# UARK# 2012-02 TOTAL THERAPY 5B

## A PHASE II TRIAL FOR HIGH-RISK MYELOMA EVALUATING ACCELERATING AND SUSTAINING COMPLETE REMISSION (AS-CR) BY APPLYING NON-HOST-EXHAUSTING AND TIMELY DOSE-REDUCED MEL-80-CFZ-TD-PACE TRANSPLANT(S) WITH INTERSPERSED MEL-20-CFZ-TD-PACE WITH CFZ-RD AND CFZ-D MAINTENANCE

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**High-Risk:**
Selection based on presence of established high-risk clinical features

↓

**INDUCTION:**
Mel 10-CFZ-TD-PACE and Peripheral Blood Stem Cell (PBSC) collection

↓

**1st TRANSPLANT:**
MEL-80 (20mg/m$^2$/d x 4d) + CFZ-TD-PACE

↓

**INTER-THERAPY:**
Mel-20 (5mg/m$^2$/d x 4d) + CFZ-TD-PACE (75%)
1cycle

↓

**2nd TRANSPLANT:**
MEL-80 (20mg/m$^2$/d x 4d) + CFZ-TD-PACE

↓

**CONSOLIDATION:**
CFZ-TD-PACE

↓

**MAINTENANCE:**
CRD (carfilzomib, Revlimid®, dexamethasone) = Cycles 1-12

CD (carfilzomib + dexamethasone) = Cycles 13-24

**Table 1: TT5B Treatment Summary**

| | |
|---|---|
| Inclusion (renal) | Creatinine < 3 mg/dL |
| **INDUCTION I** | **Mel-10+CFZ-TD-PACE #1**<br>M 10 mg/m$^2$ d 3<br>*W-GEP (optional)* *d 3 and d 5*<br>***CFZ 20 mg/m$^2$*** ***d 1,5,6***<br>T 200 mg/d d 5 – 8<br>D 40 mg/d d 5 – 8<br>P 10 mg/m$^2$/d d 5 – 8 CI<br>A 10 mg/m$^2$/d d 5 – 8 CI<br>C 400 mg/m$^2$/d d 5 – 8 CI<br>E 40 mg/m$^2$/d d 5 – 8 CI<br><br>PBSC collection ≥ 30 x 10$^6$ CD34/kg, ≥ 8 bags<br>If less, additional collection permitted - PI |
| Dose adjustment | Cisplatin for creatinine |
| ***Bridging* (Optional)*** | THAL 50 mg-DEX 20 mg |
| **Transplant-1**<br><br>**[3 weeks to 8 weeks post induction]** | **MEL-80+CFZ-TD-PACE**<br>M 20 mg/m$^2$/d d -5 – -2<br>CFZ 27 mg/m$^2$ d -5 and d -4<br>T 200 mg/d d -5 – -2<br>D 40 mg/d d -5 – -2<br>P 10 mg/m$^2$/d d -5 – -2 CI<br>A 10 mg/m$^2$/d d -5 – -2 CI<br>***C 100 mg/m$^2$/d*** d -5 – -2 CI<br>***E 80 mg/m$^2$/d*** d -5 – -2 CI<br>PBSC ≥ 3 x 10$^6$ day 0 |
| ***Bridging* (Optional)*** | THAL 50 mg-DEX 20 mg |
| ***Inter-Therapy***<br><br>**[6 weeks to 12 weeks post Transplant 1]** | **MEL-20+CFZ-TD-PACE (75%)**<br>*M 5 mg/m$^2$/d* d 1 – 4<br>*CFZ 27 mg/m$^2$* d 1 and d 2<br>*T 200 mg/d* d 1 – 4<br>*D 20 mg/d* d 1 – 4<br>***P 7.5 mg/m$^2$/d*** d 1 – 4 CI<br>***A 7.5 mg/m$^2$/d*** d 1 – 4 CI<br>***C 75 mg/m$^2$/d*** d 1 – 4 CI<br>***E 60 mg/m$^2$/d*** d 1 – 4 CI |
| ***Bridging* (Optional)*** | THAL 50 mg-DEX 20 mg |
| ***Transplant-2***<br><br>**[6 weeks to 8 weeks post Inter-Therapy]** | **MEL-80+CFZ-TD-PACE**<br>M 20 mg/m$^2$/d d -5 – -2<br>CFZ 27 mg/m$^2$ d -5 and d -4<br>T 200 mg/d d -5 – -2<br>D 40 mg/d d -5 – -2<br>P 10 mg/m$^2$/d d -5 – -2 CI<br>A 10 mg/m$^2$/d d -5 – -2 CI<br>***C 100 mg/m$^2$/d*** d -5 – -2 CI<br>***E 80 mg/m$^2$/d*** d -5 – -2 CI<br>PBSC ≥ 3 x 10$^6$ day 0 |
| ***Bridging* (Optional)*** | THAL 50 mg-DEX 20 mg |
| ***Consolidation***<br><br>**[6 weeks to 12 weeks post Transplant 2]** | *CFZ 27 mg/m$^2$ d -1 and d -2<br>T 200 mg/d d -1 – -4<br>D 40 mg/d d -1 – -4<br>P 7.5 mg/m$^2$/d d -1 – -4 CI<br>A 7.5 mg/m$^2$/d d -1 – -4 CI<br>***C 300 mg/m$^2$/d*** d -1 – -4 CI<br>***E 30 mg/m$^2$/d*** d -1 – -4 CI |
| ***Cycles 1-12***<br><br>**[4 weeks to 12 weeks post Consolidation]**<br><br>***Cycles 13-24*** | **CRD**<br>C 27 mg/m$^2$/wk d 1, 8, 15, 22<br>R 15 mg/d d 1 – 21<br>D 12 mg/wk d 1, 8, 15, 22<br><br>**CD**<br>C 27 mg/m$^2$/wk d 1, 8, 15, 22<br>D 12 mg/wk d 1, 8, 15, 22 |

# 1.0 OBJECTIVES

## 1.1 Primary Objective

Toward improving the clinical outcomes of research subjects with high-risk MM (HR-MM) in the context of the immediately preceding TT5 trial 2008-02 and TT3 trials 2003-33 and 2006-66, TT5B will attempt to accelerate and sustain, at 2 years from starting therapy, the proportion of subjects in complete remission (AS-CR-2) by reducing host-imposed toxicity and thus facilitating timely completion of highly synergistic 8-drug combination therapy, including the next generation proteasome inhibitor, Carfilzomib (CFZ). This will result in avoiding MM re-growth that, we postulate, ensued in TT3 during recovery phases from severe de-conditioning. Furthermore, we speculate that the incidence of positive minimal residual disease (MRD) will be reduced with the addition of one cycle of consolidation therapy. Toward this goal, the following approach will be implemented:

- apply a 4-day fractionated lower dose melphalan (80 mg/m2 instead of mel 200 mg/m2) together with CFZ-TD-PACE regimen in MEL80-CFZ-TD (carfilzomib, thalidomide, dexamethasone)-PACE as a hopefully less toxic and a more effective transplant regimen;
- interspersed with 1 cycle of non-transplant supported MEL-20-CFZ-TD (carfilzomib, thalidomide, dexamethasone)-PACE (in lower doses than with transplant) inter-therapy (reduced from two cycles due to prolonged thrombocytopenia);
- followed by CFZ-TD (carfilzomib, thalidomide, dexamethasone)-PACE consolidation therapy post transplant #2;
- CFZ-RD (carfilzomib, lenalidomide, and dexamethasone) maintenance for 12 cycles followed by CFZ-D for an additional 12 cycles.

## 1.2 Secondary Objectives

- To perform, 48hr after **CFZ 20 mg/m$^2$** followed by 48 hour post **melphalan 10 mg/m$^2$**, whole genome expression profiling (W-GEP) examinations of CD138-purified MM plasma cells (PC) and of bone marrow biopsy (BX) samples, and determine whether “response” and “resistance” W-GEP signatures can be identified *via* short-term GEP alterations in PC and BX, analogous to observations in TT3 with bortezomib[1].
  - A sub-aim examines whether CFZ or melphalan-induced changes are tumor cell specific or might be genetically predetermined; toward this aim, we will compare and contrast GEP in peripheral blood (PB) mononuclear cells and MM tumor cells prior to and following drug(s) test dosing.
- To perform such W-GEP examinations plus proteomic analyses on PC and BX procured from randomly sampled (RS) iliac crest bone marrow sites and from MRI-defined focal lesions (FL) under CT-guidance during defined phases of TT5B from the time of **diagnosis to remission and on to relapse, to address the following fundamental issues:**
  - Differences between RS-PC and FL-PC as well as RS-BX and FL-BX, as done in TT2 and TT3 trials, in order to continue to discern the fundamental differences in MM and host micro-environment (ME) inherent in FL versus diffuse MM growth and thus potentially define a “dormant” MM stem-cell-like, non-secretory tumor compartment that may be key to treatment failure and disease recurrence. Serial examinations during the course of therapy, in the context of 8 molecular subgroups[2] will provide insight into this newly emergent intra-patient disease heterogeneity exhibiting differential response kinetics in TT2 and TT3. These studies are also anticipated to provide a better understanding of a preferential MM sub-population cell kill as a means to distinguish whether relapse originates from the outgrowth of a minor resistant tumor sub-population or is due to further transformation during therapy
  - An important sub-aim relates to the issue of whether the *molecular subgroups elicit unique ME-associated genes (MAGs)* that partake in treatment-induced control of disease and its eventual escape.
  - A further sub-aim addresses the suitability of the ME signature in clinical remission to serve as an early surrogate for sustained complete remission (CR) when studied in comparison with normal donors.

- To perform miRNA profiling of RS-MM and FL-MM cells:
  - to asses miRNA involvement in MM pathogenesis;
  - to relate treatment success or failure to de-methylation of miRNA as a result of effective therapy.

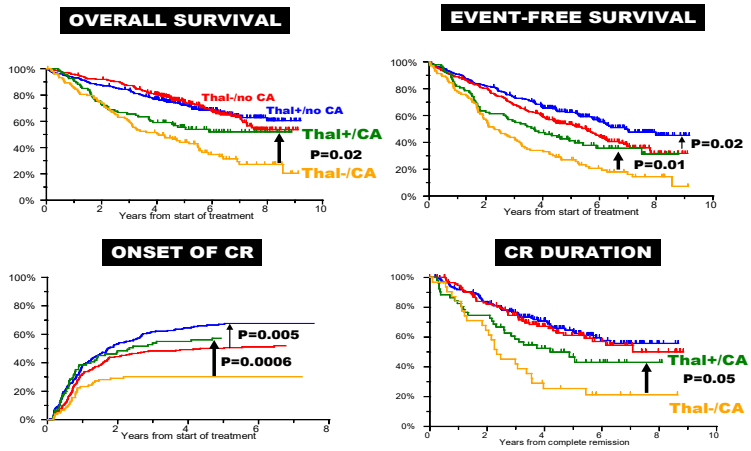
- To perform SNP profiling:
  - of MM cell DNA to determine the roles of Loss of Heterozygosity (LOH), Copy Number Abnormalities (CNA), and Uni-parental Disomy (UPD) in MM pathogenesis;
  - of germline DNA to evaluate the genetic contributions to sensitivity, resistance and toxicity to agents utilized in TT5B
- To perform aCGH profiling of RS-MM and FL-MM at baseline and progressive disease:
  - to confirm and validate current models relating CNA to W-GEP and outcome;
  - to related SNP and aCGH, proteomic profiling.
- To perform label-free proteomic analysis of MM cells in the context of W-GEP and aCGH data:
  - To validate and extend molecular classification and risk stratification models;
  - To identify protein-based risk stratification models;
  - To identify cell surface proteins on MM cells for the purpose of identifying potential new antibody-based therapeutic targets;
  - To identify post-carfilzomib protein-based alterations associated with proteasome gene induction.

# 2.0 BACKGROUND AND RATIONALE

## 2.1 Results of Total Therapy (TT) regimens TT1, TT2, TT3

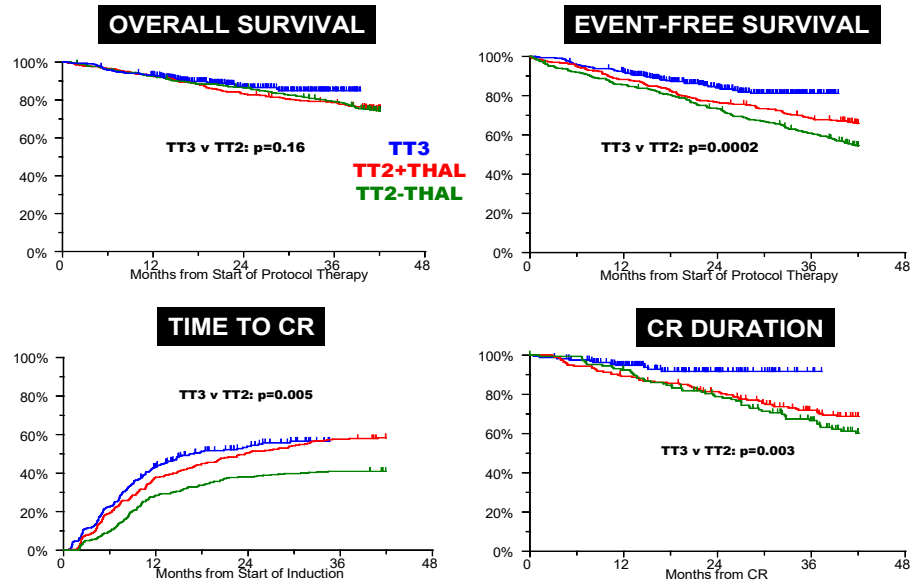
2.1.1 The median overall survival of 231 research subjects treated with TT1 was 6yr and has been extended to 9yr for 668 subjects enrolled in TT2 and is projected to reach 12yr with TT3. TT2's major advance vis-à-vis TT1 had been an outcome improvement for the two-thirds of subjects presenting without cytogenetic abnormalities ("no CA") attributable to the introduction of post-transplant consolidation chemotherapy[3], whereas the one-third with CA seemed to have benefited from thalidomide[4]. According to recent follow-up of TT2 at a median of 6 years, the experimental arm with thalidomide significantly improved not only event-free survival (EFS) both also OS and CR duration in the CA group (Figure 1).

**Figure 1. TT2: THAL Benefits CA Subgroup**



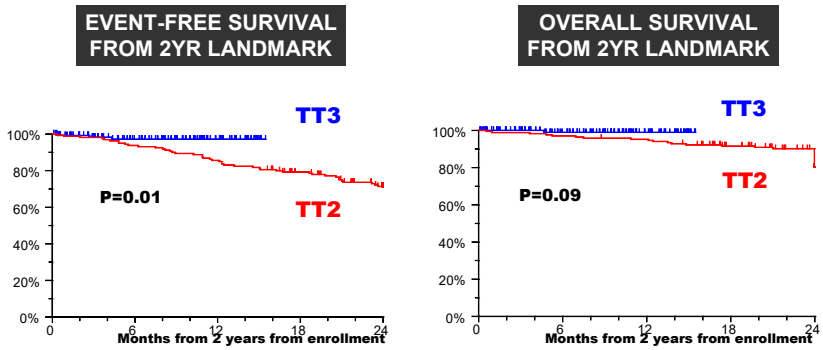
2.1.2 As we incorporated bortezomib (V) into TT3 with abbreviated induction and consolidation cycles (2 instead of 4 in TT2), both CR duration and EFS were markedly improved with a trend also noted for superior OS (Figure 2)[5].

**Figure 2. Outcome Comparisons TT3 v. TT2**



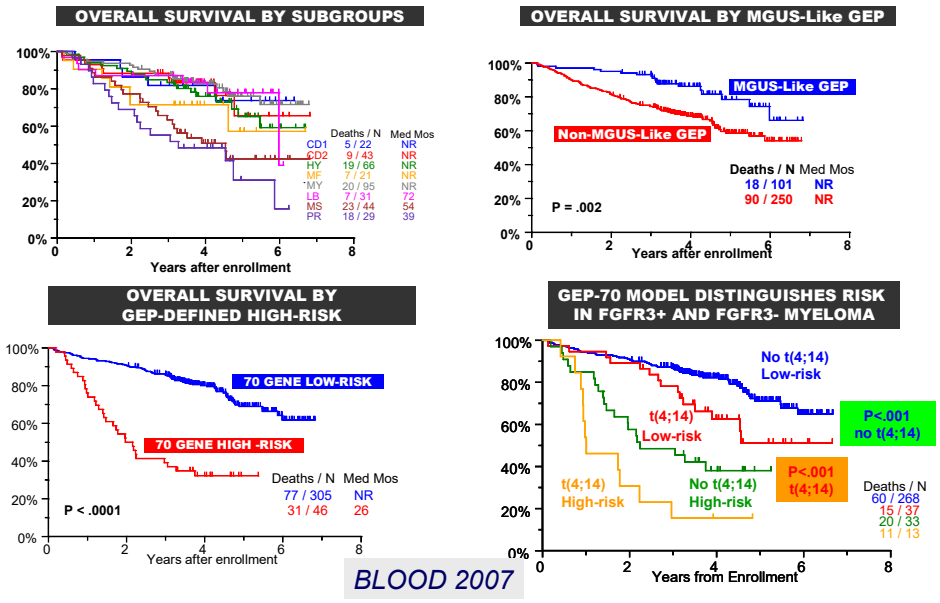

2.1.3 These results still pertained when limited to subjects who had completed all pre-maintenance components of therapy on time, suggesting that V contributed significantly to TT3's superior performance versus TT2 (**Figure 3**)[6].

**Figure 3. Outcomes in Patients with Rapid Completion of TT3 and TT2 Steps: *In Support of Bortezomib in TT3***



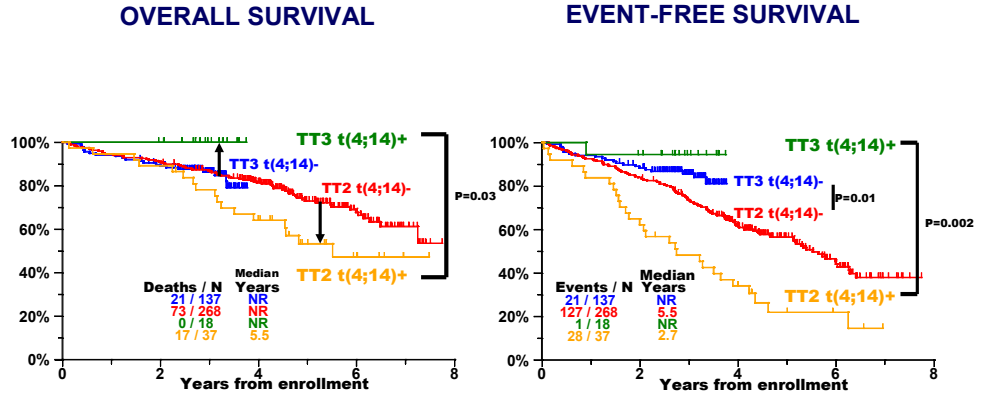
2.1.4 While CA and LDH as well as B2M and albumin all have long been recognized as baseline parameters independently and adversely affecting both OS and EFS, the recent introduction of gene expression profiling (GEP) of highly purified plasma cells (PC) has led to the recognition of a truly high-risk MM (HR-MM) subgroup with hazard ratio (HR) values exceeding 4.0 and trumping all other variables[1]. This GEP-based risk model was developed in TT2 and has been validated in TT3 as well as by other investigators applying standard and high-dose therapies[7;8]. In addition, 8 molecular subgroups were identified through unsupervised hierarchical clustering, among which MMSET/FGFR3, MAF/MAFB and Proliferation entities were associated with poor outcomes on TT2 (**Figure 4**)[2].

**Figure 4. GEP in TT2: 3 Models with Clinical Impact**



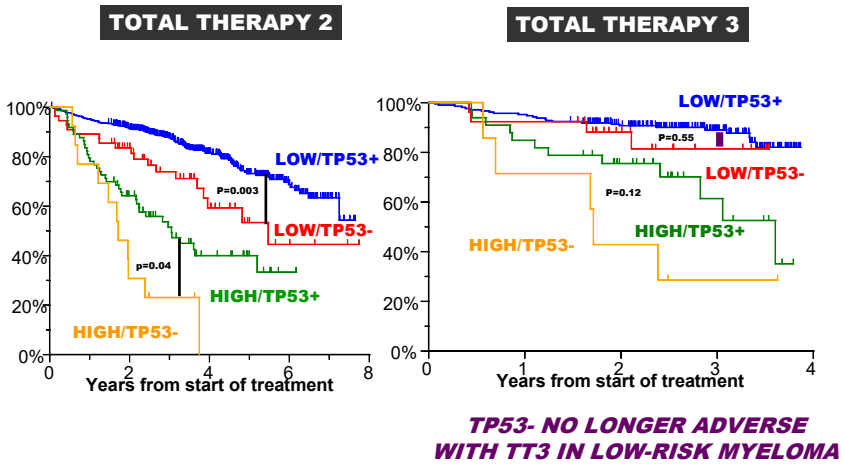

2.1.5 In a comparative analysis of TT3 v TT2 outcomes in the context of these GEP-defined risk groups and molecular entities, we observed that TT3 benefited the MMSET/FGFR3 subgroup preferentially so that it is no longer considered high-risk *per se* in bortezomib-containing therapies, an observation also made by other investigators (**Figure 5**)[5]. In fact, as is depicted in **Figure 5**, subjects with low-risk MM and exhibiting the MMSET/FGFR3-type MM experienced superior OA and EFS in comparison with those lacking this molecular translocation, while the reverse was true in the case of TT2. These data strongly support the notion that FGFR3/MMSET-type MM is exquisitely V-sensitive.

**Figure 5. TT3 Benefits FGFR3-Type Myeloma with Low-Risk as Defined by GEP**



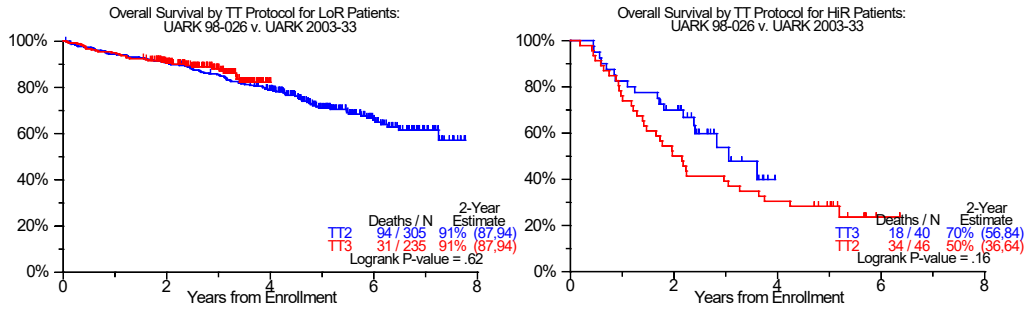
2.1.6 GEP analysis also permits the detection of TP53 deletion, as there was a strong correlation between very low expression levels of this tumor suppressor gene and mono- and bi-allelic deletion recognized by inter-phase FISH analysis. TP53 deletion represented high-risk disease in case of TT2 regardless of risk designation, whereas subjects with low-risk MM treated on TT3 fared well (**Figure 6**).

**Figure 6. TT3/TT2 Survival according to GEP Risk & TP53 Deletion**

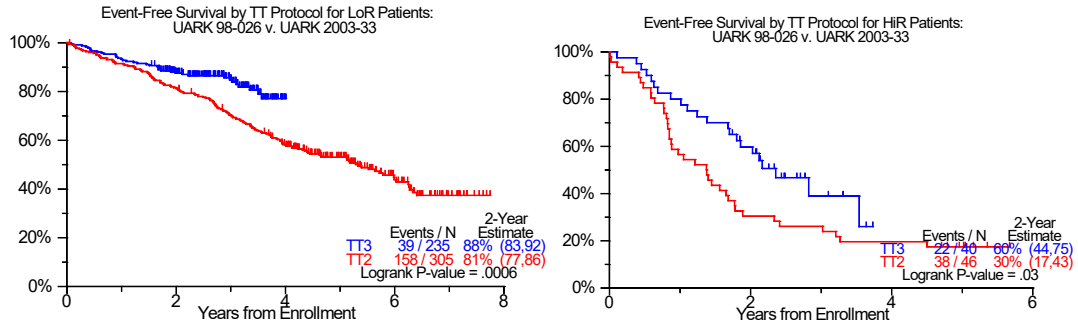



2.1.7 Furthermore, according to a recent update of TT3 v TT2 outcomes according to GEP-defined risk-groups, we observed strikingly superior EFS and CR/n-CR durations with TT3 in low-risk MM with OS trend (**Figure 7a, b, c, d**). Although trending toward superiority also in high-risk MM for TT3 versus TT2, results are unacceptably inferior to outcomes observed in low-risk disease.

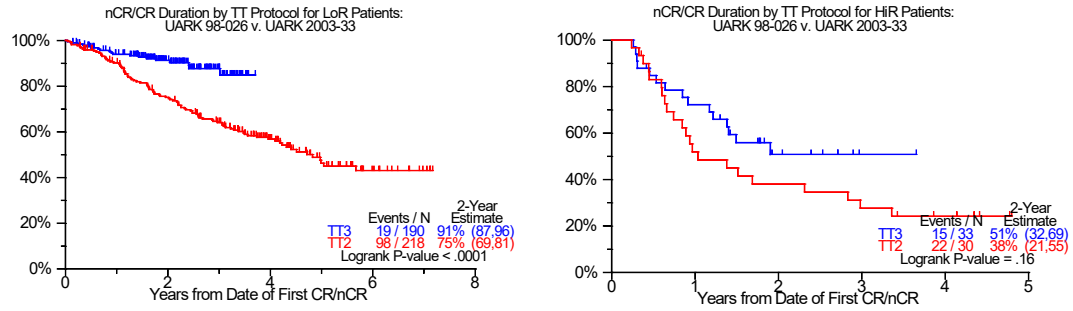
## Figure 7a. TT3 v. TT2: Overall Survival by GEP-Defined Risk



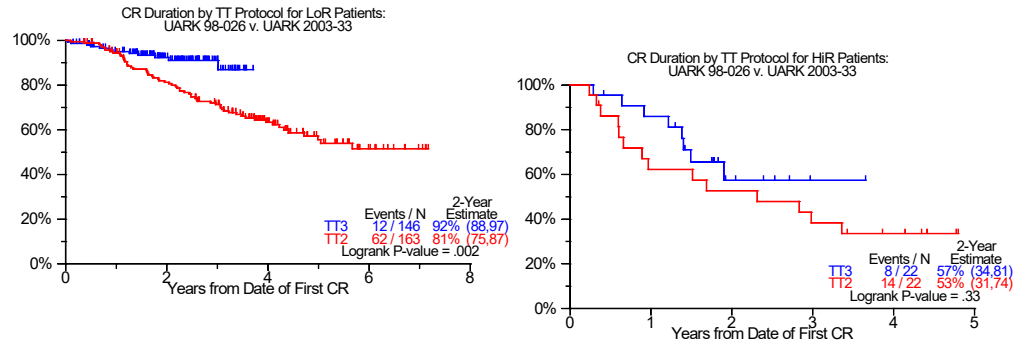

## Figure 7b. TT3 v. TT2: Event-Free Survival by GEP-Defined Risk




## Figure 7c. TT3 v. TT2: N-CR duration by GEP-Defined Risk



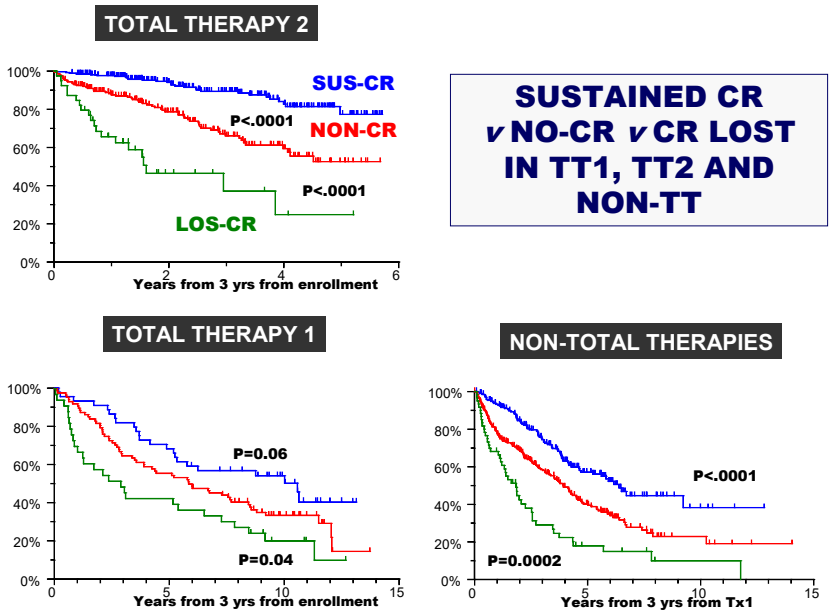

## Figure 7d. TT3 v. TT2 CR Duration by GEP-Defined Risk



2.1.8 We have also addressed the issue of attaining CR in TT trials and had noted, by multivariate analysis that CR (as a time-dependent variable) always entered as a favorable variable for both EFS and OS - until GEP-derived variables were considered[9]. Thus, in the context of GEP-defined risk groups, CR was only critical for those ~15% with HR-MM10. On the other hand, we reported that patients with MM that had evolved through a smoldering phase or from a MGUS precursor condition had superior outcomes with TT2, although the frequency of CR was significantly lower at ~10% v 40% for the remainder[5]. We interpreted this finding to reflect a re-establishment of a MGUS-like condition. Similarly, *via* GEP analysis, we were able to distinguish MGUS-like and non-MGUS-like MM; interestingly, CR frequency was significantly lower in the former category, although EFS and OS both were superior (see **Figure 4)**[11].

As CR has been embraced as a valid surrogate for OS in new agent trials, we also had recognized that the baseline features associated with high CR rates were those with negative consequences for OS and EFS, implying that more aggressive disease will be initially highly sensitive but will develop resistance rapidly either due to the expansion of a de novo resistant sub-clone or the rapid acquisition of secondary resistance, an issue well known to pertain to high-grade lymphoma[12]. Thus, while quintessential, acquiring CR status per se was not sufficient to ensure OS extension. We therefore examined, via re-iterative landmark analyses, the impact of sustained CR (sus-CR). Results with TT2 revealed that subjects with sus-CR 3yr after treatment initiation enjoyed vastly superior OS than especially those who had attained but lost CR status (los-CR) during that time interval; those who never achieved CR (non-CR) had an intermediate prognosis (**Figure 8**)[13]. These observations were confirmed in TT1 and in non-TT protocols for previously treated MM (see **Figure 8**).

**Figure 8. Sustained CR v. No-CR v. CR Lost in TT1, TT2, and non-TT**




## 2.2 Post-TT3

2.2.1 <u>TT4 for low-risk (LR)-MM:</u>

Current clinical outcome data for subjects with LR-MM on TT3 (UARK 2003-33) are so superb that TT4 (UARK 2008-11) is investigating whether, in a randomized clinical trial design, TT3-LITE (reducing induction and consolidation cycles from 2 to 1, fractionating MEL200 into 4 fractions of 50mg/m2 with the addition of VTD) can reduce treatment-related toxicities and improve tolerance and subjects compliance further while maintaining efficacy.

2.2.2 TT5 for high-risk (HR)-MM:

Little progress has been made in the management of the 15% of patients presenting with GEPdefined high risk MM. Toward improving clinical outcomes of patients with high-risk myeloma in the context of earlier Total Therapy 3 trials, Total Therapy 5 was designed to accelerate and sustain at two years from starting therapy the proportion of patients in complete remission by applying more frequent but lower doses of chemotherapy (dose-dense vs. dose- intense) to eradicate the high-risk myeloma and prevent relapse. Subjects were segregated with HR-MM out for treatment in UARK 2008-02. HR-MM was defined by GEP risk score.

Compared to high-risk subjects on TT3 a/b combined, TT5 demonstrates improved OS (2-yr estimate 88% vs 63%, p=0.02) (Figure 9), however there was no significant difference noted for PFS. These results highlight the importance of improving the rate of progression in high-risk MM as shown in Figure 10.

**Figure 9. OS TT3 HR MM vs TT5 HR MM**

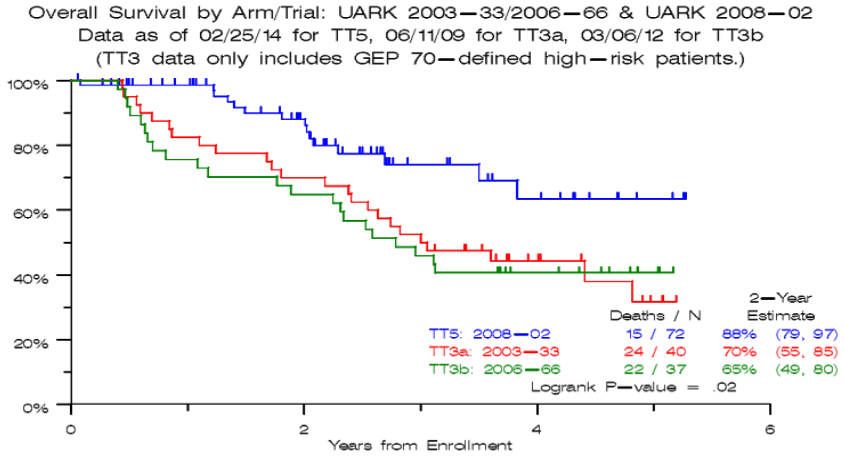
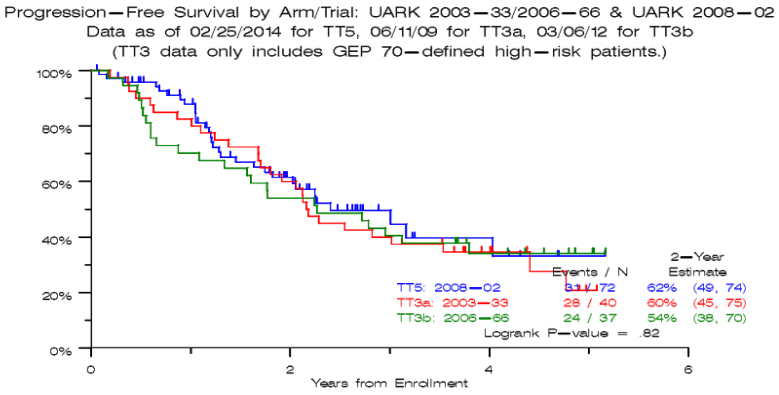



**Figure 10. PFS TT3 HR MM vs TT5 HR MM**

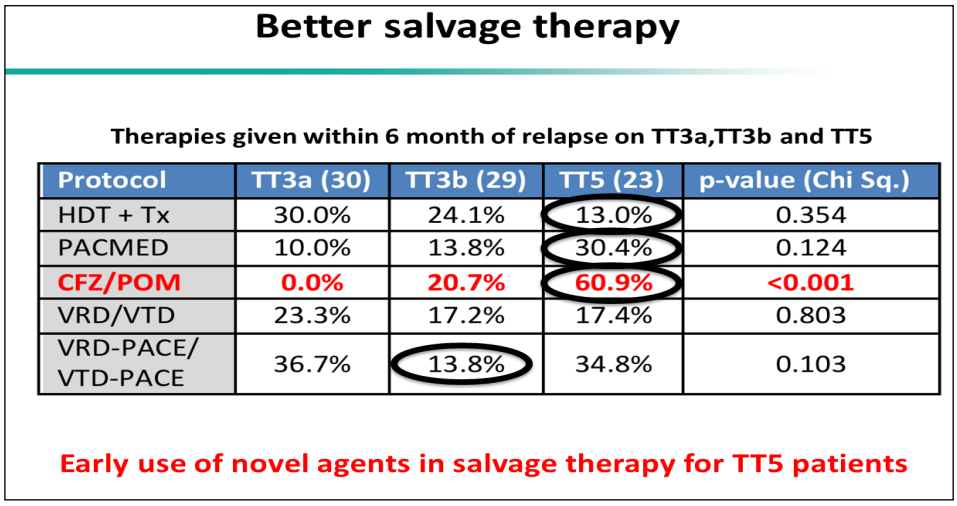



## 2.3 TT5B Rationale and Design

2.3.1 Introduction of Carfilzomib (CFZ)

As shown in the above figures, GEPdefined high-risk MM has not yet benefited from therapeutic advances observed in low-risk disease. We postulize that the superior OS in TT5 as compared to HR-MM from TT3 is due to the availability of new novel agents, such as pomalidomide and carfilzomib, used as salvage therapies (**Figure 11)**.

**Figure 11. TT3 vs TT5 Salvage Therapy**




With the introduction of proteasome inhibitors, disease-free and overall survival for most MM patients has been significantly extended. However, primary or secondary bortezomib resistance is not uncommonand treatment is often limited by dose-limiting side effects, mostly consequent to peripheral neuropathy. Although less frequent bortezomib administration at lower doses and using subcutaneous delivery may contribute to a lowered neuropathy incidence and severity without seemingly compromising efficacy, new proteasome inhibitors – the "second generation" – have now been developed and are aimed at being both more efficacious and less toxic[14]

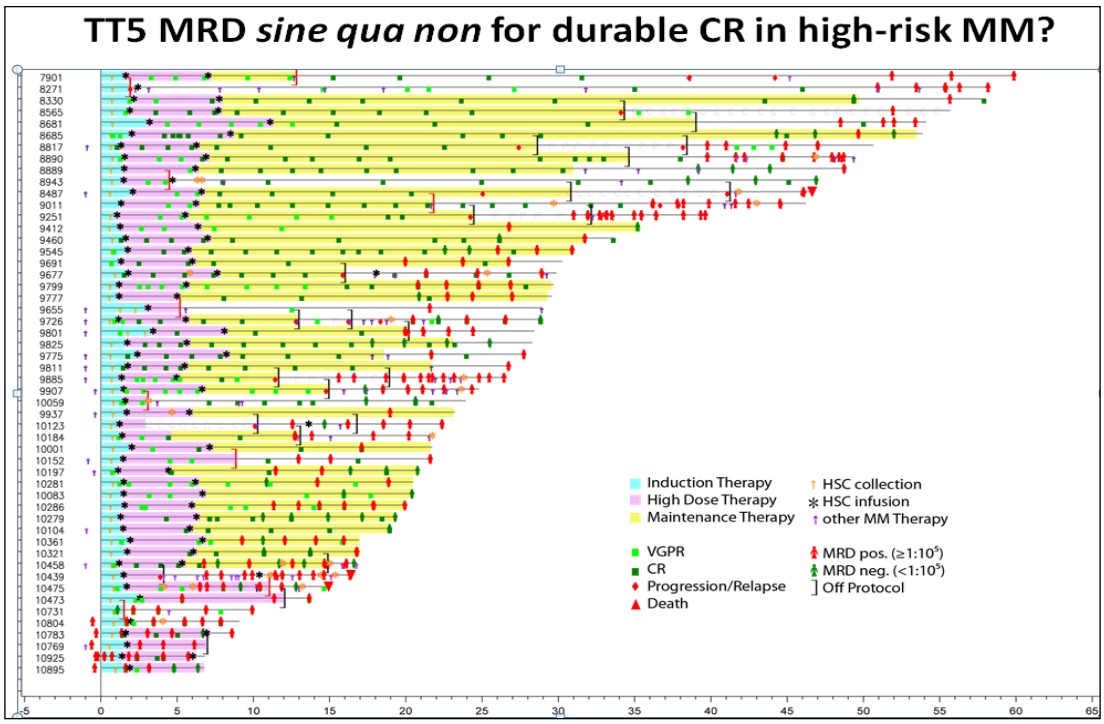
CarfilzomIb (CFZ) is a cell-permeable tetrapeptide epoxyketone analog of epoxomicin. It primarily inhibits the chymotrypsin-like site of the proteasome, and in high doses, it shows additional inhibitory effects on the trypsin-like and caspase-like sites. CFZ forms stable and irreversible adducts exclusively with the proteasome but not with other proteases. Bortezomib, in contrast, forms (slowly) reversible and less specific adducts predominantly with the chymotrypsin-like and the caspase-like site, but also with a multitude of serine proteases, potentially contributing to some of the neurotoxicity.[14]

Carfilzomib (Kyprolis®) is a proteasome inhibitor that is indicated in combinationiwth dexamethasone or with lenalidomide plus dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy, and as a single agent for the treatment of patients with relapsed or refractory multiple myeloma who have received one or more lines of therapy. However, the results of ongoing phase 2 and multiple phase 3 trials are further defining the significant role of CFZ in upfront MM.[44]

2.3.2 <u>The Addition of Consolidation Therapy</u>

As shown in our previous HR TT3 and TT5 trials, achieving VGPR or CR is not problematic, but the the long-term outcomes of patients is heterogeneous, and the majority of TT5 patients remain MRD (minimal residual disease) positive following transplant (**Figure 12**).

**Figure 12. TT5 MRD**




Several studies have shown that consolidation and maintenance post transplant can further reduce tumor burden and improve outcome. The importance of consolidation was first reported at the Myeloma Institute, prior to the introduction of novel drugs in Total Therapy 2 which employed consolidation with DCEP/EDAP and later DPACE, with TT1 patients who only received maintenance with interferon and dexamethasone. Five year rates of continuous CR (45 vs. 32%, p<0.001) and EFS (45 vs. 32%, p<0.001) were superior in patients receiving consolidation chemotherapy (43 vs. 28%, p<0.001). Further, 4-yr post ASCT OS was significantly better in patients with metaphase cytogenetic abnormalities who received post ASCT consolidation (76 vs. 47%; p=0.04).[15] The Nordic Myeloma group showed in a landmark analysis that bortezomib as consolidation produced a 7 month prolongation of PFS post ASCT compared to patients receiving placebo (27 months vs. 20 months; p=0.05), further identifying the importance of consolidation post transplant.[16]

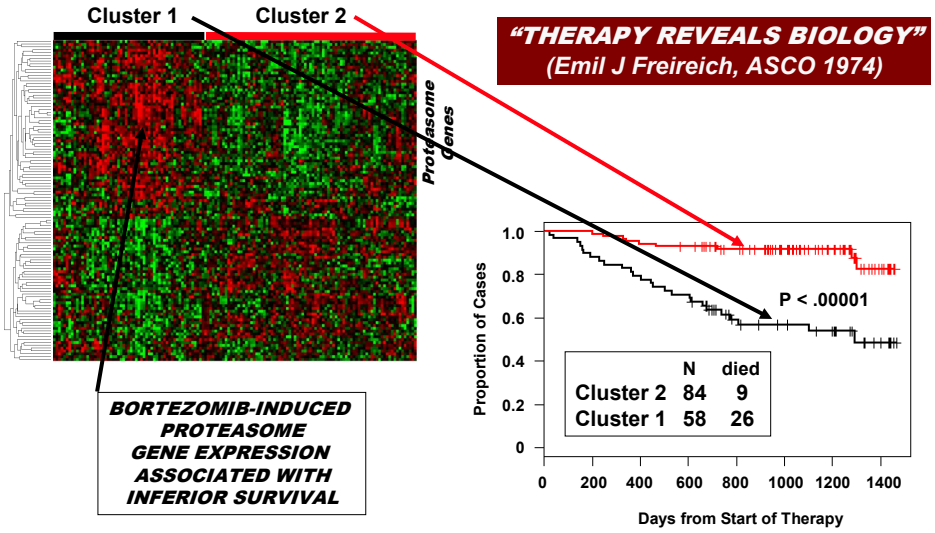
Furthermore, Paiva et al reported in a study of 241 MM patients that the two most important characteristics having prognostic influence in patients after transplant were 1)high risk cytogenetics and 2) persistent MRD by multiparameter flow cytometry (shown in 87 (36%) of the patients). After reviewing the impact of immunophenotypic CR in terms of standard and high risk patients 100 days post transplant, the best prognosis was found in the standard-risk + MRD negative group with a time to progression (TTP) of 83 months, followed by high-risk OR MRD positive group (TTP 26 months). The worst prognosis was the group where both high risk and persistent MRD were present (TTP 6 months). These results demonstrate the ongoing need for novel treatment strategies after transplant[17].

Based on the above considerations, for this trial we are proposing to start with CFZ-TD-PACE and PBSC collection, followed by the 1st of **two autotransplants employing MEL-80mg/m$^2$ in 4 daily successive doses of 20 mg/m$^2$ plus CFZ-TD-PACE plus PBSC**. Prior to the 2nd identical autotransplant, subjects will receive **1 cycle of MEL-20-CFZ-TD-PACE with MEL 5mg/m$^2$ applied in 4 fractions of 5mg/m$^2$** each. Following the second autotransplant, subjects will receive **1 cycle of CFZ-TD-PACE consolidation**. Maintenance therapy will be with **CRD** cycles every 28 days for 12 cycles, then **CD** cycles every 28 days for 12 cycles.

2.3.4 48-hour post treatment GEP

We have gained fundamental insight into disease biology, drug mechanism of action and prognosis from examination of the GEP alterations in MM-cells 48hr following a single application of bortezomib in previous trials, such as TT3. (**Figure 13**).

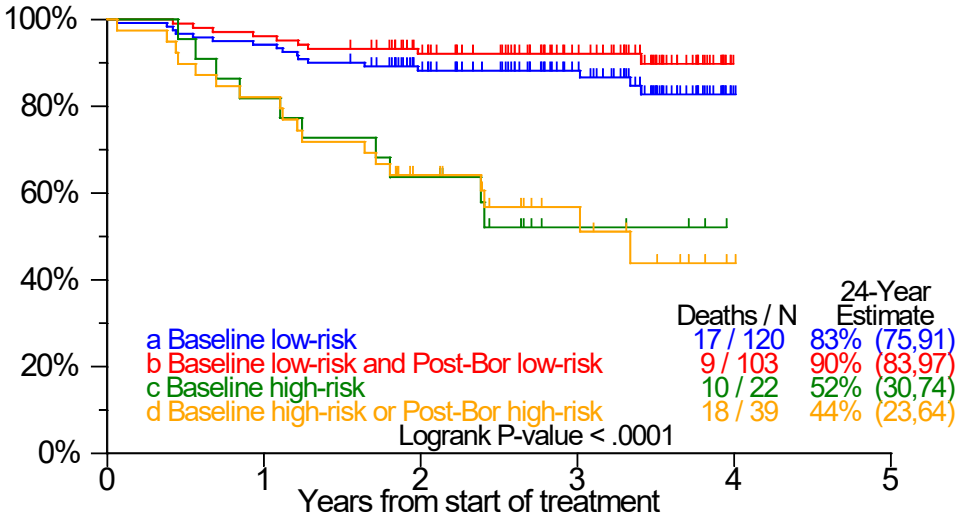
**Figure 13. TT3: Overall Survival according to 48HR Post-Bortezomib Clusters**




Two clusters were readily discerned in the above heat-map (left panel). Importantly, overall survival (right panel) and event-free survival (not shown) both were vastly inferior in subjects belonging to cluster 2 versus those in cluster 1. Cluster 2 was characterized by marked hyper-expression of proteasome genes, which therefore seems to be linked to resistance to bortezomib.

We also developed a post-bortezomib best-cut index (based on 113 genes) and a post-bortezomib 70-gene-based high-risk score (analogous to baseline risk) that identified, along with other baseline features, additional high-risk groups **(Figure 14**).

**Figure 14. TTE: Survival by Post-Bor 113-Gene Score in Context of GEP-Defined Risk Groups**



According to multivariate analysis, the post-bortezomib 113-gene index was highly significantly associated with poor survival on TT3, displacing all other baseline features out of the model (**Table 2**).

**Table 2. Bortezomib-Induced Score Significant after Adjusting for Baseline Features**

| N = 195 | | | Overall Survival | |
|---|---|---|---|---|
| | Variable | % | HR | P |
| Univariate | Age >=65 yr | 27 | 1.07 | 0.878 |
| | LDH >=190 U/L | 26 | 5.88 | <.001 |
| | B2M >=3.5 mg/L | 47 | 2.49 | 0.029 |
| | B2M >5.5 mg/L | 26 | 2.84 | 0.010 |
| | Albumin <3.5.g/dL | 30 | 1.80 | 0.158 |
| | Creatinine >=2.0 mg/dL | 9 | 2.38 | 0.113 |
| | CRP >=8 mg/L | 37 | 2.66 | 0.017 |
| | Hb <10 g/dL | 30 | 3.00 | 0.006 |
| | Cytogenetic abnormalities | 40 | 3.98 | 0.001 |
| | GEP high-risk | 21 | 4.28 | <.001 |
| | TP53 deleted | 12 | 4.17 | <.001 |
| | Post-bortezomib high-risk score | N=187 | 5.32 | <.001 |
| **Multivariate** | **Post-bortezomib high-risk score** | **N=187** | **5.40** | **<.001** |

Based on the above, we plan to gain additional insight into the disease biology, drug mechanism of action and prognosis from examining the GEP alterations in MM-cells 48 hours post single application of Carfilzumib.

As the second generation proteasome inhibitor Carfilzomib (CFZ) has proven to have superior proteasome inhibition to bortezomib in both in vitro and in vivio models, a translational research aim within the Total Therapy 5B protocol will be to study the molecular sequelae of short-term in-vivo exposure of tumor cells to low dose CZF (20mg/m2) and to correlate these results with clinical molecular features of disease, i.e. 70-gene risk, TP53 status, molecular subtype, and responses and outcomes following induction chemotherapy and melphalan 80mg/m2 followed by autologous stem cell tandem transplantation.

2.3.5 Melphalan 10mg/m$^2$ and 48hr post-treatment GEP

Melphalan has been the backbone of MM therapy since its introduction in the 1960's[21]. In the context of standard-dose regimens in the 1970's and 1980's, permutations of the standard melphalan-prednisone regimen by adding a variety of other alkylating and topoisomerase-inhibiting drugs have not advanced patients' outcomes[22]. However, with the introduction of high-dose melphalan (MEL) to 200mg/m2 requiring autotransplantation, CR rates were raise to 20% from < 5% with MP after a single and to 40% and higher with tandem applications as pioneered by us in Total Therapy 1 (TT1)[23]. These results have been confirmed in several randomized clinical trials comparing standard with single[24;25] and single with tandem transplants[26;27] . The recognition, by us, that thalidomide was the first novel agent since melphalan and glucocorticoids to exhibit anti-MM activity in advanced and refractory MM[28;29] truly ushered in a new era of MM therapeutic investigations. Thus, the thalidomide analogue, lenalidomide (Revlimid)[30;30;31], and the first-in-class proteasome inhibitor, bortezomib[32], all displayed remarkable single agent activities in advanced and refractory MM, which could be further enhanced by the addition of dexamethasone[33;34], addition of immunomodulatory agents to bortezomib[35-38] and mel to immunomodulatory agents[18;19] and to bortezomib alone[39] or in combination with immunomodulatory drugs[20]. When applied in the front-line setting, high CR rates approaching those after MEL transplants were reported especially with VTD[36], more recently, when melphalan was added to Thal-Pred (MP-T) or lenalidomide in MP-R[18;19]. The V-MP regimen has recently been reported to be superior to MP[40]. Four-drug regimens, such as V-MPT, have been noted to

be even more effective[20]. However, despite its use for MM therapy over more than 4 decades, very little is know about the mechanisms of action of standard-dose mel or high-dose MEL in MM, although some data have linked resistance to mel to LRP expression by MM-cells, which could be overcome by dose escalation to MEL[41].

As the alkylating agent melphalan represents the principal component of the Total Therapy regimen, a translational research aim within the Total Therapy 5B protocol will be to study the molecular sequelae of short-term in-vivo exposure of tumor cells to low dose melphalan (10mg/$m^2$) and to correlate these results with clinical molecular features of disease, i.e. 70-gene risk, *TP53* status, molecular subtype, and responses and outcomes following induction chemotherapy and melphalan 80mg/$m^2$ followed by autologous stem cell tandem transplantation. Preliminary in-vivo and in-vitro studies support the concept that pharmacogenomic studies of melphalan exposure will provide valuable new knowledge that might be translated into the clinical management of patients with multiple myeloma.

We are therefore proposing to study, the effects of a single application of mel 10 mg/$m^2$ (which does not affect HC collection) and compare, as in the case of bortezomib in TT3 and TT5, baseline and 48-hr W-GEP signatures in order to identify mel-uniquely regulated genes and determine, as was possible in the case of DEX and THAL in TT2[42] and bortezomib in TT3 and TT5, prognostic consequences of such GEP alterations.

To accommodate the melphalan as part of the induction CFZ-TD-PACE cycle, melphalan will be given at a dose of 10mg/$m^2$ and a 48 hr W-GEP will follow.

# 3.0 ELIGIBILITY CRITERIA

## 3.1 Inclusion criteria

3.1.1 Patients must have newly diagnosed active MM requiring treatment. Patients with a previous history of smoldering myeloma will be eligible if there is evidence of progressive disease requiring chemotherapy.

3.1.2 Patients must be either untreated or have not had more than four cycles of systemic MM therapy (e.g. RD, VRD, CVD, etc.), excluding bisphosphonates and localized radiation.

3.1.3 Participants must have clinical features of high-risk disease, which may include one or more of the following:

- 3.1.3.1 High-risk cytogenetic abnormality(ies) by conventional cytogenetics or FISH
- 3.1.3.2 Presence of extramedullary disease
- 3.1.3.3 > 3 focal lesions on FDG-PET imaging
- 3.1.3.1 ISS Stage II or III with cytogenetic abnormality
- 3.1.3.5 LDH ≥ 360 U/L (Rule out hemolysis and infection; contact PI if any doubt.)
- 3.1.3.6 Primary plasma cell leukemia

3.1.4 Zubrod ≤ 2, unless solely due to symptoms of MM-related bone disease.

3.1.5 Patients must have a platelet count of ≥ 50,000/μL, unless lower levels are explained by extensive bone marrow plasmacytosis.

3.1.6 Patients must be at least 18 years of age and not older than 75 years of age at the time of registration.

3.1.7 Participants must have a baseline serum creatinine level of < 3 mg/dL and baseline Alanine Aminotransferase (ALT) < 3x Upper Limit of Normal (ULN).

3.1.8 Participants must have an ejection fraction by ECHO or MUGA scan ≥ 45%

3.1.9 Patients must have adequate pulmonary function studies ≥ 50% of predicted on mechanical aspects (FEV1, FVC, etc) and diffusion capacity (DLCO) ≥ 50% of predicted. If the patient is unable to complete pulmonary function tests due to MM related pain or condition, exception may be granted if the principal investigator documents that the patient is a candidate for high dose therapy.

3.1.10 Patients must have signed an IRB-approved informed consent indicating their understanding of the proposed treatment and understanding that the protocol has been approved by the IRB.

### 3.2 Exclusion criteria

3.2.1 Does not have high-risk disease

3.2.2 Poorly controlled hypertension; diabetes mellitus; active or uncontrolled hepatitis; or other serious medical illness; or psychiatric illness that could potentially interfere with the completion of treatment according to this protocol.

3.2.3 Patients must not have prior malignancy**,** except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer for which the patient has not received treatment for one year prior to enrollment. Other cancers will only be acceptable if the patient's life expectancy exceeds five years.

3.2.4 Pregnant or nursing women may not participate. Women of childbearing potential must have a negative pregnancy documented within one week of registration. Subjects of reproductive potential may not participate unless they have agreed to use an effective contraceptive method.

## 4.0 TREATMENT PLAN

Throughout the study treatment regimen, the investigational agent, carfilzomib, will be administered as an intravenous (IV) infusion over ≥ 10 minutes. All other agents in the treatment regimen are considered conventional care and will be administered according to institutional standards.

### 4.1 Induction Cycle with MEL-10-CFZ-TD-PACE

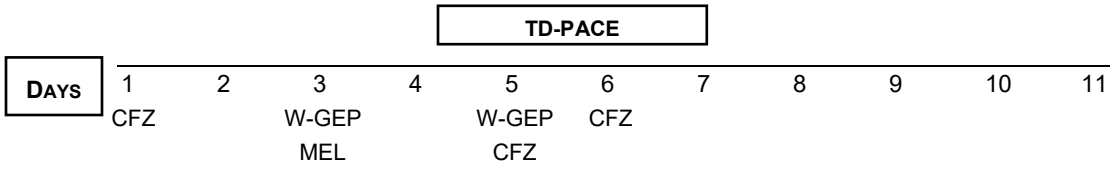
All participants will receive induction treatment with MEL 10-CFZ -TD-PACE and HC collection (goal: ≥ 30 x $10^6$ CD34/kg; minimum, 7 x $10^6$ CD34/kg):

Platelet count must be ≥ 50,000/μL un-transfused.

#### 4.1.1 Induction MEL -10-CFZ-TD-PACE Administration:

| AGENT | DOSE | ROUTE | DAYS |
|---|---|---|---|
| **C**ar**f**il**z**omib | 20 mg/$m^2$ | IV infusion | 1, 5, 6 |
| **Mel**phalan | 10 mg/$m^2$ | IV | 3 |
| **T**halidomide | 200 mg | PO | 5-8 |
| **D**examethasone | 40 mg | PO | 5-8 |
| Cis**p**latin* | 10 mg/$m^2$ | IV infusion | 5-8 |
| **A**driamycin* | 10 mg/$m^2$ | IV infusion | 5-8 |
| **C**yclophosphamide* | 400 mg/$m^2$ | IV infusion | 5-8 |
| **E**toposide* | 40 mg/$m^2$ | IV infusion | 5-8 |

For subjects with weight > 60 kg, all doses will be based on calculated body weight (actual weight + ideal body weight ÷ 2) and height, and not to exceed a BSA of 2.0 $m^2$. The daily dose of cyclophosphamide, etoposide, and cisplatin will be mixed in a 1L bag of NS for infusion. Adriamycin® will be mixed in at least 50cc normal saline.



#### 4.1.2 Peripheral Blood Stem Cell Collection

Once the subject is recovered from Induction chemotherapy, G-CSF 10 mcg/kg/day will begin on day 11 (approximately 10 days after initiation of chemotherapy) and will continue during repeated apheresis. G-CSF will be discontinued upon completion of apheresis.

PBSC collection will be initiated as soon as WBC and CD34 counts in peripheral blood are within UAMS lab's normal range. PBSC will be collected and processed according to institutional standards. These cells will be assessed by flow cytometry for the presence of CD34 for a target of ≥ 30 x $10^6$ CD34+ cells/kg (7 x $10^6$ CD34+ cells/kg minimum for tandem transplants).

PBSC will be collected upon recovery from the induction cycle with M-CFZ-TD-PACE, according to criteria established in the Apheresis Unit. The desired yield is 30 x $10^6$CD34/kg or greater, but the minimum required for 2 transplants is 7 x $10^6$CD34/kg. Re-collection is permitted with growth factors alone in case of inadequate collection or documented myeloma cell contamination exceeding 5%. If the interval between the cycle of CFZ-TD-PACE and first transplant > 3 months, patients will be removed from the study.

#### 4.1.3 DT Bridging (Optional):

4.1.3.1 Apply bridging therapy at the discretion of the treating physician. To apply DT bridging, platelets must be ≥ 50,000/µL un-transfused.

| AGENT | DOSE | ROUTE | DAYS |
|---|---|---|---|
| Thalidomide | 50 mg/day | PO | Daily |
| Dexamethasone | 20 mg/day | PO | Days 1-4 every 21days |

### 4.2 First Transplant: MEL-80-CFZ-TD-PACE

First transplant should preferably occur between 3 to 8 weeks from the 1st day of the last induction CFZ-TD-PACE, but can occur as early as 3 weeks and as late as 3 months after the Induction CFZ-TD-PACE, at the discretion of the treating physician.

#### 4.2.1 Platelet Count and Renal Function:

4.2.1.1 There is not a minimum platelet or other blood count requirement for this phase of study.

4.2.1.1 Cisplatin will be modified for renal insufficiency.

| Cisplatin dose | Creatinine |
|---|---|
| 10 mg/m$^2$ (full dose) | ≤ 1.5 mg/dL |
| 5.0 mg/m$^2$ | 1.6-2.0 mg/dL |
| 0 mg/m$^2$ (hold Cisplatin) | > 2.0 mg/dL |

4.2.1.2 Thalidomide will be modified based on peripherial neuropathy.

| Toxicity Grade | Dose delivery |
|---|---|
| 0-2 | 200 mg |
| 3-4 | 100 mg |
| 4 | 50 mg |

Treating physician has the ability to adjust Thal dose for non-hematological toxicities grade 3 and above.

4.2.1.3 Dose Adjustment for PACE:

In the unlikely event of unexpected acute toxicity traceable to any of the other drugs, the study PI will be consulted for guidance.

4.1.2.4 For subjects developing evidence of significant cardiac toxicity (arrhythmia) or cardiac failure, discontinue Adriamycin.

### 4.2.1 MEL 80-CFZ-TD-PACE Administration

The total MEL80 mg/m$^2$ will be administered in 4 successive daily fractions of 20 mg/m$^2$ (on days 1-4) along with CFZ-RD-PACE.

| AGENT | Day -5 | Day -4 | Day -3 | Day -2 | Day -1 | Day 0 |
|---|---|---|---|---|---|---|
| Melphalan | 20 mg/m$^2$ | 20 mg/m$^2$ | 20 mg/m$^2$ | 20 mg/m$^2$ | --- | --- |
| Carfilzomib | 27 mg/m$^2$ | 27 mg/m$^2$ | --- | | --- | --- |
| Thalidomide | 200 mg | 200 mg | 200 mg | 200 mg | --- | --- |
| Dexamethasone | 40 mg | 40 mg | 40 mg | 40 mg | --- | --- |
| Cisplatin | 10 mg/m$^2$ | 10 mg/m$^2$ | 10 mg/m$^2$ | 10 mg/m$^2$ | --- | --- |
| Adriamycin | 10 mg/m$^2$ | 10 mg/m$^2$ | 10 mg/m$^2$ | 10 mg/m$^2$ | --- | --- |
| Cyclophosphamide | 100 mg/m$^2$ | 100 mg/m$^2$ | 100 mg/m$^2$ | 100 mg/m$^2$ | --- | --- |
| Etoposide | 80 mg/m$^2$ | 80 mg/m$^2$ | 80 mg/m$^2$ | 80 mg/m$^2$ | --- | --- |
| PBSC Infusion | --- | --- | --- | --- | --- | **X** |

Melphalan will be diluted in normal saline for injection per Pharmacy guidelines.

The dose of melphalan will be modified based on Section 5.0 and the calculated dose reduction will be applied to all MEL doses on days 1-4.

For subjects with weight > 60 kg, all doses will be based on calculated body weight (actual weight + ideal body weight ÷ 2) and height, and not to exceed a BSA of 2.0 m$^2$. Carfilzomib will be infused over 30 (±10) minutes.

The daily dose of cyclophosphamide, etoposide, and cisplatin will be mixed in a 1L bag of NS for infusion. Adriamycin® will be mixed in at least 50cc normal saline.

### 4.2.2 Peripheral blood stem cell (PBSC) infusion

PBSC will be given intravenously on day 0, i.e., 48 hours after the last dose of melphalan. Approximately **5-6 x 10$^6$ /kg CD34 or more cells** will be infused with the 1st transplant. However, if only 7 x 10$^6$/kg CD34 cells were collected via apheresis, then minimum CD34 cells/kg infusion for second transplant is 3 x 10$^6$.

**At least 3 x 10$^6$ /kgCD34 cells will be infused with the first transplant**

### 4.2.3 DT Bridging (Optional)

4.2.1.1 Apply DT bridging therapy at the discretion of the treating phyisican. To apply DT bridging, platelets must be ≥ 50,000/µL un-transfused.

| AGENT | DOSE | ROUTE | DAYS |
|---|---|---|---|
| Thalidomide | 50 mg/day | PO | Daily |
| Dexamethasone | 20 mg/day | PO | Days 1-4 every 21days |

## 4.3 Inter-Therapy - MEL20-CFZ-TD-PACE

Inter-Therapy should preferably occur between 6 to 12 weeks from Transplant 1, but can occur earlier at the discretion of the treating physician.

#### 4.3.1 Inter-Therapy: MEL20-CFZ-TD-PACE Administration

| AGENT | DOSE | Route | Days |
|---|---|---|---|
| Melphalan | 5 mg/m$^2$ | IV | 1-4 |
| Carfilzomib | 27 mgm$^2$ | IV infusion | 1 and 2 |
| Thalidomide | 200 mg | PO | 1-4 |
| Dexamethasone | 20 mg | PO | 1-4 |
| Cisplatin | 7.5 mg/m$^2$ | IV infusion | 1-4 |
| Adriamycin | 7.5 mg/m$^2$ | IV infusion | 1-4 |
| Cyclophosphamide | 75 mg/m$^2$ | IV infusion | 1-4 |
| Etoposide | 60 mg/m$^2$ | IV infusion | 1-4 |

For subjects with weight > 60 kg, all doses will be based on calculated body weight (actual weight + ideal body weight ÷ 2) and height, and not to exceed a BSA of 2.0 m2. The daily dose of cyclophosphamide, etoposide, and cisplatin will be mixed in a 1L bag of NS for infusion. Adriamycin® will be mixed in at least 50 cc normal saline.

Melphalan will be diluted in normal saline for injection per Pharmacy guidelines.

#### 4.3.2 DT Bridging (Optional):

4.3.2.1 Apply Bridging therapy at the discretion of the treating physician. To apply DT bridging, platelets must be ≥ 50,000/µL un-transfused.

| AGENT | DOSE | ROUTE | DAYS |
|---|---|---|---|
| Thalidomide | 50 mg/day | PO | Daily |
| Dexamethasone | 20 mg/day | PO | Days 1-4 every 21days |

### 4.4 Second Transplant MEL20-CFZ-TD-PACE

#### 4.4.1 MEL80-CFZ-TD-PACE

The second cycle of high dose therapy (Mel 20 x 4 doses) plus CFZ-TD-PACE and PBSC transplant will be given as early as 6 weeks and no later than 12 weeks after Inter-Therapy, preferably between 3 to 5 months after the first transplant, irrespective of hematological recovery.

#### 4.4.2 Platelet Count and Renal Function:

4.4.2.1 There is not a minimum platelet or other blood count requirement for this phase of study

4.4.2.2 Cisplatin will be modified for renal insufficiency.

| Cisplatin dose | Creatinine |
|---|---|
| 10 mg/m$^2$ (full dose) | ≤ 1.5 mg/dL |
| 5.0 mg/m$^2$ | 1.6-2.0 mg/dL |
| 0 mg/m$^2$ (hold Cisplatin) | > 2.0 mg/dL |

4.4.2.3 Thalidomide will be modified based on peripheral neuropathy.

| Toxicity Grade | Dose delivery |
|---|---|
| 0-2 | 200 mg |
| 3-4 | 100 mg |
| 4 | 50 mg |

Treating physician has the ability to adjust Thal dose for non-hematological toxicities grade 3 and above.

4.4.2.4 Dose Adjustment for PACE:

In the unlikely event of unexpected acute toxicity traceable to any of the other drugs, the study PI will be consulted for guidance.

4.4.2.5 For subjects developing evidence of significant cardiac toxicity (arrhythmia) or cardiac failure, discontinue Adriamycin.

### 4.4.3 Transplant 2: MEL 80-CFZ-TD-PACE - Administration

The total MEL80 mg/m$^2$ will be administered in 4 successive daily fractions of 20 mg/m$^2$ (on days 1-4) along with CFZ-TD-PACE. Carfilzomib will be infused over 30 (±10) minutes.

| AGENT | Day -5 | Day -4 | Day -3 | Day -2 | Day -1 | Day 0 |
|---|---|---|---|---|---|---|
| Melphalan | 20 mg/m$^2$ | 20 mg/m$^2$ | 20 mg/m$^2$ | 20 mg/m$^2$ | --- | --- |
| Carfilzomib | 27 mgm$^2$ | 27 mgm$^2$ | --- | --- | --- | --- |
| Thalidomide | 200 mg | 200 mg | 200 mg | 200 mg | --- | --- |
| Dexamethasone | 40 mg | 40 mg | 40 mg | 40 mg | --- | --- |
| Cisplatin | 10 mg/m$^2$ | 10 mg/m$^2$ | 10 mg/m$^2$ | 10 mg/m$^2$ | --- | --- |
| Adriamycin | 10 mg/m$^2$ | 10 mg/m$^2$ | 10 mg/m$^2$ | 10 mg/m$^2$ | --- | --- |
| Cyclophosphamide | 100 mg/m$^2$ | 100 mg/m$^2$ | 100 mg/m$^2$ | 100 mg/m$^2$ | --- | --- |
| Etoposide | 80 mg/m$^2$ | 80 mg/m$^2$ | 80 mg/m$^2$ | 80 mg/m$^2$ | --- | --- |
| PBSC Infusion | --- | --- | --- | --- | --- | **X** |

Approximately **5-6 x 10$^6$ /kg CD34 or more cells** will be infused with the 2nd transplant. However, if only 7 x 10$^6$/kg CD34 cells were collected via apheresis, then minimum CD34 cells/kg infusion for second transplant is 3 x 10$^6$.

Melphalan administration, peripheral blood stem cell infusion and concomitant medications will be applied similarly as during first TT5B transplant.

The second transplant may be skipped at the discretion of the study PI. If this occurs, subjects will then proceed to consolidation therapy according to protocol schedule.

### 4.3.1 DT Bridging (Optional):

4.4.3.1 Apply Bridging at the discretion of the treating physician. To apply DT bridging, platelets must be ≥ 50,000/µL un-transfused.

| AGENT | DOSE | ROUTE | DAYS |
|---|---|---|---|
| Thalidomide | 50 mg/day | PO | Daily |
| Dexamethasone | 20 mg/day | PO | Days 1-4 every 21days |

## 4.5 Consolidation

Depending on hematologic recovery, post transplant consolidation therapy should begin 6-12 weeks after the last transplant. It can begin as early as 6 weeks after the last transplant at the treating physician's discretion, but should occur no later than 6 months after last the transplant. Consolidation for participants will consist of one cycle of CFZ-TD-PACE.

To begin CFZ-TD-PACE, platelet count should be ≥ 50,000/µL, untransfused. If platelets are < 50,000 µL, patients should proceed to maintenance. If medically necessary, patients may skip consolidation and proceed to maintenance at the treating physician's discretion.

Patients will receive Carflizomib on days 1 and 2, and TD-PACE on days 1-4.

| AGENT | DOSE | ROUTE | DAYS |
|---|---|---|---|
| Carfilzomib | 27 mg/m$^2$ | IV infusion | 1 and 2 |
| Thalidomide | 200 mg | PO | 1-4 |
| Dexamethasone | 40 mg | PO | 1-4 |
| Cisplatin | 7.5 mg/m$^2$ | IV infusion | 1-4 |
| Adriamycin | 7.5 mg/m$^2$ | IV infusion | 1-4 |
| Cyclophosphamide | 300 mg/m$^2$ | IV infusion | 1-4 |
| Etoposide | 30 mg/m$^2$ | IV infusion | 1-4 |

For patients with weight > 60 kg, all doses will be based on calculated body weight (actual weight + ideal body weight ÷ 2) and height, and not to exceed a BSA of 2.0 m$^2$. The daily dose of cyclophosphamide, etoposide, and cisplatin will be mixed in a 1L bag of NS for infusion. Adriamycin® will be mixed in at least 50cc normal saline.

If medically necessary and if a patient has sufficient stem cells in storage, a boost of stem cells can be given at any point in the consolidation phase. Boosts should be discussed with the Principal Investigator.

## 4.6 Maintenance

### 4.6.1 Cycles 1-12: CRD

Maintenance should preferably occur between 4-12 weeks post-transplant consolidation, but can occur earlier at the discretion of the treating physician.

Participants will receive CRD cycles every 28 days for cycles 1-12. At the treating physician's discretion, Thalidomide may be used in place of Revlimid*. At the discretion of the treating physician, carfilzomib, Revlimid (or Thalidomide) may have increased dose levels (see dose modifications section 5.0 for details).

| CYCLE | CRD 1 | CRD 2 | CRD 3 | CRD 4 | CRD 5 | CRD 6 | CRD 7 | CRD 8 | CRD 9 | CRD 10 | CRD 11 | CRD 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

CRD:

| AGENT | DOSE | ROUTE | DAYS | INTERVAL |
|---|---|---|---|---|
| Carfilzomib | 27 mg/m$^2$/week | IV infusion | Days 1, 8, 15, 22 (±1 day) | Every 28 days |
| Revlimid® | 15 mg/d | PO | 1-21 | Every 28 days |
| Dexamethasone | 12 mg/day | PO | Days 1, 8, 15, 22 (±1 day) | Every 28 days |
| *If Thalidomide | 100 mg/d | PO | daily | continuous |

### 4.6.2 Cycles 13-24: CD

Participants will receive CD cycles every 28 days for cycles 13-24.

| CYCLE | CD 13 | CD 14 | CD 15 | CD 16 | CD 17 | CD 18 | CD 19 | CD 20 | CD 21 | CD 22 | CD 23 | CD 24 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

CD:

| AGENT | DOSE | ROUTE | DAYS | INTERVAL |
|---|---|---|---|---|
| Carfilzomib | 27 mg/m$^2$/week | IV infusion | Days 1, 8, 15, 22 (±1 day) | Every 28 days |
| Dexamethasone | 12 mg/day | PO | Days 1, 8, 15, 22 (±1 day) | Every 28 days |

#### 4.6.3 Maintenance Treatment by Local Physicians

With the agreement of the study PI and the approval by the UAMS IRB, the subject may receive carfilzomib from their local physician if the subject is unable to return to study clinic to receive carfilzomib at scheduled intervals. The investigational drug will be shipped to the local physician by Onyx Pharmaceuticals.

After the subject completes the Pre-Maintenance testing and physician visit, the research nurse will ensure the local physician has orders and instructions for maintenance administration. The local physician will be instructed to inform MIRT on any new changes or adverse events during treatment at home. Data to be collected by MIRT Staff (CRN / CRA) prior to each cycle.

## 5.0 DOSAGE MODIFICATIONS

Subjects will be evaluated for adverse events according to the National Cancer Institute Common Terminology for Adverse Events, version 4.0 (CTCAE). All subjects who are discontinued due to an adverse event should be followed for as long as necessary to document the resolution or stabilization of the event.

All protocol treatments may be delayed or held at the treating physician's discretion if the patient's safety is considered at risk.

### 5.1 Induction - CFZ-TD-PACE

5.1.1 Modifications during Induction

5.1.1.1 Dose modifications will not be made unless there is renal dysfunction

5.1.1.2 Platelet count must be ≥ 50,000 µL un-transfused.

5.1.1.3 Dose Adjustments for PACE:

5.1.1.3.1 PACE should not be modified (except for renal dysfunction, see below).

5.1.1.3.2 However, Adriamycin will be discontinued in subjects developing evidence of significant cardiac toxicity (arrhythmia) or cardiac failure.

5.1.1.3.3 At the treating physician's discretion, in the case of profound neutropenia or thrombocytopenia, PACE chemotherapy may reduced up to 50%.

5.1.1.3.4 Cisplatin Dose Adjustments for renal function:

| Cisplatin dose | Creatinine |
|---|---|
| 10 mg/m$^2$ (full dose) | ≤ 1.5 mg/dL |
| 5.0 mg/m$^2$ | 1.6-2.0 mg/dL |
| 0 mg/m$^2$ (hold Cisplatin) | > 2.0 mg/dL |

Subsequently, the dose of cisplatin may be raised if the renal function improves.

5.1.1.4 Dexamethasone during Induction:

If life-threatening upper GI bleeding occurs or if severe diabetes mellitus develops and serum glucose is difficult to control despite treatment with insulin, dexamethasone must be discontinued or at the discretion of the treating physician, the subject may be withdrawn from the study.

5.1.1.5 Carflizomib (CFZ) during Induction:

Subjects experiencing carfilzomib related ≥ Grade 3 non-hematologic will have their dose held/further administration suspended until after further evaluation by the treating physician. CFZmay be re-introduced at the PI's discretion.

| **Carfilzomib Dose Reductions for Toxicity** | | | |
|---|---|---|---|
| **Drug** | **Full Dose** | **Level -1** | **Level -2** |
| Carfilzomib | 20 mg/m$^2$ | 15 mg/m$^2$ | Discontinue during Induction |

## 5.2 Transplant

5.2.1 Modifications during Transplant:

5.2.1.1 There is no minimum platelet or other blood count requirement for this phase of the study.

5.2.1.2 Melphalan during Transplant:

5.2.1.2.1 The total dose of melphalan will be modified to 60 mg/m2 for subjects aged ≥ 70 years, and those with a serum creatinine of ≥ 3.0 mg/dL. Melphalan may also be reduced at the discretion of the treating physician due to poor performance status, or in the case of second transplant, where significant toxicities were experienced during first transplant.

5.2.1.2.2 Melphalan may also be reduced at the discretion of the treating physician due to poor performance status, or in the case of second transplant, where significant toxicities were experienced during first transplant.

5.2.1.3 Carfilzomib during Transplant:

5.2.1.3.1 Subjects experiencing carfilzomib related ≥ Grade 3 non-hematologic or Grade 4 hematologic toxicity will have their dose held until toxicity has resolved to Grade 2 or better, and then will have their dose reduced one level from previous dose received. Once the toxicity has resolved, the drug(s) can be restarted at dose Level -1 or -2.

| Transplant Carfilzomib Dose Reductions for Toxicity | | | | |
|---|---|---|---|---|
| **Drug** | **Full Dose** | **Level -1** | **Level -2** | **Level -3** |
| Carfilzomib | 27mg/m$^2$ | 20 mg/m$^2$ | 15 mg/m$^2$ | Discontinue |

5.2.1.4 PACE

5.2.1.4.1 In the unlikely event of unexpected acute toxicity traceable to any of the other drugs, the study PI will be consulted for guidance.

5.2.1.4.2 At the treating physician's discretion, in the case of profound neutropenia or thrombocytopenia, PACE chemotherapy may be reduced up to 50%.

| Cisplatin dose | Creatinine |
|---|---|
| 10 mg/m$^2$ (full dose) | ≤ 1.5 mg/dL |
| 5.0 mg/m$^2$ | 1.6-2.0 mg/dL |
| 0 mg/m$^2$ (hold Cisplatin) | > 2.0 mg/dL |

Subsequently, the dose of cisplatin may be raised if the renal function improves.

## 5.3 Inter-Therapy

5.3.1 Modifications during Inter-Therapy:

5.3.1.1 Melphalan during Inter-Therapy:

5.3.1.1.1 Melphalan Dose Modification: Melphalan will not be modified during interim therapy. If significant toxicity occurs, discuss with principal investigator.

5.3.1.2 Dexamethasone during Inter-Therapy:

5.3.1.2.1 If life-threatening GI bleeding occurs or if severe diabetes develops despite treatment with insulin, dexamethasone must be discontinued. Some subjects may benefit from added carafate therapy, 1 gm, QID. Diuretics, tranquilizers, and increased insulin may be required in some subjects. Dose reductions (to 12 mg) are allowable if other side effects persist despite supportive care medications.

5.3.1.3 CFZ-TD-PACE Modifications during Inter-Therapy:

5.3.1.3.1 Carfilzomib dosing will be adjusted according to toxicity experienced during previous portions of the protocol, mainly concerning neuropathy, deemed to be attributable to carfilzomib. Subjects experiencing carfilzomib related ≥ Grade 3 non-hematologic or Grade 4 hematologic toxicity will have their dose held until toxicity has resolved to Grade 2 or better, and then will have their dose reduced one level from previous dose received. Once the toxicity has resolved, the drug(s) can be restarted at dose Level -1 or -2.

5.3.1.3.2 Thalidomide dosing will be adjusted according to peripheral neuropathy deemed to be attributable to thalidomide.

5.3.1.3.3 Subjects experiencing carfilzomib and/or thalidomide related ≥ Grade 3 non-hematologic or Grade 4 hematologic toxicity will have subsequent doses suspended, at the discretion of the PI.

5.3.1.3.4 Cisplatin will be adjusted according to renal function.

| Cisplatin dose | Creatinine |
|---|---|
| 7.5 mg/m$^2$ (full dose) | ≤ 1.5 mg/dL |
| 3.75 mg/m$^2$ | 1.6-2.0 mg/dL |
| 0 mg/m$^2$ (hold Cisplatin) | > 2.0 mg/dL |

5.3.1.3.5 For subjects developing evidence of significant cardiac toxicity (arrhythmia) or cardiac failure, discontinue Adriamycin.

5.3.1.3.6 Cyclophosphamide, Adriamycin and Etoposide doses should not be modified during Inter-Therapy.

5.3.1.3.7 At the treating physician's discretion, in the case of profound neutropenia or thrombocytopenia, PACE chemotherapy may be reduced up to 50%.

| **Inter-Therapy Carfilzomib and Thalidomide Dose Reductions for Toxicity** | | | | |
|---|---|---|---|---|
| **Drug** | **Full Dose** | **Level -1** | **Level -2** | **Level -3** |
| Carfilzomib | 27 mg/m$^2$ | 20 mg/m$^2$ | 15 mg/m$^2$ | Discontinue |
| Thalidomide | 200 mg | 100 mg | 50 mg | Discontinue |

## 5.4 Consolidation

5.4.1 Modifications during Consolidation:

5.4.1.1 Dose modifications will not be made unless there is renal dysfunction.

5.4.1.2 Platelet count must be > 50,000 µL un-transfused.

5.4.1.3 Dose Adjustments for PACE:

5.4.1.3.1 PACE should not be modified (except for renal dysfunction, see below).

5.4.1.3.2 However, Adriamycin will be discontinued in subjects developing evidence of significant cardiac toxicity (arrhythmia) or cardiac failure.

5.4.1.3.3 At the treating physician's discretion, in the case of profound neutropenia or thrombocytopenia, PACE chemotherapy may reduced up to 50%.

5.4.1.3.4 Cisplatin Dose Adjustments for renal function.

| Cisplatin dose | Creatinine |
|---|---|
| 7.5 mg/m$^2$ (full dose) | ≤ 1.5 mg/dL |
| 3.75 mg/m$^2$ | 1.6-2.0 mg/dL |
| 0 mg/m$^2$ (hold Cisplatin) | > 2.0 mg/dL |

Subsequently, the dose of cisplatin may be raised if the renal function improves.

5.4.1.4 Carfilzomib and Thalidomide during Consolidation:

Subjects experiencing carfilzomib related ≥ Grade 3 non-hematologic will have their dose held/further administration suspended until after further evaluation by the treating physician. CFZ may be re-introduced at the PI's discretion.

Thalidomide dosing will be adjusted according to peripheral neuropathy deemed to be attributable to thalidomide. Treating physician has the ability to adjust Thal dose for non-hematological toxicities grade 3 and above.

| Carfilzomib Dose Reductions for Toxicity | | | | |
|---|---|---|---|---|
| **Drug** | **Full Dose** | **Level -1** | **Level -2** | **Level -3** |
| Carfilzomib | 27 mg/m$^2$ | 20 mg/m$^2$ | 15 mg/m$^2$ | Discontinue during Consolidation |
| Thalidomide | 200 mg | 100 mg | 50 mg | Discontinue |

5.4.1.5 Dexamethasone during Consolidation:

If life-threatening upper GI bleeding occurs or if severe diabetes mellitus develops and serum glucose is difficult to control despite treatment with insulin, dexamethasone must be discontinued or at the discretion of the treating physician, the subject may be withdrawn from the study.

## 5.5 Maintenance

Subjects will be evaluated for possible toxicities that may have occurred with the previous dose(s). Toxicities are to be assessed according to the NCI Common Terminology for Adverse Events (CTCAE), Version 4.0.

5.5.1 CRD/CD - Maintenance Dose Modifications:

At the discretion of the treating physician, dose reduction for each drug (Revlimid®, Carfilzomib or Dexamethasone) can be done separately based on best judgment of which drug was most likely to have caused the toxicity.

At the discretion of the treating physician, dose escalation is allowed for carfilzomib, Revlimid (or Thalidomide). See table below.

5.5.1.1 Carfilzomib during Maintenance:

5.5.1.1.1 Subjects experiencing carfilzomib related ≥ Grade 3 non-hematologic or Grade 4 hematological toxicity will have their dose held until toxicity has resolved to Grade 2 or better, and then will have their dose reduced one level from previous dose received.

5.5.1.1.2 Carfilzomib for Renal Insufficiency:

Carfilzomib dosing will be adjusted for renal impairment [serum creatinine ≥ 2 x baseline or CrCl < 15 mL/min (or ≤ 50% of baseline or need for hemodialysis)] as follows:

- Withold dose and continue monitoring renal function (serum creatinine or CrCl);
  - If attributable to carfilzomib, resume dosing when renal function has recovered to within 25% of baseline; start at 1 dose level reduction;
  - If not attributable to carfilzomib, dosing may be resumed at the discretion of the physician;
- For patients on hemodialysis receiving carfilzomib, the dose is to be administered after the hemodialysis procedure.

| Carfilzomib Dose Reductions for Toxicity | | | | |
|---|---|---|---|---|
| **Drug** | **Full Dose** | **Level -1** | **Level -2** | **Level -3** |
| Carfilzomib | 27 mg/m$^2$ | 20 mg/m$^2$ | 15 mg/m$^2$ | Discontinue |

5.5.1.2 Revlimid® during Maintenance:

5.5.1.2.1 As a guideline, Revlimid® will most likely to contribute to any cytopenias. Grade 4 hematologic toxicity will have their dose held until toxicity has resolved to Grade 2 or better, and then will have their dose reduced one level from previous dose received.

5.5.1.2.3 Revlimid® for Renal Insufficiency:

| GFR mL/mn | Dose delivery |
|---|---|
| > 60 | 15 mg days 1-21 |
| 25-59 | 10 mg |
| < 25 | 5 mg |
| < 25 and dialysis | 0 |

5.5.1.3 Dexamethasone during Maintenance:

If life-threatening upper GI bleeding occurs or if severe diabetes mellitus develops and serum glucose is difficult to controldespite treatment with insulin, dexamethasone must be discontinued or at the discretion of the treating physician, the subject may be withdrawn.

| Carfilzomib, Lenalidomide and Dexamethasone Dose Reductions for Toxicity During Maintenance | | | | | |
|---|---|---|---|---|---|
| **Drug** | **Level + 1** | **Full Dose** | **Level -1** | **Level -2** | **Level -3** |
| Carfilzomib | | 27 mg/m$^2$/wk | 20 mg/m$^2$/wk | 15 mg/ m$^2$/wk | Discontinue |
| Revlimid® | 25 mg/day | 15 mg/day | 10 mg/day | 5 mg/day | Discontinue |
| Thalidomide* | 200g mg/day | 100 mg/day | 50 mg/day | 50 mg/ every other day | Discontinue |
| Dexamethasone | -- | 12 mg/weekly | 8 mg/weekly | 4 mg weekly | Discontinue |

Revlimid may be continued for up to 24 cycles. At the treating physician's discretion, Thalidomide may be substituted for Revlimid (see above)*. Subjects experiencing Thalidomide related ≥ Grade 3 non-hematologic or Grade 4 hematologic toxicity will have their dose held until toxicity has resolved to Grade 2 or better.

Subjects may continue on study as long as 2 of the 3 study drugs per cycle are administered during maintenance treatment. Dexamethasone only is not allowed. Subjects experiencing carfilzomib related ≥ Grade 3 non-hematologic or Grade 4 hematologic toxicity will have their dose held until toxicity has resolved to Grade 2 or better, and then will have their dose reduced one level from previous dose received. Once the toxicity has resolved, the drug(s) can be restarted at dose Level -1 or -2.

# 6.0 SCHEDULE OF EVALUATIONS

## 6.1 Laboratory Tests & Evaluations

**Note: Prestudy tests do not need to be repeated prior to cycle 1 Induction, as long as they were performed within 35 days prior to enrollment.**

| | Pre-study | Induction | Transplant | Inter-Therapy | Consolidation | Maintenance: Cycles 1-12 | Maintenance: Cycles 13-24 | Progressive Disease |
|---|---|---|---|---|---|---|---|---|
| **PHYSICAL ASSESSMENTS** | | | | | | | | |
| H&P[1] | X | --- | --- | | | --- | --- | |
| PE and Toxicity Evaluation | X | Prior to Induction | Prior to Transplant 1 and 2 | Prior to Inter-Therapy | Prior to Consolidation | Prior to Maint cycle 1 | Prior to Maint cycle 13 | |
| **LABORATORY** | | | | | | | | |
| CBC with differential[2] | X | Prior to Induction and weekly until blood counts recover | Prior to transplant 1 and 2; also during hematologic recovery | Prior to Inter-therapy and weekly until blood counts recover | Prior to Consolidation and weekly until blood counts recover | Every cycle | Every cycle | |
| Basic Metabolic Panel (BMP), Liver Function Tests (LFTs), BNP, Uric Acid, Albumin and CRP[2] | X | Prior to Induction | Prior to Transplant 1 and 2 | Prior to Inter-Therapy | Prior to Consolidation | Every cycle | Every cycle | |
| Pregnancy Test (WOCBP only)[6] | X | Monthly[3] | Prior to Transplant 1 and 2 | Monthly[3] | Prior to Consolidation | Every cycle[3] | Every cycle[3] | |
| Serum Protein Electrophoresis | X | Prior to Induction | Prior to Transplant 1 and 2 | --- | Prior to Consolidation | Baseline, then every 3 cycles (±1 cycle) | Every 6 cycles (±1 cycle) | |
| Serum Quantitative Immunoglobulins | X | Prior to Induction | Prior to Transplant 1 and 2 | --- | Prior to Consolidation | Baseline, then every 3 cycles (±1 cycle) | Every 6 cycles (±1 cycle) | |
| 24 hour urine for total protein & electrophoresis | X | Prior to Induction | Prior to Transplant 1 and 2 | --- | Prior to Consolidation | Baseline, then every 3 cycles (±1 cycle) | Every 6 cycles (±1 cycle) | |
| FREELITES | X | Prior to Induction if measurable at baseline | Prior to Transplant 1 and 2 | --- | Prior to Consolidation | Baseline, then every 3 cycles (±1 cycle) | Every 6 cycles (±1 cycle) | |
| Serum IFE and/or Urine[5] | X | Prior to Induction | Prior to Transplant 1 and 2 | --- | Prior to Consolidation | Baseline, then every 3 cycles (±1 cycle) | Every 6 cycles (±1 cycle) | |
| Beta-2-Microglobulin | X | Prior to Induction | Prior to Transplant 1 and 2 | Prior to Inter-Therapy | Prior to Consolidation | Baseline, then every 3 cycles (±1 cycle) | Every 6 cycles (±1 cycle) | |
| TSH | X | | --- | --- | Prior to Consolidation | Baseline, then every 6 cycles (±1 cycle) | Every 6 cycles (±1 cycle) | ± |
| REMS® | | | | | | X | | |
| S.T.E.P.S® | X | | | | | | | |
| **BONE MARROW** | | | | | | | | |
| Bone Marrow Aspirate & Biopsy[4] | X | X | X | --- | --- | Prior to cycle 1 | Prior to Maint. cycle 13 (±1 cycle) | X |
| Optional Bone Marrow GEP[4] for biology studies Section 10.0 | X | 48hr post MEL and CFZ (W-GEP | Prior to transplant 1 and 2 (W-GEP) | --- | --- | Prior to cycle1 (W-GEP) | Prior to Maint. cycle 13 (±1 cycle) (W-GEP) | W-GEP |

1. H&P to include detailed medical and treatment history, weight, height, BSA, and Performance Status
   Minimum requirements per protocol; other tests should be performed as needed, as part of standard clinical care.
2. BMP includes Na, K, Cl, CO2, BUN, Cr, and Ca; LFTs include bilirubin, SGOT, SGPT, Alkaline phosphatase, and LDH.
3. WOCBP must have a documented negative serum or urine pregnancy test (sensitivity of at least 50 mIU/mL). Female participant of child-bearing potential has agreed to a method of contraception for the duration of the study. Females of childbearing potential must adhere to the scheduled pregnancy testing as required in the Revlimid REMS® program.Male participant has agreed to use a barrier method of contraception if sexually active with a female of child-bearing potential.
4. BM Aspirate & Biopsy for pathology, plasma cell labeling index, DNA cIg. See Section 10.0 for W-GEP, aCGH, miRNA, SNP studies and timepoints.
5. Upon disappearance of the Urine M and as determined by institution's clinical lab.
6. One week prior to enrollment.

## 6.2 Radio-Imaging Studies to be Performed While On Study

| | Pre-study | Induction | Transplant | Inter-Therapy | Consolidation | Maintenance: Cycles 1-12 | Maintenance: Cycles 13-24 | Progressive Disease |
|---|---|---|---|---|---|---|---|---|
| Metastatic Bone Survey | X* if not performed within past 3 months | --- | --- | --- | --- | --- | --- | --- |
| Bone Densitometry[1] | X | --- | --- | --- | --- | --- | --- | --- |
| MRI (axial bone marrow, shoulder & sternum)[3] | X | --- | Prior to Transplant 1[3] (if abnormalities at baseline) | --- | Prior to Consolidation | Every 6 cycles[3] | Annually[3] | X |
| FDG-PET *Not mandatory, but strongly suggested | X | Prior to Induction | Prior to Transplant 1 | --- | Prior to Consolidation | Every 6 cycles | As Clinically Indicated | X |
| CT-guided FNA from MRI focal lesion[2] (after baseline: as clinically indicated) | X | --- | Prior to Transplant 1 | --- | Prior to Consolidation | As Clinically Indicated | As Clinically Indicated | If Clinically Indicated |
| Echo or MUGA | X | --- | Prior to Transplant 1 and 2 | As Clinically Indicated | As Clinically Indicated | As Clinically Indicated | As Clinically Indicated | As Clinically Indicated |
| PFTs with DLCO | X | --- | As Clinically Indicated | As Clinically Indicated | As Clinically Indicated | As Clinically Indicated | As Clinically Indicated | As Clinically Indicated |

1. Bone densitometry recommended annually, but not mandatory.
2. As Clinically Indicated: CT-guided FNA will be performed on subjects with any biopsiable focal lesions identified by MRI. Baseline is not mandatory, but strongly suggested for consenting participants.
3. MRI's after baseline are to be performed on regions of the body where clinically indicated.

# 7.0 ADVERSE EVENT REPORTING

## 7.1 Definitions

### 7.1.1. Adverse Event

An adverse event (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as AEs. Abnormal results of diagnostic procedures are considered to be AEs if the abnormality:

- results in study withdrawal
- is associated with a serious AE
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

### 7.1.2. Serious Adverse Event (SAE):

An event is “serious” if it involves considerable detriment or harm to one or more persons (who may or may not be participants), or required intervention to prevent one or more persons from experiencing considerable detriment or harm. SAEs include:

- Death
- Life-threatening experience - Disease or condition where the likelihood of death is high unless the course of the disease/condition is interrupted or diseases/conditions with potentially fatal outcomes where the end point of the clinical trial analysis is survival
- Inpatient hospitalization or prolongation of hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in participant’s offspring
- Any other important medical event that, based upon appropriate medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, the development of drug dependency or drug abuse, suicidal ideation or attempts, or the unintentional revealing of some genetic information to insurers.

### 7.1.3. Related:

An event is “related” if more likely than not it was caused by the research activity.

### 7.1.4. Unexpected:

An event is “unexpected” when its specificity, nature, severity or incidence is not accurately reflected in the consent form, protocol, or investigator’s brochure previously reviewed and approved by the IRB. Examples include a lower rate of response to treatment or a side effect that is more severe that initially expected.

### 7.1.5. Study Period

All Adverse Events (AE) will be recorded by the Investigator from the time of the start of study drug through the end of the designated follow-up period. All AEs will be recorded within the research database. All relevant historical medical conditions that are known/diagnosed prior to the administration of study drug(s) are to be recorded.

### 7.1.6. Abnormal Laboratory Values Defined as AEs

An abnormal laboratory value is considered to be an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Requires treatment, modification of study drug dose, or any other therapeutic intervention
- Is judged by the Investigator to be of significant clinical impact/importance
- Grade 3 or Grade 4 lab abnormalities regardless of significance

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded as an AE. If the laboratory abnormality was not a part of a diagnosis or syndrome, then the abnormality should be recorded as the AE.

#### 7.1.6 Unanticipated Adverse Device Effects (UADE)

An unanticipated adverse device effect is defined as “any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.”

## 7.2 Monitoring, Recording and Reporting of AEs

All AEs occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. SAEs that are still ongoing at the end of the study period must be followed up for up to 30 days to determine the final outcome. Any SAE that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

All subjects will be monitored for AE's during the study. Assessments may include monitoring the patient's clinical symptoms; laboratory, pathological, radiological, or surgical findings; physical examination; or other appropriate tests and procedures.

AE data collection and reporting, which are required as part of every study, are done to ensure the safety of subjects enrolled in the studies and those who will enroll in future protocols. AEs are to be reported in a routine fashion at scheduled times during the trial, such as with the annual reports to the IRB. Certain AEs must be reported in an expedited fashion to allow for more timely monitoring of subject safety and care. The reporting of these events depends on the characteristics of the event:

1 Seriousness (grading of event)
2 Relatedness to study therapy
3 Expectedness

Steps to Determine if the Event Requires Expedited Reporting

1. Identify the type of event using NCI CTCAE version 4.0
2. Grade the event using NCI CTCAE version 4.0
3. Determine whether the adverse event is related to the protocol therapy (investigational or commercial). Attribution categories are as follows:
   - Unrelated
   - Unlikely
   - Possible
   - Probable
   - Definite
4. Determine expectedness of event. Expected events are those previously identified resulting from administration of the agent.

An adverse event is considered unexpected when the type or severity of the event is **not** listed in:

- The investigator’s brochure or drug package insert (commercial drug)
- Consent form

Note: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event occurring more than 30 days after the last dose that is possible, probably, or definitely attributable to the agent(s) must be reported according to the instructions above.

### 7.3 Expedited Reporting of SAEs

Only adverse events meeting the UPIRTSO (Unanticipated Problem Involving Risks to Subjects or Others) will need to be reported to the UAMS IRB within the required 10 day allotment of being notified of the event.. UPIRTSO requires that an unanticipated problem meet the following qualifications: a) unanticipated or unexpected; b) related to the research; and c) involves new or increased risk to the subject(s). All other adverse events should be recorded and reported to the UAMS IRB at continuing review.

The Sponsor will be promptly notified of all SAEs that are related to the study and unanticipated/unexpected . These SAEs will be reported to the Sponsor using the FDA Medwatch 3500A.

If an unanticipated adverse device effect (UADE) occurs, the Sponsor will be notified as soon as possible, no later than 10 working days after learning of such an event, using the FDA Medwatch 3500A form.

The Sponsor will report events to FDA in accordance with 21CFR312 and 812.

All other SAEs will be reported to the Sponsor and FDA in the Annual Progress Report

**Deaths that are Related to research will be reported to the Sponsor immediately** upon Investigator notification. A death due to a terminal condition of the research participant would be considered anticipated and not related to the research and therefore not immediately reportable under this policy.

The table below summarizes Expedited Reporting requirements. All other events are compiled and submitted annually to the Institutional Review Board.

| Attribution (Relatedness) | Grade 4 | | Grade 5* | |
|---|---|---|---|---|
| | Unexpected | Expected | Unexpected | Expected |
| Unrelated or Unlikely | | | REPORT | REPORT |
| Possible, Probable, Definite | REPORT | | REPORT | REPORT |

*REPORT: Indicates an expedited report is to be submitted within 10 working days of learning of the event.*
** This includes all deaths within 30 days of the last dose of treatment regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment and is attributable and is not due to cancer recurrence must be reported according to the instructions above.*

**THE SPONSOR WILL REPORT DEATHS TO FDA IN ACCORDANCE WITH 21 CFR 312 AND 812.**

## 8.0 ETHICAL AND REGULATORY CONSIDERATIONS

### 8.1 Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol 46, No. 17, January 27, 1981, part 21CFR50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45CFR46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

### 8.2 Institutional Review

This study must be approved by the UAMS Institutional Review Board, as defined by Federal Regulatory Guidelines (Ref Federal Register Vol. 46, No. 17, January 27, 1981, part 21CFR56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

The Investigator will be responsible for preparing documents for submission to the relevant IRB and obtaining written approval for this study. The approval will be obtained prior to the initiation of the study.

Any modifications/amendments to the protocol after receipt of IRB approval must be submitted by the Investigator to the IRB for approval. The Investigator is also responsible for notifying the IRB of any serious deviations form the protocol, or anything that may involve added risk to study subjects.

### 8.3 Subject Confidentiality

MIRT affirms the subject's right to protection against invasion of privacy. In compliance with United States Federal regulations, representatives of the FDA, NCI and other regulatory authorities may review medical records and copy relevant research records in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject's statement of informed consent, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

### 8.4 Investigator Responsibilities

Investigator responsibilities are set out in the ICH guideline for Good Clinical Practice and the Code of Federal Regulations, 21CFR312 and §812.

The Investigator will permit IRB review and regulatory inspection(s) (e.g. FDA), providing direct access to the facilities where the study took place, source documents and all other study documents.

The Investigator or a designated member of the Investigator's staff must be available at some time during auditing visits to review data and resolve any queries and to allow direct access to the subject's records (e.g. medical records, office charts, hospital charts, and study related charts) for source data verification. All study documents must be made available to the auditing representative so that the accuracy and completeness of study documents may be confirmed.

### 8.5 Protocol Amendments

If modification of the protocol is necessary, the modification must be confirmed in writing, and the Sponsor will inform the FDA in accordance with 21CFR 312 and 812; the Investigator will inform the IRB. Amendments that are administrative in nature do not require IRB approval but will be submitted to the IRB for information.

### 8.6 Suspension of Study

If conditions arise requiring further clarification before the decision to proceed with or terminate the study can be reached, the study will be suspended until the situation has been resolved.

### 8.7 Protocol Deviations

When an emergency occurs that requires a deviation from the protocol for a study subject, a deviation will be made only for that subject. The Principal Investigator or other physician in attendance in such an emergency will, if circumstances and time permit, contact the Sponsor and IRB immediately by telephone. If time does not allow for this, the Investigator will notify the Sponsor and IRB no later than 5 working days of the deviation in writing.

Such contacts will be made as soon as possible to determine whether or not the subject (for whom the deviation from protocol was effected) is to continue in the study. The subjects' medical and/or research record will completely describe the deviation from the protocol and state the reasons for such deviation.

## 9.0 STATISTICAL CONSIDERATIONS

This is a phase II clinical trial with the objective to assess efficacy and safety of this treatment strategy for high-risk myeloma subjects. All subjects meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for response.

## 9.1 Definition of Success

An evaluable patient will be classified a treatment success of the primary endpoint if the patient is in sustained CR at two years after initiation of therapy. The rate of sustained CR at two years will be evaluated as the ratio of the number of evaluable subjects in sustained CR at two years and the total number of evaluable subjects registered to the trial.

## 9.2 Accrual and Study duration

Based on TT5 we anticipate an accrual rate of approximately fourteen eligible subjects per year. Thus 45 subjects will be accrued in approximately 3.2 years. The primary endpoint will be assessed after all subjects have been accrued and followed for an additional two years, approximately 5.2 years after opening of the study.

## 9.3 Sample Size and Power

For TT3 high risk subjects the sustained CR rate at two years is approximately 40%. This phase II design will be used to test the hypothesis that the true success rate is at most 40% versus the alternative that the true success rate is 60% or larger. If 24 successes are observed in the 45 evaluable subjects, this will be considered adequate evidence of promising activity and the treatment strategy will be recommended for further testing in subsequent studies. If 23 or less successes are observed in all 45 evaluable subjects, we will consider this treatment strategy insufficiently active in this patient population. Assuming the number of successes is binomially distributed, this design has a one-sided alpha of 0.05 and a power of 86% to detect a true success probability of at least 60% versus the null hypothesis success rate of 40% or less.

## 9.4 Toxicity

Toxicity and accrual monitoring is done routinely by the principal investigator and the study statistician. In addition, the maximum grade for each type of toxicity, regardless of causality will be recorded and reported for each patient and frequency tables will be reviewed to determine toxicity patterns.

All Total Therapy studies will have their data reviewed by a DSMB committee at regularly scheduled sessions. The decision of the DSMB will be reported to the UAMS IRB.

## 9.5 Secondary Endpoints

For the various endpoints based on GEP or microRNA we will use the following statistical methods. When comparing the gene expression of two groups, such as the RS-PC and FL-PC, the RS-BX and the FL-BX groups or GEP at two different time points, univariate differential analysis will be used to select the genes with the largest differential expression. To adjust for multiple comparisons the false discovery rate will be determined for each gene and only genes with a significant false discovery rate q-value will be used in further analyses. Hierarchical clustering will be used on those selected genes to determine how the subjects and genes group. To determine survival differences between different groups differentiated by GEP multivariate Cox regression analysis will be used. When developing a prognostic model based on GEP appropriate validation methods such as the 10-fold cross-validation will be employed.

The array Comparative Genomic Hybridization (aCGH) data will be normalized using a Lowess algorithm. The normalized data will be analyzed following the same procedures described above for the GEP data.

The data for the proteomics analysis will entail analyzing the abundance of approximately 2000 to 3000 proteins. After background subtraction of the proteins generally found in human tissue the same statistical methods used for the GEP data will be used to identify specific proteins.

We will identify SNPs form germline DNA that correlate to toxicity to agents utilized in TT5. We will use Fisher's Exact test as a univariate screening tool to identify the SNPs most highly correlated with the toxicity of interest. We will then use those SNPs in a recursive partitioning algorithm to identify with combination of SNPs best distinguishes patient groups with and without the toxicity of interest. Those

SNPs together with clinical standard prognostic factors will be used in a multivariate analysis. We will use appropriate validation methods, such as utilizing a training and a validation set randomly chosen from the entire data set.

OS and EFS will be assessed using the method of Kaplan and Meyer.

# 10.0 ANCILLARY STUDIES

## 10.1 Molecular studies of CD138-purified MM plasma cells (PC) and BM biopsies

Bone marrow aspirates and biopsies for whole genome expression profiling (W-GEP), aCGH, miRNA, SNP, and proteomics profiling will be performed in a selected group of subjects providing informed consent. Based on the requirement of obtaining at least 3 million plasma cells, approximately 50 ccs of bone marrow aspirate will be collected in a EDTA syringe and sent to Myeloma Health Lab and MIRT research lab for W-GEP studies. If there are insufficient plasma cells in the sample to perform gene array, an additional bone marrow pull and bone marrow biopsy may be requested. The sample should be clearly labeled “for separation for GEP, UARK 2012-02”. Samples will be collected at the following time points:

- 48-hours post 1st carfilzomib dose during Induction
- 48-hours post 1st melphalan dose during Induction
- Pre-transplant 1
- Pre-transplant 2
- Pre-Maintenance cycle 1
- Pre-Maintenance cycle 13
- Progressive Disease (PD)

## 10.2 Single Nucleotide Polymorphisms (SNP)

Samples will be collected at the same time as BM aspirate and biopsies for GEP (Only one sample per subject needed).

## 10.3 GEP Studies of MRI or PET-CT Defined Focal Lesions

At the time FNA of focal lesions are performed for clinical care, a sample will also be sent to Myeloma Health Lab and MIRT research lab for W-GEP and aCGH studies. The specimen should be labeled “FL for GEP: UARK 2012-02”

## 10.4 Studies at Disease Progression

At PD, after a chemotherapy wash-out phase of 2 weeks (if clinically feasible), RS-MM, FL-MM, RS-BX and FL-BX samples will be obtained from consenting subjects:

The PD samples will be compared to baseline samples by W-GEP, aCGH, miRNA, SNP, and proteomics to identify molecular changes related to disease progression.

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# APPENDIX I - DRUG INFORMATION

## CARFILZOMIB

DESCRIPTION

Carfilzomib is a tetrapeptide epoxyketone-based irreversible inhibitor of the chymotrypsin-like (CT-L) activity of the 20S proteasome. Proteasome inhibition leads to the accumulation of polyubiquinated protein substrates within cells and to the selective induction of apoptosis in malignant cells while sparing non-malignant cells. Carfilzomib is currently being developed for potential treatment of both hematologic and solid tumor malignancies.

Chemical Name: (2S)-N-((S)-1-((S)-4-methyl-1-(R)-2-methyloxiran-2-yl)-1-oxopentan-2-ylcarbamoyl)-2-phynylethyl)-2-((S)-2-(2-morpholinoacetamido)-4-methylpentanamide

Molecular Formula: $C_{40}H_{57}N_5O_7$

Molecular Weight: 719.9

HUMAN TOXICOLOGY

The most frequently reported AEs (those occurring in ≥ 20% of patients) included fatigue (55.0%), nausea (43.3%), anemia (42.2%), dyspnea (33.7%), diarrhea (32.3%), thrombocytopenia (31.3%), pyrexia (29.8%), headache (26.0%), cough (25.1%), upper respiratory tract infection (24.6%), vomiting (23.0%), lymphopenia (22.3%), peripheral edema (22.1%), increased blood creatinine (21.8%), constipation (20.5%), and back pain (20.5%).

Adverse events occurring in ≥ 5% of patients, but in < 20% of patients, by system organ class
(regardless of causality and inclusive of events associated with the disease under study) included the following:

1. Blood and Lymphatic System Disorders: neutropenia and leukopenia;
2. Eye Disorders: vision blurred;
3. Gastrointestinal Disorders: abdominal pain, dyspepsia, and abdominal distension;
4. General Disorders and Administrative Site Conditions: chills, asthenia, pain, and infusion site pain;
5. Infections and Infestations: pneumonia, urinary tract infection, and nasopharyngitis;
6. Investigations: electrolyte disturbances, elevated uric acid, low albumin levels, hepatic enzyme increased, weight decreased;
7. Metabolism and Nutrition Disorders: anorexia, dehydration, and decreased appetite;
8. Musculoskeletal and Connective Tissue Disorders: arthralgia, muscle spasms, myalgia, bone pain;
9. Nervous System Disorders: dizziness, hypoaesthesia, paraesthesia, PN;
10. Psychiatric Disorders: insomnia, anxiety and confusional state;
11. Respiratory, Thoracic and Mediastinal Disorders: epistaxis, pharyngolaryngeal pain, dyspnea exertional, productive cough, rhinorrhoea, and nasal congestion;
12. Skin and Subcutaneous Tissue Disorders: rash and pruritus; and
13. Vascular Disorders: hypertension and hypotension.

The most frequently reported SAEs (those occurring in ≥ 1 % of patients) included pneumonia (8.2%), disease progression (5.9%), acute renal failure (3.6%), pyrexia (3.3%), congestive cardiac failure (3.0%), dyspnea (2.1%), pathological fracture (1.8%), hypercalcemia (1.6%), sepsis (1.3%), spinal cord compression (1.3%), dehydration (1.2%), anemia (1.0%), increased blood creatinine (1.0%), mental status changes (1.0%), and renal failure (1.0%). A selective list of rare, but clinically important and potentially serious adverse events that were reported in < 1% of Phase 2 MM patients includes myocardial ischemia, cardiac failure, arrhythmia, acute respiratory failure, pulmonary hypertension, pulmonary embolism, multiorgan failure, hemoptysis, hepatic failure, hepatic encephalopathy, TLS, infusion related reaction, bleeding, transient ischemic attack, hemiparesis, and serious infections.

Females of child bearing potential should use effective contraception methods or abstain from sexual activity during and for 30 days after treatment with carfilzomib. Male subjects should use effective contraception methods or abstain form sexual activity during and for 90 days after treatment with carfilzomib.

PHARMACOLOGY

Following IV administration to patients, carfilzomib is rapidly cleared from the systemic circulation with a half-life < 1 hour and a clearance that is higher than hepatic blood flow. There is no systemic accumulation of carfilzomib after repeat doses. Exposure to carfilzomib increases dose-proportionally in the therapeutic dosage tested. No apparent effect of renal dysfunction on PK of carfilzomib has been noted to date. Carfilzomib is extensively metabolized to inactive products primarily via peptidase cleavage and epoxide hydrolysis.

Following administration of carfilzomib at doses ranging from 15 to 36 mg/m2 to patients with hematological malignancies and solid tumors, inhibition of the CT-L activity of the proteasome in PBMCs averaged approximately 85%. Recovery of proteasome activity in PBMCs was not complete on Day 8 of the dosing cycle, suggesting a prolonged period of proteasome inhibition by carfilzomib between weeks of dosing. Near complete recovery of proteasome activity was observed in PBMCs between cycles.

Formulation: Carfilzomib for Injection is supplied as a lyophilized powder in a single-use glass vial providing 2 mg/mL carfilzomib.

Storage and Stability: Lyophilized Carfilzomib for Injection is stored in a refrigerator at 2°C-8°C.

Administration: Carfilzomib doses are based on body surface area (BSA). In a typical dose of carfilzomib, 27 mg/m2 in a patient with a BSA of 2.0 m2, the dose delivered would be 54 mg carfilzomib in a volume of 27 mL. Patients with a BSA of 2.2 m2 or higher receive a dose based upon 2.2 m2 BSA.

After addition of the appropriate amount of Water for Injection and vigorous mixing, the solution is administered as an IV infusion. Please note: the use of closed system drug transfer devices, where multiple stopper punctures in close proximity to one another can occur, is not recommended as it could result in coring.

Current clinical experience indicates that carfilzomib can be safely administered IV over 2 to 10 minutes or at rates of approximately 10 mL/minute for doses up to 27 mg/m2; higher doses (> 27 mg/m2) are most often administered as a 30-minute infusion. Doses above 36 mg/m2 should always be administered as a 30-minute infusion. For IV, with dosages up to 27 mg/m2, volumes of 20-40 mL of carfilzomib may be administered from 2 to 10 minutes. For IV infusion over 30 minutes, carfilzomib should not be diluted. Based on preclinical studies, these adjustments in infusion rate and time should not affect the PDn effects in humans.

Supplier: Carfilzomib is investigational and will be provided by Onyx Pharmaceuticals.

**LENALIDOMIDE (CC-5013; REVLIMID®)**

DESCRIPTION

Celgene has developed a small molecule derivative of thalidomide, CC-5013 (also known as IMiD-3), that is a member of the IMiD class. In vitro studies have demonstrated that CC-5013 is one of the most potent of the IMiDs. Three in vitro studies have been performed to compare the activity and potency of CC-5013 and thalidomide. Two studies examined the effects of CC-5013 or thalidomide on the production of various cytokines and the other examined effects on multiple myeloma cell proliferation. In all studies, CC-5013 was approximately 50 to 2000 times more potent than thalidomide.

Inhibition of TNF-a production following LPS-stimulation of human peripheral blood mononuclear cells (PBMC) and human whole blood by CC-5013 or thalidomide was investigated in vitro. The IC50's of CC-5013 for inhibiting production of TNF-a following LPS-stimulation of PBMC and human whole blood are -100 nM (25.9 ng/mL) and -480 nM (103.6 ng/mL), respectively. Thalidomide, in contrast, has an IC50 of -194 µM (50.2 µg/mL) for inhibiting production of TNF-a following LPS-stimulation of PBMC.

Another in vitro study examined the modulation of production of various cytokines by CC-5013 and other thalidomide analogues; however, this study did not calculate IC50 values and therefore only qualitative data are included in this discussion. CC-5013 was approximately 50 to 2000 times more potent than thalidomide in stimulating the proliferation of T-cells following primary induction provided by T-cell receptor (TCR) activation. CC-5013 was also approximately

50 to 100 times more potent than thalidomide in augmenting the production of IL-2 and IFN-g following TCR activation of PBMC (IL-2) or T-cells (IFN-g). In addition, CC-5013 exhibited dose-dependent inhibition of LPS-stimulated production of the pro-inflammatory cytokines TNF-a, IL-1 b, and IL-6 by PBMC. Finally, CC-5013 increased production of the anti-inflammatory cytokine IL-10 by LPS-stimulated PBMC.

HUMAN TOXICOLOGY

Possible adverse effects associated with the use of CC-5013 are: rhinitis, headache, pruritis, rash, dry skin, numbness and tingling in the extremities, drowsiness, constipation, and hematological effects including reduced white blood cell count, reduced red blood cell count, reduced platelet count, and an abnormal blood clotting tendency.

The following are adverse events observed in completed and ongoing studies across all indications considered by an investigator to be at least possibly associated with the use of CC-5013:
**Blood and lymphatic disorder:** anemia, neutropenia, febrile neutropenia, leukopenia, thrombocytopenia, pancytopenia, myelosuppression, and bone marrow suppression

**Cardiac disorder:** atrial fibrillation, tachycardia, abnormal ECG, electrocardiogram QTc interval prolonged, and chest pain

**Eye disorder:** itchy eyes, dry eyes, blurred vision, and visual flashing

**Gastrointestinal disorders:** bloated feeling, constipation, diarrhea, dry mouth, nausea, and vomiting, indigestion, stomatitis, and gingival pain

**General disorders and administration site conditions:** achiness, fatigue, fever, headache, generalized pain, lethargy, night sweats, weakness, somnolence (sleepiness, drowsiness), anger, and rigors

**Infections:** oral thrush, rhinitis, pharyngitis, pneumonia, sinusitis, upper respiratory infection, or non-specific infection, fungal infection, and cellulitis

**Metabolism and nutrition disorders:** dehydration, hyperuricemia (increased level of uric acid in the blood), low level of thyroid hormones, increase in SGOT and/or SGPT, elevated creatinine, elevated glucose, hypokalemia, hypomagnesemia, total bilirubin increased, decreased in CD4 and CD8, and peripheral edema

**Musculoskeletal and connective tissue disorders:** back pain, bone pain, hand and leg cramps, myalgia, and arthralgia

**Nervous system disorders:** difficulty with speech (aphasia), dizziness, headache, insomnia, lightheadedness, numbness or tingling, paresthesia, peripheral neuropathy, syncope, tinnitus, altered taste (dysgeusia), loss of taste (ageusia), and tremor

**Psychiatric disorders:** depression

**Renal and urinary disorder:** urinary frequency, urinary tract infection, and low testosterone

**Respiratory, thoracic and mediastinal disorders:** congested sinuses, cough, difficulty of breathing (dyspnea), and presence of fluid in the lungs (pleural effusion), pulmonary emboli, chest or pulmonary congestion, and atelectasis

**Women and Men of Childbearing Potential**

CC-5013 should not be administered to pregnant or nursing women. Women of childbearing potential (WCBP) must have a negative serum or urine pregnancy test within 24 hours of starting study drug. In addition, sexually active men and women of childbearing potential must agree to use adequate contraceptive methods (oral, injectable, or implantable hormonal contraceptive; tuba) ligation, intra-uterine device; barrier contraceptive with spermicide; vasectomy or vasectomized partner) while on study drug. Pregnancy testing must follow pregnancy testing requirements as outlined in the Revlimid REMS® program material.

Pregnancies

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on lenalidomide, or within 28 days of the subject's last dose of lenalidomide, are considered immediately reportable events. Lenalidomide is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile or email using the Pregnancy Initial Report Form. The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form. If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form.

Male Subjects

If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking lenalidomide should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

Celgene Drug Safety Contact Information:

Celgene Corporation
Global Drug Safety and Risk Management
Connell Corporate Park
300 Connell Dr. Suite 6000
Berkeley Heights, NJ 07922
Fax: (908) 673-9115
E-mail: drugsafety@celgene.com

Formulations

Available as 5mg 10mg, 15mg and 25mg capsules

Supplier

Lenalidomide can be prescribed only by licensed prescribers and dispensed by Pharmacies that are registered with Celgene through RevAssist Program. Drug will not be supplied for the study and will need to be covered by third party payer."

**CISPLATIN (CDDP) (PLATINOL®)**

DESCRIPTION

Cis-diamminedichloroplatinum (Platinol® or cisplatin) is a heavy metal complex and is water-soluble. It is a white lyophilized powder with a molecular weight of 300.1.

Mechanism of action: It acts as a bifunctional alkylating agent.

TOXICOLOGY

Human Toxicology: Human toxicity includes anorexia, nausea, vomiting, renal toxicity (with an elevation of BUN, creatinine, serum uric acid and impairment of endogenous creatinine clearance, as well as renal tubular damage),

ototoxicity (with hearing loss which is initially in the high frequency range, as well as tinnitus), and hyperuricemia. Much more severe and prolonged toxicity has been observed in patients with abnormal or obstructed urinary excretory tracts. Raynaud's phenomena and digital ischemia has been described. Anaphylactic-like reactions including facial edema, bronchoconstriction, tachycardia and hypotension may occur within minutes of administration. Myelosuppression, often delayed erythrosuppression, is expected. In the high-dose treatment regimen with osmotic diuresis, the nadir of white cells and platelets occurred regularly at about two weeks with recovery generally at about three weeks after the initiation of therapy. Rare complications include alopecia, seizures, loss of taste, allergic reactions, and loss of muscle or nerve function. Tetany may occur due to hypomagnesiumemia and/or hypercalcemia. Other electrolyte disturbances may occur. At high doses patients have experienced optic neuritis, papilledema, cerebral blindness, blurred vision, and altered color perception. Patients have also experienced cardiac abnormalities, elevated SGOT and rash. Subsequent courses should not be given until serum creatinine returns to normal if elevated. Audiometric analyses should be monitored and courses withheld until auditory acuity is within normal limits. The occurrence of acute leukemia has been reported rarely in patients treated with anthracycline/alkylator combination chemotherapy.

PHARMACOLOGY

Kinetics: After a single IV dose, increased concentration is found in the liver, kidneys, and small and large intestines. Plasma levels of cisplatin decay in a biphasic mode with an initial half-life of 25 to 49 minutes, and a secondary phase ranging from 58 to 73 hours. This prolonged phase is due to protein binding, which exceeds 90% of the radioactivity, excreted in the first five days. The initial fractions of radioactivity are largely unchanged drugs. Although this drug seems to act as an alkylating agent, there are data to indicate that its mode and sites of action are different from those of nitrogen mustard and the standard alkylating agents. Cisplatin penetrates into CNS poorly.

Formulation: Cisplatin is available in 50 mg and 100 mg reconstituted vials.

Storage and Stability: The intact vials may be stored at room temperature (15-25°C) for the lot life indicated on the package. Do not refrigerate. The solution may be further diluted in a chloride-containing vehicle such as D5NS, NS, or D5½NS (precipitate occurs in D5W).

Administration: Cisplatin should be given as a slow intravenous infusion. Needles or intravenous sets containing aluminum parts that may come in contact with cisplatinum (Platinol) should not be used for preparation or administration, as a black precipitate is formed within 30 minutes.

Supplier: Cisplatin is commercially available, and should therefore be purchased by a third party.

**CYTOXAN® (CYCLOPHOSPHAMIDE)**

DESCRIPTION

2[bis (2chloroethyl)amino]tetrahydro-2H-1,3,2-oxazophosphorine 2-oxide mono-hydrate. Cyclophosphamide is biotransformed principally in the liver to active alkylating metabolites that cross-link to DNA.

TOXICOLOGY

Human Toxicology: Toxicity from cyclophosphamide includes bone marrow suppression which usually occurs 10 to 12 days after administration; nausea, vomiting, anorexia, abdominal discomfort, diarrhea and stomatitis; reversible alopecia; hemorrhagic cystitis which can frequently be prevented with increased hydration; fibrosis of the bladder; cardiac toxicity which may potentiate doxorubicin-induced cardiotoxicity; rare anaphylactic reaction, skin rash, hyperpigmentation, interstitial pulmonary fibrosis, cross sensitivity with other alkylating agents. Treatment with cyclophosphamide may cause significant suppression of the immune system.

Second malignancies, most frequently of the urinary bladder and hematologic systems, have been reported when cyclophosphamide is used alone or with other anti-neoplastic drugs. Malignancies may occur several years after treatment has been discontinued. Cyclophosphamide interferes with oogenesis and spermatogenesis and may cause sterility in both sexes which is dose and duration related. Cyclophosphamide has been found to be teratogenic, and

women of childbearing potential should be advised to avoid becoming pregnant. Increased myelosuppression may be seen with chronic administration of high doses of phenobarbitol. Cyclophosphamide inhibits cholinesterase activity and potentiates the effect of succinylcholine chloride. If patient requires general anesthesia within 10 days after cyclophosphamide administration, the anesthesiologist should be alerted. Adrenal insufficiency may be worsened with cyclophosphamide. Cyclophosphamide is excreted in breast milk, and it is advised that mothers discontinue nursing during cyclophosphamide administration. The occurrence of acute leukemia has been reported rarely in patients treated with anthracycline/alkylator combination chemotherapy.

PHARMACOLOGY

Kinetics: Cyclophosphamide is activated principally in the liver by a mixed function microsomal oxidase system. PO administration is well absorbed, with bioavailability greater than 75%. 5-25% of unchanged drug is excreted in the urine. Several active and inactive metabolites have been identified with variable plasma protein binding. There appears to be no evidence of clinical toxicity in patients with renal failure, although elevated levels of metabolites have been observed.

Formulation: Cyclophosphamide is supplied in 100 mg, 200 mg, 500 mg, 1 gm and 2 gm vials as a white powder. The drug should be reconstituted with sterile water for injection and may be diluted in normal saline or D5W. Cyclophosphamide is also available as a reconstituted solution available in the same size vial as the lyophilized form.

Storage and Stability: The reconstituted vial is stable for 24 hours at room temperature and 6 days when refrigerated.

Administration: The drug should be further diluted in saline or D5W and administered by slow IV infusion.

Supplier: Cyclophosphamide is commercially available, and should therefore be purchased by a third party.

**DEXAMETHASONE (DECADRON®)**

DESCRIPTION

Dexamethasone is a synthetic adrenocortical steroid and is readily absorbed from the gastrointestinal tract. Chemically, dexamethasone is 9-fluoro-11ß, 17, 21-thrihydroxy-16α-methyl-pregna-1, 4-diene-3, 20-dione.

TOXICOLOGY

Human Toxicology: Possible adverse effects associated with the use of dexamethasone are: fluid and electrolyte disturbances, congestive heart failure in susceptible persons, hypertension, euphoria, personality changes, insomnia, exacerbation of infection (e.g., tuberculosis), exacerbation or symptoms of diabetes, psychosis, muscle weakness, osteoporosis, vertebral compression fractures, pancreatitis, esophagitis, peptic ulcer, dermatologic disturbances, convulsions, vertigo and headache, endocrine abnormalities, ophthalmic changes, and metabolic changes. Some patients have experienced itching and other allergic, anaphylactic or other hypersensitivity reactions. Withdrawal from prolonged therapy may result in symptoms including fever, myalgia and arthralgia. Phenytoin, phenobarbital and ephedrine enhance metabolic clearance of corticosteroids.

Corticosteroids should be used cautiously in patients with hypothyroidism, cirrhosis, ocular herpes simplex, existing emotional instability or psychotic tendencies, nonspecific ulcerative colitis, diverticulitis, fresh intestinal anastomoses, peptic ulcer, renal insufficiency, hypertension, osteoporosis and myasthenia gravis. Immunization procedures (especially smallpox vaccination) should not be undertaken in patients on corticosteroids.

PHARMACOLOGY

Kinetics: Natural and synthetic glucocorticoids are readily and completely absorbed from the GI tract. Dexamethasone is insoluble in water. Glucocorticoids have salt-retaining properties, although dexamethasone nearly completely lacks this property. The anti-inflammatory property of this drug is its ability to modify the body's immune system. On the other hand, glucocorticoids suppress the body's response to viral as well as bacterial infections.

Formulation: Dexamethasone is available in six potencies (0.25 mg, 0.5 mg, 0.75 mg, 1.5 mg, 4 mg, and 6 mg) in capsule or tablet form. It is also available as a 4 mg/mL, 10mg/mL and 20mg/mL solution for parenteral use. All formulations of the drug can be stored at room temperature. The injectable form may be further diluted in 5% dextrose or 0.9% NaCl containing solutions and is stable for at least 24 hours at room temperature.

Storage and Stability: Dexamethasone is to be stored at room temperature.

Administration: The drug is administered by 0.5, 0.75, 1, 1.5, 2, 4 and 6 mg tablets.

Supplier: Dexamethasone is commercially available, and should therefore be purchased by a third party.

**DOXORUBICIN (ADRIAMYCIN®)**

DESCRIPTION

Mechanism of action: Doxorubicin is a cytotoxic anthracycline antibiotic different from daunorubicin by the presence of a hydroxyl group in the C-14 position. Doxorubicin is produced by fermentation from S. *peucetius* var. *caesius*. Its mechanism of action is thought to be the binding of nucleic acids, preventing DNA and possibly RNA synthesis.

TOXICOLOGY

Human Toxicology: Studies with doxorubicin have shown that the major toxic effects of this drug are alopecia, which is often total but always reversible; nausea and vomiting, which develops shortly after drug administration, occasionally persisting for 2-3 days; fever on the day of administration; and phlebitis at the site of the drug's injection. Extravasation of the drug will lead to soft tissue necrosis. Phleboscleriosis, cellulitis, vesication and erythematous streaking have also been seen. Mucositis may be seen 5-10 days after administration. Ulceration and necrosis of the colon, particularly the cecum, with bleeding and severe infection have been reported with concomitant administration of doxorubicin. Anorexia and diarrhea have also been observed. Hyperpigmentation of nail beds and dermal creases, onycholysis and recall of skin reaction from prior radiotherapy may occur. Cardiac toxicity manifested as acute left ventricular failure, congestive heart failure, arrhythmia or severe cardiomyopathy has been reported, but appears to occur predominantly in patients who receive total doses in excess of 550 mg/m2. Myelosuppression, predominantly neutropenia, is common with nadir occurring approximately two weeks after a single injection; lesser degrees of anemia and thrombocytopenia have been reported. Rapid recovery of blood counts approximately two and a half weeks after a single injection generally permits an every three-week schedule. Patients with obstructive liver disease have more severe myelosuppression due to impaired drug excretion. Thus, patients with hepatic dysfunction may need to have reduced dosage or be excluded from therapy. Renal excretion of doxorubicin is minimal, but enough to color the urine red; thus impaired renal function does not appear to increase the toxicity of doxorubicin. Other side effects include fever, chills, facial flushing, itching, anaphylaxis, conjunctivitis and lacrimation. The occurrence of acute leukemia has been reported rarely in patients treated with anthracycline/alkylator combination chemotherapy.

Safe use of doxorubicin in pregnancy has not been established. It is embryotoxic and teratogenic in rats and embryotoxic and abortifacient in rabbits. The possible effects on fertility have not been adequately evaluated. Safety in nursing women has not been proven.

PHARMACOLOGY

Kinetics: Intravenous administration is followed by a rapid plasma clearance with significant tissue binding. Urinary excretion is negligible; biliary excretion accounts for 40 to 50% of the administered dose being recovered in the bile or the feces in 7 days. The drug does not cross the blood-brain barrier.

Formulation: Doxorubicin is supplied in 10, 20, and 50 mg single use vials, and 150 and 200 mg multi-dose vials.

Storage and Stability: The doxorubicin is stable for 24 hours at room temperature and 15 days under refrigeration (2°-8°C). It should be protected from exposure to sunlight. Discard any unused solution from the vials. Bacteriostatic diluents with preservatives are NOT recommended as they might possibly worsen the reaction to extravasated drug.

Administration: Doxorubicin may be further diluted in 5% dextrose or sodium chloride injection and should be administered slowly into tubing of a freely flowing intravenous infusion with great care taken to avoid extravasation.

Supplier: Doxorubicin is commercially available, and should therefore be purchased by a third party.

**ETOPOSIDE (VP-16), (VEPESID®)**

DESCRIPTION

Chemistry: VP-16 is a semi-synthetic podophyllotoxin derivative from the plant *podophyllum pletatum*, and has antineoplastic properties in experimental animals and in man. The empiric formula C29H32O has a molecular weight of 588.

Mechanism of Action: The epipodophyllotoxins exert phase specific spindle poison activity with metaphase arrest, but in contrast to the vinca-alkaloids, have an additional activity of inhibiting cells from entering mitosis. Suppression of tritiated thymidine, uridine, and leucine incorporation in human cells in tissue culture suggests effects against DNA, RNA and protein synthesis.

Animal Tumor Data: Significant antitumor effect has been demonstrated in L1210, mouse sarcoma 37 and 180, Walker carcinosarcoma and Erlich ascites tumor. With the L1210 system, activity was schedule-dependent, having greater effect with a twice-weekly administration than with daily dosing or the administration of single large doses. The drug is active given intraperitoneally or orally in L1210. No effect was demonstrated against intracerebrally inoculated L1210.

TOXICOLOGY

Human Toxicology: Reversible myelotoxicity has been uniformly observed to be the major toxicity of VP-16 and to represent the only clinically significant side effect. Following a single IV injection, peak myelotoxicity occurs at seven to nine days. Following daily IV injections for five to seven days, myelotoxicity is maximal between 12 - 16 days from the initiation of therapy. Bone marrow suppression is mainly manifested as granulocytopenia, with thrombocytopenia and anemia occurring to a lesser extent. Gastrointestinal toxicities including transient modest nausea, vomiting and diarrhea, are common. Other reactions could include aftertaste, rash, pigmentation, pruritus, abdominal pain, constipation and dysphagia. Occasional alopecia is reported. VP-16 does not produce phlebitis, or nephrotoxicity. Rarely, anaphylactic-like reactions have been reported, as well as, hypotension. Hypotension can be managed by infusing the drug over at least a 30-minute period. Occasionally, chills, fever, peripheral neurotoxicity, stomatitis, hepatotoxicity, transient cortical blindness and radiation recall dermatitis may be a result of VP-16 administration. The occurrence of acute leukemia has been reported rarely in patients treated with VP-16 in association with other antineoplastic agents. VP-16 can cause fetal harm when administered to pregnant women.

Pregnancy and Lactation: VP-16 can cause fetal harm when administered to a pregnant woman. VP-16 has been shown to be teratogenic in mice and rats. In these studies, VP-16 caused dose-related maternal toxicity, embryo toxicity, and teratogenicity. Fetal abnormalities included decrease weight, major skeletal abnormalities, exencephaly, encephalocele, anophthalmia, and retarded ossification. No information is available on excretion of this drug in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued.

PHARMACOLOGY

Kinetics: After IV administration, disposition is biphasic with initial half-life of 1.5 hours and terminal half-life of 4 - 11 hours. Drug does not accumulate in plasma following daily administration of 100 mg/M2 for 4 - 5 days. Drug crosses blood-brain barrier poorly. Recovery after IV administration of radiolabeled VP-16 in the urine ranges from 42 - 67% and feces from 0 - 16%. The mutogenic and genotoxic potential has been established in mammalian cells.

Formulation: 100 mg of VP-16 is supplied as 5 mL of solution in Sterile Multiple Dose Vials for injection. The pH of the yellow clear solution is 3 - 4. Each mL contains 20 mg VP-16, 2 mg citric acid, 30 mg benzyl alcohol, 80 mg polysorbate 80/tween 80, 650 mg polyethylene glycol 300, and 30.5% (v/v) alcohol. VP-16 must be diluted prior to use

with either 5% Dextrose Injection, USP, or 0.9% sodium Chloride Injection, USP. The time before precipitation occurs depends on concentration, however, when at a concentration of 0.2 mg/mL it is stable for 96 hours at room temperature and at 0.4 mg/mL it is stable for 48 hours.

Storage and Stability: The drug is available as a box of 10 vials that are stored at room temperature. Each vial should be kept in the box to protect it from light. VP-16 is less stable in 5% Dextrose injection and precipitation is reported.

Administration: VP-16 is administered by slow IV infusion to reduce hypotension.
Supplier: VP-16 is commercially available, and should therefore be purchased by a third party.

**MELPHALAN (ALKERAN™)**

DESCRIPTION

Chemistry: Melphalan (L-phenylamine mustard, L-PAM, L-Sarcolysin) is an alkylating agent coupled to an amino acid.

Molecular Formula: $C_{13}H_{18}C_{12}N_2O_2$

M.W.: 305

TOXICOLOGY

Human Toxicology: Melphalan's major systemic toxicity is bone marrow depression with secondary anemia, leukopenia and thrombocytopenia, usually occurring within three to five weeks of the onset of therapy and lasting four to eight weeks. Prior chemotherapy or radiotherapy exacerbates these effects. Other side-effects include nausea, vomiting, diarrhea, stomatitis, esophagitis, colitis, increases in liver function and kidney function tests, renal/bladder necrosis, pulmonary fibrosis, respiratory distress, peripheral neuropathy, paresthesia, alopecia, fever, and hypersensitivity including edema, rash and anaphylaxis. The occurrence of acute leukemia has been rarely reported in patients treated with anthracycline/alkylator combination chemotherapy.

PHARMACOLOGY

Formulation: The intravenous preparation is available in a sterile, 50 mg vial. The product is prepared as a lyophilized powder with 20 mg of povidone per vial. Also provided is 10 mL of special diluent for use in constituting the product. The special diluent has the following composition:

| | |
|---|---|
| Sodium citrate | 0.20 g |
| Propylene glycol | 6.00 mL |
| Ethanol (95%) | 0.5 mL |
| Sterile water | qs |
| | 10.0 mL |

Solution preparation: Vial/50 mg: Constitute with 10 mL of the special diluent to yield a 5 mg/mL melphalan concentration. Prior to administration, dilute the constituted solution with 0.9% Sodium Chloride Injection, USP, to a concentration no greater than 2 mg/mL.

Storage and Stability: The intact packages of melphalan for intravenous administration should be stored at room temperature (15-30°C) protected from light. Shelf surveillance of the intact dosage form is ongoing.

Constitution with the special diluent as directed results in a solution that retains at least 90% melphalan potency for about 3 hours at 30°C. Storage at 5°C results in precipitation.

When the constituted solution is diluted to concentrations of 0.45 or 0.1 mg/mL in 0.9% Sodium Chloride Injection USP, 90% melphalan potency is retained for 45 minutes at 30°C. At 20°C, the 0.1 mg/mL concentration retained 90% potency for 3 hours. **The manufacturer recommends administration of melphalan within one hour of constitution.**

In dilute solutions of approximately 40 µg/mL, increasing amounts of chloride ion appear to enhance stability. For example, increasing the chloride content of such a solution from 0.2% to 0.9% increases the half-life from 8 to 16 hours.

Increased temperature as well as decreased chloride ion is associated with much higher degradation rates. An increase of temperature from 20°C to 25°C decreased the time to 10% decomposition by about one-half in each case.

Administration: In this protocol, melphalan will be administered intravenously.

Supplier: Melphalan is commercially available for purchase by a third party.

**THALIDOMIDE (THALOMID®)**

DESCRIPTION

Thalidomide is an N-phthaloyl-glutamic acid imide. Its chemical name is α-(N- phthalimido) glutarimide. The empirical formula is $C_{13}H_{10}N_2O_4$ and the gram molecular weight is 258.2. The CAS number of thalidomide is 50-35-1. Thalidomide is off-white to white, nearly odorless, crystalline powder that is soluble at 25°C in dimethyl sulfate (50 mg/mL) and ethanol (1 mg/mL). The glutarimide part of the molecule contains a single asymmetric center and, therefore, may exist in either of two optically active forms designated S(-) or R(+). Thalidomide is an equal mixture of the S(-) and R(+) forms and therefore has a net optical rotation of zero. The enantiomers, both the S(-) and R(+) forms differ from the racemic thalidomide in having higher solubility in water (Hague and Smith, 1988, Williams 1968, Williams et al. 1965) and undergoing faster hydrolytic cleavage. (Hague and Smith, 1988).

Contraindications and Precautions

Thalidomide causes severe birth defects. It must not be taken during pregnancy or within one month of having sexual intercourse that could result in pregnancy. Females of childbearing potential should be instructed that they must not be pregnant when thalidomide therapy is initiated. A blood test or professionally conducted urine test to rule out pregnancy prior to initiating thalidomide therapy is highly recommended. While taking thalidomide, all female patients of childbearing potential must use two methods of birth control, one barrier and one hormonal or should abstain from sexual intercourse that could result in pregnancy. It is not known if thalidomide is present in semen, therefore, it is recommended that male patients use barrier contraception while on thalidomide. Both males and females of childbearing potential should continue with the contraceptive measures described above for one month after dosing has been discontinued.

TOXICOLOGY

The most important of the adverse events reported during the administration of thalidomide are peripheral neuropathy, rash, drowsiness, and teratogenicity. Other frequent adverse events that have been reported include constipation and xerostomia. Increased appetite, loss of libido, dryness of the skin, edema of the face and limbs, nausea pruritus, headache, gastric pain, and menstrual abnormalities have occasionally been observed. In addition, hangover feeling, giddiness, or nervousness at higher doses, shivering, aural buzzing, and addiction after several months have been reported. Some patients have had a decrease in their white blood cell count and in some HIV- positive increases in the HIV RNA load has been reported. There have been reports of changes of the heart rate and rhythm. Allergic reactions include low blood pressure, rash, fever and rapid heartbeat associated with thalidomide use.

Serious dermatologic (skin) reactions including a disease called Stevens-Johnson syndrome (which could be fatal) have been reported with thalidomide. Symptoms of Stevens - Johnson syndrome include flu-like symptoms (fever, achiness), and a crusty rash may form on mouth, lips, nose and genitals. The eyes may also become red and itchy and the disease may eventually result in blindness. The disease can also affect the lungs, stomach and bowel, kidneys and heart if not treated. If any of the above-mentioned symptoms or a skin rash of any type develop, thalidomide should be discontinued until thorough evaluation of the rash can be evaluated.

Seizures, including generalized tonic-clonic convulsions, have been reported after thalidomide was approved by the FDA in clinical practice, but it has not been determined that thalidomide caused these seizures. During therapy with

thalidomide, patients with a history of seizures or with other risk factors for the development of seizures should be closely monitored for changes that could cause acute seizure activity.

Drug Interactions

Drug-drug interactions do not appear to have been systematically studied but it has been reported that thalidomide enhances the sedative effects of barbiturates, alcohol, chlorpromazine, and reserpine. Its sedative action is antagonized by methylphenidate and methyl amphetamine (Somers 1960).

Females who require treatment with rifampicin, rifabutin, barbiturates, glucocorticoids, phenytoin, or carbamazepine should not rely upon hormonal contraception since these agents have been shown to reduce the efficacy of the contraceptives.

PHARMACOLOGY

Formulations: Available as 50mg, 100mg and 200mg capsules in blister-packs of 28 capsules each and must be dispensed intact.

Administration: The drug is available in 50 mg, 100 mg, 150 mg and 200 mg capsules for oral administration.

Supplier: Thalidomide is available commercially, and therefore should be purchased by a third party payer. Thalidomide can only be marketed under a restricted distribution program. This program called the “System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.®)." Under this program, only registered prescribers and pharmacists may dispense the drug. In addition patients must be advised of, agree to and comply with the requirements of S.T.E.P.S®)."

## APPENDIX II - DIAGNOSTIC AND STAGING CRITERIA

Diagnostic Criteria:

| Revised IMWG Diagnostic Criteria for Multiple Myeloma (Rajkumar, et al, 2014) |
|---|
| Clonal bone marrow plasma cells ≥ 10% or biopsy-proven bony or extramedullary plasmacytoma[a]<br><br>And any one or more of the following myeloma defining events:<br><br>• Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:<br>o Hypercalcemia: serum calcium > 0.25 mmol/L (> 1 mg/dL) higher than the ULN or > 2.75 mmol/L (> 11 mg/dL)<br>o Renal insufficiency: CrCl < 40 mL per min[b] or SCr > 177 µmol/L (> 2 mg/dL)<br>o Anemia: Hb > 20 g/L below the LLN, or Hb <100 g/L<br>o Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT[c]<br><br>• Any one or more of the following biomarkers of malignancy:<br>o Clonal bone marrow plasma cell percentage[a] ≥ 60%<br>o Involved:uninvolved serum FLC ratio[d] ≥ 100<br>o > 1 focal lesions on MRI studies[e] |
| CrCl, Creatinine clearance; CT, computed tomography; FLC, free light chain; Hb, hemoglobin; Ig, immunoglobulin; IMWG, International Myeloma Working Group; LLN, lower limit of normal; M protein, monoclonal protein; MRI, magnetic resonance imaging; PET-CT, Positron emission tomography-computed tomography; ULN, upper limit of normal; SCr, serum creatinine<br><br>[a]Clonality should be established by showing κ/λ -light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. 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.<br>[b]Measured or estimated by validated equations.<br>[c]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.<br>[d]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.<br>[e]Each focal lesion must be 5 mm or more in size. |

Staging Criteria:

International Staging system [ISS]

| New International Staging System (Greipp, et al, JCO 2005) | | |
|---|---|---|
| Stage | Criteria | Median Survival (months) |
| I | Serum β2-microglobulin < 3.5mg/L<br>Serum Albumin ≥ 3.5 g/dL | 62 |
| II | Not stage I or III | 44 |
| III | Serum β2-microglobulin ≥ 5.5 mg/L | 29 |
| **There are two categories for stage II: serum β2-microglobulin < 3.5 mg/L but serum albumin < 3.5 g/dL; or serum β2-microglobulin 3.5 to < 5.5 mg/L irrespective of the serum albumin level.* | | |

## APPENDIX III - RESPONSE CRITERIA AND SURVIVAL OUTCOME DEFINITIONS

Timing of Response Evaluation:

Response will be evaluated according to the Schedule of Evaluations listed above (Section 6.0)

Definition of Measurable Disease:

**a.** Measurable protein criteria of the serum are defined as serum M-protein of IgG, IgA, IgD, IgE Isotype ≥ 1.0 gm/dL (10.0 g/L). Measurable protein criteria of the urine are defined as urine M-protein (Bence-Jones Protein) > 200 mg/24 hours.

**b.** Participants with IgM peaks must have either ≥ 20% bone marrow plasmacytosis or > 3 lytic lesions on skeletal survey.

**c.** Non-Secretory Disease: Participants without quantifiable M-proteins but with ≥20% bone marrow plasmacytosis will be assessed using plasma cell percentages. These participants will be evaluated for CR, no CR, and progression/relapse using the criteria above.

**Response Criteria:**

Multiple Myeloma: For the purpose of establishing one set of criteria for both Phase II and Phase III multiple myeloma studies, the following definitions will be used. These definitions are based on the International Myeloma Working Group (IMWG) Uniform Response Criteria for Multiple Myeloma[43].

**a. Measurable Disease:** Measurable, quantifiable protein criteria must be present. Acceptable protein criteria are:

- Serum M protein ≥ 1 g/dL (≥ 10 g/L), quantified by using densitometry on serum protein electrophoresis (SPEP).

  **AND/OR**

- Urine M protein [Bence-Jones Protein] ≥ 200 mg/24 hrs (> 0.2 g/24 hrs), quantified by 24-hour urine protein electrophoresis (UPEP see Appendix III: Notes,h.).

  **OR**

- Patients who have both serum M protein levels < 1 g/dL AND urine M protein levels < 200 mg/24 hrs at baseline may be followed by serum free light chain (FLC) assay if involved free light chain level ≥ 10 mg/dL (≥ 100mg/L).

**Oligosecretory and Non-secretory Disease:** Patients that do not meet the criteria for measurable disease above may only be assessed for the following objective statuses: Stringent Complete Response, Stable, and Progression.

**b. Objective Status:**

**Stringent Complete Response (sCR):**

- Meets all of the criteria for Complete Response (CR) ***and***
- normal serum free light chain ratio ***and***
- absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence

**Complete Response (CR):**

- Disappearance of all evidence of serum and urine M proteins on immunofixation electrophoresis studies ***and***
- ≤ 5% plasma cells in bone marrow ***and***
- disappearance of any soft tissue plasmacytomas

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

- Meets all of the criteria for Partial Response (PR) ***and***
- Serum and urine M proteins detectable by immunofixation but not on electrophoresis ***or***
- ≥ 90% reduction in serum M protein **and** urine M protein < 100 mg/24 hrs.

**Partial Response (PR):**

- ≥ 50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by ≥ 90% or to < 200 mg/24 h
- If the serum and urine M-protein are unmeasurable at baseline, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria
- If serum and urine M-protein are not measurable, and serum free light assay is also not measurable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30%
- In addidion to the above listed criteria, if present at baseline, a ≥ 50% reduction in the size of of soft tissue plasmacytomas is also required

**Stable Disease (SD):**

- Patient does not meet criteria for Stringent Complete Response, Complete Response, Very Good Partial Response, Partial Response, or Progression.

**Progression (PD) - Any one or more of the following:**

- Serum M protein increase ≥ 25% from lowest response value (or an increase of ≥ 1 g/dL if serum M protein was ≥ 5 g/dL at baseline), with an absolute increase of ≥ 0.5 g/dL *and/**or***
- Urine M protein increase ≥ 25% from lowest response value, with an absolute increase of ≥ 200 mg/24 hrs *and/**or***
- Only in patients without measurable serum and urine M-protein levels at baseline: ≥ 25% increase from lowest response value in the difference between involved and uninvolved serum free light chain level, with an absolute increase of > 10 mg/dL
- Only in patients without measurable serum and urine M-protein levels and without measurable disease by free light chain levels, bone marrow plasma cell percentage increase ≥ 25% from lowest response value, with the absolute plasma cell % ≥ 10%
- Definite development of new bone lesions or soft tissue plasmacytomas, or definite increase in size of existing bone lesions or soft tissue plasmacytomas (see Appendix III: Notes h.)
- Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to multiple myeloma

**NOTES: If a disease assessment indicates that a patient is experiencing a Stringent Complete Response, Complete Response, Very Good Partial Response, Partial Response, or Progression, this should be confirmed by a second disease assessment and this should be done prior to the institution of any new therapy. The second disease assessment may be done at any time.**

**CR, sCR, VGPR, and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed.**

**VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable on serum, urine, both, or neither. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed.**

**For PD, serum-M component increases of more than or equal to 1 g/dL are sufficient to define relapse if starting M-component is ≥ 5 g/dL.**

**PD for patients in CR should be defined as per the IMWG criteria. CR patients will need to progress to the same level as VGPR and PR patients to be considered PD. A positive immunofixation alone is therefore not sufficient.**

***Clarifications to IMWG criteria for coding CR and VGPR in patients in whom the only measurable disease is by serum FLC levels: CR in such patients indicates a normal FLC ration of 0.26 to 1.65 in addition to CR criteria listed above. VGPR in such patients requires a > 90% decrease in the difference between involved and uninvolved FLC levels.**

**†Clarifications to IMWG criteria for coding PD: Bone marrow criteria for PD are to be used only in patients without measurable disease by M protein and by FLC levels; "25% increase" refers to M protein, FLC, and bone marrow results, and does not refer to bone lesions, soft tissue plasmacytomas, or hypercalcemia and the "lowest response value" does not need to be a confirmed value.**

**The size of the soft tissue plasmacytomas is defined as the sum of the products of the cross-diameters of each plasmacytoma. The size of the bone lesions will be determined in a similar manner. A definite increase in the size is defined as a ≥ 50% increase (and at least 1 cm2) of this sum.**

**Survival Outcomes:**

Overall Survival: measured as the time from initial registration to death from any cause.

Event-Free Survival: measured as the time from initial registration to progression/relapse of disease or death from any cause

## APPENDIX IV - PERFORMANCE STATUS SCALE AND ADVERSE EVENT GRADING

SWOG/Zubrod Grading Scale:

Participants will be graded according to the current SWOG/Zubrod grading scale

| Grade | Scale |
|---|---|
| 0 | Fully active; able to carry on all pre-disease activities without restriction. (Karnofsky 90-100). |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work. (Karnofsky 70-80). |
| 2 | Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours. (Karnofsky 50-60). |
| 3 | Capable of only limited self-care; confined to be or chair more than 50% of waking hours (Karnofsky 30-40). |
| 4 | Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (Karnofsky 10-20). |

Adverse Event Criteria:

This study will utilize the CTCAE Version 4.0 for toxicity and performance reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP home page at http://ctep.info.nih.gov)

Additionally, the toxicities are to be reported in the appropriate data collection tools.

## APPENDIX V - CRITERIA FOR REMOVAL FROM TREATMENT AND STUDY

Criteria for Removal from Treatment:

a. Completion of protocol therapy
b. Delay in the start of subsequent cycles beyond the maximum interval allowed by the protocol for a given phase of treatment
c. Unacceptable toxicity (i.e., non-reversible Grade 3 or Grade 4 life-threatening toxicity probably or definitely related to carfilzomib)
d. Inability to collect adequate PBSCs for tandem transplant
e. Major deviation in protocol therapy
f. The patient may elect to discontinue treatment at any time for any reason

   All reasons for discontinuation of treatment must be clearly documented in source documents and database.

Criteria for Removal from Protocol Follow-Up/Off study Criteria:

a. Death
b. Progressive disease or relapse
c. Initiation of non-protocol treatment
d. Development of second neoplasm (SMN)
e. Pregnancy
f. Lost to follow-up
g. Withdrawal of consent for any further data collection

## APPENDIX VI - LIST OF ABBREVIATIONS

| | |
|---|---|
| aCGH | Microarray-based Compartive Genomic Hybridization |
| AE | Adverse Event |
| AS-CR-2 | Accelerate and sustain the proportion of subjects in complete response |
| B2M | Beta-2 Microglobulin |
| BER | Base Excision Repair |
| BM | Bone Marrow |
| BX | Biopsy |
| CA | Cytogenetic Abnormalities |
| CAD | Cyclophosphamide, Adriamycin®, Dexamethasone |
| CBC | Complete Blood Count |
| CCR | Confirmed Complete Response |
| CD | Carfilzomib and Dexamethasone |
| CFZ | Carfilzomib |
| CNA | Copy Number Abnormalities |
| CNS | Central Nervous System |
| CR | Complete Response |
| CRA | Clinical Research Assistant |
| CRD | Carfilzomib, Revlimid®, Dexamethasone |
| CRN | Clinical Research Nurse |
| CRP | C Reactive Protein |
| CTCAE | NCI Common Terminology for Adverse Events |
| DCEP | Dexamethasone, Cytoxan®, Etoposide, Cisplatin |
| delTP53 | GEP defined TP53 deletion |
| DEX | Dexamethasone |
| DISC | Death Induced Signaling Complex |
| DNA | Deoxyribonucleic acid |
| DVT | Deep Vein Thrombosis |
| EFS | Event Free Survival |
| FDA | Food and Drug Administration |
| FDG | PET Fluorodeoxyglucose - Positron Emission Tomography |
| FISH | Fluorescence *in situ* hybridization |
| FL | Focal Lesion |
| GCP | Good Clinical Practices |
| GEP | Gene Expression Profiling |
| GI | Gastrointestinal |
| H&P | History and Physical |
| HIPAA | Health Insurance Portability and Accountability Act |
| HR-MM | High Risk Multiple Myeloma |
| HS | At Bedtime |
| ICH | International Conference on Harmonization |
| IFE | Immunofixation |
| IND | Investigational New Drug |
| IRB | Institutional Review Board |
| IV | Intravenous |
| LDH | Lactate dehydrogenase |
| LOH | Loss of Heterozygosity |
| los-CR | Lost Complete Response |
| LR-MM | Low Risk Multiple Myeloma |
| MAG | Microenvironment Associated Gene |
| MDS | Myelodysplastic Syndrome |
| ME | Microenvironment |
| MEL | Melphalan |
| MGUS | Monoclonal Gammopathy of Undetermined Significance |

| | |
|---|---|
| MIRT | Myeloma Institute for Research and Therapy |
| MM | Multiple Myeloma |
| MRI | Magnetic Resonance Imaging |
| MTD | Maximum Tolerated Dose |
| NCI | National Cancer Institute |
| nCR | Near Complete Response |
| NFT | No Further Treatment |
| non-CR | Never Achieved Complete Response |
| OS | Overall Survival |
| PACE | Cisplatin, Adriamycin®, Cytoxan®, Etoposide |
| PB | Peripheral Blood |
| PBSC | Peripheral Blood Stem Cells |
| PC | Plasma Cells |
| PET-CT | Positron Emission Tomography - Computed Tomography |
| PFS | Progression Free Survival |
| PI | Principal Investigator |
| PO | By mouth |
| PR | Partial Response |
| PS | Performance Status |
| QD | Every Day |
| REV | Revlimid® (Lenalidomide) |
| RNA | Ribonucleic acid |
| RS | Randomly Sampled |
| SAE | Serious Adverse Event |
| SNP | Single Nucleotide Polymorphisms |
| SRE | Skeletal Related Events |
| sus-CR | Sustained Complete Response |
| TD | Thalidomide and Dexamethasone |
| THAL | Thalidomide |
| TSH | Thyroid Stimulating Hormone |
| TT | Total Therapy |
| TT2 | Total Therapy II: UARK 98-026 |
| TT3A | Total Therapy III: UARK 2003-33 |
| TT3B | Total Therapy III: UARK 2006-66 |
| TT4 | Total Therapy IV: UARK 2008-01 |
| TT5 | Total Therapy V: UARK 2008-02 |
| UARK | University of Arkansas for Medical Sciences |
| UPD | Uni-parental Disomy |
| V | Velcade™ (bortezomib) |
| VRD | Velcade, Revlimid®, and Dexamethasone |
| VTD | Velcade™, Thalidomide, and Dexamethasone |
| WBC | White Blood Cells |
| W-GEP | Whole Genome Expression Profiling |
| WOCBP | Women of Child Bearing Potential |
| 2D-DIGE | 2-dimensional in-gel differential gel electrophoresis |