TITLE	A randomized phase 2 study of bortezomib, cyclophosphamide and dexamethasone induction (VCD) compared with VCD and daratumumab induction followed by daratumumab maintenance (VCDD) for the initial treatment of transplant ineligible patients with multiple myeloma.
SHORT TITLE	VCDD in transplant ineligible myeloma
PROTOCOL NUMBER	AMARC 03-16
CHIEF INVESTIGATORS	Associate Professor Peter Mollee Professor Andrew Spencer
SPONSOR	Alfred Health operating through AMARC
TRIAL COMMITTEE	Associate Professor Peter Mollee Professor Andrew Spencer Associate Professor Simon Harrison Dr Hang Quach Professor Joy Ho
VERSION NUMBER	1
DATE OF PROTOCOL	27 Jan 2017
ANZCTR NUMBER	TBC

Development Protocol History

Version No	Date	Author	Reason
1	27 Jan 2017	Peter Mollee	

Approved Protocol History

Version No	Date	Author	Reason

Protocol Approval

Version No	Date	Name of person approving	Approval signature

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.

SIGNATORY ON BEHALF OF SPONSOR DATE

NAME OF SIGNATORY *(print)* 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.

PRINCIPAL INVESTIGATOR SIGNATURE DATE	PRINCIPAL INVESTIGATOR SIGNATURE DATE
PRINCIPAL INVESTIGATOR NAME *(print)*	PRINCIPAL INVESTIGATOR NAME *(print)*

CONTENTS

1. CONTACTS

Chief Investigators

Peter Mollee
Princess Alexandra Hospital
Ipswich Rd
Brisbane QLD Australia, 4102
Ph: +61 7 3176 2396
Fax: +61 7 3176 7042
Mob: +61 438109784
Email: peter.mollee@health.qld.gov.au

Andrew Spencer
Alfred Hospital
Commercial Road
Melbourne VIC Australia, 3004
Ph: +61 3 9076 3393
Fax: +61 3 9276 2298
Mob: +61 407 717 011
Email: aspencer@netspace.net.au

Statistician

A/Prof John Reynolds
Scientific Director, Biostatistics Consulting Platform, Faculty of Medicine, Nursing and Health Sciences, Monash University,
The Alfred Centre, 99 Commercial Road,
Melbourne VIC Australia 3004
Ph: +61 3 9903 0641
Email: john.reynolds@monash.edu

Sponsor

Alfred Hospital operating through AMARC
Commercial Road
Melbourne VIC Australia, 3004
Ph: +61 3 9076 2217
Fax: +61 3 9076 5531

Trial Coordinating Centre (TCC)

Nola Kennedy
Clinical Research Unit- Haematology
Alfred Hospital, Commercial Road
Melbourne VIC Australia, 3004
Ph: +61 3 9076 2217
Fax: +61 3 9076 5531
Email: N.Kennedy@alfred.org.au

TMC

TBC

Correlative Laboratory Studies Delivery:

Attention Nola Kennedy
c/o Alfred Hospital
Malignant Haematology and Stem Cell Transplantation, South Block, 1st floor
Commercial Road,
Melbourne VIC Australia, 3004
Ph: +61 3 9076 2217

SAE and pregnancy notification for all sites within 24 hours

Trial Centre : Fax: +61 3 9076 5531 **Email :** N.Kennedy@alfred.org.au
Janssen : Fax : +61 2 9888 9817 **Email** : LSO_AUST@its.jnj.com

2. ABBREVIATIONS

AE	Adverse event
ADR	Adverse drug reaction
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ASCT	Autologous stem cell transplant
AUC	Area under the curve
B2M	Beta 2 microglobulin
BMAT	Bone marrow aspirate and trephine
C	Cyclophosphamide
CI	Confidence Interval
CR	Complete Response
CRF	Case report form
CRU	Clinical Research Unit
CTN	Clinical trial notification
CTCAE	Common Terminology Criteria for Adverse Events
D	Dexamethasone
DARA	Daratumumab
DLT	Dose-limiting toxicity
ECOG	Eastern Co-operative Oncology Group
FAS	Full analysis set
FLC	Free light chain
GCP	Good Clinical Practice
GCSF	Granulocyte colony stimulating factor
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
IMiD	Immunomodulatory drugs(s)
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
MRD	Minimal Residual Disease
MTD	Maximum tolerated dose

NK	Natural killer
NCI CTC	National Cancer Institute Common Toxicity Criteria
ORR	Overall response rate
OS	Overall survival
PB	Peripheral blood
PBMC	Peripheral blood mononucelar cells
PICF	Patient Information and Consent Form
PD	Progressive disease
PFS	Progression-free survival
PI	Principal Investigator
PN	Peripheral neuropathy
PPS	Per-protocol set
PR	Partial Response
RAR	Response adaptive randomization
SAE	Serious adverse event
SD	Stable disease
SDMC	Safety and data monitoring committee
SFLC	Serum free light chain
SPEP	Serum protein electrophoresis
TCC	Trial Coordinating Centre
TGA	Therapeutic Goods Administration
TMC	Trial Management Committee
Tregs	Regulatory T cells
ULN	Upper limit of normal
VCD	Bortezomib, cyclophosphamide, dexamethasone
VCDD	Bortezomib, cyclophosphamide, dexamethasone, daratumumab

3. PROTOCOL SYNOPSIS

Title	A randomized phase 2 study of bortezomib, cyclophosphamide and dexamethasone induction (VCD) compared with VCD and daratumumab induction followed by daratumumab maintenance (VCDD) for the initial treatment of transplant ineligible patients with multiple myeloma
Study number	AMARC 03-16
Indication	Initial treatment of transplant ineligible myeloma
Rationale	Multiple myeloma (MM) is a malignant disease of monoclonal plasma cells and in the elderly has a 5-year survival rate below 50%. VCD (bortezomib, cyclophosphamide, dexamethasone) is the current standard of care in Australia for the initial tretament of transplant ineligible patients. Daratumumab, a human IgG1κ monoclonal antibody directed against CD38, has shown promising efficacy and a favorable safety profile in ongoing phase II/III studies as monotherapy and in combination with chemotherapy (lenalidomide/dexamethasone and bortezomib/dexamethasone) in patients with relapsed or relapsed, refractory MM as well as in combination with VMP in newly diagnosed MM. There has, however, been no data on the combination of daratumumab with VCD. With the increasingly important role of minimal residual disease (MRD) elimination in myeloma, the extent of MRD needs to be defined following daratumumab regimens in older, non-transplant patients.
Objectives	Primary: • To assess whether the addition of daratumumab to VCD will cause an improvement in median PFS in patients with newly diagnosed multiple myeloma who are not candidates for high dose chemotherapy and autologous stem cell transplantation Secondary: • To compare response rates to VCD and VCDD therapy as measured by IMWG criteria • To assess MRD as determined by multiparameter 8 colour flow cytometry from a bone marrow sample at the end of VCD(D) induction for all patients who have achieved VGPR or better • To assess overall survival following the addition of daratumumab to VCD compared to VCD

	• To document the safety/toxicity profile of VCDD • Change in global health status, as measured by the PRO instrument, EORTC QLQ-C30 • To evaluate quantitative and qualitative immunological changes in peripheral blood by flow cytometry and their associations with disease response.
Trial design	This is a prospective, multi-centre, open-label, phase 2 trial of VCD induction compared to VCD and daratumumab induction followed by daratumumab maintenance until disease progression or toxicity. Eligible patients will be assigned in a response adapted randomisation to receive VCDD (experimental arm) or VCD (control arm) in 35-day cycles for 9 cycles with the VCDD arm continuing on daratumumab maintenance monthly until disease progression, unacceptable toxicity, or withdrawal of consent. VCDD patients will receive daratumumab at a dose of 16mg/kg iv, day 1,8,15,22 for cycles 1 & 2, then day 1 & 15 for cycles 3-6, thereafter day 1 for cycles 7-9. In addition they will receive V 1.3mg/m2 sc day 1,8,15,22, C 300mg/m2 po and D 20mg po day 1,8,15,22 each cycle. VCD patients will receive V 1.3mg/m2 sc day 1,8,15,22, C 300mg/m2 po and D 20mg po day 1,8,15,22 each cycle. Patients will be followed up every 4 weeks for MM response until PD and then every 12 weeks for survival.
Number of participants	120 randomised
Study duration	24 to 28 months accrual. Patients will continue therapy in both the experimental (VCDD) arm and control arm (VCD) until progression, intolerance or withdrawal of consent. Follow up for PFS and OS will continue until all patients remaining on study have been followed for at least 24 months. After this point trial activities will cease and patients will be offered opportunity to continue on daratumumab until progression Thus trial duration is estimated at approximately 4 years (48 to 52 months).
Investigational product	Daratumumab
Main inclusion criteria at registration (Refer to main text for full list)	1. Male or female patients 18 years or older. 2. Patients must have a diagnosis of symptomatic multiple myeloma as per IMWG criteria (Appendix 1) 3. Measureable disease 4. Newly diagnosed and not considered candidate for high-dose chemotherapy with autologous stem cell transplantation 5. Patients must be untreated apart from a brief course of

	corticosteroids or radiotherapy 6. No contraindication to the use of any of the study drugs 7. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 (See Appendix 3). 8. Patients must meet the following clinical laboratory criteria: • ANC $\geq$ 1.0 x 10^9/L (G-CSF use is permitted) • Platelet count ≥70 x 10^9/L for subjects in whom <50% of bone marrow nucleated cells are plasma cells; otherwise platelet count >50 × 10^9/L • Total bilirubin ≤ 2 × ULN, except in subjects with Gilbert syndrome, then direct bilirubin ≤2 x ULN • ALT and AST $\leq$ 5 × ULN 9. Voluntary written consent 10. Female patients who are postmenopausal or agree to use effective contraception 11. Male patients who agree to use effective contraception 12. Study site must be able to get correlative samples to the Alfred Hospital, Melbourne, Australia, within 24 hours of collection
Main exclusion criteria at registration and randomisation **(Refer to main text for full list)**	1. Patients with AL amyloidosis, monoclonal gammopathy of uncertain significance or smouldering MM. 2. Female patients who are lactating or have a positive serum pregnancy test during the screening period. 3. Patient has $\geq$ Grade 3 peripheral neuropathy, or Grade 2 with pain on clinical examination during the screening period. 4. Subject has significant airways disease according to the following definitions: 4.1. Subject has known chronic obstructive pulmonary disease (COPD) with an Forced Expiratory Volume in 1 second (FEV1) < 50% of predicted normal. 4.2. Subject has had known moderate or severe persistent asthma within the last 2 years (see Attachment 4), or currently has uncontrolled asthma of any classification. (Note that subjects who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed in the study). 5. Evidence of current uncontrolled cardiovascular conditions, including uncontrolled hypertension, uncontrolled cardiac arrhythmias, New York Heart

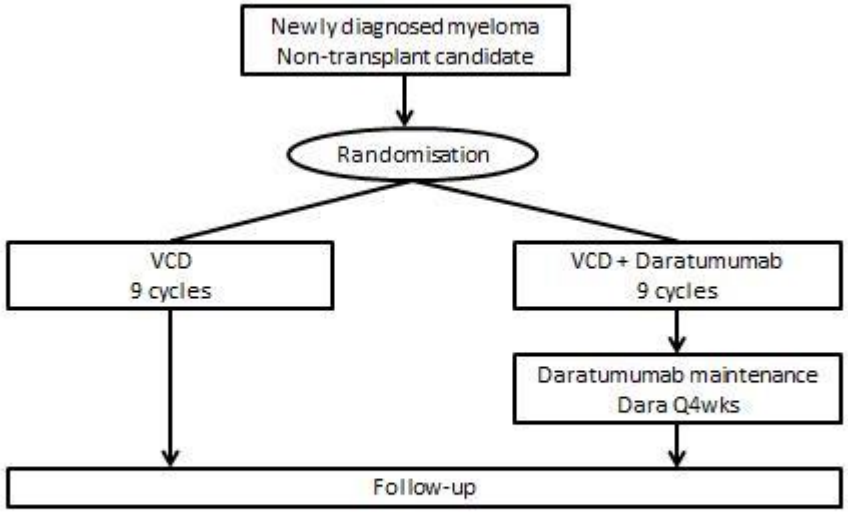
	Association (NYHA) class 3 or 4 heart failure symptoms, unstable angina, or myocardial infarction within the past 6 months. 6. Known ongoing or active systemic infection, active hepatitis B or C virus infection, or known human immunodeficiency virus (HIV) positive 7. Active malignancy with the exception of any of the following: • Adequately treated basal cell carcinoma, squamous cell carcinoma, or in situ cervical cancer • Adequately treated Stage I cancer from which the subject is currently in remission and has been in remission for 2 years • Stage I prostate cancer that does not require treatment • Any other cancer from which the subject has been disease-free for ≥ 2 years 8. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol. 9. Known allergy to any of the study medications, their analogues, or excipients in the various formulations of any agent. 10. Participation in other clinical trials for the treatment of multiple myeloma, including those with other investigational agents not included in this trial, within 30 days of the start of this trial and throughout the duration of this trial.
Efficacy assessments	PFS, OS, objective response defined as achievement of a partial or complete response (PR or CR) according to IMWG criteria (see Appendix 2).
Safety assessments	AEs, SAEs
Other assessments	Correlative studies- see text for full details
Follow-up schedule	Followed for progression free survival every 3 months until all patients remaining on study have been followed for at least 24 months.
Statistical considerations	***The design.*** After a "burn-in" period of 1:1 randomized allocation of the first 30 patients to the two study arms, we propose to use response adaptive randomization (RAR) to preferentially assign patients to the study arm that appears to be superior. Even though PFS is the primary efficacy endpoint, we will

	also incorporate information about "short-term" patient response into the RAR procedure. We will use a Bayesian mixture distribution to model the relationship between response status (after 4 cycles) and PFS. Posterior probability distributions will be used to implement both early stopping criteria and the RAR procedure. The model will be updated at frequent intervals after the burn-in period has been completed and in particular, immediately after the co-ordinating trial centre has been notified of a progression or death of a patient. General properties of the design are detailed in Huang et al, "Using short-term response information to facilitate adaptive randomization for survival clinical trials", *Statist. Med.* 2009; 28:1680-1689. We are planning to randomize up to 120 patients and anticipate an accrual rate of approximately 5 patients per month over a period of 24 to 28 months. Follow-up will continue until all patients remaining on study have been followed for at least 24 months from their date of randomization. ***The model.*** Two response categories (assessed after the first 4 induction cycles) will be utilized in the model and the RAR, namely <VGPR and ≥VGPR. We assume that the numbers of patients in a study arm that fall into the two response categories follow binomial distributions and we further assume a Beta (or Dirichlet) distribution for the prior probability distribution for the multinomial response rates. Conditional on the response being in a particular category, we assume that PFS follows an exponential distribution with a hazard rate that depends not only on the response category but also the study arm to which the patient was randomized. An inverse gamma distribution will be assumed for the prior probability distribution of the hazard rates within a study arm. ***RAR and early stopping*** Whenever the posterior probability distributions for the response rates and hazard rates are updated, the posterior probability (P) that mean PFS time in the VCD arm exceeds that in the VCDD arm will be calculated. Subsequent patients will be randomized to the VCD arm with probability P and to the VCDD arm with probability 1 – P. If at any time during the trial, including at the end of the trial, $P > 0.975$, the VCDD arm will be deemed to be inferior to the VCD arm. Similarly, if at any time during the trial, including at the end of the trial, $P < 0.025$, the VCDD arm will be deemed to be superior to the VCD arm. Accrual may be closed early if

	superiority or inferiority is established before 120 patients have been randomized. If the maximum number of patients has been randomized and, at the end of the trial, neither of the study arms have been identified as superior, the trial could be regarded as inconclusive. ***Sample size justification***. We present simulation results for this response adaptive clinical trial. An accrual rate of 5 patients per month (for up to 24 months) was assumed and 5000 trials were simulated. When the ≥VGPR response rate is 40% in the VCD arm and 60% in the VCDD arm and median PFS = 24 and 48 months respectively in the VCD and VCDD arms (HR = 0.5), the chance that the VCDD arm is declared superior to the VCD arm is estimated to be 82%. The chance that the VCDD arm is declared inferior to the VCD arm is estimated to be less than 0.1% and the chance of an inconclusive result is estimated to be 18%. The expected sample size is 113 and the expected duration of the trial is 145 weeks (33.5 months) rather than 208 weeks (48 months). Accordingly, we have made provision to randomize up to 120 patients.
Analyses	The posterior probability distributions of the response rates and the PFS hazard rates in each response category will be reported for each study arm in the form of graphs and also summarized by their 2.5, 50.0 and 97.5 percentiles (i.e. medians and 95% credible intervals). Computation of the posterior probability distributions will use minimally informative prior probability distributions for the proportion of patients and the mean survival in the two response categories or groups. The same priors will be used for each arm, so *a priori*, neither arm is favoured. The posterior probability distributions for the hazard ratio for PFS and the odds ratio for objective response will also be reported in the form of graphs together with medians and 95% credible intervals regardless of the outcome of the trial (superiority, inferiority or inconclusive). The Kaplan-Meier method will be used to summarize time-to-event outcomes (PFS and OS) by study arm. Details of all analyses, including the specifications of all prior distributions to be used in the Bayesian analyses, will be documented in a Statistical Analysis Plan (SAP) prior to database lock for the final analysis of the primary efficacy endpoint.
Trial Management Committee (TMC)	The TMC will: • Provide objective medical oversight of the clinical trial including, but not limited to, responses to queries

	raised by site PI's, • Oversee safety in real time, • Appraise updates, provided by the Trial Statistician, of the posterior probability distributions for the response rates and hazard rates and consequently give consideration to early closure of accrual, or early publication of efficacy analyses, if there is strong evidence of superiority or inferiority. A Terms of Reference (TOR) document or charter for the TMC will be established prior to trial activation. Recommendations of the TMC will be reviewed by the SDMC and the AMaRC Management Committee before implementation.

4. STUDY SCHEMA



5. SCHEDULE OF ASSESSMENTS

	Screening[a]	Cycle 1				Cycles 2-4	Cycle 5	Cycles 6-9	End of VCD(D) Induction[b]	Follow-up every 3 months[i]	At progression
Study Procedures	-28 to -1	Day 1	Day 8	Day 15	Day 22	Day 1	Day 1	Day 1			
Informed Consent	X										
Inclusion/Exclusion Criteria	X										
Demographics	X										
Medical history	X										
MM stage (Appendix 5)	X										
MM diagnostic karyotype and FISH if available	X										
Symptom-directed Physical Examination	X	X				X	X	X	X		
Neurological Assessment	X	X				X	X	X	X		
ECOG	X	X				X	X	X	X	X	
Vital Signs	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X		
Pregnancy Test[c]	X										
12-lead ECG	X										
FBE	X	X	X	X	X	X	X	X	X	X	X
Biochemistry (including serum	X	X	X	X	X	X	X	X	X	X	X

calcium corr, LDH and LFTs)											
Blood group and screen and red cell phenotyping	X										
IMWG Frailty score (Appendix 8)	X										
QOL assessment[d]	X						X		X		
Skeletal Survey	X										
Assessment of EMD if clinically indicated[e]	X					X	X	X			
B_2M	X										
LDH	X								X		
SPEP	X					X[j]	X[j]	X[j]	X[j]	X[j]	X
UPEP[f]	X					X[f]	X[f]	X[f]	X[f]	X[f]	X[f]
FLC	X					X	X	X	X	X	X
Disease response						X	X	X	X	X	X
BMAT[g]	X								X[g]		X
Correlative studies (peripheral blood collection)	X						X				
AE reporting, concomitant medications[h]	X	X				X	X	X	X	X[k]	

Abbreviations:

CR = complete response; EOT = end of treatment; FISH = fluorescent in-situ hybridization; ECOG = Eastern Cooperative Oncology Group; ECG = electrocardiogram; FBE = full blood examination; QOL = quality of life; EMD = extramedullary disease; B_2M = beta 2 microglobulin; LDH =lactate dehydrogenase; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis; SFLC = serum free light chain assay; BMAT = bone marrow aspirate and trephine; AE = adverse event.

[a] Screening should be conducted within 28 days of starting treatment.

[b] Patients who discontinue the study drug regimen for disease progression or toxicity must complete the end-of-induction (EOI) visit, which should occur within 30 days (± 1 week) after the last dose of study drug and before the start of subsequent antineoplastic therapy. Date of study cessation should be recorded.

[c] A serum pregnancy test will be performed for women of childbearing potential during screening.

[d] QLQ-C30 = Quality of Life Questionnaire.

[e] For those with documented extramedullary disease, radiographic assessments should be undertaken at screening, the end of VCD(D) induction and otherwise, only if clinically indicated. The same imaging modality used at screening (CT/PET-CT/MRI) should be used for all follow-up assessments.

[f] Only to be repeated if disease not measurable by SPEP or FLC.

[g] BMAT will be obtained at screening in all patients, at end of induction in patients who have achieved ≥ VGPR and at relapse.

[h] Including documentation of drug administration, dose adjustments, dose interruptions, AEs and concomitant medications.

[i] Patients will be followed up every three months until study closure for PFS, OS, next therapy and next therapy response data

[j] Patients with an IgG kappa paraprotein running in the same location as daratumumab in serum protein electrophoresis (typically in the late gamma region) should have response clarified by referral to a laboratory with a daratumumab-specific immunofixation electrophoresis reflex assay

[k] At first 3 month review only for VCD arm.

[l] Vital signs (blood pressure, heart rate, temperature) measured in sitting position. On Cycle 1 Day 1: immediately before the start of dara infusion; at 0.5, 1, 1.5, 2, 3.5 hr after start of infusion; at end of infusion; 0.5,1 hr after end of infusion. For all other infusions, vital signs measured immediately before start and at end of dara infusion.

6. BACKGROUND

6.1. Background

Multiple myeloma (MM) is a plasma cell malignancy characterised by an abnormal serum and /or urine immunoglobulin intact paraprotein or free immunoglobulin light chain as a result of clonal expansion of plasma cells. It is often accompanied by complications of enhanced bone loss associated with diffuse osteopenia or focal lytic lesions, renal failure, hypercalcaemia, immune suppression and anaemia. Approximately 1200 new cases are diagnosed in Australia each year and while highly responsive to treatment, always relapses and remains an incurable disease(1). While multiple myeloma is predominantly a disease of the elderly (median age at diagnosis 65-70 years), these patients are underrepresented in clinical trials. Aging is associated with co-morbidities, reduced organ function and varying degrees of frailty and disability

Since the introduction of novel agents into clinical practice, median survival of patients with MM has significantly improved although the majority of the improvement has occurred in younger patients. These therapies include the immunomodulatory drugs (IMiDs), including thalidomide, lenalidomide and pomalidomide, as well as the proteosome inhibitors bortezomib, carfilzomib and ixazomib. Currently in Australia, reimbursable options available to all patients include thalidomide, lenalidomide, pomalidomide and bortezomib. Despite the plethora of novel agents, MM is still an incurable disease, accounting for 20% of all deaths from haematologic malignancy. All patients eventually will experience relapse, developing increasing degrees of drug resistance. Improved therapeutic options for patients with myeloma remain an important goal, particularly the availablity of agents with excellent tolerability which are required for eldely patients.

6.2. Daratumumab

Daratumumab is a human IgG1κ monoclonal antibody directed against CD38. Daratumumab induces lysis of CD38-expressing tumour cells, including multiple myeloma tumour cells that were freshly isolated from patients, by a wide spectrum of potential mechanisms including: direct apoptosis through Fc-mediated cross-linking; immune-mediated tumour cell killing via complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and antibody-dependent cellular phagocytosis, through activation of complement proteins, NK cells, and macrophages, respectively (2, 3); lysis of myeloid derived suppressor cells and a subset of regulatory T cells that express CD38(4). It has demonstrated single agent activity in relapsed and refractory myeloma(5). Daratumumab has also recently been shown to significantly improve PFS in the relapsed and refractory myeloma session when added to lenalidomide and dexamethasone (6) and to bortezomib and dexamethasone (7) (HR 0.37 and 0.39 respectively). In these studies the rates of adverse events between the daratumumab and control arms were very similar as were the rates of drug cessation due to adverse events. Currently similar combinations are being examined in two large international randomized controlled trials in the upfront setting. These trials are comparing

the addition of daratumumab to lenalidomide and dexamethasone (MMY3008-MAIA) and to bortezomib, melphalan and prednisolone (MMY3007-ALCYONE). The anti-myeloma activity of daratumumab and its excellent safety profile make it an attractive agent to use in older patients.

6.3. Rationale for trial therapeutic regimen

Daratumumab has shown promising efficacy and a favorable safety profile in ongoing phase II/III studies as monotherapy and in combination with chemotherapy (lenalidomide/dexamethasone and bortezomib/dexamethasone) in patients with relapsed or relapsed, refractory MM as well as in combination with VMP in newly diagnosed MM (8). There has, however, been no data on the combination of daratumumab with bortezomib, cyclophosphamide and dexamethasone (VCD) which is the current standard of care in Australia. While prospective trial data on the VCD combination is lacking, the rationale for the widespread adoption of VCD and its use in this study is as follows. The use of cyclophosphamide in place of melphalan is thought to be of comparable efficacy based on prior randomised trials, has a lesser risk of long term marrow toxicity and is easier to use in the presence of renal failure(1). It is known from trials of VMP (bortezomib, melphalan and prednisolone) that the weekly schedule of bortezomib (4 doses in a 5 week cycle) has been shown to be more tolerable and resulted in a similar cumulative dose delivered compared to the traditional schedule of bortezomib on days 1,4,8,11 every 21 days (9). Subcutaneous bortezomib is non-inferior to IV bortezomib with respect to efficacy, but has an improved safety profile(10). Thus for transplant ineligible patients, the combination of cyclophosphamide, the weekly schedule of s/c bortezomib and dexamethasone is now considered standard of care.

6.4. Rationale for translational objectives

Response has correlated closely with survival in younger patients. With the increasingly important role of minimal residual disease (MRD) elimination in myeloma, the extent of MRD needs to be defined following daratumumab regimens in older, non-transplant patients.

In addition to daratumumab's antibody induced cytotoxicity, there are also immunomodulatory effects of daratumumab through reduction of CD38+ immunosuppressive cellular populations as well increased numbers of clonal T cells, indicating an improved adaptive immune response. The extent of this effect in the presence of chemotherapy with proteasome inhibition remains to be determined, along with their contribution to clinical responses.

7. AIMS, OBJECTIVES AND HYPOTHESES

7.1. Aim

To determine the efficacy of Daratumumab in combination with VCD in transplant ineligible patients in terms of PFS

7.2. Objectives:

7.2.1. Primary objective

- To assess whether the addition of daratumumab to VCD will cause an improvement in median PFS in patients with newly diagnosed multiple myeloma who are not candidates for high dose chemotherapy and autologous stem cell transplantation

7.2.2. Secondary objectives

- To compare response rates to VCD and VCDD therapy as measured by IMWG criteria
- To assess MRD as determined by multiparameter 8 colour flow cytometry from a bone marrow sample at the end of VCD(D) induction for all patients who have achieved VGPR or better
- To assess overall survival following the addition of daratumumab to VCD compared to VCD
- To document the safety/toxicity profile of VCDD
- Change in global health status, as measured by the PRO instrument, EORTC QLQ-C30

7.2.3. Correlative studies' objectives

- To measure NK cell numbers and subtypes assessed by flow cytometry of PBMC collected at start of induction and at end of cycle 4.
- The effect of therapy on NK-cell mediated antibody dependent cellular cytotoxicity and direct cytotoxicity (using functional and imaging assays) as well as alterations in novel pathway signaling will be compared between paired pre and post therapy patient peripheral blood samples
- In addition to NK cell numbers, to compare at baseline and end of cycle 4, the effect of receiving VCDD on:
    - B cells and T cells subsets (from peripheral blood (PB).
    - Treg numbers and function (from PB)
    - Cytokine (Th1/Th2) profile (PB)
- To quantify clonal T cell numbers at baseline and at the end of cycle 4
- Isolation of CD138 selected bone marrow plasma cell DNA at baseline and plasma cell free DNA at baseline and end of cycle 4 for exploratory biomarker analyses utilizing amplicon sequencing against a panel of pan-cancer and myeloma-specific target

regions

- Baseline NGS characterization (RNA from CD138 purified MM cells) for comparative analyses:
    - Disease outcome: VCD vs VCDD for high-risk only
    - Disease outcome: high risk vs non-high-risk for VCDD cohort
    - Disease outcome: renal failure vs normal renal function for VCDD cohort

7.3. Hypothesis

That the addition of daratumumab to VCD will improve outcomes in patients with newly diagnosed multiple myeloma who are not candidates for high dose chemotherapy and autologous stem cell transplantation

8. PATIENT SELECTION

8.1. Eligibility Criteria

Concerns regarding the eligibility of a potential patient can be directed to the trial principal investigator.

8.1.1. Inclusion criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study:

1. Male or female patients 18 years or older.
2. Patients must have a diagnosis of symptomatic multiple myeloma as per IMWG criteria (Appendix 1)
3. Measurable disease as defined by any of the following:
    - IgG myeloma: Serum monoclonal paraprotein (M-protein) level ≥10 g/L, serum iFLC ≥100mg/L with an abnormal kappa:lambda FLC ratio or urine M-protein level ≥200 mg/24 hours; or
    - IgA, IgM, IgD, or IgE multiple myeloma: serum M-protein level ≥5 g/L, serum iFLC ≥100mg/L with an abnormal kappa:lambda FLC ratio or urine M-protein level ≥200 mg/24 hours; or
    - Light chain multiple myeloma: serum iFLC ≥100mg/L with an abnormal kappa:lambda FLC ratio or urine M-protein level ≥200 mg/24 hours
4. Newly diagnosed and not considered candidate for high-dose chemotherapy with autologous stem cell transplantation due to:
    - age >65 years, or
    - in subjects ≤65 years: presence of comorbidities that, in the opinion of the investigator, preclude the patient from being a candidate for autologous stem cell transplantation
5. Untreated with the exception of short course corticosteroids (total 160mg dexamethasone or equivalent) or radiotherapy
6. No contraindication to the use of any of the study drugs
7. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 (See Appendix 3).

8. Patients must meet the following clinical laboratory criteria:
    - Absolute neutrophil count (ANC) $\geq$ 1.0 x 10^9/L (G-CSF use is permitted)
    - Platelet count ≥70 x 10^9/L for subjects in whom <50% of bone marrow nucleated cells are plasma cells; otherwise platelet count >50 × 109/L (transfusions are not permitted to achieve this minimum platelet count).
    - Total bilirubin ≤ 2 $\times$ the upper limit of the normal range (ULN). except in subjects with Gilbert syndrome, then direct bilirubin ≤2 x ULN
    - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $\leq$ 5 $\times$ ULN.

9. Voluntary written consent must be given
10. Female patients who:
    - Are postmenopausal for at least 1 year before the screening visit, OR
    - Are surgically sterile, OR
    - If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form through 120 days after the last dose of study drug, OR
    - Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g. calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

11. Male patients, even if surgically sterilized (ie, status post-vasectomy), must agree to one of the following:
    - Agree to practice effective barrier contraception during the entire study treatment period and through 120 days after the last dose of study drug, OR
    - Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)
12. Study site must be able to get correlative samples to the Alfred Hospital, Melbourne, Australia, within 24 hours of collection.

8.1.2. Exclusion criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:

1. Patients with AL amyloidosis, monoclonal gammopathy of uncertain significance or smouldering MM.
2. Female patients who are lactating or have a positive serum pregnancy test during the screening period.
3. Patient has $\geq$ Grade 3 peripheral neuropathy, or Grade 2 with pain on clinical examination during the screening period.
4. Subject has significant airways disease according to the following definitions:
    - Subject has known chronic obstructive pulmonary disease (COPD) with an Forced Expiratory Volume in 1 second (FEV1) < 50% of predicted normal. Note that FEV1

testing is required for subjects suspected of having COPD and subjects must be excluded if FEV1 <50% of predicted normal

- Subject has had known moderate or severe persistent asthma within the last 2 years (see Attachment 4), or currently has uncontrolled asthma of any classification. (Note that subjects who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed in the study).

5. Evidence of current uncontrolled cardiovascular conditions, including uncontrolled hypertension, uncontrolled cardiac arrhythmias, New York Heart Association (NYHA) class 3 or 4 heart failure symptoms, unstable angina, or myocardial infarction within the past 6 months.
6. Known ongoing or active systemic infection, active hepatitis B or C virus infection, or known human immunodeficiency virus (HIV) positive
7. Active malignancy with the exception of any of the following:
   • Adequately treated basal cell carcinoma, squamous cell carcinoma, or in situ cervical cancer
   • Adequately treated Stage I cancer from which the subject is currently in remission and has been in remission for 2 years
   • Stage I prostate cancer that does not require treatment
   • Any other cancer from which the subject has been disease-free for ≥ 2 years
8. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.
9. Known allergy to any of the study medications, their analogues, or excipients in the various formulations of any agent.
10. Participation in other clinical trials for the treatment of multiple myeloma, including those with other investigational agents not included in this trial, within 30 days of the start of this trial and throughout the duration of this trial.

9. INVESTIGATIONAL PLAN

9.1. Study Design

This is a prospective, multi-centre, open-label, response adapted randomized phase 2 trial of VCD induction compared to VCD and daratumumab induction followed by daratumumab maintenance until disease progression or toxicity. The first 30 patients registered on the study will be randomized 1:1 to the study arms. Thereafter, response adaptive randomization (RAR) will be used to assign more patients to the treatment arm that appears to have better efficacy. We are planning to randomize up to 120 patients and anticipate an accrual rate of 4 to 5 patients per month over a period of 24 to 28 months. Follow-up will be for a period of up to 24 months after the randomization of the last patient recruited to the study.

Please also see study schema Section 3.

9.2. Treatment plan

Treatment is as follows:

VCD ARM:

VCD Induction (9 x 5 weekly cycles):

- Bortezomib 1.3mg/m^2 sc day 1,8,15,22
- Cyclophosphamide 300mg/m^2 po day 1,8,15,22
- Dexamethasone 20mg po day 1,8,15,22

VCDD ARM:

VCDD Induction (9 x 5 weekly cycles):

- Bortezomib 1.3mg/m^2 sc day 1,8,15,22
- Cyclophosphamide 300mg/m^2 po day 1,8,15,22
- Dexamethasone 20mg po day 1,8,15,22
- Daratumumab 16mg/kg iv
    - Cycles 1&2: day 1,8,15,22
    - Cycles 3-6: day 1 & 15
    - Cycles 7-9: day 1

VCDD Maintenance (until progression)

- Daratumumab 16mg/kg iv once every 4 weeks

Choice of agents for anti-viral and anti-bacterial prophylaxis, anti-acid reflux and bisphosphonate therapy will be as per institutional protocol.

Before initiating a new cycle of therapy, subjects must meet the following criteria:

- Platelet count ≥70 x 10^9/L
- ANC ≥1.0 x 10^9/L

Treatment will continue until:

- failure to achieve a minimal (=minor) response after 4 cycles of VCD(D)
- disease progression
- unacceptable toxicity
- withdrawal of patient consent

9.2.1. Daratumumab Administration

Vital signs should be monitored extensively on Cycle 1 Day 1 before, during, and after the first infusion of daratumumab. For all other infusions, vital signs should be measured before the start of infusion and at the end of the infusion. If a subject experiences any significant medical event, then the investigator should assess whether the subject should stay overnight for observation.

For recommendations on daratumumab infusion rate, please refer to the Product Information or equivalent document. Brief guidance is given below.

Administer daratumumab infusion intravenously at the appropriate infusion rate. Consider incremental escalation of the infusion rate only in the absence of infusion reactions with the previous infusion of daratumumab as defined below.

	Dilution volume	**Initial rate (first hour)**	**Rate increment**	**Maximum rate**
First infusion	1000 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Second infusion[a]	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Subsequent infusions[b]	500 mL	100 mL/hour	50 mL/hour every hour	200 mL/hour

[a] Escalate only if there were no Grade 1 (mild) or greater infusion reactions during the first 3 hours of the first infusion.
[b] Escalate only if there were no Grade 1 (mild) or greater infusion reactions during a final infusion rate of ≥100 mL/hr in the first two infusions.

For infusion reactions of any grade/severity, immediately interrupt the daratumumab infusion and manage symptoms (see Section 9.2.1.2).

9.2.1.1. Guidelines for Prevention of Infusion Reactions

Preinfusion Medication
On daratumumab infusion days, subjects will receive the following medications prior to infusion:

- Paracetamol (acetaminophen) 1000 mg PO approximately 1 hour or less prior to daratumumab infusion
- An antihistamine (diphenhydramine 25-50 mg IV or PO, or equivalent H1 blocker) approximately 1 hour prior to daratumumab infusion
- Dexamethasone 20 mg IV or PO, approximately 1 hour or less prior to daratumumab infusion.
- Leukotriene Inhibitor (optional) on Cycle 1 Day 1: montelukast 10 mg PO, or equivalent, approximately 1 hour or less before the daratumumab infusion

If necessary, all PO preinfusion medications may be administered outside of the clinic on the day of the infusion, provided they are taken within 3 hours before the infusion.

Postinfusion Medication

For subjects with higher risk of respiratory complications (eg, subjects with mild asthma, or subjects with COPD who have a FEV1 <80%), the following postinfusion medications should be considered:

- Antihistamine (diphenhydramine or equivalent)
- Leukotriene inhibitor (montelukast or equivalent)
- Short-acting β2 adrenergic receptor agonist such as salbutamol aerosol
- Control medications for lung disease (eg, inhaled corticosteroids ± long-acting β2 adrenergic receptor agonists for subjects with asthma; long-acting bronchodilators such as tiotropium or salmeterol ± inhaled corticosteroids for subjects with COPD)

In addition, these at-risk subjects may be hospitalized for monitoring for up to 2 nights after an infusion. If subjects are hospitalized, then their FEV1 should be measured before discharge. If these subjects are not hospitalized, then a follow up telephone call should be made to monitor their condition within 48 hours after all infusions. If the subject has not experienced a significant medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as a serious adverse event. Investigators may prescribe bronchodilators, antihistamines, and corticosteroids that are deemed necessary to provide adequate supportive care in the event a bronchospasm occurs after subjects are released from the hospital/clinic. If an at-risk subject experiences no major infusion-related reactions, then these postinfusion medications may be discontinued after 4 full doses at the investigator's discretion.

9.2.1.2. Management of Infusion-related Reactions

Subjects in the VCDD arm should be carefully observed during daratumumab infusions. Trained study staff at the clinic should be prepared to intervene in case of any infusion-related reactions occurring, and resources necessary for resuscitation (eg, agents such as epinephrine and aerosolized bronchodilator, also medical equipment such as oxygen tanks, and a defibrillator) must be available. Attention to staffing should be considered when multiple subjects will be dosed at the same time.

If an infusion-related reaction develops, then the infusion should be temporarily interrupted. Subjects who experience adverse events during the infusion must be treated according to the investigator's judgment and best clinical practice. The following guidelines may apply:

- Subjects should be treated with paracetamol (acetaminophen), antihistamine, or corticosteroids. Intravenous saline may be indicated. For bronchospasm, urticaria, or dyspnea, subjects may require antihistamines, oxygen, corticosteroids, or bronchodilators. For hypotension, subjects may require vasopressors.

- In the event of a life-threatening infusion-related reaction (which may include pulmonary or cardiac events), or anaphylactic reaction, daratumumab should be discontinued and no additional daratumumab should be administered to the subject. Aggressive symptomatic treatment should be applied.

- If an infusion is paused, then a longer-than-anticipated infusion time may occur. Overnight stays at the hospital because of slow infusion times should not be reported as a serious adverse event. However, if the underlying cause of the delayed infusion time is an adverse event or serious adverse event, then that should be reported as such.

Infusion-Related Events of Grade 1 or Grade 2

If the investigator assesses an adverse event to be related to the daratumumab infusion, then the infusion should be paused. When the subject's condition is stable, the infusion may be restarted at the investigator's discretion. Upon restart, the infusion rate should be half of that used before the interruption. Subsequently, the infusion rate may be increased at the investigator's discretion. If the subject experiences a Grade 2 or higher event of laryngeal edema or a Grade 2 or higher event of bronchospasm that does not respond to systemic therapy and does not resolve within 6 hours from the onset, then the subject must be withdrawn from treatment.

Infusion-Related Reactions of Grade 3 or Higher

For infusion-related adverse events that are Grade 4, the infusion should be stopped and treatment with daratumumab will be discontinued for that subject.

For infusion-related adverse events that are Grade 3, the daratumumab infusion must be stopped, and the subject must be observed carefully until the resolution of the adverse event or until the intensity of the event decreases to Grade 1, at which point the infusion may be restarted at the investigator's discretion. Upon restart, the infusion rate should be half of that used before the interruption. Subsequently, the infusion rate may be increased at the investigator's discretion.

If the intensity of the adverse event returns to Grade 3 after restart of the infusion, then the procedure described in this section may be repeated at the investigator's discretion. Should the intensity of the adverse event increase to Grade 3 for a third time, then treatment with daratumumab will be discontinued for that subject.

9.2.2. Bortezomib Administration

Subjects will receive 1.3 mg/m^2 bortezomib as a SC injection once weekly (days 1,8,15,22) for nine 5-week cycles (Cycles 1 to 9; 4 doses per cycle).
Skipped doses of bortezomib will not be made up later in the cycle. Individual doses within a cycle have a ±2 day window. For example, if the patient requires overnight admission for daratumumab, then the bortezomib can be given on the day of discharge.
For subjects with unacceptable toxicity at the local injection site despite dose modifications or change in injection concentration, bortezomib can be administered intravenously as a 3 to 5 sec bolus injection.

9.2.3. Cyclophosphamide Administration

Cyclophosphamide will be administered at 300 mg/m^2 orally on days 1, 8, 15 and 22 for nine 5-week cycles (Cycles 1 to 9; 4 doses per cycle). The total calculated dose should be rounded to the closest dose that can be administered using the tablets available. No dose reduction will be made for impaired creatinine clearance but will be reduced by 50% for patients on dialysis. Administration of cyclosphamide will be approximately the same time each week and will be irrespective of daratumumab infusion. Patients should be instructed to swallow

cyclophosphamide tablets whole with or without food and not to break or chew tablets. If a dose of cyclophosphamide is missed, it should be taken as soon as possible within 72 hours of the scheduled dose. If the dose is missed for >72 hours it should not be made up. If the patient vomits after taking a dose, the patient should not repeat the dose but should resume dosing at the time of the next scheduled dose.

Patients who take more than the prescribed dose of cyclophosphamide should be instructed to seek emergency medical care if needed and contact study staff immediately. Dose reduction of cyclophosphamide for haematological toxicity should be at the investigators discretion.

9.2.4. Dexamethasone Administration

Dexamethasone will be administered at 20mg orally on days 1, 8, 15 and 22 for nine 5-week cycles (Cycles 1 to 9; 4 doses per cycle). For subjects randomized to the VCDD Arm, 20mg dexamethasone will be utilized as the treatment dose of steroid for that particular day, as well as the required pre-medication prior to daratumumab infusion. In exceptional circumstances, a subject may not tolerate sudden corticosteroid withdrawal after the dexamethasone treatment. In such an instance, a tapering regimen of dexamethasone can be prescribed. Dexamethasone tablets are to be taken with or immediately after a meal or snack, preferably in the morning. If a dose of dexamethasone is missed, it should be taken as soon as possible within 72 hours of the scheduled dose. If the dose is missed for >72 hours it should not be made up. If the patient vomits after taking a dose, the patient should not repeat the dose but should resume dosing at the time of the next scheduled dose.

All patients should receive acid reflux prophylaxis (e.g. pantoprazole 40mg daily) as per institutional protocol.

9.3. Dose Modifications and Delays

Patients will be evaluated for adverse events (AEs) at each visit with the NCI CTCAE v4.0 used as a guide for grading severity. Dosing interruptions and reductions are permitted throughout this study, refer to sections 9.3.1 to 9.3.4.

Before initiating a new cycle of therapy, subjects must meet the following criteria:

- Platelet count ≥70 x 10^9/L
- ANC ≥1.0 x 10^9/L

Unless otherwise listed in section 9.3.1 to 9.3.4, if a grade 3 or 4 adverse event occurs, hold drug(s) to be tested and re-evaluate the patient at least weekly until toxicity improves to ≤ grade 2. If the toxicity does not resolve after 2 weeks consult the principal investigator. If the toxicity resolves within or at 2 weeks to grade 2 or less, the patient will be restarted at the same dose.

In case of reappearance of the grade 3 or 4 adverse event, withhold the drug and re-evaluate the patient at least weekly until toxicity improves to ≤ grade 2. And then, the patient may be restarted on agent to be tested at the lower dose level.

Subjects who need to discontinue treatment with any one component of study treatment (bortezomib, cyclophosphamide, dexamethasone, or daratumumab) may continue to receive treatment with the other components of study treatment.

9.3.1. Daratumumab Dose Modification

Dose modification of daratumumab is not permitted; dose delay is the primary method for managing daratumumab-related toxicities.

Refer to Section 9.2.1.2 for details on management of infusion-related reactions. Only if any of the following criteria are met and the event cannot be ascribed to components of the chemotherapy regimen, the daratumumab infusion must be held to allow for recovery from toxicity. The criteria for a dose delay are:

- Grade 4 haematologic toxicity
- Grade 3 thrombocytopenia with bleeding
- Febrile neutropenia
- Neutropenia with infection, of any grade
- Grade 3 or higher nonhaematologic toxicities with the following exceptions:
    - Grade 3 nausea that responds to antiemetic treatment within 7 days
    - Grade 3 vomiting that responds to antiemetic treatment within 7 days
    - Grade 3 diarrhea that responds to antidiarrheal treatment within 7 days
    - Grade 3 fatigue that was present at baseline or that lasts for <7 days after the last administration of daratumumab
    - Grade 3 asthenia that was present at baseline or that lasts for <7 days after the last administration of daratumumab

If a daratumumab infusion does not commence within the prespecified window of the scheduled administration date, then the dose will be considered a missed dose. Administration may resume at the next planned dosing date. A missed dose will not be made up.

Any adverse event deemed to be related to daratumumab that requires a dose hold of more than 4 weeks will result in permanent discontinuation of daratumumab. After Cycle 9, any adverse event deemed to be related to daratumumab that requires a dose hold of 2 consecutive planned doses will result in permanent discontinuation of daratumumab.

9.3.2. Bortezomib Dose Modification

Dose levels for bortezomib dose modification are presented in Table 1. In addition to the bortezomib dose modification guidelines presented in Section 9.3 and Table 2, if ≥2 doses in a cycle are withheld, bortezomib dose should be reduced by 1 dose level. Once reduced due to toxicity, doses of bortezomib should not be re-escalated.

Table 1: Dose levels for bortezomib treatment modifications

Dose level	**Bortezomib dose**
Starting dose	1.3 mg/m^2
-1	1.0 mg/m^2
-2	0.7 mg/m^2
-3	Discontinue

Table 2: Dose modification guidelines for bortezomib

Neurological	Grade 1 (paresthesias and/or loss of reflexes) without pain or loss of function	No action required.
	Grade 1 with pain or Grade 2 (interfering with function but not with activities of daily living)	Reduce bortezomib by 1 dose-level or change schedule to fortnightly
	Grade 2 with pain or Grade 3 (interfering with activities of daily living)	Hold bortezomib until toxicity resolves to <Grade 2. When toxicity resolves, reinitiate with a reduction by 1 dose-level and change bortezomib treatment schedule to fortnightly
	Grade 4 (permanent sensory loss that interferes with function) and/or severe autonomic neuropathy	Discontinue bortezomib permanently.
Haematological	Neutropenia Grade 3 (without complications)	No dose reduction required of bortezomib. Consider treatment with G-CSF.

	Neutropenia associated with fever (≥38.5ºC): Grade 3 or neutropenia Grade 4	Hold therapy until recovery to baseline OR ≤ Grade 2. Upon recovery, restart bortezomib at current dose and consider G-CSF support. If recurrence is seen, consider reducing bortezomib by 1 dose-level.
	Thrombocytopenia Grade 3 (without complications)	No dose reduction.
	Platelet count ≤ 30 x 10^9/L on a bortezomib dosing day (See Section 9.3 for minimum criteria for dosing on Day 1 of a cycle)	Withhold bortezomib therapy.
	Platelet count <25,000/μL (ie, Grade 4) or Grade 3 thrombocytopenia with bleeding	Hold therapy until recovery to baseline OR ≤ Grade 2. Upon recovery, restart bortezomib at 1 dose reduced level.
Infection	Herpes Zoster activation or reactivation ANY grade	Hold therapy until lesions are dry. If not already underway, begin antiviral treatment Once the infection is resolved all medications can be restarted without a dose reduction; however, continued antiviral prophylaxis is required.

9.3.3. Cyclophosphamide Dose Modification

Table 1: Dose reductions for cyclophosphamide in renal impairment

eGFR	**Cyclophosphamide dose**
≥ 30mls/min	Full dose
< 30mls/min	25% dose reduction
On dialysis	50% dose reduction

Dose reduction of cyclophosphamide for haematological toxicity should be at the investigators discretion. Otherwise investigators are to follow the general principles in Section 9.3.

9.3.4. Dexamethasone Dose Modification

Dose reductions of dexamethasone should be at the investigators discretion. Investigators are to follow the general principles in Section 9.3.

Dosage adjustments for dexamethasone are outlined in Table 4.

Table 4 Dose modification guidelines for dexamethasone

Dose level	**Dexamethasone dose**
Starting dose	20mg
-1	8mg
-2	4mg
-3	Discontinue

Dose reduction of dexamethasone to a minimum of 4mg weekly will be allowed to manage toxicities. Dexamethasone should be discontinued if patient is unable to tolerate 4mg dose. Patients intolerant of dexamethasone 4mg weekly can continue on cyclophosphamide and bortezomib. Patients in the daratumumab arm may continue on daratumumab if they are intolerant of dexamethasone 4mg weekly only if they have not previously had a grade $\geq$2 infusion reaction.

9.4. Duration of Therapy

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

- Unacceptable toxicity/adverse event that may cause severe or permanent harm which rule out continuation of any of the study drugs
- Failure to achieve a minimal (=minor) response after 4 cycles of VCD(D) induction (as defined by IMWG – see Appendix 2)
- Relapse/progressive disease (as defined by IMWG – see Appendix 2)
- Consent withdrawal
- Major violation of the study protocol
- Suspected pregnancy
- Death

The trial may also be terminated early if safety concerns emerge with this treatment.

9.5. Treatment progression

For patients on the VCDD arm who progress on therapy, the choice of salvage regimen will be at the discretion of the treating physician.

9.6. Duration of Follow Up

Following documentation of progression or the initiation of a new anticancer therapy, patients should be followed for survival information every 3 months until all patients remaining on study have been followed for at least 24 months or when all patients have either withdrawn, died or been deemed lost to follow up. Patients in the follow up phase will have date of initiation of next therapy and regimen recorded. One or two subsequent time points may be chosen to collect long-term survival, progression and treatment data.

9.7. General Concomitant Medication and Supportive Care Guidelines

9.7.1. Permitted concomitant therapy:

- Therapies considered necessary for subject's wellbeing may be administered at the discretion of the investigator
    - Including: 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 myeloma or its therapy
- Use of bisphosphonates is permitted
- Use of haematopoietic growth factors is permitted throughout the study
    - treatment with myeloid growth factors is recommended when the ANC is less than 1.0×10^9/L
        - Subjects who fail screening due to neutropenia or anaemia will not be permitted to use growth factors to become eligible.

9.7.2. Prohibited Concomitant Therapy:

- Concomitant use of other anti-myeloma therapy while the subject is taking study drug is prohibited. Subsequent treatment for myeloma should not be initiated until progressive disease has been documented.
- Concomitant corticosteroids, other than the weekly dexamethasone as per protocol, are prohibited with the following exceptions:
    - Prednisone ≤ 10mg/day or equivalent as chronic therapy for concomitant stable medical condition
    - Initial short course corticosteroids (total 160mg dexamethasone or equivalent) to provide initial myeloma disease control prior to commencing trial therapy
    - Corticosteroids used to treat an adverse event.
- The need for radiation therapy is considered to be a treatment failure. However an exception (ie: subjects are allowed to remain on the treatment phase of the study) is made for radiation therapy to pathologic fracture site to enhance bone healing or to treat post-fracture pain that is refractory to narcotic analgesics because pathologic bone fractures do not, by themselves, fulfill a criterion for disease progression.

10. PHARMACEUTICAL INFORMATION

10.1. Investigational Agent (Daratumumab)

Janssen-Cilag will provide the Investigational product to the Sponsor for distribution until such time that the product is approved and reimbursed in Australia such that ongoing study patients can access such reimbursed product.

10.1.1 Physical Description of Study Drug

The daratumumab supplied for this study is a colorless to yellow liquid and sterile concentrate of 20 mg/mL in a vial in a 6R vial with a nominal fill volume of 5 mL (i.e. 100mg per vial).

10.1.2 Labeling

Study drug labels will contain information to meet the applicable regulatory requirements.

10.1.3 Preparation, Handling, and Storage

All study drug vials must be stored in the original carton at controlled temperatures in a refrigerator ranging from 2°C to 8°C and must not be utilized after the expiry date printed on the label. The product must be protected from light and must not be frozen. Daratumumab does not contain preservatives; therefore any unused portion remaining in the vial must be discarded.
Daratumumab will be diluted in a sterile, pyrogen-free physiological saline solution (0.9% NaCl) prior to IV administration.

For more complete information, please refer to section 9.3.1.2 and the latest version of the Investigator's Brochure.

The Alfred TCC will coordinate drug distribution for the current study.

10.1.4. Drug accountability

The investigator, or a responsible party designated by the investigator such as the Pharmacy Department at participating institutions, must maintain a careful record of the inventory and disposition of the investigative agent. A pharmacy file will be provided for the purpose and will collect information such as drug name, batch number, expiry date, amount dispensed and disposal of supplies via approved procedures at the end of the study. 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.

10.2. Registered Agents

Supplies of bortezomib, cyclophosphamide, dexamethasone and any supportive care or concomitant medications other than the investigational agent should be obtained from hospital supplies. Refer to Prescribing Information or Package Insert for more information.

11. SCHEDULE OF EVALUATIONS

Please also refer to Section 5.

11.1. Screening/Baseline:

- Informed consent
- Demographics
- Medical History
- All concomitant medications (prescription and non-prescription), treatments and therapies taken from 28 days prior to initiation of the study drug
- Adverse events
- Physical examination including neurological assessment and vitals
- ECOG (Appendix 3)
- QOL
- IMWG Frailty score
- Full blood evaluation and differential (FBE)
- Electrolytes including serum calcium (corrected) and liver function tests
- LDH, B2M, albumin
- Blood group and screen and red cell phenotyping. This is required as daratumumab binds to red blood cells and can cause a positive indirect Coombs test.
- ECG
- Pregnancy test if woman of child bearing potential
- Staging:
    - Bone marrow aspirate and trephine (BMAT)
        - IHC;
        - FISH or cytogenetics
        - Correlative study samples- purification and storage of CD138 positive MM cells for exploratory biomarker studies (see section 7.2.3)
    - SPEP +/- IF (immunofixation)
    - UPEP +/- IF
    - SFLC
    - Skeletal survey
    - Assessment of EMD
    - International Staging System (ISS) disease stage (Appendix 5)
- Peripheral blood for correlative studies

11.2. During Therapy: Day 1 of Each Cycle

- Documentation of bortezomib, cyclophosphamide, dexamethasone +/- daratumumab administration, dose adjustments, dose interruptions, AEs
- Concomitant medications
- Physical examination including neurological assessment and vitals. Vital signs (blood pressure, heart rate, temperature) measured in sitting position. On Cycle 1 Day 1: immediately before the start of dara infusion; at 0.5, 1, 1.5, 2, 3.5 hr after start of infusion; at end of infusion; 0.5,1 hr after end of infusion. For all other infusions, vital signs measured immediately before start and at end of dara infusion.
- Assessment of EMD
- Documentation of disease response (IMWG criteria- Appendix 2)
- Where applicable, dates of disease progression, study cessation and death
- ECOG (Appendix 3)
- QOL (Cycle 5, Day 1 only)
- FBE
- Electrolytes including serum calcium (corrected) and LFTs, LDH, albumin
- SPEP +/- IF
- UPEP +/-IF (only to be repeated if disease not measureable by SPEP or FLC or to confirm CR)
- SFLC
- Peripheral blood for correlative study samples (Cycle 5, Day 1 only): Immune flow cytometry- to correlate quantitative and qualitative immunological changes with disease response (see section 7.2.3)

Note: Peripheral blood for correlative studies to be collected at the end of cycle 4 (= Day 1 of cycle 5).
Note: Cycle 1, days 8,15 & 22 require FBE, biochemical profile and vitals to be performed

11.3 End of VCD(D) Induction

- Documentation of bortezomib, cyclophosphamide, dexamethasone +/- daratumumab administration, dose adjustments, dose interruptions, AEs
- Concomitant medications
- Physical examination including neurological assessment and vitals
- Assessment of EMD
- Documentation of disease response (IMWG criteria- Appendix 2)
- Where applicable, dates of disease progression, study cessation and death
- ECOG (Appendix 3)
- QOL
- FBE

- Electrolytes including serum calcium (corrected) and LFTs, LDH, B2M, albumin
- SPEP +/- IF
- UPEP +/-IF (only to be repeated if disease not measureable by SPEP or FLC or to confirm CR)
- SFLC
- BMAT for MRD studies for patients achieving ≥ VGPR

11.4 At Disease Progression:

- Concomitant medications
- Documentation of date of disease progression
- ECOG (Appendix 3)
- FBE
- Electrolytes including serum calcium (corrected) and LFTs, LDH, B2M, albumin
- SPEP +/- IF
- UPEP +/-IF
- Serum for SFLC
- Physical examination, including vital signs
- Bone marrow aspirate and trephine (BMAT)
    - Trial samples- purification and storage of CD138 positive MM cells for potential exploratory biomarker studies

11.3. Follow-Up

- Data to be collected every 3 months for:
    - Overall survival
    - Date of progression
    - Date of initiation of next therapy and regimen used
    - Response to next therapy
    - Adverse events for patients on VCDD arm

12. REGISTRATION

Before all new patients can be registered on-study, check inclusion/exclusion criteria to confirm patient eligibility, then telephone the Trial Coordinating Centre (TCC) in the Haematology Clinical Research Unit (HCRU) at the **Alfred Hospital** on (03) 9076 2217 for assignment of registration number and fax a copy of the completed registration form to the Trial Co-ordinator, Alfred Hospital on (03) 9076 5531. The Trial Co-ordinator will advise verbally of registration and then fax the allocated trial number to the study centre.

Bortezomib, cyclophosphamide, dexamethasone +/- daratumumab therapy should commence within 7 days of randomisation**.**

13. DOCUMENTATION

13.1. Informed Consent

The nature of the study and the potential risks will be explained to all candidates. Written informed consent for the clinical trial is to be obtained from each participant prior to performing screening procedures to the study. This will also include consent for additional correlative laboratory studies. Refer to section 16.1 and section 17.3 for further guidelines regarding informed consent.

13.2. Case Report Forms

Case Report Forms (CRFs) will be produced by the TCC at the Alfred Hospital and sent to participating institutions as required. All 'paper' 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 initialed and dated by an adequately qualified and authorised member of the research support team at the Trial Site. 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 sent to the TCC at the Alfred Hospital and a copy kept by the institution. All questions on the CRFs should be answered before they are sent to the TCC.

The CRFs are confidential and remain the property of AMARC.

13.3. 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 PICF and amended versions
- HREC membership list
- Any communication with the HREC
- Current version of the IB for the study drug and current PI for drugs that are already approved
- Laboratory reference ranges and accreditation
- Drug accountability logs
- 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.

13.4. 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. The master list linking identifying participant information and ID number will be maintained in a secure location separate from the participant database. Analysis of trial-related data and all ongoing queries will be via trial participant ID number only. Each institution will maintain a list of its own trial participants. Data will be analysed by ID number and initials. Samples for laboratory scientific studies will also only be analysed by ID number.

Copies of any patient reports that are to be provided with CRFs MUST be de-identified and then clearly labeled with the trial identifier, patient registration number and patient initials.

13.5. Database Management and Quality Control

Clinical trial databases will be maintained by the TCC and will not record any information that may enable the subject to be identified. The TCC will conduct all data queries with individual trial sites. Once all data has been entered and verified, the database will be locked and the final analysis performed.

13.6. Document Retention

Records from the study (both hard copy and electronic) will be retained for a minimum of 15 years after study completion in secure archiving facilities both at the trial site and at the Trial Centre. The Investigator or Trial Centre must notify AMARC prior to destroying any clinical study records. Should either the Investigator or Trial Centre wish to assign the study records to another party or move them to another location, AMARC must be notified in advance.

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and AMARC to store these in sealed containers off site so that they can be returned sealed to the investigator in case of a regulatory audit.

14. STATISTICAL CONSIDERATIONS

This is a prospective, multi-centre, open-label, response adapted randomized phase 2 trial of VCD induction compared to VCD and daratumumab induction followed by daratumumab maintenance in patients with newly diagnosed multiple myeloma.

All efficacy analyses will be intention-to-treat and based on the full analysis set (FAS), namely all randomized patients analysed "as randomized". A supportive analysis of the primary efficacy endpoint (PFS) will be conducted on the subset of patients in the FAS without major protocol deviations (the per-protocol set or PPS). Major protocol deviations will be identified and documented prior to database lock for the main analysis of PFS.

14.1. Definition of Study Endpoints

14.1.1. Primary

Progression-free survival (PFS) measured from the date of randomization to the date of the first documented progression, according to IMWG criteria, or the date of death. At the time of the final analysis, patients not deemed lost-to-follow-up, will have their PFS censored at the study censor date for PFS (the earliest of the last dates of assessment of patients not known to have progressed or died and not deemed lost to follow-up). Patients deemed lost-to-follow-up will have their PFS censored at the earlier of their last date of assessment or the study censor date for PFS.

14.1.2. Secondary

The secondary endpoint of objective response will be defined according to IMWG criteria (Appendix 2). Patients who drop out for any reason before achieving a documented objective response will be deemed to be non-responders.

Minimal residual disease (MRD) assessment by 8 colour (Euroflow) flow cytometry is a validated tool for the assessment of disease response in patients with myeloma. MRD will be assessed in the bone marrow at the completion of 9 cycles of induction therapy in patients who have achieved ≥ VGPR by IMWG criteria (or sooner if therapy ceased due to toxicity).

Overall survival (OS) will be measured from the date of randomization to the date of death. Patients not deemed lost-to-follow-up will have their OS censored at the study censor date for OS (the earliest of the last dates of contact of patients not known to have died and not deemed lost to follow-up). Patients deemed lost-to-follow-up will have their OS censored at the earlier of their date of last contact or the study censor date for OS.

To investigate the safety of therapy with VCDD and VCD for the treatment of newly diagnosed myeloma, the incidence and severity of adverse events (CTCAE Version 4) will be recorded for each patient.

To investigate the tolerability of therapy with VCDD and VCD for the treatment of newly diagnosed myeloma, the percentage of dose delivered will be calculated, based on duration of exposure and dose intensity. Duration of exposure = date of last administration of the study drug – date of first administration of the study drug + 1 day. The duration of exposure includes periods of temporary interruption. Dose intensity for patients with non-zero duration of exposure is defined as the total dose taken during the exposure period divided by the duration of exposure. The percentage of dose delivered is the actual dose intensity divided by the planned dose intensity

Quality of life during induction will be assessed using the EORTC QLQ-C30.

14.2. Sample Size and Power Calculations

Background.

PFS:

There is limited literature of PFS after VCD in non-transplant eligible patients. In a study of elderly frail patients treated with dose reduced VCP median PFS was 15.2 months (11). In the VISTA trial (12) of VMP median PFS was 24 months. In unpublished data from the Australian Myeloma and Related Disease's Registry median PFS in non-transplant eligible patients treated with VCD was 23.5 months. For this analysis we will assume a median PFS following VCD of 24 months.

In the upfront daratumumab randomized trials (MAIA and ALCYONE) it was assumed that daratumumab could reduce the risk of progression or death by 25%. In the analysed relapsed daratumumab randomized trials (POLLUX and CASTOR) the actual hazard ratio (HR) was 0.37 and 0.39 for PFS (6, 7). In this study we will conservatively assume that the addition of daratumumab to VCD will reduced the risk of progression or death by 50% (i.e. HR=0.5).

Response rates:

Assessment of response to therapy will follow the International Myeloma Working Group (IMWG) uniform response criteria. Response rates after 4 cycles of chemotherapy according to these criteria are available for patients undergoing initial bortezomib-based chemotherapy. As above (PFS section) there are limited data for response rates after VCD in non-transplant eligible patients so response rates must be inferred from transplant eligible patients treated with VCD. In transplant eligible patients the CR rate after 4 cycles ranged from 3-43% (mean 17%) and the ≥ VGPR rate ranges from 13-61% (mean 40%)(13-16). For this analysis we will assume ≥VGPR of 40% after 4 cycles of VCD.

In the relapsed daratumumab randomized trials, daratumumab increased the overall ≥VGPR rate by 30% and 32% (6, 7). Improvement in response rate after 4 cycles of chemotherapy is not available so for this study we will conservatively estimate an improvement in the ≥VGPR rate of 20%.

Impact of response on progression-free survival:

In myeloma there is a well demonstrated relationship between response and PFS, particularly in studies with novel agents (as opposed to less effective chemotherapy based

therapies). For example, in transplant eligible patients, failure to achieve ≥VGPR after 4 cycles of bortezomib-based chemo is associated with worse PFS - RR2.3 (95%CI, 1.6-3.2), p<0.0001 (17).

The design.

After a "burn-in" period of 1:1 randomized allocation of the first 30 patients to the two study arms, we propose to use response adaptive randomization (RAR) to preferentially assign patients to the study arm that appears to be superior. Even though PFS is the primary efficacy endpoint, we will also incorporate information about "short-term" patient response, as well as progression-free status, into the RAR procedure. We will use a Bayesian mixture distribution to model the relationship between the short-term response status (after 4 cycles) and PFS. Posterior probability distributions will be used to implement both early stopping criteria and the RAR procedure. The model will be updated at frequent intervals after the burn-in period has been completed and also whenever the co-ordinating trial centre has been notified of a progression or death of a patient. General properties of the design are detailed in Huang X, Ning J, Li Y, Estey E, Issa J-P and Berry DA, "Using short-term response information to facilitate adaptive randomization for survival clinical trials" (18). We are planning to randomize up to 120 patients and anticipate an accrual rate of 4 to 5 patients per month over a period of 24 to 28 months. Follow-up will be for a period of up to 24 months after the randomization of the last patient recruited to the study.

The model

Two response categories (assessed after the first 4 cycles) will be utilized in the model and the RAR process, namely <VGPR and ≥VGPR. We assume that the numbers of patients in a study arm that fall into the two response categories follow a binomial distribution and we further assume a beta (Dirichelet with k=2 categories) distribution for the prior probability distribution for the binomial response rates. Conditional on the response being in a particular category, we assume that PFS follows an exponential distribution with a hazard rate that depends not only on the response category but also on the study arm to which the patient was randomized. An inverse gamma distribution will be assumed for the prior probability distribution of the mean survival times in the response categories within a study arm.

RAR and early stopping

Whenever the posterior probability distributions for the response rates and hazard rates are updated, the posterior probability (P) that the mean PFS time in the VCD arm exceeds that in the VCDD arm will be calculated. Subsequent patients will be randomized to the VCD arm with probability P and to the VCDD arm with probability 1 – P. If at any time during the trial, including at the end of the trial, $P > 0.975$, the VCDD arm will be deemed to be inferior to the VCD arm. Similarly, if at any time during the trial, including at the end of the trial, $P < 0.025$, the VCDD arm will be deemed to be superior to the VCD arm. Accrual may be closed early if either superiority or inferiority is established before 120 patients have been randomized. Curtailment of follow-up (and early publication) is also a possibility if either superiority or inferiority is established after accrual has closed but before all randomized patients have been followed for 24 months. If the maximum number of patients has been randomized

and, at the end of follow-up, neither study arm has been identified as superior, the trial could be regarded as inconclusive; nevertheless the posterior probability distribution for the PFS hazard ratio will be published.

Sample size justification.

We present simulation results for the proposed design of the clinical trial with n=120 randomized patients (Table 5). For each scenario an accrual rate of 1 patient per week (i.e. 4 to 5 patients per month for 24 to 28 months) was assumed and 5000 trials were simulated. Scenario 1 could be described as the "null hypothesis" scenario as there is no difference between the arms in their conjectured response rates and mean PFS times. The chance that either arm is identified as superior is the "Type I error" rate and it appears to be tightly controlled at less than 5%. The mean (over the 5000 simulations) of the total number of patients randomized in each trial is close to the cap of 120. Scenario 2 represents a modest improvement in the ≥VGPR response rate in the VCDD arm (from 40% to 60%) but no improvements in the mean PFS times in each response group – accordingly it could be described as pessimistic. The corresponding conjectured increase (compared to Scenario 1) in the median PFS is slight (24.6 – 23.9 = 0.7 months) and, naturally, the trial has a low chance (estimated to be 2%) of detecting this small improvement in PFS. Scenario 3 is our conjectured scenario (median PFS = 24 and 48 months respectively in the VCD and VCDD arms; HR = 0.5) and the chance that the VCDD arm is declared superior to the VCD arm is estimated to be close to 82% (this could be described as the "Bayesian power" of the proposed design). Moreover the chance that the VCDD arm is declared inferior to the VCD arm is estimated to be less than 0.1% and the chance of an inconclusive result is estimated to be 18%. The expected sample size is 113 and the expected duration of the trial is 145 weeks (33.5 months) rather than 208 weeks (48 months).

Table 5. Operating characteristics of the design for three scenarios.

Scenario	Arm A (VCD)					Arm B (VCDD)					Mean duration (weeks)	Mean number of patients randomized to each arm			Decision (Arm B relative to Arm A)		
	Response rates		Mean PFS (months) in each response group		Median PFS (months)	Response rates		Mean PFS (months) in each response group		Median PFS (months)							
	p_1(<VGPR)	p_2 (≥VGPR)	μ_1 (<VGPR)	μ_2 (≥VGPR)	Both groups	p_1 (<VGPR)	p_2 (≥VGPR)	μ_1 (<VGPR)	μ_2 (≥VGPR)	Both groups		A	B	Total	B inferior	In-conclusive	B superior
1	0.6	0.4	32.6	37.6	23.9	0.6	0.4	32.6	37.6	23.9	207.4	59.5	60.4	119.9	0.011	0.976	0.014
2	0.6	0.4	32.6	37.6	23.9	0.4	0.6	32.6	37.6	24.6	206.9	57.6	62.2	119.8	0.010	0.968	0.022
3	0.6	0.4	32.6	37.6	23.9	0.4	0.6	58.3	77.9	47.9	144.7	37.6	75.3	112.8	0.000	0.183	0.817

Notes:

(1) The "443.R" suite of R functions developed by Professor Brad Carlin (University of Minnesota) was used to simulate a single trial. A description of the algorithm can be found in Berry SM, Carlin BP, Lee JJ and Mueller P (2011) *Bayesian adaptive methods for clinical trials*. Chapman & Hall/CRC Biostatistics Series; 38. Boca Raton, FL.

(2) All simulations used a minimally informative prior for the proportion of patients in the two response categories or groups, namely Dirichlet(γ_1=0.5, γ_2=0.5) and a minimally informative prior for the mean survival in the two response groups namely Inverse Gamma(α_1=10, α_2=10; β_1=1259, β_2=1350) which corresponds to prior means of 139.9 weeks (32.3 months) and 150.0 weeks (34.6 months) respectively for the two response groups. The same priors were used for each arm, so *a priori*, neither arm was favoured over the other.

(3) Results for each scenario are based on 5000 simulated trials.

(4) Accrual was assumed to be at the rate of approximately one patient per week (i.e. up to 120 patients accrued over a period of approximately 28 months) with total duration of the trial limited to 208 weeks (48 months).

(5) The first 30 patients were randomized 1:1 to the treatment arms. Thereafter, the allocation probability to Arm A was adapted after each new patient and based on the posterior probability (P) that the mean PFS time in the VCD arm (Arm A) exceeded that in the VCDD arm (Arm B). Subsequent patients were randomized to the VCD arm with probability P and to the VCDD arm with probability 1 – P.If at any time during the trial, including at the end of the trial, P < 0.025 the VCDD arm (Arm B) was deemed to be superior to the VCD arm (Arm A) and accrual, and/or follow-up was stopped. Similarly, if at any time during the trial, including at the end of the trial, P > 0.975, the VCDD arm was deemed to be inferior to the VCD arm and accrual, and/or follow-up was stopped.

14.3. Statistical Methods

The posterior probability distributions of the response rates and the PFS hazard rates in each response category will be reported for each study arm in the form of graphs and also summarized by their 2.5, 50.0 and 97.5 percentiles (i.e. medians and 95% credible intervals).
Computation of the posterior probability distributions will use a minimally informative prior for the proportion of patients in the two response categories or groups, namely Dirichlet (γ_1=0.5, γ_2=0.5) and a minimally informative prior for the mean survival in the two response groups namely Inverse Gamma (α_1=10, α_2=10; β_1=1259, β_2=1350) which corresponds to prior means of 139.9 weeks (32.3 months) and 150.0 weeks (34.6 months) respectively for the two response groups. The same priors will be used for each arm, so *a priori*, neither arm will be favoured over the other.
The posterior probability (P) that the mean PFS time in the VCD arm exceeds that in the VCDD arm will be calculated by sampling from the posterior (Inverse Gamma) distributions for the mean survival in each treatment arm. If at any time after the first 30 patients have been randomized, P > 0.975, the VCDD arm will be deemed to be inferior to the VCD arm. Similarly, if P < 0.025, the VCDD arm will be deemed to be superior to the VCD arm.
The posterior probability distributions for the hazard ratio for PFS and the odds ratio for objective response will also be reported in the form of graphs together with medians and 95% credible intervals regardless of the outcome of the trial (superiority, inferiority or inconclusive).

The Kaplan-Meier method will also be used to summarize time-to-event outcomes (PFS and OS) by study arm.

MRD negativity in patients achieving VGPR or better after 9 induction cycles will be summarized, by treatment arm, as proportions together with their standard errors. In an exploratory Bayesian analysis limited to this subset of the FAS, the impact of MRD negativity and treatment arm on PFS will be investigated in a Cox Proportional Hazards regression model (with minimally informative prior probability distributions for the regression parameters).

Summary tables (frequencies and percentages) of adverse events and laboratory tests (based on the worst CTCAE grade per patient), both severe (Grade ≥ 3) and of any grade, will be reported by type, treatment arm and for the following periods: by cycle for each of the first 4 cycles, for cycles 5 to 9 combined, and post-induction.

Summary tables of percentage of dose delivered by study drug and treatment arm will be reported for each of the first 4 cycles and for cycles 5 to 9 combined. Durations of exposure and reasons for discontinuation will also be summarized by study drug and by treatment arm.

Statistical analyses of the repeated assessments of each of the EORTC QLQ-C30 scales (five functional scales, one global health scale and three symptom scales) will be confined to

assessments up to the end of cycle 9. For each QLQ-C30 scale, the endpoint for statistical analyses will be the patient's profile over the first 12 cycles. In the event that a patient dies, the patient will be deemed to have "zero" global quality of life from the date of death and scales will be imputed with the appropriate lower or upper bound.

In order to deal with both drop-out, for reasons other than death, and intermittent missing data, analyses will be based on contrasts of predicted means that estimate the mean area under the time curve (AUC) for each treatment arm rather than analyses of the AUCs constructed for each individual patient. This approach avoids the biases that can occur when imputation methods are used to create individual profiles and their corresponding AUCs (Bell et al, *SAGE Open*, April-June 2014: 1-12). The repeated measurements of a scale over the first 9 cycles will be analysed by fitting linear mixed models using restricted maximum likelihood (REML) – this will allow all available data to be used without the need for imputation of missing values, the selection of the most suitable variance-covariance model for the repeated measures, using Akaike's Information Criterion, and the investigation of commonality of any nonlinear trends over time via smoothing splines. The F-test will be used to investigate a possible treatment by time interaction and any comparisons between treatment groups at each time point will be based on t-tests that utilize the predicted means and standard errors of difference that are recovered from the fitted mixed model. Of particular interest will be the two-sample, two-sided, t-test (α=0.05) that compares the contrasts of the predicted means that correspond to the trapezoidal rule for calculation of the mean AUC in a treatment arm.

Details of all analyses, including the summaries of demographics, baseline characteristics and patient disposition at the time of the analyses, and specifications of all prior distributions to be used in the Bayesian analyses, will be documented in a Statistical Analysis Plan (SAP) prior to database lock for the final analysis of the primary efficacy endpoint.

14.4. Trial Duration

Patient entry in the trial will continue until 120 patients have been randomised. The expected accrual time is 24 to 28 months. However, the Trial Management Committee (TMC) in conjunction with the AMaRC Safety and Data Monitoring Committee (SDMC) may decide to close accrual earlier if either superiority or inferiority is established before 120 patients have been randomized (providing at least 30 patients have been randomized). Patients remaining on study will be followed up for at least 24 months from the date of randomization. However, curtailment of follow-up (and early publication) is also a possibility if either superiority or inferiority is established after accrual has closed but before all randomized patients have been followed for 24 months. Unless accrual or follow-up is curtailed, the expected duration of the trial is 48 to 52 months and the main analysis of the primary efficacy endpoint (PFS) and all other endpoints will take place at this time. If the main analysis occurs earlier, due to a decision to curtail the trial, a second "update" analysis of all efficacy, safety and tolerability endpoints will occur when all randomized patients remaining on study have been followed for at least 24 months.

The trial may also be terminated early if safety concerns emerge with these treatments.

14.5. End Of Treatment

Patients should continue taking drug for the prescribed treatment period until intolerance, failure to achieve a minimal (=minor) response after 4 cycles of VCD(D) 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
- Death
- Disease progression
- Initiation of new cancer therapy
- Protocol deviation

Patients may voluntarily withdraw from the study (i.e. per-protocol) treatment at any time. Those patients who end study treatment will continue to be followed for progression and OS unless they withdraw completely from the trial. Following documentation of progression or the initiation of a new anticancer therapy, patients will be followed for survival information every 3 months until the time of the final update analysis.

14.6. Trial Modification and Safety and Data Monitoring Committee

TheAMaRC Safety and Data Monitoring Committee (SDMC) will monitor this study. The AMaRC SDMC is responsible for:

1. Conducting a clinical review of all SAEs
2. In the event of a significant incidence of SAEs, giving consideration to amending the trial
3. Reviewing summary reports, providing SDMC comments and recommendations
4. Annual review of all on-going trials, with particular reference to guidelines for early stopping
5. Review of all protocol amendments.

The SDMC will review the accumulating data approximately 6 monthly while the trial remains active. The SDMC will be responsible for ensuring that the trial is continued only if it appears ethical to do so. Consideration for earlier stopping or modification will be made if there is:

1. Unacceptable non-haematological toxicity associated with daratumumab or VCD therapy, or

2. Poor patient accrual, or
3. Serious doubt that the trial will meet its primary objective.

14.7. Ongoing Safety Monitoring

In addition to the role of the SDMC, the Trial Management Committee (TMC) will:

- Provide objective medical oversight of the clinical trial including responses to queries raised by the CI's, site PI's, SDMC, Program Manager or CRA (or Trial Centre delegate),
- Oversee safety in real time as the meetings of the SDMC are too infrequent to guarantee timely oversight,

Appraise updates, provided by the Trial Statistician, of the posterior probability distributions for the response rates and hazard rates as well as the posterior probability (P) that the mean PFS time in the VCD arm exceeds that in the VCDD arm, and, consequently give consideration to early closure of accrual, or early publication of efficacy analyses, if there is strong evidence of superiority or inferiority. The TMC may undertake additional responsibilities as determined by appropriate bodies including the SDMC, AMaRC and the Alfred TCC. A Terms of Reference (TOR) document or charter for the TMC that includes, but is not limited to, details on how blinding will be managed, will be prepared by the CI's and the Trial Statistician prior to trial activation. Recommendations of the TMC will be reviewed by the SDMC and the AMaRC Management Committee before implementation.

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 time of informed consent until 28 days following the last dose of study drugs and followed as appropriate.

15.1. Definitions

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AEs). The causal relationship can be one of the following:

- Related: There is a reasonable causal relationship between study drug administration and the AE.
- Not Related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more adverse events).

15.1.1. Serious Adverse Events

A **Serious Adverse Event (SAE)** is any untoward medical occurrence at any dose that:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see below for exceptions)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event, defined as a medical event that may not be immediately life-threatening or result in death or hospitalization but, based on appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g. medical, surgical) to prevent one of the other serious outcomes listed above. Examples of such events include but are not limited to intensive treatment in an emergency department or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.
- Potential drug-induced liver injury (DILI) is also considered an important medical event--see the DILI section below for a definition of a potential DILI event.
- Suspected transmission of an infectious agent (e.g. pathogenic or non-pathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs.

The following hospitalizations are not considered SAEs

- A visit to the emergency room or other hospital department lasting less than 24 hours that does not result in admission (unless considered an “important medical event” or a life-threatening event)
- Elective surgery planned before signing consent
- Admissions as per protocol for a planned medical/surgical procedure
- Routine health assessment requiring admission for baseline/trending of health status (e.g. routine colonoscopy)
- Medical/surgical admission other than remedying ill health state that was planned before study entry. Appropriate documentation is required in these cases
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g. lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)

15.1.2. Serious Adverse Event Collecting and Reporting

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur from consent to 60 days of discontinuing dosing. If applicable, SAEs must be collected that relate to any later protocol-specific procedure (such as follow-up skin biopsy).

The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

SAEs, whether related or unrelated to the study drug, and pregnancies must be reported to Janssen and the Alfred TCC within 24 hours.

SAEs must be recorded on the SAE Report Form; Pregnancies on a Pregnancy Surveillance Form, **and must be faxed to the Trial Centre on 03 9076 5531 and to Janssen on 02 9888 9817**

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)
If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the the Alfred TCC and Janssen (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

15.1.3. Health Authority Reporting

Investigators must adhere to local Health Authority Reporting Requirements.

Adverse drug reactions that are Serious, Unexpected, and at least Possibly Related to the drug (Suspected Unexpected Serious Adverse Reaction, SUSAR) and that have not previously been reported in the Investigators' Brochure, or reference safety information document will be reported promptly to the health authority in writing by the Principal Investigator.

A clear description of the suspected reaction should be provided along with an assessment as to whether the event is drug or disease related. The Principal Investigator shall notify the

health authority by telephone or by fax of any unexpected fatal or life threatening experience associated with the use of the drugs as soon as possible but no later than 7 calendar days after initial receipt of the information.

15.1.4. Non-Serious Adverse Events

A non-serious adverse event is an AE not classified as serious.

15.1.5. Non-Serious Event Collecting and Reporting

The collection period and the data to be collected must be specified in the clinical protocol. For study drugs with potential for delayed NSAEs (e.g. delayed excretion of the parent or active metabolites), a longer follow-up period may be warranted to allow collection of SAEs, laboratory tests and other assessments.

The collection of non-serious adverse event (NSAE) information should begin at trial registration. Non-serious adverse event information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug, or those that are present at the end of study treatment as appropriate. Non-serious Adverse Events are provided to Janssen via interim and final study reports.

15.1.6. Laboratory Test Abnormalities

The following laboratory abnormalities should be captured and reported as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than the laboratory term will be used by the reporting investigator (e.g. use the term anemia rather than low hemoglobin value).

15.1.7. Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (e.g. dose tapering if necessary for subject safety).

The investigator must immediately notify Janssen of this event via the Pregnancy Surveillance Form within 24 hours and in accordance with SAE reporting procedures as well as the Alfred Hospital TCC.

Alfred Contact Details:

Nola Kennedy
Haematology Clinical Research Unit
Alfred Hospital, Commercial Road
Melbourne, Vic 3004
Tel: +61 3 9076 2217
Fax: +61 3 9076 5531
Email: N.Kennedy@alfred.org.au

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on a Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to the Trial Centre and to Janssen. Information on this pregnancy may also be collected on the Pregnancy Surveillance Form.

15.1.8. Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as SAEs.

15.1.9. Potential Drug-Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs meeting the defined criteria must be reported as SAEs.

Potential drug induced liver injury is defined as:

1. AT (ALT or AST) elevation > 3 times upper limit of normal (ULN),

AND

2. Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),

AND

3. No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to; viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

15.1.10. Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a nonserious or serious adverse event, as appropriate, and reported accordingly.

There are some AEs that may necessitate rapid communication to regulatory authorities, such as information that may influence the benefit-risk assessment of a medicinal product, or information that would be sufficient to consider changes in medicinal product administration or in the overall conduct of a clinical investigation. Examples include an increased rate of occurrence of an expected serious ADR, or a major safety finding from a recently completed safety study. Investigators should apply appropriate medical and scientific judgement in these circumstances, and notify AMARC or designee, if they believe the event requires expedited reporting.

15.2. 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.

Grading of Adverse Reactions

- The NCI CTCAE v4.0 grading system of toxicity should be used for recording and grading of adverse events (Appendix 6).
- 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 above in section 15.1.

15.3. 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.

15.4. Adverse Event Updates

Janssen shall notify the PI and TCC via SUSAR line listings of the following information

- Any AE associated with the use of study drug in other studies that is both serious and unexpected.
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

If necessary, the PI will notify the TCC to disseminate information to the sites regarding these new serious and unexpected AE(s) or significant risks to subjects. Each individual site investigator will be responsible for notifying his/her HREC of these events. The TCC must keep copies of all AE information, including correspondence with Janssen and the sites, on file. Sites should keep record of all communications with their HREC on file.

16. CORRELATIVE STUDIES

16.1. Informed Consent

It should be noted that the correlative studies form an integral part of this protocol and informed consent for collection of these samples is implicit in informed consent for trial participation. No separate consent is necessary and collection of these samples is not optional.

16.2. Procedures for Sample Collection

For detailed procedures for collection, processing, storage and transport of samples see additional documents distributed by the TCC.

16.3. Samples Required

In addition to the routine investigations required for clinical care, correlative studies will be undertaken throughout the duration of the trial as listed below.

1. Next Generation 8-colour flow (Euroflow) bone marrow analyses at end of VCD(D) induction in patients who have achieved ≥ VGPR. Determine rates of MRD negativity in each arm and impact on disease related outcomes.
2. Sequential flow cytometric peripheral blood immune panel (NK/T-cell activation) as baseline and at the end of 4 cycles of induction. Correlate quantitative and qualitative immunological changes with disease response.
3. The effect of therapy on NK-cell mediated antibody dependent cellular cytotoxicity and direct cytotoxicity (using functional and imaging assays) as well as alterations in novel pathway signaling will be compared between paired pre and post therapy patient peripheral blood samples
4. Isolation of CD138 selected bone marrow plasma cell DNA at baseline and plasma cell free DNA at baseline and end of cycle 4 for exploratory biomarker analyses utilizing amplicon sequencing against a panel of pan-cancer and myeloma-specific target regions
5. Baseline NGS characterization (RNA from CD138 purified MM cells) for comparative analyses:
    a. Disease outcome: VCD vs VCDD for high-risk only
    b. Disease outcome: high risk vs non-high-risk for VCDD cohort
    c. Disease outcome: renal failure vs normal renal function for VCDD cohort

17. ETHICAL CONSIDERATIONS

17.1. 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 the TCC and any applicable local guidelines.

At each trial site the trial will be conducted in compliance with the Protocol, ICH GCP Guidelines in Australia, and applicable regulatory requirements.

17.2. Regulatory Requirements

If applicable, a Clinical Trial Notification (CTN) form must be submitted to the responsible HREC and returned to the TCC. 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 as instructed by the TCC.

17.3. Informed Consent

A generic PICF, written in non-technical language, will be provided by the TCC to all sites, and will contain all the information that AMARC is legally obliged to supply to all patients interested in participating in the trial. This PICF can be modified to suit individual sites but any changes must be approved by the TCC prior to submission to the responsible HREC for approval. It is the responsibility of the site investigator to obtain approval of the PICF by the responsible HREC before Trial Participants can be recruited and enrolled onto the trial.

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 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 of the Sponsor 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.

17.4. Human Research Ethics Committee (HREC)

The PI at the Trial Site must submit this protocol, and other appropriate documentation to the responsible HREC. A copy of the letter detailing HREC approval of, or advice regarding, the protocol, must be forwarded to the TCC as soon as possible after it has been received by the Trial Site. The HREC approval/advice letter must include:

- A signature from the Chairperson of the HREC
- The date of HREC review
- The trial title
- The protocol number, date and version
- The name, date and version of all other trial related documents such as the PICF
- The length of Protocol approval, if applicable
- The requirements for trial progress report submissions (eg. annual).

17.5. 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 their local HREC.

17.5.1. Protocol amendments

Any change or addition to this protocol requires a written protocol amendment that must be prepared by the PI(s) in consultation with the Study Committee, or designee. All protocol amendments will be reviewed by the SDMC prior to submission to HREC.

All protocol amendments must be submitted to the HREC of all trial sites in accordance with local requirements. Significant changes affecting the safety of subjects, the scope of the investigation or the scientific quality of the study cannot be implemented until approval is obtained. A copy of the written approval by the HREC must be sent to the TCC.

Administrative changes of the protocol are defined as minor corrections and/or clarifications that have no effect on the way the study is to be conducted, or on the safety of the subjects. These administrative changes will be agreed upon by Study Committee, or designee, and the PI(s), and will be documented in a memorandum and disseminated to all trial sites. The investigator at each site will then notify the HREC of such administrative changes.

18. PUBLICATIONS AND PRESENTATION POLICY

18.1. Reporting of Results

Access to data during the trial will be limited to the AMARC SDMC and appropriate regulatory bodies. The primary analysis of trial results for publication, and any interim analyses, will be performed by a qualified statistician approved by AMARC. The primary trial results will be published by the Principal Investigator after completion of the final report.

Acknowledgment of AMARC and Janssen support is required in all publications, abstracts and presentations. Publications must be provided to AMARC for review and approved prior to submission.

Any formal presentation or publication of data from this trial will be considered as a joint publication by the investigators, in conjunction with the AMARC. For multicentre studies, it is mandatory that the first publication is based on data from all centres. Investigators participating in multicentre studies agree not to present data gathered from one centre or a small group of centres before the full publication, unless formally agreed to by all PIs.

18.2. Trial Registration

AMARC, or designee, is responsible for registering all trials with an appropriate clinical trials registry prior to the accrual of the first patient. All AMARC trials are registered at the Australian and New Zealand Clinical Trials Registry (ANZCTR) www.anzctr.org.au.

19. REFERENCES

1. Quach H, Joshua D, Ho J, Szer J, Spencer A, Harrison S, et al. Treatment of patients with multiple myeloma who are not eligible for stem cell transplantation: position statement of the myeloma foundation of Australia Medical and Scientific Advisory Group. Intern Med J. 2015;45(3):335-43.
2. de Weers M, Tai YT, van der Veer MS, Bakker JM, Vink T, Jacobs DC, et al. Daratumumab, a novel therapeutic human CD38 monoclonal antibody, induces killing of multiple myeloma and other hematological tumors. J Immunol. 2011;186(3):1840-8.
3. Overdijk MB, Verploegen S, Bogels M, van Egmond M, Lammerts van Bueren JJ, Mutis T, et al. Antibody-mediated phagocytosis contributes to the anti-tumor activity of the therapeutic antibody daratumumab in lymphoma and multiple myeloma. MAbs. 2015;7(2):311-21.
4. Krejcik J, Casneuf T, Nijhof IS, Verbist B, Bald J, Plesner T, et al. Daratumumab depletes CD38+ immune regulatory cells, promotes T-cell expansion, and skews T-cell repertoire in multiple myeloma. Blood. 2016;128(3):384-94.
5. Lokhorst HM, Plesner T, Laubach JP, Nahi H, Gimsing P, Hansson M, et al. Targeting CD38 with Daratumumab Monotherapy in Multiple Myeloma. N Engl J Med. 2015;373(13):1207-19.
6. Dimopoulos MA, Oriol A, Nahi H, San-Miguel J, Bahlis NJ, Usmani SZ, et al. Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma. N Engl J Med. 2016;375(14):1319-31.
7. Palumbo A, Chanan-Khan A, Weisel K, Nooka AK, Masszi T, Beksac M, et al. Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma. N Engl J Med. 2016;375(8):754-66.
8. Moreau P, Mateos M-V, Bladé J, Benboubker L, de la Rubia J, Facon T, et al. An Open-Label, Multicenter, Phase 1b Study of Daratumumab in Combination with Backbone Regimens in Patients with Multiple Myeloma. Blood. 2014;124(21):176 (abstract).
9. Bringhen S, Larocca A, Rossi D, Cavalli M, Genuardi M, Ria R, et al. Efficacy and safety of once-weekly bortezomib in multiple myeloma patients. Blood. 2010;116(23):4745-53.
10. Merz M, Salwender H, Haenel M, Mai EK, Bertsch U, Kunz C, et al. Subcutaneous versus intravenous bortezomib in two different induction therapies for newly diagnosed multiple myeloma: an interim analysis from the prospective GMMG-MM5 trial. Haematologica. 2015;100(7):964-9.
11. Larocca A, Bringhen S, Petrucci MT, Oliva S, Falcone AP, Caravita T, et al. A phase 2 study of three low-dose intensity subcutaneous bortezomib regimens in elderly frail patients with untreated multiple myeloma. Leukemia. 2016;30(6):1320-6.
12. San Miguel JF, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, Kropff M, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med. 2008;359(9):906-17.
13. Bensinger WI, Jagannath S, Vescio R, Camacho E, Wolf J, Irwin D, et al. Phase 2 study of two sequential three-drug combinations containing bortezomib, cyclophosphamide and dexamethasone, followed by bortezomib, thalidomide and dexamethasone as frontline therapy for multiple myeloma. Br J Haematol. 2010;148(4):562-8.
14. Reeder CB, Reece DE, Kukreti V, Chen C, Trudel S, Hentz J, et al. Cyclophosphamide, bortezomib and dexamethasone induction for newly diagnosed multiple myeloma: high response rates in a phase II clinical trial. Leukemia. 2009;23(7):1337-41.
15. Reeder CB, Reece DE, Kukreti V, Chen C, Trudel S, Laumann K, et al. Once- versus twice-weekly bortezomib induction therapy with CyBorD in newly diagnosed multiple myeloma. Blood. 2010;115(16):3416-7.
16. Kumar S, Flinn I, Richardson PG, Hari P, Callander N, Noga SJ, et al. Randomized, multicenter, phase 2 study (EVOLUTION) of combinations of bortezomib, dexamethasone,

cyclophosphamide, and lenalidomide in previously untreated multiple myeloma. Blood. 2012;119(19):4375-82.
17. Moreau P, Attal M, Pegourie B, Planche L, Hulin C, Facon T, et al. Achievement of VGPR to induction therapy is an important prognostic factor for longer PFS in the IFM 2005-01 trial. Blood. 2011;117(11):3041-4.
18. Huang X, Ning J, Li Y, Estey E, Issa JP, Berry DA. Using short-term response information to facilitate adaptive randomization for survival clinical trials. Stat Med. 2009;28(12):1680-9.
19. Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol. 2014;15(12):e538-48.
20. Dejoie T, Corre J, Caillon H, Hulin C, Perrot A, Caillot D, et al. Serum free light chains should be the target of response evaluation in light chain multiple myeloma rather than urines. Blood. 2016.

20.

21. APPENDICES

Appendix 1: Revised IMWG Diagnostic Criteria for Symptomatic Multiple Myeloma(19)

Definition of multiple myeloma

Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary

plasmacytoma* and any one or more of the following myeloma defining events:

- Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
    - Hypercalcaemia: serum calcium >0·25 mmol/L higher than the upper limit of normal or >2·75 mmol/L
    - Renal insufficiency: creatinine clearance <40 mL per min† or serum creatinine >177 µmol/L
    - Anaemia: haemoglobin value of >20 g/L below the lower limit of normal, or a haemoglobin value <100 g/L
    - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT‡
- Any one or more of the following biomarkers of malignancy:
    - Clonal bone marrow plasma cell percentage* ≥60%
    - Involved:uninvolved serum free light chain ratio§ ≥100
    - >1 focal lesions on MRI studies¶

*Clonality should be established by showing κ / λ -light-chain restriction on fl ow cytometry, immunohistochemistry, or immunofl uorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used. † Measured or estimated by validated equations. ‡ If bone marrow has less than 10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement. §These values are based on the serum Freelite assay (The Binding Site Group, Birmingham, UK). The involved free light chain must be ≥100 mg/L. ¶Each focal lesion must be 5 mm or more in size.

Appendix 2: IMWG Response Criteria

Adapted from Kumar, S et al. Lancet Oncol 2016; 17: e328–46 and Dejoie et al. Blood 2016: Epub7-726778(20)

Note: IMWG response criteria will be followed to assess response with the exception that for patients with disease not measureable by serum M-protein (<10g/L) the serum FLC assay will be used to assess response provided disease is measureable by the FLC assay (involved FLC ≥100mg/L and abnormal FLC ratio). A 24 hour urine will only be used to assess response in patients whose disease is not measureable by either serum M-protein or serum FLC. A 24 hour urine will still be needed to defined CR and VGPR (see Dejoie et al(20)).

Stringent Complete Response (sCR)

CR as defined below plus
Normal FLC ratio and
Absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence[1]

Complete Response[2] (CR)
Negative immunofixation on the serum and urine and
Disappearance of any soft tissue plasmacytomas and
<5% plasma cells in bone marrow[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 or 90% decrease in the difference between involved and uninvolved FLC levels

Partial Response[4] (PR)
≥ 50% reduction of serum M-protein
reduction in 24 hour urinary M protein by ≥ 90% or to <200mg per 24 hour
≥ 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%

[1] Confirmation with repeat bone marrow biopsy not needed
[2] 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.
[3] Confirmation with repeat bone marrow biopsy not needed
[4] Confirmation with repeat bone marrow biopsy not needed

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

Minimal Response (previously called Minor response) (MR)
≥25% but <49% reduction of serum M protein and reduction in 24 hr BJP protein by 50-89%, which still exceeds 200mg per 24hr
In addition to the above criteria, if present as baseline, 25-49% reduction in the size of soft tissue plasmacytomas is also required.
No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response)

Stable disease (SD)
Not meeting criteria for MR, CR, VGPR, PR or progressive disease

Progressive Disease[5] (PD)
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)[6].
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 >100mg/l.
Bone marrow plasma cell percentage: the absolute % must be ≥ 10%[7].
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 hypercalcaemia (corrected serum calcium > 2.65mmol/l) that can be attributed solely to the plasma cell proliferative disorder.

NOTE: The IMWG uniform response criteria have clarified that patients in CR need to meet the same criteria for disease progression as other patients not in CR for purposes of calculating progression-free survival and time to progression.
All response categories (CR, sCR, VGPR and PR) require two consecutive assessments made at any time before the institution of any new therapy; complete, PR and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed.

[5] All relapse categories require two consecutive assessments made at any time before classification as relapse or disease progression and/or the institution of any new therapy
[6] For progressive disease, serum M component increases of ≥10gm/l are sufficient to define relapse if starting M-component is ≥50g/l
[7] Relapse from CR has the 5% cut-off versus 10% for other categories of relapse

Appendix 3: 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 4: Asthma Guidelines

Components of Severity		Classification of Asthma Severity											
		Intermittent			Persistent: Mild			Persistent: Moderate			Persistent: Severe		
		0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs
Impairment	Symptoms	≤ 2 days/week			≤ 2 days/week but not daily			Daily			Throughout the day		
	Nighttime awakenings	0	≤ 2x/month		1-2x/ month	3-4x/month		3-4x/ month	> 1x/week but not nightly		> 1x/ month	Often 7x/week	
	SABA use for symptom control (not prevention of EIB)	≤ 2 days/week			≤ 2 days/week but not daily		>2 days/ week but not daily, and not more than 1x on any day	Daily			Several time per day		
	Interference with normal activity	None			Minor limitation			Some limitation			Extremely limited		
Normal FEV$_1$/FVC: 8-19 yr 85% 20-39 yr 80% 40-59 yr 75% 60-80 yr 70%	Lung function FEV$_1$ FEV$_1$/FVC	N/A	Normal FEV$_1$ between exacerbations > 80% > 85%	Normal FEV$_1$ between exacerbations > 80% Normal	N/A	> 80% > 80%	> 80% Normal	N/A	60-80% 75-80%	60-80% Reduced 5%	N/A	< 60% < 75%	< 60% Reduced 5%
Risk	Exacerbations requiring oral systemic corticosteroids	0-1/year			≥ 2 exacerbations in 6 months requiring oral steroids or >4 wheezing episodes/1 year lasting >1 day and risk factors for persistent asthma	≥ 2/year Relative annual risk may be related to FEV$_1$.	≥ 2/year Relative annual risk may be related to FEV$_1$.	≥ 2 exacerbations in 6 months requiring oral steroids or >4 wheezing episodes/1 year lasting >1 day and risk factors for persistent asthma	≥ 2/year Relative annual risk may be related to FEV$_1$.	≥ 2/year Relative annual risk may be related to FEV$_1$.	≥ 2 exacerbations in 6 months requiring oral steroids or >4 wheezing episodes/1 year lasting >1 day and risk factors for persistent asthma	≥ 2/year Relative annual risk may be related to FEV$_1$.	≥ 2/year Relative annual risk may be related to FEV$_1$.
		← Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category. →											
Recommended Step for Initiating Treatment		Step 1			Step 2			Step 3 and consider short course of oral steroids	Step 3: medium dose ICS and consider short course of oral steroids	Step 3 and consider short course of oral steroids	Step 3 and consider short course of oral steroids	Step 3: medium dose ICS OR Step 4 and consider short course of oral steroids	Step 4 or 5 and consider short course of oral steroids
		In 2-6 weeks, evaluate level of asthma control that is achieved. 0-4 years: If no clear benefit is observed in 4-6 weeks, stop treatment and consider alternate diagnosis or adjusting therapy. 5-11 and 12+ years: adjust therapy accordingly.											

AMERICAN LUNG ASSOCIATION®
of Minnesota

Components of Control		Classification of Asthma Control								
		Well Controlled			Not Well Controlled			Very Poorly Controlled		
		0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs
	Symptoms	≤ 2 days/week but not more than once on each day		≤ 2 days/ week	> 2 days/week or multiple times on ≤2 days/week		> 2 days/ week	Throughout the day		
Impairment	Nighttime awakenings	≤ 1x/month		≤ 2x/month	> 1x/month	≥ 2x/month	1-3x/week	> 1x/week	≥ 2x/week	≥ 4x/week
	Interference with normal activity	None			Some limitation			Extremely limited		
	SABA use for symptom control (not prevention of EIB)	≤ 2 days/week			> 2 days/week			Several times per day		
	Lung function FEV$_1$ or peak flow FEV$_1$/FVC	N/A	> 80% > 80%	> 80%	N/A	60-80% 75-80%	60-80%	N/A	< 60% < 75%	< 60%
	Validated questionnaires ATAQ ACQ ACT			0 ≤ 0.75 ≥ 20			1-2 ≥ 1.5 16-19			3-4 N/A ≤ 15
Risk	Exacerbations requiring oral systemic corticosteroids	0-1/year			≥ 2/year					
		Consider severity and interval since last exacerbation								
	Reduction in lung growth/ Progressive loss of lung function	Evaluation requires long-term follow-up								
Recommended Action for Treatment		• Maintain current step • Regular follow-up every 1-6 months • Consider step down if well controlled for at least 3 months			Step up 1 step • Before step up Review adherence to medication, inhaler technique, and environmental control. If alternative treatment was used, discontinue it and use preferred treatment for that step. • Reevaluate the level of asthma control in 2-6 weeks to achieve control 0-4 years: If no clear benefit is observed in 4-6 weeks, consider alternative diagnoses or adjusting therapy. 5-11 years: Adjust therapy accordingly. • For side effects, consider alternative treatment options.	Step up at least 1 step	• Step up 1 step • Reevaluate in 2-6 weeks • For side effects, consider alternative treatment options	• Consider short course of oral steroids • Step up 1-2 steps • Before step up: Review adherence to medication, inhaler technique, and environmental control. If alternative treatment was used, discontinue it and use preferred treatment for that step. • Reevaluate the level of asthma control in 2-6 weeks to achieve control 0-4 years: If no clear benefit is observed in 4-6 weeks, consider alternative diagnoses or adjusting therapy. 5-11 years: Adjust therapy accordingly. • For side effects, consider alternative treatment options.		• Consider short course of oral steroids • Step up 1-2 steps • Reevaluate in 2 weeks • For side effects, consider alternative treatment options

Appendix 5: ISS (International Staging System) at Diagnosis

Stage 1	B_2M <3.5mg/l + Albumin ≥35g/l
Stage 2	B_2M <3.5mg/l + Albumin <35g/l or B_2M 3.5 – 5.4mg/l + Albumin ≥35g/l
Stage 3	B_2M ≥5.5mg/l

Appendix 6: Common Terminology Criteria for Adverse Events (CTCAE Version 4)

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

Appendix 7: Cockcroft-Gault Equation

For Males:

Creatinine Clearance = (140-age[years] × weight [kg]) **OR** (140–age[years] × weight [kg])

72 × (serum creatinine[mg/dL]) 0.81 × (serum creatinine[μmol/L])

For Females:

Creatinine Clearance = 0.85 (140-age[years] × weight [kg]) **OR** 0.85 (140-age[years] × weight [kg])

72 × (serum creatinine[mg/dL]) 0.81 × (serum creatinine[μmol/L])

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.

Appendix 8: IMWG Frailty score

Adapted from Palumbo et al. Blood. 2015;125(13):2068-2074. Each instrument should be scotred separately: ADL (0 to 6), IADL (0 to 8), CCI (0 to 37)

Activity of Daily Living (ADL) and Instrumental Activity of Daily Living (IADL)

The ADL scale includes six items (bathing, dressing, toileting, transferring, continence, and feeding), with a score for each item ranging from 0 (able to perform the activity) to 1 (unable to perform the activity). Total score ranges from 0 to 6. The IADL scale includes eight items (ability to use the telephone, shopping, cooking, housekeeping, doing laundry, taking own medication, making transports, and to handle finances), with a score for each item of 0 (high function, independent) or 1 (low function, dependent). The total score ranges from 0 to 8.

Score	ADL	IADL
0-1	Bathing (tub bath, shower, sponge bath)	Ability to use the telephone
0-1	Dressing (taking clothes from the wardrobe/drawers and getting dressed)	Shopping
0-1	Toileting (going to the toilet room, using toilet, arranging clothes)	Food preparation
0-1	Transferring	Housekeeping
0-1	Continence	Laundry
0-1	Feeding	Mode of transportation
0-1	-	Responsibility for own medications
0-1	-	Ability to handle finances

Charlson Comorbidity Index.

The CCI estimates the number and the severity of comorbidities, including nineteen diseases with a score varying from 1 to 6 for each of them in accordance to their severity. The score can range from 0 to 37.

Assigned weight	Condition
1	Myocardial infarction (history, not ECG changes only)
	Congestive heart failure
	Peripheral disease (includes aortic aneurysm >= 6 cm
	Cerebrovascular disease: CVA with mild or no residua or TIA
	Dementia
	Chronic pulmonary disease
	Connective tissue disease
	Peptic ulcer disease
	Mild liver disease (without portal hypertension, inlcudes chronic hepatitis)
	Diabetes without end-organ damage (excludes diet-controlled alone)
2	Hemiplegia
	Moderate or severe renal disease
	Diabetes with end-organ damage (retinopathy, neuropathy, nephropathy, or brittle diabetes)
	Tumor without metastasis (exclude if > 5 y from diagnosis)
	Leukemia(acute or chronic)
	Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumor
	AIDS (not just HIV positive)