Clinical Protocol

Rituximab, bendamustine and cytarabine followed by venetoclax (V-RBAC) in high-risk elderly patients with mantle cell lymphoma (MCL)

ID Study: FIL_V-RBAC
EudraCT number: 2017-004628-31

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3. INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug and the conduct of the study.

Investigator's Signature Date

Name of Investigator (Typed or Printed)

Institution, Address*

Phone Number*

Investigator-Sponsor Signature* Date
(where required)

Name of Coordinating Investigator (Typed or Printed)

Institution

* If the address or phone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor and will not require protocol amendment(s).

4. SYNOPSIS

Study ID	FIL_V-RBAC
Eudract N°	2017-004628-31
Title of the study	Rituximab, bendamustine and cytarabine followed by venetoclax (V-RBAC) in high-risk elderly patients with mantle cell lymphoma (MCL)
Phase of the study	II
Investigational product	ABT-199 (Venetoclax) (Abbvie)
Protocol version	1, 16 NOVEMBER 2017
Centers	40 Centers actively involved in the FIL
Protocol Definitions	Enrolled patients will be stratified in "low risk (LR)", and "high risk (HR)", depending on these 3 factors: morphology (blastoid versus others), Ki67 expression (≥30% versus others), *TP53* mutation/*TP53* deletions (present versus not). Patients with any of the three risk factors will be defined as HR.
Study Objectives and Endpoints	Primary Objective To evaluate whether the addition of venetoclax after R-BAC to *HR* patients with MCL, as defined above, improves the results of the standard R-BAC, in terms of PFS. Primary Endpoint 2-years progression-free survival (PFS) of the *HR* patients from date of enrollment Secondary Endpoints - The proportion of molecular response (analyzed in the labs of the FIL-MRD Network) - The progression-free survival (PFS) of all enrolled patients, and of different subgroups (i.e TP53 mutated patients) - The overall survival (OS) - The duration of responses (DoR) - The proportion of complete remission (CR) before and after venetoclax in the HR group and/or in the LR not responding to R-BAC. - The proportion of patients that complete the expected treatment schedule - The safety of venetoclax when administered as consolidation or maintenance after R-BAC
Study design	This is a Phase 2, one-arm, prospective multicenter study
Duration of the study	Time of enrollment: 2.5 years Minimum follow-up for the primary endpoint: 2 years Study duration: 7 years
Number of patients	52 *HR* patients (approximately 130 patients to be enrolled, overall)
Inclusion criteria	1. Previously untreated patients with MCL aged ≥65 years if they are FIT according to the geriatric CGA assessment. 2. age ≤64 years not eligible to high-dose chemotherapy plus transplantation at physician's judgement (details for non eligibility to be recorded by means of the CIRS, Cumulative Illness rating Scale). 3. Measurable nodal or extranodal disease ≥ 1.5 cm in longest diameter,

	and measurable in 2 perpendicular dimensions. 4. ECOG performance status ≤2. 5. Positivity for cyclin D1 and/or SOX11 [the latter being mandatory in cases lacking cyclin D1- or t(11;14)-negative]. 6. Adequate renal function (Creatinine clearance >50 mL/min), with preserved diuresis. 7. Adequate liver function: alanine aminotransferase (ALT)/aspartate aminotransferase (AST) <2.5 x upper limit of normal (ULN) value, total bilirubin <1.5 x ULN, unless directly attributable to the patient's tumor or to congenital causes. 8. Hepatitis B core antibody (HBcAb) positive/HBsAg negative/HBV-DNA negative patients may be enrolled if correct antiviral prophylaxis is administered at least 2 weeks before initiating protocol treatment. 9. Written informed consent.
Exclusion criteria	1. Human immunodeficiency virus (HIV) positive. 2. Previous treatment for lymphoma. 3. Disease confined to the bone marrow/peripheral blood/spleen, without any other nodal or extranodal involvement. 4. In-situ MCL. 5. Medical conditions or organ injuries that could interfere with administration of therapy. 6. Active bacterial, viral, or fungal infection requiring systemic therapy. 7. Seizure disorders requiring anticonvulsant therapy. 8. Severe chronic obstructive pulmonary disease with hypoxiemia. 9. History of severe cardiac disease: New York Heart Association (NYHA) functional class III-IV, myocardial infarction within 6 months, ventricular tachyarrhythmias, dilatative cardiomyopathy, or unstable angina. 10. Uncontrolled diabetes mellitus. 11. Active secondary malignancy. 12. Known hypersensitivity or anaphylactic reactions to murine antibodies and proteins, to Bendamustine or mannitol. 13. Major surgery within 4 weeks of study Day 1. 14. HBsAg+ 15. HCVAb+ patients with active viral replication (HCV-RNA+ with AST>2 x normal limit) 16. Any co-existing medical or psychological condition that would preclude participation in the study or compromise the patient's ability to give informed consent, or that may affect the interpretation of the results, or render the patient at high risk from treatment complications. 17. CNS involvement 18. Chronic treatment with strong or moderate CYP3A inhibitors (e.g. ketoconazole, ritonavir, clarithromycin, itraconazole, voriconazole)
Study treatment	All patients who satisfy the inclusion criteria will receive R-BAC as induction therapy (Rituximab 375 mg/m2 d1, Bendamustine 70 mg/m2 d1,2 Cytarabine 500 mg/m2 d1,2,3; q28). All patients will be treated with 4 cycles of R-BAC, recycling every 28 days. Patients will undergo histological and molecular evaluation, and then differentiated according to their risk profile. 1) Low risk patients (*LR*): these patients are meant to receive up to 6 cycles of R-BAC. Patients with PD after 4 cycles will stop treatment and be removed from protocol-specified therapy. Patients with SD after 2 cycles will be re-evaluated for response after 4 cycles and they will stop treatment if in PD. Responsive patients (CR, Cru, PR after 2 cycles; SD

<table>
<tr><td></td><td>after 2 cycles that improved their response at the end of cycle 4) will receive a total of 6 cycles. Patients experiencing excess of toxicity during any of the first 4 cycles may be treated with a total of 4 cycles (end of treatment after 4 cycles) regardless of response to treatment. Patients with less than CR after completion of induction treatment (6 or 4 cycles) will proceed to venetoclax consolidation (Vcons) and maintenance phase (Vmaint), and will be considered as HR patients.
2) <u>High risk patients (HR)</u>: these patients are meant to receive 4 R-BAC cycles before consolidation with venetoclax. However, patients with PD during or after the induction phase will stop treatment and be removed from protocol-specified therapy. Patients responsive to the initial 2 R-BAC or with SD, will be treated with 2 more R-BAC cycles (total of 4 cycles), and will proceed to consolidation phase unless they develop PD. Patients with SD at the end of R-BAC will proceed to consolidation phase. Patients experiencing an excess of toxicity satisfying stop treatment criteria during the initial 3 R-BAC cycles will proceed to Vcons after 3 cycles. Consolidation with venetoclax (V) will consist of 4 cycles lasting 28 days each (venetoclax 800 mg/die x 4 28d cycles, see ramp-up scale for initial weeks of treatment in order to reduce tumor lysis syndrome (TLS) risk). After consolidation, all patients except those experiencing PD during consolidation will proceed to V maintenance (Vmaint, single agent venetoclax 400 mg/die) for 20 months (total of 24 months including Vcons and Vmaint).</td></tr>
<tr><td>Assessments schedule</td><td>J The pretreatment (screening) phase will be 30 days for all laboratory tests and radiographic imaging and up to 90 days for bone marrow evaluation. Lymph-node or involved tissue biopsy is mandatory before study entry.
J The treatment phase will extend from the first day of the first course of R-BAC up to 6 courses for LR patients. Patients with LR not in CR after end of R-BAC will enter Vcons and Vmaint (24 months). For patients with HR disease 4 courses of R-BAC will be followed by 24 months of venetoclax treatment (consolidation+maintenance).
J The follow-up phase will begin after the completion of the treatment phase. Follow-up will continue until disease progression (PD) is documented, the patient decides to withdraw from the study, death or the study is ended (expected to be 24 months from the date the last enrolled patient will terminate maintenance phase).</td></tr>
<tr><td>Centralized analyses</td><td>
<table>
<tr><th>TEST</th><th>APPENDIX REF</th><th>REQUIRED</th><th>QUANTITY</th></tr>
<tr><td>Pathology Review/Risk profile (morphology, Ki-67 expression, TP53 mutation/deletion detection) for all enrolled patient</td><td>Appendix 9</td><td>YES</td><td>1 paraffin block (and bone marrow aspirate when the diagnosis is represented by a bone marrow biopsy)</td></tr>
<tr><td>Centralized assessment of Minimal Residual Disease (MRD) peripheral blood, bone marrow and urine sample for all enrolled patient (baseline), <u>all timepoints only for HR patients</u></td><td>Appendix 8</td><td>YES</td><td>6 timepoints</td></tr>
</table>
</td></tr>
<tr><td>Statistical considerations</td><td>The updated PFS curves of the RBAC500 trial (N= 57) has shown that the expected 2-years PFS for patients with HR disease is 40% (H0), as compared to low-risk patients (LR) that have a 2-years PFS of 100%. The addition of venetoclax to HR patients after R-BAC is expected to improve results and efficacy of this regimen in this “difficult-to-treat” population. The expected improvement given by the addition of venetoclax is a 2-years PFS benefit of 20%, testing our investigational PFS to 60% (H1). Thus, according to the one-arm study design 52 HR patients will be enrolled and followed-up</td></tr>
</table>

	for a minimum of 2 years. Overall, since HR patients will represent approximately 40-45% of newly diagnosed patients with MCL, it is estimated that 115-130 patients will be needed (52+63 or 78). All HR patients who will start therapy will be included in the efficacy analysis population, independently from completion of the scheduled treatment (i.e. those considered off-therapy will be included in the ITT analyses). The experimental drug will also be administered to LR patients that have less than CR at the end of R-BAC. Since the number of such LR patients is hardly predictable based on the present experience with RBAC500 trial, the analysis of this sub-cohort will be of exploratory nature, and thus assessed separately.

5. LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

ABBREVIATION	TERM
ADCC	Antibody-dependent cellular cytotoxicity
ADR	Adverse drug reactions
AE	Adverse Event
ALT (SGPT)	ALanine Transaminase (Serum Glutamic Pyruvic Transaminase)
ANC	Absolute neutrophil count
AST (SGOT)	ASpartate Transaminase (Serum Glutamic Oxaloacetic Transaminase)
aPTT	Activated partial thromboplastin time
β-HCG	beta-Human Chorionic Gonadotropin
BCR	B-cell antigen receptor
BICR	blinded independent central review
BM	Bone marrow
BTK	**Bruton's tyrosine kinase**
CDC	Complement-dependent cytotoxicity
CHOP	Cyclophosphamide, doxorubicin, vincristine, and prednisone
CLL	Chronic lymphocytic leukemia
CNS	Central Nervous System
CR	Complete Response
CRF	Case Report Form
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating, cell-free, tumor DNA
CTQ	clinical trial qualification
CTV	clinical target volume
DLBCL	Diffuse Large B-cell Lymphoma
DNA	Deoxyribonucleic acid
DOR	Duration of Response
DSMC	Data Safety Monitoring Committee
DSUR	Development Safety Update Report
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	Event free survival
EoT	End of therapy
EP	Efficacy population
ESA	Erythropoiesis-Stimulating Agents
FFS	Failure free survival
FIL	Fondazione Italiana Linfomi
G	Obinutuzumab
GCP	Good Clinical Practice
GTV	Gross Tumor Volume
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDT	high-dose chemotherapy
HIV	Human Immunodeficiency Virus
HR	hazard ratio
IGH	immunoglobulin heavy chain
INR	International normalized ratio
IP	Investigational Product
IRR	Infusion Related Reaction
IPI	International Prognostic Index
IRC	Independent review committee
ISRT	Involved Site Radiotherapy
IV	Intra Venous
IWCLL	International Workshop on CLL
LDH	Lactic DeHydrogenase
LVEF	Left Ventricular Ejection Fraction
MIPI	MCL International Prognostic Index
MRD	Minimal residual disease
MTV	metabolic tumour volume
NCI	National Cancer Institute
NGS	Next-generation sequencing
NHL	Non-Hodgkin's Lymphoma
NOS	not otherwise specified

ORR	Overall Response Rate
OS	Overall Survival
PB	Peripheral blood
PBPK	Physiologically-based pharmacokinetic
PCR	Polymerase Chain Reaction
PET	18F-FDG Positon Emission Tomography
PFS	Progression Free Survival
PMBL	Primary mediastinal lymphoma
PML	Progressive Multifocal Leukoencephalopathy
PO	per os
PP	polyolefine, polypropylene
PR	Partial Response
PTT	partial thromboplastin time
PUR	polyurethane
PVC	polyvinyl chloride
QA/QC	quality assurance and quality control
QPI	quantitative PET indexes
QPM	quantitative PET metrics
R	Rituximab
RBC	Red blood cell
SAE	Serious Adverse Event
SLL	Small lymphocytic lymphoma
SP	Safety population
SJS	Stevens-Johnson Syndrome
SUSAR	Suspected Unexpected Serious Adverse Reaction
SUV	Standardized Uptake Value
TLG	total lesion glycolysis
TLS	Tumor lysis syndrome
ULN	Upper Limit of normal

6. STUDY FLOW CHART

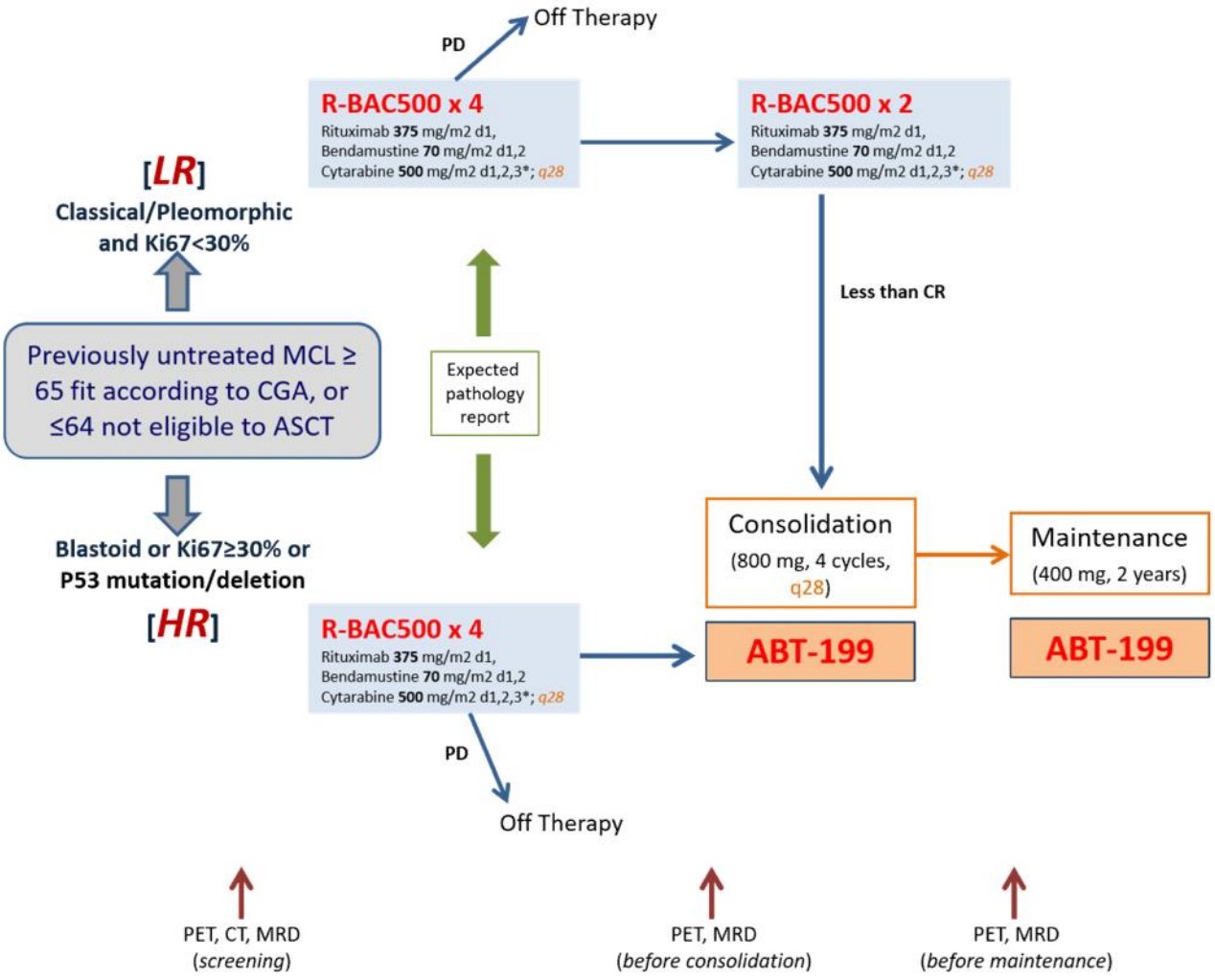


Figure 1: Study flow chart

7. BACKGROUND

7.1 Disease background: Mantle Cell Lymphoma

Mantle cell lymphoma (MCL) accounts for about 8% of all non-Hodgkin's lymphomas (NHL) and is characterized by the presence of t(11;14) and by hyper-expression of Cyclin D1[(1)].The median age at diagnosis is 63 years and patients usually present with bone marrow involvement and with an advanced stage at diagnosis[(2)]. The spleen and gastrointestinal tract are the most frequently involved sites.

7.2 Treatment options for Mantle Cell Lymphoma

The overall response rate (ORR) to chemotherapy is usually good (about 80%) with standard approaches such as Cyclophosphamide, Doxorubicin, Vincristine and Prednisolone (CHOP), CHOP-like regimens and Fludarabine-based regimens[3]. However, relapses are frequent and the prognosis is poor, with a median time to treatment failure (TTF; relapse or progression) of 1 year after an initial response[4], and a median overall survival (OS) of about 3 years[2].

The addition of Rituximab to conventional treatment such as CHOP, CHOP-like regimens or Fludarabine-based regimens has improved the response rates and median TTF in patients with MCL, but no clear-cut benefit on OS has been achieved apart from selected cohorts of patients[5]. The reported ORR is 94%, complete response (CR) of 34%, and TTF of 21 months with Rituximab-CHOP (R-CHOP) as first line treatment in patients with a median age of 61 years[6]. In younger (<65 years) selected patients the reported ORR was 96%, the CR 48% and TTF of 16 months[7].

Intensive regimens have been proposed and adopted for younger patients (<65 years) with MCL, fostering great expectations and encouraging short-term results. These regimens produced better results than conventional treatments. Rituximab with hyper-fractionated Cyclophosphamide, Vincristine, Adriamycin and Dexamethasone (R-HyperCVAD), including high-dose Cytarabine (Ara-C) and Methotrexate resulted in an OS of 82% and a 3-year TTF of 64%[8]. The use of sequential high-dose immunochemotherapy including high-dose Ara-C followed by in vivo purged stem cell autograft resulted in an OS of 89% and an event-free survival (EFS) of 79% at 54 months[9]. First-line autologous transplant following preparative regimens including high-dose Ara-C and Rituximab gave a 3-year OS of 75% and an EFS of 76%[10].

The addition of high-dose Ara-C in the above three intensive regimens seems to improve the outcome in younger patients with MCL. The use of high-dose Ara-C appears to be beneficial for patients who present with high-risk disease as well as for patients who will undergo autologous transplantation in first remission. However, all three of the above regimens (two involving autologous transplantation) are associated with a high incidence of infections and severe hematological toxicity. It is mainly because of these toxicities in older patient cohorts that the R HyperCVAD regimen produces significantly inferior responses and TTF in patients aged >65 years compared with younger patients[8].

7.3 R-BAC

The incorporation of high-dose cytarabine has been widely recognized as highly beneficial in the treatment of MCL, primarily in intensive regimens adopted for younger patients. Preclinical studies have demonstrated that bendamustine and cytarabine share distinct and synergistic mechanisms of action in MCL cell lines, especially when administered sequentially[11]. In a phase two study, the combination of rituximab (R, 375 mg/m2, day 1), bendamustine (B, 70 mg/m2, days 2 and 3), and cytarabine (800 mg/m2, on days 2 to 4) translated in impressive rates of CR (95%) in previously untreated elderly patients with MCL (RBAC500)[12]. Overall, this regimen was well tolerated, but hematologic toxicity was relevant, especially in terms of grades 3 to 4 thrombocytopenia (87% of patients).

Aiming at reducing the haematologic toxicity while preserving anti-tumor activity, the Fondazione Italiana Linfomi (FIL) designed a phase 2 trial adopting the R-BAC schedule, but lowering cytarabine dose to 500

mg/m2 (R-BAC). From May 2012 to February 2014, 57 patients with MCL from 29 centers were recruited. Median age was 71 years (range 61-79), and 91% had Ann Arbor stage III/IV disease. Mantle Cell International Prognostic Index (MIPI) was high in 45%, Ki-67 was ≥30% in 31%, and 11% had the blastoid morphological variant. Grade 3 or 4 neutropenia and thrombocytopenia were observed in 49% and 52% of cycles, respectively, with 95% of patients completing at least 4 cycles. Complete remission rate was 91%. The molecular remission rate was 76% on peripheral blood and 55% on bone marrow samples. With a median follow-up of 35 months (28-52), the 2-years PFS (± confidence interval) was 81%±5% and the OS 85%±4%. Elevated Ki-67 (≥30%), and the blastoid variant were the strongest independent predictors of adverse PFS[13].

In conclusion, the R-BAC is a highly effective treatment that can be safely administered to elderly patients with MCL. Its efficacy compares favourably with previously reported regimens in this patient population, in the absence of maintenance therapy.

7.4 ABT-199 (venetoclax)

Clinical experience with venetoclax in humans, including pharmacokinetics, safety and efficacy is summarized in the Investigator's Brochure (venetoclax, Investigator's Brochure, Current Edition).

7.4.1 Overview

Venetoclax (also referred to as ABT-199 and GDC-0199) is a novel, orally bioavailable, small-molecule B-cell lymphoma-2 (Bcl-2) family inhibitor in the biarylacylsulfonamide chemical class. Venetoclax binds with high affinity (inhibition constant [Ki] < 0.010 nM) to antiapoptotic protein Bcl-2 and with lower affinity to other antiapoptotic Bcl-2 family proteins, like Bcl-XL and Bcl-w (> 4,000-fold and > 2,000- to > 20,000-fold lower affinity than to Bcl-2, respectively).

Antiapoptotic Bcl-2 family members are associated with tumor initiation, disease progression, and chemotherapy resistance, as well as autoimmunity. Overexpression of Bcl-2 is a major contributor to the pathogenesis of some lymphoid malignancies; antagonism of the action of these proteins may enhance response to therapy and overcome resistance, and thus, these proteins are compelling targets for anti-tumor therapy[14].

7.4.2 Pharmaceutical properties

Dosage Form: Tablets

Strength: 10, 50, and 100 mg

Storage and Handling: The clinical supply should be stored at 15° to 25°C.

7.4.3 Pharmacokinetics

Following multiple-dose administration, the maximum plasma concentration of venetoclax was attained 5 to 8 hours after dosing. The harmonic mean terminal half-life (t1/2) ranged from 17 to 41 hours following a single oral dose of venetoclax. Venetoclax has been administered with food in all clinical studies, as food increased the bioavailability of venetoclax by approximately 3- to 5-fold. Venetoclax is highly bound to plasma proteins with unbound fraction (fu) < 0.01, and it is primarily eliminated as metabolites in feces with negligible renal elimination (< 0.1%).

Pharmacokinetic results were available in 106 subjects with R/R NHL in the ongoing Phase 1 first-in-human study of venetoclax (Study M12-175, Arm B). Following single doses of venetoclax 50, 100, 200, 300, and

400 mg, venetoclax plasma concentrations peaked at approximately 4 to 8 hours. The harmonic mean half-life ranged from 14.1 to 18.2 hours following single-dose administration under high-fat conditions (Week 1 Day –7). Following multiple doses of venetoclax, steady-state AUC0-24 was dose-proportional across the 200 to 800 mg dose range.

Pharmacokinetic results were available from 48 subjects with relapsed CLL in the ongoing Phase 1 combination study of venetoclax and rituximab (Study M13-365). After the lead-in period (Weeks 1 through 5), subjects within each cohort received venetoclax 200, 300, 400, 500, or 600 mg QD in combination with rituximab dose-normalized mean Cmax and AUC for venetoclax were not statistically significantly different (P > 0.05) when co-administered with rituximab (Week 6 Day 1) compared to venetoclax alone (Week 2 Day 4). Steady-state Cmax and AUC of venetoclax, when co-administered with rituximab, were dose proportional across the studied dose range of 100 to 600 mg.

Venetoclax exposures observed in subjects with NHL were similar to those observed in subjects with CLL/SLL.

7.4.4 Efficacy and safety in oncology

Multiple ongoing Phase 1/2/3 clinical studies are evaluating safety, tolerability, pharmacokinetics, and efficacy of venetoclax as monotherapy or in combination with other therapies (rituximab [R], obinutuzumab (GA101) [G], rituximab or obinutuzumab plus CHOP [cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHOP or G-CHOP, respectively], BR, bendamustine plus obinutuzumab [BG], bortezomib plus dexamethasone, azacitidine or decitabine, and cytarabine) in subjects with hematologic malignancies. Data are available from DDI studies of venetoclax interaction with ketoconazole, with rifampin, and with warfarin. Additionally, refer to the investigator brochure (IB) for further details.

Based on nonclinical and clinical data available with venetoclax administration, important identified risks are tumor lysis syndrome (TLS) and neutropenia, particularly in the CLL indication. Infection is a potential risk. Other adverse events commonly observed with venetoclax include nausea, diarrhea, and other hematological effects (including, anemia, thrombocytopenia, and lymphopenia). Decreased spermatogenesis has been observed in nonclinical studies with dogs and could present a risk to male infertility.

No carcinogenicity studies with venetoclax have been conducted to date. Nonclinical toxicology data suggest that the carcinogenic potential of venetoclax is low based on negative geneotoxicity findings and the absence of hyperplastic or neoplastic lesions in mouse (6-month) and dog (9-month) chronic toxicity studies.

7.4.5 Safety measures for TLS

Early evidence of rapid tumor cell destruction was evident in the initial cohorts of patients with CLL/SLL treated with venetoclax. TLS was noted in all 3 subjects enrolled in CLL Cohort 1, at starting doses of both 100 and 200 mg; all events were grade 3, and 2 of the events were considered serious. To mitigate the risk for TLS, a lead-in period of approximately 2 to 3 weeks with step-wise dose escalation was employed for subsequent CLL and NHL cohorts, and lower starting doses of venetoclax were used (20 to 50 mg). The dose regimen chosen for the safety expansion cohort was a weekly escalation of 20 mg – 50 mg – 100 mg – 200 mg – 400 mg [For additional details on TLS across all studies and discussion of TLS as a safety risk, refer to Section 9.2.2.1 of the Investigator's Brochure].

In NHL Cohorts 1 through 6, the starting daily dose for subjects ranged from 50 to 400 mg at Week 1, the step-up doses ranged from 100 to 800 mg, and the final designated cohort doses ranged from 200 to 1200

mg. Two subjects experienced DLTs. Both DLTs occurred at the 600 mg dose in Cohort 5 (which enrolled a total of 10 total subjects, with a 300 mg lead-in dose and 600 mg designated cohort dose). No DLTs were reported in Cohorts 6 to 8, the MTD was not reached, and subjects enrolled in safety expansion received target doses of 1200 mg.

Subjects with MCL enrolled in the NHL arm appear to be at a greater risk of experiencing TLS-associated laboratory changes with venetoclax than subjects with other NHL subtypes. Consequently, the starting dose for subjects with MCL initially remained at 200 mg, and was further lowered to the 20 mg lead-in dose. A laboratory (not clinical) nonserious grade 3 adverse event of TLS (considered probably related to venetoclax) was reported in 1 subject with MCL dosed at a 200 mg lead-in dose.

7.4.6 Subjects treated for MCL

The most common adverse events in NHL subjects, including MCL were nausea (48.1%), diarrhea (44.3%), fatigue (40.6%), and vomiting and decreased appetite (20.8% each). Adverse events grade 3 and above were reported for 54.7% subjects. The most common events grade 3 or above were anemia (16.0%) and neutropenia (12.3%). Serious adverse events were reported in 34.0% subjects. The most common serious adverse events were malignant neoplasm progression (8.5%) and diarrhea, influenza, and hyponatremia (2.8% each).

A total of 17 (16.0%) subjects experienced adverse events that led to discontinuation of venetoclax. The most common adverse events leading to discontinuation was malignant neoplasm progress (6 [5.7%] subjects) and nausea (2 [1.9%] subjects). All other events leading to discontinuation were reported in 1 subject each. A total of 9 (8.5%) subjects experienced adverse events that led to death, including 8 events of malignant neoplasm progression and 1 event of respiratory failure. All fatal events were considered to have no reasonable possibility of being related to venetoclax.

Subjects with R/R MCL had an ORR of 75% to venetoclax monotherapy in a recent report[15], and responses were observed over all adopted doses, between 200 mg and 1200 mg per day.

8. STUDY RATIONALE

The median age of patients presenting with mantle cell lymphoma (MCL) is approximately 65 years. For this reason, the majority of these patients are not candidate to intensive regimens including autologous transplant, and new active regimens are warranted for this patient population.

The R-BAC regimen is extremely active in inducing complete response in patients with MCL (93% CR), and represents the standard first-line treatment in Italy and many countries in the induction treatment of elderly fit patients with MCL. However, based on the most recent analysis (median f/u 29 mo) of patients included in the R-BAC500 FIL trial[13], patients with the blastoid variant and/or high Ki67 proliferative index (High Risk – HR-) had a significantly higher risk of relapse (2-years PFS of 40%) after completion of R-BAC, compared to classical histologies and low proliferative index (Low Risk –LR-). When treated with R-BAC, none of the LR patients experienced disease progression within 2 years from diagnosis, although no maintenance therapy was delivered.

Finally, *TP53* gene mutations in MCL patients represent an important predictor of adverse outcome, similarly to chronic lymphocytic leukemia, but have never been tested before in clinical trials enrolling elderly patients with MCL, and this represents the first trial overall using this mutation at the decisional level[16].

9. STUDY OBJECTIVES

Our aim is to improve long term results of R-BAC, consolidating patients with high-risk (HR) features (defined as: elevated Ki67 and/or blastoid cytology and/or *TP53* mutation after central pathology review) with venetoclax (ABT-199), which has demonstrated relevant single agent activity in relapsed/refractory MCL in a Phase 1-2 trial[15].

The updated PFS curves of the RBAC500 trial has shown that the expected 2-years PFS for patients with HR disease is 40% (H0), as compared to low-risk patients (LR) that have a 2-years PFS of 100%. The addition of venetoclax to *HR* patients after R-BAC is expected to improve results and efficacy of this regimen in this "difficult-to-treat" population, that represents approximately 40-45% of newly diagnosed elderly patients with MCL. It appears reasonable to treat with the experimental drug also *LR* patients that do not respond appropriately (less than CR) at the end of R-BAC. Since the number of such *LR* patients is hardly predictable based on the present experience with RBAC500 trial, the analysis of this sub-cohort will be of exploratory nature, and thus assessed separately.

The study objective is to evaluate whether the addition of venetoclax after R-BAC to HR patients improves the results of the standard R-BAC, in terms of PFS.

9.1 Primary objective and endpoint

The primary objective is to evaluate whether the addition of venetoclax after R-BAC to patients with HR MCL, as above defined, improves the results of the standard R-BAC, in terms of PFS. The primary endpoint is the progression-free survival (PFS) from date of enrollment with at least 2 years of follow-up.

9.2 Secondary Endpoints

The secondary endpoints are:

- The rate of molecular response (analyzed in the labs of the FIL-MRD Network)
- The progression-free survival (PFS) of all enrolled patients, and of different subgroups (i.e.TP53 mutated patients)
- The overall survival (OS)
- The duration of responses (DoR)
- The rate of complete remission (CR) before and after venetoclax in the HR group and/or in the LR not responding to R-BAC
- The rate of patients that complete the expected treatment schedule
- The safety of venetoclax when administered as consolidation or maintenance after R-BAC

10. STUDY DESIGN

10.1 Overview of study design

This is a Phase 2, one-arm, single arm prospective multicenter study.

10.2 Number of patients

Approximately 130 patients will be enrolled in the study, until 52 HR patients are reached (HR patients represent approximately 40-45% of newly diagnosed patients with MCL).

10.3 Duration of the study

Patients will be recruited over 30 months and followed 24 months after the end of the treatment phase, (including consolidation and maintenance phase).
From 1st patient enrolled (FPFV) to Last patient enrolled (LPFV): 30 months.
The duration of the treatment period is approximately:

- 30 months for LR patients not in CR at the end of induction (6 months for R-BAC induction phase, 4 months for ABT-199 consolidation phase and maximum 20 months for ABT-199 maintenance phase)
- 28 months for HR patients (4 months for R-BAC induction phase, 4 months for ABT-199 consolidation phase and maximum 20 months for ABT-199 maintenance phase)
- 1 months for End of Treatment (EoT) evaluation

The duration of the follow up period is 24 months.
End of study is defined by the last visit planned by the protocol of the last patient in follow-up that means 24 months after the EoT of last patient enrolled.
The Final Study Report will be provided after the end of the Study.
An extended follow-up after the end of the study requiring participating sites to provide only information on patient status (alive, dead, lost to follow-up) and to record possible events, including diagnosis of second neoplasia and long term toxicity for additional 2 years after the end of the study is planned.

11. STUDY POPULATION

Patients with an established histological diagnosis of MCL on lymph-node biopsy, bone marrow biopsy, or extranodal tissue are eligible for entry into the study.

11.1 Inclusion criteria

1. Previously untreated patients with MCL aged ≥65 years if they are FIT according to the geriatric CGA assessment.
2. age ≤64 years not eliglible to high-dose chemotherapy plus transplantation at physician's judgement (details for non eligibility to be recorded by means of the CIRS, Cumulative Illness rating Scale).
3. Measurable nodal or extranodal disease ≥ 1.5 cm in longest diameter, and measurable in 2 perpendicular dimensions.
4. ECOG performance status ≤2.
5. Positivity for cyclin D1 and/or SOX11 [the latter being mandatory in cases lacking cyclin D1- or t(11;14)-negative].
6. Adequate renal function (Creatinine clearance >50 mL/min), with preserved diuresis.

7. Adequate liver function: alanine aminotransferase (ALT)/aspartate aminotransferase (AST) <2.5 x upper limit of normal (ULN) value, total bilirubin <1.5 x ULN, unless directly attributable to the patient's tumor, or to congenital causes.
8. Hepatitis B core antibody (HBcAb) positive/HBsAg negative/HBV-DNA negative patients may be enrolled if correct antiviral prophylaxis is administered at least 2 weeks before initiating protocol treatment.
9. Written informed consent.

11.2 Exclusion criteria

1. Human immunodeficiency virus (HIV) positive.
2. Previous treatment for lymphoma.
3. Disease confined to the bone marrow/peripheral blood/spleen, without any other nodal or extranodal involvement.
4. In-situ MCL.
5. Medical conditions or organ injuries that could interfere with administration of therapy.
6. Active bacterial, viral, or fungal infection requiring systemic therapy.
7. Seizure disorders requiring anticonvulsant therapy.
8. Severe chronic obstructive pulmonary disease with hypoxiemia.
9. History of severe cardiac disease: New York Heart Association (NYHA) functional class III-IV, myocardial infarction within 6 months, ventricular tachyarrhythmias, dilatative cardiomyopathy, or unstable angina.
10. Uncontrolled diabetes mellitus.
11. Active secondary malignancy.
12. Known hypersensitivity or anaphylactic reactions to murine antibodies and proteins, to Bendamustine or mannitol.
13. Major surgery within 4 weeks of study Day 1.
14. HBsAg+
15. HCVAb+ patients with active viral replication (HCV-RNA+ with AST>2 x normal limit)
16. Any co-existing medical or psychological condition that would preclude participation in the study or compromise the patient's ability to give informed consent, or that may affect the interpretation of the results, or render the patient at high risk from treatment complications.
17. CNS involvement
18. Chronic treatment with strong or moderate CYP3A inhibitors (e.g. ketoconazole, ritonavir, clarithromycin, itraconazole, voriconazole)

11.3 Comprehensive Geriatric Assessment (CGA)

The CGA is a useful tool to assess the quality of life of elderly and to include them in clinical studies following predefined criteria. CGA includes different aspects: physical disability, nutrition conditions, psychological and psychosocial status. The presence of some functional limitations caused by comorbidity does not allow

Karnofsky Performance Status Scale Definition Rating (%) Criteria to be applicable to define all cases in the geriatric field.

This is the reason why at least three other scales which define day living have been created:

1) Scale to define the basic activities of day living (ADL) created by Katz[17]

2) Scale to define the instrumental activities of day living (IADL) created by Lawton[18]. ADL is based on 6 features: bathing, dressing, toileting, transferring, feeding, continence. IADL is based on 8 features: using the phone, shopping, cooking meals, housekeeping, doing laundry, using public transport, managing medical treatments and managing money. Some studies have showed that ADL and IADL are more appropriate to define functional deficits in elderly than PS[19-21].

In the present study CGA has been proposed in a modified version (Appendix 3), administering the CIRS comorbidity scale together with the ADL, IADL (Appendix 4).

Definition of FIT patient

According to the values obtained with the comorbidity scales, patients can be defined as FIT, UNFIT, or FRAIL. Our definition of FIT will require that patients satisfy CIRS, ADL, and IADL scales criteria, that they are not 80 years or older, and that they are not affected by any geriatric syndrome. The criteria for defining the patients are listed in Appendix 3.

12. PATIENTS ENROLLMENT

12.1 Informed consent

The Investigator(s) must obtain informed consent of a patient or his/her designee prior to any study related procedures as per Good Clinical Practices (GCP). Documentation that informed consent occurred prior to the patient's entry into the study and of the informed consent process should be recorded in the patient's source documents. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his/her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. The subject or legally acceptable representative will be given sufficient time to read the informed consent form and the opportunity to ask questions. After this explanation and before entry to the study, consent should be appropriately recorded by means of either the subject's or his/her legally acceptable representative's dated signature. After having obtained the consent, a copy of the informed consent form must be given to the subject.

If the subject or legally acceptable representative is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and personally date and sign the informed consent form after the oral consent of the subject or legally acceptable representative is obtained.

The original consent form signed and dated by the patient and by the person consenting the patient prior to the patient's entry into the study must be maintained in the Investigator's study files and a copy given to the

patient. In addition, if a protocol is amended and it impacts on the content of the informed consent, the informed consent must be revised. Patients participating in the study when the amended protocol is implemented must be re-consented with the revised version of the informed consent. The revised consent form signed and dated by the patient and by the person consenting the patient must be maintained in the Investigator's study files and a copy given to the patient.

12.2 Patient registration and data collection

Following confirmation of eligibility and written informed consent, patients should be registered online at *www.filinf.it*, in the dedicated section. An email of confirmation will be sent to the investigator. The electronic CRFs for data collection could be reached in the restricted area of the FIL website by authorized users.

13. TREATMENT

13.1 Risk definition

After enrollment of patients, every center will be asked to send paraffin blocks of the diagnostic specimen for central pathologic review and *TP53* mutations/*TP53* deletions detection as soon as possible and no later than 2 weeks from study entry. The centralized report, which is expected to be available after the patient has started the second R-BAC cycle, but before day 1 of cycle 3, will allow allocation of patients between low risk (LR) and high risk (HR), depending on these 3 factors: morphology (blastoid versus others), Ki67 expression (≥30% versus others), *TP53* mutations/*TP53* deletions (present versus not). Patients with one of these three risk factors will be defined as HR and will follow a separate consolidation and maintenance treatment.

13.2 Treatment schedule and design

Study drugs will be administered only to eligible subjects under the supervision of the investigator or identified subinvestigator(s). The treatment scheme is based on an induction phase, and is then differentiated depending on risk groups (*HR* versus *LR*). After the enrollment, the patients will undergo histological and molecular evaluation in order to assess their risk profile. The protocol treatment scheme is presented in Figure 2.

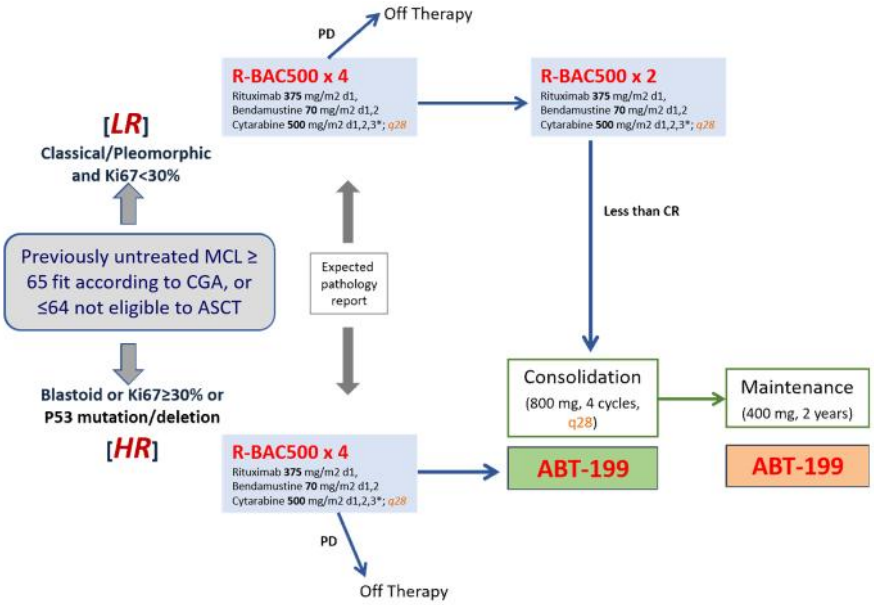


Figure 2. Treatment scheme

Basically, **all patients** will receive 4 cycles of R-BAC induction therapy.

Patients with low risk disease (*LR*) will receive 6 cycles of R-BAC overall (4 cycles are allowed for patients experiencing an excess of toxicity, see paragraph 13.4. Patients with PD during R-BAC or after 4 R-BAC will stop treatment and be removed from protocol-specified therapy. Patients not in CR after this induction will proceed to venetoclax consolidation and maintenance.

Patients with high risk disease (*HR*) at presentation (high Ki67, blastoid, or *TP53* deleted/mutated after central pathology revision), will receive 4 cycles of R-BAC before being consolidated. Patients with PD during R-BAC or at the end of the induction phase will stop treatment and be removed from protocol-specified therapy. Patients responsive to the initial 2 R-BAC or with SD, will be treated with 2 more R-BAC cycles (total of 4 cycles). Patients with SD at the end of R-BAC will proceed to the consolidation phase. Patients experiencing an excess of toxicity satisfying stop treatment criteria during the initial 3 R-BAC cycles will proceed to V_{cons} after 3 cycles.

Patients proceeding to venetoclax treatment, either *HR* and *LR*, will receive **consolidation** with single agent venetoclax 800 mg/die x 4 28d cycles (with initial ramp-up dose) of each consolidation cycle (V_{cons}).

Consolidation will be followed by **maintenance** with single agent venetoclax 400 mg/die (V_{maint}) for a total of 2 years (4 months consolidation+20 months maintenance).

A **ramp-up scale** will be performed during the first consolidation cycle of venetoclax. See scheme on Figure 3.

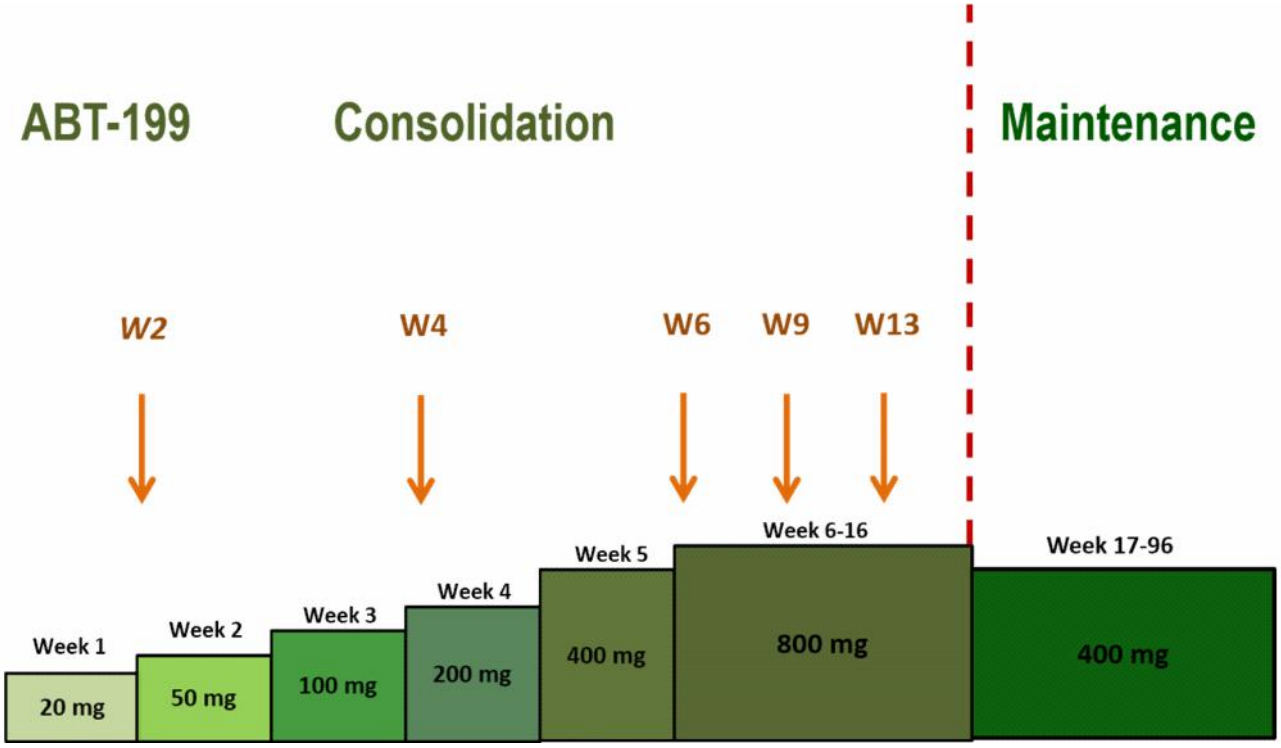


Figure 3. Venetoclax escalation strategy and maintenance

13.3 R-BAC induction (all patients)

All patients (either *LR* or *HR*) will be treated upfront with R-BAC scheme. Briefly, Rituximab will be administered intravenously at the standard dose of 375 mg/m2 on Day 1. Bendamustine will be administered intravenously at a dose of 70 mg/m2 over a 30 to 60 minute infusion on Day 2 and 3. Ara-C will be administered intravenously at the dose of 500 mg/m2 over a 2-hour infusion, 2 hours after Bendamustine administration on Day 2 and 3 and 4. Following the first cycle, if no major complication has followed Rituximab infusion, bendamustine and ara-C will be administered on day 1 following Rituximab, and the complete cycle will last for 3 days, in order to facilitate an outpatient approach. The amount (in mg) of Rituximab to be administered will be determined based on body surface area (BSA) using a standard calculation provided in Appendix 5, Suggested Body Surface Area Calculation. Instructions including calculation of the subject's dose, preparation and handling of the Rituximab infusion are provided in Appendix 6, Dispensing information for Rituximab. The amount (in mg) of Bendamustine to be administered will be determined based on body surface area (BSA) using a standard calculation provided in Appendix 5, Suggested Body Surface Area Calculation. Instructions including calculation of the subject's dose, preparation and handling of the Bendamustine infusion are provided in Appendix 7, Dispensing information for bendamustine. Bendamustine must be administered after Rituximab infusion (day 1) and before Cytarabine infusion. The amount (in mg) of Cytarabine to be administered will be determined based on body surface area (BSA) using a standard calculation provided in Appendix 5, Suggested Body Surface Area Calculation. Cytarabine must be diluted in 500 mL infusion bag of 0.9% Sodium Chloride. Cytarabine must be administered in two hours infusion, at 120 minutes after bendamustine.

It is recommended that patients presenting with high lymphocyte count in the peripheral blood, defined as total lymphocytes >20000/mmc will receive the dose of Rituximab postponed after chemotherapy, 4 days after the completion of the last dose of Ara-C (+8 from the start of therapy). Patients that still have elevated lymphocyte count at that time point will avoid Rituximab for the first cycle, maintaining the same measures for subsequent cycles.

Patients with the blastoid variant of MCL will receive prophylactic lumbar punctures on Day 1 of the first 4 cycles (4 total lumbar punctures, each with Methotrexate 15 mg and Depo-Medrol 40 mg). See paragraph 13.7 for R-BAC dose reduction, which is suggested in order to avoid an excess of toxicity.

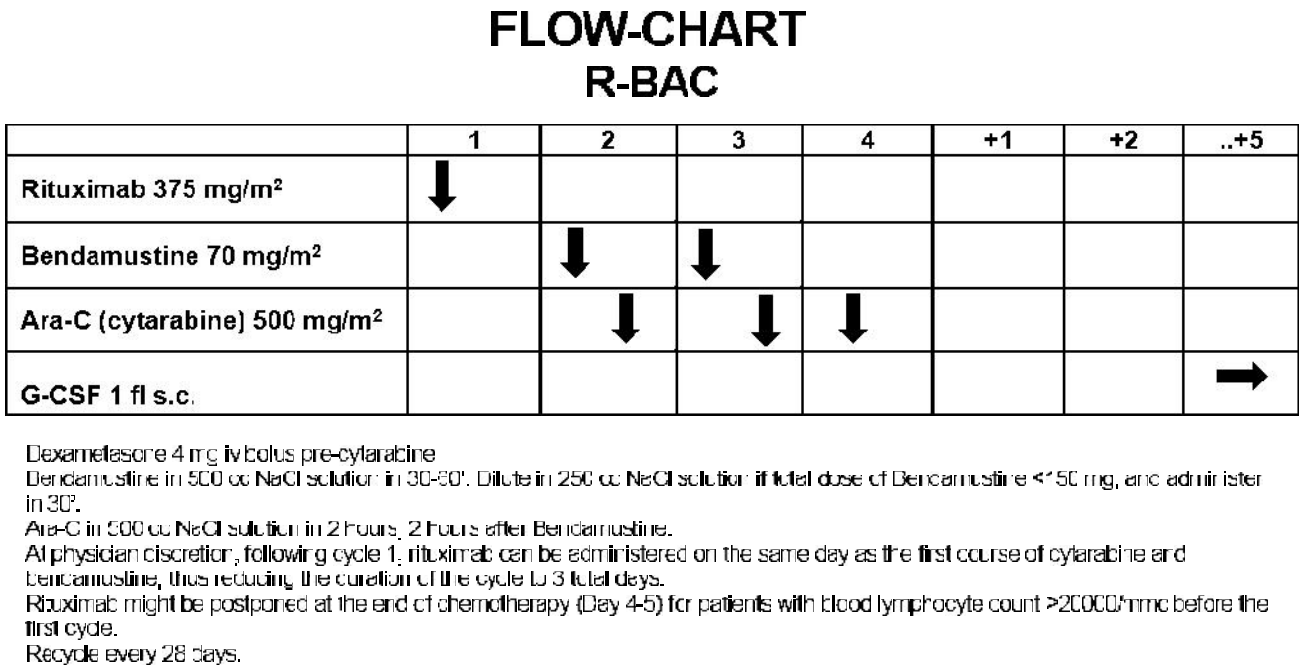


Figure 4: R-BAC treatment schedule and flow chart

13.4 Low risk patients [LR]

Low risk patients (*LR*) with PD after 2 cycles will stop treatment. LR patients that had SD after 2 cycles will be re-evaluated for response after 4 cycles and they will stop treatment if in PD. Responsive patients (CR, Cru, PR after 2 cycles; SD after 2 cycles that improved their response at the end of cycle 4 will receive a total of 6 cycles. Patients experiencing at least one episode of relevant toxicity during any of the initial cycles (see below Figure 5) may be treated with a total of 4 cycles (end of treatment after 4 cycles) regardless of response to treatment.

LR patients that are not in CR after the end of induction (either 6 or 4 R-BAC cycles), will be treated with venetoclax consolidation and maintenance similarly to HR patients. This cohort will represent an exploratory population of the study. The criteria and prerequisites for starting venetoclax in LR patients will be the same as for HR patients, and are listed in paragraph 13.8/Table 1.

13.5 High risk patients [HR]

13.5.1 R-BAC induction and Venetoclax (V_{cons}) Consolidation Phase

High risk patients (*HR*) with PD after 2 cycles will stop treatment. HR patients that had SD after 2 cycles will be re-evaluated for response after 4 cycles and they will stop treatment if in PD, thus not proceeding to V_{cons}. Responsive patients (CR, Cru, PR, SD after 2 cycles) will receive a total of 4 cycles. Patients experiencing at least one episode of relevant toxicity during any of the initial cycles (see below Figure 5) may be treated with a total of 3 cycles.

Consolidation phase will start between day 28 and day 42 of last R-BAC cycle, provided that PET scan has been performed, and criteria for starting V_{cons} are satisfied (Paragraph 13.8/Table 1). In particular, adequate bone marrow function (defined as an absolute neutrophil count of 1000 per cubic millimeter or more and a platelet count of 50,000 per cubic millimeter or more; hemoglobin level of 8 g per deciliter or more) will be required before venetoclax consolidation is started.

Patients experiencing an excess of toxicity satisfying stop treatment criteria during the initial 3 R-BAC cycles (see below Figure 5) will be allowed to proceed to V_{cons} after 3 cycles, unless they are in PD.
Consolidation will consist of 4 cycles lasting 28 days each. Venetoclax will be administered at the dose of 800 mg/die following rump-up phase (Figure 3).
At the end of consolidation phase, all patients except those experiencing PD during consolidation will proceed to V maintenance (V_{maint}) for a total of 2 years (4 months consolidation+ 20 months maintenance). Patients who discontinue study treatment for reasons other than progression should continue to have tumor assessments according to the protocol until disease progression or the end of the study. Survival information will be collected for all enrolled patients.

13.5.2 Ramp-up dose-titration for Venetoclax (TLS prevention)

The risk of TLS is being closely monitored in non-CLL indications. In general, before initiating venetoclax, subjects risk for developing TLS should be assessed.
The risk of TLS is limited to the first 4 weeks of treatment (ramp-up period). A low starting dose followed by gradual dose ramp-up allows for the tumor size to be gradually reduced and has been effective in reducing the risk of TLS. Venetoclax should be initiated with the 20 mg dose and gradually ramp-up/titrate up to 800 mg target dose over 6 weeks (Figure 3).
Prophylaxis with hydration and uric-acid reducing agents is mandatory. Creatinine levels should be evaluated before starting any venetoclax dose (see paragraph for patients with renal impairment). Clinical chemistries should be corrected. Monitor with clinical chemistries and manage promptly, as clinically indicated.
The following measures are encouraged, especially in patients that still have residual tumor burden after R-BAC induction therapy:

1. Oral hydration (6 – 8 hours/1.5 – 2 liters) for all subjects during the first 4 weeks, increased hydration at initiation and every ramp-up dose, especially in subjects at risk.

2. Start allopurinol; consider rasburicase if baseline uric acid is elevated or high risk of TLS.
3. Assess the risk for TLS based on clinical and radiological assessment (e.g., CT scan or PET) prior to initiation of venetoclax treatment, and evaluate renal function carefully.
4. Subjects with lymph nodes ≥ 5 cm or ALC ≥ 25 × 109/L, splenomegaly, renal dysfunction (< 80 mL/min), baseline clinical chemistry abnormalities, etc., could be at risk for TLS.
5. As tumor debulks following venetoclax treatment, the risk decreases. Reassessment and adjustments in the prophylaxis and monitoring measures could be considered.

For subjects at risk of TLS (lymph-nodes > 5 cm or ALC > 25× 109/L)

1. Prophylaxis with IV hydration and uric acid reducing agents per physician's clinical judgment.
2. Monitoring of clinical chemistries for the initial 4 weeks or period of risk.
3. Pre-dose: Assess clinical chemistries (e.g., creatinine, uric acid, potassium, phosphorus, and calcium) prior to initial dosing and before initiation of each ramp-up dose of venetoclax to evaluate kidney function and to correct pre-existing hyperuricemia, hyperkalemia, hyperphosphatemia, or hypocalcemia.
4. Post-dose: Monitor clinical chemistries (e.g., creatinine, uric acid, potassium, phosphorus, and calcium) for evidence of TLS at 6 – 8 hours after the first dose and after each initial ramp-up dose. Re-assess clinical chemistries before administering the second dose of each ramp-up (i.e., at 24 hours).
5. Correct relevant clinical chemistry abnormalities promptly.
6. Hospitalization is recommended for subjects with large tumor burden (e.g., lymph nodes > 10 cm or ALC > 50 × 109/L) or a subject at risk per the discretion of the treating physician. Also, based upon the judgment of the admitting physician, subjects may be hospitalized to enable more intensive monitoring of blood chemistries and other diagnostic testing, provide aggressive fluid management potentially (e.g., intravenous fluids administration), monitor and manage the likelihood of AEs, monitor subjects with severe co-morbidities (e.g., renal dysfunction, cardiac failure) and facilitate other timely supportive care.

<u>For subjects with renal impairment</u>

Patients with reduced renal function (CrCl <80 mL/min) are at increased risk of TLS. These patients may require more intensive prophylaxis and monitoring to reduce the risk of TLS when initiating treatment with venetoclax.

Trials are ongoing in subjects with renal impairment. Less than 0.1% of radioactive venetoclax dose was detected in urine. No dose adjustment is needed for patients with mild or moderate renal impairment (CrCl ≥30 mL/min) based on results of the population pharmacokinetic analysis. A recommended dose has not been determined for patients with severe renal impairment (CrCl <30 mL/min) or patients on dialysis, but these patients are excluded from the present study.

13.5.3 Venetoclax (Vmaint) Maintenance Phase

Patients that did not suspend venetoclax due to serious adverse events, and are not in PD after the consolidation phase (V_{cons}) will undergo a maintenance therapy with venetoclax monotherapy 400 mg/die (see Figure 2), for 20 months.

During maintenance phase, the same rules for drug reduction/suspension will be followed, as indicated in Table 1 and 2.

13.5.4 Venetoclax contraindications, warning and precautions

Concomitant use of venetoclax with strong CYP3A inhibitors at initiation and during the dose-titration phase is contraindicated (Section 9.2.4 of the Investigator Brochure). venetoclax should not be used with strong CYP3A inhibitors (e.g., ketoconazole, ritonavir, clarithromycin, itraconazole, voriconazole) at initiation and during ramp-up phase. For patients who have completed the ramp-up phase and are on a steady daily dose of venetoclax,

Concomitant use of strong CYP3A inhibitors may be allowed with venetoclax dose reductions by at least 75%. Concomitant use of venetoclax with moderate CYP3A inhibitors (e.g., erythromycin, ciprofloxacin, diltiazem, fluconazole, verapamil), or strong CYP3A inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's wort), or moderate CYP3A inducers (e.g., bosentan, efavirenz, etavirine) should be avoided. If a moderate CYP3A inhibitor must be used, reduce the venetoclax dose by at least 50%. Venetoclax should be administered using caution with substrates or inhibitors of P-gp or BCRP, or substrates of OATP1B1. If venetoclax is co-administered with warfarin, the international normalized ratio (INR) should be monitored closely.

Live-virus vaccines should not be given within 28 days prior to the initiation of study treatment, at any time during study treatment, or in the 30 days following last dose of study treatment.

Warfarin: In a drug-drug interaction study in healthy subjects, administration of a single dose of venetoclax with warfarin resulted in an 18% to 28% increase in Cmax and AUC∞ of R-warfarin and S-warfarin. Because venetoclax was not dosed to steady state, it is recommended that the international normalized ratio (INR) be monitored closely in patients receiving warfarin.

Fertility: venetoclax may cause fetal harm, and therefore pills should be strictly personal to the patient, to avoid accidental ingestions. Females of reproductive potential should undergo pregnancy testing before initiation of venetoclax. Based on findings in animals, male fertility may be compromised by treatment with venetoclax.

13.5.5 Missed dose

If the patient misses a dose of venetoclax within 8 hours of the time it is usually taken, the patient should take the missed dose as soon as possible and resume the normal daily dosing schedule. If a patient misses a dose by more than 8 hours, the patient should not take the missed dose and should resume the usual dosing schedule the next day.

If the patient vomits following dosing, no additional dose should be taken that day. The next prescribed dose should be taken at the usual time.

13.5.6 Venetoclax supply and accountability

Ventoclax supply and accountability wil be defined with FIL-Abbvie SOP.

13.5.7 Contraception

Male patients, even if surgically sterilized (i.e., status postvasectomy) must agree to 1 of the following: Practice effective barrier contraception during the entire study treatment period and through 6 months after the last dose of study drug, or Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods for the female partner] and withdrawal are not acceptable methods of contraception.)

13.5.8 Venetoclax oral assumption

Venetoclax should be dosed at approximately the same time each day. Each dose of venetoclax will be taken with approximately 240 mL of water within 30 minutes after completion of breakfast or the subject's first meal of the day. Tablets must be swallowed whole and must not be broken, chewed, or crushed.

13.6 Concomitant treatments

13.6.1 Recommended concomitant treatments

During induction treatment (R-BAC) the following drugs are mandatory as concomitant therapy:

- G-CSF 10 micrograms/kg from day +5 from end of therapy (usually 3 to 4 doses on alternate days), till to neutrophils > 1000 or PEG-filgrastim 6 mg to be administered within day +3
- Cotrimoxazole Bactrim 3 tablets/week (or 1 x 2/day per two days/week) or Pentamidine aerosol every 15 days in patients with Bactrim allergy or in patients with G6PD deficiency throughout the treatment and consolidation phase
- In patients with antiHBcAb +, prophylaxis against hepatitis B reactivation with Lamivudine 100 mg/die starting two weeks prior the start of the treatment to one year after the end of the treatment
- Prophylaxis with levofloxacin or ciprofloxacin in case of neutropenia <0.5 x 109/l. Ciprofloxacin should be avoided while on venetoclax therapy.

During consolidation and maintenance phase the following concomitant therapy is recommended:

- Neutropenia is frequently observed among subjects who receive venetoclax as a single agent or in combination [Grade 3 or 4 neutropenia occurred in 41% (98/240) in CLL patients, and in 12% of NHL], with slightly higher frequency observed in some combination studies.
- Granulocyte colony stimulating factors (G-CSF) should be used for supportive measures when neutrophil count <0.5 x 109/l, until recovery (>1.0 x 109/l), or in case of febrile neutropenia.
- Lymphopenia has been observed in preclinical studies. While opportunistic infections have been reported in the clinical program, data is confounded by subjects underlying disease and prior therapies.
- Antiviral prophylaxis with acyclovir 800-1200 mg per day should be implemented during the 4 months of consolidation treatment. Acyclovir prophylaxis may be stopped during maintenance phase, unless for patients with previous history of viral reactivations. Test for Cytomegalovirus (CMV)-DNA is required monthly during the consolidation phase.
- Prophylaxis of Pneumocystis Jirovecii pneumonia with Bactrim is recommended during the consolidation period and at least for the initial two months of maintenance therapy.

- Avoid the use of clarithromycin, itraconazole, voriconazole, erythromycin, ciprofloxacin, or fluconazole during venetoclax treatment.

All concomitant medications for medical conditions other than B-NHL are permitted, as clinically indicated. All supportive therapies other than anti-cancer treatment needed for the management of patients enrolled in this study are permitted.

13.6.2 Permitted concomitant therapy

The following medications and support therapies that may be used if needed during induction phase:

- Antiviral prophylaxis with acyclovir 800-1200 mg at day since the beginning of therapy is strongly recommended in patients with previous history of herpes virus infection reactivation.

Platelets and red blood cell transfusion are allowed, if needed. All hemo-components should be irradiated. Immunoglobulin assay is advisable once a month during the therapy with immunoglobulin replacement in case of IgG level < 0.3-0.5 gr/dl and frequent infectious events. Packed red cells and platelets transfusions will be given with filtered and irradiated products in case of Hb < 8 g/dL or Plts < 10 x 109/L. Erytropoietin therapy is allowed according to ASH/ASCO guidelines.

Bowel care is recommended to prevent constipation and should be administered per standard practice. Premedication for rituximab infusion with antihistamines, paracetamol/acetaminophen, prednisolone should be considered before each infusion of rituximab, because it may reduce infusion reactions.

Allopurinol should be used as prevention of tumor lysis syndrome at least for the first two weeks of treatment. The use of steroids including collirium is allowed during treatment with Ara-C, but its use should be restricted to the 3 days of treatment.

13.6.3 Prohibited concomitant therapy

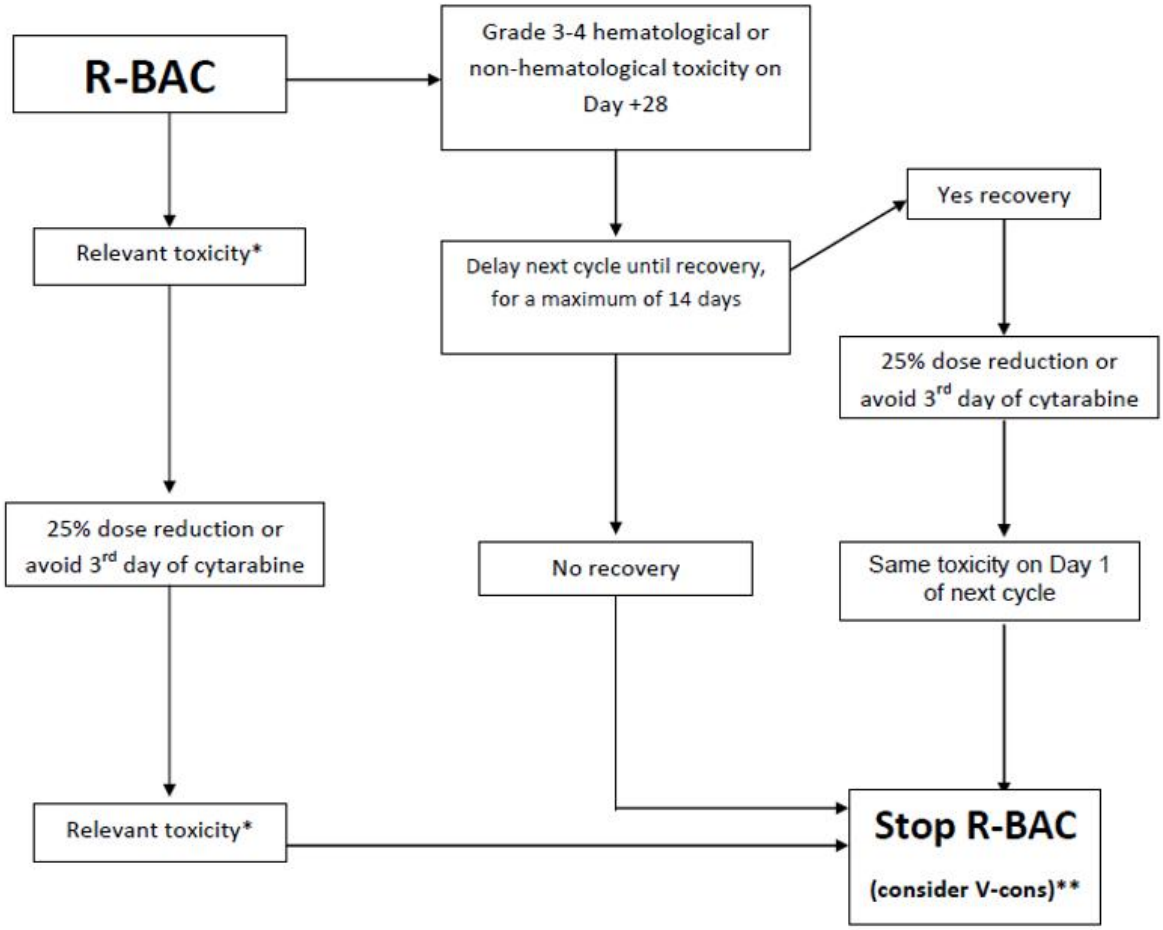
The following medications and supportive therapies are prohibited at all times:

- Any antineoplastic agent other than those planned by the study program.
- Any experimental agent.

13.7 R-BAC toxicity and dose modification, definition of relevant toxicity

The duration of the cytopenia induced by the chemotherapy or unexpected toxicities may suggest a prolongation of the interval between R-BAC cycles, and/or dose reduction (Figure 5): If any grade 3 or 4 cytopenia or grade 3-4 non-hematological toxicity persists on day 28 of any cycle, administration of subsequent cycles will be postponed of at least 2 weeks (28 days+14 days), and doses of bendamustine and Ara-C reduced by 25% for all subsequent cycles (Benda 50 mg/m2; Ara-C 375 mg/m2). Alternatevely, instead of reducing both drugs, the 3rd day of cytarabine can be avoided, maintaining the same dose of bendamustine and cytarabine for 2 days. In any case, the dose of rituximab will remain fixed.

If grade 3 or 4 cytopenia or grade 3-4 non-hematological toxicity does not resolve within the two additional weeks, or if patients still do not recover within 28 days after 25% dose reduction (or avoidance of the 3rd cyatarabine dose), R-BAC should be discontinued, and patient evaluated for starting consolidation with venetoclax (V_{cons}), if *HR* and adequate blood counts (see Figure 5 and paragraph 13.5.1 for requisites for starting venetoclax).



*Relevant toxicity: 1) Grade 4 cytopenia lasting for more than 7 days (this definition does not apply to the 1st cycle for patients that present with cytopenias defined as absolute neutrophil count<1,000 cells/μL and platelets<100,000 cells/μL which is related to marrow involvement. For this particular subgroup of patients the hematological relevant toxicity will be assessed starting from the 2nd cycle). 2) Febrile neutropenia lasting for more than 3 days. 3) Grade 3-4 non-hematologic toxicity.

** patient should be evaluated for starting consolidation with Venetoclax (Vcons), if adequate blood counts (see Figure 4 and paragraph 13.5.1 for requisites for starting Venetoclax).

Figure 5: Dose delays and reductions, treatment discontinuation

13.8 Venetoclax toxicity and dose modification, reduction, discontinuation

Dose interruptions and subsequent reductions during venetoclax therapy are summarized in Table 1 and 2, respectively, and will depend on the occurrence of TLS, neutropenia, infection, or any other drug related event. Adequate bone marrow function (defined as an absolute neutrophil count of 1000 per cubic millimeter or more and a platelet count of 50,000 per cubic millimeter or more; hemoglobin level of 8 g per deciliter or more) will be required before venetoclax consolidation is started.

During the ramp-up phase, continue the reduced dose for 1 week before increasing the dose.

Event	Occurrence	Action
Tumor Lysis Syndrome		
Blood chemistry changes or symptoms suggestive of TLS	Any	Withhold the next day's dose. If resolved within 24 to 48 hours of last dose, resume at the same dose.
For any blood chemistry changes requiring more than 48 hours to resolve, resume at a reduced dose (see Table 2)		
Non-Hematologic Toxicities		
Grade 3 or 4 non-hematologic toxicities	1st occurrence	Interrupt VENETOCLAX. Once the toxicity has resolved to Grade 1 or baseline level, VENETOCLAX therapy may be resumed at the same dose. No dose modification is required.
	2nd and subsequent occurrences	Interrupt VENETOCLAX. Follow dose reduction guidelines in Table 4 when resuming treatment with VENETOCLAX after resolution. A larger dose reduction may occur at the discretion of the physician.
Hematologic Toxicities		
Grade 3 or 4 neutropenia with infection or fever; or Grade 4 hematologic toxicities (except lymphopenia)	1st occurrence	Interrupt VENETOCLAX. To reduce the infection risks associated with neutropenia, granulocyte-colony stimulating factor (G-CSF) may be administered with VENETOCLAX if clinically indicated. Once the toxicity has resolved to Grade 1 or baseline level, VENETOCLAX therapy may be resumed at the same dose.
	2nd and subsequent occurrences	Interrupt VENETOCLAX. Consider using G-CSF as clinically indicated. Follow dose reduction guidelines in Table 2 when resuming treatment with VENETOCLAX after resolution. A larger dose reduction may occur at the discretion of the physician.
Consider discontinuing VENETOCLAX for patients who require dose reductions to less than 100 mg for more than 2 weeks. aAdverse reactions were graded using NCI CTCAE version 4.0. bClinical TLS was defined as laboratory TLS with clinical consequences such as acute renal failure, cardiac arrhythmias, or sudden death and/or seizures		

Table 1. Recommended Dose Modifications for Toxicities

Dose at Interruption (mg)	**Restart Dose (mg)**
800	**600**
600	**400**
400	**200**
200	**100**
100	**50**
50	**20**

Table 2. Dose Modification for Toxicity During venetoclax Treatment

14. REMOVAL OF SUBJECTS FROM TREATMENT AND/OR STUDY

14.1 Discontinuation from study treatment

A patient should discontinue treatment if any of the following occurs:

- completed treatment as per protocol
- inacceptable toxicity
- inadequate tumor response/tumor progression

14.2 Withdrawal of subjects from the study

Circumstances that lead to premature withdrawal of a patient from the trial must be reported by the investigator on the appropriate CRF page.
Criteria for subject withdrawal include (but are not limited to):

- death,

withdrawal of Consent 14.3 Withdrawal of Consent

Patients are free to withdraw from the study at any time without prejudice to their treatment. When a patient decides to withdraw from the study, she/he should always be contacted in order to obtain information about the reason for withdrawal and to record any adverse events. When possible, the patient should return for a study visit at the time of, or soon after withdrawal, and the relevant assessments should be performed.
If the patient explicitly states his/her wish not to contribute further data to the study, the assigned FIL Study Coordinator should be informed and the withdrawal of consent should be documented by the investigator in the patient's case report form. Information from subsequent ambulatory visits, laboratory or instrumental assessments and any other information on the patient status after consent withdrawal won't be collected in the data base or used for analysis However, both clinical data collected until patient's withdrawal as well as the data coming from the central review will still be considered as available for the study analysis.

14.4 Patients Lost to Follow up

Every effort will be made to contact patients who fail to return for scheduled visits. A patient is considered lost to follow-up if no information has been obtained when the last patient has completed the clinical phase of the study. During this time site investigator must document attempts to contact the patient either by phone or letter.

14.5 Premature termination of the study

The sponsor reserves the right to stop the trial at any time due to majeure reasons or circumnstances. The investigators will be informed of this decision in writing.
The same applies to any investigator willing to discontinue his/her participation to the trial. The investigator must immediately inform the sponsor in writing of this decision.

15. STUDY PROCEDURES TIMEPOINTS

Patients participation will include:

- The pretreatment (screening) phase will be 30 days for all laboratory tests and radiographic imaging phase and up to 90 days for bone marrow evaluation. Lymph-node or involved tissue biopsy is mandatory before study entry, and should have been performed within 6 months before study entry.
- The treatment phase will extend from the first day of the first course of R-BAC up to 6 courses for LR patients, followed by 24 months of venetoclax treatment (consolidation + maintenance), only if less than CR. For patients with HR disease 4 courses of R-BAC will be followed by 24 months of venetoclax treatment (consolidation + maintenance).
- The follow-up phase will begin after the completion of the treatment phase, and will last for 2 years after the last enrolled patient has terminated maintenance phase. Follow-up will continue until the patient decides to withdraw from the study, death or the study is ended (expected to be 2 years after the last HR enrolled patient will terminate maintenance phase).

Hematology and laboratory results must be available and reviewed by the investigator to evaluate for possible toxicities. All subjects will be monitored for adverse events throughout the study and for 30 days after the end of treatment.

15.1 Screening period

All patients must satisfy all the inclusion criteria (listed in section 11.1) and none of exclusion criteria (listed in section 11.2) and sign informed consent before the first dose of study drug can be administrated. Results of procedures performed as part of standard medical care before signing the informed consent may be used as part of the screening evaluation if performed within 30 days of beginning of therapy for laboratory tests and imaging studies, within 90 days for bone marrow biopsy and aspirate and within 6 months for lymphnode biopsy.
It is important that diagnostic specimens are centralized as soon as possible and no later than 2 weeks from study entry to the centralized pathology Lab, that will define the risk of the single patient based on

morphology, Ki-67 and *TP5*3 mutations/*TP53* deletions evaluation (see Appendix 9).

For a complete screening the following will be required in all patients:

- Written informed consent
- Complete medical history (included concomitant diseases and treatment)
- Recent clinical history (B symptoms)
- Physical examination (Vital signs, height, weight, BSA, size of lymphnodes, sign of organ involvement)
- ECOG performance status
- Bone marrow biopsy and aspirate
- PB, BM and urine sample for MRD-0 (see also section 15.10 and Appendix 8) → all patients
- Lymphnode or tissue involved biopsy. Importantly, when the diagnostic specimen is represented by a bone marrow biopsy (BOM), and no other lymphnode or extranodal tissue is available, the shipment of this specimen to the central pathology Lab should include a 2mL heparin vial of bone marrow aspirate, together with the diagnostic BOM. This is mandatory in order to allow assessment of *TP53* mutations/*TP53* deletions on this tumor sample.
- Chest and abdomen computer tomography scan (CT scan of the head and neck at the discretion of the treating physician)
- PET-scan with SUVmax determination
- ECG and echocardiogram or blood pool cardioscintigraphy
- Hematology (hematocrit, hemoglobin, RBC WBC and differential, Platelets)
- Blood chemistry (AST, ALT, serum alkaline phosphatase, gGT, total bilirubin, creatinine, Na, K, Ca, P, uric acid, total protein, albumin)
- Coagulation assessment (PTT, PT, ATIII, D-dimer, Fibrinogeno)
- Serum LDH
- Beta-2-microglobulin
- Creatinine clearance
- Tumor Lysis Syndrome (TLS) risk evaluation
- IgA, IgG, IgM
- Virology (HIV, HBsAg, HbsAb, HBVcAb and HBV-DNA, HCVAb). HBV-DNA should be tested if HBcAb+, and followed up monthly until the end of consolidation. HCV-RNA to be tested only in HCVAb+ patients.
- Diagnostic lumbar puncture (only for blastoid variants). Local diagnosis is sufficient for this purpose. Patients with cerebrospinal fluid examination positive for MCL CNS localization (either cytocentrifugate or immunophenotype) are not eligible for the study.

Additional assessments if necessary according to the local standards and if clinically indicated at the discretion of the treating physician.

15.2 Induction treatment period (R-BAC)

The treatment phase begins on Day 1 of course 1 of treatment with study drug and continues until

completion of study therapy or discontinuation of treatment with the study drug (end of treatment visit).

15.2.1 Before each course

Before each R-BAC course the following will be evaluated:

- Hematology
- Blood chemistry (AST, ALT, serum alkaline phosphatase, GGT, total bilirubin, creatinine, Na, K).
- Eligible patients whose renal function is slightly impaired should be monitored in terms of weight and diuresis, as well as for creatinine levels during each day of treatment.
- Tumor Lysis Syndrome (TLS) risk evaluation
- Cytomegalovirus DNA Detection and Quantification (CMVDNA)
- Patients with the blastoid variant of MCL will receive 4 prophylactic lumbar punctures on Day 1 of the first 4 cycles (Methotrexate 15 mg, Depo-Medrol 40 mg).
- Patients will be evaluated for possible toxicities, according to the definition of relevant toxicity reported in Appendix 11.
- Concomitant medications will also be evaluated
- Adverse event will always be notified

15.2.2 After cycle 1 and 3

- Hematology (whole blood cell counts and differential); a blood count is mandatory from day + 7 (from end of therapy) and repeated every other day till recovery of blood counts.
- Blood chemistry (AST, ALT, serum alkaline phosphatase, GGT, total bilirubin, creatinine, Na, K, uric
- acid).
- Patients will be evaluated for possible toxicities, according to the definition of relevant toxicity reported in Appendix 11. Concomitant medications will also be evaluated
- Adverse event will always be notified

Additional assessments have to be performed according to the local standards and if clinically indicated at the discretion of the treating physician.

15.2.3 After cycle 2 (All patients, either HR and LR)

Patients with any disease risk who are in PD, will go off-therapy.

- Hematology
- Blood chemistry (AST, ALT, serum alkaline phosphatase, GGT, total bilirubin, creatinine, Na, K).
- Bone marrow assessment (bone marrow biopsy) only to patients with positive bone marrow biopsy at diagnosis.
- CT scan of chest and abdomen after two cycles of treatment (Gastroscopy and colonscopy should be repeated when performed and positive at diagnosis).
- Patients will be evaluated for possible toxicities, according to the definition of relevant toxicity
- reported in Appendix 11. Concomitant medications will also be evaluated
- Adverse event will always be notified

15.2.4 After cycle 4 for HR (before consolidation, only applies to HR)

All patients with *HR* disease that will proceed to the consolidation phase will perform:

- Hematology
- TLS risk evaluation
- Blood chemistry (AST, ALT, serum alkaline phosphatase, GGT, total bilirubin, creatinine, Na, K).
- PET scan in HR patients only (to be performed between day 21 and day 35 of last R-BAC cycle, and before starting consolidation phase)
- Bone marrow biopsy will be repeated only in patients who had bone marrow involvement at diagnosis that persisted after initial two cycles.
- PB, BM and urine sample for MRD-1 (see also section 15.10 and Appendix 8) → only for HR patients Patients will be evaluated for possible toxicities, according to the definition of relevant toxicity reported in Appendix 11. Concomitant medications will also be evaluated
- Adverse event will always be notified

15.2.5 After cycle 6 for LR (or end of treatment for those in CR)

All patients with *LR* disease not in CR after end of R-BAC, that will proceed to the consolidation phase will perform:

- Physical examination
- Hematology (Whole blood cell counts and differential);
- Blood chemistry (AST, ALT, serum alkaline phosphatase, GGT, total bilirubin, creatinine, Na, K).
- PET-scan 1 month after the end of treatment (LR patients not in CR will proceed to Vcons and Vmaint,
  respectively)
- Bone marrow biopsy will be repeated only in patients who had bone marrow involvement at diagnosis that persisted after initial two cycles.
- PB, BM and urine sample for MRD-1 (see also section 15.10 and Appendix 8) - only for LR patients that are not in CR and proceed to Vcons.
- Patients will be evaluated for possible toxicities, according to the definition of relevant toxicity reported in Appendix 11. Concomitant medications will also be evaluated
- Adverse event will always be notified

15.3 During consolidation phase (for each 28 day-cycle)

- Physical examination
- Hematology
- Blood chemistry (AST, ALT, serum alkaline phosphatase, GGT, total bilirubin, creatinine, Na, K).
- CMV-DNA evaluation on Day 1 of each cycle.
- Patients will be evaluated for possible toxicities, according to the definition of relevant toxicity reported in Appendix 11. Concomitant medications will also be evaluated
- Adverse event will always be notified

15.4 After consolidation phase (after Vcons)

- Physical examination
- PET scan (to be performed at the end of consolidation and before starting maintenance phase)
- Bone marrow biopsy will be repeated only in patients who had bone marrow involvement at diagnosis that persisted after two cycles.
- PB, BM and urine sample for MRD-2 (see also section 15.10 and Appendix 8)
- Patients will be evaluated for possible toxicities, according to the definition of relevant toxicity reported in Appendix 11. Concomitant medications will also be evaluated
- Adverse event will always be notified

15.5 During maintenance phase (during Vmaint)

- Physical examination every 2 motnhs
- Hematology (Whole blood cell counts and differential); every month or according to clinical needs
- Blood chemistry (AST, ALT, serum alkaline phosphatase, GGT, total bilirubin, creatinine, Na, K); every month or according to clinical needs.
- CT scan (to be performed every 6 months)
- PB and urine sample for MRD-3 half of maintenance phase (see also section 15.10 and Appendix 8)
- Patients will be evaluated for possible toxicities, according to the definition of relevant toxicity reported in Appendix 11. Concomitant medications will also be evaluated
- Adverse event will always be notified

Additional assessments have to be performed according to the local standards and if clinically indicated at the discretion of the treating physician.

15.6 End of Treatment (within 30 days from end of treatment)

- Physical examination
- Hematology (Whole blood cell counts and differential);
- Blood chemistry (AST, ALT, serum alkaline phosphatase, GGT, total bilirubin, creatinine, Na, K).
- PET scan 1 month after the end of treatment
- Bone marrow biopsy will be repeated only in patients who had bone marrow involvement at diagnosis that persisted after consolidation phase.
- PB, BM and urine sample for MRD-4 (see also section 15.10 and Appendix 8)
- Patients will be evaluated for possible toxicities, according to the definition of relevant toxicity reported in Appendix 11. Concomitant medications will also be evaluated
- Adverse event will always be notified

15.7 During Follow-Up

Follow up visits will be assessed every 3 months for the first year of follow-up, then every 6 months for at

least one more year.

In the first year:

- Physical examination
- Hematology (Whole blood cell counts and differential);
- Blood chemistry (AST, ALT, serum alkaline phosphatase, GGT, total bilirubin, creatinine, Na, K).
- CT scan of chest and abdomen every 6 months after the end of treatment visit
- Bone marrow biopsy will be performed every 6 months only in patients who had bone marrow involvement at diagnosis that persisted after the end of treatment. Biopsies during follow-up for patients who never had bone marrow involvement, or who became negative after treatment are to be performed only if clinically indicated at the discretion of the physician
- Patients will be evaluated for possible toxicities, according to the definition of relevant toxicity reported in Appendix 11. Concomitant medications will also be evaluated
- Adverse event will always be notified
- PB and urine sample for MRD-5, 6 months after the end of maintenance (see also section 15.10 and Appendix 8)

Additional assessments if necessary according to the local standards and if clinically indicated at the discretion of the treating physician.

In the second year:

- Physical examination
- Hematology (Whole blood cell counts and differential);
- Blood chemistry (AST, ALT, serum alkaline phosphatase, GGT, total bilirubin, creatinine, Na, K). Bone marrow biopsy will be performed every 6 months only in patients who had bone marrow involvement at diagnosis that persisted after the end of treatment. Biopsies during follow-up for patients who never had bone marrow involvement, or who became negative after treatment are to be performed only if clinically indicated at the discretion of the physician
- Patients will be evaluated for possible toxicities, according to the definition of relevant toxicity reported in Appendix 11. Concomitant medications will also be evaluated
- Adverse event will always be notified

In the third and fourth years (every 6 months):

- Patient status (alive, dead, lost to follow-up);
- diagnosis of second neoplasia and long term toxicity.

15.8 Early withdrawn (discontinuation from study treatment)

- Physical Examination
- Hematology (Whole blood cell counts and differential);
- Blood chemistry (AST, ALT, serum alkaline phosphatase, GGT, total bilirubin, creatinine, Na, K).
- ECOG
- ECG and echocardiogram or blood pool cardioscintigraphy

- PET-scan
- CT scan of chest and abdomen
- Bone marrow biopsy will be repeated only in patients who had bone marrow involvement at diagnosis that persisted after two cycles.
- Patients will be evaluated for possible toxicities, according to the definition of relevant toxicity reported in Appendix 11. Concomitant medications will also be evaluated.
- Adverse event will always be notified
- PB, BM and urine sample for MRD-6 (see also section 15.10 and Appendix 8) → **all patients**

15.9 Schedule of assessments

	Screening	Induction Treatment R-BAC					Consolidation V	After consolidation	Maintenance V	EoT	FU		Early withdrawn
		Before each cycle	After cycle 1 and 3	After cycle 2	After cycle 4	After cycle 6	for each cycle		Every 2 months	+ 1 months	Every 3 months (1° year)	Every 6 months (2° year)	
Informed consent	X												
Complete medical history	X												
B symptoms	X												
Physical exam	X	X					X	X	X	X	X	X	X
ECOG	X												X
Bone marrow biopsy and aspirate	X			X[5]				X[7]		X[9]	X[10]	X	X[7]
CT of chest, abdomen[1]	X			X					X[8]		X[8]	X	X
PET-scan	X				X[6]	X		X[6]		X			X
ECG and echocardiogram or blood pool cardioscintigraphy	X												X
Hematology	X	X	X	X	X	X	X		X	X	X	X	X
Blood Chemistry	X	X	X	X	X	X	X		X	X	X	X	X
Coagulation assessment	X												
Serum LDH	X												
β-2-microglobulin	X												
Clearance creatinine	X						X						
TLS risk evaluation	X				X	X	X						
IgA, IgG, IgM	X												
Virology[2]	X												
CMVDNA							X						
Lumbar puncture (only for blastoid variants)	X[3]	X[4]											
Samples for MRD (*to be centralized*)	*See below*												
Lympho node or tissue involved biopsy* (*to be centralized asap, mandatory within 2 weeks from start of therapy*)	X												
Toxicity/ Concomitant medications			X	X	X	X	X	X	X	X	X	X	X
Adverse event		X											X[11]

1 CT scan of the head and neck at the discretion of the treating physician

2 HIV, HBsAg, HbsAb, HBVcAb, HCVAb. HBV-DNA should be tested if HBcAb+, and followed up monthly until the end of consolidation. HCV-RNA to be tested only in HCVAb+ patients.

3 Diagnostic lumbar puncture

4 Patients will receive 4 prophylactic lumbar punctures on Day 1 of the first 4 cycles (Methotrexate 15 mg, Depo-Medrol 40 mg)

5 Only to patients with positive bone marrow biopsy at diagnosis

6 Only HR patients, or LR that will receive a total of 4 R-BAC cycles and not 6, due to toxicity.

7 Only in patients who had bone marrow involvement at diagnosis that persisted after two cycles

8 Every 6 months

9 Only in patients who had bone marrow involvement at diagnosis that persisted after consolidation phase

10 Only in patients who had bone marrow involvement at diagnosis that persisted after end of treatment

11 If applicable

*When the diagnostic specimen is represented by a bone marrow biopsy (BOM), the shipment of this specimen to the central pathology Lab should include a 2mL heparin vial of bone marrow aspirate, together with the diagnostic BOM. This is mandatory in order to allow assessment of TP53 mutation on this tumor sample.

15.9.1 Schedule of assessments for MRD samples

	Screening	Induction Treatment R-BAC				Consolidation V	After consolidation	Maintenance V	EoT	FU	Early withdrawn
	Baseline				Before V_{cons}		Before V_{maint}	Half of V_{maint} after C12	End of V_{maint} after C24	6 months after EoT	Relapse/Progression
TIMEPOINTS	**MRD-0**				**MRD-1**		**MRD-2**	**MRD-3**	**MRD-4**	**MRD-5**	**MRD-6**
PB sample (*to be centralized to FIL-MRD Network Labs*) for molecular studies	X				X		X	X	X	X	X
PB sample (*to be centralized to Vicenza Lab*) for flow cytometry studies	X				X^		X^	X^	X^	X^	X
Urine sample (*to be centralized to FIL-MRD Network Labs*) for molecular studies	X				X		X	X	X	X	X
BM sample (*to be centralized to FIL-MRD Network Labs*) for molecular studies	X				X		X		X		X

All patients

All HR patients; LR not in CR treated with venetoclax

^ If the screening will be positive

15.10 Minimal Residual Disease (MRD) analysis (Appendix 8)

The present section will briefly describe the background and rationale of performing minimal residual disease (MRD) determination in the context of FIL_V-RBAC trial.

Quantification of MRD may guide therapeutic strategies in mantle cell lymphoma (MCL). The gold standard method for MRD analysis is real-time quantitative polymerase chain reaction (RQ-PCR)[21,22], but recently multicolor flow cytometry has been proposed as an alternative for the rapid sample processing and analysis[23-25].

Please note that only for HR patients, PB and BM samples will be collected according to timepoints expected for the study. LR patients' samples will be collected only at baseline and relapse/progression at the MRD lab and stored as a negative control for future analysis (i.e. mutational and clonal evolution analyses on DNA samples that will be designed and performed in a second time, after appropriate request to the Ethical Committee and relative funding derived from separate grant applications).

MRD DETECTION METHODS

1) Molecular MRD determination will be performed using the immunoglobulin heavy chain variable region gene (IGH) rearrangement and the BCL1 product of the translocation t(11;14) on peripheral blood (PB) and bone marrow (BM) samples. Based on the published experience it would be possible to obtain a molecular marker using the BCL1 in approximately 30% of patients while the rate of success with the IGH rearrangement will be around 80%[23,27-30]. Based on these premises the majority of patients will have a molecular marker suitable for MRD determination. If two markers are available, they will be both monitored. MRD will be assessed by both qualitative nested PCR and quantitative PCR. The methods for MRD determination have been already published [31-35]. As far as real time quantitative PCR is concerned data reporting will be performed according to the Euro MRD group Guidelines [22]. Moreover, for patients not showing a molecular marker identifiable by classical Sanger sequencing, next-generation sequencing (NGS) techniques, such as the IGH-based Euro Clonality NGS approach [36] or the translocation-based Targeted Locus Amplification (TLA) approach[37] will be prospectively tested in this context for the MRD analysis.

Finally, also urine samples will be collected to investigate in a pilot study the feasibility of MRD detection on cell-free tumor DNA (ctDNA)[38, 39].

2) Multicolor flow cytometry for MRD detection will be assessed on PB using two 8-color combinations of monoclonal antibodies:

1. CD20/CD23/CD5/CD19/CD200/CD62L/CD3/CD45
2. kappa/lambda/CD5/CD19/CD305/CD11a/CD3/CD45

These combinations were chosen because they have demonstrated higher sensitivity compared to the previous 4-color approach [24,25]. The MCL cells will be identified as CD62L/CD200/CD23-negative and CD19/CD5/CD20-positive cells in the first combination or as clonal (kappa or lambda) CD305/CD11a-negative and CD19/CD5-positive cells in the second.

15.11 Pathology and centralized review (Appendix 9)

The diagnosis of MCL should include the following information:

1. positivity for cyclin D1 and SOX11 (the latter being mandatory in cases lacking cyclin D1- or t(11;14)-negative);

2. expression of CD20 and CD5;
3. growth pattern (nodular, diffuse, mantle-zone);
4. cytological subtype (common, small cell, marginal zone-like, blastoid, pleomorphic);
5. negativity for CD23 and annexin 1A (in case of differential diagnosis with HCL);
6. Ki-67 rate.

Points 1 and 2 are prerequisites for case enrollment. Examples of indolent and in situ MCL should be excluded from the study.

After enrollment of patients, every center will be asked to send paraffin blocks of the diagnostic specimen for central pathologic review. The samples used for the diagnosis should be available for immunohistochemical and molecular studies aimed to explore the *TP53* status.

The review process will be organized according to the procedures described in the Appendix 9.

16. EFFICACY MEASUREMENTS AND PARAMETERS

16.1 Efficacy measurement

Patients who starting the planned therap. will be considered the Efficacy Population (EP).

Overall Response Rate (ORR): Complete Remission, Partial Remission.

A patient is defined as a responder if he has a complete or partial response. Patients without response assessment (due to whatever reason) will be considered as non-responder.

16.2. Criteria for evaluation

Recommendations for Initial Evaluation, Staging, and Response Assessment of Non-Hodgkin Lymphoma: The Lugano Classification (Cheson et al., 2014[40]) will be applied (Appendix 10).

Response criteria will be determined as follows:

Complete response (CR) requires

- Complete metabolic response
- Score 1, 2, or 3 with or without a residual mass on 5PS† [†PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma].
- It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake.
- *Response based on CT-scan*: Complete radiologic response; Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi; No extralymphatic sites of disease.

Spleen or liver should be not palpable, and any nodules disappeared.

If the bone marrow was involved by lymphoma before treatment, the infiltrate must be cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative.

Partial response (PR) requires

- Partial metabolic response
- Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size
- Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan
- *Response based on CT-scan*: The decrease in sum of the product of the diameters (SPD) of up to 6 largest dominant masses should be of >50%; no increase in size of other nodes or spleen.

No response or Stable disease (SD) is defined as a failure to attain CR/PR or PD

- No metabolic response
- Score 4 or 5† with no significant change in FDG uptake from baseline
- *Response based on CT-scan*: < 50% decrease from baseline in SPD of up to 6 dominant measurable nodes and extranodal sites; no criteria for progressive disease are met

Progressive disease (PD)

- Progressive metabolic disease
- Score 4 or 5 with an increase in intensity of uptake from baseline and/or new FDG-avid foci consistent with lymphoma
- Any new lesion or increase by > 50% of previously involved sites from nadir. Appearance of a new lesion(s) > 1.5 cm in any axis, > 50% increase in SPD of more than one node, or > 50% increase in longest diameter of a previously identifed node > 1 cm in short axis. Bone marrow. New or recurrent involvement.
- *Response based on CT-scan*: Progressive disease requires at least 1 of the following: An individual node/lesion must be abnormal with: LDi > 1.5 cm and increase by ≥ 50% from PPD nadir and an increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm. In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline. New or recurrent splenomegaly. New or clear progression of preexisting nonmeasured lesions.

16.2 Efficacy parameters

16.2.1 Primary endpoints

Progression-free survival (PFS) of the HR population from date of enrollment

16.2.2 Secondary endpoints

- The proportion of molecular response (characterized by labs of the FIL) of HR patients
- The progression-free survival (PFS) of LR patients, of all enrolled patients, and of TP53 mutated patients
- The overall survival (OS)
- The duration of responses (DoR)

- The proportion of complete remission (CR) before and after venetoclax in the HR group and/or in the LR not

responding to R-BAC.

- The proportion of patients that complete the expected treatment schedule
- The safety of venetoclax when administered as consolidation or maintenance after R-BAC

17. SAFETY MEASUREMENTS AND PARAMETERS

17.1 Safety measurements

Safety assessments will consist of monitoring and recording all adverse events (AEs) and serious adverse events (SAEs), monitoring hematology, blood chemistry, urin analysis, and measurement of vital signs and physical examinations as detailed in Table 1.

In the first stage of the study an independent panel of experts will monitor and validate the step-wise dose escalation of Ara-C to indentify the dose that will be used in the second stage. All patients who have received at least 1 dose of study medication will be considered the Safety Population (SP) and will be evaluated for toxicity from the time of their first drug administration. When toxicity occurs, it should be graded according to the NCI Common Toxicity Criteria, version 4.03 (Appendix 11).

Any SAEs will be followed until the event resolves or until the event will be stable or until sequelae and this information will be reported to the sponsor through the FIL website for transmission of SAE (17.3).

17.2 Safety parameters

17.2.1 Adverse Events (AE)

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition.

An overdose, accidental or intentional, whether or not it is associated with an AE, or abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. If an overdose is associated with an AE, the overdose and adverse event should be reported as separate terms.

17.2.2. Adverse Reaction (AR)

All untoward and unintended responses to a medicinal product related to any dose. The phrase "responses to medicinal products" means that a causal relationship between a study medication and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the sponsor as having a reasonable suspected causal relationship to the study medication qualify as adverse reactions.

17.2.3 Serious Adverse Events (SAE)

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (the term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a medically significant event:

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriated in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above.

The term “severe” is a measure of intensity, thus a severe AE is not necessarily serious. For example, “nausea of several hours” duration may be severe but may not be clinically serious.

Events not considered to be SAEs are hospitalizations for:

- A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- The administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- A procedure for protocol/disease-related investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- A procedure that is planned (i.e., planned prior to starting of treatment on study); must be documented in the source document and the CRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- An elective treatment of a pre-existing condition unrelated to the studied indication.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, both the AE page/screen of the CRF and the SAE Report Form must be completed.

For each SAE, the Investigator will provide information on severity, start and stop dates, relationship to IP, action taken regarding IP, and outcome.

17.2.4 Suspected Unexpected Serious Adverse Reaction (SUSAR)

An unlisted adverse event, the nature or severity of which is not consistent with the applicable product information. For an investigational drug, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator’s Brochure of experimental drug. For drugs with a marketing

authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the SmPC.

17.2.5 Severity

The intensity of the toxicities, AE or SAE will be graded by the investigator according to the Common Terminology Criteria for Adverse Events (CTCAE) grading system v4.03 in the toxicity categories that have recommended grading (see Investigator's file or online at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).
AEs not listed on this grading system will be graded according to the five-point system below:

- Mild (grade 1): Discomfort noticed but no disruption of normal daily activity
- Moderate (grade 2): Discomfort sufficient to reduce or affect normal daily activity
- Severe (grade 3): Incapacitating with inability to work or perform normal daily activity
- Life-threatening (grade 4): Substantial risk of dying at time of event
- Death (grade 5)

17.2.6 Causality

The Investigator(s) must determine the relationship between the administration of study drug and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:
Not related. An adverse event that is not related to the use of the investigational product. Unlikely/Doubtful. An AE for which an alternative explanation is more likely, e.g., concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely. Possible. An AE that might be due to the use of the investigational product. An alternative explanation, e.g., concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.
Probable. An AE that might be due to the use of the investigational product. The relationship in time is suggestive (e.g., confirmed by dechallenge). An alternative explanation is less likely, e.g., concomitant drug(s), concomitant disease(s).
Definite/Very likely. An AE that is listed as a possible adverse event reaction, and cannot be reasonably explained by an alternative explanation, e.g., concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (e.g., it is confirmed by dechallenge and rechallenge).
Not assessable: there is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

17.3 Serious Adverse Events reporting rules

All events that meet one or more seriousness criteria (see Section 17.2.2.) occurred after the informed consent signature until the end of the study or the study interruption for any causes, will be reported as SAE. Whenever possible, symptoms should be grouped as a single syndrome or diagnosis. The investigator should specify the date of onset, intensity, action taken regarding trial medication, corrective therapy given, outcome of all SAEs and his opinion as to whether the SAE can be related to the study drugs.
General SAE reporting rules:

- Any episode of any grade of toxicities, which meets one of the seriousness criteria, must be reported
- as "Serious Adverse Event" in the appropriate SAE form.
- Signs, symptoms and physical findings indicative of lymphoma or progression of lymphoma are not to
- be reported as "Serious Adverse Event".

- “Alopecia” toxicity (any grade) will never be reported as “Serious Adverse Event”.
- Tumor Lysis Syndrome will be reported as “Serious Adverse Event”.

All AEs that occur between the first study-related procedures and for 30 days following the last dose of investigational product will be reported.

All AEs, regardless of seriousness, severity, or presumed relationship to study therapy, must be recorded in the CRF in accordance to the CTCAE criteria (*http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE 4.03 2010-06.pdf*.). They must be recorded using medical terminology in accordance to MedDra (version 20.1) dictionary.

17.3.1 Obligations of the Investigator

Investigators must record also in the CRF their opinion concerning the relationship of the adverse event to the study therapy. All measures required for adverse event management must be recorded in the source document.

Investigators must submit reports of all SAEs, regardless of attribution to the Sponsor within 24 hours of learning of the events.

Moreover, all adverse events of tumor lysis syndrome considering not serious must be reported to the Sponsor.

For initial SAE investigators should record all case details that can be gathered on a SAE form that must be completed directly online through the FIL web site: *www.drugvigilance.filinf.it*

The initial report must be as complete as possible, including details of the current illness and serious adverse event, and an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up SAE form as soon as it becomes available and/or upon request.

The Investigator(s) must keep copies of all SAE information on file. All SAEs that have not resolved upon discontinuation of the patient’s participation in the study must be followed until either the event resolves completely, stabilizes/resolves with sequelae, or returns to baseline (if a baseline value is available).

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17.3.2 Obligations of the Sponsor

The Sponsor will inform relevant Regulatory Authorities, Ethics Committees

- Of all relevant information about serious unexpected adverse events suspected to be related to the study drugs that are fatal or life-threatening as soon as possible, and in any case no later than seven days after knowledge of such a case. Relevant follow-up information for these cases will be subsequently be submitted within an additional eight days
- Of all other serious unexpected events suspected to be related to the study drugs as soon as possible, but within a maximum of fifteen days of first knowledge by the investigator.

The FIL Pharmacovigilance will supply *AbbVie* with a copy of all SAEs which involve exposure to a [pharmaceutical company] product within 24 hours of being made aware of the event regardless of whether or not the event is listed in the reference document (e.g. IB, SmPC).
The FIL Pharmacovigilance will provide AbbVie with a copy of the development safety update report (DSUR) at the time of submission to the Regulatory Authority and Ethics Committees.

17.4 Partner Pregnancy

If a female partner of a male patient taking study drug becomes pregnant, the male patient taking study drug should notify the Investigator, and the pregnant female partner should be advised to call her healthcare provider immediately.
If a pregnancy related event is reported in a female partner of a male subject, the investigator should determine whether the female partner is willing to release her medical information to FIL Pharmacovigilance and allow the pregnancy related event to be followed-up to completion.

17.5 Follow up of AEs and SAEs

Any SAE should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or underlying condition. Any additional information known after the event has been initially reported should be sent to the FIL as soon as information becomes available via *www.drugvigilance.filinf.it*
All AEs must be documented and the outcome must be followed-up until the return to normal or consolidation of the patient's condition.
Subjects withdrawn from the study due to any AE will be followed at least until the outcome is determined even if it implies that the follow-up continues after the patient has left the trial.

17.5.1 Product Quality Complaint Handling

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide.

17.5.2 Procedures

All initial PQCs must be reported *AbbVie* by the study-site personnel within 24 hours after being made aware of the event.
If the defect is combined with a SAE, the investigational staff must report the PQC to *AbbVie* according to the SAE reporting timelines. A sample of the suspected product should be maintained for further investigation if requested by *AbbVie*.

18. STATISTICAL CONSIDERATIONS

18.1 Biostatistical definitions

Treatment

Any courses of therapy administered according to the R-BAC scheme, irrespectively of the number of delivered cycles.

Definition of "High Risk" patients (HR)

All enrolled patients that will have any of the following characteristics:

1. Ki-67 ≥ 30% (by central pathology revision) on the diagnostic specimen and/or
2. the blastoid morphological variant of MCL and/or
3. TP53 gene mutation or deletion (or p53 expression by immunohistochemistry >50%).

Investigators are encouraged to send diagnostic material to the centralized Lab within 2 weeks from start of therapy, in order to obtain a response before the start of consolidation phase (Figure 1).

Relevant toxicity

1. Grade 4 thrombocytopenia or neutropenia lasting for more than 7 days
2. Febrile neutropenia lasting for more than 3 days
3. Grade 3-4 non-hematologic toxicity.
4. This definition does not apply to the 1st cycle; relevant toxicity will be assessed starting from the 2nd cycle.

Stop treatment criteria for R-BAC cycles (Figure 4 and Table 1 and 2)

1. Occurrence of relevant toxicity for two subsequent or consecutive cycles (the protocol allows for a 25% reduction of drugs dosage/ cytarabine 3rd day avoidance, when an episode of relevant toxicity occurs for the first time).
2. Grade 3-4 hematological or non-hematological toxicity* on day +28 of a cycle not resolving within two weeks (+28 days+14 days since last cycle).
3. Grade 3-4 hematological or non-hematological toxicity on day +28 of a cycle after the 25% dose reduction/cytarabine 3rd day avoidance.
4. Patient refusal to proceed with further cycles due to perceived excessive toxicity.
5. Any unpredictable drug related event that suggests against study continuation.
6. Consider passage to Vcons in patients that cannot receive further R-BAC but are eligible for venetoclax monotherapy according to protocol definitions (see Figure 4 and paragraph 13.5.1)

18.2 Sample size calculation

As statistical tool, the one arm non parametric survival (SWOG) was adopted. The alpha-error (one tail) was 0.05, and the power was 90% (Table 3) assuming an.accrual time of 30 months and a minimum follow-up of 24 months.

Since the RBAC500 expected 2-years PFS for patients with HR disease is 40% (H0), the addition of venetoclax to all HR patients that are responsive to R-BAC is expected to improve 2-years PFS of 20%, testing our investigational PFS to 60% (H1). Thus, according to the one-arm study design, 52 HR patients will

be enrolled in the investigational arm. Overall, since HR patients will represent approximately 40-45% of newly diagnosed patients with MCL, it is estimated that 115-130 patients will be needed (52+63-78).
LR patients that do not achieve CR at the end of RBAC500 will be treated with the experimental drug. Since the number of such LR patients is hardly predictable based on the present experience with RBAC500, the analysis of this sub-cohort will be of exploratory nature, and thus assessed separately, leaving unaltered the previously calculated sample size (52 HR patients).

2-years PFS R-BAC (H0)	2-yeasr PFS R-BAC + V (H1)	Power	Patients number (Experimental arm)	Patients to be enrolled
40%	60%	90%	52	115-130

Table 3. Sample size calculation by means of SWOG one sample nonparametric survival

18.3 Statistical analysis plan

Study End points

Primary efficacy end point of the study is the progression-free survival (PFS) of the HR population from the date of starting treatment with R-BAC, defined according to Cheson criteria[40] .
Secondary end points are CR rate, MRD defined response, OS, and DoR[22]. PFS is measured from the time of enrollment until disease progression, relapse or death from any cause.
Molecular response is the proportion of patients with molecular rearrangements at baseline that become negative during treatment, measured by qualitative and quantitative PCR.
OS is measured from enrollment until death from any cause. DoR is measured from the first assessment that documents response (CR or PR) to the date of disease relapse or progression.

Safety Assessment

Safety will be assessed by documentation of adverse events (AEs), clinical laboratory results, vital signs, and physical examinations and recorded on the standard Electronic Case Report From (eCRF) pages and serious adverse event (SAE) data form. The incidence of AEs will be monitored using the National Cancer Institute (NCI) Common Terminology Criteria (CTC) version 4.0.
The safety points included among the secondary objectives of the study will be monitored and specifically reported in the CRF.

Efficacy Assessment

CR, partial response (PR), stable disease (SD), overall response (OR), and progressive disease (PD) will be assessed by CT-scan, PET, and bone marrow biopsy following Cheson criteria[40] at different time-points.

Statistical analysis

Descriptive statistics and their 95% confidence intervals will be used to summarize the activity and the safety endpoints. Time to event variables will be analysed using the Kaplan-Meier method. If the lower limit of one-sided confidence interval of the 2-year PFS in the HR group will exclude the null hypothesis (2-year PFS=40%), the experimental treatment will be judged as worthy of further investigation.

18.4 Summary of Study Endpoints

PRIMARY

OUTCOME	***TIME FRAME***	***SAFETY ISSUE?***
PFS	2 YEARS FROM ENROLLMENT for HR patients	NO

SECONDARY

OUTCOME	***TIME FRAME***	***SAFETY ISSUE?***
Molecular response	5 time points along treatment, see paragraph 15.9.1	NO
PFS	2 YEARS from ENROLLMENT for all screened patients, and different subcategories	NO
OVERALL SURVIVAL	4.5 YEARS FROM ENROLLMENT	NO
DURATION of RESPONSE	2 YEARS FROM ENROLLMENT	NO
CR RATE	Measured before and after Venetoclax	NO
RATE of Tx interruption	Measured at the end of treatment for all HR patients	YES
SAFETY (as acute and long-term toxicity)	Throughout all the active treatment period	YES

19. INDEPENDENT DATA SAFETY MONITORING COMMITTEE

The sponsor will set up an independent external Data Safety Monitoring Committee (DSMC). The DSMC consist in experts independent from the sponsor with pertinent expertise that will monitor the progress of the trial and will review accumulating data on a regular basis, if necessary.

The DSMC advises the sponsor regarding the continuity safety of trial participants and should make recommendations on the discontinuation, modification or continuation of the

trial. The independent Data Monitoring Committee will only review safety data since efficacy is controlled by the monitoring of PFS in this trial.

Frequency and contents of the DSMC meetings will be decided ongoing.

Following each meeting the DSMC will prepare a report and may recommend changes in the conduct of the trial.

20. GOOD CLINICAL PRACTICE, QUALITY CONTROL AND QUALITY ASSURANCE

20.1 Monitorings, Audits and Inspections

During the study the monitoring will be prevalently made by e-mail and telephone. The field monitor will visit the site, when needed, mainly in presence of data incongruity, to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol and to Good Clinical Practice and the progress of enrolment. Key study personnel must be available to assist the field monitor during these visits. The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. FIL Safety Monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

20.2 Investigator(s) responsibilities

Investigator responsibilities are set out in the ICH guideline for Good Clinical Practice. The investigator must give the monitor access to relevant records to confirm the above.

The Investigator(s) is responsible for keeping a record of all patients who sign an Informed Consent Form and are screened for entry into the study. For those patients who fail screening the reason(s) for exclusion must be recorded in the patient's source documents.

No procedure/assessment/measurement/test other than those outlined here, or in the schedule of study assessments, is to be performed without the prior written approval of Principal Investigator, or unless deemed by the investigator(s) as necessary for the patient's medical care. Investigator(s) and/or authorized designee(s) must enter study data onto electronic CRFs supplied by FIL. The data on the CRF will be recorded in an anonymous manner to protect the patient's identity by using a unique identifier that will prevent personal identifiable information.

The Investigator(s), or a designated member of the Investigators' staff, must be available at some time during monitoring visits to review data and resolve any queries and to allow direct access to the patient's records (e.g., medical records, office charts, hospital charts, and study related charts) for source data verification. The CRFs must be completed as soon as possible after the patient's visit, but no later than prior to each monitoring visit and be made available to the FIL representative(s) so that the accuracy and completeness may be checked.

21. ETHICAL AND REGULATORY STANDARDS

21.1 Institutional Review Board/Independent Ethics Committee Review Approval

This study will be conducted according to the Declaration of Helsinki Ethical Principles for Medical Research Involving Human Patients (see: http://www.wma.net/e/policy/b3.html for more information). The review of this protocol by the IRB/IEC and the performance of all aspects of the study, including the methods used for obtaining informed consent, must also be in accordance with principles enunciated in the declaration, as well as ICH Guidelines, Title 21 of the Code of Federal Regulations (CFR), Part 50 Protection of Human Patients and Part 56 Institutional Review Boards. Before implementing this study, the protocol, the proposed informed consent form and other information to patients, must be reviewed by a properly constituted IRB/IEC. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC must be given to FIL before the study initiation. The names and occupations of the chairman and the members of the IRB/IEC must be supplied to FIL.

The FIL as sponsor of the study, together with site Investigator(s), will be responsible for preparing documents, where ever applicable, for submission to the relevant IRB/IEC and obtaining written approval for this study. The approval will be obtained prior to the initiation of the study.

A copy of the IRB/IEC approval for the protocol and the Informed Consent is to be provided to FIL and site Investigator(s). The approval for both the protocol and informed consent must specify the date of approval, protocol number and version, or amendment number.

The Investigator(s) is responsible for notifying the FIL Safety Monitoring Office and the IRB/IEC of any serious deviations from the protocol, or anything else that may involve added risk to patients.

Any advertisements used to recruit patients for the study must be reviewed and approved by FIL and the IRB/IEC prior to use.

Before the start of the study, the FIL will provide the IRB/IEC with current and complete copies of the following documents:

1. final protocol and, if applicable, amendments
2. informed consent form (and any other written materials to be provided to the subjects)
3. Investigator's Brochure (or equivalent information) and amendments
4. information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
5. investigator's curriculum vitae or equivalent information (unless not required, as documented by IRB/IEC)
6. any other documents that the IRB/IEC requests to fulfil its obligation.

During the study the FIL according with site investigators will send the following documents to the IRB/IEC for their review and approval, where appropriate:

1. protocol amendments
2. revision(s) to informed consent form and any other written materials to be provided to subjects
3. revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
4. Investigator's Brochure amendments or new edition(s)

5. summaries of the status of the study (at least annually or at intervals stipulated in guidelines of the IRB/IEC)
6. reports of adverse events that are serious, unexpected and associated with the investigational drug
7. new information that may affect adversely the safety of the subjects or the conduct of the study
8. deviations from or changes to the protocol to eliminate immediate hazards to the subjects
9. report of deaths of subjects under the investigator's care
10. notification if a new investigator is responsible for the study at the site
11. any other requirements of the IRB/IEC

21.2 Protocol Amendments Approval

Any amendment to this protocol that seems appropriate, as the study progresses will be submitted to the IRB/IEC for written approval before the implementation of the amended version. The written signed approval from the IRB/IEC should refer specifically to the investigator(s) and to the protocol number and title and mention any amendment numbers that are applicable. Amendments that are administrative in nature do not require IRB/IEC approval but will be submitted to the IRB/IEC for information purposes.

22. ADMINISTRATIVE PROCEDURES

22.1 Curriculum vitae

An updated copy of the curriculum vitae of each investigator and sub-investigator will be provided to the FIL Start Up prior to the beginning of the study.
This study will be conducted by qualified Investigators, and Physicians with experience in treating onco-hematologic diseases.
The name of the Study Physician along with the telephone and FAX numbers of the other contact persons at the Referring Center are listed in the study site file.
The study will be monitored by qualified personnel from the FIL. Data management and statistical analyses will be the responsibility of the Principal Investigators and of the Biostatisticians referred above.

22.2 Confidentiality agreement

All goods, materials, information (oral or written) and unpublished documentation provided to the investigators (or any company acting on their behalf), inclusive of this study, the patient case report forms are the exclusive property of FIL.
They may not be given or disclosed by the investigator or by any person within his authority either in part or in totality to any unauthorized person without the prior written formal consent of FIL.
It is specified that the submission of this study and other necessary documentation to the Ethics Review Committee or a like body is expressly permitted, the Ethics Committee members having the same obligation of confidentiality.
The investigator shall consider as confidential and shall take all necessary measures to ensure that there is no breach of confidentiality in respect of all information accumulated, acquired or deduced in the course of the trial, other than that information to be disclosed by law.

22.3 Record retention in investigating centres

The investigator must maintain all study records, patient files and other source data for the maximum period of time permitted by the hospital, institution or private practice.
However national regulations should be taken into account, the longest time having to be considered.
For trials performed in the European Community, the investigator is required to arrange for the retention of the patient identification codes for at least 15 years after the completion or discontinuation of the trial.
Any center will notify the sponsor before destroying any data or records.

22.4 Ownership of data and use of the study results

The sponsor has the ownership of all data and results collected during this study. In consequence the sponsor reserves the right to use the data of the present study, either in the form of case report forms (or copies of these), or in the form of a report, with or without comments and with or without analysis, in order to submit them to the health authorities of any country.

22.5 Authorship

The first results of the trial will be published after complete data collection and evaluation of the primary endpoint. Partial or preliminary results can be published beforehand. Publication is to be initiated by the chairmen in charge of the study with approval of coordinators. Same rules apply for biological studies that are related to VR-BAC protocol.
Any publication in the form of a lecture, poster or article must be prospectively approved by the Scientific Committee of FIL.
The authors will be proposed (according to the updated FIL publication rules) by the chairmen in charge of the study, approved by coordinators and finally decided by the Steering Committee of the study.
All study data and publications are the property of the FIL.

22.6 Insurance coverage

The Investigator-sponsor of the Study must ensure that adequate insurance coverage is available to the patients, in accordance with the ICH Guidelines of Good Clinical Practice. Such coverage must extend to all damages deriving from the study, to the Protocol Study exclusion of those attributable to wilful misconduct or negligence of the institution or investigator. A copy, or excerpt, or insurer's certificate, attesting the existence and amount of such coverage at least for the duration of the study must be supplied as part of the study documentation to the review and approval of the IEC.
A specific insurance with company HDI Global SE has been concluded for patients enrolled in this study. No extra expenses, neither for therapies nor for clinical or laboratory procedures can be asked or expected to be paid by SSN or patients.

22.7 Protocol amendments procedures

It is specified that the appendices attached to this study and referred to in the main text of this study, form an integral part of the study.

No changes or amendments to this study may be made by the investigator or by the sponsor after the study has been agreed to and signed by both parties unless such change(s) or amendment(s) have been fully discussed and agreed upon by the investigator and the FIL.
Any change agreed upon will be recorded in writing, the written amendment will be signed by the investigator and by the sponsor and the signed amendment will be appended to this study.
Approval / advice of amendments by Ethics Review Committee and Competent Authorities are required prior to their implementation, unless there are overriding safety reasons.
If the change or deviation increases risk to the study population, or adversely affects the validity of the clinical investigation or the subject's rights, full approval / advice must be obtained prior to implementation. For changes that do not involve increased risk or affect the validity of the investigation or the subject's rights, approval / advice may be obtained by expedited review, where applicable.
In some instances, an amendment may require a change to a consent form. The investigator must receive approval / advice of the revised consent form prior to implementation of the change. In addition, changes to the case report forms, if required, will be incorporated in the amendment.

23. DATA HANDLING AND RECORD KEEPING

23.1 Data/documents

The investigator(s) must ensure that the records and documents pertaining to the conduct of the study and the distribution of the study drug, that is copies of CRFs and source documents original documents, data, and records (e.g., hospital records; clinical and office charts; laboratory notes; memoranda; patient's diaries or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives, microfilm, or magnetic media; x-rays; patient files) and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study are complete, accurate, filed and retained.

23.2 Data Management

Data will be entered into the clinical database as per FIL SOPs. These data will be electronically verified through use of on-line checks during data entry, and through programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary, in the form of a Data Clarification Form (DCF). Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

23.3 Retention of Records

The investigator(s) must maintain records of all study documents and supporting information relating to the conduct of the study. This documentation includes, but is not limited to, protocols, case report forms, advertising for patient participation, adverse event reports, patient source data, correspondence with health authorities and IRBs/IECs, informed consent forms, investigator(s) curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director

curriculum vitae. Patient files and other source data must be kept for the maximum period of time permitted by the hospital, institution or private practice specified below. The study monitor must be consulted if the investigator(s) wishes to assign the study files to someone else, remove them to another location or is unable to retain them for a specified period. The investigator(s) must retain study records for the time period according to local laws or requirements, whichever is longer. The monitor will inform the investigator(s) of the dates for retention. All study documents should be made available if required by relevant health authorities. The investigator(s) records must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by other applicable regulatory requirements.

24. PRIVACY OF PERSONAL DATA

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to investigate the efficacy, safety, quality, and utility of the investigational product(s) used in this study. These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations.

The investigator-sponsor ensures that the personal data will be:

1. processed fairly and lawfully
2. collected for specified, explicit, and legitimate purposes and not further processed in a way incompatible with these purposes
3. adequate, relevant, and not excessive in relation to said purposes
4. accurate and, where necessary, kept current

Explicit consent for the processing of personal data will be obtained from the participating subject (or his/her legally acceptable representative) before collection of data. Such consent should also address the transfer of the data to other entities and to other countries. The subject has the right to request through the investigator access to his/her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps should be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Patients will be registered in the study via web site the end of their staging, before beginning the treatment. The name of the patient will not be asked for not recorded at the Data Center. A sequential identification number will be automatically attributed to each patient registered in the trial. This number will identify and must be included on all case report form.

25. REFERENCES

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26. APPENDICES

APPENDIX 1: ECOG PERFORMANCE STATUS

SOURCE: *Oken MM et al, Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.*

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

APPENDIX 2: CREATININE CLEARANCE CALCULATION

Creatinine clearance for men and women will be calculated according to the Cockcroft-Gault formula as follows:

In men:

$$\frac{(140 - age) \times weight\ (kg)}{72 \times creatinine\ (mg/dL)}$$

In women:

$$\frac{(140 - age) \times weight\ (kg)}{72 \times creatinine\ (mg/dL)} \times 0.85$$

Note: Age (in years), weight (in kg), serum-creatinine (in mg/dL) 72 (normalized to 72 kg body weight and a body surface of 1.72 m^2)

APPENDIX 3: MODIFIELD COMPREHENSIVE GERIATRIC ASSESSMEN

Definition of FIT, UNFIT and FRAIL elderly patients

FIT

- non UNFIT, non FRAIL

UNFIT

- CHRONOLOGIC CRITERIA: age≥ 80 years and FIT
- CLINICAL FUNCTIONAL CRITERIA: according to ADL IADL CIRS scores

FRAIL

- CHRONOLOGIC CRITERIA: age≥ 80 years and UNFIT
- CLINICAL FUNCTIONAL CRITERIA: according to ADL IADL CIRS scores

SCALE	FIT	UNFIT	FRAIL
ADL	6	5*	≤4*
IADL	8	7-6*	≤ 5*
CIRS-G	0 score = 3-4 ≤5 score = 2	0 score = 3-4 5-8 score = 2	1 score = 3 -4 > 8 score = 2
AGE		≥ 80 FIT	≥ 80 UNFIT
Geriatric syndromes	None	1	> 1

* n. of residual functions

APPENDIX 4: QUESTIONNAIRES

Scheda attività di base della vita quotidiana (ADL)

Punteggio

A) FARE IL BAGNO (vasca, docce spugnature)

1 1. Fa il bagno da solo (entra ed esce dalla vasca da solo).
1 2. Ho bisogno di assistenza soltanto nella pulizia di una parte del corpo (es. dorso).
0 3. Ha bisogno di assistenza per più di una parte del corpo

B) VESTIRSI (prendere i vestiti dall'armadio e/o cassetti, inclusa biancheria intima, vestiti, uso delle allacciature e delle bretelle se utilizzate)

1 1. Prende i vestiti e si veste completamente senza bisogno di assistenza.
1 2. Prende i vestiti e si veste senza bisogno di assistenza eccetto che per allacciare le scarpe.
0 3. Ha bisogno di assistenza nel prendere i vestiti o nel vestirsi oppure rimane parzialmente o completamente svestito.

C) TOILETTE (andare nella stanza da bagno per la minzione e l'evacuazione, pulirsi, rivestirsi)

1 1. Va in bagno, si pulisce e si riveste senza bisogno di assistenza (può utilizzare mezzi di supporto come bastone, deambulatore o sedia a rotelle, può usare vaso da notte o comoda svuotandoli al mattino).
0 2. Ha bisogno di assistenza nell'andare in bagno o nel pulirsi o nel rivestirsi o nell'uso del vaso da notte o della comoda.
0 3. Non è in grado di recarsi in bagno per l'evacuazione.

D) SPOSTARSI

1 1. Si sposta dentro e fuori dal letto e in poltrona senza assistenza (eventualmente con canadesi o deambularore).
0 2. Compie questi trasferimenti se aiutato.
0 3. Allettato, non esce dal letto.

E) CONTINENZA DI FECI E URINE

1 1. Controlla completamente feci e urine.
0 2. "Incidenti" occasionali.
0 3. Necessita di supervisione per il controllo di feci e urine, usa il catetere, è incontinente.

F) ALIMENTAZIONE

1 1. Senza assistenza.
1 2. Assistenza solo per tagliare la carne o imburrare il pane.
0 3. Richiede assistenza per portare il cibo alla bocca o viene nutrito parzialmente o completamente per via parenterale.

TOTALE _____

Scheda attività strumentali della vita quotidiana (IADL)

Punteggio

A) ABILITA' AD USARE IL TELEFONO

1 1. Usa il telefono di propria iniziativa: cerca il numero telefonico e lo compone.
1 2. Compone solo pochi numeri ben conosciuti.
1 3. Risponde al telefono, ma non compone i numeri.
0 4. E' incapace di usare il telefono.

B) FARE LA SPESA

1 1. Si prende cura della spesa e la fa in maniera autonoma.
0 2. E' capace di effettuare solo piccoli acquisti.
0 3. Ha bisogno di essere accompagnato per qualunque tipo di acquisto.
0 4. E' completamente incapace di fare la spesa.

C) PREPARARE I PASTI

1 1. Pianifica i pasti, li prepara adeguatamente e li serve in maniera autonoma.
0 2. Prepara i pasti solo se gli forniscono tutti gli ingredienti.
0 3. E' in grado di riscaldare cibi già pronti, oppure prepara i cibi in maniera non costante tanto da non riuscire a mantenere un'alimentazione adeguata.
0 4. Ha bisogno di cibi già preparati e di essere servito.

D) CURA DELLA CASA

1 1. Riesce a occuparsi della casa autonomamente o con occasionale aiuto per i lavori pesanti.
1 2. Riesce a effettuare i lavori domestici leggeri come lavare i piatti, rifare il letto, ecc.
1 3. Riesce a effettuare i lavori domestici leggeri, ma non è capace di mantenere un livello adeguato di pulizia.
0 4. Ha bisogno di aiuto per tutte le pulizie della casa
0 5. E' completamente disinteressato a qualsiasi faccenda domestica.

E) FARE IL BUCATO

1 1. Lava tutta la propria biancheria.
1 2. Lava solo piccoli indumenti.
0 3. Tutto il bucato deve essere fatto da altri.

F) SPOSTAMENTI FUORI CASA

1 1. Viaggia autonomamente, servendosi dei mezzi pubblici o della propria automobile.
1 2. Fa uso di taxi, ma non è capace di usare mezzi pubblici.
1 3. Viaggia su mezzi pubblici solo se assistito o accompagnato.
0 4. Viaggia in macchina o in taxi quando è assistito o accompagnato da altri.
0 5. Non può viaggiare affatto.

G) ASSUNZIONE DEI PROPRI FARMACI

1 1. E' capace di assumere correttamente le medicine.
0 2. E' capace di assumere le medicine solo se in precedenza già preparate e separate.
0 3. E' incapace di assumere da solo le medicine.

H) USO DEL PROPRIO DENARO

1 1. Provvede in modo autonomo alle proprie finanze (conti, fare assegni, pagare l'affitto e le altre spese, andare in banca), controlla le proprie entrare.
1 2. Provvede alle spese e ai conti quotidiani, ma ha bisogno di aiuto per le operazioni maggiori (andare in banca, fare assegni, are grosse spese, ecc.).
0 3. E' incapace di maneggiare il denaro in modo proprio.

TOTALE _____

CIRS-G Scala geriatrica di graduazione della comorbidità

MALATTIE	PUNTEGGIO				
	0	1	2	3	4
Cardiologiche	☐	☐	☐	☐	☐
Apparato circolatorio	☐	☐	☐	☐	☐
Ematologiche	☐	☐	☐	☐	☐
Apparato respiratorio	☐	☐	☐	☐	☐
Occhi, orecchie, naso e gola e laringe	☐	☐	☐	☐	☐
Tratto gastroenterico superiore	☐	☐	☐	☐	☐
Tratto gastroenterico inferiore	☐	☐	☐	☐	☐
Fegato	☐	☐	☐	☐	☐
Reni	☐	☐	☐	☐	☐
Apparato genitourinario	☐	☐	☐	☐	☐
Apparato muscoloscheletrico/cute	☐	☐	☐	☐	☐
Sistema nervoso	☐	☐	☐	☐	☐
Endocrinopatie e dismetabolismi	☐	☐	☐	☐	☐
Malattie psichiatriche	☐	☐	☐	☐	☐

Strategia di valutazione:
0 = nessun problema
1 = problema lieve o pregresso (non interferisce con le normali attività, terapia facoltativa, prognosi eccellente)
2 = problema moderato che richiede terapia (interferisce con le normali attività, terapia necessaria, prognosi buona
3= problema severo o incontrollabile (invalidante, terapia urgente, prognosi riservata)
4 = problema estremamente severo o scompenso d'organo (Potenzialmente letale, Terapia di emergenza o inefficace, prognosi grave

APPENDIX 5: BODY SURFACE AREA CALCULATION

SOURCE: Mosteller RD., Simplified calculation of body-surface area. N Engl J Med, 317:1098, 1987

The algorithm to be used in this study is the Mosteller formula.BSA should be determinated using the appropriate following calculation:

$$BSA = \sqrt{\frac{Ht(inches) \times Wt(lbs)}{3131}}$$

OR

$$BSA = \sqrt{\frac{Ht(cm) \times Wt(kg)}{3600}}$$

APPENDIX 6: DISPENSING INFORMATION FOR RITUXIMAB

DESCRIPTION

Rituximab is a mouse/human chimeric antibody. The rituximab antibody is produced by a Chinese hamster ovary transfectoma. Rituximab will be provided in l00 mg (l0 mL) and 500 mg (50 mL) pharmaceutical grade vials at a concentration of l0.0 mg of protein per mL (actual concentration should be noted on the product label).

RECOMMENDED PREPARATION AND ADMINISTRATION

1. Refer to the clinical trial protocol for details about the dose and dose schedule.

2. Rituximab should be stored at 2-8°C. Do not freeze or store at room temperature. The product is a protein - HANDLE GENTLY AND AVOID FOAMING. The avoidance of foaming during product handling, preparation and administration is important, as foaming may lead to the de-naturing of the product proteins.

3. All transfer procedures require strict adherence to aseptic techniques, preferably in a laminar flow hood.

4. Prepare the rituximab infusion solution as follows:

(a) Refrigerate (2-8°C) all materials and solutions prior to use.

(b) Use sterile, non-pyrogenic, disposable containers, syringes, needles, stopcocks and transfer tubing, etc.

(c) Transfer of the rituximab from the glass vial should be made by using a suitable sterile graduated syringe and large gauge needle.

(d) Transfer the appropriate amount of rituximab from the graduated syringe, into a partially filled IV pack containing sterile pyrogen-free 0.9% sodium chloride solution, USP (saline solution). The final concentration of rituximab in saline solution should be a maximum of 1 mg/ml. Mix by inverting the bag gently. DO NOT USE A VACUUM APPARATUS to transfer the product from the syringe to the plastic bag.

(e) Place an IV administration into the outflow port of the bag containing the infusion solution.

(f) NOTE: DO NOT USE evacuated glass containers which require vented administration sets because this causes foaming as air bubbles pass through the solution.

5. The administration of rituximab will be accomplished by slow IV infusion. CAUTION: DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS.

6. IV pumps such as the IMED 960 may be used with the rituximab infusion. DO NOT INFUSE CONCOMITANTLY with another IV solution or IV medications. Prime the line with the rituximab solution such that approximately 30 mL are delivered

7. Administration of rituximab

Pre-administration of allopurinol (or suitable alternative):

Patients thought to be at risk of tumor lysis syndrome should be well-hydrated and treated with allopurinol (300 mg p.o.) or suitable alternative treatment for 12-24 hours before prior to the first dose of therapy with rituximab.

Caution: Do not administer rituximab as an intravenous push or bolus.

Rituximab will be administered intravenously in an out- or in-patient setting. Oral premedication (1000 mg of paracethamole and 50-100 mg diphenhydramine hydrochloride) needs to be administered 30-60 minutes prior to starting each infusion of rituximab. Prednisone/prednisolone as part of the chemotherapy protocol will be administered in the prescribed dose before the infusion of rituximab, preferably as oral medication. A peripheral or central intravenous (iv) line will be established. Before starting the infusion, there should be a ready supply of epinephrine for subcutaneous injection and diphenhydramine hydrochloride for intravenous injection, and resuscitation equipment for the emergency handling of anaphylactic reactions.

The infusion will be started at an initial rate of 50 mg/hour for the first hour. During the rituximab infusion, the patient's vital signs (blood pressure, pulse, respiration and temperature) will be monitored every 15 minutes (4x) for one hour or until stable and then hourly until the infusion is discontinued. If no toxicity is seen during the first hour, the dose rate may be escalated gradually (by increments of 50 mg/hour at 30 minute intervals) to a maximum of 300 mg/hour. If the first dose of rituximab is well-tolerated, the starting flow rate for administration of the second and subsequent infusions will be 100 mg/hour and then increased gradually (by 100 mg/hour increments at 30 minute intervals) not to exceed 400 mg/hour. Patients may experience transient fever and rigors with infusion. If any of the effects below are noted, the antibody infusion should be temporarily discontinued, the patient should be observed, and when the symptoms improve, the infusion should be continued but at half the previous rate.

Dose Rate	**Fever**	**Rigors/chills**	**Mucosal congestion Edema**	**Drop in Systolic Blood Pressure**
Decrease to 1/2 If any of these Events seen:	> 38.5°C	Mild/Moderate	Mild/Moderate	> 30 mm Hg

Following the infusion the intravenous line should be kept open for medications, as needed. If there are no complications, the intravenous line may be discontinued after one hour of observation.Dosage: 375 mg/m² body surface.

Hours	1st application mg/h *)	mg-total	further Applications mg/h *)	mg-total
0 – 1	50	50	100	100
1 – 1.5	100	100	150	175
1.5 – 2	150	175	200	275
2 – 2.5	200	275	250	400
2.5 – 3	250	400	300	550
3 – 3.5	300	550	350	725
3.5 – 4	300	700	400	925
4 – 4.5	300	850		

*) With a concentration of 1 mg/ml the values of mg/h are equal to ml/h.

Suggested Rituximab Rapid infusion

If no adverse events occurred during first Rituximab infusion,with adeguate premedication, II-III and IV Rituximab infusion will be performed as follow:

RITUXIMAB 375 mg/m^2	First dose of 100 mg in saline solution 100 ml
	Second dose (to total dose) mg in saline solution 250 ml

time	**ml/h**
0-60	100
1-180	125

APPENDIX 7: DISPENSING INFORMATION FOR BENDAMUSTINE

Refer to the clinical trial protocol for details about the dose and dose schedule.

Bendamustine should not be administered to patients with known hypersensitivity to bendamustine or mannitol.

A licensed pharmacist or a properly trained designee will prepare all doses of bendamustine. It is very important that the exact dose is accurately dispensed and administered. If possible, the same person should prepare all doses (on all dosing days). Bendamustine will be administered only to eligible subjects under the supervision of the investigator or identified subinvestigator(s).

Calculation of Dose

The amount (in mg) of bendamustine to be administered will be determined based on body surface area (BSA). BSA will be calculated based on body weight and height using a standard calculation (***Appendix 7***). The dose should be calculated on Day 1 of each cycle and remain consistent during an individual cycle. The dose administered should remain consistent across cycles unless a notable change in weight (e.g., loss or gain of ≥10%) is documented during the Day 1 weight assessment of the cycle, in which case the subject's dose should be recalculated at that time. In the event of bendamustine-associated toxicity during the study, the dose may be decreased according to the dose reduction schedules provided in protovol.

Preparation and Handling of Solution

Aseptically reconstitute each 100 mg bendamustine vial with 20 mL of only Sterile Water for Injection, USP. Shake well to yield a clear, colourless to a pale yellow solution with a bendamustine HCl concentration of 5 mg/mL. The lyophilized powder should completely dissolve in 5-10 minutes. If particulate matter is observed, the reconstituted product should not be used.

Preparation of the Infusion bag

Aseptically withdraw the volume needed for the required dose (based on 5 mg/mL concentration) within 30 minutes from reconstitution, and immediately transfer to a 500 mL infusion bag of 0.9% Sodium Chloride Injection, USP (normal saline). As an alternative to 0.9% Sodium Chloride Injection, USP (normal saline), a 500 mL infusion bag of 2.5% Dextrose/0.45% Sodium Chloride Injection, USP, may be considered. The resulting final concentration of bendamustine HCl in the infusion bag should be within 0.2 – 0.6 mg/mL. If total dose of bendamustine is <150 mg, bendamustine may be reconstituted in a 250 mL infusion bag.

After transferring, thoroughly mix the contents of the infusion bag. The admixture should be a clear and colourless to slightly yellow solution. Use Sterile Water for Injection, USP, for reconstitution and then either 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP, for dilution, as outlined above. No other diluents have been shown to be compatible. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Avoid skin contact while handling the drug.

Administration of bendamustine

The final admixture is stable 3 hours when stored at room temperature (15-30°C or 59-86°F) and room light. Administration of bendamustine must be completed within this period.

The administration of bendamustine, reconstituted and diluted according to the above prescriptions will be accomplished by slow I.V. infusion in an out- or in-patient setting over approximately 30 to 60 minutes).

CAUTION: DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS**.**

Discarding of Vials and Syringe

After administration all materials that have been used for preparation should be disposed of according to standard practices. Any unused solution should be discarded according to institutional procedures for antineoplastics.

All unused vials must be saved for reconciliation by the study monitor. A log must be kept of all disposed materials.

Procedures to follow in case of bodycontact:

Inhalation: if inhaled, remove to fresh air. If breathing becomes difficult, call a physician.

Skin: in case of skin contact, flush with copious amounts of water for at least 15 minutes. Remove contaminated clothing and shoes.

Ingestion: if swallowed, wash out mouth with water provided person is conscious. Call a physician.

Eyes: in case of contact with eyes, flush with copious amount of water for at least 15 minutes. Assure adequate flushing by separating eyelids. Always contact the investigator after any form of body contact.

APPENDIX 8: GUIDELINES MOLECULAR ASSESSMENT

MRD TIME POINTS

	All pts	*All HR patients; LR not in CR treated with venetoclax*					*All pts*
	Baseline	Before V_{cons}	Before V_{maint}	Half of V_{maint}	End of V_{maint}	+6 months	Early withdrawn
TIMEPOINTS	**MRD-0**	**MRD-1**	**MRD-2**	**MRD-3**	**MRD-4**	**MRD-5**	**MRD-6**
PB sample (*to be centralized to FIL-MRD Network Labs*) for molecular studies 3 x 7 ml EDTA tube	20 ml	20 ml	20 ml	20 ml	20 ml	20 ml	20 ml
PB sample (*to be centralized to Vicenza Lab*) for flow cytometry studies 1-3 x 3 ml TransFix/EDTA tube	9 ml	3 ml	3 ml	3 ml	3 ml	3 ml	3 ml
Urine sample (*to be centralized to FIL-MRD Network Labs*) for molecular studies 1 standard dry tube	20 ml	20 ml	20 ml	20 ml	20 ml	20 ml	20 ml
BM sample (*to be centralized to FIL-MRD Network Labs)* for molecular studies 1 standard EDTA tube	7 ml	3 ml	3 ml		3 ml		7 ml

A PB/BM/urine sample (see scheme above for details) should be collected and stored for every patient at baseline and at the moment of relapse/progression, while a number of well-defined MRD time points are planned for patients candidate to venetoclax:

1. **Baseline (MRD-0):** Screening → *all patients*
2. **MRD-1:** before consolidation therapy (before C1).
3. **MRD-2:** before maintenance therapy (after C4)
4. **MRD-3:** half of maintenance therapy (after C12) (no BM sample)
5. **MRD-4:** end of maintenance therapy (after C24)
6. **MRD-5:** 6 months after the end of maintenance therapy (no BM sample)
7. **Relapse/progression (MRD-6):** before starting a new treatment → *all patients*

SAMPLES COLLECTION

Tissues and tubes

For PB samples collection one kind of tubes will be provided by the Uffici Studi FIL: a TransFix/EDTA tube (violet tap, storage before the use at 2-8 °C) for the flow cytometry studies (to be sent to the Vicenza lab). For the MRD studies (to be sent to the FIL-MRD Network labs) no specific tube will be provided: standard 7 ml EDTA tubes are recommended for PB collection.

For BM samples collection no specific tube will be provided: standard 3 or 7 ml EDTA tubes are recommended for BM collection.

For urine samples collection no specific tube will be provided: classical 20 ml dry tubes for urine tests are recommended for urine collection.

For molecular studies for any time point both BM, PB and urine will be required. At baseline and relapse/progression at least 7 ml of BM and 20 ml of PB (three 7 ml EDTA tubes) are required for all patients. For all the other time points at least 3 ml of BM and 20

ml of PB (three 7 ml EDTA tubes) are required, only for HR patients (or LR patients receiving venetoclax). For every timepoint at least 20 ml of urine is required.
For flow cytometry studies only PB will be required. For the screening time point at least 9 ml of PB collected in TransFix/EDTA tubes are required (3 tubes). The following time points will be analyzed only if the screening will be positive. For each following time point at least 3 ml (1 tubes) of Transfix/EDTA PB are required.
The MRD analysis will be conducted in the context of the FIL-MRD Network, which includes four MRD laboratories. Every Center will refer to a different lab based on its geographic position. In particular the samples should be sent through the courier to the following addresses.

REFERENCE LABORATORIES for the molecular studies

TORINO (BLUE LAB)
The Blue lab will receive samples from: Aosta, Torino, Cuneo, Biella, Vercelli, Asti, Alessandria, Novara, Cusio-Verbano-Ossola, Imperia, Savona, Genova, Milano, Como, Varese, Lecco, Lodi, Sondrio, Bergamo, Monza, Pavia, Brescia, Cremona, Bolzano, Trento, Sassari, Olbia-Tempio, Nuoro, Oristano, Ogliastra, Medio Campidano, Carbonia-Iglesias, Cagliari.

Andress:
DR. SIMONE FERRERO - LABORATORIO BIOLOGIA MOLECOLARE
c/o laboratorio EMATOLOGIA UNIVERSITARIA 1 - Prof. Mario Boccadoro
AOU Città della Salute e della Scienza di Torino, presidio San Giovanni Battista - Molinette,
Via Genova 3, (Piano Terra) 10126 Torino.

Help-desk for the MRD study please contacts the following: Dott.ssa Daniela Barbero, Dott.ssa Daniela Drandi, Dott. Simone Ferrero. Molecular Biology Laboratory, Division of Hematology, University of Torino; TEL: +39-011-6336884; FAX: +39-011-6963737; e-mail contacts: daniela.barbero@unito.it; daniela.drandi@unito.it; simone.ferrero@unito.it

PISA (PINK LAB)
The Pink lab will receive samples from: La Spezia, Piacenza, Parma, Reggio Emilia, Modena, Massa-Carrara, Pistoia, Lucca, Prato, Pisa, Livorno, Firenze, Arezzo, Siena, Grosseto, Viterbo, Perugia, Terni, Palermo, Trapani, Messina, Catania, Enna, Caltanissetta, Agrigento, Ragusa, Siracusa.

Address:
LABORATORIO BIOLOGIA MOLECOLARE DOTT.SSA SARA GALIMBERTI
c/o U.O Ematologia - Ospedale S. Chiara
Via Roma 67
56126 Pisa

Help-desk for the MRD study please contacts the following: Dott.ssa Sara Galimberti or Dott.ssa Elena Ciabatti Molecular Biology Laboratory, Division of Hematology, University of Pisa; TEL: +39-050-992815; e-mail contacts: s.galimberti@med.unipi.it;e.ciabatti@med.unipi.it

ROMA (GREEN LAB)

The Green lab will receive samples from: L'Aquila, Rieti, Roma, Frosinone, Latina, Campobasso, Isernia, Caserta, Benevento, Napoli, Avellino, Salerno, Foggia, Barletta-Andria-Trani, Bari, Brindisi, Lecce, Taranto, Potenza, Matera, Maratea, Cosenza, Crotone, Catanzaro, Vibo Valentia, Reggio Calabria.

Address:
LABORATORIO DI BIOLOGIA MOLECOLARE
DOTT.SSA ILARIA DEL GIUDICE/DOTT.SSA IRENE DELLA STARZA
C/O Ematologia
Via Benevento 6
00161 Roma

Help-desk for the MRD study please contacts the following: Dott.ssa Ilaria del Giudice or Dott.ssa Irene della Starza, Molecular Biology Laboratory, University "Sapienza" of Roma; TEL: +39-06-441639822; e-mail contacts: delgiudice@bce.uniroma1.it, dellastarza@bce.uniroma1.it

AVIANO (ORANGE LAB)
The Orange lab will receive samples from: Trieste, Gorizia, Udine, Pordenone, Belluno, Treviso, Venezia, Vicenza, Padova, Rovigo, Verona, Ferrara, Ravenna, Bologna, Forlì-Cesena, Rimini, Pesaro-Urbino, Ancona, Macerata, Fermo, Ascoli Piceno, Pescara, Chieti.

Address:

SOC Onco-Ematologia Clinico-Sperimentale
DOTT. VALTER GATTEI
Centro di Riferimento Oncologico, I.R.C.C.S.
Via F. Gallini, 2
33081 Aviano (PN)

Help-desck for the MRD study please contacts the following: Dott. Valter Gattei or Riccardo Bomben or Massimo Degan, SOC Onco-Ematologia Clinico-Sperimentale - Centro di Riferimento Oncologico, I.R.C.C.S.;
TEL. +39 0434 659 410; e-mail contacts: vgattei@cro.it, riccardo.bomben@gmail.com, mdegan@cro.it

For flow cytometry studies all the samples will be centralized to:
DR. OMAR PERBELLINI
LABORATORIO DI CITOMETRIA
Area "De Giovanni" Ospedale S. Bortolo - ULSS 6 - Vicenza
Contra' S. Bortolo 97 - 36100 - Vicenza

APPENDIX 9: GUIDELINES PATHOLOGY REVIEW

Sample shipping and return of FFPE blocks

After enrollment of any patient, every center will be asked to send **paraffin blocks** of the diagnostic specimen as soon as possible (mandatory within 2 weeks from start of therapy) for central pathologic review and *TP53* mutation detection.
On shipment of samples, FIL will send a notification email to unita.emolinfopatologia@ieo.it containing the patient ID, the name of the courier and the airway bill number.
Blocks can be shipped at ambient temperature from Monday to Thursday.
When the diagnostic specimen is represented by a bone marrow biopsy, the shipment of this specimen to the central pathology Lab should include two 2mL heparin vial of bone marrow aspirate for *TP*53 assessment (one for FISH analysis and the other one for Sanger sequencing).
Vials must be labeled with Patient ID and should be sent from Monday to Wednesday. If the shipment will be delivered within 24 hours vials can be stored at ambient temperature; otherwise the samples should be shipped at 4°C.
Samples should be sent through the courier at the following address:
Unità di Emolinfopatologia,
Istituto Europeo di Oncologia,
via Ripamonti 435, 20141 Milano
(Building IEO1, 1° floor)
At the end of revision procedures, blocks will be returned to FIL. FIL will setup a courier service for sample return and provide detailed information to the Lab.

Histological and immunohistochemical analysis

In every case, Giemsa stain will be performed; further sections will be cut and coated on electrically charged slides suited for immunohistochemistry.
The centralized pathology Lab will confirm the diagnosis of mantle cell lymphoma and will define the risk of the single patient based on morphology and Ki-67 index.
Deparaffinization, clarification, re-hydration, rinsing and heat-based antigen retrieval will be automatically performed on DAKO PT-Links. Samples will be tested at least for CD20, CD5, cyclin D1, SOX11 and Ki67 expression; cases with blastoid morphology and/or Ki67 ≥ 30% will be additionally tested for p53 and Bcl2 expression.
P53 expression by immunohistochemistry will be used for patients risk definition when the molecular sample fails or is not available for any reason. Patients with >50% P53 expression will be defined as high risk.
All immunostains will be carried out on DAKO Autostainers with DAKO REAL alkaline phosphatase/red detection system.

TP53 analysis

- Fluorescence in situ hybridization (FISH) will be performed with Abbott LSI TP53/CEP17 probe kit.
- Molecular analysis will be technically carried out by the laboratory of Applied Genomics and Hematology Diagnostics, a IEO core facility for molecular biology, and validated by the Director of the Hamato-Lympho-Pathology Unit. *TP53* whole exonic sequence and exon-intron junctions will be PCR amplified using genomic DNA and purified before Sanger sequencing with 3500xl DX Genetic Analyzer (Applied Biosystems - Thermofisher). Cases with Sanger unsatisfactory results will be re-analyzed with Next Generation Sequencing (NGS) technique (Illumina or Thermo Fisher platforms).

APPENDIX 10: RESPONSE CRITERIA

SOURCE: *Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, Lister TA; Alliance, Australasian Leukaemia and Lymphoma Group.; Eastern Cooperative Oncology Group.; European Mantle Cell Lymphoma Consortium.; Italian Lymphoma Foundation.; European Organisation for Research.; Treatment of Cancer/Dutch Hemato-Oncology Group.; Grupo Español de Médula Ósea.; German High-Grade Lymphoma Study Group.; German Hodgkin's Study Group.; Japanese Lymphorra Study Group.; Lymphoma Study Association.; NCIC Clinical Trials Group.; Nordic Lymphoma Study Group.; Southwest Oncology Group.; United Kingdom National Cancer Research Institute.. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014 Sep 20;32(27):3059-68.*

Response Definitions for Clinical Trials (Cheson 2014).

Table 3. Revised Criteria for Response Assessment

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on EPS†	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	As individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and As increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: EPS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

†PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

APPENDIX 11: COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE)

In the present study, adverse events and/or adverse drug reactions will be recorded according to the: **Common Terminology Criteria for Adverse Events (CTCA), version 4.0**.

At the time this protocol was issued, the full CTC document was available on the NCI web site, at the following address http://ctep.cancer.gov/reporting/ctc.html.