Early stage Hodgkin’s lymphoma

Dose-dense ABVD as first line therapy in early stage unfavorable Hodgkin’s Lymphoma: a phase II, prospective, multi-center study

Study ID: FIL – DDABVD
Protocol version date: June 2011
EudraCTNumber: 2011-003191-36

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Signature of Principal Investigator

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## INDEX

1. SUMMARY ......................................................................................................................8

2. BACKGROUND AND INTRODUCTION .......................................................................13
   2.1 Hodgkin Lymphoma ..................................................................................................13
   2.2 Role of FDG- PET .......................................................................................................14

3. RATIONALE OF THE STUDY .......................................................................................15

4. OBJECTIVE OF THE STUDY .......................................................................................15
   4.1. Primary objectives ....................................................................................................15
   4.2. Secondary objectives ...............................................................................................15
   4.3. End Points .................................................................................................................15
       4.3.1. Primary End points ..........................................................................................15
       4.3.2. Secondary End points ......................................................................................16

5. PATIENT SELECTION CRITERIA ................................................................................16
   5.1. Inclusion criteria .......................................................................................................16
   5.2. Exclusion criteria ......................................................................................................16

6. STUDY DESIGN............................................................................................................17
   6.1. Number of patients ...................................................................................................18
   6.2. Study completion ......................................................................................................18
   6.3. Enrolling Centers ......................................................................................................18

7. STUDY TRATMENT......................................................................................................18
   7.1. Chemotherapeutic regimen .....................................................................................18
       7.1.1. Expected toxicity ............................................................................................19
       7.1.2. Guidelines for dose modification ......................................................................20
   7.2. Radiotherapy (Target volume, dose specification, dose fractionation) ............20
7.3. FDG PET ..........................................................................................................................22
  7.3.1. PET scan execution ..................................................................................................22
  7.3.2. Central core lab for PET reviewing .................................................................22
  7.3.3. Rules for PET-2 interpretation .........................................................................22

8. END OF TREATMENT, END OF STUDY / STUDY DISCONTINUATION ........23
  8.1. Completion ..................................................................................................................23
    8.1.1. End of treatment ...............................................................................................23
    8.1.2. End of study: .....................................................................................................24
  8.2. Therapy discontinuation ...........................................................................................24

REASONS FOR THERAPY DISCONTINUATION: ..........................................................24

9. CLINICAL EVALUATION, LABORATORY TEST AND FOLLOW UP .............24
  9.1. Screening phase (days -21 to day 0) ....................................................................25
  9.2. During treatment .....................................................................................................25
  9.3. End of therapy ..........................................................................................................26
  9.4. Follow up ..................................................................................................................27
  9.5. CRITERIA OF EVALUATION ..................................................................................27

10. STATISTICAL ANALYSIS AND SAMPLE SIZE ....................................................28

11. FORMS AND PROCEDURES FOR COLLECTING DATA AND DATA MANAGING.29

FIL DATA CENTER LOCATION .......................................................................................29

12. ADVERSE EVENT AND ADVERSE DRUG REACTION REPORT ................30
  12.1. Definition .................................................................................................................30
    12.1.1. Attribution definition .......................................................................................31
    12.1.2. Record-keeping and Identification code .......................................................33
  12.2. Reporting Procedure ..............................................................................................33
    12.2.1. All Adverse Events .........................................................................................33
    12.2.2. Serious Adverse Events ..................................................................................34
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.2.3. Serious Unexpected Suspected Adverse Reaction</td>
<td>35</td>
</tr>
<tr>
<td>13. ETICAL CONSIDERATION</td>
<td>35</td>
</tr>
<tr>
<td>13.1. Patient protection</td>
<td>35</td>
</tr>
<tr>
<td>13.2. Subject identification - Personal data protection</td>
<td>35</td>
</tr>
<tr>
<td>13.3. Informed Consent</td>
<td>36</td>
</tr>
<tr>
<td>14. CONFLICT OF INTEREST</td>
<td>37</td>
</tr>
<tr>
<td>15. DATA OWNERSHIP</td>
<td>37</td>
</tr>
<tr>
<td>16. PUBBLICATION POLICY</td>
<td>37</td>
</tr>
<tr>
<td>17. STUDY INSURANCE</td>
<td>38</td>
</tr>
<tr>
<td>18. STUDY TIME TABLE</td>
<td>38</td>
</tr>
<tr>
<td>19. REFERENCE</td>
<td>39</td>
</tr>
<tr>
<td>APPENDIX 1. TIME &amp; EVENTS SCHEDULE</td>
<td>42</td>
</tr>
<tr>
<td>APPENDIX 2 - EORTC CLASSIFICATION CRITERIA</td>
<td>43</td>
</tr>
<tr>
<td>APPENDIX 3 - ECOG PERFORMANCE STATUS</td>
<td>44</td>
</tr>
<tr>
<td>APPENDIX 4 - COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE), VERSION 4.0</td>
<td>45</td>
</tr>
<tr>
<td>APPENDIX 5 - WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI</td>
<td>46</td>
</tr>
</tbody>
</table>
Glossary of abbreviations

AE    adverse event
ASCT autologous hematopoietic stem cell transplant
ANC  absolute neutrophil count
β-HCG beta-human chorionic gonadotropin
BSA  body surface area
BUN  blood urea nitrogen
CBC  complete blood count
CR   complete response/remission
CRF  case report form
CRO  contract research organization
CTC NCI common toxicity criteria
CTCAE NCI common terminology criteria for adverse events (version 3.0)
CTV  calculated target volume
TAC  computed tomography
DFS  disease free survival
DLT  dose-limiting toxicity
ECHO Echocardiogram
ECG  12 lead electrocardiogram
ECOG Eastern Cooperative Oncology Group
CRF  case report/record form
EOT  end of treatment
EPO  erythropoietin
FDG-PET fluorodeoxyglucose positron emission tomography
G3, G4 grade 3, grade 4
GCP  good clinical practice
G-CSF granulocyte colony stimulating factor
HDT  high dose chemotherapy
HL   Hodgkin’s lymphoma
HIV  human immunodeficiency virus
IV   intravenously
ICH/ GCP International Conference on Harmonisation (ICH) / Good Clinical Practice standard
IMS  integrated medical safety
INR  international normalized ratio
IEC  Independent Ethics Committee
LLN  lower limit of normal
LVEF left ventricular ejection fraction
MoH  Ministry of Health
MRI  magnetic resonance imaging
NCI  National Cancer Institute
p.o.  per os/by mouth/orally
PBSC peripheral blood stem cell
PD   progressive disease
PFS  progression free survival
PR   partial response
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tbody>
<tr>
<td>PT</td>
<td>prothrombin time</td>
</tr>
<tr>
<td>PTT</td>
<td>partial thromboplastin time</td>
</tr>
<tr>
<td>PVT</td>
<td>calculated target volume</td>
</tr>
<tr>
<td>SAE</td>
<td>serious adverse event</td>
</tr>
<tr>
<td>SD</td>
<td>stable disease</td>
</tr>
<tr>
<td>SPD</td>
<td>sum of the product of diameters</td>
</tr>
<tr>
<td>SUSARs</td>
<td>suspected unexpected serious adverse reactions</td>
</tr>
<tr>
<td>T3</td>
<td>Triiodothyronine</td>
</tr>
<tr>
<td>T4</td>
<td>Thyroxine</td>
</tr>
<tr>
<td>TSH</td>
<td>thyroid stimulating hormone</td>
</tr>
<tr>
<td>ULN</td>
<td>upper limit of normal</td>
</tr>
<tr>
<td>WBC</td>
<td>white blood cell</td>
</tr>
<tr>
<td>WNL</td>
<td>within normal limits</td>
</tr>
<tr>
<td>WOCBP</td>
<td>women of childbearing potential</td>
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</table>
1. SUMMARY

| Title | Dose-dense ABVD (dd-ABVD) as first line therapy in early stage unfavorable Hodgkin’s lymphoma (HL) : a phase II, prospective, multi-center study. |
| Investigator Sponsor | Fondazione Italiana Linfomi (F.I.L.) |
| Study coordinator | Armando Santoro |
| Protocol identifying number | FIL-DDABVD |
| Protocol version date | June 2011 |
| Background and rationale | Dose-density has been shown to be an important factor for complete remission achievement and long-term survival in lymphomas. The aims of this study are to find out whether intensification of ABVD (dd-ABVD) is feasible and can improve the outcome of patients with early unfavorable stage HL. In view of the consolidated data on the role of early PET in defining prognosis in HL patients, the percentage of FDG-PET negativity after two cycle was chosen as the parameter to evaluate dd-ABVD activity, the obtained data will be compared with the results of historical controls using the same rules for interim-PET interpretation. |
| Phase | Phase II, multicenter study |
| Population and patient selection criteria | Patient affected by limited stage (I - II) unfavorable HL |
| Inclusion criteria | • Age 18-70 years  
• Histologically confirmed HL stage I, II unfavorable according to EORTC criteria, with exclusion of stage II B bulky.  
• Previously untreated  
• ECOG performance status 0 - 2  
• Staging with FDG-PET  
• Written informed consent  
• Adequate liver and renal function (total serum bilirubin ≤ 2.5 x ULN, AST/SGOT and/or ALT/SGPT ≤ 2.5 x upper limit of normal (ULN) or ≤ 5.0 x ULN if the transaminase elevation is due to disease involvement, serum creatinine ≤ 2.5 x ULN) |
Exclusion criteria

- Concomitant cardiac, pulmonary, neurologic, psychiatric or metabolic severe disease.
- Uncontrolled diabetes mellitus (with fasting glucose levels above 200 mg/dl).
- Other prior malignancies except for adequately treated basal cell carcinoma, squamous cell carcinoma of the skin, carcinoma in situ of the cervix, carcinoma in situ of the breast or other cancer from which the patient has been disease-free for ≥ 3 years.
- Patients with a known history of HIV seropositivity.
- Active HCV infection (PCR +; AST > 1.5-2x UN).
- Woman who is pregnant or breast feeding. Fertile patients not willing to use effective contraception during the study and 3 months after the end of treatment. Women of childbearing potential (WOCBP) are defined as sexually mature women who have not undergone a hysterectomy or who have not been naturally postmenopausal for at least 12 consecutive months. Negative pregnancy test at baseline is required (serum β HCG).
- Male patient whose sexual partner(s) are WOCBP who are not willing to use a effective contraception during the study and 3 months after the end of treatment.
- Nodular lymphocyte prevalence histological subtype.

Study design and study duration

Prospective, multicenter, Phase II trial designed to assess whether intensification of ABVD (dd-ABVD) is feasible and can improve the outcome of patients with early stage HL. The first 52 patients will be evaluated for safety analysis at completion of study treatment. In absence of severe toxicities further 34 patients (total 86 pts) will be included for activity evaluation.

The patients will be treated with standard dosage ABVD on day 1 and 8 every 21 days instead of days 1 and 15 every 28 days. Granulocyte colony-stimulating factor (G-CSF) will be administered as primary prophylaxis. The treatment phase begins on Day 1 of cycle 1 and continues until completion of the study therapy or discontinuation of treatment with the study drug. Unless in progression, all patients will receive three additional dd-ABVD cycles (total of 4 cycles) and involved-field radiation therapy (IF-RT) with total dose of 30 Gy.

Patients will undergo a baseline staging at disease onset and interim restaging after the second dd-ABVD cycle with PET-CT (PET-0 and PET-2, respectively). PET scan will be
performed with the standard-technique scanning protocol. PET-0 and PET-2 will be performed at the same PET center, with PET-CT technology. The preferred day for PET-2 scan would be the 19th or 20th day of the second cycle, just before the third cycle. Hematopoietic growth factors must be interrupted at least 48 hours before performing the FDG-PET scan, as ongoing treatment with hematopoietic growth factors may impair PET interpretation and results.

At the moment no standard rules exist for interim-PET interpretation during ABVD treatment in early or advanced-stage HL. For these reasons a review panel of nuclear medicine experts for PET reporting is mandatory. Seven reviewers with a proven experience in the field of interim PET in lymphoma will review the scans. A dedicated website will be implemented at the URL https://magic5.to.infn.it at the National Institute of Nuclear Physics (INFN) of Turin.

Since no standard criteria are available for interim-PET reviewing in ABVD-treated HL patients, the following interpretation keys will be used:

1. IHP criteria (Juweid 2007)
2. Deauville rules (Barrington 2010)

FDG-PET negativity will be defined in accord to IHP criteria (Juweid 2007) for the evaluation of primary end points.

All toxic reactions will be recorded and their grade will be assessed according to the Common Toxicity Criteria (CTC) Version 4. All patients given at least one dose of the experimental treatment will be included in the estimation of toxicity rates.

**Description of study treatment/product/intervention**

dd-ABVD will be administered intravenously on day 1 and 8 every 21 days

**Chemotherapy regimen**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Route</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin</td>
<td>25 mg/m² i.v.</td>
<td>day 1 and 8</td>
<td></td>
</tr>
<tr>
<td>Bleomycin</td>
<td>10 mg/m² i.v.</td>
<td>day 1 and 8</td>
<td></td>
</tr>
<tr>
<td>Vinblastine</td>
<td>6 mg/m² i.v.</td>
<td>day 1 and 8</td>
<td></td>
</tr>
<tr>
<td>Dacarbazine</td>
<td>375 mg/m² i.v.</td>
<td>day 1 and 8</td>
<td></td>
</tr>
</tbody>
</table>

Granulocyte colony-stimulating factor (G-CSF): days 9 to 14

**Objectives**

**Primary objectives**
- Feasibility
- Activity

**Secondary objectives**
- Comparison of PET interpretation criteria (IHP, Deauville) in predicting outcome
**Efficacy of the scheme**

- Acute and late hematological and extra-hematological toxicities

**Primary End point**

- Proportion of patient with a dose intensity reduction (lower than 85% of planned dose)
- Proportion of FDG-PET negativity after two cycle of dd-ABVD

**Secondary End point**

- Overall accuracy and Predictive Value of each interim PET interpretation criteria after a minimum follow-up of three years
- PFS and OS
- Proportion of early and late toxicities (G3/4 acute toxicities, secondary malignancies, cardiovascular and pulmonary events, infertility)

<table>
<thead>
<tr>
<th><strong>Statistical methods, data analysis, sample size</strong></th>
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<tbody>
<tr>
<td>Feasibility of dd-ABVD regimen and percentage of FDG PET negativity after 2 dd-ABVD cycles will be considered as primary endpoints.</td>
</tr>
</tbody>
</table>

Considering a proportion of patients without a dose intensity reduction of 95% in pts treated with standard ABVD, we want to exclude a reduction higher than 10% in pts treated with dd-ABVD. In order to test this difference with a one-side alpha of 0.10 and beta of 0.15, we need to evaluate 52 pts. If 5 or more pts will present a dose intensity reduction the study drug will not be considered for further evaluation and the enrolment will be ended.

Otherwise, enrolment will continue for the evaluation of second primary endpoint.

Considering a proportion of PET- of 80% in patient treated with standard ABVD, we consider of clinical interest an absolute improvement of 10% in pts treated with dd-ABVD. In order to test this difference with a one-side alpha of 0.10 and beta of 0.10, we need to evaluate 86 pts. If 74 or more PET- will be observed the study drug will be considered for further evaluation.

FDG-PET negativity will be defined in accord to IHP criteria (Juweid 2007). Patients' characteristics will be reported descriptively. The response rate, toxicity and safety data will be summarized as frequencies and proportions or as median and range. Progression free survival curves will be estimated by the Kaplan-Meier technique.
In order to evaluate the predictive value of the 2 different criteria for interim PET interpretation, the C statistic of each technique for progression free survival will be calculated and compared. Moreover sensitivity, specificity and concordance between each test result and the disease status at three years will be calculated and pairwise comparisons between pet techniques will be estimated using paired odds ratio and tested with McNeamar test. Finally the binary (k coefficient) and overall (Krippendorf alpha coefficient) concordance rate among reviewers will be calculated.

All the comparisons will be conducted for exploratory purpose.

<table>
<thead>
<tr>
<th>Study time table</th>
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<tr>
<td>- Project starting date: September 2011</td>
</tr>
<tr>
<td>- Project completion of accrual: September 2012</td>
</tr>
<tr>
<td>- Project completion of follow up: December 2015</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sponsor</th>
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<tbody>
<tr>
<td>This is a non-profit study. There is no commercial sponsor. The non-profit sponsor is the “Fondazione Italiana Linfomi (F.I.L.)”. No experimental drugs are utilized. The ABVD chemotherapy is the standard treatment for Hodgkin’s lymphoma and it is based on drugs approved for this indication.</td>
</tr>
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</table>
2. BACKGROUND AND INTRODUCTION

2.1 Hodgkin Lymphoma

Hodgkin’s Lymphoma (HL) is a lymphoproliferative malignancy, defined by the presence of the malignant Reed-Sternberg (RS) cells, which are derived from B lymphocytes, associated with a surrounding proliferation of mature T-cells.

The Ann Arbor staging system for lymphoma remains the universally accepted system for categorizing patients who have HL. Patients who have stage I/II disease are generally considered early stage, whereas patients who have stage III/IV are considered to have advanced stage disease.

Early-stage patients are stratified in two treatment subgroup defined as “favorable” and “unfavorable” (or intermediate-stage) disease according to the absence or presence of risk factors. The classification systems used by the German Hodgkin’s Study Group (GHSG), the European Organization for Research and Treatment of Cancer (EORTC), and the National Cancer Institute of Canada (NCIC) are shown in appendix 2.

Survival of patients affected by Hodgkin’s lymphoma (HL) has improved substantially during the last decades, and, to date, the overall cure rate for this neoplasm is about 80-85%. Improvement in the outcome is mostly due to the development of more active chemotherapy (CT) regimens, of a more accurate radiotherapy (RT) and of a rational combination of the different treatment modalities. The therapeutic strategies are differentiated according to disease staging at diagnosis with the aim of providing optimal disease control whilst limiting toxicity. Ongoing studies are designed employing PET oriented strategy.

According to results of EORTC H8U and GHSG HD8, the standard of care for unfavorable early stage HL is 4-6 cycle ABVD followed by Involved field radiotherapy (30-36 Gy) with a long term disease control in 80% of patient. However failure rates up to 20 % warranted further improvement.

One way is chemotherapy intensification as in HD 11 from GHSG. The German Hodgkin Study Group compared BEACOPP x 4 plus IFRT (20 or 30 Gy) with ABVD x 4 plus RT (20 or 30 Gy), but the more intensive regimen failed in the goal of
improving outcome in this subset of patients and determined a higher incidence of major toxicities BEACOPP didn’t significantly improved outcome.

A similar trial was conducted by EORTC–GELA in the H9U: the standard arm of 6 ABVD was compared with 4 ABVD + 4 BEACOPP, both arm were followed by IFRT 30 Gy. The results in term of response, EFS and OS were similar in different treatment arm at interim analysis, the chemotherapy related toxicity was higher in BAECOPP arm.

The hypothesis of dose escalation efficacy in early unfavorable HL was instead confirmed in GHSG study HD 14 where BEACOPP escalated x 2 + ABVD x 2 were compared with ABVD x 4 (improvement in PFS 6%). Still the better outcome of chemotherapy intensification is counterbalanced by more toxicity.

Russo et al. reported interesting clinical result in a study exploring dose dense (dd) and dose intense (di) ABVD in intermediate and advanced HL according to GHLSG still maintaining a low toxicity profile. Seventy patients (24 intermediate dd ABVD - 46 advanced dd-di ABVD) received 6 course of CT day 1-11 every 21 days with doxorubicin escalated to 70 mg in cycles 1-4 in dd di scheme. Respectively at early PET and at the end of chemotherapy the percentage of CR were 95% amd 98.6%. With a minimum follow up of 12 months PFS rate at 2 years in intermediate and advanced subgroup of patients is respectively 95.8% and 91.3% respectively.

In this study we propose a dose dense regimen with the aim of improving without increasing toxicity.

A lot of question about therapy intensification, chemo-radiotherapy combination and the role of PET in discriminating patient prognosis remain unresolved.

2.2 Role of FDG- PET

The FDG-PET has recently been added as a sensitive tool for the assessment of response to first-line therapy. A systematic review of 13 studies for a total of 408 patients indicated that FDG-PET has a sensitivity of 84% (CI: 71- 92) and a specificity of 90% (CI: 84-94) in detecting viable tumor after therapy. Moreover, in advanced Hodgkin’s lymphoma, early FDG-PET evaluation after two cycles of chemotherapy has recently proved to be highly predictive of outcome and to be independent from the IPS variables. Rigacci confirmed the predictive value of early PET in early stage patient. In 232 patient with HL stage I or IIA 2 yr FFS probability for PET2
negative and for PET 2 positive were 94% and 44% respectively (p0.00). The FDG PET performed after 2 cycle was positive in 14% of patients. Treatment strategy tailored on the early response to ABVD, evaluated with FDG-PET after two chemotherapy courses (PET response-adapted strategy), with an early intensification for PET-2 positive patients, is being currently investigated in numerous ongoing clinical trials.

3. RATIONALE OF THE STUDY

Dose-density has been shown to be an important factor for complete remission rate and long-term survival in lymphomas. The aims of this study were to find out whether intensification of ABVD (dd-ABVD) is feasible and can improve the outcome of patients with early stage HL. In view of emerging data on the role of early PET in defining prognosis in HL patients, the percentage of FDG-PET negativity after two cycle was chosen as the parameter to evaluate dd-ABVD activity.

4. OBJECTIVE OF THE STUDY

4.1. Primary objectives
- Feasibility of the scheme
- Activity of the scheme

4.2. Secondary objectives
- Comparison of PET interpretation criteria (IHP, Deauville) in predicting outcome
- Efficacy of the scheme
- Acute and late hematological and extra-hematological toxicities

4.3. End Points

4.3.1. Primary End points
- Proportion of patient with a dose intensity reduction (lower than 85% of planned dose)
- Proportion of FDG-PET negativity after two cycle of dd-ABVD
4.3.2. Secondary End points

- Overall accuracy and Predictive Value of each interim PET interpretation criteria after a minimum follow-up of three years
- PFS and OS
- Proportion of early and late toxicities (G3/4 acute toxicities, secondary malignancies, cardiovascular and pulmonary events, infertility)

5. PATIENT SELECTION CRITERIA

Histologically proven Hodgkin’s lymphoma, except for the nodular lymphocyte predominant subtype, Ann Arbor limited stage, unfavorable according to EORTC criteria.

5.1. Inclusion criteria

- Age 18-70 years
- Histologically confirmed HL stage I, II unfavorable according to EORTC criteria, with exclusion of stage II B bulky
- Previously untreated
- ECOG performance status 0 to 2
- FDG-PET at baseline
- Written informed consent
- Adequate liver and renal function (total serum bilirubin ≤ 2.5 x ULN, AST/SGOT and/or ALT/SGPT ≤ 2.5 x upper limit of normal (ULN) or ≤ 5.0 x ULN if the transaminase elevation is due to disease involvement, serum creatinine ≤ 2.5 x ULN)

5.2. Exclusion criteria

- Concomitant cardiac, pulmonary, neurologic, psychiatric or metabolic severe disease.
- Uncontrolled diabetes mellitus (with fasting glucose levels above 200 mg/dl).
- Other prior malignancies except for adequately treated basal cell carcinoma, squamous cell carcinoma of the skin, carcinoma in situ of the cervix, carcinoma in situ of the breast or other cancer from which the patient has been disease-free for ≥ 3 years
• Patients with a known history of HIV seropositivity
• Active HCV infection (PCR+; AST > 1.5-2x UN)
• Woman who is pregnant or breast feeding. Fertile patients not willing to use effective contraception during the study and 3 months after the end of treatment. Women of childbearing potential (WOCBP) are defined as sexually mature women who have not undergone a hysterectomy or who have not been naturally postmenopausal for at least 12 consecutive months. Negative pregnancy test at baseline is required (serum HCG).
• Male patient whose sexual partner(s) are WOCBP who are not willing to use effective contraception during the study and 3 months after the end of treatment
• Nodular lymphocyte prevalence histological subtype

6. STUDY DESIGN

Prospective, multicenter, Phase II trial designed to assess whether intensification of ABVD (dd-ABVD) is feasible and can improve the outcome of patients with early stage HL.

The first 52 patients will be evaluated for safety analysis at completion of study treatment.

In absence of severe toxicities further 34 patients (total 86 pts) will be included for activity evaluation.

After providing written informed consent, patients will be evaluated for eligibility during a 21-day screening period. If they continue to meet eligibility criteria, they will receive the first dose of dd-ABVD.

All patients will be treated with standard dosage ABVD on day 1 and 8 every 21 days instead of days 1 and 15 every 28 days. Granulocyte colony-stimulating factor (G-CSF) will be administered as primary prophylaxis.

The treatment phase begins on Day 1 of cycle 1 and continues until completion of study therapy or discontinuation of treatment with the study drug. Unless in progression, all patients will receive three additional dd-ABVD cycles (total of 4 cycles) and IF-RT 30 GY.
Patients will undergo a baseline staging at disease onset and interim restaging after the second dd-ABVD cycle with PET-CT (PET-0 and PET-2, respectively). PET scan will be performed with the standard-technique scanning protocol (see Paragraph FDG PET) and interpreted according to IHP criteria for dd-ABVD activity evaluation.

In the ancillary study, the overall accuracy of two different criteria (IHP and Deaville) for interim PET scan interpretation in predicting treatment outcome will be evaluated.

Procedures to be performed during the study are summarized on the Attachment 1, Time and Events Schedule.

6.1. Number of patients
86 evaluable patient.
Estimated accrual time is 24 months

6.2. Study completion
The first part of the study (feasibility and activity) will be completed when the last eligible patient obtain disease evaluation by PET after second dd-ABVD cycle.
The comparison of PET interpretation criteria require a minimum follow up of 3 years. This statistical analysis will be performed on a second time independently on previous points of evaluation.

6.3. Enrolling Centers
Centers from Fondazione Italiana Linfomi

7. STUDY TREATMENT

7.1. Chemotherapeutic regimen
Chemotherapy regimen

dd-ABVD will be administered intravenously on day 1 and 8 every 21 days

Doxorubicin 25 mg/m² i.v. day 1 and 8
Bleomycin 10 mg/m² i.v. day 1 and 8
Vinblastine 6 mg/m² i.v. day 1 and 8
Dacarbazine 375 mg/m² i.v. day 1 and 8

Granulocyte colony-stimulating (G-CSF) will be administered as primary prophylaxis from day 9 to 14 (6 days)
Treatment with hematopoietic growth factors must be interrupted at least 48 hours before performing the FDG-PET scan. Treatment with hematopoietic growth factors may impair PET interpretation and results.
Erythropoietin (EPO) administration is permitted according to ASCO guidelines.

7.1.1. Expected toxicity

All toxic reactions will be annotated and their grade will be assessed according to the Common Toxicity Criteria (CTC) Version 4, 2009. The rate of non-hematologic toxicity of grade 3 or greater will be the principal measure of safety. All patients given at least one dose of the experimental treatment will be included in the estimation of toxicity rates.

Acute toxicity:
- hematological toxicity: neutropenia and thrombocytopenia, the nadir may be expected near days 11-12
- bleomycin interstitial pneumonitis has been frequently reported and requires immediate stop of further bleomycin administration.
- nausea & vomiting due to doxorubicin and dacarbazine may be significant
- Subtotal/total reversible alopecia occurs in some cases

Late effects:
- Cardiac e.g. cardiomyopathy due to doxorubicin has been reported infrequently
- Early arteriosclerosis after RT to the mediastinum whether or not combined with chemotherapy is increasingly recognized as a treatment complication
- Pneumonitis due to bleomycin and or RT-induced have been reported frequently
- Gonadal toxicity may be irreversible in a not significant number of cases (oligospermia may occur in less than 10% of male patient, with full recovery in almost all of them; amenorrhea should occur in about 5%, with recovery in about 75% of female, according to the age)
- MDS and leukemia have been reported infrequently but consistently
- Second solid tumors have been reported consistently

### 7.1.2. Guidelines for dose modification

Complete blood count should be obtained before each intravenous drug administration, day 1 and day 8.

Day 1: The treatment will be administered when PMN <1500/mmc and/or PLT <100.000/mmc performing hematology evaluation every 3 days until hematological recovery. After 1 week chemotherapy will be administered according to dose reduction guidelines reported in the table.

Day 8: the treatment will be delayed when PMN< 1000/mmc and/or PLT< 75000 performing hematology evaluation every 3 days until hematological recovery

#### TAB 1 Dose modification

<table>
<thead>
<tr>
<th>PMN x 10^9</th>
<th>PLT x 10^9</th>
<th>Doxorubicin</th>
<th>Bleomycina</th>
<th>Vinblastin</th>
<th>Dacarbazin</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1.5 and</td>
<td>≥75</td>
<td>100 %</td>
<td>100 %</td>
<td>100 %</td>
<td>100 %</td>
</tr>
<tr>
<td>≥ 1.0 but &lt;1.5</td>
<td>≥50 but &lt;75</td>
<td>50 %</td>
<td>100 %</td>
<td>50 %</td>
<td>50 %</td>
</tr>
<tr>
<td>&lt; 1.0 or</td>
<td>&lt;50</td>
<td>0 %</td>
<td>0 %</td>
<td>0 %</td>
<td>0 %</td>
</tr>
</tbody>
</table>

A delay of more than 15 days in considered a treatment failure.

### 7.2. Radiotherapy (Target volume, dose specification, dose fractionation)

Involved field radiotherapy (IF-RT) should be performed 3-4 weeks after the end of last therapy (approximately 6 weeks after the start of the last chemotherapy cycle) in all responding patients.

Using conventional fractionation (1.8 – 2 Gy q.d.), a total dose of 30 Gy will be delivered to initially involved nodal areas, considering the whole lymph node region as the appropriate target volume.
A meticulous recording of initial disease at presentation, as documented by CT-scan and PET-CT scan before chemotherapy, is an absolute requirement for adequate IF-RT afterwards, together with post-chemotherapy CT-scan. It is strongly recommended that pre- and post-chemotherapy CT scans be performed, whenever possible, with patients in treatment positions. In the same way, fusion possibilities, allowing the overlapping of pre- and post-chemotherapy CT scans, are strongly recommended. CT-simulation is strongly advised when designing IFRT fields.

Definition of target volume (CTV) will incorporate the initial location and the extent of the disease, and will take into account response to chemotherapy and the displacement of normal structures. For mediastinal disease, the CTV will be the initial volume of the mediastinal mass; whenever possible, blood vessels will be avoided; in order to decrease potential lung toxicity, the length of the CTV will be the length of the mediastinal mass or nodes before chemotherapy, while the width of the CTV will be the width of the mediastinal mass or nodes after chemotherapy. The general concept is to adapt radiation fields as a best compromise between pre- and post-chemotherapy volumes. The PTV will be the CTV with a margin to take into account organ motion and set-up variations; in most situations, a 1 cm isotropic margin is considered adequate.

The prescribed dose will be 30 Gy, delivered with conventional fractionation, Monday through Friday, with a maximum weekly dose of 10 Gy. Radiation doses will be specified according to ICRU62 rules. Patients must be treated with high energy photons (6-18 MeV), depending the choice of optimal energy, as well as the choice of technical approach (3D-CRT, static IMRT, dynamic IMRT, volumetric IMRT) on different clinical scenario. Portal imaging or other new technical checks belonging to the world of IGRT (cone-beam CT, for instance) should be periodically performed. An early retrospective quality assurance program will be set up in order to ascertain any major protocol violation. The following will be considered as major deviations:
- less than 90% of the prescribed dose delivered to the PTV
- incorrect assessment of the CTV resulting in poor coverage of the initial tumor extension
- overall treatment time exceeding the normal treatment time by more than 10%

7.3. FDG PET

7.3.1. PET scan execution

PET Patients will undergo a baseline staging at disease onset and interim restaging after the second d-d-ABVD cycle with PET-CT (PET-0 and PET-2, respectively). PET scan will be performed with the standard-technique scanning protocol. PET-0 and PET-2 will be performed at the same PET centre, with PET-CT technology.

The preferred day for PET-2 scan would be the 19\textsuperscript{th} or 20\textsuperscript{th} day of the second cycle, just before the third cycle.

7.3.2. Central core lab for PET reviewing

No standard rules exist at this writing for interim-PET interpretation during ABVD treatment in early or advanced-stage HL. For these reason a review panel is mandatory. Seven nuclear medicine experts with a proven experience in the field of interim PET in lymphoma will review the scans. A dedicated website will be implemented at the URL \url{https://magic5.to.infn.it} at the National Institute of Nuclear Physics (INFN); reviewers & users will be provided with a user ID and password to enter.

7.3.3. Rules for PET-2 interpretation

Since no standard criteria are available for interim-PET reviewing in ABVD-treated HL patients. The three following rules will be used:
(1) IHP criteria (Juweid 2007): though proposed for end-treatment evaluation, these rules have been widely used for interim-PET evaluation and therefore will be also used in the present study.

(2) Deauville rules (Barrington 2010): these criteria have been purposely risen for interim-PET interpretation and rely on visual, semi-quantitative assessment according to a 5-point scale for intensity of residual FDG uptake scoring, with liver as reference organ for positivity cutoff. The 5-point scale has been proposed for interim-PET interpretation for PET-response-adapted clinical trials both for early and advanced-stage HL. However, depending on the aim of the trial (de-escalating or escalating) treatment according to interim-PET results a cutoff conservative (sensitive) or liberal (more specific) will be chosen. In the RAPID study the threshold value for PET positivity has been set for a FDG uptake higher than the mediastinum; in the RATHL study the threshold has been set for an FDG uptake higher than that of the liver (Barrington 2010). Both threshold values will be used for interim PET interpretation and the respective accuracy in predicting treatment outcome will be compared.

Overall accuracy and Predictive Value on treatment outcome will be assessed for the two rules.

However, since a minimum follow-up of three years will be needed for the evaluation of treatment outcome, the percentage of positive PET scan will be evaluated in the interim analysis and the results compared with historical controls using the same rules for interim-PET interpretation in accord to IHP criteria (Juweid 2007).

8. END OF TREATMENT, END OF STUDY / STUDY DISCONTINUATION

8.1. Completion

8.1.1. End of treatment

A patient will be classified as having completed the treatment after having completed 4 cycles of study therapy.
8.1.2. End of study:

End of study is 2 years from the activation of therapy in the last patient enrolled onto the study. The analysis of follow up data will be performed on a second time independently on previous points of evaluation determined at the end of treatment.

The timing is as follows:

- Project starting date: September 2011
- Project completion of accrual: September 2012
- Project completion of follow up: December 2015

8.2. Therapy discontinuation

Reasons for therapy discontinuation:
- Completion of planned treatment
- Disease Progression during protocol treatment
- Excessive toxicity that does not allow administration of the protocol treatment e.g. reasons to stop because of excessive hematologic toxicity, FDG-PET scan not performed after two cycles of ABVD (major protocol violation)
- Refusal of the patient to further cooperate (at any time and for any reason)
- Principal Investigator’s decision
- Pregnancy or refusal to use an effective contraception (WOCBP)

9. CLINICAL EVALUATION, LABORATORY TEST AND FOLLOW UP

The time and event schedule summarizes the frequency and timing of study related procedures (see appendix 1)

Each patient must sign and date an informed consent form prior to engaging in any procedures that is not part of routine medical care. The screening procedures must be completed on day 0.
9.1. Screening phase (days -21 to day 0)

The screening procedures that must be performed to confirm patient’s eligibility are listed below:

- Review and signing of informed consent
- Inclusion/Exclusion criteria review
- Review medical history: B-symptoms, method of contraception.
- Physical examination, including measurement of the maximum dimension of all involved lymphadenopathies and body weight
- Vital sign (blood pressure, heart rate and temperature)
- ECOG performance status (Appendix 2),
- CT scan of neck, thorax and abdomen
- Whole body FDG-PET scan
- Unilateral trephine bone marrow biopsy
- ECG and ecocardiography
- Respiratory function test
- Clinical laboratory evaluation
  - Hematology (full blood count and differential)
  - Blood chemistry (total bilirubin, creatinine, urea, uricemia, alkaline phosphatase, ALT, AST, GGT, LDH, serum albumin, ESR, K+, Na+, Cl-, Ca++, PT, PTT, Fibrinogen).
  - Serum hCG pregnancy test (where applicable)

9.2. During treatment

The following procedure are to be repeated on each treatment cycle

Day 1 and 8 of each cycle

- Vital sign (blood pressure, heart rate and temperature)
- ECOG performance status (on Day 1), see Appendix 2
- Physical examination
- Haematology (full blood count and differential)
- Adverse events assessment according to CTCAE v4.0 (appendix 3)
- Blood chemistry if clinically indicated
After 2 cycle of dd-ABVD

PET-2 scan would be the 19th or 20th day of the second cycle, just before the third cycle.

Not performing FDG-PET scan will be considered major protocol violation.

After completion of chemotherapy (4th dd-ABVD cycle or salvage)

- Physical examination
- Vital sign (blood pressure, heart rate and temperature)
- ECOG performance status (Appendix 2)
- Adverse events assessment according to CTCAE v4.0 (appendix 3)
- CT scan of neck, thorax and abdomen
- FDG-PET scan
- Clinical laboratory evaluation
  - Hematology (full blood count and differential)
  - Blood chemistry (total bilirubin, creatinine, urea, uricemia, alkaline phosphatase, ALT, AST, GGT, LDH, serum albumin, ESR, K+, Na+, Cl-, Ca++, PT, PTT, Fibrinogen).

9.3. End of therapy

- Physical examination
- Vital sign (blood pressure, heart rate and temperature)
- ECOG performance status (appendix 2)
- Adverse events assessment according to CTCAE v4.0 (appendix 3)
- CT scan of neck, thorax and abdomen
- FDG-PET scan
- Clinical laboratory evaluation
  - Hematology (full blood count and differential)
  - Blood chemistry (total bilirubin, creatinine, urea, uricemia, alkaline phosphatase, ALT, AST, GGT, LDH, serum albumin, ESR, K+, Na+, Cl-, Ca++, PT, PTT, Fibrinogen)
9.4. Follow up

From end of treatment until disease progression the patient will be monitored according to SIE/AIOM guidelines

- clinical laboratory evaluation (Hematology and Blood chemistry) and physical examination
  - For the first 2 years: every 3 months
- Neck, chest and abdomen CT scan:
  - For the first 2 years: every 6 months

9.5. CRITERIA OF EVALUATION

Response
Response will be evaluated according to 2007 Cheson’s criteria

Progression-free survival
PFS is calculated for all patients and is defined as the time from entry into the study (registration) and:

- progressive disease during protocol treatment
- relapse after reaching CR on protocol treatment
- progression after reaching PR or SD on protocol treatment

Response criteria
Disease evaluation will be performed by FDG PET and scan. FDG-PET scan after two cycles of ABVD is mandatory. The result of this FDG-PET scan is primary objective of the study and is used to guide further treatment. Response to treatment will be evaluated:

- after 2nd cycle of ABVD by FDG-PET scan
- after 4th cycle of ABVD by FDG-PET scan and CT scan
- after IN-RT by FDG-PET scan and CT scan

Response will be evaluated at around 3 weeks after the first day of the respective chemotherapy cycle and/or within 6-8 weeks after IN-RT.
Table 2. Response criteria

<table>
<thead>
<tr>
<th>Type of response</th>
<th>Definition</th>
<th>Lymph nodes</th>
<th>Spleen, liver</th>
<th>Bone marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Remission</td>
<td>Disappearance of all evidence of disease</td>
<td>Masses of any size permitted if FDG-PET negative</td>
<td>Not palpable; nodules disappeared</td>
<td>Infiltrate cleared on repeated biopsy</td>
</tr>
<tr>
<td>Partial remission</td>
<td>Regression of all miserable disease and non new site lesion</td>
<td>&gt;50% decrease in SPD of up to six largest masses; no increase in size of other nodes. One or more FDG-PET positive at previously involved sites</td>
<td>&gt;50% decrease in SPD of nodules; no increase in size of liver or spleen</td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>Failure to obtain CR or PR</td>
<td>FDG-PET positive at prior sites of disease and no new sites on CT scan or FDG-PET</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapse or Progression</td>
<td>Any new lesion or increase by &gt;50% of previously involved sites</td>
<td>Appearance of a new lesion or 50% increase in longest diameter of a previous node</td>
<td>50% increase of any previous lesion</td>
<td>New or recurrent involvement</td>
</tr>
</tbody>
</table>

10. STATISTICAL ANALYSIS AND SAMPLE SIZE

Feasibility of dd-ABVD regimen and percentage of FDG PET negativity after 2 dd-ABVD cycles will be considered as primary endpoints.

Considering a proportion of patients without a dose intensity reduction of 95% in pts treated with standard ABVD, we want to exclude a reduction higher than 10% in pts treated with dd-ABVD. In order to test this difference with a one-side alpha of 0.10 and beta of 0.15, we need to evaluate 52 pts. If 5 or more pts will present a dose intensity reduction the study drug will not be considered for further evaluation and the enrolment will be ended.

Otherwise, enrolment will continue for the evaluation of second primary endpoint.

Considering a proportion of PET - of 80% in patient treated with standard ABVD, we consider of clinical interest an absolute improvement of 10% in pts treated with dd-ABVD. In order to test this difference with a one-side alpha of 0.10 and beta of 0.10, we need to evaluate 86 pts. If 74 or more PET - will be observed the study drug will be considered for further evaluation.
FDG-PET negativity will be defined in accord to IHP criteria (Juweid 2007 Patients’ characteristics will be reported descriptively. The response rate, toxicity and safety data will be summarized as frequencies and proportions or as median and range. Progression free survival curves will be estimated by the Kaplan-Meier technique.

In order to evaluate the predictive value of the 2 different criteria for interim PET interpretation, the C statistic of each technique for progression free survival will be calculated and compared. Moreover sensitivity, specificity and concordance between each test result and the disease status at three years will be calculated and pairwise comparisons between pet techniques will be estimated using paired odds ratio and tested with McNeamar test. Finally the binary (k coefficient) and overall (Krippendorf alpha coefficient) concordance rate among reviewers will be calculated.

11. FORMS AND PROCEDURES FOR COLLECTING DATA AND DATA MANAGING

CRF is the primary data collection instruments for the study. All data requested on the CRF must be recorded, and any missing data must be explained. If a space is left blank because the procedure was not done or the question was not asked, “N/D” must be noted. If the item is not applicable to the individual case “N/A” must be noted.

To perform statistical analyses, all data collected will be recorded in a protected data base.

**FIL Data Center Location**

FIL Data Center will coordinate data collection, assess the coherence of data and monitor the study.

FIL Data Center address is:
Dipartimento ad attività integrata di Oncologia Ematologia e patologie dell’Apparato Respiratorio Università di Modena e Reggio Emilia
Centro Oncologico Modenese
c/o Policlinico, Via del Pozzo 71
41100 Modena-Italy, Tel +390594223165, FAX +390594223707
e-mail: monica.bellei@unimore.it
12. ADVERSE EVENT AND ADVERSE DRUG REACTION REPORT

12.1. Definition

**Adverse Event**

An adverse event is any untoward medical occurrence in a clinical study subject administered a pharmaceutical product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. (Definition per International Conference on Harmonization [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

**Serious Adverse Event**

A serious adverse event as defined by ICH is any untoward medical occurrence that at any dose meets any of the following conditions:

- death,
- a life-threatening event (i.e. the patient was at immediate risk of death at the time the reaction was observed),
- hospitalization or prolongation of hospitalization,
- persistent or significant disability/incapacity,
- a congenital anomaly/birth defect, or
- any other medically important condition (i.e. important adverse reactions that are not immediately life threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above).
**Unlisted (Unexpected) Adverse Event**

For an investigational product, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure/Device Manual. For a comparator product with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the Summary of Product Characteristics (SmPC).

**Associated with the use of the Drug**

An adverse event is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in the next Section.

**Adverse Drug Reaction**

Any adverse event which has at least a reasonable possibility to be related to the drug.

**Serious Adverse Drug Reaction**

Any serious adverse event which has at least a reasonable possibility to be related to the drug

**Serious Unexpected Suspected Adverse Reaction** means those events which:

- are Serious (regardless of the dosage) according to the definition contained in the preceding sub-paragraph;
- have a certain degree of probability of being harmful, as a reaction to the medicinal product under investigation, regardless of the dosage administered (in other words, may be qualified as an adverse reaction);
- are unexpected, that is to say, the nature and severity of the adverse reaction is not in agreement with the product information as recorded.

**12.1.1. Attribution definition**

Intensity (Severity) Reporting and Attribution
For both serious and non-serious adverse events, the Investigator must determine both the intensity of the event and the relationship of the event to study drug administration.

**Intensity** should be defined according to the following criteria:

- **Mild**: Awareness of sign or symptom, but easily tolerated
- **Moderate**: Discomfort enough to cause interference with normal daily activities
- **Severe**: Inability to perform normal daily activities
- **Life Threatening**: Immediate risk of death from the reaction as it occurred.

for oncological trial will be determined by using the last version of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) as a guideline, wherever possible; a copy can be downloaded from the Cancer Therapy Evaluation Program (CTEP) home page (http://ctep.cancer.gov/forms/CTCAEv4.pdf).

**Relationship** to study drug administration will be determined as follows:

- **Not related**: An adverse event which is not related to the use of the drug.
- **Unlikely/Doubtful**: An adverse event 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 adverse event which might be due to the use of the drug. 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 adverse event which might be due to the use of the drug. The relationship in time is suggestive (e.g., confirmed by
An alternative explanation is less likely, e.g., concomitant drug(s), concomitant disease(s).

- **Definite/Very Likely:** An adverse event which is listed as a possible adverse 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).

### 12.1.2. Record-keeping and Identification code

Investigator sponsor must keep detailed and accurate record of any and all adverse events reported to them by the investigators. Such records must be made available for inspection upon request of the Ministry of Health ("MoH"). Any and all communications concerning adverse events must identify the patient through a univocal code only.

### 12.2. Reporting Procedure

#### 12.2.1. All Adverse Events

All adverse events that occur between the first study-related procedure and 30 days after the last dose of study drug will be reported. All events that meet the definition of a serious adverse event will be reported as serious adverse event, regardless of whether they are protocol-specific assessments.

All adverse events, regardless of seriousness, severity, or presumed relationship to study therapy, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as “upper respiratory infection”). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to Investigator-Sponsor instructions.

All severe adverse events, considered related, must be followed until resolution of the event, or the event improves to an acceptable gravity degree related to the...
disease. The unresolved aforementioned events will be followed for a maximum of 6 months.

Serious adverse event reports will be submitted as described in the next Section

**12.2.2. Serious Adverse Events**

All serious adverse events occurring during clinical studies must be reported to the Investigator-Sponsor or his delegate by investigational staff within 24 hours of their knowledge of the event.

Information regarding serious adverse events will be transmitted to the Investigator-Sponsor or his delegate using the Serious Adverse Event Form, which must be signed by a member of the investigational staff. The initial report of a serious adverse event may be reported by fax or by telephone. It is preferable that serious adverse events be reported via fax. Subsequent to a telephone report of a serious adverse event, a Serious Adverse Event Form must be completed by the investigational staff and transmitted to the Investigator-Sponsor within 1 working day.

The cause of death of a subject in a clinical study, whether or not the event is expected or associated with the investigational agent, is considered a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject’s participation in a clinical study must be reported as a serious adverse event, except hospitalizations for:

- social reasons in absence of an adverse event
- surgery or procedure planned before entry into the study (must be documented in the CRF)
- study drug administration
- study related procedures defined in the protocol

The Investigator-Sponsor should report serious unexpected adverse events to the appropriate Independent Ethics Committee (IEC) that approved the protocol unless otherwise required and documented by the IEC. The Investigator-Sponsor
assumes responsibility for appropriate reporting of serious unexpected adverse events to Regulatory Authorities

12.2.3. Serious Unexpected Suspected Adverse Reaction
According to Italian law, Serious Unexpected Suspected Adverse Reaction reports must be entered in the Clinical Trial Electronic Module of EudraVigilance database and copied to AIFA (http://eudravigilance.emea.europa.eu/human/index.asp).

All Serious Unexpected Suspected Adverse Reaction reports must be periodically (at least every 6 months) reported to investigators and IEC as a line listing accompanied by a brief report by the sponsor highlighting the main points of concern.

13. ETHICAL CONSIDERATION

13.1. Patient protection
The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (Tokyo, Venice, Hong Kong and Somerset West amendments) or the laws and regulations of the country, whichever provides the greatest protection of the patient.

The protocol has been written, and the study will be conducted according to the ICH Guideline for Good Clinical Practice

The protocol and its annexes are subject to review and approval by the competent Independent Ethics Committee(s) (“IEC”).

13.2. Subject identification - Personal data protection
All records identifying the subject must be kept confidential and, to the extent permitted by the applicable laws and/or regulations, not be made publicly available. The name of the patient will not be asked for nor recorded at the Data Center. A sequential identification number will be automatically attributed to each patient registered in the study. This number will identify the patient and must be included on all case report forms. In order to avoid identification errors, patient initials and date of birth will also be reported on the case report forms.
Any and all patient information or documentation pertaining to a clinical trial, to the extent permitting, through a “key” kept anywhere, regardless of whether such key is supplied along with the information or documentation or not, must be considered as containing sensitive personal data of the patient, and is therefore subjected to the provisions of applicable data protection (“privacy”) regulations. Breach of such regulations may result in administrative or even criminal sanctions.

Particularly, an information sheet prepared according to such regulations and a form to evidence the consent of patients to the processing of such data must therefore accompany the informed consent administered to the patient (see paragraph 14.3 below). Such information must (i) identify the roles of the holder (“titolare”) and processor (“responsabile”, appointed by the holder) of the patient personal data (also if not directly identifying the patient), as well as the purposes of the personal data collection and processing (medical treatment and related/unrelated scientific research), (ii) adequately describe the flows of communication involving them, particularly if third parties should become involved, and (iii) seek the patient’s prior and specific consent to such processing.

Patient information or documentation may be considered “anonymous”, and as such not subject to privacy regulations, only when no key whatsoever, permitting the identification of the patient, is any longer available.

Particular attention should therefore be paid (and information/consent materials adapted accordingly) whenever patient data are supplied to third parties and may be autonomously processed, or biological samples/materials are taken and kept for future research purposes, associated or not with the pathology considered in the study.

**13.3. Informed Consent**

All patients will be informed of the aims of the study, the possible adverse events, the procedures and possible hazards to which he/she will be exposed, and the mechanism of treatment allocation. They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for study purposes by authorized individuals other than their treating
physician. An example of a patient informed consent statement is given as an appendix to this protocol.

It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever he/she wants. This will not prejudice the patient’s subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered or randomized at the Data Center. This must be done in accordance with the national and local regulatory requirements.

For European Union member states, the informed consent procedure must conform to the ICH guidelines on Good Clinical Practice. This implies that “the written informed consent form should be signed and personally dated by the patient or by the patient’s legally acceptable representative”.

14. CONFLICT OF INTEREST
Any investigator and/or research staff member who has a conflict of interest with this study (such as patent ownership, royalties, or financial gain greater than the minimum allowable by their institution) must fully disclose the nature of the conflict of interest.

15. DATA OWNERSHIP
According to the ICH Guidelines on Good Clinical Practice the sponsor of a study is the owner of the data resulting therefrom. All centers and investigators participating in the study should be made aware of such circumstance and invited not to disseminate information or data without the Institution’s prior express consent.

16. PUBLICATION POLICY
After completion of the study, the project coordinator will prepare a draft manuscript containing final results of the study on the basis of the statistical analysis. The manuscript will be derived to the co-authors for comments and after revision will be sent to a major scientific journal.
All publications, abstracts, presentations, manuscripts and slides including data from the present study will be submitted to and reviewed by the Study Coordinator for coordination and homogeneity purposes: specific advance periods for submission and review may be specified in the protocol. The timing of publications may be coordinated, and publication delayed if patentable inventions should be involved (for the time required in order to file the relevant patent applications); otherwise, according to the MoH’s Decree of May 12, 2006, investigators cannot be precluded from or limited in publishing the results of their studies (IECs must verify that no excessive restriction is contained in the protocols submitted to their review and approval).

17. STUDY INSURANCE
The Investigator-sponsor of the Study must ensure that adequate insurance coverage is available to the patients, in accordance with Section 5.8 of the ICH Guidelines of Good Clinical Practice. Such coverage must extend to all damages deriving from the study, to the exclusion of those attributable to willful 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.

Based on section 2.4 of the MoH’s decree of December 17, 2004, the insurance coverage must be supplied by the hospital or medical research department in case of no profit drug evaluation trial.

18. STUDY TIME TABLE
   Project starting date: September 2011
   Project completion of accrual: September 2012
   Project completion of data collection: April 2013
   Project data analysis: September 2013
   Project presentation of scientific report: December 2013
19. REFERENCE


Brusamolino E., Bacigalupo A., et al Classical Hodgkin’s lymphoma in adults: guidelines of the Italian Society of Hematology, the Italian Society of Experimental Hematology, and the Italian Group for Bone Marrow Transplantation on initial work-up, management, and follow-up haematologica 2009; 94


Rigacci L, et al Early FDG-PET Scan confirms its prognostic impact also in localized stage, ABVD treated Hodgkin Lymphoma patients. Haematologica 2010; Abstract book 95 (s4) s13 abs. C046


# Appendix 1. Time & Events schedule

<table>
<thead>
<tr>
<th></th>
<th>Screening visit</th>
<th>Cycl 1 - 4</th>
<th>After 2(^\text{nd}) ddABVD</th>
<th>After 4(^\text{th}) ddABVD</th>
<th>End of treatment</th>
<th>Follow up every 3/6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical/Surgical History</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Informed consent</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Inclusion/exclusion criteria</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Performance status (ECOG)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Menstrual status/contraceptive</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vital Sgn</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Weight (and Height only cycle 1)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical examination</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematology</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical chemistry(^1)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>beta HCG (if applicable)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FDG PET(^2)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>neck, chest and abdomen TAC</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Bone marrow biopsy</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECG 12 derivazioni</td>
<td>X</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF (echocardiography)</td>
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<tr>
<td>Respiratory function test</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Adverse event assessment</td>
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<td></td>
<td></td>
<td></td>
<td>THROUGHOUT</td>
</tr>
<tr>
<td>Concomitant Medication</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>THROUGHOUT</td>
</tr>
<tr>
<td>Secondary tumors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

1) Blood chemistry: total bilirubin, creatinine, urea, uricemia, alkaline phosphatase, ALT, AST, GGT, LDH, serum albumin, ESR, K+, Na+, Cl-, Ca++, PT, PTT, Fibrinogen

2) PET-2 scan would be the 19\(^{\text{th}}\) or 20\(^{\text{th}}\) day of the second cycle, just before the third cycle. Not performing FDG-PET scan will be considered major protocol violation.
## Appendix 2 - EORTC classification criteria

| RISK FACTOR | • Bulky mediastinum  
| • Age ≥ 50 years  
| • VES ≥ 50 without B symptoms or ≥ 30 with B symptoms  
| • ≥ 4 involved nodal regions |
| VOURABLE | CS I or II without risk factor |
| favorable | CS I or IIA with more than 1 risk factors |
### Appendix 3 - ECOG Performance Status

<table>
<thead>
<tr>
<th>Grade</th>
<th>ECOG</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction</td>
</tr>
<tr>
<td>1</td>
<td>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</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair</td>
</tr>
<tr>
<td>5</td>
<td>Dead</td>
</tr>
</tbody>
</table>

Appendix 4 - Common Terminology Criteria for Adverse Events (CTCAE), version 4.0

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

At the time this protocol was issued, the full CTC document was available on the NCI website, at the following address: [http://ctep.cancer.gov/reporting/ctc.html](http://ctep.cancer.gov/reporting/ctc.html)
Appendix 5 - WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964

and amended by the

29th WMA General Assembly, Tokyo, Japan, October 1975,
35th WMA General Assembly, Venice, Italy, October 1983,
41st WMA General Assembly, Hong Kong, September 1989,
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996,

and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic,
diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any
serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient’s information and to minimize the impact of the study on the subject’s physical and mental integrity and on the personality of the subject.
22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject’s freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of
interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.