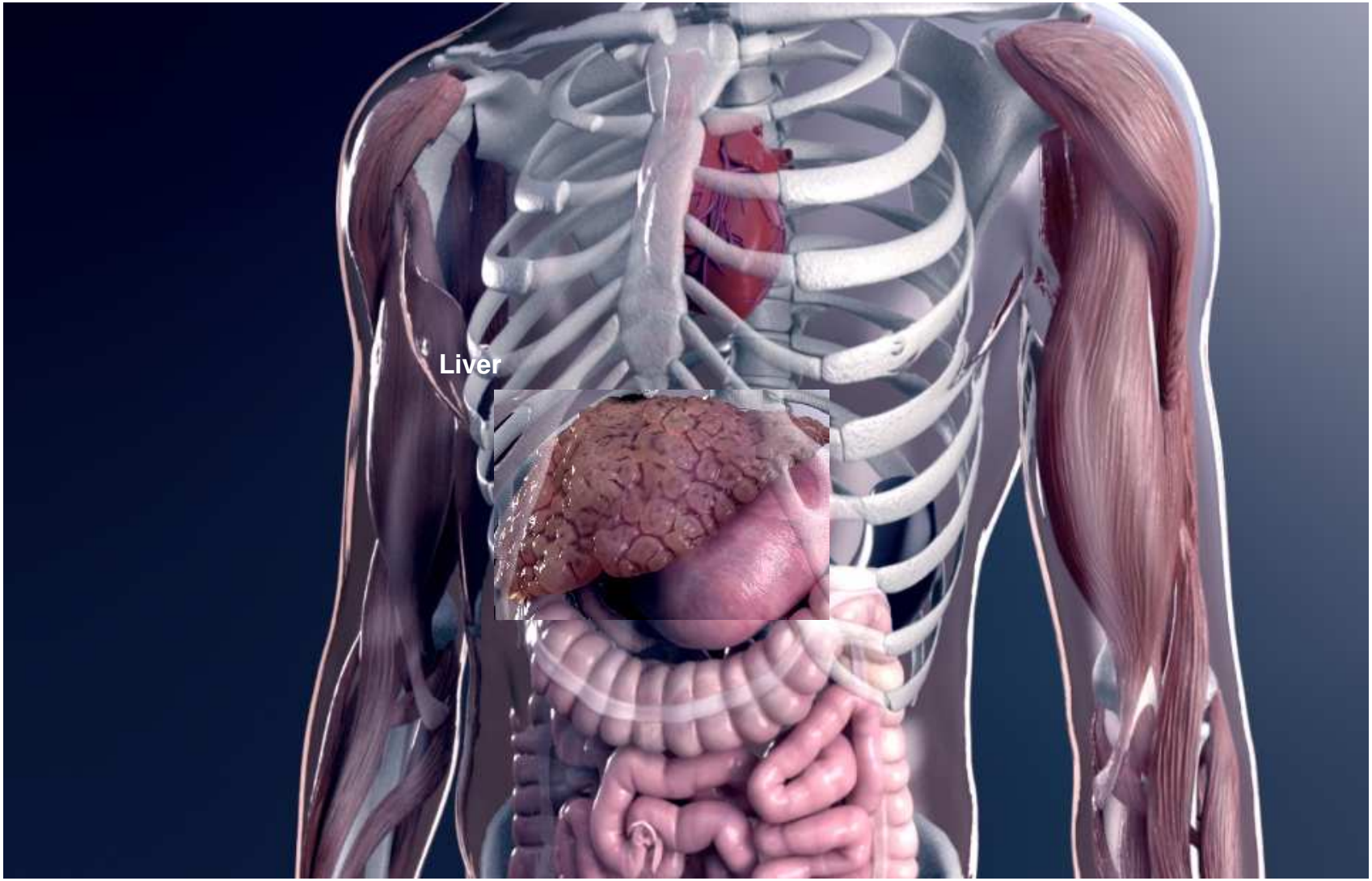
Impatto dell'infezione da HCV e ruolo dell'eradicazione in pazienti oncoematologici

Barbara Menzaghi

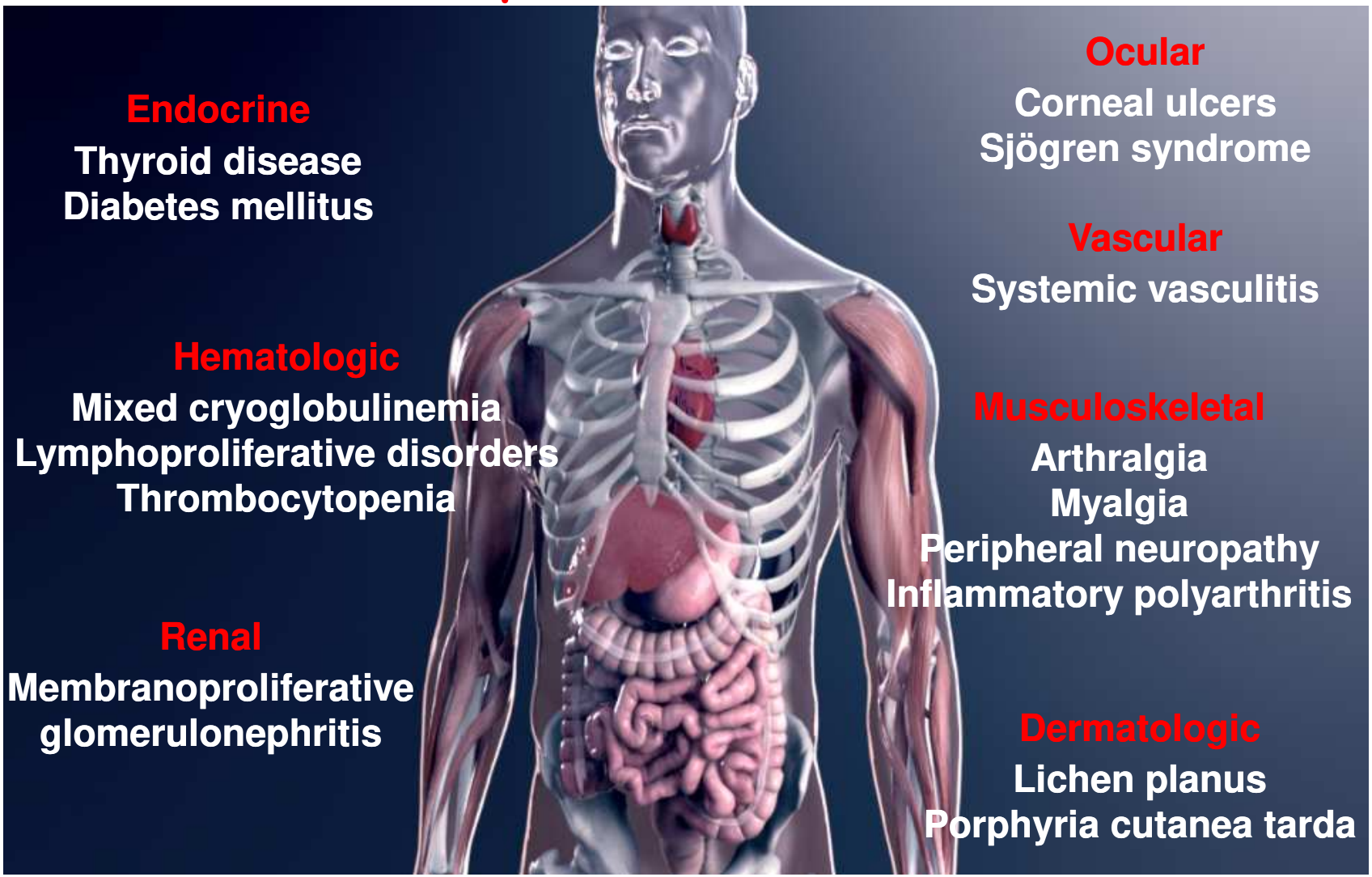
Hepatitis C

- Not only a liver disease
- What HCV "cure" means…..
- Treatment options

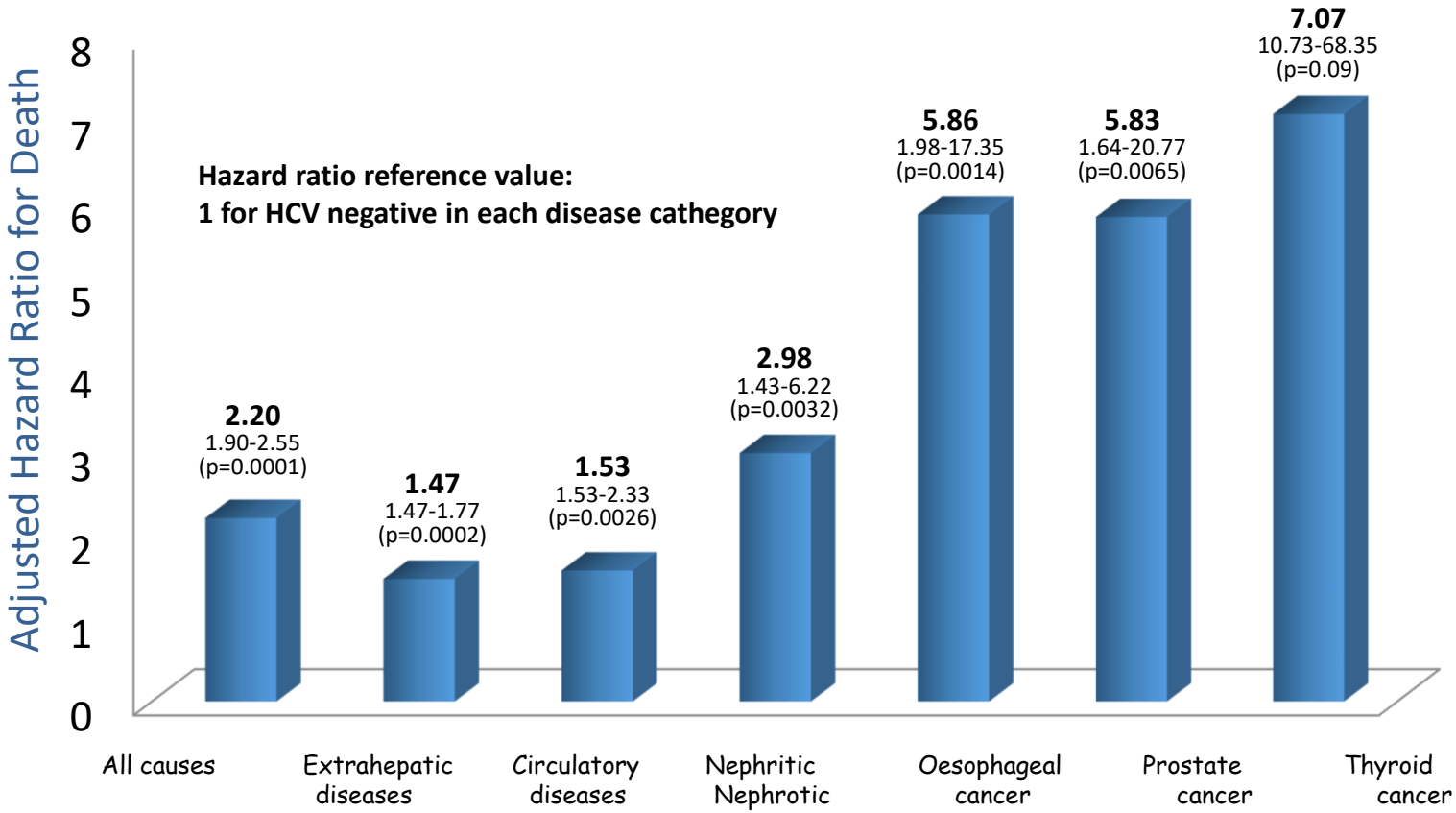
HCV and Liver Disease



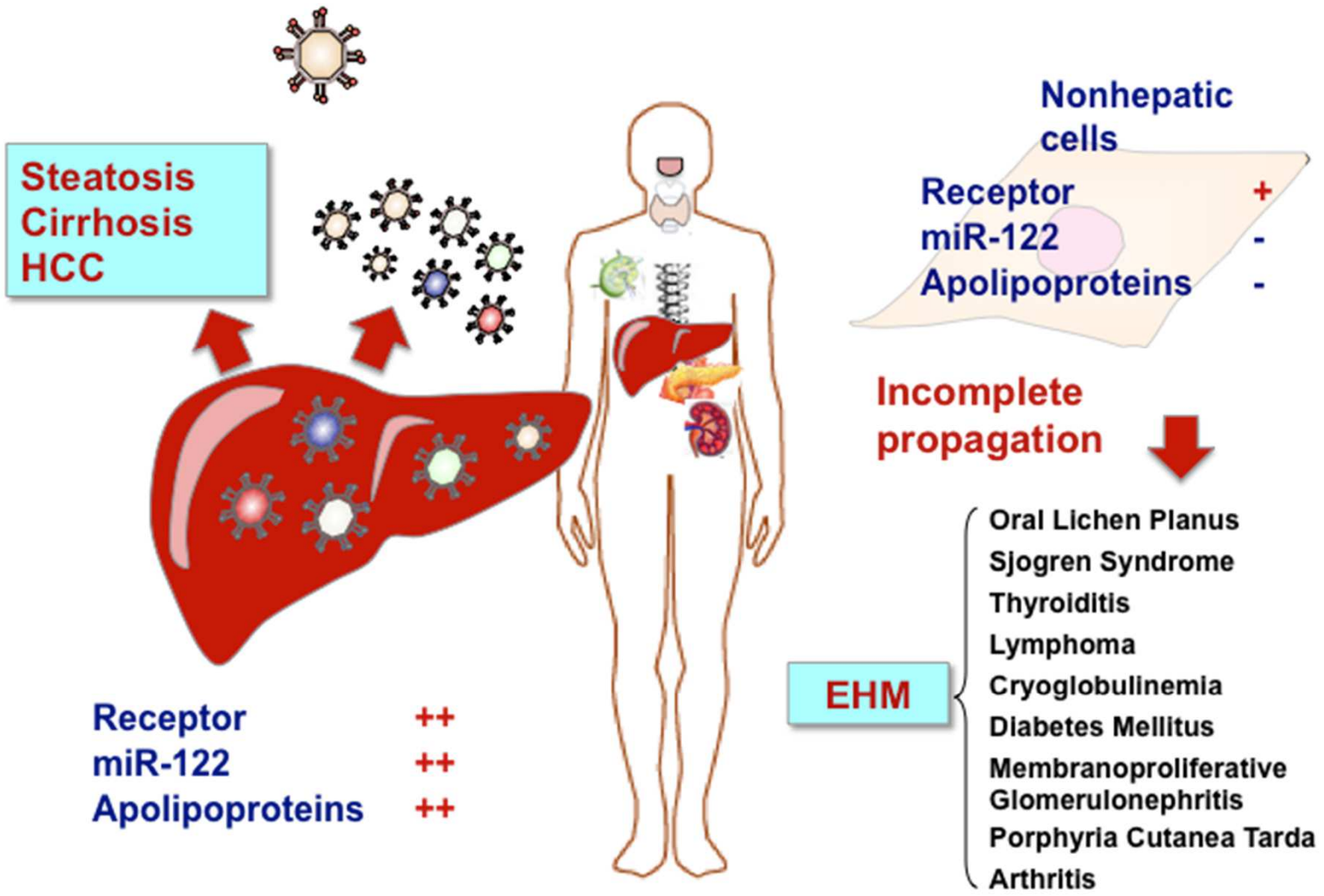
Chronic HCV Infection Also Causes Extrahepatic Manifestations



Is HCV more than a liver disease? Increased mortality "beyond" the liver The REVEAL cohort study

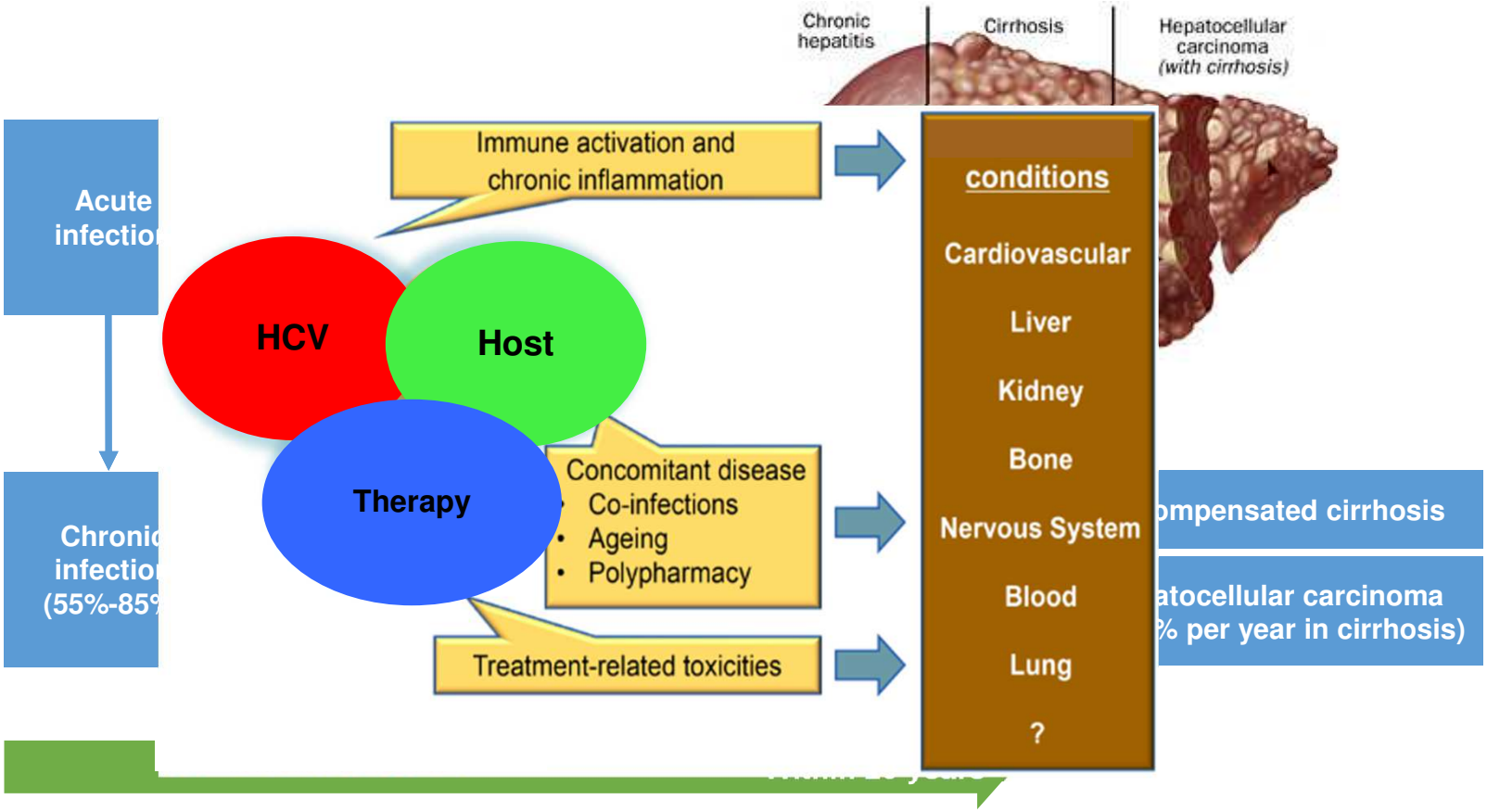


Lee et Al. J Infect Dis 2012; 206: 469-477

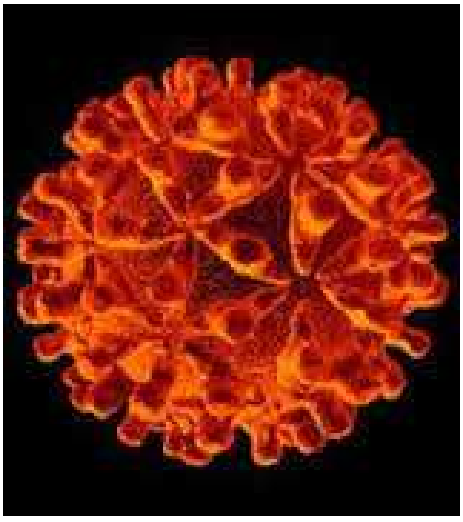


Matsuura Y, 2013; Kambara et al. JVI 2012; Fukuhara et al. JVI 2012

130–160 Million Chronic HCV Carriers Are at Risk of Developing Cirrhosis and/or HCC[1,2]



1. World Health Organization. Media Centre: Hepatitis C. April 2014. http://www.who.int/mediacentre/factsheets/fs164/en/. Accessed May 20, 2014.
2. World Health Organization. Guidelines for the screening, care and treatment of persons with hepatitis C infection. April 2014. 2002. http://www.who.int/hiv/pub/hepatitis/hepatitis-c-guidelines/en/. Accessed May 20, 2014.



Outline

- **Hematological manifestations** of HCV infection
- HCV and **iNHL**: pathogenetic role and anti-lymphoma effect of antiviral therapy
- HCV and **Diffuse Large B-Cell lymphoma**: peculiar features, increased hepatotoxicity of conventional immunochemotherapy, role of AVT

Hematological manifestation of HCV infection

- Extra-hepatic manifestations of HCV infection:
- **Thrombocytopenia**
- **Anemia** (autoimmune hemolytic anemia, aplastic anemia, pure red cell aplasia, sideroblastic anemia; ribavirin→oxydative damage and extravascular hemolysis)
- **Neutropenia**
- **Cryoglobulinemia** (type II)
- Non Hodgkin Lymphomas

Khedia S et al, Int J Prev Med 2014

HCV and incidence of cancer

- **Cases:** 12,126 chronic HCV-infected persons in the Chronic Hepatitis Cohort Study (CHeCS) contributed 39,984 person-years of follow-up from 2006 to 2010
- **Controls:** 133,795,010 records from 13 Surveillance, Epidemiology and End Results Program (SEER) cancer registries

- The **incidence** of the following cancers was significantly **higher** among patients with chronic **HCV** infection:

- liver (SRR, 48.6 [95% CI, 44.4–52.7])
- pancreas (2.5 [1.7–3.2])
- rectum (2.1 [1.3–2.8])
- kidney (1.7 [1.1–2.2])
- **non-Hodgkin lymphoma (NHL) (1.6** [1.2–2.1])
- lung (1.6 [1.3–1.9])

Allison RD et al, Journal of Hepatology 2015

Manifestazioni extraepatiche di HCV

Mediterr J Hematol Infect Dis. 2010 Mar 31;2(1):e2010004. doi: 10.4084/MJHID.2010.004.

Hepatitis C virus infection and lymphoma.

Bachy E[1], Besson C, Suarez F, Hermine O.

- L'associazione tra HCV e disturbi linfoproliferativi (LPDs) è stata recentemente ipotizzata sulla base di dati epidemiologici, studi biologici e osservazioni cliniche

- Anche se vari sottotipi di linfomi sembrano essere associati ad HCV, il Linfoma diffuso a grandi cellule B, il piccolo Linfoma linfocitico / leucemia linfatica cronica e il Llinfoma della zona marginale sembrano essere particolarmente rappresentati tra i pazienti HCV-positivi.

- Il ruolo causale di HCV in questi disordini è stata ulteriormente sostenuto dalla risposta alla terapia antivirale.

- Sebbene sia stato dimostrato che HCV possa infettare direttamente cellule mononucleari del sangue periferico, sia in vitro e, in alcuni casi, in vivo, una forte evidenza supporta anche l'ipotesi di un meccanismo di trasformazione indiretta attraverso una stimolazione antigenica sostenuta che conduce da anticorpi oligoclonali a espansione monoclonale, e a volte al linfoma, probabilmente attraverso eventi oncogenici secondari.

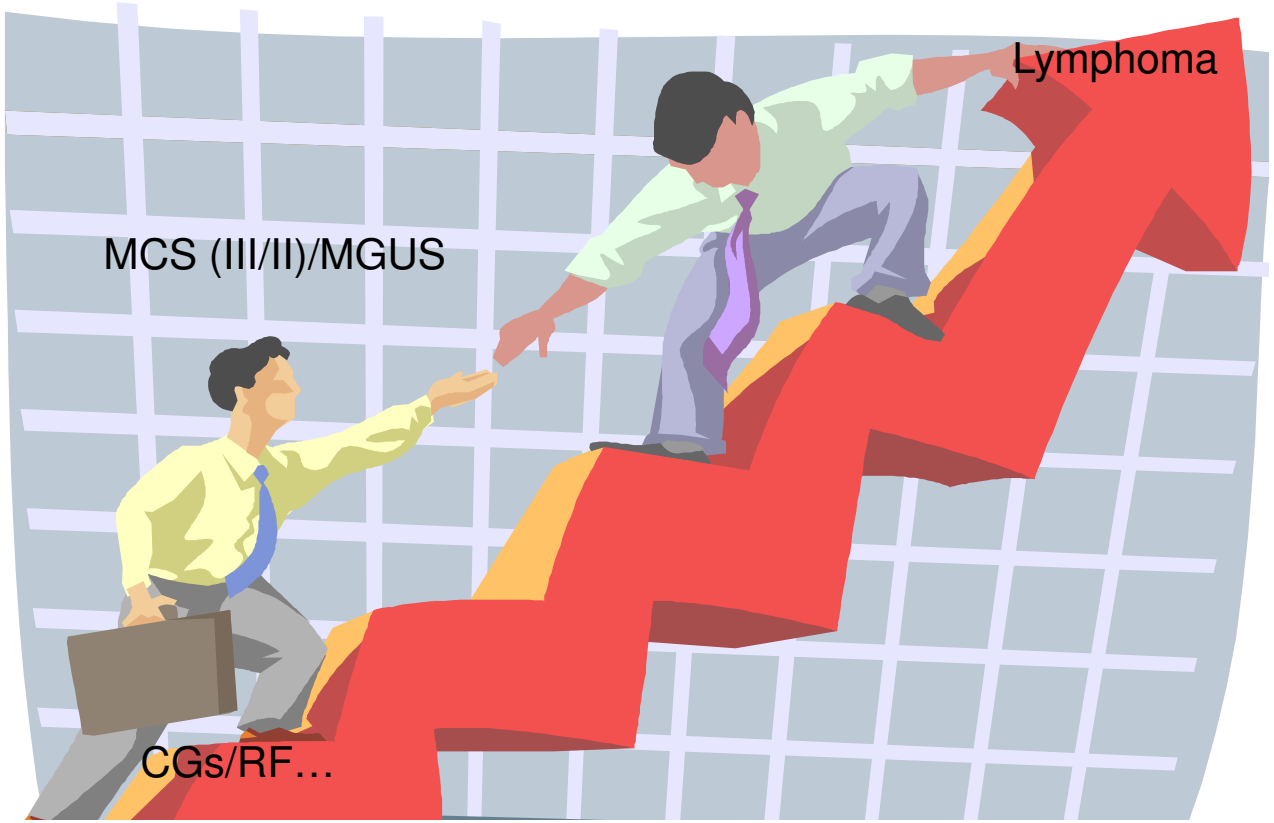
- Vi è una crescente evidenza che il virus dell'epatite C è associato Linfoma non-Hodgkin a cellule B

HCV and LPDs:
factors influencing the risk of progression

1. Genetically determined modulation of
-immune response to HCV antigens
-autoreactivity triggered by HCV

2. Viral factors

3. Environmental factors



World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.3748/wjg.v19.i44.7889

World J Gastroenterol 2013 November 28; 19(44): 7889-7895
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

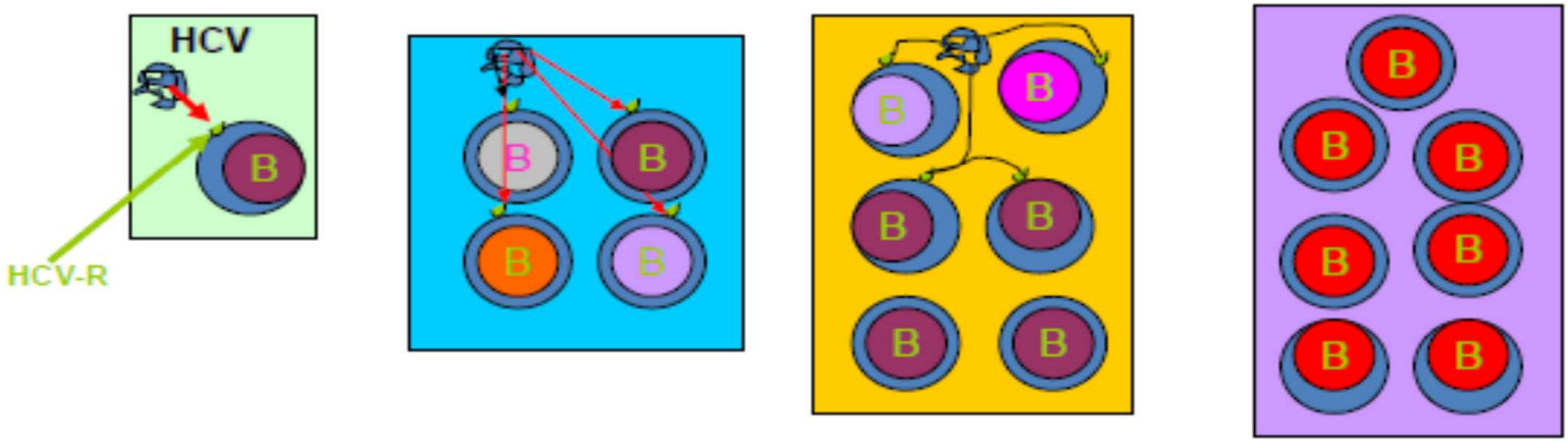
WJG 20th Anniversary Special Issues (2): Hepatitis C virus

Direct effects of hepatitis C virus on the lymphoid cells

The replication of HCV in the extrahepatic organs and, especially, lymphoid cells, might affect the pathogenesis of extrahepatic diseases with HCV infection. HCV persistent infection can cause malignant lymphoma.

Manifestazioni extraepatiche di HCV

Malattie linfoproliferative : MLDUS - LNH



Cellula B Attivata da HCV

Espansione Policlonale

Autoantic. ANA-SMA

Crioglobul.III°

Espansione Oligoclonale

MLDUS

Autoaanticorpi Monoclonali: FR

Crioglobilinemia II°

Riarr. BCl-2

Espansione Monoclonale

LinfomaNon HG

Traslocazione t (14-18)

E 2+CD81(CD19-CD21) > Ricomb.V(D)J

Manifestazioni extraepatiche di HCV

MD Anderson Cancer Center

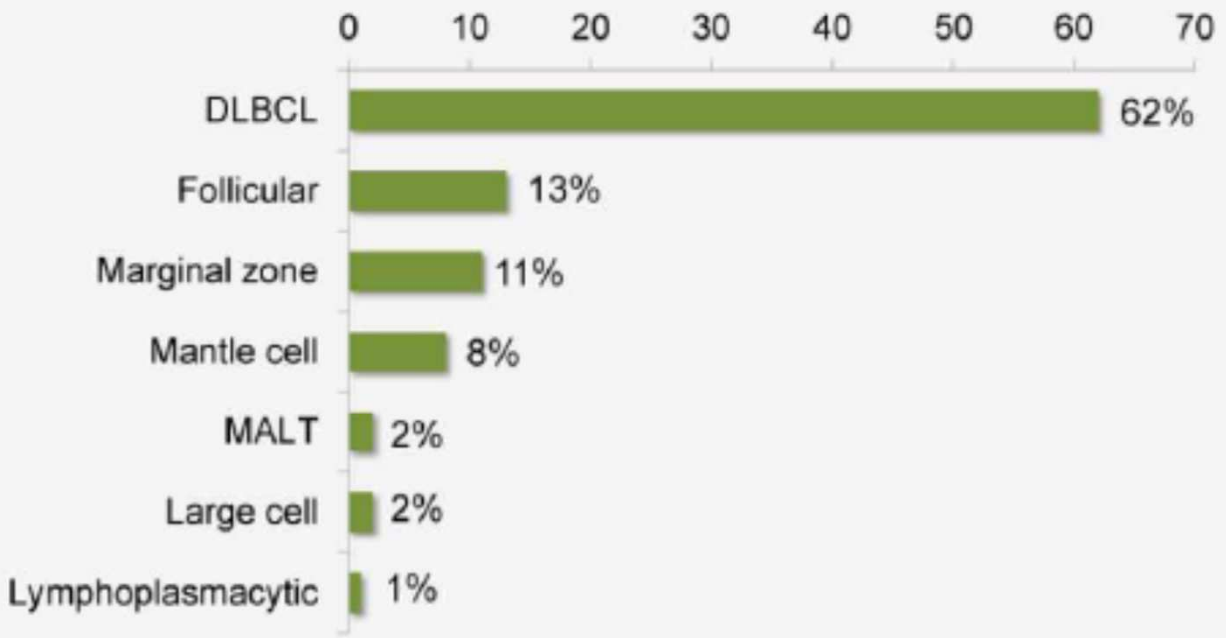
Poster # 1499

Most patients with hepatitis C virus (HCV)-associated lymphoma present with mild liver disease at cancer diagnosis: A call to revise indications for HCV treatment

Harrys A. Torres, MD, FACP; Parag Mahale, MBBS, MPH

Department of Infectious Diseases, Infection Control & Employee Health, The University of Texas MD Anderson Cancer Center

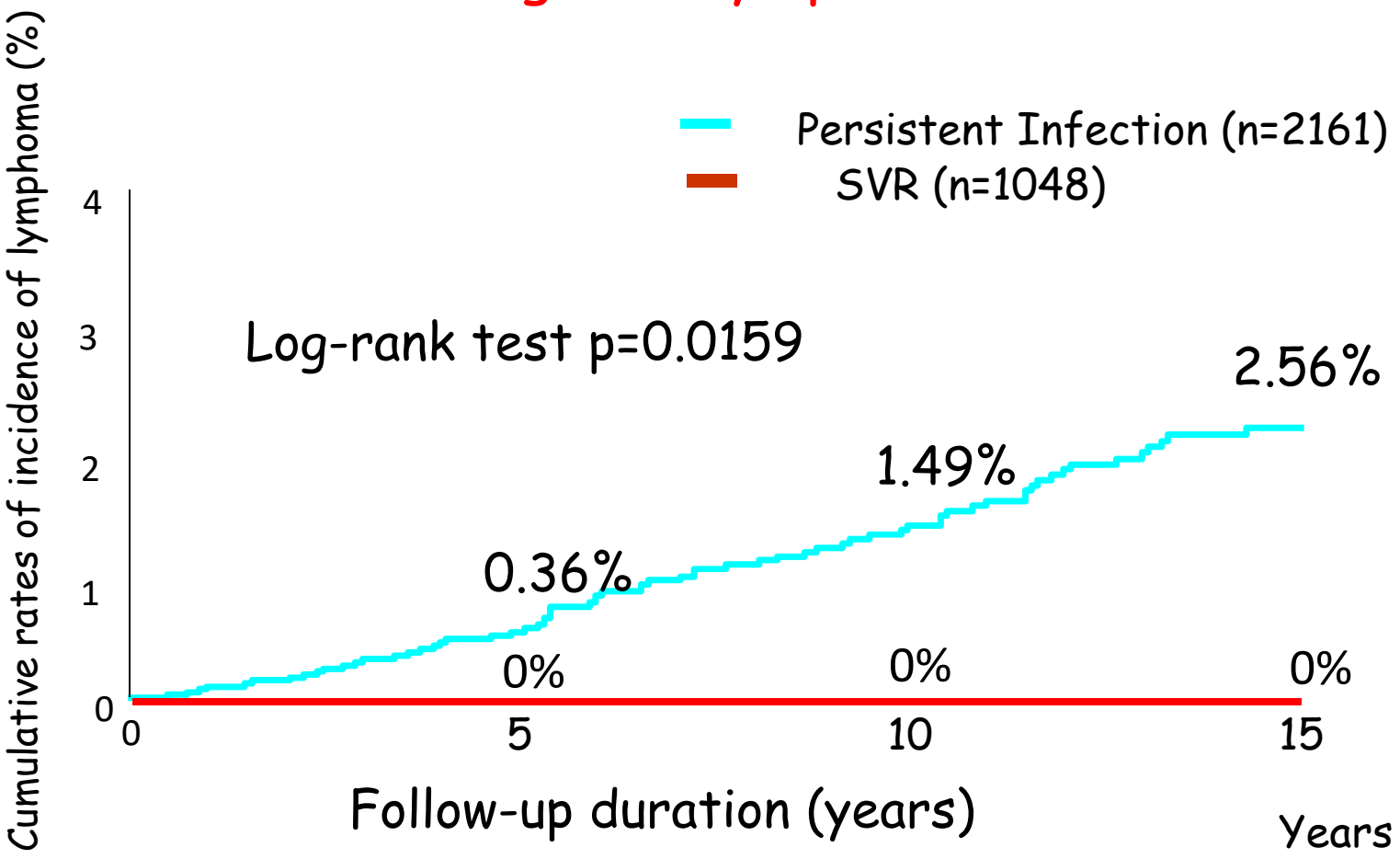
Figure 1: Types of HCV-associated B-cell NHL



DLBCL: Diffuse large B cell lymphoma, MALT: Mucosa associated lymphoid tissue

AASLD 2014

HCV Elimination Reduces The Incidence of Malignant Lymphoma

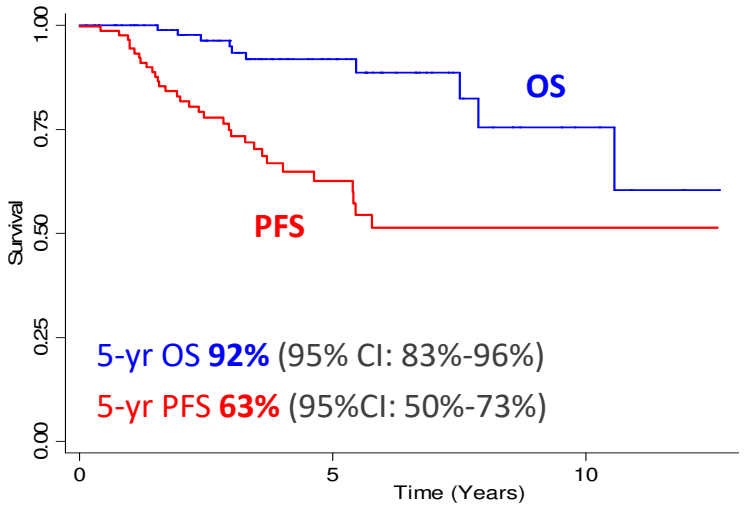


Kawamura Y, et al. Am J Med 2007;120:1034-1041

IFN-based AT in 1st line iNHL therapy: FIL study

Arcaini L et al, Ann Onc 2014

- **100 pts (retrospective)**
- 33 pts IFNα; 67 peg-IFNα (±RBV)
- 52 pts gen 2; 37 gen 1
- 60 pts MZL, 7 LPL, 27 iNHL nos
- **CR: 44%, PR 33% (ORR 77%)**
- Similar response in MZL and non-MZL (82% vs 70%, p=0.3)
- Median DOR : 33 m



- **SVR** (clearance HCV-RNA): **80 pts (80%)**
- **Hematologic response: directly related to SVR (p=0.003)**

AT in HCV+ iNHL: impact on survival

Arcaini L et al, Ann Onc 2014

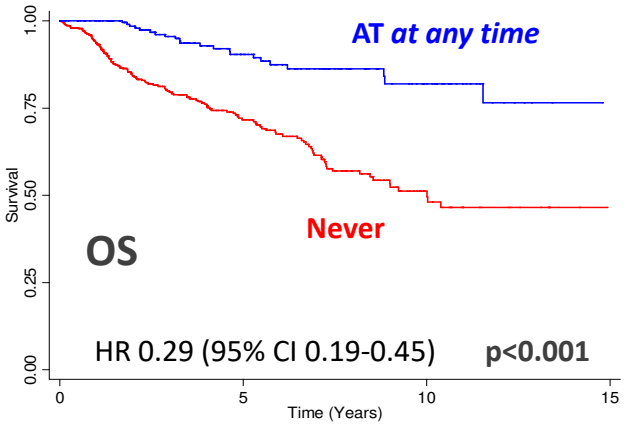
Antiviral therapy "*at any time*" (1st or ≥2nd line)

→ independent favourable prognostic impact on survival (OS)

Multivariate analysis for OS

	HR	95% CI	p
Age >60 yrs	3.89	1.71 – 8.85	0.001
Cirrhosis	2.81	1.24 – 6.35	0.013
Albumin <3.5 g/dl	3.16	1.64 – 6.09	0.001
Cryoglobulinemia	0.36	0.15 – 0.88	0.024
AT at any time	**0.21**	**0.06 – 0.73**	**0.014**

(704 consecutive pts with iNHL)



JOURNAL OF VIRAL HEPATITIS
JVH

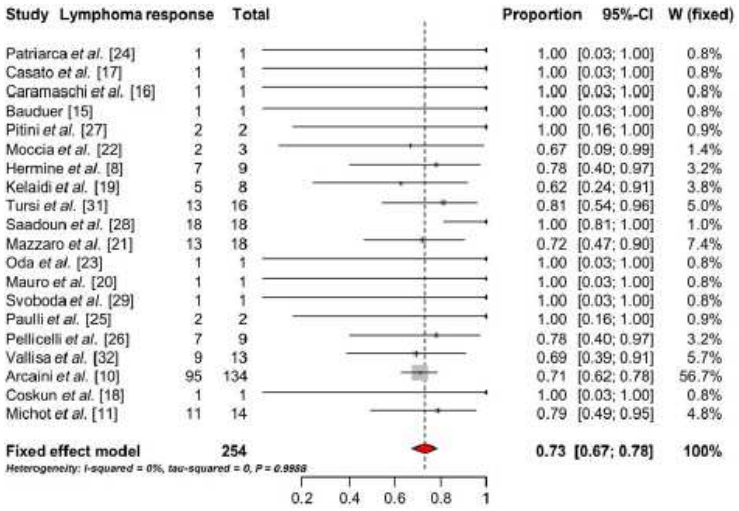
Journal of Viral Hepatitis, 2016 doi:10.1111/jvh.12518

The anti-lymphoma activity of antiviral therapy in HCV-associated B-cell non-Hodgkin lymphomas: a meta-analysis

J. Peveling-Oberhag,[1] L. Arcaini,[2,3] K. Bankov,[1] S. Zeuzem[1] and E. Herrmann[4] [1]*Department of Internal Medicine 1, Goethe-University Hospital, Frankfurt, Germany;* [2]*Department of Hematology Oncology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy;* [3]*Department of Molecular Medicine, University of Pavia, Pavia, Italy; and* [4]*Institute for Biostatistics and Mathematical Modelling, Goethe-University, Frankfurt, Germany*

20 trials
254 NHL pts
AVT: (peg)IFN+/-RIB
ORR to AVT: 73%
Predictors of response:
SVR, MZ histotype

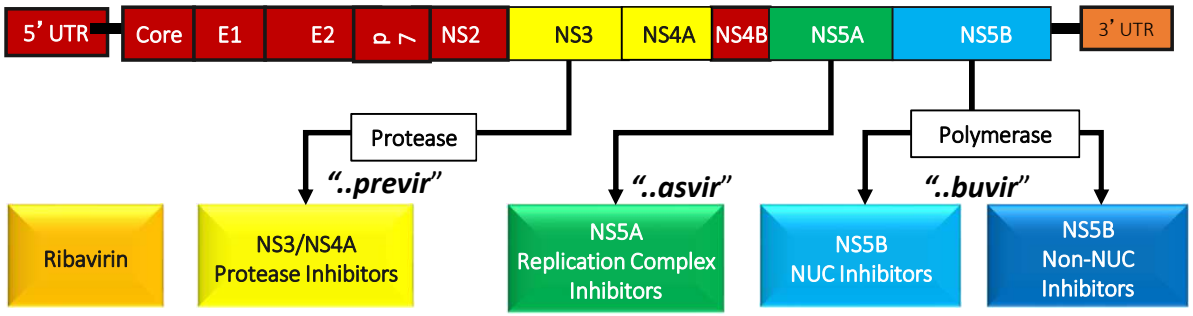
ORR



Registro Lombardo Linfomi HCV positivi

	All (n=250)	DLBCL (n=111)	MZL (n=69)	Other* (n=70)
Sex (M/F)	96/154 (38%/62%)	48/63 (43%/57%)	19/50 (28%/72%)	29/41 (41%/59%)
Age > 60 years	188 (76%)	86 (80%)	51 (74%)	51 (73%)
AST > UNL	93 (41%)	45 (45%)	26 (40%)	22 (36%)
ALT > UNL	118 (49%)	53 (48%)	30 (45%)	35 (53%)
Bilirubin > UNL	32 (18%)	19 (21%)	7 (16%)	6 (13%)
Albumin < 3.5 g/dl	37 (16%)	27 (26%)	4 (6%)	6 (10%)
Cirrhosis	38 (15.5%)	27 (24.8%)	5 (7.3%)	6 (8.8%)
B symptoms	54 (21.6%)	37 (33.3%)	7 (10.1%)	10 (14.3%)
ECOG PS > 1	39 (16%)	30 (28%)	4 (6%)	5 (7%)
Hemoglobin < 12 g/dl	65 (26.5%)	37 (34.3%)	18 (26.1%)	10 (14.7%)
Platelets < 100 x 10^9/L	23 (9.4%)	10 (9.4%)	6 (8.7%)	7 (10.3%)
LDH > UNL	78 (32.6%)	52 (48.6%)	13 (19.4%)	13 (20.0%)
Monoclonal component	73 (30.5%)	21 (20.0%)	33 (48.5%)	19 (28.8%)
Autoimmune manifestation	30 (13.1%)	1 (1.0%)	20 (29.4%)	9 (14.1%)
Cryoglobulin	42 (17.0%)	9 (8.2%)	16 (23.5%)	17 (24.6%)

The revolution of HCV antiviral therapy: DAAs *(Direct-acting Antiviral Agents)*



*Representative list; may not be fully inclusive

EASL: Indications for treatment: who should be treated?

All treatment-naïve and treatment-experienced patients with compensated or decompensated chronic liver disease due to HCV should be considered for therapy (recommendation A1)

METAVIR F3–F4	METAVIR F2	METAVIR F0–F1	Decompensated cirrhosis
Prioritise treatment	Treatment is **justified**	**Individualise** treatment	**Urgently treated** IFN-free therapy
A1	A2	B1	A1

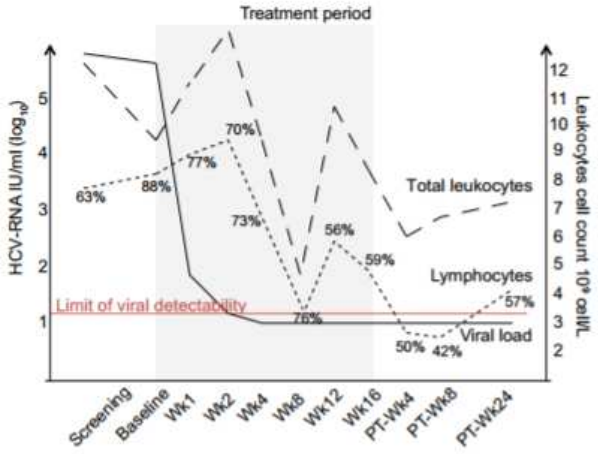
Categorie di pazienti affetti da epatite C cronica ammesse alla rimborsabilità in Italia

1) Pazienti con cirrosi in classe di Child A o B e/o con epatocarcinoma con risposta completa a terapie resettive chirurgiche o loco-regionali non candidabili a trapianto epatico nei quali la malattia epatica sia determinante per la prognosi
2) Recidiva di epatite dopo trapianto di fegato con fibrosi METAVIR[1] ≥2 (o corrispondente Ishack) o fibrosante colestatica
3) Epatite cronica con gravi manifestazioni extra-epatiche HCV-correlate (sindrome crioglobulinemica con danno d'organo, sindromi linfoproliferative a cellule B)
4) Epatite cronica con fibrosi METAVIR ≥3 (o corrispondente Ishack)
5) In lista per trapianto di fegato con cirrosi MELD <25 e/o con HCC all'interno dei criteri di Milano con la possibilità di una attesa in lista di almeno 2 mesi
6) Epatite cronica dopo trapianto di organo solido (non fegato) o di midollo con fibrosi METAVIR ≥2 (o corrispondente Ishack).
7) Pazienti con epatite cronica con fibrosi METAVIR F0-F2 (o corrispondente Ishak)

IFN-free antiviral therapy in HCV+ NHL
1st case report (SMZL)

Rossotti R et al, J Hepat 2014

- 42 y, M
- HCV genotype 1b, F0
- SMZL, spleen (17.5 cm), lymphocytosis (5.65 x 10^9/l)
- *IFN-free regimen:* **FDV** + **DLV** + **RBV** (16 w)
- SVR (4w)
- **Hematologic response** (spleen, lymphocytes) → related to SVR



FDV: *Faldaprevir*, NS3/NS4A inhibitor
DLV: *Deleobuvir,* non-nucleoside NS5B inhibitor
RBV: *Ribavirina*

IFN-free antiviral therapy in HCV+ NHL

ACG CASE REPORTS JOURNAL

CASE REPORT | LIVER

Lymphoma Remission by Interferon-Free HCV Eradication Without Chemotherapy

Lucy Y. Lim, MBBS[1], Danie La, RN, BScN[1], Christine M. Cserti-Gazdewich, MD[2], and Hemant Shah, MD, MScCH HPTE[1]

2 MZL: DAAs
1 MZL: DAAs+4xRituximab
2 DLBCL: CHT followed by DAAs

To the editor:

Regression of an HCV-associated disseminated marginal zone lymphoma under IFN-free antiviral treatment

Hepatitis C virus (HCV) is prevalent in B-cell–associated lymphomas, including marginal zone and diffuse large B-cell lymphomas.[1] A stepwise model of lymphomagenesis induced by chronic antigenic stimulation and/or a direct pro-oncogenic effect of intracellular HCV proteins is a possible mechanism.[2] Interferon-based HCV treatment may induce remission and improve prognosis of HCV-associated lymphomas.[3] Whether these effects are due to HCV clearance or to an antiproliferative effect of interferon remains unknown. We describe a patient with a complete hematologic response of an HCV-associated disseminated marginal zone lymphoma (MZL) to an interferon-free anti-HCV treatment.

1 EN MZL
Sofosbuvir+Ribavirin

Liver INTERNATIONAL

Liver International ISSN 1478-3223

RAPID COMMUNICATION

HCV-associated B-cell non-Hodgkin lymphomas and new direct antiviral agents

Paul Carrier[1,2], Arnaud Jaccard[3], Jérémie Jacques[1], Tessa Tabouret[1], Marilyne Debette-Gratien[1,2], Julie Abraham[3], Laura Mesturoux[4], Pierre Marquet[2,5], Sophie Alain[2,6], Denis Sautereau[1], Marie Essig[2,7] and Véronique Loustaud-Ratti[1,2]

1 SMZL
Sofosbuvir+Ribavirin

Regular Article

blood

LYMPHOID NEOPLASIA

Interferon-free antiviral treatment in B-cell lymphoproliferative disorders associated with hepatitis C virus infection

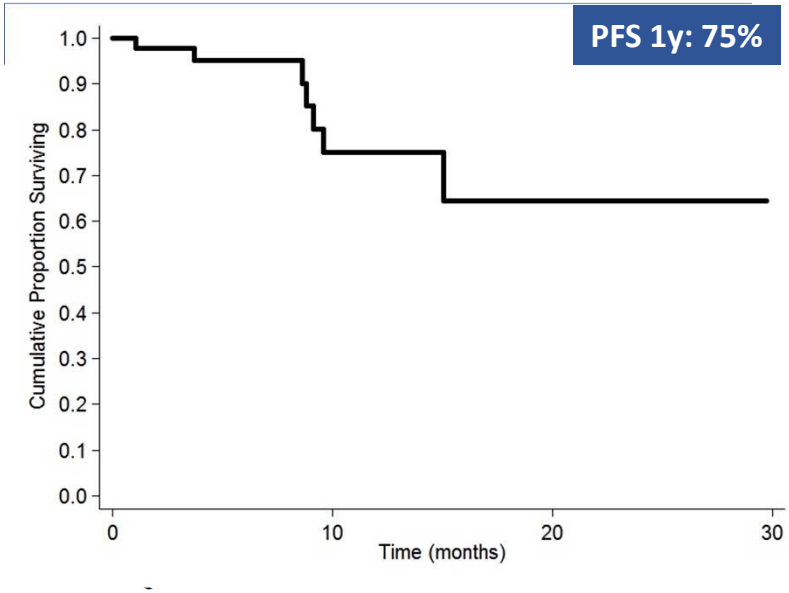
Luca Arcaini,[1,2,*] Caroline Besson,[3,*] Marco Frigeni,[1] Helene Fontaine,[4] Maria Goldaniga,[5] Milvia Casato,[6] Marcella Visentini,[6] Harrys A. Torres,[7] Veronique Loustaud-Ratti,[8] Jan Peveling-Oberhag,[9] Paolo Fabris,[10] Roberto Rossotti,[11] Francesco Zaja,[12] Luigi Rigacci,[13] Sara Rattotti,[2] Raffaele Bruno,[14,15] Michele Merli,[16] Céline Dorival,[17] Laurent Alric,[18] Arnaud Jaccard,[8] Stanislas Pol,[4] Fabrice Carrat,[17,19] Virginia Valeria Ferretti,[1] Carlo Visco,[20,†] and Olivier Hermine[21,22,†]

Blood, 2016

- **46 pts** with HCV-positive iNHL or CLL treated with DAA-based AT (IFN-free), retrospective
- 8 Italian centres (FIL), 8 French (ANRS), 1 US, 1 German
- 1^{ary} Endpoint: **ORR**
- 2^{ary} Endpoints: CR, PFS, OS

DAA-based AT in HCV+ iNHL

Arcaini L et al, Blood, 2016



Baseline pts characteristics		
HCV genotype		
1	29	63
2	12	26
3	3	7
4	2	4
Cirrhosis	7	15
Previous chemotherapy	10	22
Previous IFN-based antiviral treatment	12	26
DAAs		
Sofosbuvir-based regimen**	39	85
Other regimen***	7	15

**Sofosbuvir combined with simeprevir (n=13), ribavirin (n=15), daclatasvir (n=8), or ledipasvir (n=3)

***Paritepravir/ritonavir/ombitasvir with or without dasabuvir with or without ribavirin (n=6) or faldaprevir/deleobuvir/ribavirin (n=1)

SVR: 45/46 (98%) ORR 67%, CR 26%, PR 41%; ORR in MZL 73% No response in CLL
Significant better lymphoma response: serum MC
Trend for better lymphoma response: extranodal disease

Antiviral therapy in HCV+ iNHL: guidelines

ESMO Consensus guidelines marginal zone lymphoma

Dreyling et al, Ann Onc 2013

1.11 ***Consensus statement***

In patients with NMZL or SMZL and concurrent HCV-related chronic hepatitis who do not need immediately conventional treatment of lymphoma, antiviral treatment with pegylated interferon and ribavirin should be considered as first treatment

NCCN National Comprehensive Cancer Network® 2016

"the panel recommends initial antiviral therapy in asymptomatic patients with low-grade HCV-positive indolent B-cell NHL"

Antiviral therapy (AVT):

standard 1st line treatment in asymptomatic patients with iNHL HCV+ (who do not need immediately conventional treatment of lymphoma)

HCV positive DLBCL

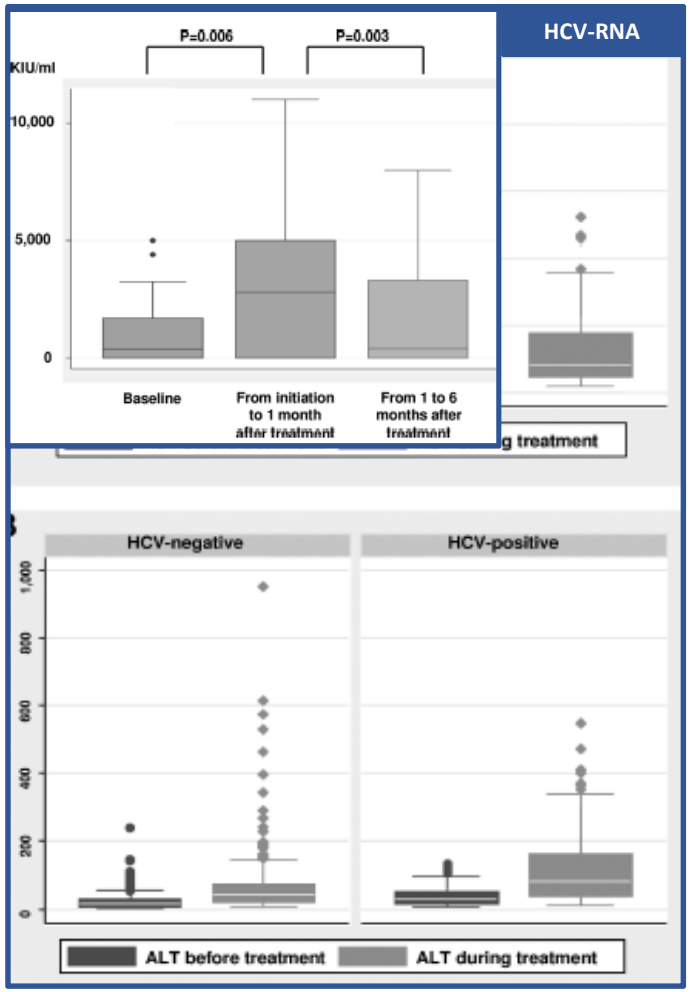
- 15% DLBCL pts are HCV infected
- Transformation from low-grade NHL, spleen involvement, high LDH: more common in HCV+ve pts
- Poorer OS: OS@2ys 56% in HCV+ve vs 80% in HCV-ve
- Greater hepatotoxicity in HCV+ve cohort
- Addition of Rituximab does not influence short-term hepatotoxicity occurence, but cases of HCV reactivation have been described

Besson C et al, JCO 2006
Visco C et al, Ann Oncol 2006
Hsieh CY et al, JCO 2008

DLBCL treated with R-CHOP

Ennishi D et al, Blood 2010

	HCV-positive (n = 131), n (%)	HCV-negative (n = 422), n (%)	*P*
Median age, y (range)	70.4 (42-86)	64.3 (20-92)	< .001
Sex, male/female	79/52	228/194	.21
LDH > normal	81 (62)	196 (46)	.002
PS > 1	16 (12)	40 (9)	.47
Stage			.48
I	28 (21)	92 (22)	
II	39 (30)	130 (31)	
III	20 (15)	84 (20)	
IV	44 (34)	116 (27)	
Extranodal sites > 1	36 (27)	75 (18)	.02
IPI: H/I, H	53 (40)	139 (33)	.01
BM involvement	12 (9)	38 (9)	.96
Spleen involvement	24 (18)	35 (8)	.001
Liver involvement	12 (9)	25 (6)	.20
t-DLBCL	5 (4)	11 (3)	.82
FL	3	5	
MZBCL	2	6	
HBsAb-positive	7/59 (12)	13/135 (10)	.24
HBcAb-positive	11/22 (50)	9/57 (16)	.03
Treatment			.12
RCHOP	96 (73)	339 (80)	
RTHPCOP	31 (24)	71 (17)	
RCEOP	4 (3)	12 (3)	
Baseline transaminase			.48
Grade 0-1	122 (93)	415 (98)	
Grade 2	7 (5)	3 (1)	
Grade 3	2 (2)	4 (1)	
Outcome of patients			
Died of lymphoma	14 (11)	45 (11)	.87
Died of hepatic failure	6 (5)	1 (0.2)	< .001
Died of other causes	4 (3)	7 (2)	.76
Hepatic toxicity			
Grade 3-4	36 (27)	13 (3)	< .001



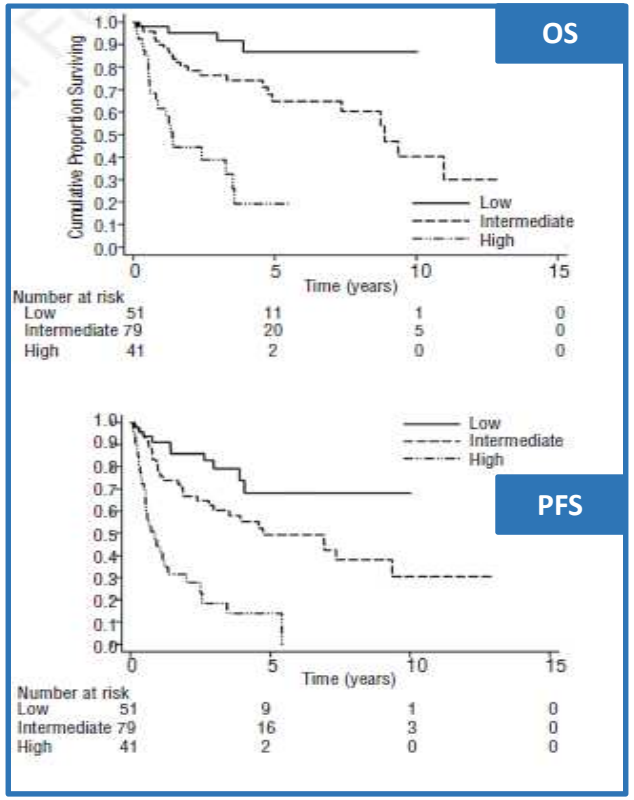
HCV positive DLBCL: a prognostic model

Table 1. Clinical characteristics of 535 patients with HCV-positive DLBCL treated with curative-intent therapy.

	N	%
Age>60	388	73
Males/females	262/273	49/51
Ann Arbor stage		
I-II	171	32
III-IV	363	68
BM involvement	102	21
Splenic involvement	171	35
Liver involvement	74	15
B symptoms	164	31
ECOG≥2	126	24
Extranodal sites ≥2	163	35
LDH elevated	279	55
IPI		
Low	107	24
Low-int	99	22
High-int	124	27
High	119	27
R-IPI		
Very good	26	5
Good	197	41
Poor	264	54

Table 5. Prognostic factors at Cox regression multivariate analysis in HCV-positive DLBCL (171 patients).

	OS			PFS		
	HR	95%CI	P	HR	95%CI	P
ECOG ≥2	4.05	2.20-7.48	<0.001	2.25	1.32-3.82	<0.001
Serum albumin <3.5 g/dL	2.42	1.31-4.48	0.005	2.72	1.64-4.53	<0.001
HCV-RNA >1000 KIU/mL	2.25	1.22-4.15	0.010	2.02	1.24-3.32	0.005

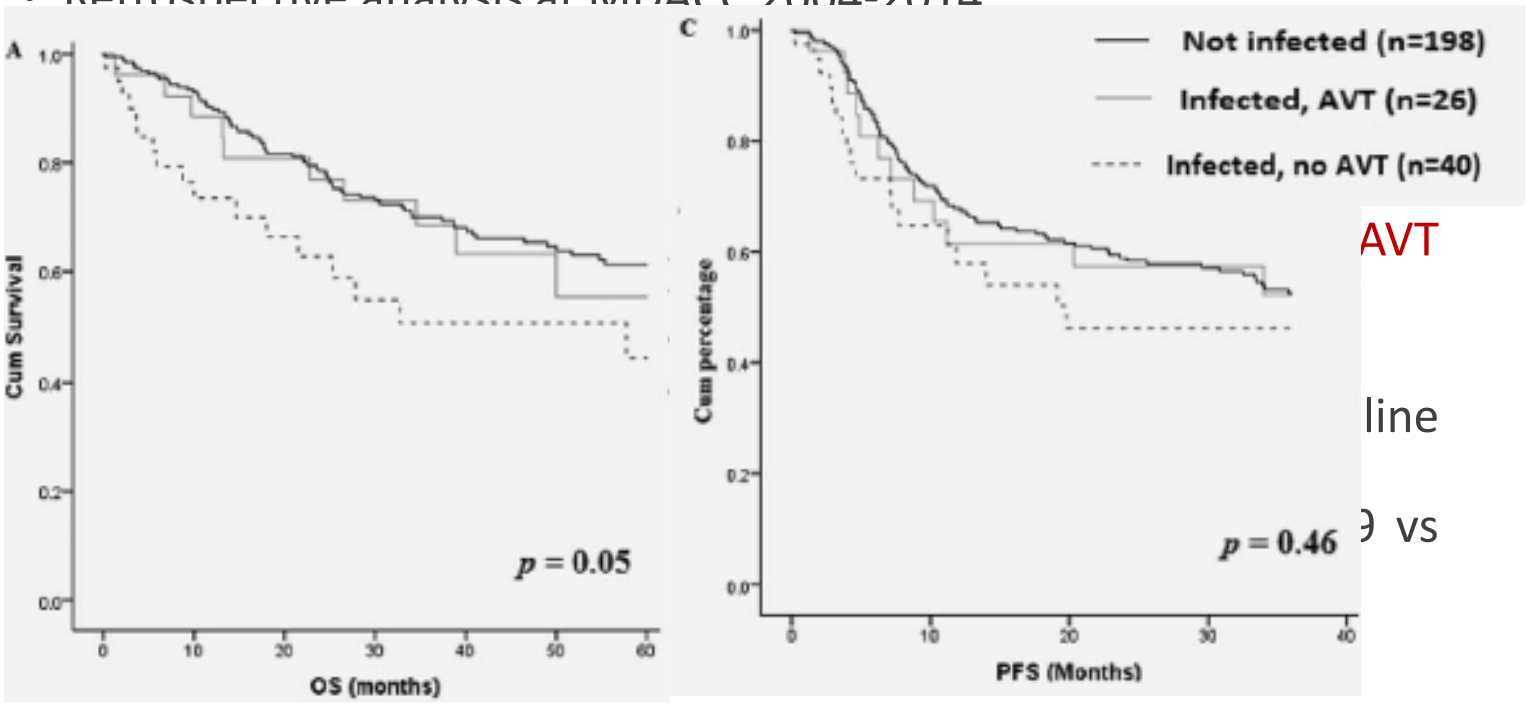


Merli M et al, Haematologica 2014

HCV positive DLBCL: role of AVT

Hosry J et al, International Journal of Cancer 2016

- Retrospective analysis at MDACC 2004-2014



AVT

line

vs

DAAs & chemotherapy

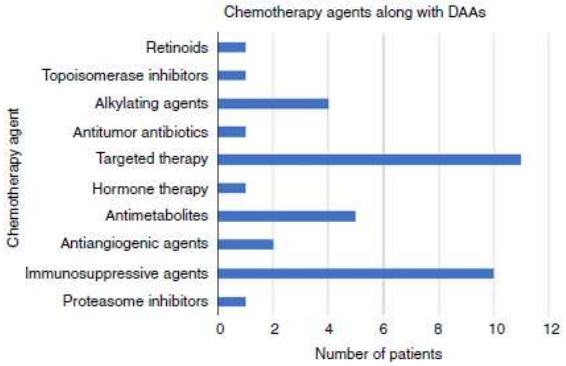
AP&T Alimentary Pharmacology and Therapeutics

Concomitant use of direct-acting antivirals and chemotherapy in hepatitis C virus-infected patients with cancer

M. P. Economides*, P. Mahale*, A. Kyvernitakis*, F. Turturo†, H. Kantarjian‡, A. Naing§, J. Hosry*, T. L. Shigle¶, A. K.

Total number of patients treated with DAAs and chemotherapy ($N = 21$)

Adverse event	N (%)
Total number of patients	21
Any adverse event	16 (76)
Type of adverse events	
Constitutional	12 (57)
Hematological	7 (33)
Gastrointestinal	7 (33)
Dermatological	6 (29)
Neurological	6 (29)
Psychiatric	4 (19)
Grade of adverse events*	
Grade 1	15 (71)
Grade 2	4 (19)
Grade 3	
Grade 4	
Grade 1 or 2	
Grade 3 or 4	



Type of direct-acting antiviral treatment	N (%)
Total	21
[illegible]irin*	11 (52)
	6 (29)
	3 (14)
	1 (5)

Conclusions

Hepatitis C virus-targeted antiviral therapy can be used concomitantly with selected anti-neoplastic agents under close monitoring for drug–drug interactions. This therapeutic intervention may prevent delays in the administration of chemotherapy in HCV-infected cancer patients.

Economides MP et al, AP&T 2016

Role of HCV in Hematology: Summary

- HCV infection can cause benign but difficult to manage hematological manifestations, being **thrombocytopenia** the most common

- Incidence of **cancer** other than HCC is increased in HCV-infected population, and **NHL** are between the most frequent extra-hepatic malignancies
- **AVT** can reduce the incidence of NHL in HCV+ve setting
- HCV has a **pathogenetic role in indolent NHL**, but multiple and complex mechanisms are still to be fully clarified

- **AVT**, both with IFN-based and IFN-free regimens, **can obtain iNHL regression**, and are considered **the gold standard for asymptomatic pts**

- **HCV+ve DLBCL** pts have higher risk disease and standard ICHT is burdened with hepatotoxicity resulting in inferior dose intensity
- **DAAs concomitant to standard chemotherapy** is under investigation


QUANDO PENSI DI AVERE TUTTE LE RISPOSTE, LA VITA TI CAMBIA TUTTE LE DOMANDE..

Grazie