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Hepatitis C – Welche Therapie für welchen Patienten

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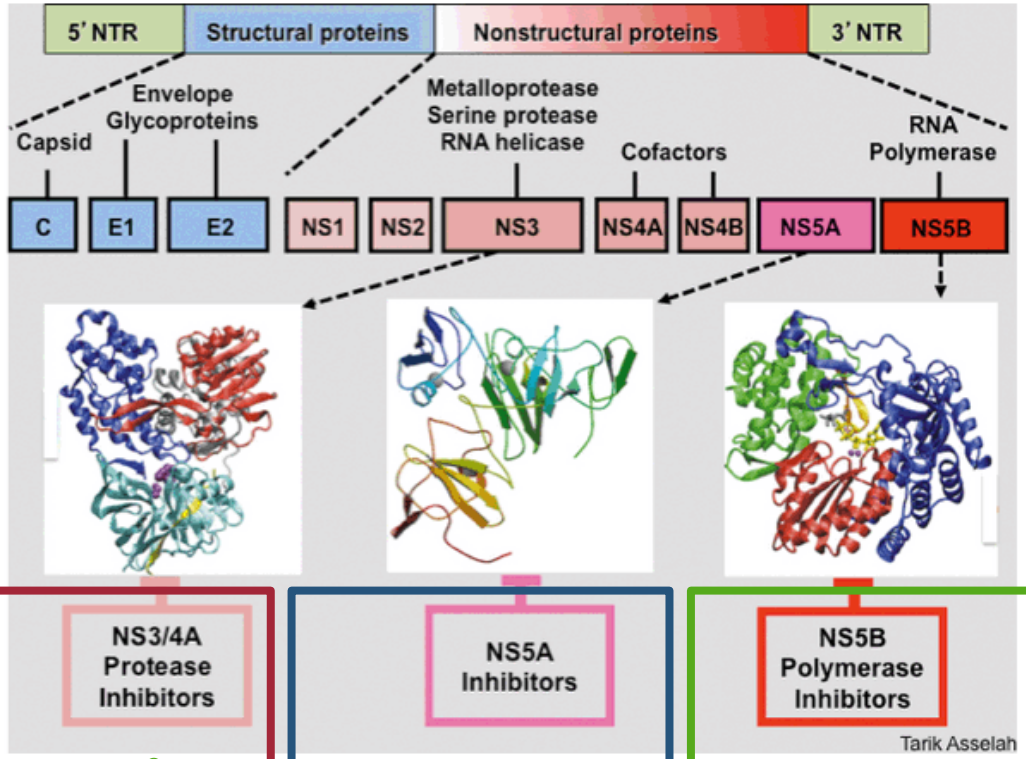
Aktuelle Wirkstoffe in der HCV Therapie



NS3/4A Protease Inhibitors

Boceprevir (Victrelis®)
Telaprevir (Incivo®)
Simeprevir (Olysio®)
Paritaprevir (ABT-450/r)
Grazoprevir [MK-5172]
GS-9451
Asunaprevir [BMS-650032]
Faldaprevir [BI-201335]

NS5A Inhibitors

Daclatasvir (Daklinza®)
Ledipasvir [GS-5885]
Ombitasvir [ABT-267]
Elbasvir [MK-8742]
Samatasvir [IDX-719]
GS-5816

NS5B Polymerase Inhibitors

NRTI
Sofosbuvir (Sovaldi®)
IDX-21437
ACH-3422
NNRTI
Dasabuvir [ABT-333]
Beclabuvir [*BMS-791325*]
Deleobuvir [BI-207127]

Cyclophilin-Hemmer

Alisporivir

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EASL HCV Guidelines 2014 Genotype 2-6

Genotype	Options for Therapy
Genotype 2*	Sofosbuvir + ribavirin: 12 wks (16-20 weeks in cirrhotic patients, especially treatment experienced) (A1)
	PegIFN/ribavirin + sofosbuvir: 12 wks for cirrhotic and/or treatment-experienced patients (B1)
Genotype 3*	Sofosbuvir + ribavirin: 24 wks (unsuitable for treatment-experienced cirrhotics, no specific alternative proposed) (A2)
	PegIFN/ribavirin + sofosbuvir: 12 wks (A2)
	Sofosbuvir + daclatasvir: 12 wks (24 wks for treatment-experienced patients) (B1)
Genotype 4*	PegIFN/ribavirin + sofosbuvir 12 weeks (B1)
	PegIFN/ribavirin + simeprevir: 12 wks, followed by 12 wks of pegIFN/ribavirin in previously untreated patients & prior relapsers (B1), or 36 wks of pegIFN/ribavirin in previous partial responders & null responders (B1)
	PegIFN/ribavirin + daclatasvir: 12 wks followed by 12 wks of pegIFN/ribavirin alone or a further 12 wks of pegIFN/ribavirin + daclatasvir (response-guided therapy) (B1)
	Sofosbuvir + ribavirin: 24 wks for interferon-intolerant patients (C2)
	Sofosbuvir + simeprevir: 12 wks (ribavirin may be added in previous nonresponders and cirrhotics) (B2)
	Sofosbuvir + daclatasvir: 12 wks in previously untreated patients; 24 wks in treatment-experienced patients (ribavirin may be added in previous nonresponders and cirrhotics) (B2)
Genotype 5/6*	PegIFN/ribavirin + sofosbuvir 12 wks (B1)
	Sofosbuvir + ribavirin: 24 wks for interferon-intolerant patients (C2)

*In settings where recommended options are not available, treatment with pegIFN/ribavirin remains acceptable.

J Hepatology. 2014; 60:392-420.

Ledipasvir-Sofosbuvir (LDV-SOF) Summary of Key Phase 3 Studies

- ION-1
  - Treatment-naïve GT 1
  - LDV-SOF with or without Ribavirin for 12 or 24 weeks
- ION-2
  - Treatment-experienced GT 1
  - LDV-SOF with or without Ribavirin for 12 or 24 weeks
- ION-3
  - Treatment-naïve non-cirrhotic GT 1
  - LDV-SOF +/- Ribavirin for 8 weeks versus LDV/SOF for 12 weeks

Ledipasvir-Sofosbuvir (LDV-SOF) Summary of Key Phase 2 Studies

- LONESTAR
  - Treatment-naïve and treatment-experienced GT 1
  - LDV-SOF fixed-dose combination with or without Ribavirin for 8 or 12 weeks
- ELECTRON (Arms 12-17 & 22)
  - Treatment-naïve and treatment-experienced GT 1
  - LDV-SOF fixed-dose combination with or without Ribavirin for 6 or 12 week
- ELECTRON-2
  - Prior SOF failure GT1; Decompensated cirrhosis GT1; Treatment naïve GT3
  - LDV-SOF fixed-dose combination with or without Ribavirin for 12 weeks
- ERADICATE
  - Treatment-naïve GT 1 and HIV coinfection
  - LDV-SOF fixed-dose combination for 12 weeks with or without HIV antiretrovirals

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LDV+SOF Fixed-Dose Combination +/- RBV Summary: ION-1, ION-2, and ION-3

Study	Population	Treatment	Duration	SVR 12 Rates
ION-1* (n= 865)	GT-1 Treatment-naïve (16% with cirrhosis)	LDV/SOF	12 weeks	99% (211/214)
		LDV/SOF + RBV	12 weeks	97% (211/217)
		LDV/SOF	24 weeks	98% (212/217)
		LDV/SOF + RBV	24 weeks	99% (215/217)
ION-2+ (n= 440)	GT-1 Treatment-experienced (20% with cirrhosis)	LDV/SOF	12 weeks	94% (102/109)
		LDV/SOF + RBV	12 weeks	96% (107/111)
		LDV/SOF	24 weeks	99% (108/109)
		LDV/SOF + RBV	24 weeks	99% (110/111)
ION-3^ (n= 647)	GT-1 Treatment-naïve (0% with cirrhosis)	LDV/SOF	8 weeks	94% (202/215)
		LDV/SOF + RBV	8 weeks	93% (201/216)
		LDV/SOF	12 weeks	95% (206/216)

*Afdhal N, et al. N Engl J Med. 2014;370:1889-98.
+Afdhal N, et al. N Engl J Med. 2014;370:1483-93.
^Kowdley, K, et al. N Engl J Med. 2014;370:1879-88.

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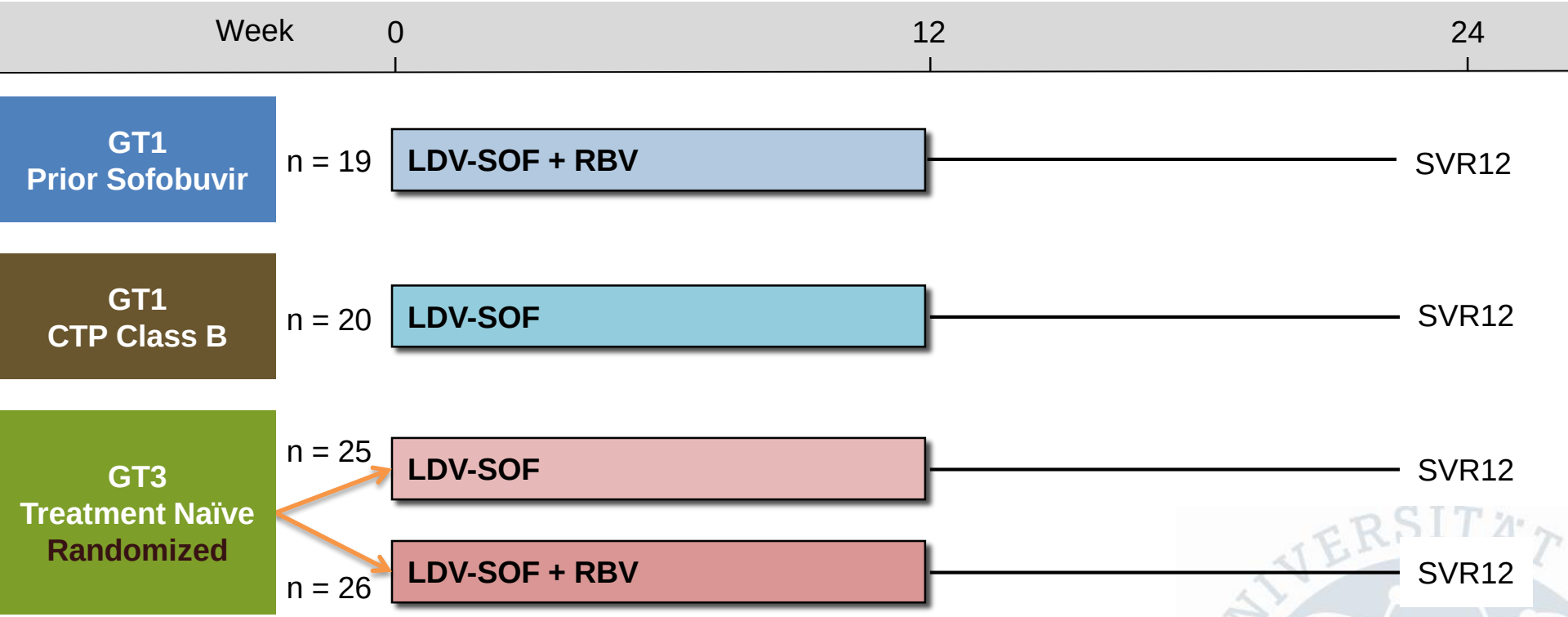
LDV+SOF +/- Ribavirin in GT 1 & 3 ELECTRON 2: Study Design



Abbreviations: LDV-SOF = ledipasvir-sofosbuvir; RBV = ribavirin

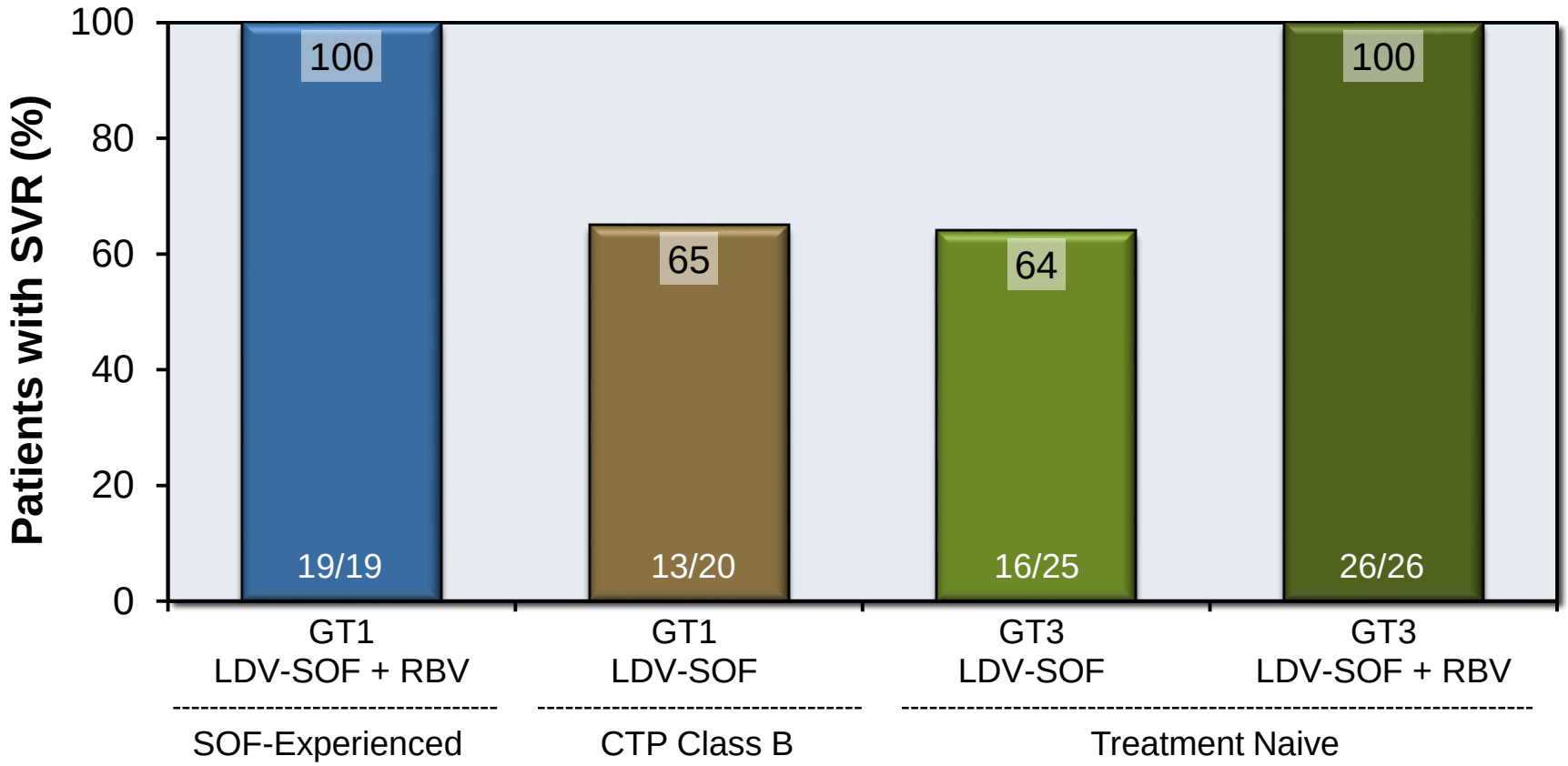
Drug Dosing

Ledipasvir-sofosbuvir (90/400 mg): fixed dose combination; one pill once daily

Ribavirin (weight-based and divided bid): 1000 mg/day if < 75 kg or 1200 mg/day if ≥ 75 kg

Source: Gane EJ, et al. 49th EASL. 2014: Abstract O6.

SOF+LDV +/- Ribavirin in GT 1 & 3 ELECTRON 2: Results



LDV-SOF = ledipasvir-sofosbuvir; RBV = ribavirin

Source: Gane EJ, et al. 49th EASL. 2014: Abstract O6.

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Sofosbuvir + Ledipasvir

Table 1 Recommended Treatment Duration for HARVONI in Patients with CHC Genotype 1

Patient Population	Recommended Treatment Duration
Treatment-naïve with or without cirrhosis	12 weeks*
Treatment-experienced** without cirrhosis	12 weeks
Treatment-experienced** with cirrhosis	24 weeks

* HARVONI for 8 weeks can be considered in treatment-naïve patients without cirrhosis who have pre-treatment HCV RNA less than 6 million IU/mL *[see Clinical Studies (14)]*.

**Treatment-experienced patients who have failed treatment with either peginterferon alfa + ribavirin or an HCV protease inhibitor + peginterferon alfa + ribavirin.

HARVONI®
ledipasvir/sofosbuvir
90 mg/400 mg tablets

seit 10.10.14 von der FDA Zugelassen

Kosten

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Kosten der aktuellen HCV-Therapie

Peg IFN	RBV	BOC	TVR	SOF	SMV	DCV	LDV	12 Wo	24 Wo	48 Wo
X	X								12.700	25.500
X	X	X							36.600	69.200
X	X		X						49.400	62.100
X	X			X				66.300		
	X			X				63.000	126.000	
				X	X			108.700		
				X		X		100.000	200.000	
					X	X		88.700		
				X			*X*	*≈75.000*	*≈150.000*	

Niereninsuffizienz dekompensierte LZ

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Studies on PK/PD in Patients With Renal and Hepatic Impairment

DAA	Primary Metabolic Pathway	Suitable in Patients With Cirrhosis			Suitable if Renal Impairment
		CTP-A	CTP-B	CTP-C	
Sofosbuvir	Renal	Yes	Yes	Yes	Not if CrCl < 30 mL/min
Simeprevir	Hepatic	Yes	No	No	Not if CrCl < 15 mL/min
Asunaprevir	Hepatic	Yes	No	No	Unknown
ABT-450/RTV	Hepatic	Yes	No	No	Unknown
Ledipasvir	Hepatic	Yes	Yes	Yes	Unknown
Ombitasvir	Hepatic	Yes	No (as combo)	No (as combo)	Unknown
Daclatasvir	Hepatic	Yes	Yes	Yes	Yes
Dasabuvir	Hepatic	Yes	No	No	Unknown

Bifano M, et al. AASLD 2011. Abstract 1362. Garimella K, et al. Clinical Pharm 2014. Abstract P43. Sofosbuvir [package insert]. Simeprevir [package insert]. Khatri A, et al. AASLD 2012. Abstract 758. German, et al. AASLD 2013. Abstract 467. Kirby R, et al. Clinical Pharm 2013. Abstract PO20.