Kronik Hepatit C'li Genotip 1-4 Olgularda Tedavi

Sofosbuvir + Ribavirin + Peg-IFN
ve
Sofosbuvir + Ledipasvir

Kombinasyon Tedavileri

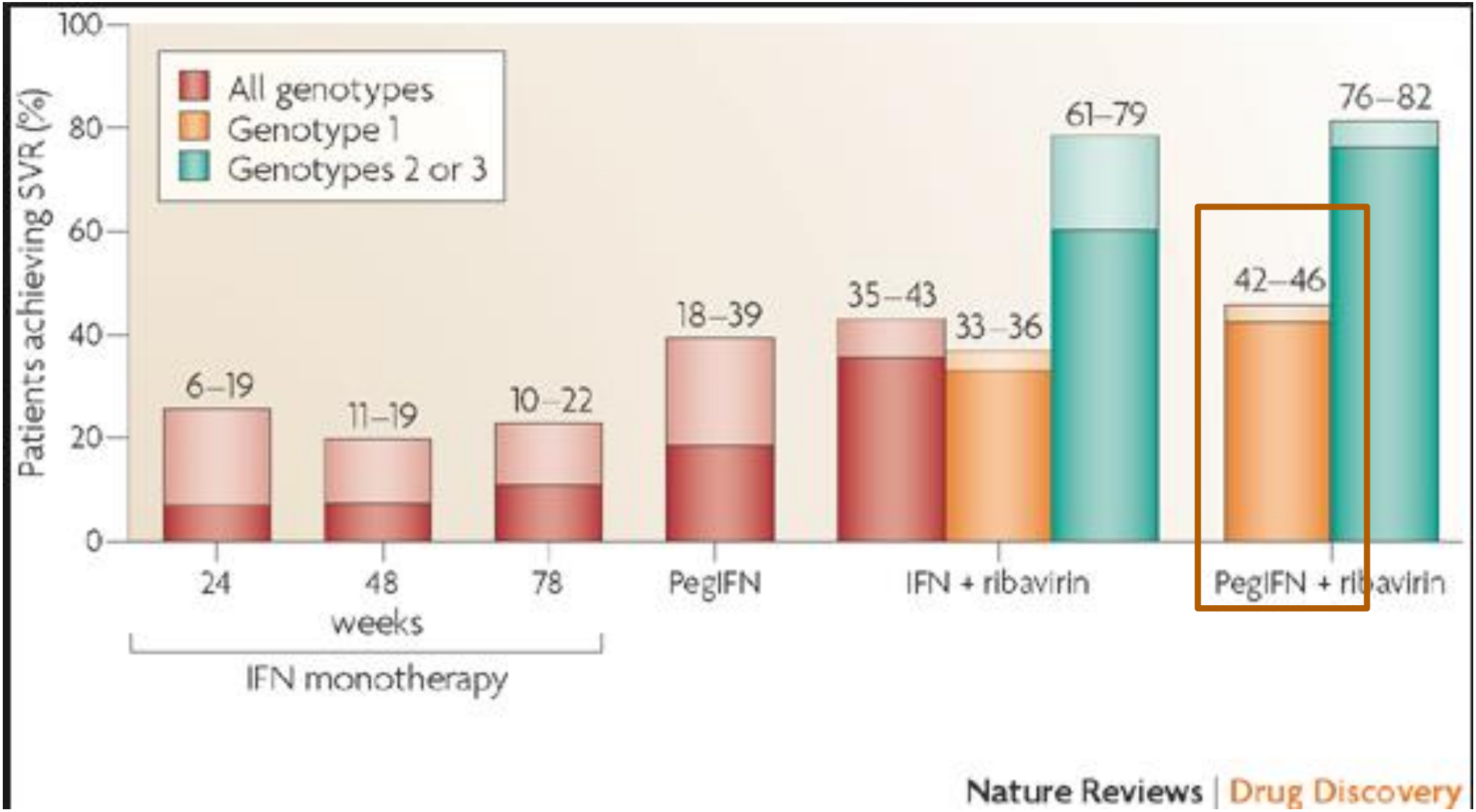
Doç Dr Aysel Kocagül Çelikbaş
Ankara Numune Eğitim ve Araştırma Hastanesi
Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji
Aralık 2015

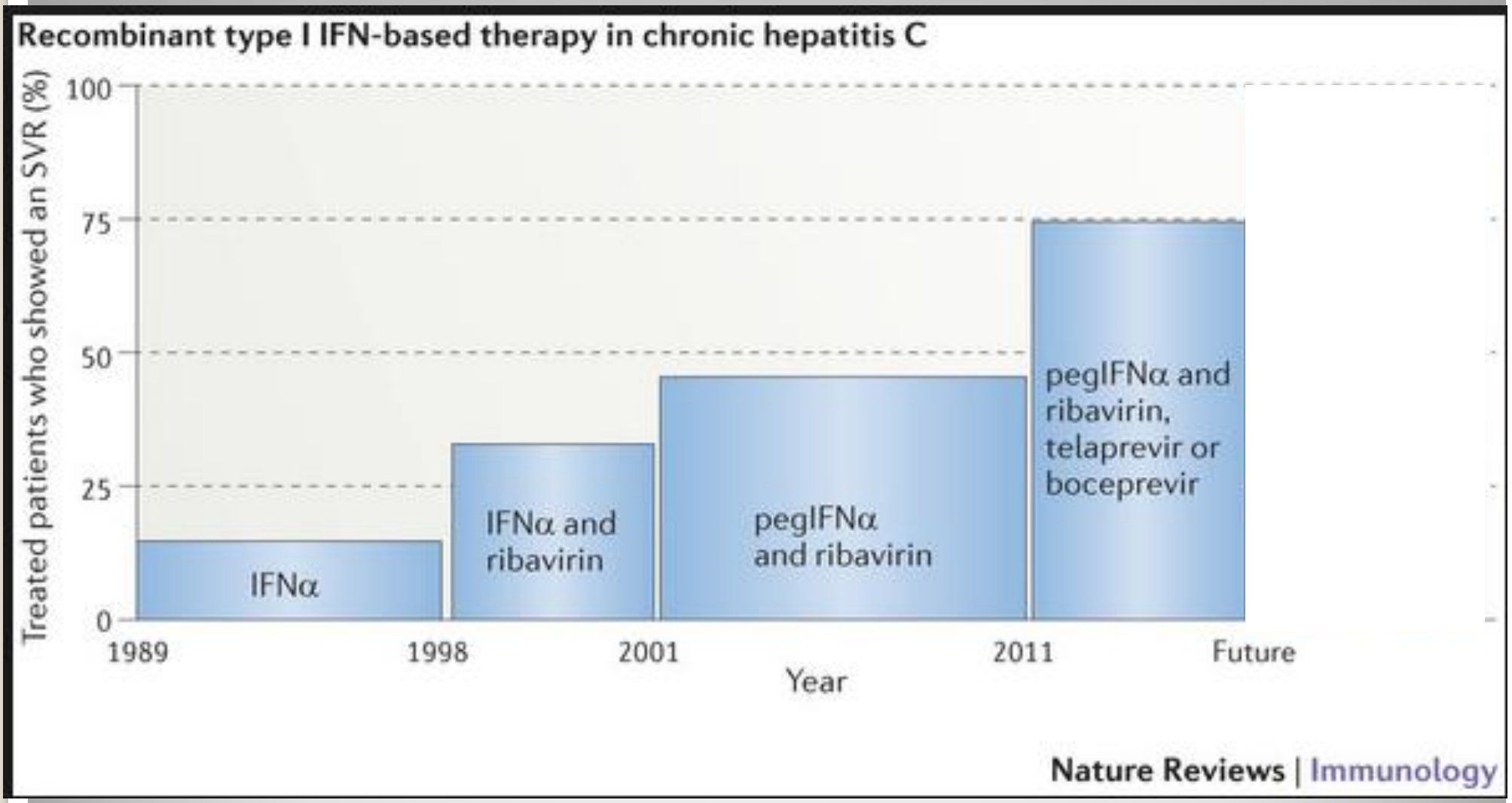
Hepatit C Tedavisi

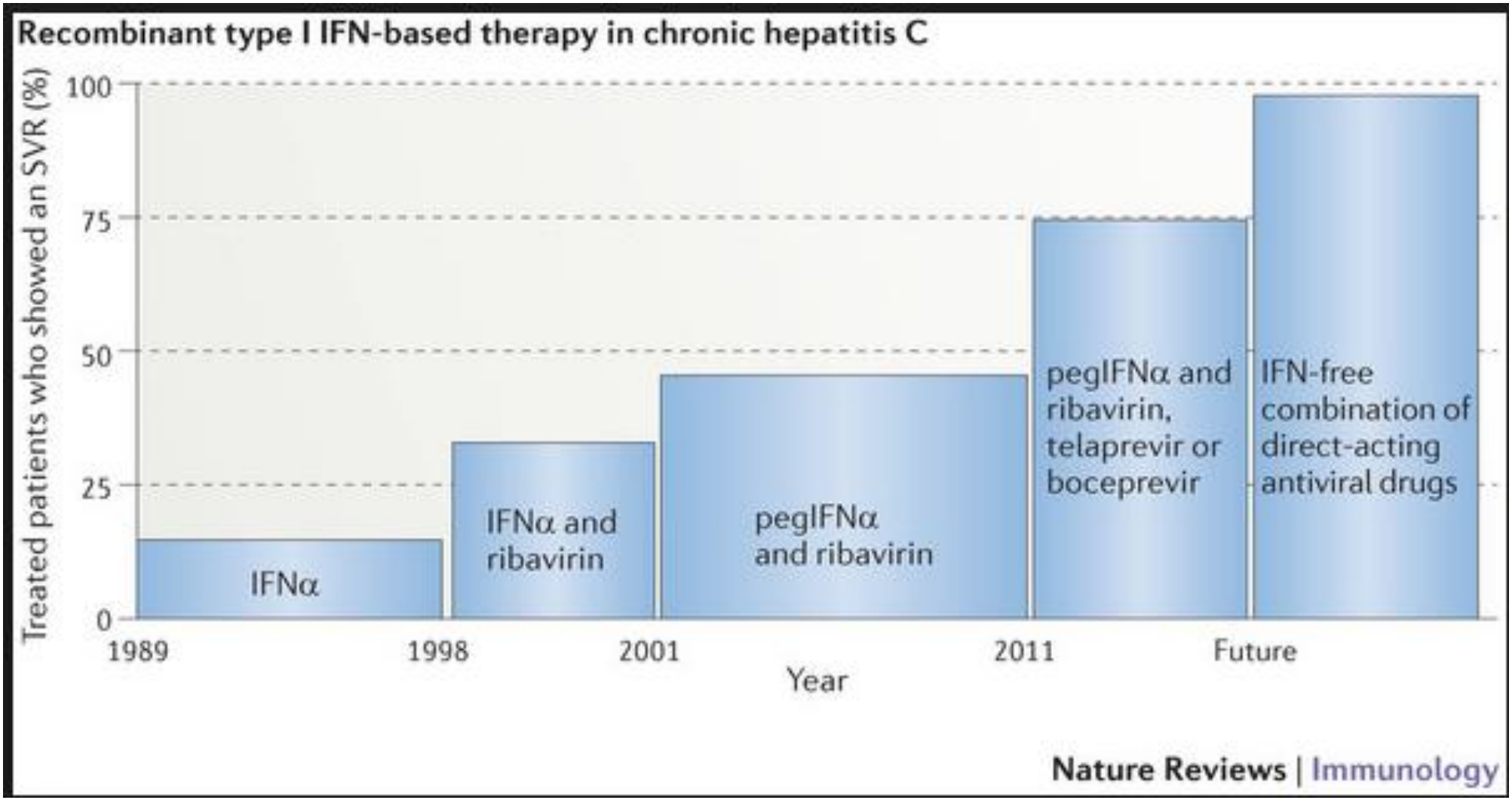
PegİNF + Ribavirin (2001)

PegİNF+ Ribavirin + PI (2011)

Depresyon, anemi, trombositopeni, döküntü, anal semptomlar


Patients achieving SVR (%)
100
80
60
40
20
0
All genotypes
Genotype 1
Genotypes 2 or 3
6–19
11–19
10–22
18–39
35–43
33–36
61–79
42–46
76–82
24
48
78
weeks
IFN monotherapy
PegIFN
IFN + ribavirin
PegIFN + ribavirin
Nature Reviews | Drug Discovery

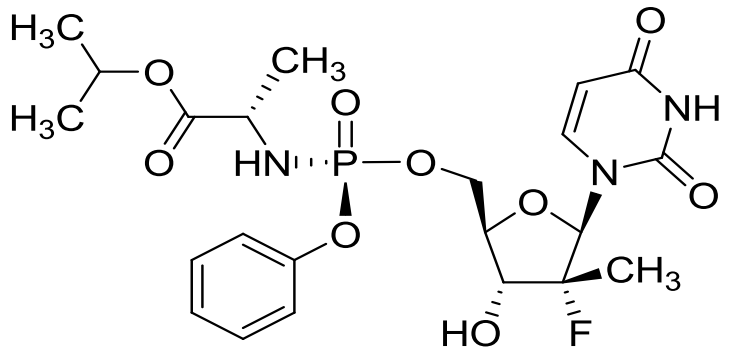

Recombinant type I IFN-based therapy in chronic hepatitis C
Treated patients who showed an SVR (%)
100
75
50
25
0
IFNα
IFNα and ribavirin
pegIFNα and ribavirin
pegIFNα and ribavirin, telaprevir or boceprevir
1989
1998
2001
2011
Future
Year
Nature Reviews | Immunology


Recombinant type I IFN-based therapy in chronic hepatitis C
Treated patients who showed an SVR (%)
100
75
50
25
0
IFNα
IFNα and ribavirin
pegIFNα and ribavirin
pegIFNα and ribavirin, telaprevir or boceprevir
IFN-free combination of direct-acting antiviral drugs
1989
1998
2001
2011
Future
Year
Nature Reviews | Immunology


2015 Eldeki ajanlar
Sofosbuvir + ribavirin ± pegIFN
Ledipasvir/ sofosbuvir
Ombitasvir/ paritaprevir/ ritonavir + dasabuvir
Simeprevir + sofosbuvir
Sofosbuvir + daclatasvir

Sofosbuvir (SOF, GS-7977)

- HCV-spesifik üridin nükleotid **NS5B polimeraz inhibitörü** (zincir sonlandırıcı)
- **Günde tek doz, oral, gıda ile alınan 400 mg tablet**
- HCV genotip 1-6' ya karşı
  güçlü antiviral aktivite
- **Uygun klinik farmakoloji profili**
  - Renal yolla klirens
  - Hepatik CYP450 metabolizması yok
  - İlaç etkileşimleri sınırlı



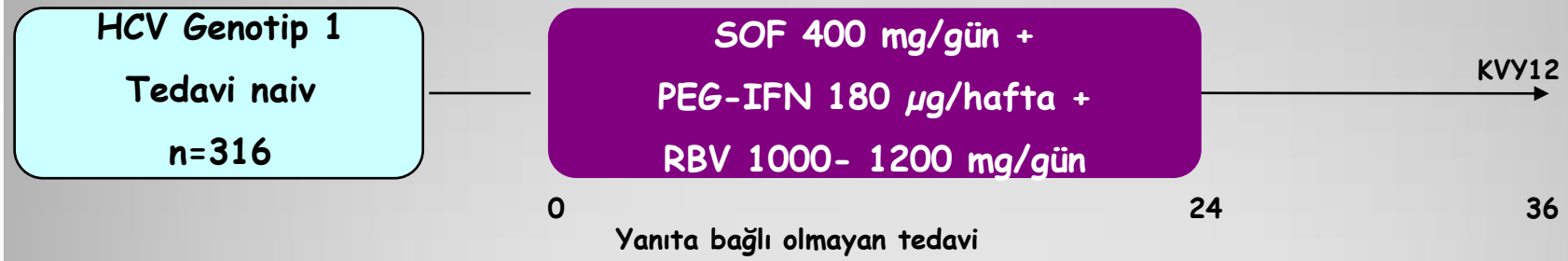
Onaya Dayanak Olan Çalışmalar

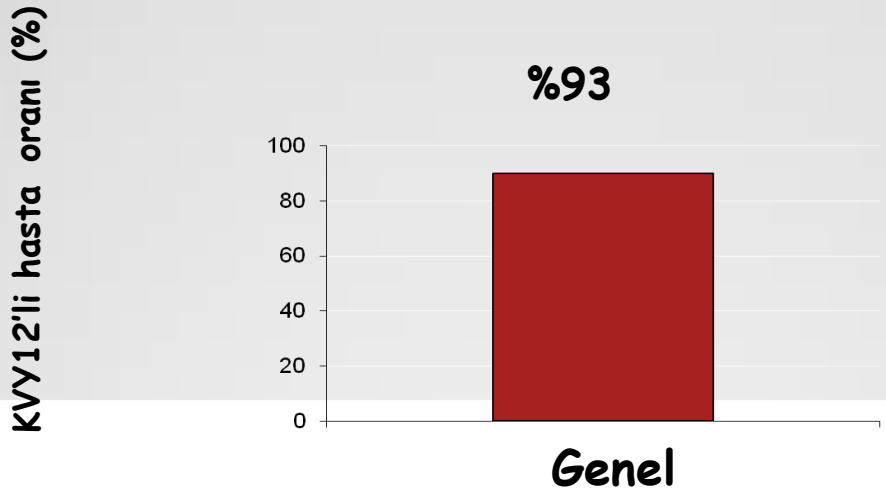
ATOMIC Genotip 1 Tedavi Naiv:

SOF + PegIFN + RBV - 24 Hafta

- Açık etiketli, randomize, çok merkezli **faz 2 etkinlik ve güvenilirlik çalışması**

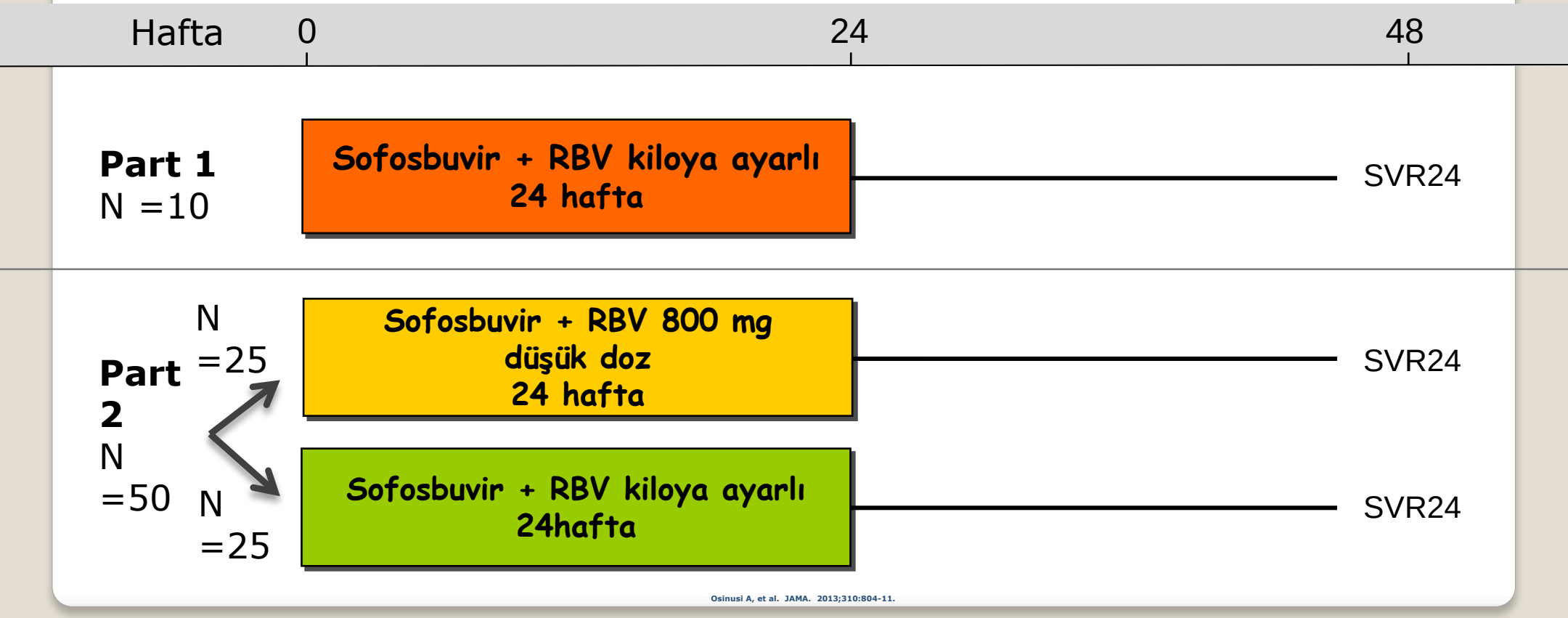
  Tedavi naiv HCV genotip-1, 316 hasta





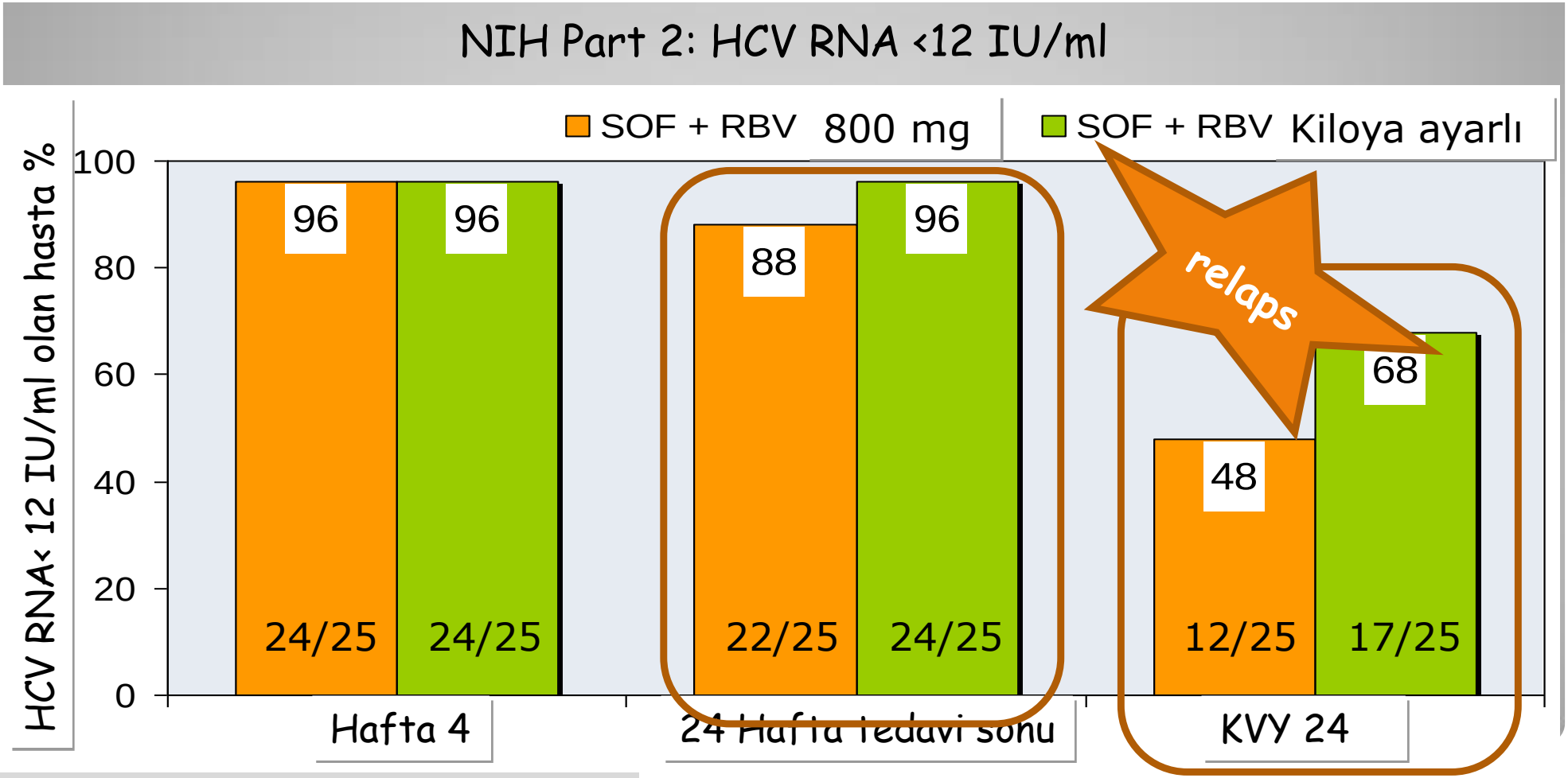
NIH SPARE çalışması: Tedavi-Naiv HCV Genotip 1olgularda Sofosbuvir ve Ribavirin (faz 2)

N=60 HCV monoenfekte hasta
Genotip 1A- 1B
Primer sonlanım noktası KVY 24
Etkinlik güvenlik çalışması



Osinusi A, et al. JAMA. 2013;310:804-11.

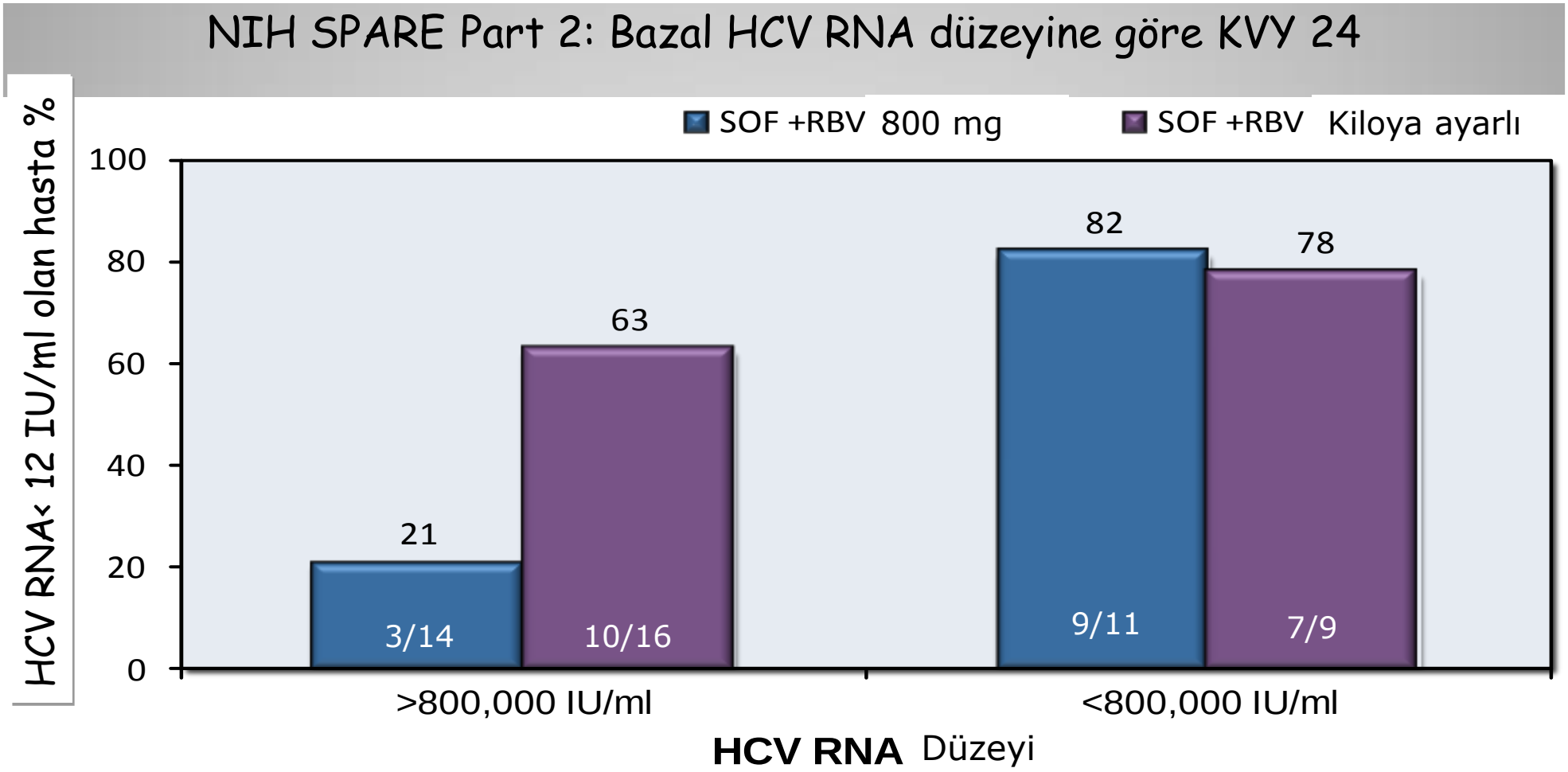
NIH SPARE:Tedavi-Naiv HCV Genotip 1 Sofosbuvir ve Ribavirin - 24 hafta



SOF = Sofosbuvir; RBV = Ribavirin

Osinusi A, et al. JAMA. 2013;310:804-11

NIH SPARE: Tedavi-Naiv HCV Genotip 1 Sofosbuvir ve Ribavirin 24 hafta



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Efficacy of Sofosbuvir and Ribavirin for treatment of Hepatitis C Genotype-1 in an Inner City Population: *Virus and Host Factors that Predict Relapse*:

A Randomized Controlled Trial

Anuoluwapo Osinusi, M.D., M.P.H.[1,2], Eric G. I tra
Bon, M.S.[3], Laura Heytens, R.N.[4], Amy Nelson li,
M.D.[1], L Barrett, M.D., Ph.D.[1], Michael Prosch na
Shivakumar, M.S.[1], Wenjuan Gu, Ph.D.[6], Richa it
Talwani, M.D.[8], Rachel Silk, R.N.[2], Colleen Kot bein,
M.D.[9], Robin Dewar, Ph.D.[6], Helene Highbarger, M.S.[6], Xiao Zhang[1], David Kleiner, M.D.[10],
Brad J. Wood, M.D.[11], Jose Chavez, M.D.[7], William Symonds, Pharm.D.[12], Mani
Subramanian, M.D.[12], John McHutchison, M.D.[12], Michael A. Polis, M.D., M.P.H.[1], Anthony
S. Fauci, M.D.[1], Henry Masur, M.D.[4], and Shyamasundaran Kottilil, M.D., Ph.D.[1]

Başlangıç viral yükü,
Erkek cinsiyet,
Vücut kitle indeksi

Re-treatment of Chronic Hepatitis C Virus Genotype 1 Infection After Relapse: An Open-Label Pilot Study

Anu Osinusi, MD; Anita Kohli, MD; Miriam M. Marti, BS; Amy Nelson, RN; Xiaozhen Zhang, MS; Eric G. Meissner, MD, PhD; Rachel Silk, RN; Kerry Townsend, BA; Phillip S. Pang, MD, PhD; G. Mani Subramanian, MD, PhD; John G. McHutchison, MD; Anthony S. Fauci, MD; Henry Masur, MD; and Shyam Kottilil, MD, PhD

[+] Article, Author, and Disclosure Information

Ann Intern Med. 2014;161(9):634-638. doi:10.7326/M14-1211

Background: The interferon (IFN)–free regimen of sofosbuvir and ribavirin for 24 weeks was recently approved to treat chronic hepatitis C virus (HCV) genotype 1 (GT-1) infection for patients ineligible for IFN. However, sofosbuvir plus ribavirin therapy is associated with relapse in 15% to 30% of patients with HCV GT-1. Neither the mechanism of relapse nor the optimal re-treatment strategy for these patients is defined.

Objective: To assess the safety and efficacy of sofosbuvir plus ledipasvir in patients with chronic HCV GT-1 that relapsed after sofosbuvir plus ribavirin therapy.

Design: Phase 2a, open-label study. (ClinicalTrials.gov: NCT01805882)

Setting: Single U.S site.

Patients: 14 patients with HCV GT-1 that relapsed after treatment with sofosbuvir plus ribavirin for 24 weeks were re-treated with sofosbuvir plus ledipasvir for 12 weeks.

Measurements: HCV RNA concentration and population sequencing to detect NS5B S282T mutations.

Results: All 14 patients treated with sofosbuvir plus ledipasvir for 12 weeks achieved a sustained virologic response, including 7 with advanced liver disease (Knodell Histology Activity Index score of 3 or 4) and 1 with a detectable NS5B S282T mutation after sofosbuvir plus ribavirin therapy. Sofosbuvir plus ledipasvir was well-tolerated with few adverse events. Four grade 3 events (elevated serum creatinine in a patient with baseline renal insufficiency, hypercholesterolemia, and hypophosphatemia) occurred. There were no grade 4 events or treatment discontinuations.

Limitation: Small sample size.

Conclusion: The fixed-dose combination of sofosbuvir plus ledipasvir was efficacious in a small cohort of patients with HCV GT-1 that relapsed after sofosbuvir plus ribavirin therapy, even in the setting of advanced liver disease. Larger studies are needed to confirm these preliminary efficacy results.

Primary Funding Source: National Institute of Allergy and Infectious Diseases, National Institutes of

NEUTRINO (Study 110)
Tedavi naiv Genotip 1,4,5 veya 6 Kronik HCV
SOF + PegIFN + RBV - 12 Hafta

- Açık etiketli, Faz 3, **güvenlik ve etkinlik** değerlendirilmesi
- **Tedavi naiv genotip 1, 4, 5(n=1) veya 6 (n=6)** kronik HCV,

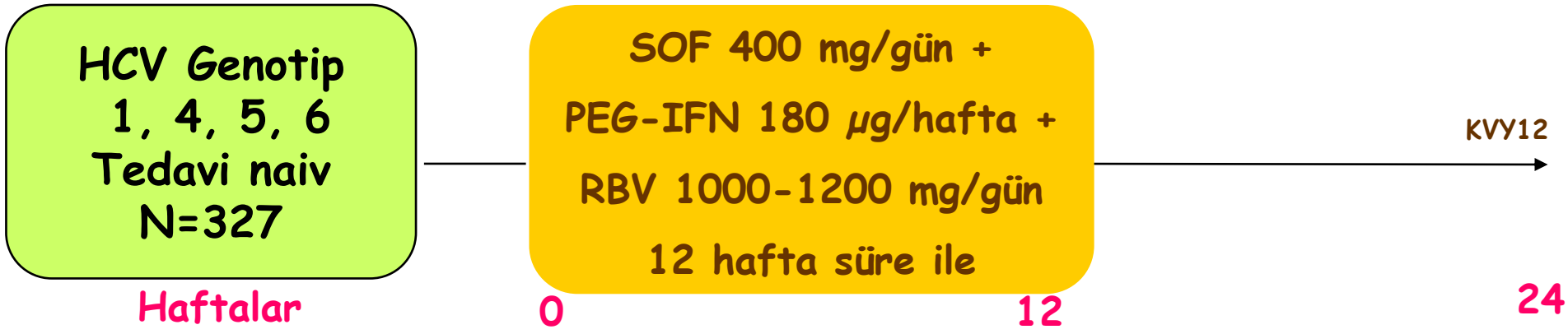
  Hastaların %20'sinin sirozlu

  - Trombosit >90.000/mm^3,
  - Nötrofilleri ≥ 1500/mm^3 ya da ≥ 1000/mm^3 (siyah) olan hastalar
- **Sofosbuvir + Peg IFN 2a + Ribavirin- 12 hafta**
- Tarihsel kontrol: geçmişte Peg IFN 2a + Ribavirin kullanmış hastalar

  FDA geçmiş tedavilere yanıt oranını %60 olarak belirledi

Lawitz et al., *N Engl J Med* 2013, 368: 1878-1887.

NEUTRINO (Study 110)
Tedavi naiv Genotip 1,4,5 veya 6 Kronik HCV
SOF + PegIFN + RBV 12 Hafta



Yanıta bağlı olmayan tedavi

- Primer sonlanma noktası: **KVY 12**

Lawitz E, et al. N Engl J Med. 2013;368(20):1878-87.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

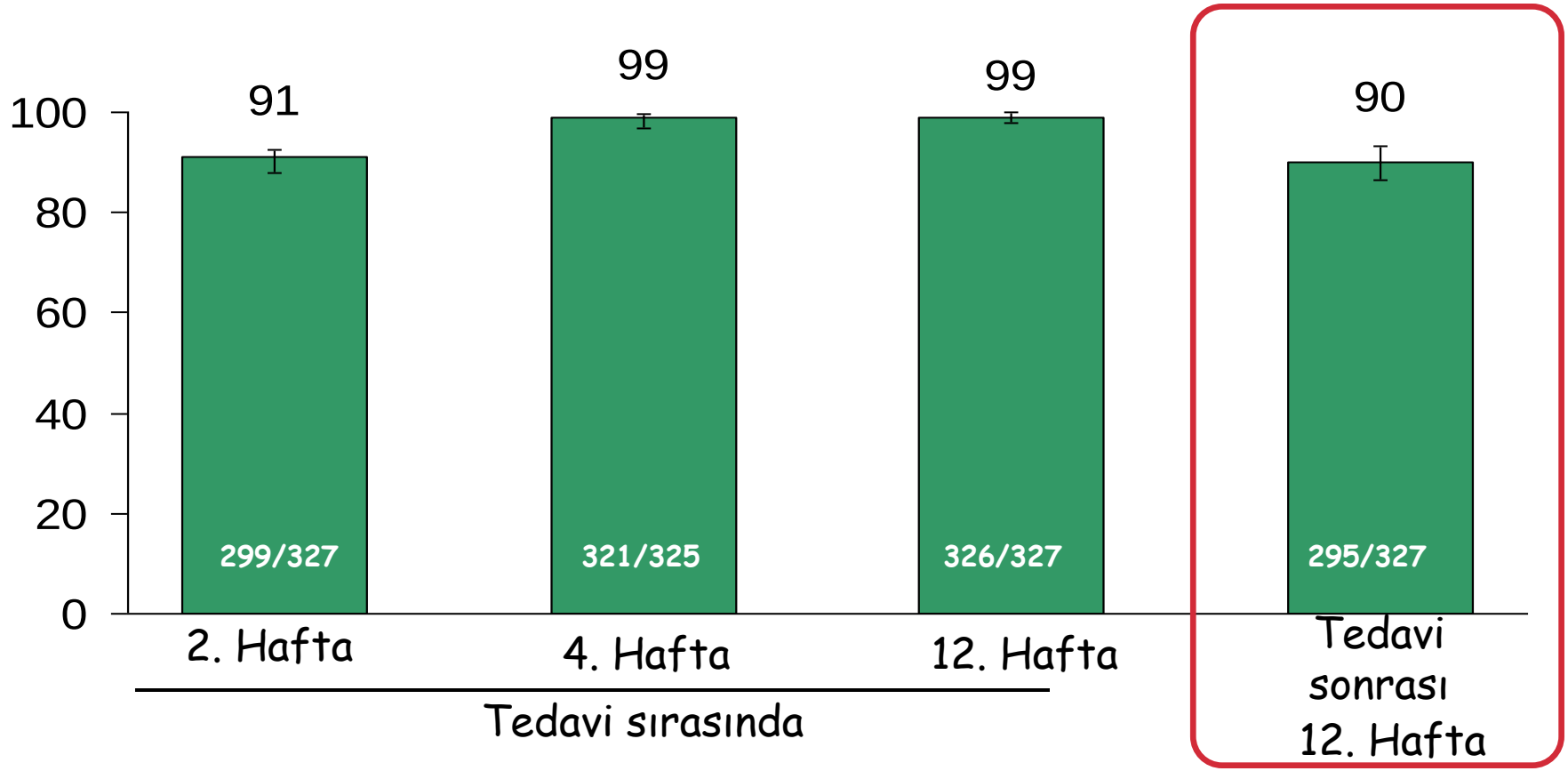
Sofosbuvir for Previously Untreated Chronic Hepatitis C Infection

Table 2. Response during and after Treatment Period.

Response	NEUTRINO Study SOF+PEG+RBV for 12 Wk (N = 327)
HCV RNA <25 IU/ml — no./total no. (%)	
During treatment	
At 2 wk	299/327 (91)
At 4 wk	321/325 (99)
At last observed measurement	326/327 (>99)
After end of treatment	
At 4 wk	302/327 (92)
At 12 wk	295/327 (90)
Virologic breakthrough during treatment — no. (%)	0
Relapse in patients with HCV RNA <25 IU/ml at end of treatment — no./total no. (%)	

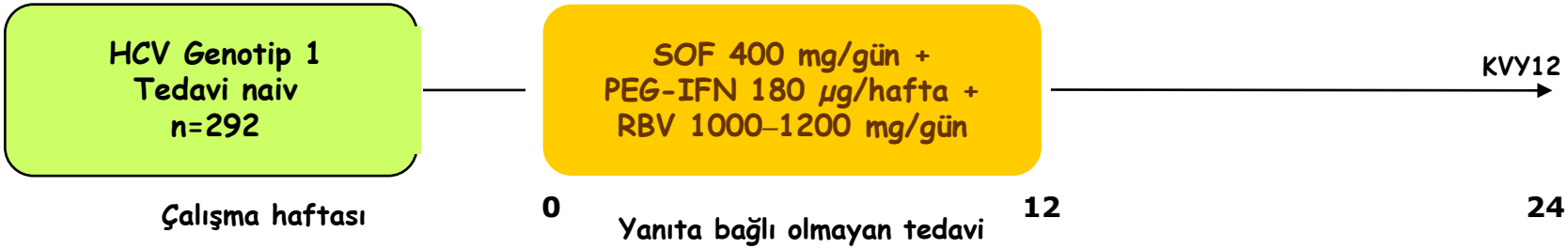
Lawitz et al., *N Engl J Med* 2013, 368: 1878-1887.

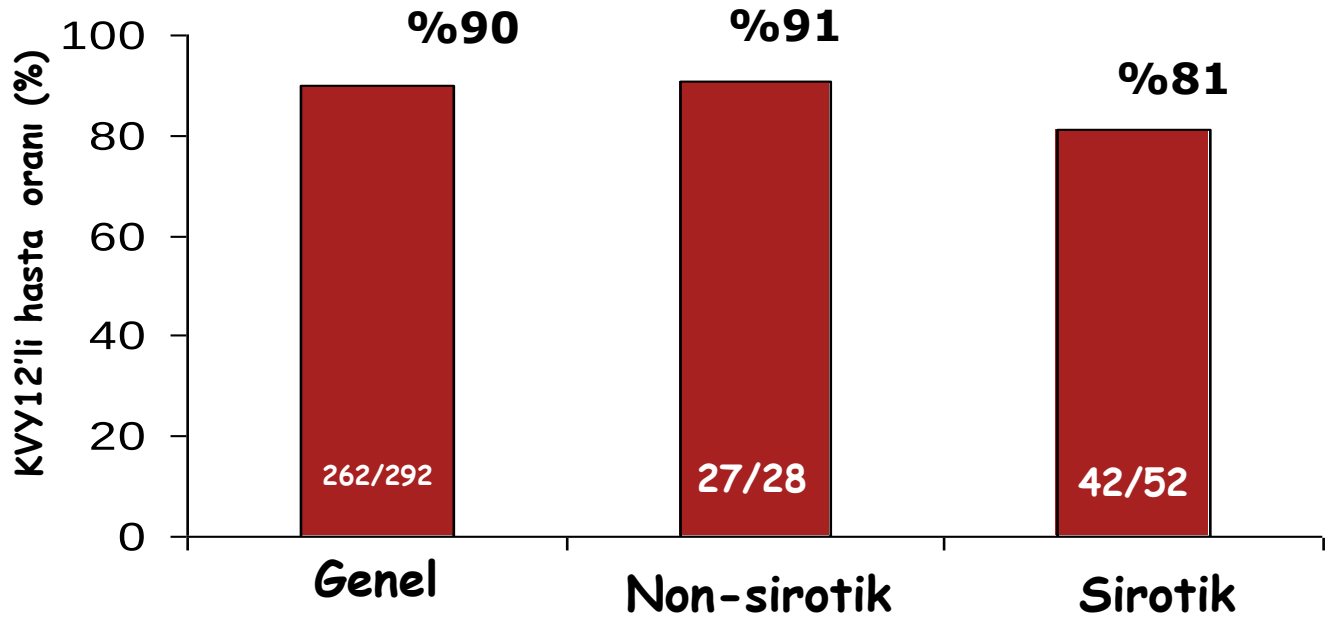
Olguların > % 90 tedavi sonrası 12. haftada KVY



Lawitz et al., *N Engl J Med* 2013, 368: 1878-1887.

NEUTRINO (Study 110)
Tedavi naiv Genotip1 SOF + PEG-IFN + RBV x 12 Hafta





Lawitz E, et al. N Engl J Med. 2013;368(20):1878-87;

PROTON Çalışması:Tedavi naiv HCV Genotip 1-3 olgular Sofosbuvir + Ribavirin + Peginterferon (faz 2 etkinlik çalışması)

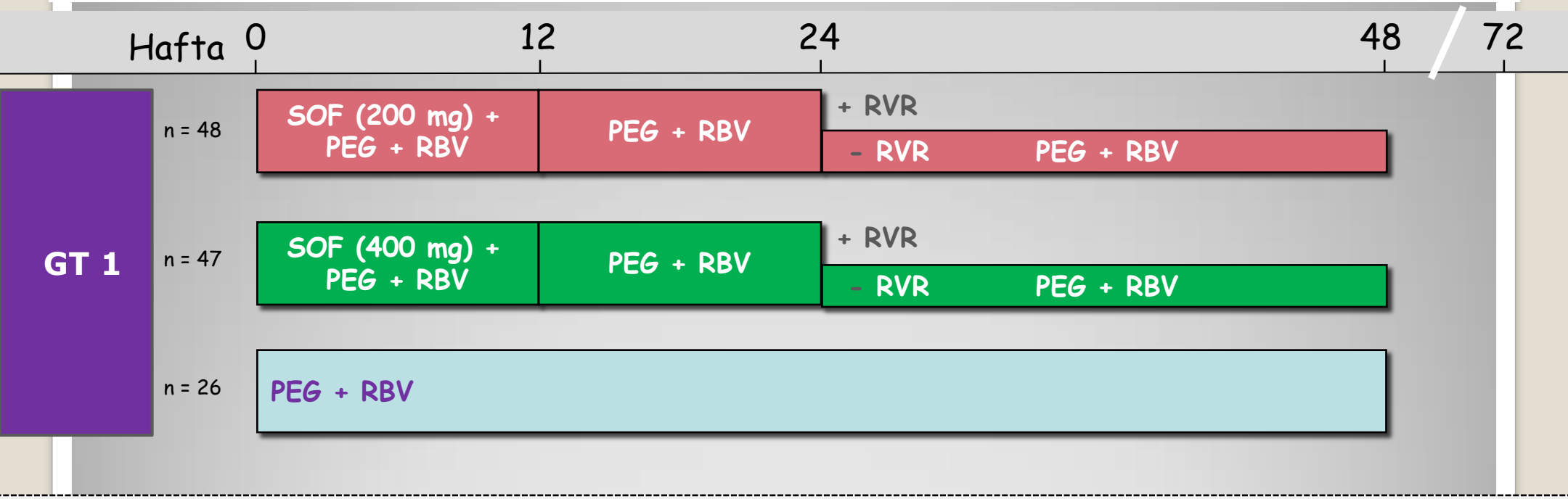
- **Alınma kriterleri**
  - **Tedavi naiv**
  - HCV RNA ≥ 50,000 IU/mL
  - **Sirozsuz**
  - GT-1 = 121
  - GT 2= 15
  - GT 3 = 10
- **Primer sonlanım noktası: KVY 24**

Sofosbuvir 200mg

Sofosbuvir 400mg

Lawitz E, et al. Lancet Infect Dis. 2013;13:401-8.

PROTON Çalışması:Tedavi naiv HCV Genotip 1-3 olgularda (faz 2 etkinlik çalışması)
Sofosbuvir + Ribavirin + Peginterferon



İlaç dozları

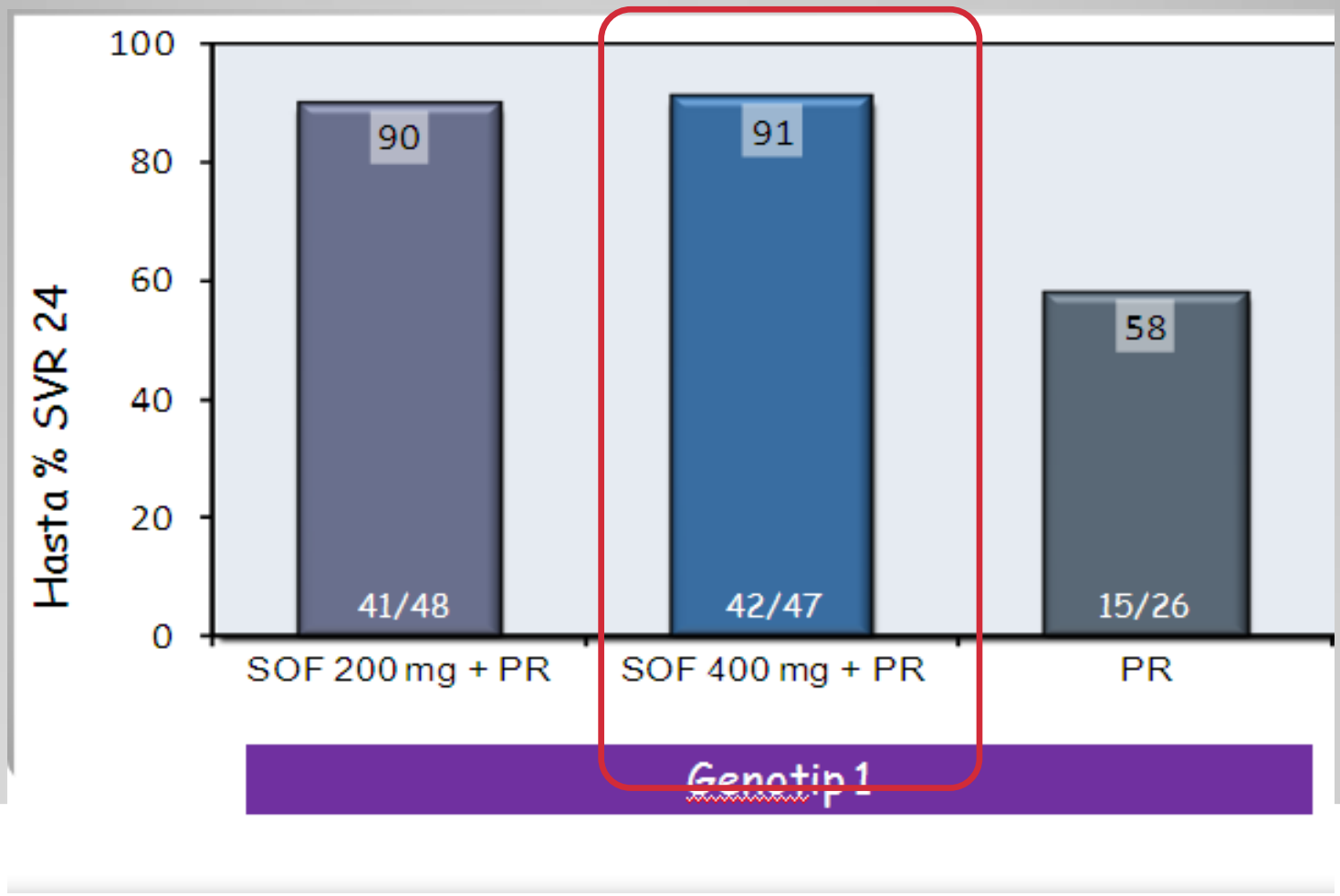
Sofosbuvir (SOF): ilk kolda 200 mg /gün, diğer kollarda 400 mg/gün,

Ribavirin (RBV) kiloya ayarlı; < 75 kg 1000 mg/gün, ≥ 75 kg 1200 mg/gün ikiye bölünmüş dozda

Peginterferferon alfa-2a (PEG): 180 µg haftada bir

Lawitz E, et al. Lancet Infect Dis. 2013;13:401-8.

PROTON Çalışması
Sofosbuvir + Ribavirin + Peginterferon

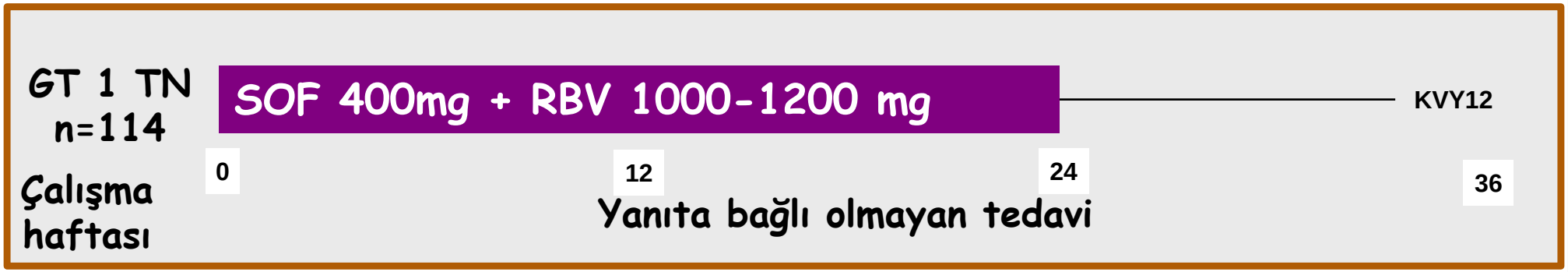


Lawitz E, et al. Lancet Infect Dis. 2013;13:401-8.

HIV/HCV koenfekte olgular

PHOTON-1

PHOTON-1 Faz 3 Çalışma (HIV/KCV Koinfeksiyonu)
SOF + RBV etkinlik ve güvenilirlik çalışması



- ✓ Geniş alınma kriterleri
  Trombosit eşik değeri olmaksızın siroza izin verildi
  Hemoglobin: ≥12 mg/dL (erkek), ≥11 mg/dL (kadın)

- ✓ ART tedavilerine izin verildi
  ART tedavisinde >8 hafta saptanamayan HIV RNA

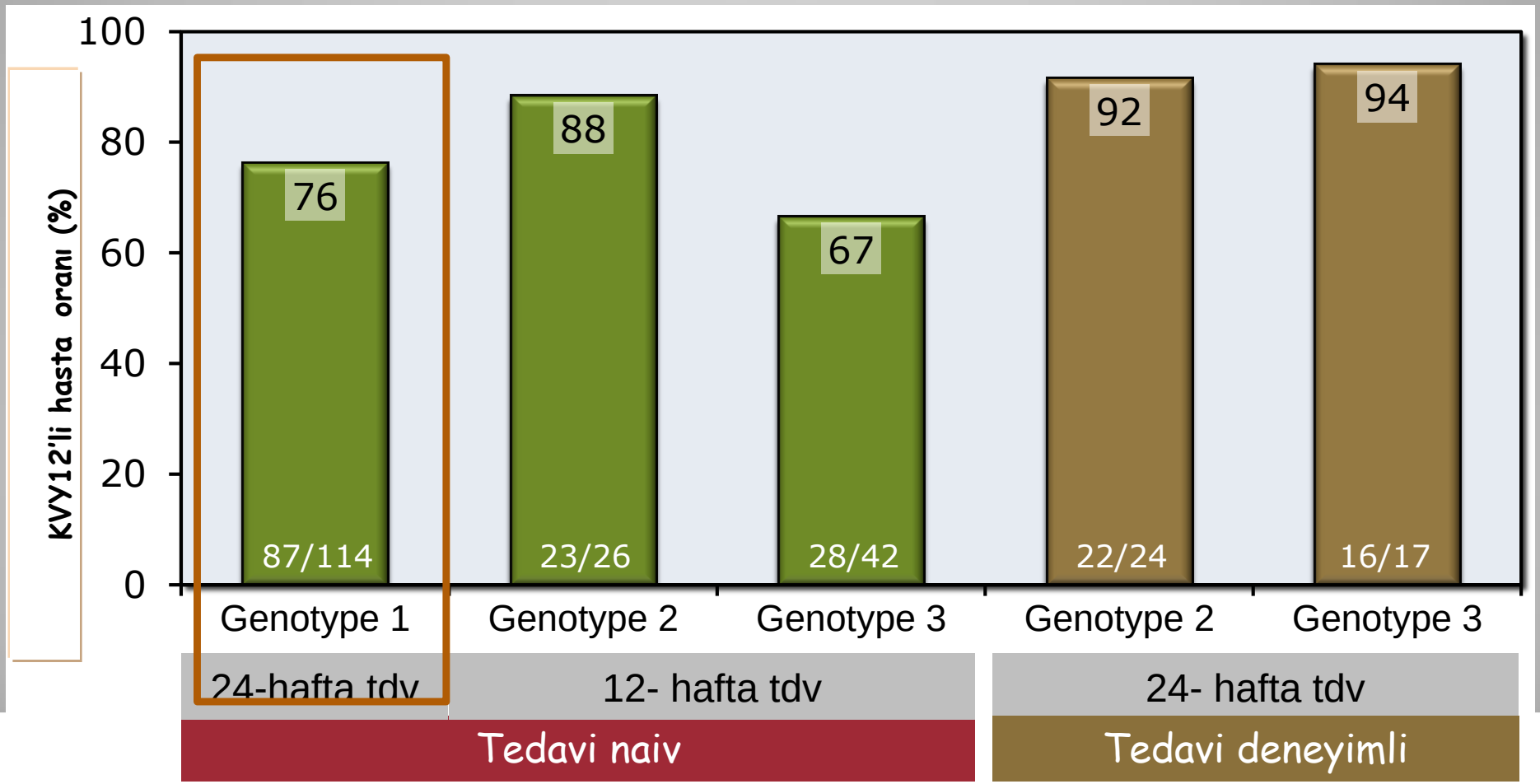
- ✓ Başlangıç CD4 sayısı;
  ART ile tedavi edilen: CD4 T-hücre sayısı >200 hücre/mm^3 ve HIV RNA < 50k/ml
  ART ile tedavi edilmeyen: CD4 T-hücre sayısı >500 hücre/mm^3

Sulkowski MS, et al. AASLD 2013. Washington, DC. Oral #212.

HCV-HIV koinfeksiyonunda Sofosbuvir +Ribavirin

PHOTON-1

PHOTON-1: Sofosbuvir + RBV x 12-24 hafta tdv ile 12 hafta KVY



Sulkowski MS, et al. JAMA. 2014;312:353-61.

SOFOSBUVİR

FDA onayı 2013

Tedavi naiv genotip 1 ve 4 olgularda

üçlü tedavide kullanılmak üzere

Sofosbuvir
+
Ribavirin
+
Peg IFN

Sofosbuvir + Ledipasvir

Ledipasvir/Sofosbuvir (Harvoni)

- Ledipasvir: NS5A inhibitörü
- Sofosbuvir : Nükleotit analogu NS5B polimeraz inhibitörü
- Doz: ledipasvir/sofosbuvir (Sabit doz 90 mg/400mg)

  Günde bir kez,

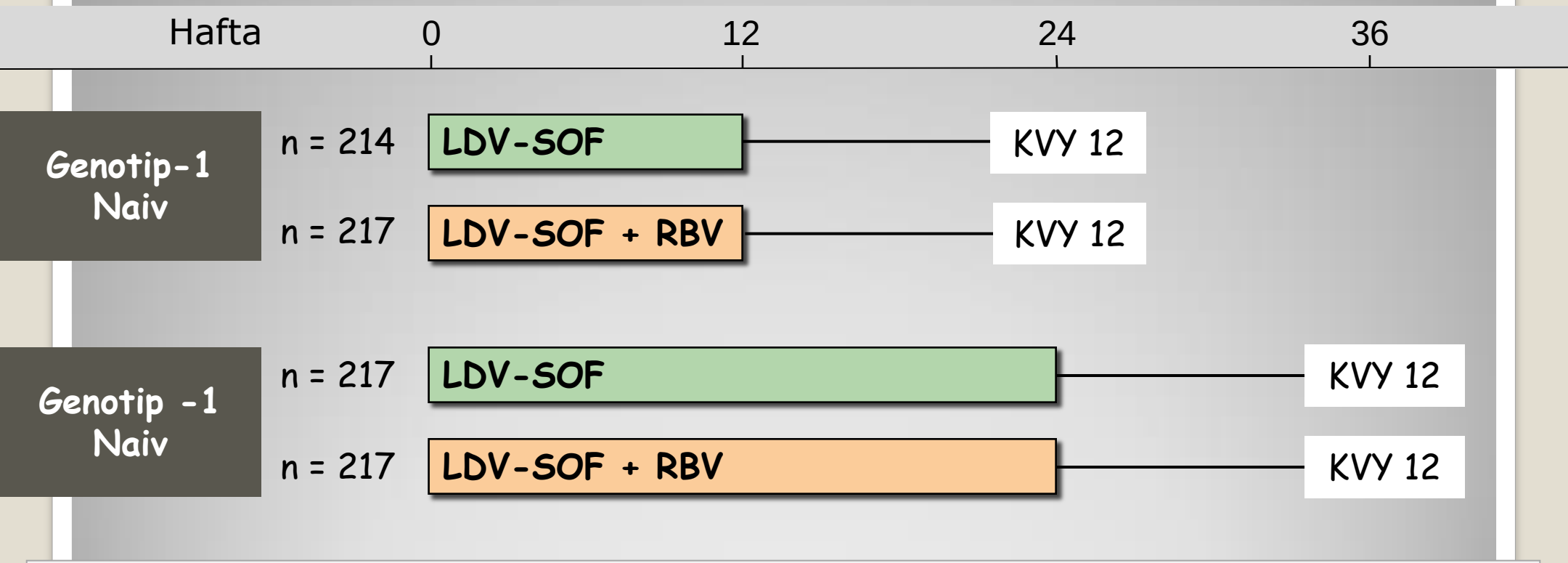
  Tek tablet yemekle veya aç.
- Endikasyonu: Genotip 1 kronik HCV hastaların tedavisi
- Yan etki: Halsizlik başağrısı
- Onay tarihi: 10. Ekim 2014

Onaya Dayanak Olan Çalışmalar

Genotip 1
Tedavi naiv olgular

ION-1

ION-1; Genotip 1 Tedavi naiv olgular Ledipasvir-Sofosbuvir +/- Ribavirin

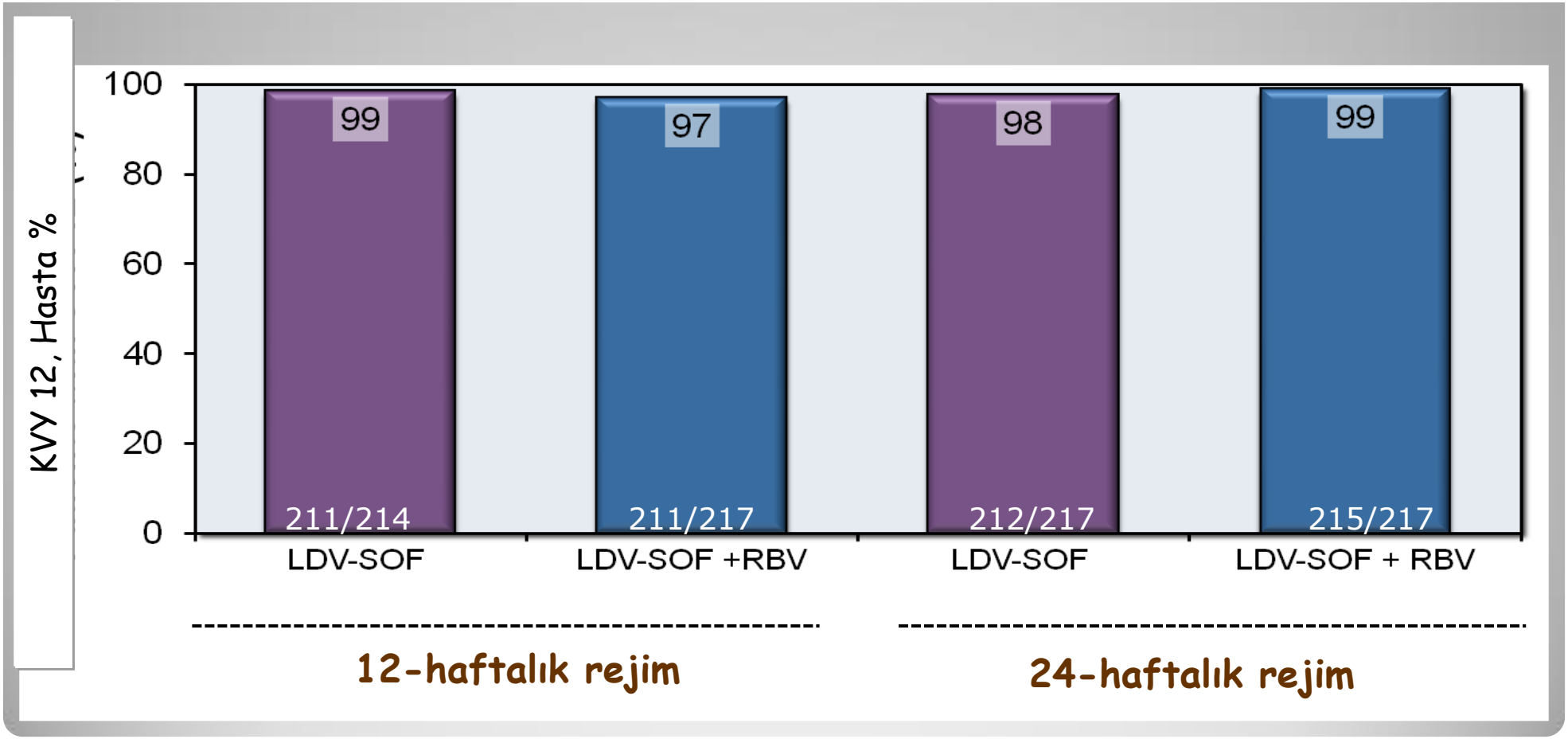


İlaç dozları: Ledipasvir-sofosbuvir (90/400 mg): bir tablet günde bir kez

Ribavirin (kiloya ayarlı ikiye bölünmüş dozda): < 75 kg, 1000 mg/gün ≥ 75 kg 1200 mg/gün

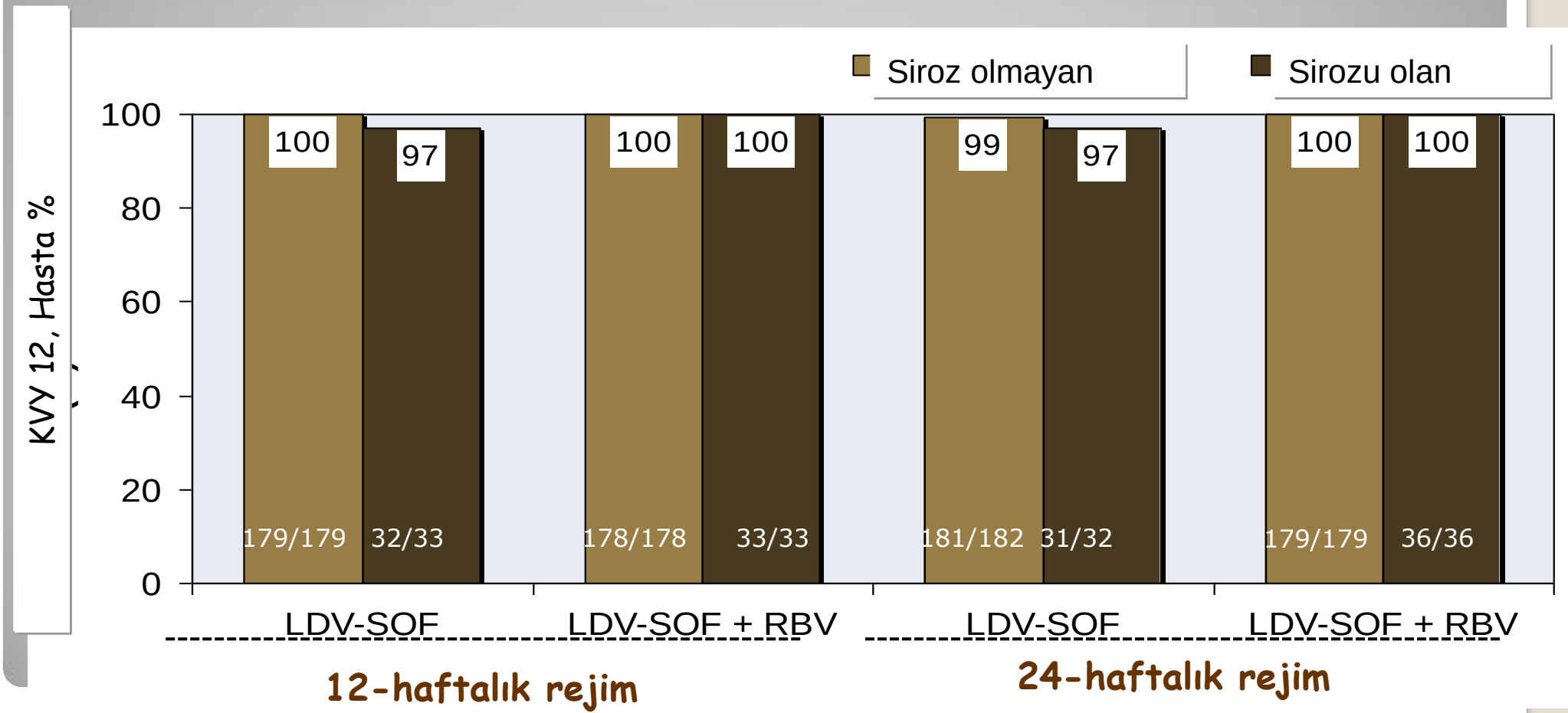
Afdhal N, et al. N Engl J Med. 2014;370:1889-98.

ION-1; Genotip 1 Tedavi naiv olgular Ledipasvir-Sofosbuvir +/- Ribavirin in HCV



Afdhal N, et al. N Engl J Med. 2014;370:1889-98.

ION-1 ; HCV Genotip 1 Tedavi naiv olgular Ledipasvir-Sofosbuvir +/- Ribavirin



Afdhal N, et al. N Engl J Med. 2014;370:1889-98.

Genotip 1
Tedavi Deneyimli Olgular

ION-2

ION-2 : Tedavi deneyimli HCV Genotip 1 olgular Ledipasvir-Sofosbuvir +/- Ribavirin (Faz 3)

Tedavi deneyimli daha önce

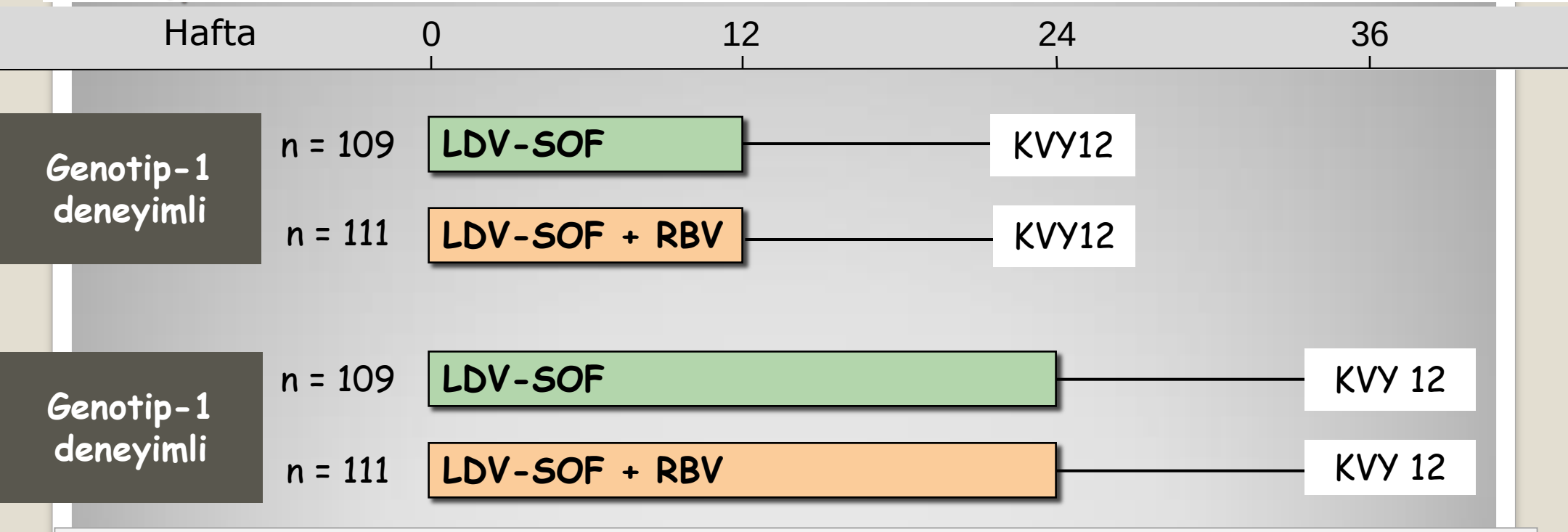
a) Peg IFN + ribavirin

b) HCV proteaz inhibitörü+ Peg IFN 2a + Ribavirin

kullanmış tedaviye yanıt alınamamış olgular

Afdhal N, et al. N Engl J Med. 2014;370:1483-93.

ION-2 : Tedavi deneyimli HCV Genotip 1 olgular Ledipasvir-Sofosbuvir +/- Ribavirin



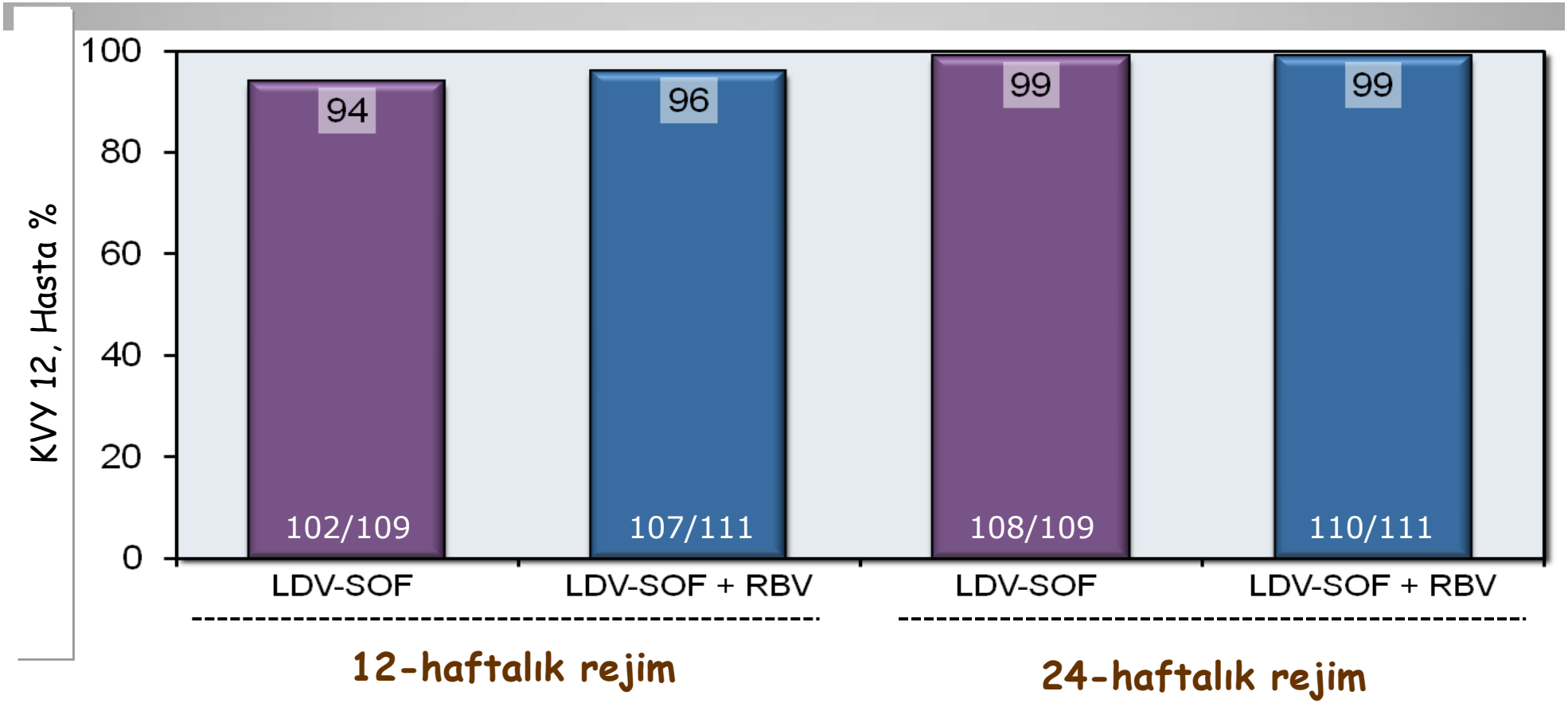
*** Olguların %20 si sirozlu**

İlaç dozları: Ledipasvir-sofosbuvir (90/400 mg): günde bir kez, bir tablet
Ribavirin (kiloya ayarlı ikiye bölünmüş dozda): < 75 kg, 1000 mg/gün
≥ 75 kg 1200 mg/gün

Afdhal N, et al. N Engl J Med. 2014;370:1483-93.

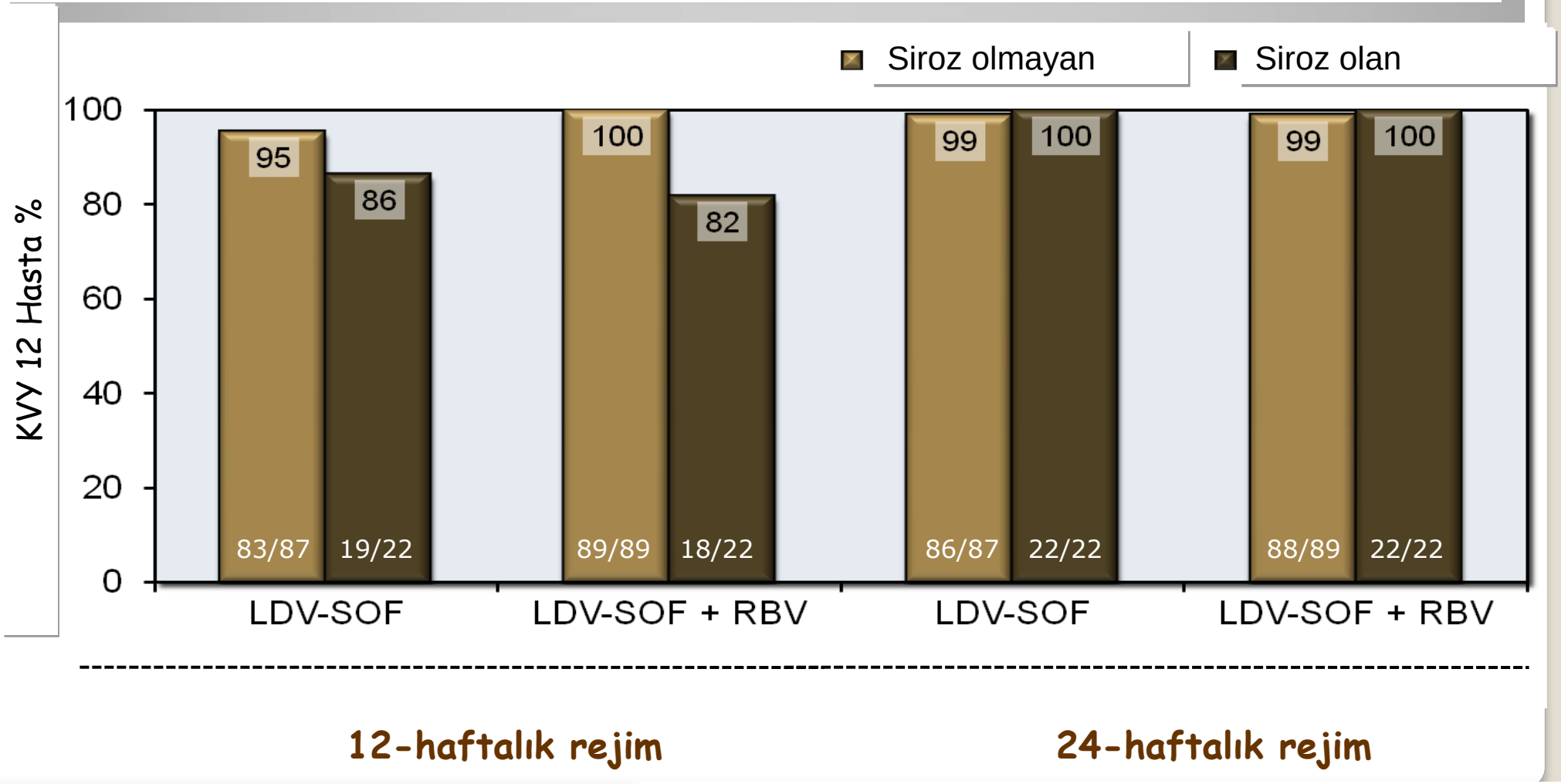
ION-2 Çalışması: Tedavi deneyimli HCV Genotip 1

Ledipasvir-Sofosbuvir +/- Ribavirin



Afdhal N, et al. N Engl J Med. 2014;370:1889-98.

ION-2 Çalışması: Tedavi deneyimli HCV Genotip 1 Ledipasvir-Sofosbuvir +/- Ribavirin

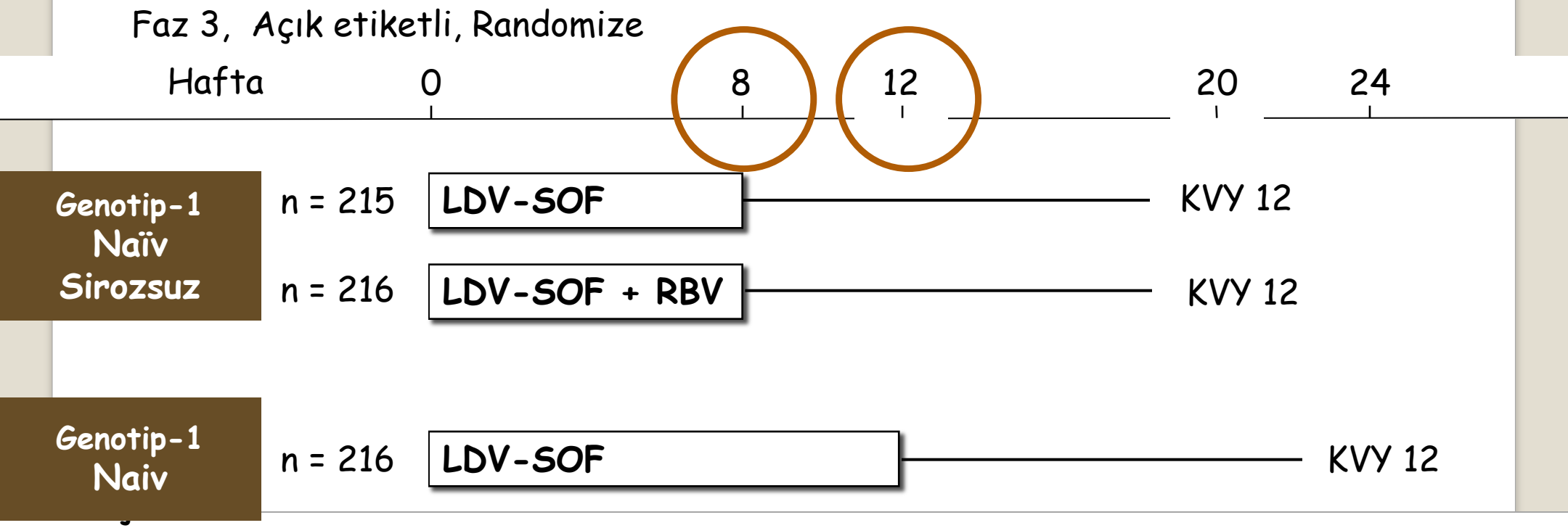


Afdhal N, et al. N Engl J Med. 2014;370:1889-98.

Genotip 1
Tedavi Naiv Nonsirotik Olgular

ION-3

ION-3 Çalışması: Tedavi naiv, nonsirotik HCV Genotip 1 Ledipasvir-Sofosbuvir+/-Ribavirin 8 hafta Ledipasvir-Sofosbuvir 12 Hafta karşılaştırması

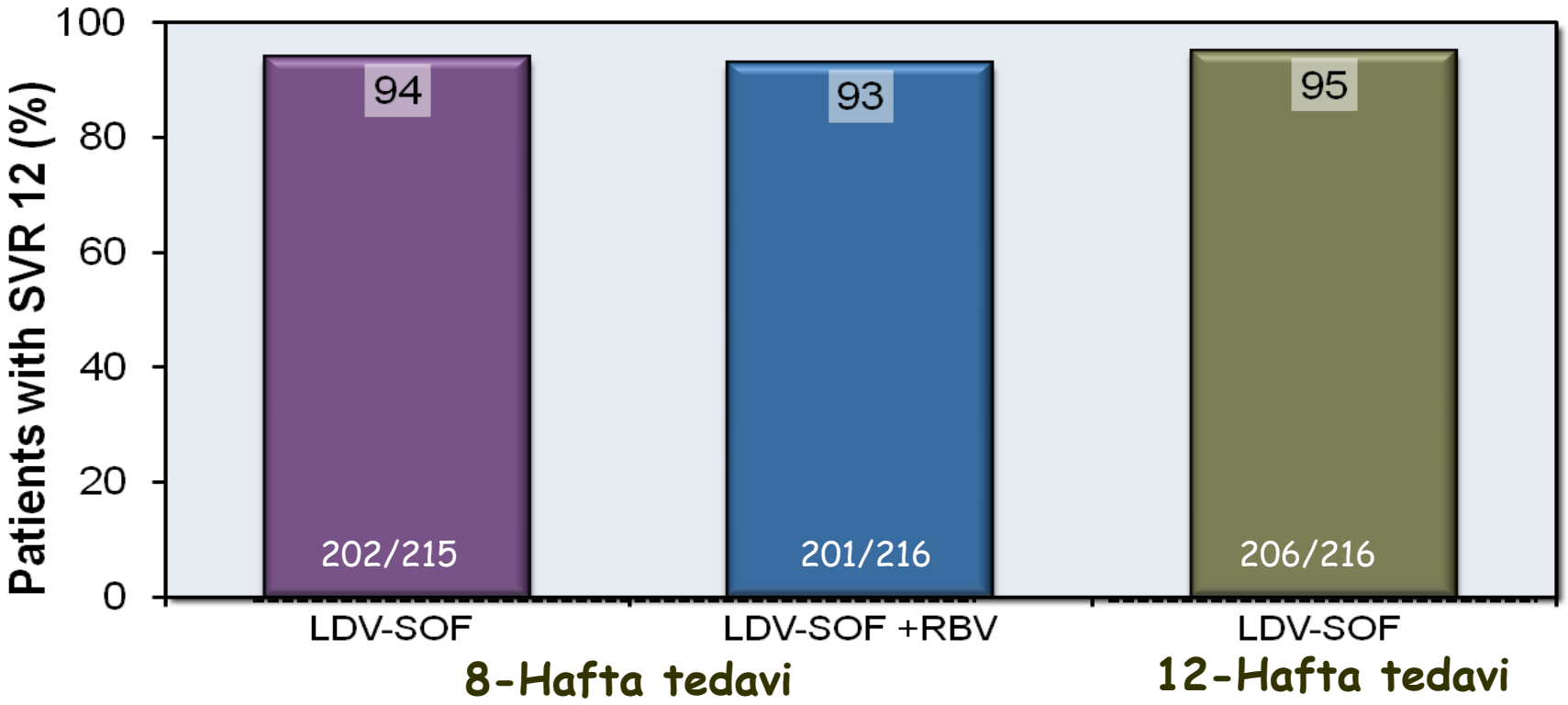


Ledipasvir-sofosbuvir (90/400 mg): tek doz tek tablet

Ribavirin (kiloya ayarlı bölünmüş iki dozda): < 75 kg, 1000 mg/gün veya ≥ 75 kg, 1200 mg/gün

Kowdley, K, et al. N Engl J Med. 2014;370:1879-88

ION-3 Çalışması: Tedavi naiv, nonsirotik HCV Genotip 1 Ledipasvir-Sofosbuvir+/-Ribavirin 8 hafta Ledipasvir-Sofosbuvir 12 Hafta karşılaştırması



Tedavi naiv sirozsuz olgularda LDV+ SOF 8 hafta tedavisi etkili bir tedavidir

Ribavirin eklemek veya tedaviyi 12 haftaya uzatmanın ek bir faydası yoktur

Kowdley, K, et al. N Engl J Med. 2014;370:1879-88

Ledipasvir/Sofosbuvir

FDA onayı 2014

Tedavi yanıtsız, ve siroz dahil genotip 1 olgularda kullanılmak üzere

Sofosbuvir
+
Ledipasvir

Genotip 1 hastalar	Tedavi süresi *
Tedavi naiv sirozlu veya sirozsuz	12 hafta
Tedavi deneyimli** sirozsuz	12 hafta
Tedavi deneyimli** sirozlu	24 hafta

*Tedavi öncesi HCV RNA düzeyi 6 milyon IU/mL altında olan tedavi naiv sirozsuz olgularda önerilen tedavi süresi 8 hafta dır.

* *Tedavi deneyimli daha önce a) pegile interferon ve ribavirin veya b) HCV proteaz inhibitörü+ peginterferon alfa + ribavirin kullanmış tedaviye yanıt alınamamış olgular

AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES
AASLD

IDSA
Infectious Diseases Society of America

Collaborating Partner
IAS–USA
International Antiviral Society–USA

Recommendations for Testing, Managing, and Treating Hepatitis C

Guidelines

CrossMark

EASL JOURNAL OF HEPATOLOGY

EASL Recommendations on Treatment of Hepatitis C 2015

European Association for the Study of the Liver *

Introduction

Hepatitis C virus (HCV) infection is one of the main causes of chronic liver disease worldwide [1]. The long-term impact of HCV infection is highly variable, ranging from minimal histological changes to extensive fibrosis and cirrhosis with or without hepatocellular carcinoma (HCC). The number of chronically infected persons worldwide is estimated to be about 160 million, but most are unaware of their infection. The implementation of extended criteria for screening for HCV is a subject of major debate among different stakeholders. Clinical care for patients with HCV-related liver disease has advanced considerably during

neurocognition and effective viral suppression is associated with reversal of cerebral magnetic resonance abnormalities [4].

Until 2011, the combination of pegylated interferon (PegIFN)-α and ribavirin for 24 or 48 weeks was the approved treatment for chronic hepatitis C [5]. With this regimen, patients infected with HCV genotype 1 had SVR rates of approximately 40% in North America and 50% in Western Europe. Higher SVR rates were achieved in patients infected with HCV genotypes 2, 3, 5, and 6 (up to about 80%, and higher for genotype 2 than for genotypes 3, 5, and 6) and intermediate SVR rates were achieved in those with HCV genotype 4 [6].

In 2011, telaprevir and boceprevir were licensed for use in

HCV GENOTİP 1 OLGULARIN TEDAVİSİ

EASL 2015
HCV Genotip 1

Genotip 1 İnterferon içeren rejim opsiyon 1

- Patients infected with HCV genotype 1 can be treated with a combination of weekly PegIFN-α, daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), and daily sofosbuvir (400 mg) 12 weeks **(A1)**

Sofosbuvir+PegINF+kiloya ayarlı ribavirin 12 hf

EASL 2015/ Genotip 1 Tedavi Naiv Sirozsuz Olgular

IFN-free options

Genotip 1 interferonsuz tedavi seçeneği 1

Genotip 1 olguların tedavisinde günde bir doz, tek tablet Sofosbuvir+ ledipasvir kullanılabilir (A1)

Tedavi naiv ve deneyimli sirozsuz olgular günde bir doz, tek tablet Sofosbuvir+ ledipasvir ile (ribavirinsiz) 12 haftada tedavi edilebilir (A1)

Tedavi naiv ve sirozsuz olgular bazal HCV RNA <6000000 IU/ml ise günde bir doz, tek tablet Sofosbuvir+ ledipasvir ile 8 haftada tedavi edilebilir (B1) Özellikle F3 olgularda dikkatli olunmalıdır.

AASLD-2015 Tedavi Naiv HCV Genotip 1 Olgular

Tedavi naiv Genotip 1 olgularda ilk seçenek interferonsuz tedaviler

Daily daclatasvir (60 mg*) and sofosbuvir (400 mg) for 12 weeks (no cirrhosis) or 24 weeks with or without weight-based RBV (1000 mg [<75 kg] to 1200 mg [>75 kg]) (cirrhosis) is recommended for treatment-naive patients with HCV genotype 1a infection.

Rating: Class I, Level B (no cirrhosis); Class IIa, Level B (cirrhosis)

Tedavi naiv genotip 1 a-b olgularda sabit doz ledipasvir/sofosbuvir 12 hafta süreyle (AI)

Seçenekler alfabetik sıraya göre dizilmiş

Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) and weight-based RBV for 12 weeks (no cirrhosis) or 24 weeks (cirrhosis) is recommended for treatment-naive patients with HCV genotype 1a infection.

Rating: Class I, Level A

Daily simeprevir (150 mg) and sofosbuvir (400 mg) for 12 weeks (no cirrhosis) or 24 weeks (cirrhosis without the Q80K polymorphism) with or without weight-based RBV is recommended for treatment-naive patients with HCV genotype 1a infection.

AASLD-2015 Peg-İNF + RBV deneyimli, sirozsuz HCV Genotip 1a ve b Olgular

Several options with similar efficacy in general are recommended for patients with HCV genotype 1a infection who do not have cirrhosis, in whom prior PEG-IFN and RBV treatment has failed (listed in alphabetic order; see text).

Daily daclatasvir (60 mg) plus sofosbuvir (400 mg) for 12 weeks is recommended for patients with HCV genotype 1a infection who do not have cirrhosis, in whom prior PEG-IFN and RBV treatment has failed.

Rating: Class IIa, Level B

Sirozsuz Peg IFN+ ribavirin deneyimli, genotip 1a-b olgularda ledipasvir/sofosbuvir, 12 hafta (A1)

Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dasabuvir (250 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks is recommended for patients with HCV genotype 1a infection who do not have cirrhosis, in whom prior PEG-IFN and RBV treatment has failed.

Rating: Class I, Level A

Daily simeprevir (150 mg) plus sofosbuvir (400 mg) for 12 weeks is recommended for patients with HCV genotype 1a infection who do not have cirrhosis, in whom prior PEG-IFN and RBV treatment has failed.

Rating: Class IIa, Level B

EASL 2015/ Genotip 1 , Kompanze Sirozlu Olgular

Tedavi naiv ve deneyimli kompanze sirozlu olgular günde bir doz, tek tablet Sofosbuvir+ ledipasvir + kiloya ayarlı ribavirin (1000-1200 mg)ile 12 haftada tedavi edilebilir (A1)

Kompanze sirozlu ribavirin kullanması kontrendike olguların, Sofosbuvir+ ledipasvir (günde bir doz, tek tablet) tedavisi 24 hafta sürdürülmelidir(B1)

without ribavirin **(B1)**

Tedavi deneyimli kompanze sirozlu olgularda cevabı negatif etkileyen bir prediktör varsa (Trombosit<75000 /µl), Sofosbuvir+ ledipasvir+ ribavirin tedavisi 24 haftada sürdürülebilir(B1)

AASLD-2015 Peg-İNF + RBV deneyimli, kompanze sirozlu HCV Genotip 1a ve b Olgular

Recommended regimens for patients with HCV genotype 1a or 1b infection who have compensated cirrhosis, in whom prior PEG-IFN and RBV treatment has failed.

Daily daclatasvir (60 mg) plus sofosbuvir (400 mg) for 24 weeks with or without weight-based RBV is recommended for patients with HCV genotype 1a or 1b infection who have **compensated cirrhosis**, in whom prior PEG-IFN and RBV treatment has failed.

Peg IFN+ ribavirin deneyimli kompanze siroz genotip 1 a-b olgularda ledipasvir/sofosbuvir, 24 hafta (A1)

Rating: Class I, Level A

Peg IFN+ ribavirin deneyimli kompanze siroz genotip 1 a-b olgularda ledipasvir/sofosbuvir + kiloya ayarlı ribavirin , 12 hafta (BI)

mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) and weight-based RBV for 24 weeks is recommended for patients with HCV genotype 1a infection and for 12 weeks without RBV for patients with HCV

HASTA ÖZELLİKLERİ	EASL 2015		AASLD 2015	
GENOTİP 1	Tedavi	Süre	Tedavi	Süre
Tedavi naiv, sirozsuz	Sof/ led	12 hafta	Sof/ led	12 hafta
Tedavi deneyimli, sirozsuz	Sof/ led	12 hafta	Sof/ led	12 hafta
Naiv kompanze siroz	Sof/led + ribavirin	12 hafta	Sof/ led + ribavirin	12 hafta
Tedavi deneyimli, sirozsuz	Sof/ led + ribavirin	12 hafta	Sof/ led + ribavirin	12 hafta
	Sof/ led	24 hafta	Sof/ led	24 hafta

AASLD-2015 Tedavi Naiv HCV Genotip 1 Olgular

HCV genotip 1 tedavi naiv hastada önerilmeyen rejimler

genotype 1.

*Sofosbuvir + kiloya ayarlı ribavirin 24 hafta AIIb

*PegIFN+ Ribavirin ± sofosbuvir, simepravir, telepravir, boceprevir AIIb

*Peg IFN, Ribavirin veya DDA monoterapisi AIII

AASLD-2015 Tedavi Sofosbuvir Ribavirin ±Peg IFN kullanıp tedavi başarısızlığı olan olgular

Recommended regimens for patients in whom a previous sofosbuvir plus RBV with or without PEG-IFN treatment has failed.

No Cirrhosis

Sirozsuz: sofosbuvir/ledipasvir+ kiloya ayarlı ribavirin 12 hafta CIII

or without PEG-IFN has failed.

Rating: Class IIb, Level C

Cirrhosis

Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with

Sirozlu: sofosbuvir/ledipasvir+ kiloya ayarlı ribavirin 24 hafta CIIa

Rating : Class IIa, Level C

Title: Retreatment of Relapsers to Sofosbuvir/Ribavirin with Sofosbuvir/Ledipasvir: Complete and Rapid Virologic Suppression By Week 4

Presenter: A. Osinusi, M. Marti, K. Townsend, A. Nelson, A. Kohli, R. Silk, P. Pang, W.T. Symonds, J. McHutchison, H. Masur, S. Kottilil, for the NIAID hepatitis C SYNERGY Team

Aims: The combination of SOF and RBV for 24 weeks is an effective regimen to treat chronic hepatitis C, GT 1 subjects, however up to a third of patients might experience relapse. The effectiveness of retreatment of SOF/RBV relapsers with other Interferon-free, directly acting antiviral agents (DAAs) is an important clinical question. In this study, we treated SOF/RBV relapsers (NIAID SPARE study) with a fixed dose combination (FDC) of SOF and LDV for 12 weeks.

Methods: Fourteen subjects were enrolled in an arm of the NIAID SYNERGY study and received SOF/LDV (400 mg/90 mg) once daily for 12 weeks. Serial measurements of safety parameters, virologic and host correlates were performed. The presence of NS5B mutations was assessed by population sequencing. The primary endpoint is SVR12.

Results: Subjects enrolled were a (mean age of 59 years, 93% male, 93% African-American, 86% IL28B CT/TT, 57% GT-1A, 50% advanced liver disease with a mean baseline HCV RNA of 6.29 log10 IU/ml). One patient demonstrated S282T mutation post SOF/RBV therapy that resolved prior to SOF/LDV initiation. All subjects achieved HCV RNA < LLOQ by week 4 with continued viral suppression. Viral decline and treatment responses are shown in Table 1. There was one grade 3 event (hypophosphatemia) but no serious adverse events (SAEs) or adverse events (AEs) leading to discontinuation.

Table 1. Viral decline on SOF/LDV FDC

	Current therapy with SOF/LDV FDC (N = 14)	Prior therapy with SOF/RBV (N = 14)
Mean (SD) baseline HCV $\log_{10}$ RNA	6.29 (0.38)	6.30 (0.40)
Mean (SD) week 4 decline	5.07 (0.44)	5.03 (0.38)
% LLOQ at week 4	100%	86%

Conclusions: A fixed dose combination of SOF/LDV appears to be a safe and effective IFN/RBV free antiviral regimen in patients who previously failed SOF/RBV therapy.

Rapid Communication

Ledipasvir-sofosbuvir plus ribavirin for patients with genotype 1 hepatitis C virus previously treated in clinical trials of sofosbuvir regimens

David Wyles, Paul Pockros, Giuseppe Morelli, Ziad Younes, Evguenia Svarovskaia, Jenny C. Yang, Phillip S. Pang, Yanni Zhu, John G. McHutchison, Steven Flamm, Eric Lawitz

View issue TOC
Volume 61, Issue 6
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Pages 1793–1797

Abstract

51 olgu
%49: Sof+ Peg IFN+ Rib
%39: Sof+ Rib
%10: Peg IFN+ Rib+ plasebo

Sofosbuvir/ledipasvir+ Rib 12 hafta tedavisi
KVY12- %98

did not achieve SVR12 was a patient with genotype 3a HCV who had been incorrectly genotyped as 1a in the previous study. Given the high rates of SVR12, no differences among patient subgroups were discernible. Of 51 patients, 41 (80%) experienced at least one adverse event (AE), but most events were mild to moderate in severity. The most common AEs were fatigue, headache, and diarrhea. One patient discontinued treatment because of an unrelated AE (bipolar disorder). *Conclusion*: Twelve weeks of LDV-SOF plus RBV was an effective and safe treatment for patients who have not achieved SVR with earlier regimens that included SOF. (HEPATOLOGY 2015;61:1793–1797)

HCV GENOTİP 4 OLGULARIN TEDAVİSİ

EASL 2015/ Genotip 4

IFN-containing options

Genotip 4 interferon içeren seçenek 1

- Patients infected with HCV genotype 4 can be treated with a combination of weekly PegIFN-α, daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or

Sofosbuvir + PegINF + kiloya ayarlı ribavirin 12 hf (B1)

EASL 2015 / Genotip 4

Genotip 4 interferonsuz tedavi seçeneği 1

Genotip 4 olguların tedavisinde günde bir doz, tek tablet Sofosbuvir+ ledipasvir kullanılabilir (A1)

Tedavi naiv ve deneyimli sirozsuz olgular günde bir doz, tek tablet Sofosbuvir+ ledipasvir ile (ribavirinsiz) 12 haftada tedavi edilebilir (A1)

Tedavi naiv ve deneyimli kompanze sirozlu olgular günde bir doz, tek tablet Sofosbuvir+ ledipasvir + kiloya ayarlı ribavirin (1000-1200 mg)ile 12 haftada tedavi edilebilir (A1)

AASLD 2015/ Genotip 4 Tedavi Naiv

Three options with similar efficacy in general are recommended for treatment-naive patients with HCV genotype 4 infection (listed in alphabetic order; see text).

Tedavi naiv olgular günde bir doz, tek tablet Sofosbuvir+ ledipasvir 12 hafta (BIIIb)

Rating: Class IIb, Level B

Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) and weight-based RBV for 12 weeks is recommended for treatment-naive patients with HCV genotype 4 infection.

Rating: Class I, Level B

Daily sofosbuvir (400 mg) and weight-based RBV for 24 weeks is recommended for treatment-naive patients with HCV genotype 4 infection.

Rating: Class IIa, Level B

AASLD 2015 HCV Genotip 4, Tedavi-naiv Olgularda Alternatif Tedavi Rejimi

Alternative regimen for treatment-naive patients with HCV genotype 4 infection.

Daily sofosbuvir (400 mg) and weight-based RBV plus weekly PEG-IFN for 12 weeks is an acceptable regimen for treatment-naive patients with HCV genotype 4 infection.

Sofosbuvir (400) + kiloya ayarlı Ribavirin + Peg IFN 12 hafta

AASLD 2015 Genotip 4, Peg IFN+ Ribavirin Deneyimli Olgularda Tedavi Seçenekleri

Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is recommended for patients with HCV genotype 4 infection, in

- Ledipasvir/sofosbuvir 12 hafta süreyle (BIIa)
- Sofosbuvir + kiloya ayarlı Ribavirin + Peg IFN 12 hafta (BIIa)
- Sofosbuvir + kiloya ayarlı Ribavirin 24 hafta (BIIa)

recommended for retreatment of patients with HCV genotype 4 infection, in whom prior treatment with PEG-IFN and RBV has failed.

Rating: Class IIa, Level B

HCV Genotip 4

HASTA ÖZELLİKLERİ	EASL 2015		AASLD 2015	
GENOTİP 4	Tedavi	Süre	Tedavi	Süre
Tedavi naiv, sirozsuz	Sof/ led	12 hafta	Sof/ led	12 hafta
Tedavi deneyimli, sirozsuz	Sof/ led	12 hafta	Sof/ led	12 hafta
Naiv kompanze siroz	Sof/led + Ribavirin	12 hafta	Sof/ led + Ribavirin	12 hafta
Tedavi deneyimli, siroz	Sof/ led + Ribavirin	12 hafta	Sof/ led + Ribavirin	12 hafta
			Sof/ led	24 hafta
			Sofosbuvir + kiloya ayarlı ribavirin + Peg IFN	12 hafta

Table 4A. Drug-drug interactions between HCV DAAs and HIV antiretroviral

		SIM	DCV	SOF	SOF/ LDV	3D
NRTIs	Abacavir	•	•	•	•	•
	Didanosine	•	•	•	•	•
	Emtricitabine	•	•	•	•	•
	Lamivudine	•	•	•	•	•
	Stavudine	•	•	•	•	•
	Tenofovir	•	•	•	•	•
	Zidovudine	•	•	•	•	•
NNRTIs	Efavirenz	•	•	•	•*	•
	Etravirine	•	•	•	•	•
	Nevirapine	•	•	•	•	•
	Rilpivirine	•	•	•	•*	•
Protease inhibitors	Atazanavir; atazanavir/ritonavir	•	•	•	•*	•
	Darunavir/ritonavir; darunavir/cobicistat	•	•	•	•*	•
	Fosamprenavir	•	•	•	•*	•
	Lopinavir	•	•	•	•*	•
	Saquinavir	•	•	•	•*	•
Entry/ Integrase inhibitors	Dolutegravir	•	•	•	•	•
	Elvitegravir/cobicistat	•	•	•	•*	•
	Maraviroc	•	•	•	•	•
	Raltegravir	•	•	•	•	•

Table 4C. Drug-drug interactions between HCV DAAs and lipid lowering drugs.

	SIM	DCV	SOF	SOF/ LDV	3D
Atorvastatin	•	•	•	•	•
Bezafibrate	•	•	•	•	•
Ezetimibe	•	•	•	•	•
Fenofibrate	•	•	•	•	•
Fluvastatin	•	•	•	•	•
Gemfibrozil	•	•	•	•	•
Lovastatin	•	•	•	•	•
Pitavastatin	•	•	•	•	•
Pravastatin	•	•	•	•	•
Rosuvastatin	•	•	•	•	•
Simvastatin	•	•	•	•	•

Yeşil: Etkileşim yok

Sarı: Potansiyel etkileşim var

doz ayarı gerekir

Kırmızı: Birlikte kullanılmamalı

Amiodarone ile birlikte kullanıldığında ciddi semptomatik bradikardi gözlendi

NATIONAL PBM BULLETIN

March 31, 2015

DEPARTMENT OF VETERANS AFFAIRS VETERANS HEALTH ADMINISTRATION (VHA)
PHARMACY BENEFITS MANAGEMENT SERVICES (PBM), MEDICAL ADVISORY PANEL (MAP),
AND CENTER FOR MEDICATION SAFETY (VA MEDSAFE)

AMIODARONE USE WITH LEDIPASVIR/SOFOSBUVIR (HARVONI) OR SOFOSBUVIR (SOVALDI) IN COMBINATION WITH ANOTHER DIRECT-ACTING ANTIVIRAL MAY CAUSE BRADYCARDIA

I. ISSUE

FDA warns of serious symptomatic bradycardia when amiodarone is taken with ledipasvir/sofosbuvir (Harvoni) or with sofosbuvir (Sovaldi) taken in combination with another direct acting antiviral for hepatitis C (e.g., simeprevir).

Güncelleme: sofosbuvir ve ledipasvir/sofosbuvir prespektüs bilgileri

5.1 Serious Symptomatic Bradycardia When Coadministered with Amiodarone

Postmarketing cases of symptomatic bradycardia, as well as fatal cardiac arrest and cases requiring pacemaker intervention, have been reported when amiodarone is coadministered with **LDV/SOF.** Bradycardia has generally occurred within hours to days, but cases have been observed up to 2 weeks after initiating HCV treatment. Patients also taking beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease may be at increased risk for symptomatic bradycardia with coadministration of amiodarone. Bradycardia generally resolved after discontinuation of HCV treatment. The mechanism for this effect is unknown.

Sofosbuvir veya Harvoni Amiodarone ile birlikte kullanıldığında ciddi semptomatik bradikardi riskini arttırabilir

http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205834s001lbl.pdf

MUTLU SONA YAKLAŞTIK