40/43
33/45
31/34
22/31
33/37
22/38
No cirrhosis
Cirrhosis
No cirrhosis
Cirrhosis
No Previous Treatment
Previous Treatment

EASL Recommendations on Treatment of Hepatitis C 2015

European Association for the Study of the Liver*

Sirotik olmayanlar

Patients	PegIFN-α, RBV and sofosbuvir	PegIFN-α, RBV and simeprevir	Sofosbuvir and RBV	Sofosbuvir and ledipasvir	Ritonavir-boosted paritaprevir, ombit-asvir and dasabuvir	Ritonavir-boosted paritaprevir, and ombitasvir	Sofosbuvir and simeprevir	Sofosbuvir and daclatasvir
Genotype 1a	12 wk	12 wk, then PegIFN-α and RBV 12 wk (treatment-naïve or relapsers) or 36 wk (partial or null responders)	No	8-12 wk, without RBV	12 wk with RBV	No	12 wk without RBV	12 wk without RBV
Genotype 1b					12 wk without RBV			
Genotype 2	12 wk	No	12 wk	No	No	No	No	12 wk without RBV
Genotype 3	12 wk	No	24 wk	No	No	No	No	12 wk without RBV
Genotype 4	12 wk	12 wk, then PegIFN-α and RBV 12 wk (treatment-naïve or relapsers) or 36 wk (partial or null responders)	No	12 wk without RBV	No	12 wk with RBV	12 wk without RBV	12 wk without RBV
Genotype 5 or 6	12 wk	No	No	12 wk without RBV	No	No	No	12 weeks without RBV

EASL Recommendations on Treatment of Hepatitis C 2015

European Association for the Study of the Liver*

Sirotik olanlarda

Patients	PegIFN-α, RBV and sofosbuvir	PegIFN-α, RBV and simeprevir	Sofosbuvir and RBV	Sofosbuvir and ledipasvir	Ritonavir-boosted paritaprevir, ombit-asvir and dasabuvir	Ritonavir-boosted paritaprevir, and ombitasvir	Sofosbuvir and simeprevir	Sofosbuvir and daclatasvir
Genotype 1a	12 wk	12 wk (treat-ment-naïve or relapsers) or 24 wk (partial or null re-sponders)	No	12 wk with RBV, or 24 wk without RBV, or 24 wk with RBV if negative predictors of response	24 wk with RBV	No	12 wk with RBV, or 24 wk without RBV	12 wk with RBV, or 24 wk without RBV
Genotype 1b					12 wk with RBV			
Genotype 2	12 wk	No	16-20 wk	No	No	No	No	12 wk without RBV
Genotype 3	12 wk	No	No	No	No	No	No	24 wk with RBV
Genotype 4	12 wk	12 wk (treat-ment-naïve or relapsers) or 24 wk (partial or null re-sponders)	No	12 wk with RBV, or 24 wk without RBV, or 24 wk with RBV if negative predictors of response	No	24 wk with RBV	12 wk with RBV, or 24 wk without RBV	12 wk with RBV, or 24 wk without RBV
Genotype 5 or 6	12 wk	No	No	12 wk with RBV, or 24 wk without RBV, or 24 wk with RBV if negative predictors of response	No	No	No	12 wk with RBV, or 24 wk without RBV

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C

IDSA
Infectious Diseases Society of America

Revised Date: August 7, 2015

INITIAL TREATMENT OF HCV INFECTION

RETREATMENT OF PERSONS IN WHOM PRIOR THERAPY HAS FAILED

II. Genotype 2

III. Genotype 3

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HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C

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Revised Date: August 7, 2015

INITIAL TREATMENT OF HCV INFECTION

RETREATMENT OF PERSONS IN WHOM PRIOR THERAPY HAS FAILED

II. Genotype 2

III. Genotype 3

Genotip 2

Önerilen rejimler	Süre	Kanıt
1*Günlük; daclatasvir** (60 mg) ve sofosbuvir (400 mg)	12 hafta	Klas IIA, Düzey B
*RBV tolere edemeyecek HCV genotip 2 enfeksiyonlu tedavi görmemiş hastalar için tavsiye edilmekte		
2a. Günlük; sofosbuvir (400 mg) ve ağırlığa göre hesaplanmış RBV	12 hafta	Klas I, Düzey A
2b. Siroz	16 hafta	Klas IIB, Düzey C
**Sitokrom P450 3A / 4 indükleyicilerle ve inhibitörleri ile eş zamanlı olarak kullanıldığında Daclatasvir dozunu artırmak veya azaltmak gerekebilir		

Genotip 2

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*RBV tolere edemeyecek HCV genotip 2 enfeksiyonlu tedavi görmemiş hastalar için tavsiye edilmekte		
2a. Günlük; sofosbuvir (400 mg) ve ağırlığa göre hesaplanmış RBV	12 hafta	Klas I, Düzey A
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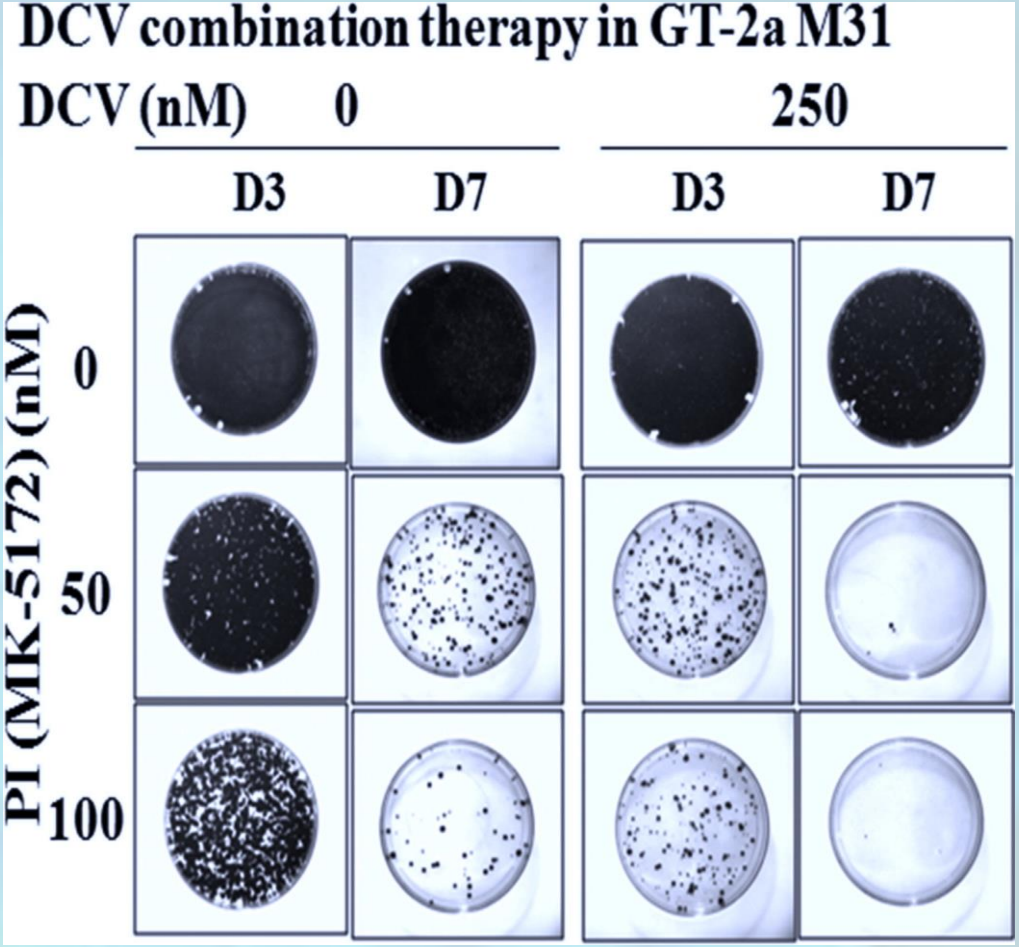
**Sitokrom P450 3A / 4 indükleyicilerle ve inhibitörleri ile eş zamanlı olarak kullanıldığında Daclatasvir dozunu artırmak veya azaltmak gerekebilir		

Daclatasvir

- GT 2 için; FDA onayı yok
- M31 polimorfizmi; kombinasyon tedavisi HCV genotipine 2a'ya etkin aktiviteye sahip



Chunfu Wang et al. Antimicrob. Agents Chemother. 2014;58:5155-5163

The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2014;370:211-21.

ORIGINAL ARTICLE

Daclatasvir plus Sofosbuvir for Previously Treated or Untreated Chronic HCV Infection

Mark S. Sulkowski, M.D., David F. Gardiner, M.D., Maribel Rodriguez-Torres, M.D., K. Rajender Reddy, M.D., Tarek Hassanein, M.D., Ira Jacobson, M.D., Eric Lawitz, M.D., Anna S. Lok, M.D., Federico Hinestrosa, M.D., Paul J. Thuluvath, M.D., Howard Schwartz, M.D., David R. Nelson, M.D., Gregory T. Everson, M.D., Timothy Eley, Ph.D., Megan Wind-Rotolo, Ph.D., Shu-Pang Huang, Ph.D., Min Gao, Ph.D., Dennis Hernandez, Ph.D., Fiona McPhee, Ph.D., Diane Sherman, M.S., Robert Hindes, M.D., William Symonds, Pharm.D., Claudio Pasquinelli, M.D., Ph.D., and Dennis M. Grasela, Pharm.D., Ph.D., for the AI444040 Study Group

Characteristic	Genotype 2 or 3, Previously Untreated		
	Group B: SOF for 7 days, then SOF and DCV for 23 wk (N = 16)	Group D: DCV and SOF for 24 wk (N = 14)	Group F: DCV and SOF plus RBV for 24 wk (N = 14)
Median age — yr	51	50	52
Male sex — no. (%)	11 (69)	6 (43)	5 (36)
Race — no. (%)†			
White	16 (100)	10 (71)	12 (86)
Black	0	2 (14)	0
Other	0	2 (14)	2 (14)
HCV RNA — $\log_{10}$ IU/ml‡	6.5±0.7	6.8±0.5	6.6±0.6
HCV genotype — no. (%)§			
1a	0	0	0
1b	0	0	0
2	9 (56)	8 (57)	9 (64)
3	7 (44)	6 (43)	5 (36)
IL28B genotype CC — no. (%)	8 (50)	5 (36)	7 (50)
Metavir score for fibrosis — no. (%)¶			
F0 or F1: none or minimal	6 (38)	6 (43)	6 (43)
F2 or F3: moderate	7 (44)	7 (50)	6 (43)
F4: clinically significant	3 (19)	1 (7)	2 (14)

Virologic Response	Genotype 2 or 3, Previously Untreated			
	Group B: SOF for 7 days, then SOF and DCV for 23 wk (N=16)	Group D: DCV and SOF for 24 wk (N=14)	Group F: DCV and SOF plus RBV for 24 wk (N=14)	Total: Groups B, D and F (N=44)
	number of study participants (percent)			
During treatment				
Week 2				
HCV RNA <25 IU/ml	13 (81)	12 (86)	12 (86)	37 (84)
HCV RNA undetectable	5 (31)	4 (29)	4 (29)	13 (30)
Week 4				
HCV RNA <25 IU/ml	16 (100)	14 (100)	14 (100)	44 (100)
HCV RNA undetectable	14 (88)	11 (79)	9 (64)	34 (77)
End of treatment‡				
HCV RNA <25 IU/ml	15 (94)§	14 (100)	14 (100)	43 (98)
HCV RNA undetectable	15 (94)§	13 (93)	14 (100)	42 (95)
After treatment				
Week 4				
HCV RNA <25 IU/ml	14 (88)¶	14 (100)	12 (86)‖**	40 (91)
HCV RNA undetectable	14 (88)¶	14 (100)	11 (79)‖**	39 (89)
Week 12				
HCV RNA <25 IU/ml	14 (88)	14 (100)	12 (86)**	40 (91)
HCV RNA undetectable	14 (88)	13 (93)	12 (86)**	39 (89)
Week 24				
HCV RNA <25 IU/ml	14 (88)	14 (100)	13 (93)	41 (93)
HCV RNA undetectable	14 (88)	14 (100)	13 (93)	41 (93)

Treatment Group	Patient *IL28B* Genotype	HCV Genotype	Reason	Virologic Outcome	Comments
SOF × 7 days, then DCV+SOF × 23 weeks (B)	C/C	3	Slow virologic suppression defined as virologic breakthrough	SVR_{24}	HCV RNA became undetectable at week 3. At week 8 and again at week 10, HCV RNA was detectable and <25 IU/mL, meeting a protocol definition of virologic breakthrough. HCV RNA became undetectable prior to the addition of peginterferon/ribavirin at week 12. The patient achieved SVR_{24} following 24 weeks of rescue therapy.
SOF × 7 days, then DCV+SOF × 23 weeks (B)	T/T	3	Virologic relapse	Virologic relapse	HCV RNA became undetectable at week 2 and remained undetectable until week 24 (end of treatment). At post-treatment week 4, HCV RNA was 158603 IU/mL (5.2 $\log_{10}$ IU/mL). An NS5A-A30K polymorphism was detected at baseline and also at relapse.
DCV+ SOF+RBV × 24 weeks (F)	C/C	2	Lost to follow-up	Unknown	The patient was lost to follow-up after treatment week 18. HCV RNA was undetectable at the last measurement, obtained at treatment week 14.
DCV+ SOF+RBV × 24 weeks (F)	C/C	2	Missing	SVR_{24}	The patient completed 24 weeks of treatment and did not return for the post-treatment week 4 and post-treatment week 12 visits, but returned at post-treatment week 24 with HCV RNA undetectable.

Number of Patients	HCV Genotype	Polymorphism(s) at NS5A Amino Acid Positions	Virologic Outcome
13	2	L31M	SVR_{48} (all)
1	2	L31M-P58S	SVR_{24}
1	3	A30K	Relapse
1	3	A30K, L31M	SVR_{48}
3	3	Y93H	SVR_{48} (all)

Adverse Event	Previously Untreated					Previously Treated	
	Treatment for 24 Wk			Treatment for 12 Wk		Treatment for 24 Wk	
	Groups A and B: Lead-in SOF and DCV (N = 31)	*Groups C and D: DCV and SOF (N = 28)*	*Groups E and F: DCV and SOF and RBV (N = 29)*	*Group G: DCV and SOF (N = 41)*	*Group H: DCV and SOF and RBV (N = 41)*	*Group I: DCV and SOF (N = 21)*	*Group J: DCV and SOF and RBV (N = 20)*
	number of study participants (percent)						
Any adverse event	25 (81)	26 (93)	26 (90)	38 (93)	38 (93)	16 (76)	20 (100)
Adverse event occurring in ≥25% of patients in any group*							
Fatigue	9 (29)	14 (50)	9 (31)	16 (39)	15 (37)	6 (29)	9 (45)
Headache	5 (16)	8 (29)	11 (38)	14 (34)	9 (22)	7 (33)	7 (35)
Nausea	5 (16)	9 (32)	9 (31)	8 (20)	8 (20)	0	2 (10)
Grade 3 or 4 adverse event	0	2 (7)†	2 (7)	1 (2)	1 (2)	0	1 (5)
Discontinuation of treatment due to adverse event‡	0	1 (4)	1 (3)	0	0	0	0
Serious adverse event§	2 (6)	4 (14)	2 (7)	1 (2)	0	0	1 (5)
Grade 3 or 4 laboratory abnormality occurring in ≥3 patients across all groups							
Phosphorus <2.0 mg/dl	0	1 (4)	1 (3)	0	3 (7)	0	0
Glucose							
Fasting value >250 mg/dl	0	1 (4)	1 (3)	1 (2)	0	1 (5)	0
Random value >250 mg/dl	0	0	1 (5)¶	0	0	1 (5)	1 (5)

Genotip 2 için alternatif rejim

- **AASLD/IDSA HCV 2015 rehberinde alternatif tedavi önerilmemekte**

Kullanılması önerilmeyen rejimler:	
1. PEG-IFN ve RBV 24 hafta	Klas IIb, Düzey A
2. Monoterapi olarak PEG-IFN, RBV ya da doğrudan etkili anti-viraller	Klas III, Düzey A
3. Telaprevir-, boceprevir- veya ledipasvir içeren rejimler	Klas III, Düzey A

Tedavi deneyimli hastalarda

- **Öncesinde PEG-IFN ve RBV tedavisi başarısız hastalarda**
  - **SOF 400 mg ve ağırlığa göre hesaplanmış RBV**

    16 - 24 hafta

    Klas I, Düzey A
- **IFN kullanabilen fakat öncesinde PEG-IFN ve RBV tedavisi başarısız olan hastalarda**
  - **SOF 400 mg, ağırlığa göre hesaplanmış RBV ve haftalık PEG-IFN**

    12 hafta

    Klas IIa, Düzey B

SOF ve RBV başarısız

- **DCV 60 mg, SOF 400 mg ve/veya ağırlığa göre hesaplanmış RBV**

  24 hafta

  Klas IIa, Düzey C

- **IFN kullanabilen hastalarda; SOF 400 mg, ağırlığa göre hesaplanmış RBV ve haftalık PEG-IFN**

  12 hafta

  Klas IIa C Seviyesi

PEG-IFN ve RBV başarısız hastalarda önerilmeyen tedaviler

- **PEG-IFN ve RBV ve/veya Telaprevir veya Boseprevir**

  Klas IIb, Düzey A

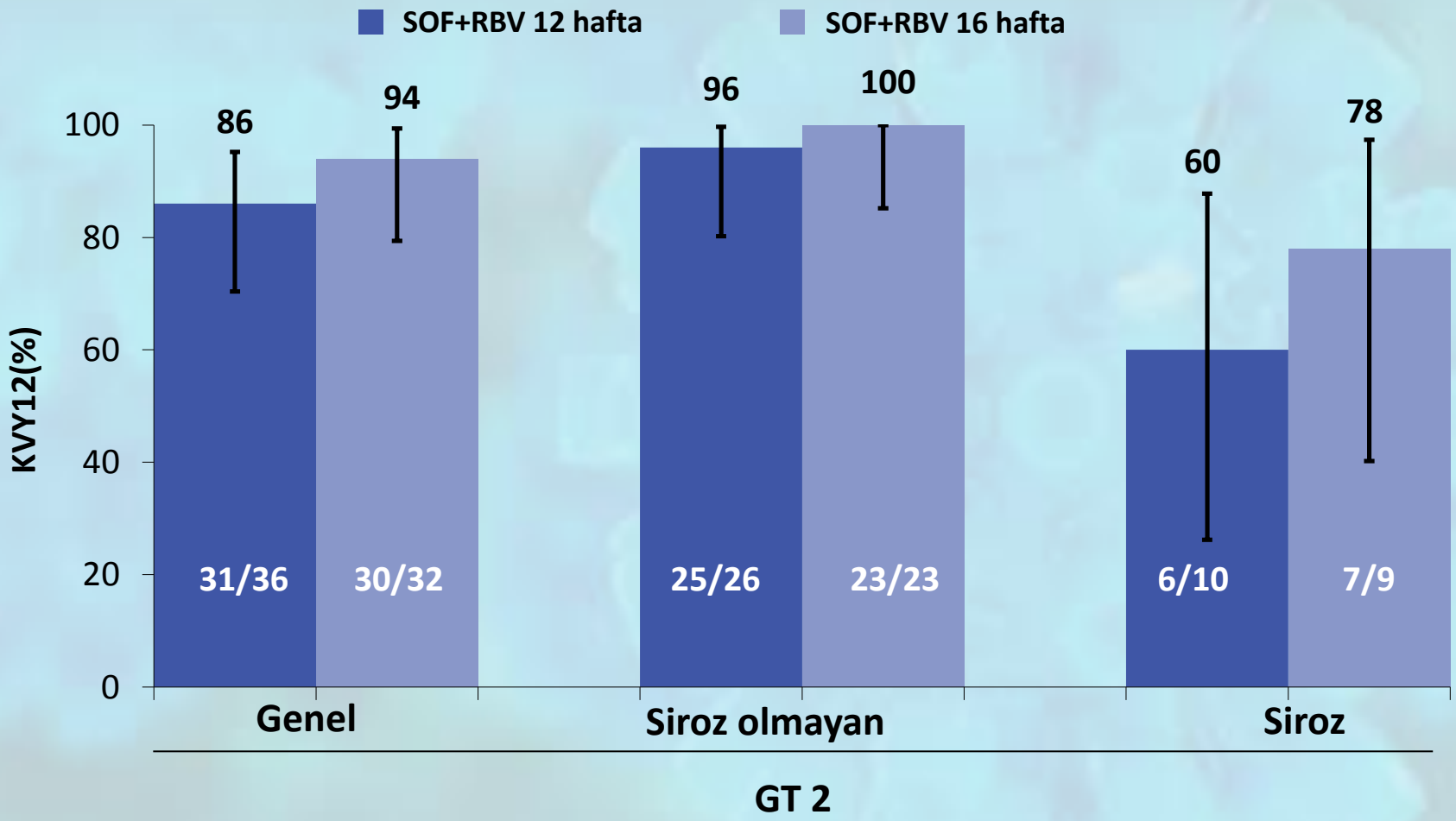
- **Ledipasvir / sofosbuvir**

  Klas III, Düzey A

- **PEG-IFN, RBV veya doğrudan etkili anti-viral monoterapi**

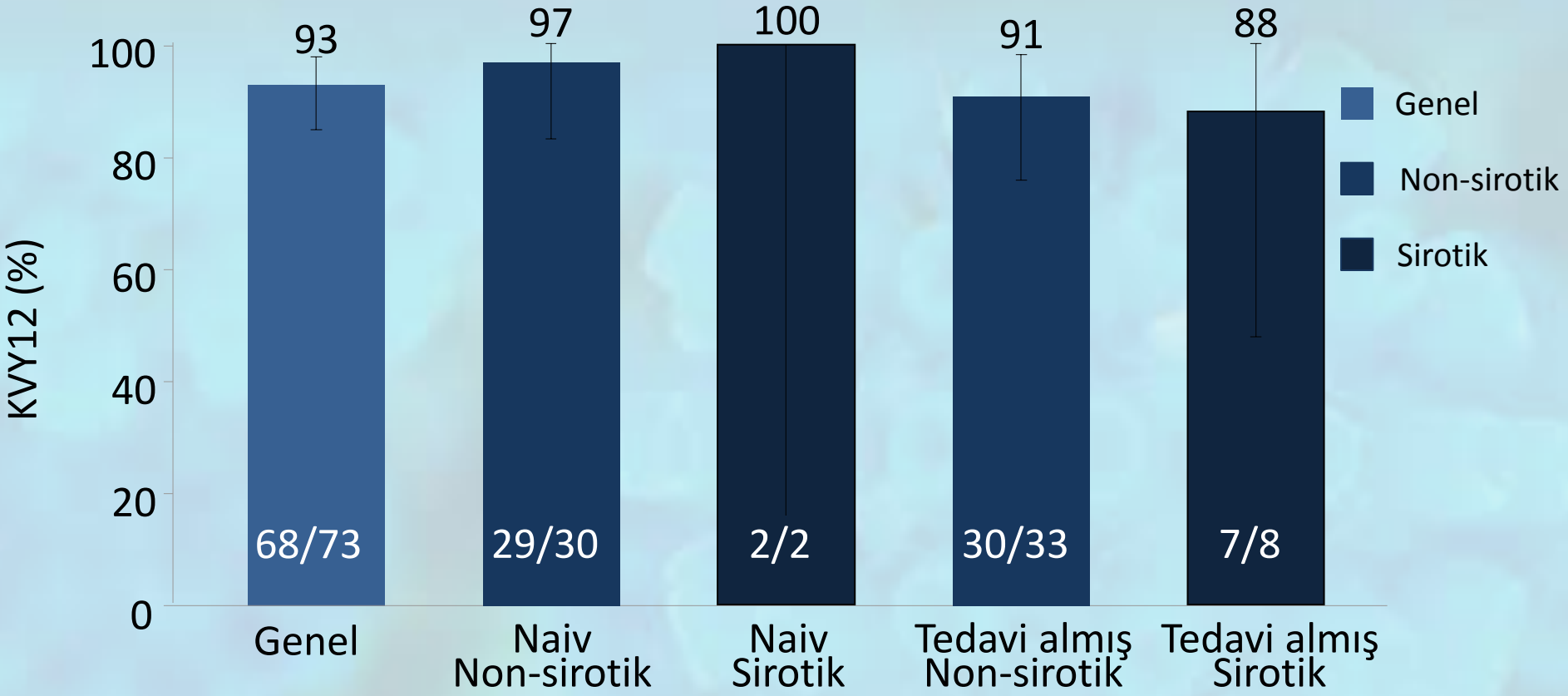
  Klas III, Düzey A

FUSION; Genotip 2 için KVY12 Tedavi Almış: SOF + RBV (12 vs. 16 Hafta)



Nelson DR, et al. EASL 2013. Amsterdam, The Netherlands. Oral #6;
Jacobson IM, et al. N Engl J Med. 2013;368(20):1867–77.

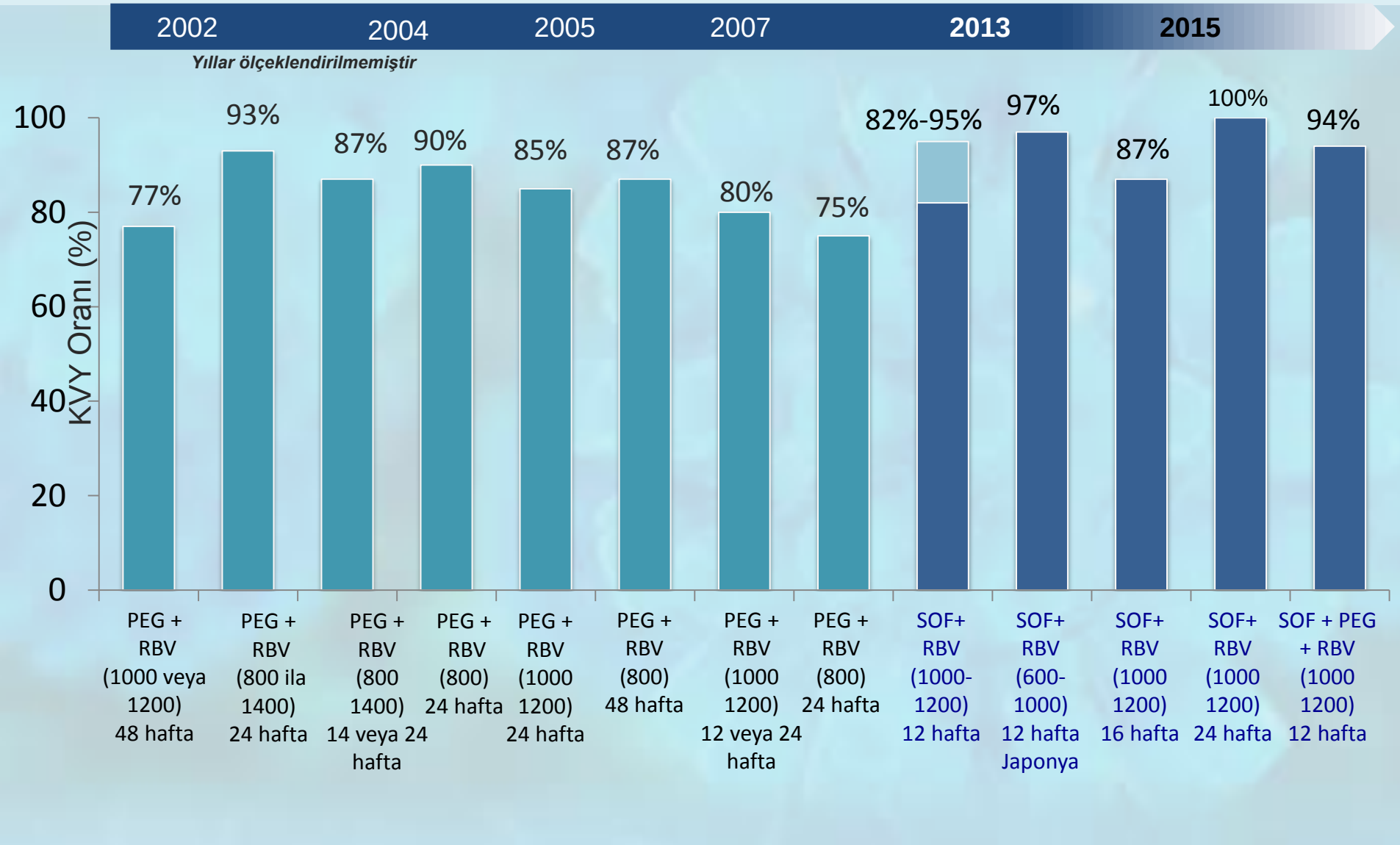
VALENCE: Genotip 2 için KVY12
Tedavi Naiv ve Almış: SOF + RBV
12 Hafta



- Hastaların %100'ü 4. haftada HCV RNA < LLOQ düzeyine sahipti
- Tedavinin bitimi sonrası nüks; tüm virolojik başarısızlıklar

Zeuzem S, et al. AASLD 2013. Washington, DC. #1085.

HCV Genotip 2 Hastalarında Mevcut Tedavilerin KVY Oranları



- Zeuzem S, et al. *J Hepatol* 2004;40:993-9;
- Dalgard O, et al. *Hepatol* 2004;40:1260-5;
- Hadziyannis S, et al. *Ann Intern Med* 2004;140:346-55; Hadziyannis S, et al. /Fried M, et al. *N Engl J Med* 2002;347:975-82;
- Mangia A, et al. *N Engl J Med* 2005;352:2609-17;
- Shiffman M, et al. *N Engl J Med* 2007;357:124-34;
- SOVALDI® [PI]. Gilead Sciences, Inc. Foster City, CA March 2015;
- Omata M, et al. *J Viral Hep* 2014;21:762-768;
- Foster, G et al, L05, EASL 2015

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C

IDSA
Infectious Diseases Society of America

Revised Date: August 7, 2015

INITIAL TREATMENT OF HCV INFECTION

RETREATMENT OF PERSONS IN WHOM PRIOR THERAPY HAS FAILED

II. Genotype 2

III. Genotype 3

Genotip 3

Önerilen rejimler	Süre	Kanıt
1a. Daclatasvir (60 mg) sofosbuvir (400 mg)±ağırlığa göre hesaplanmış RBV	12 hafta	Klas I, Düzey A
1b. Siroz	16 hafta	Klas IIa, Düzey C
2. Sofosbuvir (400 mg), ağırlığa göre hesaplanmış RBV ve PEG-IFN (IFN kullanabilecek hastalar)	12 hafta	Klas I, Düzey A
Alternatif rejim		
24 hafta süreyle günlük sofosbuvir (400 mg) ve ağırlığa göre hesaplanmış RBV (IFN kullanılamayan)	24 hafta	Klas I, Düzey A

Kullanılması önerilmeyen rejimler:	
1. PEG-IFN ve RBV; 24-48 hafta	Klas IIb, Düzey A
2. Monoterapi olarak PEG-IFN, RBV ya da doğrudan etkili anti-viraller	Klas III, Düzey A
3. Telaprevir-, boceprevir- veya simeprevir içeren rejimler	Klas III, Düzey A

Tedavi deneyimli hastalarda

- **Öncesinde PEG-IFN ve RBV tedavisi başarısız hastalar**

  1. Daclatasvir (60 mg) ve Sofosbuvir (400 mg)

  12 hafta

  Klas I, Düzey A

  2. Sofosbuvir (400 mg), ağırlığa göre hesaplanmış RBV ve haftalık PEG-IFN (IFN uygulanabilen hastalar)

  12 hafta

  Klas I, Düzey A

Tedavi deneyimli hastalarda

- **PEG-IFN ve RBV ile önceden tedavi başarısız siroz hastaları**

1. Daclatasvir (60 mg), sofosbuvir (400 mg) ve ağırlığa göre hesaplanmış RBV

24 hafta

Klas IIa, Düzey C

2. Günlük sofosbuvir (400 mg), ağırlığa göre hesaplanmış RBV ve haftalık PEG-IFN IFN

12 hafta

Klas I, Düzey A

Tedavi deneyimli hastalarda

- **Sofosbuvir ve RBV tedavisi başarısız hastalar**

  1. Daclatasvir (60 mg), sofosbuvir (400 mg) ve ağırlığa göre hesaplanmış RBV

  24 hafta

  Klas IIa, Düzey C

  2. Sofosbuvir (400 mg), ağırlığa göre hesaplanmış RBV ve haftalık PEG-IFN

  12 hafta

  Klas IIa, Düzey C

Önerilmeyen tedaviler

1. PEG-IFN ve RBV; 24 - 48 hafta

Klas IIb, Düzey A

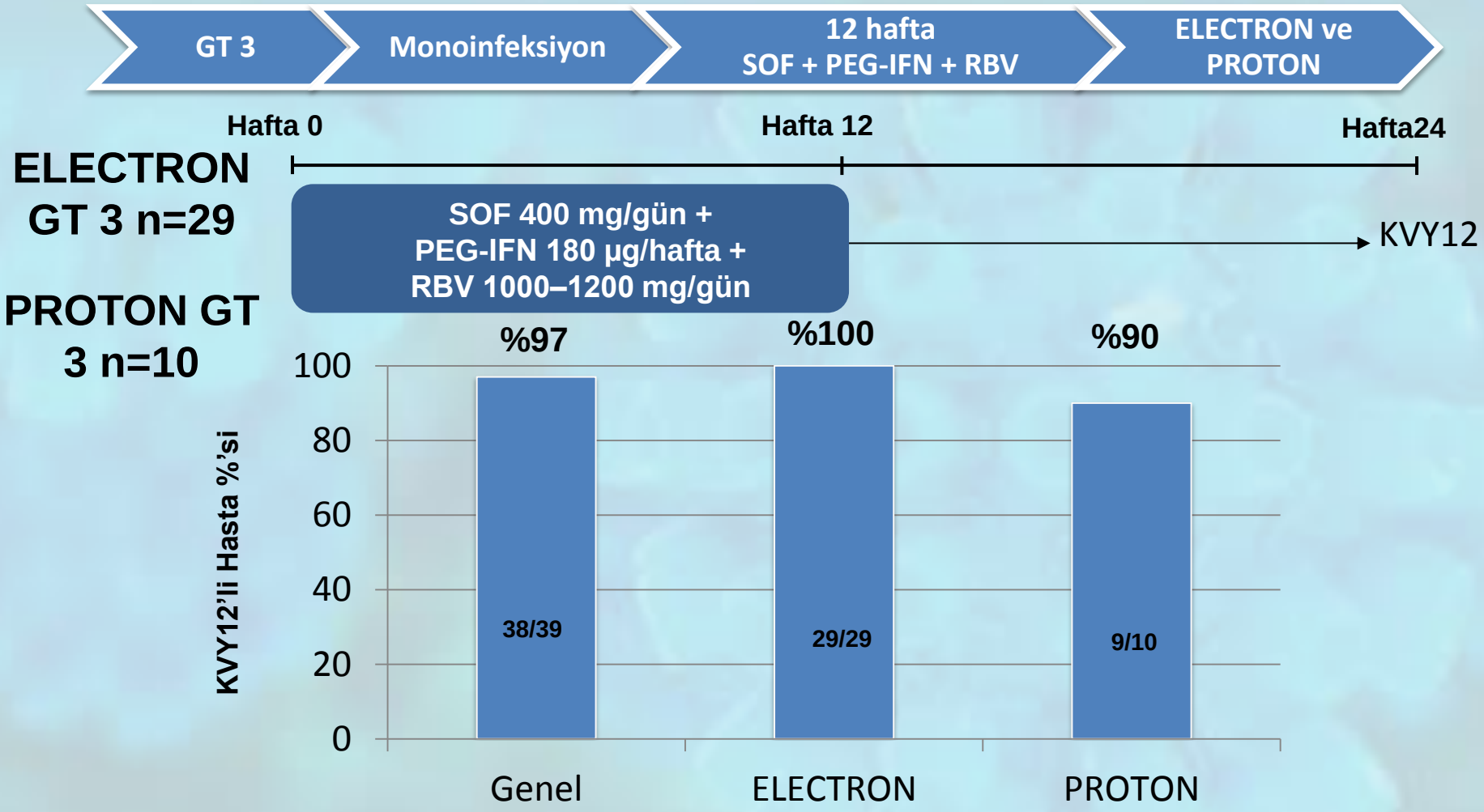
2. PEG-IFN, RBV veya doğrudan etkili anti-viral monoterapi

Klas III, Düzey A

3. Telaprevir, boceprevir veya simeprevir bazlı rejimler

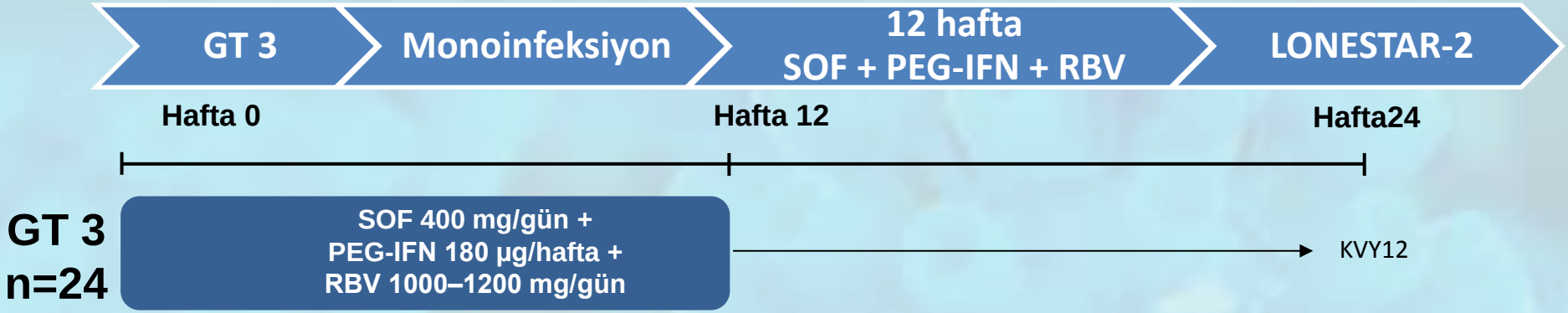
Klas III, Düzey A

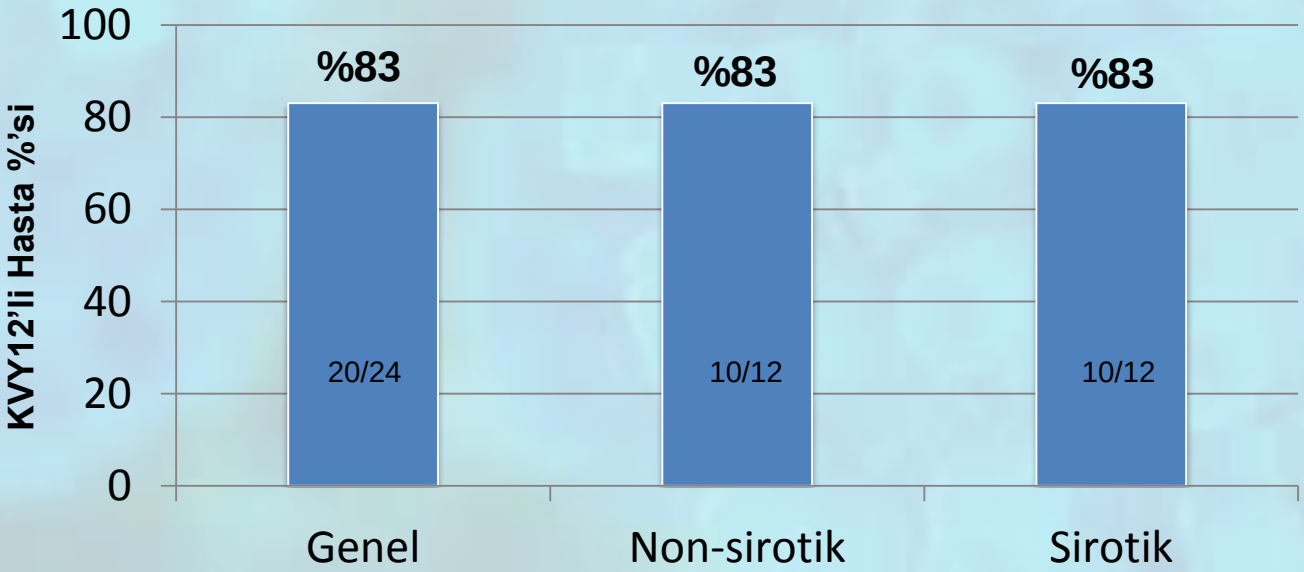
ELECTRON ve PROTON
GT 3 Tedavi Naiv: 12 Hafta SOF + PEG-IFN + RBV



Gane E, et al. N Engl J Med 2013;368:34–44; .

LONESTAR-2
GT 3 Tedavi Almış: SOF + PEG-IFN + RBV x 12 Hafta



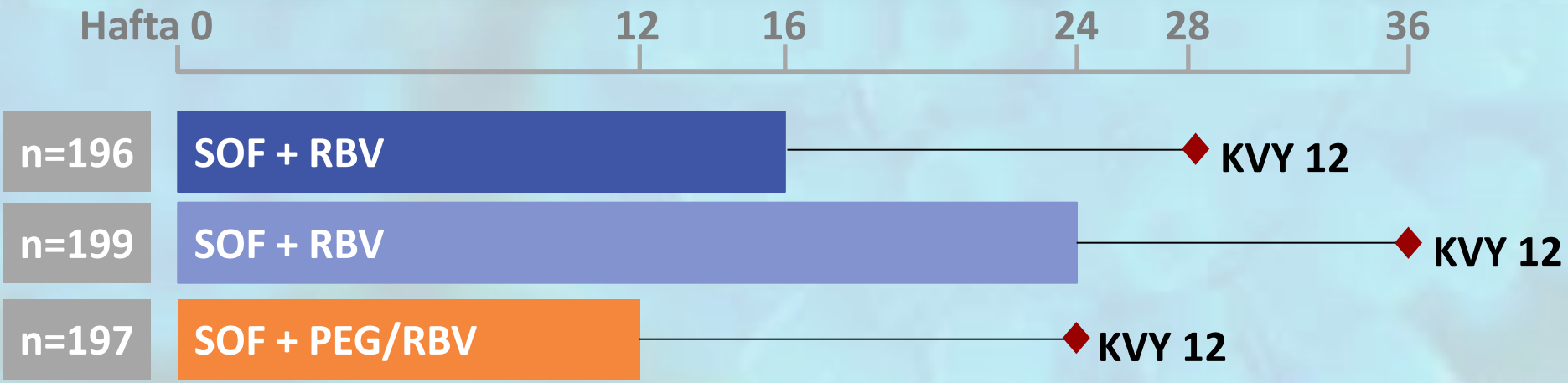


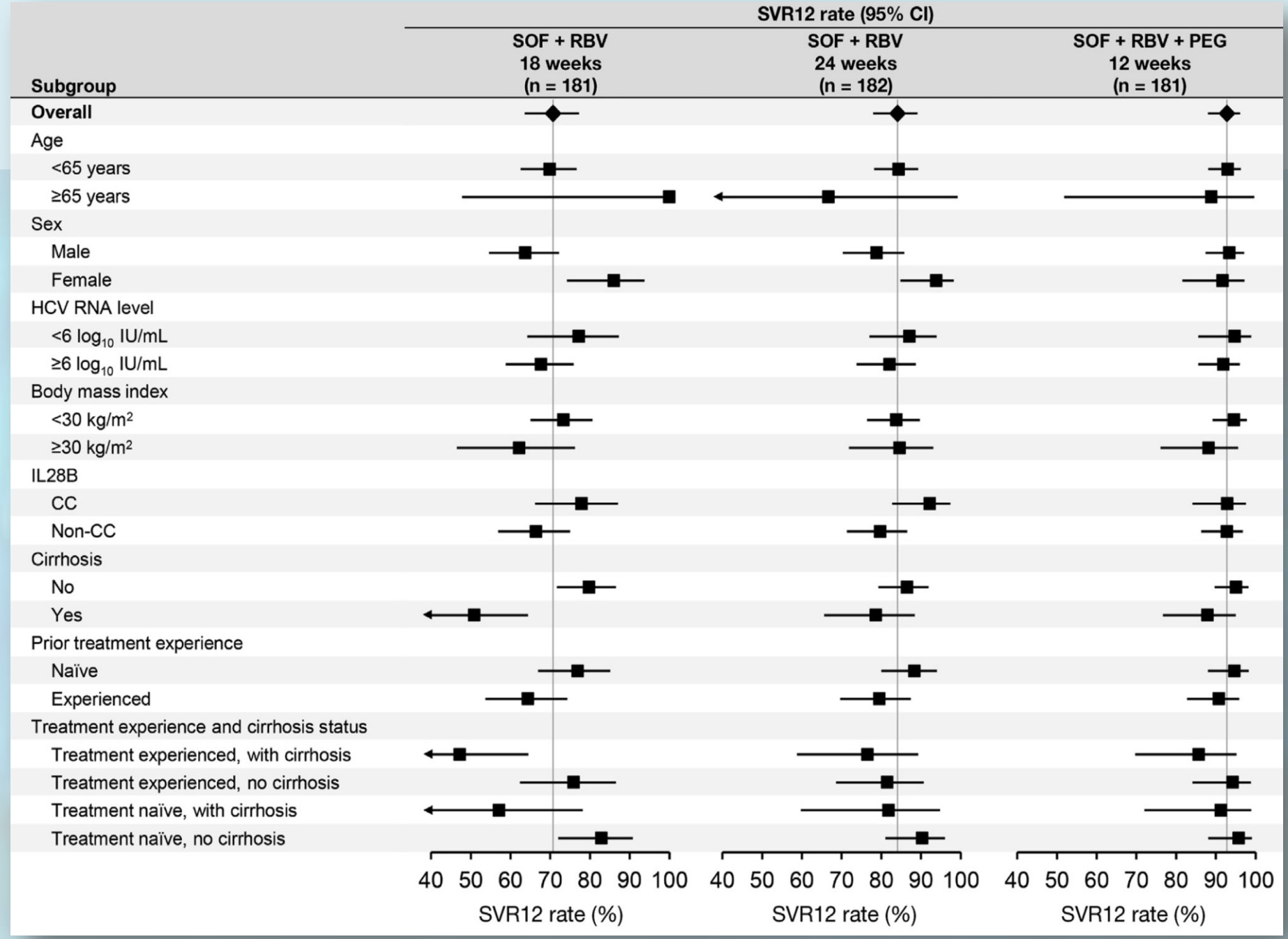
Lawitz E, et al. AASLD 2013. Washington, DC. Oral #LB-4;.

Gastroenterology 2015;149:1462–1470

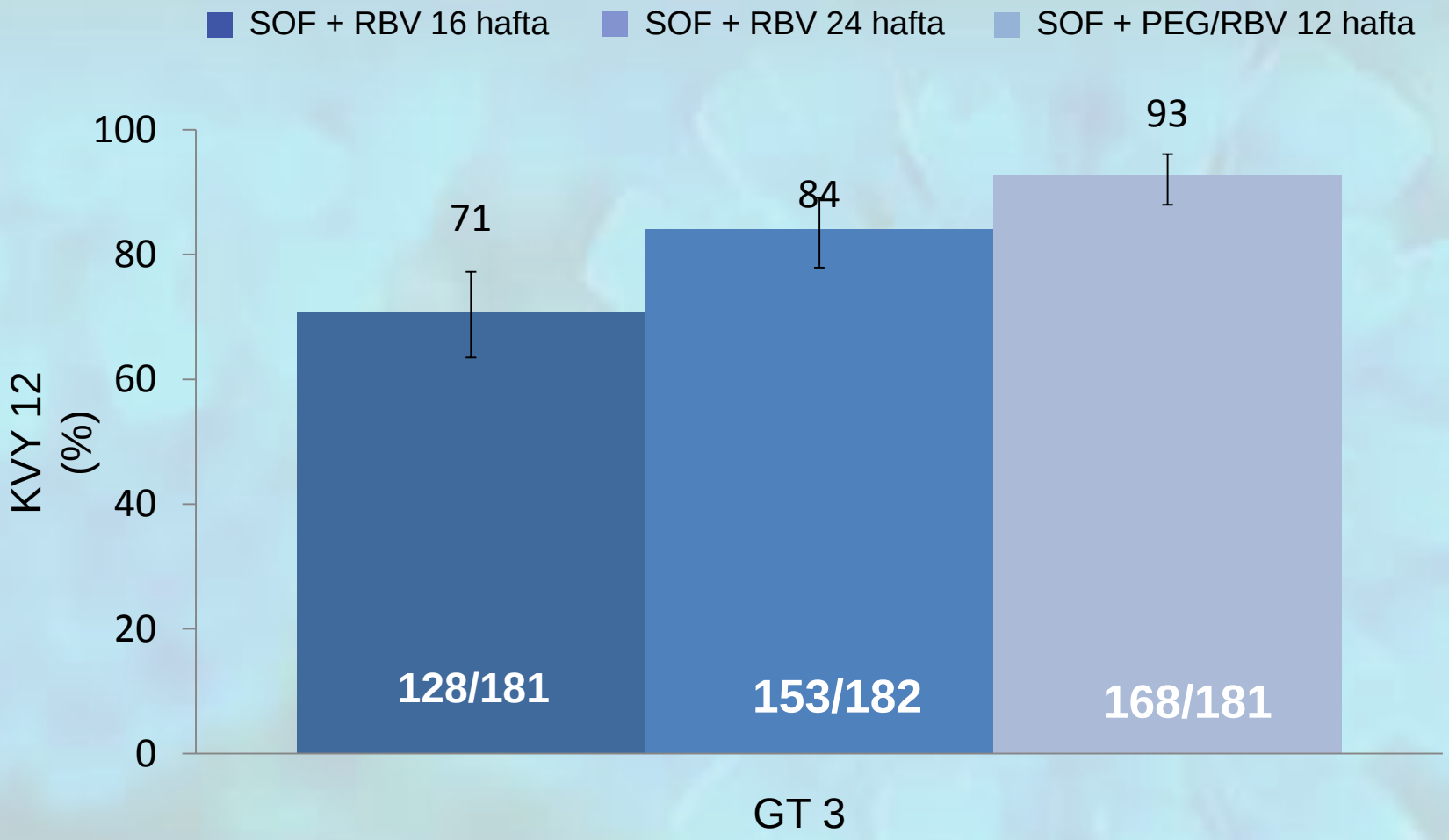
Efficacy of Sofosbuvir Plus Ribavirin With or Without Peginterferon-Alfa in Patients With Hepatitis C Virus Genotype 3 Infection and Treatment-Experienced Patients With Cirrhosis and Hepatitis C Virus Genotype 2 Infection

Graham R. Foster,[1] Stephen Pianko,[2] Ashley Brown,[3] Daniel Forton,[4] Ronald G. Nahass,[5] Jacob George,[6] Eleanor Barnes,[7] Diana M. Brainard,[8] Benedetta Massetto,[8] Ming Lin,[8] Bin Han,[8] John G. McHutchison,[8] G. Mani Subramanian,[8] Curtis Cooper,[9] and Kosh Agarwal,[10] the BOSON Study Group

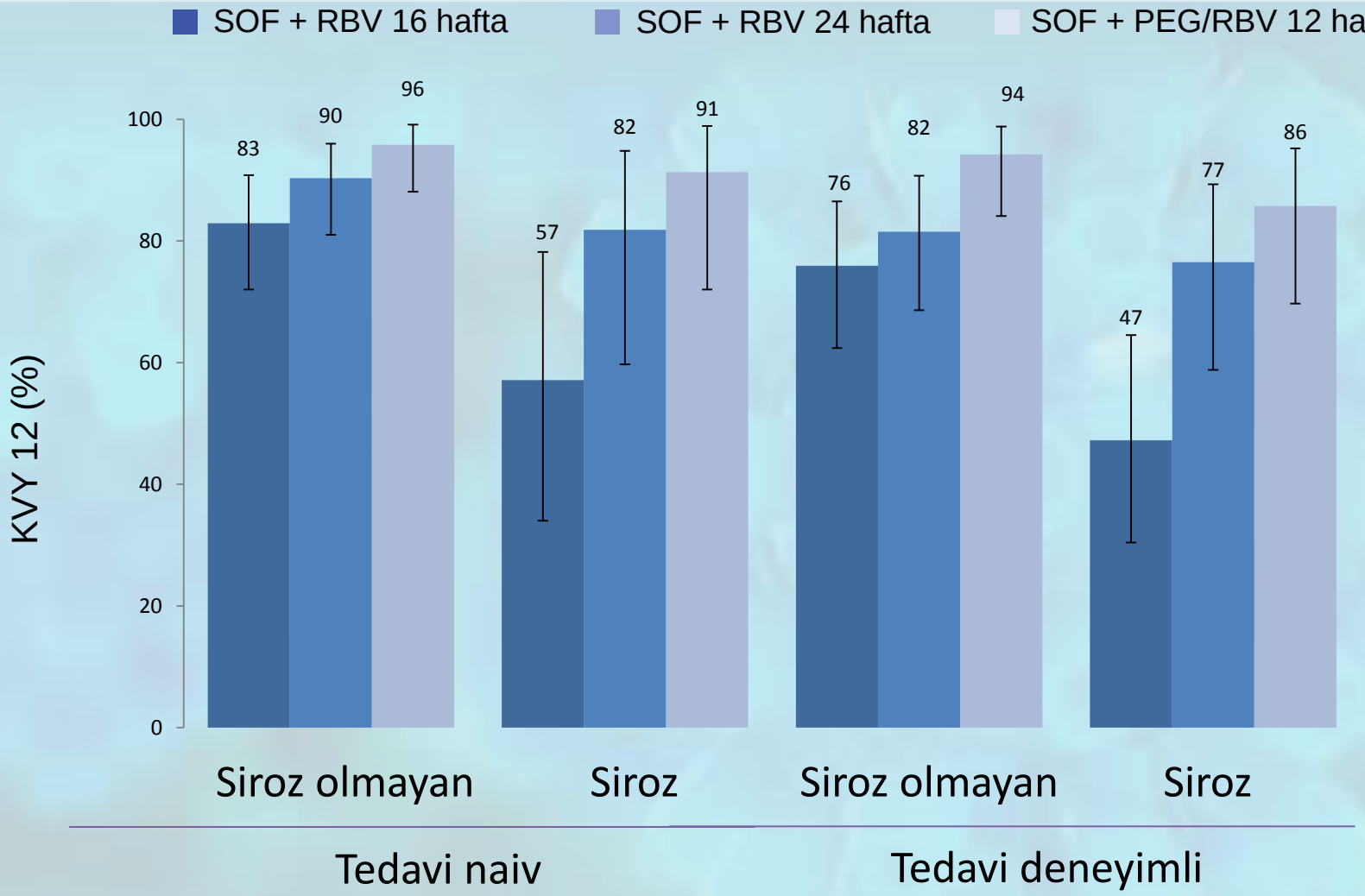



SVR12 rate (95% CI)
Subgroup
SOF + RBV 18 weeks (n = 181)
SOF + RBV 24 weeks (n = 182)
SOF + RBV + PEG 12 weeks (n = 181)
Overall
Age
<65 years
≥65 years
Sex
Male
Female
HCV RNA level
<6 log10 IU/mL
≥6 log10 IU/mL
Body mass index
<30 kg/m2
≥30 kg/m2
IL28B
CC
Non-CC
Cirrhosis
No
Yes
Prior treatment experience
Naïve
Experienced
Treatment experience and cirrhosis status
Treatment experienced, with cirrhosis
Treatment experienced, no cirrhosis
Treatment naïve, with cirrhosis
Treatment naïve, no cirrhosis
40 50 60 70 80 90 100
SVR12 rate (%)
40 50 60 70 80 90 100
SVR12 rate (%)
40 50 60 70 80 90 100
SVR12 rate (%)

KVY12 GT 3


SOF + RBV 16 hafta
SOF + RBV 24 hafta
SOF + PEG/RBV 12 hafta
KVY 12 (%)
100
80
60
40
20
0
71
84
93
128/181
153/182
168/181
GT 3

KVY 12 GT 3; problem devam ediyor!!!



Nedenler?

- **Kc yağlanması ve etkileyen diğer riskler (yüksek yağlı diyet, kronik alkol tüketimi, dislipidemi, obezite, kronik ilaç tüketimi, diyabet, insülin direnci), alkolik ve non-alkolik steatoz**
  - **HCV GT-3a; GT-1 ve 2'ye göre daha yüksek steatoz**
  - **HCV GT-3 spesifik sitopatik etki**

Liver INTERNATIONAL
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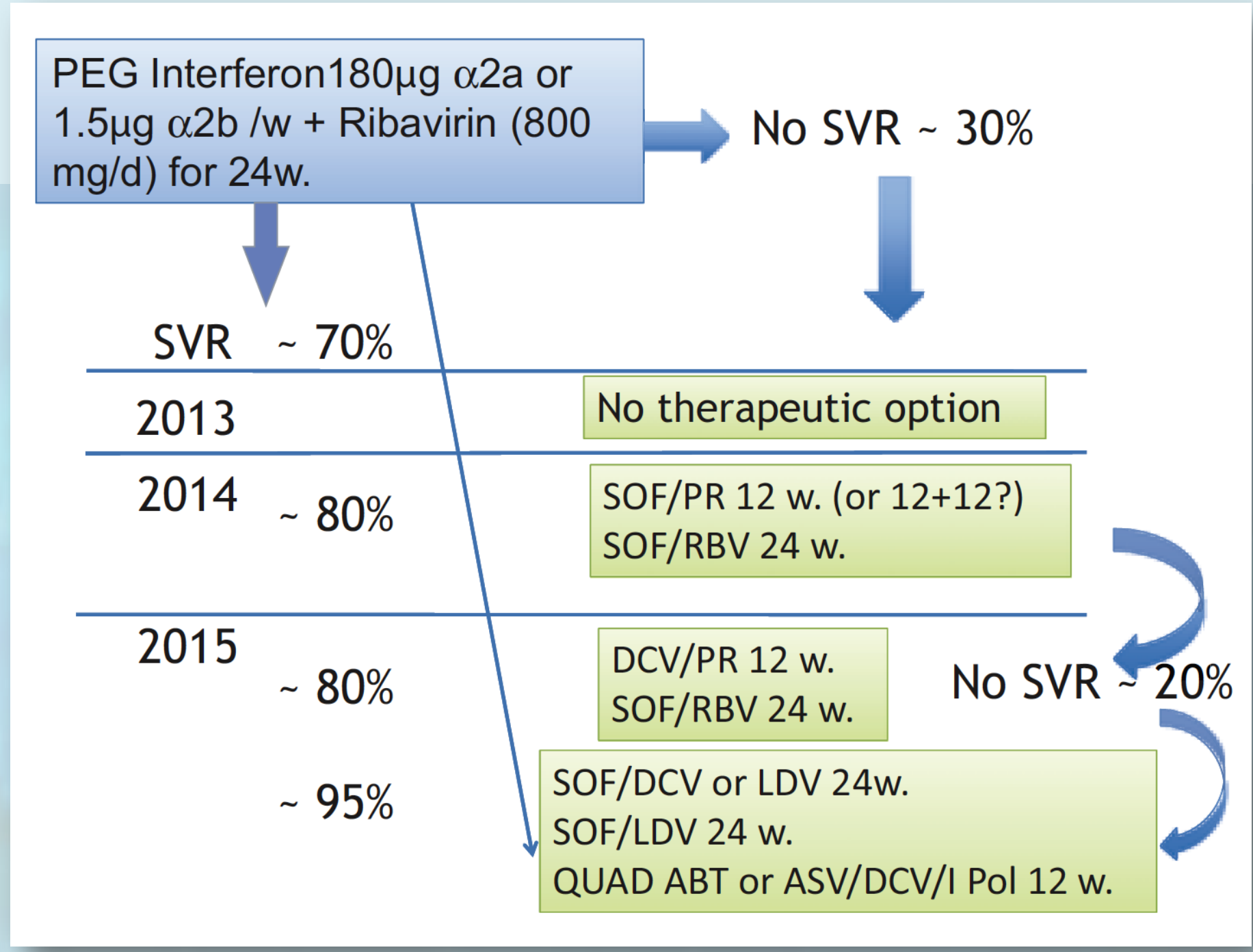
Liver International ISSN 1478-3223

REVIEW ARTICLE

Treatment of hepatitis C virus genotype 3-infection

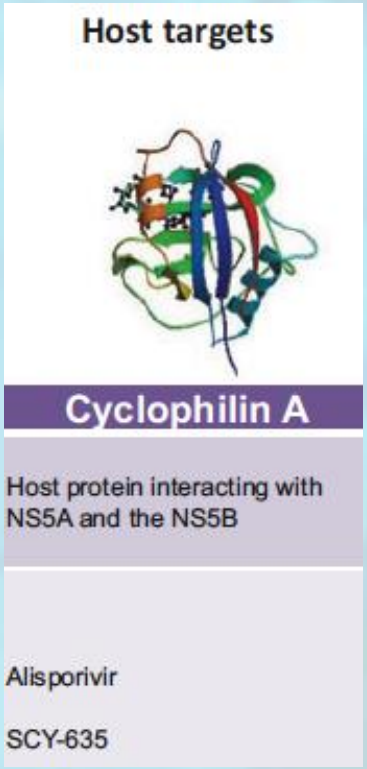
Stanislas Pol, Anaïs Vallet-Pichard and Marion Corouge

- **İlk jenerasyon NS3 / NS4A proteaz inhibitörleri genotip 3'e etkinliği zayıf**
- **İkinci jenerasyon NS3 / NS4A proteaz inhibitörleri PEG-IFN ile birlikte kullanımı genotip 3'e sınırlı etkiye sahip**
  - **Pangenotipik aktiviteye sahip Simeprevirin genotip 3 karşı etkinliği düşük**


PEG Interferon180µg α2a or 1.5µg α2b /w + Ribavirin (800 mg/d) for 24w.
No SVR ~ 30%
SVR ~ 70%
2013
No therapeutic option
2014
~ 80%
SOF/PR 12 w. (or 12+12?)
SOF/RBV 24 w.
2015
~ 80%
DCV/PR 12 w.
SOF/RBV 24 w.
No SVR ~ 20%
~ 95%
SOF/DCV or LDV 24w.
SOF/LDV 24 w.
QUAD ABT or ASV/DCV/I Pol 12 w.

VITAL-1

- Faz IIb; naiv genotip 2 ve 3-hasta siklofilin inhibitörü Alisporivir (600 -1000 mg / gün)
- Alisporivir ±RBV kolunda; %81-83
- Alisporivir+PEG-IFN; % 77
- RBV+PEG IFN; % 58



GT 2 ve 3 eredikasyonu

- **GT 2;**
  - **SOF+ Velpatasvir kombinasyonu**
  - **SOF+DCV kombinasyonu**
- **GT 3;**
  - **Eşlik eden problemlerin tedavisi**
  - **SOF+DCV (12-16 hafta) SOF+ağırlığa göre hesaplanmış RBV + PEG-IFN (24 hafta)**
  - **Yeni tedaviler.....**

Umarım uyandırabilmişimdir