Nouveaux traitements du VHC en néphrologie

JNI, symposium MSD
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Liens d’intérêt

- Orateur : GSK, BMS, Boehringer Ingelheim, Janssen, Vertex, Novartis, Sanofi, Gilead, Roche, MSD, Abbvie

- Bourses: BMS, Gilead, Roche, MSD

- Membre de board : BMS, Boehringer Ingelheim, Janssen, Gilead, Roche, MSD, Abbvie

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- Pourquoi guérir le VHC en général?

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- Comment traiter?

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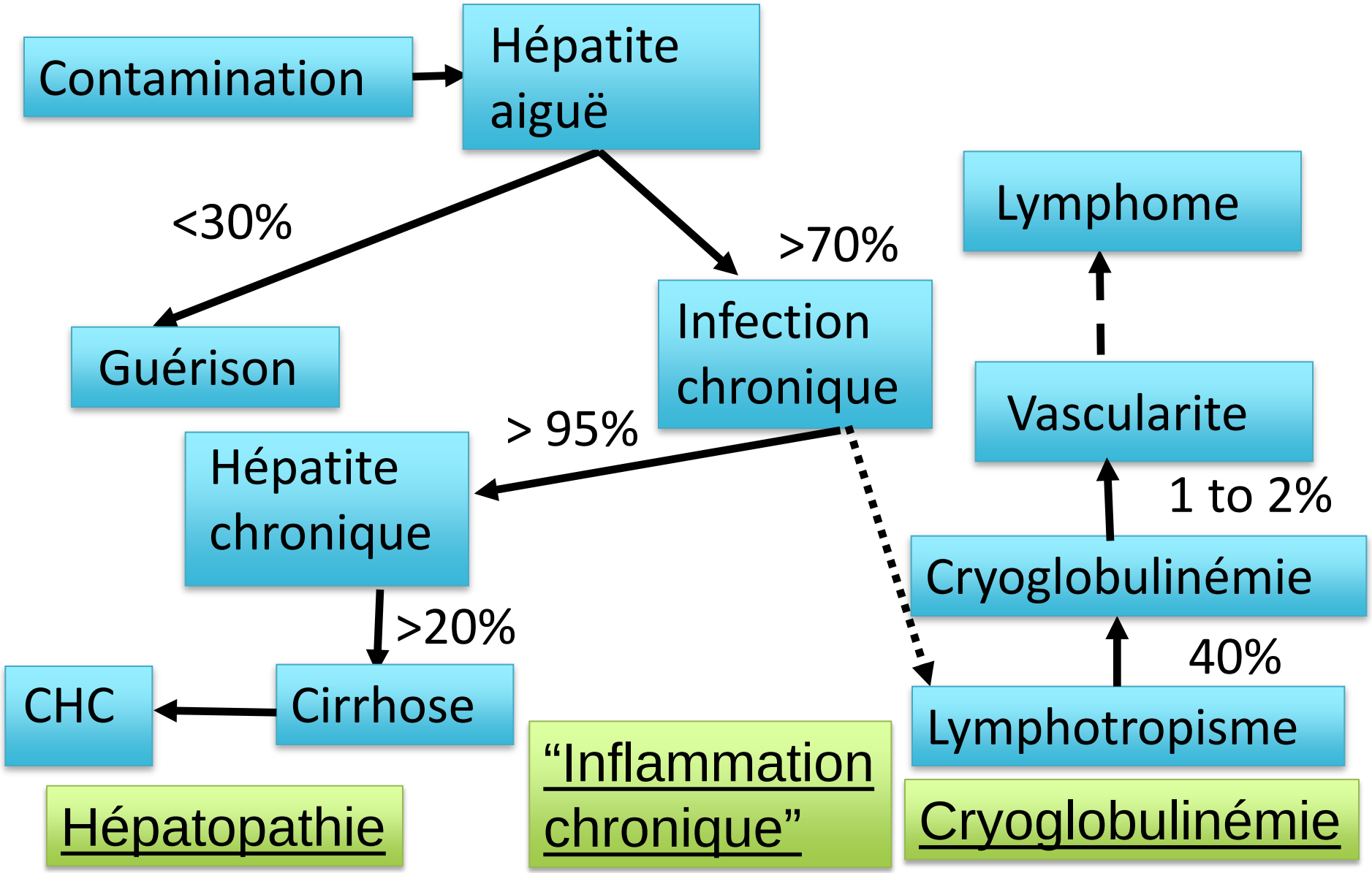
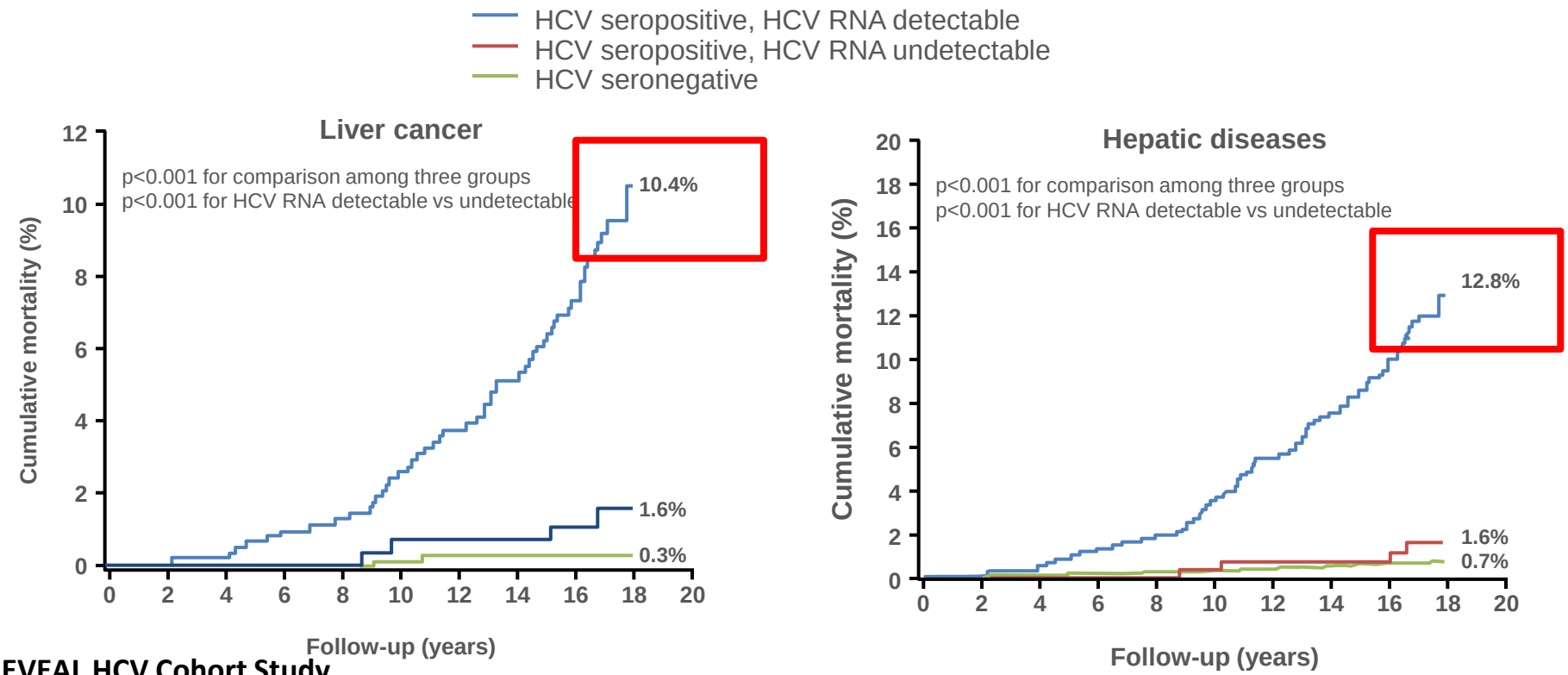
L'hépatite C est une maladie systémique



Une virémie C persistante est associée à une sur-mortalité hépatique



The REVEAL HCV Cohort Study

23 820 adults, Taiwan

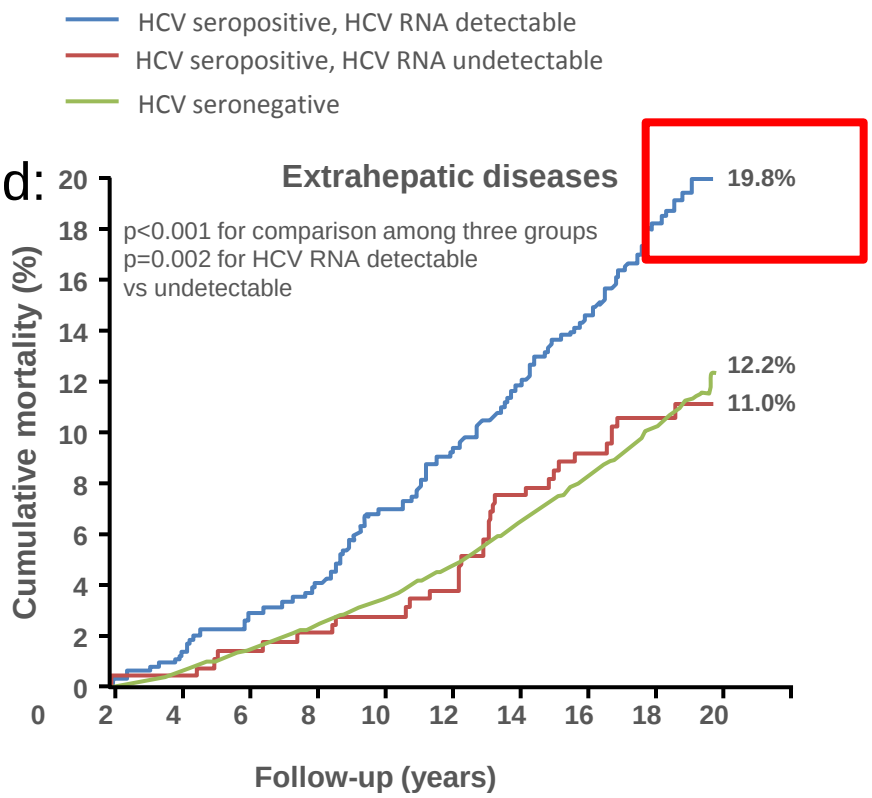
1095 anti-HCV positive; 69.4% with detectable HCV RNA

Lee M-H et al, J Infect Dis 2012;206:469–477

Une virémie C persistante est associée à une sur-mortalité extra-hépatique

Significant association between HCV and:

- **diabetes** (OR = 1.8)
- **cardio-vascular mortality** (OR=2.37)
- **cerebro-vascular mortality** (OR= 2.7)
- **renal disease** (HR for ESRD < 59 y= 7.8 vs. 3.2)
- **extra-hepatic** (breast: OR=2) **cancers**



White D et al. J Hepatol 2008;49:831–844

Kakinami L et al. Int J Clin Pract 2013;67:6–13

Lee M-H et al. Stroke 2010;41:2894–2900

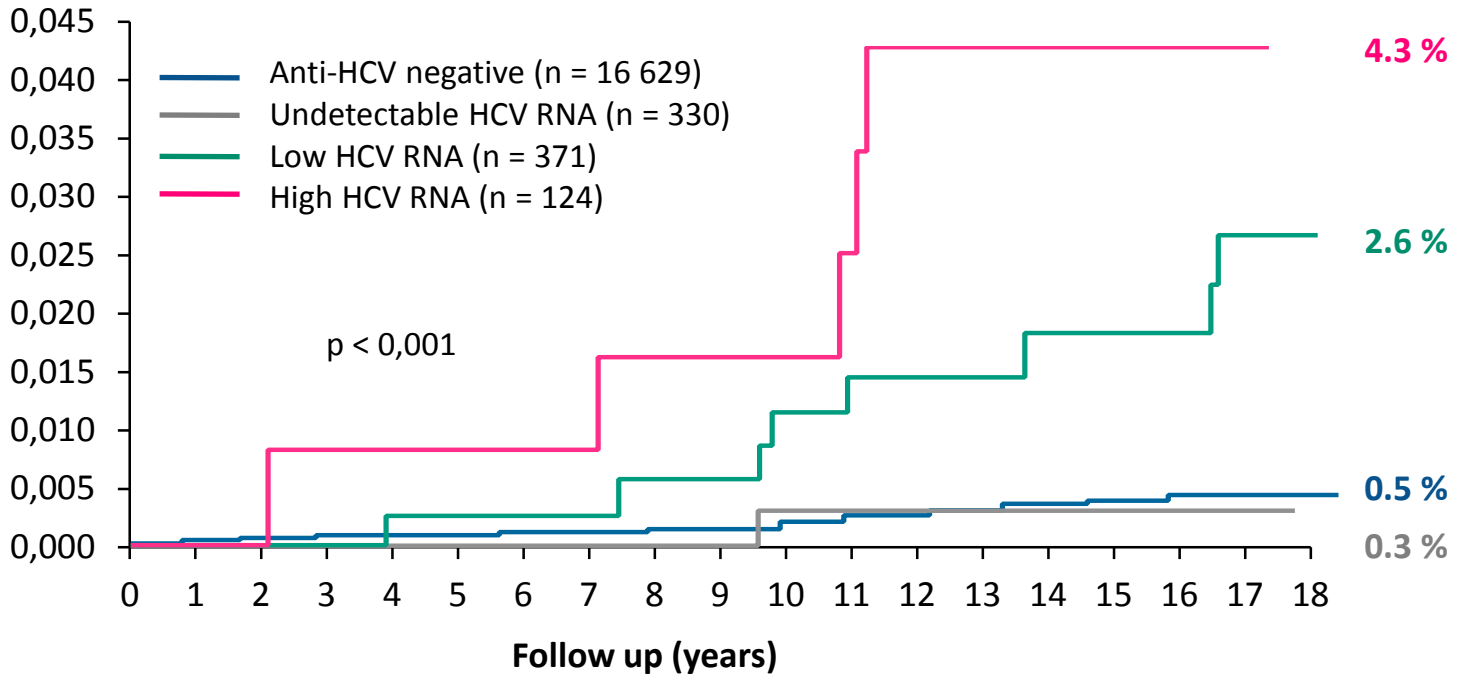
Su F-H et al. Am J Kidney Dis 2012;60:553−560

Su F-H et al. BMC Cancer 2011;11:495

Lee M-H et al, J Infect Dis 2012;206:469–477

L'hépatite C est une maladie systémique

Cumulative risk of death related to renal disease according to HCV status



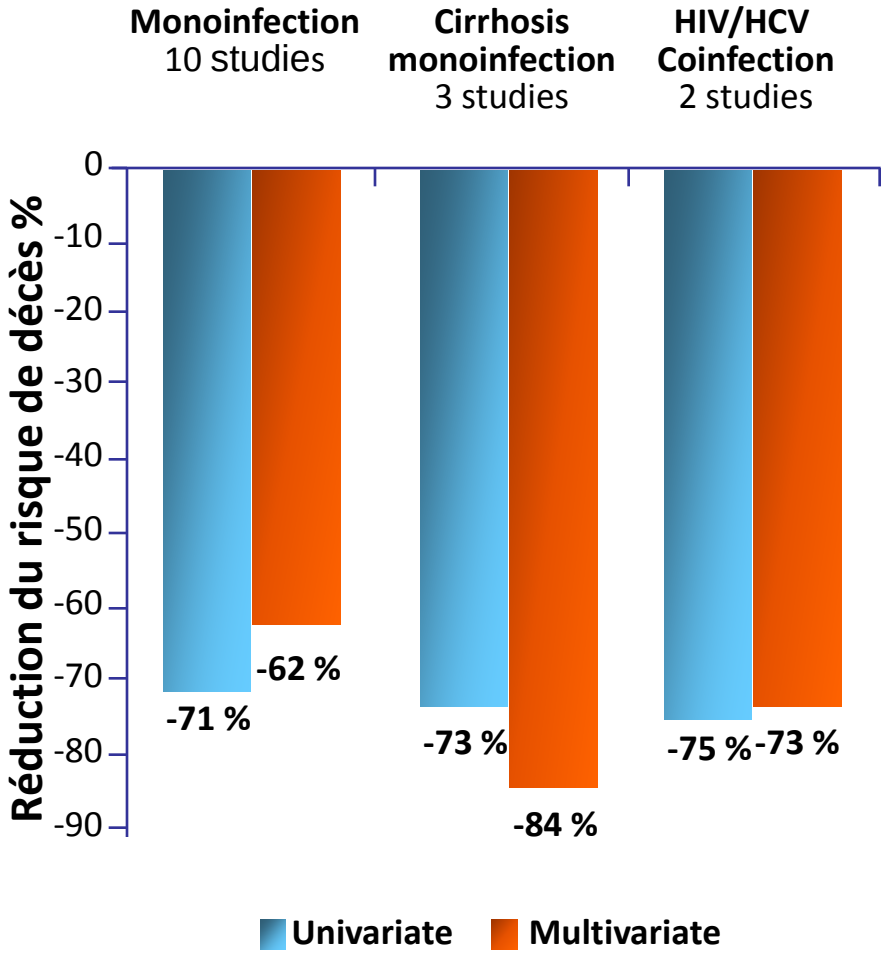
Reveal HCV Longitudinal taïwanese study in 23 785 patients

➜ **HCV infection is associated with an increased risk of renal disease, ESRD and renal-related mortality**

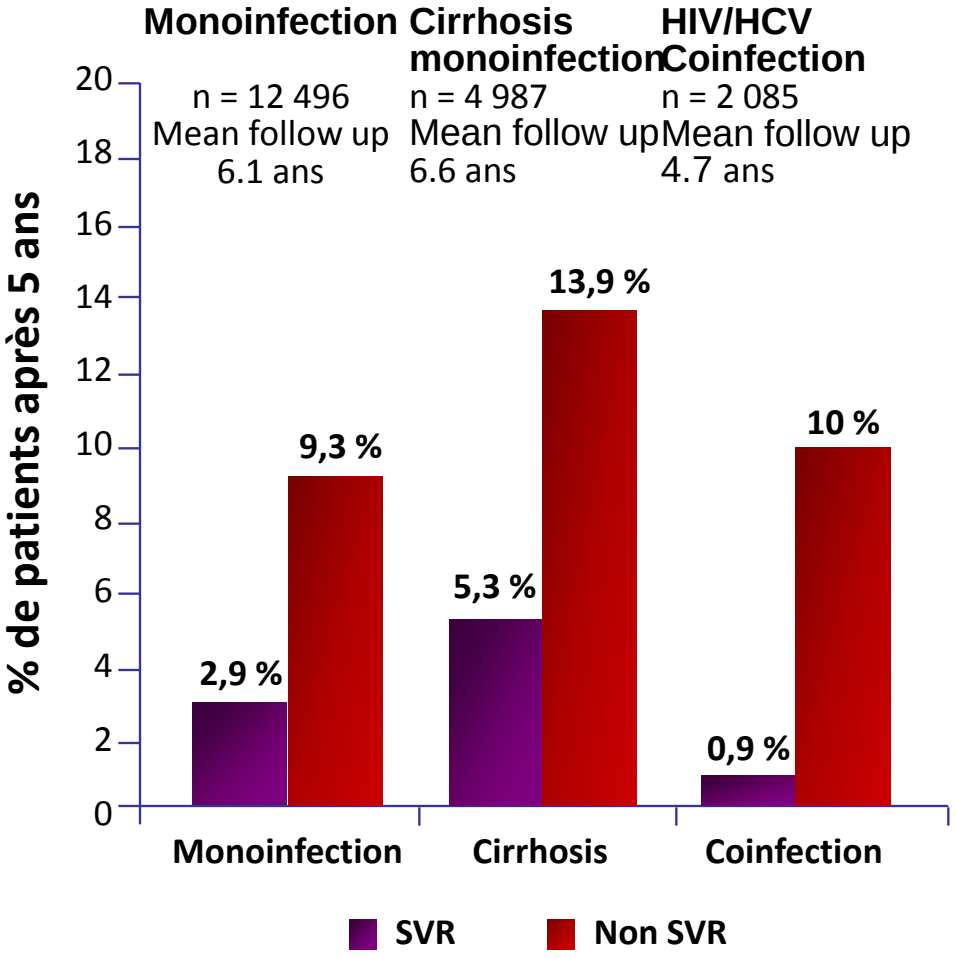
Lai TS et al., AASLD 2014 abstr. 172

L'infection active par le VHC est un facteur de mortalité hépatique et extra-hépatique

Mortalité globale et RVS



Rique de cancer à 5 ans



Hill AM et al. AASLD 2014, Abs. 44

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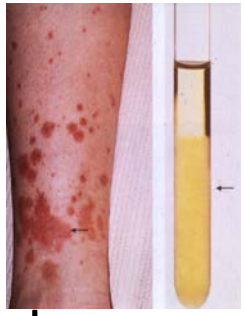
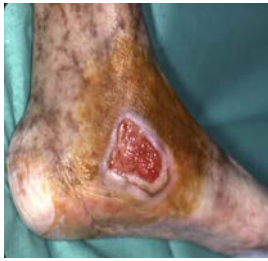
Impact négatif du VHC en néphrologie



- Fréquence plus élevée de l'infection VHC chez les IR que dans la population générale

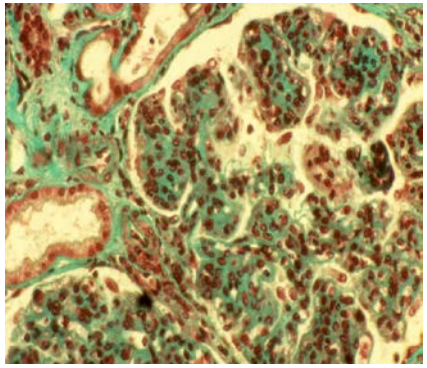
- Vascularite cryoglobulinémique (GNMP) et insuffisance rénale



- Morbidité (DNID, maladies vasculaires) et mortalité supérieures des dialysés VHC+ vs. VHC-

- Morbidité (GNMP de novo, néphropathie du rejet) et mortalité supérieures des transplantés rénaux VHC+

- Traitements Interferon contre-indiqués chez les transplantés, mal tolérés chez les dialysés et Ribavirine de maniement difficile



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  Les possibilités thérapeutiques

Traitement de l'hépatite C

2011	2017	2020	> 2020	RVP (GT1)
Combinaison PEG-IFN – RBV				45%
DAAs				65-75%
Combinaisons DAAs (IP/I Pol/NS5A) RBV…			→ **Traitements sans IFN**	> 90%

- Inhibiteurs Cyclophylline
- Inhibiteurs d'entrée?
- Vaccinothérapie?
- Cytokines ? Autres immuno-modulateurs?

- Bi-
- Tri-
- Quadri-
- Penta-thérapie

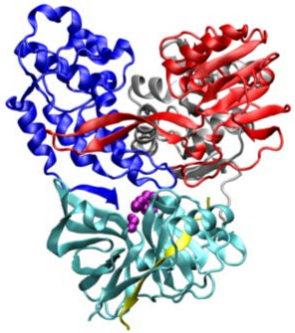
Gane E et al. Lancet 2010
Lok A et al. NEJM 2012

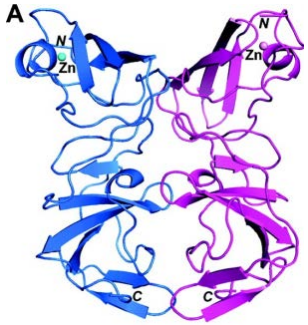
Clinical Practice Guidelines for the Diagnosis, Prevention and Management of Hepatitis C in CKD

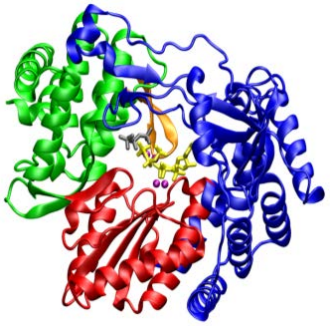
Obsolete: 2003!

Les Antiviraux Directs du VHC

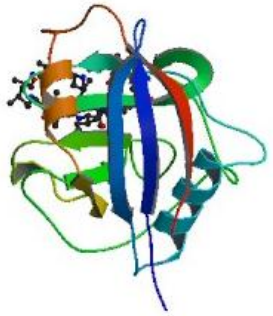
Cibles Virales





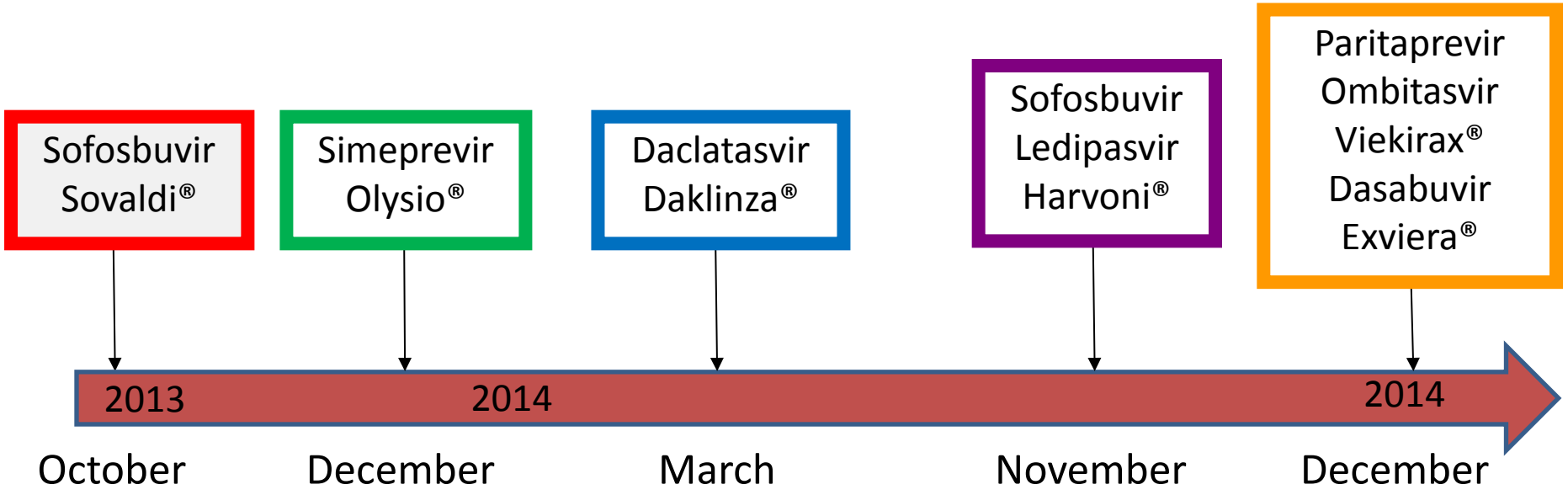


Cibles d'Hôte



NS3	NS5A	NS5B	Cyclophilin A
Protéase sérine NS3/4A essentielle au processing post-traductionnel de la polyprotéine du VHC	Phosphoprotéine multifunctionnelle essentielle au complexe de réplication de l'ARN VHC	ARN Polymérase ARN dépendante NS5B spécifique du VHC	Protéine de l'hôte impliquée dans la réplication du VHC via l'interaction avec la protéine NS5A et la polymérase
-PREVIR **Boceprevir** **Telaprevir** **ABT-450/r, ACH-1625** **Asunaprevir,** **Simeprevir, BI-201335** **MK-5172**	**-ASVIR** **-Daclatasvir** **Ledipasvir (GS-5885)** **GS-5816** **ABT-267 (Ombitasvir)** **PPI-668** **Elbasvir**	**-BUVIR** **-<u>Nucleos(t)ide analogue</u>** **Sofosbuvir,** **IDX-184*** **<u>Non-nucleoside analogue</u>** **ABT-333 (Dasabuvir)** **ABT-072, BMS-791325**	**Alisporivir** **SCY-635**

Flux des ATU/AMM en France



Restricted to
« priority » patients

- F3F4
- Symptomatic cryoglobulinemic vasculitis
- Waiting for liver or renal transplantation
- After liver transplantation

Nouveaux traitements du VHC en néphrologie

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  Les adaptations pharmacocinétiques

Pharmacocinétique du sofosbuvir et insuffisance rénale

	Normal Renal Function eGFR > 80 mL/ min/ 1.73 m²	Mild Renal Impairment eGFR ≥ 50 and ≤ 80 mL/min/1.73 m²		Moderate Renal Impairment eGFR ≥ 30 and < 50 mL/min/1.73 m²	
PK Parameter	**Mean (%CV) (n=6)**	**Mean (%CV) (n=6)**	**%GMR (90% CI) (n=6)**	**Mean (%CV) (n=6)**	**%GMR (90% CI) (n=6)**
GS-331007 AUC_{inf}, ng•h/mL	12,700 (19.1)	19,600 (14.3)	155 (88.3, 273)	24,100 (23.3)	188 (107, 331)
GS-331007 C_{max}, ng/mL	1360 (42.3)	1640 (16.3)	128 (94.3, 175)	1460 (33.2)	110 (80.8, 150)
SOF AUC_{inf}, ng•h/mL	590 (29.9)	964 (36.6)	161 (109, 239)	1310 (50.4)	207 (139, 307)

AUC_{inf}=area under the curve; CI=confidence interval; C_{max}=maximum observed plasma concentration of drug; CV=coefficient of variation, GMR=geometric mean ratio, PK=pharmacokinetic.

Cornpropst M, et al. EASL 2012. Barcelona, Spain. #1101

Pharmacocinétique du sofosbuvir et insuffisance rénale

	Normal Renal Function eGFR >80 mL/min /1.73 m^2	ESRD: Period 1 (Dose Pre-Dialysis)		ESRD: Period 2 (Dose Post-Dialysis)	
PK Parameter	**Mean (%CV) (n=6)**	**Mean (%CV) (n=3 to 5)**	**%GMR (90% CI)**	**Mean (%CV) (n=3 to 5)**	**%GMR (90% CI)**
GS-331007 $AUC_{inf,}$ ng•h/mL	12,700 (19.1)	226,000 (78.6)	1380 (693, 2760)	358,000 (70.7)	2170 (1090, 4330)
GS-331007 $C_{max,}$ ng/mL	1360 (42.3)	1470 (39.5)	110 (81.0, 150)	2420 (35.0)	180 (132, 246)
SOF $AUC_{inf,}$ ng•h/mL	590 (29.9)	785 (42.7)	128 (84.5, 193)	948 (32.9)	160 (106, 242)

AUCinf=area under the curve; CI=confidence interval; Cmax=maximum observed plasma concentration of drug; CV=coefficient of variation, GMR=geometric mean ratio, PK=pharmacokinetic.

Cornpropst M, et al. EASL 2012. Barcelona, Spain. #1101

Pharmacocinétique du sofosbuvir et insuffisance rénale en pratique

- No dosing adjustement of sofosbuvir for eGFR > 30 mL/mn

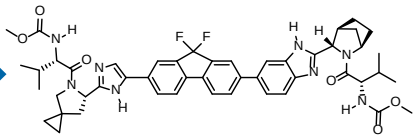
- for eGFR < 30 mL/mn, no clear data:

Contra-indicated or ½ pill (200 mg)/d or 400 mg/2d or 400 mg after each dialysis?

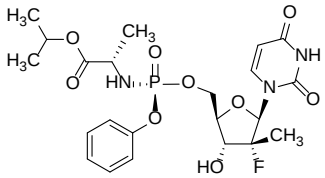
Ledipasvir / Sofosbuvir: coformulation en STR

- **Ledipasvir**
  - Picomolar potency against HCV GT 1a and 1b[1]
  - Effective against NS5B RAV S282T[2]
  - Once-daily, oral, 90 mg

LDV NS5A inhibitor



- **Sofosbuvir**
  - Potent antiviral activity against HCV GT 1–6
  - High barrier to resistance
  - Once-daily, oral, 400-mg tablet



SOF - NS5B nucleotide polymerase inhibitor

- **Ledipasvir/Sofosbuvir STR**
  - Once-daily, oral fixed-dose (90/400 mg) combination tablet
  - No food effect
  - >2000 patients treated

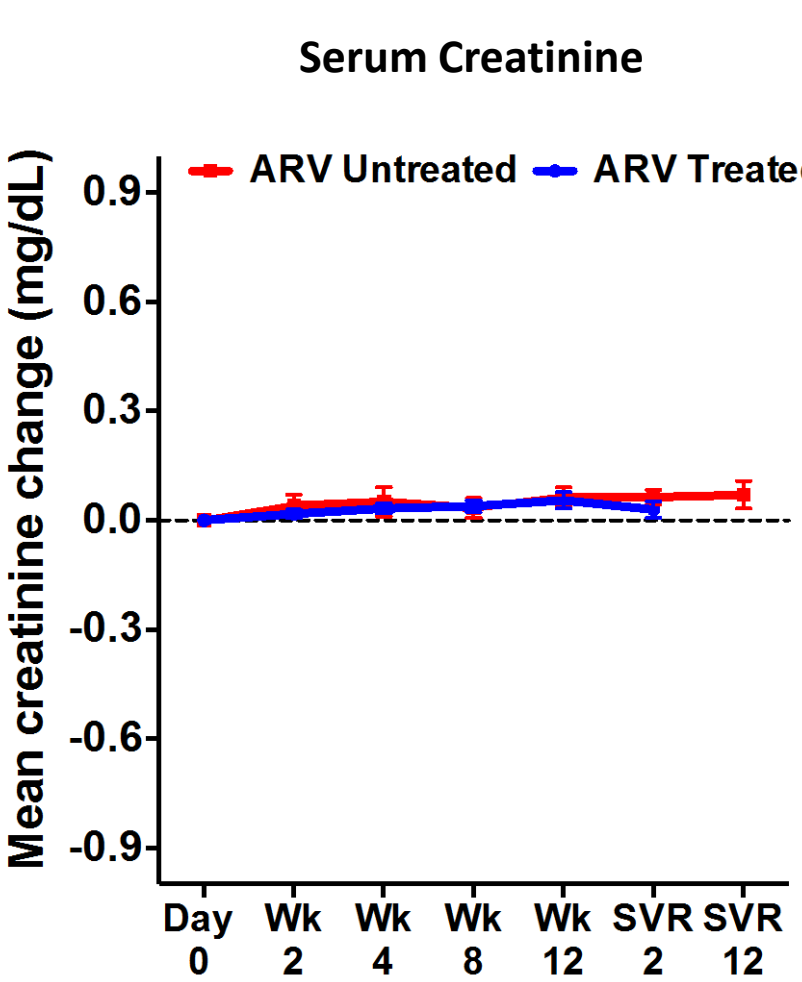
LDV NS5A inhibitor

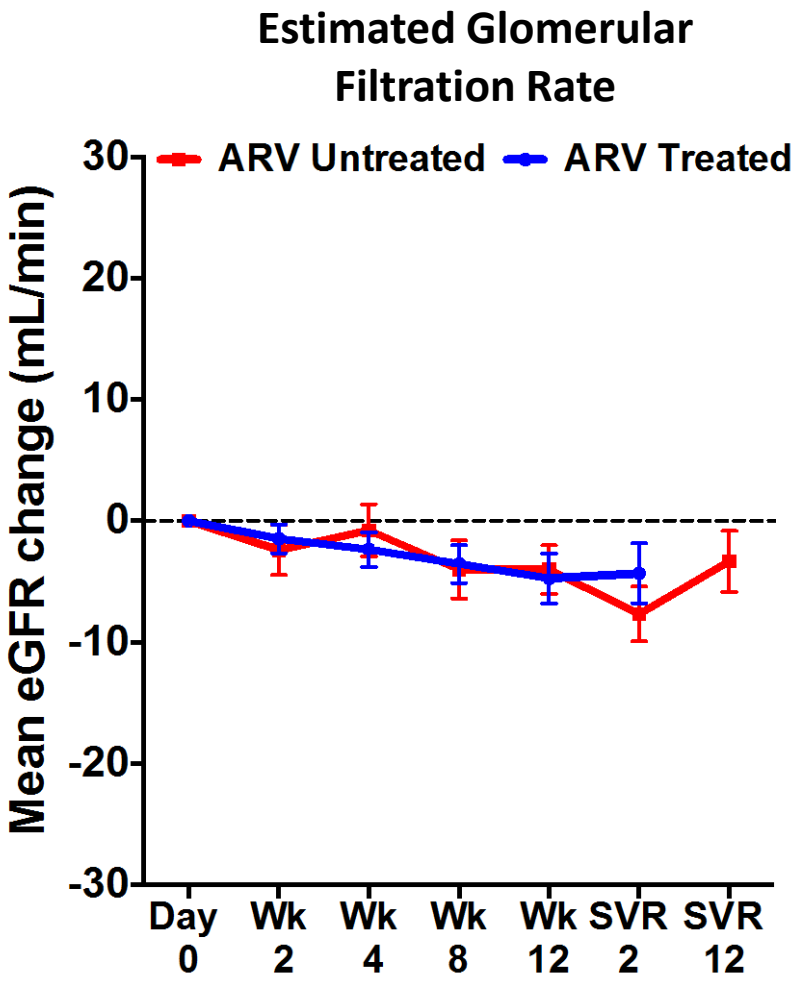
SOF - NS5B nucleotide polymerase inhibitor

EMA Granted LDV/SOF Accelerated Assessment (27 March, 2014)
FDA Granted Priority Review and Breakthrough Status (PDUFA: 10 Oct, 2014)

1. Lawitz E, et al. EASL 2011, poster 1219; 2. Cheng G, et al. EASL 2012, poster 1172

Pas de variations des paramètres rénaux sous SOF/LDV





- There was no change in serum creatinine or estimated GFR over time within groups (*P*>0.05) : *mixed model analysis*

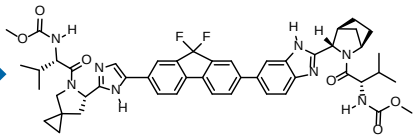
ERADICATE Study (NIAID, LDV/SOF)

Osinusi A, EASL, 2014, O14

Ledipasvir/Sofosbuvir: coformulation in STR

- **Ledipasvir**
  - Picomolar potency against HCV GT 1a and 1b[1]
  - Effective against NS5B RAV S282T[2]
  - Once-daily, oral, 90 mg

LDV NS5A inhibitor



- **Sofosbuvir**
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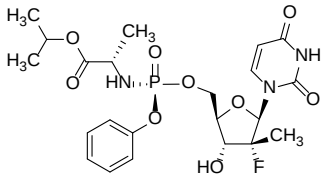

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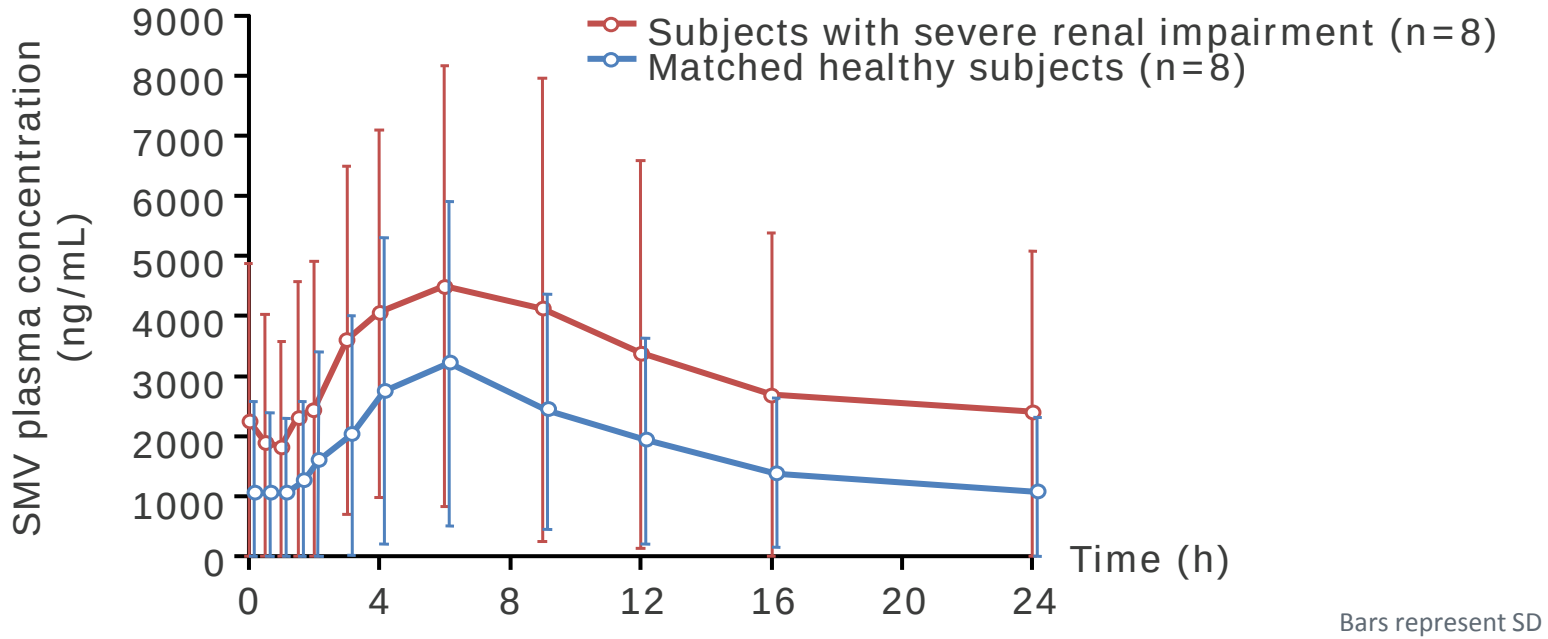
LDV NS5A inhibitor

SOF - NS5B nucleotide polymerase inhibitor

Trial begun in October 2014 in G1 or G4 kidney recipients with eGFR > 40 mL/mn

Pharmacocinétique du simeprevir et insuffisance rénale

Linear mean plasma concentration–time profiles of SMV comparing severely renal impaired and matched healthy subjects



- For subjects with severe renal impairment, SMV C_{min}, C_{max} and AUC_{24h} were about 71%, 34% and 62% higher, respectively, compared with matched healthy controls
  - For t_{max}, no relevant differences were observed between the groups

SMV, simeprevir

Simion et al. HCV Clin Pharm Workshop 2013

Pharmacocinétique du Simeprevir et insuffisance rénale en pratique

- No dosing adjustement of simeprevir (150 mg/d) and other protease inhibitors

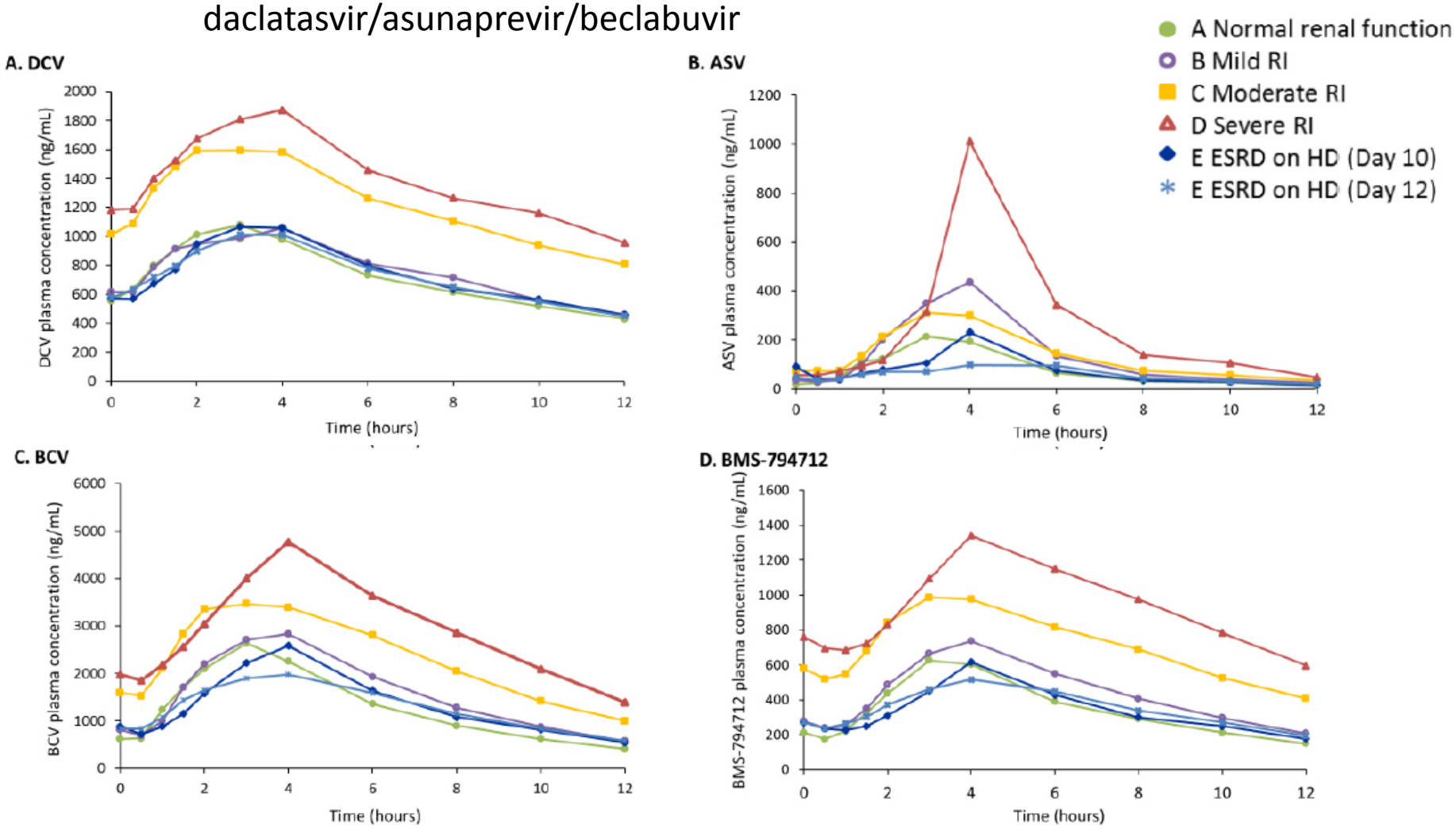
- But dosing adjustement of calcineurin inhibitor under simeprevir (1/4 to ½ dose and drug monitoring)

Pharmacocinétique du Daclatasvir et insuffisance rénale en pratique

- No dosing adjustement of daclatasvir (one pill of 60 mg/j) and other NS5A inhibitors of the replication complex
- No dosing adjustement of calcineurin inhibitor under NS5A inhibitors

Pharmacocinétique du Daclatasvir et combinaisons BMS

daclatasvir/asunaprevir/beclabuvir



Adapted from: Adamczyk R. ILC 2015, #PO790

Pharmacocinétique du Daclatasvir et combinaison Trio BMS et insuffisance rénale

- Safety
  - DCV-TRIO was generally well tolerated in subjects with normal renal function, and in subjects with variying degrees of RI.
- Conclusion
  - No dose adjustment is recommended for RI except for subjects with severe RI that are not on hemodialysis, where once-daily dosing of DCV-TRIO is recommended instead of BID dosing

Adapted from: Adamczyk R. ILC 2015, #PO790

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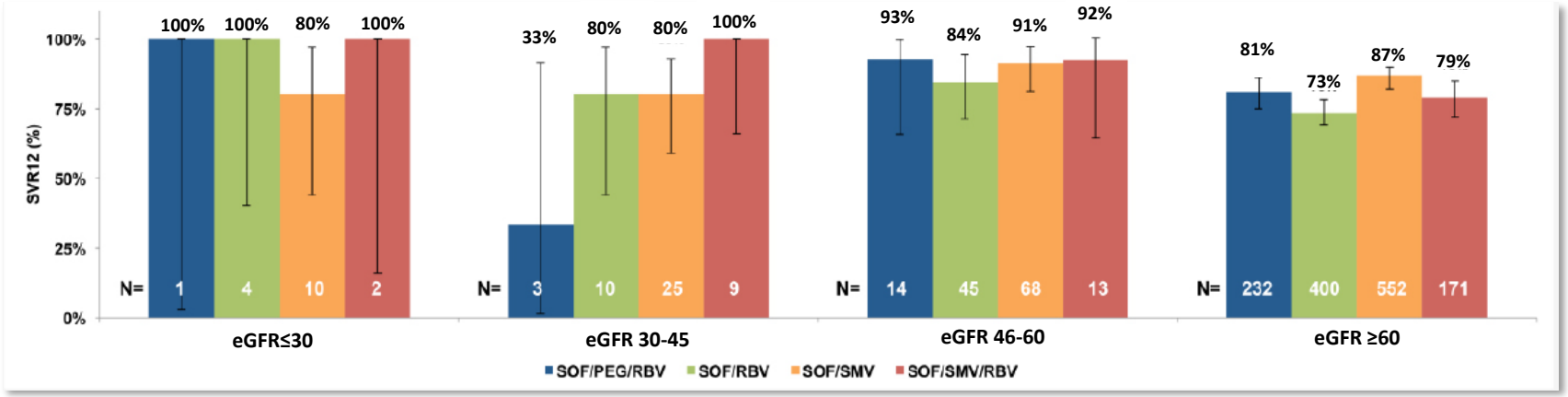
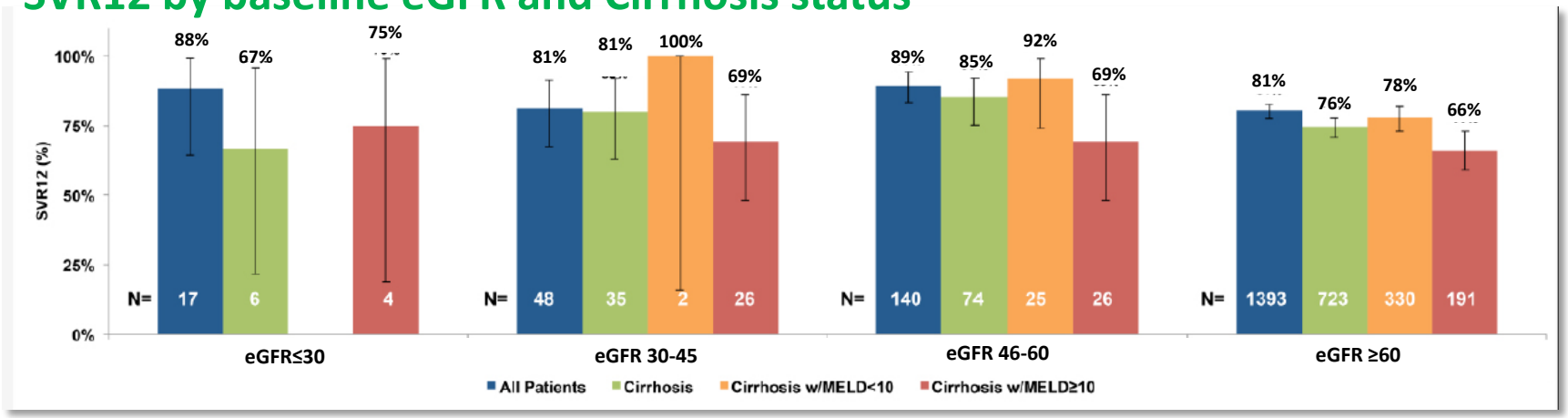
  Les résultats des nouvelles molécules

Données de la cohorte US Target des associations avec sofosbuvir et rein

SVR12 by baseline eGFR and by treatment regimen



SVR12 by baseline eGFR and Cirrhosis status



***Among patients with known outcomes**

Adapted from: Saxena V. ILC 2015, #LP08

Données de la cohorte US Target des associations avec sofosbuvir et rein

Table 2: Safety Outcomes by Baseline eGFR*

Dichotomous = no (%) Continuous = mean (range)	eGFR ≤ 30 (N=17)	eGFR 30-45 (N=56)	eGFR 46-60 (N=157)	eGFR>60 (N=1,559)
Common AEs				
Fatigue	3 (18)	19 (34)	56 (36)	543 (35)
Headache	1 (6)	9 (16)	19 (12)	274 (18)
Nausea	3 (18)	8 (14)	33 (21)	247 (16)
Anemia AE	**6 (35)**	**16 (29)**	**37 (24)**	**246 (16)**
Required Transfusion(s)	2 (12)	5 (9)	3 (2)	31 (2)
Erythropoietin Start on Treatment	1 (6)	8 (14)	14(9)	50 (3)
RBV[$]				
Reduction in RBV due to Anemia	3 (38)	8 (30)	33 (42)	185 (19)
RBV Discontinuation	0 (0)	4 (15)	1 (1)	12 (1)
Worsening Renal Function[]	**5 (29)**	**6 (11)**	**4 (3)**	**14 (1)**
Renal or Urinary System AEs[Φ]	**5 (29)**	**6 (11)**	**13 (8)**	**84 (5)**
Any Serious AEs	**3 (18)**	**13 (23)**	**8 (5)**	**100 (6)**
Cardiac Serious AEs	**1 (6)**	**2 (4)**	**8 (5)**	**53 (3)**
Early Treatment Discontinuation	**1 (6)**	**4 (6)**	**6 (4)**	**68 (4)**
Early Treatment Discontinuation AE	**1 (6)**	**2 (3)**	**4 (2)**	**39 (3)**
Death[§]	**1 (6)**	**0 (0)**	**2 (1)**	**10 (1)**

*Among all patients who completed therapy; [$] Among patients treated with RBV; [] includes acute on chronic renal insufficiency, outcome abstracted from treatment documentation; [Φ] includes acute renal failure, dysuria, hematuria, urinary retention and other similar renal/urinary problems; [§] eGFR ≤ 30 patient that died: Liver transplant recipient with baseline MELD of 26 who died from worsening renal failure and hepatic decompensation

Adapted from: Saxena V. ILC 2015, #LP08

Efficacité de 12 semaines de la 3D Abbvie avec (GT1a) ou sans RBV (GT1B): Ruby1

- No discontinuations or treatment-related serious AEs
- All patients completing treatment to date had virologic response

Timepoint	N	Virologic Response (n)	Percent
End of Treatment	14	14	100
Post-treatment Week 4	10	10	100
Post-treatment Week 12	2	2	100

Adapted from: https://ilc-congress.eu/cpgs/summary (21-4-2015)

Efficacité de 12 semaines de la 3D Abbvie avec (GT1a) ou sans RBV (GT1B): Ruby1

	GT1b 3D N=7	GT1a 3D+RBV N=13
Event[a] (experienced by 2 or more patients)	n	
Anemia	0	8
Fatigue	2	4
Diarrhea	1	4
Nausea	0	5
Dizziness	1	2
Headache	0	3
Decreased appetite	0	2
Irritability	0	2
Edema peripheral	1	1
Weight decreased	0	2

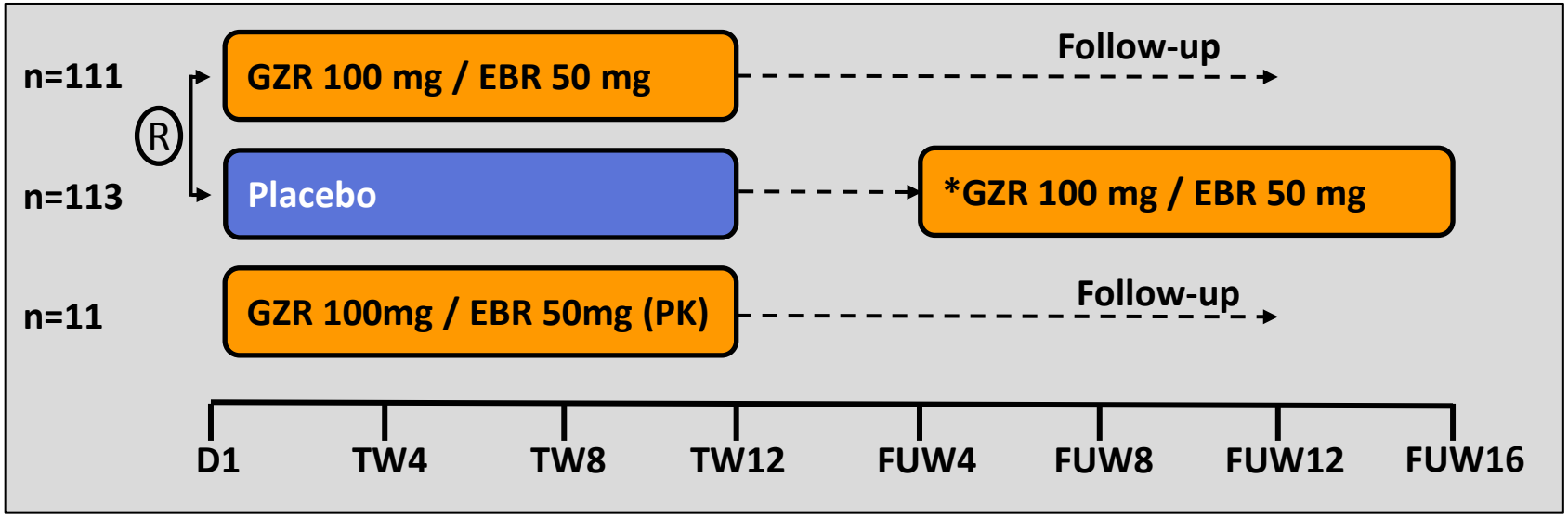
[a]Adverse event as reported by investigator.

Adapted from: https://ilc-congress.eu/cpgs/summary (21-4-2015)

C-Surfer

Grazoprevir (IP 2nd) + Elbasvir(NS5A 2nd) chez GT1 CrCl <30 mL/min

<1% of grazoprevir and elbasvir are renally excreted

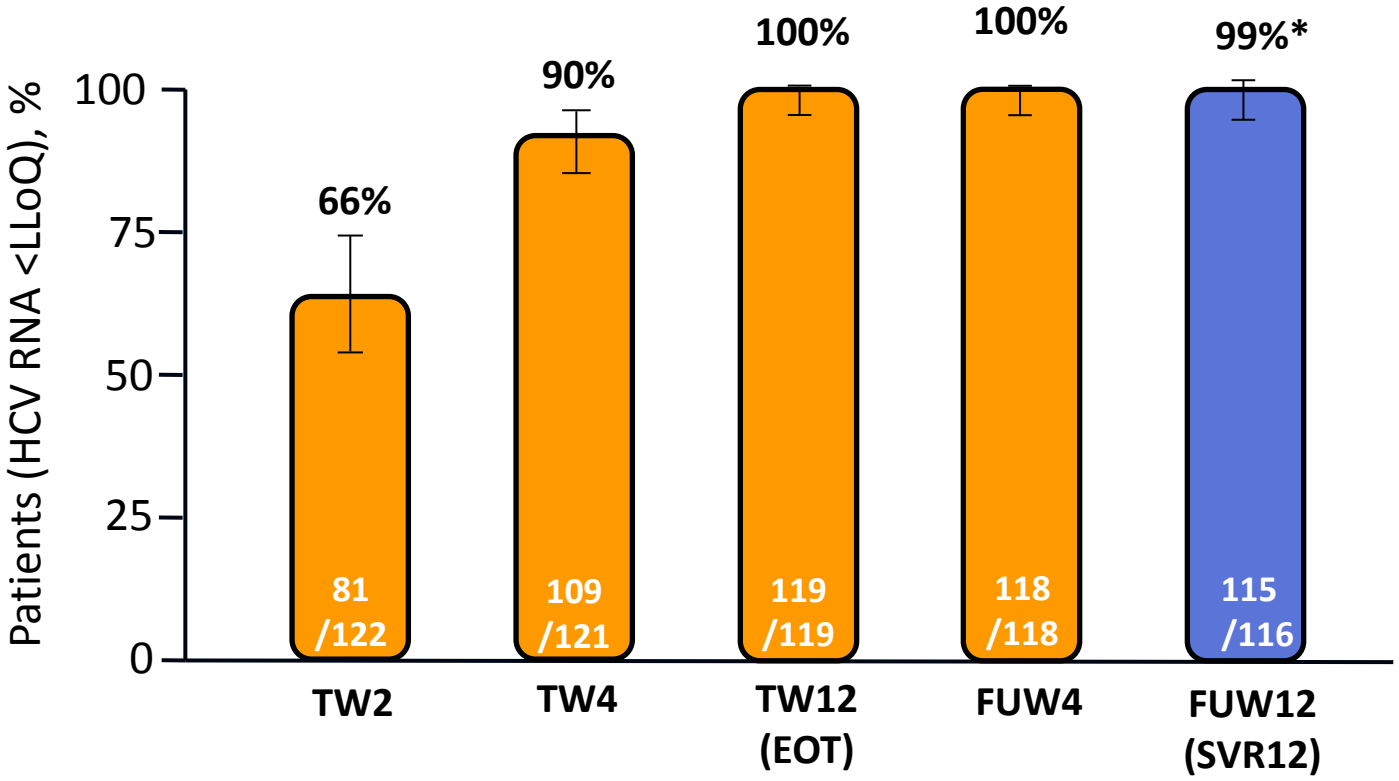


- Randomized, parallel-group, multi-site, placebo-controlled trial
- Stratification by diabetes (yes/no) and hemodialysis status (HD/non-HD)
- 224 patients randomized to immediate treatment with GZR/EBR or deferred treatment where patients received placebo for 12 weeks then open-label GZR/EBR starting at FUW4
- 11 patients in open-label GZR/EBR arm underwent intensive pharmacokinetic sampling

*Deferred open-label treatment arm (all randomized patients remained blinded to treatment until FW4)
GZR and EBR were administered as separate entities in the immediate and PK arms, and as a fixed dose-combination in the deferred arm. CKD = chronic kidney disease; GT = genotype; HD = hemodialysis; R = randomized

C-Surfer: réponses virologiques

1 noncirrhotic patient with HCV GT1b infection relapsed at FW12

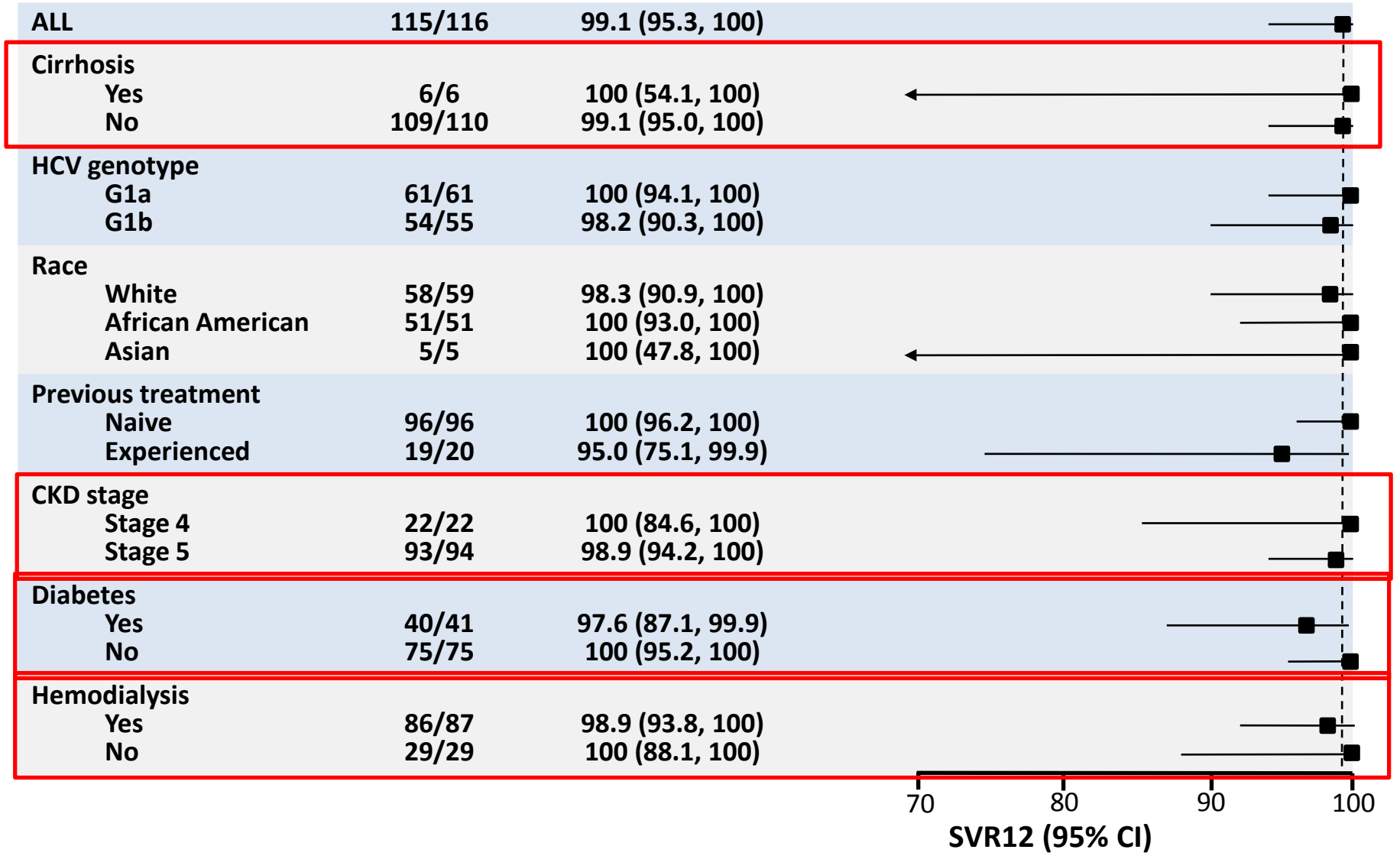


*Efficacy is presented for the modified full analysis set population (mFAS). Full Analysis set: patients with SVR12 94%

6 patients were excluded from the per protocol: lost to follow-up (n=2), n=1 each for death, non-compliance, withdrawal by subject, and withdrawal by physician (due to violent behavior)

Roth D et al. Lancet 2015

C-Surfer: réponses virologiques



Roth D et al. Lancet 2015

*modified full analysis set population (mFAS)

C-Surfer: tolérance

	GZR / EBR (ITG) (n=111)	Placebo (DTG) (n=113)	Difference in % Estimate (95% CI)
Adverse events*, n (%)	84 (75.7)	95 (84.1)	-8.3 (-18.9, 2.2)
Headache	19 (17.1)	19 (16.8)	0.3 (-9.6, 10.4)
Nausea	17 (15.3)	18 (15.9)	-0.6 (-10.3, 9.1)
Fatigue	11 (9.9)	17 (15.0)	-5.1 (-14.1, 3.7)
Insomnia	7 (6.3)	12 (10.6)	-4.3 (-12.2, 3.2)
Dizziness	6 (5.4)	18 (15.9)	-10.5 (-19.1, -2.6)
Diarrhea	6 (5.4)	15 (13.3)	-7.8 (-16.1, -0.2)
Serious AEs, n (%)	16† (14.4)	19 (16.8)	-1.5 (11.2, 8.1)
Discon due to an AE, n (%)	0 (0)	5 (4.4)	-4.4 (10.0, -1.0)
Deaths‡, n (%)	1 (0.9)	3 (2.7)	-1.8 (-6.7, 2.5)

*Reported in ≥10% of patients in either treatment group (ASaT)
†One SAE in the ITG was considered drug-related (elevated lipase)
‡One ITG patient died from cardiac arrest and 3 DTG patients died from aortic aneurysm, pneumonia, and unknown cause
AE = adverse event; DTG = deferred treatment group; ITG = immediate treatment group; SAE = serious adverse event

Roth D et al. Lancet 2015

Nouveaux traitements du VHC en néphrologie: conclusions

- Les AVD du VHC: révolution thérapeutique puisque tous les patients vont guérir

- Adaptations posologiques selon les classes d'AVD et le DFG (SOF)

- Usage encore contraint en 06.2015 mais les nouvelles recommandations vont permettre de traiter tous les dialysés et tous les transplantés rénaux

Recommandations AFEF sur la prise en charge des hépatites virales C

AFEF

ASSOCIATION FRANÇAISE POUR L'ETUDE DU FOIE

1. **Pour les patients ayant une insuffisance rénale modérée (clairance de la créatinine > 30 ml/min/1,73 m2), aucun ajustement de dose n'est nécessaire (A)**

2. Pour les patients ayant une clairance de la créatinine < 30 ml/min/1,73m2, il est recommandé de prendre l'avis d'un centre expert (AE)

3. Le traitement de l'hépatite C est recommandé chez tous les patients hémodialysés sans projet de transplantation rénale (A)

4. Chez les patients hémodialysés, les schémas thérapeutiques sans ribavirine sont à privilégier (A)

5. Chez les patients de génotype 1 ayant une clairance de la créatinine < 30 ml/min/1,73m2, le traitement par Grazoprevir + Elbasvir pendant 12 semaines sera le schéma thérapeutique recommandé (A)