CORSO EDUCAZIONALE

GRUPPO LINFOMI IN PAZIENTI CON IMMUNODEFICIT

Milano, Starhotels Anderson

24 maggio 2024

Coinfezione HIV/HCV e linfomi

Michele Merli

Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico

Milano

Disclosures of Michele Merli

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Regeneron			X		X		
Janssen							X
Roche							X

HIV and HCV coinfection: “A Tale of two viruses”

- **2.3 million individuals worldwide coinfected with HIV/HCV**
- **6.2%** of *people living with HIV* (**PLWH**) carry **HCV coinfection**
- Odds of HCV: 6 times higher in PLWH than HIV-negative counterpart
- Higher prevalence in *intravenous drug users* (**IDU**) and *men who have sex with men* (**MSM**), due to the same transmission route
- HIV coinfection: detrimental impact on the natural history of HCV (e.g. higher viral loads, accelerated progression of liver fibrosis and of end-stage liver disease)
- HCV coinfection impacts HIV disease progression in PLWH receiving ***antiretroviral therapy (ART),*** by negatively affecting CD4+ counts homeostasis, facilitating viral replication and viral reservoir persistence

Gobran S *et al*, *Front Immunol 2021*

DAAs in HIV/HCV coinfected patients

- Early studies suggested lower *sustained virologic response* (**SVR**) rates to ***direct-acting antivirals*** **(DAAs)** than monoinfected pts (86.4 vs 94.9%)
- Recent studies reported comparable SVR between HIV/HCV and monoinfected individuals
- Same predictor of failure to achieve SVR under DAAs: sex, immune status, HCV-RNA load, severity of liver disease and suboptimal DAAs regimens
- Negative predictors of SVR and barrier to treatment may be higher in HIV/HCV coinfected
- Clear benefit of HCV cure in limiting liver disease progression and hepatocellular carcinoma (HCC) development in PLWH, especially if treated at an early fibrosis stage

Gobran S *et al*, *Front Immunol 2021*

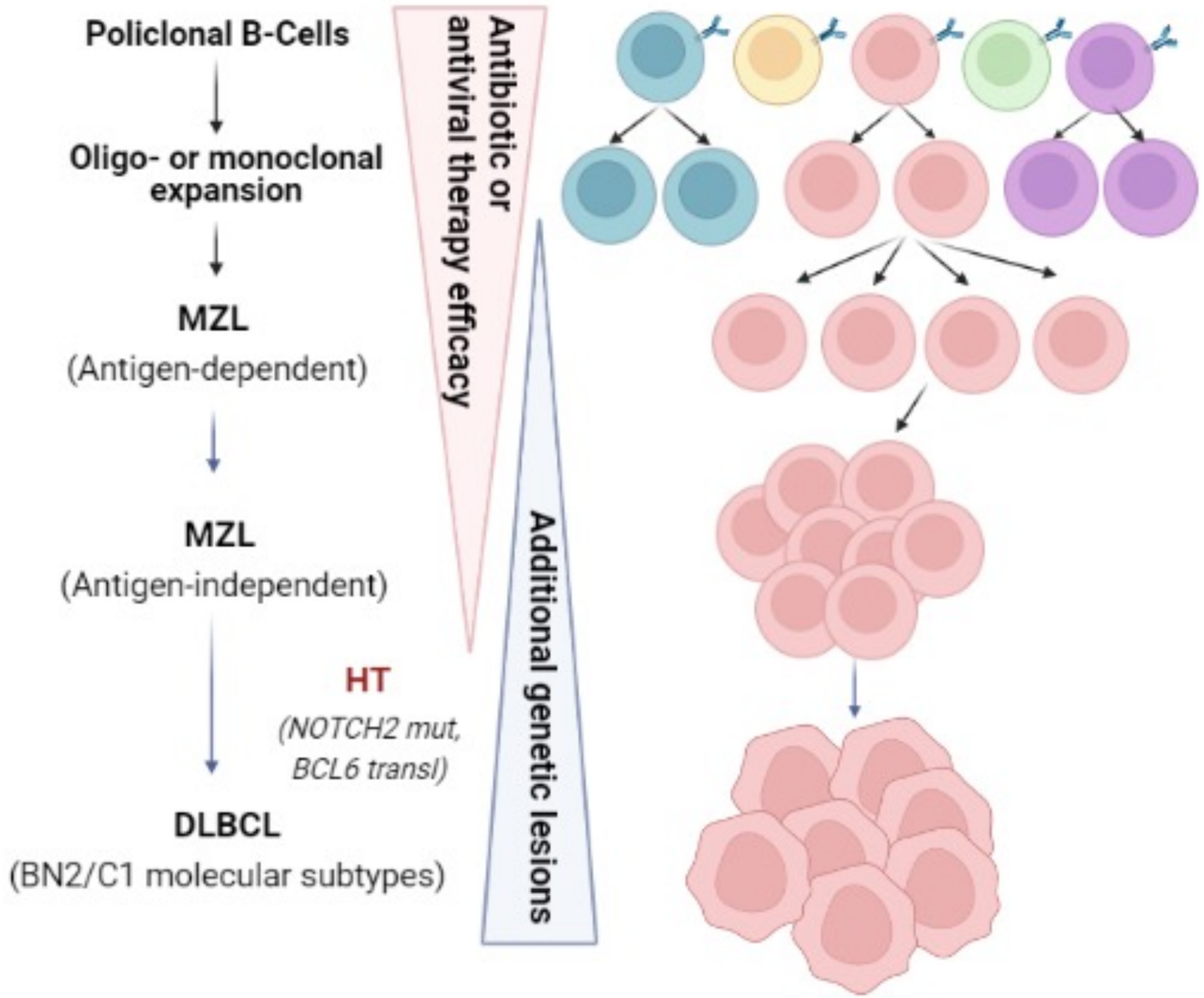
HIV/HCV coinfected patients and NHL

- **HCV** chronic infection:
  - associated with increased risk of *non-Hodgkin lymphoma* **(NHL)** in **PLWH**
  - trend of inferior OS in HIV-related NHL in the modern **ART** era[1]
- **DAAs:**
  - SVR in nearly all treated pts with negligible toxicity
  - HIV/HCV coinfected pts (careful attention to interactions with ART)
- DAAs' administration during or after immuno-chemotherapy may improve long-term outcome in HIV-negative HCV-associated DLBCL pts[2-3]
- Only scant data about the **use of DAAs in HIV/HCV coinfected NHL patients** are available

[1]**Besson C *et al***, *AIDS. 2020;* [2]**Merli M *et al***, *Oncologist. 2019;* [3]**Arcari A** *et al, BJH 2023*

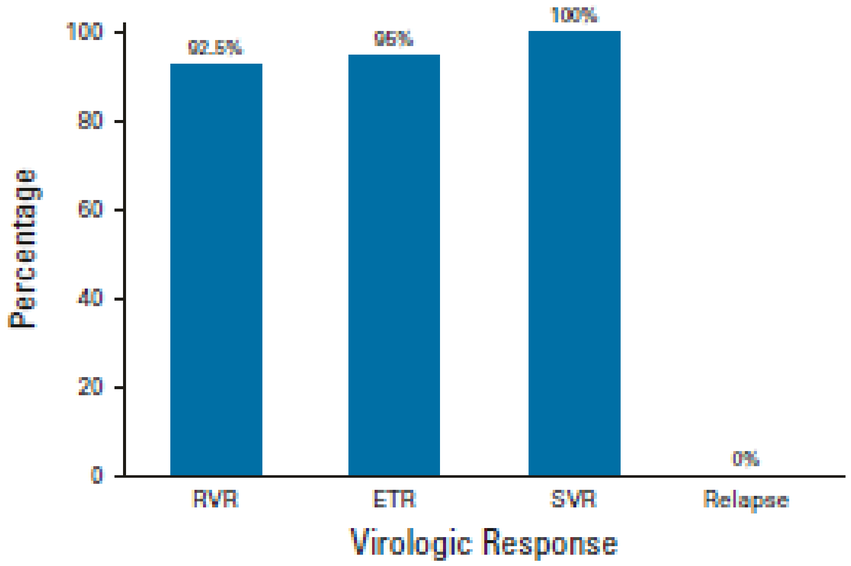
Pathogenetic model of HCV-associated NHL

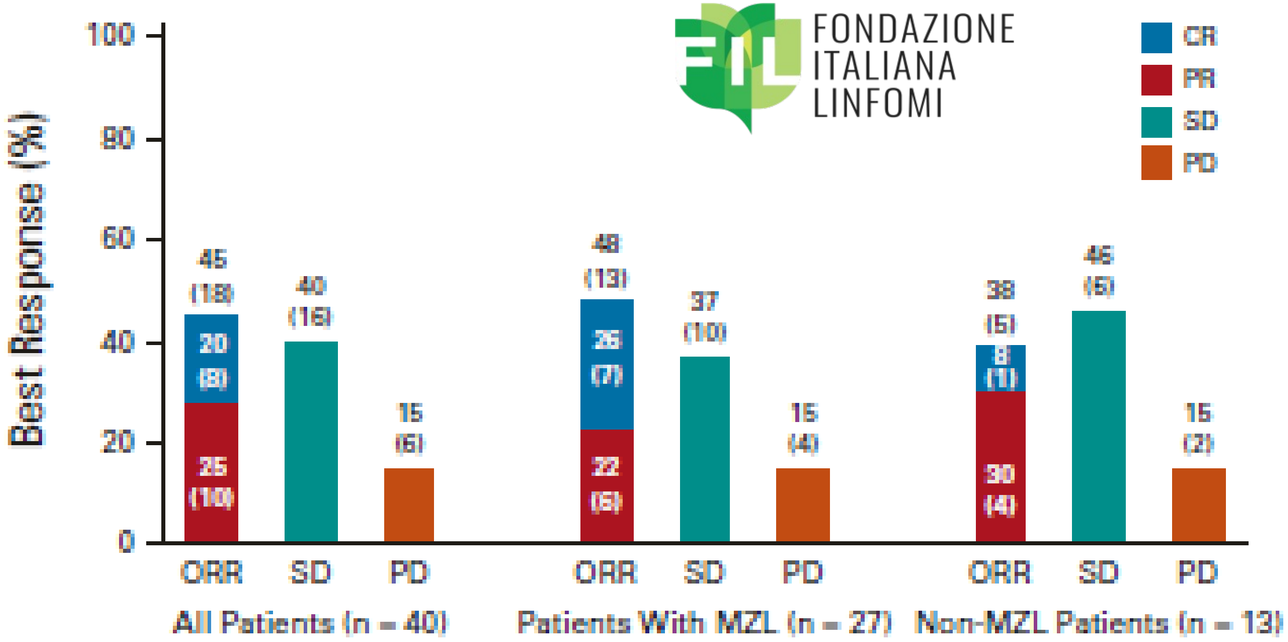
- Antigen-driven model of lymphomagenesis
- Pathogenetic treatment: DAAs
- HCV eradication (100%)
- Variable rates of **lymphoma responses** (PR, CR), especially in the early phases *(antigen-dependent)*



Merli M & Arcaini L,
ASH Educational Book 2022

HCV- iNHL treated with DAAs as first-line: the *FIL_BArT study*





- **SVR**: 40/40 **(100%)**
- **ORR**: no differences MZL vs non-MZL
- **ORR 48% in MZL (26% CR)**
- MALT 71% > NMZL 43% > SMZL 0% (p=0.014)
- Nodal 33%, Extranodal 71%
- Spleen 30%, BM 32%

Histology	Response				
	CR	**PR**	**SD**	**PD**	**ORR**
All (N=40)	**8 (20)**	**10 (25)**	**16 (40)**	**6 (15)**	**18 (45)**
MZL (N=27, 68%)	7 (26)	6 (22)	10 (37)	4 (15)	13 (48)

Merli M *et al. JCO 2022*

DLBCL HCV(HIV-negative)-associated genetic landscape

54 HCV-associated DLBCL cases

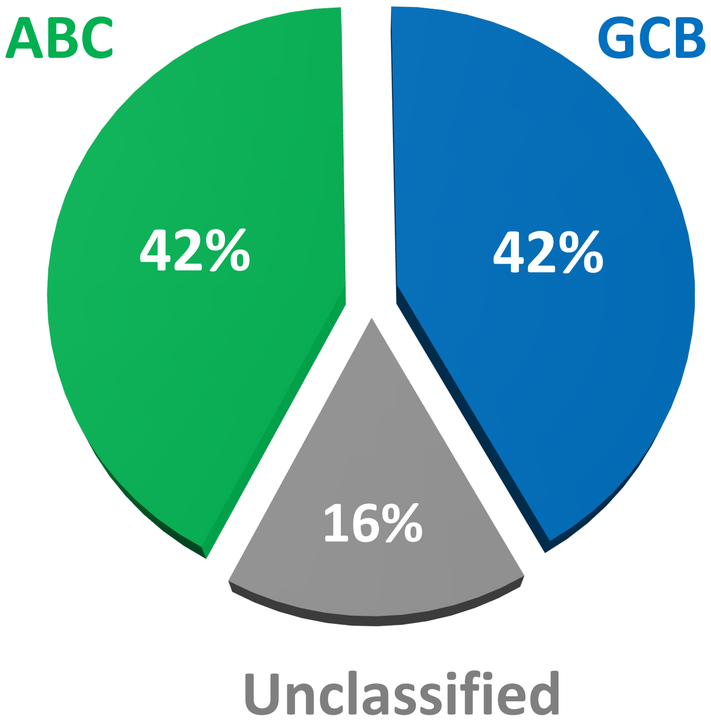
FISH

52% BCL6 fusion
13% MYC fusion
4% BCL2 fusion

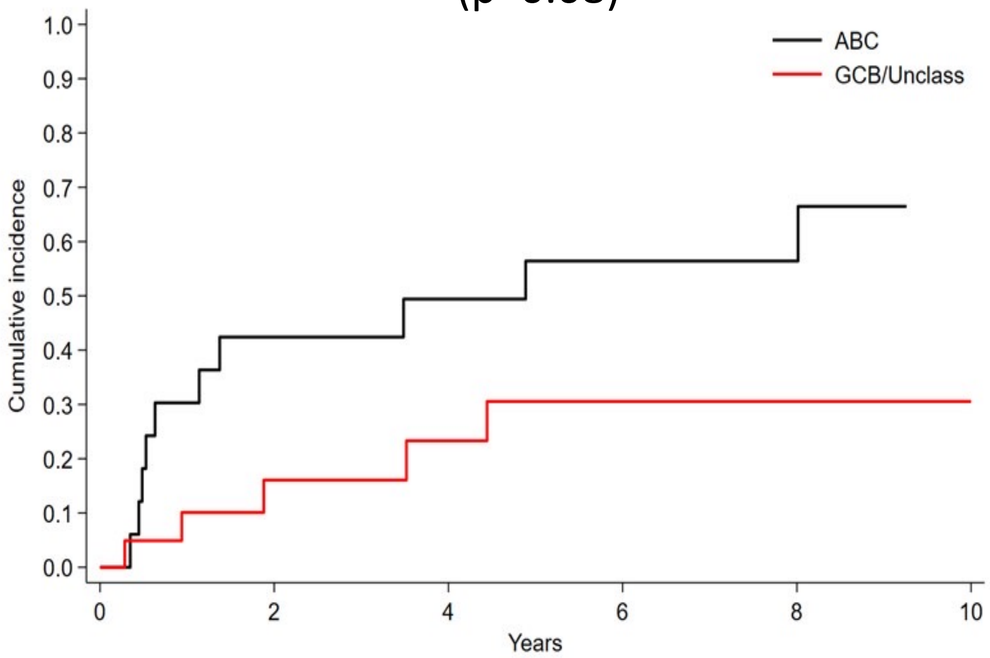
3 DHL cases (5.6%)

(1 MYC/BCL2; 2 MYC/BCL6)

GEP (Lymph2Cx)

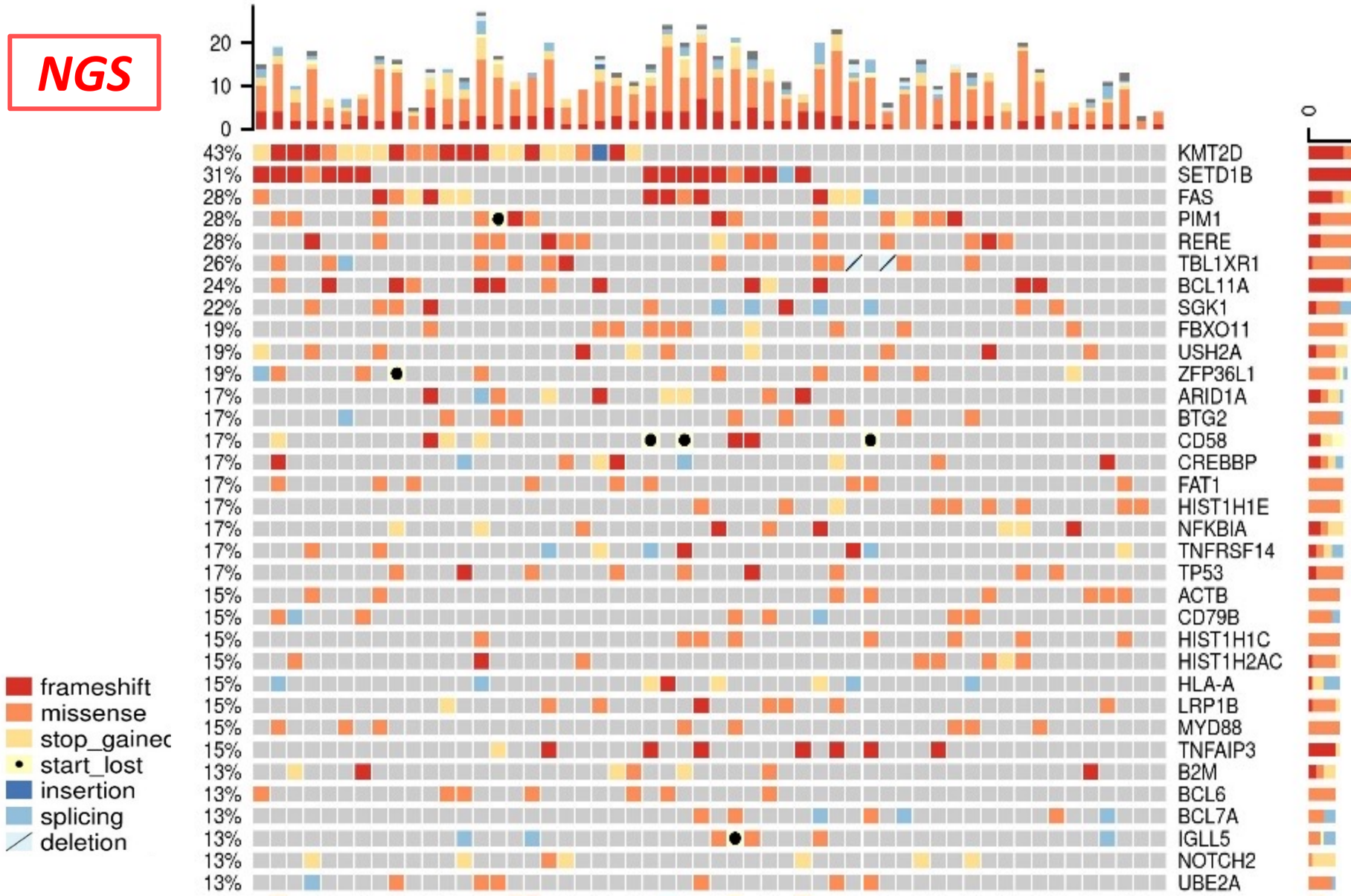


Lymphoma-related mortality
(p=0.08)



Sciarra R, Merli M *et al*, *BJH 2024*

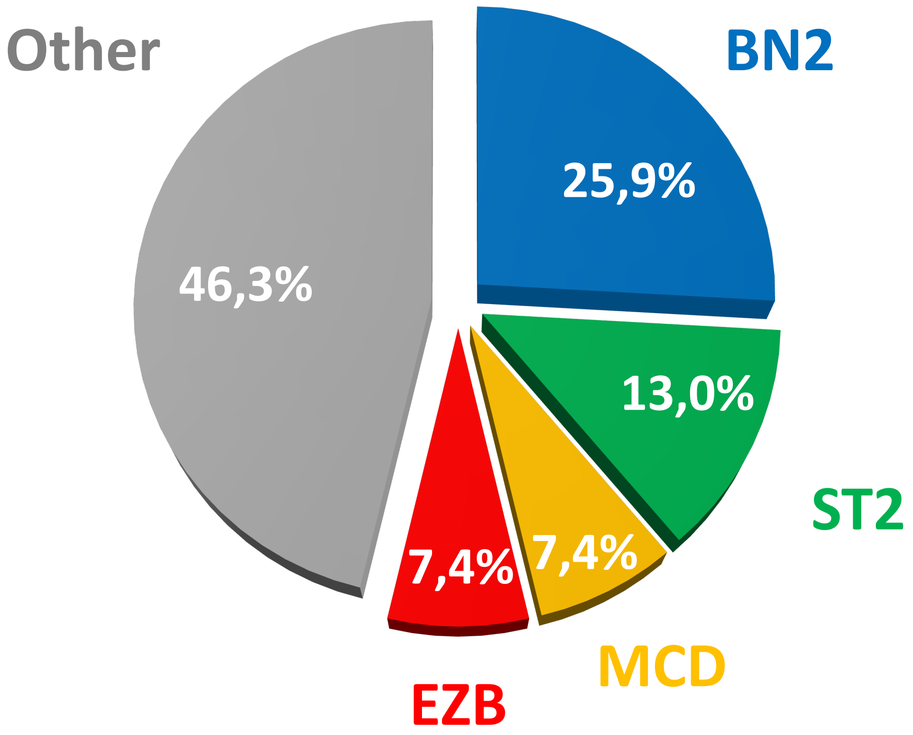
NGS

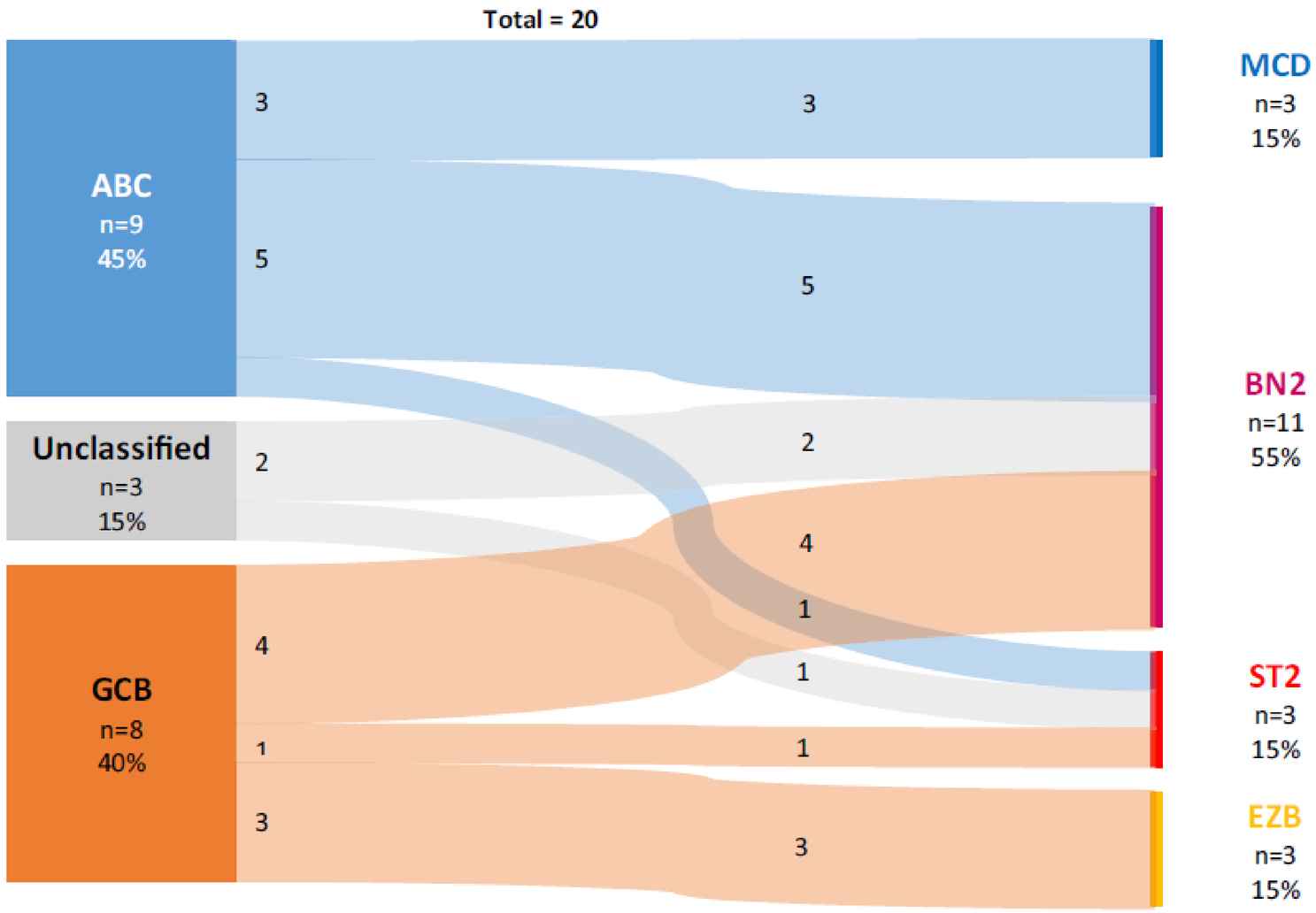


- **Recurrently mutated genes:** *SETD1B, RERE, BCL11A, TBL1XR1, ZFP36L1*
- Different from HCV-neg DLBCL

Sciarra R, Merli M *et al*, *BJH 2024*

LymphGen





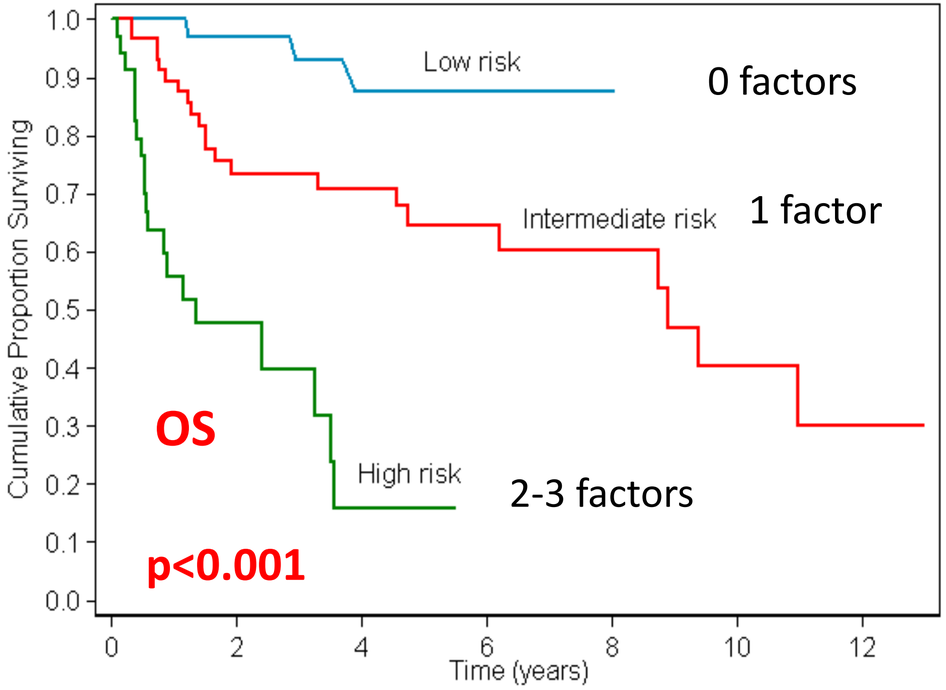
- **Preferential MZL origin**

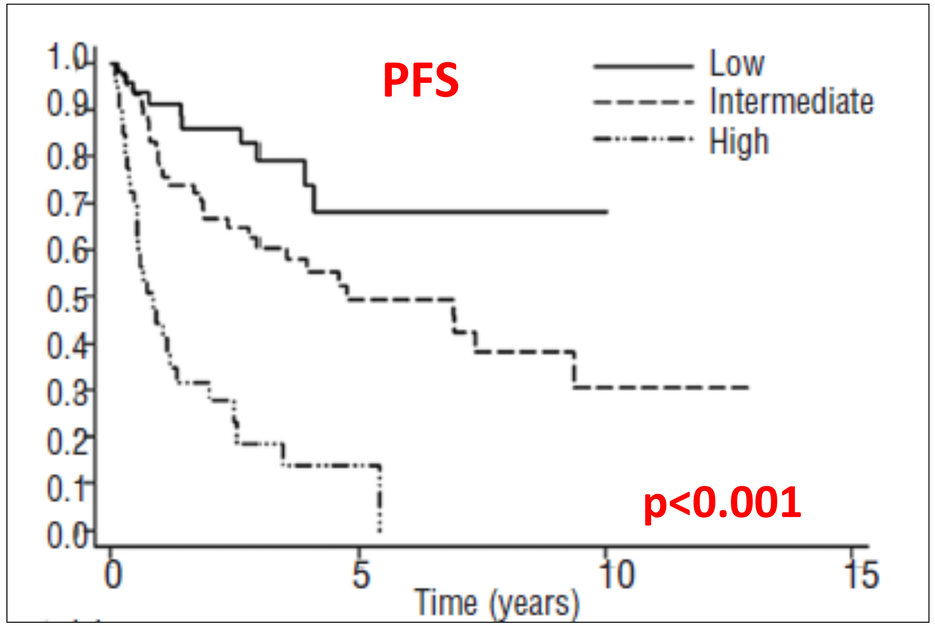
Sciarra R, Merli M *et al*, *BJH 2024*

HCV-associated DLBCL: prognosis in the pre-DAAs era

- **3-yr OS 71%** and 3-yr PFS 58% with R-CHOP (232 pts)
- Not inferior to HCV-negative DLBCL historical survival rates
- Specific prognostic score (*Hepatitis-C prognostic score*, **HPS**)

1) ECOG≥2
2) Albumin <3.5 g/dl
3) HCV-RNA >1000 KIU/ml



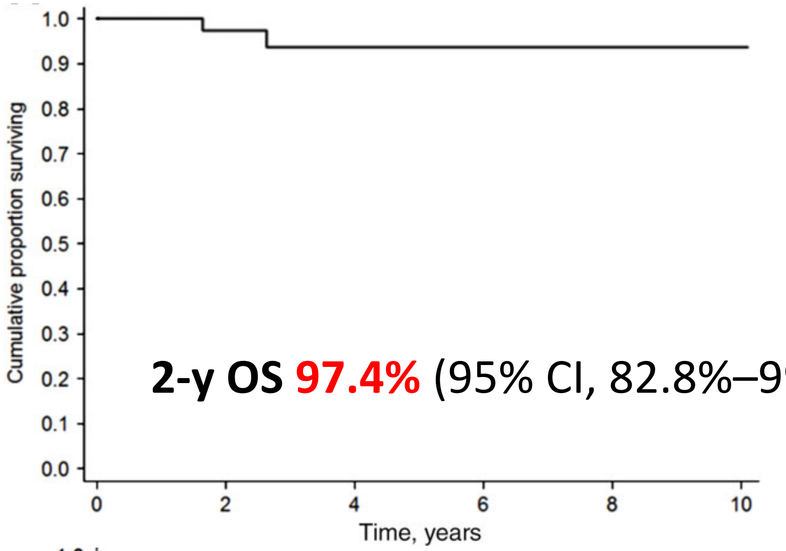


FONDAZIONE ITALIANA LINFOMI

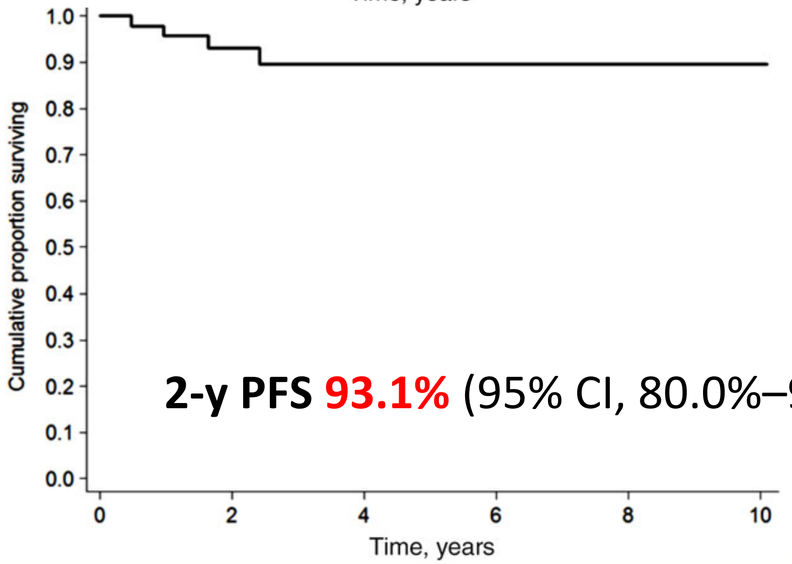
Merli M *et al, Haematologica 2014*

HCV+/HIV- DLBCL treated with R-CHOP + DAAs

- Retrospective study, 23 Centers (Italy, France)
- 47 consecutive pts with HCV+ DLBCL
- R-CHOP + DAAs
  - Concurrently (n=9)
  - Subsequently (n=38)
- Sofosbuvir-based in 45 pts
- Grade 1-2 events in 11 pts
- CR 98%, SVR 96%
- **Long-term favorable outcome**



2-y OS 97.4% (95% CI, 82.8%–99.6%)



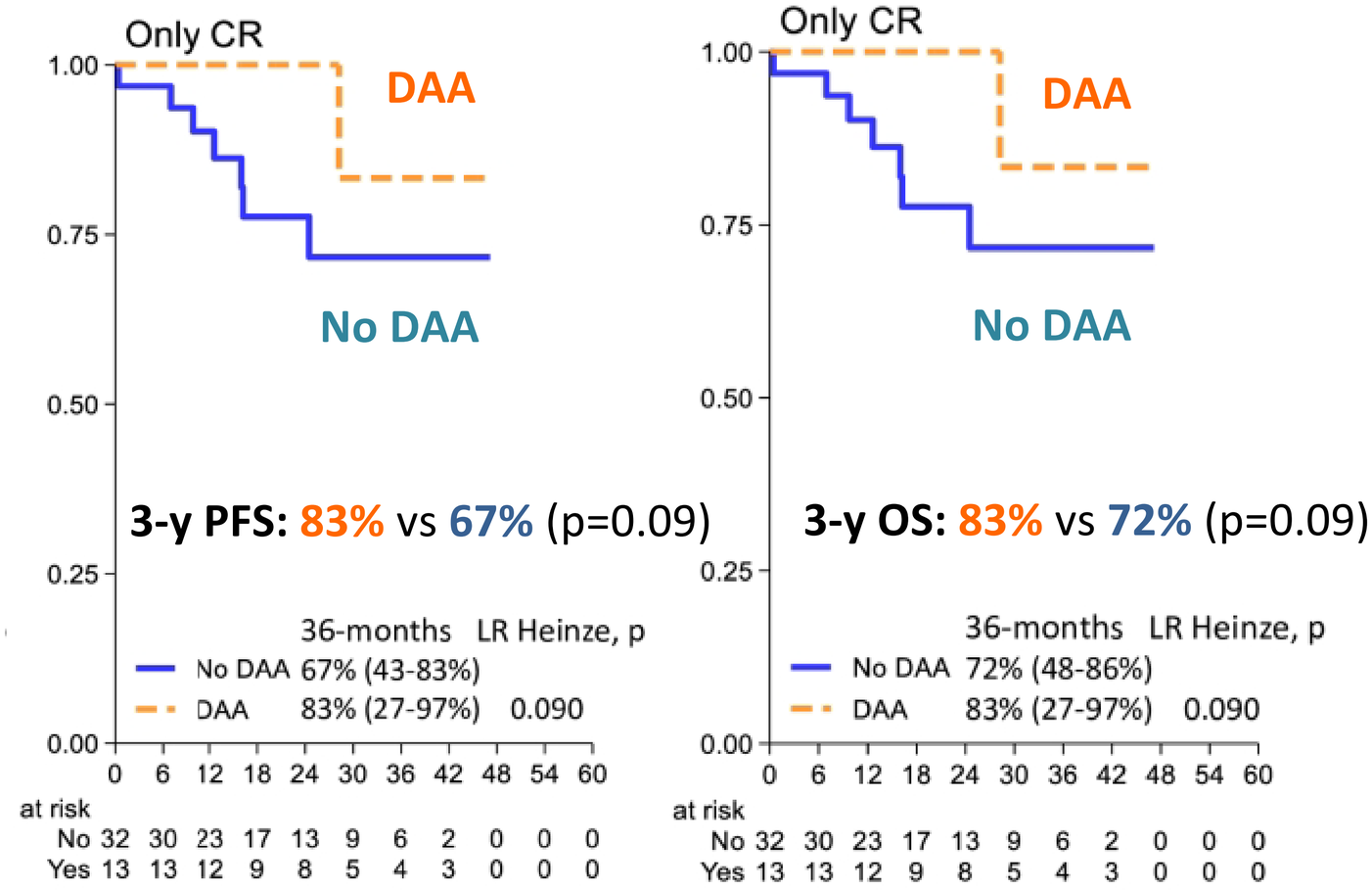
2-y PFS 93.1% (95% CI, 80.0%–97.7%)

Merli M *et al*, *Oncologist 2019*

FIL Elderly Project: elderly HIV-/HCV+ DLBCL

FONDAZIONE ITALIANA LINFOMI

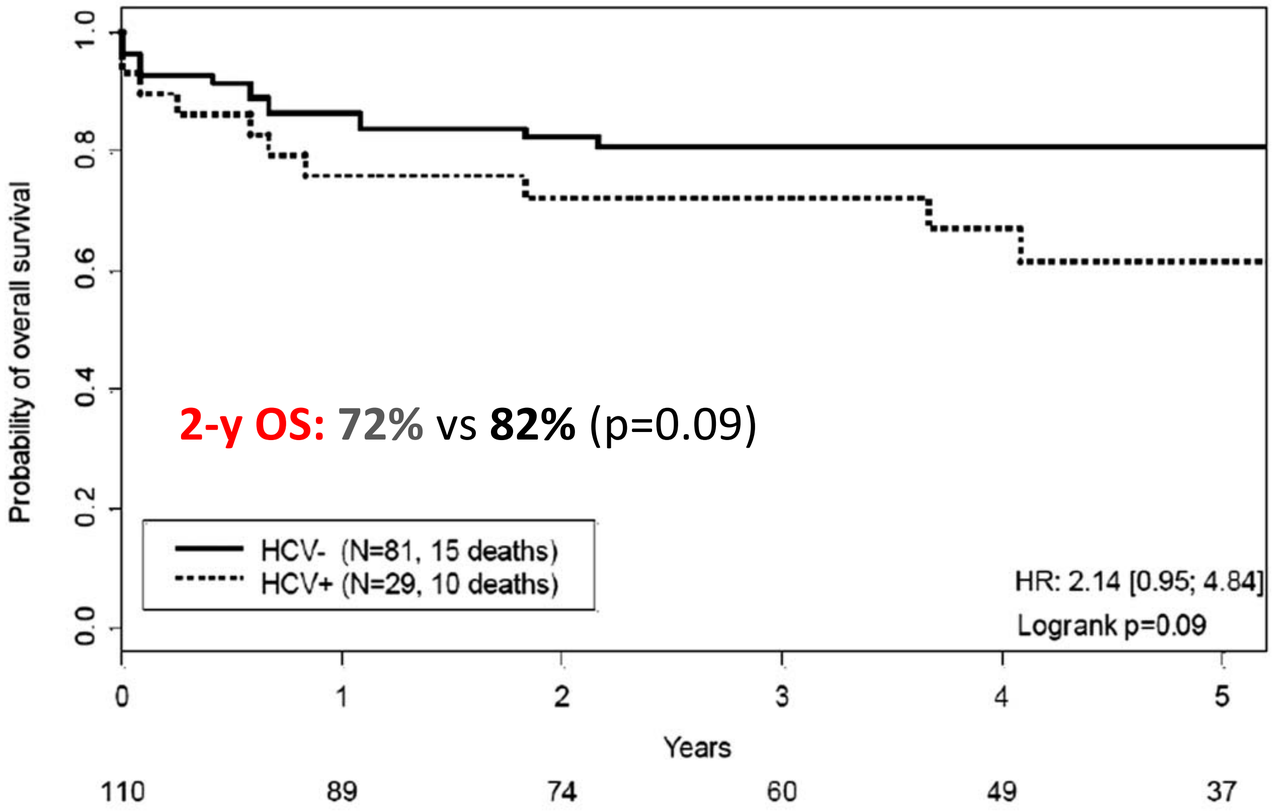
- Prospective observational study
- 89 HCV+ DLBCL pts out of 1095 (8.1%)
- Elderly (≥65 yrs)
- sGA: 45% fit, 29% unfit, 26% frail
- R-CHOP/COMP 49%,
  R-miniCHOP/COMP 36%
- 20 pts treated with DAAs (Conc n=3)
- No grade 3-4 events
- **Long-term favorable outcome**



Arcari A *et al, BJH 2023*

HCV infection and lymphoma risk in PLWHIV

- **French Lymphovir-ANRS-CO16 cohort** (2008-2015), 179 HIV-related lymphomas: 110 NHL, 69 HL
- **Modern antiretroviral therapy (ART) era**
- Prevalence of HCV was higher in pts with HIV+ NHL than in HIV+ pts without NHL (HIV French Hospital Database): **26% *vs* 14%, OR 2.15** (95% CI 1.35–3.32)
- No association between HCV and HL
- **HCV+/HIV+ NHL: trend of inferior OS (*vs* HCV-)**



[1]Besson C *et al*, *AIDS. 2020*

Characteristics of B-NHL in HIV/HCV coinfected pts

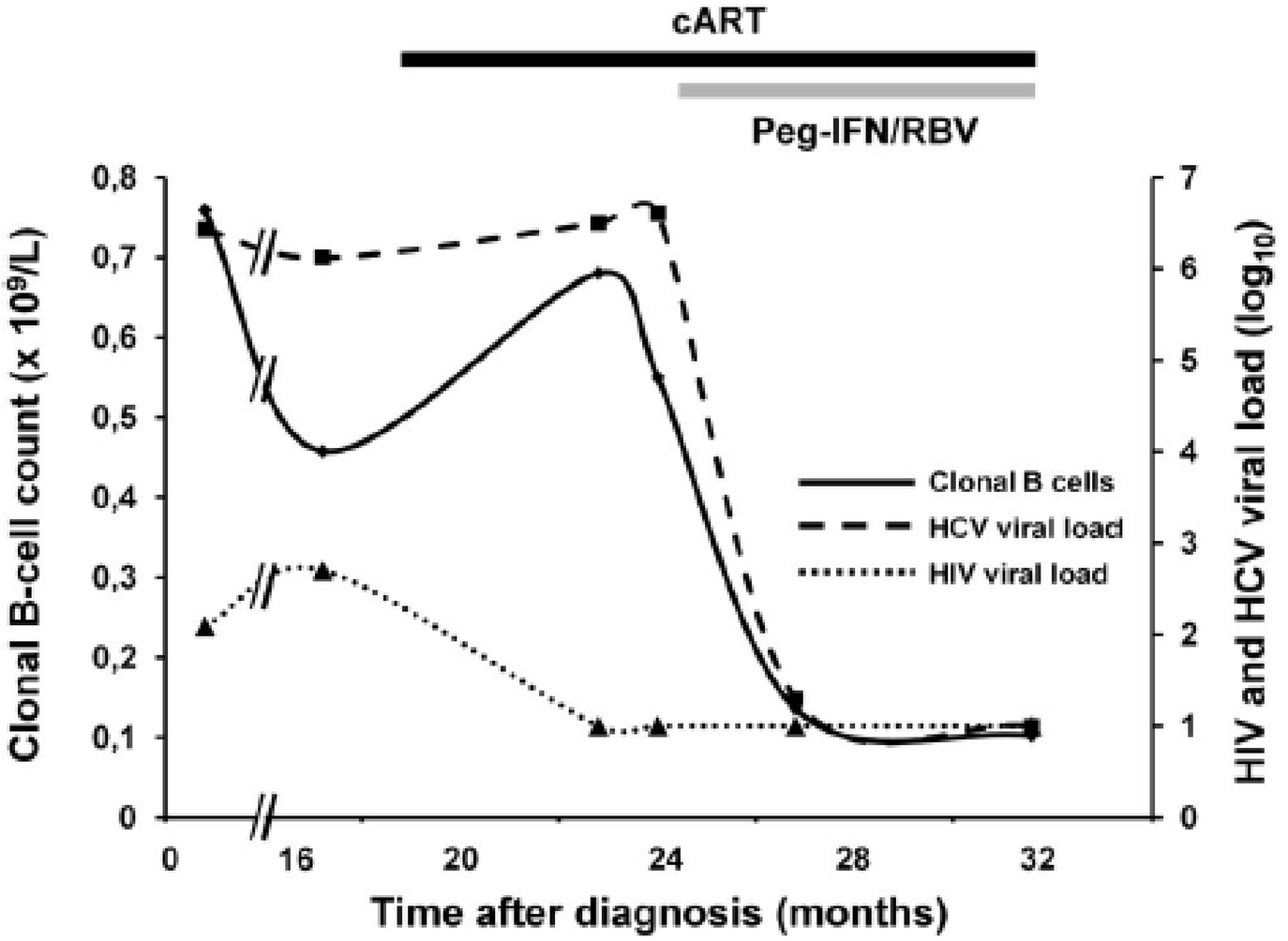
- Only few clinical data (6 pts), all in the pre-DAAs era *(ANRS-CO16 Lymphovir study)*

	Pretreatment Characteristics of NHL					Treatment and Outcome				
Patient	NHL Subtypes	Extranodal Involvement	$CD4^+$ T-Cell Count (/mm^3)	HIV/HCV Viral Load (log_{10})	M Component/ RF	Chemotherapy	cART/ Anti-HCV Therapy	NHL Response	Follow-Up (Months)	Death/ Cause
1	LPL/PBL	Bone marrow, lymph node	550	<1.6/5.8	IgMκ; 65 g/L/No	—	—	—	0.1	Cardiac ischemia
2	MALT/ DLBCL	Stomach	200	5.9/7.1	No/no	R-CHOP; COPADM CYVE	Yes/no	Remission	21	No
3	DLBCL	Bone marrow, liver	347	<1.6/5.9	No/no	R-CHOP-MTX	Yes/no	—	5	Severe infection
4	LPL	Small intestine	235	<1.6/6.1	No/no	R-CVP	Yes/no	Remission	13	No
5	Suggestive MALT	Duodenum	614	<1.6/5.4	No/no	CHL	Yes/no	Remission	25	No
6	SMZL	Spleen, liver	1322	2.1/6.4	No/no	No	Yes/yes	Remission	32	No

Terrier B *et al, JAIDS 2013*

B-NHL HIV/HCV coinfected pts and antiviral therapy

- 1 SMZL coinfected pt responded to peg-IFN + RBV (along with continuing ART)



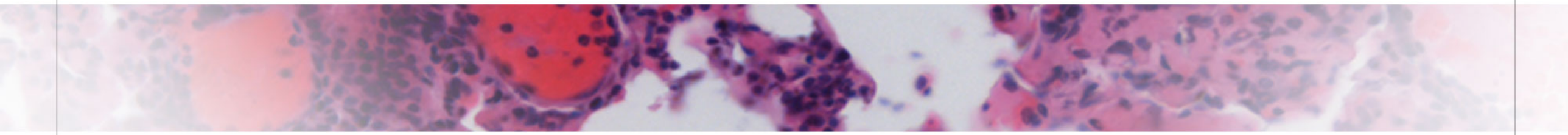
Terrier B *et al, JAIDS 2013*

A retrospective study to evaluate the activity of direct-acting antivirals in patients with HIV- and HCV-associated non-Hodgkin lymphomas

(HIV/HCV-NHL-DAA-2021)

- **Study design:**
  - Retrospective collection of clinical and virological features, treatments and outcome data of all consecutive **pts with NHL *and* HIV/HCV co-infection (HCV-RNA positive)**
  - *Special focus* on **pts affected by DLBCL** and **treated with DAAs**
  - Only pts who received **ART** were included (diagnosis beginning from 2010)
- **15 Centers**

American Society of Hematology
Helping hematologists conquer blood diseases worldwide



Impact of Direct-Acting Antivirals on the Outcome of HIV/HCV Coinfected Patients with Non-Hodgkin Lymphomas in the Modern Anti-retroviral Therapy Era: a Retrospective Multicenter Study of 74 Cases

Michele Merli[1], Alessandro Re, Michele Bibas, Davide Dalu, Emanuele Ravano, Guido Gini, Carlo Visco, Maria Chiara Tisi, Emanuele Cencini, Dario Marino, Massimo Gentile, Roberta Sciarra, Cristina Rovelli, Valentina Zuccaro, Valentina Mazzotta, Cinzia Fasola, Vittorio Ruggero Zilioli, Costanza Fraenza, Benedetta Bianchi, Rosa Daffini, Carmela Pinnetti, Benedetta Lombardi Stocchetti, Barbara Mora, Caterina Cristinelli, Paolo Grossi, Francesco Passamonti, Michele Spina *and* Luca Arcaini

Blood, Vol 138, Suppl 1, 23 Nov 2021, Page 1434

Patients characteristics: clinical features

- **84 HIV/HCV coinfected NHL pts**
  - 58 DLBCL (60% nonGC)
  - 14 Burkitt
  - 4 T-NHL
  - 2 indolent NHL
- Median age: 51 (22-67)
- Previous AIDS: 19 pts (23%)
- 51 pts (69%): **IDU**
- Stage III/IV: 70 pts (83%)
- aaIPI ≥2: 63 pts (75%)
- ≥2 Extranodal sites: 17 pts (29%)

Parameter	All patients (n=84)	DLBCL (n=58)
Age, median (range)	51 (22-67)	52 (22-67)
Gender, M/F (%)	78/6 (93/7)	53/5 (91/9)
Years of HIV before NHL, median (range)	20 (0-37)	21 (0-37)
Previous AIDS defining event, N (%)	19 (23)	13 (22)
HIV transmission group		
Intravenous drug users	56 (67)	35 (60)
Men who have sex with men	15 (18)	11 (19)
Heterosexual	12 (14)	11 (19)
Vertical	1 (1)	1 (2)
Histology		
DLBCL	58 (69)	58 (including 3 DH HGBL, 1 DLBCL transformed from MALT)
Burkitt Lymphomas	14 (17)	
Plasmablatic Lymphomas	6 (8)	
ALCL ALK-	1 (1)	
T – Lymphoblastic Lymphoma	1 (1)	
Peripheral T-Cell lymphoma, NOS	2 (2)	
Gastric MALT	1 (1)	
Lymphoplasmacytic Lymphoma	1 (1)	

Merli M *et al*, *ASH 2021 (updated unpublished data)*

Patients characteristics: virological features

- CD4+ <200/mmc: 38% of pts
- ≥400 HIV-RNA copies/ml: 31% of pts
- ARL-IPI score[1]: interm/high in 64%
- HCV genotype: 1 in 29 pts (58%), 3 in 14 (28%), 4 in 7 (14%)
- Cirrhosis: 37% of pts
  - Child-Pugh B/C in 19% of all pts

[1]**Barta SK *et al*,** *Haematologica. 2014*

Merli M *et al*, *ASH 2021 (updated unpublished data)*

Parameter		All patients (n=84)	DLBCL (n=58)
CD4+/mmc [n=80]	<50	6 (7)	3 (5)
	50-199	25 (31)	16 (30)
	200-499	30 (38)	22 (41)
	≥500	19 (24)	13 (24)
HIV-RNA copies/ml [n=80]	<400	55 (69)	41 (76)
	400-9999	10 (12)	6 (11)
	≥10000	15 (19)	7 (13)
ARL-IPI *(Barta 2014)*			
Low		30 (36)	21 (36)
Intermediate		43 (51)	31 (54)
High		11 (13)	6 (10)
HCV-genotype [n=50]	1	29 (58)	20 (61)
	3	14 (28)	8 (24)
	4	7 (14)	5 (15)
Cirrhosis, N (%) [n=71]		26 (37)	18 (37)
Child-Pugh A/B/C, N		10/11/5	5/8/5
HBsAg pos, N (%)		8 (10)	6 (10)

First-line lymphoma treatments and responses

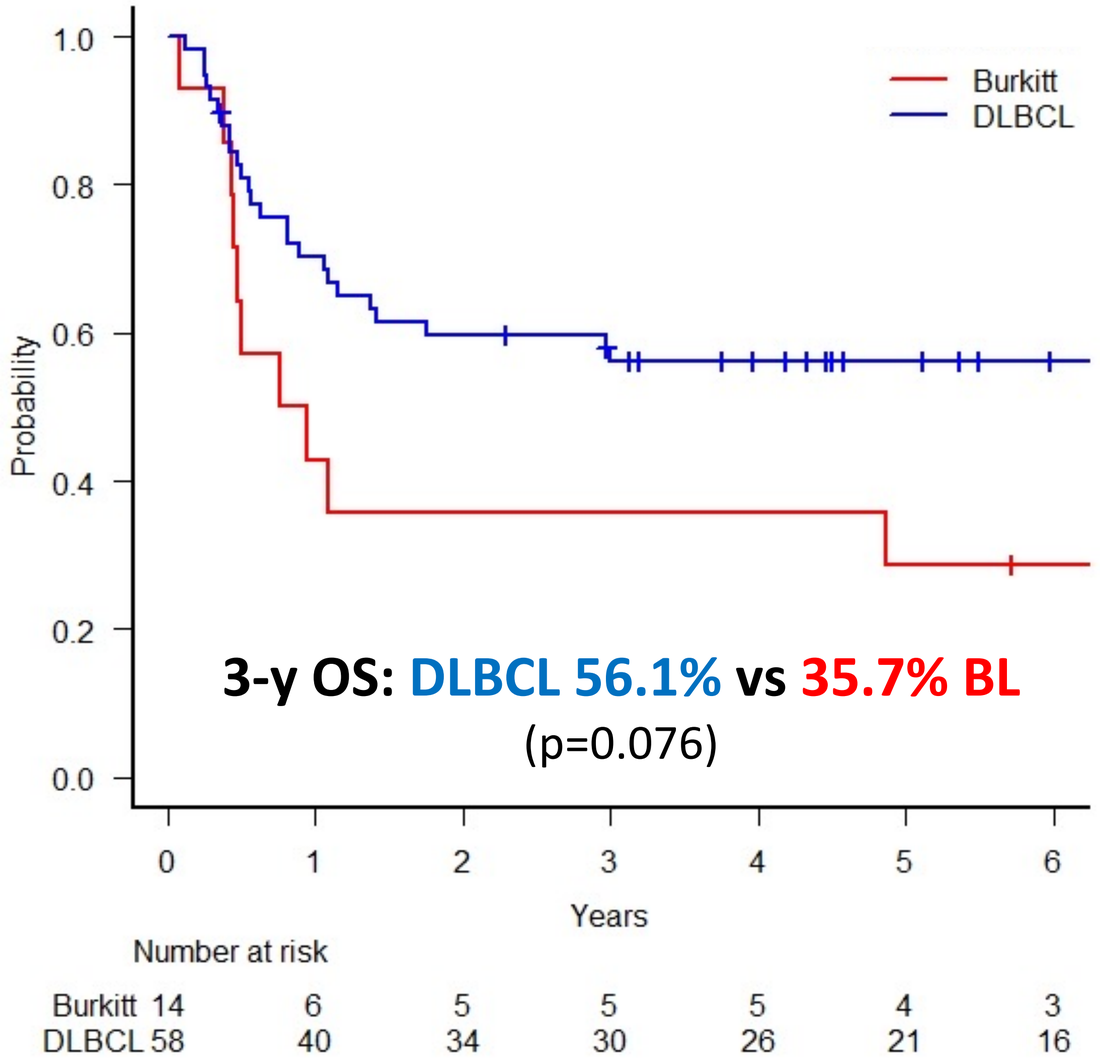
- 80 out of 84 pts (95%) underwent curative first-line therapy alongside ART
- Rituximab was used in 61% of B-NHL pts (64% in DLBCL)
- ASCT in 5 pts (6%)
- (R-)CHOP-like in 57 (68%), (R-)EPOCH in 10 (12%), (R-)CODOX-M/IVAC in 5 (6%)
- 51 pts (64%) achieved a CR, 10 (12%) a PR, 19 (24%) did not respond or progressed (NR/PD)

	DLBCL (n=58)	Burkitt (n=14)	Plasmablastic (n=6)
Regimen			
(R-)-CHOP (-like), n (%)	48 (83)	1 (7)	5 (83)
(R-)-DA-EPOCH, n (%)	5 (9)	4 (29)	1 (17)
(R-)-CODOX/IVAC, n (%)	1 (1)	4 (29)	-
Carmen, n (%)	-	3 (21)	-
Other, n (%)	1 (1)	1 (7)	-
Not treated, n (%)	3 (6)	1 (7)	-
Rituximab use, n (%)	35 (64)	7 (54)	-
ASCT consolidation, n (%)	3 (5)	-	1 (17)
Response			
CR	37 (67)	7 (54)	3 (50)
PR	6 (11)	1 (8)	2 (33)
NR/PD	12 (22)	5 (38)	1 (17)

Merli M *et al*, *ASH 2021 (updated unpublished data)*

Outcomes: PFS and OS

- At a ***median follow-up of 3.1 years***:
  - 37 pts (44%) progressed
    - **3-year PFS 49.2%** (95%CI 38.0-59.4)
  - 46 pts (55%) died
    - **3-year OS 56.3%** (95% CI 44.9-66.3)
    - **Causes of death:**
      - 34 lymphoma progression
      - 9 infection (COVID n=1)
      - 3 second cancer (HCC n=1)



3-y OS: DLBCL 56.1% vs 35.7% BL
(p=0.076)

Merli M *et al*, *ASH 2021 (updated unpublished data)*

Anti-HCV antiviral therapy

- 15 pts received IFN-based regimens
  - 6 SVR (40%)
- After 2016, 26 pts (14 DLBCL) received various DAAs regimens after I-CT (Sofosbuvir-based in 25)
- Sequential in 21, concurrent with I-CT in 5
- Toxicity of DAAs was minimal, with only 2 G≥2 AEs (insomnia and peripheral neuropathy)
- **SVR was achieved in 25/26 pts (95%)**
  - 25/25 (100%) in pts treated *per protocol**

Merli M *et al*, *ASH 2021 (updated unpublished data)*

Parameter	All pts (n=84)	DLBCL (n=58)
ART, N (%)	84 (100)	58 (100)
(peg-) interferon (+/- RBV), N	15	10
SVR, N (%)	6 (40%)	4 (40%)
DAAs, N	26	17
Sofosbuvir + Ribavirin	1	1
Sofosbuvir + Simeprevir	1	0
Sofosbuvir + Daclatasvir	4 (+RBV in 2)	2 (+RBV in 1)
Ledipasvir-Sofosbuvir	8 (+ RBV in 1)	5 (+ RBV in 1)
Sofosbuvir-Velpatasvir	11	8
Grazoprevir-Elbasvir	1	1
SVR after DAAs (ITT), N (%)	25/26 (96%)	16/17 (94%)
(per-protocol), N (%)	25/25 (100%)	16/16 (100%)

** The only patient who did not achieve SVR discontinued DAAs autonomously after few weeks*

Details of 2 patients with indolent lymphomas

1. M, 59 years, IDU, gastric EMZL, genotype 1A

   ART (Tenofovir Afenamide, Emtricitabina, Darunavir, Ritonavir

   Treated with anti-HP antibiotic therapy, CR, along with ART)

   pegIFN + RBV: failed to achieve SVR

   Sofosbuvir + Daclatasvir + Ribavirin (2015): SVR

   Alive, CR, SVR

2. F, 47 years, IDU, lymphoplasmacytic lymphoma (abdominal wall), genotype 1A

   ART (dolutegravir, lamivudine)

   Treated with chlorambucil, NR

   pegIFN + RBV + Teleprevir: **SVR and CR of lymphoma**

   Alive, CR, SVR

Merli M *et al*, *ASH 2021 (updated unpublished data)*

Prognostic factors - Univariate analysis (OS)

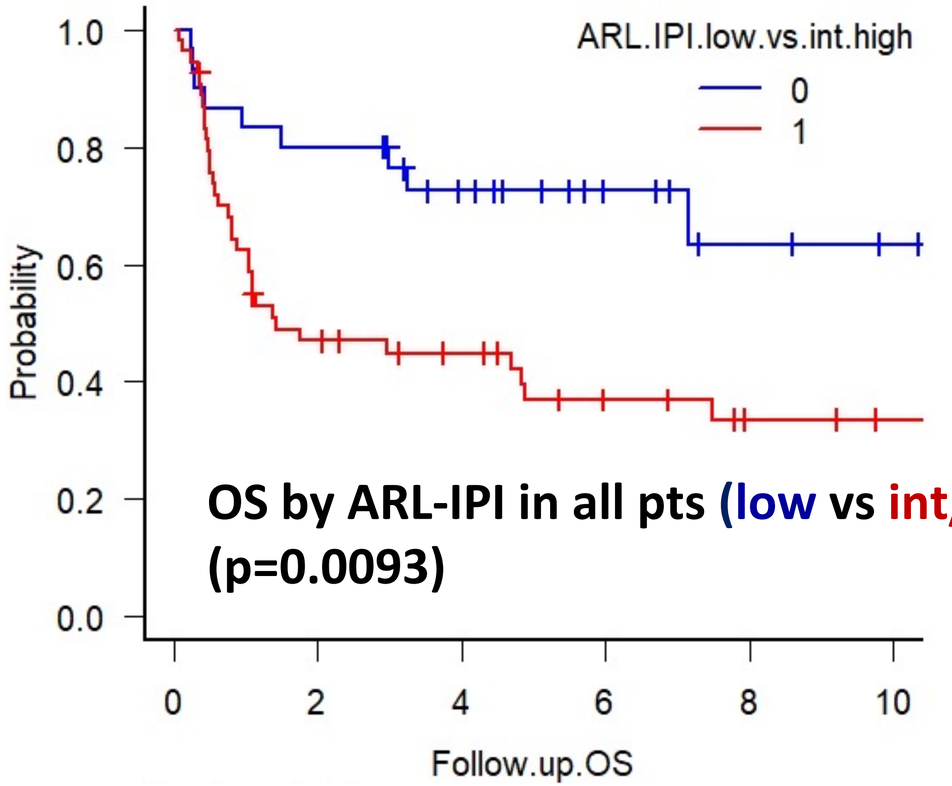
	All pts			DLBCL		
	HR	95% CI	p level	HR	95% CI	p level
ECOG ≥2	2.11	1.10-4.03	0.023	1.74	0.78-3.88	0.171
ARL-IPI	2.27	1.12-4.61	0.022	2.83	1.14-7.05	0.025
SVR after IFN or DAAs	0.32	0.14-0.79	0.003	0.24	0.08-0.71	0.009

Merli M *et al*, *ASH 2021 (updated unpublished data)*

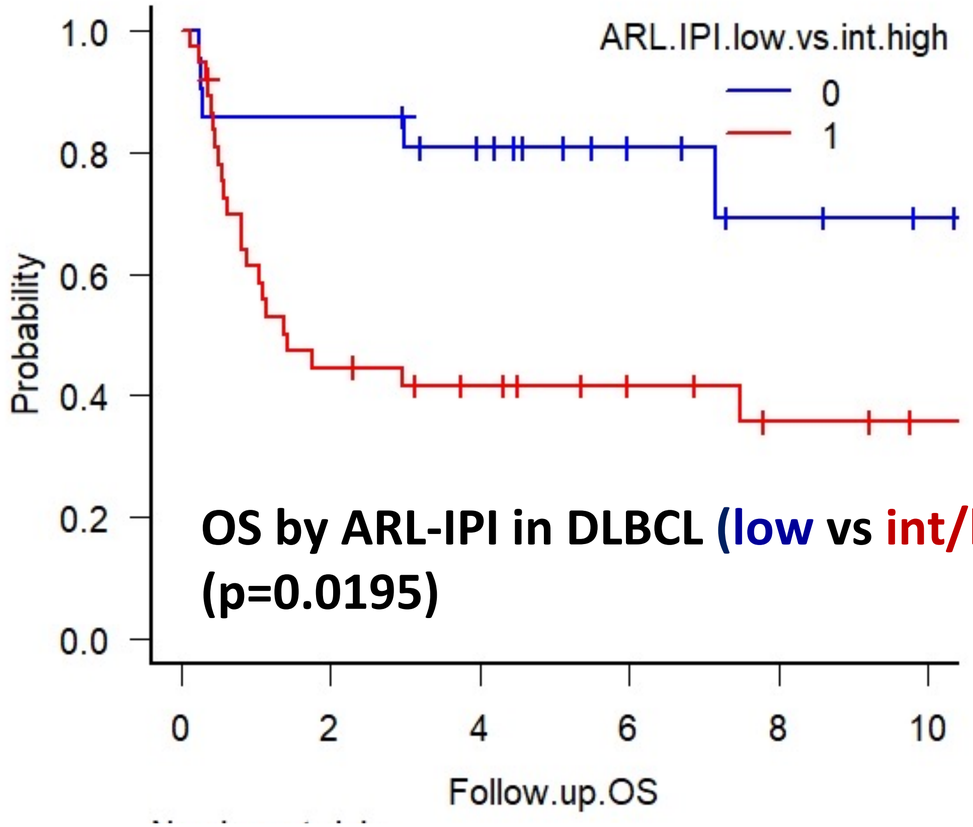
ARL-IPI and OS

- ARL_IPI is composed by aaIPI (x2), extranodal sites, HIV score (composed of CD4+ count, HIV viral load and previous history of AIDS)

[1]**Barta SK *et al*,** *Haematologica. 2014*



OS by ARL-IPI in all pts (low vs int/high) (p=0.0093)



OS by ARL-IPI in DLBCL (low vs int/high) (p=0.0195)

Merli M *et al*, *ASH 2021 (updated unpublished data)*

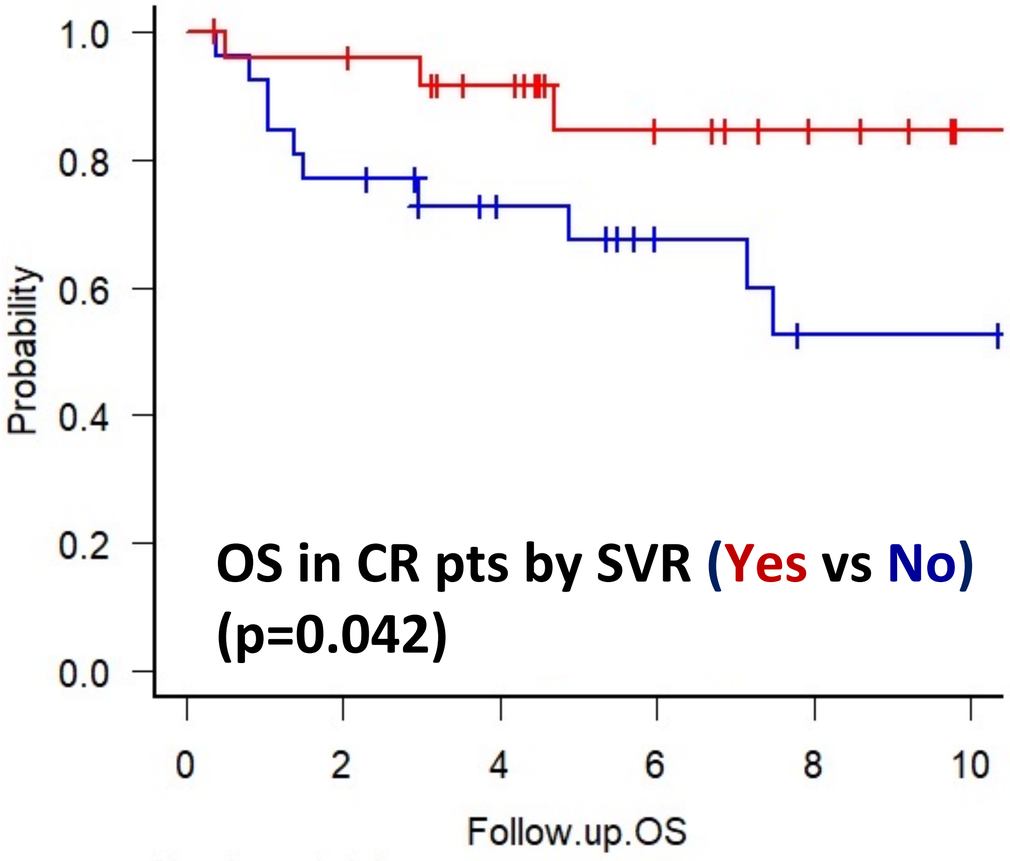
Prognostic Factors Multivariable analysis (OS)

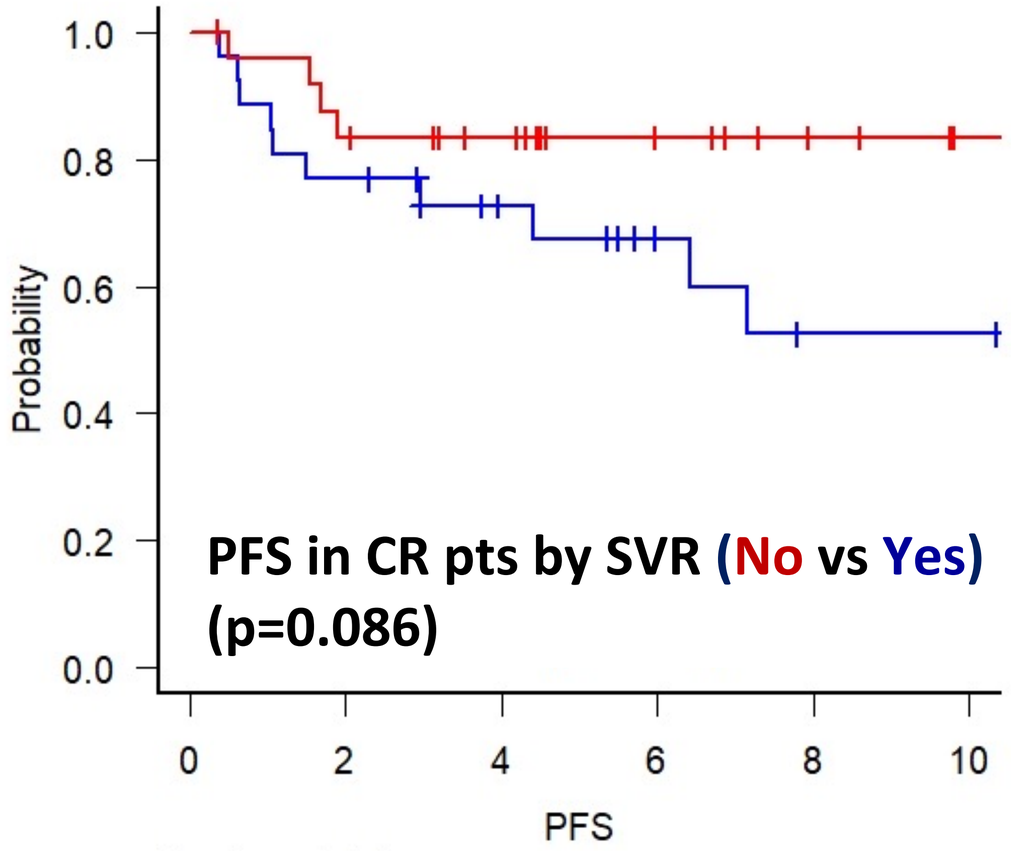
All pts	HR	95% CI	p level
ARL-IPI	2.27	1.12-4.61	0.022
SVR after IFN or DAAs	0.32	0.14-0.79	0.003
DLBCL pts			
ARL-IPI	2.52	1.01-6.3	0.048
SVR after IFN or DAAs	0.27	0.09-0.78	0.016

Merli M *et al*, *ASH 2021 (updated unpublished data)*

Anti-HCV therapy and Outcome (all patients in CR)

- The achievement of SVR after IFN or DAAs was associated with significantly better OS (p=0.042) and with a borderline better PFS ***in patients who achieve CR after first-line I-CT***

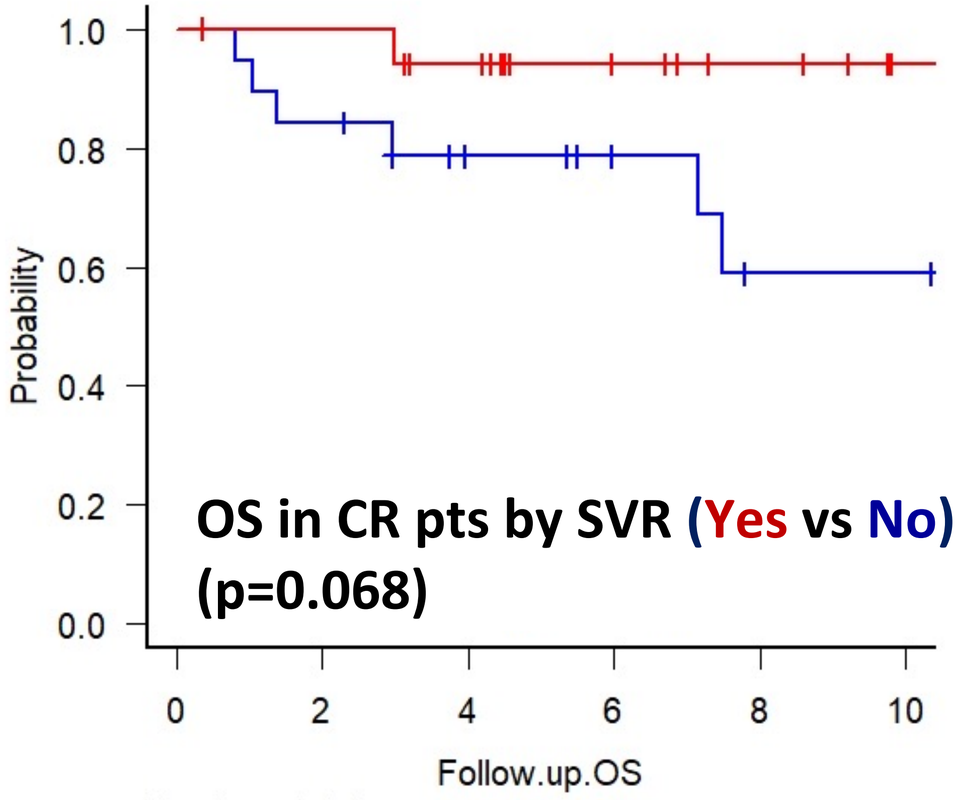




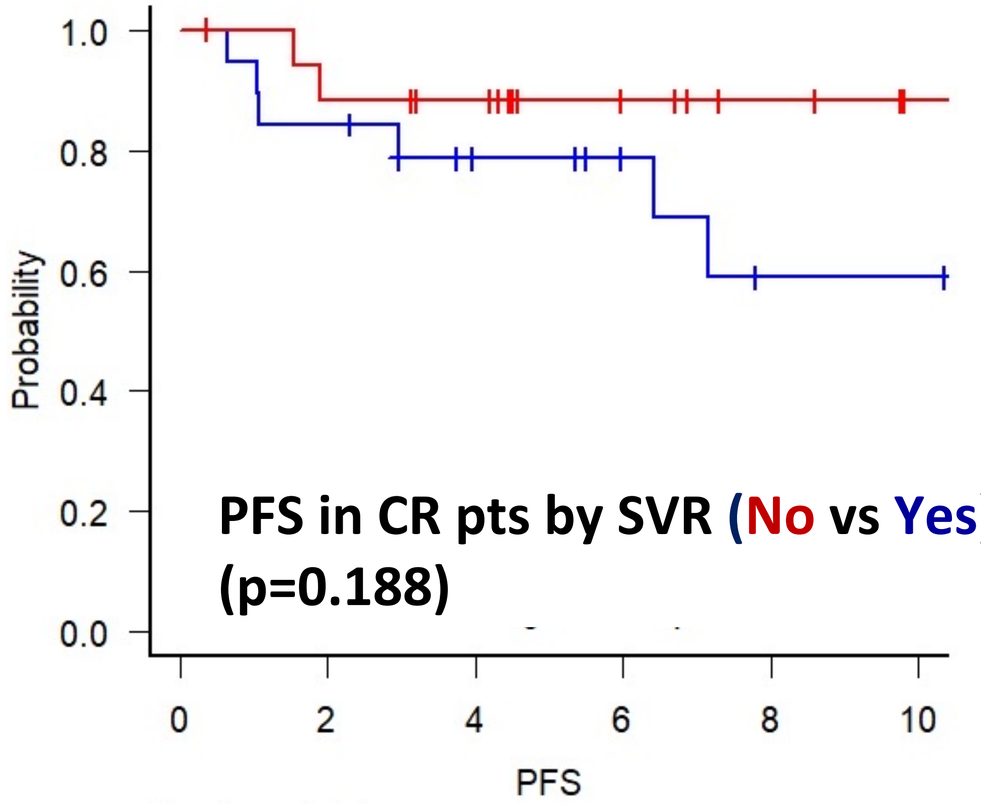
Merli M *et al*, *ASH 2021 (updated unpublished data)*

Anti-HCV therapy and Outcome (DLBCL pts in CR)

- The achievement of SVR after IFN or DAAs was associated with a borderline better OS (p=0.042) ***in patients who achieve CR after first-line I-CT***



OS in CR pts by SVR (Yes vs No) (p=0.068)



PFS in CR pts by SVR (No vs Yes) (p=0.188)

Merli M *et al*, *ASH 2021 (updated unpublished data)*

Conclusions

- In this very high-risk series of HIV/HCV coinfected patients with NHL, mainly represented by DLBCL, the administration of DAAs during or after immuno-chemotherapy, and along with ART, resulted feasible and effective (SVR 95%)
- SVR after DAAs or IFN displayed an independent favourable influence on OS
- These results strongly support DAAs' use in this *hard to treat* population