PROTOCOLLI FIL

LINFOMI INDOLENTI NON FOLLICOLARI

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COMMISSIONE LINFOMI INDOLENTI

PROTOCOLLI
LINFOMI INDOLENTI

Macroglobulinemia di Waldenstrom → **FIL-BRB**

Linfomi HCV + → **Studio BArT**
(**B**-cell Lymphoma **A**ntivi**r**al **T**reatment)

MACROGLOBULINEMIA DI WALDENSTRÖM

"Studio di fase II con Bortezomib, Rituximab e Ribomustin -BRB- in pazienti affetti da linfoma non Hodgkin infoplasmocitico/Morbo di Waldenstrom in prima recidiva"

ID study: FIL BRB
EudraCT Number: 2013-005129-22

SPONSOR
Fondazione Italiana Linfomi (FIL)

COORDINATORI DELLO STUDIO
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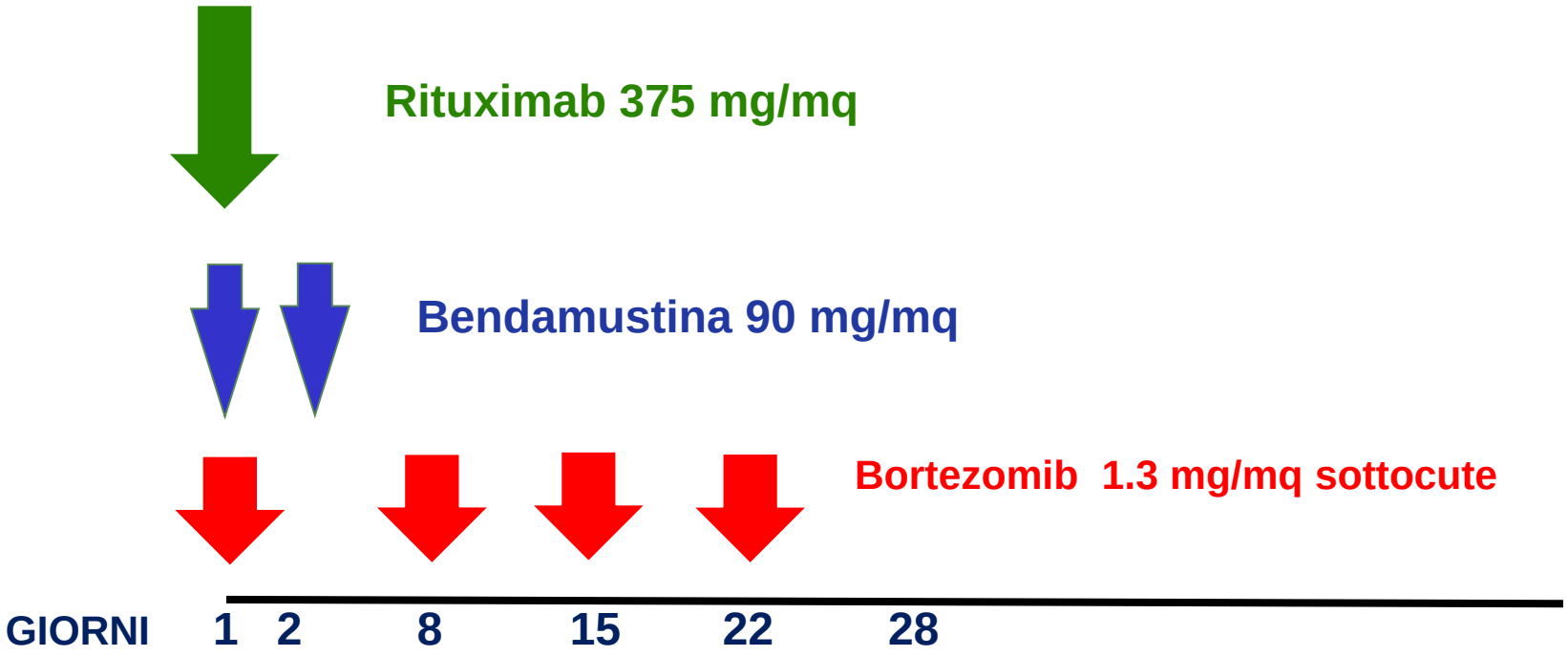
PROTOCOLLO FIL-BRB

6 Cicli ripetuti ogni 28 giorni



Bortezomib verrà fornito dalla Janssen Cilag

MACROGLOBULINEMIA DI WALDENSTRÖM

OBIETTIVO PRIMARIO

- Valutare la sopravvivenza libera da progressione di malattia.

Lo studio ha come obiettivo l'ottenimento di una migliore PFS a 18 mesi, almeno pari al 65%, rispetto al 50% ottenibile con altre terapie riportate in letteratura

OBIETTIVI SECONDARI

- Valutare il tasso di risposta globale
- Valutare la sopravvivenza globale
- Valutare il profilo di tossicità

DIMENSIONE DEL CAMPIONE

- Durata dello studio **65 mesi** (→ 4 anni nella versione pre-arruolamento): arruolamento 41 mesi (→ 24 nella versione pre-arruolamento) e follow-up 24 mesi dall'ultimo paziente arruolato
- Dimensione campionatura: **38 pazienti** (→ 61 nella versione pre-arruolamento)

PROTOCOLLO FIL-BRB

CRITERI DI INCLUSIONE

- ✓ Esame istologico (midollo osseo o biopsia linfonodale) lymphoplasmacytic/citoid lymphoma/ Waldenström macroglobulinemia
- ✓ Pazienti con malattia in recidiva/progressione dopo una iniziale risposta ad una prima linea di chemioterapia o con malattia resistente ad una linea chemioterapica
- ✓ *Possono essere inseriti pazienti trattati in I linea con Bendamustina o Bortezomib (almeno una remissione parziale durata 24 mesi)*
- ✓ Malattia attiva: sintomi costituzionali e/o citopenia e/o organomegalia e/o sindrome da iperviscosità e/o malattia bulky
- ✓ Età ≥ 18 anni
- ✓ ECOG performance status 0-2

CRITERI DI ESCLUSIONE

- ✓ Malattia attiva di HCV, HBV
- ✓ HIV positività
- ✓ Clearances creatininica < 30 ml/min
- ✓ Neuropatia di grado > 2

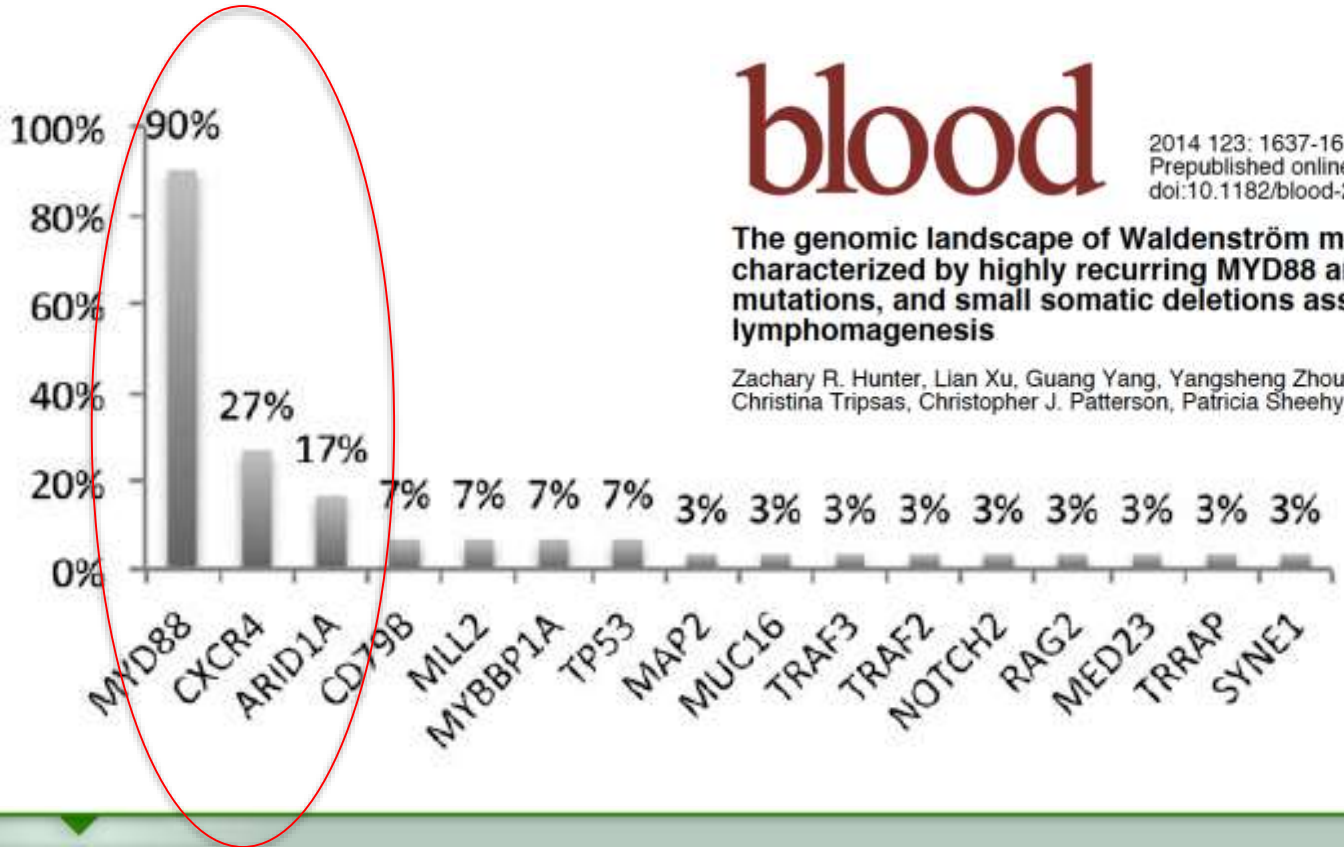
Valutazione della Tossicità Neurologica
sec. Criteri NCI

Tossicità sensoriale e motoria su una scala da 0 a 4 (appendice B)

BIO-BRB STUDY

BIOLOGICAL BACKGROUND

The panorama of somatic mutations in Waldenström Macroglobulinemia (WM) is being rapidly unraveled. **The recent discovery of recurring, acquired somatic point mutation affecting some crucial genes, as MYD88, CXCR4 and ARID1A**, has improved considerably our understanding of the pathogenesis of WM. Interestingly, some of these mutations impact on prognosis and drug resistance[1].



blood

2014 123: 1637-1646
Prepublished online December 23, 2013;
doi:10.1182/blood-2013-09-525808

The genomic landscape of Waldenström macroglobulinemia is characterized by highly recurring MYD88 and WHIM-like CXCR4 mutations, and small somatic deletions associated with B-cell lymphomagenesis

Zachary R. Hunter, Lian Xu, Guang Yang, Yangsheng Zhou, Xia Liu, Yang Cao, Robert J. Manning, Christina Tripsas, Christopher J. Patterson, Patricia Sheehy and Steven P. Treon

BIO-BRB study

Mutational characterization of Waldenström Macroglobulinemia and minimal residual disease monitoring in the context of BRB phase II trial by Fondazione Italiana Linfomi (FIL)

Referente per lo studio biologico: Simone Ferrero Ematologia U Torino

SPECIFIC AIMS

- **Mutational screening** of baseline samples for the most frequently mutated genes in WM: MYD88, CXCR4 and ARID1A
- **MRD quantitative evaluation** on $MYD88^{L265P}$ by the sensitive ddPCR approach at baseline and after BRB treatment on BM and PB
- Development of a sensitive, **plasma-based ddPCR tool** to detect $MYD88L^{265P}$ on circulating tumor DNA

ARRUOLAMENTO PAZIENTI

ARRUOLAMENTI CONCLUSO 38

(17 pazienti inseriti nello studio biologico)

Paziente	Interruzione dopo…	Causa
GI.CA.0006BRB	5° ciclo	hematological toxicity - thrombocytopenia
AMM0008BRB	3° ciclo	hematological toxicity - persistent neutropenia
CB0011BRB	5° ciclo	hematological toxicity - thrombocytopenia, neutropenia
GS0013BRB	4° ciclo	progressive disease
0028BRB	4° ciclo	extra hematological toxicity - lipothymia
0030BRB	5° ciclo	extra hematological toxicity - ischemic event

"A multicenter study to evaluate the anti-viral activity of an interferon-free treatment for patients with hepatitis C virus-associated indolent B-cell lymphomas"

ID Study: FIL_BArT (B-cell Lymphoma **A**ntivira**l** **T**reatment, **BArT study)**

EudraCT number: 2015-004830-81

STUDY COORDINATOR

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Michele Merli, *Varese*

PATHOLOGY REVIEW

Marco Paulli, *Pavia*

MOLECULAR STUDIES

Simone Ferrero, *Torino*

ENDPOINTS

Primary endpoint

- Sustained virologic response at 12 weeks (**SVR12**)

Secondary endpoints

- Overall response rate (**ORR**) of lymphoma

  (Lymphoma response will be assessed 12 weeks after the end of AT)

- **PFS, EFS, OS**

- Reduction of peripheral lymphocytes, lymph nodes and splenomegaly and amelioration of cytopenias during AVT (monthly evaluation)

- **Rate of virological responses**: *rapid virologic response* (RVR), *extended RVR* (eRVR), *early virologic response* (EVR), *early responders*, *partial response*, *breakthrough*, *end-of-treatment response* (ETR), *relapse*, *null-response*

- **Toxicity** (CTCAE version 4.03), evaluated by incidence of severe/life-threatening events (grade 3, 4 and 5) and/or SAE

INCLUSION CRITERIA (1)

1. Age > 18 years
2. **Indolent B cell lymphoma:**
    - ***Marginal Zone Lymphoma*** *(MZL):*
        - ***Nodal*** *(NMZL)*
        - ***Extranodal*** *(EMZL, MALT-type)*
        - ***Splenic*** *(SMZL)*
        - ***Disseminated***
    - ***Lymphoplasmacytic lymphoma*** *(LPL)*
    - ***Small Lymphocytic Lymphoma*** *(SLL)*
    - ***Follicular lymphoma*** *(FL)* ***grade 1-2***
    - ***CD5-negative B-cell lymphoma NOS***
3. **HCV-RNA positive** patients
4. **Assessable HCV genotype**
5. **No previous therapy for lymphoma**

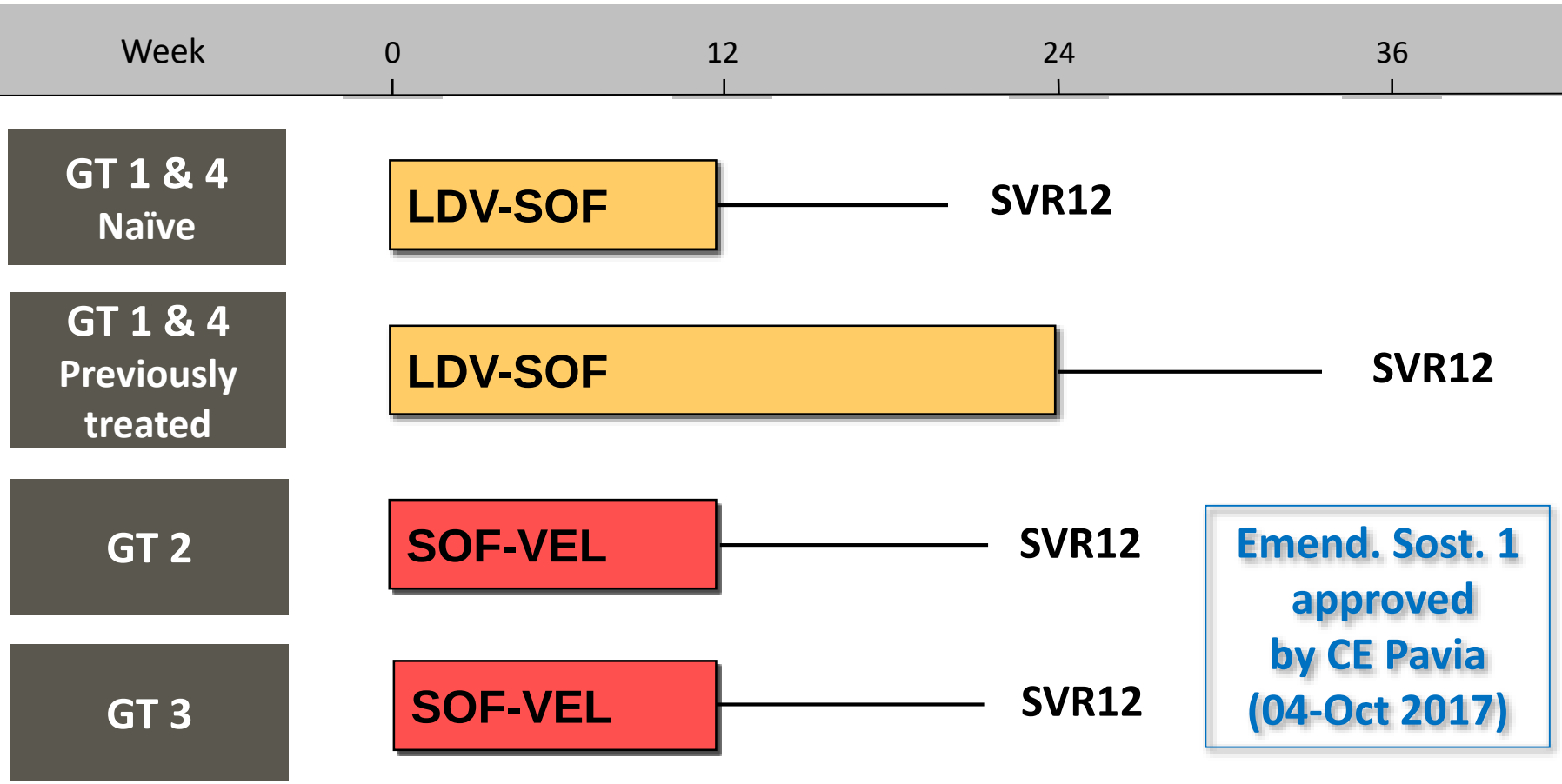
INCLUSION CRITERIA (2)

6. **Measurable disease** after diagnostic biopsy (*longest axis ≥1.5 cm for nodal and ≥1 cm for extranodal lesions)* **and/or evaluable disease** *(quantifiable BM infiltrate and >5 x10^9/L clonal B-cells in PB in case of exclusive BM/leukemic disease)*
7. **No need for immediate lymphoma treatment**, defined by the ***absence of all the following criteria***:
   - systemic symptoms
   - bulky (>7 cm) and symptomatic nodal or extranodal mass
   - symptomatic splenomegaly
   - progressive leukemic phase
   - serous effusions
8. Performance status < 2 according to ECOG scale
9. **Adequate haematological counts**:
   - ANC > 1 x 10^9/l
   - Hb > 9 g/dl (transfusion independent)
   - Plt > 50 x 10^9/l (transfusion independent)

MAIN EXCLUSION CRITERIA

- Diagnosis of lymphoblastic lymphoma, Burkitt lymphoma, mantle cell lymphoma, follicular lymphoma grade 3, diffuse large B-cell lymphoma, primary mediastinal lymphoma
- Previous anti-HCV antiviral treatment with SVR
- Diagnosis of **cirrhosis** (histological *or* Stiffness >12 KpA at fibroscan)
- Uncontrolled diabetes or severe cardiovascular disease
- Concomitant therapy with **amiodarone**
- History of any other clinically relevant disease or metabolic disturbances (including ongoing bacterial, fungal or viral infections)
- HIV positivity
- **HBV positivity** (HBsAg+ or HBV-DNA+) with the exception of HBcAb+, HBsAg-, HBsAb+/- with HBV-DNA negativity
- If female: pregnant or breast-feeding

NEWS FOR G2 E G3 (EMEND. SOST. 1)



LDV-SOF: Ledipasvir-Sofosbuvir (90/400 mg) one pill once daily (***Harvoni***, *Gilead*)

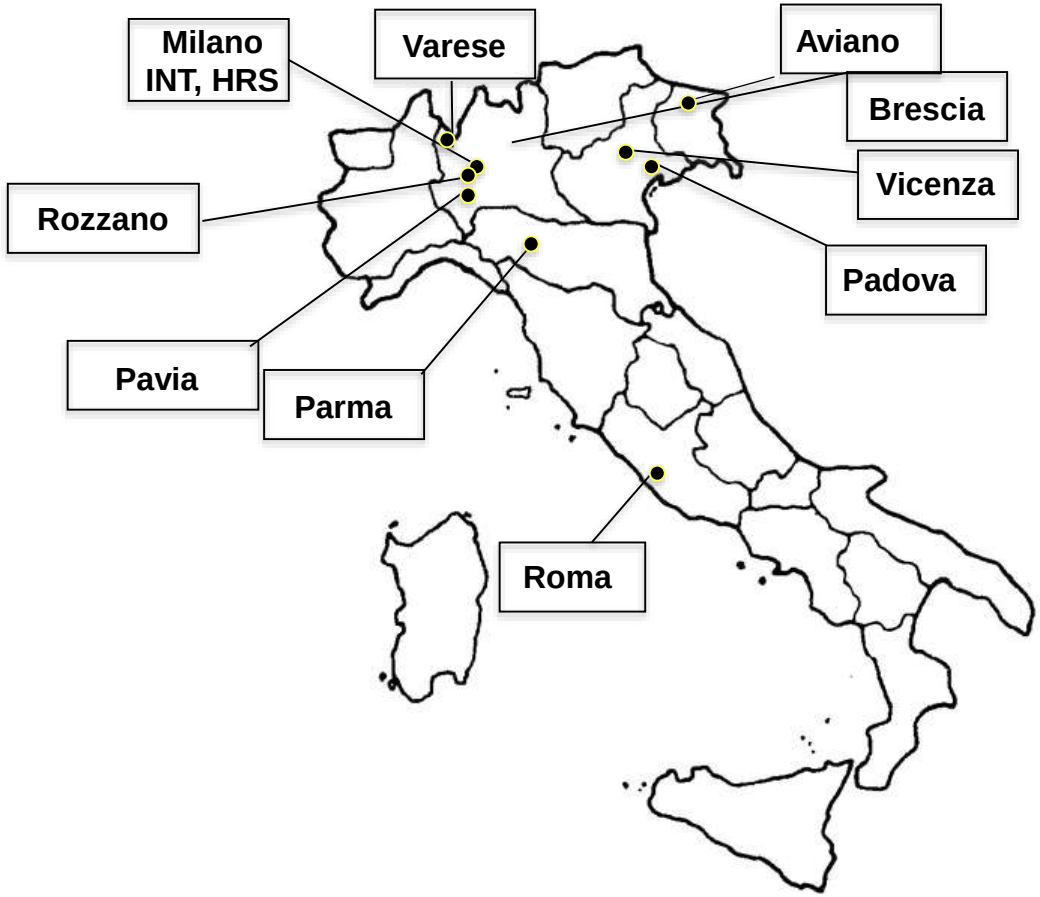
SOF-VEL: Sofosbuvir-Velpatasvir (400/100 mg) one pill once daily (***Epclusa***, *Gilead*)

STATUS ARRUOLAMENTO (25/10/17)

22 pazienti arruolati (44 previsti)

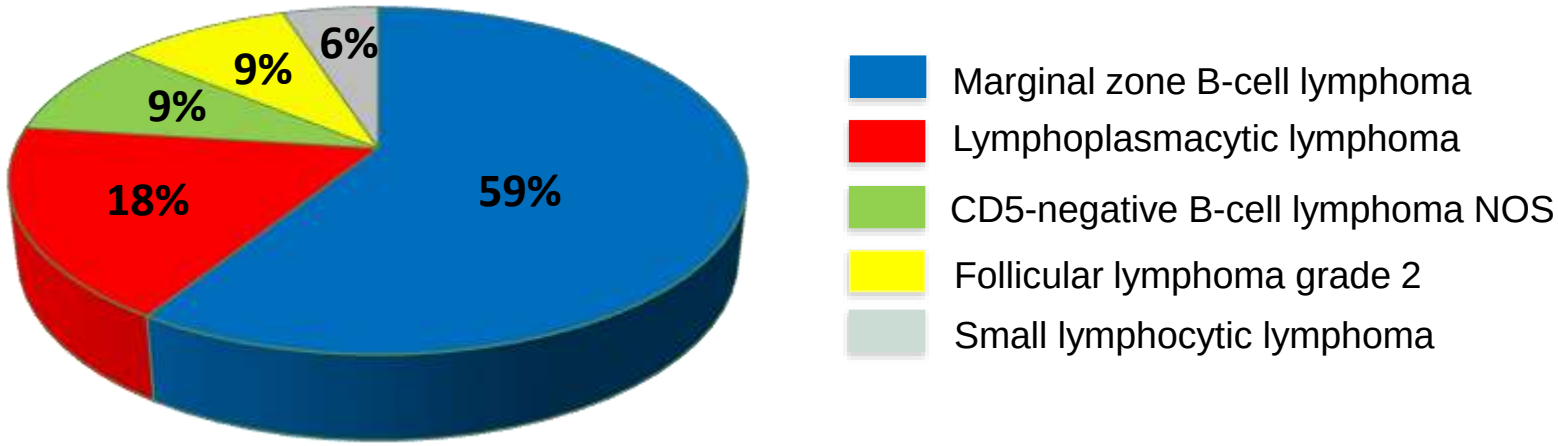
Centri attivi che hanno arruolato almeno 1 paziente (11/14):

- Aviano
- Brescia
- Milano INT
- Milano S. Raffaele
- Milano Humanitas
- Padova
- Parma
- Pavia
- Roma La Sapienza
- Varese
- Vicenza



PATIENT CHARACTERISTICS (N=22)

Histology	N	%
Marginal zone B-cell lymphoma	13	59
Lymphoplasmacytic lymphoma	4	18
CD5-negative B-cell lymphoma NOS	2	9
Small lymphocytic lymphoma	2	9
Follicular lymphoma grade 2	1	5



PATHOLOGICAL REVIEW AND MOLECULAR STUDIES

External pathology review: Prof. Marco Paulli, *University of Pavia*

- Paraffin block or 20 unstained slides

Molecular studies *("Bio-BArT"):* Dr. Simone Ferrero, *University of Torino*

Perspective collection of biological samples (BM and/or PB) at screening, during treatment, post-treatment, follow-up and at progression, for:

- **MRD analysis by ASO-quantitative PCR (*IgH* rearrangement)**
  - Correlation of MRD kinetics with viral response
- **Profiling of the immunoglobulin gene repertoire** of HCV-driven lymphomas
  - Correlation with treatment response
- **Mutational screening** of baseline samples
  - Correlation with treatment response
  - Comparison of the mutational landscape found in different tissues: BM, PB and lymph nodes

MOLECULAR STUDIES (BIO-BART)

External pathology review: Prof. Marco Paulli, *University of Pavia*

- Paraffin block or 20 unstained slides

Molecular studies *("Bio-BArT"):* Dr. Simone Ferrero, *University of Torino*

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  - Comparison of the mutational landscape found in different tissues: BM, PB and lymph nodes

500€ + IVA for each shipping!
("infected biological samples")

STUDIO BART

Per segnalare pazienti da arruolare nello studio contattare

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Ematologia dott. Vitolo

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