CLINICAL STUDY PROTOCOL

DART4MM

Title:	A Pilot study on the efficacy of Daratumumab in Multiple Myeloma (MM) patients in >VGPR/MRD-positive by next generation flow (NGF)
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PROTOCOL APPROVAL

The Investigators:

- Approve this protocol

- declare that the study will be conducted in compliance with the provisions of this protocol

Dott. Alessandro Gozzetti	20/4/18 Data
Dott. Gabriele Buda	23/04/18 Data
Dott. Piero Galieni	23/4/2018 Data
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STUDY BACKGROUND

Multiple myeloma (MM) is a plasma cell malignancy characterized by clonal proliferation of plasma cells in the bone marrow microenvironment and associated organ damage (CRAB= increased calcium, renal insufficiency, anemia, bone lesions) (1). The organ damage is due to a monoclonal protein produced in the blood or urine. It represents about 10% of hematological cancers and 1% of all cancers. Median age at diagnosis is 70 years. In the last decades we experienced a great improvement in myeloma survival both in young and old patients (2,3). A more evident increase was seen in the age group younger than 65 years, leading to 5- and 10-year relative survival of 56% and 41%. By contrast, only moderate improvement was seen in the age group >65 years, and no substantial improvement was achieved among patients older than 75 years (3).

New drugs era

The clinical progresses are due to the introduction of novel drugs (bortezomib, thalidomide, lenalidomide) and to autologous stem cell transplantation (ASCT). These approaches resulted in an increased rate of complete response (CR) that translated into prolonged survival(4). Nonetheless a better understanding of plasma cell biology and myeloma pathways has resulted in the identification of novel targets for therapy. New agents deriving from already approved and active agents (such as second- and third generation proteasome inhibitors, thalidomide, lenalidomide) have been developed and also new drugs with novel mechanisms of action are under investigation in clinical trials. Although advancements have been outstanding in the field of myeloma, there is still a small group of patients (10-15%) that has a dismal prognosis, i.e. .del 17p and t(4;14) patients, in which novel therapeutic approaches are urgently warranted (5-7).

CR and MRD

The introduction of novel therapies for the treatment of MM patients has significantly improved clinical outcome, but it has been difficult to define precisely a complete response since until few years ago CR was defined by negative immunofixation and less than 5% bone marrow plasma cells. This definition of clinical response criteria and clinical end points has largely remained the same over the past 15 years and presents several relevant limitations. The challenge is to identify the patients that despite reaching CR status relapse very quickly (unsustained response) compared to other patients that only achieve partial response but have prolonged survival. Moreover, within the treatment options, new drugs are becoming available that seem to increase the depth of response. Improving CR rates have made the measurement and monitoring of MRD in MM a relevant task. Most patients who achieve MRD-negative status eventually relapse, indicating that the sensitivity and specificity of traditional techniques for MRD assessment can be improved. Flow studies have been employed in latest years, with 4-6 colours cytometry and sensitivity of 10^{-3} or 10^{-4}. Recent

data suggest that a lower cut-off provided by more sensitive assays like next generation flow at 8 colours will likely improve outcome prediction further. Accordingly, 10^{-5} should currently be considered as the target cut-off level for definition of MRD negativity.

To achieve a complete remission (CR) is a prerequisite for long term progression free survivals (PFS) and ultimately overall survivals (OS) and cure both in young and old patients with MM. CR rate can be up to 85% after single or double autologous transplant (ASCT) and up to 40% in the ASCT ineligible (old) patient with new drugs regimens (such as bortezomib, thalidomide, lenalidomide, carfilzomib)(8-10). Nonetheless a minimal residual disease (MRD positive) can be demonstrated in the majority of patients in CR with molecular or flow methodologies. Moreover most patients who achieve MRD-negative status eventually relapse, indicating that the sensitivity and specificity of traditional techniques for MRD assessment can be improved. Recent data suggests that a lower cut-off provided by more sensitive assays (e.g., next generation sequencing (NGS) or high-sensitive flow cytometry (NGF)) can improve outcome prediction further. Two 8 colours tubes panel developed by the EuroFlow Consortium can detect MRD-positive cases with a sensitivity near to the molecular detection and can be applied as standardized method. The IMWG guidelines for response criteria definitions of MRD recommend NGF or NGS as complementary methods or both and by PET/CT as imaging methods.
NGF is more convenient than NGS in terms of applicability in daily laboratory practice.
Long term remission have been reported to be frequent in MRD neg MM patients only after allogeneic transplant and few studies have been done in other drug settings.
The combination of bortezomib-thalidomide-dexamethasone (VTD) has proved to be superior to thalidomide-dexamethasone (TD) as induction therapy before ASCT resulting in a 3-year PFS of 68 % for the VTD arm vs. 56% for the TD arm (11). CR rate was 55%. VTD was also superior in a spanish study associated with thalidomide maintenance (12).Novel drugs have been explored in clinical trials in the induction therapy of younger patients (13-18).

Novel therapeutic strategies: consolidation

Therapy consolidation (usually two cycles after ASCT to increase responses) and maintenance (continuous therapy until progression) are being explored to improve outcome after ASCT as an alternative to perform a second autotransplant with the idea to achieve the same efficacy but with less toxicity. In one study VTD consolidation increased CR from 15 % to 49 % in patients who had previously achieved VGPR after double ASCT (19). Molecular remissions by allele- specific polymerase chain reaction (AS-PCR) following VTD treatment had a better outcome: the PFS at 42 months for patients with a low tumor load was 100% versus 57% for patients with a higher tumor load after VTD. Another study confirmed these findings (20-21). Two cycles of consolidation therapy with TD or VTD were given after the second ASCT. In the TD arm, consolidation improved the CR rate from 40% to 47%. In the VTD arm, the CR rate increased from 49% to 61%. Several studies are ongoing to better evaluate the role of consolidation therapy.

Initial treatment of non-transplant eligible myeloma patients

About two-thirds of MM patients are more than 65 years old at the time of the first diagnosis (22). Therefore the majority of patients are usually not eligible for high-dose therapy followed by ASCT. Achieving at least a very good partial response (VGPR) has been demonstrated to be related to an improvement of the long-term outcome also in the elderly patients (23-33). Standard frontline treatment for elderly patients has been for long time the combination of the oral alkylating agent melphalan with prednisone (MP). This schedule is well tolerated even in frail patients and can be administered as outpatient regimen with maintenance of a good quality of life but the overall response rate obtained is dismal. The introduction of novel agents, such as thalidomide, lenalidomide and bortezomib, has led to better responses also in this setting of patients. Since the CR is an independent predictor of longer PFS and OS regardless of age and International Staging System (ISS), a novel agent is recommended in the induction therapy (34). A randomized phase III study compared bortezomib-melphalan-prednisone (VMP) to MP in the elderly. VMP significantly increased the CR rate (from 4% to 30 %), PFS (from 16 to 23 months), and OS (from 43 to 56 months) with respect to MP (34). Subsequently a reduced bortezomib schedule (from twice- to once-weekly administration) was shown to be better tolerated without affecting the outcome (35). Today, both MPT and VMP are considered the standard therapies for elderly patients (Table 2).

Daratumumab in clinical trials and study rationale

Daratumumab is an immunoglobulin G1 kappa (IgG1κ) human mAb against CD 38 antigen,
produced in a mammalian cell line (CHO) using recombinant DNA technology. (see Investigational Brochure, IB)
Daratumumab has been explored as a single agent in relapsed and refractory patients (GEN501,NCT00574288. In the dose-expansion phase 30 patients received 8 mg/kg and 42 patients 16 mg/kg once weekly (8 doses), twice monthly (8 doses) then monthly up to 24 months. Patients had received a median number of 4 to 5 lines of therapy with 54% of patients refractory to bortezomib and 72% to lenalidomide. Low grade infusion-related reactions were initially observed in up to 75% of patients but were considerably attenuated by the delivery in a large infusion volume. Thirty five percent of patients receiving a dose of 16 mg/kg responded, with 15% of complete or very good partial responses. These encouraging results were confirmed in the multicenter phase 2 study SIRIUS (NCT01985126). In this study, 106 heavily pretreated myeloma patients received daratumumab monotherapy (16 mg/kg). Patients had received a median of 5 prior therapies and the majority of them were refractory to bortezomib, lenalidomide and pomalidomide. Partial response was achieved by 29.2% of patients and the median duration of response was 7.4 months.

A pooled analysis of the patients of the GEN 501 and the SIRIUS trials who had received daratumumab monotherapy at the dose of 16 mg/kg (n=148) showed an overall response rate of 31.1% and a median PFS and OS of 4 and 20 months, respectively. Patients achieving only stable disease or minimal response reached a promising median overall survival of 18.5 months, which is unexpected in this population of very advanced myeloma patients. The quality of response was correlated with the expression intensity of CD38 by neoplastic plasmocytes. Daratumumab was granted accelerated approval in 2015 by the FDA to treat patients with multiple myeloma who had received at least three prior treatments.

Daratumumab is also being studied in combination with many other agents including lenalidomide, bortezomib, carfilzomib or pomalidomide. The phase 3 randomized trial CASTOR recently confirmed a strong advantage of the addition of daratumumab to bortezomib/dexamethasone, in 498 relapsed myeloma patients (NCT02136134). The triplet combination was associated with a significantly better response rate, including 82.9% of PR or better and 19.2% of CR or better. The 1-year rate of progression free survival was 60.7% in the daratumumab group versus 26.9% in the control arm. The updated results of this trial have confirmed this strong PFS benefit for the patients in the daratumumab arm, especially for the patients in first relapse (12-months PFS : 77.3% vs 24.7%, $p<10^{-4}$). Daratumumab also clearly improved the median PFS of patients with high-risk cytogenetic. In this relapse setting, the POLLUX trial also demonstrated a strong advantage of the addition of daratumumab to lenalidomide and dexamethasone, in terms of both response rate and PFS (NCT02076009) . In this trial, patients in the daratumumab group reached an overall response rate of 93% (including 43% CR) and had a 63% reduction in the risk of progression. The updated results of this trial confirmed this significant PFS advantage even in lenalidomide-naïve patients and in patients with high-risk cytogenetic. Minimal Residual disease (MRD) assessed by NGS analysis in patients included in CASTOR and POLLUX trials revealed an unprecedently observed rate of patients with MRD negative disease. Indeed, 32% (vs 9%) and 18% (vs 4%) of patients reached a 10^{-4} MRD negative in the daratumumab (versus control) arms of POLLUX and CASTOR, respectively. In particular the rate of MRD negativity (10^{-5}) has increased continuosly after month 6 in patients receiving Daratumumab monotherapy in the CASTOR trial. (36)

The addition of daratumumab is currently being assessed in the context of previously untreated myeloma patients. The phase 3 randomized study Cassiopeia is currently evaluating the role of daratumumab in combination with VTD in induction, and its role as maintenance after high-dose therapy (NCT02541383). In patients not eligible for transplant, the phase 3 randomized trial MAIA is evaluating the addition of daratumumab to lenalidomide-dexamethasone (NCT02252172).

In the ALCYONE trial (Dara-VMP vs VMP) in patients inelegible to transplant MRD negativity (10^{-5}) has increased continuosly after cycle 10 with daratumumab monotherapy.(37)

The potential benefit of daratumumab has also been recently evaluated in high-risk smoldering myeloma patients in the phase 3 randomized CENTAURUS (NCT02316106).

Daratumumab monotherapy can increase response and in particular MRD negativity, which correlates with PFS and OS. To our knowledge the use of daratumumab in multiple myeloma patients with suboptimal response (in particular with a >VGPR/MRD+) has not yet been explored.
To achieve a better response can ameliorate patient outcome and survival.

STUDY OBJECTIVES

Aim of this study is to evaluate Daratumumab effect on MRD-positive patients with MM who achieved >VGPR after any therapy (ASCT, VMP, Rev-Dex). Daratumumab 16 mg/kg administered at weekly intervals for 8 weeks, +every 2 weeks for an additional 16 weeks, will be given to 50 MM patients who achieved a >VGPR defined by monoclonal component disappearance in serum or urine, immunofixation positive/negative and MRD-positivity (by NGF). Free light chain (FLC) and CT/PET will be evaluated at time 0. NGF will be done on marrow aspirate at time 0, at 2 months and every 6 months for 2 years. If patients will be still MRD positive after 6 months of therapy , treatment will be continued up to 2 years.

Primary objectives

Primary objective of the study is Daratumumab efficacy: in particular capacity to determine increase of response by MRD negativity, detected by NGF assessment on bone marrow specimens

Secondary objectives

Rate of acute and late toxicity according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) criteria.

STUDY DESIGN

No -profit, , prospective , uncontrolled, multi-institutional phase II study, open label, single arm.
Start of recruitment: June 2018
Planned termination of recruitment: December 2019
Planned termination of follow-up: June 2020

Final study report: December 2020

Patient population

Hospital setting, outpatient. 50 patients are planned to be enrolled and treated
Other satellite centers that will enroll patients and treat patients

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SUBJECT ELIGIBILITY

Inclusion criteria

Patients are eligible to be included only if they meet all of the following criteria:

- Age 18-85 years at the time of signing the informed consent form
- Able to adhere to the study visit schedule and other protocol requirements
- >VGPR/MRD-positive by NGF measured by 2-tubes optimized 8-color antibody panel, (OneFlow PCST e PCD BD Biosciences)
- Patients should be at enrollment at least 12 weeks from any therapy for myeloma after diagnosis or at any subsequent relapse
- Eastern Cooperative Oncology Group performance status score of 0, 1, or 2
- Laboratory values and electrocardiogram within protocol-defined parameters at screening
- All previous MM therapy, including radiation, cytostatic therapy and surgery, must have been terminated at least 4 weeks prior to treatment in this study, without corticosteroid therapy.
- Laboratory test results within these ranges:
  - Absolute neutrophil count 1.0 x 10^9/L
  - Platelet count 75 x 10^9/L
  - Creatinine clearance > 30 ml/h)
  - Total bilirubin □ 1.5 mg/Dl
  - Aspartate aminotransferase (AST; SGOT) and alanine aminotransferase (ALT; SGPT) □ 2 x ULN

- Disease free of prior malignancies for 5 years with exception of curatively treated basal cell, squamous cell carcinoma of the skin, or carcinoma "in situ" of the cervix or breast
- Fertile patients must use effective contraception during and for 6 months after study treatment
- Patients must sign on an Informed Consent Form

No study treatment or any other procedure within the framework of the trial (except for screening) will be performed in any patient prior to receipt of written informed consent.

Exclusion criteria

Patients will be excluded from the study if they meet any of the following criteria:

- Received daratumumab or other anti-CD38 therapies previously
- Nonsecretory multiple myeloma
- Previously received an allogenic stem cell transplant or has received an autologous stem cell transplantation within 12 weeks
- Known chronic obstructive pulmonary disease, persistent asthma, or a history of asthma within 5 years
- Absence of the Informed Consent Form signed by the patient
- Pregnant or breast feeding females
- Use of any other experimental drug or therapy within 28 days of baseline.
- Known hypersensitivity to the study drugs
- Known positive for human immunodeficiency virus (HIV) or infectious hepatitis, type A, B or C.
- Plasma cell leukemia, Waldenstrom's macroglobulinemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes), or amyloidosis

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

- Surgically sterile
- If of childbearing potential, agree to practice 2 effective methods of contraception from the time of signing of the step 2 informed consent form through 6 months after the last dose of study drug
- 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 6 months after the last dose of study drug
- 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.

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
USER INDEPENDENT Highly Effective Methods That Are User Independent *Failure rate of ≤1% per year when used consistently and correctly.*
Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
Intrauterine device (IUD)
Intrauterine hormone-releasing system (IUS)
Bilateral tubal occlusion
Vasectomized partner *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 74 days.)*
USER DEPENDENT Highly Effective Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*

Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] oral intravaginal transdermal injectables
Progestogen-only hormone contraception associated with inhibition of ovulation[b] oral injectable
Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.)*
NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of >1% per year)
Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
Male or female condom with or without spermicide[c]
Cap, diaphragm, or sponge with spermicide
A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
Periodic abstinence (calendar, symptothermal, post-ovulation methods)
Withdrawal (coitus-interruptus)
Spermicides alone
Lactational amenorrhea method (LAM)
a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study intervention.

c) Male condom and female condom should not be used together (due to risk of failure with friction).

STUDY TREATMENT

Patients will receive: Daratumumab 16 mg/Kg day every week for 8 weeks intravenous (8 infusions) Daratumumab 16mg/kg day every 2 weeks for 16 weeks intravenous (8 more infusions) If MRD positive by NGF: Daratumumab 16 mg/kg every 4 weeks for 80 weeks intravenous
Treatment duration will be 6 months total (8 infusions = 2 months; + 8 infusions = 4 months) for patients achieving MRD negativity after 6 months; 2 years for patients MRD positive after 6 months

Treatment Duration: interim analysis of bone marrow MRD will be done at months 2 and 6 . Patients achieving an MRD negative status at 6 months can stop treatment (as per primary endpoint). As exit strategy patients still with detectable MRD will continue Daratumumab until MRD negativity is confirmed after 6 months and every 6 months up to two years. Hence, pts still MRD-positive after 6 months dara treatment will continue until MRD turns to negative (i.e. at intermediate MRD evaluations planned at 6,12,18 months), with a maximum treatment duration of 24 months.

STUDY DRUG

Please See IB

General drug characteristics and mechanism of action

Description of Daratumumab

Daratumumab is an immunoglobulin G1 kappa (IgG1κ) human mAb against CD 38 antigen, produced in a mammalian cell line (CHO) using recombinant DNA technology.

Pharmacological Properties

Daratumumab binds to the C-terminus of CD38. While binding of daratumumab antibody to CD38 in vitro has some effect on enzyme activity (inhibiting cyclase and stimulating hydrolase activity), the main effect of daratumumab antibody binding to CD38+ myeloma cell lines is cell lysis through CDC, ADCC or ADCP, or by direct apoptosis following crosslinking of the antibody molecules. These mechanisms are likely to be involved in daratumumab activity in vivo, although the primary mechanism of action in patients is not fully elucidated. Elevated expression of CD38 on myeloma cells allows daratumumab to bind relatively selectively to those cells. Thus daratumumab produces a potent immunologic antitumor effect.

Dosage and Administration

Daratumumab has been administered as monotherapy at doses up to 24 mg/kg and as combination therapy at doses up to 16 mg/kg.

The daratumumab infusion should be intravenously administered at the appropriate initial infusion rate, as presented in Table below. Incremental escalation of the infusion rate should be considered only if the previous infusion of daratumumab was well-tolerated as defined in Table below.

Infusion Rates for Daratumumab Administration via IV

	Dilution Volume	Initial Infusion Rate (first hour)	Increments of Infusion Rate[a]	Maximum Infusion Rate
First infusion	1000 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Second infusion[b]	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Subsequent infusions[c]	500 mL	100 mL/hour	50 mL/hour every hour	200 mL/hour

a Consider incremental escalation of the infusion rate only in the absence of infusion reactions

b Dilution volume of 500 mL should be used only if there were no Grade 1 (mild) or greater infusion reactions during the first 3 hours of the first infusion. Otherwise, continue to use a dilution volume of 1000 mL and instructions for the first infusion.

c Use a modified initial rate for subsequent infusions (i.e. third infusion onwards) only if there were no Grade 1 (mild) or greater infusion reactions during a final infusion rate of ≥100 mL/hr in the first two infusions. Otherwise, continue to use instructions for the second infusion.

Treatment scheme

Patients will receive: Daratumumab 16 mg/Kg day every week for 8 weeks intravenous (8 infusions) Daratumumab 16mg/kg day every 2 weeks for 16 weeks intravenous (8 more infusions) If MRD positive by NGF: Daratumumab 16 mg/kg every 4 weeks for 80 weeks intravenous
Treatment duration will be 6 months total (8 infusions = 2 months; + 8 infusions = 4 months) for patients achieving MRD negativity after 6 months; 2 years for patients MRD positive after 6 months

Treatment Duration: interim analysis of bone marrow MRD will be done at month 2 and 6 . Patients achieving an MRD negative status at 6 months can stop treatment (as per primary endpoint). As exit strategy patients still with detectable MRD will continue Daratumumab until MRD negativity is confirmed on two bone marrow consecutive determination one month apart up to two years. Hence, pts still MRD-positive after 6 months Dara treatment will continue until MRD turns to negative (i.e. at intermediate MRD evaluations planned at 6,12,18 months confirmed after 1 month each for MRD neg Pts), with a maximum treatment duration of 24 months.

Study drug management

The relevant information on the drug characteristics, storage, application, mode of action and adverse reactions is included in the Summary of Product Characteristics (SmPC). Hospital Pharmacy will prepare the drug as usually in daily routine.

Adherence to treatment

NA

RECOMMENDED CONCOMITANT THERAPIES

Pre-infusion therapy

In order to reduce the risk of IRRs, a pre-infusion therapy should be administered to all patients 1-3 hours before each infusion of DARZALEX as follows:

• Corticosteroids (with long or intermediate action)

Monotherapy:

Methylprednisolone 100 mg, or equivalent, administered intravenously. After the second infusion, the dose of corticosteroids may be reduced (methylprednisolone 60 mg orally or intravenously).

Combination therapy:

Dexamethasone 20 mg, given before each infusion of DARZALEX (see section 5.1).

Dexamethasone is administered intravenously before the first infusion of DARZALEX and oral administration may be considered before subsequent infusions.

• Antipyretic (paracetamol 650-1.000 mg by mouth)

• Antihistamine (diphenhydramine 25-50 mg or orally or intravenously equivalent).

Post-infusion therapy

To reduce the risk of delayed infusion-related reactions, post-infusion therapies should be administered as follows:

Monotherapy:

The oral corticosteroid (methylprednisolone 20 mg or equivalent dose of an intermediate or long-acting corticosteroid according to local standards) should be administered in each of the following two days all infusions (starting from the day after the infusion).

Combination therapy:

Consider administration of low-dose methylprednisolone (≤ 20 mg) by the oral route or equivalent the day after the DARZALEX infusion. However, if a regimen-specific base corticosteroid (eg, dexamethasone) is given the day after infusion of DARZALEX, additional post-infusion medications may not be necessary (see section 5.1 rcp).

In addition, for patients with a history of chronic obstructive pulmonary disease, post-infusion therapy including short- and long-acting bronchodilators and inhaled corticosteroids should be considered. After the first four infusions, if the patient does not have major IRRs, these post-infusion inhaler medicines may be discontinued at the discretion of the physician.

Prophylaxis of reactivation of the Herpes zoster virus

Antiviral prophylaxis should be performed to prevent the re-activation of herpes zoster virus.

Pneumocystis Cariini (PCP) Prophylaxis *should be considered with TRIMETHOPRIM/SULFAMETAZOL 800mg po twice a day for two days consecutive weekly*

Concomitant medication

Per le specifiche vedi sezione del prodotto sperimentale.
In general, the patients should continue to take their previous therapies (for non-malignant conditions) according to the recommendations of the responsible physician. The following concomitant therapies will not be allowed:

- any other antineoplastic treatment
- other investigational therapies
- initial prophylactic use of G-CSF, GM-CSF and other growth factors

Concomitant medication, which is relevant for the study assessments, have to be recorded. Additionally, any diagnostic, therapeutic or surgical procedure performed during the study period should be reported.
Supportive care for treatment-related symptoms will be offered as needed to all patients in this study. Prophylactic treatment with antibiotics is not recommended, even in case of grade 4 neutropenia (without fever), but the decision is up to the local investigator's preference. Prophylactic hematopoietic growth factors (i.e., G- or GM-CSF) are not recommended, but secondary prophylaxis after a previous episode of neutropenia is up to the discretion of the investigator. Use of any supplementary growth factor must be documented in the patient record. Growth factors must be discontinued at least 48 hours prior to initiation of the next cycle of chemotherapy.

Emergency management

In case of an emergency the coordinating investigator can be approached via the following phone/fax connection:+39 0577- 586798/+39 0577-586185

Prohibited concomitant medication

Other drugs active in multiple myeloma (chemotherapy, proteasome inhibitors, IMID's, radiotherapy)

Risk-benefit evaluation in the patient population

The benefit should be superior to risks in this population of patients. In fact the potential MRD negativity for patients can translate in longer survivals. The risks are derived mainly from infectious complications that can arise in MM patients.

Subject completion/discontinuation of study treatment

A subject will be considered to have completed the studt if he or she has finished all protocol-specified procedures before the end of the study, has not been lost to follow up, and has not withdrawn consent for study partecipation before the end of the study

Withdrawal of the study subject and treatment modifications

Patients will be removed from protocol treatment for the following reasons:

- disease progression
- development of unacceptable toxicity
- treatment delay more than four weeks or if three consecutive planned doses of Daratumumab are missed for reasons other than toxicity
- administration of any other anti-neoplastic medication or any other experimental drug
- consent withdrawn
- investigator decision in the best interest of the patient
- pregnancy or insufficient contraception
- loss to follow-up
- death

The time point of and reason for removal of a patient must be documented on the case report form. The investigator will attempt to complete all discharge procedures at the time a patient is discontinued from study treatment and to record further follow-up data, if required.

Early termination or suspension of the study

At any time, the sponsor/coordinating investigator of the study may terminate the trial participation of an individual patient, as well as the whole trial, provisionally or permanently, if this is required by stringent medical, administrative or legal reasons (including insufficient patient recruitment), especially if severe and/or frequent adverse events occur, requiring a new risk/benefit evaluation

STUDY ENDPOINTS

MRD negativity will be the primary endpoint

Primary endpoint: MRD negativity will be measured at time 2, 6, 12, 18, 24 months by Flow cytometry on bone marrow aspirate. MRD negativity will be defined as absence of monoclonal plasma cells with a sensitivity of $1x10^5$ cells analyzed by Euro flow protocols.

Time point assessments: primary endpoints will be at 2,6,12,18 and 24 months.

Secondary endpoints:. Complete remission rate (CR), Duration of response (DoR) and progression free survival (PFS).

Time point assessments: primary endpoints will be at 2,6,12,18 and 24 months.

STUDY ASSESSMENTS

Study flowchart

STUDY PARAMETERS	pre-study	day 1 of each cycle	day 8, 15, 22 of cycle 1-2	Day 1 cycle 3-4-5-6	Response evaluation after cycles 2 and 6 (EoT)	Follow-up[6]
Informed consent	χ1					
Medical history	χ1					
Physical exam	χ2	X		X	X	X
Height, body weight	χ2	X		X	X	X
Vital signs	χ2	X	X	X	X	X
Neurological exam	χ2				X	
Performance status	χ2	X		X	X	X
Pregnancy test[4]	χ1	X		X		
CBC/differential blood count[7]	χ2	X	X	X	X	
Serum chemistry, general[8]	χ2	X		X	X	
Serum chemistry, myeloma-specific[9]	χ2	X		X	X	X

Beta-2 microglobulin	X					
Urinalysis[10]	X2	X		X	X	X
Free light chains	X	X		X	X	X
Bone biopsy	X3				X	X[5]
BM aspiration	X3				X	X[6b]
FISH (opt.) At dx	X					
Next Generation flow	X3				X	X[6b]
Toxicity/symptoms (NCI CTC, app. 3)	X2	X	X	X	X	X
Concomitant medication	X	x	X	X	X	X
Tumor assessment, incl. skeletal status	X3				X	
Chest X ray	X3					
ECG	X2					
Echocardiography	X3					
PET/CT	X				X11	X6b

1. Within 14 days prior to the start of therapy.
2. Within 7 days prior to the start of therapy.
3. Within 21 days prior to the start of therapy.
4. In case of women with childbearing potential.
5. As clinically indicated.
6. Every 3 months for two years (or until last dose of study treatment or confirmed disease progression)

6b Every 6 months for two years

7. Hb, WBC, granulocytes, platelets
8. Calcium, creatinine, uric acid, SGOT, SGPT, LDH, alk. phosphatase, total protein, albumin, blood sugar, CRP, VES
9. M protein, immunelectrophoresis, immunoglobulins

10. Urine electrophoresis (Bence-Jones protein), immunelectrophoresis, sugar
11. If complete response after cycle 6 (End of Treatment)

Screening phase

Patient will be referred to study after obtaining at least VGPR to prior treatment. The following baseline assessments will be conducted or obtained within three weeks prior to start of study treatment unless otherwise indicated:

- A condition from prior treatment of >VGPR/ CR-MRD positivity by NGF should be met. In particular:

  - >VGPR: Serum and urine M protein detectable by immunofixation but not on electrophoresis or 90% reduction in serum M protein plus urine M protein level <100mg per 24 h ;

  - CR/MRD positive by NGF: Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and 5% PCs in BM, positive flow by 8 colour analysis and >1 million BM cell analyzed

- Signed written informed consent (within 14 days prior the start of therapy)
- Complete medical history including dates and description of initial diagnosis of multiple myeloma, pre-treatment, ISS and Durie Salmon stage, FISH at diagnosis when available, documentation and measurement of tumor parameters and lesions, tumor related symptoms, relevant concurrent illnesses and relevant concomitant medication (within 14 days prior the start of therapy)
- .Physical examination including: weight, height, WHO performance status and complete neurological examination (within 7 days prior to treatment).
- Vital signs: blood pressure, pulse rate and oral temperature within 7 days prior to treatment.

- Residual toxicities from prior therapies should be recorded using the NCI Common Toxicity Criteria.
- 12 lead ECG.
- Urine or serum HCG if patient is of childbearing potential.
- Hematological tests: Complete blood count (CBC) including neutrophil and platelet count within 7 days prior to treatment.
- General serum chemistry: Calcium, creatinine, uric acid, SGOT, SGPT, LDH, alk. phosphatase, total protein, albumin, blood sugar, CRP, VES
- Myeloma-specific serum chemistry: M protein, immunelectrophoresis, immunoglobulins
- Free Light Chains (FLC)
- Urinalysis: Urine electrophoresis (Bence-Jone protein), immunelectrophoresis, sugar,
- Bone marrow analysis : percentage of plasma cells, percentage of cellularity, Next generation flow (centralized to Siena LAB)
- Recent Skeletal status, recent chest X ray, echocardiography within four weeks prior to treatment
- PET/CT within 4 weeks prior to treatment.

The above tests and procedures are summarized in the Study Flow Sheet in section 6.1.

Tumor response evaluation

Tumor response will be assessed according to the "International uniform response criteria for multiple myeloma" issued in 2006 by the International Myeloma Working Group and the International Myeloma Foundation[i].

Time to best response

Time to best response is defined as the time from treatment start to the first detection of the best response category according to Tab. 2, calculated for all patients, which are not primarily refractory.

Progression-free survival

Progression-free survival (PFS) will be defined as the time from the initial dose of chemotherapy to the time of disease progression (cf. Table 3) or death, or to the date of last assessment without any such event (censored observation).

Time to progression

This will be defined as the time from baseline to the development of progressive disease, as defined in Table 3.

Overall survival

The duration of survival will be determined by measuring the time interval from initial dose to the date of death or last observation (censored).

DATA MANAGEMENT

Data collection

All patient-related data are recorded in a pseudonomized way. Each patient is unequivocally identified by a trial subject number, attributed at recruitment into the study. The investigator has to keep a patient identification log, including the full name and address of the subject and eventually

additional relevant personal data such as hospital record number, home physician etc. In addition, patients who were screened in order to be entered into the study, but who could not be recruited for whatever reason (informed consent not given, not fulfilling selection criteria etc.) are recorded in a "patient reject log".
All the data retrieved during the conduct of the study are entered into the appropriate case record forms (CRF) by the investigator or another person authorized by the investigator (co-investigator). The CRFs are provided by the study secretariat and are explained to the investigator by the study monitor.
All recorded data have to be plausible and complete. Please respect the following technical details when using the CRFs:

- Use black or blue ballpoint pens only in order to insure that all copies are legible.
- Write only one letter or numeral into each of the open boxes of the respective data fields. Closed boxes have to be crossed only (check boxes).
- All data fields have to be filled, except for those referring to open questions. If a specific test was not performed or an information item is definitely not available or applicable, information on this should be provided (not done= ND, not applicable, not available = NA, unknown= UK).
- If a date is not known exactly, please fill in the respective field according to the following example: - - 08 05.
- If any corrections have to be performed in the CRF by the investigator or co-investigator, they have to be performed according to GCP principles, i.e. the original entry has to be crossed out but remain legible.
- The correct version is then written legibly beside or above the original one.
- The correction (or addition) has to be dated and signed or initialed.

Version to be corrected:

1	2	1	3	0	3
day		month		year	

corrected version:

2 date, initials

1	2	1	~~3~~	0	3
day		month		year	

- Please write legibly and use printing letters

The investigator is obliged to complete the case report forms within a reasonable time period after retrieval of the data (i.e. usually within 2 weeks). The completed forms are signed by the investigator, where necessary. The original has to be sent to the data management office or handed

over to the monitor in case of on-site visits. A copy remains with the investigator. The study office or monitor checks the forms for completeness and plausibility. In case of queries, the form or a photocopy of it will be sent or given back to the investigator for clarification/correction/ completion. Queries have to be handled within 4 weeks.
After finalization of the data checks by the study office/monitor the originals or fair copies are sent to the biostatistical center. If additional queries arise there during computer data entry, they are handled by the investigator via monitor or study office contacts.

Data archiving

The original forms of all relevant study documents including CRFs are stored at the office of the coordinating investigator/sponsor for at least 10 years after completion of the final study report. The investigators have to archive major administrative documents (correspondence with ethical committee, authorities, sponsor etc.), the patient identification log, the signed informed consent forms, and the main study documents (protocol, amendments) for the same time period. The original patient records have to be archived according to the standard procedures of the respective institution, but at least for 10 years.

STATISTICAL METHODS AND DATA ANALYSIS

General design

The present trial is designed as a phase II study that aims at estimating the activity of Daratumumab as consolidation therapy after initial therapy. The achievement on MRD negative status defined by next generation flow (NGF), divided by the total intent-to-treat patient number is chosen as primary activity endpoint.
The estimation of the activity rate is to be based on an explorative pilot study, since immediate embarking on a large-scale comparative activity trial would not be acceptable from the point of view of resources. Moreover, this would induce ethical objections, as it does not seem to be justifiable to expose a large number of patients to an experimental approach without sufficient exploratory indications of an improved risk-benefit ratio.

Sample size calculation

The main objective of the trial is to assess, whether the experimental regimen shows a promising activity profile in treatment of MM minimal residual disease. The primary endpoint is the response rate.

Multiple myeloma patients achieving CR and MRD negativity after autotransplant are around 60% and 20% of the total, respectively. MM patients that achieve an MRD negative status after VMP (velcade , melphalan prednisone) are not known. Since CR achievement after VMP is 30%, MRD negativity is probably < 5% of the patients. Statistical analysis will be provided on 50 patients, assuming the power to show an increase in MRD negativity from 20% to at least 50% of the patients treated.
In summary, the trial design is based on the following assumptions:
The activity of the experimental therapy would be rated as insufficient, if the actual response rate was only 20% or lower.
On the other hand, the regimen would be considered to be a promising candidate for further development (e.g. in a phase III trial), if the true ORR amounted to 50% or more.
To show effectiveness of daratumumab to give a negative MRD; only descriptive statistics will be performed.
Statistical Power Calculations:*
This is a phase 2 interventionalopen-label, single arm study, thus no formal calculation of sample size and statistical power is necessary. This notwithstanding, a sample size of 50 patients produces a two-sided 95% confidence interval with a width equal to 16.6% when the sample proportion (eg, for percentage of patients with MRD negative at months 2) is 10%, equal to 25.4% when the sample proportion is 30%, and a maximum width equal to 27.7% when the sample proportion is 50%. This calculation was performed using PASS v.11 software (NCSS, LLC. Kaysville, Utah, USA).

All parameters will be evaluated in an explorative or descriptive manner, providing means, medians, ranges, standard deviations and/or confidence intervals. If p values are calculated (e.g. in subgroup comparisons), they will be presented explicitly without referring to hypotheses or a significance level. Usually, no error adjustment for multiple testing will be performed. Thus the p values will reflect the comparison-wise error and not the experiment-wise error. All p values will be two-sided if not stated otherwise. The statistical methods described in this section are suited for the data and distributions usually expected in this type of trials. The suitability will be checked after data entry. If necessary, the statistical method will be modified accordingly, with critical discussion of the original and modified results.
Response, toxicity and event rates at pre-specified time points are calculated, providing confidence intervals. In case of comparison between patient groups, these rates will be analyzed by Fisher´s exact test, χ^2 test or Mantel-Haenszel test (or trend test according to COCHRAN/ARMITAGE), respectively.
Event related data like time to response, progression-free or overall survival will be estimated by the product limit method[ii] and compared using the log-rank test. If the Peto log-rank test is not appropriate because of violation of the proportional hazard assumption[iii], Gehan's generalization of the Wilcoxon rank sum test for censored data (GEHAN 1965) will be applied, preferably in its

modification by PETO (1972) and PRENTICE (1978). If appropriate, prognostic strata will be taken into account (PETO, 1977).
Multivariate analyses will eventually be performed by suitable regression models (logistic regression, proportional hazard regression model.

The main biometrical evaluation of the study and the compilation of the statistical report as part of the integrated clinical/biometrical report will be performed two years after termination of patient recruitment as well as after completion and/or correction of all case report forms.

SAFETY MANAGEMENT

Definition

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

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

Collection of adverse events starts with the signing of the ICF until the last study related procedure. A serious adverse event 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
- Is life-threatening (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.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- 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 Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate 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 subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the study drug and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For Daratumumab, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure.

Adverse Event Associated With the Use of the Drug

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

Severity Criteria

An assessment of severity grade will be made using the following general categorical descriptors:
Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

Adverse events recording

All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the subject's last study-related procedure, which may include contact for follow-up of safety. Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study drug, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments. Anticipated events will be recorded and reported as described in Safety Reference Information section.

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

The Sponsor-Investigator assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor-Investigator will also report to the investigators (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs).

Serious Adverse Events

All serious adverse events occurring during the study must be reported to the appropriate Sponsor-Investigator contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the

study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be made by facsimile (fax).

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, should 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 drug 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 (eg, 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 treatment 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 (refer to Section Adverse Event Definitions and Classifications).

Pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the sponsor-investigator by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form.

Any subject who becomes pregnant during the study must be promptly withdrawn from the study.

Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported as noted above.

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

Causal link

Not Related

An adverse event that is not related to the use of the drug

Doubtful

An adverse event for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An adverse event that might be due to the use of the drug. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An adverse event that might be due to the use of the drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very Likely

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

Adverse events reporting

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

Anomalies in the laboratory parameters

Please see IB

ADMINISTRATIVE PROCEDURES

Study financing

The sponsor/coordinating investigator will take care of the financing/funding of the study. The funding is based partially from the pharmaceutical industry (Jansenn).

Insurance coverage

Insurance will be given by AOUS

Indipendent data monitoring committee (IDMC)

Since the study is a phase2 including 50 patients as total , IDMC is not required.

General revision

The study will be monitored externally by regular site visits, query letters and telephone calls to the investigator by authorized personnel of the principal investigator. Queries or monitoring visits may take place before, during and after recruitment of patients into the study. The number of contacts will depend on the characteristics of the respective center, e.g. the number of recruited patients.

According to the investigator's agreement, the monitor is allowed to access the trial documentation and the patients' personal medical records in the participating center.
In order to assure the quality of the data, all entries into the CRFs are formally inspected for completeness and plausibility. During site visits, an additional control with respect to identity of the data recorded in the personal patient records and in the CRF (Source Data Verification) may be performed. In addition, the monitor should review original patient records, drug accountability records and document retention (study file). Additionally, the monitor should observe study procedures and will discuss any problems with the investigator.

Amendments to the protocol

Any modifications to the protocol which may impact on the conduct of the study, potential benefit of the study, or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendment will be agreed upon by the investigators and the sponsor. It requires a new application to the competent authority and to the competent ethical committee prior to implementation, according to EC regulations.
Administrative or technical changes of the protocol such as minor corrections and/or clarifications that have no effect on the way the study is to be conducted, nor on the risk-benefit-ratio, will be agreed upon by the sponsor and the investigator(s) and will be documented in a memorandum to the protocol. The competent ethical committee may be notified of such changes at the discretion of the sponsor/coordinating investigator.

The sponsor/coordinating investigator has to assure, that all amendments have been added to the study documents at any site involved in the trial.

Ethical considerations

The study will be conducted according to the principles of Good Clinical Practise (GCP) as reported in current Italian and European legislation and in agreement with the last revision of the declaration of Helsinki and current the Italians laws and regulations. Patients will be enrolled only after giving a free written informed consent (see attach). The patient’s confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations (Decreto Legislativo 30/6/2003 n. 196 e successive modificazioni). Each participating Hematology Unit must submit the study protocol to local Ethics Committee/IRB for approval.

Acquisition of the informed consent

Before recruitment into the clinical trial each patient will be informed, that participation in the study is completely voluntary, and that he or she may withdraw the participation in the trial at any time without any declaration of reasons. This will not lead to any disadvantage for the respective patient. If the withdrawal is caused by any adverse drug events, the patient should inform the investigator about this fact.
The treating physician will inform the patient about the drugs to be used and their possible adverse effects. At the same time he/she will be informed on the nature and objectives of the study, expected advantages of the participation, possible hazards of the study and alternatives of treatment. The patient will also receive the necessary information on the trial specific insurance and his obligations with this respect. The patient will have sufficient time for his decision and opportunity to ask additional questions. Moreover, the patient will receive a written "patient information", containing all relevant information for the patient's decision and the course of the study. Information about all biological sampling during the study will be given.
The consent of the patient to participate must be obtained in writing before recruitment into the study. The informed consent form must be dated and signed by the patient. Thereby, he declares his voluntary consent to participate in the study and his willingness to comply with the requirements of the trial and the instructions of the treating investigator during the course of the study.
There are two copies of the informed consent form: one for the patient and one to be kept by the investigator in his study documents. The informed consent is only valid after receiving the patient's signature. Thereafter, the patient can be entered into the study if he/she fulfils the selection criteria.
With the declaration of consent the patient agrees that data on his disease are recorded within the framework of the clinical trial and that they are transferred to the sponsor in a pseudonymized way. Moreover, the patient agrees that delegates from the responsible authorities or the sponsor may have direct access to his/her original medical records for trial related monitoring, audit, review and regulatory inspection.

Confidentiality

All Investigators in the study will maintain confidentiality about all data coming from the trial , personal data regarding patients involved before, during and after trial.

Conflicts of interest

No conflicts of interest are present by investigators.

RESPONSABILITY AND PUBLICATION POLICY

No Profit Promoter

The promotor of the study is a no profit public institution (UOC Ematologia, Azienda Ospedaliera Universitaria Senese)

Data properties

All data produced are property of study Promoter. Each participating center will send all requested patients data to the study promoter (in anonymous form); after publication of experimental results, collected data (always in anonymous form) may be transferred also to Countries outside UE.

Publication

The promoter only will decide how and when to publish the results of the research.

Other financing

Even if private subjects will contribute with additional funds to the project, this would not give any right of data property to the private subject or right of veto for data publication.

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