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ΜΕΤΑΠΤΥΧΙΑΚΗ ΔΙΠΛΩΜΑΤΙΚΗ ΕΡΓΑΣΙΑ

ΜΑΡΚΙΔΗΣ ΜΙΧΑΗΛ

# *''Second line therapy using Lenalidomide/Dexamethasone, in Greek and Cypriot patients with refractory/relapsed multiple myeloma. An observational retrospective study''*

*Ο συνδυασμός Λεναλιδομίδης/Δεξαμεθαζόνης ,ως θεραπεία δεύτερης γραμμής σε Έλληνες και Κύπριους ασθενείς με ανθεκτικό/υποτροπιάζων πολλαπλό μυέλωμα.Μια πολυκεντρική,αναδρομική μελέτη παρατήρησης.*

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## ΕΛΛΗΝΙΚΗ ΣΥΝΟΨΗ ΜΕΤΧΑΠΤΥΧΙΑΚΗΣ ΔΙΠΛΩΜΑΤΙΚΗΣ ΕΡΓΑΣΙΑΣ

### Τίτλος μελέτης

Ο συνδυασμός Λεναλιδομίδης/Δεξαμεθαζόνης ,ως θεραπεία δεύτερης γραμμης σε Έλληνες και Κύπριους ασθενείς με ανθεκτικό/υποτροπιάζων πολλαπλό μυέλωμα.Μια πολυκεντρική,αναδρομική μελέτη παρατήρησης.

### Τύπος μελέτης και σχεδιασμός

Πρόκειται για μια πολυκεντρική ,αναδρομική μελέτη παρατήρησης.

Θα αναζητηθούν από τους ερευνητές ,τα ιατρικά αρχεία ασθενών με ανθεκτικό/υποτροπιάζων πολλαπλό μυέλωμα ,οι οποίοι λάβανε ως θεραπεία δεύτερης γραμμής ,τον συνδυασμό λεναλιδομίδης/δεξαμεθαζόνης .

Κύριο καταληκτικό σημείο της μελέτης ,είναι η μέτρηση και η εκτίμηση της επιβίωσης χωρίς εξέλιξη της νόσου(PFS).

Δευτερεύων καταληκτικό σημείο είναι η παρατήρηση και αξιολόγηση του χρόνου ,από την αρχή της θεραπείας δεύτερης γραμμής μέχρι την υποτροπή της νόσου ή τον θάνατο του ασθενούς από οποιοδήποτε αίτιο.

Στη μελέτη αυτή θα συμπεριληφθούν το ελάχιστο 195 ασθενείς και θα παρατηρηθεί η PFS για 12 μήνες.

Τα κέντρα που θα εντάξουν ασθενείς στη μελέτη θα είναι 15 συνολικά σε Ελλάδα και Κύπρο.

# CLINICAL TRIAL PROTOCOL

TITLE OF STUDY

**Second line therapy using Lenalidomide/Dexamethasone, in Greek and Cypriot patients with refractory/relapsed multiple myeloma. An observational retrospective study.**

Protocol Version: 1.0

Date : 2017

Study sponsor : “Sponsor pharmaceuticals”

# TABLE OF CONTENTS

## 1 LIST OF ABBREVIATIONS

AE Adverse Event

ASCT Autologous Stem Cell Transplantation

ASH American Society of Hematology

CI Confidence Interval

CR Complete Response CRF Case Report Form

CT Computed Tomography

EBMT European Group for Blood and Marrow Transplantation

ECOG Eastern Cooperative Oncology Group

EFS Event-Free Survival

FDA Food and Drug Administration

FLC Free Light-Chain

GPP Good Pharmacoepidemiology Practice

HDT High-Dose Therapy

IBMTR International Bone Marrow Transplant Registry

ICF Informed Consent Form

IGF-1 Insulin Growth Factor 1

IL-6 Interleukin 6

IRB Institutional Review Board

ISS International Staging System

MGUS Monoclonal gammopathy of undetermined significance

MM Multiple Myeloma

MR Minor Response

MRI Magnetic Response Imaging

NCCN National Comprehensive Cancer Network

nCR Near Complete Response ORR Overall Response Rate

OS Overall Survival

PD Progressive Disease

PFS Progression-Free Survival

PR Partial Response

REC Research ethics committee

RRMM Relapsed or Refractory Multiple Myeloma

SD Stable Disease

TNF-α Tumor Necrosis Factor aplha

TtNT Time to Next Treatment

TTP Time to Progression

VEGF Vascular Endothelial Growth Factor

## 2. PROTOCOL SYNOPSIS

### Study title

"Second line therapy using Lenalidomide/Dexamethasone in Greek and Cypriot patients with Refractory/Relapsed Multiple Myeloma.An observational retrospective study."

### Study type and design

This observational ,retrospective study aims to evaluate disease progression and survival rates as well as to record treatment strategies used in common clinical practice with relapsed/refractory multiple myeloma patients after first relapse ,in Greece and Cyprus.

### Primary endpoint

Evaluation of the 12 month progression-free survival rate in patients treated with Lenalidomide/Dexamethasone at 1$^{st}$ relapse.

### Secondary endpoint

Time(months) from second line treatment initiation upon to disease progression or death from all causes,whatever comes first,in patients receiving therapy with Lenalidomide/Dexamethasone after first relapse.

### Time frame

12 months

**Number of sites enrolling participants:** 15

**Number of participants :** 195

# 3. INTRODUCTION

## 3.1 Background

### 3.1.1 Epidemiology and pathogenesis of multiple myeloma

Multiple myeloma is a hematologic disorder which is characterized by a proliferation of malignant, monoclonal plasma cells in the bone marrow (BM) and/or extramedullary sites, that appears in association with monoclonal protein in serum and/or urine, decreased normal immunoglobulin (Ig) levels, and lytic bone disease.[1]

The American Cancer Society's estimates for multiple myeloma in the United States for 2017, say that about 30,280 new cases will be diagnosed and about 12,590 deaths are expected to occur [2]. In Europe, 38.928 incidents of multiple myeloma and 24.283 deaths were reported during 2012. In Greece, 567 new diagnoses and 380 deaths were recorded(2012). Multiple myeloma incidence and death rates are slightly higher for men compared to women [3,4]. Furthermore multiple myeloma is twice as common in black population compared to the white population.[5]

Multiple myeloma evolves from a premalignant condition clinically recognized as Monoclonal gammopathy of undetermined significance .MGUS is present in 3% to 4% of the general population older than 50 years. Because MGUS is mostly asymptomatic and often detected as an incidental laboratory finding, only 10% of the patients with newly diagnosed multiple myeloma have a history of preexisting MGUS. However, studies have found that MGUS almost always precedes multiple myeloma and is associated with a risk for progression of approximately 1% per year. Smoldering multiple myeloma is an intermediate stage between MGUS and MM and is associated with a higher risk for progression of approximately 10% per year.[5]

Although there are treatment strategies available from early to relapsed multiple myeloma, it is thought to be an incurable disease due to the interactions between the bone marrow and the multiple myeloma plasma cells. It has been found that the bone marrow environment strengthens multiple myelomas growth with secretion of cytokines, growth factors and anti-apoptosis factors like tumor necrosis factor alpha (TNF-a),interleukin 6 (IL-6),insulin-like growth factor 1 (IGF-1) and vascular endothelial growth factor (VEGF). As a result, factors that not only block the proliferation of the multiple myeloma cells but also affect the bone microenvironment, are definitely more beneficial in its treatment.

### 3.1.2 Diagnosis and Staging

Diagnosis of symptomatic multiple myeloma is based on the detection of a monoclonal paraprotein (M-protein) in the plasma with levels of ≥30 g/L and/or ≥10 % of clonal plasma cells of bone marrow and/or proven by biopsy plasmacytoma along with one (or more) of the CRAB symptoms. CRAB symptoms are hypercalcemia, renal problems, anemia and bone damage like thinning (osteoporosis) or lytic sessions [6].

Multiple myeloma staging is based on Durie-Salmon criteria developed in 1975, or on the recently developed International Staging for Multiple Myeloma criteria (ISS). ISS criteria are based on beta-2-microglobulin and albumin levels [7,8].

### 3.1.3 Treatment strategies

Different therapeutic strategies exist, for patients dealing with multiple myeloma. Although there are clear guidelines for dealing with the disease when the first diagnosis occurs, there is not a generally accepted treatment strategy for patients dealing with relapsed and refractory multiple myeloma. [9,10]

For patients with symptomatic multiple myeloma, who are eligible for transplantation, first line therapy strategy includes initial

induction with chemotherapy and later autologous stem cell transplantation followed (or not) by maintenance therapy. Maintenance therapy after ASCT aims in improving progression-free survival (PFS) and overall survival(OS) [11,12].

For patients who are not eligible for transplantation, first line therapy includes chemotherapeutic factors use like melphalan with prednisolone. Furthermore, the addition of drugs like lenalidomide, thalidomide and bortezomib has shown great response and overall survival results [13,14,15]

### 3.1.4 Refractory/Relapsed multiple myeloma definition and treatments

Relapsed/refractory multiple myeloma (RRMM) is defined as a disease which becomes non-responsive or progressive on therapy or within 60 days from the last treatment in patients who had achieved a minimal response or better on previous therapy.

Relapsed multiple myeloma is regarded as a recurrence of the disease after previous response, and has been defined based on objective laboratory and radiological criteria: ≥ 25 % increase of the serum or urine monoclonal protein (M-protein) or ≥ 25 % difference between involved and uninvolved serum free light chains from its nadir, respectively, or the development of new plasmacytomas or hyperkalaemia. In patients with non-secretory disease, relapse is defined as an increase of the bone marrow plasma cells. In general, an indication for relapse treatment has been defined as either the appearance or reappearance of one or more CRAB criteria or a rapid and consistent biochemical relapse.

The relapse criteria have been developed by the European Bone and Marrow Transplantation team in association with the Autologous Blood and Marrow Transplant Registry team and the International Bone Marrow Transplant Registry team. These criteria are known as the “EBMT criteria” [28]

Even though there are some therapeutic choices for multiple myeloma, it is an incurable disease with 1/3 of patients showing no

response to first line therapy and all of the patients relapsing some time after initial therapy [9,10].

Treatment choices for refractory/relapsed multiple myeloma are lenalidomide,thalidomide, bortezomib, alkylating agents, anthracyclines and corticosteroids as a monotherapy or different combinations [16,17,18] .Therapy must be individualized, taking upon consideration the first line treatment, the response to the first line treatment and the physical condition of the patient [19].

The combination of lenalidomide and dexamethasone has improved the outcome of patients with refractory/relapsed multiple myeloma. Randomized, phase III, clinical trials MM-009 and MM-010 that tested the Len/Dex combination in comparison with dexamethasone monotherapy revealed improved response and survival rates for RRMM patients. It has been proved that Lenalidomide/Dexamethasone combination has improved outcomes when administered after the $1^{st}$ relapse. It is important to mention that patients receiving this combination after $1^{st}$ relapse had better TTP,ORR and OS than those receiving the combination as a next line therapy ($3^{rd}$ or more). More specific TTP was 17,1 months (after $1^{st}$ line) against 10,6 months (later), ORR was 66,9% (after $1^{st}$ line) against 56,8% (later) and OS was 42 months(after $1^{st}$ line) against 35,8 months (later) [22,31]

Starting dose of lenalidomide should be monitored when in combination with dexamethasone in patients with RI or cytopenia. In addition, creatinine clearance and complete blood count (CBC) must be recorded before starting the Lenalidomide/Dexamethasone treatment. For patients with renal dysfunction starting dose must be reduced depending on the level of dysfunction [29]

## 4 NECESSITY OF THE TRIAL

Lenalidomide and dexamethasone therapy has prolonged patients' with refractory and relapsed multiple myeloma survival. Efficacy and safety of these drugs are sufficiently evidence based. Nevertheless, there is a lack of objective data regarding efficacy and the usage of this drug combination as second line therapy.

As it is well known, the study population of a certain clinical trial must fulfill strict inclusion and exclusion criteria that may lead to a population, that is not necessarily representative of the patient population with refractory and relapsed multiple myeloma. Additionally, the outcomes of a certain clinical trial are observed under strictly controlled conditions that do not necessarily reflect the usual clinical practice.

Due to the lack of knowledge regarding the patient outcomes in refractory and relapsed multiple myeloma receiving lenalidomide and dexamethasone combination treatment, this retrospective study aims to evaluate disease progression and survival rates as well as to record the treatment strategies used in common clinical practice with patients with RRMM after the first relapse in Greece and Cyprus.

## 5 STUDY ENDPOINTS

### 5.1 Primary endpoind

Evaluation of 12 month progression free survival (PFS), of patients under Lenalidomide/Dexamethasone treatment after first relapse.

### 5.2 Secondary endpoind(s)

- Time (in months) from second line treatment initiation up to disease progression or death from all causes, whatever comes first, in patients receiving therapy with Lenalidomide/Dexamethasone after first relapse (clinical or laboratory).

- Time (in months) from second line treatment initiation up to disease progression or death from all causes, whatever comes first, in patients receiving therapy with Lenalidomide/Dexamethasone after symptomatic relapse (clinical).
- Time (in months) from second line treatment initiation up to disease progression or death from all causes, whatever comes first in patients receiving therapy with Lenalidomide/Dexamethasone after asymptomatic relapse (laboratory).
- Percentage of multiple myeloma patients achieving more or same partial response after second line treatment initiation (ORR rate).
- Causes of choosing the Lenalidomide/Dexamethasone combination treatment including renal dysfunction, age, co-morbidities and other factors.

# 6 STUDY DESIGN

## 6.1 Type of study

It is a multicenter, two-countries, non-interventional, retrospective study of patients' medical records with refractory/relapsed multiple myeloma, who fulfill the inclusion criteria.

All the information needed for the purposes of this study, will be gathered in the electronic web-based Case Report Form (e- CRF).

## 6.2 Clinical sites

This clinical study will take place in 15 clinical sites around Greece and Cyprus, where clinical hematologists work. Doctors will be asked to retrieve the required information and fill the CRF.

## 6.3 Study population

This study will include 195 patients with refractory/relapsed multiple myeloma that received second line therapy with lenalidomide and dexamethasone combination between 1 January 2012 until 31 December 2015 and fulfill all the study inclusion criteria depending on the investigators' judgment.

# 7 STUDY ENROLLMENT

Patients with refractory/relapsed multiple myeloma (EBMT criteria), alive or not, who started second line therapy with lenalidomide/dexamethasone between 1 January 2012 to 31 December 2015 will be detected through their medical history files.

Patients will be included in the study consecutively, starting from the ones who received second line therapy with Lenalidomide/Dexamethasone closest to the endpoint date of 1 January 2012.

Inclusion of patients who have died is permitted only after REC/IRB's approval that confirms that individual consent need not be obtained. In the case of not approving the exception of consent, patients who died will not be included in the study.

## 7.1 Inclusion criteria

Patients included in the study must fulfil **ALL** of the following criteria:

- Male and female patients aged 18 or older.
- Subjects must have a relapsed or refractory multiple myeloma diagnosis according to EBMT criteria.

- Subjects must have initiated second-line therapy with lenalidomide/dexamethasone between 1st January 2012 and 31 December 2015.
- Subjects must have available medical files/records and detailed historical data on their disease course and clinical management.
- Provision of signed ICF for collecting and analyzing medical data pertinent to the objectives of this study.

### 7.2 Exclusion criteria

For the candidate subjects **NONE** of the following criteria should apply:

- Prior malignancy (within the 3 years preceding initial diagnosis of multiple myeloma).
- Subject participation in another interventional study.
- Concurrent administration of anti-cancer regimens for malignancies other than multiple myeloma.

## 8 STUDY PROCEDURE AND EVALUATIONS

### 8.1 Study procedure

Upon inclusion to the study the investigator must follow the procedures mentioned bellow:

a) History file check and personal history in order to check compliance with the inclusion/exclusion criteria

b) Explanation of the study goal to the patient. Let him take his time and read the informed consent.

c) Retrieval of old data from the patient's medical record and CRF completion.

d) Provision of the completed CRF of every new patient to the clinical trial monitor and store a copy.

## 8.3 Study evaluations

For the study purposes, the principal investigator (doctor) will collect and complete the CRF with the following patient information:

- Signed informed consent
- Patient eligibility for inclusion to the study (inclusion/exclusion criteria)
- Demographics (age, gender, race)
- Anthropometrics upon diagnosis and upon initiation of second line therapy
- Medical history
- Initial diagnosis information (including disease staging according to staging criteria of ISS) (prior to first relapse)
- Laboratory findings (including blood screening with white blood cell type and blood smear testing, biochemical tests, including calcium and creatinine clearance, SPE, immunoprecipitation, urinary albumin and protein M, bone marrow biopsy and imaging studies). The information above will be collected from the medical records and will be at the closest timing since the initial diagnosis of the multiple myeloma, before initiation of second line therapy, at the first, documented response and upon relapse.
- Information regarding first line therapy including starting date, the exact drugs used and the duration of treatment.
- Data regarding the best response to the first line therapy
- Data regarding diagnosis of refractory/relapsed multiple myeloma prior to the second line therapy.
- Patient functional status prior to the second line therapy initiation.
- Data of second line therapy (starting day, dose, date and cause for stopping or adjusting the dose).
- Evaluation of disease progression during second line therapy.

## 9 STATISTICAL CONSIDERATIONS

### 9.1 Sample size considerations

The sample size is determined by the primary endpoint of the study, which is the percentage of the study population with 12 months PFS (progression free survival).

There is lack of published studies related to 12 month PFS. Because of that, we will use data from two clinical trials MM-009 and MM-010, which claim that 14 month PFS of Lenalidomide/Dexamethazone as second line treatment approaches 50%. In order to estimate our sample size, we will use the 50% PFS for the 12 months.

Therefore, supposing the PFS is 0,50 the number of patients is calculated:

$$n \geq \frac{1.96^2 s^2}{\delta^2}$$

and $s = (1-p)\, p$

n is the number of patients

z=1,96

δ=0,07 is the precision and

p=0,05 is the given percentage

Thus we may have sufficient precision if we use at least 195 patients.

Given the above, the 95% confidence interval (CI) of the FPS percentage will be 43,0 - 57,0.

Thus we may have sufficient precision if we use at least 195 patients.

{Sample size calculations were performed using SPSS 24 software}

## 9.2 Statistical methods and data analysis

This study has a descriptive nature and it doesn't aim in the confirmation or rejection of some hypothesis. Descriptive statistical analysis and epidemiological methods will be used for all the study data.

Shapiro-Wilk control will be used to test the normality of the continuous variables distribution in order to determine the use of parametric or non-parametric methods for the data analysis.

Continuous variables will be presented with the use of descriptive statistics (Mean, median, standard deviation) and categorical variables will be presented in frequency tables (N, %).

Data related to study end-points (PFS, ORR, biochemical relapse, clinical relapse) will be calculated with their 95% confidence intervals.

Logistic regression analysis will also be used to evaluate the effect of confounding factors in the percentage of Multiple Myeloma patients treated with Lenalidomide/Dexamethasone from the 1$^{st}$ relapse and didn't have another relapse or did not die within 12 months from the initiation of the second line treatment with Lenalidomide/Dexamethasone (PFS).

In addition, Kaplan-Meier method will be used for secondary end-points, having to do with evaluations of time-to-event and estimation of PFS and TtNT. Relevant diagrams will also be made.

Differences in PFS and TtNT between study groups of patients will be evaluated with Log-Rank testing. Furthermore, the effects of demographic, anthropometric and clinical characteristics in the PFS and TtNT will be evaluated by Cox regression analysis.

Every statistical testing will have a 0,05 significance level.

## 10 COLLECTION AND REPORT OF SAFETY DATA

This is a non interventional, retrospective study and because of that there is no active collection and reporting of safety data. All the adverse events have been mentioned before and must have been noted by the doctors, according to pharmacovigilance requirements. However, if a serious adverse event is noted in the CRF, it will be asked from the investigators to report it in special adverse event report files so as to be processed.

## 11 DATA HANDLING AND RECORD KEEPING

### 11.1 Important documentation

Before the initialization of the study the following files must be collected and archived:

- Curriculum vitae of principal investigator and co-investigators (recent ones, signed and dated).
- Dated and signed principal investigators agreement to the protocol.
- Dated and signed principal investigators agreement to changes of the protocol (if needed).
- Copy of approval correspondence from the responsible authorities in compliance with the local law for each of the clinical sites included in the study.
- Investigators contract.
- Financial contracts.

## 11.2 Important files and storage

- The investigator should maintain complete and accurate trial documents in a safe place (fire and water protected).
- Special attention should be paid to updated documents.
- Attention should be paid to any e-records that must be used within an adequate document management system that is validated and the access protected by password and specific identification. Adding or changing e-data must be controlled by an audit trail. Maintain a security system that prevents unauthorized access to the data
- The investigator should take measures to prevent accidental or premature destruction of these documents.

## 11.3 Case report forms

Because electronic CRF will be used, attention should be paid to any e-records that must be used within an adequate document management system that is validated and the access protected by password and specific identification.

Adding or changing e-data must be controlled by an audit trail. Maintain a security system that prevents unauthorized access to the data

## 11.4 Protocol deviation

Protocol deviations/changes are permitted only with written agreement from the sponsor and documented approval from the REC.

## 11.5 Premature discontinuation of the trial

### 11.5.1 Investigator termination

If the investigator decides to terminate or suspend a trial, the sponsor and the REC should both be informed promptly and given a written explanation for termination.

### 11.5.2 Sponsor termination

If the sponsor decides to terminate or suspend a trial the investigator should inform the institution and provide the REC with a written explanation.

### 11.5.3 REC termination

If the REC terminates or suspends a trial, the investigator should inform the institution, the health authorities where applicable and the sponsor, and provide the latter with a written explanation.

## 12 ETHICAL ISSUES

### 12.1 Ethical standard

This trial was designed and will be conducted in accordance to the Helsinki Declaration(lastly published on Oct 2008),to the guidelines of good pharmacoepidemiology practice and to the local regulations.

### 12.2 Institutional review board

The protocol, informed consent forms, recruitment materials and all participant materials will be submitted to the local IRB for review and approval.

Approval of both the protocol and the consent form must be obtained before any participant is enrolled.

### 12.3 Consent procedures and documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. The investigator will explain the research study to the participant and answer any questions that may arise.

The participants may withdraw consent at any time throughout the course of trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

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