

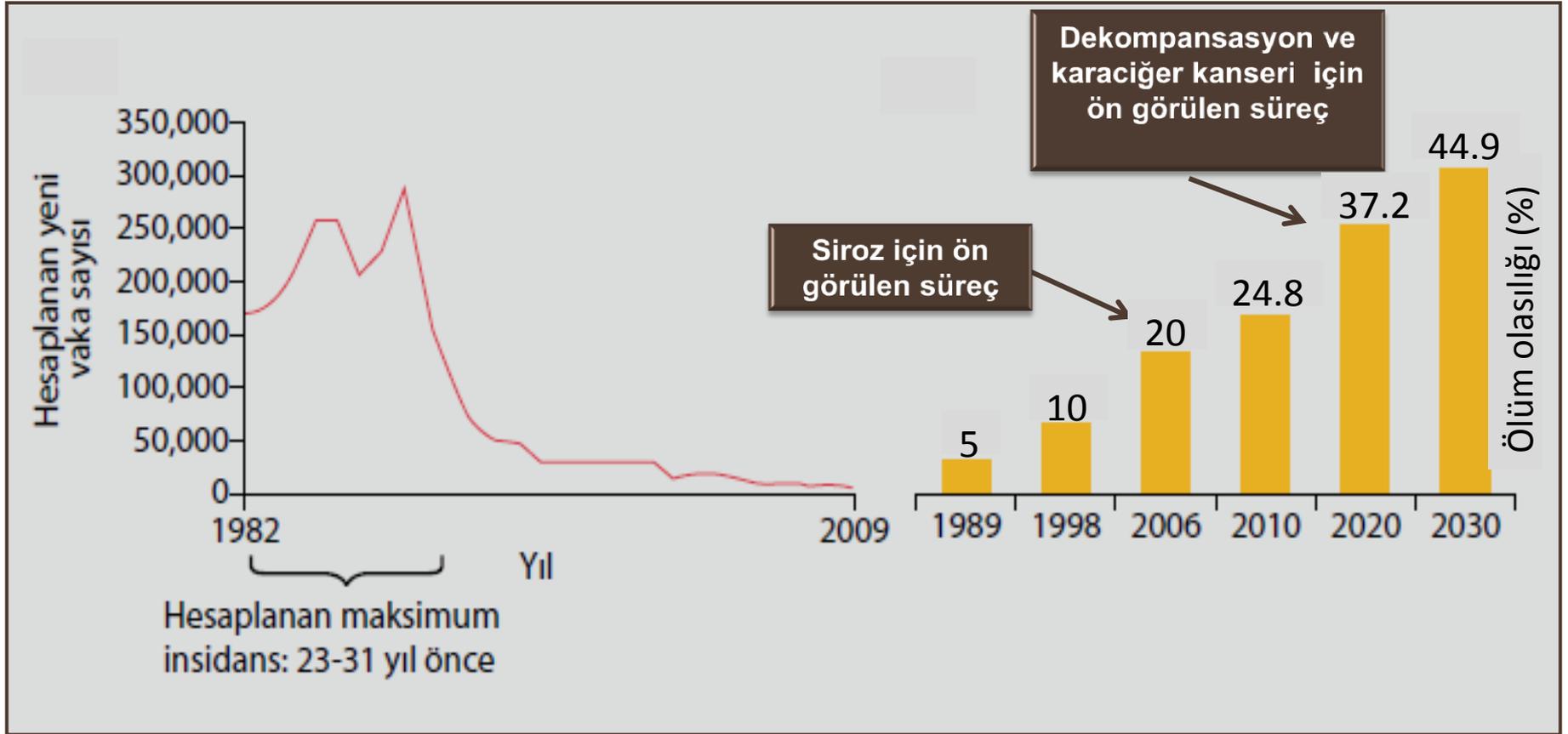
# KRONİK HEPATİT C'Lİ GENOTİP 1 VEYA 4 İLE İNFEKTE HASTALARDA TEDAVİ

- OMBİTASVİR / PARİTAPREVİR / RİTONAVİR – DASABUVİR ± RİBAVİRİN  
TEDAVİLERİ -

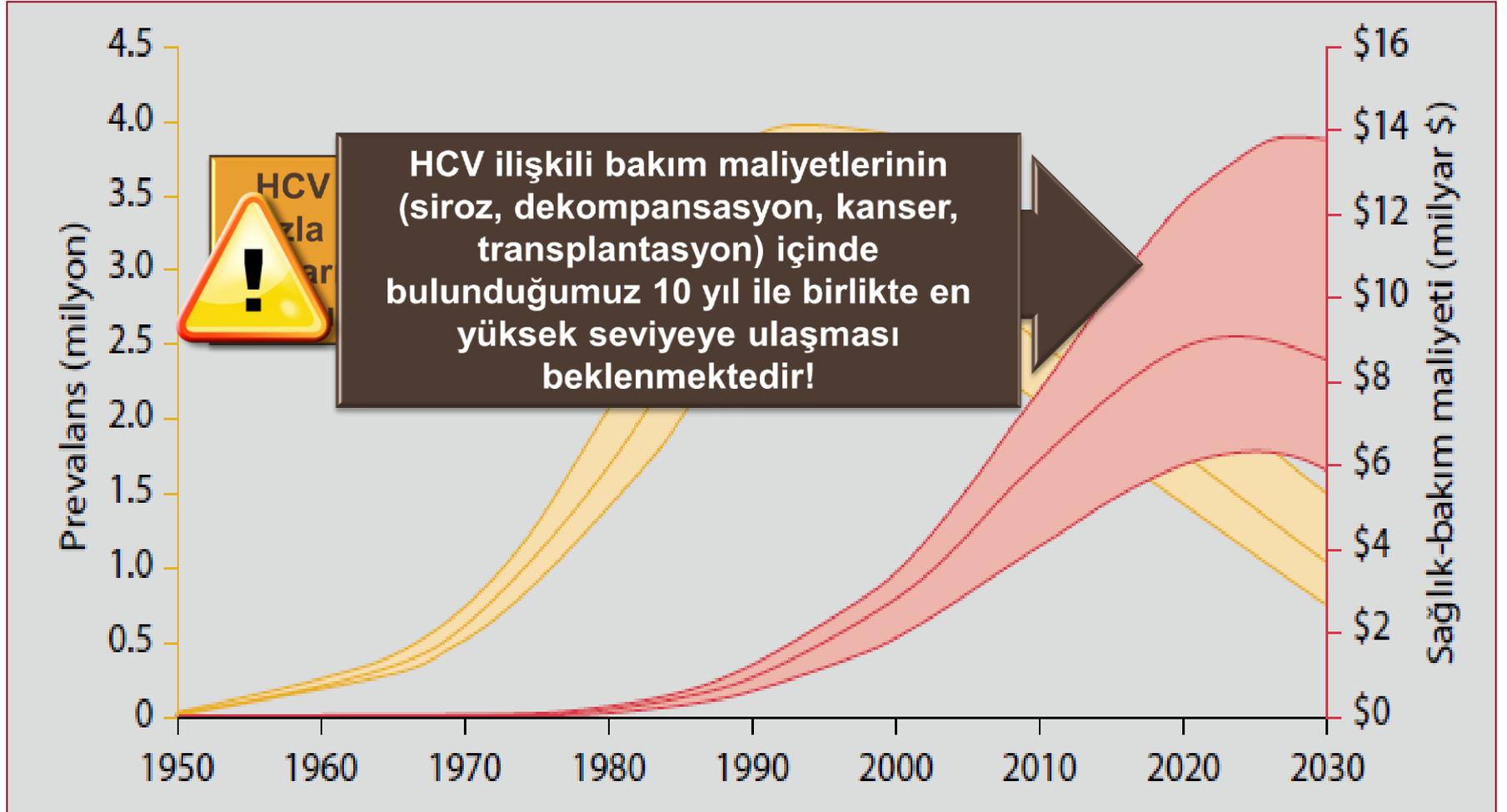
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Klinik Mikrobiyoloji ve İnfeksiyon Hastalıkları Anabilim Dalı  
KAYSERİ

# HCV infeksiyonu ve beklenen ölüm oranı



# HCV infeksiyonu ve ekonomik boyut



# Hepatit C virusu

Tutunma: Virus karaciğer hücresine reseptör aracılığı ile bağlanır. Bu işlem için en az dört farklı protein gerekir

Penetrasyon ve giriş: Karaciğer hücresi içe doğru kıvrılıp virüsü alır

Füzyon sonrası viral RNA salınımı: Virus protein kılıfından soyunur RNA hücre içine salınır

Viral protein sentezi: Viral RNA karaciğer hücresini kullanarak kendi proteinlerini sentezletir

Viral protein işlenmesi: Karaciğer enzimleri sentezlenen viral proteinleri uygun biçimde keser hazırlar

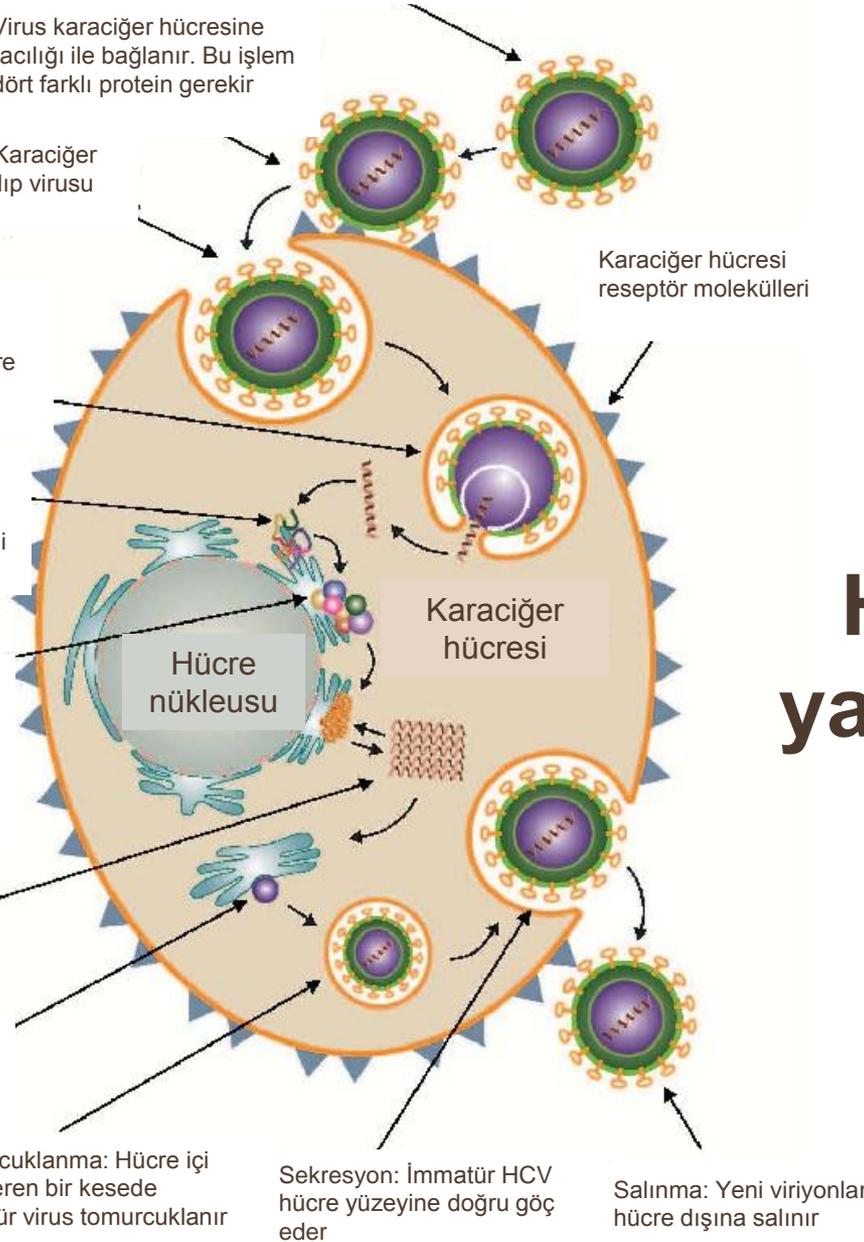
Replikasyon: Yüzlerce HCV RNA kopyası sentezlenir

Viral montaj: Protein kapsid RNA'yı çevreleyip yeni viriyonları oluşturur

Tomurcuklanma: Hücre içi sıvı içeren bir kesede immatür virus tomurcuklanır

Sekresyon: İmmatür HCV hücre yüzeyine doğru göç eder

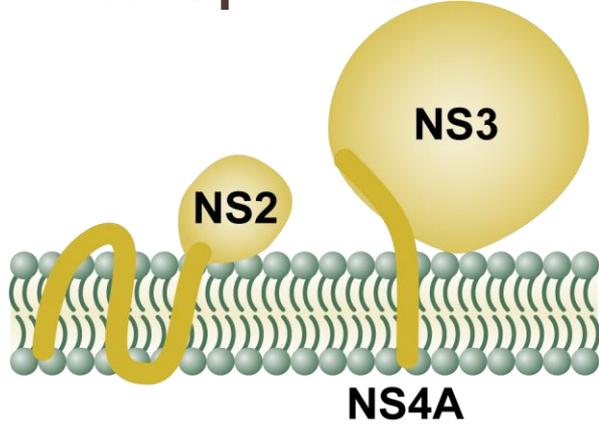
Salınma: Yeni viriyonlar hücre dışına salınır



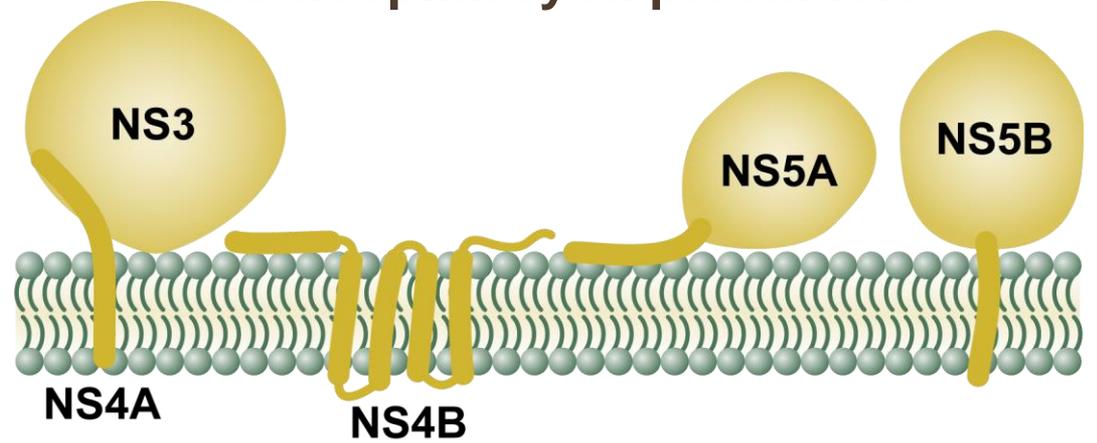
## Hepatit C'nin yaşam döngüsü

# HCV replikasyonunda rol alan esansiyel proteinler

## Viral proteazlar



## Viral replikasyon proteinleri



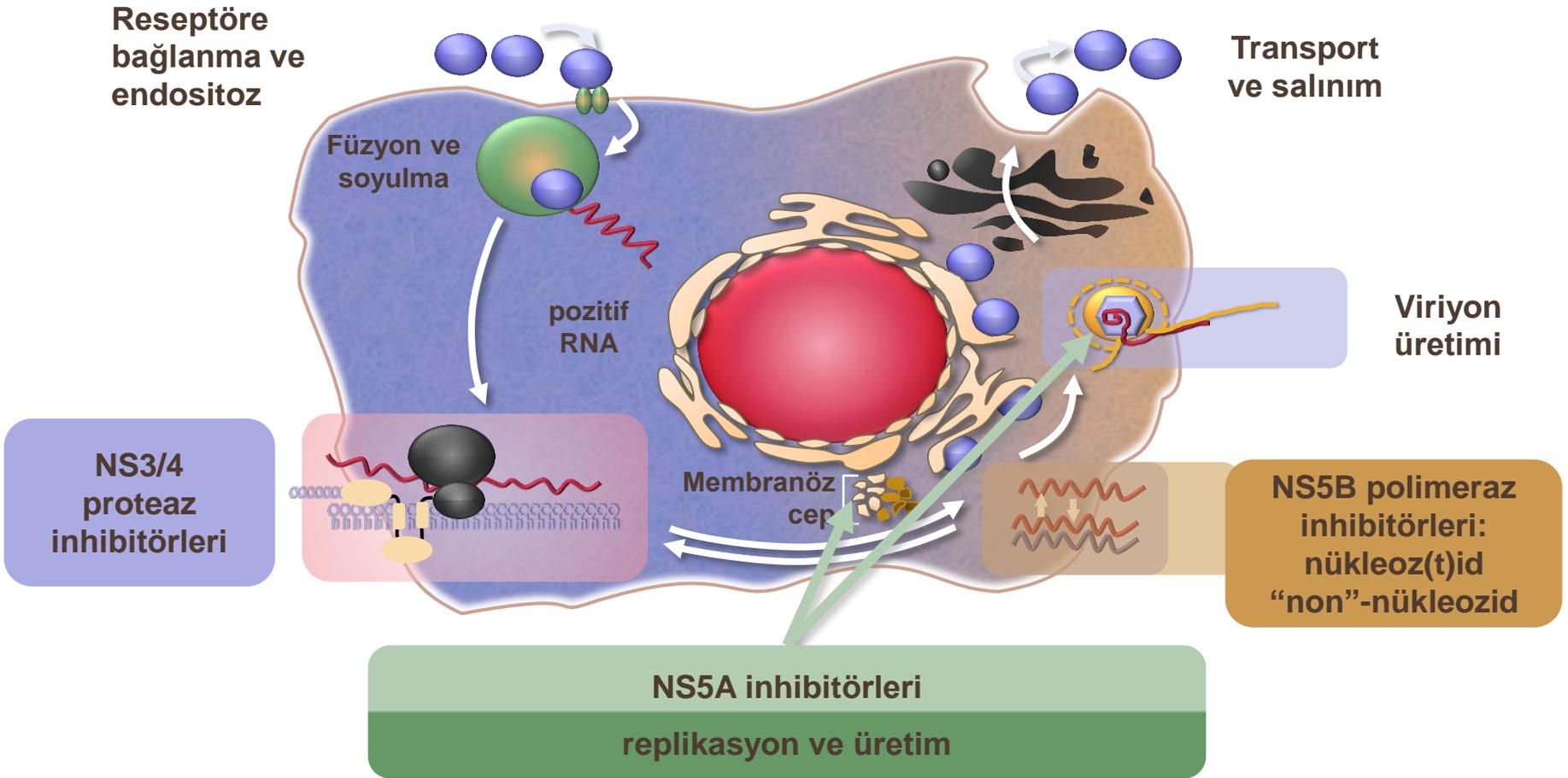
### - Viral proteazlar:

- Viral sistein proteaz (NS2)
- Esas viral serin proteaz (NS3)
- NS4A proteini NS3 proteaz için ko-faktör

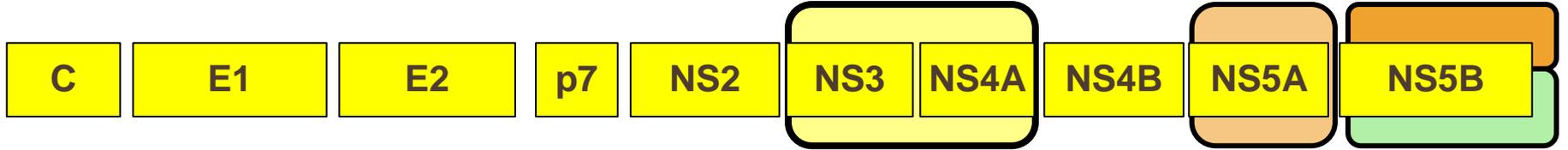
### - Viral proteinler HCV RNA 'yı çoğaltmak için replikasyon kompleksi yapar:

- NS3/4A kompleksi
- NS4B
- NS5A
- HCV RNA polimeraz (NS5B)

# Doğrudan etkili antiviral ajanlar için hedefler



# Doğrudan etkili antiviral ajanlar



## NS3/4A Proteaz inhibitörleri (Pi)

Yüksek potens

Sınırlı genotipik kapsam

Düşük direnç bariyeri

Telaprevir  
Boceprevir  
Simeprevir  
Danoprevir  
Faldaprevir  
Asunaprevir  
Paritaprevir  
Grazoprevir  
Vaniprevir  
Sovaprevir

## NS5B Nükleoz(t)id inhibitörleri (NI)

Orta ve yüksek potens

Pangenotipik kapsam

Yüksek direnç bariyeri

Sofosbuvir  
Mericitabine  
IDX-184  
ALS-2200

## NS5A inhibitörleri

Yüksek potens

Multigenotipik kapsam

Düşük direnç bariyeri

Daklatasvir  
Ledipasvir  
Ombitasvir  
Elbasvir  
Samatasvir  
GS-5885  
GS-5816 (Velpatasvir)  
PPI-668 (Ravidasvir)  
GSK2336805  
ACH-3102  
MK-8742

## NS5B "Non"- nükleozid inhibitörleri (NNI)

Orta potens

Sınırlı genotipik kapsam

Düşük direnç bariyeri

ABT-072  
ABT-333  
BI-207127  
BMS-791325  
GS-9669  
Setrobuvir  
Tegobuvir  
Dasabuvir  
Deleobuvir  
PPI-383  
VX222

# Doğrudan etkili antivirallerin etkinlik/yan etki profilleri

Özellik	Proteaz inhibitörü*	Proteaz inhibitörü**	NS5A inhibitörü	Nük. polimeraz inhibitörü	“Non”-nük. polimeraz inhibitörü
Direnç profili	●	●	●	●	●
Tüm genotiplere etkinlik	●	●	●	●	●
Antiviral potens	●	●	●	●	●
Yan etkiler	●	●	●	●	●

● İyi profil

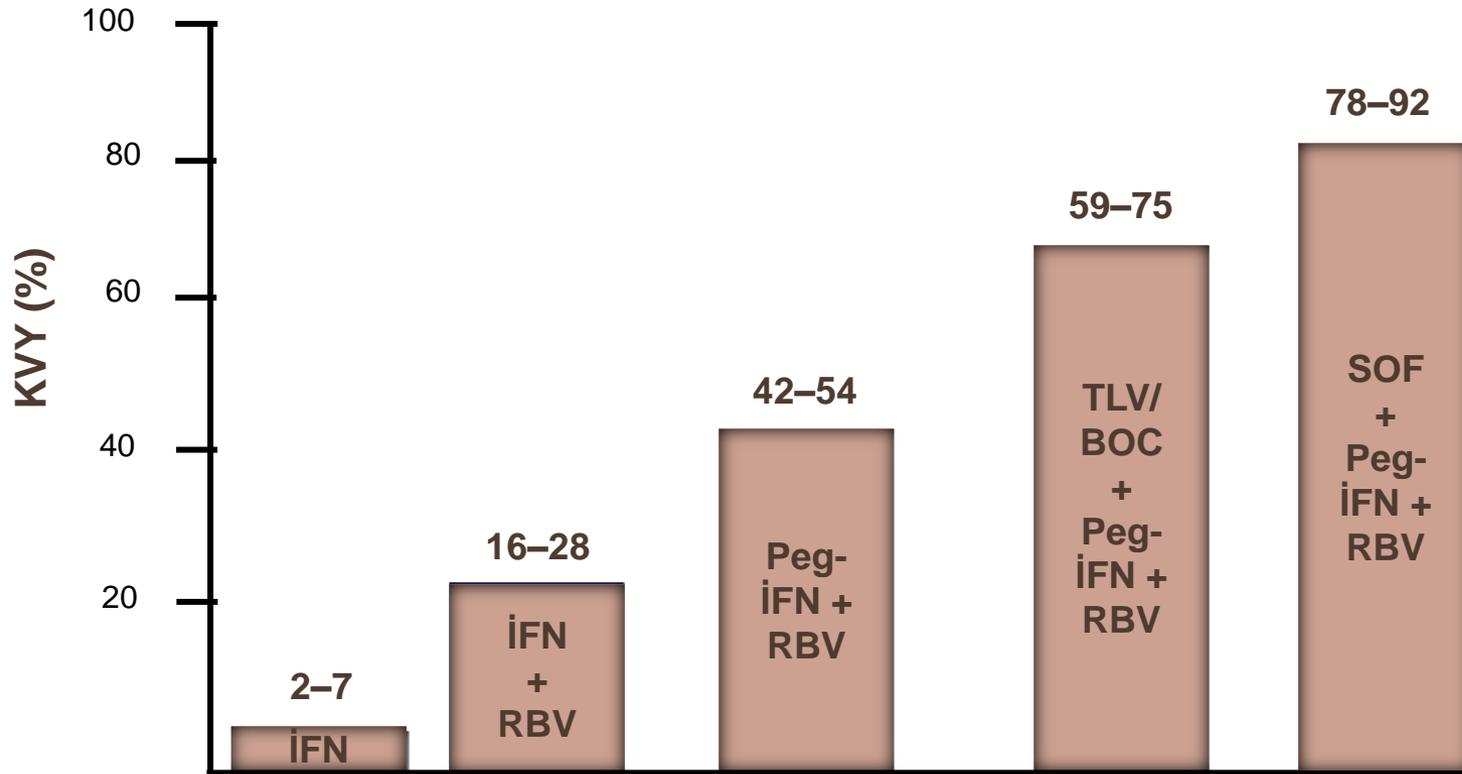
● Orta profil

● Kötü profil

\*Birinci jenerasyon

\*\*İkinci jenerasyon

# Tedavideki süreç



# Tedavi hedefi



- Daha etkili
- Daha iyi tolere edilebilen
- Daha kısa tedavi süresi olan
- Daha kolay kullanılabilen



**Kronik hepatit C tedavisinde  
ombitasvir/paritaprevir/ritonavir + dasabuvir  
kombinasyonu**



# Üç direkt etkili antiviral kombinasyonu

- ❖ **Ombitasvir (OBV):** HCV NS5A inhibitörü
- ❖ **Paritaprevir (PTV):** HCV NS3/4A proteaz inhibitörü
- ❖ **Ritonavir (RTV):** HCV'ye karşı aktif değil, paritaprevirin sistemik etkinliğini artıran CYP3A inhibitörü



-Kombine preparat-

12,5 mg ombitasvir / 75 mg paritaprevir / 50 mg ritonavir (**viekirax**)

+

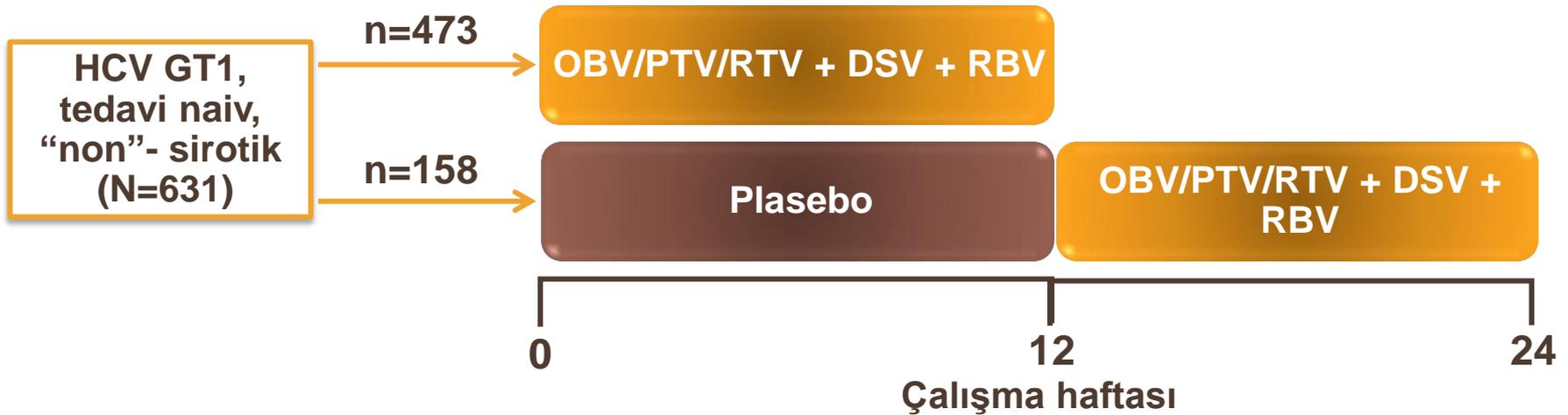
- ❖ **Dasabuvir (DSV):** HCV RNA-bağımlı RNA polimeraz NS5B “non”-nükleozid inhibitörü  
250 mg dasabuvir (**exviera**)

**Genotip 1 ile infekte naiv veya tedavi deneyimli,  
sirotik olmayan hastalarda  
ombitasvir/paritaprevir/ritonavir + dasabuvir  $\pm$   
ribavirin kombinasyon tedavisi**

# SAPPHIRE-I:

## Naiv, sirotik olmayan hastalarda tedavi

### -Çalışma tasarımı-

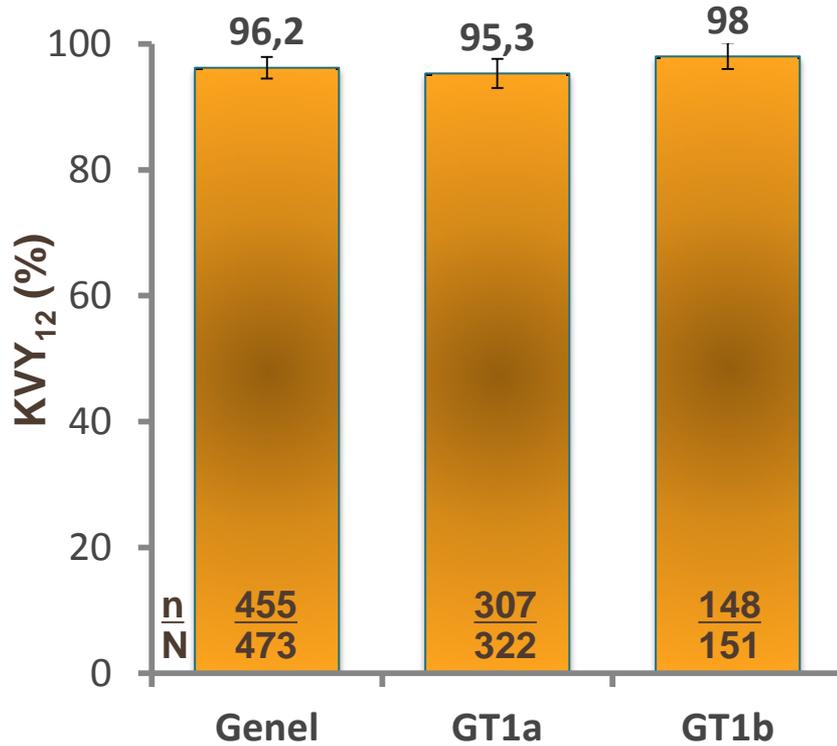


- OBV/PTV/RTV 25 mg/150 mg/100 mg (sabah 2 tablet/gün)
- DSV 250 mg – 2x1 tablet/gün
- RBV kiloya bağlı olarak günde iki kez

# Demografik özellikler

Hasta özellikleri	OBV/PTV/RTV + DSV + RBV (n= 473)	Plasebo (n= 158)
Erkek, n (%)	271 (57.3)	73 (46.2)
İrk, n (%)		
Beyaz	428 (90.5)	144 (91.1)
Siyah	26 (5.5)	8 (5.1)
Diğer	19 (4)	6 (3.8)
Hispanik veya Latin, n (%)	27 (5.7)	5 (3.2)
Yaş (yıl), ortalama	49.4 (18-70)	51.2 (21-70)
VKİ (kg/m <sup>2</sup> ), ortalama	25.7 (18-38.4)	26.2 (18.5-39.4)
Fibroz düzeyi ≥ F2, n (%)	110 (23.3)	42 (26.6)
İL28B CC genotipi, n (%)	144 (30.4)	50 (31.6)
HCV genotipi, n (%)		
1a	322 (68.1)	105 (66.5)
1b	151 (31.9)	53 (33.5)
HCV RNA log <sub>10</sub> İÜ/ml, ortalama	6.4 ± 0.62	6.47 ± 0.65

# Subtiplere göre KVV<sub>12</sub> oranları ve tedavi sonuçları



Sonuçlar	OBV/PTV/RTV + DSV + RBV N/n (%)
KVV <sub>12</sub>	455/473 (96.2)
Virolojik başarısızlık	
Alevlenme	1 (0.2)
Relaps	7 (1.5)
Yan etkiye bağlı çalışma ilacına devamsızlık	3 (0.6)
Tedavi sonrası takipte kayıp	2 (0.4)

# SAPPHIRE-II:

## Tedavi deneyimli, sirotik olmayan hastalarda tedavi-Çalışma tasarımı-



- OBV/PTV/RTV 25 mg/150 mg/100 mg (sabah 2 tablet/gün)
- DSV 250 mg – 2x1 tablet/gün
- RBV kiloya bağlı olarak günde iki kez

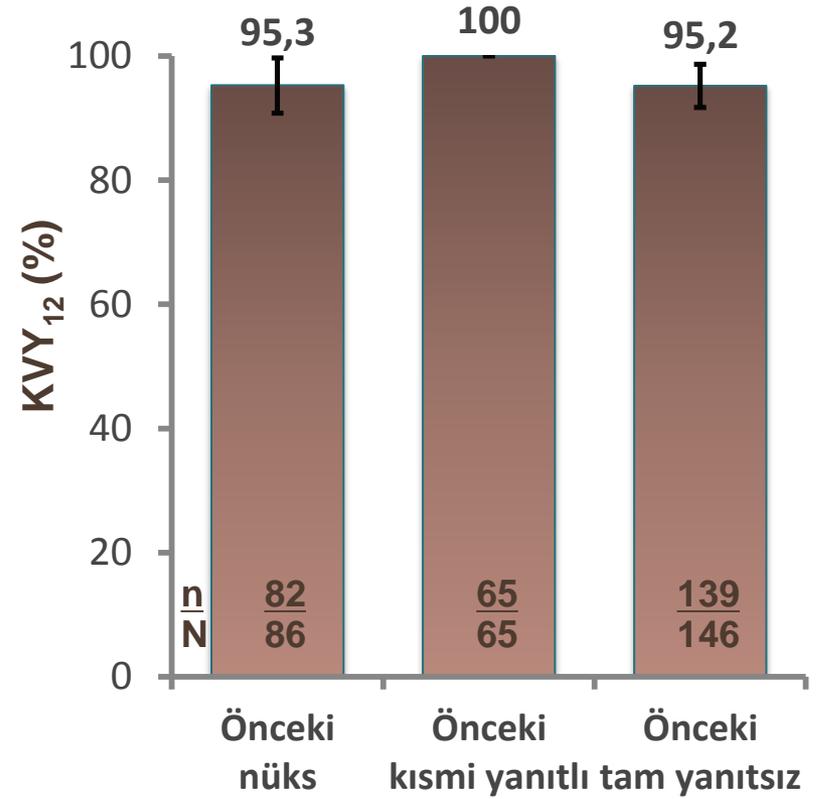
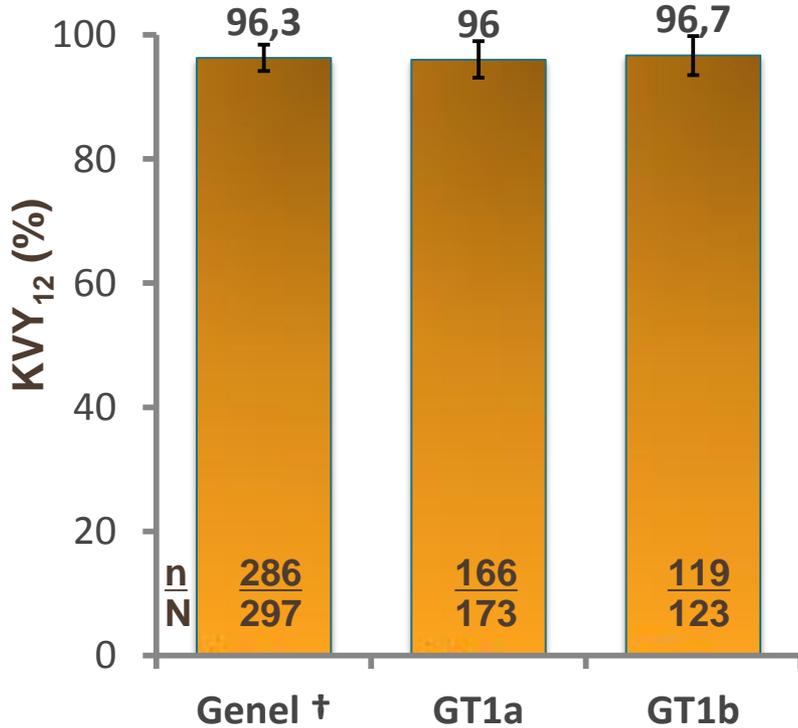
# Demografik özellikler (1)

Hasta özellikleri	OBV/PTV/RTV + DSV + RBV (n= 297)	Plasebo (n= 97)
<b>Erkek, n (%)</b>	167 (56.2)	60 (61.9)
<b>İrk, n (%)</b>		
Beyaz	269 (90.6)	86 (88.7)
Siyah	22 (7.4)	10 (10.3)
Asya	6 (2)	0 (0)
<b>Hispanik veya Latin, n (%)</b>	22 (7.4)	3 (3.1)
<b>Coğrafya, n (%)</b>		
Kuzey Amerika	136 (45.8)	33 (34)
Avrupa	150 (50.5)	61 (62.9)
Avustralya veya Yeni Zelanda	11 (3.7)	3 (3.1)
<b>Yaş (yıl), ortalama</b>	51.7 (19-71)	54.9 (30-69)
<b>VKİ (kg/m<sup>2</sup>), ortalama</b>	26.3 (18.1-38.1)	26.4 (18.5-36.7)

# Demografik özellikler (2)

Hasta özellikleri	OBV/PTV/RTV + DSV + RBV (n= 297)	Plasebo (n= 97)
Fibroz düzeyi (F2 veya F3), n (%)	95 (32)	32 (33)
İL28B CC genotipi, n (%)	34 (11.4)	7 (7.2)
HCV genotipi, n (%)		
1a	173 (58.2)	57 (58.8)
1b	123 (41.4)	40 (41.2)
HCV RNA log <sub>10</sub> İÜ/ml, ortalama	6.55 (4.61-7.70)	6.52 (5.20-7.55)
Önceki Peg-İFN/RBV tedavisi, n (%)		
Tam yanıtızsız	146 (49.2)	47 (48.5)
Kısmi yanıtlı	65 (21.9)	21 (21.6)
Relaps	146 (49.2)	29 (29.9)

# Subtiplere göre ve önceki tedavi yanıtlarına göre KVV<sub>12</sub> oranları



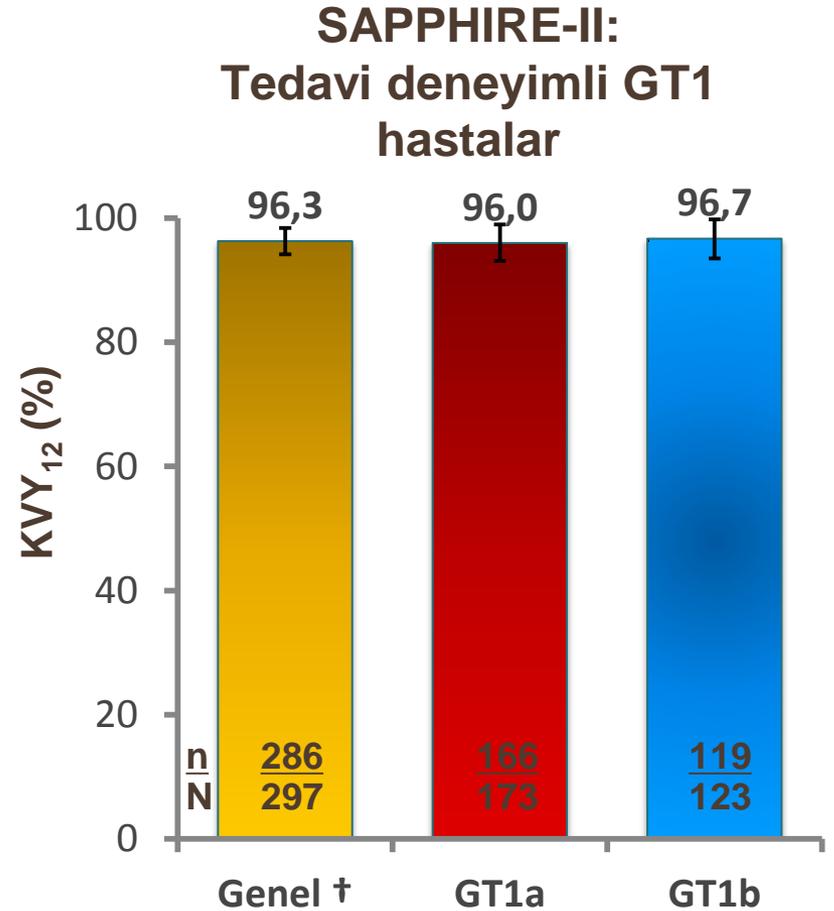
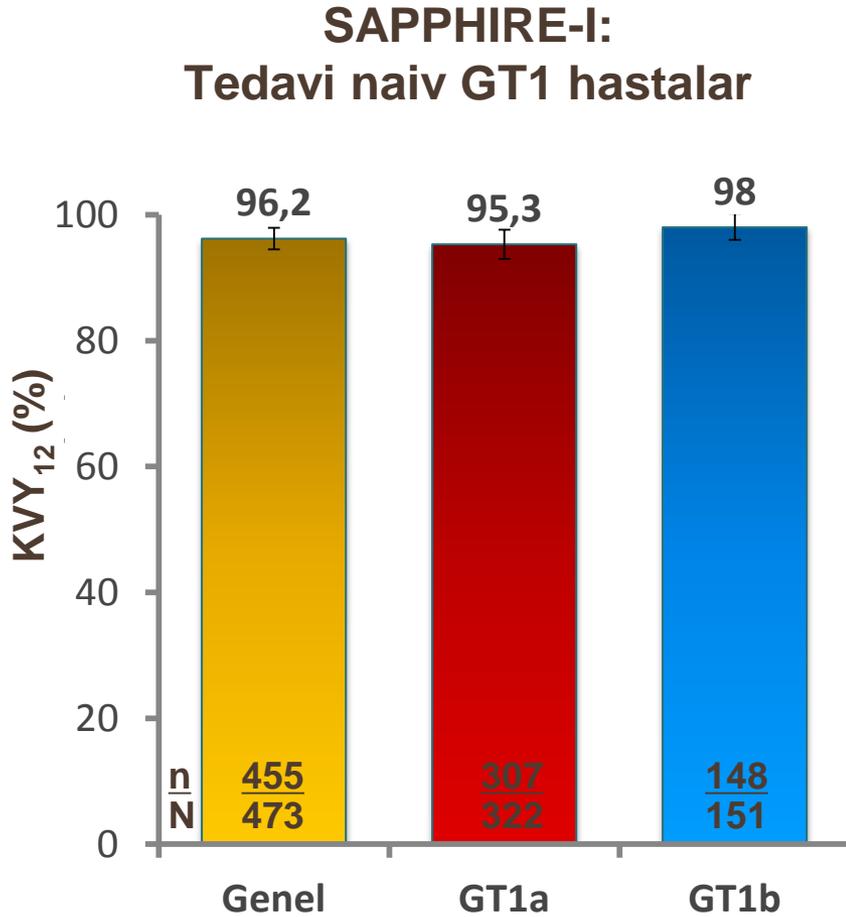
† Bir hastada suptipleme yapılamamış (%95 güvenlik aralığı)

# Tedavi sonuçları

	<b>Tüm hastalar (N= 297)</b>	<b>PR relaps (N= 86)</b>	<b>PR kısmi yanıtlılar (N= 65)</b>	<b>PR tam yanıtsızlar (N= 146)</b>
<b>KVY<sub>12</sub>, n/N (%)</b>	<b>286/297 (96.3)</b>	<b>82/86 (95.3)</b>	<b>65/65 (100)</b>	<b>139/146 (95.2)</b>
<b>Virolojik başarısızlık, n (%)</b>				
<b>Alevlenme</b>	<b>0 (0)</b>	<b>0 (0)</b>	<b>0 (0)</b>	<b>0 (0)</b>
<b>Relaps</b>	<b>7 (2.4)</b>	<b>1 (1.2)</b>	<b>0 (0)</b>	<b>6 (4.1)</b>
<b>Çalışma ilacını erken bırakma,* n (%)</b>	<b>4 (1.4)</b>	<b>3 (3.5)</b>	<b>0 (0)</b>	<b>1 (0.6)</b>

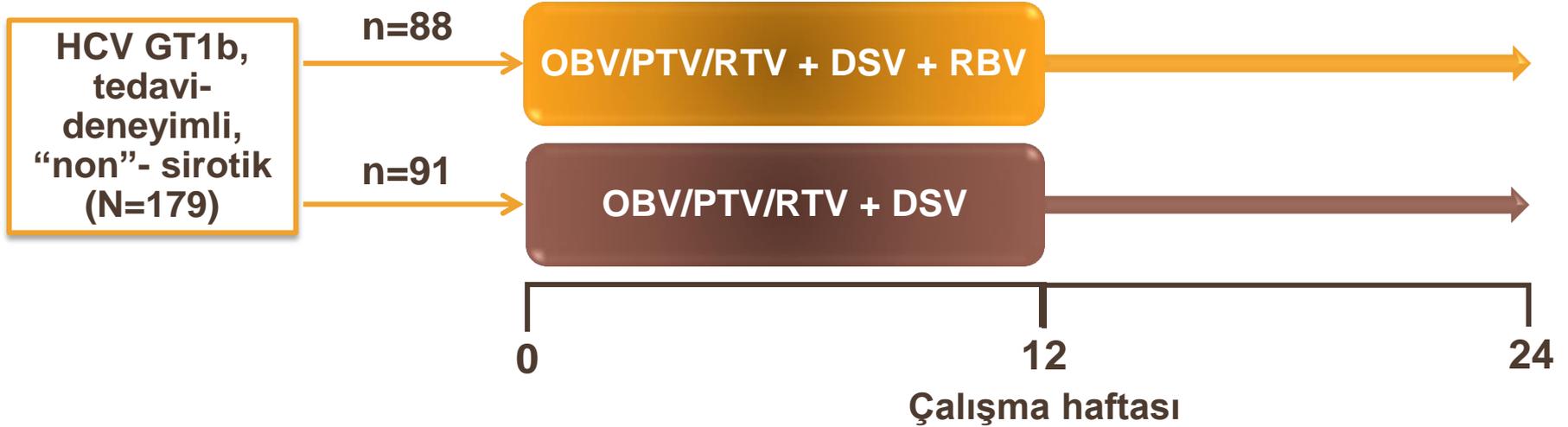
\*Alevlenme olmaksızın

# SAPPHIRE-I ve SAPPHIRE-II: Etkinlik



# PEARL-II:

## Tedavi deneyimli, sirotik olmayan hastalarda tedavi-Çalışma tasarımı-



- OBV/PTV/RTV 25 mg/150 mg/100 mg (sabah 2 tablet/gün)
- DSV 250 mg – 2x1 tablet/gün
- RBV kiloya bağlı olarak günde iki kez

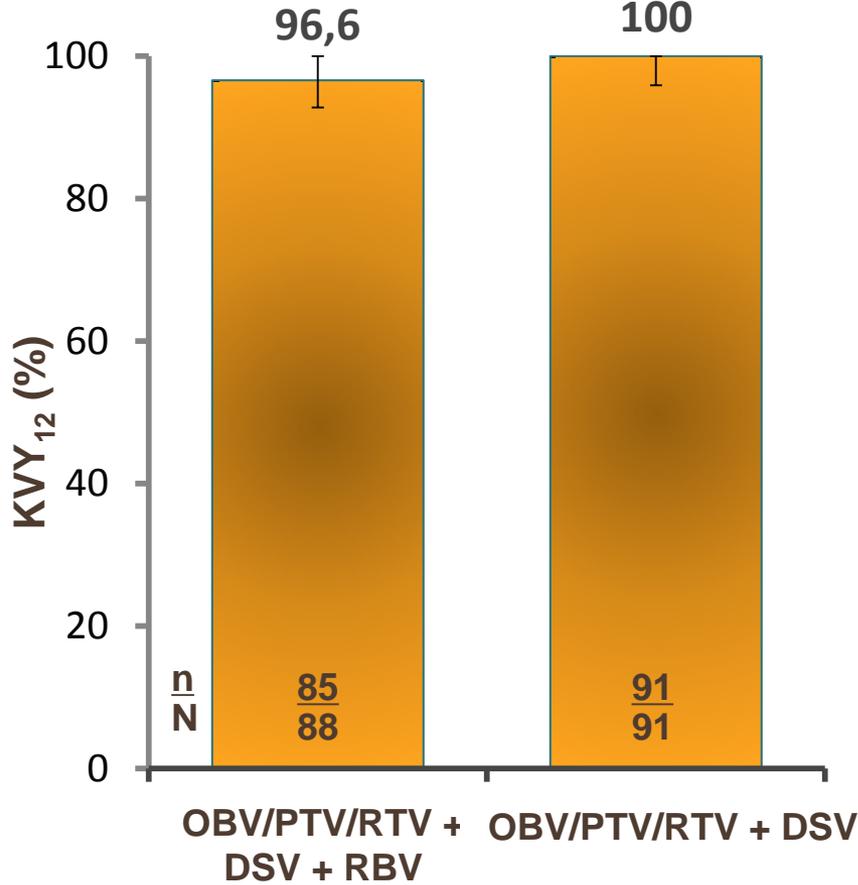
# Demografik özellikler (1)

Hasta özellikleri	OBV/PTV/RTV + DSV + RBV (n= 91)	OBV/PTV/RTV + DSV (n= 95)
Erkek, n (%)	45 (49.5)	57 (60)
İrk, n (%)		
Beyaz	84 (92.3)	86 (90.5)
Siyah	3 (3.3)	26 (6.3)
Hispanik veya Latin, n (%)	4 (4.4)	2 (2.1)
Coğrafya, n (%)		
Kuzey Amerika	14 (15.4)	19 (20)
Avrupa	77 (84.6)	76 (80)
Yaş (yıl), ortalama $\pm$ SD	54.1 $\pm$ 10.9	54.2 $\pm$ 10.5
VKİ (kg/m <sup>2</sup> ), ortalama $\pm$ SD	26.2 $\pm$ 4.1	27.5 $\pm$ 4.3

# Demografik özellikler (2)

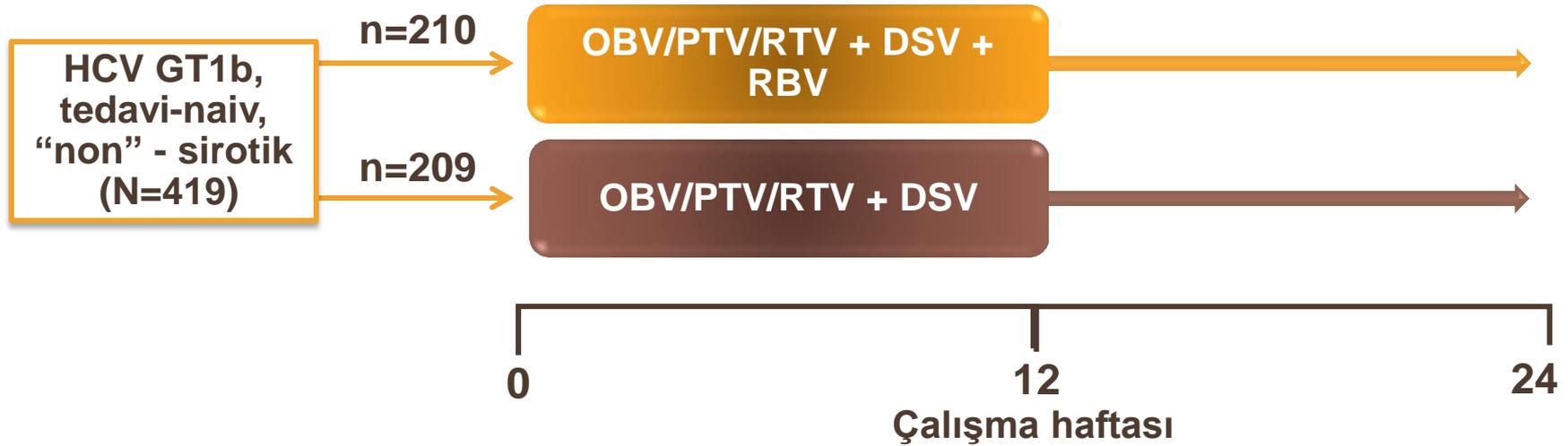
Hasta özellikleri	OBV/PTV/RTV + DSV + RBV (n= 100)	OBV/PTV/RTV + DSV (n= 205)
IL28B CC genotipi, n (%)	10 (11)	7 (7.4)
HCV RNA log <sub>10</sub> İÜ/ml	6.56 ± 0.56	6.48 ± 0.53
Önceki Peg-İFN/RBV tedavisi, n (%)		
Tam yanıtız	32 (35.2)	33 (34.7)
Kısmi yanıtlı	26 (28.6)	27 (28.4)
Nüks	33 (36.3)	35 (36.8)
METAVIR fibroz düzeyi		
F0 veya F1	64 (70.3)	61 (64.2)
F2	13 (14.3)	21 (22.1)
F3	14 (15.4)	13 (13.7)

# Tedavi sonuçları



Sonuçlar	OBV/PTV/RTV + DSV + RBV N/n (%)	OBV/PTV/RTV + DSV N/n (%)
KVV <sub>12</sub>	85/88 (96.6)	91/91 (100)
Virolojik başarısızlık		
Alevlenme	0 (0)	0 (0)
Relaps	0 (0)	0 (0)
Çalışma ilacını bırakma	2 (2.3)	0 (0)
Tedavi bitimi sonrası takipte kayıp	1 (1.1)	0 (0)

# PEARL-III: Naiv, sirotik olmayan hastalarda tedavi -Çalışma tasarımı-

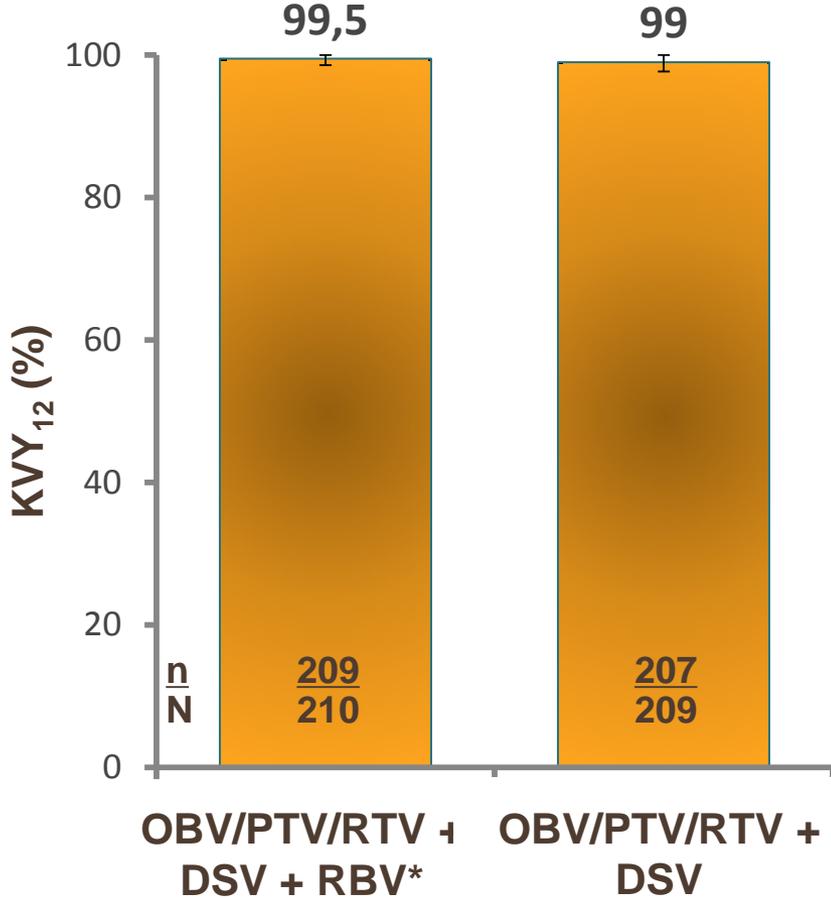


- OBV/PTV/RTV 25 mg/150 mg/100 mg (sabah 2 tablet/gün)
- DSV 250 mg – 2x1 tablet/gün
- RBV kiloya bağlı olarak günde iki kez

# Demografik özellikler

Hasta özellikleri	OBV/PTV/RTV + DSV + RBV (n= 210)	OBV/PTV/RTV + DSV (n= 209)
Erkek, n (%)	106 (50.5)	86 (41.1)
İrk, n (%)		
Beyaz	198 (94.3)	196 (94.2)
Siyah	10 (4.8)	10 (4.8)
Diğer	2 (1)	2 (1)
Hispanik veya Latin, n (%)	2 (1)	5 (2.4)
Coğrafya, n (%)		
Kuzey Amerika	48 (22.9)	47 (22.5)
Avrupa	162 (77.1)	162 (77.5)
Yaş (yıl), ortalama ± SD	48.4 ± 11.9	49.2 ± 12
VKİ (kg/m <sup>2</sup> ), ortalama ± SD	25.8 ± 3.8	26.1 ± 4.2
METAVİR fibroz düzeyi		
F0 veya F1	150/210 (71.4)	141/208 (67.8)
F2	38/210 (18.1)	47/208 (22.6)
F3	22/210 (10.5)	20/208 (9.6)
İL28B CC genotipi, n (%)	44 (21)	44 (21.1)
HCV RNA log <sub>10</sub> İÜ/ml	6.29 ± 0.77	6.33 ± 0.67
HCV RNA ≥ 800,000 İÜ/ml, n (%)	159 (75.7)	148 (70.8)

# Tedavi sonuçları

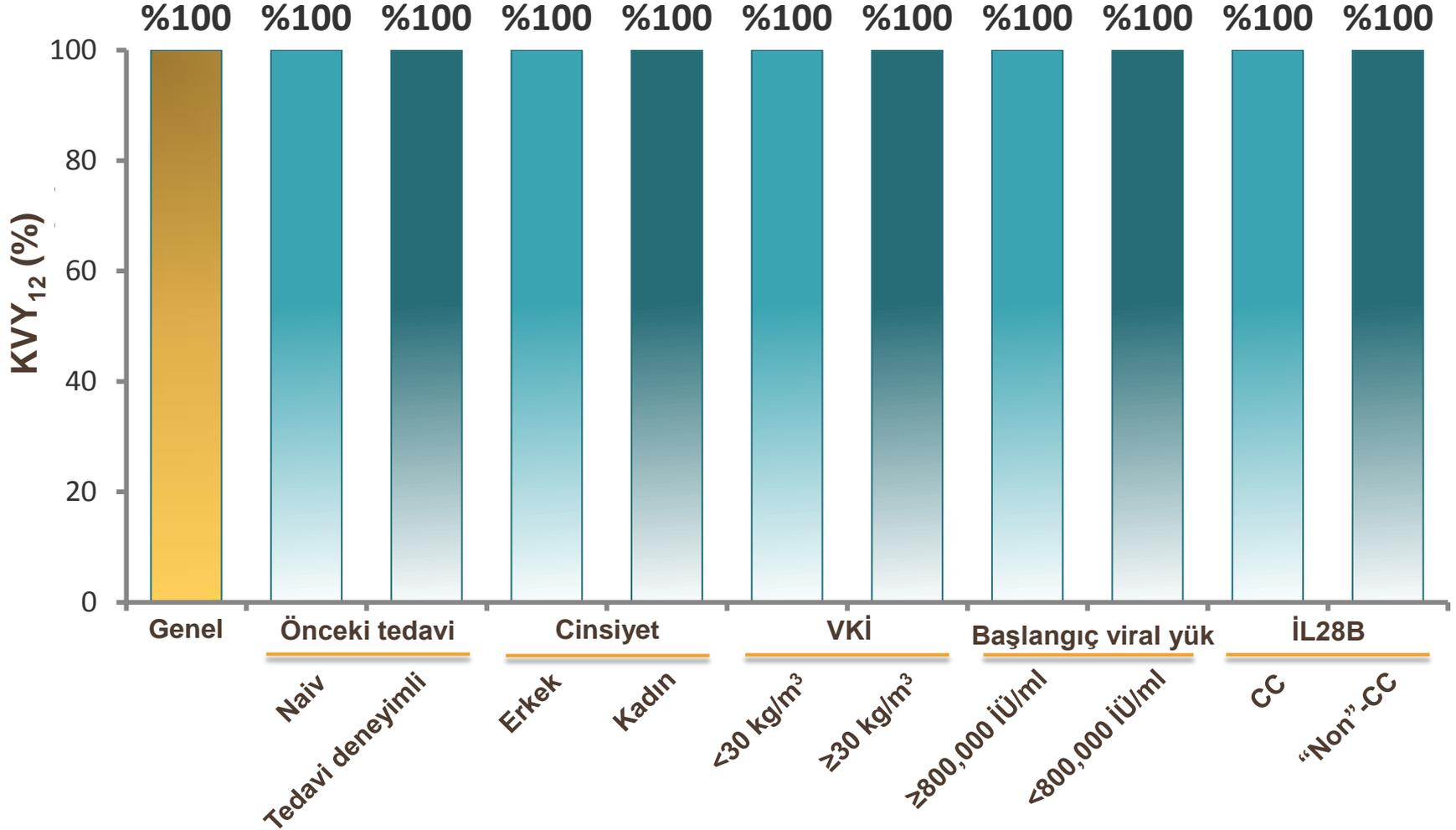


Sonuçlar	OBV/PTV/RTV + DSV + RBV N/n (%)	OBV/PTV/RTV + DSV N/n (%)
KVV <sub>12</sub>	209/210 (99.5)	207/209 (99)
Virolojik başarısızlık		
Alevlenme	1 (0.5)*	0 (0)
Relaps	0 (0)	0 (0)
Çalışma ilacını bırakma	0 (0)	0 (0)
Tedavi bitimi sonrası takipte kayıp	0 (0)	2 (1)†

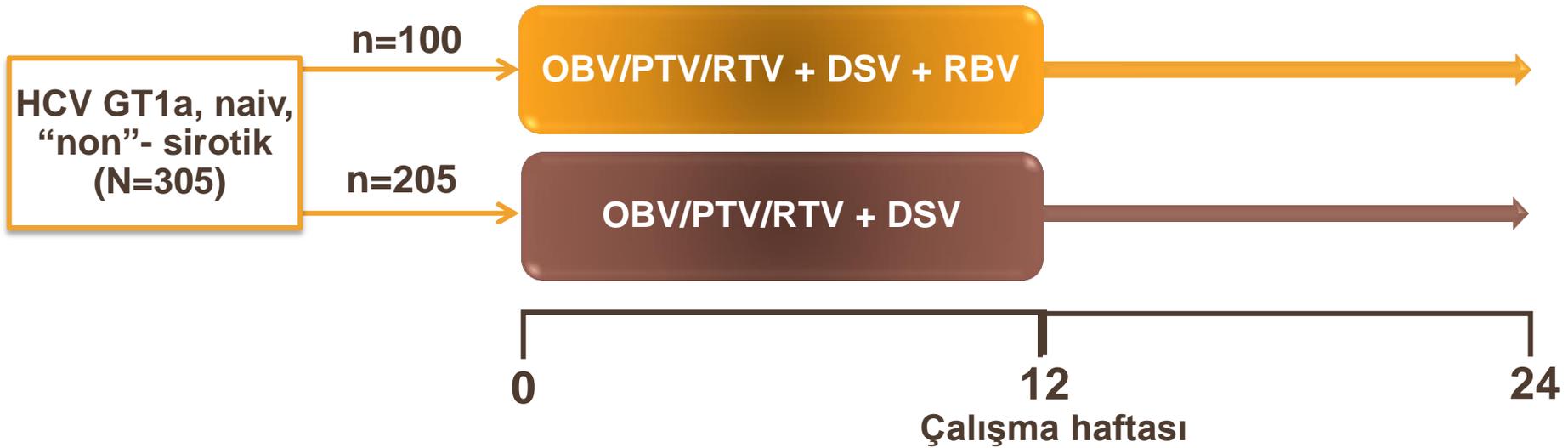
\* Alevlenme olan bir hastada NS5A Y93H polimorfizmi

† İki hasta takip eilememiş, ancak ikisi de KVV<sub>24</sub>'e ulaşmış (%95 güvenlik aralığı)

# PEARL-II ve PEARL-III: Etkinlik



# PEARL-IV: Naiv, sirotik olmayan hastalarda tedavi -Çalışma tasarımı-

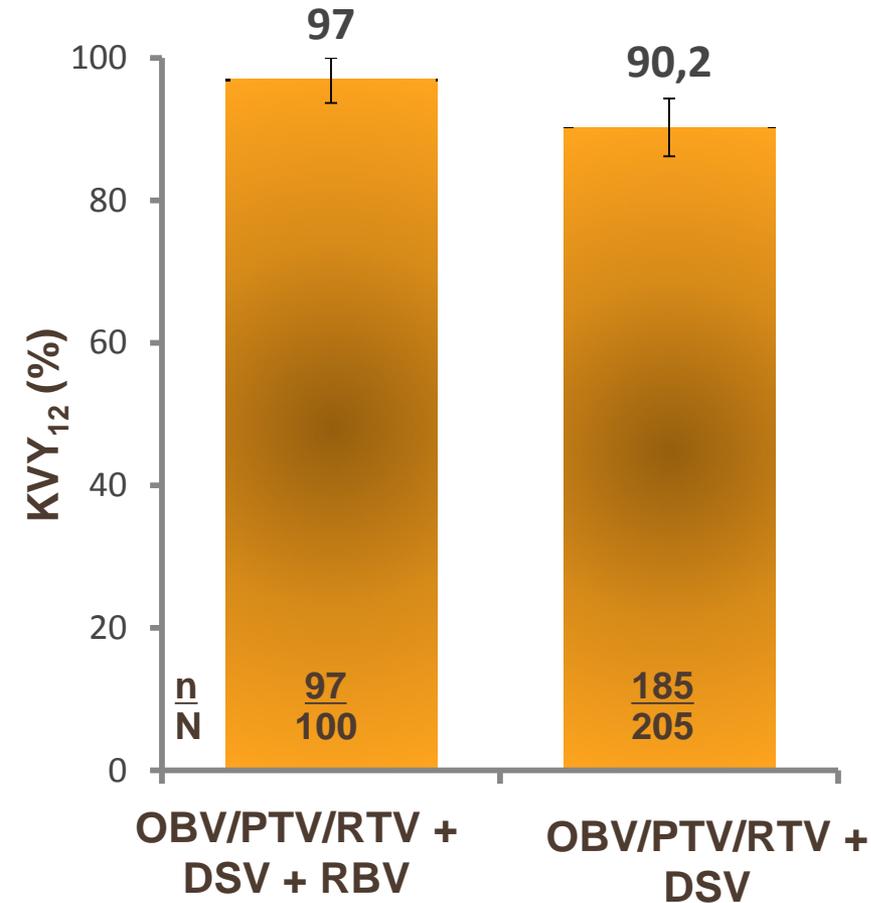


- OBV/PTV/RTV 25 mg/150 mg/100 mg (sabah 2 tablet/gün)
- DSV 250 mg – 2x1 tablet/gün
- RBV kiloya bağlı olarak günde iki kez

# Demografik özellikler

Hasta özellikleri	OBV/PTV/RTV + DSV + RBV (n= 100)	OBV/PTV/RTV + DSV (n= 205)
<b>Erkek, n (%)</b>	70 (70)	129 (62.9)
<b>İrk, n (%)</b>		
Beyaz	86 (86)	171 (83.4)
Siyah	10 (10)	26 (12.7)
Diğer	4 (4)	8 (3.9)
<b>Hispanik veya Latin, n (%)</b>	10 (10)	18 (8.8)
<b>Coğrafya, n (%)</b>		
Kuzey Amerika	92 (92)	186 (90.7)
Avrupa	8 (8)	19 (9.3)
<b>Yaş (yıl), ortalama ± SD</b>	51.6 ± 11	51.4 ± 10.6
<b>VKİ (kg/m<sup>2</sup>), ortalama ± SD</b>	26.9 ± 4	26.7 ± 4.3
<b>METAVİR fibroz düzeyi</b>		
F0 veya F1	63/100 (63)	132/205 (64.4)
F2	21/100 (21)	35/205 (17.1)
F3	16/100 (16)	38/205 (18.5)
<b>IL28B CC genotipi, n (%)</b>	31 (31)	63 (30.7)
<b>HCV RNA log<sub>10</sub> İÜ/ml</b>	6.64 ± 0.5	6.53 ± 0.68
<b>HCV RNA ≥ 800,000 İÜ/ml, n (%)</b>	92 (92)	172 (83.9)

# Tedavi sonuçları

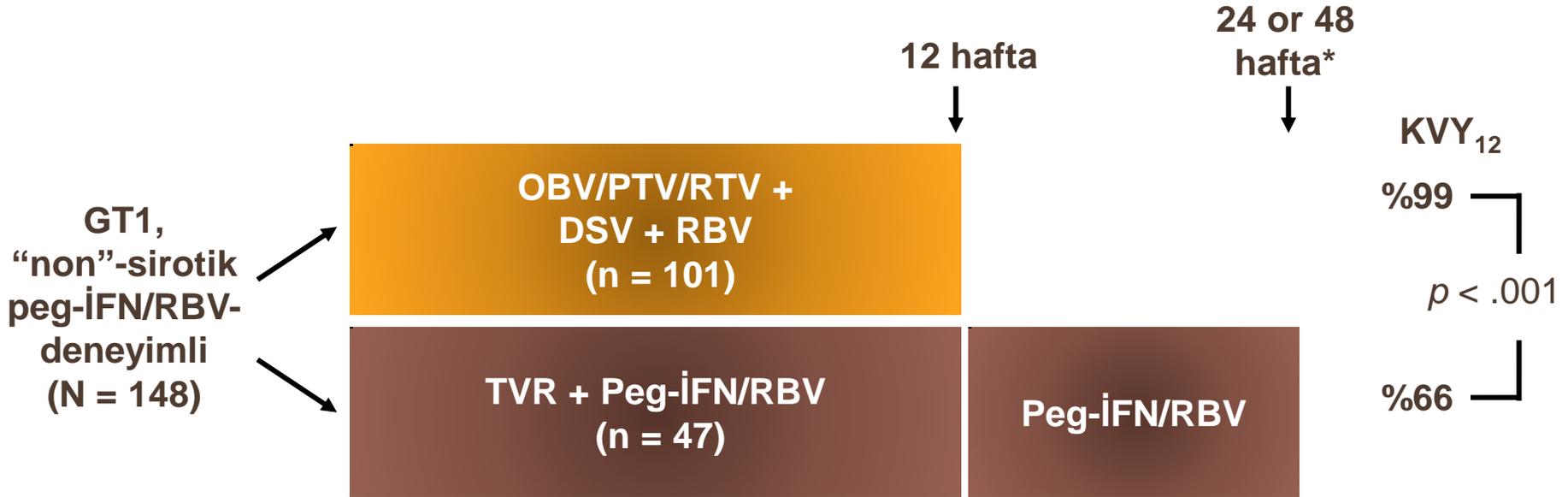


Sonuçlar	OBV/PTV/RTV + DSV + RBV N/n (%)	OBV/PTV/RTV + DSV N/n (%)
KVV <sub>12</sub>	97/100 (97)	185/205 (90.2)
Virolojik başarısızlık		
Alevlenme	1 (1)	6 (2.9)
Relaps	1 (1)	10 (5.2)
Çalışma ilacını bırakma	0 (0)	3 (1.5)
Tedavi bitimi sonrası takipte kayıp	1 (1)	1 (0.5)

(% 95 güvenlik aralığı)

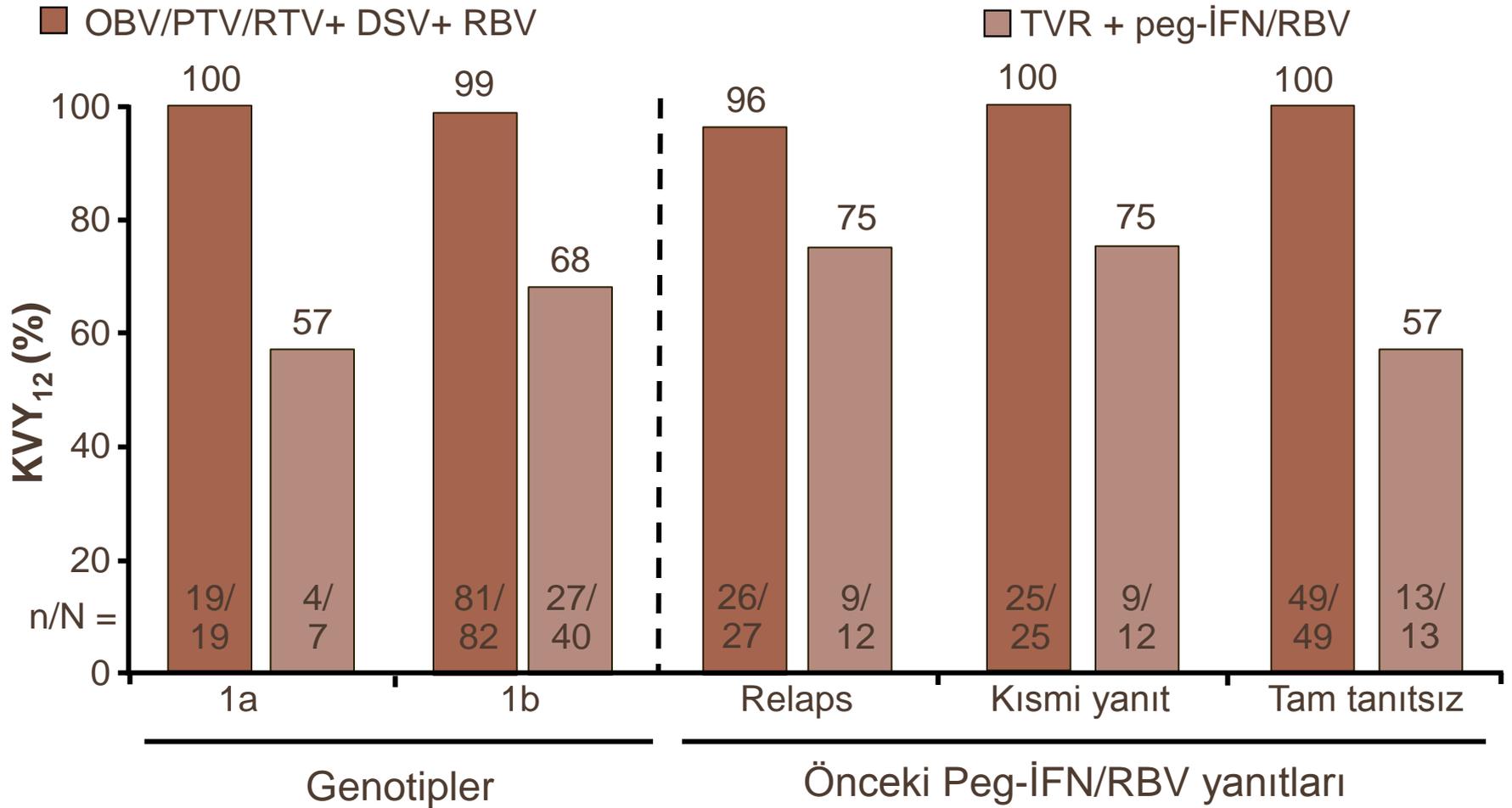
# MALACHITE-II: Tedavi deneyimli hastalarda OBV/PTV/RTV + DSV + RBV tedavisi ile Peg-İFN + RBV + TPV tedavisinin karşılaştırılması

- ❖ Çok merkezli, açık etiketli, randomize faz III çalışma
  - ❖ Hastaların %6'sında fibroz F3 veya üstü, %49'u peg-İFN+RBV'ye tam yanıtızsız, %91'inde *IL28B* genotipi CC dışı, %18'i GT1a infeksiyonu, %100'ü beyaz ırk, ortalama HCV RNA:düzeyi 6.37-6.39 log<sub>10</sub> İÜ/ml

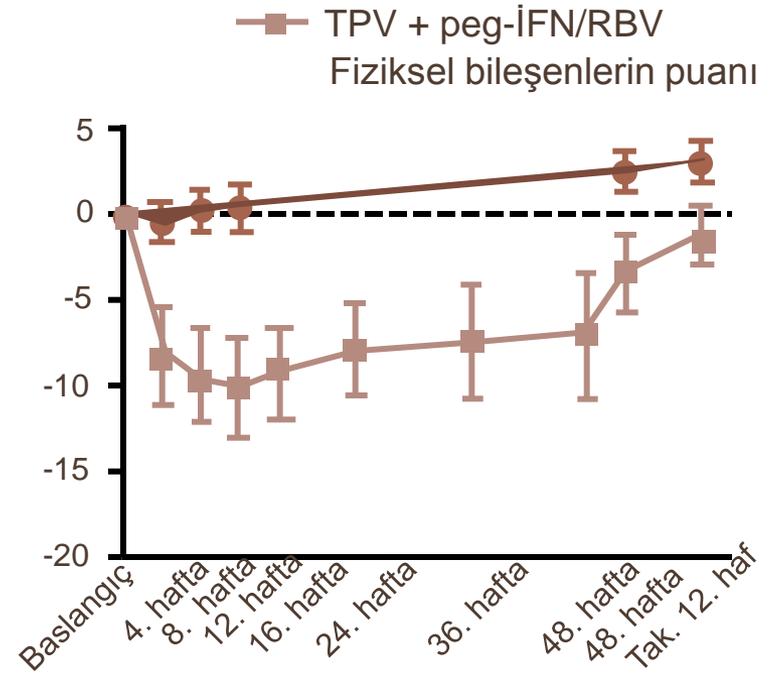
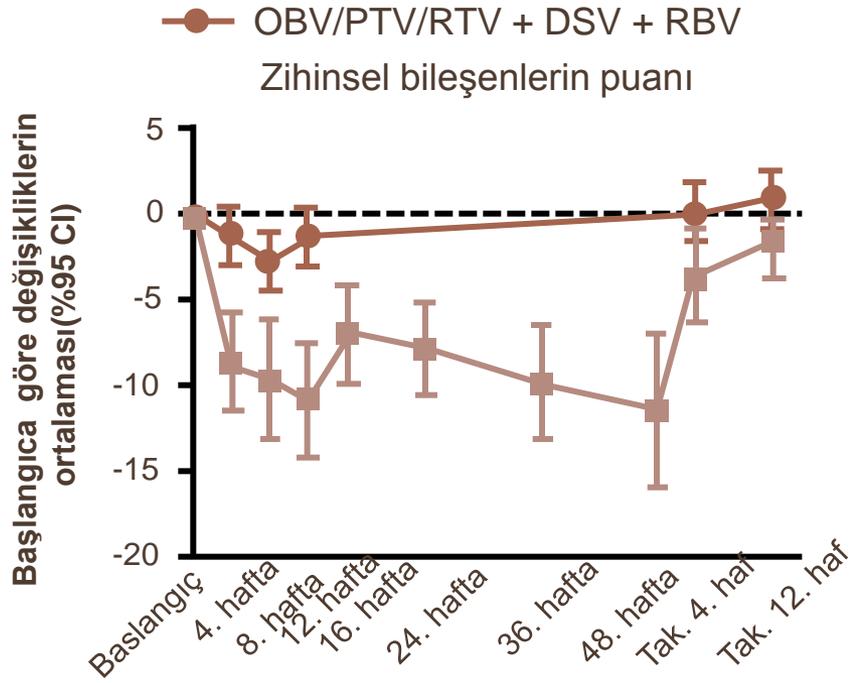


- OBV/PTV/RTV 25 mg/150 mg/100 mg (sabah 2 tablet/gün)
- DSV 250 mg – 2x1 tablet/gün
- TVR 750 mg – 3x1
- Peg-İFN/RBV - TVR'siz 12-36 hafta

# Subgruplara göre KVV<sub>12</sub> oranları



# Yaşam kalitesi ve laboratuvar bulguları

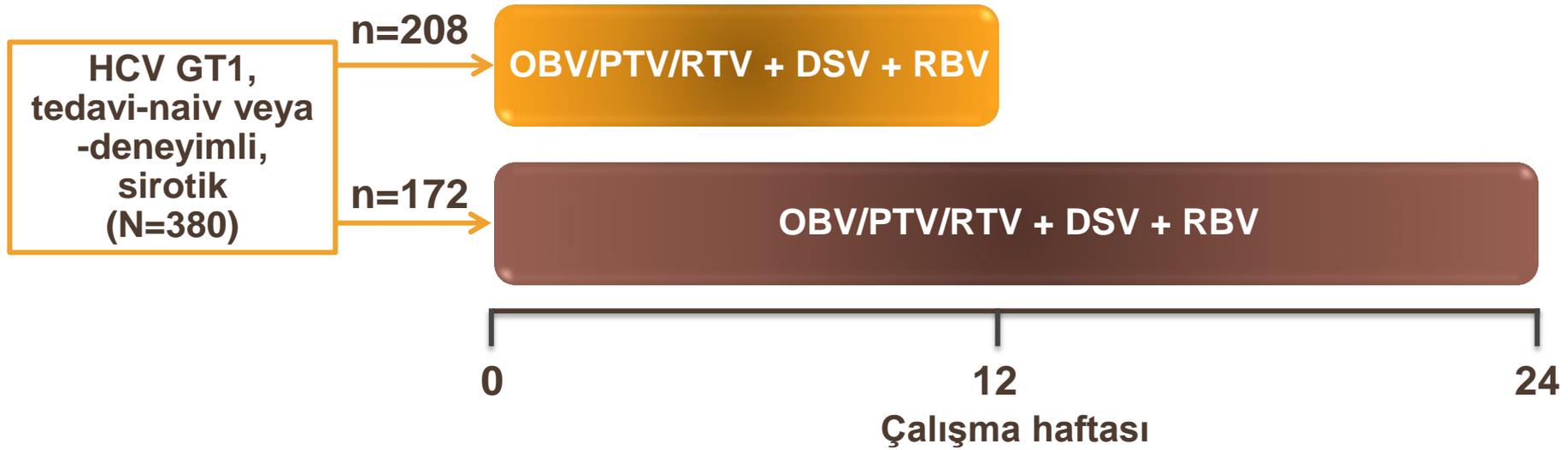


Laboratuvar bozuklukları, %	OBV/PTV/RTV + DSV + RBV (n = 101)	TPV + peg-İFN/RBV (n = 47)
Hemoglobin 8 < 10 g/dl	4	26
Hemoglobin < 8 g/dl	0	9
ALT > 5 x NÜL	1	6

**Genotip 1 ile infekte naiv veya tedavi deneyimli,  
sirotik hastalarda  
ombitasvir/paritaprevir/ritonavir + dasabuvir  $\pm$   
ribavirin kombinasyon tedavisi**

# TURQUOISE-II: Tedavi naiv veya deneyimli, sirotik hastalarda tedavi

## -Çalışma tasarımı-

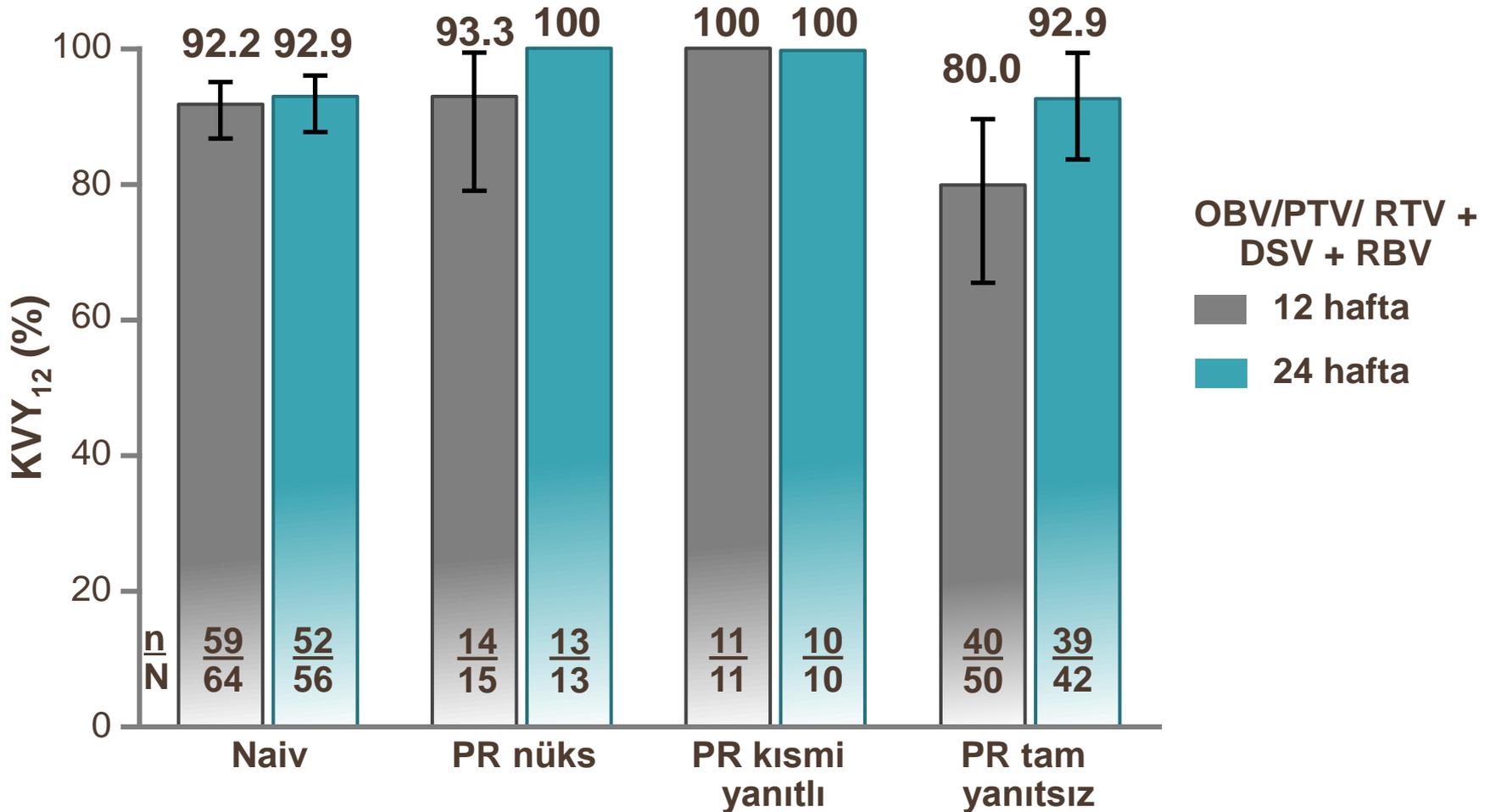


- OBV/PTV/RTV 25 mg/150 mg/100 mg (sabah 2 tablet/gün)
- DSV 250 mg – 2x1 tablet/gün
- RBV kiloya bağlı olarak günde iki kez

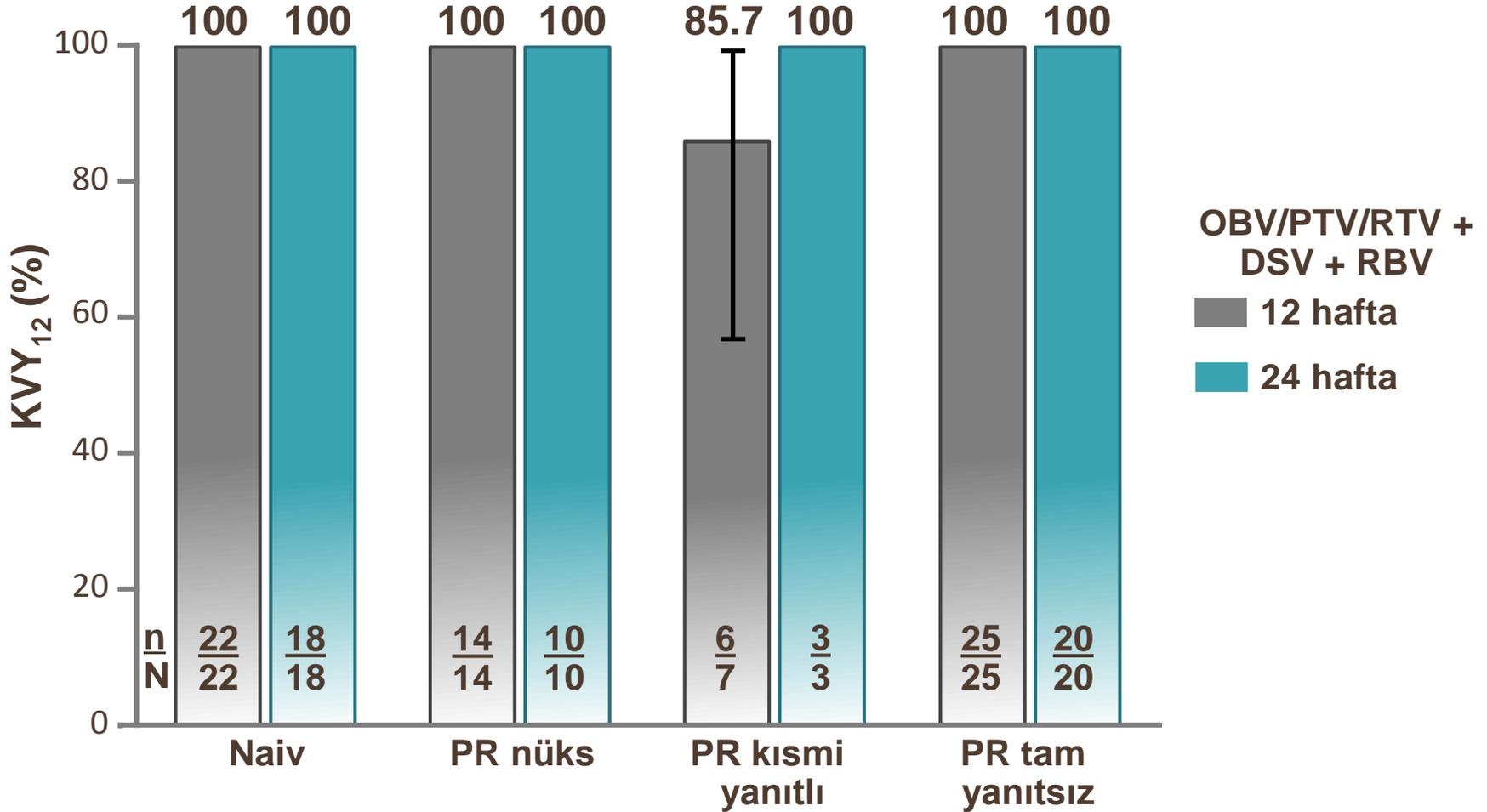
# Demografik özellikler

Hasta özellikleri	12 hafta (n= 208)	24 hafta (n= 172)
Erkek, n (%)	146 (70.2)	121 (70.3)
İrk, n (%)		
Beyaz	199 (95.7)	161 (93.6)
Siyah	6 (2.9)	6 (3.5)
Asya	3 (1.4)	5 (2.9)
Hispanik veya Latin, n (%)	25 (12)	20 (11.6)
Yaş (yıl), ortalama $\pm$ SD	57.1 $\pm$ 7	56.5 $\pm$ 7.9
VKİ (kg/m <sup>2</sup> ), ortalama $\pm$ SD	27.9 $\pm$ 4.1	27.9 $\pm$ 4.3
İL28B “non”- CC, n (%)	173 (83.2)	138 (80.2)
HCV RNA (log <sub>10</sub> İÜ/ml), ortalama $\pm$ SD	6.41 $\pm$ 0.62	6.53 $\pm$ 0.52
Önceki Peg-İFN/RBV tedavisi		
Tam yanıtız	75/122 (61.5)	62/98 (63.3)
Kısmi yanıtılı	18/122 (14.8)	13/98 (13.3)
Nüks	29/122 (23.8)	23/98 (23.5)
Platelet sayısı, x 10 <sup>9</sup> /l		
Ortalama	140 (104-188.5)	142.5 (105-183)
Albumin, g/l		
Ortalama	40 (37-42)	39 (37-42)

# Önceki tedavi yanıtına göre GT1a ile infekte hastalarda $KVY_{12}$ oranları



# Önceki tedavi yanıtına göre GT1b ile infekte hastalarda $KVY_{12}$ oranları



# TURQUOISE-III: Tedavi naiv veya deneyimli, kompanse sirotik hastalarda tedavi -Çalışma tasarımı-

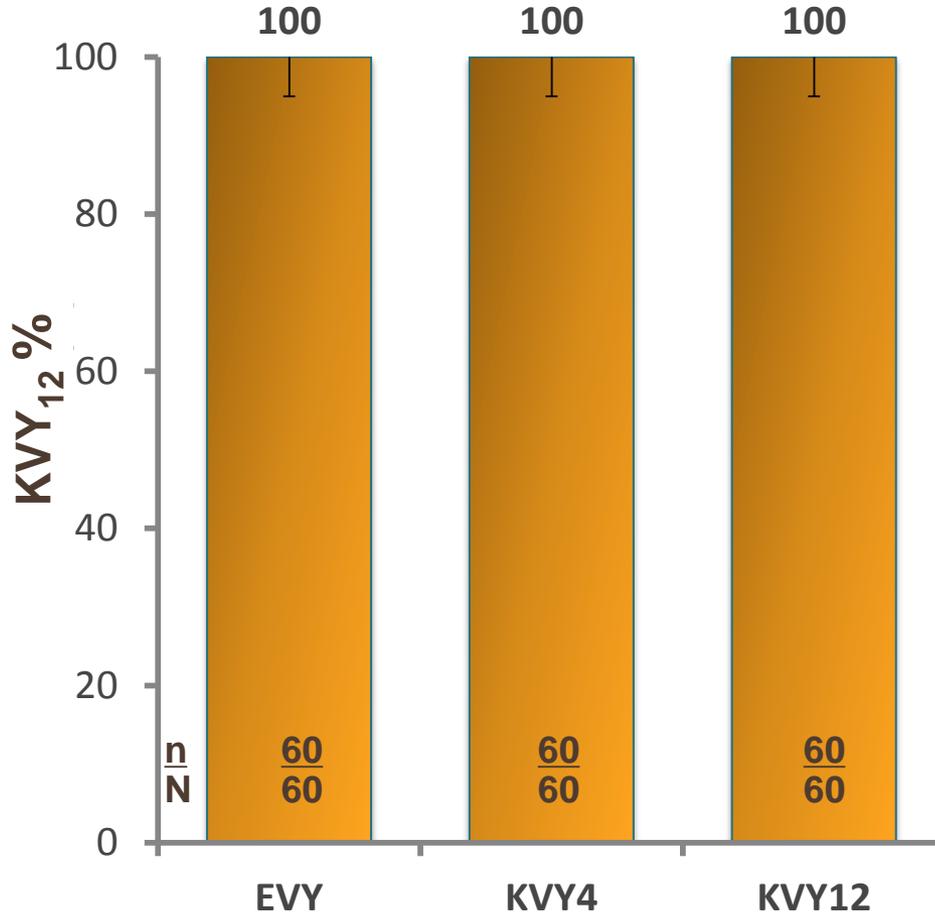


- OBV/PTV/RTV 25 mg/150 mg/100 mg (sabah 2 tablet/gün)
- DSV 250 mg – 2x1 tablet/gün
- RBV kiloya bağlı olarak günde iki kez

# Demografik özellikler

Hasta özellikleri (n= 60)	
Erkek, n (%)	37 (62)
Siyah, n (%)	7 (12)
Yaş (yıl), ortalama $\pm$ SD	59.5 $\pm$ 9.5
VKİ (kg/m <sup>2</sup> ), ortalama $\pm$ SD	27.8 $\pm$ 5.4
İL28B “non”- CC, n (%)	50 (83)
HCV RNA (log <sub>10</sub> İÜ/ml), ortalama $\pm$ SD	6.6 $\pm$ 0.6
Peg-İFN/RBV tedavi deneyimi, n (%)	33 (55)

# KVY<sub>12</sub> oranları

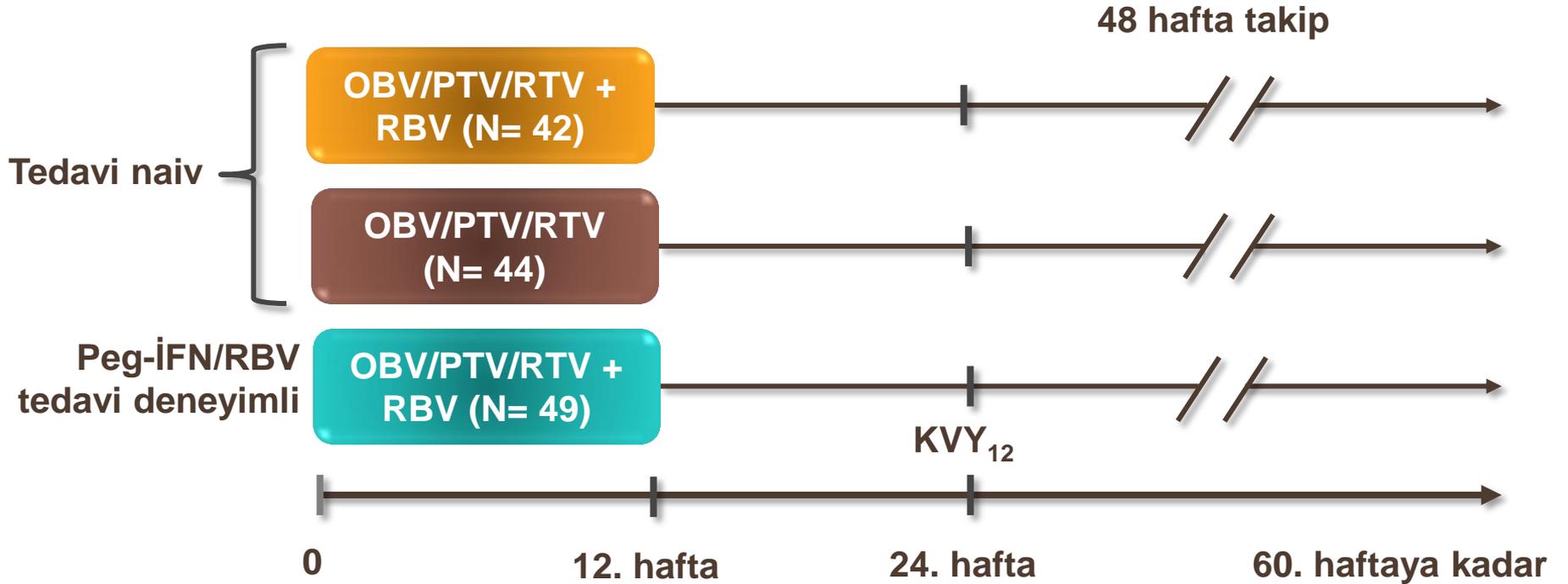


EVY: Erken virolojik yanıt

- ❖ Hastaların tümünde tedavinin dördüncü haftasında HCV RNA değerleri negatifleşmiş
- ❖ Tüm hastalar tedaviyi tamamlamış ve KVY<sub>12</sub> elde edilmiş

**Genotip 4 ile infekte hastalarda  
ombitasvir/paritaprevir/ritonavir  $\pm$  ribavirin  
kombinasyon tedavisi**

# PEARL-I: Çalışma tasarımı



- OBV/PTV/RTV 25 mg/150 mg/100 mg (sabah 2 tablet/gün)
- RBV kiloya bağlı olarak günde iki kez

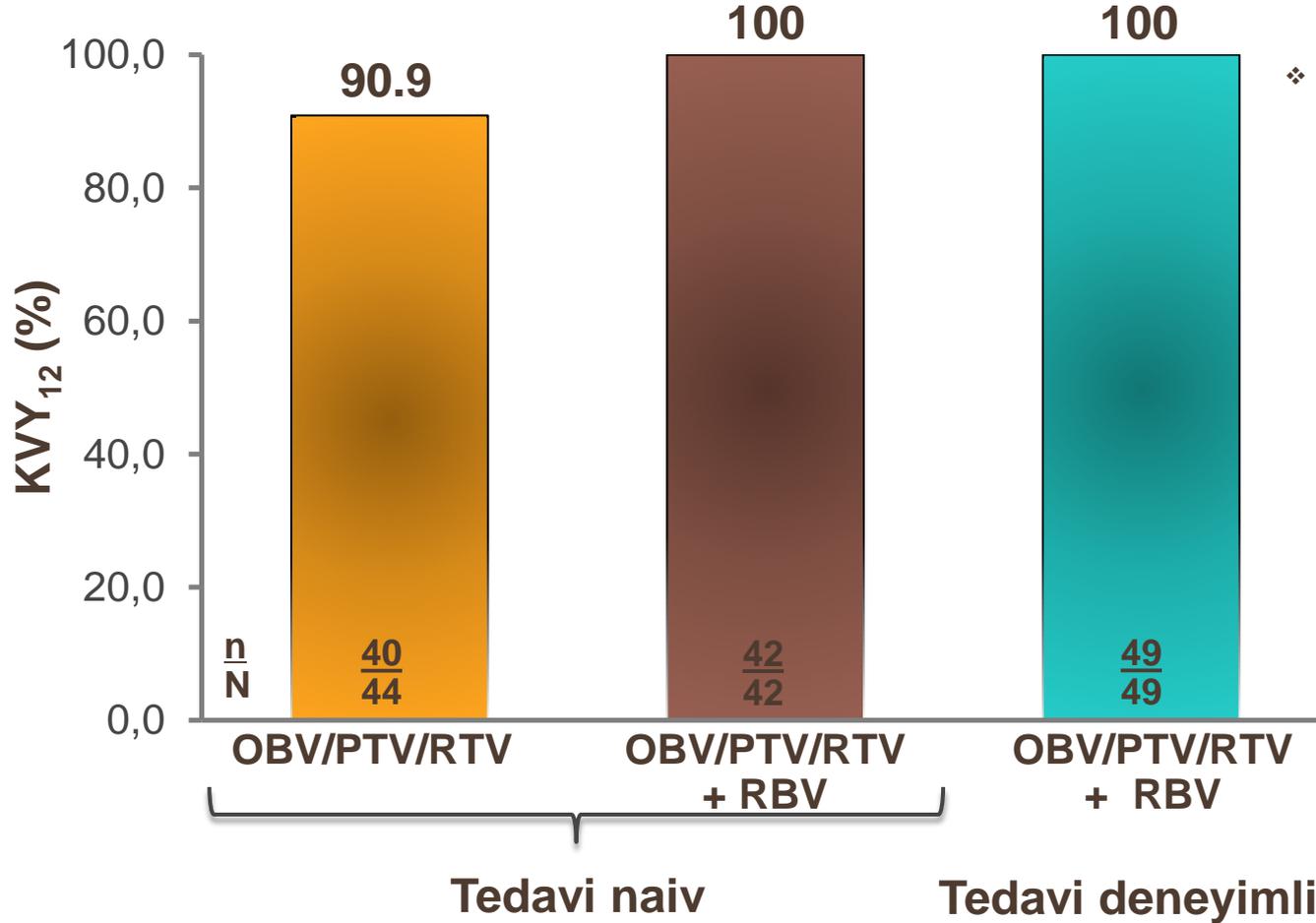
# Demografik özellikler (1)

Hasta özellikleri	Tedavi naiv		Tedavi deneyimli
	OBV/PTV/RTV (n= 44)	OBV/PTV/RTV + RBV (n= 42)	OBV/PTV/RTV + RBV (n= 49)
Erkek, n (%)	24 (55)	28 (67)	36 (74)
Coğrafya, n (%)			
Avrupa	38 (86)	36 (86)	42 (86)
Kuzey Amerika	6 (14)	6 (14)	7 (14)
Yaş (yıl), ortalama	49.0 ± 10	44.0 ± 13	51.0 ± 10
VKİ (kg/m <sup>2</sup> ), ortalama	25.0 ± 4	25.0 ± 4	27.0 ± 4
HCV RNA log <sub>10</sub> İÜ/ml, ortalama	6.1 ± 0.6	6.1 ± 0.6	6.3 ± 0.5
HCV RNA ≥800,000 İÜ/ml	27 (61)	30 (71)	37 (76)

# Demografik özellikler (2)

Hasta özellikleri	Tedavi naiv		Tedavi deneyimli
	OBV/PTV/ RTV (n= 44)	OBV/PTV/ RTV + RBV (n= 42)	OBV/PTV/ RTV + RBV (n= 49)
<b>İL28B genotipi, n (%)</b>			
CC	12 (27)	11 (26)	6 (12)
CT	24 (55)	26 (62)	32 (65)
TT	8 (18)	5 (12)	11 (22)
<b>Fibroz düzeyi, n (%)</b>			
F0-F1	38 (86)	33 (79)	33 (67)
F2	4 (9)	6 (14)	11 (22)
F3	2 (5)	3 (7)	5 (10)
<b>Önceki Peg-İFN/RBV tedavisi n (%)</b>			
Tam yanıtızsız			23 (47)
Kısmi yanıtılı			9 (18)
Relaps			17 (35)

# Tedavi sonuçları



- ❖ Naiv grupta bir hastada alevlenme ve iki hastada relaps
  - ❖ Bu üç hasta da genotip 4d infeksiyonu
  - ❖ Virolojik başarısızlık sırasında bulunan direnç ile ilişkili varyantlar (ağırlıklı olarak NS3'te D168V, NS5A'da L28S veya L28V) tedavi başlangıcında da var
  - ❖ Bu üç hastanın ikisinde İL28B CT, diğerinde ise İL28B TT genotipi

# OBV/PTV/RTV + DSV ± RBV ile yapılan faz III çalışmalarının özeti

Çalışma	Hasta popülasyonu	Tedavi şeması	KVY <sub>12</sub> (%)	Nüks (%)	Vir. başarı-sızlık* (%)
SAPPHIRE-I (n=631)	GT1, “non” sirotik, naiv	OBV/PTV/RTV + DSV + RBV, 12 hafta (n=473) Plasebo, 12 hafta (n=158)	96.2	1.5	0.2
SAPPHIRE-I (n=394)	GT1, “non” sirotik, PR deneyimli	OBV/PTV/RTV + DSV + RBV, 12 hafta (n=297) Plasebo, 12 hafta (n=97)	96.3	2.4	0
PEARL-II (n=179)	GT1b, “non” sirotik, PR deneyimli	OBV/PTV/RTV + DSV + RBV, 12 hafta (n=88) OBV/PTV/RTV +DSV, 12 hafta (n=91)	96.6 100	0	0
PEARL-III (n=419)	GT1b, “non” sirotik, naiv	OBV/PTV/RTV + DSV + RBV, 12 hafta (n=210) OBV/PTV/RTV +DSV, 12 hafta (n=209)	99.5 99	0	0.5 0
PEARL-IV (n=305)	GT1a, “non” sirotik, naiv	OBV/PTV/RTV + DSV+ RBV, 12 hafta (n=100) OBV/PTV/RTV + DSV, 12 hafta (n=205)	97 90.2	1 5.2	1 2.9
TURQUOISE-II (n=380)	GT1, sirotik, naiv ve PR deneyimli	OBV/PTV/RTV + DSV + RBV, 12 hafta (n=208) OBV/PTV/RTV + DSV + RBV, 12 hafta (n=172)	91.8 95.9	5.9 0.6	0.5 1.7
TURQUOISE-III (n=60)	GT1, sirotik, naiv ve PR deneyimli	OBV/PTV/RTV + DSV + RBV, 12 hafta (n=60)	100	0	0

# Ombitasvir/ paritaprevir/ ritonavir + dasabuvir kombinasyonunun özellikleri (1)

- ❖ RBV ile birlikte kullanımda kontrasepsiyon yöntemleri uygulanmalıdır— gebelik kategorisi B (tedavi süresince ve tedavi bitiminden sonra 6 ay süreyle)
- ❖ Emziren kadınlarda kullanılmamalıdır
- ❖ Pediyatrik hastalarda farmakokinetik araştırılmamıştır, 18 yaş altı kullanılmamalıdır
- ❖ Geriyatrik hastalarda, hafif-orta-şiddetli böbrek yetmezliğinde ve hafif-orta karaciğer yetmezliğinde (Child-Pugh A ve B) doz ayarlaması gerekli değildir
- ❖ Şiddetli karaciğer yetmezliğinde (Child-Pugh C) kullanılmamalıdır

# Ombitasvir/ paritaprevir/ ritonavir + dasabuvir kombinasyonunun özellikleri (2)

- ❖ Bir OMV/RTV/RTV dozunun kaçırılması halinde, diğer doz 12 saat içerisinde alınabilir ve ilacın alınması gereken zamanın üzerinden 12 saatten fazla geçmişse kaçırılan doz alınmamalıdır
- ❖ DSV dozunun kaçırılması halinde diğer doz 6 saat içerisinde alınabilir ve ilacın alınması gereken zamanın üzerinden 6 saatten fazla geçmişse kaçırılan doz alınmamalıdır
- ❖ OBV(12.5 mg)/ PTV(75 mg)/ RTV(50 mg) kombinasyonu günde bir kez yemekle beraber iki tablet, DSV (250 mg) günde iki defa bir tablet
- ❖ Kombine tedavi ile RBV'yi birlikte alan hastalarda en sık görülen yan etkiler yorgunluk ve bulantı
  - ❖ Diğer yan etkiler anemi, uykusuzluk, kaşıntı ve asteni

# Ombitasvir/ paritaprevir/ ritonavir + dasabuvir kombinasyonunun özellikleri (3)

## ❖ OBV/PTV/RTV

- ❖ Genotip 1 ve 4 HCV infeksiyonunda etkilidir
- ❖ İçeriğinde etinilestradiol bulunan tıbbi ürünler, atazanavir ve darunavir dışındaki HIV proteaz inhibitörleri, CYP3A4 substratları, enzim indükleyicileri, CYP3A4 inhibitörleri ile birlikte kullanılmamalıdır
- ❖ Daha önce NS3/4A veya NS5A inhibitörleri ile tedavi alan hastalarda etkililiği gösterilmemiştir

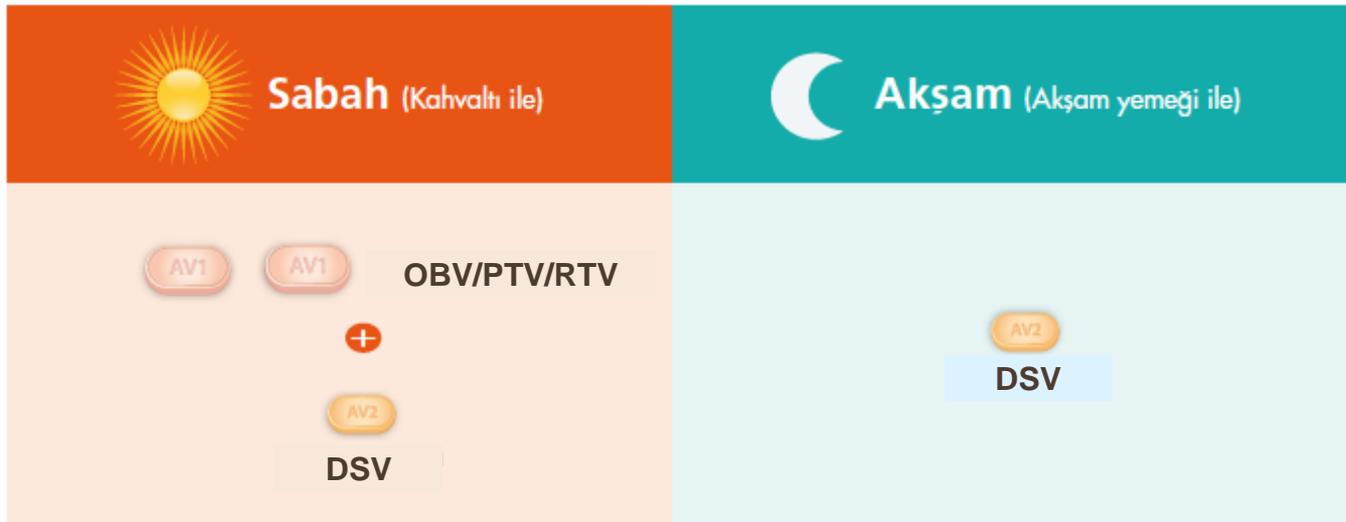
## ❖ DSV

- ❖ Genotip 1 HCV infeksiyonunda etkilidir
- ❖ İçeriğinde etinilestradiol bulunan tıbbi ürünler ve enzim indükleyicileri ile birlikte (CYP3A4, CYP2C19, CYP2D6 veya CYP1A2 tarafından metabolize edilen ve CYP2C8'i inhibe eden tıbbi ürünler...) kullanılmamalıdır

# OBV/PTV/RTV kombinasyonunun genotip 1 HCV infeksiyonunda kullanım şeması

Hasta Popülasyonu	Tedavi	Süre
Genotip 1b non-sirotik	OBV/PTV/RTV + DSV	12 Hafta
Diğer Genotip 1 (sirotik veya non-sirotik)*	OBV/PTV/RTV + DSV +RBV	

\*Genotip 1a kompanse sirotik hastalarda OBV/PTV/RTV + DSV +RBV 24 hafta!



# OBV/PTV/RTV kombinasyonunun genotip 4 HCV infeksiyonunda kullanım şeması

Hasta Popülasyonu	Tedavi	Süre
GT 4*	OBV/PTV/RTV + RBV	12 Hafta

\*Genotip 4 kompanse sirotik hastalarda OBV/PTV/RTV + RBV 24 hafta!



# OBV/PTV/RTV + DSV kombinasyonu

- ❖ 25 ülkede 2600'den fazla hasta ile (özel hasta grupları dahil) yapılan çalışmalar sonucunda yüksek oranda kür sağlayan
  - ❖ Genotip 1b hastalarda %100
  - ❖ Genotip 1 hastalarda %97
  - ❖ Genotip 4 hastalarda %100
- ❖ Düşük yan etki profiline sahip
- ❖ Yüksek tedavide kalma oranı olan
- ❖ Böbrek yetmezliği hastalarında doz ayarlaması gerektirmeyen

**12 haftalık interferonsuz, oral tedavi rejimidir!**

# Hepatitis C Guidance: AASLD-IDSAs Recommendations for Testing, Managing, and Treating Adults Infected With Hepatitis C Virus

AASLD/IDSA HCV Guidance Panel\*

## Preamble

The pace of hepatitis C virus (HCV) drug development in recent years has accelerated dramatically. For patients to benefit from these impressive advances, practitioners need access to the most up-to-date data and to advice from experienced experts. Such information and advice can be difficult to access readily given the diverse sources from which information is available and the sometimes lengthy time needed for publication of original articles and scholarly perspectives. Traditional practice guidelines for more established areas of medicine and care often take years to develop and bring to publication. In the new era in hepatitis C treatment, such a process would not be nimble or timely enough to address the needs of patients with HCV infection, practitioners caring for these patients, or payers approving therapies for use. A living document made available in a web-based system, such as that used by the US Department of Health and Human Services for human immunodeficiency virus (HIV) treatment recommendations (<http://aidsinfo.nih.gov/guidelines>), was selected as the best model to provide timely recommendations for hepatitis C management. In 2013, the two major membership societies supporting liver and infectious disease specialists (American Association for the Study of Liver Diseases [AASLD] and Infectious Diseases Society of America [IDSA]) joined forces to develop guidance for the management of hepatitis C in this rapidly moving field. The International Antiviral Society-USA, which has experience in developing treatment guidelines in HIV disease, was invited to join the effort as a collabo-

rating partner responsible for managing the panel and the guidance development process.

The goal of the hepatitis C guidance is to provide up-to-date recommendations for HCV care practitioners on the optimal screening, management, and treatment for adults with HCV infection in the United States, using a rigorous review process to evaluate the best available evidence. This review provides a condensed summary of recommendations from the guidance. The complete guidance, which is updated regularly, is available at [www.hcvguidelines.org](http://www.hcvguidelines.org).

## Process

This was conceived to be a living document that would reside online and undergo real-time revisions as the field evolved. To lead the process, two cochairs selected by the governing boards of each founding society were joined by a fifth cochair representing the International Antiviral Society-USA. These cochairs selected 10 panel members from each society. The panel members were chosen to represent expertise in the diagnosis, management, treatment, research, and patient care from the fields of hepatology and infectious diseases. At least 51% of the panelists could have no substantive industry support other than research advisory boards, data safety monitoring boards, or research funding that went to the member's employer.

The panel first convened in person in October 2013. Panel members were divided into teams to review available data and to propose preliminary guidance in three areas: (1) testing and linkage to care, (2) initial treatment of HCV infection, and (3) retreatment of patients

*Abbreviations:* AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; anti-HCV, antibody to HCV; CDC, Centers for Disease Control and Prevention; CTP, Child-Turcotte-Pugh; DAA, direct-acting antiviral; eGFR, estimated glomerular filtration rate; FDA, US Food and Drug Administration; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDSA, Infectious Diseases Society of America; IFN, interferon; NS3, nonstructural protein 3; PEG-IFN, pegylated IFN; PrO2D, paritaprevir/tritona virilombitasvir plus dasabuvir; RAV, resistance-associated variant; RBV, ribavirin; SVR, sustained virological response.

Received June 3, 2015; accepted June 3, 2015.

These recommendations have been approved by the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America.

All AASLD Practice Guidelines are updated annually. If you are viewing a Practice Guideline that is more than 12 months old, please visit [www.aasld.org](http://www.aasld.org) for an update in the material.

\*The names and affiliations of all authors are listed at the end of the article.

# Genotip 1 HCV ile infekte hastalar

Tedavi seçenekleri	
SMV + PR	Önerilmez
SOF + PR	Önerilmez
SOF + RBV	Önerilmez
LDV/ SOF	Önerilir
<b>OBV/PTV/RTV + DSV ± RBV</b>	<b>Önerilir</b>
SMV+ SOF ± RBV	Önerilir

# Genotip 1 HCV ile infekte naiv hastalar

	LDV/ SOF*	OBV/PTV/RTV + DSV	SOF + SMV
Genotip 1a, sirotik olamayan	12 hafta	12 hafta+ RBV	12 hafta ± RBV*
Genotip 1a, kompanse sirotik	12 hafta	24 hafta + RBV	24 hafta ± RBV*
Genotip 1b, sirotik olamayan	12 hafta	12 hafta	12 hafta ± RBV
Genotip 1b, kompanse sirotik	12 hafta	12 hafta	24 hafta ± RBV

\* Q80K mutasyonu yoksa tercih edilmeli!

# Genotip 1 HCV ile infekte peg-İFN/RBV deneyimli hastalar

	LDV/ SOF	OBV/PTV/RTV + DSV	SOF + SMV
Genotip 1a, sirotik olamayan	12 hafta	12 hafta + RBV	12 hafta
Genotip 1a, kompanse sirotik	24 hafta 12 hafta+ RBV	24 hafta + RBV	24 hafta ± RBV*
Genotip 1b, sirotik olamayan	12 hafta	12 hafta	12 hafta
Genotip 1b, kompanse sirotik	24 hafta 12 hafta+ RBV	12 hafta	24 hafta ± RBV

\* Q80K mutasyonu yoksa tercih edilmeli!

# Genotip 1 HCV ile infekte proteaz inhibitörü deneyimli hastalar

	LDV/ SOF	OBV/PTV/RTV + DSV	SOF + SMV ± RBV
Genotip 1a, sirotik olamayan	12 hafta	Hayır	Hayır
Genotip 1a, kompanse sirotik	24 hafta 12 hafta + RBV	Hayır	Hayır
Genotip 1b, sirotik olamayan	12 hafta	Hayır	Hayır
Genotip 1b, kompanse sirotik	24 hafta 12 hafta + RBV	Hayır	Hayır

# Genotip 4 HCV ile infekte naiv ve peg-İFN/RBV deneyimli hastalar

Tedavi Rejimi				
Genotip 4 naiv	LDV/ SOF 12 hafta	OBV/PTV/RTV + RBV 12 hafta*	SOF + RBV 24 hafta	
Alternatif Rejim				
Genotip 4 naiv	SOF + RBV + Peg- İFN 12 hafta	SOF + SMV ± RBV 12 hafta		
Tedavi Rejimi				
Genotip 4 tedavi deneyimli	LDV/ SOF 12 hafta, sirotik ise 24 hafta	OBV/PTV/RTV + RBV 12 hafta*	SOF + RBV + Peg- İFN 12 hafta	SOF + RBV 24 hafta

\* Sirotik olmayanlarda

## 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 the last two decades, thanks to an enhanced understanding of the pathophysiology of the disease, and because of developments in diagnostic procedures and improvements in therapy and prevention.

These EASL Recommendations on Treatment of Hepatitis C are intended to assist physicians and other healthcare providers, as well as patients and other interested individuals, in the clinical decision-making process by describing the current optimal management of patients with acute and chronic HCV infections. These recommendations apply to therapies that have been approved in the European Union at the time of their publication.

### The standard of care up to 2014

The primary goal of HCV therapy is to cure the infection. A sustained virological response (SVR) is defined as undetectable HCV RNA 12 weeks (SVR12) or 24 weeks (SVR24) after treatment completion. The infection is cured in more than 99% of patients who achieve an SVR. The SVR is generally associated with resolution of liver disease in patients without cirrhosis. Patients with cirrhosis remain at risk of life-threatening complications; however hepatic fibrosis may regress and the risk of complications such as hepatic failure and portal hypertension is reduced. Recent data suggest that the risk of HCC and all-cause mortality is significantly reduced, but not eliminated, in cirrhotic patients who clear HCV compared to untreated patients and non-sustained virological responders [2,3]. HCV may also affect

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

Until 2011, the combination of pegylated interferon (PegIFN)- $\alpha$  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 genotype 1 infection. These two drugs are first-wave, first-generation direct-acting antivirals (DAAs). Both target the HCV NS3-4A serine protease and are thus referred to as protease inhibitors. Both telaprevir and boceprevir must be administered in combination with PegIFN- $\alpha$  and ribavirin. In the Phase III trials of boceprevir and telaprevir in HCV genotype 1 treatment-naïve patients, triple therapy regimens achieved higher SVR rates than PegIFN- $\alpha$  and ribavirin dual therapy, of the order of 65% to 75% [7-10]. However, the side effect profiles of these triple combination therapies and the costs per SVR in patients with advanced hepatic fibrosis are such that they should ideally no longer be used in patients infected with HCV genotype 1, as soon as other, more efficacious and better tolerated options are available.

Three new HCV DAAs have been licensed in the EU in 2014, for use as part of combination therapies for HCV infection. Sofosbuvir, a pangenotypic nucleotide analogue inhibitor of HCV RNA-dependent RNA polymerase, has been approved in January 2014. Simeprevir, a second-wave, first-generation NS3-4A protease inhibitor active against genotypes 1 and 4 has been approved in May 2014. Daclatasvir, a pangenotypic NS5A inhibitor, has been approved in August 2014.

Each of these three DAAs can be used as a component of a triple combination regimen with PegIFN- $\alpha$  and ribavirin, yielding SVR rates of 60-100% according to the DAA used, the HCV genotype, the presence of detectable pre-existing amino acid substitutions conferring resistance to the DAA used and the severity of liver disease. Although these combinations are better tolerated than triple combination including telaprevir or boceprevir, their side effect profiles and management remain challenging because of the use of PegIFN- $\alpha$  and of ribavirin.

With three new HCV DAAs approved, IFN-free combinations were broadly used across Europe in 2014, initially as part of early access programs, essentially in patients with advanced liver disease (fibrosis METAVIR score F3 or F4). The combination of sofosbuvir and ribavirin is indicated in patients infected with HCV

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# HCV genotip 1 veya 4 ile infekte, sirotik olmayan naiv veya peg-İFN/RBV deneyimli hastalar

Tedavi	HCV Genotip		
	1a	1b	4
SOF + PR	12 hafta		12 hafta
SMV + PR	12 hafta (naiv veya relaps) 24 hafta (parsiyel/ "null")		12 hafta (naiv veya relaps) 24 hafta (parsiyel/ "null")
LDV/SOF	8-12 hafta <sup>†</sup>		12 hafta
<b>OBV/PTV/RTV + DSV</b>	RBV ile birlikte 12 hafta	12 hafta	Önerilmiyor
<b>OBV/PTV/RTV</b>	Önerilmiyor		12 hafta + RBV
SOF + SMV	12 hafta		12 hafta
SOF + DCV	12 hafta		12 hafta

<sup>†</sup> Naiv, sirotik olmayan ve bazal HCV RNA düzeyi < 6 milyon İÜ/ml olan hastalarda 8 hafta verilebilir (özellikle F3 fibroz hastalarında)

# HCV genotip 1 veya 4 ile infekte, kompanse sirotik naiv veya peg-İFN/RBV deneyimli hastalar

Tedavi	HCV Genotip		
	1a	1b	4
SOF + PR	12 hafta		12 hafta
SMV + PR	12 hafta (naiv veya relaps) 24 hafta (parsiyel/ "null")		12 hafta (naiv veya relaps) 24 hafta (parsiyel/ "null")
LDV/SOF	RBV ile 12 hafta veya RBV'siz 24 hafta veya RBV ile 24 hafta (negatif göstergeler varsa)		RBV ile 12 hafta veya RBV'siz 24 hafta veya RBV ile 24 hafta (negatif göstergeler varsa)
<b>OBV/PTV/RTV + DSV</b>	RBV ile 24 hafta	RBV ile 12 hafta	Önerilmiyor
<b>OBV/PTV/RTV</b>	Önerilmiyor		24 hafta + RBV
SOF + SMV	RBV ile 12 hafta veya RBV'siz 24 hafta		RBV ile 12 hafta veya RBV'siz 24 hafta
SOF + DCV	RBV ile 12 hafta veya RBV'siz 24 hafta		RBV ile 12 hafta veya RBV'siz 24 hafta



**AASLD 2015...**

# Preliminary Safety and Efficacy Results From TOPAZ-II: A Phase 3b Study Evaluating Long-Term Clinical Outcomes in HCV Genotype 1-Infected Patients Receiving Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir ± Ribavirin

Nancy Reau<sup>1</sup>, Fred Poordad<sup>2</sup>, Jeffrey V. Eneosa<sup>3</sup>, Asma Siddique<sup>4</sup>, Humberto Aguilar<sup>3</sup>, Jacob Lalezari<sup>6</sup>, Franco Felizarta<sup>7</sup>, Peter J. Ruane<sup>8</sup>, Peter Marunok<sup>6</sup>, David E. Bernstein<sup>10</sup>, Douglas Dieterich<sup>11</sup>, Gregory E....

## INTROOU

Following treatment with HCV, a sustained virologic response (SVR) reduces decompensation and all-cause mortality.

## Multi-target Regimen

Long-term sustained virologic response rates have not been reported in patients treated with...

## OBJECTIVE

To evaluate the efficacy of OPV/PTV/r + DSV ± RBV in HCV genotype 1-infected patients with compensated liver disease.

## METHOD

TOPAZ-II is a 52-week, multicenter, randomized, controlled study comparing 30 weeks of treatment with OPV/PTV/r + DSV ± RBV to 48 weeks of treatment with OPV/PTV/r + DSV ± RBV in HCV genotype 1-infected patients with compensated liver disease.

❖ HCV genotip 1 ile infekte, sirozu olan veya olmayan, naiv veya tedavi deneyimli hastalarda 12 veya 24 haftalık OPV/PTV/r + DSV ± RBV tedavisi ile KVV elde etme oranı yüksektir (ITT analizi %95.3, mITT analizi %97.3)

❖ Tedavi iyi tolere edilmiştir ve tedavi kesilmesini gerektirecek yan etki oranı düşüktür

... (n = 1), pruritus (n = 1), and altered mental status (n = 1) ...

# Long-Term Efficacy of Ombitasvir/Paritaprevir/r and Dasabuvir With or Without Ribavirin in HCV Genotype 1-Infected Patients With or Without Cirrhosis

Stefan Zeuzem<sup>1</sup>, Ira M Jacobson<sup>2</sup>, Jordan J Feld<sup>3</sup>, Heiner Wedemeyer<sup>4</sup>, Xavier Forns<sup>5</sup>, Pietro Andreone<sup>6</sup>, Massimo G Colombo<sup>7</sup>, David E Bernstein<sup>8</sup>, Fred Poordad<sup>9</sup>, Christophe Hezode<sup>10</sup>, Thomas Podsadecki<sup>11</sup>, Wangang Xiang<sup>12</sup>, Jiwang Guo<sup>13</sup>, Josep L Garcia-Arribas<sup>14</sup>, Josep L Garcia-Roma<sup>15</sup>, Josep L Garcia-Saiz<sup>16</sup>, Josep L Garcia-Tenorio<sup>17</sup>, Josep L Garcia-Tenorio<sup>18</sup>, Josep L Garcia-Tenorio<sup>19</sup>, Josep L Garcia-Tenorio<sup>20</sup>, Josep L Garcia-Tenorio<sup>21</sup>, Josep L Garcia-Tenorio<sup>22</sup>, Josep L Garcia-Tenorio<sup>23</sup>, Josep L Garcia-Tenorio<sup>24</sup>, Josep L Garcia-Tenorio<sup>25</sup>, Josep L Garcia-Tenorio<sup>26</sup>, Josep L Garcia-Tenorio<sup>27</sup>, Josep L Garcia-Tenorio<sup>28</sup>, Josep L Garcia-Tenorio<sup>29</sup>, Josep L Garcia-Tenorio<sup>30</sup>, Josep L Garcia-Tenorio<sup>31</sup>, Josep L Garcia-Tenorio<sup>32</sup>, Josep L Garcia-Tenorio<sup>33</sup>, Josep L Garcia-Tenorio<sup>34</sup>, Josep L Garcia-Tenorio<sup>35</sup>, Josep L Garcia-Tenorio<sup>36</sup>, Josep L Garcia-Tenorio<sup>37</sup>, Josep L Garcia-Tenorio<sup>38</sup>, Josep L Garcia-Tenorio<sup>39</sup>, Josep L Garcia-Tenorio<sup>40</sup>, Josep L Garcia-Tenorio<sup>41</sup>, Josep L Garcia-Tenorio<sup>42</sup>, Josep L Garcia-Tenorio<sup>43</sup>, Josep L Garcia-Tenorio<sup>44</sup>, Josep L Garcia-Tenorio<sup>45</sup>, Josep L Garcia-Tenorio<sup>46</sup>, Josep L Garcia-Tenorio<sup>47</sup>, Josep L Garcia-Tenorio<sup>48</sup>, Josep L Garcia-Tenorio<sup>49</sup>, Josep L Garcia-Tenorio<sup>50</sup>, Josep L Garcia-Tenorio<sup>51</sup>, Josep L Garcia-Tenorio<sup>52</sup>, Josep L Garcia-Tenorio<sup>53</sup>, Josep L Garcia-Tenorio<sup>54</sup>, Josep L Garcia-Tenorio<sup>55</sup>, Josep L Garcia-Tenorio<sup>56</sup>, Josep L Garcia-Tenorio<sup>57</sup>, Josep L Garcia-Tenorio<sup>58</sup>, Josep L Garcia-Tenorio<sup>59</sup>, Josep L Garcia-Tenorio<sup>60</sup>, Josep L Garcia-Tenorio<sup>61</sup>, Josep L Garcia-Tenorio<sup>62</sup>, Josep L Garcia-Tenorio<sup>63</sup>, Josep L Garcia-Tenorio<sup>64</sup>, Josep L Garcia-Tenorio<sup>65</sup>, Josep L Garcia-Tenorio<sup>66</sup>, Josep L Garcia-Tenorio<sup>67</sup>, Josep L Garcia-Tenorio<sup>68</sup>, Josep L Garcia-Tenorio<sup>69</sup>, Josep L Garcia-Tenorio<sup>70</sup>, Josep L Garcia-Tenorio<sup>71</sup>, Josep L Garcia-Tenorio<sup>72</sup>, Josep L Garcia-Tenorio<sup>73</sup>, Josep L Garcia-Tenorio<sup>74</sup>, Josep L Garcia-Tenorio<sup>75</sup>, Josep L Garcia-Tenorio<sup>76</sup>, Josep L Garcia-Tenorio<sup>77</sup>, Josep L Garcia-Tenorio<sup>78</sup>, Josep L Garcia-Tenorio<sup>79</sup>, Josep L Garcia-Tenorio<sup>80</sup>, Josep L Garcia-Tenorio<sup>81</sup>, Josep L Garcia-Tenorio<sup>82</sup>, Josep L Garcia-Tenorio<sup>83</sup>, Josep L Garcia-Tenorio<sup>84</sup>, Josep L Garcia-Tenorio<sup>85</sup>, Josep L Garcia-Tenorio<sup>86</sup>, Josep L Garcia-Tenorio<sup>87</sup>, Josep L Garcia-Tenorio<sup>88</sup>, Josep L Garcia-Tenorio<sup>89</sup>, Josep L Garcia-Tenorio<sup>90</sup>, Josep L Garcia-Tenorio<sup>91</sup>, Josep L Garcia-Tenorio<sup>92</sup>, Josep L Garcia-Tenorio<sup>93</sup>, Josep L Garcia-Tenorio<sup>94</sup>, Josep L Garcia-Tenorio<sup>95</sup>, Josep L Garcia-Tenorio<sup>96</sup>, Josep L Garcia-Tenorio<sup>97</sup>, Josep L Garcia-Tenorio<sup>98</sup>, Josep L Garcia-Tenorio<sup>99</sup>, Josep L Garcia-Tenorio<sup>100</sup>

## INTRODUCTION

- Hepatitis C virus (HCV) is a worldwide, common chronic infection.
- Phase 3 trials of 12-week regimens of ombitasvir, paritaprevir, and dasabuvir with or without ribavirin (OPV/PTV/r ± DSV ± RBV) in HCV genotype 1 (GT1)-infected patients showed high sustained virologic response (SVR12) rates.

## Multi-targeted NS5A inhibitors



- Following 12-week treatment of patients who were RNA post-SVR12, relapse occurred in 4.8% of patients.
- We present the long-term efficacy of OPV/PTV/r ± DSV ± RBV in GT1-infected patients.

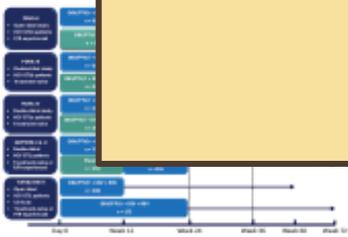
## OBJECTIVE

- To examine the long-term efficacy of OPV/PTV/r ± DSV ± RBV in GT1-infected patients up to post-treatment week 104.

## METHODS

- Treatment-naïve or -experienced GT1-infected patients were randomized to receive OPV/PTV/r (25 mg/150 mg) twice daily, 8 weeks, with or without DSV (1200 mg) and RBV (800 mg) daily.

Figure 1. Phase 3 Study Design



Genotype	Group	n	SVR12 (%)	Relapse (%)	SVR12 (%)	Relapse (%)
GT1a	OPV/PTV/r ± DSV ± RBV	595	95.1	4.8	95.1	4.8
	OPV/PTV/r	121	95.1	4.8	95.1	4.8
GT1b	OPV/PTV/r ± DSV ± RBV	301	95.1	4.8	95.1	4.8
	OPV/PTV/r	68	95.1	4.8	95.1	4.8

- ❖ HCV genotip 1 ile infekte hastalarda OPV/PTV/r + DSV ± RBV ile KVV oranı  $\geq$  %95
- ❖ Uzun süreli takipte (tedavi sonrası 48 hafta) KVV devamlılık oranı %99.5
- ❖ Filogenetik analizlerle doğrulanan relaps oranı %0.4



# TURQUOISE-III: 12-Week Ribavirin-Free Regimen of Ombitasvir/Paritaprevir/r and Dasabuvir for Patients With HCV Genotype 1b and Cirrhosis

Fred Poordad<sup>1</sup>, Jordan J Feld<sup>2</sup>, Roger Trinh<sup>3</sup>, Yves Horsmans<sup>4</sup>, Magdy Elkhatab<sup>5</sup>, Stefan Bourgeois<sup>6</sup>, Samuel S Lee<sup>7</sup>, Christophe Moreno<sup>8</sup>, David E Bernstein<sup>9</sup>, Ziad Younes<sup>10</sup>, Akshanth R Polepally<sup>5</sup>, Kevin Hov...

<sup>1</sup>The Texas Liver  
<sup>2</sup>Toronto Liver  
<sup>3</sup>GastroOne, C

## BACKGRO

- Patients with cirrhosis have without cirrho
- Treatment with regimens of ombitasvir (OSI) + paritaprevir (PTV) + dasabuvir (DSB) demonstrated post-treatment (GT) 1b infection rates of ~100% in non-cirrhotic patients

## Multi-target



## OBJECTIV

- The TURQUOISE-III study of OSB/PTV/r without RBV in compensated

## METHOD

### STUDY DESIGN

- TURQUOISE-III is a single-arm, open-label, parallel-group, phase 3 study
- All patients received treatment daily + D
- Efficacy was assessed by quantification of HCV RNA
- Safety and tolerability were assessed by adverse events (AEs)

### ELIGIBILITY CR

- HCV treatment-naïve patients, ≥18 years of age, with HCV RNA >10<sup>6</sup> IU/mL and history of decompensated cirrhosis
- Patient laboratory values: total bilirubin <2.0 mg/dL, aspartate aminotransferase (AST) <25 × 10<sup>3</sup> IU/L, creatinine clearance ≥30 mL/min

❖ 12 haftalık RBV içermeyen 3D kombinasyonu ile 60 HCV genotip 1b ile infekte sirotik hastada (33'ü tedavi deneyimli) KVV oranı %100'dür

❖ Tedavi iyi tolere edilmiştir ve tedavi kesilmesini gerektirecek yan etki gözlenmemiştir

❖ Bulgular sirotik hastalarda 3D tedavisine RBV eklenmesinin gerekli olmadığını ortaya koymuştur

• 100% of patients achieved SVR4 and SVR12

• No HCV-related deaths were observed

Treatment Week



# Efficacy, Change in MELD Score, and Safety by Baseline MELD Score in Patients With Compensated Cirrhosis Receiving Ombitasvir/Paritaprevir/r and Dasabuvir Plus Ribavirin in the Phase 3 TURQUOISE-II Trial

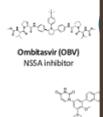
Ira Jacobson<sup>1</sup>, TM Welzel<sup>2</sup>, Hugo F Vargas<sup>3</sup>, Marcos Pedrosa<sup>4</sup>, Norah Terrault<sup>5</sup>, Douglas Dieterich<sup>6</sup>, Fredric D Gordon<sup>7</sup>, Kris V Kowdley<sup>8</sup>, Guy Neff<sup>1\*</sup>, Ran Liu<sup>4</sup>, Juan Carlos Lopez-Talavera<sup>4\*</sup>, Stefan Zeuzem<sup>2</sup>

<sup>1</sup>Weill Cornell Medical College  
<sup>2</sup>Mount Sinai School of Medicine

## BACKGROUND

- Patients with hepatitis C virus (HCV) cirrhosis are at high risk of portal hypertension, liver-related and extrahepatic complications
- The model for end-stage liver disease (MELD) scoring system has been used for short- and intermediate-term prognosis in patients with cirrhosis<sup>1</sup>
- MELD score is used for Organ Sharing (OS) allocation for patients with end-stage liver disease
- Curing HCV infection and preventing decompensation have been shown to reduce mortality<sup>2</sup>
- The 3 direct-acting antiviral (DAA) co-formulated oral paritaprevir (PTV)/ombitasvir (OBV)/ritonavir (RT) plus weight-based (WT) ribavirin (RBV) regimen achieved SVR response rates of 95% in genotype (GT) 1 patients

## Multi-targeted (3D) Regimen



PTV was identified by AbbVie and Janssen; other DAA were not.

## OBJECTIVE

- Evaluate the efficacy of the multi-targeted (3D) regimen in terms of MELD score and SVR in patients with compensated cirrhosis receiving OBV/PTV/r + DSV + RBV

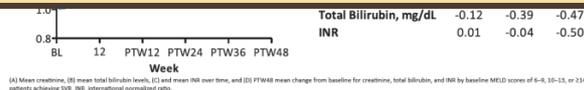
## METHODS

- 380 treatment-naïve patients with compensated cirrhosis were randomized to receive either the 3D regimen (n = 208) or the standard of care (SOC) regimen (n = 172) in TURQUOISE-II
- Analyses were performed in patients with baseline MELD scores of 6–14 and ≥14
- Efficacy was assessed in terms of SVR in patients achieving SVR at post-treatment week 48 (PTW48) and laboratory abnormalities were assessed in all patients receiving at least 1 dose of study drug

❖ Sirotik hastalarda OPV/PTV/r + DSV + RBV kombinasyonu ile MELD skoru ne olursa olsun elde edilen KVV oranı yüksektir

❖ Hasta sayısı az olmakla beraber KVV elde edilen, MELD skoru yüksek olan hastalarda da tedavi sonrası skorda düzelme olmuştur

❖ KVV elde edilen hastalarda bilirubin düzeyinin azalması skorun düzeleceğini gösteren önemli bir bulgudur



• The safety profile in patients with various MELD scores were similar (Table 3), though conclusions about safety in patients with MELD scores ≥14 are limited due to the small sample size



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the risk of liver transplant, analysis of 229 studies in American Association for 2014.

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# QUARTZ-I: Retreatment of HCV Genotype 1 DAA-failures With Ombitasvir/Paritaprevir/r, Dasabuvir, and Sofosbuvir

LB-20

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## BACKGROUND

- Retreatment of patients who have failed a first course of direct-acting antiviral (DAA) therapy is clearly defined
- Prior treatment with a DAA (including ombitasvir/paritaprevir/rasburic acid/sofosbuvir) increases the response rate up to 98 weeks of treatment
- The 3-DAA (DDA) regimen (ombitasvir/paritaprevir/rasburic acid/sofosbuvir) achieves high sustained virologic response (SVR) rates in HCV genotype 1 patients
- Sofosbuvir (SOF) is a nucleoside analog that is active against all HCV genotypes
- There are no known drug-drug interactions between the DAA and SOF
- The multi-targeted DAA regimen (DDA) is a promising treatment for patients with HCV genotype 1

## Multi-targeted DAA

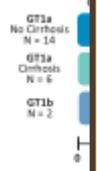


## OBJECTIVE

- Investigate the efficacy and safety of the multi-targeted DAA regimen (DDA) in patients with HCV genotype 1

## METHODS

Figure 1. QUANTITATIVE ANALYSIS OF SVR



- Patients with HCV genotype 1 infection with cirrhosis received Ombitasvir/Paritaprevir/rasburic acid/sofosbuvir (DDA) + Dasabuvir (DSV) + Sofosbuvir (SOF) + Rasburic acid (RBV) for 24 weeks (Figure 1)
- Patients with HCV genotype 1 infection with or without cirrhosis received Ombitasvir/Paritaprevir/rasburic acid/sofosbuvir (DDA) + Dasabuvir (DSV) + Sofosbuvir (SOF) for 12 weeks (Figure 1)

❖ DEA tedavi deneyimi olan HCV genotip 1 ile infekte hastalarda (GT 1a infeksiyonu 20 hasta, GT1b 2 hasta) dirençli varyantların varlığına rağmen 12-24 haftalık OBV/PTV/r + DSV + SOF ± RBV tedavisi ile KVV oranı %93'tür

❖ Tedavi iyi tolere edilmiştir ve tedavi kesilmesini gerektirecek yan etki gözlenmemiştir



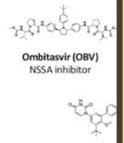
# Ombitasvir/Paritaprevir/r and Dasabuvir ± Ribavirin is Better Tolerated Than Telaprevir + Peginterferon/Ribavirin With Less Frequent and Less Severe Anemia in the MALACHITE-I and MALACHITE-II Trials

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## INTRODUCTION

- Although new antiviral (DAA) regimens for hepatitis C virus (HCV) are available, telaprevir + peginterferon + ribavirin (TPV) is still widely available in many regions including Europe.
- TPV has demonstrated efficacy and safety in phase 3 trials with high rates of sustained virologic response (SVR12).
- Trials directly comparing DAA-containing regimens to TPV have demonstrated superior efficacy and safety for DAA-containing regimens.
- Phase 3 trials of telaprevir, paritaprevir, ombitasvir, paritaprevir, dasabuvir have demonstrated superior virologic response in GT1-infected patients with cirrhosis<sup>2</sup>.

## Multi-targeted Regimen



PTV was identified by AbbVie and is a protease inhibitor. Ribavirin does not have antiviral activity.

- MALACHITE-I and MALACHITE-II trials directly compare the OBV/PTV/r + DSV ± RBV regimen of care (TPV + peginterferon + ribavirin) to treatment-experienced patients without cirrhosis.
- Efficacy and overall safety were similar in MALACHITE-II trials.
  - MALACHITE-I<sup>1</sup>
    - 97–99% SVR12
    - 78–82% SVR12 with pegIFN/RBV
  - MALACHITE-II<sup>2</sup>
    - 99% SVR12 with pegIFN/RBV
    - 66% SVR12 with pegIFN/RBV

## OBJECTIVE

- We report exploratory analyses of the frequency of adverse events (AEs) and management of anemia by treatment regimen in the MALACHITE-I and -II trials.

- ❖ OPV/PTV/r + DSV ± RBV ile 12 haftalık tedavi:
- ❖ Yan etkilerin görülme sıklığı TPV (12 hafta) + PR (24-48 hafta) kombinasyonuna göre daha düşüktür
- ❖ Anemi sıklığı (3D kollarında:%1-%5, TVR'li kolda: %41) ve ciddiyeti daha azdır
- ❖ Anemi nedeniyle kan transfüzyonu ve eritropoetin kullanımı gerekmemiştir

OBV/PTV/r + DSV; only headache occurred in >20% of patients receiving OBV/PTV/r + DSV + RBV (Table 3)

achieved SVR12

– 12 (9.8%) received blood transfusion and 1 (0.8%) received erythropoietin



# Clinical Management of Ribavirin Dosing in HCV-Infected Patients With Anemia-Related Events Receiving Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir in Combination With Ribavirin

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<sup>5</sup>AbbVie, North Chicago, Illinois, USA  
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## INTRODUCTION

- In the current era, direct-acting antiviral (DAA) regimens have been shown to be difficult-to-cure genotype (GT) 1 patients.
- RBV can cause weight loss and declines in hemoglobin (Hb).
- Anemia-related events are managed through various strategies. However, optimal management requires an understanding of hemoglobin levels and the impact of patients with anemia on treatment response.
- Phase 3 trials of a regimen of ombitasvir/paritaprevir/ritonavir (OPV/PTV/r) + dasabuvir (DSV) + RBV demonstrate a high response rate at p24 in GT1-infected patients who are compensated.

## Multi-Targeted



## OBJECTIVES

- To describe the clinical management of patients with anemia receiving OPV/PTV/r + DSV + RBV combination

## METHODS

### STUDY DESIGN

- Patients received OPV/PTV/r + DSV + RBV for 12 or 24 weeks
- RBV was initially dosed according to body weight (1000 mg if <75 kg, or 1200 mg if ≥75 kg)
- All patients who modified RBV dose due to anemia-related events were included in this analysis

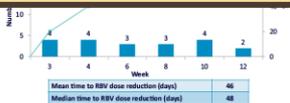
❖ OPV/PTV/r + DSV + RBV tedavisi alan 1548 HCV genotip 1 hastasında RBV doz azaltma oranı %6.5

❖ Doz modifikasyon gereksinimi özellikle ilk 6 hafta içinde ve başlangıç Hb düzeyi düşük hastalarda risk fazla

❖ Doz azaltılması KVV oranını etkilememiştir

Parameter	1000 mg (n=102)	1200 mg (n=107)
BMI, mean kg/m <sup>2</sup> ± SD	26.8 ± 4.5	26.4 ± 4.2
P-10, mean ng/L ± SD*	720.7 ± 982.2	484.4 ± 449.7
Hemoglobin, mean g/dL ± SD	14.0 ± 1.4	14.8 ± 1.3

\*For patients with and without RBV dose reductions, data from 7 and 584 patients were missing, respectively.  
 P-10, paritaprevir; BMI, body mass index; P-10, gamma interferon inducible protein 10.



predictors of anemia were evaluated

- By regression analysis, the only factor significantly associated with developing anemia (hemoglobin <10 g/dL), among the 100 patients that modified RBV dose, was low baseline hemoglobin (P < .001) (Table 4)

## Modification\*

Parameter	Odds ratio	95% CI	P-value
Baseline hemoglobin level (g/dL)	0.379	0.243, 0.590	<.001

\*Independent baseline variables that were considered: age (year), sex (male, female), race (Black, Asian, White), ethnicity (Hispanic/Latino, other), BMI (kg/m<sup>2</sup>), hemoglobin (g/L), creatinine clearance (mL/min), platelet count (10<sup>3</sup>/L), albumin (g/L), prior pegIFN/RBV experience (yes, no).

P Ferenci: Advisory Committees/Speaker: Roche; Consultant: Boehringer Ingelheim, Janssen, Bristol-Myers Squibb, Achillion, GlaxoSmithKline, Gilead, MSD/Merck; Research Grants: Roche, Austria.



of patients due to V GT1a not achieve Day 15, prior on before /mL); among ed with ily during oglobin g a RBV emia and it declines obin levels 12 rates participated the writing, support was by AbbVie.

and, Janssen, Merck; Merck; Gilead, Bristol-Myers Squibb, Roche; Sponsor: Gilead, AbbVie, BMS; Gilead, Merck, Novartis, Astellas, Roche, Merck, AbbVie, BMS; employees of AbbVie and may hold AbbVie stock or options.



# Efficacy and Safety of Ombitasvir/Paritaprevir/Ritonavir Co-Administered With Ribavirin in Adults With Genotype 4 Chronic Hepatitis C Infection and Cirrhosis (AGATE-I)

Tarik Asselah<sup>1</sup>, Tarek I Hassainein<sup>2</sup>, Roula B Qaqish<sup>3</sup>, Jordan J Feld<sup>4</sup>, Christophe Hezode<sup>5</sup>, Stefan Zeuzem<sup>6</sup>, Peter Ferenci<sup>7</sup>, Tami Pilot-Matias<sup>3</sup>, Yao Yu<sup>3</sup>, Rebecca Redman<sup>3</sup>, Niloufar Mobashery<sup>3</sup>

<sup>1</sup>Centre de Recherche  
<sup>2</sup>Toronto Centre

## INTRODUCTION

- Chronic hepatitis C is a major global health challenge, affecting approximately 170 million people.
- HCV genotype 4 accounts for 13% of global HCV infections.
- The Phase 2b PEACE trial demonstrated the efficacy and safety of the ombitasvir (OBV)/paritaprevir (PTV)/ritonavir (R) co-therapy with weight-based ribavirin (RBV) in adults with genotype 4 chronic hepatitis C infection without cirrhosis.
- The sustained virologic response (SVR) rates were high (85% and 90% at 12 and 24 weeks, respectively).
- In many countries, HCV genotype 4 is the most common genotype in compensated cirrhosis, and it is the highest priority genotype for treatment due to the high burden of disease in this population is impacted.



PTV was identified by AbbVie and other sponsor data not have entered.

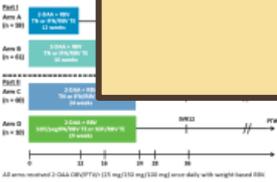
## OBJECTIVE

- AGATE-I evaluated the efficacy and safety of the combination of OBV/PTV/r + RBV in an excluded population with exploratory assessment of virologic failure, relapse, and treatment discontinuation with options.

## METHODS

### STUDY DESIGN

Figure 1. Study Design in Genotype 4-Infected Compensated Cirrhosis



❖ HCV genotip 4 ile infekte, naiv veya tedavi deneyimli, kompanse sirotik hastalarda (n: 120) 12-16 haftalık OBV/PTV/r + RBV tedavisi ile yüksek oranda (%96 ve %100) KVV elde edilmiştir

❖ Tedavi iyi tolere edilmiştir

❖ Yan etkiler nedeniyle tedavi kesilmesi gerekmemiştir

and sequenced from the baseline samples from all patients  
• Phylogenetic analysis was conducted on the resulting sequences in order to determine the GT4 subtype

History of diabetes, n (%)  
21 (5.8) 13 (21.7)  
\*One patient originally randomized in Arm B but prematurely discontinued treatment at week 12 is included in Arm A for demographic and baseline analysis. The patient remains at lower level of week 12 (0.2%) at post-treatment week 0.  
†Risk factors may include: GT4 genotype in HCV, Hepatitis C virus, RNA, ribonucleic acid.  
‡Samples could not be obtained from 1 patient; sample failed testing with 1 other patient. Both patients were from the 24-week treatment group.

emergent variants present in NS3  
- In NS5A, polymorphism P58L was present at baseline, and treatment-emergent variants L28L/M and Y93Y/H in addition to P58L were present at the time of virologic failure

• Bilirubin elevation was the most common laboratory abnormality, primarily indirect bilirubin and was not associated with significant changes in liver transaminases



OBV/PTV/r + RBV for 12 or 16 weeks and was well tolerated and associated to SVR12 (96.0%, n=114/119), SVR24 (96.0%, n=114/119), and relapse (0.0%, n=0/119).  
\*To evaluate the efficacy of OBV/PTV/r with RBV in the treatment of HCV genotype 4 infection in patients with compensated cirrhosis or with

and to the design, interpretation of the publication, and to ensure the accuracy of writing support from E. Fischer of AbbVie. AbbVie funded

and/or consultant to the study, including: Gilad, Sofonea, and Roche. Other authors: AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Eisai, Gilead, Janssen, Merck Sharp & Dohme, and Theravance.

Mobashery are not affiliated with any of the sponsors. All authors performed the study and contributed to the design, interpretation of the publication, and to ensure the accuracy of writing support from E. Fischer of AbbVie. AbbVie funded

AbbVie, BMS, Gilead, Janssen, Merck Sharp & Dohme, and Theravance.

advisory boards/speakers bureaus for Roche, AbbVie, Boehringer Ingelheim, Eisai, and Janssen. This study was supported by a research grant from Roche.

# Efficacy and Safety of Co-Formulated Ombitasvir/Paritaprevir/Ritonavir With Ribavirin in Adults With Chronic HCV Genotype 4 Infection Without Cirrhosis and With Compensated Cirrhosis in Egypt (AGATE-II)

Gamal Esmat<sup>1</sup>, Wahid Doss<sup>2</sup>, Roula B Qaqish<sup>3</sup>, Imam Waked<sup>4</sup>, Gamal Shiha<sup>5</sup>, Ayman Yosry<sup>2</sup>, Mohamed Hassany<sup>2</sup>, Jennifer King<sup>1</sup>, Carolyn Setze<sup>1</sup>, Rebecca Redman<sup>3</sup>, Niloufar Mobashery<sup>3</sup>

<sup>1</sup>Cairo Univ

❖ HCV genotip 4 ile infekte, naiv veya tedavi deneyimli sirotik olmayan 100 hastada 12 hafta ve kompanse sirotik 60 hastada 12 veya 24 haftalık OBV/PTV/r + RBV tedavisi ile yüksek oranda (sırasıyla % 94, %97,%97) KVY elde edilmiştir

❖ Tedavi iyi tolere edilmiştir

❖ Yan etkiler nedeniyle tedavi kesilmesi gerekmemiştir

## BACKG

- Chronic HCV is a major cause of liver disease and 1 of the 5 leading causes of death worldwide.
- Although 13% of HCV infections are self-clearing, 87% is 93%<sup>1</sup>
- Pegylated interferon (IFN) with sustained virologic response (SVR) poorly tolerated.
- Direct-acting antiviral (DAA) regimens have shown high efficacy in clinical studies.
- The 2-DAA regimens (OBV/PTV/r + RBV) are the most effective for HCV patients.



PTV was identified as a potent NS5B inhibitor.

## OBJEC

- AGATE-II was a phase 3, randomized, controlled, parallel, multicenter study of OBV/PTV/r + RBV vs. IFN-α/peg-IFN-α in Egyptian HCV GT4 patients with compensated cirrhosis.

## METH

### STUDY DESIGN

Figure 1. Study Design in Egyptian HCV GT4 Patients With Compensated Cirrhosis



All patients received 2-DAA (OBV/PTV/r + RBV) with weight-based RBV.

Laboratory abnormalities were assessed in all patients receiving at least 1 dose of study drug.

Missing SVR12 data	1/100 (0.1%)	0/0	NA <sup>a</sup>
Drop 1 (n=15-8) (n=8)	0	0	0
Drop 2 (n=5-4.5) (n=1)	0	0	0

<sup>a</sup>Includes 1 patient with compensated cirrhosis who was unresponsive to non-DAA therapy at the time of enrollment and was assigned to arm 2. <sup>b</sup>Includes 1 subject withdrawn severely. <sup>c</sup>NA, Not available; study ongoing.

<sup>d</sup>SVR, treatment-emergent adverse event.  
<sup>e</sup>The subject died of pain treatment only 12<sup>th</sup> week which was unrelated to study drug.



# High Rates of SVR in Patients With HCV Genotype 2 or 3 Infection Treated With Ombitasvir/Paritaprevir/r and Sofosbuvir With or Without Ribavirin

Stephen Shafran<sup>1</sup>, David Shaw<sup>2</sup>, Eric Cohen<sup>3</sup>, Koshi Agarwal<sup>4</sup>, Graham R Foster<sup>5</sup>, Manal Abunimeh<sup>6</sup>, Bo Fu<sup>7</sup>, Daniel E Cohen<sup>8</sup>, Edward Gane<sup>9</sup>

<sup>1</sup>University of  
<sup>2</sup>Queen Mary

## BACKGR

- Hepatitis C is worldwide, v
- Few interferon infection and (SVR12) are l
- Currently ap ribavirin (RB with lowest, peginterfero
- The 2 direct with paritap to treat GT3

Q

## OBJECTI

- The QUA12 in patients w

## METHOD

Figure 1. Q

Q

- Patients with SOF 1400 mg
- Patients with or without w
- Patients were treatment-ex
- Efficacy was the last dose
- Adverse even patients need

## ELIGIBILITY CRITERIA

- Chronic HCV GT2 or GT3 infection (HCV RNA > 10000 IU/mL) at screening
- Absence of cirrhosis
- Treatment-naïve or treatment-experienced with pegIFN/RBV or SOF

HCV GT2 OBV/PTV/r + SOF + RBV	HCV GT3 OBV/PTV/r + SOF	HCV GT3 OBV/PTV/r + SOF + RBV

• 1 serious AE (pneumonia) was reported and not considered related to study drugs  
• Grade 3 laboratory abnormalities were infrequent



- ❖ 12 haftalık OBV/PTV/r + SOF ± RBV tedavisi ile HCV genotip 3 ile infekte, sirotik olmayan hastalarda (n: 20) KYY oranı %91-100
- ❖ HCV genotip 2 ile infekte, sirotik olmayan 10 hastanın 9'unda 8 haftalık OBV/PTV/r + SOF + RBV tedavisi ile KYY elde edilmiştir (Tüm hastalardaki KYY 8 oranı %90)
- ❖ Bulgular bu kombinasyonun genotip 2 ve 3 ile infekte hastalarda yeni bir tedavi seçeneği olabileceğini göstermektedir

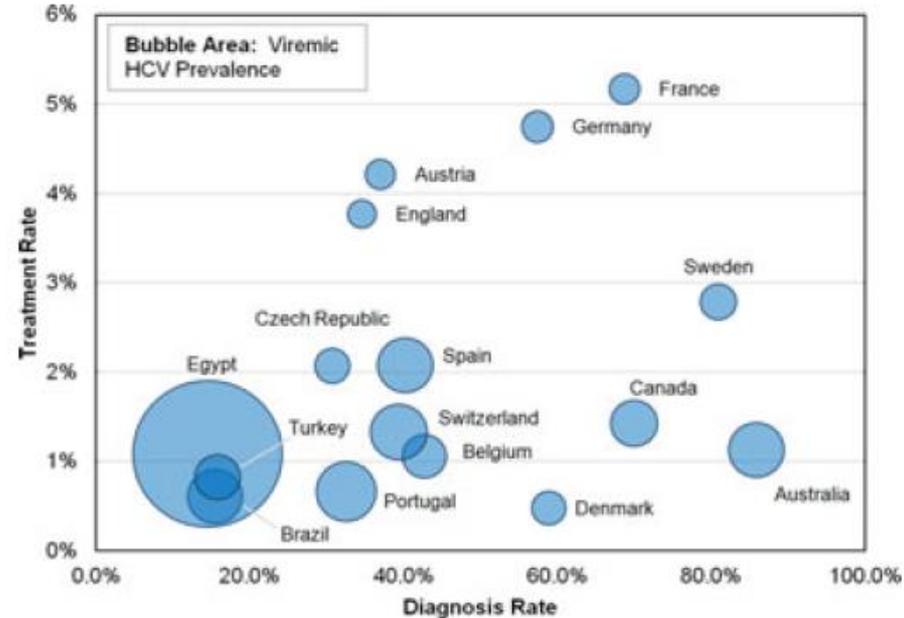
# Türkiye ve hepatit C

HCV



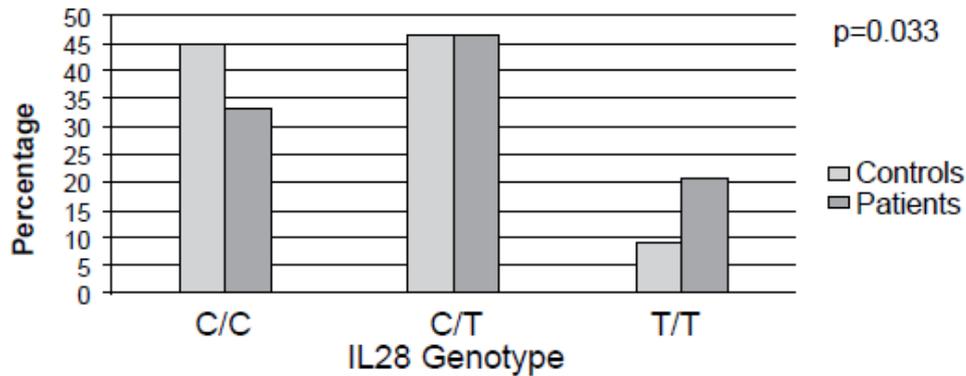
2013 yılı verilere göre ülkemizde tanı oranı %20'nin, tedavi oranı ise %1'in altındadır!

Dore GJ, et al. J Viral Hep 2014;21 (suppl1):1-4.

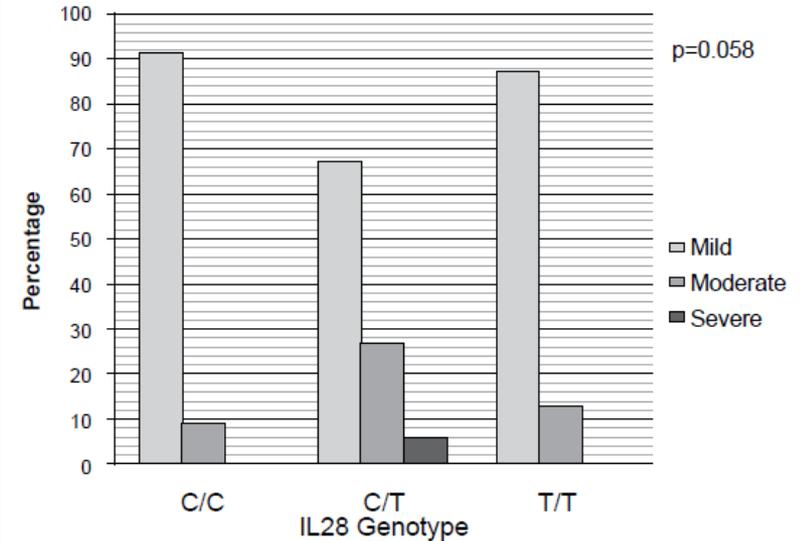


## Characterization of the Interleukin-28B Gene rs12979860 C/T Polymorphism in Turkish Chronic Hepatitis C Patients and Healthy Individuals

Serpil Taheri<sup>1,3</sup>, Bilgehan Aygen<sup>2</sup>, Keziban Korkmaz<sup>3</sup>, Orhan Yıldız<sup>4</sup>, Gökmen Zararsız<sup>5</sup>, Halit Canatan<sup>1</sup>



**FIG. 1.** IL28B rs12979860 C/T polymorphism in control and in patients with chronic HCV infection



**FIG. 2.** The relationship between fibrosis score and IL28B rs12979860 C/T polymorphism in patients with chronic HCV infection

**Results of pegylated interferon plus ribavirin for treatment-naïve Turkish patients with hepatitis C virus infection in real life setting: a multicenter, observational study**

**Y .Gurbuz<sup>1</sup>, N. E. Tulek<sup>2</sup>, E. E. Tutuncu<sup>1</sup>, S. T. Koruk<sup>3</sup>, B. Aygen<sup>4</sup>, N. Demirturk<sup>5</sup>, S. Kinikli<sup>2</sup>, A. Kaya<sup>6</sup>, T. Yildirmak<sup>7</sup>, K. Suer<sup>8</sup>, F. Korkmaz<sup>9</sup>, O. Ural<sup>10</sup>, S. Akhan<sup>11</sup>, and Viral Hepatitis Study Group of Turkish Society of Clinical Microbiology and Infectious Diseases\***

**Background:** Although pegylated interferon alpha plus ribavirin have been the standard therapy for patients with chronic hepatitis C since years, the efficacy of therapy have been reported to be inconsistent in clinical trials and observational studies in many countries. In this multicenter study, we aimed to report the “real life” results of pegylated interferon and ribavirin treatment in treatment-naïve Turkish patients.

**Methods:** The study was performed retrospectively with 1214 treatment naïve-patients treated with pegylated interferon alpha 2a or 2b plus ribavirin according to current guidelines. The patients’ data were gathered from 22 hospitals using a standard excel file prepared for this study. Data included demographic and clinical characteristics (gender, age, body weight, initial HCV RNA level, disease staging) as well as treatment course (treatment duration, outcomes, discontinuations and adverse events). The efficacy of treatment was evaluated according to the patient demographic features, baseline HCV RNA levels, HCV genotype, fibrosis stage.

**Results:** One thousand two hundred and fourteen patients were included in the study. There were 513 (42.3 %) males and 701 (57.7 %) females, with the mean age of  $50.8 \pm 11.7$  years. Since HCV genotype 1 is the most dominant genotype in Turkey, some hospitals do not perform genotype analysis and treat all patients as genotype 1. As a result, data regarding HCV genotype were not available for 267 patients. Eight hundred and sixty-nine patients (91.8 %) were found to be genotype 1. Thirty-eight (4 %), 16 (1.7 %) and 24 (2.5 %) patients were genotype 2, 3 and 4, respectively. Baseline HCV RNA level was  $>800000$  IU/ml in 511 (42.1 %) patients. A baseline liver biopsy was obtained from 898 patients showing stage 0 fibrosis in 127 (14.1 %), stage 1 in 419 (46.7 %), stage 2 in 182 (20.3 %), stage 3 in 148 (16.5 %) and stage 4 in 22 (2.4 %) patients according to METAVIR. Overall sustained virological response (SVR) to therapy was achieved in 761 (62.7 %) patients. SVR rate was 59.1 % in genotype 1, 89.4 % in genotype 2, 93.8 % in genotype 3, and 33.3 % in genotype 4 patients. The predictors of SVR were age less than 40 years, genotype 2/3, low baseline viral load, low fibrosis stage, achievement of early virological response, cumulative drug dose more than 80 % of the planned dose. The rate of treatment discontinuation due to adverse events was 2.7 %.

**Conclusions:** This study comprises the “real life” results of pegylated interferon alpha plus ribavirin therapy in a large group of treatment-naïve Turkish patients. Our data suggest that the rate of SVR to pegylated interferon alpha plus ribavirin therapy was higher than those reported in randomized controlled trials



Asian Pacific Association for The Study of the Liver  
Brisbane 12 – 15 March 2014

## Impact of Interleukin 28B Genotype on the Virological Responses in Chronic Hepatitis C Treatment

Bilgehan Aygen<sup>a</sup>, Orhan Yildiz<sup>a, b</sup>, Sila Akhan<sup>b</sup>, Ozgur Gunal<sup>c</sup>, Serpil Taheri<sup>d</sup>, Gokmen Zararsiz<sup>e</sup>, Murat Sayan<sup>f</sup>, Aydin Rustemoglu<sup>g</sup>, Elif Sargin Altinok<sup>f</sup>

**Table 3.** Distribution of IL28B rs12979860 C/T Genotypes and Alleles in Patients With Sustained Virologic Response and Non-Responder

	IL28B	SVR (n = 83), n (%)	Non-response (n = 103), n (%)	P	OR (95% CI)
rs12979860 alleles	C	98 (59)	84 (41)	< 0.001	-
	T	68 (41)	122 (59)	< 0.001	
rs12979860 genotypes	CC	28 (66.7)	14 (33.3)	0.001	1
	CT	42 (42.9)	56 (57.1)		0.38 (0.18 - 0.80)
	TT	13 (28.3)	33 (71.7)		0.20 (0.08 - 0.49)

SVR: sustained virologic response; OR: odds ratio; CI: confidence interval.

**Table 4.** Relationship Between IL28B Genotype and Response to Treatment Rates

Variables, n (%)	C/C (n = 42)	C/T (n = 98)	T/T (n = 46)	P
RVR	23 (54.8)	39 (41.9) <sup>a</sup>	18 (39.1)	0.216
cEVR	37 (88.1)	57 (58.2)	22 (47.8)	< 0.001
EVR (cEVR + pEVR)	41 (97.6)	71 (72.4)	29 (63.0)	< 0.001
ETR	38 (90.5)	61 (62.2)	26 (56.5)	0.001
SVR	28 (66.7)	42 (42.9)	13 (28.3)	0.001
Relapse	11 (26.2)	20 (20.4)	14 (30.4)	0.400
PR	1 (2.4)	8 (8.2)	3 (6.5)	0.443
NR	1 (2.4)	25 (25.5)	16 (34.8)	0.001
Breakthrough	1 (2.4)	3 (3.1)	0 (0.0)	0.495

RVR: rapid virological response; cEVR: complete early virological response; EVR: early virological response; pEVR: partial early virological response; ETR: end-of-treatment response; SVR: sustained virological response; PR: partial response; NR: null response. <sup>a</sup>Five patients were not evaluated for RVR.

## Retreatment of Chronic Hepatitis C Infection with Telaprevir: Preliminary Results in Turkey

Bilgehan Aygen<sup>1</sup>, Orhan Yıldız<sup>1</sup>, Sıla Akhan<sup>2</sup>, Mustafa Kemal Çelen<sup>3</sup>, Onur Ural<sup>4</sup>, Süda Tekin Koruk<sup>5</sup>, Şükran Köse<sup>6</sup>, Fatime Korkmaz<sup>7</sup>, Ziya Kuruüzüm<sup>8</sup>, Nazan Tuna<sup>9</sup>, Serpil Taheri<sup>10</sup>, Murat Sayan<sup>11</sup>, Nazlım Aktuğ Demir<sup>4</sup>, Şua Sümer<sup>4</sup>, Elif Sargın Altınok<sup>2</sup>

**TABLE 2.** Treatment responses

Patients	RVR n/total (%)	EVR n/total (%)	eRVR n/total (%)	24 <sup>th</sup> week of treatment n/total (%)
Relapse (n=80)	69/80 (86.3)	73/80 (91.3)	67/80 (83.8)	71/80 (88.8)
Null response (n=25)	14/25 (56)	14/25 (56)	12/25 (48)	14/25 (56)
Partial response (n=6)	3/6 (50)	5/6 (83.3)	3/6 (50)	4/6 (66.7)
p	0.002	<0.001	<0.001	<0.001

RVR: rapid virological response; EVR: early virological response; eRVR: extended rapid virological response

**TABLE 3.** Adverse events during the overall treatment period

Adverse events	no. (%)	Adverse events	no. (%)
Fatigue	90 (81.1)	Psychiatric disorders	
Headache	87 (78.4)	Depression <sup>b</sup>	25 (22.5)
Malaise	79 (71.2)	Anxiety	12 (10.8)
Pyrexia	29 (26.1)	Insomnia	9 (8.1)
Weight loss <sup>a</sup>	17 (15.3)	Mood impairment	7 (6.3)
Cough	14 (12.6)	Emotional lability	3 (2.7)
Gastrointestinal disorders		Decrease in laboratory value	
Anorexia	87 (78.4)	Hemoglobin <sup>f</sup>	
Dyspeptic complaints	48 (43.2)	To 8.5 to ≤10 g/dL	62 (55.9)
Nausea	45 (40.5)	To <8.5 g/dL	27 (24.3)
Stomachache	29 (26.1)	Neutrophil	
Diarrhea	24 (21.6)	To 500 to <750/mm <sup>3d</sup>	4 (3.6)
Vomiting	21 (18.9)	To <500/mm <sup>3e</sup>	2 (1.8)
Dry mouth	15 (13.5)	Platelet count	
Constipation	16 (14.4)	To 25.000 to <50.000 mm <sup>3d</sup>	9 (8.1)
Dysgeusia	9 (8.1)	To <25.000 mm <sup>3e</sup>	2 (1.8)
Anorectal problems		Other adverse events	
Discomfort	28 (25.2)	Hypothyroidism <sup>f</sup>	2 (1.8)
Hemorrhoid	25 (22.5)	Infection <sup>f</sup>	2 (1.8)
Pruritus	23 (20.7)	Reason for discontinuation	
Hemorrhage	17 (15.3)	Anorectal problems	3 (2.7)
Skin and subcutaneous tissue disorders		Excessive nausea, vomiting	3 (2.7)
Pruritus	70 (63.0)	Major depression	1 (1.8)
Dry skin	67 (60.4)	Severe rash	1 (1.8)
Rash	53 (47.7)	Upper gastrointestinal bleeding (Mallory-Weiss)	1 (1.8)
Mild	35 (66.0)	Hemoptysis	1 (1.8)
Moderate	16 (30.2)	Constitutional symptoms	1 (1.8)
Severe	1 (1.8)		











## KRONİK HEPATİT C

✓ Tedavi seçenekleri arttı!

✓ Seçilmiş hastalarda proteaz inhibitörleri dahil DEA + peg-İFN + RBV halen önemli bir tedavi seçeneği!

✓ Oral kullanılan DEA kombinasyonları gündemde!

✓ İkili veya üçlü DEA kombinasyonları ile %90 ve üzerinde başarılı sonuçlar var!

✓ Daha az yan etkiler söz konusu!

✓ Tedavi süreleri kıaldı!

✓ Kullanılan ilaçlar ve virolojik özellikler RBV'nin önemini farklılaştırdı!

✓ Zor hasta gruplarında da peg-İFN/RBV içermeyen DEA kombinasyonlarının başarısı gösterildi!

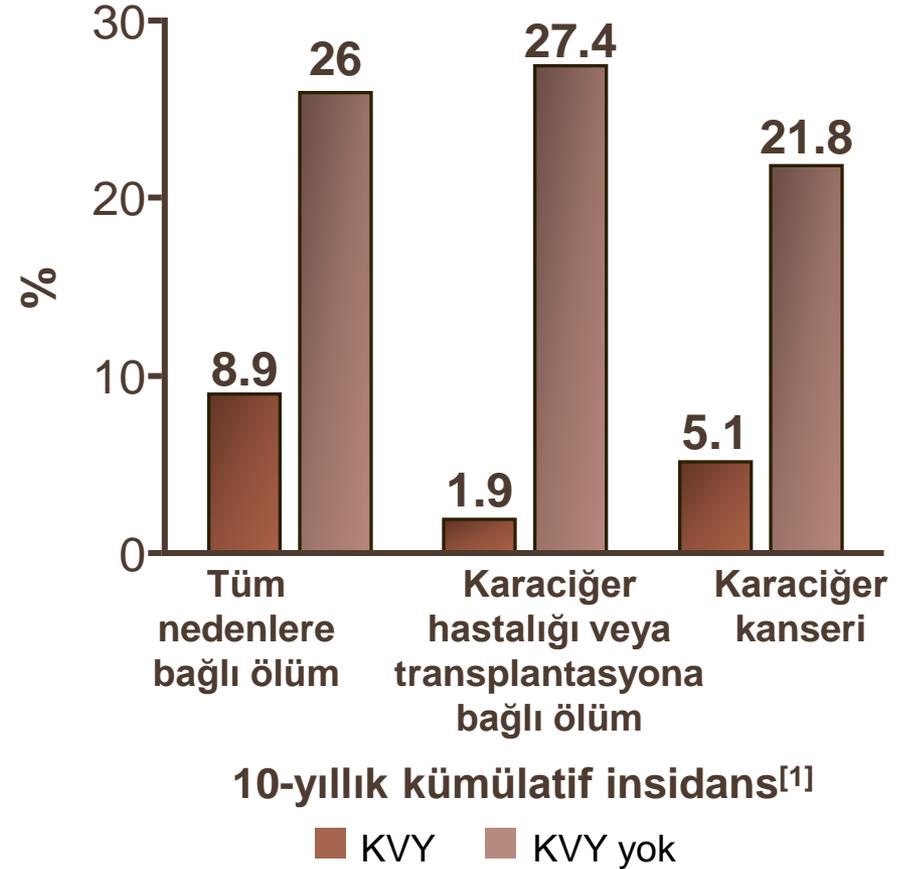
# HCV tedavisinin sağlıklı yaşama katkısı

## ❖ İleri fibroz veya siroz

- ❖ Çok merkezli çalışma<sup>[1]</sup>
  - ❖ 5 hastane Avrupa, Kanada)
- ❖ HCV ile infekte 530 hasta
  - ❖ İFN tedavileri--- 1990-2003
  - ❖ Ortalama takip süresi: 8.4 yıl

## ❖ Erken evre hastalık

- ❖ Ekstra-hepatik tablolar<sup>[2]</sup>  
ve
- ❖ Yaşam kalitesi düzelir<sup>[3]</sup>



1. van der Meer AJ, et al. JAMA 2012;308:2584-93. 2. van der Meer AJ. Expert Rev Gastroenterol Hepatol 2015;9:559-66. 3. Younossi Z, et al. Clin Gastroenterol Hepatol 2014;12:1349-59.

# Dünya...



**2015  
Antiviraller**

**Sofosbuvir +  
ribavirin ± peg-  
İFN**

**Ledipasvir/  
sofosbuvir**

**Sofosbuvir +  
daclatasvir**

**Ombitasvir/  
paritaprevir/  
ritonavir +  
dasabuvir**

**Simeprevir +  
sofosbuvir**

# Dünya...

**Sofosbuvir +  
GS-5816**

**Grazoprevir +  
elbasvir**

**Daclatasvir +  
asunaprevir +  
beclabuvir**

**Sofosbuvir +  
daclatasvir**

**Sofosbuvir +  
ribavirin**

**Sofosbuvir +  
ledipasvir**

**Paritaprevir/  
ritonavir +  
dasabuvir +  
ombitasvir**

**Simeprevir +  
sofosbuvir**

# Dünya...

**Araştırmaları devam eden DEA kombinasyonları**

**Sofosbuvir +  
GS-5816**

**Grazoprevir +  
elbasvir**

**Daclatasvir +  
asunaprevir +  
beclabuvir**

**Sofosbuvir +  
daclatasvir**

**Sofosbuvir +  
ribavirin**

**Sofosbuvir +  
ledipasvir**

**Paritaprevir/  
ritonavir +  
dasabuvir +  
ombitasvir**

**Simeprevir +  
sofosbuvir**

# Ülkemizdeki geri ödeme koşulları...

- ❖ Mevcut tedaviler HCV infeksiyonunu kontrol etmede yetersiz!
- ❖ Birçok hastada defalarca tedavi alıyor...



- ❖ Hastaların tedavi toleransında azalma
  - ❖ Maliyet artışı
  - ❖ Viral direnç artışı

- ❖ Bakanlık düzeyinde güncel klavuz örneği ile gerçek maliyet-etkinlik etkinlik çalışmaları

### Özellikle:

- Tedavi deneyimli hastalar
- Yan etkiler nedeniyle tedaviyi alanlar  
Proteaz inhibitörleri  
Peg-İFN
- Uzun süreli tedaviyi tercih edenler
- Genotip 4 ile infekte olanlar

### Proteaz inhibitörleri: güvenlik ve tolerabilite

- ✓ Peg-İFN+RBV tedavisi ile ortak yan etkiler: Anemi, nötropeni, depresyon, yorgunluk, baş ağrısı, bulantı, ateş, miyalji, huzursuzluk, uykusuzluk, raş

Peg-İFN + RBV 48 haftalık tedavi ile KVY oranı düşüktür

- ✓ Ülkemizde KVY oranı %33.3!
- ✓ Pİ kombinasyonlu tedavilerde de başarı oranı düşük!

# Türkiye...



**Bir Ömür, Bir Son İçin Bekler İnsan!**



*Teşekkürler...*