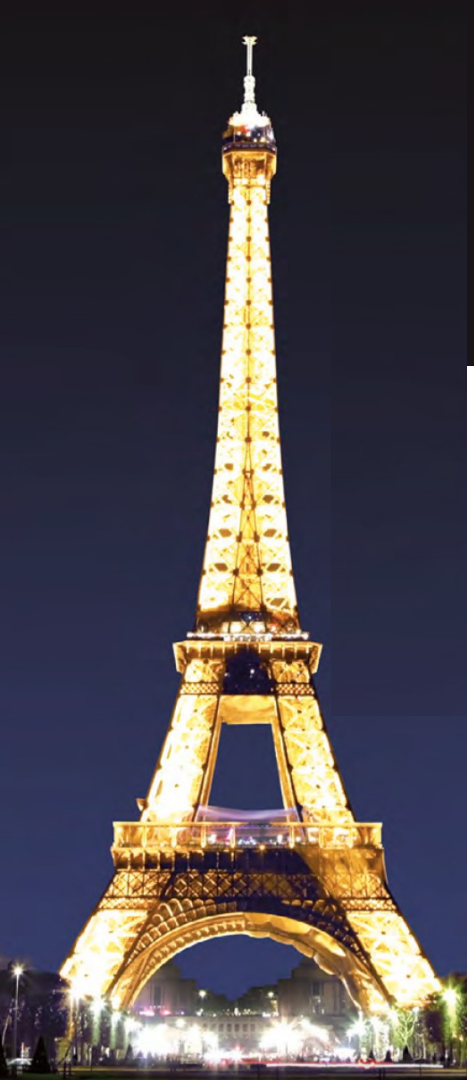


2019
12th Paris Hepatology Conference
PHC 2019
14 & 15 January 2019
PARIS - Palais des Congrès

Do DAAs decrease the risk of HCC?

Massimo Levrero

Cancer Research Center of Lyon (CRCL) and INSERM U1052, Lyon, France
Hopital de la Croix-Rousse - Hospices Civils de Lyon, Lyon, France

Sapienza Università di Roma
Dipartimento di medicina interna e specialitA' mediche

iit @Sapienza Istituto Italiano di Tecnologia

Inserm Institut national de la santé et de la recherche médicale
CRCL
Hospices Civils de Lyon

Disclosures

Advisory Committees or Review Panels:
- BMS
- Jansen
- Gilead
- Arbutus
- Galapagos
- Assembly Pharma
- Sanofi/Aventis

Speaking and Teaching:
- MSD
- Roche
- BMS
- Jansen
- Gilead

Annals of Internal Medicine | Review

Eradication of Hepatitis C Virus Infection and the Development of Hepatocellular Carcinoma

A Meta-analysis of Observational Studies

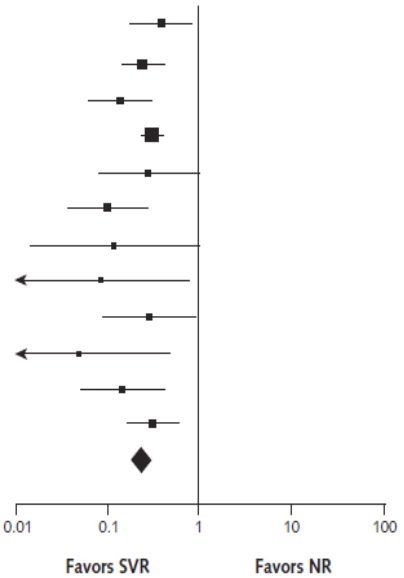
Rebecca L. Morgan, MPH; Brittney Baack, MPH; Bryce D. Smith, PhD; Anthony Yartel, MPH; Marc Pitasi, BS; and Yngve Falck-Ytter, MD

Forest Plot Of Adjusted Hazard Effects In Persons At All Stages Of Fibrosis

Study, Year (Reference)	log(Hazard Ratio)	SE	Total SVR	Total NR	Weight, %	Hazard Ratio IV, Random (95% CI)
Asahina et al, 2010 (36)	–0.944	0.388	686	1356	9.2	0.39 (0.18–0.83)
Hung et al, 2011 (46)	–1.423	0.273	1027	443	15.3	0.24 (0.14–0.41)
Kawamura et al, 2010 (50)	–1.985	0.407	1081	977	8.5	0.14 (0.06–0.31)
Kramer et al, 2011 (27)	–1.182	0.126	4292	10 276	31.2	0.31 (0.24–0.39)
Kurokawa et al, 2009 (51)	–1.277	0.631	139	264	4.0	0.28 (0.08–0.96)
Okanoue et al, 2002 (53)	–2.294	0.512	375	586	5.8	0.10 (0.04–0.28)
Osaki et al, 2012 (50)	–2.130	1.053	185	197	1.5	0.12 (0.02–0.94)
Pradat et al, 2007 (17)	–2.481	1.132	87	103	1.3	0.08 (0.01–0.77)
Sinn et al, 2008 (56)	–1.246	0.596	296	194	4.4	0.29 (0.09–0.93)
Takahashi et al, 2011 (57)	–3.022	1.163	89	114	1.3	0.05 (0.00–0.48)
Tateyama et al, 2011 (58)	–1.968	0.537	139	234	5.3	0.14 (0.05–0.40)
Yoshida et al, 1999 (61)	–1.164	0.324	789	1568	12.1	0.31 (0.17–0.59)
Total			9185	16 312	100.0	0.24 (0.18–0.31)

Heterogeneity: tau-square = 0.04; chi-square = 14.05; $P = 0.23$; $I^2 = 22\%$

Test for overall effect: $Z = 10.80$; $P < 0.001$



Morgan et al, Ann Int Med 2013;158:329-337

Annals of Internal Medicine | Review

Eradication of Hepatitis C Virus Infection and the Development of Hepatocellular Carcinoma

A Meta-analysis of Observational Studies

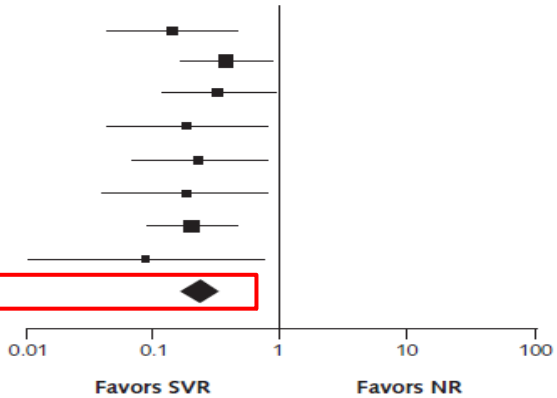
Rebecca L. Morgan, MPH; Brittney Baack, MPH; Bryce D. Smith, PhD; Anthony Yartel, MPH; Marc Pitasi, BS; and Yngve Falck-Ytter, MD

Figure 2. Forest plot of adjusted hazard effects in persons with advanced liver disease.

Study, Year (Reference)	log(Hazard Ratio)	SE	Total SVR	Total NR	Weight, %	Hazard Ratio IV, Random (95% CI)
Braks et al, 2007 (37)	−1.966	0.601	37	76	11.2	0.14 (0.04–0.45)
Bruno et al, 2007 (38)	−0.954	0.425	124	759	22.4	0.39 (0.17–0.89)
Cardoso et al, 2010 (40)	−1.120	0.514	103	204	15.3	0.33 (0.12–0.89)
Hasegawa et al, 2007 (64)	−1.690	0.755	48	57	7.1	0.18 (0.04–0.81)
Hung et al, 2006 (65)	−1.468	0.622	73	59	10.4	0.23 (0.07–0.78)
Morgan et al, 2010 (52)	−1.721	0.764	140	309	6.9	0.18 (0.04–0.80)
van der Meer et al, 2012 (63)	−1.592	0.416	192	338	23.4	0.20 (0.09–0.46)
Velosa et al, 2011 (60)	−2.433	1.108	39	91	3.3	0.09 (0.01–0.77)
Total			756	1893	100.0	0.23 (0.16–0.35)

Heterogeneity: tau-square = 0.00; chi-square = 3.64; $P = 0.82$; $I^2 = 0\%$

Test for overall effect: $Z = 7.21$; $P < 0.001$



Conclusion: Sustained virologic response after treatment among HCV-infected persons at any stage of fibrosis is associated with reduced HCC. The evidence was determined to be of moderate quality.

Morgan et al, Ann Int Med 2013;158:329-337

Meta-analysis: interferon improves outcomes following ablation or resection of hepatocellular carcinoma

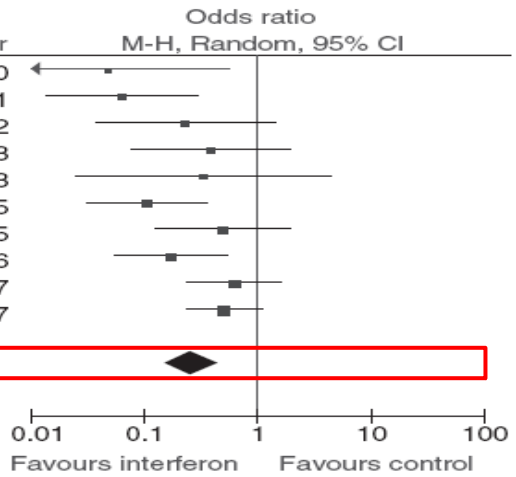
A. K. Singal*, D. H. Freeman Jr† & B. S. Anand‡

10 studies (5 randomized) were included treating initial HCC with resection (3 studies), ablation (5 studies) and ablation + resection (2 studies)

Study or Subgroup	Interferon Events	Interferon Total	Control Events	Control Total	Weight	Odds ratio M-H, Random, 95% CI	Year
Ikeda *et al.*	1	10	7	10	4.2%	0.05 [0.00, 0.56]	2000
Suou *et al.*	4	18	18	22	8.6%	0.06 [0.01, 0.30]	2001
Kubo *et al.*	9	15	13	15	6.9%	0.23 [0.04, 1.41]	2002
Shiratori *et al.*	40	49	23	25	8.2%	0.39 [0.08, 1.94]	2003
Lin *et al.*	5	8	5	6	3.9%	0.33 [0.03, 4.40]	2003
Sakaguchi *et al.*	6	24	25	33	11.8%	0.11 [0.03, 0.36]	2005
Hung *et al.*	11	16	27	33	10.1%	0.49 [0.12, 1.94]	2005
Mazzaferro *et al.*	57	76	70	74	12.8%	0.17 [0.06, 0.53]	2006
Jeong *et al.*	28	42	32	42	15.2%	0.63 [0.24, 1.63]	2007
Kudo *et al.*	24	43	60	84	18.3%	0.51 [0.23, 1.09]	2007
Total (95% CI)		301		344	100.0%	0.26 [0.15, 0.45]	
Total events	185		280				

Heterogeneity: $Tau^2 = 0.27$; $Chi^2 = 14.41$, df = 9 ($P = 0.11$); $I^2 = 38\%$

Test for overall effect: $Z = 4.84$ ($P < 0.00001$)



Benefit of IFN in reducing the risk of HCC recurrence. However, this strategy was not included in HCC guidelines.

Singal et al, Aliment Pharmacol Ther 2010; 32: 851-858

- In hepatitis C virus (HCV) infection, all-cause mortality and the risk of HCC occurrence are reduced among patients who achieved sustained virologic response (SVR) with interferon (IFN) - based therapies; 1

- patients with cirrhosis acquired a reduced HCC incidence after SVR, even if a relevant risk remains. 1,2

- there is no conclusive evidence that IFN-based therapy can prevent or delay HCC recurrence after curative HCC treatment. 3

1. Morgan et al. Ann Intern Med. 2013
2. Di Marco et al. Gastroenterology 2016
3. EASL-EORTC guidelines: management of HCC. J Hepatol. 2012

Semantics of Hepatocellular Carcinoma (HCC)

- ***OCCURRENCE (developement):*** **De novo appearance of HCC in a subject (with or without liver disease) with no history or previous evidence of a liver tumor** (INTERMEDIATE RISK)

- ***RECURRENCE*:** **Reappearance of HCC in a subject (with or without liver disease) with a previous HCC judged to be radically cured by any technique (TACE, RFTA, resection,…)** (HIGH RISK)

DAAs for HCV infection

- Direct-acting antivirals (DAAs) have revolutionised the treatment of hepatitis C virus (HCV) infection, with very high rates (>90%) of SVR, very few contraindications and low rate of adverse events;

- However, there are no data from RCTs on the effect of HCV eradication by DAAs in patients with advanced or decompensated liver disease, and in patients who were successfully treated for HCC.

2016: relevant alarm from “field-practice” studies!

Research Article

EASL JOURNAL OF HEPATOLOGY

Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy☆

María Reig[1,†], Zoe Mariño[2,†], Christie Perelló[3], Mercedes Iñarrairaegui[4], Andrea Ribeiro[1], Sabela Lens[2], Alba Díaz[5], Ramón Vilana[6], Anna Darnell[6], María Varela[7], Bruno Sangro[4], José Luis Calleja[3], Xavier Forns[2,‡], Jordi Bruix[1,*,‡]

Research Article

EASL JOURNAL OF HEPATOLOGY

Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct-acting antivirals

Fabio Conti[1,†], Federica Buonfiglioli[1,†], Alessandra Scuteri[2], Cristina Crespi[2], Luigi Bolondi[3], Paolo Caraceni[3], Francesco Giuseppe Foschi[4], Marco Lenzi[1], Giuseppe Mazzella[3], Gabriella Verucchi[1], Pietro Andreone[1,‡], Stefano Brillanti[1,*,‡]

[1]*Research Centre for the Study of Hepatitis, Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Italy;* [2]*Department of Digestive Diseases, Policlinico S.Orsola-Malpighi, Bologna, Italy;* [3]*Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Italy;* [4]*Division of Internal Medicine, Ospedale di Faenza, Italy*

Incidence and pattern of “de novo” hepatocellular carcinoma in HCV patients treated with oral DAAs.

Romano A, Capra F, Piovesan S, Chemello L, Cavalletto L, Anastassopoulos G, et al.

Hepatology 2016; 64: Abstract 19.

DDA, SVR and HCC

- **(Early) HCC occurrence**
- **HCC pattern**
- **(Early) HCC recurrence**

Research Article

CrossMark

EASL JOURNAL OF HEPATOLOGY

Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct-acting antivirals

Fabio Conti[1,†], Federica Buonfiglioli[1,†], Alessandra Scuteri[2], Cristina Crespi[2], Luigi Bolondi[3], Paolo Caraceni[3], Francesco Giuseppe Foschi[4], Marco Lenzi[1], Giuseppe Mazzella[3], Gabriella Verucchi[1], Pietro Andreone[1,‡], Stefano Brillanti[1,*,‡]

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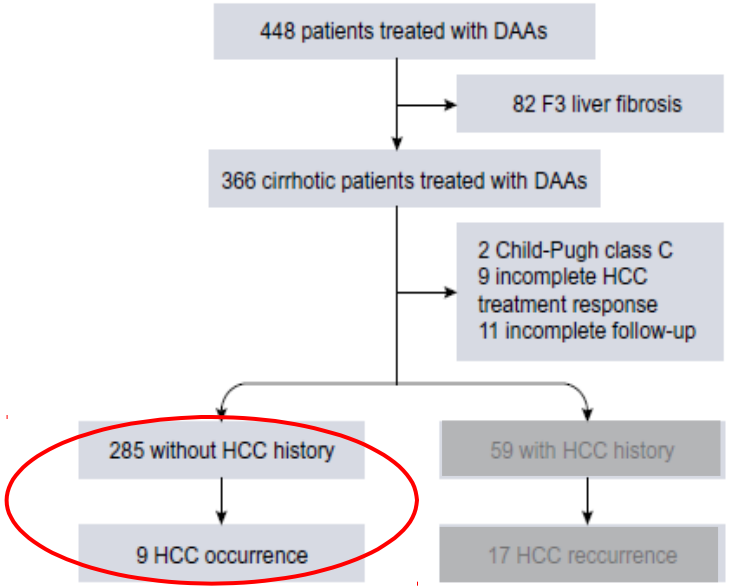
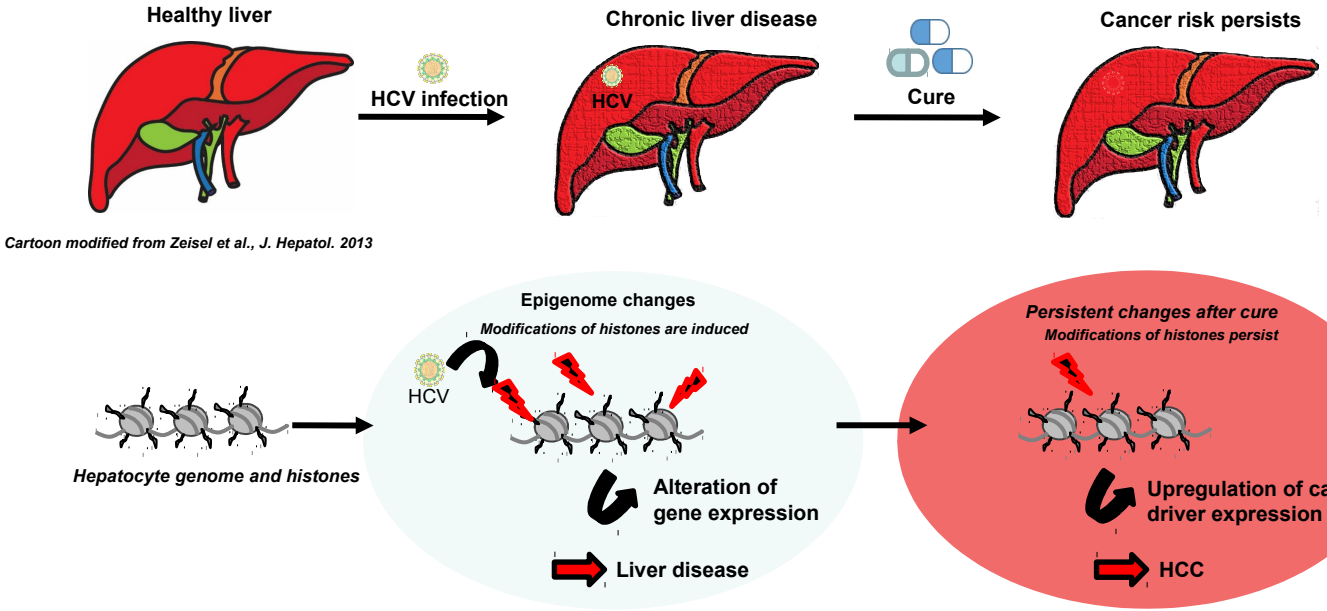


During the 24-week post-treatment evaluation HCC occurrence rate was 3,1% (9/285).

- Retrospective study
- Short follow-up
- No control group
- Crude (not actuarial) rate

DAAs and cancer risk:
Viral cure does not eliminate HCV-induced epigenetic changes



Hepatitis C virus-induced epigenetic and transcriptional changes persist post cure

F. Jühling[1,2], S. Bandiera[1,2], N. Hamdane[1,2], C. Thumann[1,2], S.C. Durand[1,2], H.E. Saghire[1,2], I. Davidson[3,4,5], F. Habersetzer[1,6], P. Pessaux[1,6], N. Bardeesy[7], C. Schmidl[8,9,10], C. Bock[8,9,10], Y. Hoshida[11], M.B. Zeisel[1,2], T.F. Baumert[1,2,6].

Journal of Hepatology **2017** vol. 66 | S1–S32

Host immune modulations by DAA

- Quick resolution of anti-HCV immune response
  (memory T cell de-differentiation, restoration of CD4, CD8 T cells, deactivation of NK cells)

(Spaan, JID 2016, Serti, Gastro 2015, Burchill, JVH 2015, Martin, J Hep 2014, Perello, CGH 2016)

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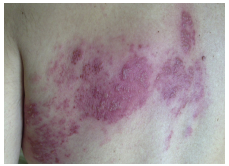

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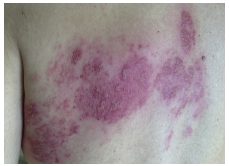

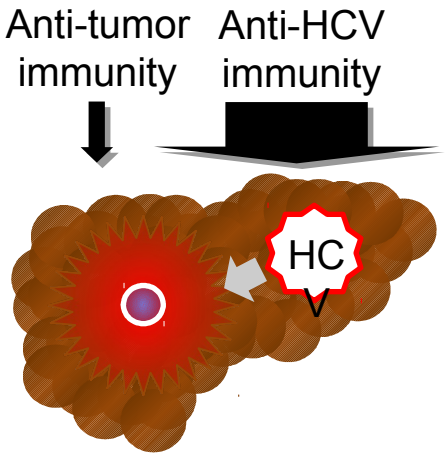

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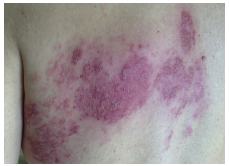

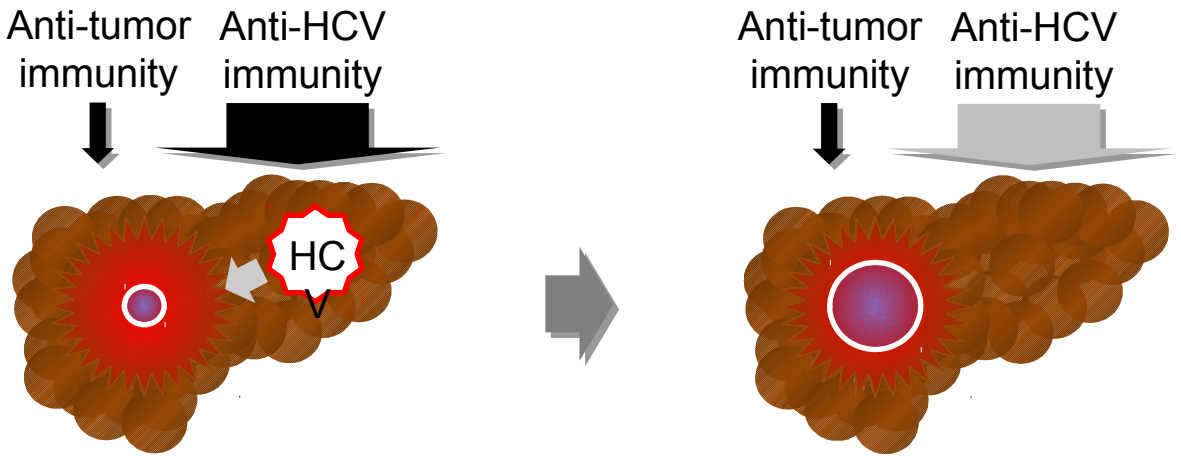

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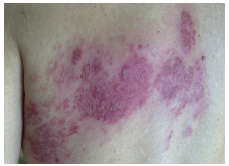
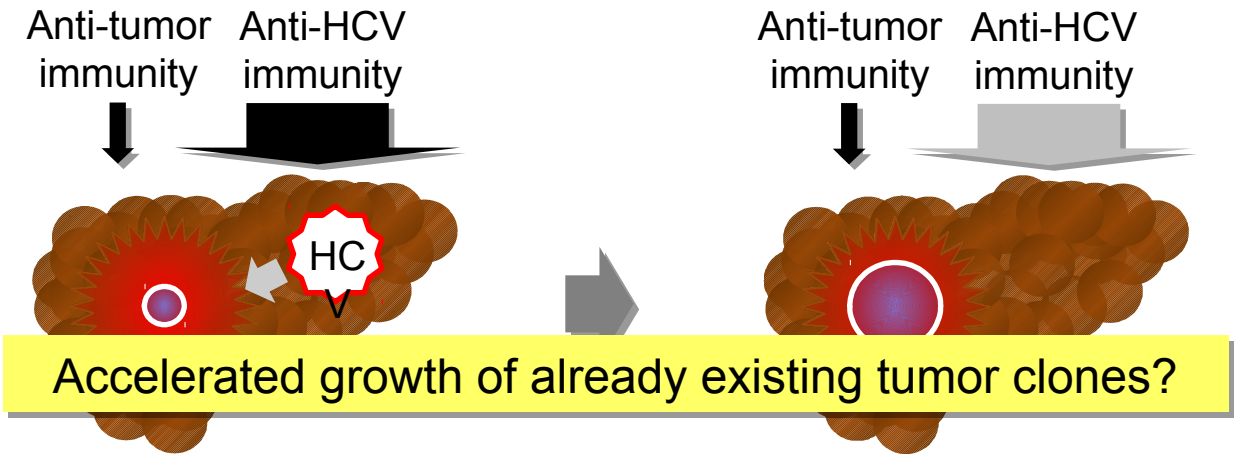




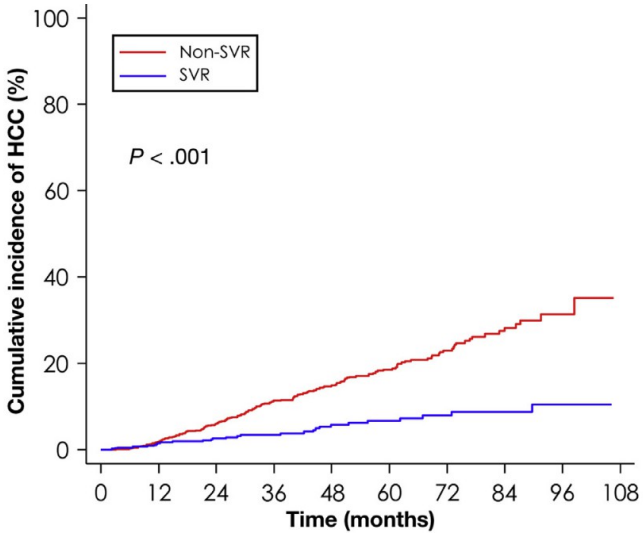
(Spaan, JID 2016, Serti, Gastro 2015, Burchill, JVH 2015, Martin, J Hep 2014, Perello, CGH 2016)

Eradication of Hepatitis C Virus Infection in Patients With Cirrhosis Reduces Risk of Liver and Non-Liver Complications

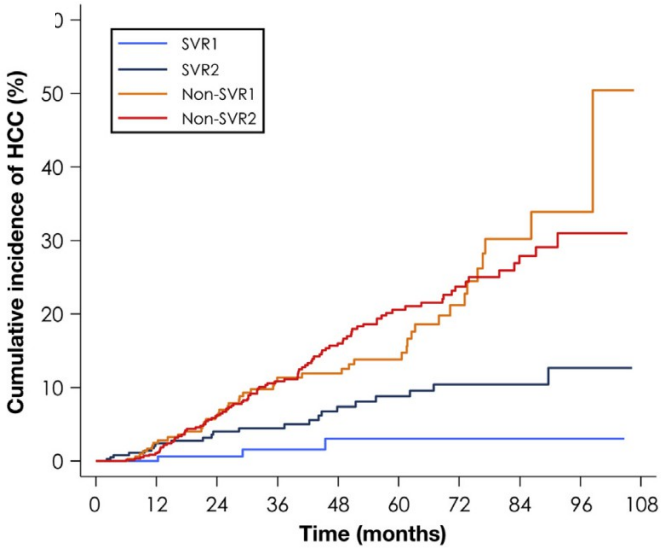
Pierre Nahon,[1,2,3] Valérie Bourcier,[1] Richard Layese,[4] Etienne Audureau,[4] Carole Cagnot,[5] Patrick Marcellin,[6] Dominique Guyader,[7] Hélène Fontaine,[8] Dominique Larrey,[9] Victor De Lédinghen,[10] Denis Ouzan,[11] Fabien Zoulim,[12] Dominique Roulot,[13] Albert Tran,[14,15] Jean-Pierre Bronowicki,[16] Jean-Pierre Zarski,[17] Vincent Leroy,[17] Ghassan Riachi,[18] Paul Calès,[19] Jean-Marie Péron,[20] Laurent Alric,[21] Marc Bourlière,[22] Philippe Mathurin,[23] Sébastien Dharancy,[23] Jean-Frédéric Blanc,[24] Armand Abergel,[25] Lawrence Serfaty,[26] Ariane Mallat,[27] Jean-Didier Grangé,[28] Pierre Attali,[29] Yannick Bacq,[30] Claire Wartelle,[31] Thông Dao,[32] Yves Benhamou,[33] Christophe Pilette,[34] Christine Silvain,[35] Christos Christidis,[36] Dominique Capron,[37] Brigitte Bernard-Chabert,[38] David Zucman,[39] Vincent Di Martino,[40] Vincent Thibaut,[41] Dominique Salmon,[42] Marianne Ziol,[2,3,43,44] Angela Sutton,[44,45,46] Stanislas Pol,[8,47] and Françoise Roudot-Thoraval,[4] for the ANRS CO12 CirVir Group

Gastroenterology

Patients with metabolic features BMI ≥ 25 kg/m2 and/or diabetes and/or dyslipidemia.



	Number at risk (events)
Non-SVR	1033 (17) 866 (34) 731 (38) 562 (20) 447 (17) 311 (14) 192 (10) 99 (3) 26 (1) 2
SVR	653 (8) 483 (5) 381 (3) 296 (6) 221 (2) 174 (2) 123 (1) 73 (1) 30 (0) 3



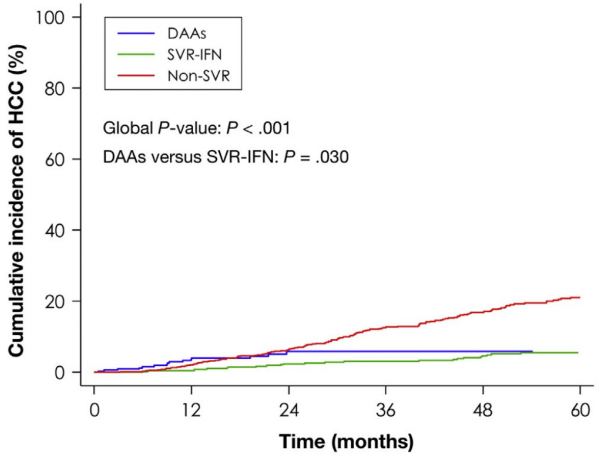
	Number at risk (events)
SVR1	208 (0) 152 (1) 118 (1) 89 (1) 59 (0) 40 (0) 25 (0) 15 (0) 8 (0) 2
SVR2	378 (8) 289 (4) 230 (1) 186 (5) 147 (2) 121 (2) 91 (0) 56 (1) 22 (0) 1
Non-SVR1	316 (7) 264 (9) 214 (11) 172 (1) 142 (3) 100 (7) 53 (5) 22 (1) 5 (1) 0
Non-SVR2	624 (6) 524 (25) 447 (21) 342 (18) 272 (13) 187 (6) 126 (5) 71 (2) 20 (0) 2

Gastroenterology 2017;152:142–156

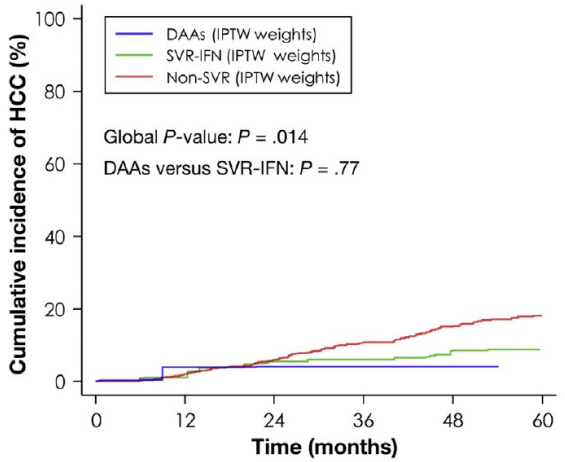
Incidence of Hepatocellular Carcinoma After Direct Antiviral Therapy for HCV in Patients With Cirrhosis Included in Surveillance Programs

Pierre Nahon,[1,2,3] Richard Layese,[4] Valérie Bourcier,[1] Carole Cagnot,[5] Patrick Marcellin,[6] Dominique Guyader,[7] Stanislas Pol,[8,9] Dominique Larrey,[10] Victor De Lédinghen,[11] Denis Ouzan,[12] Fabien Zoulim,[13] Dominique Roulot,[14] Albert Tran,[15,16] Jean-Pierre Bronowicki,[17] Jean-Pierre Zarski,[18] Ghassan Riachi,[19] Paul Calès,[20] Jean-Marie Péron,[21] Laurent Alric,[22] Marc Bourlière,[23] Philippe Mathurin,[24] Jean-Frédéric Blanc,[25] Armand Abergel,[26] Lawrence Serfaty,[27] Ariane Mallat,[28] Jean-Didier Grangé,[29] Pierre Attali,[30] Yannick Bacq,[31] Claire Wartelle,[32] Thông Dao,[33] Dominique Thabut,[34] Christophe Pilette,[35] Christine Silvain,[36] Christos Christidis,[37] Eric Nguyen-Khac,[38] Brigitte Bernard-Chabert,[39] David Zucman,[40] Vincent Di Martino,[41] Angela Sutton,[42,43,44] Françoise Roudot-Thoraval,[4] and Etienne Audureau,[4] for the ANRS CO12 CirVir Group

Gastroenterology



Groups	Number at risk (events)										
DAAs	336	(12)	263	(3)	117	(0)	13	(0)	6	(0)	4
SVR-IFN	495	(2)	474	(9)	436	(3)	391	(6)	352	(3)	260
Non-SVR	923	(17)	797	(33)	676	(42)	518	(22)	400	(18)	288



Groups	Number at risk (events)					
DAAs (IPTW weights)	956	698	384	92	53	43
SVR-IFN (IPTW weights)	1076	1043	965	849	771	532
Non-SVR (IPTW weights)	1029	892	760	613	478	357

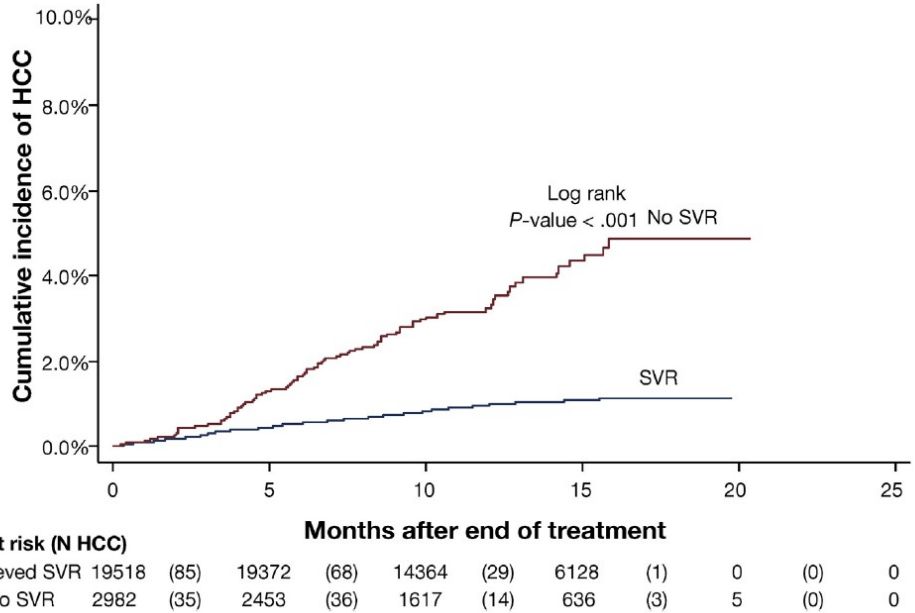
Inverse probability of treatment and censoring weights (IPTCW)

Gastroenterology 2018;155:1436–1450

Risk of Hepatocellular Cancer in HCV Patients Treated With Direct-Acting Antiviral Agents

Fasiha Kanwal,[1,2,3] Jennifer Kramer,[1,3] Steven M. Asch,[4,5] Maneerat Chayanupatkul,[2] Yumei Cao,[3] and Hashem B. El-Serag[1,2,3]

Gastroenterology



129 VAHs = 22,500 patients treated with DAA

- 19,518 with SVR
- 2982 without SVR)
- 271 new cases of HCC (183 in patients with SVR)

- SVR = reduced risk of HCC (HR 0.28, 95% CI 0.22–0.36)

- HCC after SVR: cirrhosis 1.82 / 100 py
  no cirrhosis 0.34 / 100 py

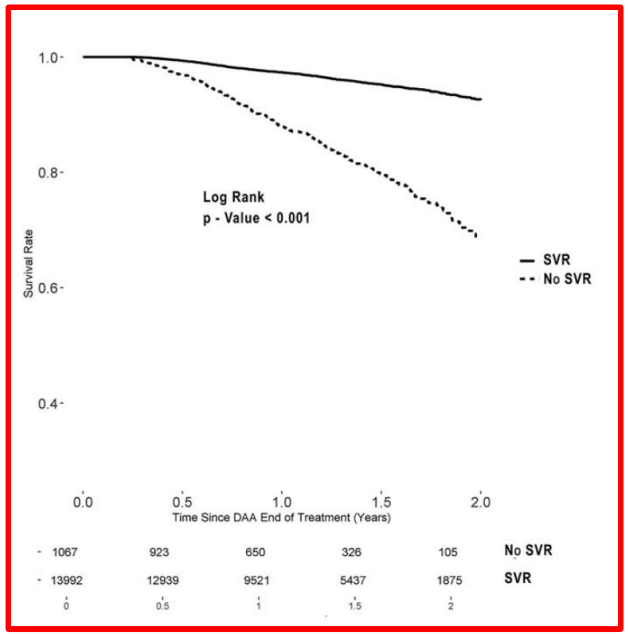
Retrospective study

Gastroenterology 2017;153:996–1005

Impact of Sustained Virologic Response With Direct-Acting Antiviral Treatment on Mortality in Patients With Advanced Liver Disease

Lisa I. Backus, Pamela S. Belperio, Troy A. Shahoumian, and Larry A. Mole

HEPATOLOGY AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES



Patients with HCV infection, FIB-4 > 3.25 in VA HCV Clinical Case Registry (N = 15,059)

- 1,067 patients did not achieve SVR (no SVR)
- 13,992 patients achieved SVR
- follow-up 1.6 years

SVR with DAA therapy significantly lowered incident HCC by 84%

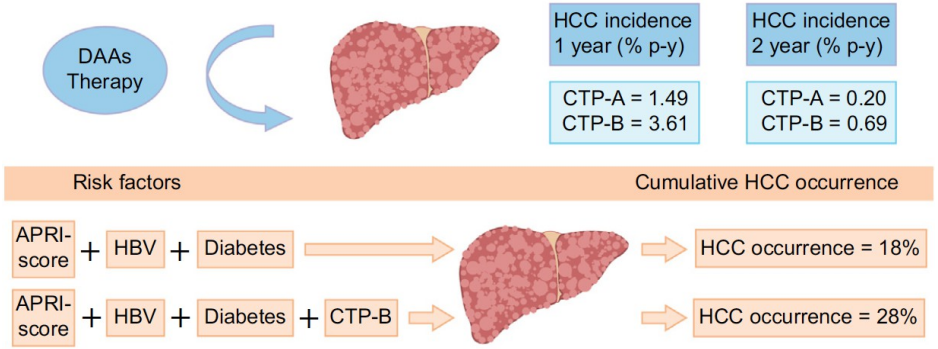
Retrospective study

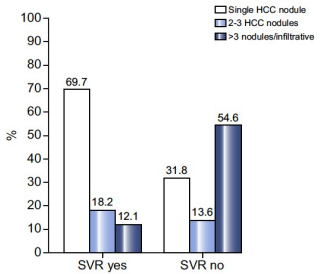
Backus LI, et al. Hepatology. 2017

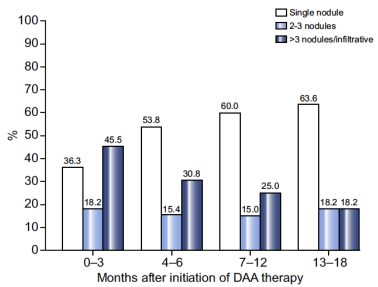
Newly diagnosed hepatocellular carcinoma in patients with advanced hepatitis C treated with DAAs: A prospective population study

Antonietta Romano[1], Paolo Angeli[1], Sara Piovesan[2], Franco Noventa[2], Georgios Anastassopoulos[2], Liliana Chemello[1], Luisa Cavalletto[1], Martina Gambato[3], Francesco Paolo Russo[3], Patrizia Burra[3], Valter Vincenzi[4], Pier Giorgio Scotton[5], Sandro Panese[6], Diego Tempesta[7], Tosca Bertin[8], Maurizio Carrara[9], Antonio Carlotto[10], Franco Capra[11], Giada Carolo[12], Giovanna Scroccaro[13], Alfredo Alberti[2,*]

EASL JOURNAL OF HEPATOLOGY







NAVIGATORE Platform

HCC incidence

- **first year: 0.46% (95% CI 0.12–1.17) in F3,**
  1.49% (1.03–2.08) in CTP-A
  3.61% (1.86–6.31) in CTP-B
- **second year 0%, 0.2%, 0.69%**

Multivariate analysis,
aspartate AST/platelet ratio ≥2.5 (HR 2.03; 1.14–3.61; p = 0.016)
HBV co-infection (HR 3.99; 1.24–12.91; p = 0.021)

no SVR (HR 9.09; 5.2–16.1; p = 0.0001)

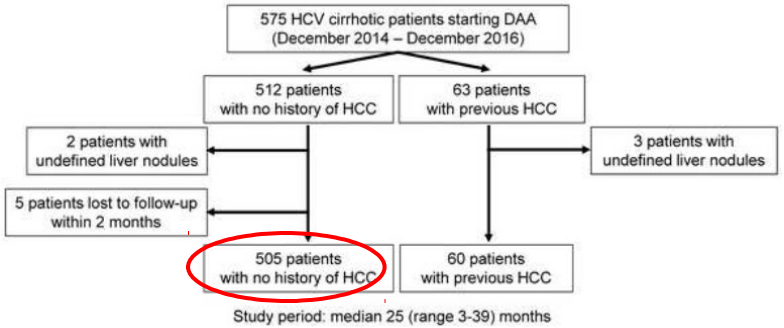
29% of patients with HCC had an aggressive tumor, often seen in the early phase of treatment.

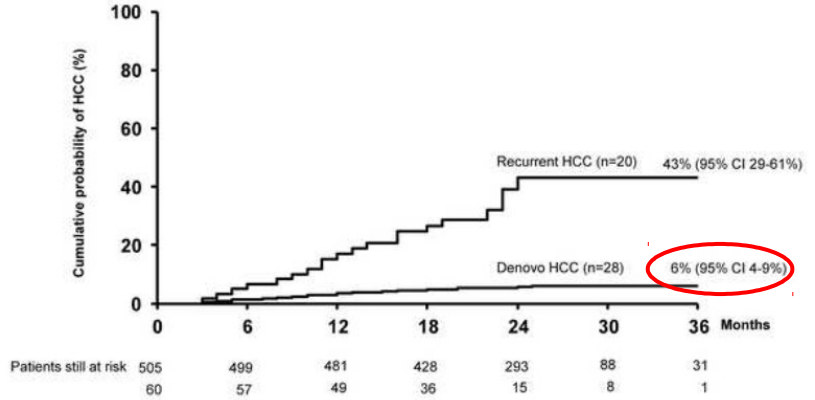
- Prospective study
- Follow-up: 536.2 ± 197.6 days (median 523 days)

Factors Associated With Increased Risk of De Novo or Recurrent Hepatocellular Carcinoma in Patients With Cirrhosis Treated With Direct-Acting Antivirals for HCV Infection

Clinical Gastroenterology and Hepatology

Elisabetta Degasperi,* Roberta D'Ambrosio,* Massimo Iavarone,* Angelo Sangiovanni,* Alessio Aghemo,[‡,§] Roberta Soffredini,* Marta Borghi,* Giovanna Lunghi,[‖] Massimo Colombo,[§] and Pietro Lampertico*





De novo HCC :

- **75% had a single tumor**
- **82% of these were Barcelona liver cancer stage 0–A**
- **alpha-fetoprotein (median): 6 ng/mL (range, 1.0–9240 ng/mL)**

- **male sex (HR, 6.17; 95% CI, 1.44–26.47; P = .01)**
- **diabetes (HR, 2.52; 95% CI, 1.08–5.87; P = .03)**
- **LSM (HR, 1.03; 95% CI, 1.01 £1.06; P = .01)**
- **FIB-4 score (HR, 1.08; 95% CI, 1.01–1.14; P = .01)**

- Retrospective study
- Short follow-up
- No control group

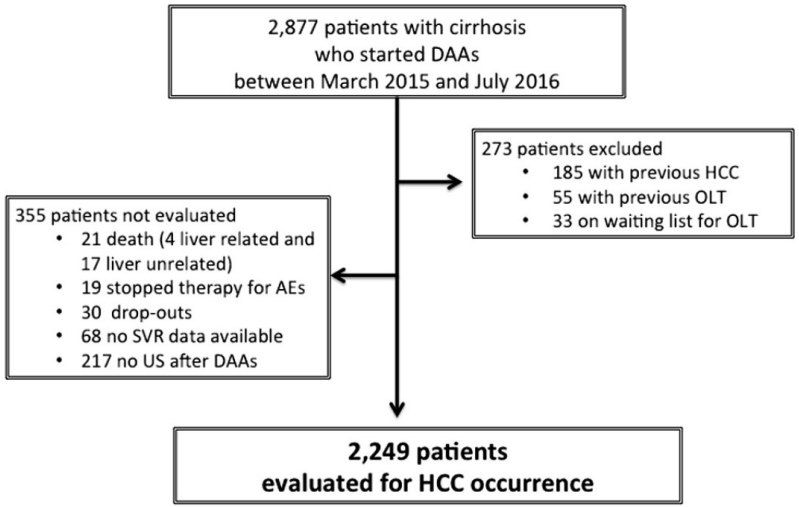
Degasperi E. et al. GC&H. In press

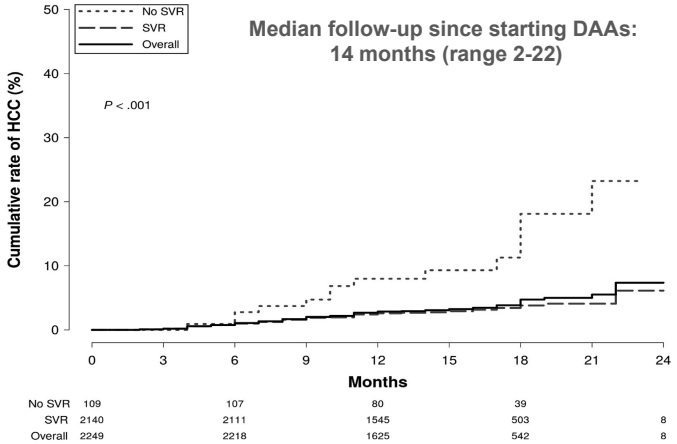
Incidence of Hepatocellular Carcinoma in Patients With HCV-Associated Cirrhosis Treated With Direct-Acting Antiviral Agents

Vincenza Calvaruso,[1] Giuseppe Cabibbo,[1] Irene Cacciola,[2] Salvatore Petta,[1] Salvatore Madonia,[3] Alessandro Bellia,[4] Fabio Tinè,[5] Marco Distefano,[6] Anna Licata,[7] Lydia Giannitrapani,[7] Tullio Prestileo,[8] Giovanni Mazzola,[9] Maria Antonietta Di Rosolini,[10] Licia Larocca,[11] Gaetano Bertino,[12] Antonio Digiacomo,[13] Francesco Benanti,[14] Luigi Guarneri,[15] Alfonso Averna,[16] Carmelo Iacobello,[17] Antonio Magro,[18] Ignazio Scalisi,[19] Fabio Cartabellotta,[20] Francesca Savalli,[21] Marco Barbara,[1] Antonio Davì,[10] Maurizio Russello,[4] Gaetano Scifo,[6] Giovanni Squadrito,[2] Calogero Cammà,[1] Giovanni Raimondo,[2] Antonio Craxì,[1] and Vito Di Marco[1] on Behalf of Rete Sicilia Selezione Terapia–HCV (RESIST-HCV)

Gastroenterology

Prospective study





Overall HCC occurrence

Time	Events, N. (%)	Cumulative Rate (Kaplan – Meier estimates x 100)
6 months	24 (1.0)	1.0%
12 months	59 (2.4)	2.7%
18 months	73 (2.9)	4.4%
24 months	78 (3.1)	7.4%

Gastroenterology 2018;155:411–421

Incidence of Hepatocellular Carcinoma in Patients With HCV-Associated Cirrhosis Treated With Direct-Acting Antiviral Agents

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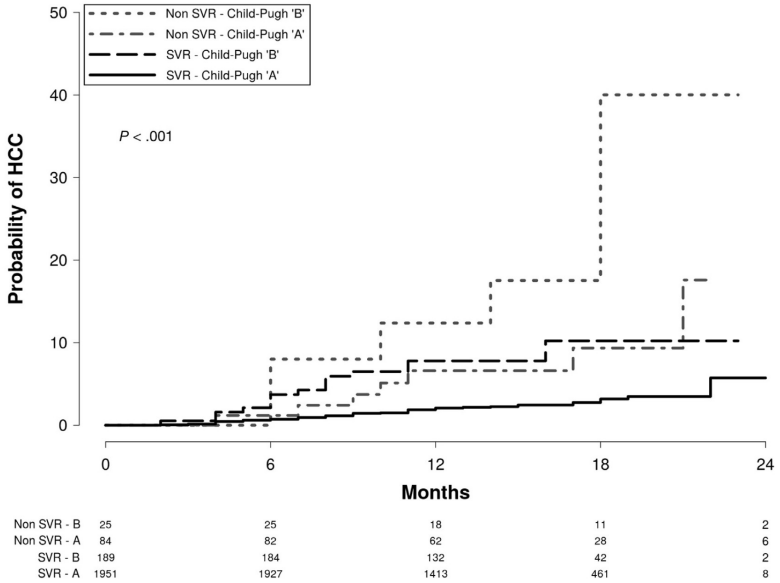
Gastroenterology



	Multivariate Cox regression		
	HR	95% CI	*P* value
Albumin ≥3.5 vs <3.5 mg/dL	1.77	1.12–2.82	.015
Platelet count ≥120 vs <120 × 10^3/dL	3.97	2.23–7.09	<.001
SVR_{12} vs no SVR_{12}	3.40	1.89–6.12	<.001

EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma 2018

- ✓ Once cirrhosis has been established, antiviral therapy is beneficial in preventing cirrhosis progression and decompensation.
- ✓ **Successful antiviral therapy reduces but does not eliminate, the risk of HCC development** (evidence moderate). Antiviral therapies should follow EASL guidelines for the management of chronic HCV infection.
- ✓ HCC occurrence or recurrence is different between patients receiving DAA or IFN therapy
- ✓ The HCC occurrence rate after DAA-therapy may be due to the broader spectrum of patients receiving antiviral therapy in the DAA era: more patients with a higher risk of developing HCC are treated (more advanced stages of cirrhosis, in unselected Child Pugh B class or with significant portal hypertension) since DAA therapy can be offered to patients with more advanced liver disease who would not have been considered suitable for IFN treatment.

European Association for the Study of the Liver, J Hepatol 2018

DDA, SVR and HCC

- (Early) HCC occurrence
- HCC pattern
- **(Early) HCC recurrence**

Risk of HCC recurrence after DAAs

Study	Method	Number of patients, n		Last treatment of HCC	Median observation period (months)	HCC recurrence, n (%)		Conclusion: Did DAAs accelerate recurrence?
		DAA	Control			DAA	Control	
Reig, 2016[11]	Retrospective	58	0	Resection, ablation, or TACE	5.7	16 (27.6)	–	Yes
ANRS CO22, 2016[8]	Retrospective	189	78 (no treatment)	Resection or ablation	21.6 (DAA), 26.1 (no treatment)	24 (12.7)	16 (20.5)	No
ANRS CO12, 2016[8]	Retrospective	13	66 (no treatment)	Resection or ablation	21.3 (all patients)	1 (7.7)	31 (47.0)	No
ANRS CO23, 2016[8]	Retrospective	314	0	Transplantation	7 (mean)	7 (2.2)	–	No
Conti, 2016[10]	Retrospective	59	0	Resection, ablation, PEI, or TACE	37 (with Rec.*),12 (without Rec.†)	17 (28.8)	–	Yes
Minami, 2016[12]	Retrospective	27	38 (IFN), 861 (no treatment)	Ablation	16 (DAA), 36 (IFN, no treatment)	8 (29.6)	26 (68.4) (IFN), 553 (64.2) (no treatment) at 3 years	No
Torres, 2016[15]	Prospective	8	0	Resection, ablation,or proton therapy	12	0 (0)	–	No
Zeng, 2016[16]	Retrospective	8	0	Ablation	15	0 (0)	–	No
Cabibbo, 2017[9,‡]	Prospective	143	0	Resection, ablation, or TACE	8.7	29 (20.3)	–	No
Ikeda, 2017[17,‡]	Retrospective	177	89 (no treatment)	Resection, ablation, TACE or PRT	20.7 (DAA, No treatment)	30.1% (12 months) 38.9% (24 months)	25% (12 months), 46.5% (24 months)	No
Kolly, 2017[18]	Retrospective	47	0	Resection, ablation,or TACE	9.6	Disease-free rate 77% (6 months), 58% (12 months)	–	No
Nagata, 2017[19]	Retrospective	83	60 (IFN)	Resection or ablation	28 (SVR DAA§), 74 (SVR IFN‖)	22.9% (SVR), 40% (Non–SVR) at 3 years	47.1% (SVR), 77.1% (Non–SVR) at 5 years	No
Petta, 2017[20]	Retrospective	58 (SVR DAA§)	57 (SVR IFN‖) 328 (HCV active¶)	Resection or ablation	18 (SVR DAA§), 34 (SVR IFN‖), 17 (HCV active¶)	16 (27.6)	22 (38.6) (SVR IFN†), 142 (43.3) (HCV active‡)	No
Virlogeux, 2017[21]	Retrospective	23	45 (no treatment)	Resection, ablation, TACE, or combination	17.4 (DAA with Rec.*), 10.1 (No treatment with Rec.†), 35.7 (DAA without Rec.*), 15.4 (No treatment without Rec.†)	11 (47.8)	33 (73.3)	No
Zavaglia, 2017[22]	Retrospective	31	0	Resection, ablation, or TACE	8	1 (3.2)	–	No
Kinoshita (The current study)‡	Retrospective	147	156 (IFN)	Ablation	22 (DAA), 86 (IFN)	80 (54.4)	136 (87.2)	No

Kinoshita et al. J Hepatology 70, 78-86, 2019

Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing IFN-free therapy

Research Article

JOURNAL OF HEPATOLOGY

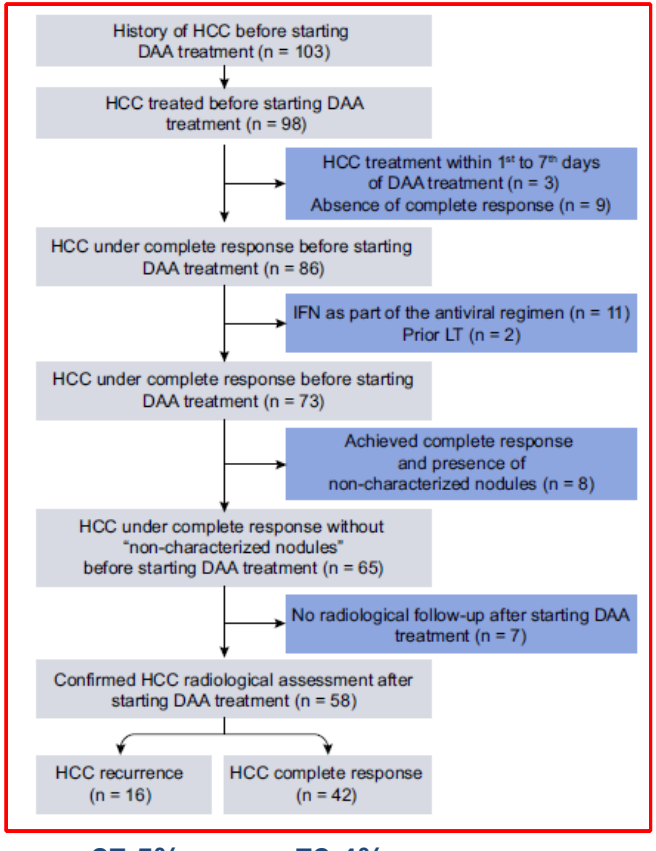
Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy☆

María Reig[1,†], Zoe Mariño[2,†], Christie Perelló[3], Mercedes Iñarrairaegui[4], Andrea Ribeiro[1], Sabela Lens[2], Alba Díaz[5], Ramón Vilana[6], Anna Darnell[6], María Varela[7], Bruno Sangro[4], José Luis Calleja[3], Xavier Forns[2,‡], Jordi Bruix[1,*,‡]

HCC recurrence rate of almost 28%

- Multicenter, retrospective study
- Small population (16 HCC in 58 pts)
- Short follow-up (5.7 mo, range 0.4-24.6)
- Crude (not actuarial) rate

Reig M. J Hepatol. 2016



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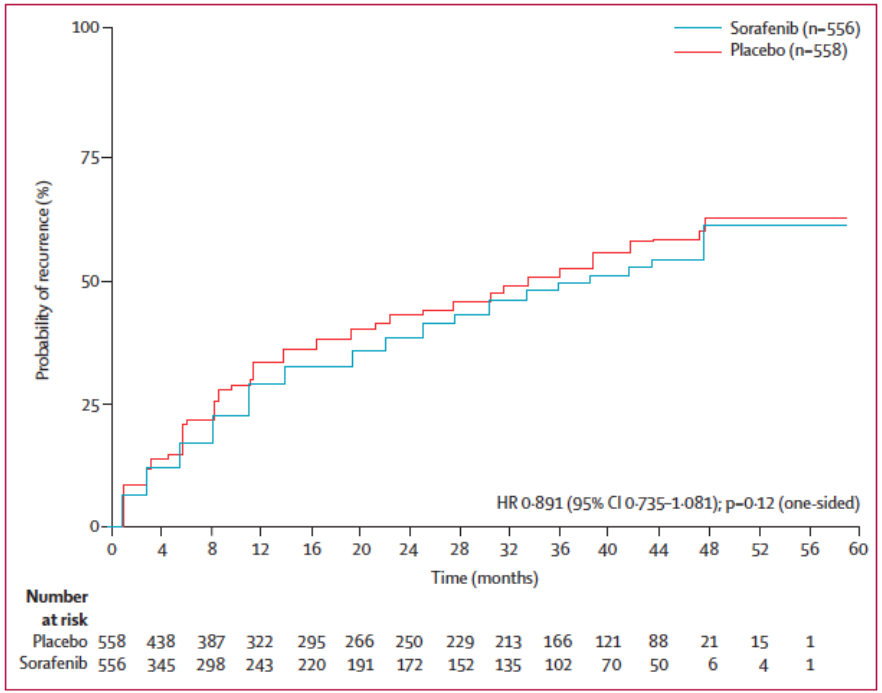

Figure 3: Kaplan-Meier analysis of time to recurrence based on independent assessment
HR=hazard ratio.

Bruix et al. Lancet 2015

Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing IFN-free therapy

Research Article

JOURNAL OF HEPATOLOGY

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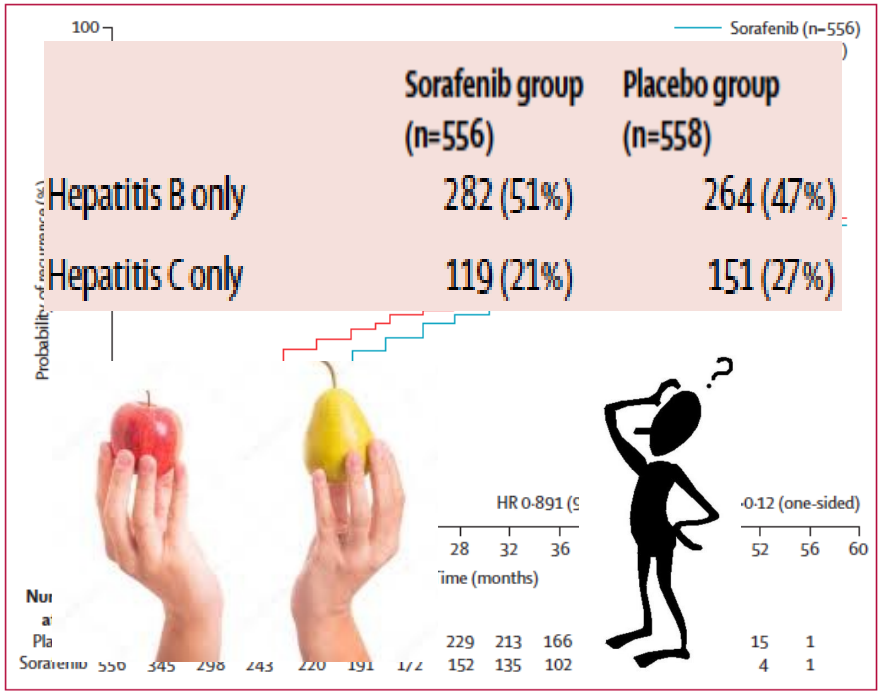


Figure 3: **Kaplan-Meier analysis of time to recurrence based on independent assessment**
HR=hazard ratio.

Bruix et al. Lancet 2015

Research Article

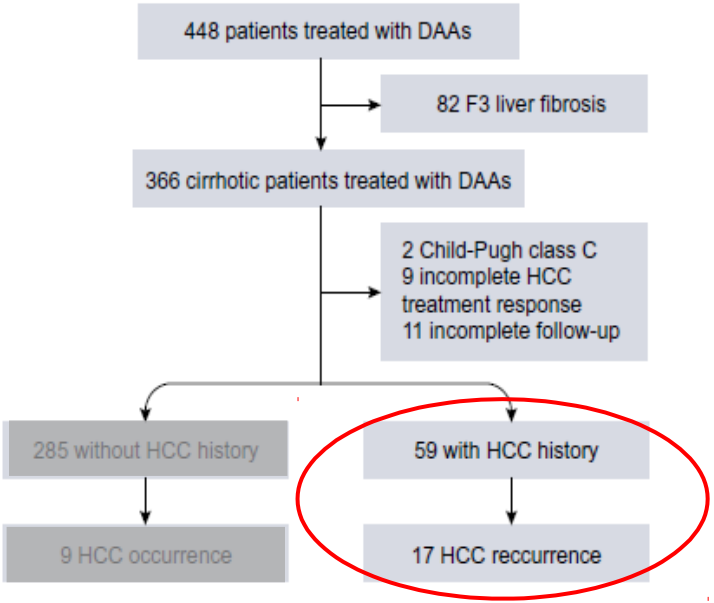
CrossMark

EASL JOURNAL OF HEPATOLOGY

Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct-acting antivirals

Fabio Conti[1,†], Federica Buonfiglioli[1,†], Alessandra Scuteri[2], Cristina Crespi[2], Luigi Bolondi[3], Paolo Caraceni[3], Francesco Giuseppe Foschi[4], Marco Lenzi[1], Giuseppe Mazzella[3], Gabriella Verucchi[1], Pietro Andreone[1,‡], Stefano Brillanti[1,*,‡]

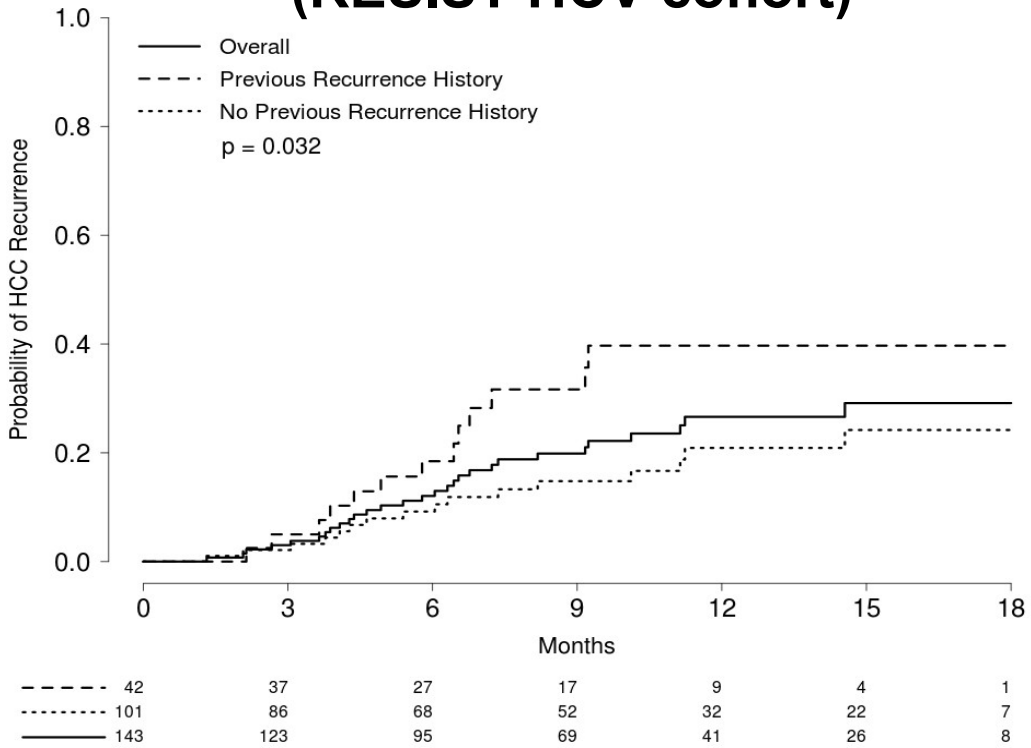
[1]*Research Centre for the Study of Hepatitis, Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Italy;* [2]*Department of Digestive Diseases, Policlinico S.Orsola-Malpighi, Bologna, Italy;* [3]*Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Italy;* [4]*Division of Internal Medicine, Ospedale di Faenza, Italy*



During the 24-week post-treatment evaluation HCC recurrence rate was 28.8 % (17/59).

- Retrospective study
- Short follow-up
- No control group
- Crude (not actuarial) rate

Early Recurrence of Hepatocellular Carcinoma (RESIST-HCV cohort)



Overall 6- 12- and 18-month HCC recurrence rate: 12%, 26.6% and 29.1% respectively.

G. Cabibbo et al. Aliment Pharmacol Ther. 2017;46:688–695.

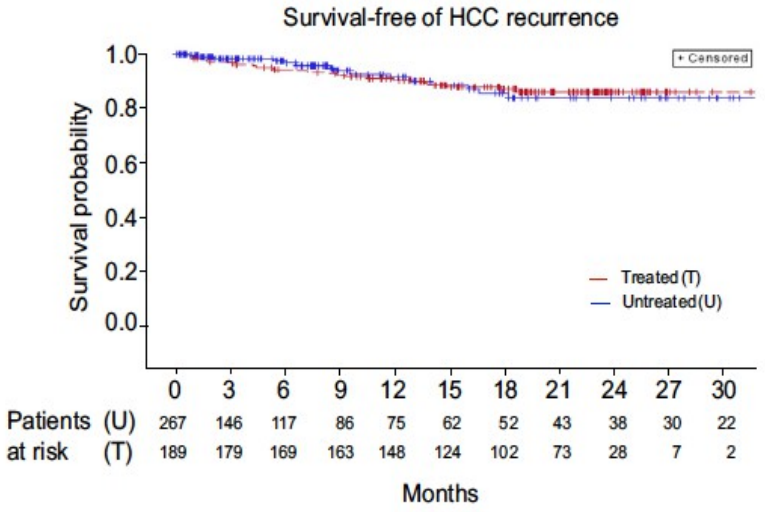
Lack of evidence of an effect of direct-acting antivirals on the recurrence of hepatocellular carcinoma: Data from three ANRS cohorts

The ANRS collaborative study group on hepatocellular carcinoma
(ANRS CO22 HEPATHER, CO12 CirVir and CO23 CUPILT cohorts)*

Cohort ANRS	N with HCC	N with HCC treated with DAA	HCC Recurrence Rate in DAA –treated group per 100 person-months	HCC Recurrence Rate in No-DAA group per 100 person-months
HEPATHER	267	189	0.73	0.66
CIRVIR	79	13	1.11	1.73
CUPILT (LT)	314	314	3.1	--

Retrospective study

- All included patients had therapies with curative potential (resection, RFA, LT)
- No evidence of increased risk of HCC recurrence in DAA-treated patients



Pol S, J Hepatol 2016

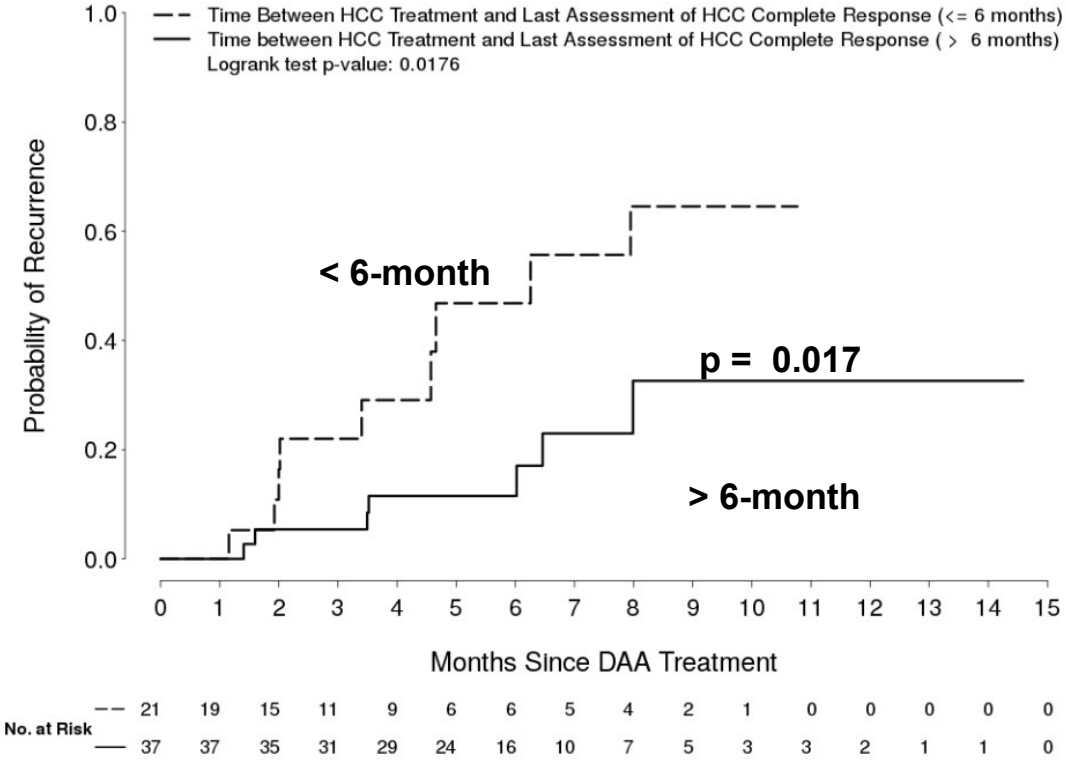
DAA & HCC recurrences: controversies

- **Study design (no randomised, retrospective or prospective)**
- **(Lack of) control group**
- Heterogeneous inception point
- **Time lag between tumor cure and start of DAA**
- **Heterogeneous baseline pts and tumor characteristics**
- Type of curative HCC treatment
- Assessment of complete radiological response
- HCC recurrence definition (early/late and local/distant)
- Schedules of follow-up after HCC treatment
- History of prior HCC recurrences
- Impact of Competitive risk on survival

Cabibbo G et al. Liv Int 2018

JOURNAL OF HEPATOLOGY

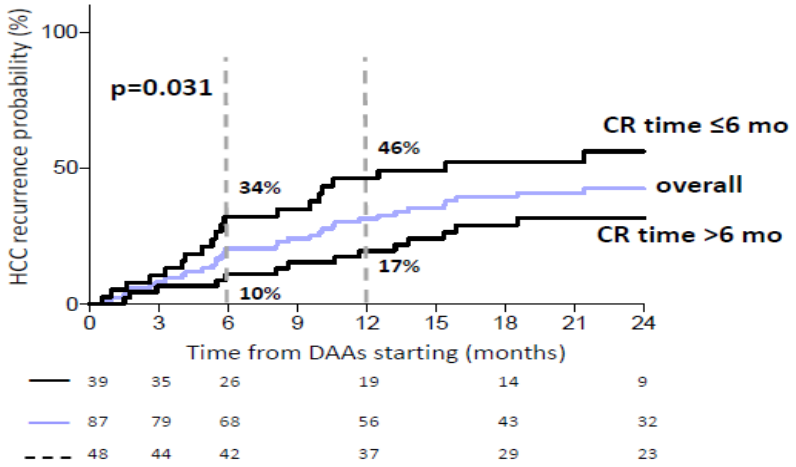
Direct antiviral agents and risk for HCC early recurrence: Much ado about nothing



Cammà C, Cabibbo G, Craxì A. J Hepatology 2016

HCC RECURRENCE IN THE NAVIGATORE DATABASE

Results: HCC recurrence from DAAs starting

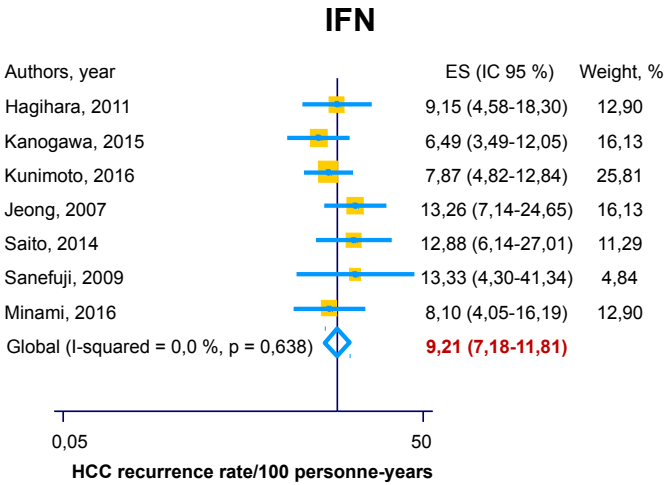


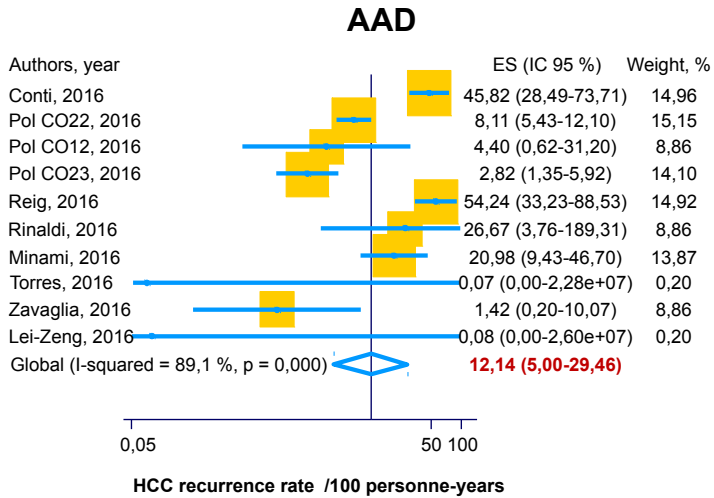
Patients with complete response (CR) confirmed for more than 6 months before DAAs initiation showed lower early HCC recurrence than those with less than 6 months of CR

Gambato M, et al. ILC 2018, #PS-153

HCC Risk after DAAs treatments : meta-analysis

HCC recurrence following SVR





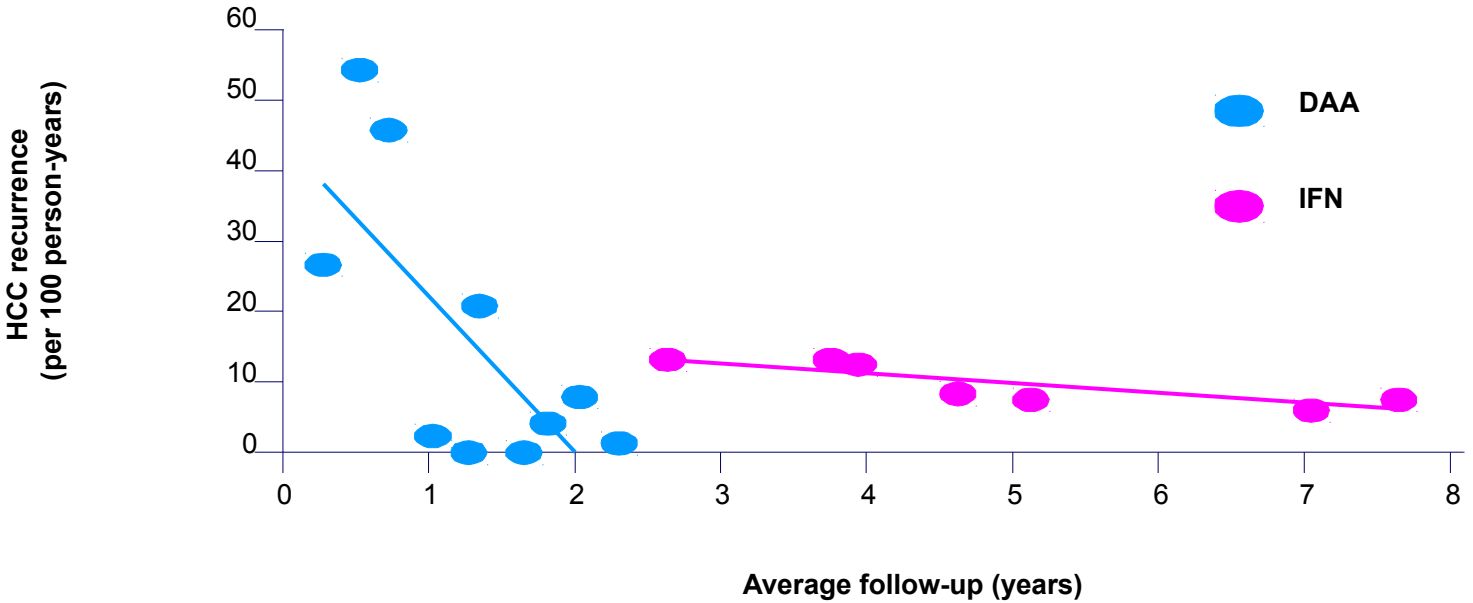
Meta regression of HCC recurrence

	RR non adjusted	RR adjusted	IC 95 %	P value
Average follow-up	0,86	0,79	0,55-1,15	0,19
Average Age	1,11	1,11	0,96-1,27	0,14
Treatment	1,36	0,62	0,11-3,45	0,56

Waziry et al J Hepatol 2017;67:1204- 1212.

HCC Risk after DAAs treatments : meta-analysis

Impact of follow-up on HCC recurrence by average follow-up



➔ **HCC recurrence decrease with longer follow-up**

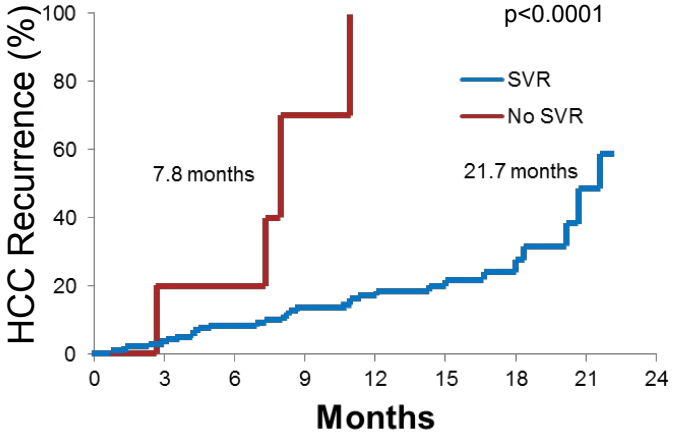
➔ **No data on HCC severity**

Waziry et al J Hepatol 2017;67:1204- 1212.

SVR as a Predictor of Recurrent HCC in HCV Patients

Multicenter, prospective cohort of 1927 patients with HCV cirrhosis, including 161 with previously treated HCC

38/161 patients had a recurrence of HCC; average annual incidence of 24.8%

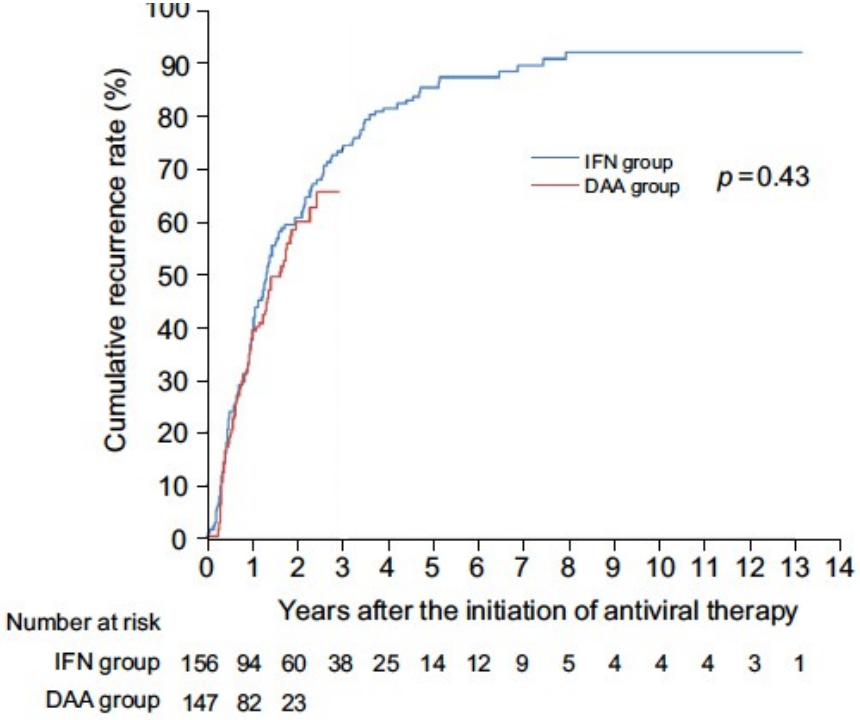


		Univariate		Multivariate	
		HR (95% CI)	P-value	HR (95% CI)	P-value
Years since HCC	≥12 vs. <12 months	2.20 (1.00-4.83)	**0.05**	2.09 (0.94-4.61)	0.07
HCC Treatment	Curative vs. palliative	1.32 (0.46-3.76)	0.61	-	
SVR		8.43 (2.85-24.9)	**0.0001**	**5.21 (1.75-15.5)**	**0.003**
Alpha-fetoprotein	≥10 ng/dL	**6.32 (1.82-21.9)**	**0.004**	**6.19 (1.81-21.2)**	**0.004**

SVR to DAA regimens is associated with a significantly lower rate of recurrence of HCC

Lleo, EASL 2018, SAT-PS-154

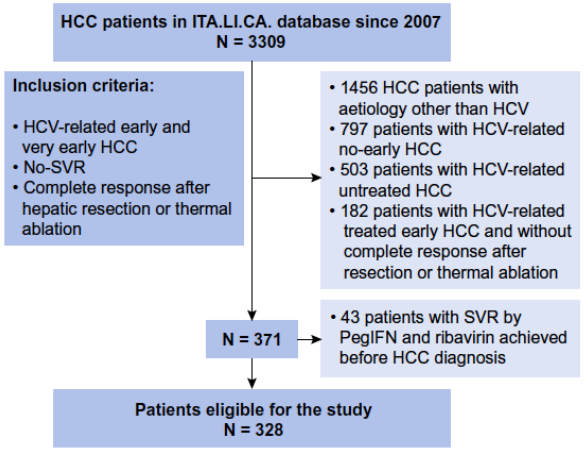
Impact of direct-acting antivirals on early recurrence of HCV-related HCC: Comparison with interferon-based therapy

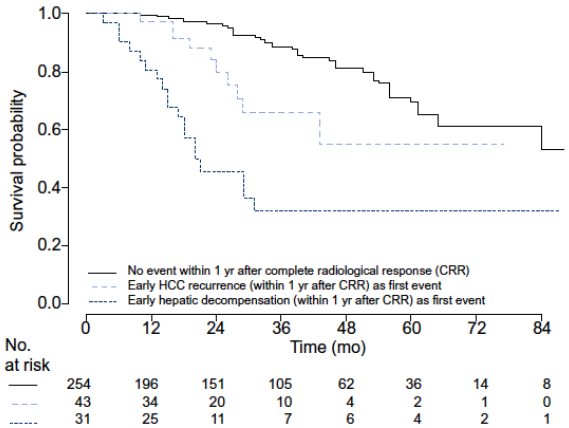


- There was no significant difference in the early HCC recurrence rate and pattern between IFN-based and DAA therapy.
- High AFP-L3, short recurrence-free period, and history of multiple HCC treatments were risk factors for early recurrence.
- Eradication of HCV after curative HCC treatments could preserve liver function, regardless of antiviral therapy regimen.

Kinoshita et al. J hep 2018

Hepatic decompensation is the major driver of death in HCV-infected cirrhotic patients with successfully treated early hepatocellular carcinoma

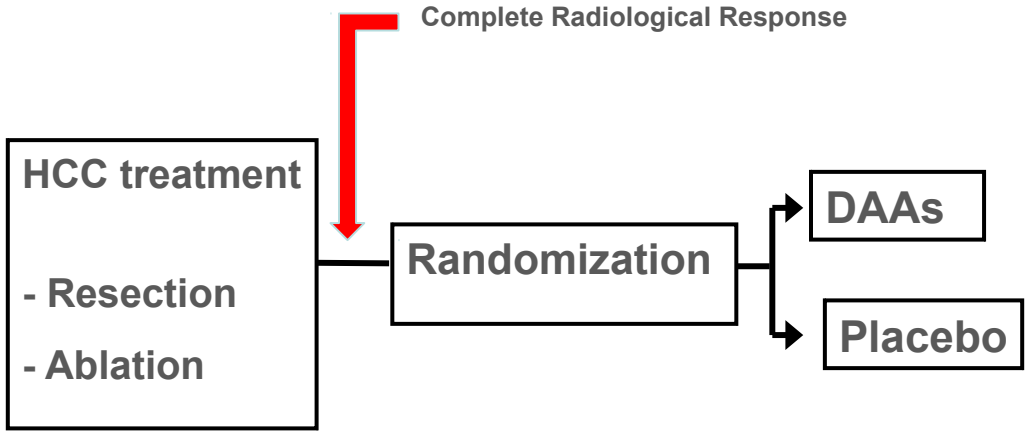




Conclusion: Survival in HCV infected patients with cirrhosis and successfully treated HCC, is mainly influenced by early hepatic decompensation. HCV eradication after treatment with DAA could improve overall survival of HCC patients through long-term preservation of liver function.

Cabibbo et al, on behalf ITA.LICA. Group. J Hep 2017

“Adjuvant” use of DAAs in successfully treated HCC and HCV related cirrhosis



Endpoints

- Overall Survival
- HCC Recurrence
- Hepatic Decompensation
- Biomarkers
- Other

Ideal RCT → **No longer feasible**

EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma 2018

✓**Patients with HCV-associated cirrhosis and HCC treated by curative intent maintain a high rate of HCC recurrence even after subsequent directly acting antiviral (DAA) therapy**. It is presently unclear whether this presents the inherent risk of advanced cirrhosis to develop HCC or if DAA therapy increases recurrence rates. Thus, further research is encouraged.

✓To adequately assess the risk of HCC recurrence/development it is essential to determine if treated patients were properly screened for HCC before DAA initiation, how and for how long follow-up screening was performed and finally, if the incidence of HCC during follow-up was one of the endpoints of retrospective analysis.

✓**Currently, in these patients close surveillance is advised and the benefit of viral cure must be outweighed against a potentially higher recurrence risk** (evidence low; recommendation high).

European Association for the Study of the Liver, J Hepatol 2018

HCC recurrence after DAAs: the take-home message

- Patients with HCV cirrhosis and a previously cured HCC remain at risk of cancer recurrence after HCV eradication

- The **risk of HCC recurrence is lower than in non-eradicated patients**, and is proportional to previous HCC recurrence and tumor size

- Preliminary data in patients with previous cured HCC suggest that the response rate to DAAs is excellent and that survival may be higher in SVR patients despite HCC recurrence

- **DAAs should not be withheld in these patients**

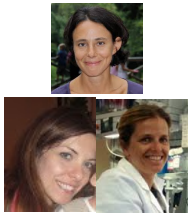
INSERM U1052 - Equipe 23

Massimo Levrero
Mirjam Ziesel
Marie Laure Plissonnier
Francesca Guerrieri
Natali Abeywickrama Samarakoon
Vincenzo Alfano
Oceane Floriot
Alexia Paturel
Anna Delest
Mohamed Ibachi

Paul Deny
Jean Claude Cortay
Claude Caron de Fromentel

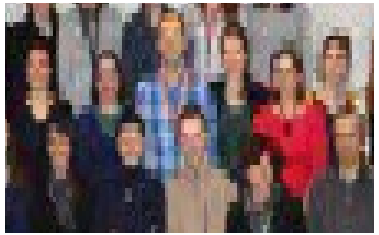
Jean Yves Mabrut
Michael Lesurtel
Mohkan Kayvan

Lab of Gene Expression



Massimo Levrero
Francesca Guerrieri
Natalia Pediconi
Laura Belloni
Ludovica Calvo
Debora Salerno

INSERM U1052 – Equipe 15



Fabien Zoulim
Barbara Testoni
Fanny Lebossé
Caroline Scholtes

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Collaborations:

Jane Mc Keating – Oxford, UK
Ourania Andrisani – Purdue IN, USA
Maura Dandri - Hamburg, Germany
Carlo Ferrari - Parma, IT
Letizia Chiodo, Giancarlo Ruocco – Roma, IT
Sabrina Strano, Giovanni Blandino – Roma, IT