FONDAZIONE ITALIANA LINFOMI

Clinical Protocol

A phase II, open label, multicenter trial of Daratumumab in combination with Gemcitabine, Dexamethasone and Cisplatin (D-GDP) in patients with relapsed/refractory CD38 positive peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL) and other nodal lymphomas of TFH cell origin

ID Study: FIL_Dara-GDP

EudraCT number: 2018-002644-91

INVESTIGATOR SPONSOR:

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REGISTRATION (REFER TO CHAPTER 12)	www.filinf.it
SAE REPORTING (REFER TO CHAPTER 17)	www.drugvigilance.filinf.it/

Version and date of Protocol: Version 1.0 of March 29, 2019

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2. TABLE OF CONTENTS

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_Dara-GDP
EudraCT N°	2018-002644-91
Title of the study	A phase II, open label, multicenter trial of Daratumumab in combination with Gemcitabine, Dexamethasone and Cisplatin (D-GDP) in patients with relapsed/refractory CD38 positive peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL) and other nodal lymphomas of TFH cell origin
Phase of the study	Prospective, multicenter, phase II single arm study.
Investigational product	Daratumumab
Protocol version	Version 1.0 of March 29, 2019
Centers	20 centers in Italy part of Fondazione Italiana Linfomi
Study Objectives and Endpoints	***Primary Objective*** To evaluate the efficacy of 4 courses of D-GDP in terms of complete response in patients with PTCL-NOS, AILT and other nodal lymphomas of TFH cell origin refractory/relapsed after at least one and no more than two previous lines of therapy. ***Secondary Objectives*** - To evaluate the Overall Response Rate (ORR) (Lugano 2014); - To evaluate the efficacy in terms of Overall survival (OS); - To evaluate the efficacy in terms of Progression-free survival (PFS); - To evaluate the safety of D-GDP combination. ***Explorative objectives*** - To assess the role of daratumumab maintenance; - To evaluate the association between intensity of CD38 expression and response. ***Primary Endpoint*** CR (Complete Response) Rate (CRR) after 4 cycles of D-GDP. CR will be defined according to the Lugano 2014 criteria ***Secondary Endpoints*** 1) ORR (=CR + Partial Response, PR) (Lugano 2014) 2) OS (defined as the time from treatment start and death from any cause) (Lugano 2014) 3) PFS (defined as the time from treatment start and progression/relapse or death from any cause) (Lugano 2014) 4) The occurrence of relevant toxicity evaluated in terms of: - grade 4 neutropenia lasting for more than 7 days regardless adequate G-CSF primary prophylaxis/treatment - grade 4 thrombocytopenia lasting for more than 7 days - delay ≥ 15 days in the next course administration - any relevant grade 3-4 non-hematological toxicity drug related (excluding alopecia, laboratoristic data and infusion-related reaction, IRR); - febrile neutropenia lasting for more than 7 consecutive days Toxicity will be recorded and classified according to the definitions of the NCI criteria “Common Terminology Criteria for Adverse Events (CTCAE)”, version 5.0.

	Explorative efficacy endpoints - Role of daratumumab maintenance by comparison of CRR before and after maintenance, and by evaluation of rate of conversion in CR with daratumumab maintenance for patients in PR after the induction. - Association between intensity of CD38 expression and response. The extent of CD38 expression evaluated by the central FIL designed laboratory will be correlated with response measured according to the Lugano 2014 criteria at various timepoints.
Study design	This is an open-label, multicenter, single arm, single-stage phase II trial. After the patient signs the written informed consent the patient will enter the screening phase planning baseline assessments and a concomitant upfront confirmation of diagnosis of PTCL-NOS, AITL or nodal lymphoma of TFH cell origin and a central evaluation of immunohistochemical positivity of CD38 on bioptic material used to perform local diagnosis of relapsed disease, or that used for the more recent biopsy in the case of refractory patients. A core needle biopsy is considered sufficient for review and CD38 evaluation. Evaluation at central laboratory can be performed in bone marrow sections in those patients with only bone marrow lymphoma infiltration. Only patients with confirmed eligible diagnosis and a percentage of CD38 positive tumor cells ≥ 5% will be considered eligible for study treatment. The treatment consists of an induction phase and a maintenance phase. ***Induction phase:*** 4-6 courses (according to response after cycle 4 and to patient compliance) of D-GDP every 21 days pursuant to the following schedule: • Daratumumab cycle 1: 8 mg/kg i.v. on day 2 and on day 9; cycle 2-6: 16 mg/kg i.v. on day 2 and day 9) • Gemcitabine 1000 mg/sm i.v. day 1 and day 8 (gemcitabine on day 8 to be skipped in case of grade 3-4 toxicity) • Cisplatin 75 mg/sm i.v. day 1 • Dexamethasone 40 mg i.v. or po days 1-2-3-4-9 • G-CSF from day 3 to 6, and from day 10 to 13 (to be prolonged if necessary) After 4 courses of D-GDP, patients in CR/PR and eligible for allogeneic stem cell transplantation (allo-SCT) will be addressed to allo-SCT consolidation. Otherwise, patients in CR will enter the maintenance phase at this point of the study. Patients in PR (not eligible for allogeneic stem cell transplantation) or in SD after D-GDP x 4 can receive 2 additional courses of D-GDP before maintenance or can move directly to maintenance, according to center choice (based on patient condition, performance status and quality of response). Patients who respond (CR/PR) after 6 courses of induction phase (end of induction, EOI) and eligible to allo-SCT will be addressed to allo-SCT consolidation. Patients who respond to the induction phase (CR/PR) and are not eligible for allo-SCT and patients in SD at EOI, will move to the maintenance phase. Patients in PD at any time will discontinue treatment, as well as patients experiencing at any time unacceptable toxicity.

	Maintenance phase: starting 28 days after the beginning of cycle 4 or 6 (or, in case of toxicity grade > 1, after toxicity is resolved) and up to 24 cycles from start of D-GDP according to the following schedule: • Daratumumab 16 mg/kg single administration every 28 days Treatment with D-GDP or daratumumab single agent will be discontinued before completion of 24 cycles in case of: • decision of the investigator to consolidate D-GDP response with allogeneic stem cell transplant • disease progression • unacceptable toxicity • withdrawal of consent • investigator determines that further therapy is not in the patient's best interest (e.g., due to non-compliance, toxicity, etc.) Adverse events (CTCAE v. 5.0) will be monitored from the first study-related procedure, throughout treatment, maintenance and for 30 days after the end of treatment with the study drug.
Duration of the study	Patients will be recruited over 18 months. The median expected duration of the treatment period is approximately 6 months. End of study is defined by the visit planned by the protocol 24 months after the start of treatment of the last patient, for a total study duration of approximately 42 months (3.5 years).
Number of patients	A total of 35 patients will be enrolled in the study.
Inclusion criteria	• Histologically documented diagnosis of CD38 positive PTCL-NOS, AITL and other nodal lymphomas of TFH cell origin as defined in the 2017 edition of the World Health Organization (WHO) classification. Patients with only bone marrow involvement are eligible. ***Note:*** Only patients with a centrally assessed percentage of CD38 positive tumor cells ≥ 5% in the relapse biopsy, or in the more recent biopsy in the case of refractory patients, will be considered eligible for protocol study treatment. • Age 18-75 years • Relapsed or refractory to at least one and a maximum of two previous lines of treatment • Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2 • At least one site of measurable nodal disease at baseline ≥ 2.0 cm in the longest transverse diameter as determined by CT scan (MRI is allowed only if CT scan cannot be performed). Note: Patients with only bone marrow involvement are eligible • Adequate hematological counts defined as follows: - Absolute Neutrophil count (ANC) > 1.0 x 10^9/L unless due to bone marrow involvement by lymphoma - Platelet count ≥ 50.000/mm^3 unless due to bone marrow involvement by lymphoma • Adequate renal function defined as follows: - Creatinine clearance ≥ 40 mL/min (Cockcroft-Gault formula) • Adequate hepatic function per local laboratory reference range as follows: - Aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 3.0 x ULN - Bilirubin ≤1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin)

	• Subject understands and voluntarily signs an informed consent form approved by an Independent Ethics Committee (IEC), prior to the initiation of any screening or study-specific procedures • Subject must be able to adhere to the study visit schedule and other protocol requirements • Life expectancy ≥ 3 months • Women must be: - postmenopausal for at least 1 year (must not have had a natural menses for at least 12 months) - surgically sterile (have had a hysterectomy or bilateral oophorectomy, tubal ligation, or otherwise be incapable of pregnancy), - completely abstinent (periodic abstinence from intercourse is not permitted) or if sexually active, be practicing two highly effective methods of birth control (e.g., prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, double barrier method (e.g.: condoms, diaphragm, or cervical cap, with spermicidal foam, cream, or gel, male partner sterilization) as local regulations permit, before entry, and must agree to continue to use the same method of contraception throughout the study. They must also be prepared to continue birth control measures for at least 3 months after terminating treatment. - Women of childbearing potential must have a negative pregnancy test at screening • Men must agree to use an acceptable method of contraception (for themselves or female partners as listed above) for the duration of the study. Men must agree to use a double barrier method of birth control and to not donate sperm during the study and for 3 months after receiving the last dose of study drug. • Male even if surgically sterilized (i.e., status post vasectomy) must agree to 1 of the following: - practice effective barrier contraception during the entire study treatment period and through 3 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, post ovulation methods for the female partner] and withdrawal are not acceptable methods of contraception)
Exclusion criteria	• Histological diagnosis different from CD38 positive PTCL-NOS, AITL, and other nodal lymphomas of TFH cell origin • More than two lines of previous treatment (autologous stem cell transplant performed as part of consolidation to a previous line of therapy should not be considered as a line of therapy) • Previous treatment with Gemcitabine or Platinum based regimens; patients who received a single course of Platinum based course (i.e. DHAP) are not excluded • Prior therapy with monoclonal antibody antiCD38 • Concomitant experimental therapy • Relapse after allo SCT • CNS involvement with lymphoma • Subject has received any anti-cancer therapy including chemotherapy, immunotherapy, radiotherapy, investigational therapy, including targeted small molecule agents within 14 days prior to the first dose of study drug

<table>
<tr><td></td><td>

Chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) requiring treatment
Subject is:

Known to be seropositive for human immunodeficiency virus (HIV)
Seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]). Subjects with resolved infection (i.e., subjects who are HBsAg negative but positive for antibodies to hepatitis B core antigen [anti-HBc] ± antibodies to hepatitis B surface antigen [anti-HBs]) must be screened using real-time polymerase chain reaction (PCR) measurement of hepatitis B virus (HBV) DNA levels. Those who are PCR positive will be excluded. EXCEPTION: Subjects with serologic findings suggestive of HBV vaccination (anti-HBs positivity as the only serologic marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV DNA by PCR
Known to be seropositive for hepatitis C (except in the setting of a sustained virologic response [SVR], defined as aviremia at least 12 weeks after completion of antiviral therapy)

Cardiovascular disease (NYHA class ≥2)
Creatinine Clearance < 40 mL/min (Cockcroft–Gault formula)
Significant history of neurologic, psychiatric, endocrinological, metabolic, immunologic, or hepatic disease that would preclude participation in the study or compromise ability to give informed consent
Any history of other active malignancies within 3 years prior to study entry, with the exception of adequately treated in situ carcinoma of the cervix uterine, basal cell carcinoma of the skin or localized squamous cell carcinoma of the skin, previous malignancy confined and surgically resected with curative intent.
Uncontrolled and/or active systemic infection (viral, bacterial or fungal)
Evidence of any other clinically significant uncontrolled condition(s)
If female, the patient is pregnant or breast-feeding

</td></tr>
<tr><td>Study treatment and response assessment</td><td>Daratumumab will be administered in combination with GDP during the induction phase and as single agent during the maintenance phase; treatment will be continued up to 24 cycles from start of D-GDP or will be discontinued in case of decision to consolidate D-GDP response with allogeneic stem cell transplant, disease progression, unacceptable toxicity, withdrawal of consent and/or the investigator determines that further therapy is not in the patient best interest (e.g., due to non-compliance, toxicity, etc.)

Response will be evaluated according to the Lugano 2014 criteria.</td></tr>
<tr><td>Assessments schedule</td><td>Response evaluation will be performed during the induction phase after cycles 4 and 6 (only for those patients who will receive 6 D-GDP) from the beginning of treatment; during the maintenance phase response evaluation will be performed every 3 cycles up to cycle 12, every 4 cycles from cycle 13 to 24.</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>Diagnosis review and CD38 expression evaluation</td><td>Appendix E</td><td>YES</td><td>1 BLOCK or 20 UNSTAINED SLIDES</td></tr>
</table>
Upfront centralized diagnosis review and evaluation of immunohistochemical positivity of CD38 will be performed during the screening phase in the relapse biopsy, or in the more recent biopsy in the case of refractory patients: this</td></tr>
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<table>
<tr><td></td><td>procedure is compulsory for treatment start, but the local pathology report is enough to enroll patient. Only patients with a confirmed diagnosis of PTCL-NOS, AITL or nodal lymphomas of TFH cell origin and a percentage of CD38 positive tumor cells ≥ 5% will be considered eligible to study protocol treatment.</td></tr>
<tr><td>Statistical considerations</td><td>It is expected for the current trial that D-GDP will improve the CR rate to 40% with an absolute improvement of 20%, while the toxicity rate is maintained at 30%.
Sample size:
A'Hern's Single-Stage Phase II design will be used. The study sample size has been calculated according to the primary efficacy endpoint.
Based on data from the literature, the null hypothesis that the true proportion of CR after four courses of D-GDP is 0.20 will be tested against an alternative CR proportion of 0.40 with an absolute improvement of 0.20, considered clinically promising with the experimental treatment.
Assuming a type I error rate of 5% and a power of 80% when the CR proportion is 40% overall 35 patients will be accrued. The null hypothesis will be rejected if 12 or more CR out of 35 patients are observed after four courses of D-GDP.
Safety monitoring and stopping rules:
In order to monitor the safety and the activity of the treatment in small cohorts of patients, we will use the Bayesian approach of Thall et al. (1995), as extended by Thall and Sung (1998).
Monitoring of relevant toxicity after 4 cycles of D-GDP will be done to ensure that it is not higher than an acceptable toxicity of 30% (as defined in the safety endpoints) and the monitoring of activity after 4 cycles of D-GDP will be done to ensure that CR proportion is not lower than 40%.
The prior probability of toxicity and activity are modeled by beta distributions [Beta (0.6,1.4) and Beta (0.8,1.2), respectively].
We will stop the enrolment if the posterior probability of the treatment being more toxic or less active than expected is greater than 95%.
Patients will be monitored according to the following stopping boundaries in cohorts of five patients:
<table>
<tr><th>Number of patients enrolled</th><th>Stop the enrollment if the cumulative relevant toxicities after 4 cycles are greater or equal to:</th><th>Stop the enrollment if the number of cumulative CR after 4 cycles are lower or equal to:</th></tr>
<tr><td>5</td><td>4</td><td>-</td></tr>
<tr><td>10</td><td>6</td><td>1</td></tr>
<tr><td>15</td><td>9</td><td>2</td></tr>
<tr><td>20</td><td>11</td><td>4</td></tr>
<tr><td>25</td><td>13</td><td>5</td></tr>
<tr><td>30</td><td>15</td><td>7</td></tr>
<tr><td>35</td><td>17</td><td>8</td></tr>
</table>

The primary efficacy analysis will be performed after enrolment of 35 patients. The primary efficacy analysis will consist of an estimate of CRR on the efficacy population after 4 cycles of D-GDP therapy, with 90% confidence intervals</td></tr>
</table>

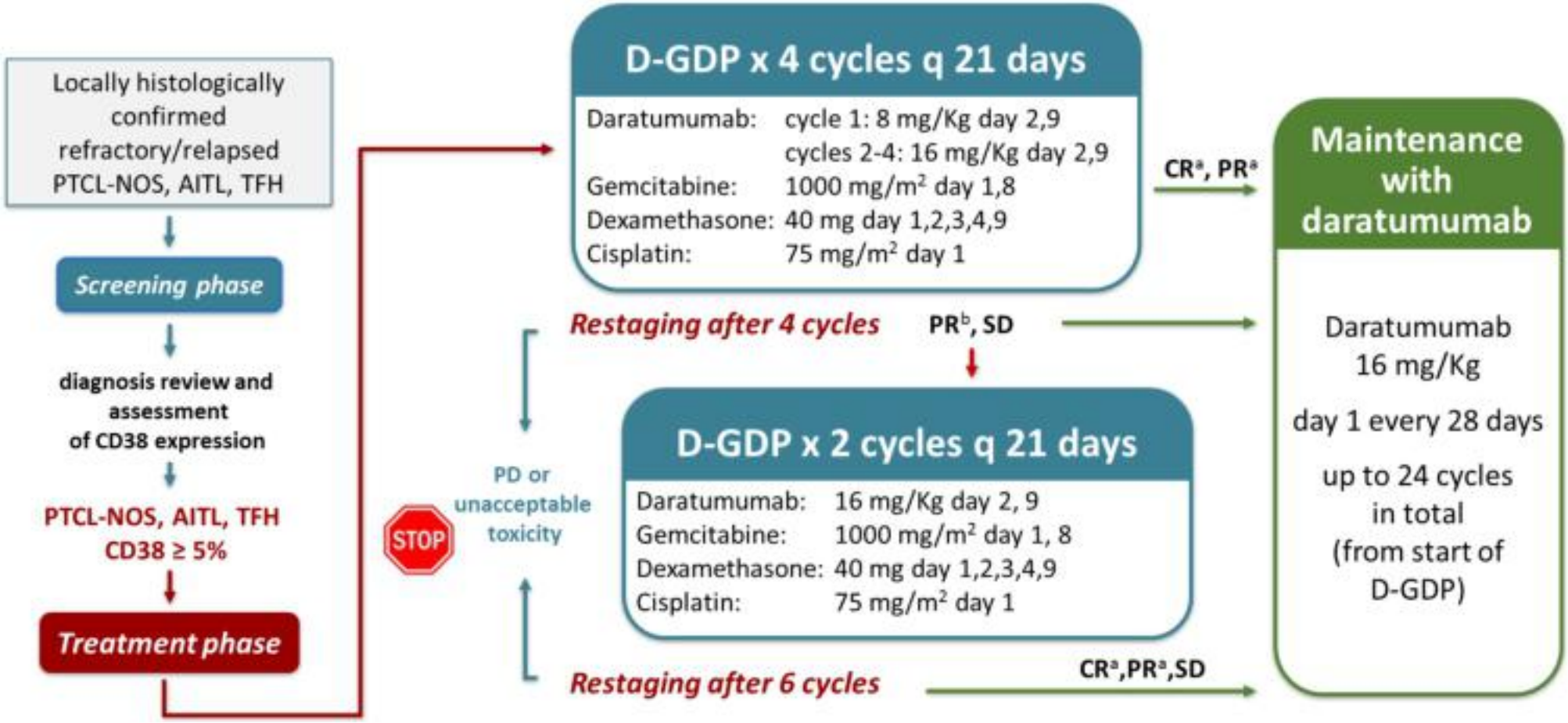
	(according to 1-sided alpha error of 0.05). To conclude that the new treatment is promising, the minimum number of patients with a CR is 12/35. The time-to-event functions (OS and PFS) will be estimated by the Kaplan-Meier product-limit method. Subgroup analyses on primary efficacy parameter (CRR) will be performed to assess the role of daratumumab maintenance and to explore potential prognostic role of CD38 expression. A logistic regression model will be used and the effect (CRR) and its 95%CI will be presented. For safety analysis, both at patient level and at therapy cycle level, summaries of incidence rates (frequencies and percentages) and intensity of individual adverse events by CTCAE v. 5.0 will be reported. The results of this study will support the rationale of a phase III randomized trial if both efficacy and safety endpoints will be considered promising.

5. LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

ABBREVIATION	TERM
AE	Adverse Event
AITL	Angioimmunoblastic T cell lymphoma
ALC	Absolute Lymphocyte Count
ALCL	Anaplastic Large Cell Lymphoma
ALT	Alanine Transaminase
ANC	Absolute neutrophil count
AST	Aspartate Transaminase
BSA	Body Surface Area
CNS	Central Nervous System
CR	Complete Response
CrCl	Creatinine Clearance
CRF	Case Report Form
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTCL	Cutaneous T-cell Lymphoma
D	Daratumumab
DNA	Deoxyribonucleic acid
DoR	Duration of Remission
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOR	End of treatment Response
ESR	Erythrocyte Sedimentation Rate
FIL	Fondazione Italiana Linfomi
FPFV	First Patient First Visit
GCP	Good Clinical Practice
GDP	Gemcitabine, Dexamethasone, Cisplatin
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
ICH	Immunohistochemical
IP	Investigational Product
LDH	Lactic Dehydrogenase
LPFV	Last patient Fist Visit
LPLV	Last patient Last Visit
LVEF	Left Ventricular Ejection Fraction
MF	Mycosis Fungoides
MRI	Magnetic Resonance Imaging
NHL	Non-Hodgkin’s Lymphoma
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PET	18F-FDG Positron Emission Tomography
PFS	Progression Free Survival
PR	Partial Response

ABBREVIATION	TERM
PS	Performance Status
PTCL	Peripheral T Cell Lymphoma
PTCL-NOS	PTCL-not otherwise specified
R/R	Relapse or Refractory
SAE	Serious Adverse Event
SD	Stable Disease
SUSAR	Suspected Unexpected Serious Adverse Reaction
TFH	T-cell lymphomas of T-follicular helper origin
TLS	Tumor Lysis Syndrome
TTR	Time To Response
ULN	Upper Limit of Normal
WOCBP	Women of childbearing potential

6. STUDY FLOW CHART



[a] Responsive Pts (CR, PR), if eligible, will be addressed to allo-SCT after cycle 4/6

[b] After cycle 4, Pts in PR not eligible to allo-SCT or in SD can receive 2 additional cycles of D-GPD or be addressed directly to maintenance

7. BACKGROUND

7.1. OVERVIEW OF PERIPHERAL T-CELL LYMPHOMAS

Peripheral T-cell lymphomas (PTCLs) are rare aggressive lymphomas, accounting for 5-10% of all non-Hodgkin's lymphomas in western countries. They arise from the proliferation of mature post-thymic lymphocytes and comprise different histologic subtypes among whom the most frequent in western countries are: peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL) and other nodal T-cell lymphomas of T-follicular helper origin (TFH), anaplastic large cell lymphoma (ALCL) ALK-positive (ALCL-ALK+) and ALK-negative (ALCL-ALK-) [1]. These different histologic subtypes, with the exception of ALCL-ALK+, share an aggressive clinical behavior and a poor prognosis. Response to induction chemotherapy is often inadequate and/or short-living. Nearly 50% of patients relapse or progress within one year from first-line therapy (CHOP or CHOEP). High-dose chemotherapy followed by autologous stem cell rescue is an option for younger patients, but many of them eventually relapse after transplant. The prognosis of relapsed refractory (R/R) patients is dismal, with an expected survival of less than one year. There is no standard of care in R/R patients [2, 3]. Gemcitabine-based regimens are frequently used in R/R patients, with overall response rate (ORR) ranging from 30 to 70% and a median progression-free survival (PFS) ranging from 4 to 11 months [4–6]. During the last few years, many efforts have been made to find new agents and therapeutic approaches for PTCLs. Unfortunately, with the exception of brentuximab-vedotin that showed remarkable activity in cutaneous T-cell lymphomas and ALCLs [7, 8], the results achieved with other agents are much less impressive. The two HDAC inhibitors romidepsin and belinostat as well as the antimetabolite pralatrexate, approved by FDA for the treatment of R/R PTCLs, showed nearly 30% ORR with median PFS of only few months [9–12].

Recent advances in the understanding the biology of PTCLs have been made, leading to the identification of BCL2, CD38 and PD-1 as potential therapeutic targets. A recent FIL study found that CD38 is expressed in 20/25 of AITL (80%) with variable scores; in particular 12 of the 24 positive cases (50%) resulted to be score 3 (percentage of positive tumor cells 50-75%) or 4 (percentage of positive tumor cells >75%). Fifty-seven % of PTCLs-NOS were CD38 positive, also in this case with variable numbers of stained tumor cells and a level of score 3-4 positivity that overall appeared to be less than that of AITL (7/20, 35%). The probability of CD38 positivity in ALCLs was on the contrary very low, resulting 6/36 (17%) and 0/10 of evaluable cases of ALK- and ALK+ ALCLs, respectively [13].

7.2. CURRENT THERAPIES FOR RELAPSED REFRACTORY PTCLS

Several novel agents have been evaluated in single-arm phase I and II studies in patients with relapsed/refractory disease including: immunoconjugates, immunotherapies, and immunomodulators; histone deacetylase (HDAC) inhibitors; antifolates; fusion proteins and nucleoside analogs. The efficacy of these agents is reported in the Table 1 below (adapted from a review by Coiffier et al [3]).

Table 1. Current therapies for R/R PTCLs

Drug/regimen	N. of patients	Type of patients	ORR%	Median DoR (months)	Median PFS (months)
Alemtuzumab	14	PTCL	36	NR	NR
	10	PTCL-NOS and MF	60	7	NR
Alisertib	48	NHL (including PTCL)	27	NR	NR

Table 1. ***(cont.)***

Belinostat	120	PTCL	26	8.3	NR
Bendamustine	60	PTCL and CTCL	50	3.5	3.6
Bortezomib	12	PTCL and CTCL	67	NR	NR
Denileukin diftitox	27	PTCL	48	NR	6
Gemcitabine	13	PTCL NOS and MF	69	NR	NR
	10	PTCL NOS and CTCL	60	13.5	NR
	39	PTCL-NOS and MF	51	NR	NR
Lenalidomide	23	PTCL	30	NR	3.2
	10	PTCL NOS	30	NR	NR
Mogamulizumab	37	CCR4+ PTCL/CTCL	35	NR	3.0
Pentostatin	37	NHL (including PTCL)	13	8	NR
	44	T-cell leukemias/lymphomas	55	4.3	2.1
	14	T-cell NHL	50	NR	6
Plitidepsin	29	PTCL	21	2.2	1.6
Pralatrexate	29	T-cell NHL	54	NR	NR
	109	PTCL	29	10.1	3.5
Romidepsin	45	PTCL and CTCL	38	8.9	NR
	130	PTCL	25	28	4
Tipifarnib	93	NHL (including PTCL)	20 (50 in PTCL NOS)	7.5	NR
Zanolizumab	21	PTCL	24	NR	NR

7.3. STUDY DRUG BACKGROUND: DARATUMUMAB

7.3.1. Mechanism of action

CD38 is a transmembrane glycoprotein (48 kDa) expressed on the surface of hematopoietic cells, including multiple myeloma and other hematopoietic cell types and tissues [14, 15] and has multiple functions, such as receptor mediated adhesion, signaling, and modulation of cyclase and hydrolase activity. Daratumumab is an IgG1κ human monoclonal antibody that binds CD38-expressing malignant cells with high affinity and has direct and indirect antitumor activity and diverse mechanisms of action, including: induction of apoptosis; immune-mediated actions, including complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP); and immunomodulatory functions that target and deplete CD38-positive regulator immune suppressor cells, which leads to T-cell expansion and activation in patients who have a response [16–20].

7.4. PRECLINICAL STUDIES

7.4.1. Pharmacodynamics

Daratumumab has been shown to potently inhibit the in vivo growth of CD38-expressing tumor cells. Based on in vitro studies, daratumumab may utilize multiple effector functions, resulting in immune mediated tumor cell death. These studies suggest that daratumumab can induce tumor cell lysis through complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and antibody-dependent cellular phagocytosis in malignancies expressing CD38. A subset of myeloid derived suppressor cells (CD38+MDSCs), regulatory T cells (CD38+Tregs) and B cells (CD38+Bregs) are decreased by daratumumab mediated cell lysis. T cells (CD3+, CD4+, and CD8+) are also known to express CD38 depending on the stage of development and the level of activation. Significant increases in CD4+ and CD8+ T cell absolute counts, and percentages of lymphocytes, were observed with daratumumab treatment in peripheral whole blood and bone marrow. In addition, T-cell receptor DNA sequencing verified that T-cell clonality was increased with daratumumab treatment, indicating immune modulatory effects that may contribute to clinical response.
Daratumumab induced apoptosis in vitro after Fc mediated cross-linking. In addition, daratumumab modulated CD38 enzymatic activity, inhibiting the cyclase enzyme activity and stimulating the hydrolase activity. The significance of these in vitro effects in a clinical setting, and the implications on tumor growth, are not well-understood.

A recent preclinical experience with daratumumab in a large panel of T-ALL patient-derived xenografts (PDX) [21]demonstrated striking efficacy of the drug in 14/15 different PDX. These results demonstrated that CD38 is a novel target with broad potential, and daratumumab is a promising novel therapy in the treatment of T-ALL.

7.4.2. Non-clinical toxicology: Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or genotoxicity studies have been conducted with daratumumab. No animal studies have been performed to evaluate the potential effects of daratumumab on reproduction or development, or to determine potential effects on fertility in males or females

7.4.3. Animal Toxicology

Toxicology data have been derived from studies with daratumumab in chimpanzees and with a surrogate anti-CD38 antibody in cynomolgus monkeys. No chronic toxicity testing has been conducted.

7.5. CLINICAL PHARMACOLOGY

7.5.1. Pharmacodynamics

NK cells express CD38 and are susceptible to daratumumab mediated cell lysis. Decreases in absolute counts and percentages of total NK cells (CD16+CD56+) and activated (CD16+CD56dim) NK cells in peripheral whole blood and bone marrow were observed with daratumumab treatment.

7.5.2. Pharmacokinetics

Over the dose range from 1 to 24 mg/kg as monotherapy or 1 to 16 mg/kg of DARZALEX® in combination with other treatments, increases in area under the concentration-time curve (AUC) were more than dose-proportional.
Following the recommended dose of 16 mg/kg when daratumumab was administered as monotherapy or in combination therapy, the mean serum maximal concentration (Cmax) value at the end of weekly dosing, was approximately 2.7 to 3-fold higher compared to the mean serum Cmax following the first dose. The mean ± standard deviation (SD) trough serum concentration (Cmin) at the end of weekly dosing was 573

± 332 µg/mL when daratumumab was administered as monotherapy and 502 ± 196 to 607 ± 231 µg/mL when daratumumab was administered as combination therapy. When daratumumab was administered as monotherapy, daratumumab steady state was achieved approximately 5 months into the every 4-week dosing period (by the 21st infusion), and the mean ± SD ratio of Cmax at steady-state to Cmax after the first dose was 1.6 ± 0.5.

7.5.2.1. Distribution

At the recommended dose of 16 mg/kg, the mean ± SD central volume of distribution was 4.7 ± 1.3 L when daratumumab was administered as monotherapy and 4.4 ± 1.5 L when daratumumab was administered as combination therapy.

7.5.2.2. Elimination

Daratumumab clearance decreased with increasing dose and with multiple dosing. At the recommended dose of 16 mg/kg of daratumumab as monotherapy, the mean ± SD linear clearance was estimated to be 171.4 ± 95.3 mL/day. The mean ± SD estimated terminal half-life associated with linear clearance was 18 ± 9 days when daratumumab administered as monotherapy and a mean of 22-23 days when daratumumab was administered as combination therapy.

7.5.2.3. Special populations

The following population characteristics have no clinically meaningful effect on the pharmacokinetics of daratumumab in patients administered with drug as monotherapy or as combination therapy: sex, age (31 to 93 years), mild [total bilirubin 1 to 1.5 times upper limit of normal (ULN) or aspartate aminotransaminase (AST)>ULN] and moderate (total bilirubin 1.5 to 3 times ULN and any AST) hepatic impairment, or renal impairment [Creatinine clearance (CrCl) 15 -89 mL/min]. The effect of severe (total bilirubin >3 times ULN and any AST) hepatic impairment is unknown. Increasing body weight increased the central volume of distribution and clearance of daratumumab, supporting the body weight-based dosing regimen.

7.5.2.4. Drug Interactions

Effect of Other Drugs on Daratumumab

The coadministration of lenalidomide, pomalidomide or bortezomib with daratumumab did not affect the pharmacokinetics of daratumumab.

Effect of Daratumumab on Other Drugs

The coadministration of daratumumab with bortezomib or pomalidomide did not affect the pharmacokinetics of bortezomib or pomalidomide.

7.6. CLINICAL TRIALS

7.6.1. Relapsed/Refractory Multiple Myeloma

Two trials scheduling the administration of daratumumab monotherapy were conducted on relapsed/refractory heavily pretreated multiple myeloma (MM) patients, both showing encouraging efficacy with a favorable safety profile in this population of patients.

The SIRIUS trial evaluated daratumumab monotherapy at a dosage of 16 mg/Kg per week for 8 weeks (cycles 1 and 2), then every 2 weeks for 16 weeks (cycles 3-6), and then every 4 weeks thereafter (cycle 7 and higher, until unacceptable toxicity or disease progression) in a cohort of 106 multiple myeloma patients who were previously treated with at least three lines of therapy (including proteasome inhibitors and immunomodulatory drugs), or were refractory to both proteasome inhibitors and immunomodulatory drugs [22]. Patients had received a median of 5 prior lines of therapy, and 85 (80%) patients had previously received autologous stem cell transplantation (ASCT). Overall response rate (partial response [PR] + very good PR [VGPR]+ complete response [CR] + stringent CR [sCR]) was recorded in 31 (29.2%) of patients (sCR: 3, 2.8%; CR:0; VGPR: 10, 9.4%; PR: 18, 17.0%).

The study GEN501 population consisted of relapsed or refractory MM patients who had received at least 2 different prior cytoreductive therapies [23]. Forty-two patients received 16 mg/Kg once weekly (8 doses),

twice monthly (8 doses), and monthly for up to 24 months, or until unacceptable toxicity or disease progression). Patients had received a median of 5 prior lines of therapy, in 74% of them including ASCT. The overall response rate was 36%: 15 patients had a partial response or better, including 2 with a complete response and 2 with a very good partial response). The median progression-free survival was 5.6 months (95% confidence interval [CI], 4.2 to 8.1), and 65% (95% CI, 28 to 86) of the patients who had a response did not have progression at 12 months. The median duration of response was not estimable (range: 2.2 to 13.1+ months).

Two phase III randomized trials comparing two different background therapies +/- daratumumab were conducted almost contemporaneously and published in 2016.

The POLLUX phase III trial compared treatment with daratumumab 16 mg/kg in combination with lenalidomide (25 mg once daily orally on Days 1-21 of repeated 28-day cycles) and low-dose dexamethasone (oral or intravenous dexamethasone 40 mg/week) (DRd) to treatment with lenalidomide and low-dose dexamethasone (Rd) at the same doses in patients with multiple myeloma who had received at least one prior therapy [24]. Treatment was continued in both arms until disease progression or unacceptable toxicity. A total of 569 patients were randomized; 286 to the DRd arm and 283 to the Rd arm. Patients had received a median of 1 prior line of therapy. Sixty-three percent (63%) of patients had received prior ASCT. The majority of patients (86%) received a prior proteasome inhibitor, 55% of patients had received a prior immunomodulatory agent, including 18% of patients who had received prior lenalidomide; and 44% of patients had received both a prior proteasome inhibitor and immunomodulatory agent. Overall response rate (partial response [PR] + very good PR [VGPR]+ complete response [CR] + stringent CR [sCR]) was 91.3% and 74.6% in the DRd and Rd arm, respectively (P<0.0001), with sCR, CR, VGPR and PR of 17.8%, 24.5%, 32.2%, 16.8% and 7.1%, 11.7%, 24.4%, 31.4% in DRd and Rd arm, respectively. POLLUX demonstrated an improvement in PFS in the DRd arm as compared to the Rd arm; the median PFS had not been reached in the DRd arm and was 18.4 months in the Rd arm (hazard ratio [HR]=0.37; 95% CI: 0.27, 0.52; p<0.0001), representing 63% reduction in the risk of disease progression or death in patients treated with DRd. The median duration of response had not been reached in the DRd group (range: 1+ to 19.8+ months) and was 17.4 months (range: 1.4 to 18.5+ months) in the Rd group. With a median follow-up of 13.5 months, 75 deaths were observed; 30 in the DRd group and 45 in the Rd group [24].

The CASTOR phase III trial compared treatment with daratumumab 16 mg/kg in combination with bortezomib and dexamethasone (DVd), to treatment with bortezomib and dexamethasone (Vd) in patients with multiple myeloma who had received at least one prior therapy [25]. Bortezomib was administered by SC injection or IV infusion at a dose of 1.3 mg/m^2 body surface area twice weekly for two weeks (Days 1, 4, 8, and 11) of repeated 21-day treatment cycles, for a total of 8 cycles. Dexamethasone was administered orally at a dose of 20 mg on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each of the 8 bortezomib cycles (80 mg/week for two out of three weeks of the bortezomib cycle). Bortezomib and dexamethasone were given for 8 three-week cycles in both treatment arms; whereas daratumumab was given until disease progression. A total of 498 patients were randomized; 251 to the DVd arm and 247 to the Vd arm. Patients had received a median of 2 prior lines of therapy and 61% of patients had received prior ASCT. Sixty-nine percent (69%) of patients had received a prior proteasome inhibitor (66% received bortezomib) and 76% of patients received an immunomodulatory agent (42% received lenalidomide). Overall response rate (partial response [PR] + very good PR [VGPR]+ complete response [CR] + stringent CR [sCR]) was 79.3% and 59.9% in the DVd and Vd arm, respectively (P<0.0001), with sCR, CR, VGPR and PR of 4.4%, 13.9%, 38.2%, 22.7% and 2.0%, 6.5%, 19.0%, 32.4% in DVd and Vd arm, respectively. CASTOR demonstrated an improvement in PFS in the DVd arm as compared to the Vd arm; the median PFS had not been reached in the DVd arm and was 7.2 months in the Vd arm (HR [95% CI]: 0.39 [0.28, 0.53]; p-

value < 0.0001), representing a 61% reduction in the risk of disease progression or death for patients treated with DVd versus Vd. The median duration of response had not been reached in the DVd group (range: 1.4+ to 14.1+ months) and was 7.9 months (1.4+ to 12+ months) in the Vd group. With a median follow-up of 7.4 months, 65 deaths were observed; 29 in the DVd group and 36 in the Vd group were observed [25].

Finally, EQUULEUS was an open-label trial in which 103 patients with multiple myeloma who had received a prior proteasome inhibitor and an immunomodulatory agent, received 16 mg/kg daratumumab in combination with pomalidomide and low-dose dexamethasone until disease progression [26]. Pomalidomide (4 mg once daily orally on Days 1-21 of repeated 28-day cycles) was given with low dose oral or intravenous dexamethasone 40 mg/ week. Patients in the study had received a median of 4 prior lines of therapy. Seventy-four percent (74%) of patients had received prior ASCT. Ninety-eight percent (98%) of patients received prior bortezomib treatment, and 33% of patients received prior carfilzomib. All patients received prior lenalidomide treatment, with 98% of patients previously treated with the combination of bortezomib and lenalidomide. Efficacy results shown an overall response rate of 59.2%: sCR: 7.8%; CR:5.8%; VGPR: 28.2%; PR: 17.5%). The median duration of response was 13.6 months (range: 0.9+ to 14.6+ months).

7.6.2. Newly Diagnosed Multiple Myeloma

Few months ago, the results of the first trial testing daratumumab for the front-line treatment of MM was published. The phase III study ALCYONE compared treatment with daratumumab 16 mg/kg in combination with bortezomib, melphalan and prednisone (D-VMP), to treatment with VMP in patients with newly diagnosed multiple myeloma [27]. Bortezomib was administered by subcutaneous (SC) injection at a dose of 1.3 mg/m2 body surface area twice weekly at Weeks 1, 2, 4 and 5 for the first 6-week cycle (Cycle 1; 8 doses), followed by once weekly administrations at Weeks 1, 2, 4 and 5 for eight more 6-week cycles (Cycles 2-9; 4 doses per cycle). Melphalan at 9 mg/m2, and prednisone at 60 mg/m2 were orally administered on Days 1 to 4 of the nine 6-week cycles (Cycles 1-9). Daratumumab treatment was continued until disease progression or unacceptable toxicity. A total of 706 patients were randomized: 350 to the D-VMP arm and 356 to the VMP arm. Overall response rate was 90.9% and 73.9% in the D-VMP and VMP arm, respectively (P<0.0001), with sCR, CR, VGPR and PR of 18.0%, 24.6%, 28.6%, 19.7% and 7.0%, 17.4%, 25.3%, 24.2% in D-VMP and VMP arm, respectively. The MRD negativity rate was also assed, resulting 22.3% in D-VMP and 6.2% in VMP arm, respectively (P<0.0001). ALCYONE demonstrated an improvement in PFS in the D-VMP arm as compared to the VMP arm; the median PFS had not been reached in the D-VMP arm and was 18.1 months (95% CI:16.53, 19.91) in the VMP arm (hazard ratio [HR]=0.5; 95% CI: 0.38, 0.65; p<0.0001), representing 50% reduction in the risk of disease progression or death in patients treated with D-VMP The median duration of response had not been reached in the D-VMP group and was 21.3 months (range: 0.5+, 23.7+) in the VMP group [27].

7.6.3. Clinical Activity in other hematological malignancies

Expression of CD38 has been associated with a number of diseases. Most notably, CD38 is expressed in a large number of hematological malignancies. In addition to MM, consistent expression has been observed the malignant cells of CLL [28, 29], and was also reported in Waldenström's macroglobulinemia [30], mantle cell lymphoma [31], acute lymphoblastic leukemia [32], acute myeloid leukemia [32, 33], NK cell leukemia [34] and NK/T-cell lymphoma [21, 35, 36].

The expression of CD38 as a target-molecules has not been extensively investigated in PTCLs, limiting the possible use of targeted therapies in these lymphoid tumors. A study by Wang et al on 94 patients diagnosed with Extranodal NK/T-cell lymphoma (ENKTL) taken from the database of Sun Yat-sen University Cancer Center of China and treated with chemo/radiotherapy from Jan 2002 to Dec 2013,

reported a strong CD38 expression in this subset of extranodal PTCL (47 patients, 50%), and demonstrated a poor prognosis for strong CD38 expressor patients (Progression-free survival: HR=2.535 with 95%CI:1.258–5.109, *P= 0.009*), thus indicating the potential role of CD38 as a therapy target [35]. Hari and coworkers [36] published a case report of a 56-year old woman with stage IE nasal-type ENKTL at diagnosis who was heavily pretreated (5 lines, including allo-SCT) due to extensive relapsed, refractory disease and who then received off-label therapy with daratumumab at a dose of 16 mg/Kg/week achieving a CR after 6 weeks of treatment, reconfirmed at 21 weeks of follow-up.
A recent FIL study [13] found that CD38 is expressed in 20/25 of AITL (80%) with variable scores; in particular 7 of the 20 positive cases (35%) resulted to be score 3 (percentage of positive tumor cells 50-75%) or 4 (percentage of positive tumor cells >75%). Fifty-seven % of PTCL-NOS were CD38 positive, also in this case with variable numbers of stained tumor cells and a level of score 3-4 positivity of 12/24 (50%). The probability of CD38 positivity in ALCLs was on the contrary very low, resulting 6/36 (17%) and 0/10 of evaluable cases of ALK- and ALK+ ALCLs, respectively [13]. Actually, 9 cases classified by the study as PTCL-NOS according to the WHO 2008, would have been identified as nodal T-cell lymphomas with TFH phenotype according to the WHO 2016, indicating that also these entities express CD38.

8. STUDY RATIONALE

Patients with relapsed/refractory PTCLs have a dismal prognosis. With available treatments, responses are short-living and overall survival is usually less than one year. New treatment options are therefore urgently needed. Recent insights into the biology of PTCLs have provided the basis for the use of targeted therapies in this setting. In particular, the discovery that CD38 is over-expressed in the majority of patients with PTCL-NOS, AITL and nodal lymphomas of TFH origin makes CD38 a suitable therapeutic target.
Aim of this study is to evaluate if the addition of Daratumumab to an induction Gemcitabine-Dexamethasone-Cisplatin regimen (GDP) followed by a maintenance therapy with Daratumumab could represent a novel salvage treatment for patients with R/R CD38 positive PTCL-NOS, AITL and nodal lymphoma of TFH origin.

The rationale of this study is based on:

- the activity daratumumab has been demonstrated in multiple myeloma and, occasionally, in some other hematological disorders including T-cell neoplasia [21, 36]
- the safety profile of daratumumab is good
- daratumumab has been safely and effectively combined with other cytotoxic agents in multiple myeloma
- CD38 is expressed in a significant proportion of PTCL-NOS, AITL and nodal lymphomas of TFH origin
- the good results observed in previous studies in NHL when a monoclonal antibody was combined to standard chemotherapy
- the choice of GDP was made because this regimen has been extensively adopted as salvage therapy for R/R PTCL [6, 37–48] and therefore the results of this study will be compared to historical GDP controls.

9. STUDY OBJECTIVES

9.1. PRIMARY OBJECTIVE

The primary objective of the study is to evaluate the efficacy of 4 courses of D-GDP in terms of complete response in PTCL-NOS, AILT and TFH phenotype patients, refractory and/or relapsed after at least one and a maximum of two lines of previous therapy (autologous stem cell transplant performed as part of consolidation to a previous line of therapy should not be considered as a line of therapy).

9.2. SECONDARY OBJECTIVES

- To evaluate the Overall Response Rate (ORR);
- To evaluate the efficacy in terms of Overall survival (OS);
- To evaluate the efficacy in terms of Progression-free survival (PFS);
- To evaluate the safety of D-GDP.

9.3. EXPLORATIVE OBJECTIVES

- To assess the role of daratumumab maintenance;
- To evaluate the correlation between intensity of CD38 expression and response.

10. STUDY DESIGN

10.1. OVERVIEW OF STUDY DESIGN

This is an open-label, multicenter, single arm, single-stage phase II trial in patients aged 18-75 years, with refractory/relapsed CD38 positive PTCL-NOS, AITL and other nodal lymphomas of TFH cell origin.

During the screening (within 4 weeks before treatment start) the central diagnosis review and evaluation of CD38 expression are to be done in concomitance with other planned procedures. The patient will be asked to give his/her consent prior to centralize the material collected and used for local diagnosis of refractory/relapsed PTCL-NOS, AITL or TFH lymphoma to the FIL central designated laboratory.
The material that will be used for central diagnosis confirmation and evaluation in immunohistochemistry of CD38 expression is that coming from the relapse biopsy or from the more recent biopsy in the case of refractory patients: this is a preclusive procedure to confirm patients are eligible to receive the experimental treatment including daratumumab (see *Appendix E* for details).
Only patients with confirmed diagnosis of PTCL-NOS, AITL or TFH lymphoma and a percentage of CD38 positive tumor cells ≥ 5% will be included onto the study. A core needle biopsy is considered sufficient for central evaluations. Tests at central laboratory can be carried out in bone marrow sections in those patients with only bone marrow lymphoma infiltration.

The treatment phase consists of an induction phase and a maintenance phase.
After 4 courses of D-GDP, patients in CR/PR eligible for allo-SCT will be addressed to allo-SCT consolidation.
Otherwise, patients in CR will enter the maintenance phase at this point of the study.
Patients in PR (not eligible for allo-SCT) or in SD after D-GDP x 4 can receive 2 additional courses of D-GDP before maintenance or can move directly to maintenance, according to center choice (based on patient condition, performance status and quality of response).
Patients who respond (CR, PR) after 6 courses of induction phase (end of induction, EOI) and eligible to allo-SCT will be addressed to allo-SCT consolidation.
Patients in PD at any time will discontinue treatment, as well as patients experiencing at any time unacceptable toxicity.

Procedures to be performed during the study are summarized on schedule of assessment (see *Chapter 15, "Study procedures timepoints"*).

10.2. NUMBER OF PATIENTS

A total of 35 patients satisfying the inclusion criteria will be enrolled in the study, will receive the experimental treatment and will be evaluated for the study endpoints. Patients that after the screening will have no confirmation of diagnosis of PTCL-NOS, AITL or TFH phenotype, and those with CD38 expression < 5% will be considered screening failures.

10.3. DURATION OF THE STUDY

Patients will be recruited over 18 months.
The median expected duration of the treatment period is approximately: 6 months on an average (for induction + maintenance). Last patient followed for final analysis: 24 months from the start of treatment.
End of study is defined by the last visit planned by the protocol 24 months after the start of treatment of the last patient (LPLV), that means approximately 42 months (3.5 years) after the study start.
The Final Study Report will be provided after the end of the Study.

11. STUDY POPULATION

11.1. INCLUSION CRITERIA

- Histologically documented diagnosis of CD38 positive PTCL-NOS, AITL, and other nodal lymphomas of TFH cell origin as defined in the 2017 edition of the World Health Organization (WHO) classification [1]. Only patients with percentage of CD38 positive tumor cells ≥ 5% in the relapse biopsy or in the more recent biopsy in the case of refractory patients will be included onto the study (a core needle biopsy is considered sufficient for CD38 evaluation); CD38 can be evaluated in bone marrow sections in those patients with bone marrow lymphoma infiltration
- Age 18-75 years
- Relapsed or refractory to at least one and a maximum of two previous lines of treatment
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2
- At least one site of measurable nodal disease at baseline ≥ 2.0 cm in the longest transverse diameter as determined by CT scan (MRI is allowed only if CT scan cannot be performed). Note: Patients with only bone marrow involvement are eligible
- Adequate hematological counts defined as follows:
  - Absolute Neutrophil count (ANC) > 1.0 x 10^9/L unless due to bone marrow involvement by lymphoma
  - Platelet count ≥ 50.000/mm^3 unless due to bone marrow involvement by lymphoma
- Adequate renal function defined as follows:
  - Creatinine clearance ≥ 40 mL/min (Cockcroft–Gault formula)
- Adequate hepatic function per local laboratory reference range as follows:
  - Aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 3.0 x ULN
  - Bilirubin ≤1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin)
- Subject understands and voluntarily signs an informed consent form approved by an Independent Ethics Committee (IEC), prior to the initiation of any screening or study-specific procedures
- Subject must be able to adhere to the study visit schedule and other protocol requirements

- Life expectancy ≥ 3 months
- Women must be:
  - postmenopausal for at least 1 year (must not have had a natural menses for at least 12 months)
  - surgically sterile (have had a hysterectomy or bilateral oophorectomy, tubal ligation, or otherwise be incapable of pregnancy),
  - completely abstinent (periodic abstinence from intercourse is not permitted) or if sexually active, be practicing two highly effective methods of birth control (e.g., prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, double barrier method (e.g.: condoms, diaphragm, or cervical cap, with spermicidal foam, cream, or gel, male partner sterilization) as local regulations permit, before entry, and must agree to continue to use the same method of contraception throughout the study. They must also be pre-pared to continue birth control measures for at least 3 months after terminating treatment.
  - Women of childbearing potential must have a negative pregnancy test at screening
- Men must agree to use an acceptable method of contraception (fort them-selves or female partners as listed above) for the duration of the study. Men must agree to use a double barrier method of birth control and to not donate sperm during the study and for 3 months after receiving the last dose of study drug.
- Male even if surgically sterilized (i.e., status post vasectomy) must agree to one of the following:
  - practice effective barrier contraception during the entire study treatment period and through 3 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, post ovulation methods for the female partner] and withdrawal are not acceptable methods of contraception)

11.2. EXCLUSION CRITERIA

- Histological diagnosis different from CD38 positive PTCL-NOS, AITL, and other nodal lymphomas of TFH cell origin
- More than two lines of previous treatment (autologous stem cell transplant performed as part of consolidation to a previous line of therapy should not be considered as a line of therapy)
- Previous treatment with Gemcitabine or Platinum based regimens; patients who received a single course of Platinum based course (i.e. DHAP) are not excluded
- Prior therapy with monoclonal antibody antiCD38
- Concomitant experimental therapy
- Relapse after allo-SCT
- CNS involvement with lymphoma
- Subject has received any anti-cancer therapy including chemotherapy, immunotherapy, radiotherapy, investigational therapy, including targeted small molecule agents within 14 days prior to the first dose of study drug
- Chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) requiring treatment
- Subject is:
  - Known to be seropositive for human immunodeficiency virus (HIV)
  - Seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]). Subjects with resolved infection (i.e., subjects who are HBsAg negative but positive for

antibodies to hepatitis B core antigen [anti-HBc] ± antibodies to hepatitis B surface antigen [anti-HBs]) must be screened using real-time polymerase chain reaction (PCR) measurement of hepatitis B virus (HBV) DNA levels. Those who are PCR positive will be excluded. EXCEPTION: Subjects with serologic findings suggestive of HBV vaccination (anti-HBs positivity as the only serologic marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV DNA by PCR.

  - Known to be seropositive for hepatitis C (except in the setting of a sustained virologic response [SVR], defined as aviremia at least 12 weeks after completion of antiviral therapy).
- Cardiovascular disease (NYHA class ≥2)
- Creatinine Clearance < 40 mL/min (Cockcroft–Gault formula)
- Significant history of neurologic, psychiatric, endocrinological, metabolic, immunologic, or hepatic disease that would preclude participation in the study or compromise ability to give informed consent
- Any history of other active malignancies within 3 years prior to study entry, with the exception of adequately treated in situ carcinoma of the cervix uterine, basal cell carcinoma of the skin or localized squamous cell carcinoma of the skin, previous malignancy confined and surgically resected with curative intent
- Uncontrolled and/or active systemic infection (viral, bacterial or fungal)
- Evidence of any other clinically significant uncontrolled condition(s)
- If female, the patient is pregnant or breast-feeding

12. PATIENTS ENROLLMENT

12.1. INFORMED CONSENT

The Investigator(s) must obtain informed consent of a patient 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 their disease. Subjects will be told that alternative treatments are available if they refuse to take part in the study and that such refusal will not prejudice future treatment. The subject 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 the subject's dated signature. After having obtained the consent, a copy of the informed consent form must be given to the subject.

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 local diagnosis of refractory/relapsed PTCL-NOS, AITL or TFH, check of inclusion/exclusion criteria and written informed consent signature, patients should be registered online at www.filinf.it, in the

study dedicated section. An email of confirmation will be sent to the local investigator, to coordinating investigator of the study and to the FIL Trial office staff. If the patient is confirmed with a diagnosis eligible for the study and with CD38 tumor expression ≥ 5%, the information will be promptly provided to the local investigator and the protocol treatment can be started. All CRFs for patient's registration and data collection could be reached in the restricted area of the FIL website by authorized users.

13. TREATMENT

13.1. TREATMENT SCHEDULE AND DESIGN

13.1.1. Pre- and Post- infusion Medications

Pre- and post- daratumumab infusion medications should be instituted as needed (see *paragraph 13.3.1 "Recommended concomitant medications")*.

13.1.2. Treatment during induction phase

GDP will be prepared and administered according to the standard preparation and infusion procedures at each investigational site.
Daratumumab (D): will be given intravenously (i.v.) at a dose of 8 mg/Kg on day 2 and 9 of cycle 1; from cycle 2 it will be given at a dose of 16 mg/Kg on day 2 and 9 of each cycle.

Induction phase:
4-6 courses (according to response after cycle 4 and patient compliance) of D-GDP every 21 days according to the following schedule:

Cycle 1		**Q21 days**
Daratumumab	8 mg/Kg i.v.	days 2 and 9
Gemcitabine	1000 mg/m^2, i.v.	days 1 and 8
Cisplatin	75 mg/m^2, i.v.	day 1
Dexamethasone	40 mg/day, i.v. or po	days 1-2-3-4-9

Gemcitabine at day 8 skipped in case of grade 3-4 toxicity

G-CSF support should be given from day 3 to 6, and from day 10 to 13 (to be prolonged if necessary).

Cycles 2-4/6		**Q21 days**
Daratumumab	16 mg/Kg i.v.	days 2 and 9
Gemcitabine	1000 mg/m^2, i.v.	days 1 and 8
Cisplatin	75 mg/m^2, i.v.	day 1
Dexamethasone	40 mg/day, i.v. or po	days 1-2-3-4-9

Gemcitabine at day 8 skipped in case of grade 3-4 toxicity

G-CSF support should be given from day 3 to 6, and from day 10 to 13 (to be prolonged if necessary).

Patients in CR/PR after 4/6 cycles of D-GDP will be shift to allo-SCT, if eligible. Patients not eligible to transplant or achieving at least a SD after induction will receive maintenance.

13.1.3. Treatment during maintenance phase

Maintenance phase will start 28 days after the beginning of cycle 4 or 6 (or, in case of toxicity grade > 1, after toxicity is resolved) and up to 24 cycles from start of D-GDP according to the following schedule:

Maintenance schedule		**Q28 days**
Daratumumab	16 mg/Kg i.v.	single administration on day 1

Treatment will be continued up to 24 cycles from start of D-GDP.

13.1.4. Treatment discontinuation

Treatment with D-GDP or daratumumab single agent will be discontinued in case of:

- decision of the investigator to consolidate D-GDP response with allogeneic stem cell transplant
- disease progression
- unacceptable toxicity
- withdrawal of consent
- investigator determines that further therapy is not in the patient's best interest (e.g., due to non-compliance, toxicity, etc.)

13.2. DARATUMUMAB

13.2.1. Supplier

DARZALEX® (daratumumab) will be supplied by Janssen as 100 mg (5 ml) or 400 mg (20 ml) vials (20 mg/ml concentrate for solution for infusion to be diluted prior to administration). Study drug will be supplied by Janssen to the Sponsor for the entire period of the study. The Sponsor will be responsible for sending the drugs to all participating sites. Drugs will be delivered to sites only after having received the registration form and the drug request form, correctly filled and signed by the Investigator.

13.2.2. Dosage form, packaging and labeling

Daratumumab will be administered intravenously (i.v.) in combination with GDP (during the induction phase) or as a single agent (during the maintenance phase).

13.2.3. Receipt of study drug

The Sponsor is responsible for taking an inventory of each shipment of study drug received, and comparing it with the accompanying study drug accountability form. The Sponsor will verify the accuracy of the information on the form, sign and date it, retain a copy in the study file and return a copy to Janssen or its representative.

13.2.4. Storage and handling

At the study site, all investigational study drugs will be stored in a locked, safe area to prevent unauthorized access. The study drug should be stored in a refrigerator (2 °C-8 °C). Do not freeze.
Store in the original package in order to protect from light.
Storage conditions after dilution of the medicinal product: from a microbiological point of view, unless the method of opening/dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and should be no more than 24 hours at refrigerated conditions (2 °C-8 °C) protected from light, followed by 15 hours (including infusion time) at room temperature (15°C - 25°C) and room light.

13.2.5. Unused study drug supplies

The sponsor will inform the investigators on the return or destruction of unused study drug. If any study drug is lost or damaged, its disposition should be documented in the source documents. Study drug supplies will be retained at the clinical site pending instructions for disposition by the sponsor.

13.3. ADMITTED/EXCLUDED CONCOMITANT MEDICATION

13.3.1. Recommended concomitant medications

Steroids

For patients with B symptoms, bulky disease, tumor circulating cells count > 20 x 10^9/L, or if judged of clinical benefit by the treating physician during the screening phase, it is allowed pre-treatment with Prednisone 0.25-0.5 mg/kg/d, to be suspended within the first month of therapy. If clinically indicated a single administration of Vincristine 1 mg before initiating treatment is admitted.

Pre-infusion medication

Pre-infusion medications should be administered to reduce the risk of IRRs to all patients 1-3 hours prior to every infusion of Daratumumab as follows.

- Corticosteroids
  - during induction daratumumab is administered with GDP. Dexamethasone should be administered prior to every daratumumab infusion. Dexamethasone dose (40 mg) could be split to half before and half after daratumumab infusion. Dexamethasone is given intravenously prior to the first daratumumab infusion and oral administration may be considered prior to subsequent infusions.
  - During daratumumab monotherapy maintenance, long-acting or intermediate-acting corticosteroids administration is recommended: methylprednisolone 100 mg, or equivalent, administered intravenously before daratumumab. Following the second infusion, the dose of corticosteroid may be reduced (oral or intravenous methylprednisolone 60 mg);
- Antipyretics (oral paracetamol 650 to 1,000 mg);
- Antihistamine (oral or intravenous diphenhydramine 25 to 50 mg or equivalent).

Post-infusion medications

Post-infusion corticosteroids medication should be administered to reduce the risk of delayed infusion-related reactions.

When daratumumab is administered in monotherapy, oral corticosteroid (20 mg methylprednisolone or equivalent dose of an intermediate-acting or long-acting corticosteroid in accordance with local standards) should be administered on each of the two days following all infusions (beginning the day after the infusion).

Since during induction the background regimen contains dexamethasone, if the steroid is administered the day after the daratumumab infusion, additional post-infusion medications may not be needed. If not, administering low-dose oral methylprednisolone (≤ 20 mg) or equivalent the day after daratumumab infusion may be considered.

Additionally, for patients with a history of chronic obstructive pulmonary disease, the use of post-infusion medications including short and long acting bronchodilators, and inhaled corticosteroids should be considered. Following the first four infusions, if the patient experiences no major IRRs, these inhaled post-infusion medications may be discontinued at the discretion of the physician.

13.3.2. Other concomitant admitted medications

Concomitant therapy includes any prescription medications or over-the-counter preparations used by a patient between the 7 days preceding the baseline evaluations and the end of last study visit.
All concomitant medications should be reported to the investigator and recorded on the appropriate CRF.
The following are supportive therapies that are admitted:

- Omeprazole 20 mg/day orally or equivalent therapy for peptic ulcer;
- 5HT3 antagonists or equivalent anti-emetics;
- Loperamide for the treatment of diarrhea, starting at the time of the first watery stool. The loperamide dose regimen should be according to standard practice;
- Bowel care is recommended to prevent constipation and should be administered per standard practice;
- Platelets and red blood cell transfusion are allowed, if clinically indicated according to local policy;
- Erythropoietin therapy is allowed if clinically indicated according the ASCO guidelines [49].

13.3.3. Excluded medications

Use of the following therapies is **prohibited** during the study:

- Cytotoxic chemotherapy (other than study treatment)
- Other experimental agents
- Immunotherapy
- Hormone therapy (other than hormone-replacement therapy, or megestrol acetate)
- Any therapies intended for the treatment of lymphoma whether European Medicines Agencies (EMA) or US Food and Drug Administration (FDA) approved or experimental (outside of this study).

Patients who require the use of any of these agents will be discontinued from study treatment.
Treatment with other concomitant anti-tumor agents not defined in this protocol as study treatment or other concurrent investigational agents of any type will result in withdrawal of patients from study treatment.

13.4. PROPHYLACTIC MEASURES

13.4.1. Hospitalization during the first cycle of therapy

The first course of D-GDP will be provided as inpatient care, at least until administration of daratumumab on day 2 is completed. Following cycles will be administered as outpatient care.

13.4.2. Prevention of daratumumab infusion-related reactions (IRRs)

Pre-infusion medications should be administered to reduce the risk of infusion-related reactions (IRRs) prior to treatment with daratumumab (see also *paragraph 13.7.3*).
Patients should be pre-medicated with antihistamines, antipyretics and corticosteroids to reduce the risk of IRRs prior to treatment with daratumumab.
To reduce the risk of delayed IRRs, oral corticosteroids should be administered to all patients following daratumumab infusions. Additionally, the use of post-infusion medications (e.g. inhaled corticosteroids, short and long acting bronchodilators) should be considered for patients with a history of chronic obstructive pulmonary disease to manage respiratory complications should they occur (see *paragraph 13.3.1*).
Daratumumab infusion should be interrupted for IRRs of any severity. Medical management/supportive treatment for IRRs should be instituted as needed. The infusion rate should be reduced when re-starting the infusion (see *paragraph 13.7.3*).

13.4.3. Prophylaxis for tumor lysis syndrome (TLS)

For patients with high tumor burden and who are considered by the investigator to be at risk for tumor lysis syndrome, tumor lysis prophylaxis with hydration and uric-acid reducing agents is recommended prior to the initiation of treatment, as per clinical practice. Clinical chemistries should be corrected. Monitor with clinical chemistries and manage promptly, as clinically indicated.

Patients should be well hydrated. Starting 1 or 2 days before the first dose of daratumumab, it is desirable to maintain a fluid intake of approximately 3 L/day. In addition, all patients with high tumor burden considered at risk for tumor lysis syndrome should be treated with 300 mg/day of allopurinol PO or a suitable alternative uric-acid reducing agents treatment starting 48–72 hours prior to Cycle 1, Day 1 of treatment and hydration. Patients should continue to receive repeated prophylaxis with allopurinol and adequate hydration prior to each subsequent infusion, if deemed appropriate by the investigator.

13.4.4. Mandatory primary neutropenia prophylaxis

Primary neutropenia prophylaxis is required during the induction period of the treatment. G-CSF should be used after each D-GDP cycle from day 3 to 6, and from day 10 to 13; the administration of G-CSF can be prolonged after day 13 according to patient requirement and/or local policy and in accordance with ASCO guidelines [50].

13.4.5. Prevention of Herpes Zoster infection and Pneumocystis Jiroveci Pneumonia

Herpes Zoster:

- Antiviral prophylaxis with acyclovir 800 mg at day or valaciclovir 500 mg at day according to local policy during the induction and maintenance phases;

Pneumocystis Jiroveci Pneumonia (PCP):

- Co-Trimoxazole 800 mg/160 mg Forte Tablets 1 tablet on Monday, Tuesday, Friday or Pentamidine aerosol every 28 days in patients with Co-Trimoxazole allergy/intolerance or in patients with G6PD deficiency according to local policy during the induction and maintenance phase.

13.4.6. Anti-Hyperuricemic therapy

Allopurinol or other antihyperuricemic drug according to local policy. Consider use of rasburicase if subjects baseline uric acid level is elevated.

13.4.7. Prevention and Management of Hepatitis B Virus Reactivation

Patients with chronic hepatitis B virus (HBV) requiring treatment are excluded from the study.

Patients with active hepatitis B virus (HBV) are excluded from the study.

Primary antiviral prophylaxis is permitted as per local standard of care. Per protocol, HBV DNA testing by PCR is mandatory for subjects at risk for HBV reactivation (see *Section 15.4*).

The following categories of patients HBV positive but with no evidence of active hepatitis may be considered for the study:

- HBsAg positive with HBV DNA < 2000 UI/ml (inactive carriers); HBV DNA > 2000 UI/ml is criteria of exclusion
- HBsAg negative but anti-HBs positive
- HBsAg negative but anti-HBc positive
- HBsAg positive with HBV DNA < 2000 UI/ml and HBsAg negative but anti-HBc ± anti-HBs positive will be eligible for the study only if they accept to receive prophylactic Lamivudine 100 mg/daily for all the period of treatment and at least for 12 months after the end of therapy. Treatment should be stopped in case of hepatitis reactivation.

As far as the monitoring of these patients, the protocol plans:

- Patients HBsAg positive with HBV DNA < 2000 UI/ml (inactive carriers): monthly evaluation of transaminases and liver function, and bi-monthly evaluation of HBV DNA by PCR; in case of hepatitis reactivation or HBV DNA > 2000 UI/ml, treatment should be stopped;
- Patients HBsAg negative but anti-HBc ± anti-HBs positive: monthly evaluation of transaminases, liver function and bi-monthly evaluation of HBV DNA by PCR

As far as prophylactic treatment with Lamivudine:

- Lamivudine 100 mg/daily should be given for all the period and at least for 12 months after the end of therapy in inactive carriers (HBsAg positive with HBV DNA < 2000 UI/ml) and in patients HBsAg negative but anti-HBc ± anti-HBs positive.

For subjects who are diagnosed with HBV reactivation while on treatment, study treatment should be interrupted until the infection is adequately controlled. If the benefits outweigh the risks, study treatment may be resumed with concomitant antiviral prophylaxis as per local standard of care. Consult a liver disease specialist as clinically indicated.

Subjects with serologic findings suggestive of HBV vaccination (anti-HBs positivity as the only serologic marker) and a known history of prior HBV vaccination, do not need to be tested for HBV DNA by PCR, and should be considered eligible for the study.

13.4.8. HCV positive patients

Patients with chronic hepatitis C virus (HCV) requiring treatment are excluded from the study.
Patients with active hepatitis C virus (HCV) are excluded from the study.
Patient with no evidence of active hepatitis and/or advanced chronic liver disease according to liver biopsy or fibro-scan evaluation may be included into the study.
To monitor hepatic function, it is recommended to have a monthly evaluation of transaminases and liver function.

Treatment with D-GDP should be stopped in case of hepatitis reactivation.

13.5. CONTRACEPTION

No clinical or preclinical studies have been performed to evaluate the potential effects of daratumumab on reproduction or development.
Non-sterilized female patients of reproductive age group and male patients should use effective methods of contraception through defined periods during and after study treatment as below specified.
Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, or
- Surgically sterile, or
- If of childbearing potential, agree to practice 2 effective methods of contraception from the time of signing of the informed consent form through 3 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, post ovulation methods) and withdrawal are not acceptable methods of contraception.

Male patients, even if surgically sterilized (i.e., status post vasectomy) must agree to 1 of the following:

- Practice effective barrier contraception during the entire study treatment period and through 3 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, symptom-thermal, post ovulation methods for the female partner) and withdrawal are not acceptable methods of contraception.

13.6. GDP TOXICITY

Expected Risks and Toxic Effects of gemcitabine

Safety data presented below are based on single-agent gemcitabine given as treatment for a wide variety of malignancies; adverse effects are graded according to World Health Organization (WHO) toxicity criteria.

Hematologic. Myelosuppression is an expected effect of gemcitabine therapy. WHO grade 3 or 4 hemoglobin toxicity was recorded for 10.5 % of patients. The clinical significance of these results is difficult to assess due to disease-related anemia and because investigators differed in the extent to which they transfused patients. WHO grade 3 or 4 white blood cell toxicity was seen in 14.4%; incidence of neutropenia (WHO grade 3 or 4) was 21.9% and of thrombocytopenia (WHO grade 3 or 4) 10.1%. Hemorrhage of grade > 1 WHO was reported in 8.9% of patients (only 0.6% grade 3 or 4).

Gastrointestinal. Elevated liver function tests, primarily in serum transaminases, occur in roughly one half of patients, but rarely (0.1%) required discontinuation of therapy, even in combination studies. WHO grade 3 or 4 toxicities occurred in 7.1%, 7.2%, 5.6%, and 1.6% of patients for ALT, AST, alkaline phosphatase, and bilirubin, respectively. Nausea and vomiting, usually of mild or moderate severity, have been commonly reported (63.3%); 11.4% were WHO grade 3 (vomiting severe enough to require therapy) and 0.7% grade 4 (intractable vomiting). Variability in use of prophylactic antiemetics confounds this assessment. Overall, nausea/ vomiting was frequent but rarely dose limiting, manageable with standard antiemetics. Grade 2 WHO oral toxicity was reported in 3.3% of patients (erythema or ulcers, no need for liquid diet); grade 3 was seen in 0.3%; there were no WHO grade 4 oral toxicities (i.e. rendering alimentation impossible). Diarrhea of any severity was reported by 15.6% of patients.

Renal. Mild (WHO grade 1) proteinuria and hematuria were commonly reported. Hemolytic-uremic syndrome (HUS) has been reported; however, renal events outside HUS are very rare, and no causal association with gemcitabine can be fully established.

Fever/Infection. Infections of > WHO grade 1 were reported in 14.5% of patients, 1.9% grade 3 or 4. The overall incidence of fever was 36.5%, an indication that gemcitabine may cause fever in the absence of clinical infection. Fever was frequently associated with other flu-like symptoms.

Cutaneous/Hair. A maculopapular rash of mild to moderate severity may appear within 2-3 days of starting treatment (27.4% of patients). Mild alopecia was reported in 14.6% of patients. Injection site pain or other local reaction was noted in < 3% of patients.

Neurologic. Somnolence (WHO grade 1 or greater) was reported in 11.5% of patients, asthenia in 8.8%, and muscle weakness in 0.4%. Peripheral neurotoxicity, mild and not progressive, was reported for 8.1%. Constipation was reported for 20.1% of patients, the majority mild (WHO grade 1).

Pulmonary. Dyspnea of any severity was reported in 18.8% of patients, WHO grade 3 or 4 (dyspnea at rest and dyspnea requiring complete bed rest, respectively) in 3.9%. Occasionally the dyspnea also involved bronchospasm (<3% of patients) and was temporally related to the administration of gemcitabine. It should be noted that many patients treated in gemcitabine clinical trials had lung cancer or pulmonary manifestations of other malignancies. Pulmonary toxicity associated with gemcitabine presents most commonly as an acute dyspnea that is not serious; however, serious toxicity including progressive dyspnea, pulmonary edema, pneumonitis, and ARDS have been reported.

Cardiac. WHO grade 4 cardiac function toxicity (symptomatic dysfunction not responsive to therapy) was seen in 0.4% of patients, and WHO grade 4 (symptomatic dysfunction responsive to therapy) in 1.3%. Cardiac rhythm toxicity (multifocal premature ventricular contractions) WHO grades 3 and 4 have been rarely reported.

Expected Risks and Toxic Effects of cisplatin

The dose-limiting toxicity of cisplatin is ***nephrotoxicity***, which may be acute or chronic. While acute renal failure may occur within 24 hours of administration in 5-10% of patients, especially those with inadequate hydration, renal dysfunction is usually mild and partially reversible in patients receiving < 100 mg/m^2/cycle, as in this study. Hyperuricemia may indicate cisplatin induced renal toxicity.

Cumulative ***ototoxicity*** has been documented in up to one third of patients treated with cisplatin.

Neurotoxicity, typically manifested as a sensory peripheral neuropathy, usually reversible, can occur during or after cisplatin therapy; treatment should be discontinued if the patient experiences neurological symptoms such as loss of motor function, areflexia, loss of proprioception, and aphasia.

Visual impairment (e.g. blurred vision, altered color perception) is a frequent problem, rarely severe (e.g. optical neuritis) and usually reversible.

Severe ***nausea and vomiting*** are a certainty in all patients not pretreated with antiemetics; delayed nausea/ vomiting and anorexia occur frequently in patients in whom the acute symptoms are controlled.

Patients with a prior exposure to platinum (e.g. working in the electronic industry) are particularly susceptible to ***anaphylactoid reactions*** (facial edema, flushing, wheezing, tachycardia, and hypotension).

Cisplatin causes less bone marrow suppression than other antineoplastic agents; ***anemia, neutropenia, and thrombocytopenia*** may occur between days 18-23 following treatment.

Tissue necrosis after extravasation of >20 ml of concentrated solution has been reported.

The risk of ***secondary malignancy*** increases with cumulative doses > 500 mg.

Other reactions include hiccups, elevated hepatic enzymes, and alopecia.

Expected Risks and Toxic Effects of dexamethasone

Because dexamethasone has been widely used in various situations in medicine for many years, its toxicity profile is well known. Reported side effects include hyperglycemia, osteoporosis, mental disturbances, gastritis, peptic ulceration, Cushing's syndrome, and adrenal suppression, but these problems are rare when dexamethasone is used for short periods only.

13.7. DARATUMUMAB TOXICITY

13.7.1. Indications and Use

Daratumumab is being developed for the treatment of adult patients with multiple myeloma (MM), that highly express CD38 in the malignant cells. Moreover, CD38 is expressed in a large number of hematological malignancies and identified as a promising target for antibody-based therapies.

As of July 2017, daratumumab (DARZALEX®) has been approved in dozens of countries for indications as single agent and/or in polychemotherapy; MM who have received at least one prior therapy (second-line treatment), in association with lenalidomide/dexamethasone or bortezomib/dexamethasone; MM who have received at least two prior therapies including lenalidomide and a proteasome inhibitor (third-line treatment), in combination with pomalidomide and dexamethasone; MM who have received at least three prior lines of therapy including a proteasome inhibitor and an immunomodulatory agent or who are double-refractory to a proteasome inhibitor and an immunomodulatory agent (fourth-line treatment), as monotherapy. In May 2018 has been approved by FDA for treatment of newly diagnosed MM (first-line treatment) who are ineligible for autologous stem cell transplant in combination with bortezomib, melphalan, and prednisone.

13.7.2. Contraindications

Daratumumab is contraindicated in subjects who have known hypersensitivity (e.g., anaphylactic and anaphylactoid reactions) to daratumumab or to the excipients in its formulation.

13.7.3. Special warnings and precautions for use of daratumumab

Adverse reactions are adverse events (AEs) that were considered to be reasonably associated with the use of daratumumab based on the comprehensive assessment of the available AE information. A causal relationship with daratumumab cannot be reliably established in individual cases. Furthermore, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The most frequent adverse reactions (> 20%) in individual randomized controlled studies were infusion reactions, fatigue, nausea, diarrhea, muscle spasms, pyrexia, cough, dyspnea, neutropenia, thrombocytopenia and upper respiratory tract infection. In addition, in combination with bortezomib, peripheral edema and peripheral sensory neuropathy were frequently reported. Serious adverse reactions were pneumonia, upper respiratory tract infection, influenza, pyrexia, diarrhea, atrial fibrillation.

A list of expected adverse reactions is provided in ***Appendix F***.

Infusion-related reactions

Pre- and post-infusion medications should be administered to reduce the risk of infusion-related reactions (IRRs) with daratumumab.

Infusion-related reactions (IRRs) were reported in approximately half of all patients treated with daratumumab. Monitor such patients throughout the infusion and the post-infusion period.

The majority of IRRs occurred at the first infusion. Four percent of all patients had an IRR at more than one infusion. Nearly all reactions occurred during infusion or within 4 hours of completing daratumumab. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnea, hypertension, laryngeal edema and pulmonary edema. Signs and symptoms may include respiratory symptoms, such as nasal congestion, cough, throat irritation, as well as chills, vomiting and nausea. Less common symptoms were wheezing, allergic rhinitis, pyrexia, chest discomfort, pruritus and hypotension.

For IRRs of any grade/severity, immediately interrupt the daratumumab infusion and manage symptoms. Management of IRRs may further require reduction in the rate of infusion, or treatment discontinuation of daratumumab as below outlined.

- Grade 1-2 (mild to moderate): Once reaction symptoms resolve the infusion should be resumed at no more than half the rate at which the IRR occurred. If the patient does not experience any further IRR symptoms, infusion rate escalation may be resumed at increments and intervals as clinically appropriate up to the maximum rate.
- Grade 3 (severe): Once reaction symptoms resolve, restarting of the infusion may be considered at no more than half the rate at which the reaction occurred. If the patient does not experience additional symptoms, infusion rate escalation may be resumed at increments and intervals as appropriate. The procedure above should be repeated in the event of recurrence of Grade 3 symptoms. Permanently discontinue daratumumab upon the third occurrence of a Grade 3 or greater infusion reaction.
- Grade 4 (life-threatening): Permanently discontinue daratumumab treatment.

Infections

In patients receiving daratumumab combination therapy, Grade 3 or 4 infections were reported with daratumumab combinations and background therapies, with a variable frequency of 19%-28%. Pneumonia was the most commonly reported severe (Grade 3 or 4) infection across studies. Discontinuations from treatment were reported in 2% to 5% of patients. Fatal infections were reported in 0.8% to 2% of patients across studies, primarily due to pneumonia and sepsis.

Hemolysis

There is a theoretical risk of hemolysis. Continuous monitoring for this safety signal will be performed in clinical studies and post-marketing safety data.

Tumor lysis syndrome (TLS)

Tumor lysis syndrome may be a potential for side effect during daratumumab therapy. There is no data in T cell lymphoma and for this reason TLS should be closely monitored during treatment, particularly during cycle 1. In general, before initiating treatment, subject risk for developing TLS should be assessed. Prophylaxis with hydration and uric-acid reducing agents is recommended. Clinical chemistries should be corrected. Monitor with clinical chemistries and manage promptly, as clinically indicated.

Interference with Serological Testing

Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (Indirect Coombs test or IAT). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab infusion. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum [51]. The determination of a patient's ABO and Rh blood type are not impacted.

Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received daratumumab. Type and screen patients prior to starting daratumumab.

If an emergency transfusion is required, non-cross-matched ABO/RhD-compatible RBCs can be given per local blood bank practices.

Neutropenia

Daratumumab may increase neutropenia induced by GDP (see *paragraph 13.7.1*). Daratumumab dose delay may be required to allow recovery of neutrophil count.

Monitor complete blood cell counts periodically during treatment according to timepoints reported in *Chapter 15 "Study procedures timepoints"*. Monitor patients with neutropenia for signs of infection.

No dose reduction of Daratumumab is recommended. Consider supportive care with transfusions or growth factors.

Thrombocytopenia

Daratumumab may increase thrombocytopenia induced by GDP (see *paragraph 13.7.1*). Daratumumab dose delay may be required to allow recovery of platelets.

Monitor complete blood cell counts periodically during treatment according to timepoints reported in *Chapter 15 "Study procedures timepoints"*. No dose reduction of Daratumumab is recommended. Consider supportive care with transfusions.

13.7.4. Adverse Drug Reactions

The most frequently reported adverse reactions (incidence ≥20%) were infusion reactions, neutropenia, thrombocytopenia, fatigue, nausea, diarrhea, constipation, vomiting, muscle spasms, arthralgia, back pain, pyrexia, chills, dizziness, insomnia, cough, dyspnea, peripheral edema, peripheral sensory neuropathy and upper respiratory tract infection. See Daratumumab Reference Safety Information (***Appendix F***).

13.7.5. Special Populations

Elderly

No dose adjustments are considered necessary. No clinically important influence of age on the exposure to daratumumab was observed in the population pharmacokinetic analyses in patients receiving both monotherapy or combination therapies. The difference in exposure was within 6% between younger (age < 65 years, n = 352; or age < 75 years, n = 630) and older subjects (age ≥ 65 years, n = 342; or age ≥ 75 years, n = 64).

Renal impairment

No formal studies of daratumumab in patients with renal impairment have been conducted. Based on population pharmacokinetic analyses no dosage adjustment is necessary for patients with renal impairment. No clinically important differences in exposure to daratumumab monotherapy were observed

between patients with renal impairment and those with normal renal function. Additional population pharmacokinetic analyses in patients receiving combination treatments also demonstrated no clinically important differences in exposure to daratumumab between patients with renal impairment (mild, n = 264; moderate, n = 166; severe, n = 12) and those with normal renal function (n = 251).

Hepatic impairment

No formal studies of daratumumab in patients with hepatic impairment have been conducted. Changes in hepatic function are unlikely to have any effect on the elimination of daratumumab since IgG1 molecules such as daratumumab are not metabolized through hepatic pathways. Based on population pharmacokinetic analyses, no clinically important differences in the exposure to daratumumab were observed between patients with hepatic impairment and those with normal hepatic function. No dosage adjustments are necessary for patients with hepatic impairment.

13.7.6. Fertility, pregnancy and lactation

Women of child-bearing potential/Contraception

Women of child-bearing potential should use effective contraception during, and for 3 months after cessation of daratumumab treatment.

Pregnancy

There are no human or animal data to assess the risk of daratumumab use during pregnancy. IgG1 monoclonal antibodies are known to cross the placenta after the first trimester of pregnancy. Therefore, daratumumab should not be used during pregnancy unless the benefit of treatment to the woman is considered to outweigh the potential risks to the fetus. If the patient becomes pregnant while taking this medicine, the patient should be informed of the potential risk to the fetus.

Breast-feeding

It is not known whether daratumumab is excreted into human or animal milk.

Maternal IgG is excreted in human milk but does not enter the neonatal and infant circulations in substantial amounts as they are degraded in the gastrointestinal tract and not absorbed.

The effect of daratumumab on newborns/infants is unknown. A decision should be made whether to discontinue breast-feeding or to discontinue daratumumab therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

No data are available to determine potential effects of daratumumab on fertility in males or females (see *paragraph 7.4.2.*).

13.7.7. Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

As an IgG1κ monoclonal antibody, renal excretion and hepatic enzyme-mediated metabolism of intact daratumumab are unlikely to represent major elimination routes. As such, variations in drug-metabolizing enzymes are not expected to affect the elimination of daratumumab. Due to the high affinity to a unique epitope on CD38, daratumumab is not anticipated to alter drug-metabolizing enzymes.

13.8. DRUGS DOSE MODIFICATION

13.8.1. GDP

The GDP regimens has been extensively adopted as salvage therapy for R/R PTCL [6, 37–48] and therefore the results of this study will be compared to historical GDP controls.

Doses of GDP will be reduced according to the development of severe hematological or non-hematological toxicities.

If Hematological Toxicity

- In case of febrile neutropenia, grade 4 thrombocytopenia or grade 4 neutropenia for 7 days: doses of gemcitabine and cisplatin will be reduced by 25% in following cycles; if the same grade 4 hematological toxicity will occur again, doses will be reduced by 50% of the initial dosage.

If non-hematological Toxicity

- In case of any grade 3 non-hematological toxicities (except alopecia), doses of gemcitabine and cisplatin will be reduced by 25% in following cycles; if the same grade 3 non-hematological toxicity will occur again, doses will be reduced by 50% of the initial dosage.
- In case of grade 2 neurological toxicity, dose of cisplatin will be reduced by 50% in following cycles; cisplatin will be discontinued with the occurrence of > grade 2 neurological toxicity.
- D-GDP therapy will be discontinued with the occurrence of any grade 4 non-hematological toxicities.

Alcohol content of gemcitabine: Doses of gemcitabine not available as ready- made infusions contain up to approximately 11g of ethanol (1.5units). Patients should be advised not to drive on the day of treatment. Where alcohol content is a concern please contact pharmacy for advice about alternative formulations.

13.8.2. Daratumumab

No dose reductions of daratumumab are recommended. Dose delay may be required to allow recovery of blood cell counts in the event of hematological toxicity.
Daratumumab may increase neutropenia and thrombocytopenia induced by GDP (see *paragraphs 13.7.3. and 13.8.1*).
Monitor complete blood cell counts periodically during treatment according to what reported in *Chapter 15 "Study procedures timepoints"*. Monitor patients with neutropenia for signs of infection.
Consider supportive care with transfusions or growth factors.

14. REMOVAL OF SUBJECTS FROM TREATMENT AND/OR STUDY

14.1. DISCONTINUATION FROM STUDY TREATMENT

A subject must be discontinued from study treatment in case of:

- patient withdraws consent to receive protocol treatment;
- disease progression at any time;
- occurrence of an unacceptable toxicity at any time;
- the investigator believes that for safety reasons it is in the best interest of the subject to discontinue the treatment.

14.2. WITHDRAWAL OF SUBJECTS FROM THE STUDY

A subject has the right to withdraw from the study at any time and for any reason without prejudice to his or her future medical care by the physician or at the institution.
Circumstances that lead to premature withdrawal of a patient from the trial must be reported by the investigator on the appropriate CRF page.
If the patient withdraws the consent or doesn't fulfill the inclusion criteria, he must be considered off protocol.
At the time of withdrawal all study procedures outlined for the end of treatment should be completed.

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 to record any adverse events and all the evaluable study endpoints. 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, in agreement with the DSMC, may decide to prematurely stop the trial at any time based on the following criteria:

- one the stopping rules has been reached (see paragraph 18.3);
- there is evidence of other unacceptable risks for study patients beyond the safety stopping rules;
- it will not be possible to reach the planned sample size within reasonable time;
- other justified reasons (i.e., availability of new very effective treatments).

The sponsor will inform of this decision in writing all concerned investigators, IECs and regulatory authorities. The sponsor will provide information regarding the timelines of study termination and instructions regarding treatment and data collection of enrolled patients.
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, giving assurance of providing data for all patients already enrolled.

15. STUDY PROCEDURES TIMEPOINTS

15.1. SCREENING PERIOD

Within 4 weeks prior to start of the therapy

Screening procedures are per clinical practice of refractory/relapsed PTCL. All screening assessments must be completed within 28 days prior to the beginning of therapy with the exception of the tumor biopsy and the bone marrow biopsy, which may occur up to 3 months prior to C1D1, and the PET and CT scans, which may occur up to 6 weeks prior to C1D1. Relapse biopsy, or in the more recent biopsy in the case of refractory patients, will be centralized to the FIL designated laboratory for centralized pathology assessment and CD38 positivity after the subject has signed the informed consent. A core needle biopsy is considered sufficient for diagnosis review and CD38 evaluation; ***Note:*** Patients with only bone marrow

involvement are eligible. In patients with only bone marrow lymphoma infiltration central diagnosis review and CD38 evaluation can be performed in bone marrow sections.
Only patients with percentage of CD38 positive tumor cells ≥ 5% will be considered eligible for protocol study treatment.

The screening period procedures include:

- Check for inclusion/exclusion criteria
- Written Informed Consent;
- Complete Medical History;
- Lymph Node/Tumor biopsy material (formalin-fixed, paraffin-embedded) available to centralize (mandatory) (see *Chapter 20* and *Appendix E*);
- Physical Examination including height and weight;
- ECOG performance status;
- Vital Signs (blood pressure, pulse rate and body temperature);
- B symptoms;
- Hematology including hemoglobin, hematocrit, platelet (PLT), red blood cell (RBC), white blood cell count (WBC) with absolute differential count (neutrophils, lymphocytes, monocytes, basophils, and eosinophils);
- Biochemistry including AST, ALT, serum alkaline phosphatase, gGT, total bilirubin, LDH, creatinine, Na, K, Ca, uric acid, total protein, albumin and creatinine clearance;
- IgA, IgG, IgM;
- Coagulation assessment: PTT, PT;
- Determination of ABO and Rh blood type and Indirect Coombs test (IAT);
- Serology for HBV (refer also to *paragraph 15.4*):
    - hepatitis B surface antigen (HBsAg)
    - hepatitis B surface antibody (Anti-HBs)
    - hepatitis B core antibody (Anti-HBc)

  Subjects who are positive for Anti-HBc or Anti-HBs will undergo testing for hepatitis B DNA by PCR;
- Serology for HCV, HIV;
- Contrast enhanced CT scan including neck, chest, abdomen and pelvis (MRI can be used alter-natively to CT scan) plus PET scan or, in alternative, a PET-CT scan;
- ECG;
- LVEF by bi-dimensional echocardiogram;
- Pregnancy test (if applicable);
- Bone marrow biopsy;
- Concomitant medications;
- Reporting of AE occurred during the screening phase.

15.2. INDUCTION PHASE

<u>During cycle 1: weekly evaluation of</u>

- Physical Examination;
- ECOG performance status;
- Vital Signs (blood pressure, pulse rate and body temperature);
- Hematology including hemoglobin, hematocrit, PLT, RBC, WBC with absolute differential count;
- Biochemistry including potassium, uric acid, phosphorus, calcium and creatinine;

<u>Before each subsequent cycle therapy (Cycles 2-6)</u>

- Physical Examination;

- ECOG performance status;
- Vital Signs (blood pressure, pulse rate and body temperature);
- Hematology including hemoglobin, hematocrit, PLT, RBC, WBC with absolute differential count;
- Biochemistry including AST, ALT, serum alkaline phosphatase, gGT, total bilirubin, LDH, creatinine, Na, K, Ca, uric acid;
- Concomitant medications reporting;
- Reporting of AE occurred during the previous cycle.

During each subsequent cycle of therapy (Cycles 2-6): weekly evaluation of

- Hematology including hemoglobin, hematocrit, PLT, RBC, WBC with absolute differential count.

15.3. MAINTENANCE PHASE

Before each maintenance cycle

- Physical Examination;
- ECOG performance status;
- Vital Signs (blood pressure, pulse rate and body temperature);
- Hematology including hemoglobin, hematocrit, PLT, RBC, WBC with absolute differential count;
- Biochemistry including AST, ALT, serum alkaline phosphatase, gGT, total bilirubin, LDH, creatinine, Na, K, Ca, uric acid;
- Concomitant medications reporting;
- Reporting of AE occurred during previous cycle (starting from cycle 2).

15.4. HBV STUDY EVALUATIONS

- ***HBV Serology***

All subjects will be tested locally for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (Anti-HBs), and hepatitis B core antibody (Anti-HBc) at Screening.

- ***HBV DNA Tests***

Subjects who are positive for Anti-HBc or Anti-HBs will undergo testing for hepatitis B DNA by PCR.

Subjects with serologic findings suggestive of HBV vaccination (Anti-HBs positivity as the only serologic marker) and a known history of prior HBV vaccination do not need to be tested for HBV DNA by PCR.

During and following study treatment, subjects who have history of HBV infection (HBsAg negative and anti-HBc ± anti-HBs positive and with undetectable HBV DNA levels at screening) will be closely monitored for clinical and laboratory signs of reactivation of HBV: HBV DNA levels in PCR must be followed approximately every 2 months for up to 12 months after the last dose of daratumumab.

Where required by local law, the results of HBV testing may be reported to the local health authorities.

15.5. RESTAGING AFTER 4 COURSES OF INDUCTION

To be performed on day 12 to 19, cycle 4

- Physical Examination;
- ECOG performance status;
- Vital Signs (blood pressure, pulse rate and body temperature);
- Hematology including hemoglobin, hematocrit, PLT, RBC, WBC with absolute differential count;
- Biochemistry including AST, ALT, serum alkaline phosphatase, gGT, total bilirubin, LDH, creatinine, Na, K, Ca, uric acid;
- IgA, IgG, IgM;
- ECG;

- LVEF by bi-dimensional echocardiogram;
- Contrast enhanced CT scan including neck, chest, abdomen and pelvis (or MRI, if used at baseline staging);
- Bone marrow biopsy (if positive at baseline) only to confirm a CR (NB: once a CR has been confirmed no other bone morrow biopsies are required);
- Any other radiological (PET or PET/CT scan included), clinical and laboratory procedures if indicated to confirm a CR or if clinically indicated;
- Response assessment according to Lugano 2014 criteria [52], Appendix D;
- Reporting of AE occurred during cycle 4.

15.6. RESTAGING AT EOI (END OF INDUCTION PHASE)

To be performed on day 15 to 25, cycle 6

- Physical Examination;
- ECOG performance status;
- Vital Signs (blood pressure, pulse rate and body temperature);
- Hematology including hemoglobin, hematocrit, PLT, RBC, WBC with absolute differential count;
- Biochemistry including AST, ALT, serum alkaline phosphatase, gGT, total bilirubin, LDH, creatinine, Na, K, Ca, uric acid;
- Contrast enhanced CT scan including neck, chest, abdomen and pelvis (or MRI, if used at previous assessments);
- Response assessment according to Lugano 2014 criteria [52], Appendix D;
- Bone marrow biopsy (if positive at baseline) only to confirm a CR;
- Any other radiological (PET or PET/CT scan included), clinical and laboratory procedures if indicated to confirm a CR or if clinically indicated;
- Reporting of AE occurred during cycle 6.

15.7. RESTAGING DURING MAINTENANCE

Every 3 cycles up to cycle 12, then every 4 cycles from cycle 13 to 24

- Physical Examination;
- ECOG performance status;
- Vital Signs (blood pressure, pulse rate and body temperature);
- Hematology including hemoglobin, hematocrit, PLT, RBC, WBC with absolute differential count;
- Biochemistry including AST, ALT, serum alkaline phosphatase, gGT, total bilirubin, LDH, creatinine, Na, K, Ca, uric acid;
- Contrast enhanced CT scan including neck, chest, abdomen and pelvis (or MRI, if used at previous assessments);
- Bone marrow biopsy (if positive at baseline) only to confirm a CR;
- Any other radiological (PET or PET/CT scan included), clinical and laboratory procedures if indicated to confirm a CR or if clinically indicated;
- Response assessment according to Lugano 2014 criteria [52], Appendix D;

15.8. RESTAGING AT THE EOT (REGARDLESS OF THE REASON FOR DISCONTINUATION)

- Physical Examination;
- ECOG performance status;
- Vital Signs (blood pressure, pulse rate and body temperature);
- Hematology including hemoglobin, hematocrit, PLT, RBC, WBC with absolute differential count (neutrophils, lymphocytes, monocytes, basophils, and eosinophils);

- Biochemistry including AST, ALT, serum alkaline phosphatase, gGT, total bilirubin, LDH, creatinine, Na, K, Ca, uric acid, total protein, albumin;
- IgA, IgG, IgM;
- ECG;
- LVEF by bi-dimensional echocardiogram;
- Contrast enhanced CT scan including neck, chest, abdomen and pelvis (or MRI, if used at previous assessments);
- Response assessment according to Lugano 2014 criteria [52], Appendix D;
- Bone marrow biopsy (if positive at baseline) only to confirm a CR;
- Any other radiological (PET or PET/CT scan included), clinical and laboratory procedures (including biopsy of suspicious extranodal sites) if indicated to confirm a CR or if clinically indicated;
- Reporting of AE occurred during the last cycle administered.

15.9. ASSESSMENTS DURING FOLLOW-UP

After treatment discontinuation, both in the case the protocol treatment was fully administered and in the case of an early discontinuation, patients will be followed-up according to clinical practice timeline and procedures, and information on patient status (progression/relapse, alive/dead, lost to follow-up) will be collected till the end of the study (LPLV), planned 24 months after the start of induction treatment of last patient enrolled. In case of progression/relapse during follow-up, the patients will be then followed-up for survival till the study end.

15.10. SCHEDULE OF ASSESSMENTS

	Screening (All)	Induction				Maintenance			FU
	-28 to D1 as per clinical practice	Cy 1	Cy 2-6	After Cy 4	EOI	Before each cycle	Every 3 cycles Cy 1-12 and every 4 cycles Cy 12-24	EOT*	as per clinical practice
	D1	D1	D1			D1			
Informed consent	X								
Inclusion/Exclusion	X								
Lymph Node/Tumor biopsy material available for central review	X								
Medical History	X								
Physical exam [a]	X	X[w]	X	X	X	X	X	X	
Pregnancy test [b]	X								
ECOG PS	X	X[w]	X	X	X	X	X	X	
B symptoms	X								
Hematology tests [c]	X	X [c, w]	X [c, w]	X [c]	X [c]	X	X	X	
Biochemistry [d]	X	X[w]	X	X	X	X	X	X	
IgA, IgG, IgM	X			X				X	
Coagulation (PT, PTT)	X								
ABO/Rh and IAT	X								
Bone marrow biopsy [g]	X			X [g]	X [g]		X [g]	X [g]	
Tumor assessment (TB CT scan, MRI, PET) [h]	X			X	X		X	X	
ECG	X			X				X	
LVEF echo	X			X				X	

Other procedures [i]				X	X		X	X	
Response assessment				X	X		X	X	
Serology	X [e]	X [f]							
Concomitant medications [j]	Recorded from screening through 30 days after the last dose of treatment.								
Adverse event reporting [k]	Recorded from signing of the informed consent through 30 days after the last dose of treatment.								
Serious adverse event [k]	Recorded from signing of the informed consent form through LPLV.								

* *EOT for any reason, including early withdrawal and PD/relapse*

a. *Physical examination including vital signs (blood pressure, pulse rate, height, weight) with measurement of all palpable disease.*

b. *For women of childbearing potential only: pregnancy test within 7 days prior to study drugs administration (or within 14 days if with a confirmatory urine pregnancy test within 7 days prior to the first study drugs administration).*

c. *Clinical laboratory evaluations (blood count with differential white count) to be performed weekly during induction*

d. *Biochemistry (AST, ALT, serum alkaline phosphatase, gGT, total bilirubin, LDH, creatinine, Na, K, Ca, uric acid, total protein, albumin, creatinine clearance). During cycle 1 weekly assessment of biochemistry including potassium, uric acid, phosphorus, calcium and creatinine*

e. *Standard HIV and HCV; HBV serology includes HBsAg, anti-HBc, anti-HBs and HBV-DNA in PCR in patients positive to anti-HBc ± anti-HBs;*

f. *In patients who are HBsAg negative and anti-HBc ± anti-HBs positive and with undetectable HBV DNA levels at screening, HBV DNA levels by PCR must be followed approximately every 2 months for up to 12 months after the last dose of daratumumab (see paragraph 15.4).*

g. *Bone marrow to be repeated at restaging with the aims to confirm a CR, and only if positive at baseline. If bone marrow clears during treatment, no additional test to be performed.*

h. *During the screening, contrast enhanced CT scan, including neck, chest, abdomen and pelvis (or MRI, if CT-scan cannot be done)) + PET scan or alternatively, a combined PET-CT (allowed if CT resolution meets Central Radiology's minimum threshold); during subsequent evaluation PET is allowed if of clinical relevance but not mandatory.*

i. *Any other radiologic, clinical and laboratory procedures (including biopsy of suspicious sites) if indicated to confirm a CR or if clinically indicated.*

j. *Concomitant medications must be collected from the time of informed consent signature, throughout the treatment period and up to and including 30 days post-study follow-up period.*

k. *Adverse events must be collected from the time of signature of informed consent throughout the treatment period and until completion of the last subject's related procedure which includes contact for follow-up of safety. All SAEs must be reported within 24 hours. All AEs and SAEs must be followed up until resolution unless in the opinion of the investigator the condition is unlikely to resolve due to the patient's underlying disease.*

w. *weekly evaluation of hematology including hemoglobin, hematocrit, PLT, RBC, WBC with absolute differential count.*

16. EFFICACY MEASUREMENTS AND PARAMETERS

16.1. EFFICACY MEASUREMENT

The primary analysis population for all efficacy and safety analyses includes all 35 subjects who received at least 1 dose of planned therapy.

Efficacy will be measured by:

- Computed tomography (CT) scans with contrast of the neck, chest, abdomen and pelvis plus Positron emission tomography (PET) scan of the whole body or a CT-PET will be performed at baseline and after 3 cycles of treatment. Subsequently, CT scan will be performed every 3 cycles during the first 12 cycles and every 4 cycles from cycle 13 to 24; PET will be repeated only to confirm a CR status evaluated with CT. For those patients still on therapy after 24 cycles, the response evaluation, after this time, will be performed every 6 cycles.
- MRI may be used instead of CT scan in patients for whom CT scans with contrast are contraindicated.
- Bone marrow biopsy will be performed at baseline and subsequently to confirm first CR only in patients who were positive for lymphoma infiltration at baseline.
- For the evaluation of response, the response criteria (PET-based or CT-based of the Lugano Classification will be adopted) [52].

16.2. EFFICACY PARAMETERS

16.2.1. Primary efficacy endpoint

Complete Response Rate (CRR) after 4 cycles of D-GDP. CRR will be defined as the proportion of patient in CR according to Lugano classification response Criteria (***Appendix D***) [52] after the first 4 cycles of D-GDP. In case of early discontinuation, efficacy will be assessed at the EOT visit. Patients without response assessment (due to whatever reason) will be considered as non-responders.

16.2.2. Secondary efficacy endpoints

Overall Response Rate (ORR). ORR will be assessed after the first 4 cycles and at each restaging and defined according to the Lugano 2014 criteria (***Appendix D***) [52], including the sum of CR + PR. Response assessment will be done at each restaging. The best overall response will be defined as the best response between the date of beginning of therapy and the last restaging. Patients without response assessment (due to whatever reason) will be considered as non-responders.

Overall Survival (OS) will be defined from the date of starting therapy and the date of death from any cause. Patients alive and those who are lost to follow-up at the time of the final analysis will be censored at the date of the last contact.

Progression-Free Survival (PFS) will be defined from the date of starting therapy and the date of disease progression, relapse or death from any cause. Responding patients according to the Lugano classification response Criteria (***Appendix D***) [52] and patients who are lost to follow-up will be censored at their last assessment date.

16.2.3. Explorative efficacy endpoints

Role of daratumumab maintenance by comparison of CRR before and after maintenance, and by evaluation of rate of conversion in CR with daratumumab maintenance for patients in PR after the induction.

Association between intensity of CD38 expression and response. The extent of CD38 expression evaluated by the central FIL designed laboratory will be correlated with response measured according to the Lugano 2014 criteria at various endpoints.

17. SAFETY MEASUREMENTS AND PARAMETERS

17.1. SAFETY MEASUREMENTS

All patients who have received at least 1 dose of study medication will be considered for the safety analysis 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 5.0.

During the first 4 cycles of therapy, ADRs and AEs will be evaluated with the aim of monitoring toxicity for stopping rules assessment according to the modalities hereafter reported. The same modalities will be applied also for further evaluation at timepoints reported in *Chapter 15.*

17.1.1. Definition of relevant toxicity

Relevant toxicity will be defined as the proportion of patients experiencing one or more of the following events:

- grade 4 neutropenia lasting more than 7 days regardless adequate G-CSF primary prophylaxis/treatment;
- grade 4 thrombocytopenia lasting more than 7 days;
- this definition does not apply to the 1st cycle for patients presenting 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, hematological relevant toxicity will be assessed starting from the 2nd cycle;
- any grade 3-4 non-hematological toxicity drug related with special regard to infections and tumor lysis syndrome (excluding alopecia, laboratoristic data and IRR);
- delay ≥ 15 days in the next course administration;
- febrile neutropenia lasting for more than 7 consecutive days.

17.2. SAFETY PARAMETERS

17.2.1. Adverse Events (AEs) and Adverse Drug Reactions (ADRs)

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal (investigational or non-investigational) product and which does not necessarily have to have a causal relationship with this treatment [Dir 2001/20/EC Art 2(m)].
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 (investigational or non-investigational) product, whether or not considered related to the medicinal (investigational or non-investigational) product. 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.
In the context of a clinical trial: any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment [Reg (EU) No 536/2014 Art 2(2)(32)]
Adverse drug reaction (ADR) is a response to a medicinal product which is noxious and unintended [DIR 2001/83/EC Art 1(11)], this meaning that if there is at least a reasonable possibility of a causal

relationship between a medicinal product and an adverse event, it should be sufficient reason for reporting.
Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure [DIR 2001/83/EC Art 101(1)]. Use outside the marketing authorization includes off label use, overdose, misuse, abuse and medication errors.

17.2.2. Serious Adverse Events (SAE)

A serious adverse event (SAE) based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death (the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe);
- 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 (hospitalization is defined as an inpatient admission, regardless of length of stay);
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect;
- Is a suspected transmission of any infectious agent via a medicinal product;
- 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.

If an AE is considered serious, both the AE page/screen of the CRF and the SAE Report Form on www.drugvigilance.filinf.it must be completed.
For each SAE, the Investigator will provide information on severity, start and stop dates, relationship to investigational product (IP), action taken regarding IP, and outcome.

17.2.3. Suspected Unexpected Serious Adverse Reaction (SUSAR)

An unlisted adverse event, the nature or severity of which is not consistent with the applicable product reference safety 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 (IB) 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 related reference safety information document (IB or SMPC).

17.2.4. 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 v 5.0 in the toxicity categories that have recommended grading (follow the link or see Investigator's file).
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)	Fatal

17.2.5. 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).

17.3. SERIOUS ADVERSE EVENTS REPORTING RULES

All events that meet one or more criteria of seriousness (see *paragraphs 17.2.2 and the present paragraph*) occurred after the informed signature until completion of the last subject's related procedure which includes contact for follow-up of safety, which may include contact for follow-up of safety and regardless of the relationship to the study treatment, will be reported as SAE.
The SAE that occurs during the follow-up period, if considered related to the study medication, will be reported.
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 adverse events, which meets one of the seriousness criteria, must be reported as "Serious Adverse Event" on the FIL drugvigilance platform www.drugvigilance.filinf.it.
- 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".

All **AEs** that occur from the time a signed and dated ICF is obtained until completion of the last subject's related procedure which includes contact for follow-up of safety will be recorded in the source documents and the CRF.
All **SAEs** that occur between the study informed consent signature and until completion of the last subject's related procedure which includes contact for follow-up of safety will be notified to the sponsor by study-site personnel within 24 hours of their knowledge of the event through the FIL platform www.drugvigilance.filinf.it by using the FIL Serious Adverse Event reporting rules.
The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All AEs and SAEs regardless of seriousness, severity, or presumed relationship to study therapy, must be recorded in the CRF and source documents in accordance to the CTCAE criteria v 5.0.
All safety information must be recorded using **Medical Dictionary for Regulatory Activities Terminology (MedDRA)**.
Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide.

Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events or serious adverse events. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about adverse event occurrence.

Solicited Adverse Events
Solicited adverse events are predefined local and systemic events for which the subject is specifically questioned.

Unsolicited Adverse Events
Unsolicited adverse events are all adverse events for which the subject is specifically not questioned.

Special Reporting Situations
Safety events of interest on a clinical trial that may require expedited reporting or safety evaluation include, but are not limited to:

- drugs exposure during pregnancy (paternal, maternal)
- suspected transmission of any infectious agent via administration of the medicinal products
- exposure to the medicinal products from breastfeeding
- overdose of the medicinal products
- medication error, intercepted medication error or potential medication error
- suspected abuse/misuse of the medicinal products,

- unexpected therapeutic benefit or clinical benefit from use of the medicinal products inadvertent or accidental exposure to the medicinal products

Special reporting situations (including SRSs not associated to an event) must be reported using the Serious Adverse Event Form following the rules and timelines of SAE reporting, as a sponsor procedure.

17.3.1. Obligations of the Investigator

Investigator(s) 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 and reported according to promoter instructions.
Investigators must submit reports of all SAEs, regardless of attribution, Pregnancy Reports, Special Reporting Situations, Product Quality Complaints to the Sponsor **within 24 hours** of learning of the events.
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 by the end of the study, or that have not resolved upon discontinuation of the patient's participation in the study must be followed until any of the following occurs:

- The event resolves;
- The event stabilizes;
- The event returns to baseline, if a baseline value/status is available;

- The event can be attributed to agents other than the study intervention or to factors unrelated to study conduct;
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts).

Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event.

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as a serious adverse event, ***except hospitalizations for the following***:

- Hospitalizations not intended to treat an acute illness or adverse event (e.g., social reasons such as pending placement in long-term care facility);
- Surgery or procedure planned before entry into the study (must be documented in the CRF). ***Note:*** Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event;
- For convenience the investigator may choose to hospitalize the subject for the duration of the intervention period.

Disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition.

Contact Details for Pharmacovigilance

Name: *FIL Pharmacovigilance Department*
☎: +39.0131.033156
Fax: +39.0131.263455
Email: drugvigilance@filinf.it
Website: www.drugvigilance.filinf.it

17.3.2. Obligations of the Sponsor

The sponsor-investigator assumes responsibility for appropriate reporting of serious unexpected suspected adverse reactions (SUSARs) occurred in the study and preparation and reporting of the development safety update report (DSUR) according to the current regulation.
In particular, the Sponsor assumes responsibility for reporting to Italian Regulatory Authority through Eudravigilance, to all other Investigators that participate in the study and to the Ethic Committee of the coordinating center what described hereafter:

- all relevant information about serious suspected unexpected adverse events (SUSAR) to be related to the study drugs that are fatal or life-threatening will be reported 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
- all other serious unexpected adverse events suspected (SUSAR) to be related to the study drugs will be reported as soon as possible, but within a maximum of fifteen days of first knowledge by the investigator;

- reporting of all SUSARs related to the study drugs, as received by Janssen, to the Principal Investigators of all clinical sites participating in the trial.

Moreover, the Sponsor-investigator will prepare and provide the copy of the DSUR to Italian Regulatory Authority and all relevant Ethics Committees.

The FIL Pharmacovigilance will supply Janssen with a copy of all SAEs which involve exposure to a Janssen 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 supply Janssen with a copy of all Pregnancy Reports and/or Special Reporting Situations and/or Product Quality Complaints (PQC) occurred during the study within 24 hours of their knowledge of the event.

The FIL Pharmacovigilance will provide Janssen with a copy of the annual development safety update report (DSUR) at the time of submission to the Regulatory Authority and Ethics Committees.

17.4. PREGNANCY

17.4.1. Females of Childbearing Potential

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject or partners of male subjects occurring while the subject is on study drug, or within 3 months after the last dose of study treatment, are considered events to be reported by the study-site personnel within 24 hours of their knowledge of the event to FIL Pharmacovigilance on the appropriate **Pregnancy Form**.

Email: drugvigilance@filinf.it
Fax: +39.0131.263455

Any subject who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study intervention.
The exposure of any pregnant female (e.g., caregiver or pharmacist) to study drug is also an immediately reportable event.

The female should be referred to an obstetrician/gynecologist preferably one experienced in reproductive toxicity for further evaluation and counseling.
The Investigator will follow the female subject until completion of the pregnancy and must notify FIL immediately about the outcome of the pregnancy (either normal or abnormal outcome).
Abnormal pregnancy outcomes (e.g., spontaneous or therapeutic abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events and must be reported through www.drugvigilance.filinf.it within 24 hours of the Investigator's knowledge of the event.

All neonatal deaths that occur within 30 days from birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 30 days that the Investigator suspects is related to the in-utero exposure to the study drug should also be reported to FIL within 24 hours of the Investigator's knowledge of the event through www.drugvigilance.filinf.it.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

17.4.2. Male patients

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, including ADRs 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.

17.6. PRODUCT QUALITY COMPLAINT HANDLING

Any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a product after it is released for distribution. A complaint is any indication of the failure of the product to meet consumer or user expectations for quality or to meet performance specifications. It may allege an adverse reaction, injury, or malfunction associated with the use of the product. It may also involve the design, literature, packaging, advertising, availability, physical appearance, or promotion of a product..

Procedures

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

18. STATISTICAL CONSIDERATIONS

18.1. STUDY DESIGN

This is a prospective, multicenter, single arm, single-stage phase II trial in patients aged 18-75 years, with refractory/relapsed CD38 positive PTCL-NOS, AITL and TFH, with centrally assessed CD38 expression ≥ 5%.
It is expected for the current trial that D-GDP will improve the CR rate to 40% with an absolute improvement of 20%, while the toxicity rate is maintained at 30%.

18.2. SAMPLE SIZE CALCULATION

A'Hern's Single-Stage Phase II design will be used. The study sample size has been calculated according to the primary efficacy endpoint.

Based on data from the literature, the null hypothesis that the true proportion of CR after four courses of D-GDP is 0.20 will be tested against an alternative CR proportion of 0.40 with an absolute improvement of 0.20, considered clinically promising with the experimental treatment.
Assuming a type I error rate of 5% and a power of 80% when the CR proportion is 40% overall 35 patients will be accrued. The null hypothesis will be rejected if 12 or more CR out of 35 patients are observed after four courses of D-GDP.

18.3. SAFETY MONITORING AND STOPPING RULES

In order to monitor the safety and the activity of the treatment in small cohorts of patients, we will use the Bayesian approach of Thall et al. (1995) [53], as extended by Thall and Sung (1998) [54].
Monitoring of relevant toxicity **after 4 cycles of D-GDP** will be done to ensure that it is not higher than an acceptable toxicity of 30% (as defined in the safety endpoints) and the monitoring of activity **after 4 courses of D-GDP** will be done to ensure that CR proportion is not lower than 40%.
The prior probability of toxicity and activity are modeled by beta distributions [Beta (0.6,1.4) and Beta (0.8,1.2), respectively].
The enrolment in the study will be stopped if the posterior probability of the treatment being more toxic or less active than expected is greater than 95%.
Patients will be monitored according to the following stopping boundaries in cohorts of five patients, according to the rules summarized in the following Table:

Number of patients enrolled	Stop the enrollment if the cumulative relevant toxicities after 4 cycles are greater or equal to:	Stop the enrollment if the number of cumulative CR after 4 cycles are lower or equal to:
5	4	-
10	6	1
15	9	2
20	11	4
25	13	5
30	15	7
35	17	8

18.4. STATISTICAL ANALYSIS PLAN

18.4.1. Analysis population

Both efficacy and safety analysis will be conducted on all patients receiving at least one dose of planned therapy including the investigational drug.

18.4.2. Demographics and other baseline characteristics

Demographic and baseline characteristics will be presented for all patients. Discrete variables will be summarized by frequencies and percentages. Continuous variables will be summarized by use of standard measures of central tendency and dispersion (mean and standard deviation or median and interquartile range).

18.4.3. Final Efficacy analysis

The primary efficacy analysis will be performed after enrolment of 35 patients. The primary efficacy analysis will consist of an estimate of CRR on the efficacy population after 4 cycles of D-GDP therapy, with 90% confidence intervals (according to 1-sided alpha error of 0.05). To conclude that the new treatment is promising, the minimum number of patients with a CR is 12/35.

The time-to-event functions (OS and PFS) will be estimated by the Kaplan-Meier product-limit method.

Subgroup analyses on primary efficacy parameter (CRR) will be performed to assess the role of daratumumab maintenance and to explore potential prognostic role of CD38 expression. A logistic regression model will be used and the effect (CRR) and its 95%CI will be presented.

18.4.4. Final Safety analysis

The analysis of safety assessments in this study will include summaries of the following categories of safety and tolerability data collected for each subject:

- Drug Exposure
- Adverse Events
- ADRs and SAEs
- AEs leading to withdrawal
- Any Deaths

Duration of study drug exposure, cumulative dose, and dose intensity will be summarized at patient level and at therapy cycle level.
For safety analysis, both at patient level and at therapy cycle level, summaries of incidence rates (frequencies and percentages) and intensity of individual AEs by CTCAE v. 5.0 will be reported. Each patient will be counted only once within each preferred term during the therapy. If a patient experiences more than one AE within a preferred term during the therapy, only the AE with the greatest intensity will be included in the summaries. If, during the same therapy cycle, the patient experiences more than one AE within a preferred term, only the AE with the greatest intensity will be included in the summaries.

According to categorization of CTCAE v 5.0, the cumulative incidence of first severe, life-threatening, fatal (CTCAE grade 3, 4 and 5) and/or SAEs (Infusion-related reactions) commencing during and up to 24 hours after study drug infusion and at any time during therapy and follow-up will be calculated; the cumulative incidence will be calculated using the method of Gooley et al [55], considering death from any cause as a competing event.

18.4.5. Final analysis

The results of this study will support the rationale of a phase III randomized trial if both efficacy and safety endpoints will be considered promising.

19. INDEPENDENT DATA SAFETY MONITORING BOARD (DSMB)

The FIL on its own initiative and responsibility set up an independent external DSMB. The DSMB consist in experts independent from the sponsor.

The selection of DSMB members is extremely important, as DSMB responsibilities relate to the trial safety participants. The ability of DSMBs is to provide the anticipated additional assurance of patient safety and trial integrity.

The aim of the DSMB is to assess, at intervals during the course of the trial, the progress of the trial, the trial safety data and the trial outcome data with a view to recommending whether the trial should continue, be modified or be terminated.
The DSMB composition include relevant expertise, experience in clinical trials and in serving on other DSMBs, and absence of serious conflicts of interest. The objectives and design of the trial and the scope of the responsibilities given to the DSMB determine the types of expertise needed for a particular DSMB.

Roles of DSMB (suggested, not exclusive):

1) To review ongoing safety and efficacy data throughout the study according to the efficacy and safety analyses described in *paragraphs 18.4.3 and 18.4.4* and according to possible additional DSMB requests;
2) To monitor evidence for treatment benefit and thus decide when/whether the main trial question has been answered;
3) To monitor evidence for treatment harm (toxicity);
4) To decide whether to recommend changes to the protocol;
5) To decide whether to recommend that the trial continues to recruit participants or whether recruitment should be terminated;
6) To review final analysis of the data;
7) To discuss final data with PI and the sponsor.

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

20. INDEPENDENT EXTERNAL PATHOLOGY REVIEW

An independent pathology panel will review the lymph node/tumor/bone marrow for confirmation of the diagnosis of cases classified by local pathologist as PTCL-NOS, AITL, TFH and for assessment of CD38 expression. The investigative site must submit the requested samples as part of the screening phase to allow for a histological review.
The review process will be organized at the FIL designated central laboratory according to the procedures described in ***Appendix E***.

21. GOOD CLINICAL PRACTICE, QUALITY CONTROL & QUALITY ASSURANCE

21.1. MONITORING, 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 inconsistencies, 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.

21.2. INVESTIGATOR(S) RESPONSIBILITIES

Investigator(s) 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 Investigator's 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.

22. ETHICAL AND REGULATORY STANDARDS

22.1. INDEPENDENT ETHICS COMMITTEE REVIEW APPROVAL

This study will be conducted according to the Declaration of Helsinki Ethical Principles for Medical Research Involving Human Patients. The review of this protocol by the 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 IEC. A signed and dated statement that the protocol and informed consent have been approved by the IEC must be given to FIL before the study initiation. The names and occupations of the chairman and the members of the IEC must be supplied to FIL.

The FIL as sponsor of the study, together with site Investigator(s), will be responsible for preparing documents, wherever applicable, for submission to the relevant IEC and obtaining written approval for this study. The approval will be obtained prior to the initiation of the study.
A copy of the 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 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 IEC prior to use.
Before the start of the study, the FIL will provide the 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 IEC);
6) any other documents that the IEC requests to fulfil its obligation.

During the study the FIL, in common accord with site investigators, will send the following documents to the 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 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 IEC.

22.2. PROTOCOL AMENDMENTS APPROVAL

Any amendment to this protocol that seems appropriate, as the study progresses will be submitted to the IEC for written approval before the implementation of the amended version. The written signed approval from the 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 IEC approval but will be submitted to the IEC for information purposes.

23. ADMINISTRATIVE PROCEDURES

23.1. 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.

23.2. 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 during the trial, other than that information to be disclosed by law.

23.3. RECORD RETENTION IN INVESTIGATING CENTERS

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 studies performed in the European Community, the investigator is required to arrange for the retention of the patients' identification codes according to the applicable laws and regulations on Clinical Trials.
Any center will notify the sponsor before destroying any data or records.

23.4. 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.

23.5. AUTHORSHIP

The first results of the trial will be published after completion of 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.
Any publication in the form of a lecture, poster or article must be approved by the Scientific Committee of FIL before release.
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.

23.6. 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, with 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.
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.

23.7. PROTOCOL AMENDMENTS PROCEDURES

It is specified that the appendices attached to this study and referred to in the main text of this stud, 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.

24. DATA HANDLING AND RECORD KEEPING

24.1. 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.

24.2. DATA MANAGEMENT

Data will be entered into the clinical online 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) or a Query. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

24.3. 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 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.

25. 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 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 at the end of their staging and 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.

26. REFERENCES

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27. APPENDICES

APPENDIX A: 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* [56].

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 housework, 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 B: CREATININE CLEARANCE CALCULATION

SOURCES: *Cockcroft DW, Gault MH, Prediction of creatinine clearance from serum creatinine. Nephron 16, 31-41,1976* [57].

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 C: COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS V. 5.0

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 5.0**.
Click on CTCAE, version 5.0 to download the document in pdf.

APPENDIX D: RESPONSE ASSESSMENT BY CT AND PET SCANS

SOURCE: *Cheson et al., J Clin Oncol. 2014 Sep 20;32(27):3059-68* [52].

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 5PS†	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	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
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions

(continued on following page)

Table 3. Revised Criteria for Response Assessment (continued)

Response and Site	PET-CT–Based Response	CT-Based Response
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: 5PS, 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 E: GUIDELINES FOR PATHOLOGY REVIEW

The review process will be organized at the FIL designated central laboratory according to the procedures below described. Lymph node/tumor/bone marrow biopsy documenting relapse of PTCL-NOS/AILT/other nodal lymphoma of TFH cell origin, or the more recent biopsy in the case of refractory patients, will be used for central review and for CD38 expression evaluation in immunohistochemistry. Central review and CD38 expression assessment are mandatory for the study.

The investigative site must submit the requested samples as part of the screening phase to allow for an upfront histological review and for CD38 expression evaluation by immunohistochemistry.
Samples shipment will be set up by FIL

For each patient a formalin-fixed paraffin embedded (FFPE) tissue block should be provided to the central laboratory. Sites are encouraged to provide a block, since some nuclear antigens to be tested are labile, and the risk for false negative results on cut sections is high.
The block will be promptly returned to the local site upon completion of the central review process and CD38 assessment.

In the case a block is absolutely not available, the site can choose one on the two following options:

a) to send 20 unstained sections;
b) to send one H&E or GIEMSA stained slide from each block, and all immunostains performed for local diagnosis plus 15 unstained sections. The institution's H&E, GIEMSA and immunostains will be returned promptly after the review is done.

In both cases, an anonymized copy of the local diagnostic reports, including the description, the final diagnosis, and the immunohistochemical and/or flow cytometry results and molecular results, if done, are also to be provided.

Tests to be performed at central laboratory

Central review and confirmation of diagnosis

All tumor samples will be centrally revised according to the 2017 revised edition of the WHO-classification of Tumours of the Haematopoietic and Lymphoid Tissues [1].

Samples will be tested with the following panel of markers: CD2, CD3, CD4, CD5, CD7, CD8, CD30, CD15, CD20, CD21, PD-1, BCL6, CD10, CXCL13, TIA-1, Granzyme B, perforin, FOXP3, Ki-67/MIB-1, and CD38.

Evaluation of CD38 expression

Immunohistochemical assessment (ICH) of expression of CD38 will be performed on fresh sections cut from the paraffin block (or on unstained sections), and the percentage of positive tumor cells will be scored according to Bossard C. et al [58] as follows: 4: >75%; 3: 50-75%; 2: 25-49%; 1: 5-24%; 0: <5%.

Only patients with a percentage of CD38 positive tumor cells ≥ 5% (score ≥ 1) will receive the study treatment, while cases with an insufficient amount of tumor tissue cells (score =0) will be considered as "not evaluable" and will not be included into the study.

Details on results of centralized review and CD38 expression assessment will be collected on a dedicated CRF.

FIL designated central laboratory for central review and CD38 expression assessment:

Prof. Stefano Pileri, Dr. Valentina Tabanelli, Dr. Stefano Fiori
Divisione di Diagnosi Emolinfopatologica
Building IEO1, 1° piano
IEO - Istituto Europeo di Oncologia
via Ripamonti 435, Milano
Phone: +39 02 57489522 Fax: +39 02 94379320
Email: stefano.pileri@ieo.it; divisione.emolinfopatologia@ieo.it

The laboratory has entered into an agreement with FIL to carry out the centralized review of the samples of patients registered in the trial.

APPENDIX F: REFERENCE SAFETY INFORMATION DARATUMUMAB

(Serious Expected Terms Associated with Daratumumab Coded by MedDRA version 20.0)

IB edition 15.0. Approval date: 14 Dec 2018. Data cut-off date: *evaluated safety data from 8 clinical studies (GEN501,GEN503, MMY1001, MMY1002, MMY2002, MMY3003, MMY3004, and MMY3007) and post-marketing experience up to* ***15 Nov 2018***

Table 9: Serious Adverse Reactions (SAR) for Daratumumab Considered Expected for Safety Reporting Purposes

	All Grades
Infections and infestations	
Pneumonia	Common
Sepsis	Common
Upper respiratory tract infection	Uncommon
Lower respiratory tract infection	Uncommon
Bronchitis	Uncommon
Herpes zoster	Uncommon
Influenza[d]	Uncommon
Epiglottitis[a,n]	Uncommon
Lung infection	Uncommon
Pneumonia aspiration[a,n]	Uncommon
Pneumonia bacterial[o]	Uncommon
Pneumonia viral	Uncommon
Bacterial sepsis[a,g]	Uncommon
Bronchitis bacterial[a]	Uncommon
Pneumococcal sepsis[a,p]	Uncommon
Pneumonia cytomegaloviral[a]	Uncommon
Pneumonia influenzal[a]	Uncommon
Pneumonia pneumococcal[a,c]	Uncommon
Pulmonary sepsis[a]	Uncommon
Respiratory syncytial virus infection[a]	Uncommon
Respiratory tract infection[a]	Uncommon
Respiratory, thoracic and mediastinal disorders	
Dyspnoea[b]	Common
Hypoxia[b,m,e]	Uncommon
Pneumonitis	Uncommon
Pulmonary oedema[e,b]	Uncommon
Bronchospasm[b]	Uncommon
Laryngeal oedema[b]	Uncommon
Cough[a,b]	Uncommon

	All Grades
Wheezing [a,b]	Uncommon
Blood and lymphatic system disorders	
Anaemia[i]	Uncommon
Febrile neutropenia	Uncommon
Thrombocytopenia[j]	Uncommon
Neutropenia[h]	Uncommon
General disorders and administration site conditions	
Pyrexia[e,q]	Common
Oedema peripheral[a,n]	Uncommon
Fatigue	Uncommon
Chest discomfort [a,b]	Uncommon
Pyrexia [a,b]	Uncommon
Gastrointestinal disorders	
Diarrhoea	Uncommon
Nausea[a,n]	Uncommon
Vomiting[a,n]	Uncommon
Vascular disorders	
Hypertension[b,l]	Uncommon
Hypotension [a,b,k]	Uncommon
Investigations	
Crossmatch incompatible	Uncommon
Nervous system disorders	
Peripheral sensory neuropathy[a,n]	Uncommon
Headache[a]	Uncommon
Cardiac disorders	
Atrial fibrillation	Uncommon
Injury, poisoning and procedural complications	
Infusion related reaction [a,b]	Uncommon
Immune system disorders	
Anaphylactic reaction[f]	Rare

Incidence is based on those serious events considered possibly, probably, or very likely related to daratumumab by the investigator, unless otherwise indicated.
Based on 1166 multiple myeloma patients treated with daratumumab.
[a]Serious cases have been reported in at least two subjects in clinical trials irrespective of investigator causality and/or during postmarketing experience. After thorough, cross-program assessment of this term by the sponsor, there is reasonable evidence of a causal relationship to daratumumab.
[b]Preferred term (PT) was reported by the investigator to be a sign or symptom of an infusion related reaction (IRR) and would be expected in the context of an IRR. Although investigators varied in their selection of reported SAR terms, these IRRs represent the same serious medical phenomenon.
[c]MedDRA PT considered a synonymous medical term with Pneumonia pneumococcal: Pneumonia streptococcal.
[d]MedDRA PT considered a synonymous medical term with influenza: H1N1 influenza, H2N2 influenza.
[e]Preferred term was also reported outside of the context of an IRR.
[f]Identified from post-marketing experience. Frequency category based on spontaneous reporting rate.
[g]MedDRA PT considered a synonymous medical term with Bacterial sepsis: Bacteraemia.
[h]MedDRA PT considered a synonymous medical term with Neutropenia: Granulocyte count decreased, Granulocytopenia, Neutrophil count decreased.
[i]MedDRA PT considered a synonymous medical term with Anaemia: Haemoglobin decreased, Haematocrit decreased.
[j]MedDRA PT considered a synonymous medical term with Thrombocytopenia: Platelet count decreased.
[k]MedDRA PT considered a synonymous medical term with Hypotension: Blood pressure decreased.
[l]MedDRA PT considered a synonymous medical term with Hypertension: Blood pressure increased.
[m]MedDRA PT considered a synonymous medical term with Hypoxia: Oxygen saturation decreased.
[n]Frequency category calculation is based on serious clinical trial reports irrespective of investigator causality.
[o]MedDRA PT considered a synonymous medical term with Pneumonia bacterial: Lower respiratory tract infection bacterial.
[p]MedDRA PT considered a synonymous medical term with Pneumococcal sepsis: Pneumococcal bacteraemia.
[q]MedDRA PT is listed twice, with different frequency category reported for occurrence as an IRR.

Table 10: Serious Life Threatening or Fatal Adverse Reactions in Patients Treated with Daratumumab Considered Expected for Safety Reporting Purposes

	Life Threatening	Fatal
Infections and infestations		
Pneumonia[a,b]	6 (1%)	6 (1%)
Sepsis[a,c]	5 (< 1%)	1 (< 1%)
Blood and lymphatic system disorders		
Thrombocytopenia[d]	1 (< 1%)	0
Immune system disorders		
Anaphylactic reaction[e]	Rare	

Incidence is based on those serious events considered possibly, probably or very likely related to daratumumab by the investigator, unless otherwise indicated.
Based on 1166 multiple myeloma patients treated with daratumumab.
[a]Frequency calculation is based on clinical trial reports irrespective of investigator causality.
[b]MedDRA PTs considered synonymous medical terms with life-threatening and fatal Pneumonia: Lung infection, Pneumonia bacterial, Pneumonia viral, Pulmonary sepsis.
[c]MedDRA PT considered a synonymous medical term with life-threatening and fatal Sepsis: Septic shock.
[d]MedDRA PT considered a synonymous medical term with Thrombocytopenia: Platelet count decreased.
[e]Identified from post-marketing experience. Frequency category based on spontaneous reporting rate.