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| **TITLE**  | ***Phase 2 Clinical Trial of Dichloroacetate in Plateau Phase Myeloma***  |
| PRINCIPALINVESTIGATOR | Dr Samuel Bennett |
| CO-INVESTIGATORS | Dr James D’Rozario (Clinical)Dr Philip Crispin (Clinical)Dr Anneke BlackburnDr Lucy Coupland |
| VERSION NUMBER  | 1.0 |
| DATE OF PROTOCOL  | August, 2014 |
| ANZCTR NUMBER | Pending Ethics Approval |

**FOREWORD**

Information in this protocol should not be disclosed other than to those involved in the execution or

ethical review of the study without written authorisation from the investigators.

**This protocol complies with the Guidelines for Good Clinical Practice in clinical research.**

This document is intended to describe a phase 2 clinical trial and to provide information about trial procedures. It is not intended that the Protocol be used as a guide for the treatment of patients not enrolled on the trial.

No data will be accepted for analysis unless the Human Research Ethics Committee

(HREC) has approved this trial for patient enrolment and participation.

Any future amendments to this document will be forwarded to the ACT HREC for review prior to protocol circulation. If in doubt about which is the correct version of the protocol please contact the Principal Investigator.

The Protocol and all other trial related documentation including the Patient Information Sheet (PIS) and Patient Consent Form (PCF) and Case Report Forms (CRF) must be written in English and under no circumstances be translated into another language without prior written approval from the investigators

**Protocol History**

|  |  |  |  |
| --- | --- | --- | --- |
| Version No | **Date** | **Author**  | **Reason** |
| 1.0 | August 2014 | S Bennett | HREC review |

**SPONSOR SIGNATURE**

I have read and approve this protocol. My signature, in conjunction with the signature of the investigator, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and all applicable local laws and regulations including, but not limited to, the International Conference on Harmonisation Guideline for Good Clinical Practice (ICH GCP), the ethical principles that have their origin in the Declaration of Helsinki and

applicable privacy laws

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NAME OF SIGNATORY *(print)*

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POSITION OF SIGNATORY

**PRINCIPAL INVESTIGATOR SIGNATURE**

I have read and approve this protocol. My signature, in conjunction with the signature of the

sponsor, confirms the agreement of both parties that the clinical study will be conducted in

accordance with the protocol and all applicable local laws and regulations including, but not

limited to, the ICH GCP, the ethical principles that have their origin in the Declaration of

Helsinki and applicable privacy laws.

Nothing in this document limits the authority of a physician to provide emergency medical care

under applicable regulations.

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CONTENTS

**1 Contacts...............................................................................................................** **11**

**2 Abbreviations ...................................................................................................... 12**

**3 Protocol Synopsis ................................................................................................. 14**

**4 Study Schema ...................................................................................................... 19**

**5 Schedule of assessments ...................................................................................... 20**

**6 Background ........................................................................................................ 22**

**7 .0 Objectives and Hypothesis ............................................................................ 30**

7.1 PRIMARY OBJECTIVE ............................................................................................................................................... 30

7.2 SECONDARY OBJECTIVES *...............................................................................................................................................* 30

7.3 HYPOTHESIS:

............................................................................................................................................... 30

**8.0 Patient Selection........................................................................................ 31**

8.1 ELIGIBILITY CRITERIA ................................................................................................................................................ 31

8.2 EXCLUSION CRITERIA

.................................................................... ........................................................................... 32

**9.0 Investigational Plan ..................................................................................... 33**

9.1 STUDY DESIGN ............................................................................................................................................... 33

9.2 AGENT ADMINISTRATION

............................................................................................................................................... 33

9.3 DOSE MODIFICATIONS AND DELAYS ................................................................................................................................................ 34

9.4 DURATION OF THERAPY & ‘STOPPING RULES’ .............................................................................................................................................. 35

9.5 DURATION OF FOLLOW-UP

............................................................................................................................................... 36

9.6 GENERAL CONCOMITANT MEDICATION & SUPPORTIVE CARE GUIDELINES ............................................................................................................................................... 36

*9.6.1 Permitted concomitant therapy: ......................................................................................................................* 36

*9.6.2 Prohibited concomitant therapy: .......................................................................................................................* 36

**10 Pharmaceutical Information....................................................................**.......... **37**

10.1 DICHLOROACETATE *.................................................................................................................................................* 37

10.2 DRUG ACCOUNTABILITY *................................................................................................................................................* 37

**11 Registration ...................................................................................................... 37**

**12 Documentation ................................................................................................** **38**

12.1 INFORMED CONSENT ................................................................................................................................................ 38

12.2 CASE REPORT FORMS ................................................................................................................................................ 38

12.3 ESSENTIAL DOCUMENTS .................................................................................................................................................. 38

12.4 CONFIDENTIALITY .................................................................................................................................................. 38

12.5 DOCUMENT RETENTION ................................................................................................................................................. 39

**13 Statistical Considerations ..................................................................................** **39**

13.1 DEFINITION OF STUDY ENDPOINTS ................................................................................................................................................. 40

*13.1.1 Primary*

*.........................................................................................................* 40

*13.1.2 Secondary*

*.........................................................................................................* 40

13.2 SAMPLE SIZE AND POWER CALCULATIONS ................................................................................................................................................. 40

13.3 STATISTICAL METHODS ................................................................................................................................................ 41

13.4 END OF TREATMENT ................................................................................................................................................ 41

13.5 TRIAL MODIFICATION & SAFETY & DATA MONITORING COMMITTEE ................................................................................................................................................ 42

**14 Assessment of Response ................................................................................. 43**

14.1 Complete Response (CR) .............................................................................................................................................. 43

14.2 Stringent Complete Response (sCR) ............................................................................................................................................... 43

14.3 Very Good Partial Response (VGPR) .............................................................................................................................................. 43

14.4 Partial Response (PR) .............................................................................................................................................. 43

14.5 Stable disease (SD) .............................................................................................................................................. 43

14.6 Progressive Disease (PD) ............................................................................................................................................ 44

**15 Adverse Event Reporting .............................................................................. 44**

15.1 DEFINITIONS ................................................................................................................. 44

*15.1.1 Adverse Event ...........................................................................................................................................* 44

*15.1.2 Serious Adverse Event ...........................................................................................................................................* 45

*15.1.2.1 SAE Exceptions*

*...........................................................................................................................................* 45

*15.1.3 Immediate reporting of serious adverse events ...........................................................................................................................................* 46

*15.1.4 Pregnancy Related Events ............................................................................................................................... ............* 46

15.2 SAE REPORTING RESPONSIBILITIES

............................................................................................................................................ 47

15.3 ADVERSE EVENT SEVERITY ............................................................................................................................................ 47

15.4 ADVERSE EVENT TREATMENT RELATIONSHIP GUIDELINES

............................................................................................................................................ 48

**16 Ethical Considerations................................................................................... 48**

16.1 ETHICAL PRINCIPLES ........................................................................................................................................... 48

16.2 REGULATORY REQUIREMENTS ........................................................................................................................................... 48

16.3 INFORMED CONSENT

........................................................................................................................................... 48

16.4 ADHERENCE TO PROTOCOL........................................................................................ 49

**17 Publications and presentation policy .............................................................. 49**

17.1 TRIAL REGISTRATION ............................................................................................................................................ 49

**19 REFERENCES .................................................................................................. 49**

**Appendix 1 WHO Diagnostic Criteria .................................................................. 52**

**Appendix 2 ECOG Performance status criteria ..................................................... 53**

**Appendix 3 Pregnancy prevention risk management plan .................................... 54**

**Appendix 4 ISS (International Staging System) at diagnosis .................................. 60**

**Appendix 5 Common Terminology Criteria for Adverse Events (CTCAE Version 4) 61**

**Appendix 6 Total Neuropathy Score (Clinical)......................................... 62**

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**SAE and pregnancy notification within 24 hours**

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**2 Abbreviations**

AE Adverse event

ADR Adverse drug reaction

ALP Alkaline phosphatase

ALT Alanine transaminase

ASCT autologous stem cell transplant

B2M Beta 2 microglobulin

BMAT Bone marrow aspirate and trephine

CMP Calcium, Magnesium & Phosphate

CR Complete Response

CK Creatine Kinase

CRF Case report form

CRU Haematology Clinical Research Unit

CTN Clinical trial notification

CTCAE Common Terminology Criteria for Adverse Events

DCA Dichloroacetate

Dex Dexamethasone

DLT Dose-limiting toxicity

ECOG Eastern Co-operative Oncology Group

FCBP Female of childbearing potential

FLC Free light chain

GCP Good Clinical Practice

GCSF Granulocyte colony stimulating factor

GSTZ1 Glutathione S-Transferase Zeta 1

GGT Gamma-glutamyltransferase

HIV Human immunodeficiency virus

HREC Human Research Ethics Committee

ICH-GCP International Conference on Harmonisation, Good Clinical Practice

ID Identification

IF immunofixation

IHC immunohistochemistry

IIT Investigator Initiated Trial

IMiDs Immunomodulatory drugs

IMWG International Myeloma Working Group

ITT Intention-To-Treat

LDH Lactate dehydrogenase

LFT Liver function test

MTD Maximum Tolerated Dose

MM Multiple myeloma

MR Minor response

MTD Maximum tolerated dose

NHMRC National Health and Medical Research Council

OS Overall survival

PB Peripheral blood

PICF Patient Information and Consent Form

PD Progressive disease

PFS Progression-free survival

PI Principal Investigator

PR Partial Response

QTc Corrected QT interval

SAE Serious adverse event

SD Stable disease

SFLC Serum free light chain

SPEP Serum protein electrophoresis

TCA Tricarboxylic Acid

TGA Therapeutic Goods Administration

UEC Urea, Electrolytes and Creatinine

ULN Upper limit of normal

**3 Protocol Synopsis**

*Note: This is a synopsis. The body of the protocol must be referred to for the complete study information.*

|  |  |
| --- | --- |
| **Title** | ***Phase 2 Clinical Trial of Dichloroacetate in Plateau Phase Myeloma***  |
| ***Abbreviated Title*** | *DiCAM* |
| **Indication** | *Treated myeloma in plateau phase* |
| **Rationale** | *Some cancers show heightened anaerobic glycolytic activity. Some cases of plasma cell myeloma also show this property. Dichloroacetate is an orally bioavailable compound which is known to inhibit pyruvate dehydrogenase kinases (PDKs) and shift cellular metabolic activity towards aerobic glycolysis and the TCA cycle, and is relatively non-toxic. DCA shows evidence of activity in a number of cancers in pre-clinical models and has been tested in phase I and II studies in solid (non-haemopoietic malignancies).**The plateau phase of myeloma treatment (where patients have achieved a maximal response to other traditional glucocorticoid, IMiD and proteasome inhibitor based therapy but show evidence of residual disease based on the persistence of a paraprotein) is an ideal setting to test the efficacy of DCA.* *With non-invasive monitoring of the paraprotein level while taking DCA over 12 weeks, the study will establish if DCA shows any in vivo evidence of anti-myeloma activity.*  |
| ***Objective: Primary*** | 1. *Establish if there is evidence of clinical efficacy of DCA in myeloma in plateau phase as measured by at least a >25% fall in paraprotein / light chain levels over 12 weeks.*
 |
| ***Objectives: Secondary***  | *Establish the achievable maximum drug levels of DCA in vivo with the dosing schedule as outlined in* ***section 6****-* ***Background:******Dosing schedule & Pharmacokinetics.***1. *Confirm the tolerability and safety of DCA at these doses*
2. *Genotype patients for Glutathione transferase zeta (GSTZ1) and correlate with DCA levels and tolerability.*
 |
| **Hypothesis** | *H0 = <10% of patients respond to the DCA i.e. H0: patients achieving ORR < 10% of study participants**Ha = 12 weeks of oral DCA will cause at least a 25% reduction in paraprotein or light chains in at least 30% of participants* |
| **Trial design** | *This is a prospective non-randomised open label, phase 2, two-stage clinical trial.* |
| **Number of participants** | *First phase = 15. Second phase = 10. Total participants numbers = 25* |
| **Study Duration** | *Participants will receive 12 weeks of study drug only. Follow up will continue for 6 months after accrual achieved i.e. (after the 25th patient has received 3 months of therapy).* |
| **Investigational product** | ***Dichloroacetate (DCA)*** |
| **Main inclusion criteria at registration** | * ***Diagnosis of Plasma Cell Myeloma (at any time) according to WHO criteria***
* *Aged 18 years or older*
* *Eastern Co- operative Oncology Group Performance status ≤2*
* *Life expectancy due to myeloma or co- morbid conditions in the opinion of the treating physician likely to exceed 3 months*

***AND*** * ***..has measurable residual disease***
	+ *Quantifiable serum paraprotein on electrophoresis at least 1g/L* ***OR***
	+ *Elevated free kappa (>21mg/L) or lambda light chains (>30mg/L) AND a minimum difference between level of involved/uninvolved light chain of 150mg/L AND an abnormal serum free light chain ratio (normal κ:λ = 0.26-1.26)*
* *AND*
* ***.. is in a ‘Plateau- Phase’***
	+ ***A period of neither progression nor response at least 28 days following the last change in myeloma treatment***
	+ ***Progression*** *defined as per IWMG*
		- *an increase in the paraprotein by >= 25% and at least 5g/L*
		- *In light chain only patients, >25% increase in difference between involved and uninvolved light chain level, with an absolute increase of >0.1g/L*
		- *development of new lytic lesions*
		- *development of new end organ damage (Renal disease, marrow failure, lytic lesions, hypercalcaemia) attributable to myeloma or new plasmacytomas*
	+ ***Response*** *defined as*
		- *reduction in the paraprotein by ≥ 25% OR in the case of light chain only myeloma, 25% decrease in the difference between the involved and uninvolved light chain and an absolute reduction of at least 100mg/L.*
	+ *Blood samples to assess for plateau phase must be ≥ 28 days apart*
 |
| **Exclusion criteria**  | * *Unable to give informed consent*
* *Non-secretory myeloma*
* *Receipt of any active anti-myeloma therapy (excluding bisphosphonates) in the 16 weeks prior to enrolment, with the exception that patients on stable doses of long- term maintenance therapy will be allowed (no dose alteration in the prior 8 weeks).*
* *Pregnant or breastfeeding*
* *Unwilling to avoid pregnancy and use birth control (if applicable) during the study and for 4 weeks after completion of the study*
* *Unable to swallow capsules*
* *Major surgery within the last 28 days*
* *Enrolled in another trial or have discontinued from another clinical trial within the last 14 days*
* *Any serious pre-existing medical condition that, in the opinion of the study doctor would keep you from being on this trial*
* *Any peripheral motor or sensory neuropathy, neuralgia or paraesthesia (of grade 3 or worse)*
* *Any pre-existing severe ataxia or tremor (grade 3 or worse)*
* *Known history of liver disease (cirrhosis established by imaging studies or biopsy) or abnormal liver function tests within the last 14 days (AST or ALT > 3 x ULN or ALP >2.5 x ULN or total bilirubin > 1.5 x ULN)*
* *Any more than moderate renal impairment i.e. Calculated Creatinine Clearance by Cockcroft Gault formula of ≤ 30 mL/min*
* *Inadequate cardiac function defined as:*
	+ *Electrocardiographic (ECG) evidence of*
		- *Acute ischemia*
		- *Active clinically significant conduction system abnormalities*
		- *>Grade 2 (>480 ms) (QTc) prolongation*
	+ *Uncontrolled angina or severe ventricular arrhythmias*
	+ *Myocardial infarction within the last 6 months*
	+ *Class 3 or higher New York Heart Association Congestive Heart Failure*
* *Haematological*
	+ *Haemoglobin < 80g/L*
	+ *Absolute Neutrophil Count (ANC) ≤ 1.0 x 10^9/L*
	+ *Platelet Count ≤ 50 x 10^9/L*
* *Any active fungal, bacterial and/or known active viral infection including HIV or hepatitis (A, B, or C).*
* *A second malignancy which in the opinion of the investigator may affect the interpretation of results*
 |
| **Efficacy assessments** | *Overall Response Rate (ORR) = the proportion of participants achieving at least 25% and at least 1g/L reduction in paraprotein OR at least a 25% reduction in the difference between involved and uninvolved light chains (and a minimum absolute reduction in difference between the involved & uninvolved light chain of at least 100mg/L)* |
| **Safety assessments** | *AEs, SAEs, Total Neuropathy Score (TNSc)* |
| **Other assessments** | *DCA plasma levels* *GSTZ1 genotyping* |
| **Follow-up schedule** | *Physical examination and paraprotein level at 3 and 6 months post completion of therapy* |
| **Statistical considerations** | *The study will have 80% power to detect a true effect of the DCA therapy (at a significance level of 0.05), if 25 patients are recruited.*  |
| **First major analysis** | ***After the 15th participant has completed 12 weeks of therapy.*** |
| **Final/other analyses** | *A study close-out (censor) date will be 9 months from D1 of the 25th trial participant’s commencement of the treatment schedule.*  |

**4 Study Schema**

Consent &

SCREENING **screening failure**

**Oral DCA for 12 WEEKS**

**Follow-up Assessments**

5 Schedule of assessments

|  |  |  |  |
| --- | --- | --- | --- |
| **Study Visit** | **Time Between Visits** | **Approx Visit****Length** | **Study Procedures/ Activities** |
| **Screen visit****Occurs between 1 and 28 days** **of starting study drug.** |  | Approx. 2 hours | **During this time period, which may consist of multiple visits, you will have the following done to determine if you are eligible to participate in this study:*** You will sign the informed consent form
* Your complete medical history will be taken
* You will be asked how well you are able to perform the normal activities of daily living (a performance status evaluation)
* You will be asked about any other drugs you may be taking , including over-the counter medication
* You will have a physical exam, which will include measuring your height, blood pressure, heart rate, weight and assessment for pre-existing nerve damage (neuropathy)
* Women who are able to have children must take a blood pregnancy test
* You will have an electrocardiogram (“ECGs”, tests that measure the electrical activity of the heart) taken
* Urine will be collected for urinalysis and microscopy
* Blood (about 3.3 teaspoons) will be taken for routine tests and to confirm you are eligible for the study (FBP, UEC, LFT, LDH, glucose, CK, CMP, Lipase + EPP/SFLC\*, HIV, HBV, HCV)

**\*If the last measurement of the paraprotein was more than 28 days prior to the screening visit then the EPP/SFLC needs to be rechecked** * If this blood test doesn’t yet confirm a “plateau” phase, you may still be eligible but will need to have a repeat blood test (about 1.7 teaspoons) in 4 weeks’ time until a stable paraprotein/light chain level (<20% change) is confirmed
 |
| **Day 1** | 24 hrs after confir-med eligible  | Approx. 8 hours | * If more than 14 days has elapsed from screening visit you will have a physical exam, which will include measuring your height, blood pressure, heart rate, weight, electrocardiograms (“ECGs”, tests that measure the electrical activity of the heart) taken.
* You will be asked how well you are able to perform the normal activities of daily living (a performance status evaluation)
* You will be asked about any other drugs you may be taking , including over-the counter medication
* An intravenous cannula (IV) will be inserted and samples of blood (around half a teaspoon) taken just prior to the first dose of DCA. These are to test your genes to see how well your body processes the DCA, and ensure the baseline level of DCA in the blood is zero.
* You will be given the first dose of DCA (a single dose of 25mg/kg)
* Further samples of blood (a maximum of half a teaspoon each time) will then be taken from the cannula 1, 2, 3, 4, 5, 6 hrs after the dose of DCA is given to check the levels of DCA in the blood
 |
| **Day 2** |  |  | * You will have a brief clinical assessment by a study doctor to ensure you are not having any problems after the first dose
* A blood sample (around half a teaspoon) will be taken to check the level of DCA in the blood 24hrs after the first dose
* You will take 25mg/kg now and again in the evening
 |
| **Day 3** |  |  | * You continue to take 25mg/kg in the morning and in the evening
 |
| **Day 4** |  |  | * You will reduce your dose to 6.25mg/kg twice a day (ie morning and evening)
 |
| **Day 8** | 7 days after D1  | Approx.8 hours | * You will have a physical exam, which will include measuring your height, blood pressure, heart rate, weight and a check for evidence of “neuropathy” or nerve damage
* You will have an ECG
* Urine will be collected for urinalysis and microscopy
* An intravenous cannula will be inserted and blood (about 3.8 teaspoons) will be taken for routine tests (FBP, UEC, LFT, LDH, glucose, CK, CMP, Lipase) and to test the level of DCA in the blood **before you take this morning’s dose of DCA**
* Further samples of blood (a maximum of half a teaspoon each time) will then be taken from the cannula after 1, 2, 3, 4, 5, 6 hours to check the levels of DCA in the blood
 |
| **Day 28****(1 month)** | 20-22 days after D8 | Approx 2 hours | * You will have a physical exam, which will include measuring your height, blood pressure, heart rate, weight and a check for evidence of “neuropathy” aka nerve damage and tests of balance.
* Blood (about 3.8 teaspoons) will be taken for routine tests\*\*, and to check the DCA levels and to check the level of paraprotein or light chains in your blood
 |
| **Day 56****(2 months)** | 28- 30 days after D28 | Approx. 2 hours | * You will have a physical exam, which will include measuring your height, blood pressure, heart rate, weight and a check for evidence of “neuropathy” aka nerve damage and tests of balance
* Blood (about 3.8 teaspoons) will be taken for routine tests\*\*, and to check the level of DCA in the blood and to check the level of paraprotein or light chains in your blood (DCA taken after drug, adherence level assessment)
 |
| **Day 84****(3 months)** | 28-30 days after D56 | Approx. 2 hours | * You will have a physical exam, which will include measuring your height, blood pressure, heart rate, weight and a check for evidence of “neuropathy” or nerve damage
* You will be asked how well you are able to perform the normal activities of daily living (a performance status evaluation)
* You will have your blood pressure and electrocardiograms (“ECGs”, tests that measure the electrical activity of the heart) taken
* Blood (about 3.8 teaspoons) will be taken for routine tests\*\*, and to check the level of DCA in the blood and to check the level of paraprotein or light chains in your blood
* **Today is the last day that you will take the DCA**
 |
| **Day 168****(6 months)** | 84-91 days after D 84 | Approx 2hrs | * You will have a physical exam and check for evidence of neuropathy (nerve damage).
* You will have blood taken (around 1.7 tspn) to check the paraprotein level.
 |
| **Day 252****(9 months)** | 84-91 days after D 168 | Approx 2hrs | * You will have a physical exam and check for evidence of neuropathy (nerve damage)
* You will have blood taken (around 1.7 tpsn) to check the paraprotein level.
 |

\*\*(FBP, UEC, LFT, LDH, , glucose, CK, CMP, Lipase)

**6 Background**

Plasma cell myeloma, commonly known as Multiple Myeloma (MM) is a cancer comprised of a clonal expansion of plasma cells manifesting as bone disease, hypercalcaemia, renal disease and anaemia3 With current treatment the disease is incurable and average survival is in the order of 3- 7 years3

Most cases of myeloma are associated with intact monoclonal immunoglobulin production (i.e. “paraprotein”) or “free light chains” which can be used as a surrogate marker for disease burden and response to treatment, or sign of impending relapse or progression.

The recommended current treatment for symptomatic MM is1,4

1. 3-6 cycles of induction chemotherapy.
2. autologous stem cell transplantation (ASCT) in patients who respond to

induction therapy, who are <70 years of age with a good performance status and who do not have significant co-morbidities. Transplant ineligible patients will normally receive further cycles of chemotherapy (up to 8)

1. subsequent monitoring +/- maintenance therapy for those who respond to

ASCT

1. second-line therapies at disease progression include cytotoxic chemotherapy, lenalidomide and bortezomib based regimens.
2. subsequent relapses can be treated with repeat courses, or by introducing

agents to which patients have not been exposed.

Those patients who do not respond to induction chemotherapy undergo treatment with salvage induction therapy and, if a response if achieved proceed to ASCT. If only a partial response to the initial ASCT is achieved a second ASCT may be advised.

A plateau phase is achieved in the majority of patients following ASCT or following induction chemotherapy in patients not suitable for ASCT. This phase of the disease may last for weeks to months prior to disease progression and plateau phase may also be seen after subsequent courses of therapy. Although there is no consensus as to what constitutes a plateau phase, previous phase 2 studies have adopted various definitions with the core underlying concept being a “stable” paraprotein level6. During these periods, no therapy, bone strengthening agents alone or maintenance therapy with thalidomide, lenalidomide or steroids may be used. A philosophical issue in Multiple Myeloma therapy is the role of treatment to achieve a response plateau: to reserve future therapy for disease progression versus treatment to achieve the deepest response up-front and then maintaining that response4. The aim of maintenance therapy is to prolong the plateau phase or improve the depth of response.

***Dichloroacetate (DCA)***

DCA is an agent that has, in recent years, been demonstrated to have anti-cancer properties – either anti-proliferative or pro-apoptotic – across a range of cancers7 . Dr Anneke Blackburn’s group at The John Curtin School of Medical Research are recognised internationally for their work on the effect of DCA in breast cancer in vitro and in vivo using mouse models. Others groups have published work on the effectiveness of DCA across a range of cancer types8.

Specific to this application, multiple myeloma cells lines have recently been demonstrated to be sensitive to DCA treatment, DCA increased MM cell sensitivity to Bortezomib treatment and the administration of DCA plus Bortezomib to myeloma-bearing mice increased their survival9,10

The preliminary evidence on the benefits of DCA as a cancer treatment is mounting and, due to the availability of information on the internet, patients with cancer are already accessing DCA in an uncontrolled way. It is imperative, therefore, that clinical trials are performed to determine whether there is, in fact, benefit to be gained from DCA treatment in a variety of cancers.

The aim of this proposal is to study the effect of DCA in patients with MM who are in plateau phase and attending clinics at The Canberra Hospital.

***Mechanism of DCA***

DCA targets a very fundamental change in cancer cells – the high rate of glycolysi*s (*glucose breakdown) in the presence of adequate oxygen (known as the Warburg effect). The high rate of glycolysis is accompanied by high glucose uptake into cells, a property now used in Positron Emission Tomography (PET) scans with 16F-DG PET imaging of cancers. These scans identify metabolically active tumours with high glucose uptake. The metabolic signature of cancers is in part due to the proliferative drive of cancer cells.

The enzyme pyruvate dehydrogenase (PDH) governs the conversion of pyruvate to acetyl Co-A (Figure 1A) and therefore can control the flow of metabolites from glycolysis to the citric acid cycle, thereby regulating the generation of ATP from glucose. PDH activity is regulated by 6 other enzymes - 4 kinases and 2 phosphatases. The four pyruvate dehydrogenase kinase (PDK) isoforms, PDK1-4, inhibit PDH activity by phosphorylating serine residues Ser232, 293 and 300 on the two E1α subunits of PDH4,whereas the two phosphatases (PDP1-2) reactivate PDH by dephosphorylating any of the 3 sites. PDK2 is ubiquitously expressed while other isoforms are expressed only in selected tissues11 , however expression can be deregulated in cancer cells12,13



***Figure 1: DCA is effective against cancer.***

*(A) Redirection of pyruvate metabolism by DCA, away from lactate to acetyl-CoA production and into mitochondrial metabolism. (B) DCA halted the growth of established primary mouse mammary tumours in vivo (gangB13). (C) Enhanced cytotoxicity of a novel arsenic-based drug PENAO (5-7uM) by DCA (5mM) in human breast, colon, pancreatic and prostate cancer cells. Toxicity is low in non-cancerous MCF10A cells*

The PDH-PDK axis can integrate signals from growth factors, oncogenes and the microenvironment and is a central regulatory hub for tumour metabolism and a target for cancer therapy. DCA redirects the metabolism of pyruvate away from lactate production and into mitochondrial oxidation via the inhibition of PDKs (Figure 1A). It is a pan-PDK inhibitor that is most effective against PDK211, but can also inhibit other isoforms at higher concentrations (Ki for inhibition of PDK1-4 by DCA are 1.0, 0.2, 8.0 and 0.5 mM, respectively14.

DCA has been proposed as a novel and relatively non-toxic anti-cancer agent15 because it targets a change undergone during tumorigenesis, and can be effective against cancer cells without toxicity to normal cells. DCA can inhibit cancer growth in vitro and in vivo via the inhibition of PDKs, resulting in decreased lactate and increased ROS production8. In our own studies, we have demonstrated the effectiveness of DCA against the growth of breast cancer cell lines in vitro, and against a metastatic rat mammary adenocarcinoma in vivo7,16, which correlated with the reversal of the glycolytic phenotype as measured by lactate production.

In a second in vivo model, BALB/c mice were injected subcutaneously with V14 cells (derived from a spontaneous mammary adenocarcinoma arising in a BALB/c-Trp53+/- mouse17) and mice with established tumours were treated with DCA in the drinking water. DCA treatment (1.5 g/L, ~200 mg/kg/day, from 11 days after cell injection) halted the growth of the established tumours (Figure 1B). DCA is also able to enhance the cytotoxicity of mitochondrial toxins such as arsenic trioxide (ATO)16 and 4-(N-(S- penicillaminylacetyl)amino) phenylarsonous acid (PENAO)(Figure 1C).

These results demonstrate that DCA has anti-proliferative properties in addition to pro-apoptotic properties, and can be effective against established tumours and metastatic disease in vivo, highlighting its potential for clinical use*.*

***Clinical use of DCA against cancer.***

DCA has been used to lower lactate levels in phase III clinical trials for the treatment of chronic lactic acidosis in congenital mitochondrial disorders18,19. This history of patient use has enabled DCA to move quickly into the clinic for cancer applications. Six clinical trials are registered with clinicaltrials.gov for the use of DCA against brain (x2), metastatic solid (x2), and head and neck cancers (x2). The wide spread publicity of Bonnet et al’s report15. Together with the ready access and oral availability of DCA has created patient demand for DCA.

While there are no available results from randomised clinical trials of DCA in cancer, there are several reports of the successful use of DCA alone in the clinical management of a broad range of cancer types, including complete remission in two cases of recurrent non-Hodgkin lymphoma20,21 and one case of metastatic renal squamous cell carcinoma22, illustrating the potential for DCA to be effective against difficult cancer types. Michelakis et al report stable disease in 4/5 glioblastoma patients taking DCA in addition to their standard therapy. Dose-dependent, reversible peripheral neuropathy was the only apparent toxicity, with no signs of hematologic, hepatic, renal or cardiac toxicity23.

In vitro studies on 49 primary glioblastoma samples indicated the ability of DCA to reverse the Warburg effect in vitro, and trough plasma concentrations in glioblastoma patients of ~0.5 mM DCA were in line with PDK2 inhibition (Ki 0.2 mM), supporting the proposed mechanism23. Further, the palliation of a carcinoma of unknown origin in an elderly patient demonstrates another potential application of DCA in the management of cancer24.

There is clearly support in the medical community for clinically testing DCA in cancer therapy hence our proposal for a clinical trial in myeloma patients.

***DCA is effective against myeloma cells in vitro.***

Myeloma cells have been characterised to have a glycolytic phenotype9,10,25,26, with approximately half of the cell lines examined showing high levels of lactate production. Examination of the Oncomine gene expression database27 indicates that MM cells do not overexpress PDK1 or PDK3 mRNA compared to normal plasma cells28. Sanchez et al10 and Fujiwara et al9 report that DCA combined with bortezomib showed additive cytotoxic effects in some MM cell lines. Thus, we expect that a significant fraction of MM patients will be good candidates for growth control or enhanced apoptosis mediated by DCA*.*

While these studies are encouraging, there are several shortcomings in these studies performed on myeloma cells. Sanchez et al10 and Fujiwara et al9 report that DCA combined with bortezomib showed additive cytotoxic effects in some MM cell lines, however, this work required DCA concentrations of 10 mM or higher, and confirmation that DCA is active at concentrations relevant to PDK inhibition and relevant to patient plasma concentrations is needed.

The expression of PDK1 was reported to be higher in MM cells than in plasma cells from MGUS patients9 however the other isoforms of PDK were not investigated. Only 1 primary cell sample has been tested for sensitivity to DCA, and the combination of DCA with other myeloma therapies other than bortezomib has not been tested.

***Pharmacology of DCA***

*Therapeutic**Range*

The therapeutic range necessary for successful treatment of cancer with DCA has not yet been reported. While Michelakis et al report trough levels achieved in glioblastoma patients, maximum levels are not reported and the long term therapeutic outcomes for these patients has not been published23 We propose a predicted therapeutic range based on the Ki for the Pyruvate Dehydrogenase Kinases (PDKs), the enzymes targeted by DCA. The Ki for inhibition of PDKs by DCA is 1.0, 0.2, 8.0 and 0.5 mM for isoforms 1 to 4 of PDK, respectively14 Gene expression databases indicate that PDK3 is not overexpressed in myeloma cells27 Further, preliminary reports of serum DCA concentrations achieved at tolerable doses of DCA in cancer patients suggest that 8 mM is unlikely to be achieved. Therefore, we aim to inhibit isoforms PDK1, PDK2 and PDK4 by achieving DCA serum levels in the range of 0.5 – 2.5 mM (65 – 325 ug/ml), 2.5 times the Ki. This concentration range is also consistent with our in vitro studies showing inhibition of cancer cell growth via on-target effects of DCA at concentrations of 1 mM.

***Dosing schedule & Pharmacokinetics***

 The first dose of DCA is cleared from plasma more rapidly than subsequent doses29 due to the irreversible inactivation by DCA of GSTZ1, the enzyme responsible for the metabolism of DCA to glyoxylate30 Stacpoole and colleagues29 have performed pharmacokinetics on oral DCA in healthy adults, including the plasma levels and half life after a single dose or after 5 doses. Michelakis et al report on the DCA trough levels in 4 glioblastoma patients treated with DCA. After 3 months on 6.25 mg/kg po bid, serum DCA trough levels ranged from 0.26 – 0.63 mM23, however trough DCA levels were not detectable for the first 2 – 3 months. Based on these reports, we have devised a dosing schedule to rapidly achieve and maintain DCA in our predicted therapeutic range, by administering a high loading dose of DCA to increase its half life, followed by a lower maintenance dose.

DCA is rapidly and almost completely absorbed from oral administration, with an oral dose of 25 mg/kg resulting in peak plasma concentrations of 94 ug/ml (0.7mM) in healthy adults. After 5 days of oral dosing of 25 mg/kg, the Cmax was increased to 158 ug/ml (1.2 mM), with an increase in the AUC from 196 to 1275 hr.ug/min and an increase in the half life from 0.9 to 10.5 hrs29 The 10 hr half-life was achieved after 5 doses of 25 mg/kg, given as a single dose per day (total 125 mg/kg over 5 days). We will administer this amount of DCA over 3 days.

**Day 1: 25 mg/kg single initial dose**

An initial oral dose of 25 mg/kg will be given on day 1 and pharmacokinetics will be performed on this dose. The administration of DCA would then proceed as follows:

**Days 2 and 3: 25 mg/kg bd**. (total 125 mg/kg over 3 days).

The half life should then be ~10 hr.

**Days 4 to 7: 6.25 mg/kg bd** (as per Michelakis experience).

Maintenance dose.

**Day 8: 25 mg/kg single dose**

Determine trough concentration of DCA first, and then repeat pharmacokinetic measurements on a single 25 mg/kg dose to confirm changes in half life.

**Day 9-14: 6.25 mg/kg bd.**

Return to maintenance dose.

**Day 28, 56, 84: 6.25 mg/kg bd.**

Determine trough DCA concentration after 6.25 mg/kg dose.

We estimate that this dosing schedule will keep trough plasma concentrations in the range of 0.2 – 0.6 mM (based on Michelakis measurements at this dose23) and peak concentrations in the range of 0.4 – 1.2 mM (twice the trough levels, as half-life is approx 12 hrs). We expect that the actual levels achieved will vary between patients but that dosing will only be reduced or treatment deferred in the event of emerging toxicity.

Measurements of serum DCA levels will be made for determination of pharmacokinetics of DCA on day 1 and day 8 of the study. Patients will take 25 mg/kg orally on an empty stomach. Blood will be collected at time 0, 60, 120 min, 3, 4, 5, 6 and 24hrs after administration of DCA, and processed for measurement of DCA levels. We will retrospectively analyse the pharmacokinetic data and look for correlation between efficacy or toxicity and serum DCA levels.

***Metabolism of DCA****.*

The pharmacokinetics of DCA may be influenced by different isoforms of glutathione transferase Zeta (GSTZ1), the enzyme responsible for the major route of metabolism of DCA. Four common isoforms of GSTZ1 exist in humans that are able to metabolise DCA at different rates in vitro31,32 A rare variant of GSTZ1 was recently associated with a very long half life for DCA initial dose33. DCA is also a suicide substrate for GSTZ1, irreversibly inactivating the enzyme during its metabolism, and this inactivation also occurs at different rates for the different isoforms30 . Recent evidence from patients suggests that genotypes for this enzyme may alter the rate of metabolism, resulting in different plasma concentrations from the same dose in both healthy volunteers and in glioblastoma patients33 . Thus knowledge of GSTZ1 genotype is important when assigning dosing regimens to subjects participating in clinical trials of DCA. However, genotype-phenotype information is presently too limited to predict whether slow DCA metabolism per se is an independent risk factor for drug toxicity.

Thus, in addition to determining the pharmacokinetics of DCA in patients, we will determine the genotype for GSTZ1 in patients. DNA will be isolated from blood samples drawn for plasma DCA levels, and genotypes determined by PCR using methods established by Dr Blackburn31,32 (common variants) and Shroads et al33 (rare variant). The plasma concentration of DCA and the occurrence of side effects / tolerated dose will be examined for any correlation with genotypes. The DNA samples will be kept for no longer than 3 years after the completion of the study for auditing purposes.

1. **Objectives and Hypotheses**
	1. **Primary Objective**

Establish if there is evidence of clinical efficacy of DCA in myeloma in plateau phase as measured by at least a >25% fall in paraprotein / light chain levels over 12 weeks in at least 30% of participants treated with the study drug.

* 1. **Secondary Objectives**

Establish the achievable maximum drug levels of DCA in vivo with the dosing schedule as outlined in section 6 and confirm the tolerability and safety of DCA at these doses

Genotype patients for Glutathione transferase zeta (GSTZ1) and correlate with DCA levels and tolerability.

* 1. **Hypothesis**

DCA administration for 12 weeks in plateau phase patients will lead to at least an Objective Response in at least 30% of participants. We defined an Objective Response as at least a 25% reduction in paraprotein & at least 1g/L, or in the case of light chain only myeloma, 25% reduction between involved and uninvolved light chains, and an absolute decrease of at least 100mg/L.

The null hypothesis is that <10% of trial participants show evidence of an Objective Response.

**8.0 Patient Selection**

**8.1 Eligibility criteria**

Concerns regarding the eligibility of a potential patient should be directed to the trial principal

investigator.

* Diagnosis of Plasma Cell Myeloma (at any time) according to WHO criteria\* **(see Appendix 1)**
* Aged 18 years or older
* Eastern Co- operative Oncology Group Performance status\* ≤2 **(see Appendix 2)**
* Life expectancy due to myeloma or co- morbid conditions in the opinion of the treating physician likely to exceed 3 months
* **Measurable residual disease**
	+ Quantifiable serum paraprotein on electrophoresis at least 1g/L **OR**
	+ Elevated free kappa (>21mg/L) or lambda light chains (>30mg/L) AND a minimum difference between level of involved/uninvolved light chain of 150mg/L AND an abnormal serum free light chain ratio (normal κ:λ = 0.26-1.26)
* **Plateau phase of disease**
	+ Plateau phase is a recognised phase of stable disease in myeloma, although there is no consensus definition in the literature.
	+ In this study we have *adapted* the definition used by Rajkumar et al6 to be:
	+ **A period of *neither* progression *nor* response at least 28 days following the last change in myeloma treatment**
	+ **Progression** defined as per IWMG
		- an increase in the paraprotein by >= 25% and at least 5g/L
		- In light chain only patients, >25% increase in difference between involved and uninvolved light chain level, with an absolute increase of >0.1g/L
		- development of new lytic lesions
		- development of new end organ damage (Renal disease, marrow failure, lytic lesions, hypercalcaemia) attributable to myeloma or new plasmacytomas
	+ **Response** defined as
		- reduction in the paraprotein by ≥ 25% OR in the case of light chain only myeloma, 25% decrease in the difference between the involved and uninvolved light chain and an absolute reduction of at least 100mg/L.
	+ Blood samples to assess for plateau phase must be ≥ 28 days apart

**8.2 Exclusion criteria**

* Unable to give informed consent
* Non-secretory myeloma
* Receipt of any active anti-myeloma therapy (excluding bisphosphonates) in the 16

weeks prior to enrolment, with the exception that patients on stable doses of long- term maintenance therapy will be allowed (no dose alteration in the prior 8 weeks).

* Pregnant or breastfeeding
	+ All females of childbearing potential (FCBP) **(see appendix 3)** must agree to have a negative

 pregnancy test within 72 hrs before commencing DCA.

* Unwilling to avoid pregnancy and use birth control (if applicable) during the study and for 4 weeks after completion of the study
	+ During the 12 week study drug administration and for 4 weeks after completion of the study, two reliable methods of contraception must be used simultaneously or otherwise complete abstinence from any sexual contact be maintained
* Unable to swallow capsules
* Major surgery within the last 28 days
* Enrolled in another trial or have discontinued from another clinical trial within the last 14 days
* Any serious pre-existing medical condition that, in the opinion of the study doctor would keep you from being on this trial
* Any peripheral motor or sensory neuropathy, neuralgia or paraesthesia (of grade 3 or worse)
* Any pre-existing severe ataxia or tremor (grade 3 or worse)
* Known history of liver disease (cirrhosis established by imaging studies or biopsy) or abnormal liver function tests within the last 14 days (AST or ALT > 3 x ULN or ALP >2.5 x ULN or total bilirubin > 1.5 x ULN)
* Any more than moderate renal impairment i.e. Calculated Creatinine Clearance by Cockcroft Gault formula of ≤ 30 mL/min
* Inadequate cardiac function defined as:
	+ Electrocardiographic (ECG) evidence of
		- Acute ischemia
		- Active clinically significant conduction system abnormalities
		- >Grade 2 (>480 ms) (QTc) prolongation
	+ Uncontrolled angina or severe ventricular arrhythmias
	+ Myocardial infarction within the last 6 months
	+ Class 3 or higher New York Heart Association Congestive Heart Failure
* Haematological
	1. Haemoglobin < 80g/L
	2. Absolute Neutrophil Count (ANC) ≤ 1.0 x 10^9/L
	3. Platelet Count ≤ 50 x 10^9/L
* Any active fungal, bacterial and/or known active viral infection including HIV or hepatitis (A, B, or C).
* A second malignancy which in the opinion of the investigator may affect the interpretation of results

**9.0 Investigational Plan**

**9.1 Study Design**

This study is a two-stage, phase 2, non-randomised study of the efficacy of DCA in plateau phase myeloma. The primary efficacy endpoint will be the Objective Response Rate **(see definition section** **7.3)**. This will encompass any patient who has a complete response, very good partial response or partial response as defined by the IMWG standard response criteria40 but also includes those with a minor response but not achieving PR. The more generous response rate definition deliberately reflects the fact that as drug exposure is short (<12 weeks), tumour burden is already low and thus the depth of responses may be limited.

**9.2 Agent administration**

Oral Dichloroacetate as the sodium salt, will be administered by mouth twice daily for 12 weeks according to the following dosing schedule.

**Day 1: 25 mg/kg single initial dose**

**Days 2 and 3: 25 mg/kg bd**.

**Days 4 to 7: 6.25 mg/kg bd**

**Day 8: 25 mg/kg single dose**

**Day 9-84: 6.25 mg/kg bd.**

**9.3 Dose modifications and delays**

In the event of any grade III toxicity attributable to the study drug, medical

interventions to alleviate toxicity will be instituted where such a medically appropriate

intervention exists (e.g. electrolyte supplementation in the event of low potassium or

magnesium etc). The toxicity must resolve to grade II or lower after 3 weeks of medical

intervention. ***If there is failure to resolve the toxicity to less than grade II after 3 weeks of medical***

***intervention the participant will come off study***.

In the event of ***grade III toxicity, where no supportive medical intervention exists***, the study

drug will be ***withheld for 14 days***, and at the end of this period, if that toxicity has resolved

to less than or equal to grade II, study drug can be recommenced at 75% of the

previously administered dose.

This protocol is summarised in the flow chart below.

**9.4 Duration of Therapy & ‘Stopping Rules’**

All participants will be planned to receive 12 weeks of therapy. No further drug will be supplied beyond this time period.

Patients will continue on therapy unless any of the following occurs:

1. **Dose-limiting toxicity as defined by a**
* CTCAE grade IV toxicity
* CTCAE grade III toxicity that results in hospitalisation
* CTCAE grade III toxicity that fails to improve to at least grade II after interruption of therapy for 2 weeks.
* CTCAE grade III toxicity that fails to improve to at least grade II after 3 weeks of medical intervention

1. **Evidence of accelerated myeloma progression / relapse (IMWG criteria)**
* Confirmed development of new bony lesions or soft tissue plasmacytomas or increase in size >50% and at least 1cm
* Drop in Hb >20g/L without other explanation
* New onset hypercalcaemia (corr > 2.6mmol/L) attributable to the myeloma
* Rise in serum creatinine to >177 without other explanation
* Any relative increase in the paraprotein of >25% with at least an absolute increase of 5g/L\*
* In light chain only patients, >25% increase in difference between involved and uninvolved light chain level, with an absolute increase of >0.1g/L
1. **Consent withdrawal**
2. **Major violation of the study protocol**
3. **Suspected or confirmed pregnancy**
4. **Other significant concern raised by study investigators about the wellbeing of the patient that is**
	* **attributable to the study drug**
	* **not covered under sections a) or b), at the discretion of the study investigators.**

**The entire trial will be terminated in the event of**

* Any death directly attributable to study drug.
* 25% or more patients in the first stage have any grade III or greater toxicity attributable to study drug that fails to resolve to less than or equal to grade 2.

**9.5 Duration of Follow-up**

All trial participants will continue to be followed-up following cessation of the study drug. This will involved 2 visits at 3 monthly intervals after the 12 week DCA administration is complete (i.e. at month 6 and month 9) of the study.

In the event of an individual being withdrawn from further study drug administration due to toxicity or progression as outlined in **section 9.4**, follow-up visits will occur at 3 and 6 months after the last day of study drug administration.

In the event a patient withdraws consent for continued administration of the study drug, they may at their discretion continue to be followed up at 3 and 6 months post the last day of study drug administration *or* withdraw from the study entirely.

**9.6 General concomitant medication and supportive care guidelines**

**9.6.1 Permitted concomitant therapy**

Therapies considered necessary for subject’s well-being may be administered at the

discretion of the investigator including but not limited to: antibiotics, analgesics, antihistamines, or other medications and transfusions of red cells, platelets or fresh, frozen plasma (FFP) given to assist in the management of complications associated with MM or its therapy.

The use of bisphosphonates is permitted.

The use of haematopoietic growth factors is permitted throughout the study

 and treatment with myeloid growth factors is recommended when the ANC is less than 1.0 x 109/L

***However*** subjects who fail screening due to cytopenias will not be permitted to use growth factors to become eligible.

Ongoing administration of stable doses of long- term maintenance therapy for myeloma (e.g. Lenalidomide, Thalidomide) will be allowed however, no dose alteration in the 8 weeks prior to commencing DCA is permitted.

**9.6.2 Prohibited concomitant therapy**

No active anti-myeloma therapy, including glucocorticoids (excluding bisphosphonates) is permitted to be administered in the 16 weeks prior to enrolment, with the exceptions noted in 9.8.1.

No immunosuppressant medications are permitted.

Radiation therapy is not permitted.

**10 Pharmaceutical Information**

**10.1 Dichloroacetic acid (DCA)**

Dichloroacetic acid is an organohalide. Dichloroacetic acid for this study will be supplied as gelatine capsules containing the sodium salt in 3 sizes, 25mg, 125mg and 500mg.

The exact capsule contents in addition to active study drug will be determined at a later point once the contract for compounding the study drug is confirmed. These contents will be printed on a label attached to the study medication.

The contents of the capsule may be an irritant to the skin, eyes or respiratory tract and thus contact should be avoided.

**10.2 Drug accountability**

Under no circumstances will the investigator supply study drug to a third party or allow the study drug to be used in any other ways than as directed by this protocol

**11 Registration**

Before all new patients can be registered on-study, check inclusion/exclusion criteria to

confirm patient eligibility. A unique study ID will then be allocated according to the order the patient is enrolled on to the study (e.g. DCA001 for the first patient enrolled)- followed by a hyphen- followed by the patient initials.

The study drug should commence 24 hours after confirmation of eligibility and registration to the study.

**12 Documentation**

**12.1 Informed consent**

Consent for the clinical trial should be obtained at the screening visit to the study. Some patients may not be eligible to commence study drug immediately if they have not had a recent paraprotein measurement (**see Schedule of Assessments- 5**) but can return for a follow-up visit after 28 days to confirm eligibility.

**12.1 Case Report Forms**

Case Report Forms (CRFs) should be completed in black ink. A correction should be made by striking through the incorrect entry with a single line and by entering the correct information adjacent to it. The correction must be initialled and dated by an adequately qualified and authorised member of the research support team. If an item is not available or is not applicable, this fact should be indicated; do not leave a space blank.

The ORIGINAL of each completed CRF must be kept by the institution. All questions on the CRFs should be answered. The CRFs are confidential and remain the property of the CTU at Canberra Hospital. These documents will be kept for 15 years.

**12.3 Essential documents**

Essential trial documents to be maintained at the trial site include, but are not limited to:

• HREC- approved study protocol and amended versions

• all source documents and laboratory records

• Sample CRF and completed CRF copies

• HREC-approved PIS and CF and amended versions

• HREC membership list

• Any communication with the HREC

• Laboratory reference ranges and accreditation

• Protocol deviation logs

• Staff curriculum vitae and training logs

• Signature sheet and delegation of responsibilities log

• Copies of PICF for each subject

Source documents pertaining to the trial must be maintained by investigational sites. Source

documents may include, but are not limited to, a subject's medical records, hospital charts,

clinic charts, the investigator's subject study files, treatment prescriptions, treatment

administration sheets, X-rays, CT scans and laboratory tests.

**12.4 Confidentiality**

The study will be conducted in accordance with applicable Privacy Acts and Regulations. All

data generated in this study will remain confidential. All information will be stored securely

and will only be available to staff directly involved with the study. Personal data identifying

trial subjects will be held securely at the treating institution for the purpose of follow up after

the conclusion of the protocol-specified period.

Trial participants will be allocated a unique identification (ID) number. Analysis of trial-related data will be by ID number and initials. Copies of any patient reports that are to be maintained with CRFs MUST be de-identified and then clearly labelled with the patient ID number only.

**12.5 Document retention**

Records from the study will be retained for a minimum of 15 years after study completion either on site (in the locked clinical trial unit office) or at a secure archiving facility.

**13 Statistical Considerations**

A Simon’s Mini-max 2-stage design will be used to conduct the trial. This trial design will optimise safety by exposing fewer patients to a potentially inactive treatment34.

With this study design a total of 25 patients are needed to achieve 80% power with an alpha of 0.05.

The null hypothesis is that <10% of patients respond to the DCA i.e. H0: patients achieving ORR < 10% of study participants.

The alternative hypothesis is that at least 30% of patients will have a response to the DCA: Ha: patients achieving ORR ≥ 30% of study participants

The decision to terminate the study and reject the drug after the first stage of the study will be based on the number of responses observed. If at least 1 of the first 15 evaluable patients in stage 1 achieve a response as defined above, the study will continue to stage 2 until a total of 25 evaluable patients have been recruited.

If in the final analysis more than 5 patients have an ORR then the null hypothesis will be rejected i.e. confirming evidence of the efficacy of DCA in deepening responses in plateau phase patients.

The primary efficacy analysis of ORR will be performed when the required number of evaluable patients has been enrolled. The study population is defined as all registered patients who have received at least 12 weeks of treatment. A final evaluation of the proportion of patients achieving ORR will be calculated and a corresponding 95% CI reported.

The expected enrolment period is 12 months. To account for potential non-adherence or early dropout, we envisage that up to an additional 5 patients may be enrolled in the first stage and that these additional enrolments may continue, only until such time as 15 patients have successfully completed the 3 month exposure to the study drug. Once the first 15 patients have completed this treatment period, no further enrolment will occur until the initial efficacy analysis is complete.

If the study proceeds to the second phase, a study “close-out” date will be applied. This date will be the day in which the last of 25 patients to complete the 12 week study drug administration period, has their 6 month follow-up visit.

**13.1 Definition of Study endpoints**

**13.1.1 Primary**

Overall Response Rate (ORR) = the proportion of patients achieving

at least 25% *and* at least 1g/L) reduction in paraprotein

OR

at least a 25% reduction in the difference between involved and uninvolved light chains (and a minimum absolute reduction in difference between the involved & uninvolved light chain of at least 100mg/L)

Genotype patients for Glutathione transferase zeta (GSTZ1) and correlate with DCA levels and tolerability

In instances of a dramatic response to the DCA, the response assessment should be recorded according to IMWG criteria (see section 15). Where the paraprotein or light chain assessment suggests a Complete Response, this should be confirmed with a repeat marrow aspirate and trephine.

**13.1.2 Secondary**

Genotype patients for Glutathione transferase zeta (GSTZ1) and correlate with DCA levels and adverse events if any.

Establish the range of drug levels of DCA in vivo achieved with the dosing schedule as outlined in **section 9.2**

**13.2 Sample Size and Power calculations & Interim Analysis**

The *in vivo* cyototoxic efficacy of DCA (if any) is entirely unknown. For this reason, accurate estimates of the expected magnitude of any change in paraprotein levels with exposure of patients to DCA are not possible. However, there are preliminary *in vitro* data suggesting that DCA may be effective as an anti-myeloma therapy.

Sanchez et al (2013) found that 3 out of 6 myeloma cell lines used glycolysis as a bioenergetic pathway.  2 out of 2 of these glycolytic cell lines tested showed sensitivity to DCA as indicated by altered metabolism and decreased cell viability10.

Fujiwara et al (2013) found that 4 out of 6 cell lines were highly glycolytic and were sensitive to lactate dehydrogenase (LDH) inhibition. Further, in primary myeloma cell samples, expression of glycolysis-related genes (LDH) was highly elevated in approximately 30% of 59 cases examined9.

Thus we have made a relatively conservative estimate that 30-50% of myeloma cases may be responsive to inhibition of the glycolytic phenotype with DCA. We also assume that if <10% of patients show any response then the study drug is likely ineffective and does not merit further analysis.

Based on these assumptions and taking into account the Mini-max 2 stage design as outlined above, a study analysing the data of 25 patients will be adequately powered (80%) to demonstrate a significant effect of the DCA at an alpha of 0.05

Thus, recruitment will continue until 25 patients have completed therapy.

However, the 2 stage design obviates the need for analysis beyond 15 patients. Once the 15th patient has completed their 12th week of DCA therapy, further enrolment will be halted and an interim analysis of the data performed. If at this stage no patient has demonstrated an OR, then the trial will be discontinued.

**13.3 Statistical Methods**

Descriptive statistics of the baseline characteristics of all registered patients will be reported.

The primary outcome measures will be the change (if any) in paraprotein over the 12 week period.

All analyses of the primary endpoint will include only eligible patients who conformed to their allocated treatment as stated in the protocol. Patients will be designated as either a “Responder” or “Non-responder” according to the presence or absence of an OR.

The data reported will be the proportion of patients achieving an OR.

Secondary analyses based on myeloma characteristics recorded at registration (Paraprotein isotype, baseline paraprotein level, ISS stage at diagnosis, disease duration and number of prior treatment episodes, cytogenetics/FISH where available) will also be undertaken.

Two-tailed P-values will be used for all comparisons, and all statistical tests will be performed two-sided using a significance level of 5%. When confidence intervals are calculated, they will be two-sided, 95% intervals.

**13.4 End Of Treatment**

Patients should continue taking drug for the prescribed treatment period until intolerance or

disease progression. However, patients may discontinue study treatment for a myriad of

reasons. Whenever a patient discontinues treatment, for whatever reason, the End of treatment

CRF must be completed and one of the following reasons must be identified:

* + - Adverse event(s)
		- Abnormal laboratory value(s)
		- Abnormal test procedure results
		- Treatment duration completed as per protocol
		- Patient withdrew consent
		- Patient withdrew consent from study therapy administration and the study but is still willing to be followed for OS
		- Lost to follow-up
		- Administrative problems
		- Death
		- Disease progression
		- Suspected pregnancy
		- Protocol deviation

Patients may voluntarily withdraw from the study treatment at any time. Those patients who

withdraw consent from treatment have the option to continue to be followed. If they choose to continue to be followed they must sign an appropriate consent form indicating their agreement.

**13.5 Trial Modification and Safety and Data Monitoring Committee**

The investigators will internally monitor the study.

The PI and one other *clinician* investigator will review all SAEs. In the event of a significant incidence of SAEs, they will give consideration to amending the trial. Proposed amendments to the trial protocol, PIS or CF beyond the version initially approved by the HREC will require signatures of all co-investigators

The PI and one other *clinician investigator* will review all instances where individuals come off study due to toxicity or progression and applying stopping rules if appropriate.

The interim analysis of the first 15 patients for efficacy will also include an analysis of toxicity and the trial stopping rule applied where 25% or more patients in the first stage have any grade III or greater toxicity attributable to study drug that fails to resolve to less than or equal to grade 2.

The PI will also meet with one other *clinician investigator* 3 monthly over the course of the trial and give consideration to stopping the study if there is either

* + Poor patient accrual, or
	+ Any serious doubt that the trial will meet its primary objective.

**14 Assessment of Response**

Adapted from International Myeloma Working Group response criteria35 after Kyle and

Rajkumar

**14.1 Complete Response (CR)**

* Negative immunofixation on the serum and urine and
* Disappearance of any soft tissue plasmacytomas and
* <5% plasma cells in bone marrowp

**14.2 Stringent Complete Response (sCR)**

* CR as defined below plus
* Normal FLC ratio and
* Absence of clonal cells in bone marrow by immunohistochemistry or
* Immunofluorescenceq

**14.3 Very Good Partial Response (VGPR)**

* Serum and urine M-protein detectable by immunofixation but not on electrophoresis
* or 90% reduction in serum M-protein plus urine M-protein <100mg per 24 hour

**14.4 Partial Response (PR)**

* ≥ 50% reduction of serum M-protein and reduction in 24 hour urinary M protein by ≥90% or to <200mg per 24 hour
* If the serum and urine M protein are unmeasurable, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M- protein criteria.
* If serum and urine M-protein are unmeasurable, and serum free light

assay is also unmeasurable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30%

* In addition to the above listed criteria, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required.

Note clarification to IMWG criteria for coding CR and VGPR in patients in whom the only measurable disease is by serum FLC levels: CR in such patient is defined as a normal FLC ratio of 0.26-1.65 in addition to CR criteria listed above. VGPR in such patients is defined as a >90% decrease in the difference between involved and uninvolved FLC levels.

p Confirmation with repeat bone marrow biopsy not needed

q Confirmation with repeat bone marrow biopsy not needed

**14.5 Stable disease (SD)**

Not meeting criteria for MR, CR, sCR, VGPR, PR or progressive disease

**14.6 Progressive Diseases (PD)**

Progressive disease: requires any one or more of the following:

* Increase of ≥25% from lowest response level in Serum M component and/or (the absolute increase must be ≥0.5g/dL) the urine M-component and/or (the absolute increase must be ≥ 200mg/24 hour)
* Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels. The absolute increase must be >10mg/dl.
* Bone marrow plasma cell percentage: the absolute % must be ≥ 10%
* Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas
* Development of hypercalcemia (corrected serum calcium >11.5 mg/dl or 2.65mmol/l) that can be attributed solely to the plasma cell proliferative disorder

**15 Adverse Event Reporting**

Information about all AEs whether volunteered by the patient, discovered by the investigator

questioning, or detected through physical examination, will be collected and recorded from

the day of study drug commencement until 28 days following the last dose of DCA and

followed as appropriate.

**15.1 Definitions**

**15.1.1 Adverse Event**

An adverse event (AE) is any unintended change in structure (signs) or function (symptoms)

of the body, whether or not considered drug related. Laboratory abnormalities are only

considered AEs if they fulfil one of the following criteria:

* + - Accompanied by clinical symptoms;
		- Leading to a change in study medication (e.g. dose modification, interruption or permanent discontinuation);
		- Requires a change in concomitant therapy (e.g. addition or change in a concomitant medication, therapy or treatment).
		- Unexpected toxic side effect of treatment

Any medical condition or clinically significant laboratory abnormality with an onset date

before the first date of study product administration is considered to be pre-existing, and

should be documented in the CRF as medical history.

**15.1.2 Serious Adverse Event**

A serious adverse event (SAE) is any AE which:

* + - Results in death
		- Is life-threatening (i.e., in the opinion of the Investigator(s) the subject is at immediate risk of death from the AE)
		- Requires inpatient hospitalization or prolongation of existing hospitalization
		- Results in persistent or significant disability/incapacity (a substantial disruption of the subject’s ability to conduct normal life functions)
		- Is a congenital anomaly/birth defect
		- Constitutes an important medical event
		- Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above.

Any case of second cancers or leukaemias detected during follow-up must also be

reported as serious adverse events as soon as the investigator becomes aware of the

event.

The following must be also be reported immediately:

* Any occurrence of pregnancy
* All reports of elevated/questionable or indeterminate beta human chorionic

gonadotropins (βhCGs) or positive urine pregnancy tests.

Any case of second cancers or leukaemias detected during follow-up must also be

reported as serious adverse events as soon as the investigator becomes aware of the event.

***15.1.2.1 SAE Exceptions***

The following will not be considered SAEs:

Any event that results in hospitalisation or prolongs an existing hospitalisation if the only reason

for the hospitalisation or prolongation was for:

* administration of study procedures and not associated with any deterioration in condition
* placement of a permanent intravenous catheter
* pre-study scheduled elective surgery not related to the studied indication or it’s treatment
* outpatient hospitalisation for procedures such as;
	+ elective day surgery or
	+ convenience purposes, eg. transportation difficulties
* an emergency, outpatient visit that did not result in overnight hospitalisation

However, these events should be recorded in the CRFs.

**15.1.3 Immediate reporting of serious adverse events**

Any AE that meets the criterion for an SAE requires the completion of an SAE Report Form

in addition to being recorded on the AE pages of the CRF. The Investigator(s) is required to

ensure that the data on these forms is accurate and consistent. This applies to all SAEs,

regardless of relationship to study drug, that occur during the study, those made known to the

Investigator(s) within 28 days after a subject’s last dose of study drug, and those made known

to the investigator(s) at any time that are suspected of being related to study drug.

The SAE must be reported immediately (i.e., within 24 hours of the Investigators’ knowledge

of the event) to the PI who will confer with another *clinician investigator* (NOT the primary clinician involved in the patient’s care), review the SAE and consider modifications to the study or whether applying any of the stopping rules is appropriate.

Until the SAE has been reviewed, and an appropriate course of action implemented, no further patient registration to the trial should occur.

**15.1.4 Pregnancy Related Events**

Pregnancy-related events occurring while the patient is on study drug or within 4 weeks after

the patient’s last dose of study drug are considered SAEs. If the patient

is on study drug it must be discontinued immediately and any unused portion should be

returned to the CTU. The pregnancy-related event must be reported

by completing a Pregnancy Report Form.

The patient should be referred to an obstetrician/gynaecologist experienced in reproductive toxicity for further evaluation and counselling. The Investigator will follow the patient until resolution and must notify the PI of the outcome as specified below. The Investigator will provide this information as a follow-up to the initial pregnancy report.

The following pregnancy related events should also be considered grounds for stopping the trial:

* If the outcome of the pregnancy results in spontaneous abortion [any congenital

anomaly detected in an aborted fetus is to be documented]

* stillbirth,
* neonatal death
* congenital anomaly
* all neonatal deaths within 28 days of birth should be reported, without regard to

causality, as SAEs.

* any infant death after 28 days that the Investigator(s) suspects is related to the in utero exposure to the study drug

**15.2 SAE** **Reporting Responsibilities**

Upon receipt of an SAE report by the PI, those events deemed to be both serious and unexpected

and related to the study intervention must be reported to the TGA using a ‘blue

form’ ADRAC card downloaded from: http://www.health.gov.au/tga/adr/bluecard.pdf and sent

to the following address.

The Secretary, ADRAC

Reply Paid 100

Woden ACT 2606

Fax: (02) 6232 8392

For those serious, unexpected events deemed to be related to the study drug, this report to the

TGA should occur as soon as possible, but no later than 7 days after the PI gained first

knowledge of the event. Incomplete reports must be completed and forwarded as soon as

possible within 8 additional calendar days.

**15.3 Adverse event severity**

The investigator should seek to elicit any clinical or objective reactions from patients being

treated and determine the relationship to the treatment. The severity of the adverse event and

relationship should be assessed according to the specific guidelines described below.

The NCI CTCAE v4.0 grading system of toxicity should be used for recording and

grading of adverse events (Appendix 5- see internet link).

Reaction(s), not covered by the above grading system, should be graded on the

following scale;

1 = mild . awareness of sign, symptom or event, but easily tolerated

2 = moderate . discomfort enough to cause interference with usual activity

and may warrant intervention

3 = severe incapacitating with inability to do usual activities or

significantly affects clinical status, and warrants intervention

4 = life threatening . immediate risk of death

5 = death

"Severity" and "Serious" are not synonymous. “Severity” refers to the intensity of a

reaction (i.e. mild, moderate, severe, etc.). "Serious" refers to a regulatory definition for

the outcome of an event (i.e. fatal, life-threatening, resulted in hospitalisation, etc.), as

described in section 16.1.2..

Please note the separate requirement for neuropathy monitoring using the ‘Total neuropathy Score-Clinical’ **see Appendix 6**

**15.4 Adverse event treatment relationship guidelines**

The investigator must assess the relationship of any adverse event to the use of the study

drug(s) using the following guidelines;

0 = Not related . no temporal association, or the cause of the event has been identified

1 = Possibly related . temporal association, but other aetiologies are likely to be the cause.

2 = Probably related . temporal association, other aetiologies are possible but unlikely.

3 = Related established temporal or other association and

event not reasonably explained by the patient's known clinical state or any other factor.

**16 Ethical Considerations**

**16.1 Ethical Principles**

This Protocol has been designed to comply with the Declaration of Helsinki and any

subsequent amendments, the ICH Guidelines for Good Clinical Practice (CPMP/ICH/153/95)

annotated with TGA comments (July 2000), the NHMRC National Statement on Ethical

Conduct in Research involving Humans (2007), the policies and procedures of ALLG and any

applicable local guidelines.

**16.2 Regulatory Requirements**

A Clinical Trial Notification (CTN) form will be submitted to the HREC. It is the responsibility of the investigator to not enter patients onto the trial before CTN acknowledgment is received from the TGA and all other documentation is completed

**16.3 Informed Consent**

A generic PICF, written in non-technical language, will be provided by to potential trial participants

and will contain all relevant details as required by the HREC.

Prior to the commencement of any study-related procedure (e.g Screening tests to fulfil

eligibility criteria), the investigator must obtain written informed consent from each

participant. The investigator ( or delegate) must explain to each subject (or legally authorized

representative) the nature of the study, its purpose, the procedures involved, the expected

duration, the potential risks and benefits involved and any discomfort it may entail. Each

subject must be informed that participation in the study is voluntary, that he/she may

withdraw from the study at any time and that withdrawal of consent will not affect his/her

subsequent medical treatment or relationship with the treating physician.

In addition, the patient should be informed that participation in the trial includes consent to appropriate regulatory authorities and representatives to inspect patient medical records in order to verify trial-related data. The subject should read and consider the PICF before signing and dating it, and should be given a copy of the signed document. No patient can enter the study before his/her informed consent has been obtained.

**16.4 Adherence to Protocol**

Except for an emergency situation in which proper care for the protection, safety and well

being of the trial participant requires that an alternative treatment be used, the trial shall be

conducted exactly as described in the approved protocol. It is the responsibility of the

investigator to document any protocol deviations in the appropriate log and the subject’s

CRF, accompanied by a suitable explanation and to satisfy any reporting requirements of the

HREC.

**17 Publications and presentation policy**

Access to data during the trial will be limited to the investigators (or their delegates).

The primary analysis of trial results for publication, and any interim analyses, will be

performed by the investigators with the assistance of a qualified statistician.

The primary trial results will be published by the Principal Investigator after completion of the final report.

**17.1 Trial registration**

The PI will register the trials with the Australian and New Zealand Clinical Trials Registry (ANZCTR) [www.anzctr.org.au](http://www.anzctr.org.au). PRIOR to any patient accrual AND following HREC approval of the study.

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**Appendix 1**- **WHO Diagnostic Criteria for Symptomatic Plasma Cell Myeloma**

* **M-protein in serum or urine (lower-level not specified)**
* **Bone marrow clonal plasma cells (lower-level not specified) or plasmacytomas**
* **Related organ or tissue impairment (e.g. hypercalcaemia, renal insufficiency, anaemia, bone lesions, hyperviscosity, recurrent infection)**

**Appendix 2 ECOG Performance status criteria**

Grade Status

**0** Able to carry out all normal activity without restriction.

**1**  Restricted in physically strenuous activity but ambulatory and able to do light

work.

**2** Ambulatory and capable of all self-care but unable to carry out any work. Up

and about more than 50% of waking hours.

**3** Capable of only limited self-care, confined to bed or chair more than 50% of

waking hours.

**4** Completely disabled. Cannot carry on any self-care. Totally confined to bed

or chair.

**Appendix 3 Pregnancy prevention risk management plan**

**DCA Pregnancy Prevention Risk Management Plan**

Appendix 3 applies to all patients receiving DCA therapy. The following Pregnancy

Risk Minimization Plan documents are included in this Appendix:

**DCA Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control**

**Methods** (Section 1.1.1.2);

**DCA Pregnancy Education and Counselling Checklist** (Section 1.1.1.3);

The DCA Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control

Methods document (Section 1.1.1.2) provides the following information:

* Potential risks to the fetus associated with DCA exposure
* Definition of Female of Childbearing Potential (FCBP)
* Pregnancy testing requirements for patients receiving DCA who are females of childbearing potential
* Acceptable birth control methods for both female of childbearing potential and male patients receiving DCA in the study
* Requirements for counselling of all study patients receiving DCA about pregnancy precautions and the potential risks of fetal exposure to DCA

DCA Pregnancy Education and Counselling Checklist (Section 1.1.1.3) must be completed and signed by either an Investigator or delegate at the screening visit and prior to initial dispensing of DCA study treatment, as well as at D8, D28, D56 and D84 visits. A copy of these documents must be maintained in the patient records.

**1.1.1.2. DCA Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods Risks Associated with Pregnancy**

DCA at very high doses was found to be teratogenic in developmental studies in rat and mouse embryos. The risk of DCA in pregnancy in humans is unknown but given its effect in some animals, should be avoided in this situation. There is some evidence DCA effects spermatogenesis in dogs. The following section outlines a management plan to prevent pregnancy in subjects taking DCA.

**Criteria for females of childbearing potential (FCBP)**

This protocol defines a female of childbearing potential as a sexually mature woman who:

1) has not undergone a hysterectomy or bilateral oophorectomy or

2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

**Counselling**

For a female of childbearing potential, DCA is contraindicated unless all of the following are met

(ie, all females of childbearing potential must be counselled concerning the following risks and

requirements prior to the start of DCA study therapy):

* She understands the potential teratogenic risk to the unborn child
* She understands the need for effective contraception, without interruption, 28 days before starting study treatment, throughout the entire duration of study treatment, dose interruption and 28 days after the end of study treatment
* She should be capable of complying with effective contraceptive measures
* She is informed and understands the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy
* She understands the need to commence the study treatment as soon as study drug is dispensed following a negative pregnancy test
* She understands the need and accepts to undergo pregnancy testing based on the frequency outlined in this protocol (Section 1.1.1.2)

The investigator must ensure that females of childbearing potential:

* Comply with the conditions for pregnancy risk minimization, including confirmation that she has an adequate level of understanding
* Acknowledge the aforementioned requirements

Male patients taking DCA must meet the following conditions (ie, all males must be counselled

concerning the following risks and requirements prior to the start of DCA study therapy):

* Understand the potential teratogenic risk if engaged in sexual activity with a pregnant female or a female of childbearing potential
* Understand the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a pregnant female or a female of childbearing potential.

**Contraception**

Females of childbearing potential (FCBP) enrolled in this protocol must agree to use **two** reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual contact during the following time periods related to this study:

1) From the time of the screening visit

2) while participating in the study;

3) dose interruptions; and

4) for at least 28 days after study treatment discontinuation.

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. FCBP must be referred to a qualified provider of contraceptive methods if needed. The following are examples of highly effective and additional effective methods of contraception:

* Highly effective methods:
* Intrauterine device (IUD)
* Hormonal (birth control pills, injections, implants)
* Tubal ligation
* Partner’s vasectomy
* Additional effective methods:
* Male condom
* Diaphragm
* Cervical Cap

**Pregnancy testing**

Medically supervised pregnancy tests must be performed for females of childbearing potential, including females of childbearing potential who commit to complete abstinence, as outlined below.

**Before starting study drug**

*Female Patients:*

FCBP must have a negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting study drug. The pregnancy test must be performed within 72hrs prior to the start of study drug. The patient may not receive study drug until the study doctor has verified that the results of these pregnancy tests are negative.

*Male Patients:*

Must practice complete abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for at least 28 days following study drug discontinuation, even if he has undergone a successful vasectomy.

**During study participation and for 28 days following study drug discontinuation**

*Female Patients:*

* FCBP must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while on study, at study discontinuation, and at day 28 following study drug discontinuation.
* At each visit, the Investigator or Delegate must confirm with the FCBP that she is continuing to use two reliable methods of birth control.
* If pregnancy or a positive pregnancy test does occur in a study patient, study drug must be immediately discontinued.
* Pregnancy testing and counselling must be performed if a patient misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Study drug treatment must be discontinued during this evaluation.
* Females must agree to abstain from breastfeeding during study participation and for at least 28 days after study drug discontinuation.

*Male Patients:*

* Confirmation of the requirement for complete abstinence or condom use during sexual contact with a pregnant female or a female of childbearing potential and the potential risks of fetal exposure to DCA must be conducted at each visit.
* If pregnancy or a positive pregnancy test does occur in the partner of a male study patient during study participation, the investigator must be notified immediately.

*Additional precautions*

* Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to the study doctor at the end of treatment.
* Patients should not donate blood during therapy and for at least 28 days following

discontinuation of study drug.

* Male patients should not donate semen or sperm during therapy or for at least 28 days following discontinuation of study drug.

**1.1.1.3. DCA Pregnancy Education and Counselling Checklist (to be completed at Screening, Prior to Dispensing Study Drug, D8, D28, D56, D84)**

Patient Study ID \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**(Check the appropriate box to indicate risk category or completion of counselling task)**

Female:

If female, check one:

FCBP (Female of childbearing potential):

NOT FCBP

Male:

**Do Not Dispense study drug if:**

* The patient is pregnant.
* No pregnancy tests were conducted for a FCBP.
* The patient states she did not use TWO reliable methods of birth control (unless practising complete abstinence of heterosexual contact) [from the screening visit, during therapy and during dose interruption].

**For ALL participants**

I counselled the participant

* NEVER share study drug with anyone else.
* Do not donate blood while taking study drug and for 28 days after

stopping study drug.

* Do not breastfeed a baby while participating in this study and for at

least 28 days after study drug discontinuation.

* Do not break, chew, or open study drug capsules.
* Return unused study drug to the study doctor.

**For a FCBP:**

I confirmed that the initial pregnancy test at screening and *all* subsequent

pregnancy tests results are negative.

I counselled the FCBP regarding the following:

* Potential risk of fetal exposure to DCA: If DCA is taken during pregnancy, it

may cause birth defects and that the participant must agree not to become pregnant while taking DCA

* Using TWO reliable methods of birth control at the same time or complete abstinence from heterosexual contact [from the screening visit, during therapy, during dose interruption and 28 days after discontinuation of study drug
* That even if she has amenorrhea she must comply with advice on contraception
* Weekly pregnancy tests will be required for the first 28 days of study and then monthly thereafter, including 28 days post completion of study drug
* DCA should & will be ceased at any time if there is a suspicion of pregnancy based on testing or new unexplained irregularity in menstrual cycle.
* Use of one highly effective method and one additional method of birth control AT THE SAME TIME

Highly effective methods:

o Intrauterine device (IUD)

o Hormonal (birth control pills, injections, implants)

o Tubal ligation

o Partner’s vasectomy

Additional effective methods:

o Male condom

o Diaphragm

o Cervical Cap

**For a FEMALE NOT OF CHILDBEARING POTENTIAL**

See “ALL PARTICIPANTS”

**For a MALE:**

I counselled the Male patient regarding the following:

* Potential risk of fetal exposure to DCA or effects on spermatogenesis
* To engage in complete abstinence or use a condom when engaging in sexual

contact (including those who have had a vasectomy) with a pregnant female or a

female of childbearing potential, while taking study drug, during dose

interruptions and for 28 days after stopping study drug.

* Males should notify their study doctor when their female partner becomes

pregnant and female partners of males taking study drug should be advised

to call their healthcare provider immediately if they get pregnant

Investigator/Counselor Name (Print):

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Investigator/Counselor Signature:

 \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Date:

\_\_\_\_\_/\_\_\_\_\_/\_\_\_\_\_

**Appendix 4 ISS (International Staging System) at diagnosis**

**Stage 1** B2M <3.5mg/l + Albumin ≥35g/l

**Stage 2** B2M <3.5mg/l + Albumin <35g/l

or

Albumin ≥35g/l but B2M 3.5 – 5.4mg/l

**Stage 3** B2M ≥5.5mg/l

**Appendix 5 Common Terminology Criteria for Adverse**

**Events (CTCAE Version 4)**

<http://evs.nci.nih.gov/ftp1/CTCAE/About.html>

**Appendix 6- Total Neuropathy Score (Clinical)**

\*autonomic symptoms: new onset of fainting, impotence, constipation, loss of bowel and bladder control.

Based on TNSc score as outline in Cavaletti G et al 2006. Multicenter assessment of the Total Neuropathy Score for chemotherapy induced peripheral neurotoxicity. *Journal of the Peripheral Nervous System, 11 (2), 135-141*

Patient ID \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Day of Assessment \_\_\_\_\_\_\_\_\_\_\_\_\_

Sensory \_\_\_\_\_\_\_\_\_\_\_\_\_

Motor \_\_\_\_\_\_\_\_\_\_\_\_\_

Autonomic\* \_\_\_\_\_\_\_\_\_\_\_\_\_

Pin ­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­\_\_\_\_\_\_\_\_\_\_\_\_\_

Vibration \_\_\_\_\_\_\_\_\_\_\_\_\_

Strength \_\_\_\_\_\_\_\_\_\_\_\_\_

Tendon \_\_\_\_\_\_\_\_\_\_\_\_\_

**TOTAL score \_\_\_\_\_\_\_\_\_\_\_\_\_**