台灣肝臟研究學會(TASL)
2014 C型肝炎治療之建議

(Draft)

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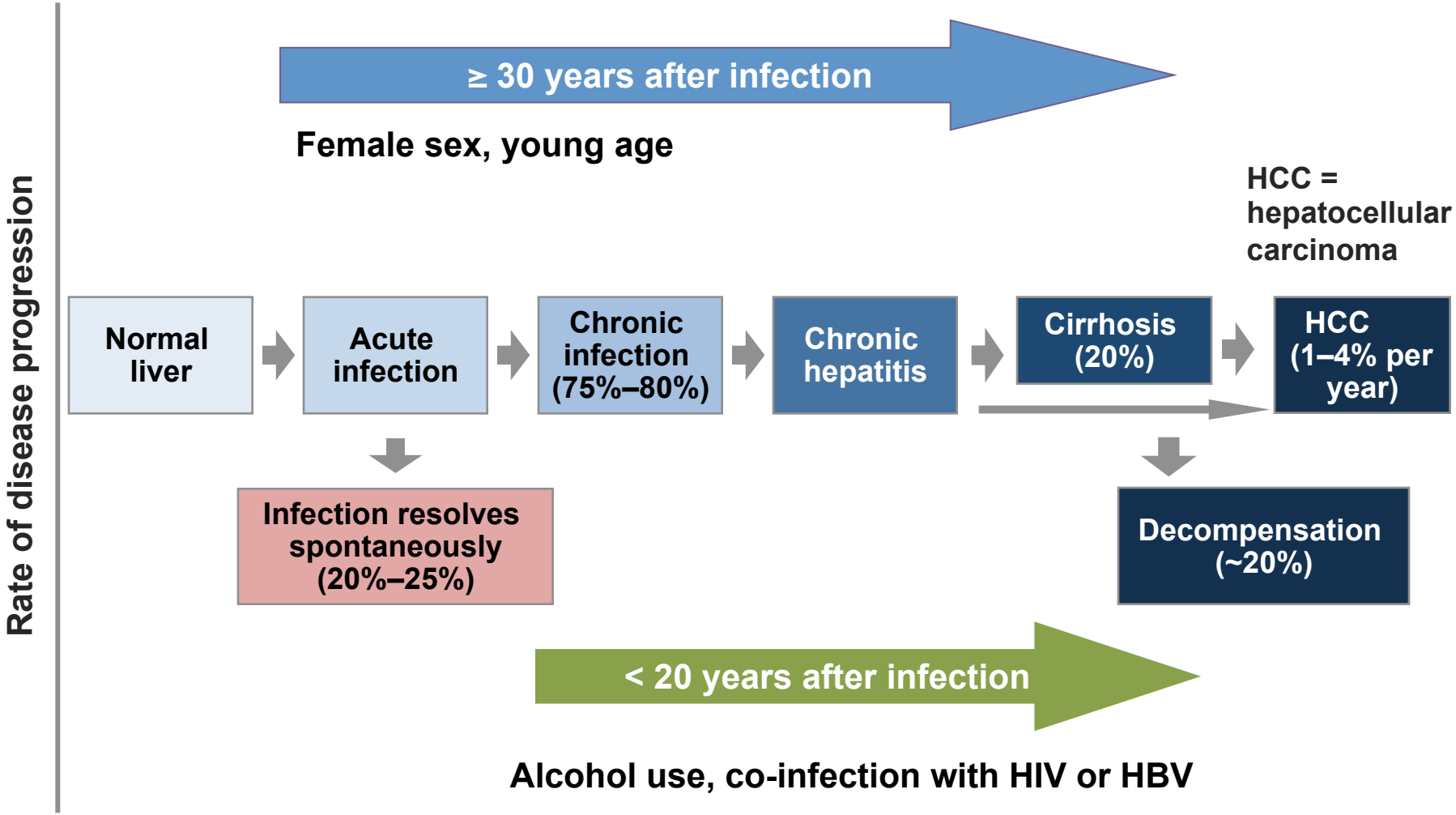
Landmarks of HCV Management

- 2006 NHRI-TASL C型肝炎治療之建議

1. **Interleukin-28B (IL28B) polymorphisms in HCV G1 response to PegIFN/RBV (Nature, 2009)**
2. **First Directly-acting antiviral agents (DAA) approved in combination with PegIFN/RBV for HCV G1 patients in 2011 (NEJM, 2011)**
3. **First IFN-free DAA regimen for HCV G2/3 in 2013 (NEJM, 2013)**
4. **First IFN/RBV-free DAA regimen for HCV G1b in 2014 (Lancet, 2014)**
5. **First IFN/RBV-free DAA regimen for HCV G1 in 2014 (NEJM, 2014)**

- 2014 TASL C型肝炎治療之建議

Disease progression in HCV

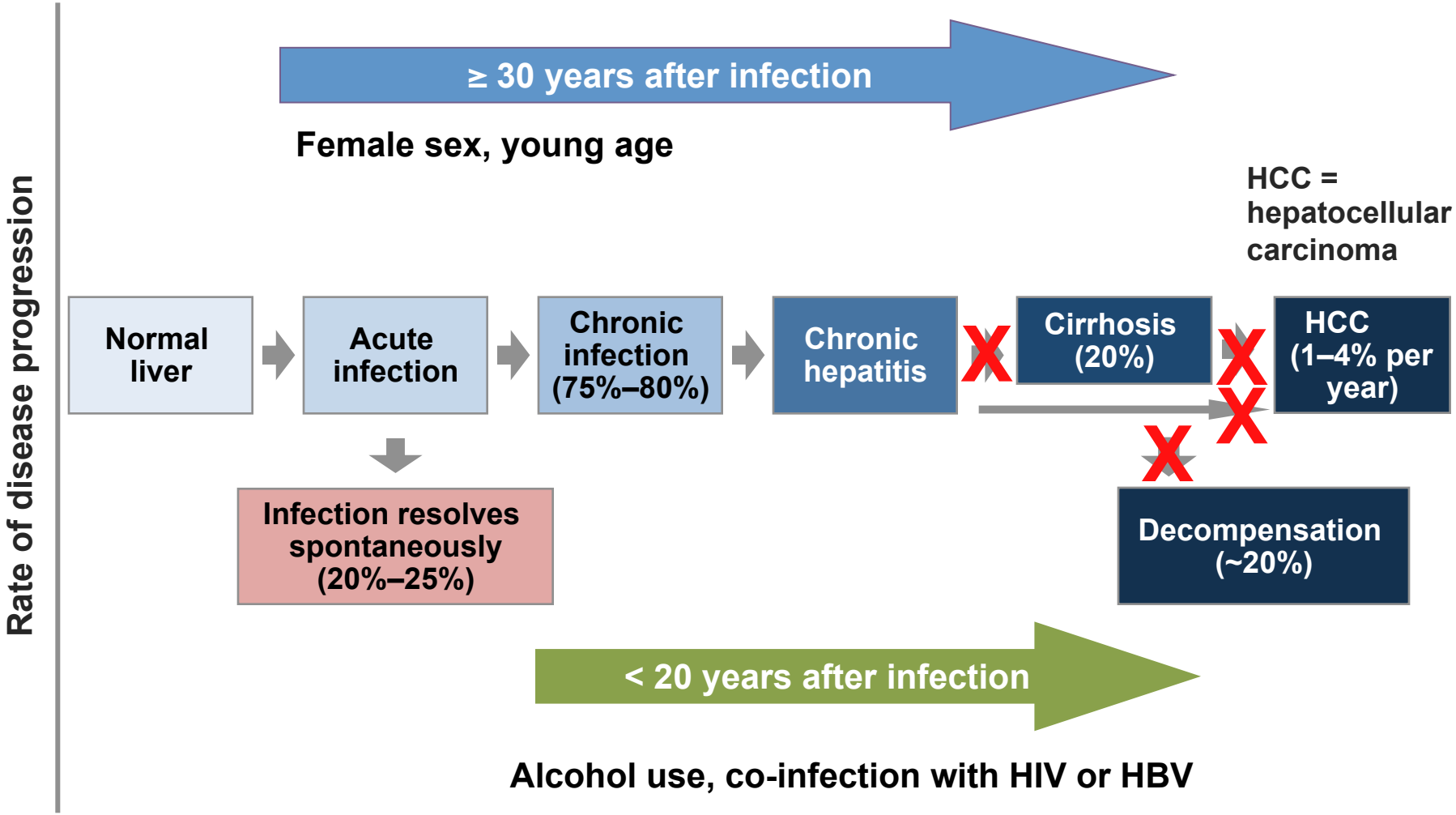


HBV, hepatitis B virus; HCC, hepatocellular carcinoma.

Lauer G & Walker B. *N Engl J Med* 2001; 345:41.

Yu-3

Disease progression in HCV



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Hepatitis C Treatment: Objectives

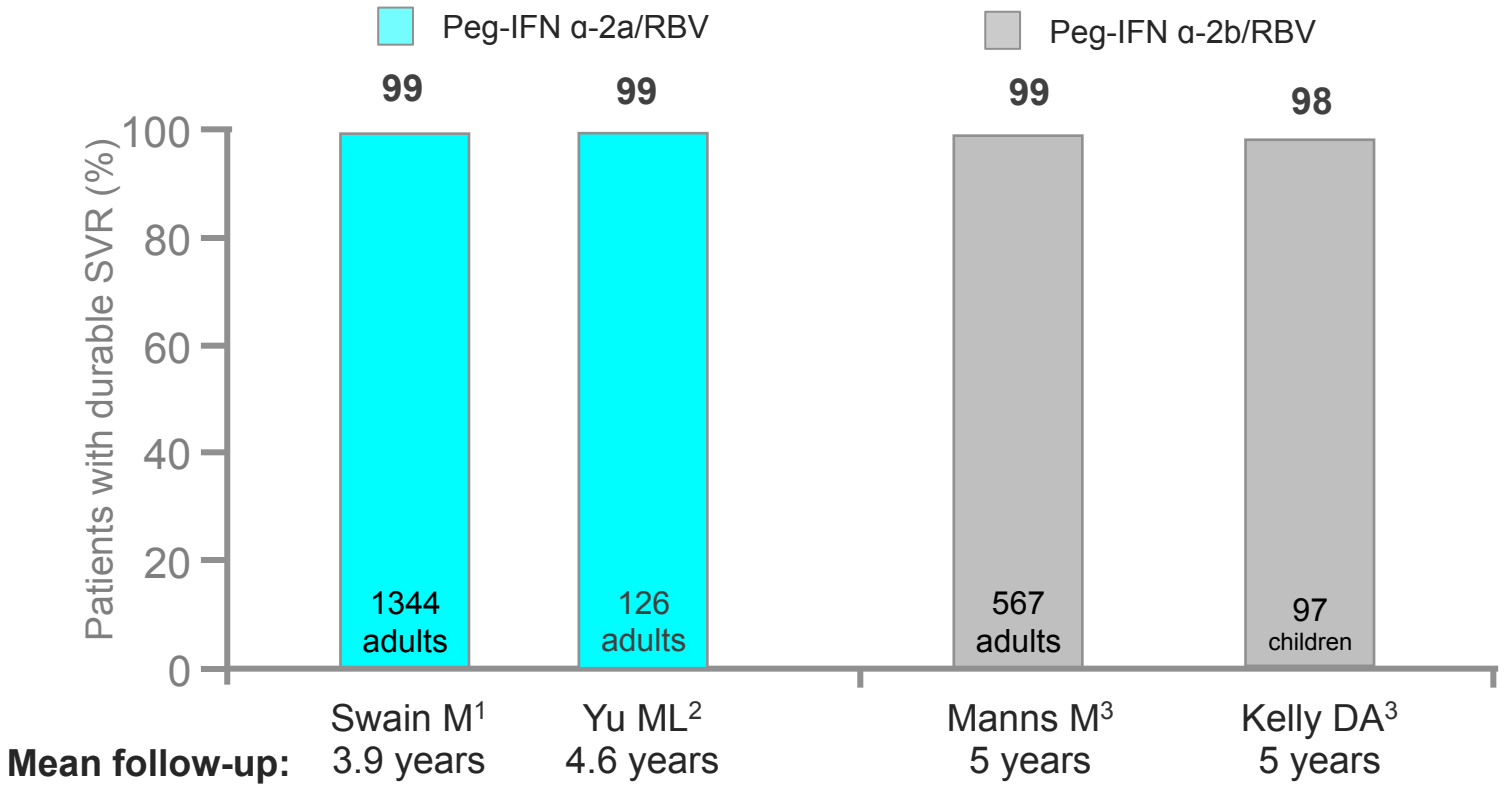
* **Goal: Viral eradication**
  - Sustained virological response (SVR),
    serum HCV-RNA persistently undetectable (<50 IU/ml)
    for 24 weeks after end-of-treatment

* **SVR associated with improved outcome**
  - Leads to improved histology
  - Leads to clinical benefits
    - Decreases risk of cirrhosis
    - Decreases decompensation
    - Prevents de novo esophageal varices
    - Decreases risk of hepatocellular carcinoma
    - Decreases mortality

Huang JF, Yu ML, et al., Aliment Pharmacol Ther. 2007;25:1029.
Yu ML, et al., Antiviral Therapy, 2006;11:985.
Yu ML, et al., Hepatology, 2006;44:1086.
Bruno S, et al. Hepatology. 2010;51:2069.
Veldt BJ, et al. Ann Intern Med. 2007;147:677.
Maylin S, et al. Gastroenterology. 2008;135:821.

Achieving an SVR should be considered as a cure for chronic HCV infection

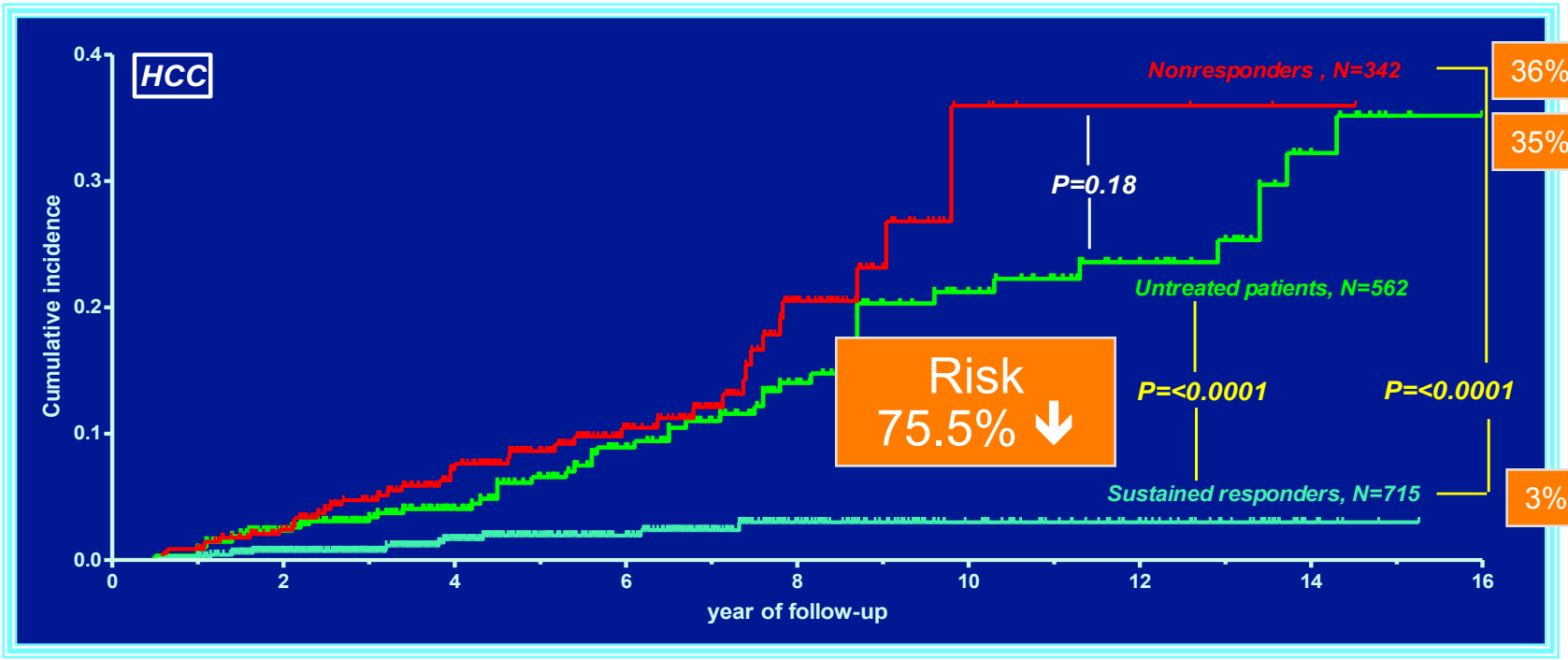
SVR is long lasting and clinical relapse is extremely rare



1. Swain M, et al. Gastroenterology 2010; 139: 1593
2. Yu ML, et al. Hepatology. 2013;57:2135-42.
3. Manns M, et al. . J Viral Hep 2013; doi:10.1111/jvh.12074
4. Kelly DA, et al. J Viral Hepat 2011;1365-2893.

Successful antiviral therapy reduces risk of HCC Development in HCV Patients

- 1619 pts from LK-CGMH, KCGMH, KMUH
- IFN-based therapy, 1057; untreated, 562
- mean FU, 5.16 y (1-16 y)

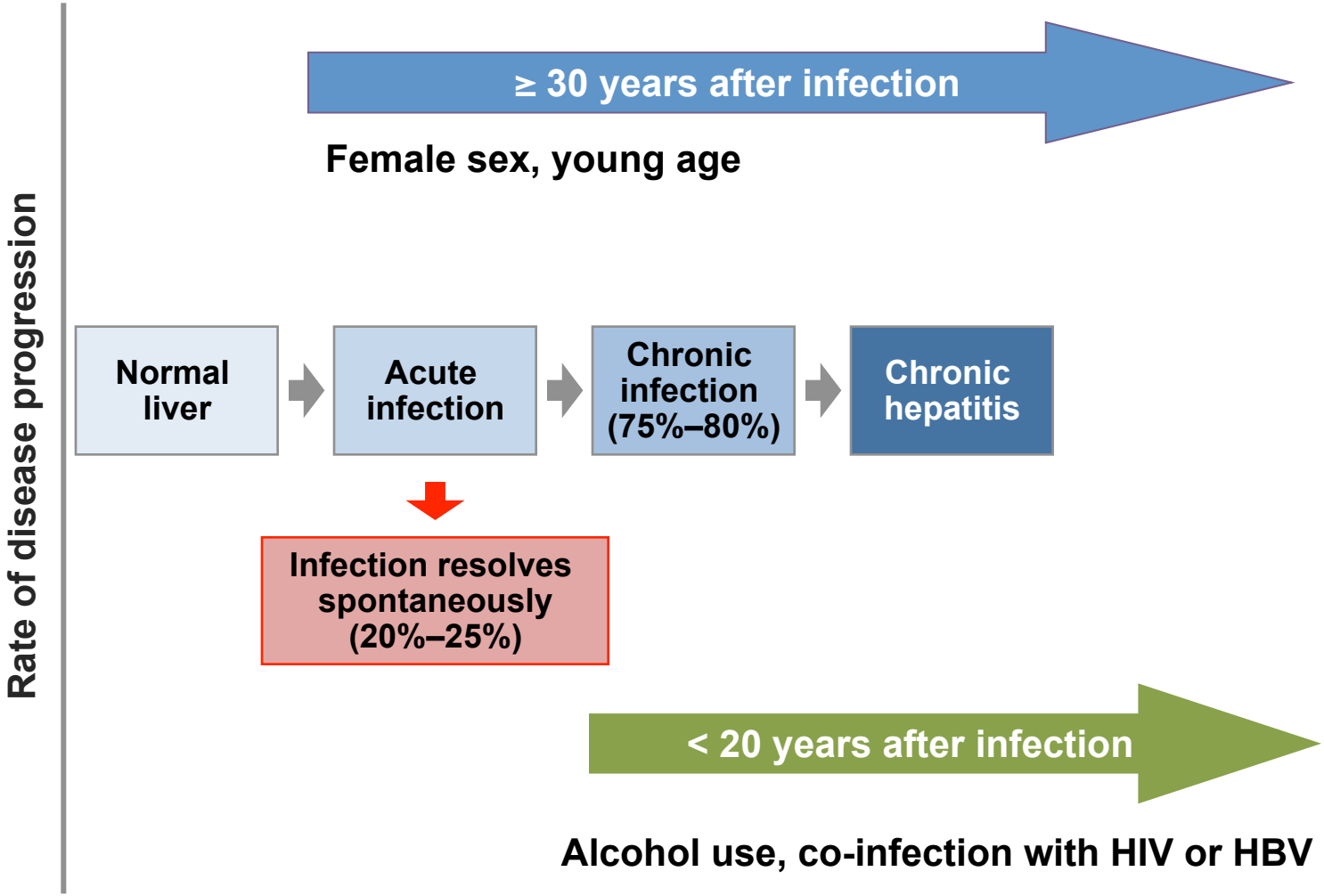


Yu ML, et al., Antiviral Therapy, 2006;11:985-94.
Yu ML, et al., Hepatology, 2006;44:1086-97.

2014 TASL C型肝炎治療之建議
（實證等級）

1. 持續病毒反應（SVR）為C型肝炎治療之目標(I)

Disease progression in HCV



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2014 TASL C型肝炎治療之建議
（實證等級）

Anti-HCV (+) Population	HCV RNA (+)		Reference
	%	n/N	
General	78.0%	1,922/2565	Yang JF, et al., Yu ML. KJMS 2010
Uremics	74.6%	214/287	Yu ML, et al. J Hepatol 2014
HIV/HCV	91.2%	196/215	Hseih MH, et al, Yu ML. Plos One 2014
HBV/HCV	54.7%	41/75	Dai CY, et al., Yu ML. Gut 2007

2014 TASL C型肝炎治療之建議（實證等級）

1. 持續病毒反應（SVR）為C型肝炎治療之目標(I)

2. 血清C型肝炎抗體（anti-HCV）陽性之C型肝炎病毒感染患者應檢驗血清 HCV RNA (III)

Anti-HCV (+) Population	HCV RNA (+)		Reference
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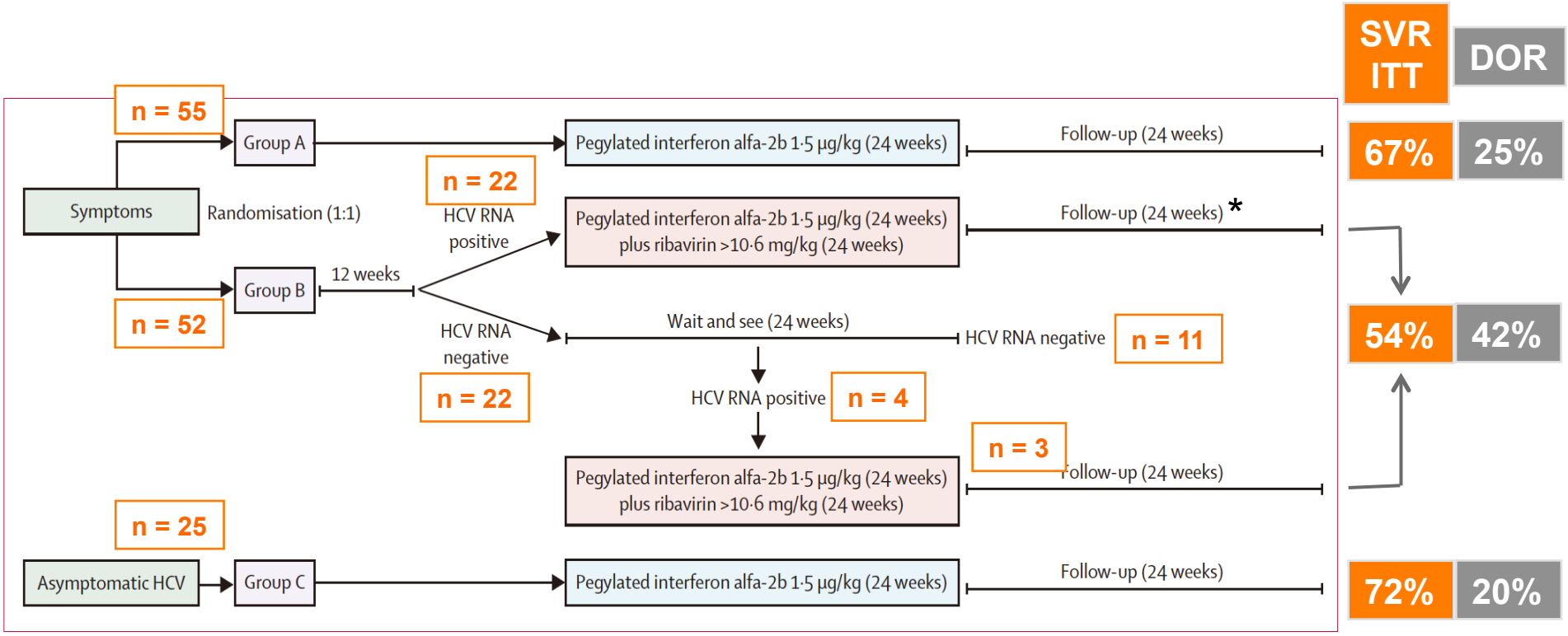
C型肝炎治療之建議
(實證等級)

3. 急性C型肝炎之診斷為Anti-HCV陽轉，同時原來正常之肝轉氨酶值（ALT）於發病時大於100 IU/L以上，血清C型肝炎病毒（HCV RNA）陽性，且排除其他原因所造成之ALT異常 (II)

4. 有症狀之急性C型肝炎患者可先觀察二至四個月，若血清HCV RNA未消失，則給予抗病毒藥物治療 (III)

Immediate vs. delayed treatment for Acute hepatitis C, Phase III, RCT



*14 (100%) patients who received delayed antiviral treatment and completed follow-up achieved SVR.
SVR, sustained virologic response based on ITT analysis; DOR, drop out rate

2014 TASL C型肝炎治療之建議（實證等級）

3. 急性C型肝炎之診斷為Anti-HCV陽轉，同時原來正常之肝轉氨酶值（ALT）於發病時大於100 IU/L以上，血清C型肝炎病毒（HCV RNA）陽性，且排除其他原因所造成之ALT異常 (II)

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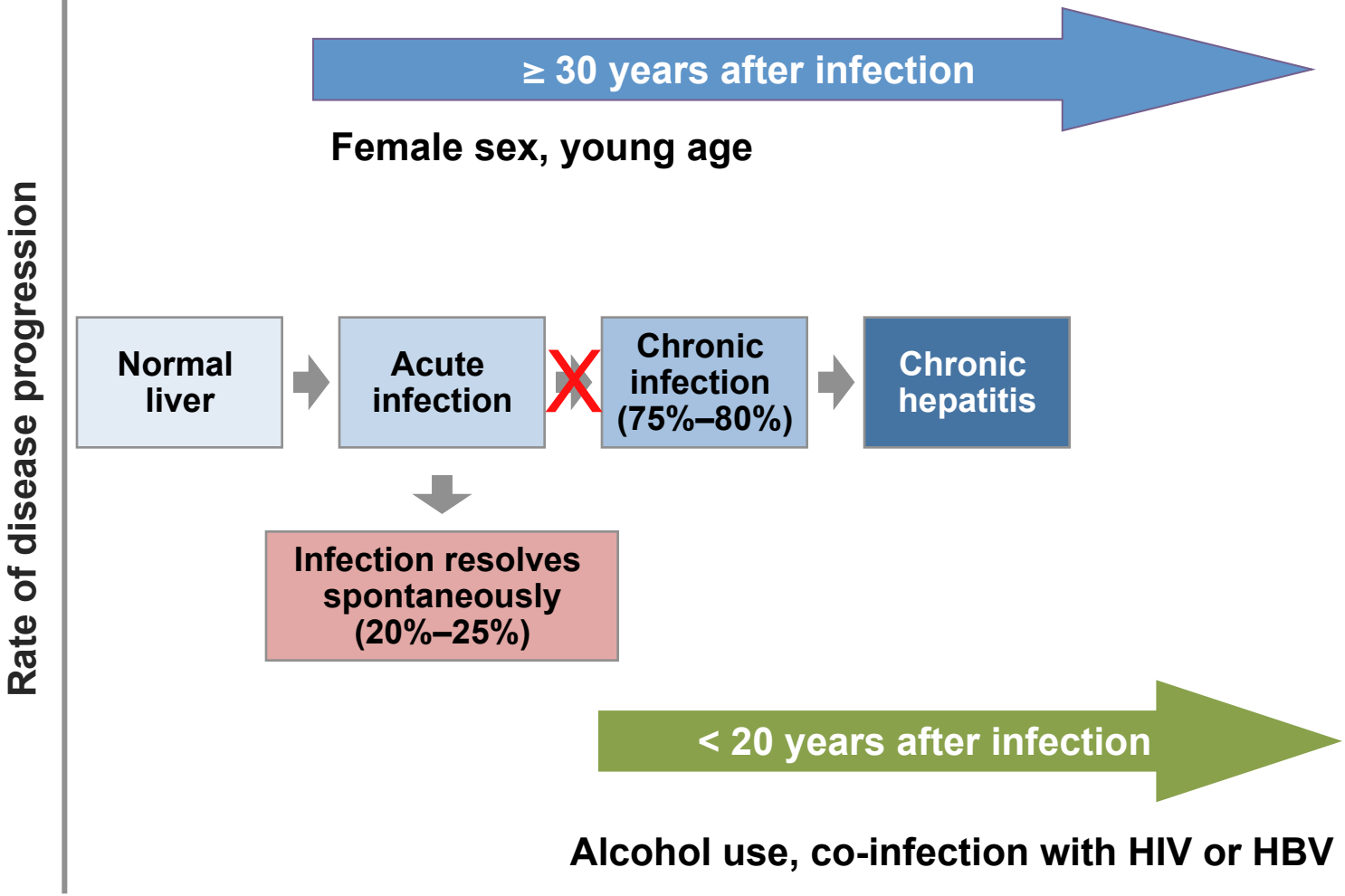
Disease progression in HCV



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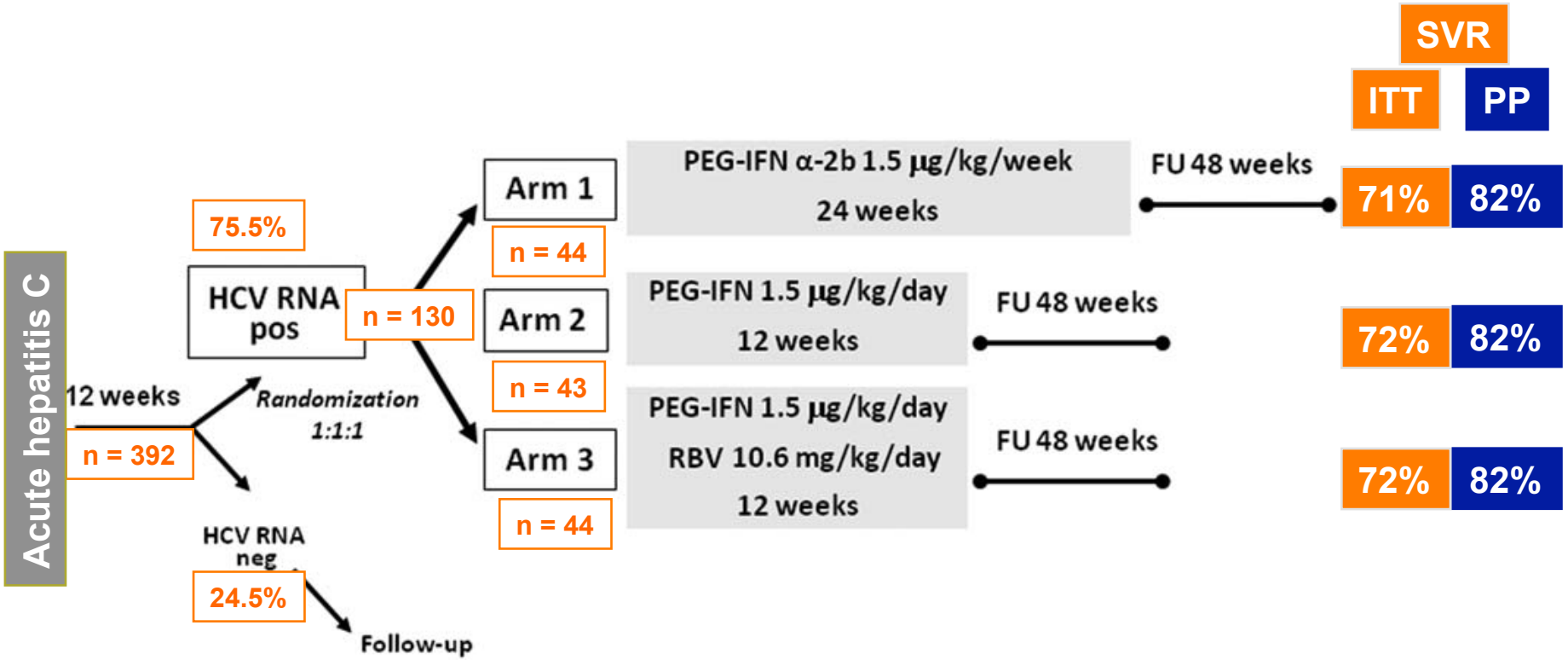
2006 NHRI-TASL C型肝炎治療之建議（實證等級）

5. 對於急性C型肝炎應積極給予治療，以避免變為慢性C型肝炎 (II)，長效型干擾素(Pegylated Interferon)與傳統型干擾素均可使用，治療期間為24週 (II)

6. 目前未有證據顯示合併雷巴非林(Ribavirin) 治療能加強干擾素治療急性 C 型肝炎之療效 (II)

12w PegIFN is optimal for delayed treatment of Acute hepatitis C

- A 3-arm RCT -



SVR, sustained virologic response
ITT, intention-to-treat analysis
PP, per-protocol analysis

2014 TASL C型肝炎治療之建議
（實證等級）

5. 對於急性C型肝炎應積極給予治療，以避免變為慢性C型肝炎 (II)。建議使用長效型干擾素 (Pegylated Interferon)與傳統型干擾素，治療期間為2412週 (II)

6. 目前未有證據顯示合併雷巴非林(Ribavirin) 治療能加強干擾素治療急性 C 型肝炎之療效 (II)

2014 TASL C型肝炎治療之建議（實證等級）

7. 慢性C型肝炎病患接受抗病毒藥物治療前，應檢測病毒基因型以提供抗病毒用藥之選擇，決定治療時間及預知可能療效 (I)

8. 血清HCV RNA陽性之慢性C型肝炎患者不論ALT值是否異常，皆應考慮抗病毒藥物治療。患者接受抗病毒藥物之前，可考慮接受肝穿刺檢查或非侵襲性纖維化評估*，以提供抗病毒用藥之選擇(II)->(I)以決定肝組織發炎活性級別及纖維化期別(III)，尤其是基因型第一型與第四型慢性C型肝炎病毒感染患者(III)。若肝穿刺檢查發現有第一期或以上之肝纖維化時，患者應接受治療(II)

*Fibrotest, Fibroscan, ARFI, etc.

2014 TASL C型肝炎治療之建議（實證等級）

9.若肝穿刺檢查發現沒有肝纖維化，慢性C型肝炎患者接受臨床觀察即可。除非患者有極強烈意願選擇接受根除性治療，否則並不需要馬上施予治療(II)。但患者血清ALT值異常且肝臟發炎指數在A2以上時，亦可考慮治療(III)

10.未接受治療之慢性C型肝炎患者，應每3至6個月定期追蹤肝功能(III)。臨床追蹤5~10年後，可考慮重複肝穿刺檢查或非侵襲性纖維化評估(III)，若患者組織學上顯示肝病惡化，應給予治療(III)

2014 TASL C型肝炎治療之建議（實證等級）

11.慢性C型肝炎病患接受抗病毒藥物治療前需檢測血清病毒濃度(I)，但在基因型第二型與第三型慢性C型肝炎患者此項檢查非絕對必要

12.慢性C型肝炎病患接受抗病毒藥物治療，若停藥時病毒消失，應於停藥十二週*或二十四週後再次檢測病毒，以決定是否有持續病毒反應 SVR (II)

*DAA regimens: SVR12 = SVR24

2014 TASL C型肝炎治療之建議（實證等級）

13.基因型第一型與第四型慢性C型肝炎患者如治療中無干擾素反應(治療四週時病毒量下降 <1 logs)或無早期病毒反應(治療十二週時病毒量下降 < 2 logs)可以考慮停藥(I)。但必須依個人治療中耐受度、肝病嚴重度、及是否有部份病毒或生化反應來決定 (III)

14.長效型干擾素合併Ribavirin為治療基因型第一型與第四型慢性C型肝炎首選用藥 (I)，Ribavirin起始劑量建議七十五公斤以下每天一千毫克，七十五公斤以上每天一千二百毫克(I)

Week 4 Rapid stopping rule for naïve HCV-1

All 528 HCV-1 patients treated with 48w PegIFN/RBV from NTUH & KMUH

Week 4 viral loads and IL28B rs8099917 genotype	Non-SVR (n = 136)	SVR (n = 392)	P value	SEN	SPE	PPV	NPV	ACC
	n(%)	n(%)		%	%	%	%	%
Gr A: < 1 log_{10} IU/mL decline	40 (29)	1 (0.3)	<0.001	99.7	29	80	98	82
Gr B: > 10,000 IU/mL/non-TT	47 (35)	3 (1)	<0.001	99	35	81	94	83
Poor W4 responses: Gr A or B	59 (43)	3 (1)	<0.001	99	43	84	95	85

IL-28B rs8099917 genotype

Yu ML, et al. PLOS ONE 2012, 7(12): e52048. doi:10.1371/journal.pone.0052048

2014 TASL C型肝炎治療之建議（實證等級）

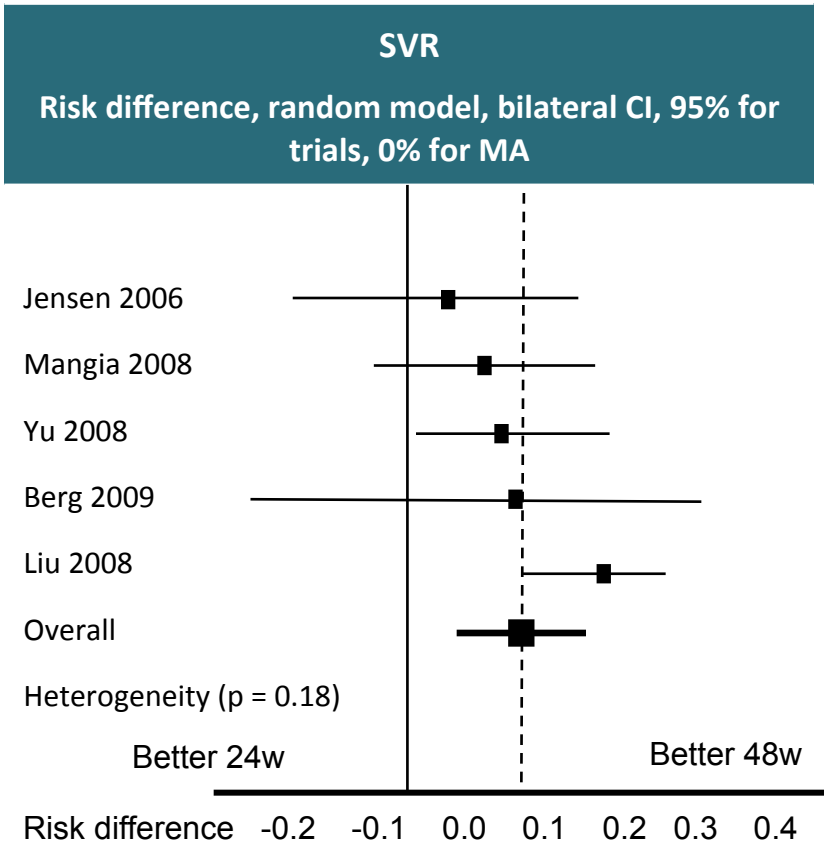
15.基因型第一型與第四型慢性C型肝炎患者建議治療時間為四十八週。

若病人治療前病毒濃度較低(<400,000 IU/mL)且治療第四週時病毒消失(快速病毒反應，RVR)，可考慮接受二十四週治療(II) -> (I)。

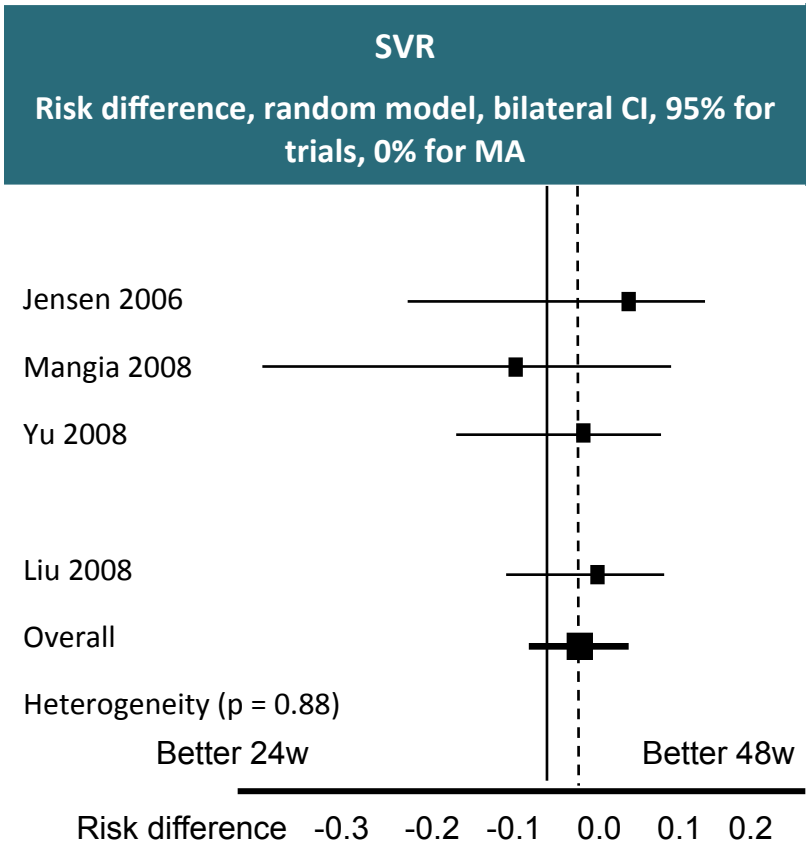
若病人治療第十二週仍為病毒陽性反應且有早期病毒反應(治療十二週時病毒量下降 ≥ 2 logs)，可考慮延長至七十二週治療 (I)。

Shortened Treatment Duration in Treatment-Naïve HCV-1 Patients with RVR: Meta-Analysis

- Systemic review of RCT comparing 24 weeks to 48 weeks of treatment : 5 trials (624 patients with RVR)



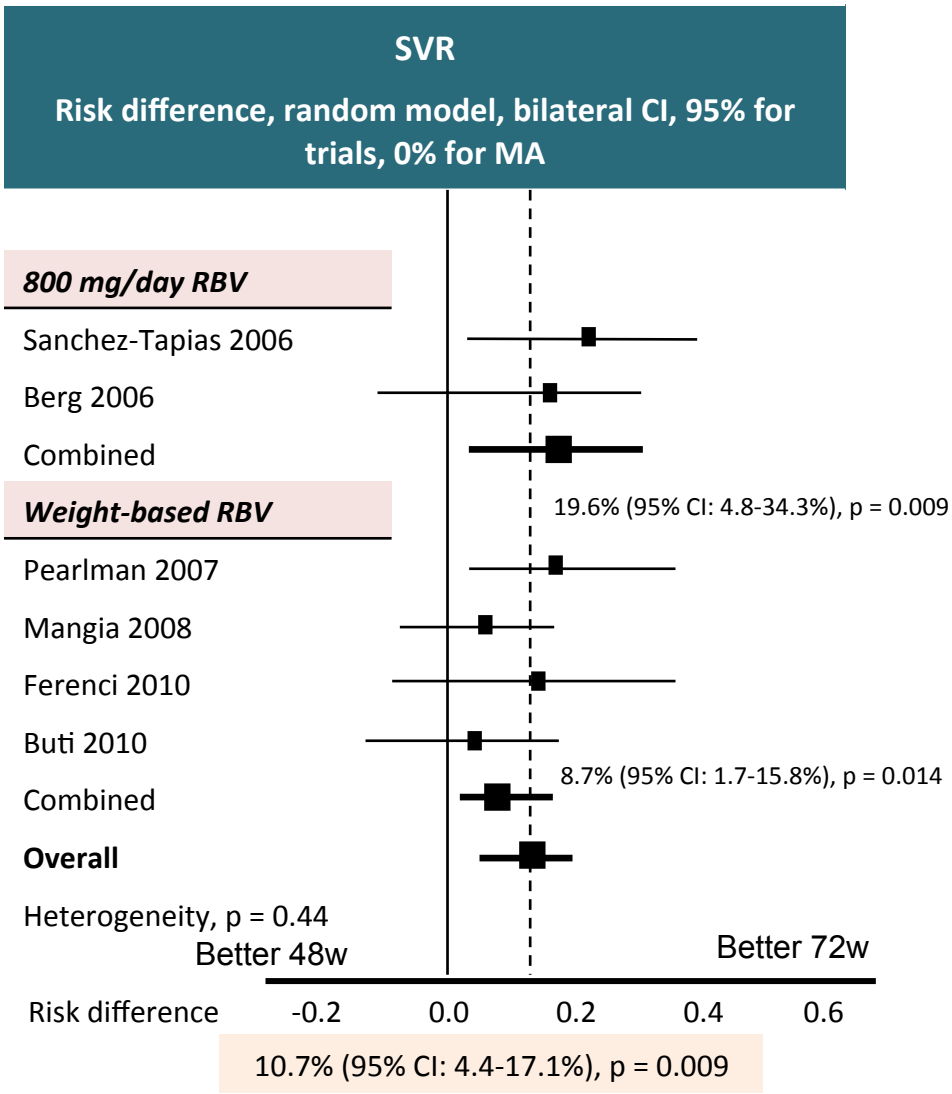
Patients with RVR
12.5% (95% CI: 5.8-19.2%), p < 0.0001

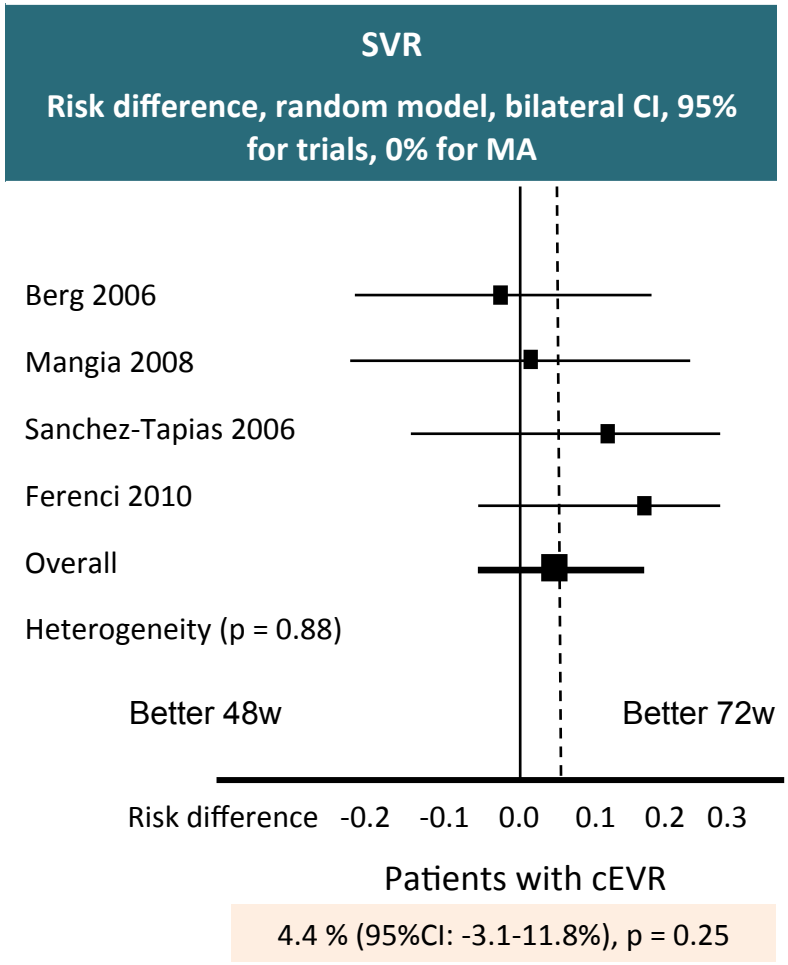


Patients with RVR & low baseline viral load (< 400,000 IU/mL)
4.4 % (95%CI: -1.0-9.8%), p = 0.11

Extending to 72w for HCV-1 Slow Responders: Meta-Analysis

- Systemic review of RCT comparing 48 weeks to 72 weeks of treatment : 6 trials





Di Martino V, et al. Hepatology 2011;54:789-800

2014 TASL C型肝炎治療之建議（實證等級）

16.基因型第二型與第三型慢性C型肝炎患者建議使用長效型干擾素或傳統型干擾素合併Ribavirin每天八百至一千二百毫克治療，治療時間為二十四週(I)。

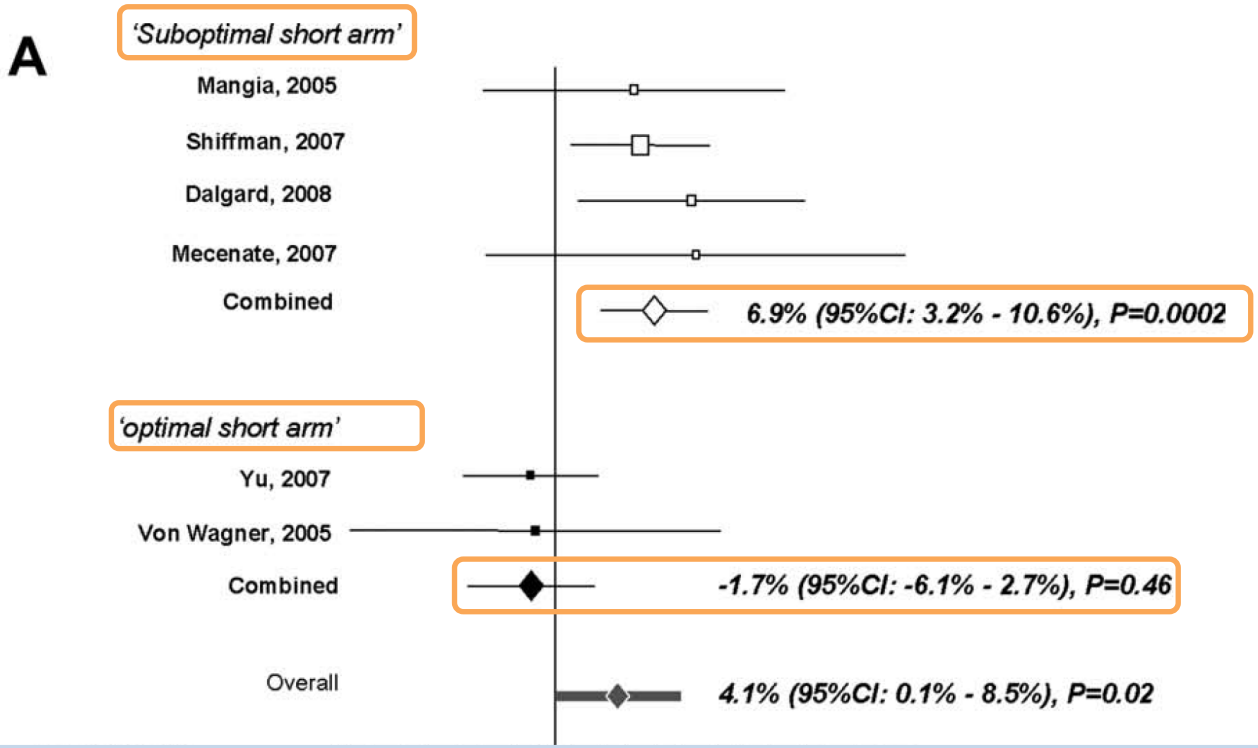
若病人接受長效型干擾素合併每天1000至1200毫克Ribavirin治療，於治療第四週時病毒已消失(有RVR)，可考慮只接受12至16週治療即可(I)

若病人治療第四週仍為病毒陽性反應(無RVR)，且有早期病毒反應(治療十二週時病毒量下降 ≥ 2 logs)，可考慮延長至四十八週治療 (II)。

Meta-analysis for HCV-2/3 RVR+ve pts

Comparable SVR rate between optimal short therapy and 24w SOC

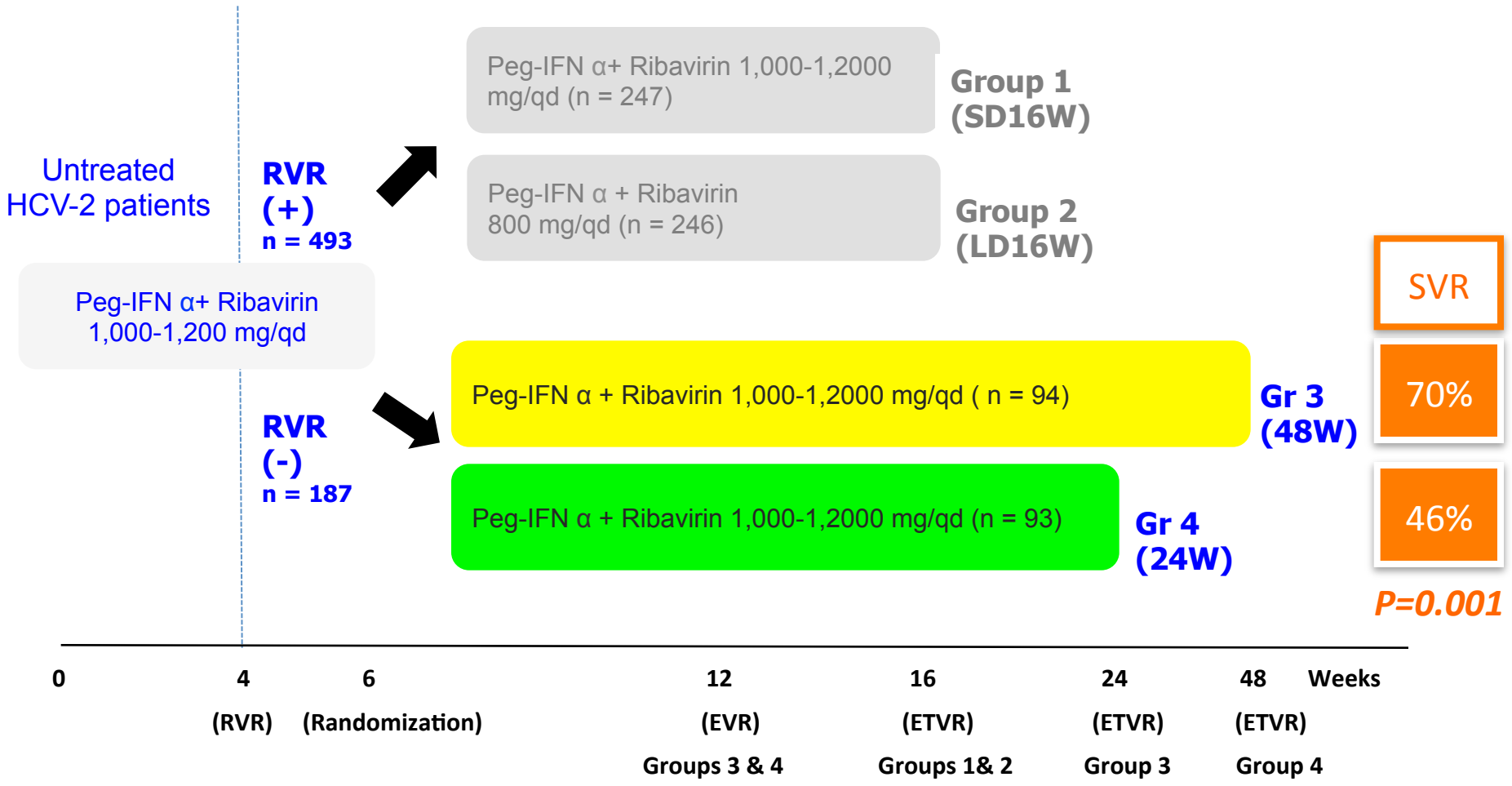
- Category of HCV-2/3 patient by regimens (6 RCTs, 2004-2008)
  - Suboptimal short therapy: 12-14 wks Tx or fixed-LD RBV (n=1782)
  - Optimal short therapy: 16 wks Tx and weight-based RBV (n=272)



Shorter treatment for HCV-2/3 patients with a RVR should be a 16-week regimen with weight-based dose of RBV

Di Martino V, et al. Hepatology 2011; 54:789-800.

TARGET-2 study: Individualized Therapy for HCV-2



Primary end point: SVR_{24} (Cobas Taqman v.2.0, limit of detection 15 IU/mL)
Clinical trial number: NCT00532701

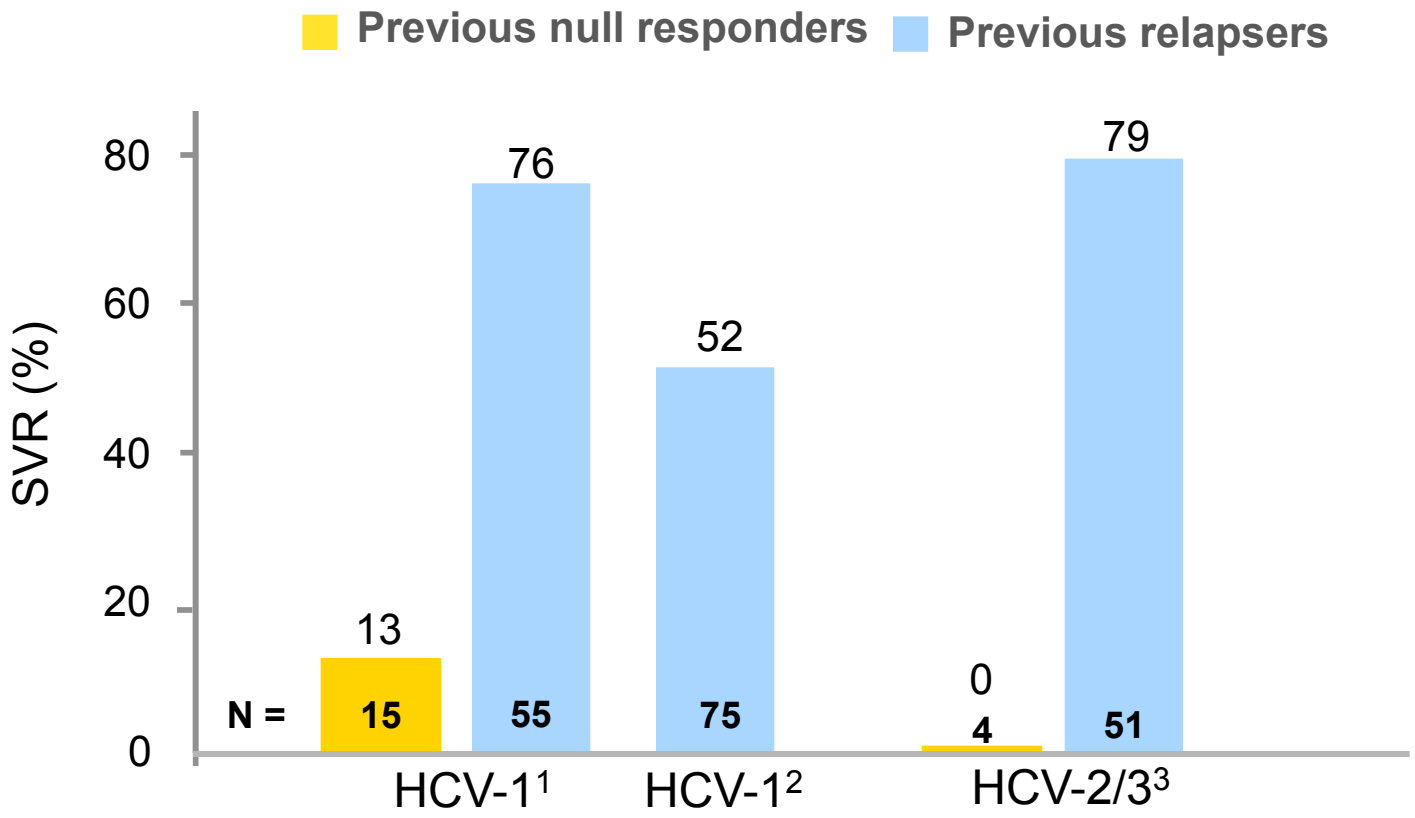
2014 TASL C型肝炎治療之建議（實證等級）

17.慢性C型肝炎病患若先前以非長效型干擾素為基底之治療復發者或失敗且有明顯纖維化或肝硬化，應考慮以長效型干擾素合併 Ribavirin 重複治療二十四至四十八週(II)。，但最適合的治療時間與干擾素及 Ribavirin 之劑量尚未確立若先前以干擾素為基底之治療為部分反應者(治療期間病毒量下降 >2 logs、但從未消失)或無反應者(治療期間病毒量下降從未>2 logs)，不建議再接受長效型干擾素合併 Ribavirin 之重複治療(II)

18.長效型干擾素與Ribavirin合併治療前與治療中，應定期接受理學檢查、病毒學檢查、血清生化學檢查、血液學檢查與甲狀腺功能檢查，必要時需評估心臟、肺部及精神狀態，以處理干擾素與Ribavirin之副作用及評估療效(II)

Treatment-experienced HCV patients Retreatment with PegIFN/RBV in Taiwan

48w PegIFN/RBV for HCV-1; 24w PegIFN/RBV for HCV-2/3



1. Huang CF, et al., Yu ML. J Gastroenterol Hepatol, 2013 ;28(9):1515-20.
2. Chen MY, et al. J Gastroenterol Hepatol 2014;29:102-9
3. Huang CF, et al., Yu ML, PLoS ONE, 2013;8(3):e58882.

2014 TASL C型肝炎治療之建議
（實證等級）

19. 長效型干擾素與Ribavirin合併治療期間與治療後六個月內，必須執行避孕措施(IV)

20. 治療後，所有病患仍需接受定期肝功能、甲型胎兒蛋白(AFP)與腹部超音波檢查，尤其是治療無效者，或年齡較高、有糖尿病、與嚴重肝臟纖維化者更須注意(III) ->(II)

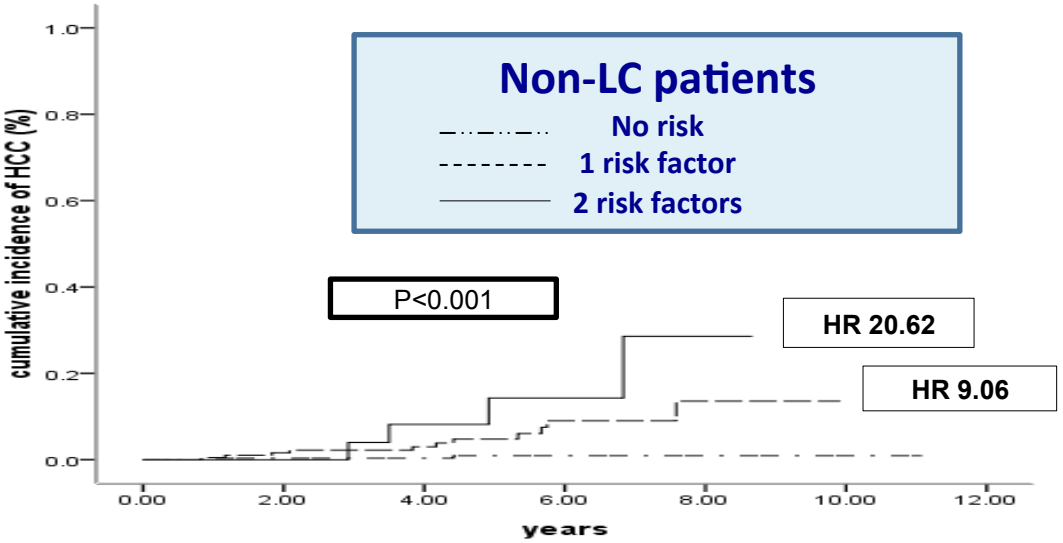
Risk of HCC development in SVR patients with advanced liver disease -Meta-analysis

- 10 cohorts in Europe & Canada
- Median age: 53 (IQR:45-60)
- LC: 85%, bridging fibrosis:15%
- DM: 14 %
- 51 of the 1000 patients (5.1%) developed HCC over median follow-up of 5.7 years
- Annual incidence of HCC: 1%

	OR (95 % C.I.)	P value
Age, yrs		
<45	1	
45-60	8.54 (1.13-64.65)	0.038
>60	8.91 (1.12-70.77)	0.039
PLT counts		
per 1000 cells/mm^3 increase	0.94 (0.87-1.00)	0.048
DM		
No	1	
Yes	2.36 (1.02-5.42)	0.044

van der Meer et al. AASLD 2013

Risks of HCC among cirrhotic patients and non-cirrhotic patients who carried different risk factors



Risk factors in non-cirrhotic patients :
1. high *r*-GT levels
2. age≥ 60 of years

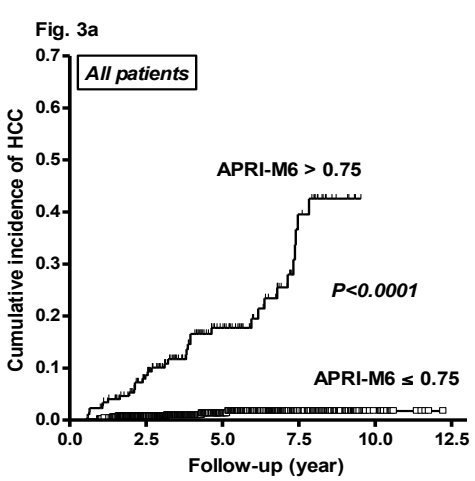
	HCC incidence (per person-year)	OR	95% C.I.	P value
LC	4.54 %	1		
Non-LC with 2 risk factors	2.80 %	0.59	0.20-1.75	0.34
Non LC with 1 risk factor	1.22 %	0.26	0.12-0.56	0.001
Non-LC without any risk factor	0.14 %	0.03	0.007-0.13	<0.0001

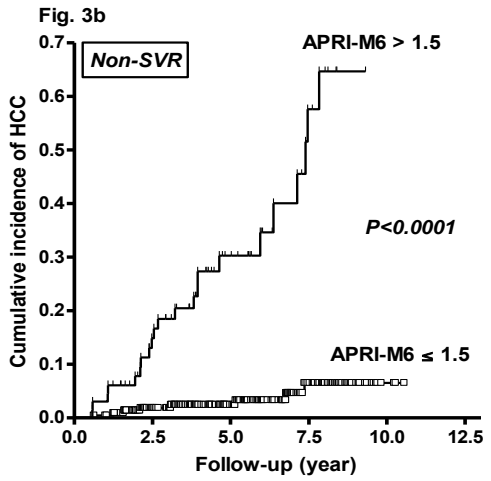
Variables	HCC, n (%)	Non-HCC, n (%)	P	SEN	SPE	PPV	NPV	ACC
r-GT> 74 IU/L	10 (58.8)	128 (23.7)	0.003	59	76	7	98	76
Age> 60 yrs	9 (52.9)	125 (23.2)	0.009	53	77	7	98	76
r-GT> 74 IU/L or age>60 yrs	15 (88.2)	226 (41.9)	<0.001	88	58	6	99	59
r-GT> 74 IU/L and age>60 yrs	4 (23.5)	27 (5.0)	0.01	24	95	13	98	93

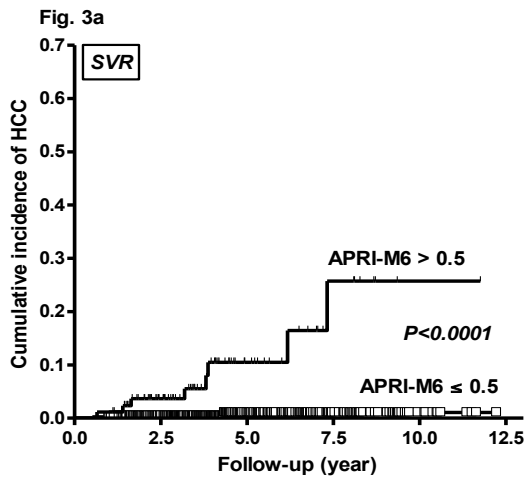
Huang CF…Yu ML et al. J Hepatol 2014

High APRI-M6 after SVR remains at risk of HCC

- **APRI-M6 (APRI 6 months after EOT), indicating the degree of liver fibrosis, predicts 12-y outcome with AUROC of 0.87 accuracy of 0.81**







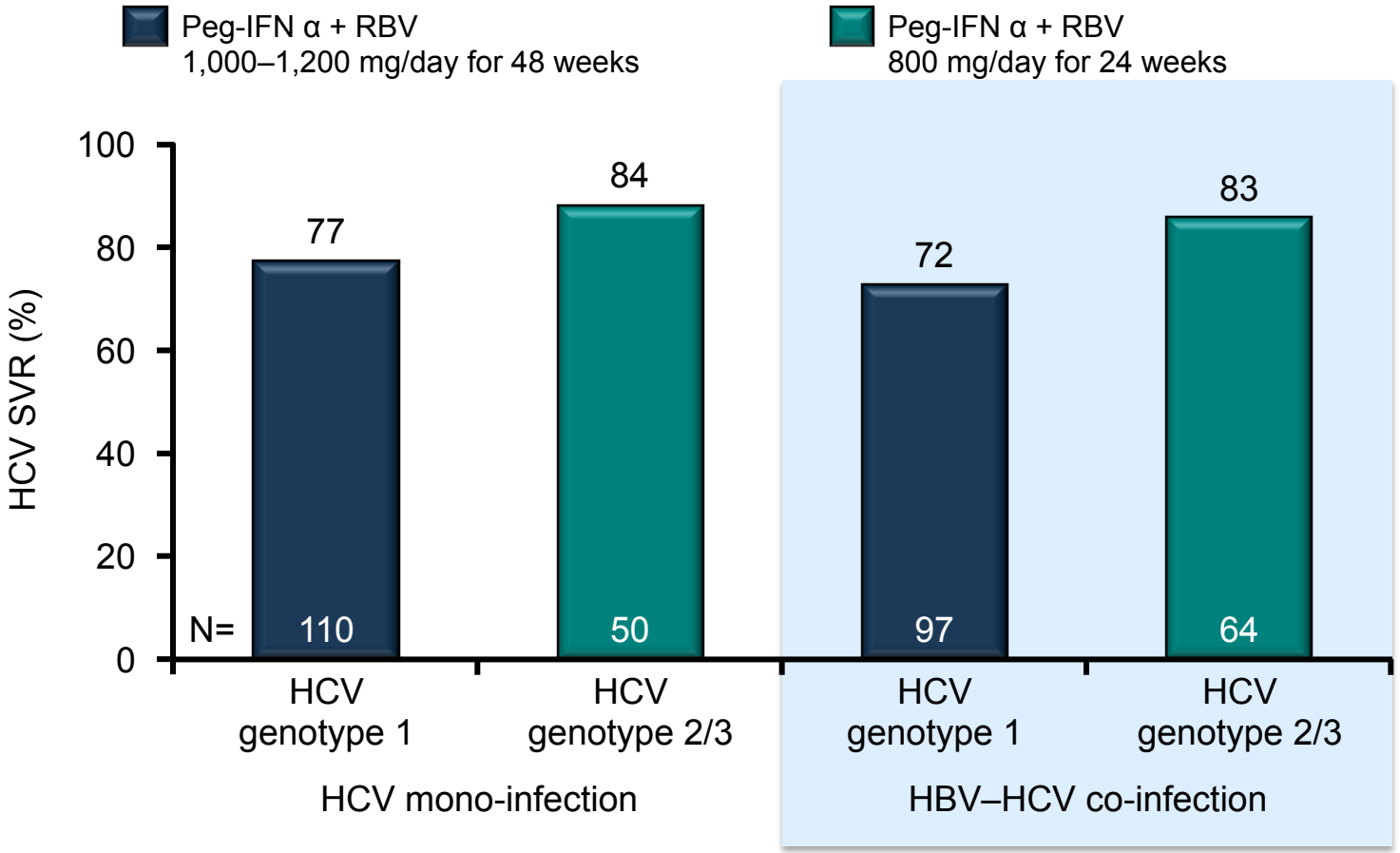
APRI: (AST level/upper limit of normal range)/PLT counts (10^9/L) × 100

2014 TASL C型肝炎治療之建議（實證等級）

慢性B型與C型肝炎病毒雙重感染的治療

1. 面對慢性C型肝炎患者，應例行檢驗HBsAg；面對慢性B型肝炎患者，也應例行檢驗anti-HCV。當遇到高危險族群如靜脈毒癮者時，更應進行相關檢驗 (IV)。
2. 當HBsAg檢驗結果為陰性時，應進一步檢驗anti-HBs及anti-HBc。當anti-HBs及anti-HBc皆是陰性時，應建議患者接受完整三劑之B肝疫苗注射 (IV)。
3. 針對雙重C型和B型肝炎病毒感染患者，每3至6個月，應定期追蹤肝功能，每6至12個月，應定期追蹤HBsAg、HBeAg、及anti-HBe (IV)。
4. 依據雙重病毒感染者之慢性肝病嚴重程度，應每3-6個月進行肝細胞癌篩檢，項目包括腹部超音波檢查和甲種胎兒蛋白(AFP) (III)。
5. 在雙重病毒感染患者接受治療前，應進行相關病毒學檢驗以釐清何種病毒活性較強 (III)。C型肝炎病毒活性較強之雙重病毒感染患者，應採用與C型肝炎病毒單一感染患者相同之治療準則，長效型干擾素合併Ribavirin，病毒基因型第一型為期四十八週、病毒基因型第二型為期二十四週(I)。
6. B型肝炎病毒活性較強之雙重病毒感染患者，治療策略仍有待研發 (IV)。

Similar SVR rates in Asian HBV–HCV co-infected and HCV mono-infected patients



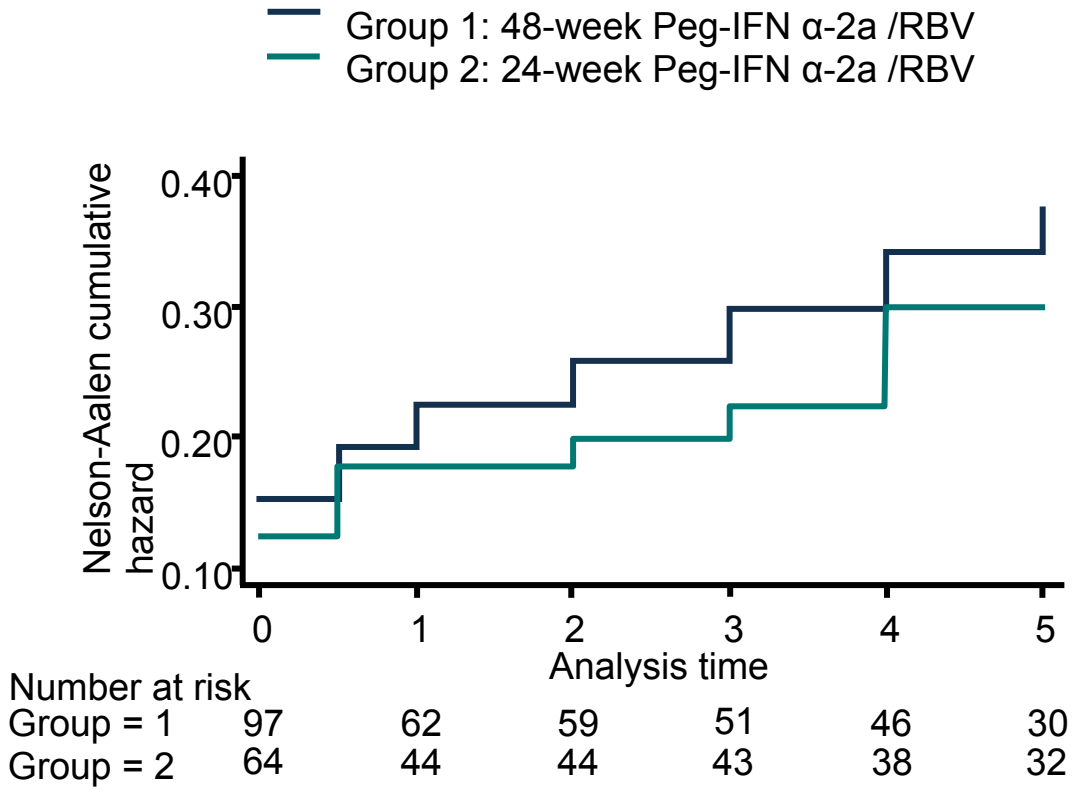
ITT population
SVR = sustained virological response

Factors predictive of HCV SVR

- **Low baseline HCV RNA; non-LC**

Liu CJ, *et al. Gastroenterology* 2009;136:496–504.

Around 30% of patients cleared HBsAg 5 years after treatment with Peg-IFN α-2a /RBV



Factors associated with HBsAg loss

- Neither HBV genotype, PC/BCP mutant, nor HCV SVR
- BL HBV DNA < 200 IU/ml
- BL and EOT HBsAg < 10 IU/ml

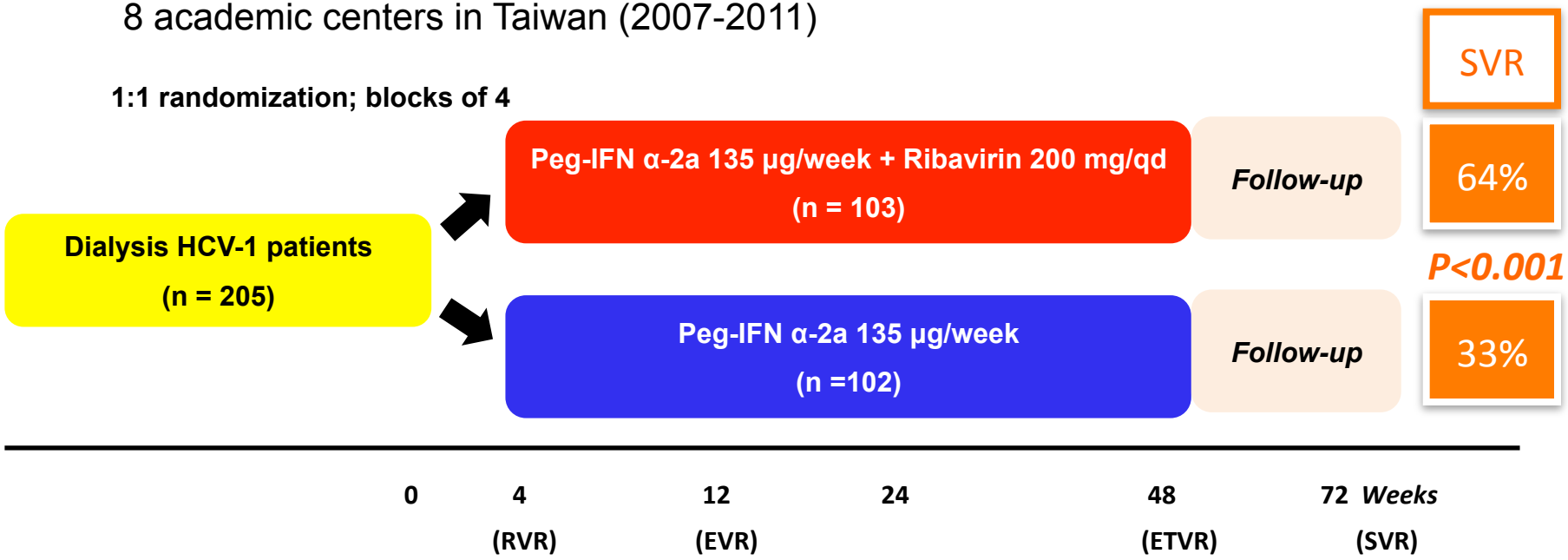
Yu ML, *et al. Hepatology* 2013;57:2135–42.

2014 TASL C型肝炎治療之建議
（實證等級）

末期腎病變血液透析患者慢性C型肝炎感染的治療

Peginterferon α-2a ± Low Dose Ribavirin for Treatment-Naïve Hemodialysis HCV-1Patients: HELPER-1 Trial

- HELPER-1: Hemodialysis Low Dose Peginterferon and Ribavirin for HCV-1 Patients
- Randomized, multicenter, open-label trial, 2-arm parallel, active control trial (n = 205) in 8 academic centers in Taiwan (2007-2011)



Primary efficacy endpoint: SVR rate

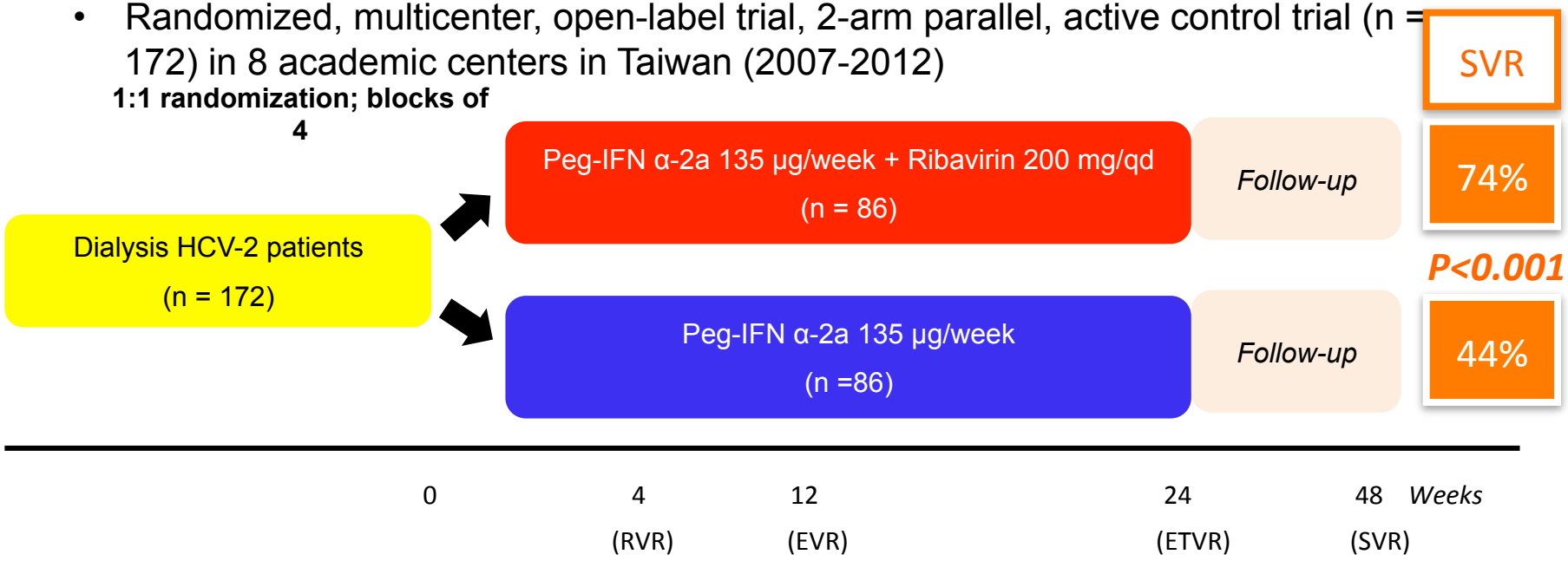
Primary safety endpoint: adverse event (AE)-related withdrawal rate

Clinical trial number: NCT00491244

Liu CH, et al. Ann Intern Med 2013;159:729-38

Peginterferon α-2a ± Low Dose Ribavirin for Treatment-Naïve Hemodialysis HCV-2 Patients: HELPER-2 Trial

- HELPER-2: Hemodialysis Low Dose Peginterferon and Ribavirin for HCV-2 Patients
- Randomized, multicenter, open-label trial, 2-arm parallel, active control trial (n = 172) in 8 academic centers in Taiwan (2007-2012)



Primary efficacy endpoint: SVR rate

Primary safety endpoint: adverse event (AE)-related withdrawal rate

Clinical trial number: NCT00491244

Liu CH, et al. Gut 2014, in press

Dosage Modification for Impaired Renal Function [Peginterferon α -2a & Peginterferon α -2b]

Ccr	Peg-IFN alfa-2a, µg/wk	Peg-IFN alfa-2b, µg/kg/wk	Ribavirin Daily
30-50 mL/min	180	1.125	Alternating doses, 200 mg and 400 mg every other day
Less than 30 mL/min	135	0.75	200 mg/day
Hemodialysis	135	0.75	200 mg/day

FDA, Peginterferon alfa-2a and peginterferon alfa-2b package insert

2014 TASL C型肝炎治療之建議（實證等級）

末期腎病變血液透析患者慢性C型肝炎感染的治療

1.末期腎病變血液透析患者應例行檢驗anti-HCV(IV)。

2.針對C型病毒感染患者，每3至6個月，應定期追蹤肝功能 (IV)。

3.依據C型病毒感染者之慢性肝病嚴重程度，應每3-6個月進行肝細胞癌篩檢，項目包括腹部超音波檢查和甲種胎兒蛋白(AFP) (III)。

4.末期腎病變血液透析患者之慢性C型肝炎接受治療前，應進行病毒學檢驗以決定是否需要治療及作為療程之參考 (II)。

5.末期腎病變血液透析患者慢性C型肝炎之治療建議為：長效型干擾素(alfa 2a, 135微克/週; alfa 2b, 0.75微克/公斤/週)合併Ribavirin200毫克/天，病毒基因型第一型為期四十八週、病毒基因型第二型為期二十四週(I)。

2014 TASL C型肝炎治療之建議（實證等級）

- HIV合併HCV感染時之追蹤和治療建議
- 孕婦慢性C型肝炎之處置
- 兒童慢性C型肝炎治療

2014 TASL C型肝炎治療之建議（實證等級）

- 小分子直接抗C型肝炎病毒藥物於慢性C型肝炎之治療 (DAA containing regimens) (I)

- 符合干擾素適應症暨可耐受者
  - DAA 合併長效型干擾素及Ribavirin療程
  - DAA 無干擾素療程

- 不符合干擾素適應症或干擾素耐受不良者
  - DAA 無干擾素療程

Direct Acting Antivirals (DAA) with Approval or Filing for NDA

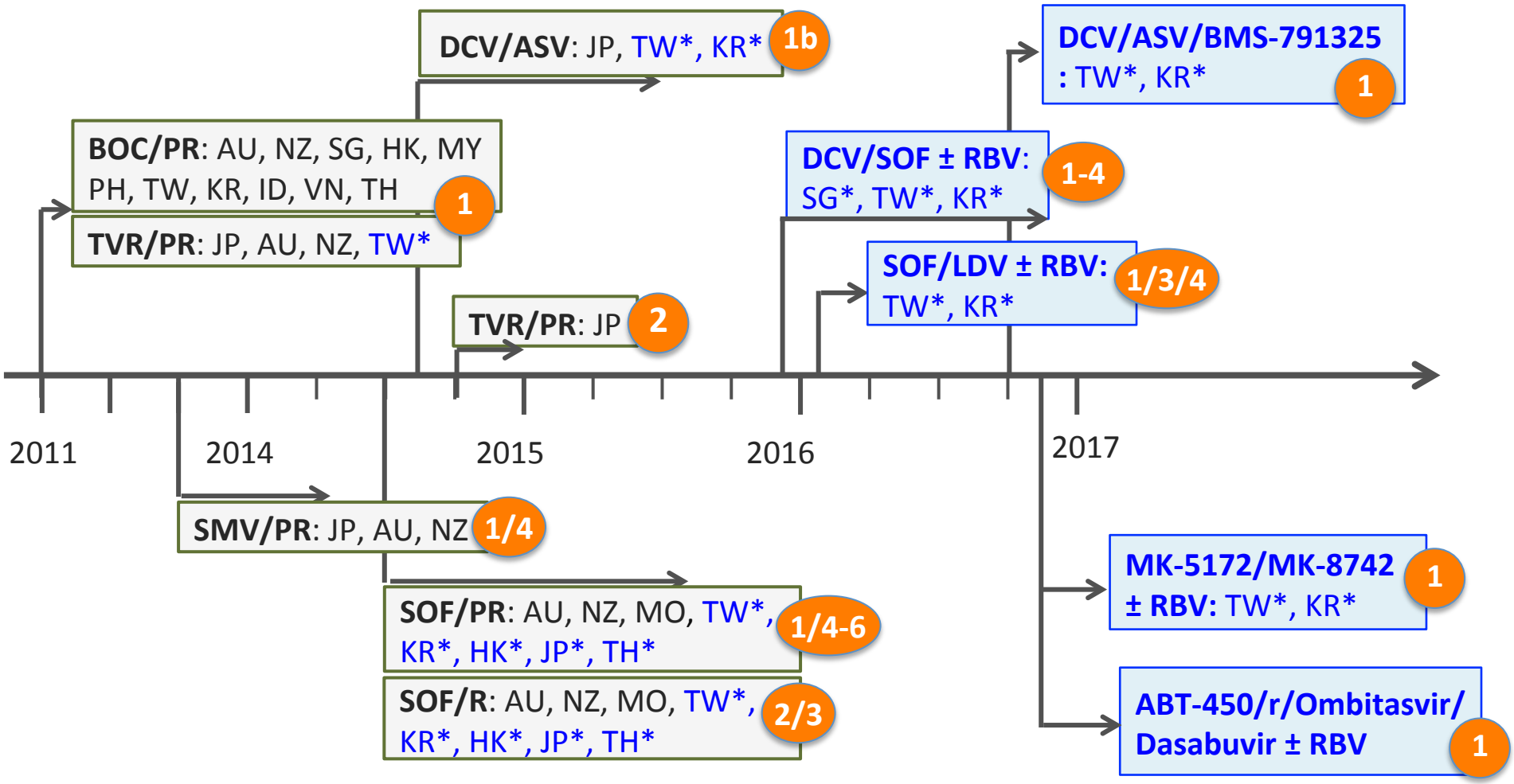
2011

- NS3/4A Protease-Inhibitors
  - Boceprevir (Taiwan, Mar 2014)
  - Telaprevir (Taiwan, Oct 2014)

2013
2014

- Nucleotide Polymerase inhibitor
  - Sofosbuvir
- NS3/4A Protease-Inhibitors
  - Simeprevir
  - Faldaprevir X (withdrawal)
- NS5A-Inhibitor
  - Daclatasvir
- IFN-free combinations
  - Sofosbuvir + RBV
  - Daclatasvir + Asunaprevir
  - Sofosbuvir + Ledipasvir (FDC)
  - ABT450/r + Ombitasvir + Dasabuvir +/- RBV

Expected DAA to be approved in Asia



Expected indications of DAA regimens in Asia countries

DAA Regimen	Treatment duration	HCV Genotype	Decompensated Liver diseases
Interferon-containing regimens			
*BOC + PR, RGT (BOC 800 mg q8hr, 24-44w)	28-48 weeks	G1	No
*TVR + PR, RGT (TVR 1125 mg q12hr, 12w)	24-48 weeks	G1/2	No
*SMV + PR (SMV 150 mg qd, 12w)	24-48 weeks	G1/4	No
*SOF + PR (SOF 400 mg qd, 12w)	12 weeks	G1/3-6	No
*DCV + PR, RGT (DCV 60 mg qd, 24w)	24-48 weeks	G4	No
Interferon-free regimens			
*SOF + RBV	12-24 weeks	G1-6	Yes
**SOF + SMV ± RBV	12 weeks	G1	No
*DCV + ASV	24 weeks	G1b	No
*DCV + SOF ± RBV	12-24 weeks	G1–4	Yes
*SOF + LDV ± RBV	8-24 weeks	G1/3/4	Yes
#ABT-450/r + Ombitasvir + Dasabuvir ± RBV	12-24 weeks	G1	Yes
##DCV + ASV + BMS-791325	12 weeks	G1	No
##MK-5172 + MK-8742 ± RBV	12 weeks	G1–6	No

DAA, directly-acting antiviral agents; RGT, response-guided therapy; BOC, boceprevir; P, peginterferon; R or RBV, ribavirin, TVR, telaprevir; SMV, simeprevir; SOF, sofosbuvir; DCV, daclatasvir; ASV, asunaprevir; LDV, ledipasvir *Approved regimens in US, EU or Japan; **off-label regimen; #regimen awaiting approval; ##regimens of ongoing phase 3 trials. Underline indicated fixed-dose combination

Yu ML, Chuang WL. Clinical Liver Disease, 2014 in press

HCV Practice Recommendation for IFN-eligible naïve patients in Asia-Pacific countries with DAA available

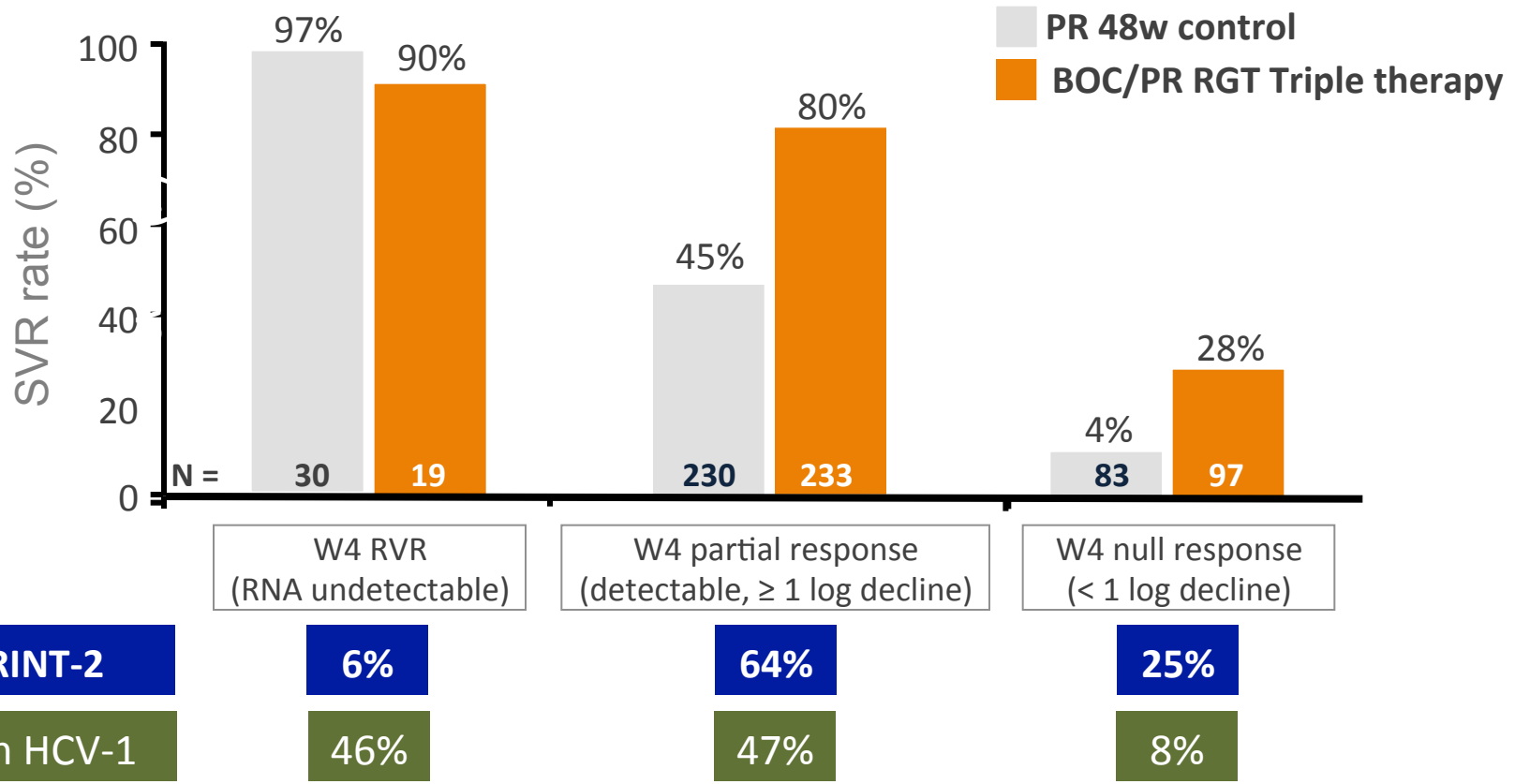
SVR rates of DAA + PR Tx Regimen for HCV-1 Patients

(Not head-to-head comparisons)

	Boceprevir	Teleprevir	Simeprevir	Sofosbuvir
Tx shortening Naive pts	**56 %**	**58-65 %**	**88%**	**(100%)**
Naïve pts	63-66 %	74-79 %	**80 %**	**90 %**
HCV -1a	59-63 %	75 %	84 % w/o Q80K 58 % with Q80K	**92 %**
HCV-1b	66-70 %	84 %	85 %	82 %
IL28 B CT/TT	62-68 %	67 %	75 %	**87 %**
Cirrhosis	38 %	54-71 %	60 %	**80 %**
Relapsers	75 %	84 %	79 %	*No data*
Partial resp	52 %	61-69 %	70 %	*No data*
Null resp	38 %	31-46 %	44 %	*No data*
Cirrhosis	Numbers too small	19-31 %	25 %	*No data*

Poorded et al, Sprint-2, NEJM 2011, 364: 1195-1206; Bacon et al, Respond-2, NEJM 2011; 364:1207-17; Vierting et al, Provide, J Hepatol 2014; 60:748-750, Jacobson et al, Advance, NEJM 2011:364: 2405-16; Sherman et al, NEJM 2011; 365: 1014-24, Zeuze et al, Realize, NEJM 2011; 364:2417-26, Jacobson et al, Quest-1 , EASL 2013, Forms et al, AASLD 2013; Reddy et al, APASL; Ferenci et al, Startverso-1, EASL 2013; Jensen et al, Startverso-2, AASLD 2013, Jacobson et al, Startverso-3, AASLD 2013, Lawitz et al, Neutrino, NEJM 2013; 368:1878-87.

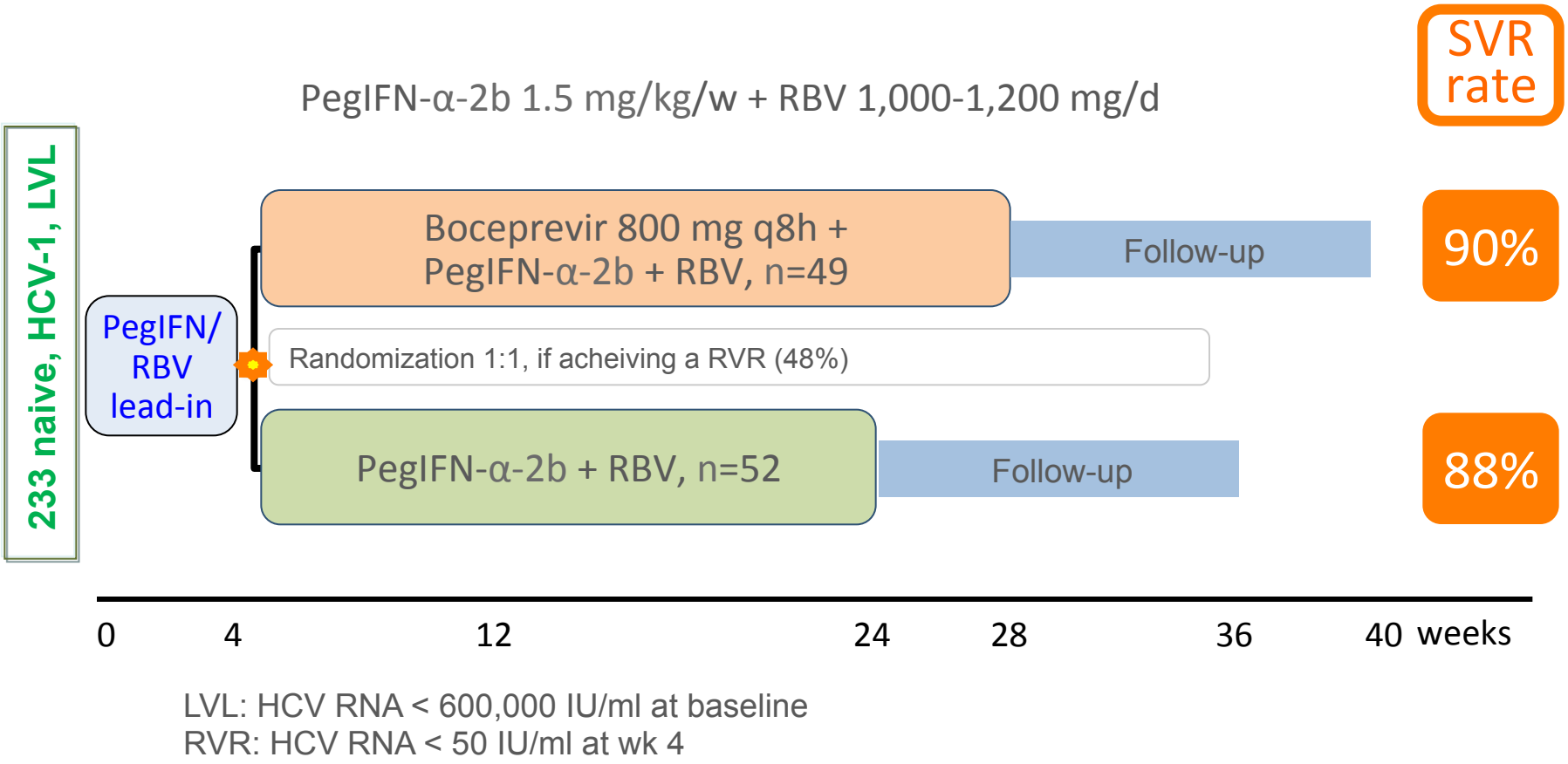
No benefit of adding BOC to PegIFN/RBV for HCV-1 patients with RVR



Lim SG, Yu ML, et al. 2013 APASL Liver Week 2013
Yu ML, et al. PLoS ONE 2012

HCV-1 patients with an LVL and RVR

Whether 28w LI-BOC/PR is superior to 24w PR?



LVL: HCV RNA < 600,000 IU/ml at baseline
RVR: HCV RNA < 50 IU/ml at wk 4

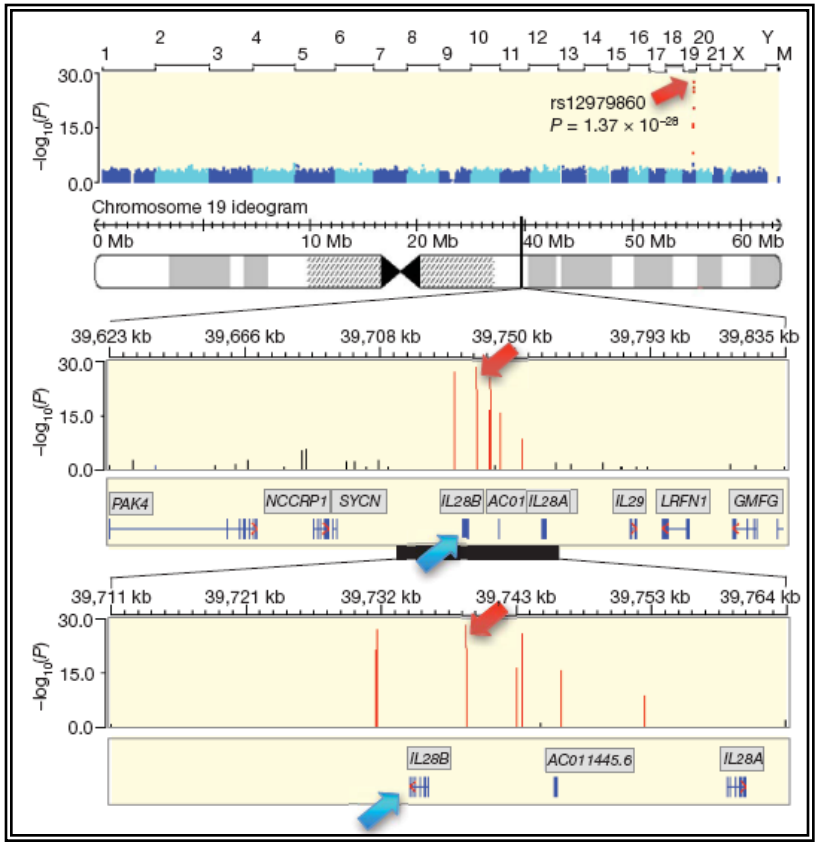
HCV-1 patients with LVL and RVR to PegIFN/RBV Obviates a Protease Inhibitor

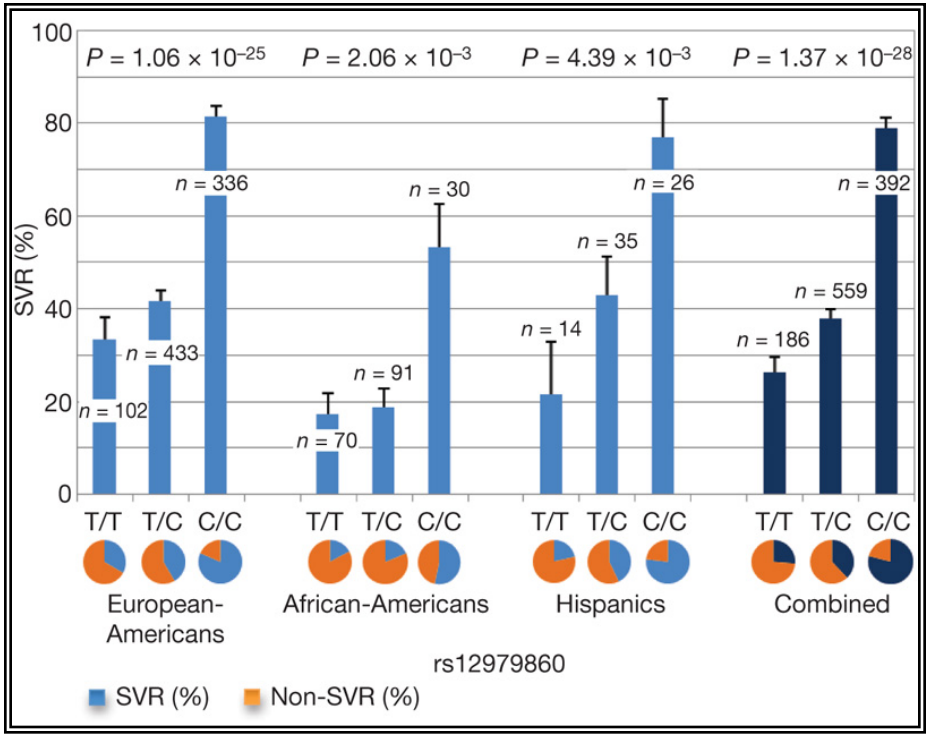
Pearlman **BL, et al. Hepatology. 2013.**

How to identity HCV-1 patients who will respond to 24 weeks of PegIFN/ RBV before starting treatment?

IL-28B SNPs & SVR in HCV-1 to SOC

- Genome-wide association study more than 1,600 patients in IDEAL study
- IL-28B (IFN-λ-3) genetic polymorphisms: chromosome 19, rs12979860





Strong linkage disequilibrium between the two most used IL28B gene SNPs

IL28B SNP	rs12979860	rs8099917
Alternative name	**Duke SNP**	**Triple “9” SNP**
Favorable genotype	CC	TT
Unfavorable genotype	Non-CC	Non-TT

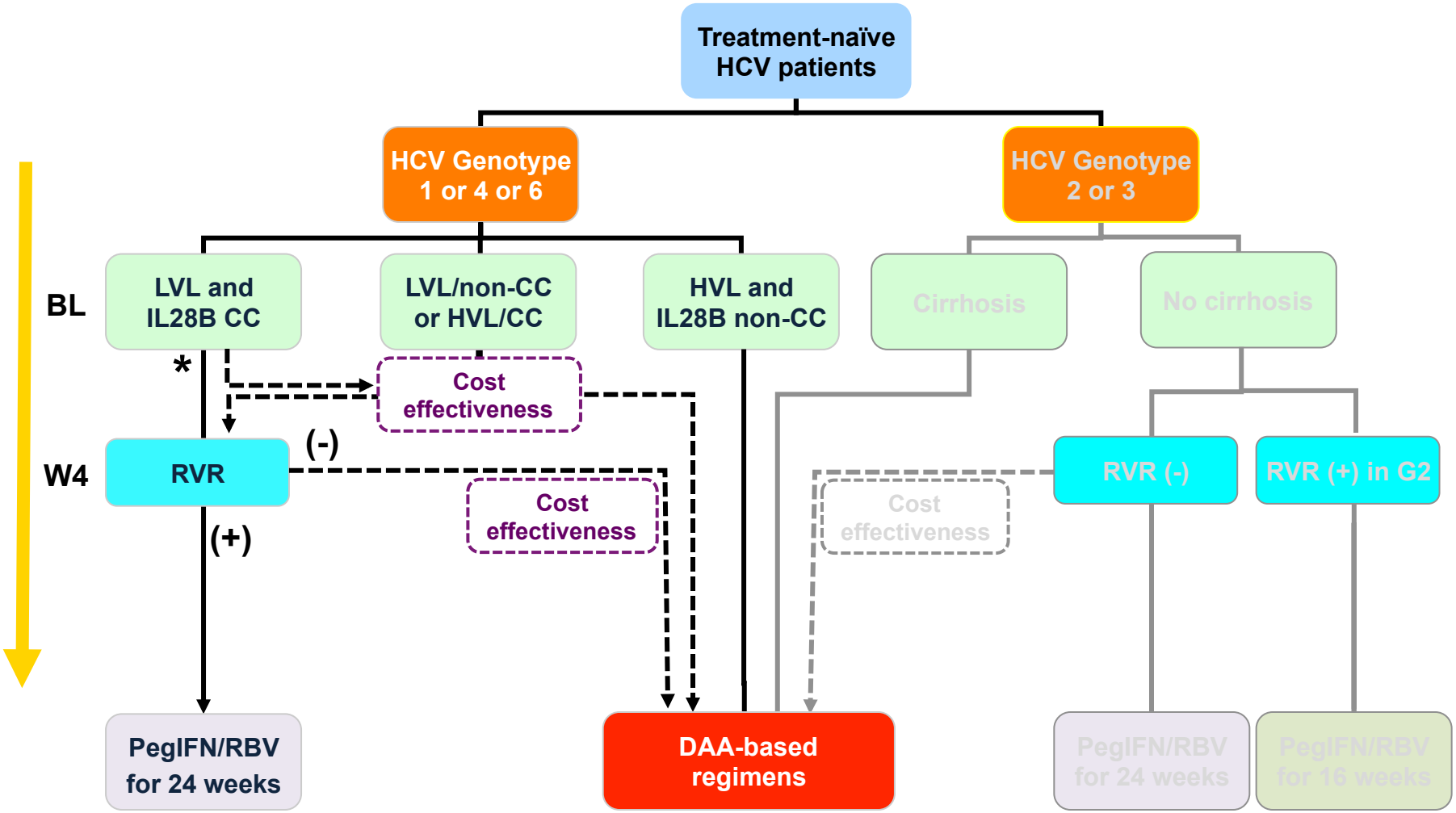
Identify HCV-1 super-responders before starting the antiviral therapy

Variables	SVR	Non-SVR	P value	SEN	SPE	PPV	NPV	ACC
Baseline factor	n (%)	n (%)		%	%	%	%	%
	n =131	n =95						
Positive predictor								
LVL	81 (62)	26 (27)	<.001	62	73	76	58	66
TT	121 (92)	66 (70)	<.001	92	31	65	74	66
LVL+TT	73 (56)	18 (19)	<.001	56	81	**80**	57	66
Negative predictor								
HVL	50 (38)	69 (73)	<.001	62	73	76	58	66
GT/GG	10 (8)	29 (31)	<.001	92	31	65	74	66
HVL+GT/GG	2 (2)	21 (22)	<.001	99	22	64	**91**	66

- IL28B rs8099917 genotype combined with baseline VL helps identify HCV-1 patients who will not benefit from a shorter 24w regimen before starting therapy.

Huang CF, et al., Yu ML. J Hepatol, 2012, 56: 34-40.

HCV Practice Recommendation for IFN-eligible naïve patients in Asia-Pacific countries with DAA available



Dot lines indicated options of choice, based on cost-effectiveness of available DAA regimens

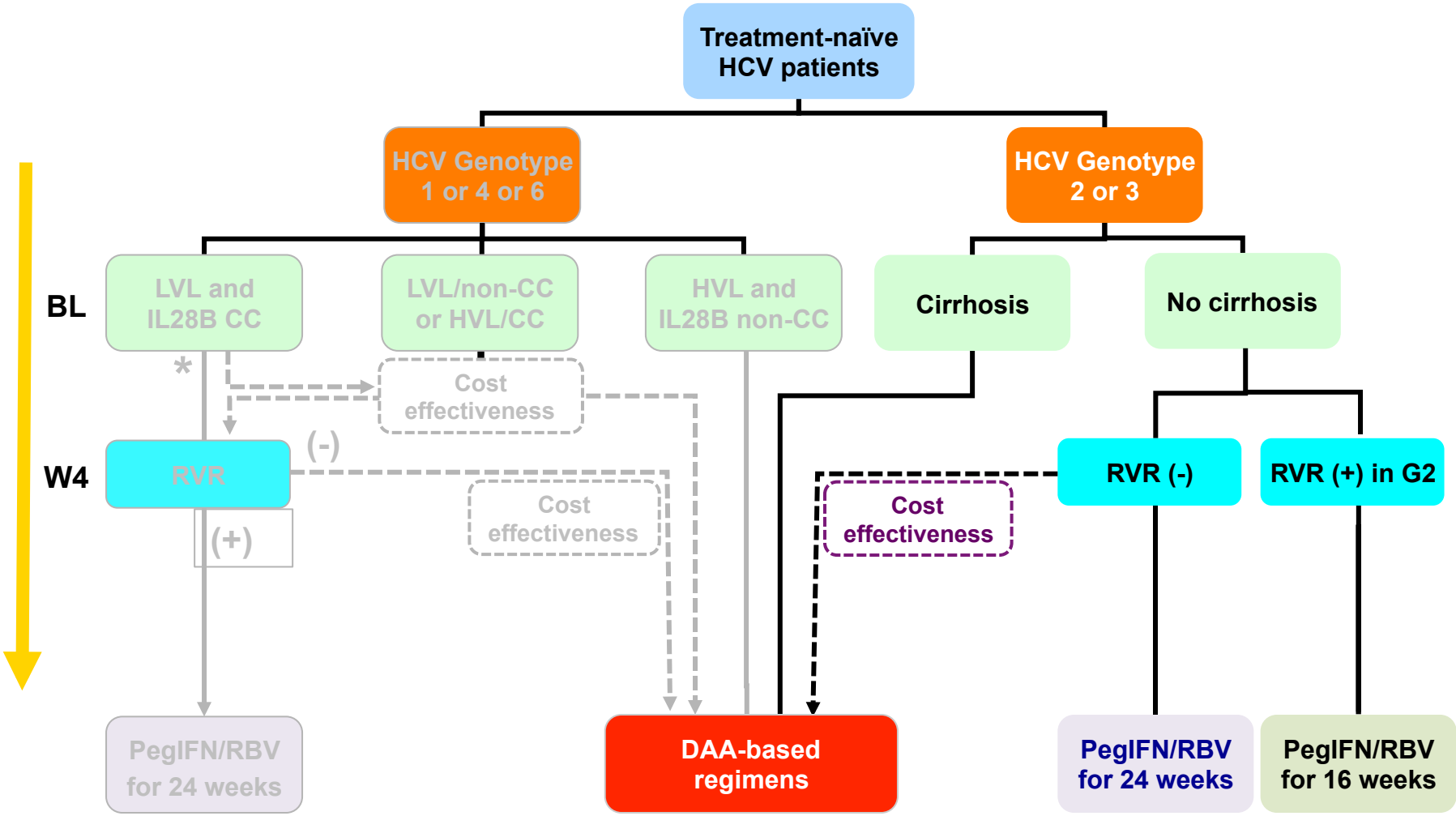
* **For areas with only boceprevir/PR, telaprevir/PR, simeprevir/PR, daclatasvir/PR available**

Yu ML, Chuang WL. Clinical Liver Disease, 2014 in press

Emerging IFN-free DAA regimens for HCV

NS3/4 PI	NS5A RCI	NS5B NNI	NS5B NI	RBV	wk	HCV	SVR
Asunaprevir	Daclatasvir				24	G1b TN G1b TE	90% 82%
Asunaprevir	Daclatasvir	BMS791325			12	G1a	92%
ABT-450/r	Ombitasvir	Dasabuvir		RBV	12 24	G1 TN/E 1a/LC/NR	96% 93%
MK-5172	MK-8742			RBV	12	G1	90-98%
			Sofosbuvir	RBV	12 24	G2 G1/3	93% 68/92%
Simeprevir			Sofosbuvir	RBV	12	G1	> 93%
	Daclatasvir		Sofosbuvir	RBV	24	G1 G2/3	100% 93%
	Ledipasvir		Sofosbuvir	RBV	8	Non-LC, G1 TN	94%
	Ledipasvir		Sofosbuvir	RBV	12	G1	> 94%

HCV Practice Recommendation for IFN-eligible naïve patients in Asia-Pacific countries with DAA available



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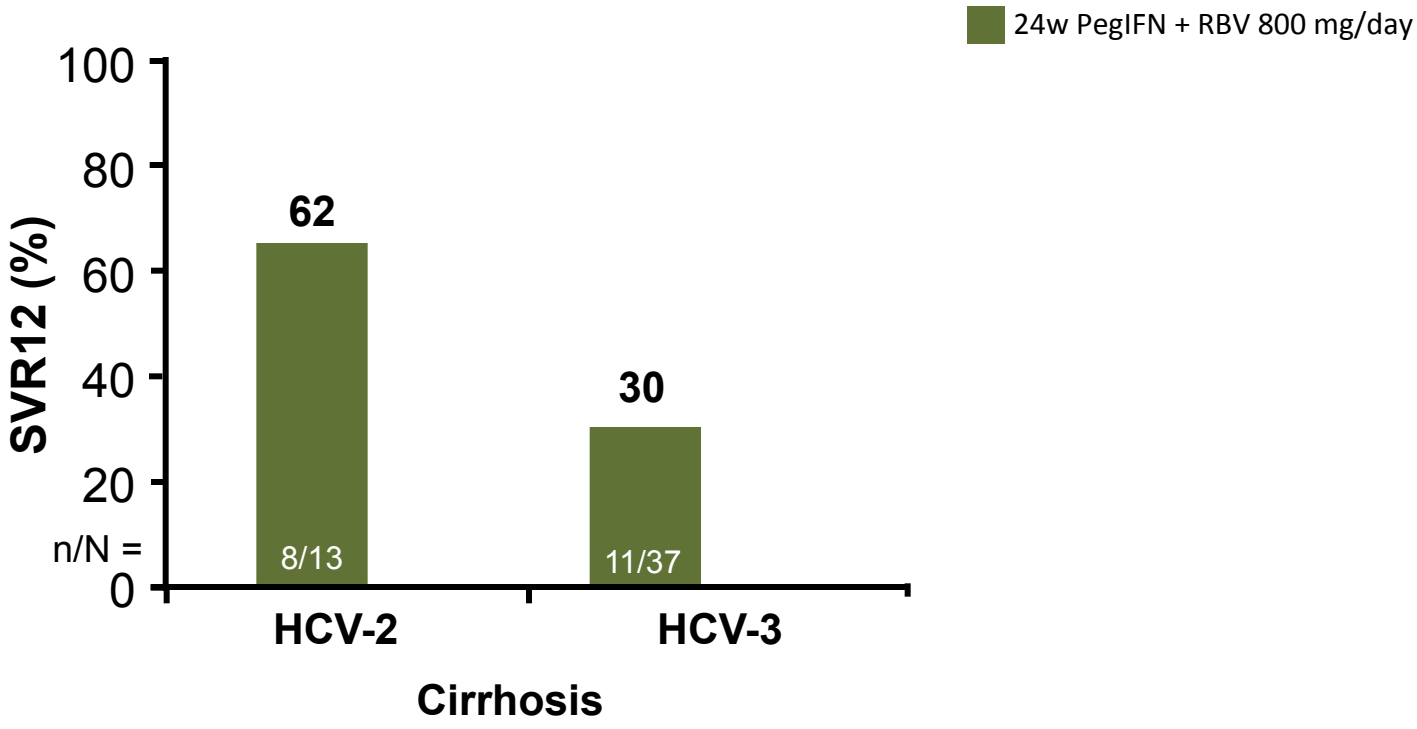
Yu ML, Chuang WL. Clinical Liver Disease, 2014 in press

SVR12 Naïve G2/3 cirrhotic patients

- **2 Randomized, open-label phase III trial**
  - **Fission, Valence**



Lawitz E, et al. N Engl J Med. 2013;368:1878-1887.
Zeuzem S, et al. AASLD 2013. Abstract 1085.

SVR12 Naïve G2/3 cirrhotic patients

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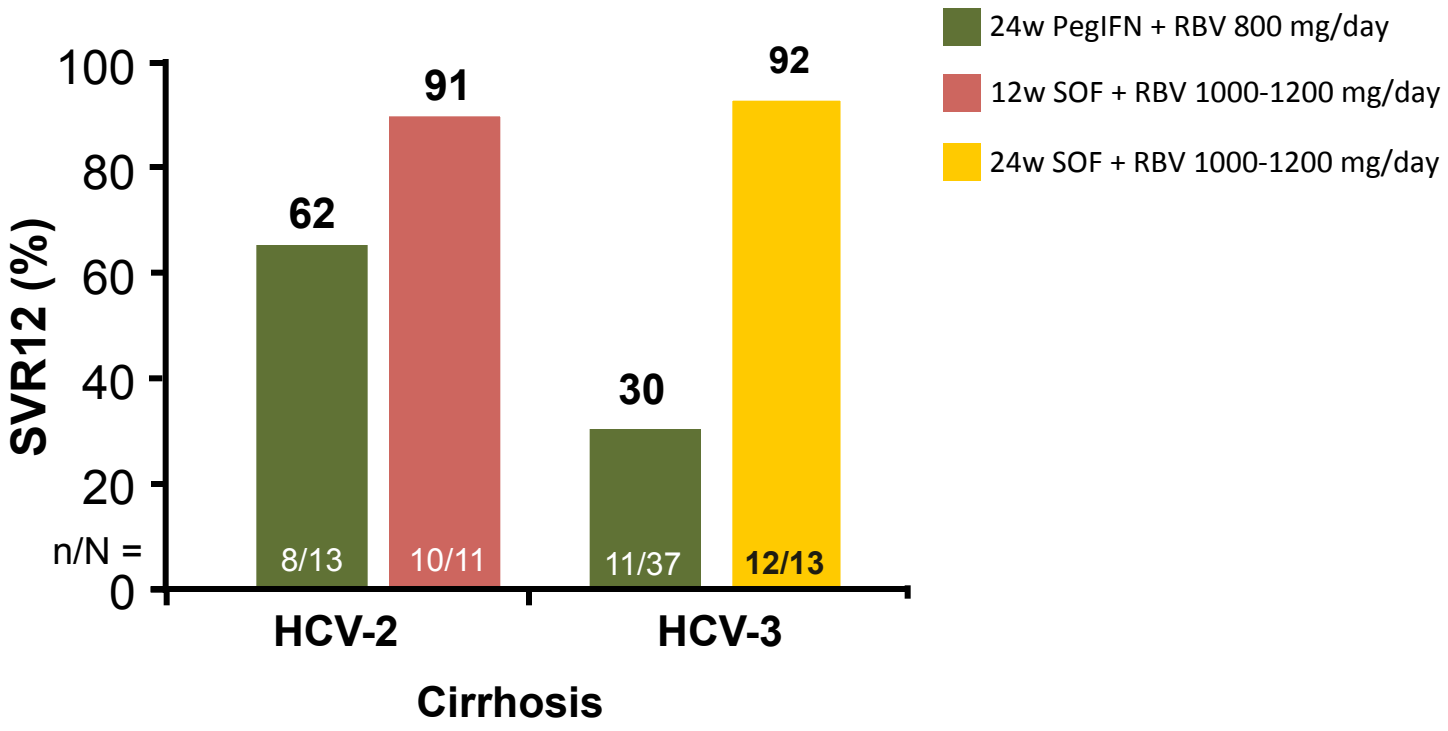
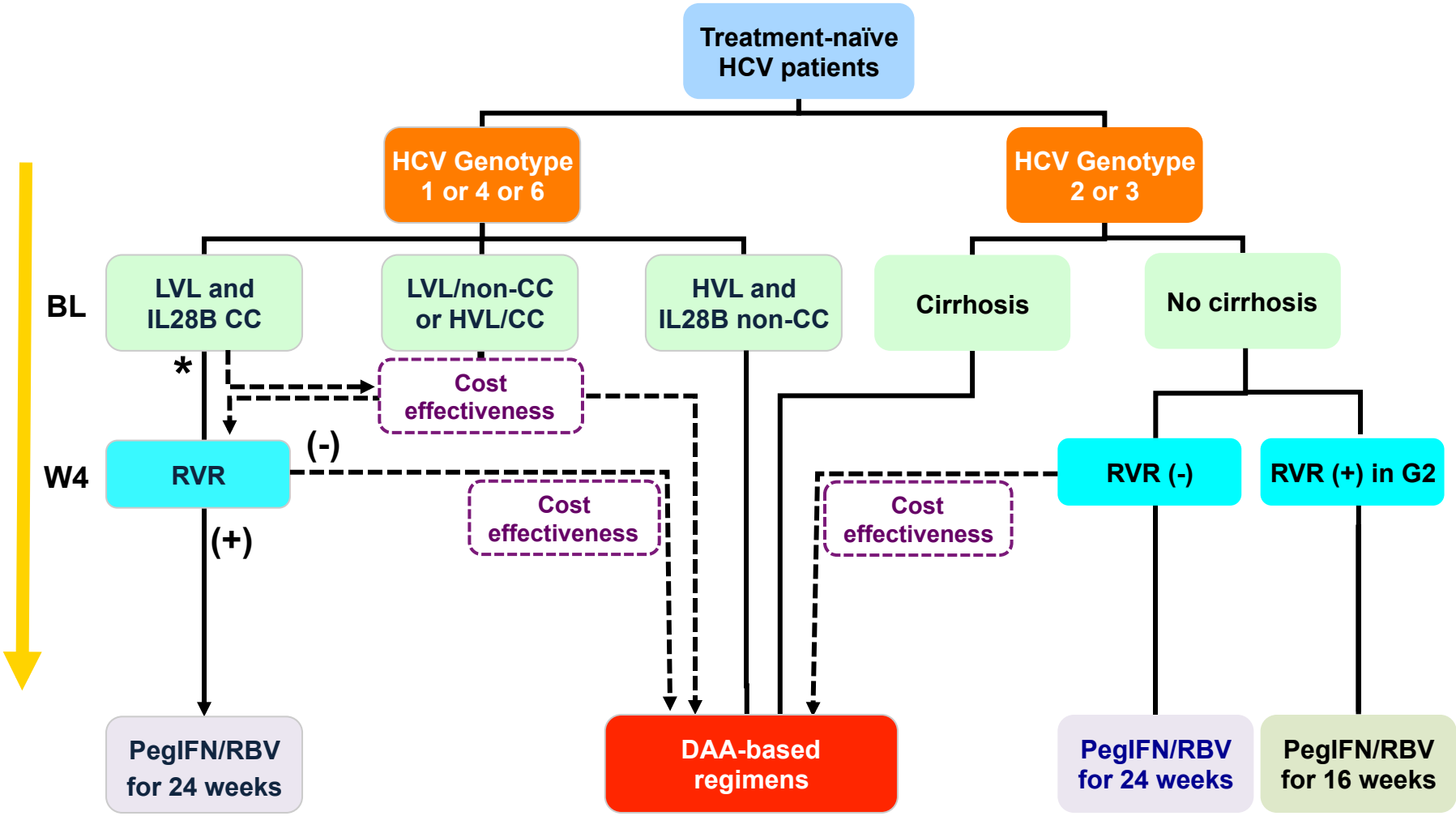


Lawitz E, et al. N Engl J Med. 2013;368:1878-1887.

Zeuzem S, et al. AASLD 2013. Abstract 1085.

HCV Practice Recommendation for IFN-eligible naïve patients in Asia-Pacific countries with DAA available



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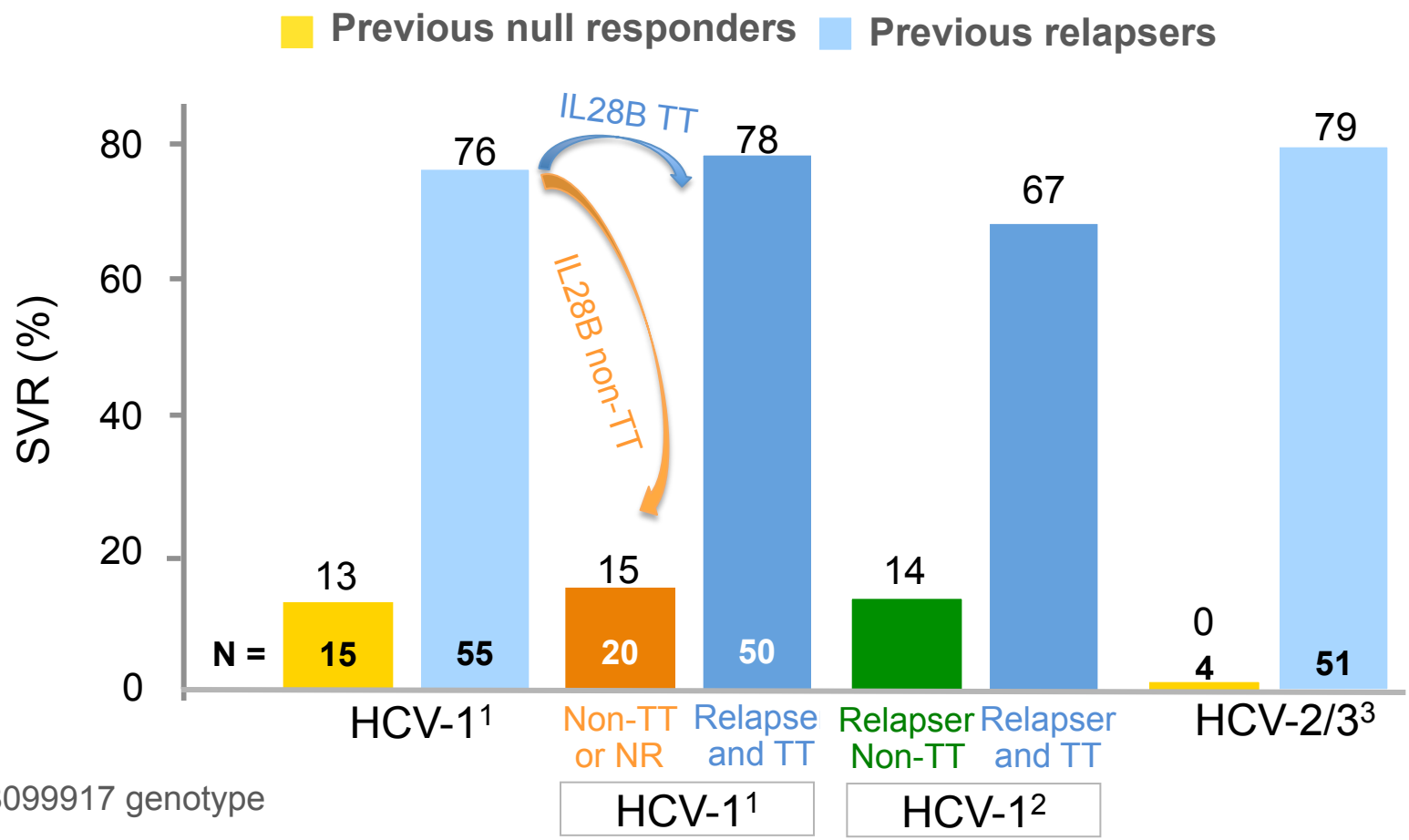
Yu ML, Chuang WL. Clinical Liver Disease, 2014 in press

HCV Practice Recommendation for IFN-experienced patients in Asia-Pacific countries with DAA available

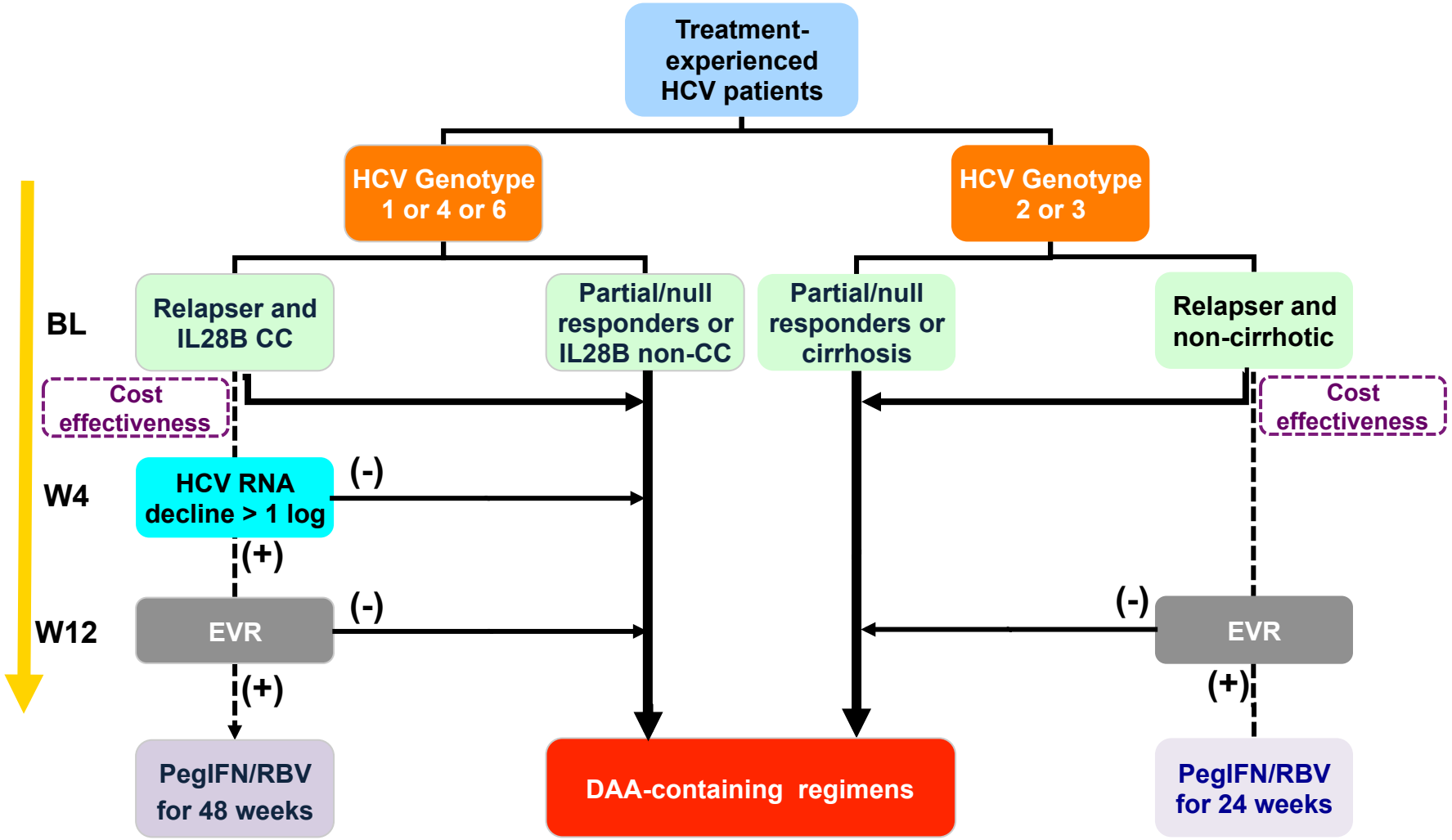
Treatment-experienced HCV patients Retreatment with PegIFN/RBV in Taiwan

48w PegIFN/RBV for HCV-1; 24w PegIFN/RBV for HCV-2/3



1. Huang CF, et al., Yu ML. J Gastroenterol Hepatol, 2013 ;28(9):1515-20.
2. Chen MY, et al. J Gastroenterol Hepatol 2014;29:102-9
3. Huang CF, et al., Yu ML, PLoS ONE, 2013;8(3):e58882.

HCV Practice Recommendation for IFN-experienced patients in Asia-Pacific countries with DAA available



Dot lines indicated options of choice, based on cost-effectiveness of available DAA regimens

Yu ML, Chuang WL. Clinical Liver Disease, 2014 in press

Options for treating decompensated HCV patients

DAA Regimen	Treatment duration	HCV Genotype	Decompensated Liver diseases
Interferon-containing regimens			
*BOC + PR, RGT (BOC 800 mg q8hr, 24-44w)	28-48 weeks	G1	No
*TVR + PR, RGT (TVR 1125 mg q12hr, 12w)	24-48 weeks	G1/2	No
*SMV + PR (SMV 150 mg qd, 12w)	24-48 weeks	G1/4	No
*SOF + PR (SOF 400 mg qd, 12w)	12 weeks	G1/3-6	No
*DCV + PR, RGT (DCV 60 mg qd, 24w)	24-48 weeks	G4	No
Interferon-free regimens			
*SOF + RBV	12-24 weeks	G1-6	**Yes**
**SOF + SMV ± RBV	12 weeks	G1	No
*DCV + ASV	24 weeks	G1b	No
*DCV + SOF ± RBV	12-24 weeks	G1–4	**Yes**
*SOF + LDV ± RBV	8-24 weeks	G1/3/4	**Yes**
#ABT-450/r + Ombitasvir + Dasabuvir ± RBV	12-24 weeks	G1	**Yes**
##DCV + ASV + BMS-791325	12 weeks	G1	No
##MK-5172 + MK-8742 ± RBV	12 weeks	G1–6	No

DAA, directly-acting antiviral agents; RGT, response-guided therapy; BOC, boceprevir; P, peginterferon; R or RBV, ribavirin, TVR, telaprevir; SMV, simeprevir; SOF, sofosbuvir; DCV, daclatasvir; ASV, asunaprevir; LDV, ledipasvir *Approved regimens in US, EU or Japan; **off-label regimen; #regimen awaiting approval; ##regimens of ongoing phase 3 trials. Underline indicated fixed-dose combination

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Future anti-HCV regimens

5S

- Super: potent, pan-genotypic
- Safer: well tolerated, no DDI
- Simpler: once daily, no RGT
- Shorter: duration (8-12w)
- Surprise: in price!

One size/tablet fit all!

Thank You for Your Attention !