Indolent Lymphoma Workshop

May 15-16, 2017

Bologna,
Royal Hotel Carlton

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Antiviral approaches

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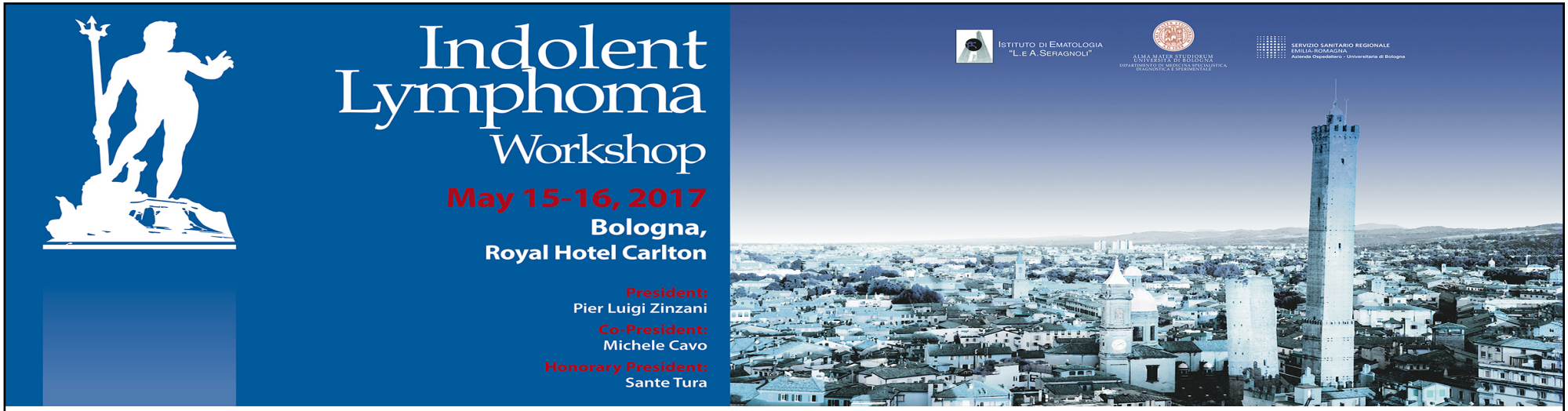


Disclosures of NAME SURNAME

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Celgene			x			x	
Roche			x			x	
Gilead	x					x	
Pfizer						x	
Sandoz						x	

Criterion for causality	Comment	Microbial agent and evidence for causality	
Bradford Hill		HIV	HCV
1. Biological plausibility	*In vitro*, molecular, or animal data	+	+
2. Analogy	Comparison with other disease models	+	+
3. Coherence	Lack of conflict with other information	+	+
4. Specificity	~1 : 1 correspondence of agent to disease	+	
5. Consistency	Repeated demonstration across studies	+	
6. Strength of association	Magnitude of relative risk	+	
7. Biological gradient	Dose–response relationship	+	
8. Temporality	Exposure precedes disease	+	+
9. Experimental evidence	Human experiment		
Fredericks and Relman		*Borrelia burgdorferi*	*Chlamydia psittaci*
1. Molecular detection in disease	Microbial sequences in host tissues	+	+
2. Localization	Microbe localized within tumour	+	+
3. Only low level detection in the absence of disease	Quantitative testing	+	+
4. Resolution/relapse	Detection parallels disease		+
5. Temporality	Detection precedes disease		
6. Coherence	Microbe characteristics consistent with disease	+	+
7. Reproducibility	Repeated demonstration across studies		

From Hjalgrim & Engels J Intern Med 2009

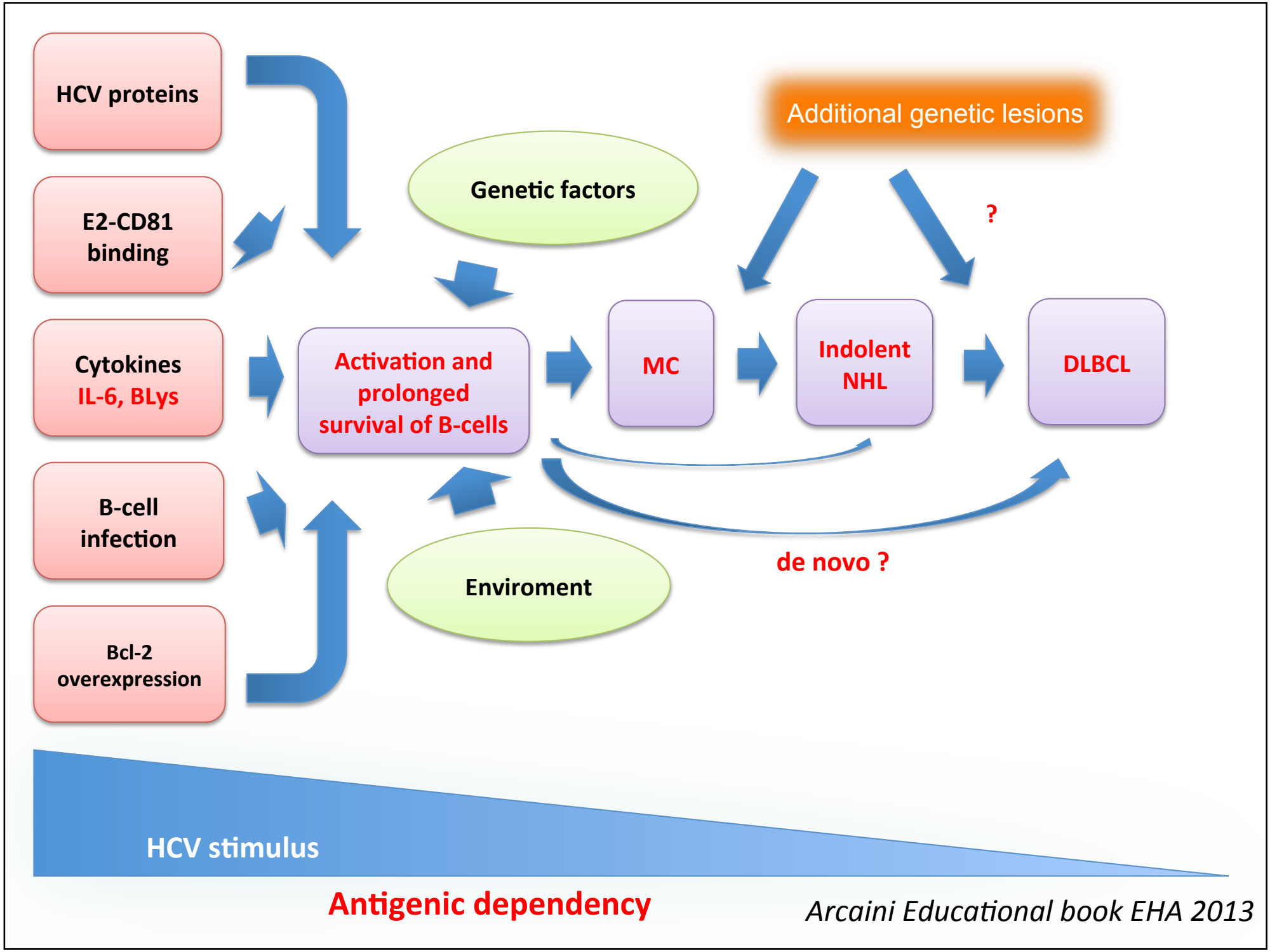
Bradford Hill Proc Royal Soc Med 1965
Fredericks Relman Clin Microbiol Rev 1996

IARC classification

Six human viruses classified as "carcinogenic to humans" (Group 1) based on sufficient evidence supporting their etiologic association with human cancer:

- EBV
- HBV
- HPV of several types
- HTLV-1
- **HCV** (HCC and **NHL**)
- HHV-8

WHO IARC Monograph Working Group. Lancet Oncol. 2009



Arcaini Educational book EHA 2013

META-ANALYSIS

- All cohort studies: RR 1.9
- All case-control studies: RR 2.5
- All studies: **RR 2.5**
- NHL attributable to HCV in countries with high prevalence: **10%**
- NHL attributable to HCV in countries with low prevalence: **<1%**

Dal Maso, Cancer Epidemiol Biomarkers Prev 2006

International Lymphoma Epidemiology Consortium (InterLymph)

- Pooled case-control study
- 4,784 NHL and 6,269 controls
- HCV infection in 172 cases of NHL (3.6%) and 169 (2.7%) controls
- HCV is associated with:

  Marginal zone lymphoma (OR, 2.47)

  Lymphoplasmocytoid lymphoma (OR 2.57)

  Diffuse large B cell lymphoma (OR 2.24)

de Sanjose et al, Clin Gastroenterol Hepatol. 2008

Registry of HCV-associated lymphomas

- Since January 2008, 250 consecutive pts with lymphoma and HCV infection diagnosed in the participating centres
- Median age at dg 68 yrs (range 32-90)
- **DLBCL** 44%
- **MZL** 28%
- **Low-grade NHL NOS** 11%

Manuscript in preparation

CLINICAL FEATURES

- Extranodal lymphoma: 63%
- Detection of HCV+ before NHL in 67%
- At dg of lymphoma, HCV-RNA+ 90%
- Cryoglobulinemia and serum monoclonal component associated with indolent histotypes (p=0.002)

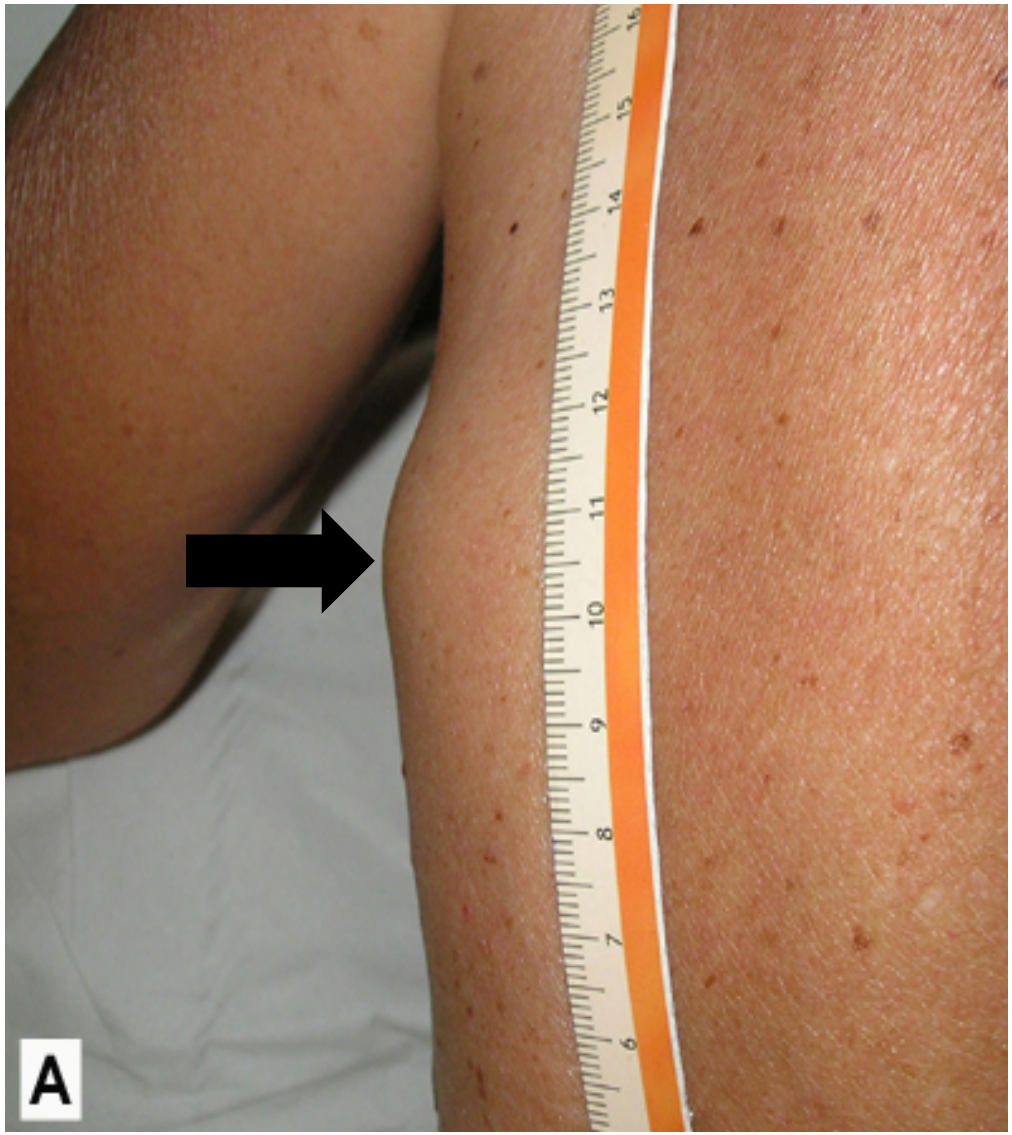
Manuscript in preparation

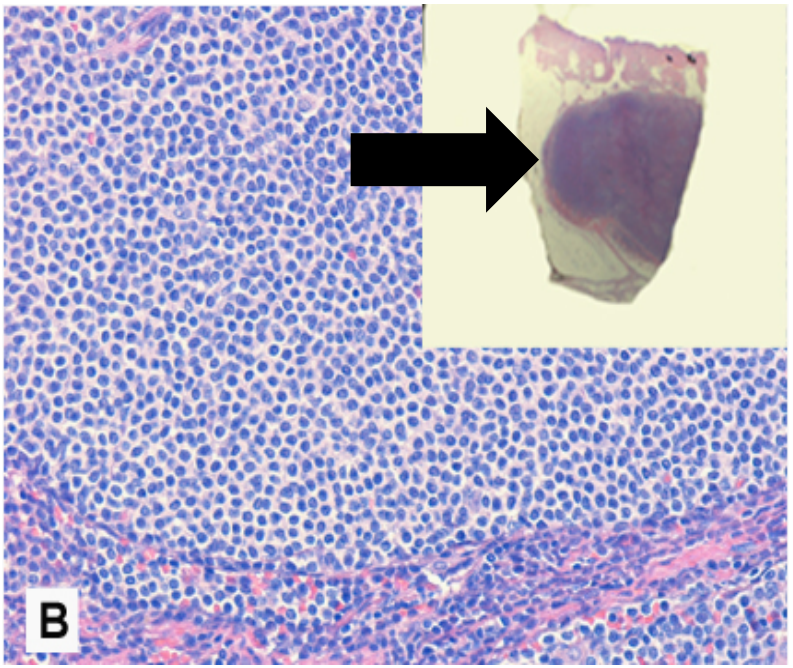
Lipoma-like marginal zone lymphoma

- 12 pts with primary subcutaneous MZL
- 10 F, 2 M; median age 69 yrs
- HCV serology: 12/12 positive
- HCV-RNA+: 10/10
- Single or multiple subcutaneous nodules
- Clinical appearance similar to lipomas
- Regression with antiviral treatment

Paulli et al, Annals of Oncology 2010

Lipoma-like marginal zone lymphoma





HCV PREVALENCE IN SMZL

	%
HCV+	19
HCV genotype	
1b	67
2b	7
2a/2c	26

Arcaini et al, Blood 2006

HCV+ SLVL treated with AT

- 9 pts with SLVL and HCV infection
- IFN-a 3 MU 3 times/wk for 6 months
- 7 pts: HCV-RNA- + CR
- 2 NR → Ribavirin → HCV-RNA- 1 CR, 1 PR
- 1 relapse with HCV-RNA+
- No molecular response
- 6 pts with SLVL HCV-neg: NR

Hermine et al, NEJM 2002

SLVL associated with MC and HCV infection: a new entity?

- 18 pts with SLVL
- Median age 58 years
- Predominantly female (F 78%)
- Symptomatic type II MC : 72%
- Symptoms preceding dg of SLVL in 7 (mean 3.5 years)
- Genotype 1: 54%
- Haematological + virological response: 78%
- HCV genotype 1: 54% (4 / 7 responders)
- Only 2 molecular responses

Saadoun et al, Blood 2004

EFFECT OF ANTIVIRAL TREATMENT ON SURVIVAL OF PATIENTS WITH INDOLENT B-CELL LYMPHOMAS ASSOCIATED WITH HEPATITIS C VIRUS INFECTION: A MULTICENTRE COHORT STUDY OF THE FONDAZIONE ITALIANA LINFOMI

FIL multicentric study

- 704 HCV+ pts with indolent NHL
- HCV-RNA+: 92%
- Genotype 1: 50%
- Genotype 2: 44%
- Cryoglobulinemia in 104 pts
- HBsAg+ 2%
- Cirrhosis 4%

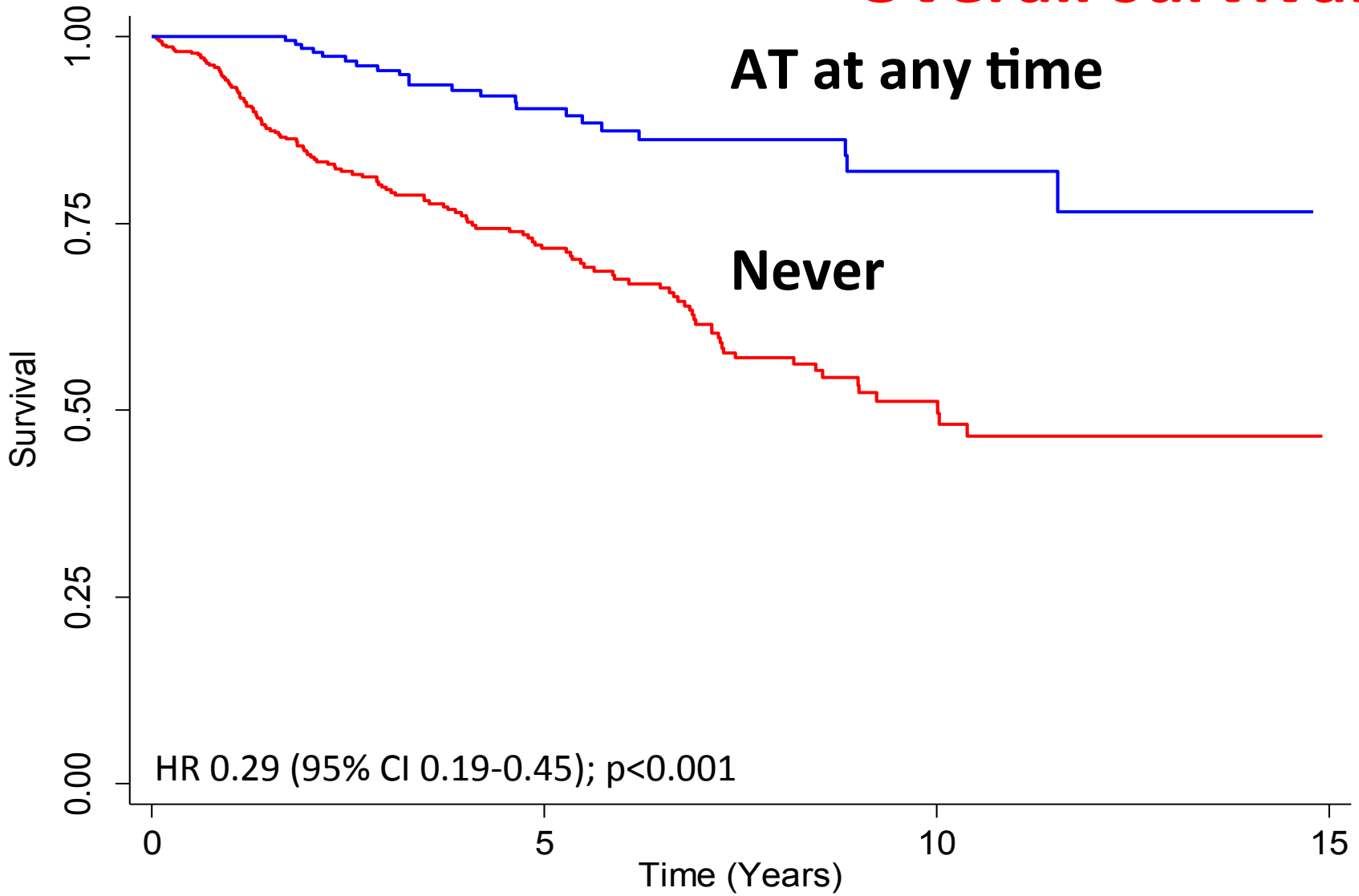
Arcaini et al Annals of Oncology, 2014

Multivariate analysis

Prognostic variables independently associated with a shorter OS:

- **Age >60 yrs**
- **Albumin <3.5 g/dl**
- **No AT at any time**

Overall survival



N at risk

AT	222	102	33	7
never	465	154	34	10

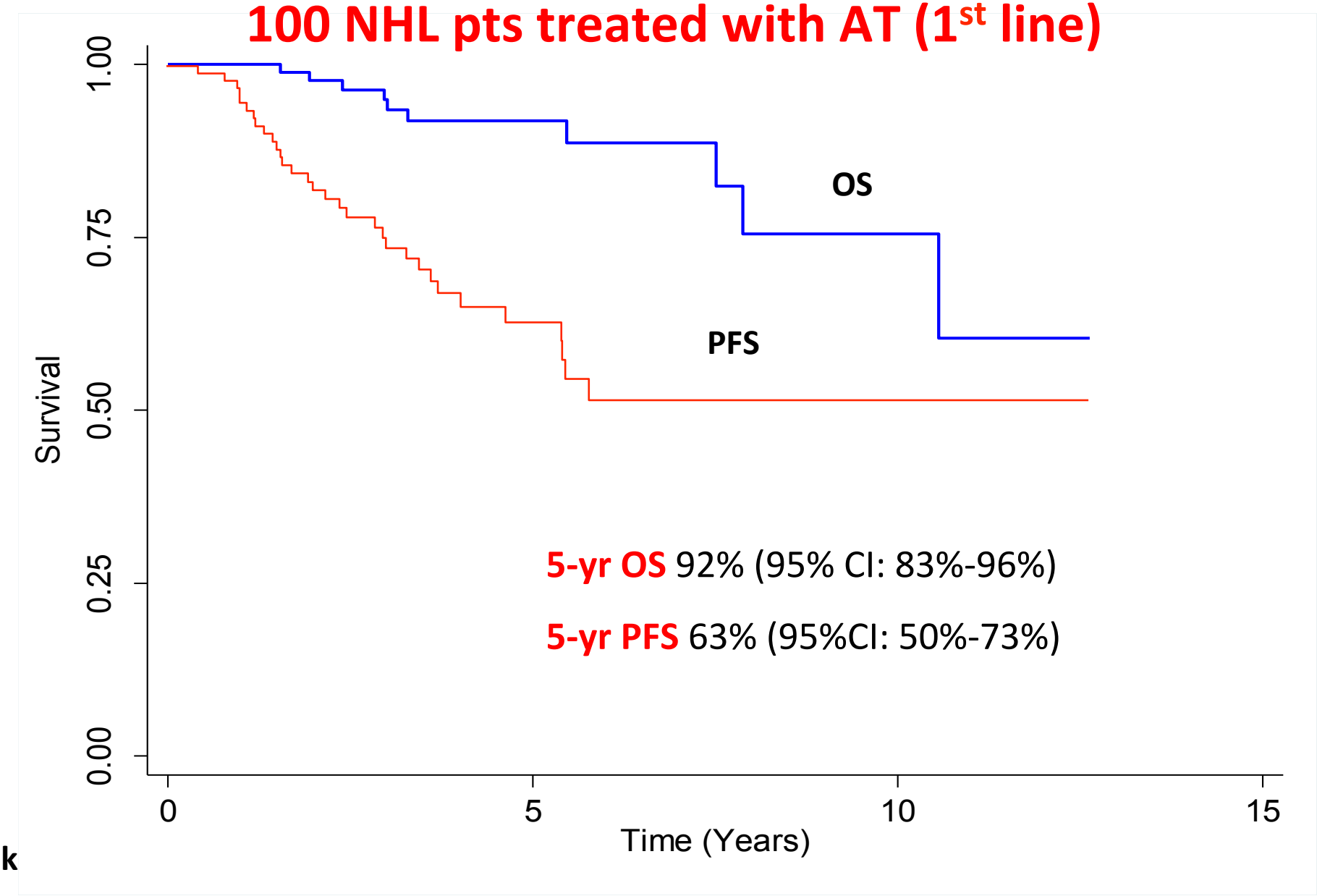
AT as NHL treatment (1st line)

- 33 with IFN and 67 with peg-IFN
- 60 MZL
- Genotype: 2 in 52 pts and 1 in 37
- 7 interrupted for NHL progression
- CR: 44/100
- PR: 33/100
- HCV-RNA clearance in 80 pts **related to lymphoma response**

AT as NHL treatment (1st line)

- Lymphoma response not different between MZL and non-MZL (ORR= 82% vs. 70%)
- Lower in SMZL respect to other MZL cases (ORR: 65% vs. 92%; p=0.02)
- ORR 83% in genotype 2 carriers and 70% in genotype 1 carriers (p=0.3)

100 NHL pts treated with AT (1st line)



N at risk

OS	100	36	7	2
PFS	99	27	6	2

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

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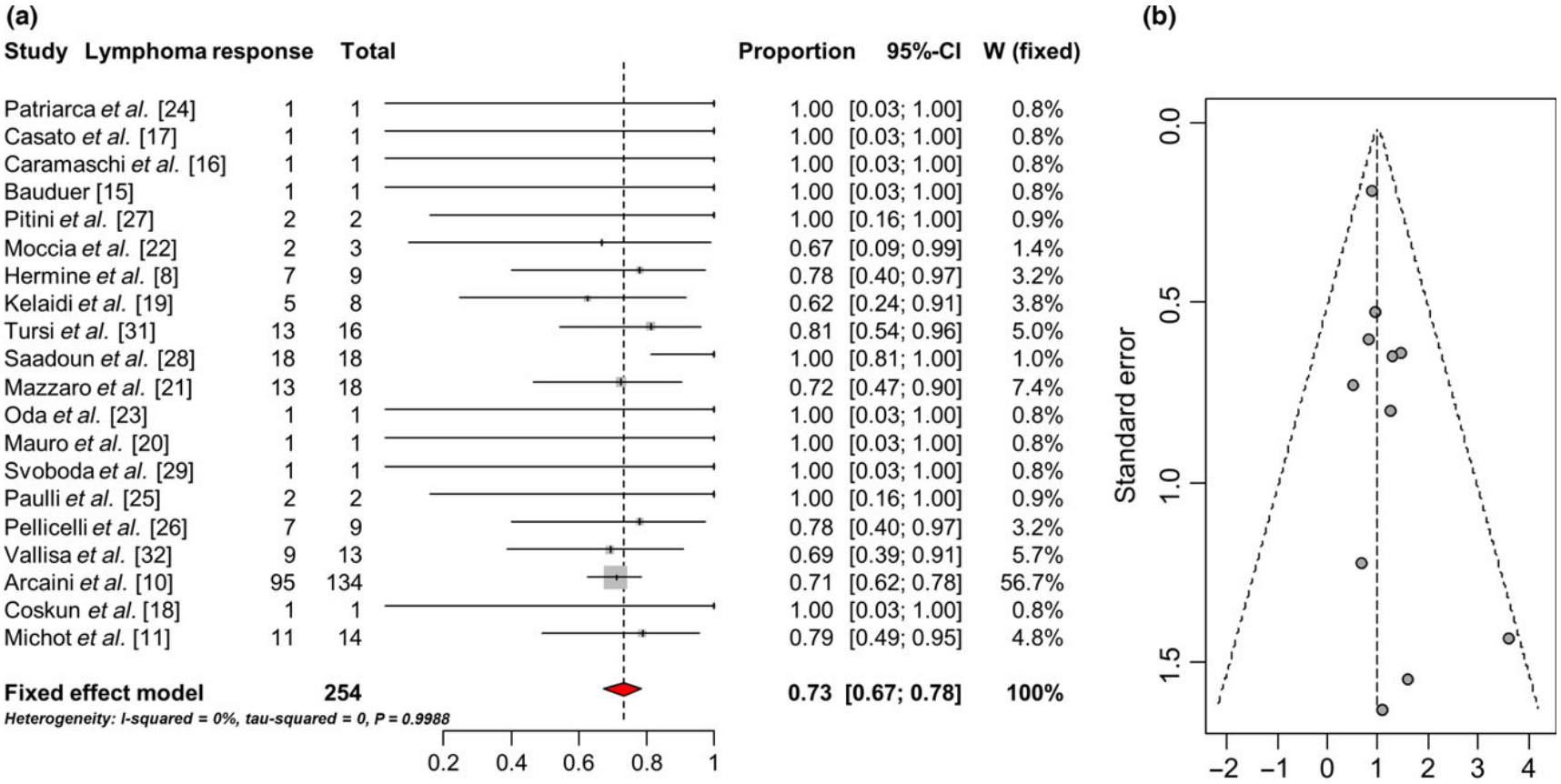
	N° pts*	Year	Antiviral treatment	Diagnosis	Virologic response	NHL response
Bauduer *et al.* [17]	1	1996	IFN	MZL/MALT	1	1 PR
Caramaschi *et al.* [18]	1	1999	IFN	MZL/MALT	NA	1 CR
Moccia *et al.* [24]	3	2001	IFN	SMZL	NA	2 CR
Patriarca *et al.* [26]	1	2002	IFN	LPL	1	1 CR
Casato *et al.* [19]	1	2002	IFN	MZL	HCV-RNA decrease	1 CR
Hermine *et al.* [10] [9] [8]	9	2004	IFN	SLVL	7	7 CR
Pitini *et al.* [29]	2	2004	IFN	SMZL	2	2 CR
Kelaidi *et al.* [21]	8	2004	IFN + RBV	SMZL (n = 4), MZL/MALT (n = 4)	5 SVR, 2 NSVR	5 CR
Tursi *et al.* [33]	16	2004	IFN + RBV	MZL/MALT	11	16 CR
Saadoun *et al.* [30]	18	2005	IFN (n = 8) IFN + RBV (n = 10)	SLVL	14 CR, 4 NSVR	14 CR, 4 PR
Svoboda *et al.* [31]	1	2005	Peg-IFN + RBV	MZL/MALT	1	CR
Vallisa *et al.* [34]	13	2005	Peg-IFN + RBV	SMZL (n = 4), MZL/MALT (n = 4), FL (n = 1), LPL (n = 4)	7 SVR, 1 NSVR	7 CR, 2 PR
Mazzaro *et al.* [23]	18	2009	IFN + RBV (n = 8) Peg-IFN + RBV (n = 10)	SLVL (n = 1), FL (n = 1), LPL (n = 16)	3 SVR, 4 NR, 1 NSVR 6 SVR, 2 NR, 2 NSVR	3 CR, 2 PR 6 CR, 2 PR
Paulli *et al.* [27]	2	2009	Peg-IFN + RBV	MZL/MALT	2 CR	1 CR, 1 PR
Oda *et al.* [25]	1	2010	Peg-IFN + RBV	B-NHL (liver)	SVR	CR
Pellicelli *et al.* [28]	9	2011	Peg-IFN + RBV	SMZL (n = 3), MZL (n = 4), FL (n = 2)	7 SVR, 2 NSVR	5 CR, 2 PR
Mauro *et al.* [22]	1	2012	Peg-IFN + RBV	LPL	SVR	CR
Coskun *et al.* [20]		2013	Peg-IFN + RBV	MZL	SVR	CR
Arcaini *et al.* [12]	134	2014	Peg-IFN + RBV	SMZL (n = 35), MALT (n = 31), LPL (n = 9), FL (n = 12), Other (n = 33)	102 SVR, 30 NSVR, 2 NA	95 CR/PR
Michot *et al.* [13]	14	2015	Peg-IFN + RBV	MZL	11 SVR, 3 NSVR	11 CR/PR

Tot 254 pts

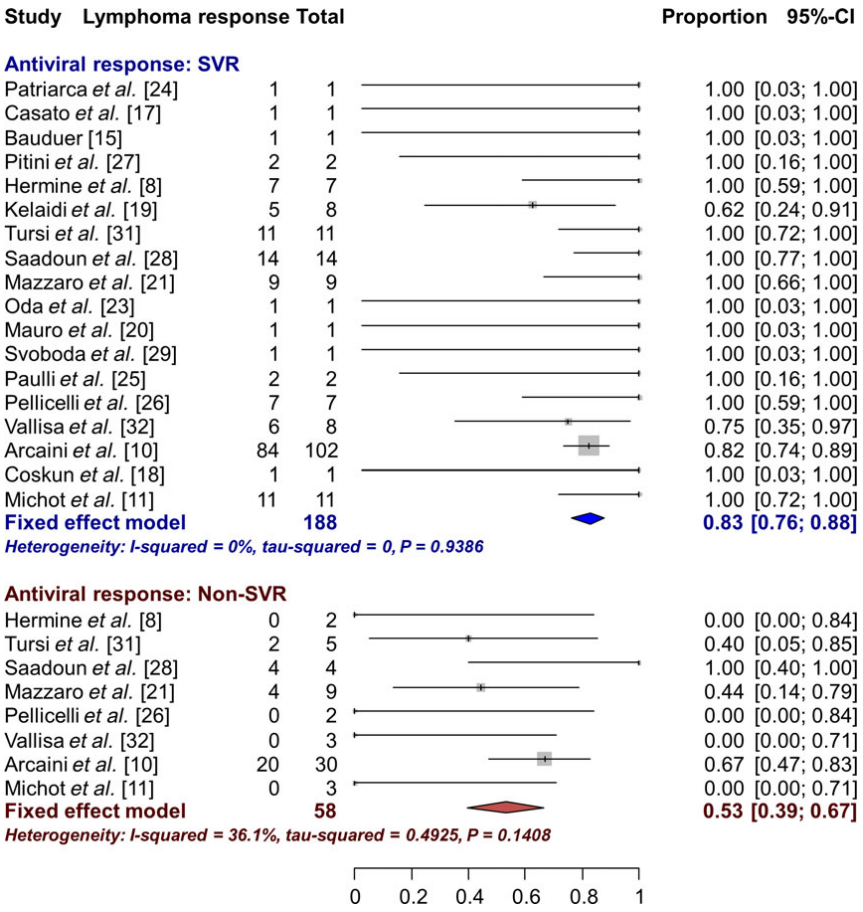
Lymphoma response

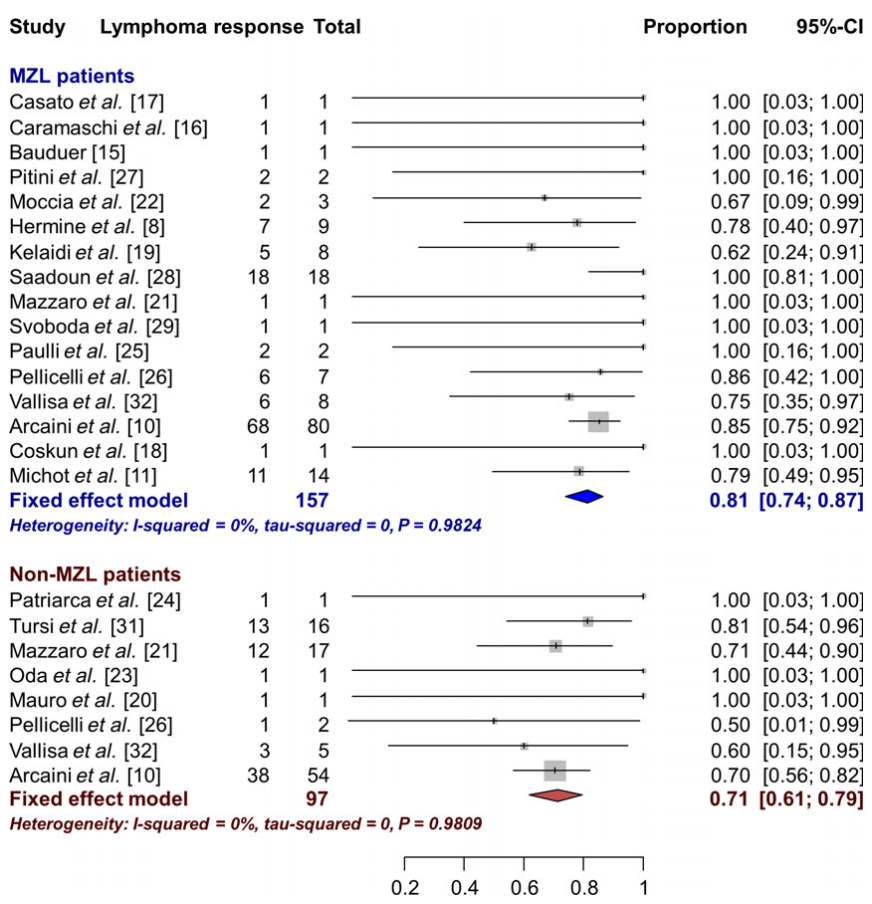


ORR 73%

SVR and histotype

157 MZL





83 % vs 53%

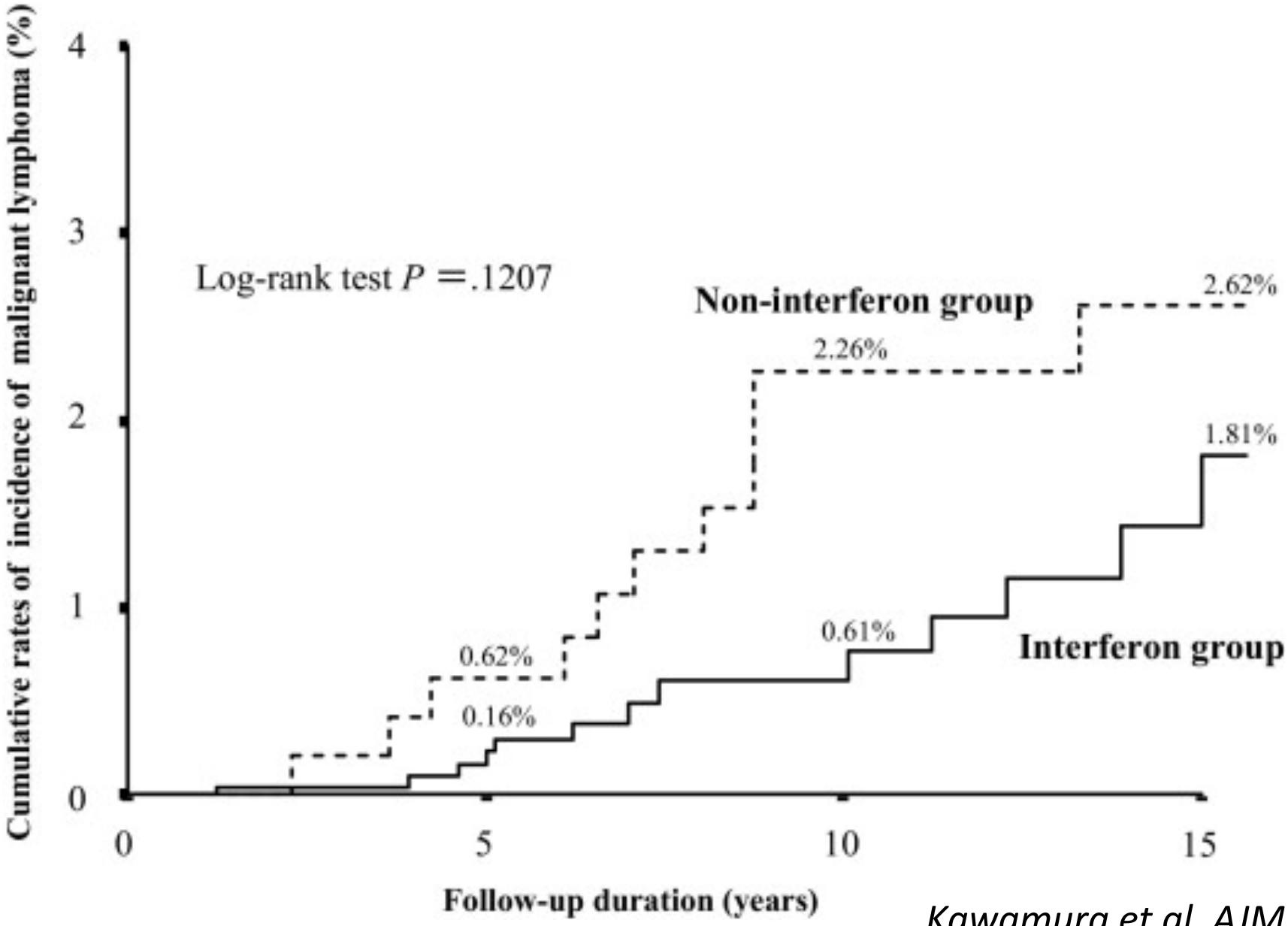
81 % vs 71%

Antiviral therapy and risk of lymphoma

- 501 HCV+ pts never treated
- 2,708 HCV+ pts treated with IFN
- Cumulative rates at 5, 10 and 15 yrs:
- **Non-IFN group**: 0.6%, 2.3% and 2.6%
- **IFN-group with SVR**: 0%, 0% and 0%
- **IFN-group with persistent infection**: 0.4%, 1.5% and 2.6%

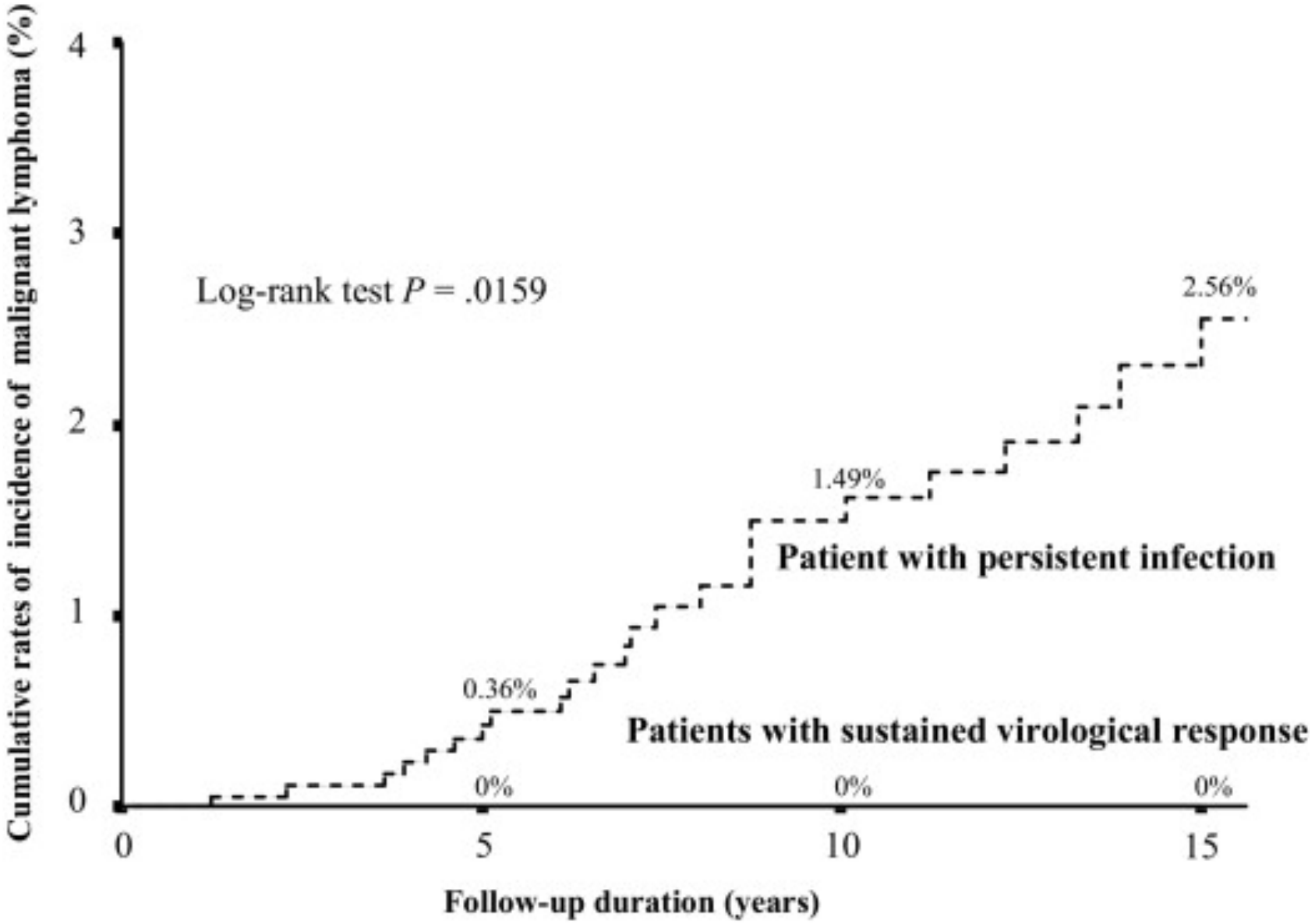
Kawamura et al, AJM 2007

Antiviral therapy and risk of lymphoma



Kawamura et al, AJM 2007

Antiviral therapy and risk of lymphoma



Kawamura et al, AJM 2007

HCV-associated lymphoma present with mild liver

- MD Anderson Cancer Center (2008-2014)
- 89 pts
- Genotype 1 62%
- DLBCL 62%
- Detectable HCV RNA 90%
- Advanced liver disease (Metavir stage ≥ 3) 18%
- All 53 patients with chronic HCV infection documented before lymphoma diagnosis were seen by HCV treating physicians. Providers did not recommend AVT in almost one half of cases (44%), mostly because of the lack of advanced liver disease at HCV diagnosis (38%)

Torres et al, Liv Int 2015

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

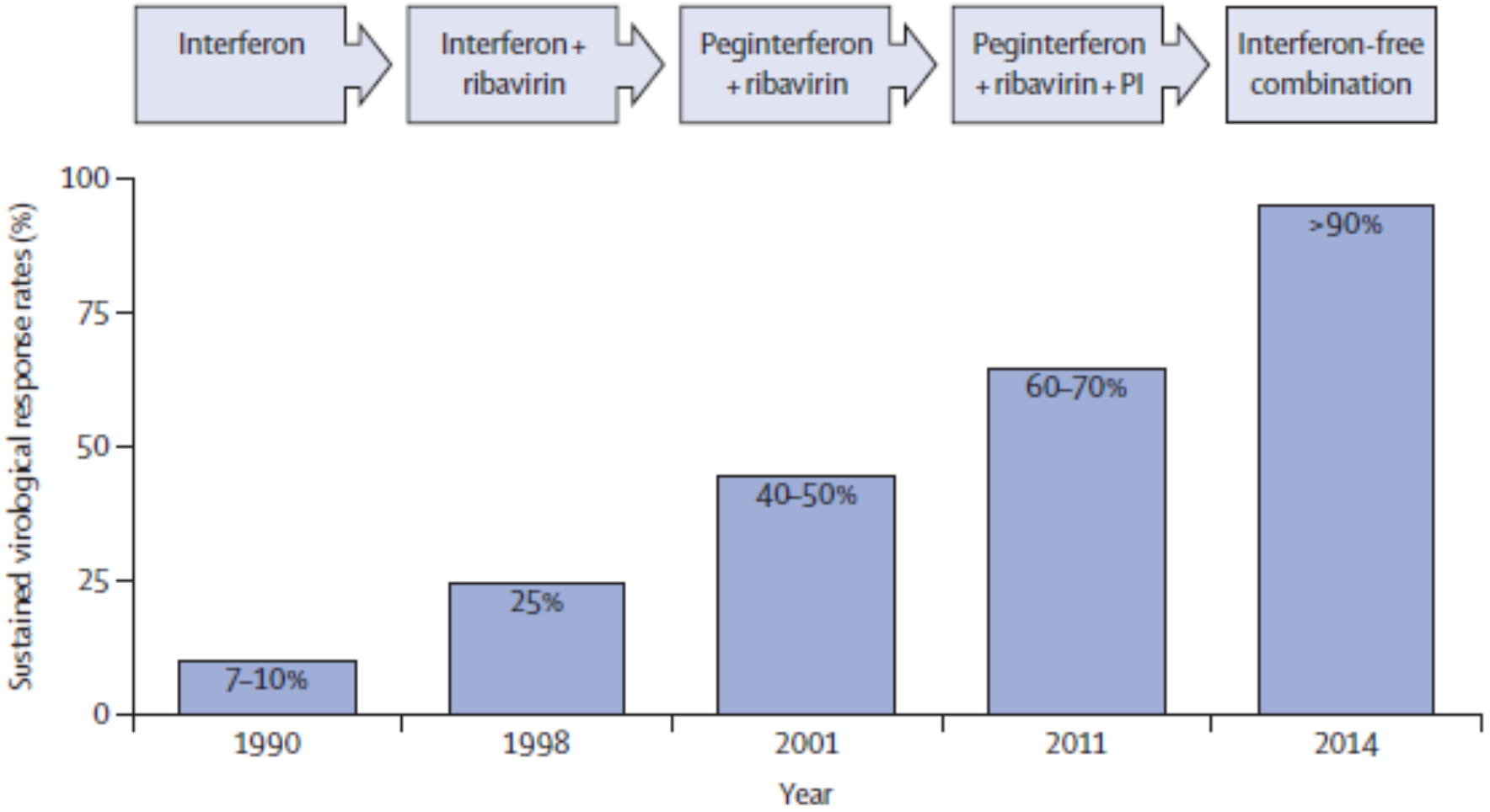
NCCN National Comprehensive Cancer Network® 2015

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

Antiviral therapy (AVT):

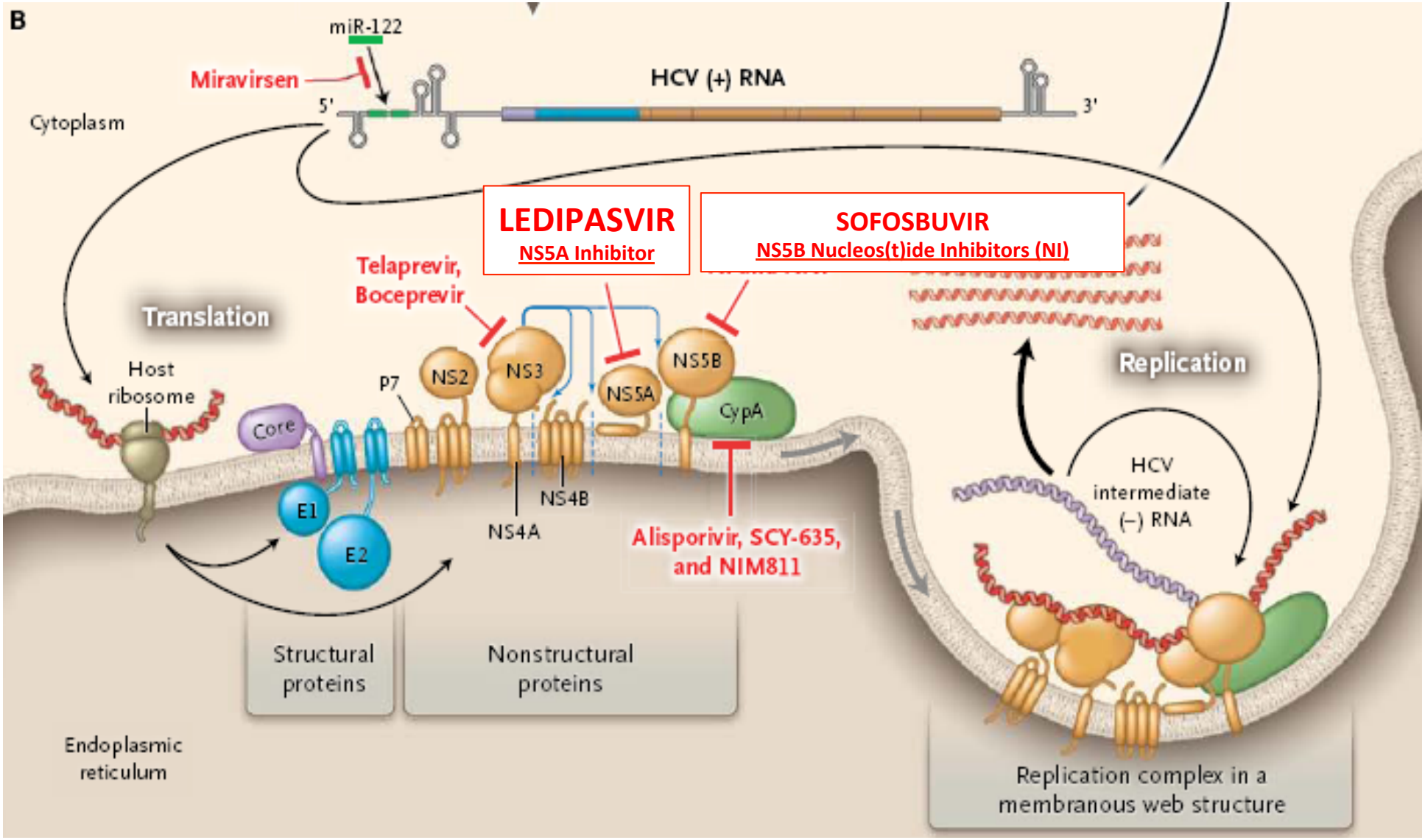
standard 1st line treatment in asymptomatic patients with iNHL HCV+ (who do not need immediately conventional treatment of lymphoma)

The advent of *IFN-free therapy*: SVR >90% also in genotype 1



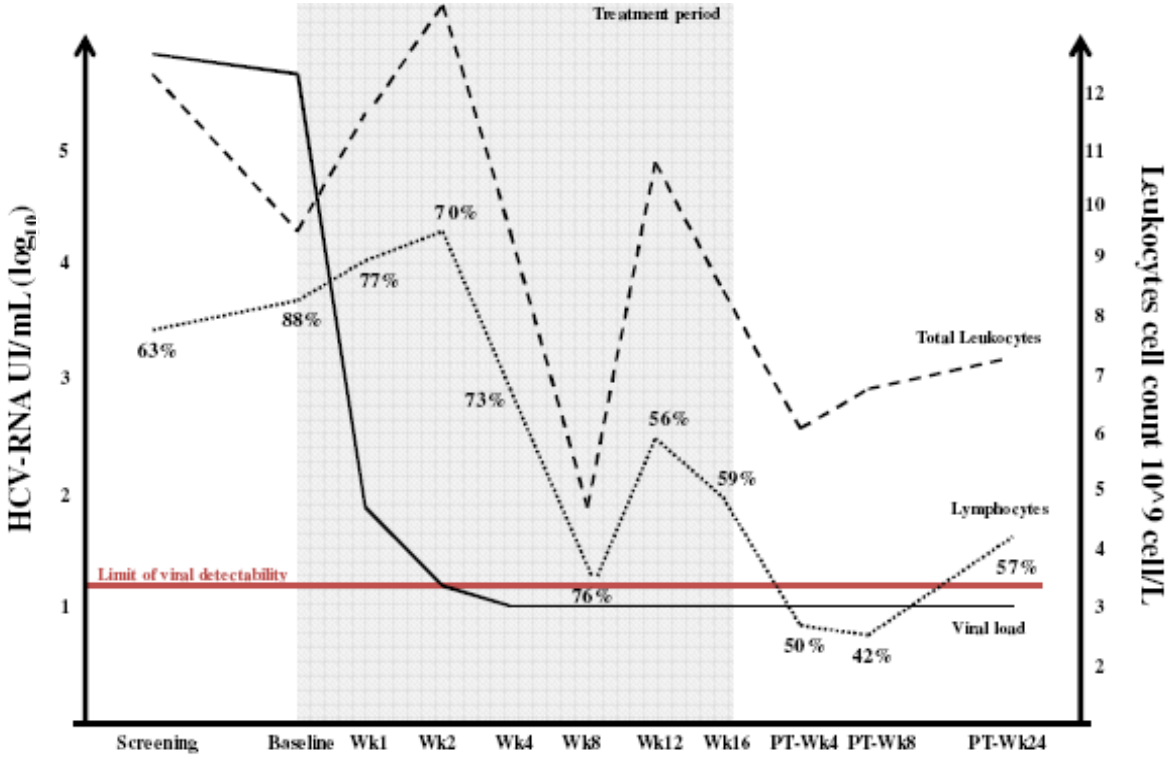
Webster et al. Lancet 2015

Direct-Acting Antiviral Agents: mechanisms of action



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

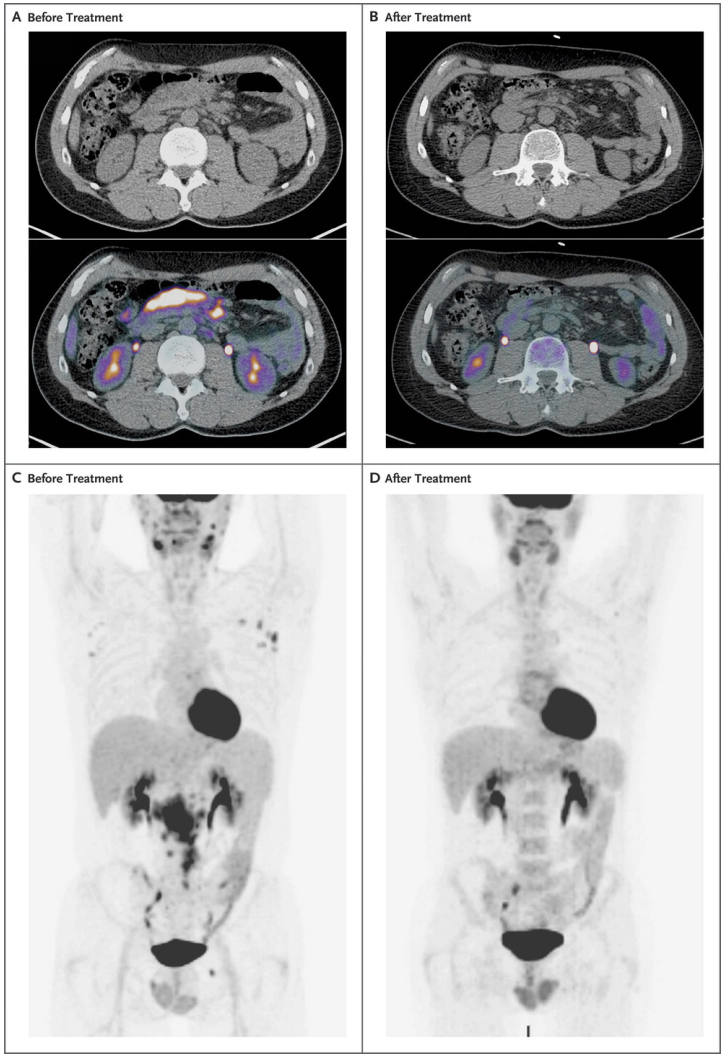
- 42 y, M
- HCV genotype **1b**, F0
- SMZL, spleen 17.5 cm, lymphocytosis (5.65 x 10^9/l)
- *IFN-free regimen:*
  FDV + **DLV** + **RBV** (16 w)
- SVR (4w)
- Hematologic response (spleen, lymphocytes)
  → related to SVR



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

Rossotti R et al, J Hepat 2014

Remission of Follicular Lymphoma after Treatment for Hepatitis C Virus Infection



Maciocia N et al, NEJM 2016

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] Hélène 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,†]

Clinical features

	n	%
Male/female	18/28	39/61
MZLs	37	80
Splenic	17	37
Nodal	1	2
Extranodal	15	32
Leukemic	4	9
Others*	5	11
CLL/SLL	4	9
Ann Arbor stage III-IV	35/42	83
B symptoms	6	13
ECOG performance status ≥ 2	1	2
Hemoglobin <12 g/dL	14/45	31
Platelets $<100 \times 10^9$/L	10/45	22
Lactate hydrogenase $>$ UNL	10/40	25
β_2-Microglobulin $>$ UNL	20/26	77
Albumin <3.5 g/dL	6/40	15
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

Lymphoma response

	CR, n	PR, n	SD, n
All (N = 46)	12	19	11
MZLs (n = 37)	11	16	6
Splenic (n = 17)	4	7	5
Nodal (n = 1)	1	0	0
Extranodal (n = 15)	5	7	0
Leukemic (n = 4)	1	2	1
Follicular lymphoma (n = 2)	0	2	0
Lymphoplasmacytic lymphoma (n = 2)	0	1	1
Low-grade B-NHL NOS (n = 1)	1	0	0
CLL/SLL (n = 4)	0	0	4

ORR 67%: 26 % CR, 41% PR - ORR in MZL 73%; no response in CLL

Predictive factors

- **Univariate analysis**: higher risk of non response in pts with nodal disease and with low hb levels
- In contrast, extranodal disease and serum MC a trend toward a lower risk of nonresponse

- **Multivariate analysis**:, risk of nonresponse lower in pts with a serum MC (OR, 0.1; 95% CI, 0.1-1.0; P 5 .048) and a trend with extranodal disease

14th International Conference of Malignant Lymphoma (Lugano, 14-7 June 2017)

- Frigeni et al. "**Interferon-Free Antiviral Treatment in B-cell Lymphoproliferative Disorders associated with Chronic Hepatitis-C Virus Infection**" (nr. 136). oral presentation in the **SESSION 12: "MARGINAL ZONE LYMPHOMA"**, Saturday, June 17th from 10:15 to 11:15 in Room A

- Merli et al. **"Direct-acting Antivirals during or after Immuno-chemotherapy in Hepatitis C Virus-associated Diffuse Large B-cell Lymphomas" poster presentation**

A multicenter study to evaluate the antiviral activity of an interferon-free treatment with sofosbuvir + ledipasvir ± ribavirin (G1, 3 and 4) and sofosbuvir + ribavirin (G2) for patients with hepatitis C virus-associated indolent B-cell lymphomas

ID Study: FIL_BArT (B-cell lymphoma **A**ntiviral **T**reatment**)**

EudraCT number: 2015-004830-81

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