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Walden University
2015

Abstract

Survival Analysis of Total Therapy 3 in Newly Diagnosed Multiple Myeloma

by

Scott Edward Bowman Miller

BS, Baker University, 1992

Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

Doctor of Philosophy

Public Health

Walden University

November 2015

Abstract

Multiple Myeloma (MM) is a hematologic malignancy that accounts for approximately 1% of all adult cancers. This study investigated the impact of patient distance traveled to MM care sites, which was not considered in previous research on any disease-specific staging or prognostic schema despite evidence suggesting that distance impacts patient outcome. This study investigated the impact of patient distance from the site of care on survival outcomes using a group of 480 clinical trial participants. Andersen's behavioral model of health services use functioned as the theoretical model for this study. The independent variable was patient travel distance, controlling for established measures of risk, including ISS Stage and Gene Expression Profiling based risk stratification. A Cox proportional hazard model was used to analyze time to progression and/or death outcome. Analysis revealed that patients who lived <120 miles from the site of care were 1.73 times more likely to experience cancer progression or death than those who lived ≥ 121 miles. When controlling for ISS Stage and GEP risk, participants who lived <120 miles from the site of care were 1.67 times more likely to experience cancer progression or death than those who lived ≥ 121 miles. Participants aged ≥ 65 years who lived <120 miles were 1.88 times more likely to experience cancer progression and 1.75 times more likely to die than those who lived ≥ 121 miles. Statistically significant results (p = <.05) were obtained for all PFS and OS outcomes with the exception of gender. This study promotes social change by improving the care of patients through science-based communications with healthcare providers and policy makers. Results from this trial may be readily applied to other more common hematologic malignancies.

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Dedication

I am very grateful for the love, understanding, and motivation from my family in allowing me the time to purse my education. This work is dedicated to patients who have and continue to participate in Total Therapy trials and their families.

Acknowledgments

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Chapter 1: Introduction to the Study

Introduction

Multiple Myeloma (MM) is a hematologic malignancy of plasma cells that is characterized by bone marrow failure, anemia, destruction of skeletal bone, renal dysfunction, and impaired immune response (Agarwal & Ghobrial, 2013; Mahindra et al., 2012; Rajkumar, 2011). Despite advances with modern therapy, including autologous hematopoietic stem cell transplantation (ASCT), MM has traditionally been characterized as an incurable disease (Bianchi, Richardson, & Anderson, 2014; Landgren et al., 2014). However, this view has been challenged by investigators citing the long-term outcomes of 1,202 patients on Total Therapy protocols (Barlogie et al., 2014) and other published evidence indicating that a cure is possible for select groups of patients (Hajek, 2013; San-Miguel & Mateos, 2011). Cure of MM is functionally defined as no evidence of disease by any detection method 10 years after therapy cessation.

In 2011, the reported median overall survival (OS) for those with newly diagnosed symptomatic MM (NDxMM) was reported as 4.4–7.1 years (de Weers et al., 2011). Significant progress in the treatment of MM in recent years has markedly improved both progression-free survival (PFS) and OS (Morgan & van Rhee, 2014), with a portion of patients having been cured of their disease. This favorable outcome is limited in scope, however. For the majority of MM patients, the disease course is characterized by an initial response to therapy, tumor resistance to therapy marked by tumor progression, tumor relapse, and death (Mahindra et al., 2012).

This chapter presents the background of MM and discuss both progress and challenges confronting public health and medical professionals who are responsible for the care of patients with the disease. MM is a late clinical manifestation resulting from malignant transformation of plasma cells that inappropriately proliferate and accumulate in the bone marrow. Defective and malignant plasma cells found in the bone marrow and rarely in extramedullary anatomical sites (Usmani et al., 2012) that produce abnormal amounts of monoclonal protein (M-protein), which can damage vital organs (Sigurdardottir et al., 2015). At the time of this study, there was broad agreement that only symptomatic MM which meets appropriate clinical and laboratory criteria requires systematic treatment (Mikhael et al., 2013; Palumbo & Anderson, 2011). This consensus in the clinical literature is reflected in the National Comprehensive Cancer Network (NCCN) treatment guidelines (Anderson et al., 2014).

There is not a single, unifying treatment schema that has been demonstrated as appropriate for all persons with multiple myeloma. The NCCN is an alliance of 25 cancer centers in the United States that produces guidelines for diagnosis and therapy based on peer-reviewed evidence and input from experts in the fields of hematology and oncology. The NCCN and other groups, including individual physicians, make choices for systematic therapy for MM based on clinical evidence, their preferenced, logistical considerations, and patient choice. There are well-known barriers to care for those with cancer, including socioeconomic status, physical performance status, lack of appropriate clinical trials, and geographic location (Chambers & Hyde, 2015). The distance patients must travel from their home to their site of care has been identified as a factor which may

influence treatment decisions and outcome (Huang, Dignan, Han, & Johnson, 2009; Lenhard, Enterline, Crowley, & Ho, 1987; Lipe, Lansigan, Gui, & Meehan, 2012; Meilleur et al., 2013; Tariman, Doorenbos, Schepp, Becker, & Berry, 2014).

There are many appropriate therapeutic regimens available to treat symptomatic MM. Treatment regimens for MM may be broadly classified as those intended for patients who are candidates for ASCT and those for patients who are not candidates for ASCT (Mikhael et al., 2013). Multidrug combinations are routinely used for initial or "induction" therapy in NDxMM. Current guidelines and practice patterns routinely include between two and three drugs, with some centers utilizing up to seven anti-MM drugs for induction therapy (Anderson et al., 2014; Bianchi et al., 2014; Mikhael et al., 2013; Rajkumar, 2011). This study investigated the impact of patient distance traveled to MM care sites, which was not considered in previous research on any disease-specific staging or prognostic schema despite evidence suggesting that distance impacts patient outcome. This study specifically investigated the impact of patient distance from the site of care on survival outcomes using a group of 480 clinical trial participants. Andersen's behavioral model of health services use functioned as the theoretical model for this study.

Background of the Problem

Advances in treatment over time have significantly changed the OS for patients with MM. The median OS for patients with MM was 17 months prior to the introduction of melphalan, an alkylator type of anti-neoplastic drug (National Cancer Institute, 2015b) used in combination with the corticosteroid prednisolone (M+P; Alexanian et al., 1972). Combination therapy with M+P resulted in an improvement in OS ranging between 19

and 39 months (Gregory, Richards, & Malpas, 1992). Thereafter, little progress was noted until the introduction of both thalidomide (Thalomid) and bortezomib (Velcade) as investigational agents in the late 1990s (R. A. Kyle & Rajkumar, 2014).

Thalidomide is the first of the immunomodulatory (IMiD) class of drugs and bortezomib is the first of the proteasome inhibitor class of medications. These classes of medications are commonly referred to as *novel therapy* in the MM literature (Kumar et al., 2008). The introduction of thalidomide and bortezomib in the treatment of both NDxMM and relapsed/refractory MM has resulted in significantly improved PFS and OS. Kumar (2008) reported a 50% improvement in OS for those diagnosed with MM in the years 2001-2006, owing to the use of novel therapy when compared to historic controls.

Therapy for MM typically involves combination classical chemotherapy with the inclusion of one or more novel therapies, independent of the eligibility for the patient to undergo future ASCT (Anderson, 2014). Classical chemotherapy agents used in induction therapy for MM include doxorubicin (Adriamycin), liposomal doxorubicin (Doxil), cisplatin (Platinol), melphalan (Alkeran), etoposide (VePesid), cyclophosphamide (Cytoxan), and vincristine (Vincar) (Anderson, 2014). These agents are used in treatment regimens consisting of single agents, multi-agents, and in combination with corticosteroids (prednisolone, dexamethasone) and/or novel therapies such as thalidomide (Thalidomide), lenalidomide (Revlimid), pomalidomide (Pomalyst), bortezomib (Velcade) or carfilzomib (Kyprolis), or other approved and investigational agents (Barlogie et al., 2014; Berenson et al., 2014; Mikhael et al., 2013; Rajkumar et al., 2010; Stewart, 2012). The use of novel agents in combination with one another but without

classic chemotherapy is now an NCCN-approved strategy for therapeutic intervention (Anderson et al., 2014).

Combination therapy utilizing multiple classes of medications has improved both PFS and OS for MM, but comes at the expense of significant toxicities and disruptions to activities of daily living (Anderson, 2014; Tariman et al., 2014). A hallmark feature of multiple myeloma is bone pain associated with lytic bone lesions and impending or current vertebral, rib, or long bone fractures (Jethava, Pena, Yoon, Stein, & Zangari, 2015). Very little qualitative data regarding the impact of therapy and the disease process on the quality of life for those undergoing anti-MM therapy were available at the time of this study (Baz et al., 2015). Known consequences of untreated disease include fatigue, anemia, infection, neuropathy, bleeding, renal dysfunction, hazy vision, headaches, hyperviscosity of the blood leading to blood clot formation, decreased performance status, and early death (Durie, 2012; Gundrum & Neuner, 2013). Adverse events associated with anti-MM therapeutics vary by drug, dose intensity, and drug combination. Significant adverse events associated with classical chemotherapy, corticosteroids, and novel agents include anemia, bone marrow suppression (anemia, thrombocytopenia, neutropenia), constipation, somnolence, cardiac failure, edema, rash, neuropathy, and deep vein thrombosis/pulmonary embolism (DVT/PE; Mateos, 2010).

There are multiple models for staging and prognostication of MM. These models include:

- the European Group for Blood and Marrow Transplantation (EBMT) criteria (Bladé et al., 1998)(Bladé et al., 1998; Appendix A),

- Durie-Salmon Staging System (Durie & Salmon, 1975; Appendix B),

- the International Staging System (ISS; Greipp et al., 2005; Appendix C),

- the International Myeloma Working Group (IMWG) CRAB criteria (Rajkumar et al., 2014; Appendix D),

- Gene Expression Profiling (GEP70; Shaughnessy et al., 2007), and seperately

- the Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) Consensus Guidelines 2013 (Mikhael et al., 2013), which utilize a broad array of clinical features, laboratory, imaging, cytogenetic, and genetic information to guide therapy and prognosticate for survival.

Orally administered treatment regimens, including thalidomide-dexamethasone, lenalidomide-dexamethasone, pomalidomide-dexamethasone, or melphalan-prednisone, are often chosen by physicians and patients as they do not require patients to undergo central line placement or make frequent visits to the infusion clinic. At the time of this study, no quantitatively designed disease staging, prognostication, disease response systems, or clinical care guidelines considered the potential impact of the distance a patient must travel to the site of cancer care as a variable in therapy.

Statement of the Problem

This study was designed to close a gap in literature with regard to the potential impact of patient distance traveled in the era of novel therapies, improved autologous stem cell transplantation (ASCT) outcomes, and supportive care for those with NDxMM. Previous findings on the potential impact of distance traveled on PFS for patients with MM are inconsistent (Abou-Jawde et al., 2006; Lenhard et al., 1987; Lipe et al., 2012).

Previously published work on this topic revealed a lack of consistent patient populations studied, were based on data that were published 25 years ago and therefore did not include novel therapies, and contained significant methodological errors (Lenhard et al., 1987; Ojha et al., 2007). In a retrospective report based on 27,987 patients with NDxMM from 1998-2000 derived from the National Cancer Center Data Base, 7.9% survived > 10 years (Raghavendra, Al-Hamadani, & Go, 2013). Amongst the small fraction of patients who survived > 10 years, residence in a metropolitan area, high education level, high income, ASCT, and initial treatment at an academic medical center were significantly associated with > 10 year survival; however, multivariate analysis demonstrated that the geographic location of residence, sex, ethnicity, or household median income were not significant factors associated with OS (Raghavendra et al., 2013). Raghavendra et al. (2013) concluded that sociodemographic and other significant healthcare disparities exist for those who are treated for NDxMM.

ASCT is not an appropriate or feasible treatment option for a subset of patients with NDxMM, including older adults and those with poor performance status (Anderson et al., 2014; Palumbo et al., 2011). Investigators from the Dartmouth Hitchcock Medical Center, who retrospectively evaluated the impact of multiple prognostic variables, including distance from the cancer center for those who did undergo ASCT, concluded that increasing distance from the cancer center was associated with improved OS and disease free survival (Lipe et al., 2012). Lipe et al. (2012) acknowledged the limitations of their analysis, including a selection bias to only include patients who were eligible for ASCT and small sample size. Investigators from the Cleveland Clinic Myeloma Research

Program also performed a retrospective analysis examining, among other variables, the impact of patient distance traveled on clinical outcomes among Black patients with both NDxMM and relapsed/refactory MM, concluding that socioeconomic status, race, and distance traveled did not affect outcome (Abou-Jawde et al., 2006). A rejoinder to Abou-Jawde et al. (2006) by Ojha et al. (2007) identified methodlogical flaws including over estimation of the impact of serum albumin and β-2 microglobulin, inconsistent patient populations studied, and insufficient statistical power, raising serious concerns regarding the results of the research.

This study addressed the gap in the literature utilizing data from The Myeloma Institute for Research and Therapy (MIRT) located at the University of Arkansas for Medical Sciences (UARK, a.k.a, UAMS) in Little Rock, Arkansas, USA. MIRT is the largest dedicated research and treatment center for MM in the world. As an international and state reference center for MM, MIRT attracts and treats patients from all over the globe (Arkansas Online, 2014; Talk Business and Politics, 2014). Research originating from MIRT includes the discovery of thalidomide as an active anti-myeloma drug (Singhal et al., 1999), the use of gene expression profiling as a tool to differentiate high risk multiple myeloma (HRMM) from low risk multiple myeloma (LRMM) (Shaughnessy et al., 2007), and the performance of both single and tandem ASCT on outpatients. The *Total Therapy* approach of applying all therapeutically active pharmaceutical drugs and procedures, including ASCT in the treatment of newly diagnosed MM has been applied in successive clinical trials at MIRT, originating with Total Therapy 1 in 1989 to Total Therapy 6, which is still accruing subjects in late 2015.

There is a clear need to identify the potential impact of the distance from a patient's home to MIRT on PFS and OS for those treated at MIRT for NDxMM. At the time of this study, MIRT had never formally investigated the potential impact of patient distance traveled on PFS and OS. Given the central Arkansas location of MIRT, volume of patients with NDxMM treated, the role of MIRT/UARK as a state-operated medical facility, and its worldwide referral base, MIRT has the data and capacity to inform the community by investigating the potential impact of patient distance traveled on PFS and OS for those with NDxMM in a quantitative, retrospective study. Owing to the large sample size, uniform treatment, and long term follow up of subjects with NDxMM, the TT3 dataset was chosen to inform this study. The TT3 trials were among the first to prospectively combine novel therapies with ASCT and consolidation in the newly diagnosed setting and are among the most mature trials for long-term follow up in this patient population. The TT3 trials evaluated PFS and OS that are measured in days and reported as months/years.

Purpose of the Study

The purpose of this study was to determine if those patients with NDxMM who live within close proximity to MIRT have different PFS or OS outcomes than those who live outside of close proximity to MIRT in the TT3 clinical trials. TT3 is one of the first prospective clinical trials that combined novel therapy with chemotherapy, followed by ASCT and novel drug maintenance therapy in NDxMM patients (see Appendix E and Appendix F). The distance of <121 miles from MIRT was chosen to include most of the State of Arkansas and UARK-affiliated regional health centers (formerly known as

AHECs), and because this distance corresponds to MIRT being reasonably reachable with approximately 2 hours of travel time by automobile.

This study was designed to produce findings that will positively influence the delivery of MM care and other more common hematologic malignancies such as leukemia and lymphoma. It specifically tested whether or not proximity to the site of care was associated with longer PFS. Findings from translational and clinical research in MM have been applied to more commonly encountered hematologic malignancies, including leukemia and lymphoma. For example, the novel therapies lenalidomide and bortezomib, first studied in MDS and MM, are now routinely utilized in the management of mantle cell lymphoma and are FDA approved for use in this disease. Findings from studies utilizing ASCT for MM are commonly applied to those who are undergoing the procedure for diffuse large B cell lymphoma.

Many U.S. insurance companies do not provide financial benefits to allow a patient and/or family to travel to a distant site for cancer care. Hospital admission may be the only mechanism to provide room and boarding for a patient with cancer (Alonso-Zaldivar, 2014). High socioeconomic status (SES) has been associated with better outcomes among a variety of health conditions, including multiple myeloma (Paul, Hall, Carey, Cameron, & Clinton-McHarg, 2013; Raghavendra et al., 2013). This suggests that high SES may enable a person with NDxMM to travel to a reference center for the disease and have the ability to temporarily relocate to the area to allow for protocol enrollment or off-protocol therapy. This ability to travel and temporarily relocate for care

is not covered by many insurance companies and those with limited financial resources are less likely to be able to temporarily relocate to the site of care for their disease.

Research Questions and Hypotheses

The primary objective of this study was to determine if there qs a difference in PFS or OS for those with NDxMM who live <121 miles from MIRT compared to those who live ≥ 121 miles from MIRT in TT3. The hypothesis suggests there may be a difference in PFS and OS due to logistical or patient care challenges in both planned and nonscheduled visits (owing to complications attributable to the disease or treatment related toxicities). In many rural practice settings, the specialized medical expertise required to treat MM, along with medical complications of the disease or its treatment, may not be readily available.

Several research questions were used to investigate the study hypothesis. Key terms used in the research questions were:

- GEP70 – Gene expression profiling of 70 genes related to MM, to define the risk classification of multiple myeloma as HRMM or LRMM (Shaughnessy et al., 2007; van Laar et al., 2014). GEP70 is a molecular diagnostic.

- Close proximity to MIRT – Distance from a patient's zip code of residence to MIRT is < 121 miles.

- Outside close proximity to MIRT –- Distance from a patient's zip code of residence to MIRT is ≥ 121 miles.

Research Question 0

Research Question 0 (RQ0): Does close proximity to MIRT impact PFS and OS in TT3?

Null hypothesis (H_{00}): There is no statistically significant difference to PFS or OS based on a patient's close proximity to MIRT.

Alternative Hypothesis (H_{A0}): There is a statistically significant difference to PFS or OS based on a patient's close proximity to MIRT, when controlling for GEP70-defined risk and ISS Stage.

Research Question 1

Research Question 1 (RQ1): Does close proximity to MIRT impact PFS and OS in TT3, when controlling for GEP70-defined risk and ISS Stage?

Null hypothesis (H_{01}): There is no statistically significant difference to PFS or OS based on a patient's close proximity to MIRT, when controlling for GEP70-defined risk and ISS Stage.

Alternative Hypothesis (H_{A1}): There is a statistically significant difference to PFS or OS based on a patient's close proximity to MIRT, when controlling for GEP70-defined risk and ISS Stage.

Research Question 2

Research Question 2 (RQ2): Does patient age ≥ 65 years and close proximity to MIRT impact PFS and OS in TT3, when controlling for GEP70-defined risk and ISS Stage?

Null hypothesis (H_{02}): There is no statistically significant difference in PFS or OS based on a patient age ≥ 65 years and close proximity to MIRT after controlling for GEP70-defined risk and ISS Stage.

Alternative Hypothesis (H_{A2}): There is a statistically significant difference in PFS or OS based on a patient age ≥ 65 years and close proximity to MIRT after controlling for GEP70-defined risk and ISS Stage.

Research Question 3

Research Question 3 (RQ3): Does patient gender and close proximity to MIRT impact PFS and OS in TT3, when controlling for GEP70-defined risk and ISS Stage?

Null hypothesis (H_{03}): There is no statistically significant difference on PFS or OS based on patient gender and close proximity to MIRT after controlling for GEP70-defined risk and ISS Stage in TT3.

Alternative Hypothesis (H_{A3}): There is a statistically significant difference on PFS or OS based on patient gender and close proximity to MIRT after controlling for GEP70-defined risk and ISS Stage in TT3.

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Theoretical Basis of the Study

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The theoretical framework used for this study was Andersen's behavioral model of health services utilization (BMH). BMH was originally created in the 1960s to explain why families use healthcare services, but has been updated to reflect individual choices in healthcare services consumption (Andersen, 1995). The behavioral model of health services utilization posits that there are three critical factors (predisposing factors, enabling factors, and need factors) that influence an individual's use of health care

services (Anderson, 1995). Andersen's model has been subsequently adapted for use in a variety of medical and social research applications, including cancer screening (Rahman, Dignan, & Shelton, 2005).

Anderson (1995) described three sets of factors:

- predisposing factors consisting of demographic descriptors of a population, such as age and ethnicity;

- enabling factors that allow a person to access health services, including financial resources, health insurance, and geographic location; and

- need factors consisting of motivating reasons that a person would seek to access healthcare such as health screening, acute illness, or trauma (Anderson, 1995).

MM is the late manifestation of the accumulation of malignant plasma cells in the bone marrow or extramedullary anatomical sites, which may cause anemia, bone pain, fracture, or immune suppression leading to infection (Colson, 2015). The application of Andersen's model to NDxMM and this study allows for predisposing factors associated with MM, enabling factors, and need factors to be used to explain any potential differences in patient outcome.

In this study, the three essential factors of the BMH model were utilized and evaluated as either dependent or independent variables. This study analyzed secondary data obtained from a prospective clinical trial; the factors that prompted to present to MIRT (opposed to another cancer center) for therapy are not were recorded in the original dataset. Table 1 shows the alignment of the three essential BMH factors with study variables.

Table 1

BMH Constructs and Relationship to Study Variables

BMH Construct	Description	Database	Study variable
Age	Predisposing factor	Age at enrollment	Independent
Ethnicity	Predisposing factor	Not reported	N/A
SES Status	Enabling	Not collected	Potential Confounder
Geographic location	Enabling	<121 miles, or >= 121 miles	Independent
NDxMM diagnosis	Need	ISS Stage	Independent

Nature of the Study

The study was a quantitative, retrospectively based secondary analysis of data obtained from MIRT's TT3a (Barlogie, 2003) and TT3b protocols (Barlogie, 2006) that enrolled patients with NDxMM. The study investigated PFS and OS outcomes where PFS is measured as the time from study enrollment to disease progression/relapse or death from any cause, and OS is measured as the time from study enrollment to death from any cause, according to the EBMT criteria (Bladé et al., 1998). The dependent variables are PFS and OS. Independent variables include close proximity to MIRT based on patient zip code at TT3 study registration, gender, age ≥ 65 years, GEP70-defined risk status (HRMM or LRMM), and ISS stage. The data to inform this study were collected from prospective clinical trials for those with NDxMM conducted at MIRT. The data collected for clinical decision-making and research purposes originated from the TT3 clinical trials, which were approved by the Institutional Review Board (IRB) at UARK and by appropriate U.S. regulatory agencies, including the U.S. Food and Drug Administration. The secondary dataset that was analyzed in the study was void of personally identifiable, protected health information. The Institutional Review Board

(IRB) at both UARK and Walden University approved this study. All persons meeting eligibility criteria who were enrolled on TT3 will be evaluated. The National Cancer Institute (NCI) (grant CA 55813) supported the TT3 trials. Bart Barlogie, M.D., Ph.D., was the principal investigator (PI) for both trials. In the TT3a protocol, 303 patients were enrolled, with an additional 177 enrolled on the extension trial TT3b. In total, data from all 480 patients enrolled to both trials was evaluated in a survival analysis defined by PFS and OS.

The Cox proportional hazard (PH) model was utilized to analyze the data for time to event for PFS and OS outcomes. Covariates were chosen and are founded in the peer-reviewed MM literature. Additional Cox PH analysis was performed to determine if distance impacts PFS or OS while controlling for GEP70-defined risk and ISS stage. A result is considered statistically significant if a p value is < .05.

In the TT3 protocols, patients must have met the CRAB criteria (*C*alcium elevation, *R*enal insufficiency, *A*nemia, and *B*one lesions), indicating that systemic treatment for MM was medically indicated (Kyle et al., 2003). MM was staged according to the ISS criteria (Greipp et al., 2005). Disease response and progression are defined by the EBMT criteria (Bladé et al., 1998). Retrospective review was chosen for this study based on three primary considerations. First, data and outcomes are available for patients treated on two prospective clinical trials (TT3a/b), the results of which have been published in the peer-reviewed literature (Barlogie et al., 2007; Nair et al., 2010). Second, if the data and analysis indicate that those who live in close proximity to MIRT have longer PFS and/or OS, with other factors being controlled for, this provides rationale to

implement policy change. Third, the time required to prospectively collect these data and analyze for the primary objective of the study puts patients at undue risk of harm, if the null hypothesis cannot be rejected.

Definition of Key Terms

The following list provides definitions of key terms and variables, which are used to describe multiple myeloma, and research terminology. A list of abbreviations is located in Appendix G.

Adverse event (AE): Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure (Cancer Therapy Evaluation Program, 2003, p. 1). In the TT3 protocols, all adverse events are graded according to the NCI Common Terminology for Adverse Events, Version 3.0 (Cancer Therapy Evaluation Program, 2003).

European Group for Blood and Marrow Transplantation (EBMT): A European cooperative group focusing on research related to bone marrow transplantation.

GEP70: Gene expression profiling of 70 genes related to MM, utilizing purified plasma cells (CD138+) and the Affymetrix U133Plus2.0 gene micro array, (Shaughnessy et al., 2007).

GEP70 Low Risk MM: Low-risk MM according to the GEP70 model, with a 77% probability of 5-year event-free survival (Shaughnessy et al., 2007; van Laar et al., 2014).

GEP70 High Risk MM: High-risk multiple myeloma according to the GEP70 model, with a 34% probability of 5-year event-free survival (Shaughnessy et al., 2007; van Laar et al., 2014).

International Staging System (ISS): A validated schema to classify and stratify patients diagnosed with MM risk that is used in research and standard practice (Greipp et al., 2005).

Monoclonal Gammopathy of Undetermined Significance (MGUS): The presence of an M-protein <30g/L, bone marrow clonal plasma cells <10%, no end organ damage, and no evidence of B-cell lymphoma or other disease known to produce an M-protein. A pre-neoplastic condition (Surveillance, Epidemiology, and End Results Program (SEER), 2015).

Myeloma Institute for Research and Therapy (MIRT): A center for clinical care and research that is located at the University of Arkansas for Medical Sciences.

Multiple Myeloma: A hematologic malignancy of plasma cells that produce abnormal amounts of immunoglobulin or immunoglobulin protein fragments, which meets the CRAB clinical criteria (Kyle et al., 2003; see Appendix D).

Overall Survival: Time from study enrollment to death from any cause (Barlogie, 2003).

Progression Free Survival: Time from study enrollment to disease progression or death from any cause (Barlogie, 2003).

Tandem Transplant: Two planned autologous stem cell transplants during initial therapy.

Total Therapy 3a/b (TT3): Prospective clinical trials of 480 newly diagnosed persons with MM (Barlogie, 2003, 2006).

University of Arkansas for Medical Sciences (UARK): The University of Arkansas for Medical Sciences located in Little Rock, Arkansas.

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Assumptions, Limitations, and Scope of Study

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Four major assumptions were made for this research study: (a) the data from TT3 were nonbiased, accurate and were recorded accurately in the multiple myeloma database (MMDB); (b) the patients who were enrolled and evaluated on TT3 provided written informed consent, met the eligibility criteria as established by the respective protocols, and were compliant with the treatments and procedures that informed the protocols; (c) patients that were enrolled to the TT3 protocols were representative of NDxMM patients who were treated at an academic medical center during the years the respective studies were actively accruing; and (d) the data evaluated in the study would adequately answer the research questions in the study.

Assumptions

The Total Therapy 3a/b protocols were subject to UARK IRB and FDA oversight, and were audited for protocol compliance, disease progression, and death attribution by an independent, outside group of study auditors, led by Raymond Weiss. It was assumed that the data analyzed in this study are without bias and reliable as the data were obtained from research and clinical records. Known sources of bias which may be present in this study include data from a single center (Bellomo, Warrillow, & Reade, 2009) and the use of PFS as an endpoint (Booth & Eisenhauer, 2012; Korn & Crowley, 2013).

Limitations

A known limitation of this study was the use of secondary data for analysis. Although data obtained from the TT3 protocols were collected specifically to address PFS and OS in the study population, the investigational variable of distance was not considered at the time of data collection. The TT3 protocols were not randomized trials. The data collected and recorded were not originally intended to collect geographic data, thus if a subject changed geographic location during the study period, this information would not have been collected and could therefore confound the planned analysis.

The TT3 protocols were designed and implemented by a group of hematologists who are experts in the diagnosis and treatment of MM. MM is a relatively rare condition, accounting for approximately 1% of adult neoplastic disease (Palumbo & Anderson, 2011). The expertise and resources available to treat MM may not be available in other treatment settings, independent of geographic location or socioeconomic status of patients. Socioeconomic status of study participants was not evaluated as a part of the TT3 protocols and will not be analyzed in this research. Factors that influenced an individual subject to participate in the TT3 trials are unknown; however, a diagnosis of MM was confirmed per TT3 protocol.

Disparities in outcomes of patients with cancer, including MM, based on multiple factors including socioeconomic status, race, and geographic location are well described in the literature (Chambers & Hyde, 2015; Landgren et al., 2014; Waxman et al., 2010). As a state-operated medical center, UARK is duty bound to treat patients without regard to their ability to pay or any demographic descriptor. The pre-malignant condition of

MGUS is a known risk factor for the development of MM; however, with the exceptions of avoiding exposure to pesticides, avoiding obesity, and potentially a trial of a therapeutic agent to treat MGUS if diagnosed, there are no known health related behaviors or socioeconomic status which may prevent MM (Landgren et al., 2014; Rajkumar, 2011). Lastly, when the TT3 protocol was initiated, the EBMT (Bladé et al., 1998) criteria were used to categorize disease response; these criteria have subsequently been replaced by the IMWG criteria in research and clinical practice (Rajkumar et al., 2014).

Scope of Study

This study sought to address a gap in the peer-reviewed literature with regard to the potential impact of patient distance traveled on PFS for those with NDxMM. MM therapy has significantly improved outcomes in the past decade (Barlogie et al., 2014; Morgan & van Rhee, 2014). Although geographic location and patient distance traveled are factors for consideration in clinical care and clinical trial participation (Tariman et al., 2014), the role of distance is not considered in any prognostication, treatment, or disease staging system. MIRT is a world recognized leader in the research and treatment of MM and is one of the most commonly cited references in the peer-reviewed literature specific to MM (J.-P. Andersen et al., 2015). TT3 study results have been published in the peer-reviewed literature and have influenced the treatment of MM patients worldwide (J.-P. Andersen et al., 2015; Anderson, 2014). This study did not incorporate findings from a recently published manuscript from investigators at MIRT who demonstrated that *CYR61/CCN1* overexpression in the bone marrow microenvironment was associated with

superior survival and reduced bone disease in patients treated on the TT3 protocol

(Johnson et al., 2014). The data to inform the report from Johnson and associates (2014)

was obtained retrospectively, have not been validated in other data sets, and represent

experimental findings that are not likely to be reproducible in other research or clinical

settings.

The results from this study may influence treatment and clinical trial decision-

making based on patient distance from MIRT in the future, and these findings may also

be applicable to other medical centers that treat hematologic malignancies. If distance is

found to be a significant variable which impacts outcome, special procedures and

protocols, such as the Very Immunocompromised Patient (VIP) protocol (Schindler,

2015), could be considered for implementation at MIRT.

<div align="center">**Potential for Positive Social Change**</div>

MM is generally regarded as an incurable malignancy impacting older persons

(Libby et al., 2014; Rajkumar, 2011) that necessitates chemotherapeutic treatment to

delay progression of the disease. Despite significant progress in the treatment of MM,

measured by increased PFS and OS in recent years, most patients relapse from their

disease (Ferrero et al., 2015; Heuck et al., 2014). Improvement in PFS and OS has also

resulted in peripheral neuropathy, cardiac events, and financial toxicity (Boland et al.,

2013; Colson, 2015; Khera, 2014). The distance from a patient's home to the site of

therapy for MM is not considered in established prognostic or therapeutic designs,

despite the potential of distance to impact PFS or OS. This study utilized Andersen's

theoretical framework of the BMH (Andersen, 1995) and quantitative analysis of two

large clinical trials TT3a/b (Barlogie, 2003, 2006) to determine if living in close proximity to MIRT has an impact on PFS or OS. The peer-reviewed literature is limited and contradictory on the potential of patient distance traveled to impact PFS and OS for those undergoing treatment for NDxMM in the era of novel therapy. The clinical protocols TT3a/b prospectively investigated PFS and OS in NDxMM at MIRT and represent one of the largest datasets utilizing novel therapies, ASCT, and maintenance therapy in the first line setting. The data derived from TT3 will serve to inform the research questions raised in this research study.

Significance of the Study

MIRT is one of the few centers in the world where GEP data and clinical outcomes are collected for nearly all patients on a longitudinal basis, thus presenting the opportunity to conduct the largest trial ever reported investigating the potential impact of patient distance traveled in NDxMM in the era of novel therapy in combination with planned ASCT, followed by multi-agent maintenance therapy. This study is unique as MIRT has the largest database of clinical outcomes and genetic material from CD138+ (multiple myeloma tumor cells) in the world that has undergone GEP. Patients with NDxMM, independent of risk stratification, face significant health challenges due to drug toxicity, infection, tumor lysis, renal complications, skeletal fractures, and other disease related sequela. Access to appropriate and specialized medical care for the treatment of these morbidities is critical. The distance from a patient's home to the site of care may be a significant variable on clinical outcomes.

Summary and Transition

Treatment of MM is reserved for those persons who have symptomatic MM meeting the CRAB diagnostic criteria Therapeutic regimens for MM have improved OS and PFS in the preceding decade (Barlogie et al., 2014; Kumar et al., 2008; Nair et al., 2010); however, treatment for MM often results in decreased quality of life, frequent clinic visits, and toxicities (Baz et al., 2015; Boland et al., 2013; Paul et al., 2013). Although there have been multiple peer-reviewed articles which address the question of patient distance traveled and the potential impact on PFS and OS, none of the peer-reviewed and expert-generated guidelines for MM disease prognostication and treatment address the variable of patient distance traveled to the site of care.

This study sought to address a gap in the literature through an analysis of secondary data obtained from the TT3 clinical trials for persons with NDxMM. The TT3 clinical trial dataset contained all necessary information to investigate the potential impact of patient distance travelled on PFS and OS outcome. The use of a dataset that contained genetic and classic disease staging information allowed for these known influencers on disease outcome to be controlled for in the analysis.

Chapter 2: Literature Review

Introduction and Background

The purpose of this quantitative study of 480 clinical trail participants was to investigate the impact of patient distance from the site of care on survival outcomes for patients enrolled on two clinical trials for newly diagnosed multiple myeloma. Previous, peer-reviewed studies have yielded inconsistent conclusions regarding the issue of patient distance traveled to the site of care for multiple myeloma (MM) treatment. This chapter presents a critical review of the peer-reviewed literature to provide background on the pathophysiology of MM and its treatment, as well as a review of published data regarding the impact of distance on outcomes, and expected outcomes after therapy. The chapter begins with a review of the search strategy for contemporary literature review. The functional role of a healthy plasma cell in immunity, epidemiology, pathophysiology, and other essential elements to characterize MGUS and MM, including disease staging, risk stratification, and common treatments are presented.

Literature Search Strategy

The primary research strategy utilized the electronic review of publically available databases, including PubMed, EBSCO, Cochrane Collection, Web of Science, relevant English literature, peer-reviewed journals, and medical textbooks. It also included a review of proceedings from the respective annual meetings of the American Society of Clinical Oncology (ASCO) and the American Society for Hematology (ASH), because these organizations are among the most reputable sources of information to inform cancer research and treatment. The search was performed using keyword searches

on the Google Scholar search engine, relating to the purpose and research questions of the study, including *multiple myeloma, myeloma, newly diagnosed, MM, MGUS, monoclonal gammopathy of undetermined significance, plasma cell dyscrasia, plasma cell leukemia, health belief model, behavioral model of health services, distance, epidemiology, geography, site of care, gene expression profiling, paraproteinemias, risk stratification, treatment, Total Therapy, autologous stem cell transplant, ASCT, and cytogenetics* as singular terms and in key word combinations with the Boolean operators "*AND*," "*OR*," "*NOT*." The majority of the data used in this literature review was obtained from peer-reviewed literature published from 2011 to 2015, and was focused on clinical outcomes and human data. Peer-reviewed literature older than 2011 was used when more recent data were limited or when the resources were essential reports in the history, diagnosis and treatment of multiple myeloma which were published prior to 2011.

Theoretical Framework

The theoretical framework used for this study was a modified version of Andersen's behavioral model of health services utilization (BMH; Anderson, 1995). BMH was originally developed in the 1960s to explain why families use healthcare services, and has been subsequently updated and modified by its original author. Progressive phases of the model have been published and purport to better inform individual healthcare decision making and its influences on patient outcomes. Phase four of the Andersen model was chosen to inform this study as it has been widely utilized in health related behavior research (Anderson, 1995). The behavioral model of health

services utilization describes three critical factors that influence an individual's use of

health care services:

- predisposing factors,

- enabling factors, and need factors (Anderson, 1995).

Figure 1 presents Phase 4 of Andersen's model.

ENVIRONMENT   **POPULATION CHARACTERISTICS**   **HEALTH BEHAVIOR**   **OUTCOMES**
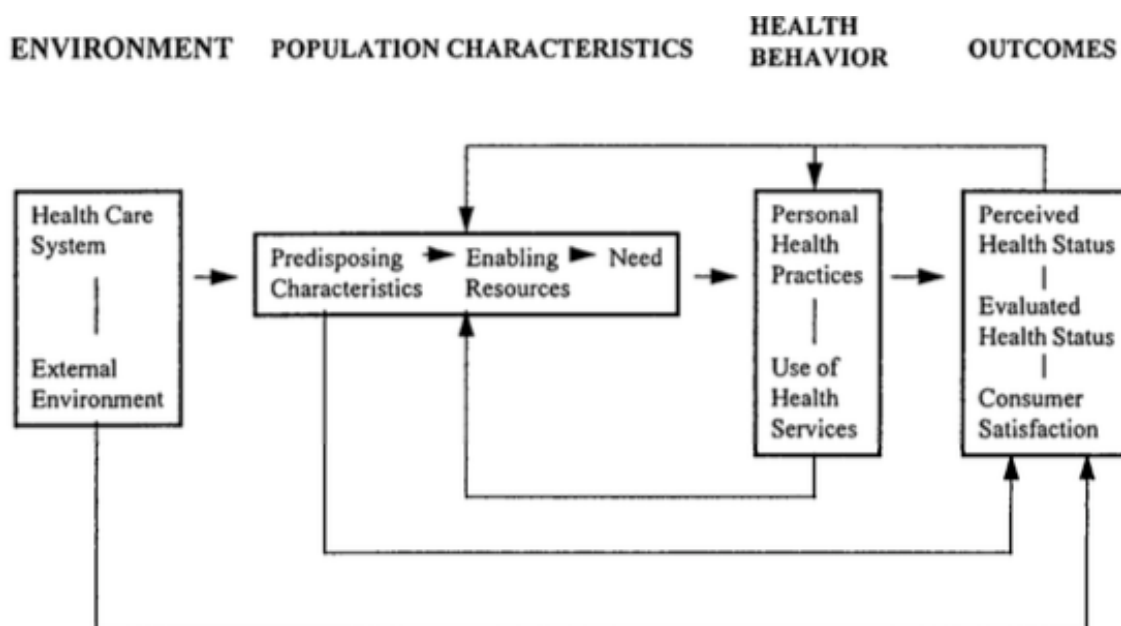
Figure 1. Phase 4 of Andersen's BMH model put for by Anderson. Andersen, R.M. (1995). Revisiting the behavioral model and access to medical care: Does it matter? *Journal of Health and Social Behavior, 36*, 1-10. Copyright 1996 Journal of Health & Social Behavior, property of the American Sociological Association. *Reprinted with permission*. (See Appendix N).

One predisposing factor of an individual to access healthcare services is age. The

data to inform this study originated from two prospective clinical trials that, by protocol

design, only allowed persons aged 18 years or older to participate. MM is associated with

increasing age and is most commonly diagnosed in the seventh decade of life (National

Cancer Institute, 2015c). Participant age is noted by Andersen to impact health care decision making as influenced by social interaction and networks and culture (Andersen, 1995). Age over 65 years was an independent variable in this study.

Ethnicity is another predisposing factor in Andersen's BMH model. Applied to this study, ethnicity information was collected but not analyzed, as the sample population was not large enough to allow for stratification based on ethnicity. Ethnicity and race are known to impact the incidence of MM at the population level. This scope of this study and sample population did not allow ethnicity as a variable; however, additional information regarding race and ethnicity is provided in this chapter. Andersen posits that the choice to access health care services is multifactorial and is influenced by individual beliefs and external factors that have feedback mechanisms. Andersen (1995) suggested that genetic information could be considered as a potential predisposing characteristic; the development of MM is associated with heritability, however the use of genetic screening is not currently in routine clinical practice. Genetic information was obtained from CD138+ cells and analyzed in this study but germline mutations were not analyzed.

Andersen (1995) described enabling factors such as an individual's financial resources, health insurance, and geographic location as elements that enable them to access healthcare services. SES, geographic location, and the existence of a health care provider undoubtedly influence access to care (Andersen, 1995, p. 3). Enabling factors such as health insurance status have broad influence on health care outcomes and health policy is beyond the scope of this study. As a theoretical model, the BMH acknowledges

that culture, biologic necessity, and access to care all influence health care services utilization (Andersen, 1995).

Geographic location is an enabling factor in the BMH model and as applied to this study is a dependent variable. MM is a rare disease in the general population and is typically treated, within the confines of a U.S. medical system model by an oncologist or hematologist. Many rural communities do not have a local oncologist/hematologist, which is a limiting factor according to the BMH model. The current study utilizes distance, measured in miles, from MIRT as a potential influencer of PFS and OS outcome. The medical expertise and resources to diagnose and treat MM may not be present in all communities, thus distance may be an enabling factor to access care and influence treatment. Andersen suggests that burdens to access health care, such as distance or living in a rural community without ready access to the resources required to treat a disease may influence an individual's decision to seek care for their condition (Andersen, 1995). The current study did not examine the factors that influenced an individual's choice to seek care at MIRT; rather it used geographic distance from MIRT as a surrogate for ready access to specialized medical care.

Andersen (1995) suggests that realized access to care is the actual use of services and for the purposes of this study; all participants had access to care and were able to meet eligibility criteria for enrollment on a Phase II clinical trial. The ability to access a specialized tertiary care facility is a complex issue such that a wide spectrum of SES is represented. SES is an acknowledged influencer of health status, health service utilization and a potential confounder in this study.

The need to seek medical care was described by Andersen (1995) as a variable that is subject to interpretation by an individual and their perceptions of health or financial factors. Perceptions of need to seek treatment for asymptomatic conditions such as hypertension are likely different from high symptomatic conditions, such as MM. MM is clinically notable for variety of clinical symptoms including anemia, bone pain and fracture (Colson, 2015). MM is an uncommon malignancy and it is unlikely that the general public would not have any knowledge of the need to be treated for MM unless and until the disease was detected or there was a family history of MM. The need to seek care for MM was not directly assessed in this study; however, the disease burden as measured by the ISS was assessed and may be used as a proxy for need, such that life expectancy is correlated with ISS stage. A limitation of this construct in the current setting is the protocol driven study procedures and therapeutic regimen; the TT3 trials are aggressive trials aimed at disease cure not palliation or pain control. As applied to BMH model, this study does not address the dimension of need for those who are unfit, unwilling, or unable to undergo aggressive therapy for NDxMM.

Role of Normal Plasma Cells in Human Immunity

Plasma cells (PCs) are terminally differentiated B-cells that produce immunoglobulins (Igs), which are utilized by the human immune system to identify and neutralize pathogenic organisms including viruses, bacteria and cancer cells via recognition of antigens (Pellat-Deceunynck & Defrance, 2015; Tai & Anderson, 2011). Five major isotypes of Igs have been identified in humans: IgA, IgD, IgE, IgG, and IgM (Brioli et al., 2014). The five major Igs are known as heavy chain isotypes, with two

accompanying kappa (κ) or lambda (λ) light chains (Munshi, Longo, & Anderson, 2012). In MM, excess proteins derived from clonal plasma cells are secreted into the serum and urine, which is known as an "M spike." When excess proteins caused by clonal plasma cells are detected only in the urine, this is known as Bence-Jones protein. MM may be caused by any of the major heavy or light chain proteins. The κ/λ ratio is used clinically to monitor the disease/tumor burden (Anderson, 2014; Brioli et al., 2014). In the normally functioning immune system, Igs form the basis of circulating antibodies that are critical to the humoral immune response. Each combination of heavy chains and light chains produces a specific immunoglobulin molecule (protein).

Disease Definitions

MGUS is defined by the IMWG as the presence of an M-protein < 30 g/L in serum, bone marrow clonal PCs < 10% and low level of PC infiltration in a trephine biopsy, no evidence of other B-cell proliferative disorders, and no organ or tissue impairment, including bone lesions (Kyle et al., 2003, p. 752).

Smoldering MM (SMM) is defined as serum protein (IgG or IgA) ≥ 30 g/L or urinary monoclonal protein ≥ 500 mg per 24 hours and/or clonal bone marrow PCs 10%-60% and the absence of myeloma defining events (Rajkumar et al., 2014, p. 541).

The revised IMWG diagnostic criteria define (clinical/symptomatic) MM by the presence of ≥ 10% clonal PCs in the bone marrow and/or presence of a biopsy-proven bony or extramedullary plasmacytoma (Rajkumar et al., 2014) and myeloma defining events defined by the CRAB criteria (Kyle et al., 2003). The following biomarkers are

also indicative of MM, clonal bone marrow PC $\geq$ 60%; involved/uninvolved serum free light chain ratio § $\geq$ 100; > 1 focal lesion by MRI (Rajkumar et al., 2014, p. 541).

Plasma Cells, Monoclonal Proteins, and MGUS

Plasma cells secrete antibodies into the circulation to assist in normal immune function. In MGUS, single plasma cells proliferate (clones) without antigen exposure, and produce a single monoclonal (M) protein that may be detectable in urine, serum or other tissues (R. Kyle & Rajkumar, 2015). This nonantigen stimulated production of an M protein is the manifestation of abnormal plasma cell function. MGUS is characterized by the detection of M protein without end-organ damage or other benign or hematological conditions (R. Kyle & Rajkumar, 2015). MGUS almost universally precedes MM. The rate of "conversion" from MGUS to MM is approximately 1% per year (Rajkumar, 2015).

MGUS is frequently referred to as a single disease state in the literature, although there are multiple "classifications" of MGUS based on Ig subtype (Agarwal & Ghobrial, 2013; Landgren, 2013) and risk of conversion to MM (Gundrum & Neuner, 2013; Mateos et al., 2013). In a prospective cancer screening study of more than 77,000 patients aged 55-74 years, nearly all of the 71 patients who were diagnosed with MM had a preceding MGUS diagnosis (Landgren, Kyle, Pfeiffer, et al., 2009). In this literature review and research study, MGUS is defined as a single entity according to the IMWG criteria.

MGUS is typically associated with older age, which may also be associated with comorbidities that require more frequent medical care, thus leading to laboratory

investigations which revealed MGUS, when it would have gone undiagnosed in patients who did not seek frequent medical care (R. Kyle & Rajkumar, 2015). In a large study investigating the outcomes of patients with MGUS, it was concluded that patients with MM who were aware of a prior MGUS diagnosis had better OS (median 2.8 years) compared to those patients who were not previously diagnosed with MGUS (median 2.1 years), suggesting that MGUS patients who were clinically monitored at regular intervals experienced earlier detection of MM (Sigurdardottir et al., 2015). Clinical guidelines suggest that patients with MGUS be monitored for disease progression to MM but that no treatment for the disease be offered, owing to the low rate of conversion to MM and the toxicities associated with treatment (Anderson, 2014; R. Kyle & Rajkumar, 2015; Rajkumar et al., 2014).

Historically, treatment with anti-MM agents directed towards MGUS resulted in toxicity with little clinical benefit. One recent study demonstrated that the anti-MM therapy combination of lenalidomide + dexamethasone, for those with high risk MGUS or high risk SMM (nonsymptomatic MM) improved OS (Mateos et al., 2013), but no therapy was suggested outside of a clinical trial (Landgren, 2013).

Epidemiology of MGUS

MGUS is an asymptomatic disease affecting 1 in 25 persons ≥ 50 years of age, and it is commonly detected by routine laboratory secondary to other medical concerns (Rajkumar, 2015). MGUS diagnosis is primarily made in persons aged 50 years or older, with increasing age correlating with a higher incidence of the condition (Agarwal & Ghobrial, 2013). The prevalence of MGUS is 3-4% of the adult population in the United

States, with males having a slightly higher incidence compared to females (Wadhera & Rajkumar, 2010; Landgren, Kyle, Pfeiffer, et al., 2009). However, the true incidence and prevalence is not known, as the condition is not routinely screened for in the "at risk" population of adults in the United States (Carson, Bates, & Tomasson, 2014). It is unlikely that a prospective study comparing detection and follow-up frequency for MGUS will be conducted owing to the requirements of a large sample size, long follow-up time, and cost (Sigurdardottir et al., 2015). Additionally, any intervention, including watchful waiting and close monitoring, must be associated with a significant increase in OS with minimal or no toxicity of any type, owing to the nonsymptomatic nature of MGUS and the relatively low transformation of MGUS to MM requiring therapy (R. Kyle & Rajkumar, 2015).

The age adjusted prevalence rate of MGUS was three times higher for Blacks when compared to Whites in a study of U.S. veterans (Landgren et al., 2006). Racial and ethnic differences in the prevalence of MGUS suggest a potential role of genetic and environmental factors in the development of the disease (Agarwal & Ghobrial, 2013). From a clinical and/or public health perspective, obesity was the only identified health related, modifiable factor which potentially can reduce the incidence of MGUS (Carson et al., 2014; Landgren et al., 2010; Rajkumar, 2015). In some studies exposure to pesticides was associated with a higher incidence of MGUS (Landgren, Kyle, Hoppin, et al., 2009; Pahwa et al., 2012; Wadhera & Rajkumar, 2010).

A recent study sponsored by the NCI-supported Southwest Oncology Group (SWOG) revealed that four genes predict progression from SMM to MM, with 85.7% of

patients transitioning from SMM to MM in 24 months (Khan, et al., 2015). Early

detection of high risk SMM may also be associated with earlier detection of MM and

better outcomes, as it was demonstrated that close monitoring of MGUS resulted in

improved OS for those with MM (Agarwal & Ghobrial, 2013; Rajkumar, 2015). The

utility of a four-gene model to predict those who converted from SMM to MM is

consistent with the observation that early detection of genetic changes in PCs, which

results in transformation from MGUS to SMM to MM, may result in improved clinical

outcomes. A limitation of the four-gene model is the need for sampling of bone marrow

to obtain CD138+ cells (Khan, et al., 2015).

In summary, MGUS is a premalignant condition in those aged over 50 years, with

increased prevalence in Blacks (5.9%–8.4%) when compared to Whites (3.0%–3.6%),

that is slightly more common in males (Wadhera & Rajkumar, 2010). MGUS transforms

to SMM at a relatively low rate of 1% per year, over the age of 50, with some variations

during the sixth to eighth decade of life (Rajkumar, 2015). SMM is genetically and

clinically similar to MM (Khan, et al., 2015) but does not meet the required elements of

the CRAB criteria, thus pharmacologic intervention is not indicated outside of a clinical

trial (Gundrum & Neuner, 2013). MGUS is not a preventable condition, with the possible

exceptions of the avoidance of pesticide exposure and obesity, and it is a precursor state

of MM.

Epidemiology of Multiple Myeloma

The American Cancer Society reported that in 2015, approximately 26,850

persons will be newly diagnosed with MM, with 11,240 persons expected to die from the

disease in the United States (American Cancer Society, 2015, p. 4). MM is thought to result from transformation of the premalignant plasma cells (MGUS) to MM by environmental and genetic factors (Rajkumar, 2015). There are no validated predictors of transformation from MGUS to MM that are in routine clinical practice (Alexander et al., 2007). The median age of MM diagnosis is 65 years (Rajkumar, 2011). The prevalence of MM in Blacks is double the prevalence in Whites, and the disease is twice as common among males when compared to females (Baris, Brown, Andreotti, & Devesa, 2013). Globally, the highest incidence of MM occurs in Black Americans, followed by White Americans, with the least common incidence occurring in Asians, regardless of living in America (Martino, 2011).

Data obtained from the SEER database indicate the incidence of MM is 6.3 per 100,000 men and women, with 3.3 deaths per 100,000 based on 2008-2012 data (SEER Cancer Statistics Factsheets: Myeloma & National Cancer Institute, 2015). The lifetime risk of developing MM is 0.7% for both men and women, based on 2008-2012 data (SEER Cancer Statistics Factsheets: Myeloma & National Cancer Institute, 2015). MM is exceedingly rare in those under age 20 (Crusoe et al., 2015). There is one case report in the literature describing biopsy proven, symptomatic MM in a child of 8 years who underwent standard anti-MM chemotherapy, relapsed, was administered subsequent salvage therapy, and who was scheduled for allogeneic transplant (Crusoe et al., 2015).

Non-Modifiable Risk Factors for Development of Multiple Myeloma

Advanced age is a risk factor for MM; age adjusted incidence rates of MM increase with age over 40, with continued and increasing risk until the eighth decade of

life (Alexander et al., 2007). Development of MGUS is a risk factor for MM as it is a premalignant precursor to MM (Rajkumar, Gahrton, & Bergsagel, 2011). MGUS may be the result of pesticide exposure or other environmental exposures over the course of a lifetime (Landgren, Kyle, Hoppin, et al., 2009), but there is not a definitive action or avoidance strategy which will prevent MGUS. Early detection of MGUS is associated with increased survival of MM (Agarwal & Ghobrial, 2013), but this is due to close clinical observation. There are investigational techniques involving next generation sequencing (NGS) and GEP of CD138+ cells (plasma cells) to determine genetic features which are correlated to increased transformation to MM (Agnelli, Tassone, & Neri, 2013; Braggio, Egan, Fonseca, & Stewart, 2013; López-Corral et al., 2012; Mateos et al., 2013). The widely used technique of analyzing serum free light chains (FLCs) to determine risk of MGUS transformation to MM has been validated in the literature (Dispenzieri et al., 2008). Infections, due to a defective immune system as a consequence of the disease or due to immunocompromised status as a result of treatment, was identified as the leading cause of MM related death (Blimark et al., 2015).

Modifiable Risk Factors for Development of Multiple Myeloma

Obesity is a modifiable risk factor associated with the development of MM; in a meta-analysis of prospective clinical trials, increased body mass index (BMI) correlated to a higher incidence of MM (Wallin & Larsson, 2011). There are sparse contemporary data available which report the potential of diet to impact the incidence of MM. A series of older studies conducted primarily with Swedish fishermen concluded that the type of fish (lean versus fatty) and a lack of vegetable intake were associated with MM

development, but these data are not representative of population level data (Martino, 2011). Tobacco and alcohol, as variables in the development of MM, have not been studied in large populations and the data are not conclusive (Alexander et al., 2007). It should be noted that both alcohol and tobacco use have been associated with the development of multiple other tumor types (American Cancer Society, 2015).

Heritability of Multiple Myeloma

There are a number of epigenetic, genetic, transcriptional, and phenotypic changes associated with the development of MGUS and MM (Agarwal & Ghobrial, 2013). The Online Mendelian Inheritance in Man (OMIM) database reported 74 Mendelian disorders including cancer or a susceptibility to develop cancer as a phenotypic manifestation (McKusick, 2007). Genome-Wide Association Studies (GWAS) and other epidemiologic investigations have reported an increased incidence of MM among those who have a first degree relative with the disease (Koura & Langston, 2013; Pruitt et al., 2014). A biological family history that includes any type of cancer is associated with increased MM risk overall (OR=1.73, 95% CI 1.14-2.60; P=0.008), as well as among African Americans (P=0.03) and participants less than 65 years of age (P=0.0005) (Pruitt et al., 2014).

A limitation of many previous investigations into the role of heritability of MM include relatively small sample sizes in case control study designs, a lack of geographic diversity, and most investigations having been conducted among Whites only (Koura & Langston, 2013). Current research investigating genetic traits of those with MGUS and MM indicate that an autosomal dominant heredible hyperphosphorlyated paratarg -7 [pP-

7] has been frequently identified in Blacks, which may be responsible for the increased incidence of the disease in this group of patients (Koura & Langston, 2013).

The Role of Race in Multiple Myeloma

Differences in the incidence and prevalence of MM between Blacks and Whites is amongst the most profound across all tumor types (Greenberg et al., 2015). The increased risk of MM among Blacks is thought to be associated with their two- to three-fold increase in the incidence of MGUS when compared to Whites (Landgren et al., 2014). Data obtained from the SEER database indicated that Blacks consistently have a higher incidence of MM and higher mortality from the disease when compared to other races (Waxman et al., 2010). Waxman et al. (2010) noted that mortality reflected the combined impact of cancer care and incidence, whereas survival is a measure of cancer survival. The increased incidence of MGUS and MM in Blacks does not correlate with poorer survival as a function of race or genetics, but it may reflect poorer access to care. In a 91-subject prospective study that utilized ASCT as part of the therapeutic regimen in an environment where equal access to care was assured, there was no difference in survival outcomes by race (Verma, Howard, & Weiss, 2008).

Among patients diagnosed with MM between 1973 and 2005, Waxman et al. (2010) found that Black MM patients had better disease-specific survival outcomes when compared to White patients ($p < .001$) when the patients were aged over 50 years, and there was no difference among races when the disease was diagnosed before 50 years (Waxman et al., 2010, p. 5503). In a randomized study conducted by SWOG, Black and White patients diagnosed with MM had equal survival outcomes when treated on either

of the two possible randomized treatments (Modiano, Villar-Werstler, Crowley, &

Salmon, 1996). In a large, retrospective study evaluating the impact of race on MM

outcomes of more than 40,000 patients, Black patients had similar survival rates

compared to White patients by multivariate analysis (Kaya et al., 2012).

Pathophysiology of Multiple Myeloma

MGUS is the result of the transformation and accumulation of abnormal PCs that

produce abnormal amounts of a single Ig. MGUS is an asymptomatic disease that is

hypothesized to transform to MM based on multiple oncogenic events within the plasma

cell or the bone marrow itself (Agarwal & Ghobrial, 2013). Genetic events leading to the

development of MM include chromosome 1 abnormalities, IgH translocations, Cyclin D

dysregulation, *RAS* or *FGFR3* mutation, deletion of chromosome 13 and hypodiploidy

(Agarwal & Ghobrial, 2013; Caltagirone et al., 2014; Heuck et al., 2014; Kalff &

Spencer, 2012; Palumbo & Anderson, 2011). Although MM is a hematological

malignancy, it is characterized by multiple genetic aberrations resulting in overexpression

of oncogenes, loss of functional tumor-suppressor genes, which is more associated with

solid tumor biology (Anderson, 2014) and the presence of an altered bone marrow

microenvironment (Bam et al., 2013; Cives, Ciavarella, Dammacco, & Silvestris, 2013).

SMM is the result of progression of MGUS (Rajkumar, Landgren, & Mateos,

2015). SMM may be differentiated from MGUS in that it is a malignant disease, but it is

not associated with the clinical symptoms described by the CRAB criteria (Khan, et al.,

2015; Rajkumar et al., 2015). Figure 1 illustrates the linear development from a singular,

defective plasma cell, ending in plasma cell leukemia. MM is the result of a

transformation—of defective plasma cells proliferating, changing to the premalignant condition of MGUS, further clinical progression from MGUS to SMM, then upon evidence of clinical symptoms, the diagnosis of MM may be rendered, according to the IMWG criteria (Rajkumar et al., 2014). Plasma cell leukemia is the most aggressive plasma cell dyscrasia, representing systemic extramedullary MM, and it has a median OS of 7 months (van de Donk, Lokhorst, Anderson, & Richardson, 2012). Figure 1 illustrates the progression of PC expansion to symptomatic MM, ending in plasma cell leukemia.
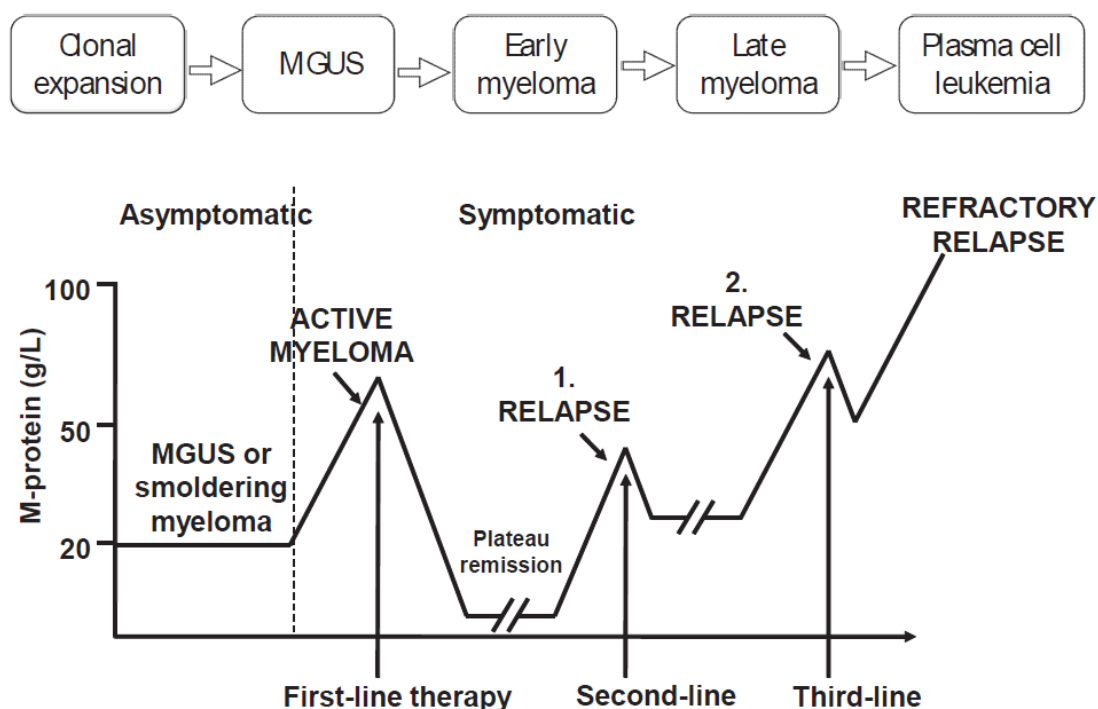
Figure 2. The progression of multiple myeloma: Its pathogenesis and clinical course from MGUS to Plasma Cell Leukemia. From *Multiple myeloma: A quick reflection on the fast progress* by R. Hajek, 2013, InTech Publishing, http://dx.doi.org/10.5772/55366. Used under the Creative Commons BY 3.0 license.

MM has multiple clinical signs and symptoms requiring therapy, including bone pain, bone fracture, lytic lesions, anemia, renal insufficiency, increased infections, poor vision, back pain, DVT/PE formation, bleeding, neuropathy, and hypercalcemia (Boland et al., 2013; Colson, 2015). As abnormal PCs proliferate and bind to the bone marrow stroma, the bone marrow microenvironment secretes substances which serve as survival signals, including interleukin (IL)-6 and vascular endothelial growth factor (VEGF), which initiates angiogenesis to abnormal PCs (K.C. Anderson & Carrasco, 2011; Singhal et al., 1999). As a result of the proliferation of abnormal PCs occupying space within the

limited volume of the bone marrow and the altered bone marrow microenvironment, normal hematopoiesis is interrupted, resulting in the abnormally low production of normal components of blood, including red blood cells, white blood cells and platelets (Bruns et al., 2012).

Abnormal PCs/MM cells are bound to the bone marrow stroma via intracellular adhesion molecules (ICAMs) (K.C. Anderson & Carrasco, 2011; Palumbo & Anderson, 2011). The adhesion of PCs to the bone marrow stimulates bone marrow microenvironment changes that support abnormal PCs/MM cells by increased IL-6 production, which is a growth factor for MM cells, increased resistance to chemotherapy, increased VEGF production, which initiates neovascularization to tumor cells and further supports their growth, and other chemokine and cytokine interactions within the bone marrow(K.C. Anderson & Carrasco, 2011; Johnson et al., 2014; Machal et al., 2013; Nishida, Yano, Nishida, Kamura, & Kojiro, 2006). As MM cells adhere to the bone marrow stroma they increase cell proliferation and increase anti-apoptotic proteins, and this adhesion then induces the bone marrow stroma to react by increasing pro-MM cell signals, resulting in a paracrine loop optimized for MM cell survival (Manier, Sacco, Leleu, Ghobrial, & Roccaro, 2012). This paracrine system loop promotes tumor survival and disease proliferation. This interaction between the MM cell and the bone marrow microenvironment and the survival advantages conveyed to MM cells via binding to the bone marrow stroma, allow for increased cell survival, proliferation, angiogenesis, and chemotherapy resistance (Mahindra et al., 2012).

As MM tumor volume increases, in addition to the disruption of normal hematopoiesis, other biological processes initiate changes and clinical sequela to the bone and other tissues. Under normal hematopoietic conditions, bone is remodeled constantly by the normal regulation of osteoblasts, which serve to support new bone development, and osteoclasts, which are designed to assist in bone reabsorption (Jethava et al., 2015; Mhaskar et al., 1996). Bone pain is frequently the clinical symptom which prompts medical care for MM (Kane, Hoskin, & Bennett, 2015; R. A. Kyle, Gertz, et al., 2003). Bone disease, evident by pain, fracture or focal lesions identified by imaging studies, is the net result of increased osteoclast activity resulting in bone destruction and hypercalcemia (Heuck et al., 2014; Mikhael et al., 2013). Bone destruction and reabsorption results in increased calcium in the serum (Mhaskar et al., 1996; Mikhael et al., 2013). Increased serum calcium (hypercalcemia) may lead to renal insufficiency, which is associated with early death and poor outcomes despite aggressive anti-MM therapy (Khan, Apewokin, et al., 2015).

Multiple Myeloma Disease Staging and Risk Stratification

Treatment and therapy for MM is reserved for those meeting diagnostic criteria for the disease (Rajkumar et al., 2014) and who have myeloma defining events, according to the CRAB criteria:

- [C] Calcium elevation in the blood (serum calcium > 10.5 mg/l or upper limit of normal)

- [R] Renal insufficiency (serum creatinine >2 mg per 100 ml)

- [A] Anemia (hemoglobin <10 g per 100 ml or 2 g < normal)

- [B] Lytic bone lesions or osteoporosis

Neither MGUS nor smoldering MM require anti-MM therapy, but should be monitored closely for the development or transformation to MM, which requires therapy (Anderson, 2014; Mateos et al., 2013; Palumbo & Anderson, 2011). MM is defined by the criteria established in the IMWG (Rajkumar et al., 2014), and it is classically associated with an elevation in M-protein and end organ damage. MM is stratified by risk to identify appropriate treatment strategies to optimize outcomes while minimizing toxicities and other treatment burdens. There are multiple disease risk and staging systems that utilize clinical, genetic, and imaging to assess risk and tumor burden at diagnosis and through varying stages of disease progression (Amin et al., 2014; Mikhael et al., 2013; van Laar et al., 2014).

A complete response (CR) to therapy, as defined by the Bladé criteria or other disease response criteria, have been associated with superior clinical outcomes in a variety of clinical trials, including TT3 (Barlogie et al., 2014). Approximately 30% of patients who were able to achieve CR due to introduction of novel therapy in the induction and relapse treatment setting (Chanan-Khan & Giralt, 2010). A meta-analysis of 4,990 patients selected from both prospective and retrospective studies investigating

the impact of attaining a CR during induction or post-transplant, revealed CR attainment is associated with prolonged OS ($p = < .00001$) and PFS ($p = < .00001$) (Chanan-Khan & Giralt, 2010, p. 2614). Most patients relapse despite a period of CR owing to minimal residual disease (MRD) and intraclonal heterogeneity (Heuck et al., 2014; Papanikolaou et al., 2013; Sarasquete et al., 2005).

The use of mutliparameter flow cytometry, real-time quantitative polymerase chain reaction (RT-PCR), and NGS enable detection of MRD (Ladetto et al., 2012; Paiva et al., 2008; Sarasquete et al., 2005); however, MRD detection is only appropriate in the research setting, has very high cost, limited therapeutic options and is not included in the NCCN guidelines. In one report, the majority of patients with both NDxMM and R/R MM were reported to be MRD + (Vij et al., 2014); however, the inclusion of patients not in CR confounds this finding. Most currently available techniques used for MRD detection require bone marrow sampling or radiography guided/directed fine needle aspiration of MM focal lesions. In the future, NGS based testing of peripheral blood without the need for paired bone marrow sampling for MRD may be viable, validated, and routine.

Durie-Salmon Staging System

The Durie-Salmon (DS) (Appendix B) staging system was published in 1975 and utilized measurements obtained from peripheral blood and skeletal surveys (utilizing X-rays) to define risk and tumor burden in MM (Durie & Salmon, 1975). The DS was utilized in both research and clinical practice to stratify risk and prognosticate for survival, and it served as the standard staging system in MM for more than two decades.

The DS categorized MM disease stage as Stage I, II, or III, based on tumor burden, number of lytic lesions, and renal function (R. Kyle & Rajkumar, 2009). There are several known limitations to the DS including interoperator variability (in assessing the number of lytic lesions by radiograph), a lack of agreed and standardized laboratory normal values for serum creatinine and albumin, the inability to detect nonsecretory MM, and the lack of genetic information to inform disease risk (Greipp et al., 2005; Mikhael et al., 2013; Sawyer, 2011).

EBMT Criteria

Definitions of disease response and relapse were defined by three major cooperative research groups representing MM experts from the European Group for Blood and Marrow Transplantation (EBMT), Autologous Blood and Marrow Transplant Registry (ABMTR), and the International Bone Marrow Transplant Registry (IBMTR) in 1998 (Bladé et al., 1998). The criteria published by the three groups are known as the Bladé criteria. ASCT as a singular therapeutic modality and in combination with novel therapies has been demonstrated to improve patient outcomes in MM (Anderson, 2014; Barlogie et al., 1997; Jagannath et al., 1997; Mikhael et al., 2013; Palumbo et al., 2011). The Bladé criteria established definitions of response and relapse in MM that are obtained using standardized methodologies and are reproducible across multiple practice settings. Additionally, the Bladé criteria utilized repeated measurements of MM markers in peripheral blood and urine, rather than repeated bone marrow aspiration to assess response, limited the number of bone marrow aspirations required, and further reduced the need of repeated radiologic examination to confirm response.

The Bladé criteria did not incorporate modern imaging techniques such as MRI or PET/CT to guide disease stage or detect extramedullary disease. The lack of modern imaging techniques coupled with a complex set of guidelines limited the use of the Bladé criteria outside of an academic setting. The Bladé criteria were utilized in the TT3 protocols to define disease response and relapse. The IMWG guidelines for disease response and relapse have widely replaced the Bladé criteria and were used to define disease response in the TT 4, 5, and 6 clinical trials at UARK beginning in 2008.

International Staging System

The ISS (Appendix C) was published in 2005 and replaced the DS as the standard model for MM staging and risk stratification (R. Kyle & Rajkumar, 2009). The ISS utilizes the commonly obtained laboratory values of serum albumin and serum β-2 microglobulin to categorize MM as Stage I, II, or III. The advantage of the ISS compared to the DS is the lack of interoperator variability in determining the number of lytic lesions by skeletal survey. Importantly, the cost of obtaining the necessary information to stage the disease is minimal and may be utilized throughout treatment. The ISS is validated, available in any modern medical practice, and is obtained by computing results from a peripheral blood draw.

Limitations of the ISS include the reliance on the serum β-2 microglobulin level, which may be elevated simply due to renal failure or tumor burden; the ISS may not be utilized in the setting of MGUS or SMM; it does not utilize genetic information; and it has not been validated when novel therapies are administered (R. Kyle & Rajkumar, 2009). The ISS does not consider molecularly defined risk but relies on clinical values

obtained from peripheral blood. The ISS is used in both the research and standard practice setting and is commonly reported in current clinical trials, as this practice allows for comparison of patients in different clinical trials (Rajkumar et al., 2014). The ISS does not utilize genetic information obtained from conventional cytogenetics or fluorescent in situ hybridization (FISH) analysis obtained from tumor cells to assess disease risk. The ISS was utilized as the staging system in TT3 clinical trials.

IMWG Criteria

The IMWG criteria for the diagnosis, staging, and risk stratification of MM were first published in 2003 and were last updated in 2014 (Kyle et al., 2003; Rajkumar et al., 2014). The purpose of the IMWG criteria was to provide clinicians updated diagnostic and response criteria in recognition of the impact of novel therapies, improved detection of the disease, genetic information obtained from both conventional cytogenetics and FISH, new imaging techniques, and to provide a common schema to compare study populations (Rajkumar et al., 2014). The updated IMWG criteria were established by a group of MM experts representing international collaboration and were created in acknowledgement of the impact of novel therapies to improve OS with early intervention. The IMWG incorporates the use of CT, MRI, and PET-CT to detect extramedullary disease and the number and volume of focal and lytic bone lesions; however, the use of these modalities in routine practice is not recommended and is associated with very high cost (Anderson, 2014; McAfee, 2013; Mikhael et al., 2013).

Multiple Myeloma Risk Assessment

Extending survival and attaining cure in MM result from the use of induction therapy, high dose therapy followed by ASCT, consolidation, and maintenance therapy, although cure is relatively uncommon and is only possible in approximately 10% of patients with existing therapy (Barlogie et al., 2014; Hajek, 2013). Host-related risk factors include age, performance status, renal function, SES, and potentially distance from home to the site of cancer care (Greipp et al., 2005; Lenhard et al., 1987; Meilleur et al., 2013; Mikhael et al., 2013; Paul et al., 2013). Tumor-related risk factors include the genetic abnormalities observed in tumor cells, involving hyperdiploid/nonhyperdiploid status, alteration or deletion of chromosome 1,13 or 17, and other chromosome abnormalities (Furukawa & Kikuchi, 2015; Greipp et al., 2005; Mikhael et al., 2013; Sawyer, 2011; Van Wier et al., 2013).

MM survival is correlated with the depth of response to therapy measured by the attainment of CR. Therapy and other variables including genetic risk observed in the tumor cell by various techniques impact the achievement and duration of CR including patient age, renal function, serum albumin level, serum β2-microglobulin; ISS stage, and potentially patient distance to their site of care (Greipp et al., 2005; Kapoor et al., 2010; Lenhard et al., 1987; Lipe et al., 2012; Mikhael et al., 2013; Morgan, Walker, & Davies, 2012). Risk stratification should be performed to identify patients who are at high risk of early progression due to aggressive disease associated with high risk features described below and not for treatment decisions (Rajkumar, Harousseau, et al., 2011).

Risk stratification methodologies based on information available by measurement

of albumin, β2-microglobulin, C-reactive protein, and lactate dehydrogenase (LDH)

obtained from peripheral blood have been validated, are consistent across multiple

laboratories, and are relatively inexpensive (Bataille, Boccadoro, Klein, Durie, & Pileri,

1992; Greipp et al., 1993; Greipp et al., 2005; Patel et al., 2012). The ISS stage is

determined by obtaining serum levels of albumin and β2-microglobulin, which are

readily measured from peripheral blood utilizing standard laboratory examination that has

been widely adopted in both research and clinical practice (Anderson, 2014; Rajkumar et

al., 2014). Strengths of the ISS and other methods to evaluate risk based on laboratory

values obtained from peripheral blood include low cost, standardized measurement,

simply calculated risk assessment, and a noninvasive approach. Limitations to risk

assessment utilizing peripheral blood sampling include the lack of genetic information to

inform risk, the inability to monitor plasma cell cellularity within the bone marrow, and a

lack of radiographic evidence of disease progression or response to therapy.

Genetic information has been demonstrated to provide valid prognostic

information and as a result, the NCCN and other organizations recommend risk

stratification by a variety of genetic testing methods, including conventional karyotyping

and FISH (Anderson, 2014; Kapoor et al., 2010; Mikhael et al., 2013). A more detailed

review of genetic testing of MM based on testing methodology will be provided.

Genetically Defined Risk

MM is a genetically diverse disease noted for complex cytogenetics, multiple

genetic aberrations, and intraclonal heterogeneity, which change due to time and selective

pressure of therapy (Heuck et al., 2014; Morgan et al., 2012). Although MM is thought to arise from a single mutated plasma cell, it is recognized that progression from MGUS to symptomatic MM involves multiple genetic changes in multiple plasma cell clones (Morgan et al., 2012). This intraclonal heterogeneity evolves over time, due to host and tumor biology. Bone lesions and/or extramedullary foci of MM vary by anatomical site, such that a sample obtained from one anatomical location may have different genetic features when compared to another sample obtained from the same patient, at the same point in time, from another site (Lohr et al., 2014). There is no single genetic alteration that characterizes MM for diagnostic purposes (Keats et al., 2003).

MM may be categorized genetically into two groups, hyperdiploid (≥ 47 and < 75 chromosomes) or nonhyperdiploid based on the number of chromosomes detected in CD138+ plasma cells (Van Wier et al., 2013). Non-hyperdiploid MM is clinically more aggressive than hyperdiploid MM, and it is associated with shorter PFS and OS (Mikhael et al., 2013; Van Wier et al., 2013). Investigators at the Mayo Clinic cite *ploidy* status as hyperdiploid or nonhyperdiploid in the stratification of risk in MM (Mikhael et al., 2013). Diploid status is not detectable utilizing conventional cytogenetics, thus more advanced pathologic techniques, including FISH or GEP, are required to quantify this known risk factor in individual patients (Keats et al., 2003). The mechanisms of hyperdiploid plasma cell transformation are not well described, but it is reported that the most common hyperdiploidy is trisomy 11, which is implicated in cyclin D1 overexpression (Furukawa & Kikuchi, 2015). Importantly, biologic samples used to determine ploidy status must originate from tumor samples and may not be obtained from peripheral blood.

Gender in MM

The Medical Research Council (MRC) is a United Kingdom (UK) based research collaborative that supports and conducts research in a variety of medical disciplines. The MRC Myeloma IX trial evaluated long-term outcomes of $N = 1970$ patients with MM in the UK, a planned analysis of gender disparities and tumor genetics in MM indicated that the low risk genetic feature of hyperdiploidy status was discovered in 62% of males and 50% females ($p = .001$) and secondary genetic defects, including the high risk feature del(13q) were more frequent in 52% of females and 41% of males ($p = .042$) (Boyd et al., 2011). Female gender was associated with inferior OS, 44.8 months for females and 49.9 months for males ($p = .0.020$) (Boyd et al., 2011).

In contrast to the findings of the MRC Myeloma IX trial, an analysis of data collected from more than 1200 participants treated at UARK through 2010, did not reveal any adverse prognostic impact of female gender (Szymonifka et al., 2010). PFS and OS stratified by gender are not routinely reported in the literature although the numeric frequency of the disease in males is reflected in clinical trial reports. There are no data in the peer-reviewed literature indicating any drug or treatment regimen is more or less effective based on gender. The potential of gender to influence PFS and OS outcome in NDXMM is not well described in the literature.

Age as a Risk Factor in MM

MGUS, the likely obligate precursor to MM is associated with increasing age and is reported in 5% of all adults aged over 70 years (Mikhael et al., 2013). MM is regarded as a diagnosis of older persons, with the incidence of the disease increasing with

increased age; older age is a prognostic risk factor according to multiple treatment and diagnostic guidelines (Kristinsson, Anderson, & Landgren, 2014; Mikhael et al., 2013). Age is a recognized prognostic variable for consideration for ASCT. ASCT is a standard therapy for patients who qualify for the procedure based on performance status; performance status is independent of chronologic age in the Karnofsky and ECOG performance status criteria (Eastern Cooperative Oncology Group, 2015; National Cancer Institute, 2015a). In consideration of available evidence, the Centers for Medicare and Medicaid Services, has limited the availability of ASCT to persons under the age of 77 years who have adequate performance status and meet other eligibility criteria for the procedure. Age over 77 years is a disqualifying factor based on current Medicare guidelines regarding coverage for ASCT in MM (Hill, 2000). The age limit for Medicare payment for ASCT may be viewed as problematic as the median age of MM diagnosis is reported to be between 65-70 years and 35-40% of patients are older than 75 years at diagnosis (Zweegman, Palumbo, Bringhen, & Sonneveld, 2014).

The introduction of novel therapy has increased PFS and OS for most patients; however, patients with GEP70 defined HRMM and persons over the age of 65 have not benefitted robustly from the introduction of new therapeutics and advances in supportive care (Kumar et al., 2008; Usmani et al., 2012; Zweegman et al., 2014). In one study, French and Italian patients ≥ 75 years who were treated with novel therapy were found to have equal OS outcomes compared to historic controls (Zweegman et al., 2014). It has been noted that although there are genetic differences in tumors noted between younger

and older patients with MM, these differences do not correlate with more aggressive disease (Zweegman et al., 2014).

Gene Expression Profiling in MM

GEP is an analysis of the genes from CD138+ plasma cells, obtained from bone marrow sampling, to stratify the risk of MM progression. GEP is not included as a standard of care in the diagnosis or monitoring of MM in clinical practice (Anderson, 2014), but this technique is utilized in the research setting and at some tertiary care facilities that have a research interest in MM (Decaux et al., 2008; Mikhael et al., 2013; van Laar et al., 2014; Zhan et al., 2002). The GEP70 model has been validated as an independent predictor of disease risk in both newly diagnosed and relapsed/refractory MM (Shaughnessy et al., 2007; van Laar et al., 2014). GEP-based risk stratification is superior to FISH, conventional cytogenetic, or serum based risk stratification schemas (Mikhael et al., 2013; van Laar et al., 2014).

The GEP70 model was created at UARK and has subsequently been licensed to Signal Genetics, Inc., as the MyPRS® test (van Laar et al., 2014). In the research setting at UARK, the GEP70 model is performed by UARK staff and serves as the prospective risk stratification methodology in all Total Therapy Trials beginning with TT4, although the ISS is also utilized to provide information on patient risk. MyPRS® is available as a clinical test to any clinician who is authorized to order the exam and able to provide a bone marrow aspirate. There is no significant difference in risk scores between the test as performed by UARK versus using the MyPRS® test (van Laar et al., 2014).

GEP is a molecular examination of tumor cells performed on purified CD138+ cells obtained from bone marrow or bony focal lesions; the test has not been validated utilizing peripheral blood and in contrast to the ISS, it is an invasive test. Microarray analysis utilizing the Affymetrix U133Plus 2.0 chip and computation of genetic information identified 51 up-regulated genes and 17 down-regulated genes that are predictive of high risk and low risk MM disease (Shaughnessy et al., 2007). The GEP70 score is highly predictive of both PFS and OS and has been utilized in clinical trials that were submitted to the U.S. FDA in support of the approval of bortezomib in MM (Jagannath et al., 2006; Richardson et al., 2007).

GEP70 performed at UARK results in a numeric score indicative of MM risk. As described by Shaughnessy and associates, a GEP70 score ≤ 0.66 is indicative of low risk disease and a score ≥ 0.661 indicates high risk disease on an open-ended scale(Shaughnessy et al., 2007). The 5-year event free survival for those with newly diagnosed GEP70-defined low risk disease is 60% compared to 18% for high risk disease, $p < .001$, HR = 4.51; 5-year OS in low risk disease is 78%, contrasted to 28% in high risk disease, $p < .001$, HR = 5.16 (Shaughnessy et al., 2007, p. 2279). GEP70-defined high risk disease represents approximately 13% of all cases (Shaughnessy et al., 2007).

Limitations of GEP-based risk stratification for MM include the need for bone marrow sampling, extensive sample preparation, a lack of agreement in the peer-reviewed literature regarding ideal candidate genes for risk assessment, and a lack of therapy-specific response signatures by GEP (Amin et al., 2014; Anderson, 2014; van

Laar et al., 2014). The NCCN currently identifies GEP as a research procedure; as a result, GEP utility is limited and not used in routine practice. The mSMART guidelines for the treatment of MM, published by investigators from the Mayo Clinic, also identify GEP as an investigational test (Mikhael et al., 2013).

GEP-Defined Molecular Subgroups

Investigators at UARK utilized GEP to identify seven genetically distinct subgroups of MM (Zhan, Huang, et al., 2006). In a group of 414 patients with NDxMM who went on to receive high dose therapy followed by tandem ASCT, GEP of CD138+ plasma cells identified seven unique gene expression signatures associated with different clinical consequences and statistically significant differences in PFS and OS (Zhan, Huang, et al., 2006). GEP-defined subgroups have been utilized to guide therapy based on genetic risk and expected clinical course in both NDxMM and R/R MM at UARK. According to Zhan and associates (2006), HY, CD-1, CD-2, and LB subgroups have been correlated with improved PFS and OS when compared to the PR, MS, and MF subgroups (see definitions below).

GEP-based subgroups are not utilized for disease stratification outside UARK—they are used exclusively for research purposes elsewhere. Identification of a response signature to bortezomib has been accomplished at UARK (Shaughnessy et al., 2011) based on GEP-defined molecular subgroups. The identification of patients who respond by MS is only applicable to those who are treated at UARK on TT research protocols.

CD-1: Multiple Myeloma subgroup characterized by overexpression of Cyclin D1 (CCND1), Cyclin D3 (CCND3), and the Kelch-like 4 (*KLHL4*) gene.

CD-2: Multiple Myeloma subgroup characterized by overexpression of CCND1 and CCND3, as well as *MS4A1/CD20* and the early B cell marker, *PAX5*.

Hyperdiploidy (HY): Multiple Myeloma subgroup characterized by trisomies of odd number chromosomes, not including chromosome 1.

Low Bone (LB): Multiple Myeloma subgroup characterized by low bone disease, defined by a low number of MRI-defined focal lesions.

MF: Multiple Myeloma subgroup characterized by an overexpression of the *c-MA*F and *MAFB* proto-oncogenes.

MS: Multiple Myeloma subgroup characterized by *MMSET* overexpression, with or without overexpression of *FGFR3*.

Proliferation (PR): Multiple Myeloma subgroup characterized by overexpression of cell proliferation genes and a high cell proliferation index.

Risk Assessment by Conventional Karyotyping

It has been established that risk associated with MM can be, at least in part, due to the genetics of the myeloma cell (Morgan et al., 2012; Peterson, Chavan, Bauer, Heuck, & Johann, 2014; Sawyer, 2011; Zhuang et al., 2014). Hyperdiploid MM is associated with lower risk disease (Van Wier et al., 2013; Zhan, Huang, et al., 2006). In a large study of the genetics of MM, Blacks were found to have more frequent hyperdiploid disease than Whites and less frequent chromosomal translocations, including t(11;14) or t(4;14) that are associated with high risk disease (Greenberg et al., 2015; Kalff & Spencer, 2012; Keats et al., 2003). The NCCN guidelines for the diagnostic workup of MM include conventional karyotyping analysis by cytogenetic examination and FISH

examination of tissue obtained from a bone marrow biopsy (Anderson, 2014). Metaphase cytogenetic (conventional karyotyping) examination is performed on dividing MM cells which have been isolated from bone marrow and cultured in vivo. The bone marrow and bone marrow microenvironment support the growth, proliferation, and division of MM cells (Bam et al., 2013; Johnson et al., 2014; Palumbo & Anderson, 2011). When removed from the supportive bone marrow microenvironment, approximately 33% of MM cells will continue to divide; these cells have complex cytogenetic features and are associated with aggressive disease (Zhan, Sawyer, & Tricot, 2006).

There are known limitations of conventional cytogenetic analysis. Nearly 70% of all MM cells will not yield any results by cytogenetic examination, as they will not divide outside of the bone marrow; thus, meaningful information cannot be derived from the vast majority of samples obtained. There are other drawbacks of cytogenetic examination, including the necessity of tissue obtained by bone marrow biopsy, the expertise needed to prepare a sample for examination, and the costs associated with this specialized test (Anderson, 2014; Mikhael et al., 2013). Disease risk assessed by cytogenetic examination is based on the deletion of chromosome 13 and detection of complex karyotypes (Mikhael et al., 2013).

Risk Assessment Using Fluorescence in situ Hybridization (FISH)

FISH-based cytogenetic testing does not require actively dividing cells and therefore may be performed on appropriately prepared CD138+ cells obtained from bone marrow biopsy (Ross et al., 2012). FISH testing is intended to reveal specific genetic abnormalities that have been implicated in risk stratification, and this test should be used

in conjunction with conventional cytogenetic testing (Anderson, 2014). The routine use and widespread availability of FISH testing in MM has revealed that the true incidence of genetic abnormalities in MM is much higher than previously understood utilizing classic cytogenetics (Ross et al., 2012). If a clinician is unable to obtain both FISH and classic cytogenetic test results from bone marrow biopsy, FISH is the preferred test, owing to its specificity and accuracy and the impact of specific genetic abnormalities which may be identified by FISH but not by classic cytogenetic analysis (Mikhael et al., 2013). In Table 2, FISH-based detection of specific genetic abnormalities and their relative frequency are described from a group of 484 patients with NDxMM treated at the Mayo Clinic (Kumar et al., 2012).

Table 2

*Genetic Abnormalities Detected by FISH (*N* = 484)*

FISH abnormality	Frequency *n* (%)
Any translocations	22 (46)
t(11;14)	86 (18)
t(4;14)	47 (10)
t(14;16)	24 (5)
t(6;14)	3 (<1)
t(14;20)	1 (<1)
Other IgH locus abnormality	59 (12)
Any trisomy	275 (57)
1 chromosome	42 (9)
2 chromosomes	1
3 chromosomes	<1
4 chromosomes	7
≥ 5 chromosomes	60 (12)
Monosomy	236 (49)
Monosomy 13/Del 13q	228 (47)
Monosomy 14	38 (8)
Monosomy 16	14 (3)
P53 abnormality	62 (13)
Del 17p	49 (10)
Other (all tetraploidy)	3 (<1)
Normal	15 (3)

Note. Adapted from "Trisomies in multiple myeloma: impact on survival in patients with high-risk cytogenetics" by Kumar et al., 2012, *Blood*, *119*(9), p. 2101. Copyright 2013, American Society of Hematology.

High Risk MM

The designation of HRMM for those with NDxMM, based upon genetic features

of plasma cell clones, may be accomplished utilizing different methods including FISH,

GEP, and NGS (Bianchi et al., 2014; Heuck et al., 2014; Mikhael et al., 2013; Palumbo et

al., 2011). In addition to the ploidy status of the disease by chromosome counts, specific

genetic mutations are associated with high risk disease. The frequency of HRMM varies

by detection method, but it is reported to impact between 10% and 20% of patients at

initial diagnosis (Bianchi et al., 2014). PFS and OS outcomes for those with HRMM are

significantly shorter when compared to LRMM (Greenberg et al., 2014). The proteasome inhibitor bortezomib has been shown to abrogate the risk associated with t(4;14), which is a commonly detected genetic feature in HRMM (Anderson, 2014; Sawyer, 2011; Sonneveld et al., 2012).

Impaired Renal Function

Impaired renal function occurs frequently in MM due to the excretion of high amounts of calcium, protein, and light chains in blood, which causes damage and decreased functioning of the renal tubules (Khan, Apewokin, et al., 2015; Tosi et al., 2015). As tumor burden increases, the amount of defective plasma cells which excrete light chains also increases; as light chain levels increase this induces the increased production of the pro-inflammatory and pro-MM cytokines IL-6 and tumor necrosis factor alpha (TNF-α) (Anderson, 2014; Tosi et al., 2015). Therapy intended to treat MM may also contribute to impaired renal function due to tumor lysis syndrome, whereby the cellular contents of plasma cells destroyed by therapy are carried into the renal tubules by blood, resulting in renal tubule trauma (Tosi et al., 2015).

Unregulated bone reabsorption due to an increase in osteoclast activity results in bone destruction, pain, and increasing serum levels of calcium (Palumbo & Anderson, 2011). Treatment with bisphosphonate drugs has been demonstrated to prevent and treat bone events in MM and has been incorporated into the standard of care (Anderson, 2014; Mhaskar et al., 1996; Schmitt et al., 2013). Bisphosphonate drugs are inhibitors of osteoclasts and have been demonstrated in multiple clinical trials and in a Cochrane Systematic review to reduce fractures and pain associated with symptomatic MM

(Mhaskar et al., 1996). The toxicities associated with bisphosphonate therapy include hypercalcemia, osteonecrosis of the jaw, and renal toxicity (Schmitt et al., 2013).

Patient Distance Traveled as a Risk Factor

Studies assessing the impact of patient distance traveled in other tumor types have demonstrated a correlation between increasing distance traveled and the type of therapy received (Lamont et al., 2003; Wheeler et al., 2014). A review of the literature reveals inconsistent patient populations studied when assessing the potential of distance to impact patient outcomes with MM. Contributing to the confounding conclusions drawn from previous studies associating distance with risk in MM are data obtained prior to the availability of novel agents, methodological errors, small patient populations studied, the retrospective nature of many studies, a lack of consistent measurements of socioeconomic status, and short follow-up (Abou-Jawde et al., 2006; Colson, 2015; Lenhard et al., 1987; López-Corral et al., 2012; Ojha et al., 2007; Paul et al., 2013; Shank, Brown, & Schwartz, 2015; Tariman et al., 2014).

Socioeconomic status (SES) has an impact on cancer survivorship across all tumor types (Chang et al., 2012; Siegel, Naishadham, & Jemal, 2012). Socioeconomic data were not collected in the TT3 trials and data are not available to characterize individual patients who were enrolled. Furthermore, it is a known limitation of this study that a number of TT3 protocol participants did temporarily relocate to Little Rock for at least a portion of their treatment. The lack of SES data in this study is a recognized limitation. Demographic data obtained at the U.S. zip code level are available but are inconsistent and do not adequately characterize financial or social factors at an individual

level (Berkowitz, Traore, Singer, & Atlas, 2015). It has been reported, that in diffuse large B cell lymphoma, another hematologic malignancy, that poorer economic status negatively impacts survival (Flowers & Nastoupil, 2014; Tao, Foran, Clarke, Gomez, & Keegan, 2014). SES status may be measured by cash on hand, education level, access to care, zip code of residence, and the number of persons living in a domicile, but none of these measures is adequate in a population-level study (Khera, 2014; Paul et al., 2013). Further confounding the interpretation of SES as a predictor of risk in cancer is the variability of care and services available in rural areas when compared to tertiary care centers in urban environments (Meilleur et al., 2013; Wheeler et al., 2014). In care settings where universal access to health care is available, it has been reported that poorer economic status is still associated with poorer survival (Landgren et al., 2006; Tariman et al., 2014).

The effect of distance traveled to care site on survival of patients with cancer was assessed in an NCI-supported study that collected data on 240,531 patients at 21 comprehensive cancer centers from 1977-1982 (Lenhard et al., 1987). Among these patients, 1,479 had an MM diagnosis. Consistent with other reports in the MM literature, Lenhard and associates (1987) reported that among the MM subjects included in their manuscript the median age at diagnosis was 63.6 years, with more male and White patients (Baris et al., 2013; Hajek, 2013; Lenhard et al., 1987). In both univariate and multivariate analysis, Lenhard and associates (1987) reported patients who lived $\geq$ 150 miles from the site of cancer care had significantly improved OS ($p = .007$). The investigators noted a trend consistent with increasing distance from the site of care

correlating with increased OS, even when controlling for all other known covariates, including SES. As reported by Lenhard and colleagues (1987), distance has an impact on OS. In the context of a literature review performed in 2015, these data must be interpreted with the knowledge that MM therapy, in the measured time frame, did not incorporate novel agents, that generally all therapy was delivered intravenously and although the study did report data from a generally representative population of those with MM, there was the potential for selection bias as only data from comprehensive care centers were included in the research. It is possible that the necessity for intravenous delivery of chemotherapy also introduced selection bias favoring patients with better performance status. Further limiting the utility of these results is the lack of patient staging according to the DS criteria. The lack of DS staging data in the report impairs interpretation of findings, as the ability to travel due to advanced stage disease may have impacted subject participation and therefore may have enriched the study with patients who had a lower disease burden. The finding that distance does have an impact on OS in MM has prompted others to further investigate this finding.

In a study conducted by a group of MM experts from the Cleveland Clinic, neither subject race, SES, nor distance traveled to the site of care were found to be significant prognostic factors for OS in both NDxMM and R/R MM (Abou-Jawde et al., 2006). The study reported OS outcomes for 292 patients with NDxMM and 124 with R/R MM in a retrospective fashion and included patients who were treated both on and off research protocols. The report by Abou-Jawde and associates (2006) did utilize SWOG patient staging criteria and also included information on serum albumin and β2-

microglobulin that are consistent with other published reports. The research as presented

has several limitations. The data that informed the research were obtained from both

newly diagnosed and relapsed refractory patients. The inclusion of R/R MM patients in

the analysis naturally shortens OS, owing to disease that is refractory to therapy, and thus

limits the interpretation of the data.

Second, the research did not include patients who received the standard of care

during the years of study data collection, which included induction chemotherapy

followed by ASCT (no patients in this report underwent ASCT). Importantly, there were

no data reported on the number and type of genetic abnormalities in patients, which

further limits the application of this information into research or clinical practice. It is

unknown if there was selection bias favoring those with high risk disease or poor

performance status, as data concerning cytogenetic risk and the ability to meet criteria for

ASCT were not reported. The use of novel agents was limited to thalidomide in this

report, although the Cleveland Clinic did have access to bortezomib on a commercial

basis. The use of bortezomib in genetically defined high risk patients was known to

mitigate the impact of t(4;14) when the data were reported. Bortezomib is only

administered by needle; the necessity for a venous access line or the impracticality of

travel to receive a subcutaneous injection may have further biased patient selection in this

trial. Abou-Jawde and colleagues (2006) reported that race had no prognostic impact on

OS, yet only 13% of trial participants were Black. The small number of Black patients

included in the trial and the inclusion of both NDxMM and R/R MM patients limit the

impact of the report.

In a rejoinder to the report by Abou-Jawde and associates (2006), errors in study methodology include over-controlling for the influence of serum albumin and β2-microglobulin as independent prognosticators of risk, as they are included in the SWOG disease staging system, a general lack of valid epidemiologic methods, and insufficient power to detect statistically significant changes (Ojha et al., 2007). The inclusion of both NDxMM and R/R patients in a Cox proportional hazard model is methodologically inappropriate as the survival probabilities are not constant (Ojha et al., 2007). The lack of genetically defined risk factors was not noted in the rejoinder, but the lack of other prognostic information, including LDH levels, was noted.

The most recent peer-reviewed report investigating the potential impact of patient distance traveled on outcome in MM was conducted by investigators from the NCI-designated comprehensive cancer center located at Dartmouth Hitchcock medical center (Lipe et al., 2012). In a retrospective analysis of 77 consecutive patients with NDxMM who underwent ASCT, increasing distance from the cancer center was associated with improved OS ($p = .004$) but had no impact on PFS ($p = .26$) (Lipe et al., 2012). In contrast to other reports, the novel agents thalidomide, lenalidomide, and bortezomib were utilized in the majority (69%) of patients (Lipe et al., 2012). Among these 77 patients, the median OS for those who lived > 50 miles from the medical center was 81.6 months compared to 50.4 months for those who lived < 50 miles from the site ($p = .03$). The investigators utilized the ISS to categorize risk but they did not analyze genetic data, which limits the interpretation and application of these data. Limited genetic information

was included in the report but was not included as a variable in the Cox regression model that was used to evaluate the relationship between distance and OS.

The authors reported several limitations of the study, including the small number of patients studied over a 7-year accrual period, the lack of a consistent pre-transplant induction regimen, and referral bias (Lipe et al., 2012). The investigators concluded that distance from the transplant center should not be considered a negative prognostic variable for transplant, but the investigators did not address the question in a nontransplant population. Table 3 presents selected features of risk categorized by patient factors, tumor biology and tumor burden.

Table 3

Selected Risk Features in MM

Patient Associated	Tumor Biology Associated	Tumor Burden Associated
Physical Health / Performance Status	Ploidy Status	Extramedullary Disease
Age	Alterations on Chromosome 1	Plasma Cell Proliferation Rate
Renal Function	Deletion of Chromosome 13 by Conventional Karyotyping	Serum β2-microglobulin Level
Distance from site of care[+]	High Risk GEP Score 17p − (p53 deletion) t(4;14) t(6;14) t(11;14) t(14;16)	Serum Albumin Level Serum LDH Level

Note. Adapted from "Management of newly diagnosed symptomatic multiple myeloma: Updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) Consensus Guidelines 2013". Mikhael, J. R., Dingli, D., Roy, V., Reeder, C. B., Buadi, F. K., Hayman, S. R., … Lacy, M. Q. (2013). *Mayo Clinic Proceedings*, *88*(4), 360–376. Copyright, 2013, Mayo Foundation for Medical Education and Research.
[+] Investigational Variable

CRAB Criteria - Laboratory and Clinical Information

The CRAB criteria are associated with laboratory findings and clinical symptoms defined by the IMWG (Kyle et al., 2003).

Elevated Calcium: Serum calcium levels are elevated in MM due to the imbalance between osteoblasts and osteoclasts. Osteoclasts are associated with increased bone reabsorption, resulting in excess calcium being released into the serum. Excess serum calcium may lead to hypertension, weakness, altered mental status, cardiac arrest, and renal failure (Levey & Coresh, 2012).

Renal Dysfunction: Renal dysfunction in MM is caused both by elevated serum calcium in the serum and interstitial nephritis caused by excess κ and λ light chains (FLC) being deposited in the glomerulus of the kidney (Anderson, 2011; Khan, Apewokin, et al., 2015; Miguel & Mateos, 2011). Renal dysfunction is associated with poor survival (Khan, Apewokin, et al., 2015) and is complicated by the use of pharmacologic agents intended to treat the disease which cause significant renal impairment, including bisphosphonates (Mhaskar et al., 1996; Schmitt et al., 2013; Tosi et al., 2015).

Summary and Transition

Normal PCs are terminally differentiated B cells that serve to produce and secrete antibodies, a critical component of human humoral immunity to pathogenic organisms. Genetic and host factors are thought to contribute to changes in PCs which lead to mutations causing the abnormal proliferation of a single PC, giving rise to an expanding number of PC clones. Clonal expansion occurs within the bone marrow but does not

cause clinical signs or symptoms of disease. Expanding PC clones that meet the criteria established by the IMWG are known as MGUS.

MGUS is a premalignant condition, generally occurring in persons older than age 50 that is often diagnosed when medical care is sought for other reasons. Genetic and epigenetic originated mutations to PC clones may lead to the development of MM, although the risk of conversion from MGUS to MM only occurs at the rate of 1% per year. There is no known behavior or therapy that can prevent the conversion of abnormal PCs to MGUS or to MM. MGUS disproportionally affects Blacks compared to Whites and is more common in males compared to females. The heritability of MGUS and MM is not well established in large trials, but there is evidence that the conditions are more common in persons that have a first-degree relative with the conditions.

MM causes pain, anemia, and skeletal fractures and is diagnosed according to the IMWG criteria; therapy is indicated when the CRAB criteria are met. Therapy is complex, involves the administration of multi-agent chemotherapy and novel therapies, ASCT in patients who are able to undergo the procedure, and maintenance therapy. MM is staged according to multiple schemas, including the DS, ISS, and IMWG. MM risk is stratified according by ISS, GEP, FISH, and cytogenetic tests, with each methodology having known strengths and weaknesses.

With appropriate therapy LRMM is associated with median OS of 8 −10 years, with HRMM having a median OS of less than 3 years (Mikhael et al., 2013). Projected 5-year and median PFS and OS vary by risk stratification methodology. The standard of care dictates that conventional cytogenetics and FISH studies be performed in NDxMM

to identify the genetically identified risk factors associated with HRMM. GEP is a more advanced methodology to describe genetic features of the disease, but it is associated with higher cost and is currently considered by NCCN to be an investigational test.

Non-genetic/nontumor related risks in MM include impaired renal function, older age, and potentially distance traveled to obtain care for the disease. Age, renal dysfunction, and poor performance status are known risk factors for early disease progression and shorter response to MM therapy and may limit treatment options, including ASCT. Multiple investigations have been completed that examined the impact of distance on PFS and OS for those with cancer, including MM. A current literature review focusing on the impact of distance as a prognostic variable revealed inconsistent findings and nonrepresentative populations studied. This study sought to address a gap in the contemporary literature regarding the potential impact of distance traveled to obtain care on PFS and OS in NDxMM in the era of novel therapy followed by ASCT and maintenance therapy.

Chapter 3: Research Method

Introduction

The purpose of this quantitative study of 480 clinical trial participants was to investigate the impact of patient distance from the site of care on survival outcomes for patients enrolled on two clinical trials for newly diagnosed multiple myeloma (NDxMM). Multiple Myeloma (MM) is a hematologic malignancy resulting from clonal expansion of defective plasma cells leading to organ damage, skeletal fractures, anemia, and other clinical symptoms. The following sections describe the research design, study setting and sample, Total Therapy 3 (TT3) entry criteria, including baseline blood chemistry values, and bone marrow biopsy proven, NDxMM, data acquisition, description of variables, proposed statistical procedures and ethical considerations and protection of participants' rights in the study.

Research Design

This study was a quantitative, retrospective analysis of secondary data obtained from the TT3 at The Myeloma Institute for Research and Therapy located at the University of Arkansas for Medical Sciences that enrolled patients with NDxMM. The data to inform this study were collected from prospective clinical trials for those with NDxMM conducted at MIRT. This study and the original TT3 trials investigated progression free survival (PFS) and overall survival (OS) outcomes utilizing the Bladé criteria to define disease progression. The dependent variables are PFS and OS. Independent variables include close proximity to MIRT based on patient zip code at TT3 study registration, gender, age $\geq$ 65 years, GEP70-defined risk status (HRMM or

LRMM), and ISS stage. Prospective clinical trials utilizing standardized criteria to evaluate disease response allow a researcher to a priori collect all information necessary to answer the primary objectives of the clinical trial. In TT3, disease staging and responses were conducted utilizing the ISS and EBMT criteria respectively.

A retrospective cohort design was selected as the most appropriate design for this study due to the time and logistical requirements to prospectively accrue data. Retrospective trial designs to evaluate the investigational variable of patient distance traveled on PFS and OS outcomes are appropriate. The earlier TT3 trials prospectively collected data for PFS and OS outcome measurement. The independent variables include patient distance traveled, GEP70 status, ISS stage, gender, and age $\geq$ 65 years. Confounding variables include a lack of SES data and minor differences between TT3a/b. All 480 participants provided written informed consent for treatment and research purposes on TT3, which was conducted under the auspices of UARK IRB approval and was subject to FDA oversight. The TT3 protocols were also subject to review by an independent Data Safety and Monitoring Board to ensure participant safety and 80% of subject records were subjected to audit for attribution of toxicity, response, and response duration. The NCI supported the TT3 protocols via grant CA 55813.

Setting and Sample

The TT3 clinical trials are among the largest prospective clinical trials ($N = 480$) that have investigated PFS and OS in NDxMM patients who underwent induction therapy with novel agents, tandem ASCT, and multidrug maintenance therapy. Clinical data, PFS and OS outcomes continue to be collected from patients that enrolled on TT3 trials and

are still alive. The updated data are entered into the clinical record and MMDB at UARK. The research participants in the studies are persons with NDxMM, aged ≥ 18 years, who met the eligibility criteria, and enrolled on TT3. The TT3a/b trial designs were similar although there are slight differences in the maintenance portions of the trials. TT3a mandated that bortezomib be administered in combination with thalidomide and dexamethasone in the maintenance phase of the study in year 1 only, in maintenance years 2-3, only thalidomide and dexamethasone were to be administered. In TT3b, bortezomib was administered in combination with lenalidomide and dexamethasone in all 3 years of maintenance. The substitution of thalidomide in favor of lenalidomide in the maintenance phase of TT3b was done to mitigate the common toxicity of peripheral neuropathy associated with long-term exposure to thalidomide. Although there a minor protocol differences in TT3a/b, the pooled analysis of TT3a/b results were accepted in peer-reviewed journal *Blood*, in keeping with the confirmatory intent and design of TT3b (Nair et al., 2010).

TT3 Entry Criteria

All participants in the TT3 trials were treated at MIRT, were recruited and screened for study participation by MIRT physicians and research staff. The TT3 trials were posted on the publically available clinical trial registries, including http://www.clinicaltrials.gov. All patients enrolled on TT3 were required to provide written, informed consent to participate in the research protocol. Participants were required to have had completed all baseline studies to determine trial eligibility within 35

days of study registration, with the exception of a skeletal survey that must have been completed 90 days prior to registration. Additional study entry criteria included:

- Patients must have had NDxMM, symptomatic MM requiring therapy according to the CRAB criteria (Kyle et al., 2003);

- Protein criteria must have been present (quantifiable M-component of IgG, IgA, IgD, IgE and/or urinary κ or λ light chains, Bence-Jones protein, or free κ/λ light chains. Non-secretory MM patients were eligible to participate if they have > 20% plasmacyotis, or >3 focal lesions on MRI;

- Patients may not have received more than one cycle of prior chemotherapy for MM;

- Patients must have been ≤ 75 years at protocol registration;

- Cardiac ejection fraction by ECHO or MUGA ≥ 40% performed within 60 days prior to registration;

- Patients must have adequate pulmonary function with PFT's ≥ 50% of predicted within 60 days prior to registration;

- Performance status 0-2 based on the SWOG criteria; performance status of 3-4 was permitted if attributable only to bone pain;

- Patients must have been willing and able to comply with study procedures, including contraception.

TT3 Exclusion Criteria

Patients were excluded from participation in the TT3 protocols if any of the following conditions were present:

- Platelet count < 30 x 10^9/L, unless myeloma-related;

- Grade > 2 peripheral neuropathy;

- Hypersensitivity to bortezomib, boron, or mannitol;

- Uncontrolled diabetes;

- Recent (< 6 months of study registration) myocardial infarction, unstable angina, difficult to control congestive heart failure, uncontrolled hypertension, or difficult to control cardiac arrhythmias;

- Evidence of chronic obstructive or chronic restrictive pulmonary disease;

- light chain deposition disease or serum creatinine > 3 mg/dl;

- 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 were only acceptable if the patient's life expectancy exceeded five years);

- no significant comorbid medical conditions or uncontrolled life-threatening infections; and

- pregnant or nursing status.

In addition, women of child-bearing potential were required to have a negative pregnancy test documented within one week of study registration. Women and men of reproductive potential could not participate unless they agreed to use an effective contraceptive method.

Power Analysis

This study was a retrospective analysis of previously collected data from the prospective TT3 clinical trials. A power analysis tests the probability of rejecting the null hypothesis when the alternative hypothesis is true. The research plan for this study relied on previously collected data, thus an a priori power analysis was possible. A post-hoc analysis was technically possible but such an analysis requires observations from analysis of data and is often conducted when analysis reveals a statistically insignificant result (Hoenig & Heisey, 2001) and was not selected for use in this trial.

As the essential data elements required for the planned research were prospectively obtained and the results of proposed analysis were unknown prior to IRB approval, the power analysis was performed on an a priori basis. The test family of t tests was used to determine the power of the study, utilizing G*Power version 3.1 (Dusseldorf Universitat, 2014), and guided by the statistical procedures for power calculations in linear regression authored by the developers of G*Power (Faul, Erdfelder, Buchner, & Lang, 2009).Table 4 shows the results of the G*Power calculation and demonstrates that the study had more participants than is required to have power of .95, an error probability of 0.05, and test for the research question-based number of predictors.

Table 4

G*Power Analysis Calculator (a priori) t tests - Linear Multiple Regression: Fixed Model, Single Regression Coefficient

Parameter	Calculation
Effect size f2	0.15
A err prob	0.05
Power (1-β err prob)	0.95
Number of tested predictors	2
Noncentrality parameter **δ**	3.6537652
Critical t	1.9879342
df	86
Total sample size	89
Actual power	0.9508043

Data Acquisition

The study was informed by data obtained from the Multiple Myeloma Data Base (MMDB) at the Myeloma Institute for Research and Therapy (MIRT) located at The Univeristy of Arkansas for Medical Sciences (UAMS/UARK) that was collected for the TT3 clinical trials. Per UAMS policy, appropriately credentialed clinical research professionals who have completed training, utilize MIRT standard operating procedures, and are authorized to access the database perform data entry in MMDB. Data obtained from MMDB have been utilized for research purposes, have been audited by qualified external reviewers, has been used for publication in peer-reviewed journals, and are subject to UARK IRB supervision. The data to inform this trial was obtained and/or analyzed with IRB permission from both UARK, IRB#204088, Expires 04/02/2016 and Walden University, IRB # 09-17-15-0232203, expires N/A.

Variables

Dependent Variables

There were two dependent variables in this study: PFS and OS. PFS and OS are commonly reported in oncology based clinical trials and were both prospectively defined endpoints in the TT3 trial. The definitions of PFS and OS originally used in the TT3 trials will be used in the planned research. TT3 defined PFS as time from study registration to disease progression/relapse of disease or death from any cause; OS was time from study registration to death from any cause (Barlogie, 2003, 2006). Progression/relapse of disease is defined according to the Bladé/EBMT criteria. PFS and OS are measured in days and reported as months/years. In this study, PFS and OS were calculated from the day of study registration to the date of progression or death, as recorded in MMDB on the data cutoff day of April 30, 2015.

Independent Variables

There are multiple independent variables in this study: (a) subject proximity to MIRT based on patient zip code, (b) GEP70-defined risk status (HRMM or LRMM), (c) ISS stage, (d) patient gender, and (e) age $\geq$ 65 years. All independent variables were recorded upon enrollment to TT3. Patient proximity to MIRT will be calculated based on distance from participant U.S. zip code to MIRT. Proximity was defined as:

- Close proximity to MIRT: A distance from a patient's zip code of residence to MIRT of < 121 miles.

- Outside close proximity to MIRT: A distance from a patient's zip code of residence to MIRT of $\geq$ 121 miles.

The honest broker managing the data utilized SAS 9.3 to compute the distance from subject home zip code at study registration to MIRT and provided the data to the principal investigator.

GEP70 status (HRMM or LRMM) is determined by gene expression profiling of 70 genes related to MM as described by Shaughnessy and associates (2007) and performed at UARK on CD138+ purified plasma cells obtained from bone marrow biopsy. GEP70 is a validated prognostic test used to determine the risk of early progression in MM.

ISS Stage (1, 2, 3) is a validated system for patient classification and risk stratification. The ISS stratifies patients by obtaining levels of β2-microglobulin and albumin obtained from serum. The ISS staging system is utilized in both clinical and research practice to allow comparison of patient groups in different clinical trials.

Data Analysis Plan

The Cox proportional hazards model was utilized to analyze the limited dataset for the time to event outcomes, PFS and OS, using the statistical software *R* (R Core Team, 2015) *powerSurvEpi* package (Qiu, Chavarro, Lazarus, Rosner, & Ma, 2012). Covariates were chosen and are founded in the peer-reviewed MM literature. A result is considered statistically significant if a *p* value is < .05.

The study was expected to reject the null hypothesis in the research questions below:

Research Question 0

Research Question 0 (RQ0): Does close proximity to MIRT impact PFS and OS in TT3?

Null hypothesis (H_{00}): There is no statistically significant difference to PFS or OS based on a patient's close proximity to MIRT.

Research Question 1

Research Question 1 (RQ1): Does close proximity to MIRT impact PFS and OS in TT3, when controlling for GEP70-defined risk and ISS Stage?

Null hypothesis (H_{01}): There is no statistically significant difference to PFS or OS based on a patient's close proximity to MIRT, when controlling for GEP70-defined risk and ISS Stage.

To investigate Research Question 1, a univariate Cox PH model was used to separately examine the potential impact of the independent variable of proximity on the dependent variables of PFS and OS, while controlling for GEP70-defined risk and ISS Stage.

Research Question 2

Research Question 2 (RQ2): Does patient age $\geq$ 65 years and close proximity to MIRT impact PFS and OS in TT3, when controlling for GEP70-defined risk and ISS Stage?

Null hypothesis (H_{02}): There is no statistically significant difference in PFS or OS based on a patient age $\geq$ 65 years and close proximity to MIRT after controlling for GEP70-defined risk and ISS Stage.

To investigate Research Question 2, a Cox PH model was used to separately examine the potential impact of the independent variable, patient age ≥ 65, on the dependent variables of PFS and OS, while controlling for GEP70-defined risk and ISS Stage.

Research Question 3

Research Question 3 (RQ3): Does patient gender and close proximity to MIRT impact PFS and OS in TT3, when controlling for GEP70-defined risk and ISS Stage?

Null hypothesis (H_{03}): There is no statistically significant difference on PFS or OS based on patient gender and close proximity to MIRT after controlling for GEP70-defined risk and ISS Stage in TT3.

To investigate Research Question 3, a Cox PH model was used to separately examine the potential impact of the independent variable, patient gender, on the dependent variables of PFS and OS, while controlling for GEP70-defined risk and ISS Stage.

<div align="center">

Threats to Validity

</div>

The TT3 clinical protocols are nonrandomized Phase II, prospective clinical trials that evaluated PFS and OS outcomes of 480 participants who were newly diagnosed with MM and treated at MIRT. The TT3 trials are closed to new patient accrual but outcomes for patients who remain alive have been updated weekly through the data cutoff date of the proposed trial. Internal threats to the validity of the proposed study include a lack of randomization in the TT3 trial design and the passage of time between TT3a and TT3b. Although the TT3 trials were not randomized, the results from the trials have been

published in peer-reviewed journals, cited in multiple peer-reviewed articles, and the findings have been incorporated in the treatment of MM in the United States and Internationally (Anderson, 2014; Muchtar et al., 2014). SES data were not collected from participants on TT3.

The criteria used to determine disease progression were subject to human interpretation but the interpretations were guided by laboratory information that is deemed to be highly accurate as the data were originated in a CLIA certified centralized pathology department at the University of Arkansas for Medical Sciences. External threats to validity of this study include the potential that patients enrolled on the TT3 protocol were not representative of the general NDxMM population. Objective entry and exclusionary criteria for study enrollment guided subject eligibility but it is recognized that these results originate from a single center.

Ethical Procedures

This study is a review of secondary data that was determined to impose minimal risk to patients and was granted a waiver of informed consent and approved by the UARK IRB on April 3, 2015 as noted in the approval IRB approval letter (UARK IRB Approval #204088) (Appendix H). The UARK IRB approved amendment 1 to UARK 2015-06 on May 12, 2015 (Appendix I). The UARK protocol review and motoring committee (PRMC) acknowledged the study on April 15, 2015 (Appendix J). A letter of cooperation from MIRT/UARK is noted in Appendix L. The UARK IRB committee chairperson acknowledged the lack of need for a data use agreement (Appendix K) for the PI to utilize UARK 2015-06 as the data source for this study. The TT3 protocols were

conducted in compliance with institutional, state and federal guidance and were performed in accordance with the Declaration of Helsinki, subject to external audit and oversight by an independent Data Safety Monitoring Board (Nair et al., 2010). The data to inform this study were originally collected for research and clinical purposes, during which all participants provided written informed consent prior to TT3 enrollment.

The study protocol mandated the use of an *honest broker* to prepare the data for submission to the PI. The honest broker was an authorized data manger from UARK who was responsible to remove all personally identifiable information from requested data sets subject to UARK IRB review and approval. The honest broker removed all personally identifiable data from the limited dataset and replaced study participant name coded in MMDB as *PatID* with an additionally encrypted coded number named *Codeid*. The PI will never possess or have access to the encryption key, thereby ensuring that personally identifiable information was protected.

The honest broker verified that the data was retrieved from MMDB, coded accurately and provided a de-identified, limited data set to the PI in a Microsoft Excel spreadsheet. The data cut-off date of the study was April 30, 2015. The electronic limited dataset is stored on a password-protected computer.

The study was also subject to Walden University IRB approval and data analysis did not occur until authorized by the Walden University IRB (Approval # 09-17-15-0232203; Appendix M). The only risk to participants is the potential for a loss of privacy. To minimize the risk to participants, the study was conducted utilizing a limited dataset that contained no personally identifiable information.

The PI further completed training on protection of human patients in Biomedical Research via the Collaborative Institutional Training Initiative (CITI) program and the National Institutes of Health Office of Extramural Research training course Protecting Human Research Participants.

No contact with any study participant was anticipated or occurred during this study. In the event of the loss of the limited dataset or inadvertent loss of confidentiality of any subject, the event will be reported to the IRB of both UARK and Walden University. The data will be kept in accordance with UARK IRB policy and destroyed in 5 years from IRB approval.

Data Dissemination

The limited dataset was not being shared with any nonUARK IRB authorized individual or entity. It is anticipated that the research findings from this dissertation will be presented publically in aggregate form, but no personally identifiable information will ever be disclosed. Consistent with Walden University's commitment to social change, the findings from this study will be shared with clinicians and health policy leaders.

Summary and Transition

Chapter 3 described the methodology of this retrospectively based, quantitative analysis of survival outcomes of patients treated on the TT3 protocols for NDxMM. The research design selected was utilized to determine if proximity to MIRT impacted PFS or OS when controlling for known risk factors associated with MM. The sample population selected is comprised from all patients treated on TT3 who consented to research and treatment and is believed to be representative of NDxMM patients treated at an academic

medical center. The use of the Cox PH model is accepted as an appropriate statistical tool to measure survival outcome in cancer trials and the data to inform the trial was obtained from clinical and research records obtained with UARK IRB approval. The research questions originated from a detailed literature review and variables chosen are accepted in the peer-reviewed literature. The data collected from subjects treated on TT3 has been presented publically in peer-reviewed journals and has been audited for quality by qualified investigators from the U.S. Food and Drug Administration and NCI supported investigators. UARK IRB review, monitoring and evaluation of study procedures by the U.S. Food and Drug Administration ensured protection of the rights of human subjects.

This study was reviewed and approved by the appropriate IRB's from Walden University and UARK. The data to inform the study was obtained by an authorized honest broker at UARK and consisted as a limited data set, void of personally identifiable information. The research methodology evaluated the limited data set to determine PFS and OS outcomes of patients treated on TT3 to determine if patient proximity to MIRT impacted outcome when other known risk factors are controlled.

Chapter 4: Results

Introduction

The purpose of this quantitative study of 480 clinical trial participants was to investigate the impact of patient distance from the site of care on survival outcomes for patients enrolled on two clinical trials for newly diagnosed multiple myeloma. The study hypotheses suggested that there was a difference in progression free survival (PFS) and overall survival (OS) due to logistical or patient care challenges in both planned and nonscheduled visits (owing to complications attributable to the disease or treatment related toxicities). This chapter will include a description of the data collected and the methodology for collection. Any deviation from the data collection or analysis described in Chapter 3 will be documented. Baseline descriptive participant characteristics and statistical analysis for each unique research question are presented.

Data Collection

This retrospective study utilized secondary data obtained from the Total Therapy 3 clinical trials at the Myeloma Institute for Research and Therapy at the University of Arkansas for Medical Sciences (UAMS/UARK). All clinical and geographic information necessary to conduct this study was obtained prospectively and recorded in the MMDB. The participants' geographic locations were reported at the zip code level, but not analyzed as a potential variable to impact PFS and OS in Total Therapy 3 protocols. This study evaluated the dependent variables of PFS and OS outcome for all 303 patients enrolled on Total Therapy 3a from February 2004 – July 2006 and the 177 patients

enrolled on Total Therapy 3b from November 2006 – September 2008. Unless a study participant had withdrawn consent, was lost to follow up, or died, researchers from the Myeloma Institute for Research and Therapy actively followed them for disease progression and outcome. Protocol specific procedures mandated that a bone marrow specimen was to be obtained for the purpose GEP, serum chemistry studies obtained from peripheral blood, and that imaging studies be performed. Measurement of baseline serum albumin and β-2 microglobulin were used to determine the ISS Stage (Appendix C). Information obtained for this study included a "Codeid" as a unique participant identifier, gender (male or female), ethnicity, protocol (TT3a or TT3b) enrollment, GEP70 Status (low or high risk), date enrolled on protocol, age at baseline (protocol enrollment), date of progression, date of death, date of last contact, reason for removal from protocol, distance from MIRT and ISS Stage. Table 5 presents baseline demographic information of study participants at protocol enrollment.

Table 5

Descriptive Statistics at Study Enrollment

Variable	*n*	*N*	*%*
Distance < 121 miles	72	480	15
Age >= 65 yrs.	130	480	27
Female	179	480	37
at least 1 cycle of prior therapy	51	480	11
ISS Stage 1	196	478	41
ISS Stage 2	166	478	35
ISS Stage 3	116	478	24
GEP-70 High Risk	80	469	17
Asian	5	480	1
Black	33	480	7
Native American	1	480	0
Pacific Islander	1	480	0
White	428	480	89
Refused/Blank	12	480	3

Note. Baseline GEP70 results were not available for 11 participants.

The variance between all enrolled subjects in Total Therapy 3 and baseline characteristics reported in this study is the lack of available GEP70 and/or the necessary information to assign an ISS Stage within the time allowed in the original protocols. The most common reason for the lack of GEP information was failed bone marrow sampling or insufficient quality of the sample. In the event of a failed sample, a repeat bone marrow sample was sought. In total, of the 480 participants enrolled on Total Therapy 3, 11 participants were not assigned a baseline GEP70 risk status. This study excluded participants whose records did not have both a GEP70 risk status assignment and ISS Stage within the time period required by the original study protocols. In this study, 469 participants are considered evaluable.

The population in this study was generally representative of the population of those persons with NDxMM based on the standardized criteria established by the DS. The proportion of male to female participants was consistent with data reported in the SEER database and by the NCCN (Anderson, 2014; National Cancer Institute, 2015c). GEP information was not available for the majority of persons diagnosed with MM as the test is considered investigational (Anderson, 2014). The median age of study participants was 59 years (30-74) and the median followup was 8.9 years later.

The original ISS data were obtained from 10,750 untreated patients with NDxMM (Greipp et al., 2005). The TT3 trials have a higher proportion of patients with Stage 1 and 2 disease when compared to the original ISS data; however, patients may have received one line of treatment prior to study enrollment if urgent therapy was required (Barlogie, 2003, 2006). A rapid change in ISS stage is biologically and therapeutically feasible with the administration of one cycle of anti-MM treatment. Table 6 presents the distribution of ISS Stage at diagnosis between the original ISS report and the 469 evaluable participants in this study.

Table 6

ISS Stage Distribution at Diagnosis

ISS Stage	ISS Participants %	Total Therapy 3 %
Stage 1	28	41
Stage 2	33	35
Stage 3	39	24

Note. Adapted from "International staging system for multiple myeloma" by Greipp, P. R., San Miguel, J., Durie, B., Crowley, J. J., Barlogie, B., Bladé, J., … Kyle, R. (2005). *Journal of Clinical Oncology*, *23*(15), 3412–3420. Copyright, The American Society of Clinical Oncology.

A Cox regression analysis was performed to determine the hazard ratio (HR) for risk of PFS or OS based on close proximity to MIRT. Additional Cox regression was performed to determine the HR for PFS and OS based on distance and covariates that are known to influence survival, including GEP-70 risk status, age $\geq$ 65 years, and gender. The Cox PH model is generally used to provide an estimate of HR and the bounding confidence interval and is one of the most commonly used models in outcome research (Spruance, Reid, Grace, & Samore, 2004) as it is applicable to many disease states.

When assigned to outcomes research, a HR <1.0 indicates that the group or research variable of interest, is less likely to experience the event of interest. An HR = 1.0 indicates that the groups have an equal risk of the event of interest. A HR > 1.0 indicates that the group or research variable of interest, is more likely to experience the event of interest. In this study, participants were stratified by distance traveled to MIRT, the groups are defined as those who live in either close proximity to MIRT (<121 miles from MIRT) or those not in close proximity to MIRT ($\geq$ 121 miles).

Research Question 0

Research Question 0 (RQ0): Does close proximity to MIRT impact PFS and OS in TT3?

Null hypothesis (H_{00}): There is no statistically significant difference to PFS or OS based on a patient's close proximity to MIRT.

Alternative Hypothesis (H_{A0}): There is a statistically significant difference to PFS or OS based on a patient's close proximity to MIRT, when controlling for GEP70-defined risk and ISS Stage.

Research Question 0: PFS Result

480 participants were evaluated for PFS outcome without regard to GEP-70 defined

risk and ISS Stage. Close proximity to MIRT was associated with a statistically

significant shorter PFS result HR 1.73, 95% CI [1.22 - 2.46], p = .001. The Wald statistic

showed that the overall effect of close proximity to MIRT on PFS in TT3 was significant,

p = 0.001. The hazard ratio obtained for this result was 1.73, indicating close proximity to

MIRT was associated with increased risk of shorter PFS compared to those outside of
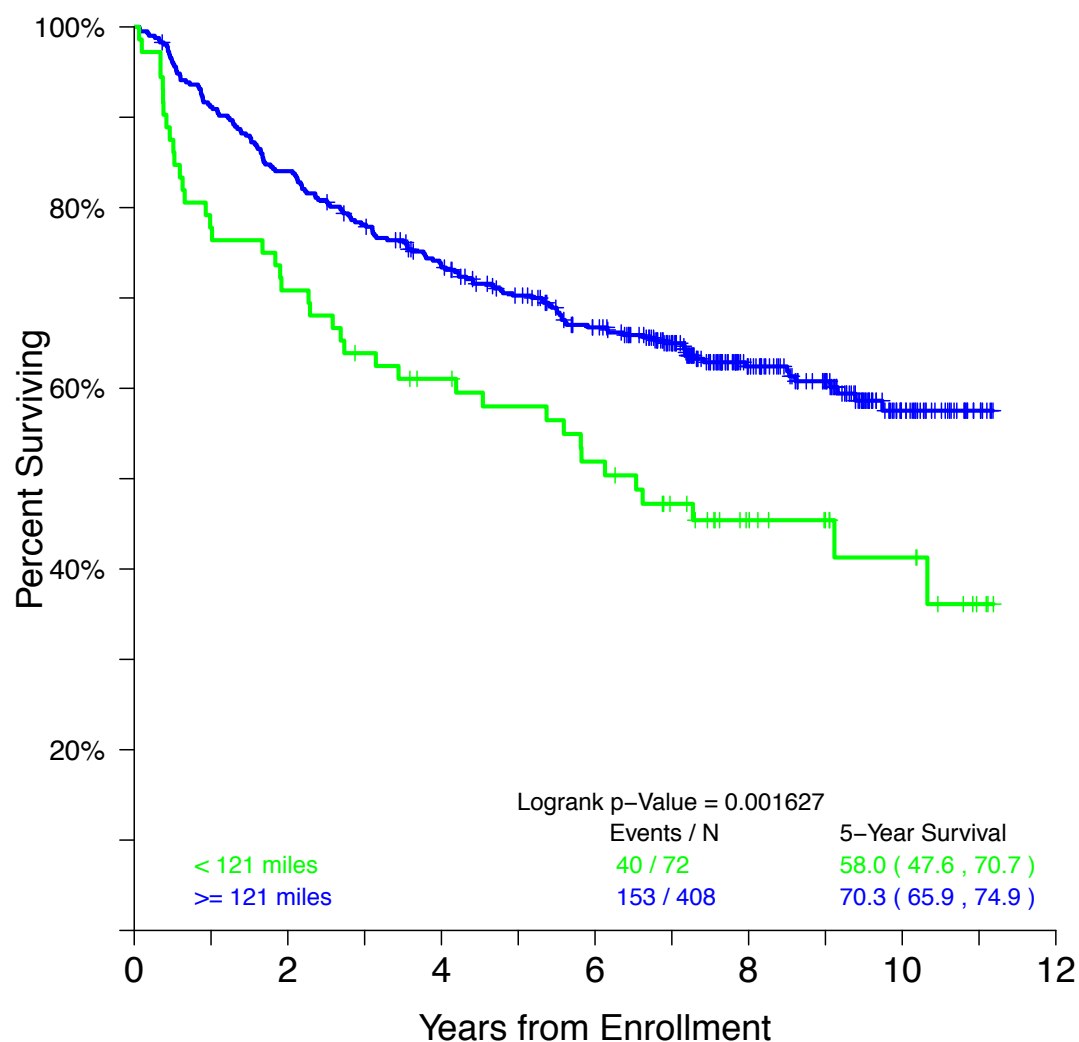
close proximity.

Figure 3. Research Question 0 PFS results.

Research Question 0: OS Result

480 participants were evaluated for OS outcome without regard to GEP-70 defined

risk and ISS Stage. Close proximity to MIRT was associated with a statistically

significant shorter OS result HR 1.73, 95% CI [1.22 - 2.45], *p* = .002. The Wald statistic

showed that the overall effect of close proximity to MIRT on PFS in TT3 was significant,

p = 0.002. The hazard ratio obtained for this result was 1.73, indicating close proximity to MIRT was associated with increased risk of shorter OS compared to those outside of close proximity.
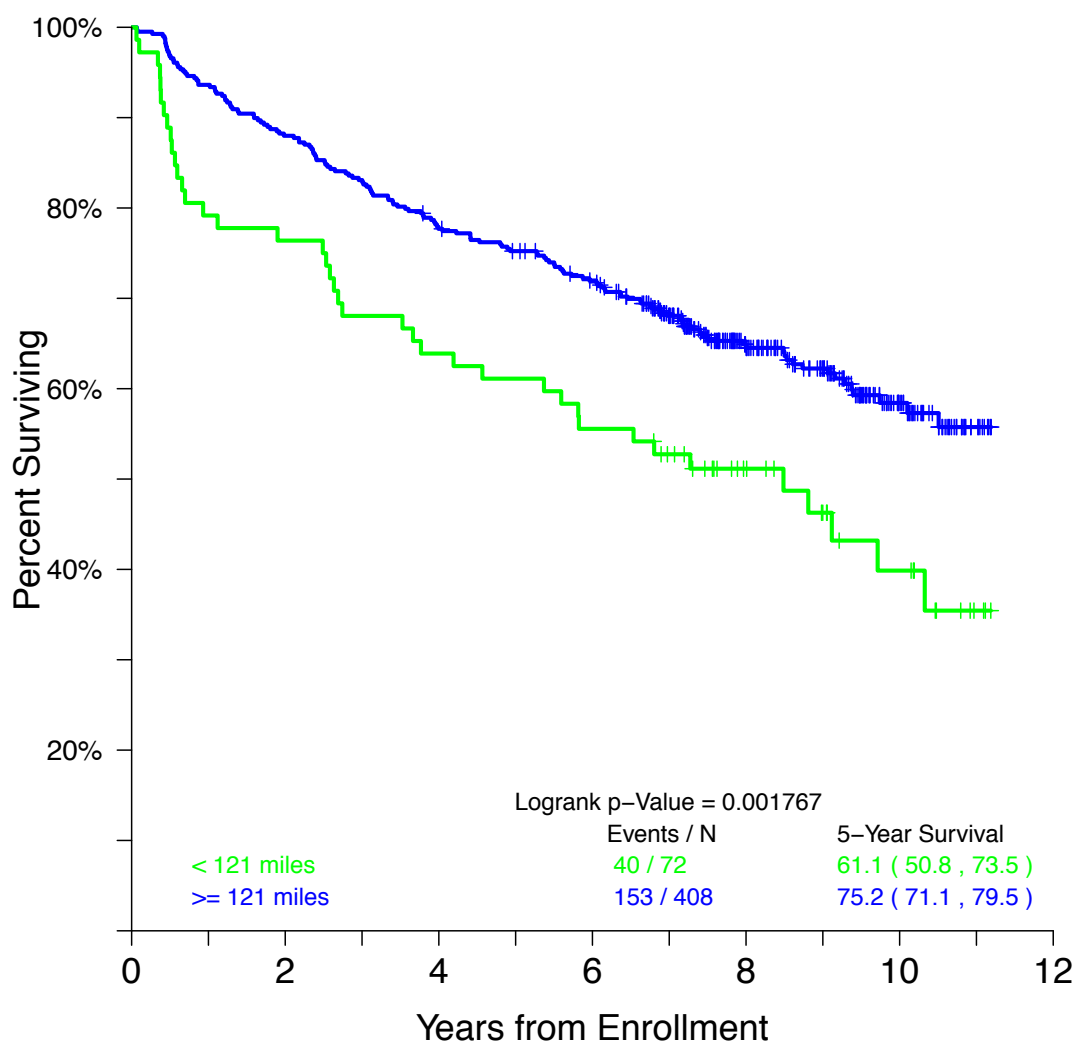
Figure 4. Research Question 0 OS results.

Table 7

Regression Results for Research Question 0

Variable	PFS/OS	HR	SE HR	z	*p*
Distance (<121 miles)	PFS	1.73	.177	3.11	.001
Distance (<121 miles)	OS	1.73	.177	3.08	.002

Research Question 0 results indicate that distance from MIRT was associated with statistically significant differences in PFS and OS outcome. Research Questions 1-3 tested the hypothesis when controlling for established factors associated with MM, including GEP-70 status, ISS Stage, and gender.

Research Question 1

Research Question 1 (RQ1): Does close proximity to MIRT impact PFS and OS in TT3, when controlling for GEP70-defined risk and ISS Stage?

Null hypothesis (H_{01}): There is no statistically significant difference to PFS or OS based on a patient's close proximity to MIRT, when controlling for GEP70-defined risk and ISS Stage.

Alternative Hypothesis (H_{A1}): There is a statistically significant difference to PFS or OS based on a patient's close proximity to MIRT, when controlling for GEP70-defined risk and ISS Stage.

Research Question 1: PFS Result

469 of 480 participants had baseline GEP and ISS Stage results. Close proximity to MIRT was associated with a statistically significant shorter PFS result HR 1.67, 95% CI [1.17 - 2.38], *p* = .004 in TT3 after controlling for the effect of GEP70-defined risk and ISS Stage. The Wald statistic showed that the overall effect of close proximity to MIRT

on PFS in TT3 was significant, $p = 0.000$. The hazard ratio obtained for this result was 1.67, indicating close proximity to MIRT was associated with increased risk of shorter PFS compared to those outside of close proximity when controlling for GEP70-defined risk and ISS Stage. The null hypothesis is rejected.

Research Question 1: OS Result

469 of 480 participants had baseline GEP and ISS Stage results. Close proximity to MIRT was associated with a statistically significant shorter OS result HR 1.67, 95% CI [1.17 - 2.39], p = .004 in TT3 after controlling for the effect of GEP70-defined risk and ISS Stage. The Wald statistic showed that the overall effect of close proximity to MIRT on PFS in TT3 was significant, $p = 0.000$. The hazard ratio obtained for this result was 1.67, indicating close proximity to MIRT was associated with increased risk of shorter PFS compared to those outside of close proximity when controlling for GEP70-defined risk and ISS Stage. The null hypothesis is rejected.

Figure 5. Research Question 1 OS results. Note. Figure abbreviations, HR = GEP-70 High Risk; LR = GEP-70 Low Risk

Table 8

Regression Results for Research Question 1

Variable	PFS/OS	HR	SE HR	z	p
Distance (<121 miles)	PFS	1.67	.181	2.83	.004
Distance (<121 miles)	OS	1.67	.181	2.85	.004

The results of the analysis compel rejection of the null hypothesis for research question one that there is no statistically significant difference on PFS or OS based on a patient's close proximity to MIRT, when controlling for GEP70-defined risk and ISS Stage. Results support the alternative hypothesis that there is a statistically significant difference on PFS or OS based on a patient's close proximity to MIRT, when controlling for GEP70-defined risk and ISS Stage.

Research Question 2

Research Question 2 (RQ2): Does patient age $\geq$ 65 years and close proximity to MIRT impact PFS and OS in TT3, when controlling for GEP70-defined risk and ISS Stage?

Null hypothesis (H_{02}): There is no statistically significant difference in PFS or OS based on a patient age $\geq$ 65 years and close proximity to MIRT after controlling for GEP70-defined risk and ISS Stage.

Alternative Hypothesis (H_{A2}): There is a statistically significant difference in PFS or OS based on a patient age $\geq$ 65 years and close proximity to MIRT after controlling for GEP70-defined risk and ISS Stage.

Research Question 2: PFS Result

One hundred and thirty (n=130) of 480 participants were $\geq$ 65 years at study enrollment; 126 of 130 participants $\geq$ 65 years had both baseline GEP and ISS Stage results available and were evaluated in this research question. Patient age $\geq$ 65 years and close proximity to MIRT was associated with a statistically significant shorter PFS result HR 1.88, 95% CI [1.07 - 3.28], p = .026 in TT3 after controlling for the effect of GEP70-defined risk and ISS Stage. The Wald statistic showed that the overall effect of close proximity to MIRT on PFS in TT3 was significant, p = .0000. The hazard ratio obtained for this result was 1.88, indicating close proximity to MIRT was associated with increased risk of shorter PFS compared to those outside of close proximity when controlling for GEP70-defined risk and ISS Stage. The null hypothesis is rejected.
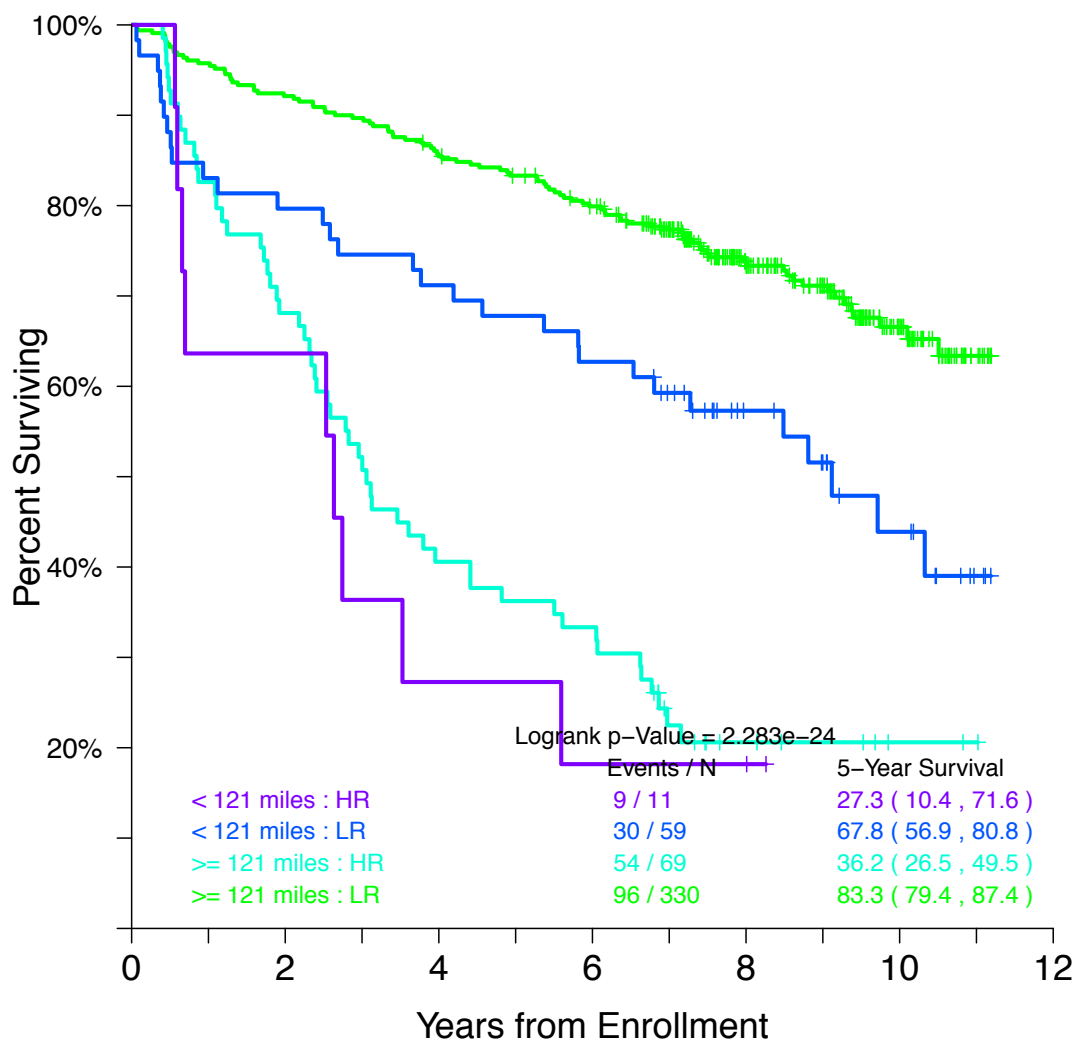
Research Question 2: OS Result

One hundred and thirty (n=130) of 480 participants were ≥ 65 years at study enrollment; 126 of 130 participants ≥ 65 years had both baseline GEP and ISS Stage results available and evaluated in this research question. Patient age ≥ 65 years and close proximity to MIRT was associated with a statistically significant shorter PFS result HR 1.75, 95% CI [1.00 – 3.06], p = .049 in TT3 after controlling for the effect of GEP70-defined risk and ISS Stage. The Wald statistic showed that the overall effect of close proximity to MIRT on PFS in TT3 was significant, p = .0000. The hazard ratio obtained for this result was 1.75, indicating close proximity to MIRT was associated with increased risk of shorter OS compared to those outside of close proximity when controlling for GEP70-defined risk and ISS Stage. The null hypothesis is rejected.

Figure 6. Research Question 2 OS results. HR = GEP-70 High Risk; LR = GEP-70 Low Risk

Table 9

Regression Results for Research Question 2

Variable	PFS/OS	HR	SE HR	z	p
Distance (<121 miles)	PFS	1.88	.284	2.21	.026
Distance (<121 miles)	OS	1.75	.285	1.96	.049

The results of the analysis compel rejection of the null hypothesis for research question two that there is no statistically significant difference in PFS or OS based on a patient age $\geq$ 65 years and close proximity to MIRT after controlling for GEP70-defined risk and ISS Stage. Results support the alternative hypothesis that there is a statistically significant difference in PFS or OS based on a patient age $\geq$ 65 years and close proximity to MIRT after controlling for GEP70-defined risk and ISS Stage.

Research Question 3

Research Question 3 (RQ3): Does patient gender and close proximity to MIRT impact PFS and OS in TT3, when controlling for GEP70-defined risk and ISS Stage?

Null hypothesis (H_{03}): There is no statistically significant difference on PFS or OS based on patient gender and close proximity to MIRT after controlling for GEP70-defined risk and ISS Stage in TT3.

Alternative Hypothesis (H_{A3}): There is a statistically significant difference on PFS or OS based on patient gender and close proximity to MIRT after controlling for GEP70-defined risk and ISS Stage in TT3.

Research Question 3: PFS Result

There were 179 females and 301 males in the TT3 clinical trials. Baseline GEP results were available for 175 females and 294 males. Gender and GEP baseline information was available for 469 of 480 participants. Patient gender and close proximity to MIRT did not significantly impact PFS in TT3, HR 1.01, 95% CI [.75 – 1.35], $p = .94$. The hazard ratio obtained for this result was 1.01, indicating close proximity to MIRT was not associated with increased risk of shorter PFS compared to those outside of close proximity, when controlling for GEP70-defined risk and ISS Stage. The null hypothesis cannot be rejected.
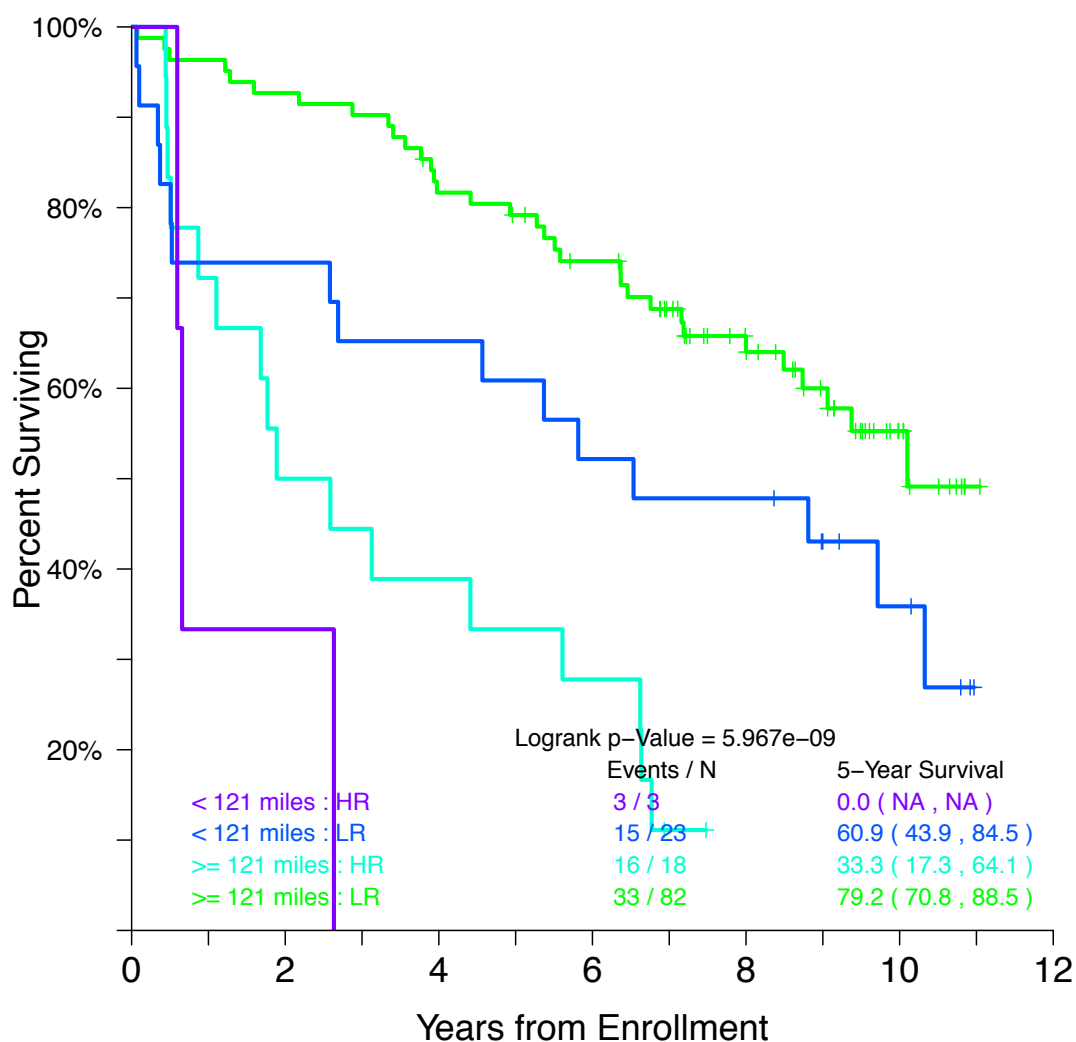
Research Question 3: OS Result

There were 179 females and 301 males in the TT3 clinical trials. Baseline GEP results were available for 175 females and 294 males. Gender and GEP baseline information was available for 469 of 480 participants. Patient gender and close proximity

to MIRT did not significantly impact PFS in TT3, HR .99, 95% CI [.73 – 1.33], p = .96. The hazard ratio obtained for this result was .99, indicating close proximity to MIRT was not associated with increased risk of shorter PFS compared to those outside of close proximity when controlling for GEP70-defined risk and ISS Stage. The null hypothesis cannot be rejected.
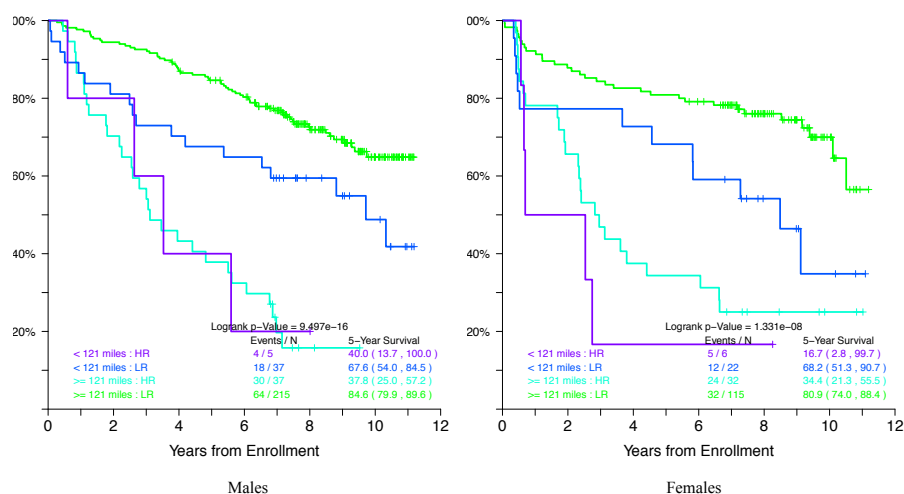

Figure 7. Research Question 3 OS results. HR = GEP-70 High Risk; LR = GEP-70 Low Risk.

Table 10

Regression Results for Research Question 3

Variable	PFS/OS	HR	SE HR	z	p
Distance (<121 miles)	PFS	1.01	.150	.075	.940
Distance (<121 miles)	OS	.99	.150	-0.05	.960

The results of the model did not compel rejection of the null hypothesis for research question three that there is no statistically significant difference on PFS or OS based on patient gender and close proximity to MIRT after controlling for GEP70-defined risk and ISS Stage in TT3. Results demonstrated that close proximity to MIRT had a significant impact on both PFS and OS after controlling for GEP70-defined risk and ISS Stage in TT3, while gender did not have a statistically significant impact on PFS or OS.

Summary

This study sought to determine if patient travel distance to MIRT impacted PFS or OS outcome in the TT3 trials for NDxMM. Patient travel distance was categorized as either in close proximity, defined as residence in a zip code that is <120 miles from MIRT, whereas those outside of proximity to MIRT live in a zip code ≥ miles from MIRT. The results of this study indicate that close proximity to MIRT is associated with statistically significant differences in PFS and OS which are associated with shorter PFS and OS. ISS Stage and GEP-70 defined risk are known to influence PFS and OS in NDxMM. This study determined that patient distance traveled in TT3 does impact PFS and OS, this determination is statistically significant in a Cox PH model where distance traveled, ISS Stage, and GEP-70 risk stratification are both included and controlled for. The variables of age ≥ 65 and gender were also evaluated in the Cox PH model. When controlling for ISS Stage and GEP-70 risk stratification, age ≥ 65 was statistically significant as a negative modifier on PFS and OS, but gender was not associated with a

statistically significant risk. The null hypothesis was rejected in the first two research

questions in this study, but cannot be rejected in the third question.

Chapter 5: Discussion, Conclusions, and Recommendations

Introduction

The purpose of this quantitative study of 480 clinical trial participants was to investigate the impact of patient distance from the site of care on survival outcomes for patients enrolled on two clinical trials for newly diagnosed multiple myeloma. Current diagnostic and prognostic schemas do not incorporate patient distance traveled to the site of care for MM despite evidence that it may impact PFS and OS. This study addressed this gap by retrospectively examining prospectively collected data including distance from the patient's home to MIRT, ISS Stage, age, GEP-70 risk stratification to determine if near proximity (distance <120 miles from MIRT) impacted PFS or OS compared to a proximity ≥ 121 miles.

The results of this study indicate that patients in close proximity to MIRT have an increased hazard of progression and death. The conclusions that close proximity to MIRT is associated with an increased hazard of early progression and death was determined to be statistically significant; this conclusion was also determined to be valid when known predictors of risk, including ISS Stage, GEP-70 based risk, and age ≥ 65 were introduced into the Cox PH model. Gender was not determined to be associated with an increased risk of progression or death.

Interpretation of the Findings

Previous studies examining the potential of patient distance traveled to impact PFS or OS have yielded inconsistent findings and have not been tested in a large sample after the introduction of novel therapy followed by autologous stem cell transplant

(ASCT). The results of this study are consistent with the major findings of Lenhard and associates (1987) and Lipe et al., 2012, such that patient distance traveled did impact overall survival (OS). The baseline demographic characteristics in this trial were consistent with previously reported studies of NDxMM. In contrast to the majority of the existing literature investigating the role of distance in PFS and OS in NDxMM, this study used a singular treatment regimen and strict entry criteria for study participation. This is the largest currently reported study investigating the role of patient distance traveled to impact PFS and OS outcome where all patients received combination novel therapy induction, tandem ASCT, and three year, three drug maintenance therapy.

Several additional facets make this study unique in its contribution and expansion of the literature. The NCCN recommends that NDxMM patients who are eligible for ASCT, be treated with novel drug based induction therapy, ASCT, and maintenance therapy; this study represents long-term follow up of patients treated in a similar fashion to current NCCN recommendations. This study is also unique in that it included both the ISS Staging System, which is available in most clinical practices and the research based GEP-70 risk based stratification of NDxMM. The application of both routine and investigational risk stratification schemas in the analysis of distance as a risk factor in NDxMM, allows for the application of this information in both academic and community based practice settings. This information is of interest to the broad community of health care providers who treat MM as this study analyzed novel therapy in combination with classic chemotherapy and utilized two ASCT procedures and planned multiyear maintenance therapy. The findings that distance from the site of care impacts PFS and OS

for those undergoing therapy for multiple myeloma should be a clinical concern and variable to consider at diagnosis.

The findings from this study are confounded by the lack of SES data collection and analysis in the original study from which data were obtained. An assumption of this trial is that participants who lived ≥ 121 miles from MIRT had the financial resources, physical ability, and desire to travel to Arkansas for treatment. Those without the ability to travel to Arkansas/MIRT for treatment could not have been enrolled on the TT3 protocols; persons who lived < 121 miles from MIRT, by definition, are residents of the State of Arkansas and may have been eligible for TT3 participation, even if they were financially indigent. Placed in the historical context of MM treatment in 2003, the use of novel drug combination chemotherapy in the NDxMM setting, followed by tandem ASCT, and three year, three drug maintenance therapy was not routine, was investigational, and not the standard of care. The choice to travel to MIRT from outside of the State of Arkansas and participate in TT3 implies higher health literacy and SES status.

Theoretical Framework of the Study

Andersen's behavioral model of health services (BMH) use (1995) serves as the theoretical framework of this study. The BMH has been widely utilized as a framework for health services and outcomes and has undergone revision since its introduction in the 1960's to be applicable to individual decision making with respect to healthcare services use. The application of the BMH to the this study is predicated on the hypothesis that patient distance traveled to the site of care for MM may be impactful on PFS and OS and

is consistent with Andersen's assertion that distance and availability of healthcare services are key factors in an individual's choice to access the healthcare system.

Limitations of the Study

This study is a retrospective analysis of secondary data collected from TT3. Although the data analyzed in this study did not originate from a randomized clinical trial investigating the research questions in the study. This study originated from data collected at a single center, which may limit the applicability of the results.

Socioeconomic Status (SES) status is known to impact PFS and OS in cancer and the results from this study are likely confounded by the lack of SES data. SES data was not collected or analyzed in this study. Furthermore, gross measures of SES associated with zip code of residence or "cash on hand" may not adequately inform the likelihood of drug regimen persistence, compliance to treatment plans/protocol. This study is unique in that the median follow up, as of the date of data cut-off is nearly 9 years. The relatively large sample size of this study combined with the consistency of the baseline demographics of the population implies that this study is trustworthy, valid, and repeatable.

Recommendations

The results from this trial indicate that distance should be examined in future studies as an impactful variable on progression and death in NDxMM. Results from this trial should be used as a proof of concept, or as a "training set" to retrospectively analyze the Total Therapy 4-6 clinical trials. If future analysis of TT4-6 confirms these findings, the prospective collection of distance and SES information should be included on future

clinical trials at MIRT. One confirmed in multiple retrospective trials and one prospective trial, the information should be made available to professional organizations involved in NDxMM disease prognostication schemas, including the International Myeloma Working Group, NCCN, and the American Society of Hematology. Furthermore, the application of these findings to other cancer centers that collect data concerning long-term outcomes and have publically available data is another recommended practice. In the event that distance, as a prognostic variable is evaluated in a prospective clinical trial, a team of qualified public health practitioners, policy makers, hematologists, social workers, and outcome research specialists should be convened to plan an ideal data collection and analysis plan.

Implications for Social Change

This study affirms the applicability of Anderson's (1995) model of behavioral health services to a relatively rare adult hematologic malignancy. Although MM is a relatively rare cancer, findings from this study may be applied to any planned therapeutic regimen which incorporates ASCT. ASCT is a standard of care in many more common malignancies, including some lymphomas and leukemias. Distance as a prognostic variable may also be viewed in the context of access to healthcare.

This study promotes positive social change by demonstrating the potential of patient travel distance to shorten life expectancy. It also raises additional and troubling questions regarding the role of SES to impact cancer survivorship. As the U.S. healthcare delivery system is adapting to recent legislative changes, the application of these findings to healthcare policy decisions regarding the ability of a person to travel outside of their

local health "network" to seek optimal care should be addressed. The ability of a person to access healthcare and experience better outcomes as a function of distance traveled for care or SES is a known and policy modifiable healthcare inequity.

Conclusion

MM is a rare malignant transformation of plasma cells that is characterized by bone pain, anemia, skeletal fracture, and shortened life span. Recent advances in the treatment of NDxMM have extended the PFS and OS for patients with the disease. Distance to the site of care for MM has been demonstrated to impact PFS and OS and this study confirms this observation in the TT3 trials for NDxMM. The TT3 trials are notable for the use of combination novel therapy based induction, tandem ASCT, multi-year, multi-drug maintenance therapy, and long-follow up. With a median of nearly 9 years of follow up, patient travel distance to the site of care has been shown to impact PFS and OS outcome, favoring those who live beyond 121 miles of MIRT. This quantitative, retrospective study of 480 participants with NDxMM has demonstrated that patient travel distance, and likely, SES is prognostic variables for survival. This study is the largest study reporting PFS and OS outcomes for patients who were treated for NDxMM in the era of novel therapy. Comparisons of survival from clinical trials which differ in design are not scientifically appropriate; however, it should be noted that OS reported in this trial exceeds published reference standards of 2003 and 2015.

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Appendix A: EBMT Criteria

Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation

Adapted from Blade et al. (1998, p. 1119).

Complete response (CR) requires all of the following:
1. Absence of the original monoclonal paraprotein in serum and urine by immunofixation, maintained for a minimum of 6 weeks. The presence of oligoclonal bands consistent with oligoclonal immune reconstitution does not exclude CR.
2. < 5% plasma cells in a bone marrow aspirate and also on trephine bone biopsy, if biopsy is performed. If absence of monoclonal protein is sustained for 6 weeks it is not necessary to repeat the bone marrow, except in patients with nonsecretory myeloma where the marrow examination must be repeated after an interval of at least 6 weeks to confirm CR.
3. No increase in size or number of lytic bone lesions (development of a compression fracture does not exclude response).
4. Disappearance of soft tissue plasmacytomas.

Patients in whom some, but not all, the criteria for CR are fulfilled are classified as PR, providing the remaining criteria satisfy the requirements for PR. This includes patients in whom routine electrophoresis is negative but in whom immunofixation has not been performed.

Partial response (PR) requires all of the following:
1. ≥50% reduction in the level of the serum monoclonal paraprotein, maintained for a minimum of 6 weeks.
2. Reduction in 24 h urinary light chain excretion either by >90% or to <200 mg, maintained for a minimum of 6 weeks.
3. For patients with nonsecretory myeloma only, >50% reduction in plasma cells in a bone marrow aspirate and on trephine biopsy, if biopsy is performed, maintained for a minimum of 6 weeks.
4. >50% reduction in the size of soft tissue plasmacytomas (by radiography or clinical examination).
5. No increase in size or number of lytic bone lesions (development of a compression fracture does not exclude response).

Patients in whom some, but not all, the criteria for PR are fulfilled are classified as MR, provided the remaining criteria satisfy the requirements for MR.

Minimal response (MR) requires all of the following:

1. 25–49% reduction in the level of the serum monoclonal paraprotein maintained for a minimum of 6 weeks.
2. 50–89% reduction in 24 h urinary light chain excretion, which still exceeds 200 mg/24 h, maintained for a minimum of 6 weeks.
3. For patients with nonsecretory myeloma only, 25–49% reduction in plasma cells in a bone marrow aspirate and on trephine biopsy, if biopsy is performed, maintained for a minimum of 6 weeks.
4. 25–49% reduction in the size of soft tissue plasmacytomas (by radiography or clinical examination).
5. No increase in the size or number of lytic bone lesions (development of a compression fracture does not exclude response).

MR also includes patients in whom some, but not all, the criteria for PR are fulfilled, provided the remaining criteria satisfy the requirements for MR.

No change (NC)

1. Not meeting the criteria of either minimal response or progressive disease.

Plateau

1. Stable values (within 25% above or below value at the time response is assessed) maintained for at least 3 months.

Time point for assessing response

1. Response to the transplant procedure will be assessed by comparison with results immediately prior to conditioning.
2. If transplant is part of a treatment programme, response to the whole treatment programme will be assessed by comparison with the results at the start of the programme.

Relapse from CR requires at least one of the following:

1. Reappearance of serum or urinary paraprotein on immunofixation or routine electrophoresis, confirmed by at least one further investigation and excluding oligoclonal immune reconstitution.
2. ≥5% plasma cells in a bone marrow aspirate or on trephine bone biopsy.
3. Development of new lytic bone lesions or soft tissue plasmacytomas or definite increase in the size of residual bone lesions (development of a compression fracture does not exclude continued response and may not indicate progression).
4. Development of hypercalcaemia (corrected serum calcium >11·5 mg/dl or 2·8 mmol/l) not attributable to any other cause.

Progressive disease (for patients not in CR) requires one or more of the following:

1. >25% increase in the level of the serum monoclonal paraprotein, which must also be an absolute increase of at least 5 g/l and confirmed by at least one repeated investigation.
2. >25% increase in the 24 h urinary light chain excretion excretion, which must also be an absolute increase of at least 200 mg/24 h and confirmed by at least one repeated investigation.
3. >25% increase in plasma cells in a bone marrow aspirate or on trephine biopsy, which must also be an absolute increase of at least 10%.
4. Definite increase in the size of existing bone lesions or soft tissue plasmacytomas.
5. Development of new bone lesions or soft tissue plasmacytomas (development of a compression fracture does not exclude continued response and may not indicate progression).
6. Development of hypercalcaemia (corrected serum calcium >11·5 mg/dl or 2·8 mmol/l) not attributable to any other cause.

Appendix B: Durie-Salmon Criteria

(Adapted from Durie & Salmon (1975)

Stage I	All of the following: ▪ Hb > 10g/dL ▪ normal calcium ▪ Skeletal survey: normal or single plasmacytoma or osteoporosis ▪ Serum paraprotein level < 5 g/dL if IgG, < 3 g/dL if IgA ▪ Urinary light chain excretion < 4 g/24h
Stage II	Fulfilling the criteria of neither I nor III
Stage III	One or more: ▪ Hb < 8.5g/dL ▪ high calcium > 12 mg/dL ▪ Skeletal survey: Three or more lytic bone lesions ▪ Serum paraprotein > 7g/dL if IgG, > 5 g/dL if IgA ▪ Urinary light chain excretion > 12g/24h
Sub-classification	**A** = Relatively normal renal function (serum creatinine value < 2.0 mg/100 ml) **B** = Abnormal renal function (serum creatinine value $\geq$ 2.0 mg/100 ml)

Appendix C: International Staging System (ISS)

International Staging System (Greipp, San Miguel, Durie, Crowley, Barlogie, Bladé, Boccadoro, Child, Avet-Loiseau, & Kyle, 2005)

International Staging System		
Stage	Criteria	Median Survival (months)
I	Serum $\beta2$-microglobulin < 3.5mg/L Serum Albumin > 3.5 g/dL	62
II	Not stage I or III	44
III	Serum $\beta2$-microglobulin > 5.5 mg/L	29
There are two categories for stage II: serum $\beta2$-microglobulin < 3.5 mg/L but serum albumin < 3.5 g/dL; or serum $\beta2$-microglobulin 3.5 to < 5.5 mg/L irrespective of the serum albumin level.		

Appendix D: CRAB Criteria

Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group

Adapted from Kyle et al. (2003).

Diagnosis	Diagnostic Criteria: All Three Required
Symptomatic Multiple Myeloma[a]	Monoclonal plasma cells in the bone marrow ≥ 10% and/or presence of a biopsy-proven plasmacytoma Monoclonal protein present in the serum and/or urine[b] Myeloma-related organ dysfunction (≥ 1)[c] [C] Calcium elevation in the blood (serum calcium > 10.5 mg/l or upper limit of normal) [R] Renal insufficiency (serum creatinine > 2 mg per 100 ml) [A] Anemia (hemoglobin < 10 g per 100 ml or 2 g < normal) [B] Lytic bone lesions or osteoporosis[d]

a These criteria identify Stage IB and Stages II and III A/B myeloma by Durie/Salmon stage. Stage IA becomes smoldering or indolent myeloma.
b If no monoclonal protein is detected (nonsecretory disease), then ≥ 30% monoclonal bone marrow plasma cells and/or a biopsy-proven plasmacytoma required.
c A variety of other types of end-organ dysfunctions can occasionally occur and lead to a need for therapy. Such dysfunction is sufficient to support classification as myeloma if proven to be myeloma related.
d If a solitary (biopsy-proven) plasmacytoma or osteoporosis alone (without fractures) is the sole defining criteria, then ≥ 30% plasma cells are required in the bone marrow.

Appendix E: Total Therapy 3a Treatment Plan

	VTD-PACE #1
Induction I	V 1.0 mg/m^2 d 1, 4, 8 and 11 T 200 mg/d d 4 – 7 D 40 mg/d d 4 – 7 P 10 mg/m^2 d 4 – 7 CI A 10 mg/m^2 d 4 – 7 CI C 400 mg/m^2 d 4 – 7 CI E 40 mg/m^2 d 4 – 7 CI PBSC collection > 20 x 10^6 CD34/kg
Bridging	THAL 50 mg-DEX 20mg
	VTD-PACE #2
Induction 2 **[6 weeks to 8 weeks post Induction 1]**	V 1.0 mg/m^2 d 1, 4, 8 and 11 T 200 mg/d d 1 – 4 D 40 mg/d d 1 – 4 P 10 mg/m^2 d 1 – 4 CI A 10 mg/m^2 d 1 – 4 CI C 400 mg/m^2 d 1 – 4 CI E 40 mg/m^2 d 1 – 4 CI
Bridging	THAL 50 mg-DEX 20mg
Transplant 1 **[3 weeks to 12 weeks post Induction 2]**	MEL 200 M 200 mg/m^2 d -1 D 40 mg/d d -2 to +1
Bridging	THAL 100 mg-DEX 20mg
Transplant 2 **[8 weeks to 6 months post Transplant 1]**	MEL 200 M 200 mg/m^2 d -1 D 40 mg/d d -2 to +1
Bridging	THAL 100 mg-DEX 20mg
Consolidation 1 **[6 weeks to 6 months post Transplant 2]**	VTD-PACE V 1.0 mg/m^2 d 1, 4, 8 and 11 T 200 mg/d d 1 – 4 D 40 mg/d d 1 – 4 P 7.5 mg/m^2 d 1 – 4 CI A 7.5 mg/m^2 d 1 – 4 CI C 300 mg/m^2 d 1 – 4 CI E 30 mg/m^2 d 1 – 4 CI
Bridging	THAL 100 mg-DEX 20mg
Consolidation 2 **[8 weeks to 12 weeks post Consolidation 1]**	VTD-PACE V 1.0 mg/m^2 d 1, 4, 8 and 11 T 200 mg/d d 1 – 4 D 40 mg/d d 1 – 4 P 7.5 mg/m^2 d 1 – 4 CI A 7.5 mg/m^2 d 1 – 4 CI C 300 mg/m^2 d 1 – 4 CI E 30 mg/m^2 d 1 – 4 CI
Maintenance Year 1: **[4 weeks to 4 months post Consolidation 2]** **Maintenance Year 2-3**	Treatment for 3 years: **VTD** V 1.0 mg/m^2/wk d 1, 4, 8, 11 T 100 mg/d d 1 – 28 D 20 mg/wk d 1-4 and 8-11 **VTD weekly** V 1.0 mg/m^2/wk d 1, 8, 15, 22 T 100 mg/d d 1 – 28 D 20 mg/wk d 1, 8, 15, 22 **Or** **TD** T 100/mg/d d 1-28 D 20 mg/d d 1-4

Appendix F: Total Therapy 3b Treatment Plan

	VTD-PACE #1
Induction I	V 1.0 mg/m^2 d 1, 4, 8 and 11 T 200 mg/d d 4 – 7 D 40 mg/d d 4 – 7 P 10 mg/m^2 d 4 – 7 CI A 10 mg/m^2 d 4 – 7 CI C 400 mg/m^2 d 4 – 7 CI E 40 mg/m^2 d 4 – 7 CI PBSC collection > 20 x 10^6 CD34/kg
Bridging	THAL 50 mg-DEX 20mg
	VTD-PACE #2
Induction 2 **[6 weeks to 8 weeks post Induction 1]**	V 1.0 mg/m^2 d 1, 4, 8 and 11 T 200 mg/d d 1 – 4 D 40 mg/d d 1 – 4 P 10 mg/m^2 d 1 – 4 CI A 10 mg/m^2 d 1 – 4 CI C 400 mg/m^2 d 1 – 4 CI E 40 mg/m^2 d 1 – 4 CI
Bridging	THAL 50 mg-DEX 20mg
Transplant 1 **[3 weeks to 12 weeks post Induction 2]**	**MEL 200** M 200 mg/m^2 d -1 D 40 mg/d d -2 to +1
Bridging	THAL 100 mg-DEX 20mg
Transplant 2 **[8 weeks to 6 months post Transplant 1]**	**MEL 200** M 200 mg/m^2 d -1 D 40 mg/d d -2 to +1
Bridging	THAL 100 mg-DEX 20mg
Consolidation 1 **[6 weeks to 6 months post Transplant 2]**	**VTD-PACE** V 1.0 mg/m^2 d 1, 4, 8 and 11 T 200 mg/d d 1 – 4 D 40 mg/d d 1 – 4 P 7.5 mg/m^2 d 1 – 4 CI A 7.5 mg/m^2 d 1 – 4 CI C 300 mg/m^2 d 1 – 4 CI E 30 mg/m^2 d 1 – 4 CI
Bridging	THAL 100 mg-DEX 20mg
Consolidation 2 **[8 weeks to 12 weeks post Consolidation 1]**	**VTD-PACE** V 1.0 mg/m^2 d 1, 4, 8 and 11 T 200 mg/d d 1 – 4 D 40 mg/d d 1 – 4 P 7.5 mg/m^2 d 1 – 4 CI A 7.5 mg/m^2 d 1 – 4 CI C 300 mg/m^2 d 1 – 4 CI E 30 mg/m^2 d 1 – 4 CI
Maintenance Year 1: **[4 weeks to 4 months post Consolidation 2]** **Maintenance Year 2-3**	**Treatment for 3 years:** **VRD** V 1.0 mg/m^2/wk d 1, 4, 8, 11 R 15 mg/d d 1 – 20 R 5 mg/d d 21 – 28 D 20 mg/wk d 1-4 and 8-11 **VRD weekly** V 1.0 mg/m^2/wk d 1, 8, 15, 22 R 15 mg/d d 1 – 20 R 5 mg/d d 21 – 28 D 20 mg/wk d 1, 8, 15, 22

Appendix G: List of Abbreviations

ACS	American Cancer Society
ASCT	(peripheral blood) Autologous Stem Cell Transplant
AE	adverse event
B2M	β 2 microglobulin
BMH	Andersen's behavioral model of health services utilization
BRAF	v-raf murine sarcoma viral oncogene homolog B
CBC	complete blood count (hematology)
Chem7	Basic metabolic panel (chemistry)
CR	complete response
CRF	case report form
CT	x-ray computed tomography
CYP	Cytochrome P
DLT	dose-limiting toxicity
DWIBBS	diffusion weighted imaging with background body signal suppression
DVT/PE	Deep Vein Thrombosis / Pulmonary Embolism
EBMT	European Group for Blood and Marrow Transplantation
ECOG	Eastern Cooperative Oncology Group
ERK	Extracellular signal-regulated kinase
FDA	Food and Drug Administration
FLC	free light chain
GEP	Gene expression profiling
GEP70	Gene expression profiling of 70 genes related to multiple myeloma
GWAS	Genome-Wide Association Studies
HRMM	High Risk Multiple Myeloma
ICF	informed consent form
ICH	International Conference on Harmonization
IFE	Immunofixation electropheresis
IFN	interferon
Ig	immunoglobulin
IL	interleukin
IMiD	Immunomodulatory drug
IMWG	International Myeloma Working Group
IRB	Institutional review board
kg	kilogram
KRAS	kirsten rat sarcoma viral oncogene homolog
LFT	Liver function test
LRMM	Low Risk Multiple Myeloma
MAPK	mitogen-activated protein kinase
MM	Multiple myeloma
MMDB	Multiple Myeloma Database
M-protein	monoclonal protein
MGUS	Monoclonal Gammapathy of Undermined Significance

MIRT	Myeloma Institute for Research and Therapy
MR	minor response
MTD	maximum tolerated dose
MUGA	Multi gate acquisition scan to assess cardiac function
NCI	National Cancer Institute
NCI-CTCAE	NCI Terminology Criteria for Adverse Events
NDxMM	Newly Diagnosed Multiple Myeloma
NRAS	neuroblastoma RAS viral oncogene homolog
OMIM	Online Mendelian Inheritance in Man database
OS	Overall Survival
PCs	Plasma Cells
PET	positron emission tomography
PFS	Progression Free Survival
PG	Pharmacogenomics
P-gp	phosphoglycoprotein
PHI	protected health information
PK	Pharmacokinetics
PR	partial response
PT	Prothrombin time
R/R MM	relapsed/refractory multiple myeloma
SAE	serious adverse event
sCR	stringent complete response
SMM	Smoldering Multiple Myeloma
SPEP	serum protein electrophoresis
TNF-α	tumor necrosis factor α
TT3 a/b	Total Therapy 3 a/b
UARK	University of Arkansas for Medical Sciences
UPEP	urine protein electrophoresis
VDT	Velcade (bortezomib), Dexamethasone, Thalidomide (thalidomide)
VDT-PACE	Velcade (bortezomib), Dexamethasone, Thalidomide (thalidomide), cisplatin, doxorubicin, cyclophosphamide, etoposide
VGPR	very good partial response
VIP	Very Immunocompromised Patient (Protocol)
VRD	Velcade, Revlimid, Dexamethasone
VTD	Velcade, Thalidomide, Dexamethasone
VMP	Velcade, Melphalan, Dexamethasone

Appendix H: UARK IRB Approval Letter

UAMS

UNIVERSITY OF ARKANSAS
FOR MEDICAL SCIENCES

Institutional Review Board
4301 West Markham, #636
Little Rock, AR 72205-7199

█████████████ ███

http://irb.uams.edu/

FWA00001119

04/03/2015

PI Name: Miller, Scott

PI Department: MYEL Myeloma Business Planning

Protocol Number: 204088
Protocol Title: UARK 2015-06: PFS and OS Analysis in Molecularly Defined Risk and Distance Traveled in Newly Diagnosed Multiple Myeloma

NEW SUBMISSION APPROVAL, EXPEDITED

The Institutional Review Board approved this study on 04/03/2015, based on Title 45 CFR 46.110, using expedited review procedures under category 5.

This approval period runs from 04/03/2015 to 04/02/2016

The IRB determined the risk for adults who enter this study to be minimal.

The IRB waived the requirement for obtaining informed consent.

The IRB granted a waiver of HIPAA authorization for the PHI described in the submission as follows:
overall and progression-free survival, GEP70 defined risk status (high or low), distance from MIRT based on subject zip code at presentation, transplant status, age < 65, and molecular subgroup

The IRB determined that the research cannot practicably be conducted without access to or use of this PHI, and cannot practicably be carried out without the waiver.

The IRB determined that the research uses the following methods to ensure minimal risk to privacy of subjects:

- A plan to protect the identifiers from improper use or disclosure.
- A plan to destroy the identifiers at the earliest opportunity consistent with the conduct of research, unless there is a health or research justification for retaining the identifiers or retention is required by law.
- An assurance that the PHI will not be re-used or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research as permitted by the HIPAA regulations.

Reminder: All other HIPAA requirements, including Minimum Necessary Rule, still apply.

Committee Notes/Comments:

The following documents were received:

- Protocol v2.03.31.2015 tracked (**Type:** Protocol)
- Protocol v2.03.31.2015 clean (**Type:** Protocol)

If you have any questions, please contact an IRB administrator at 501-██████.
Click here to access study.

Appendix I: UARK IRB Approval Letter (Amendment 1)

UAMS

UNIVERSITY OF ARKANSAS
FOR MEDICAL SCIENCES

Institutional Review Board
4301 West Markham, #636
Little Rock, AR 72205-7199

http://irb.uams.edu/

FWA00001119

05/12/2015

PI Name: Miller, Scott PI Department: MYEL Myeloma Business Planning

Protocol Number: 204088

Protocol Title: UARK 2015-06: PFS and OS Analysis in Molecularly Defined Risk and Distance Traveled in Newly Diagnosed Multiple Myeloma

MODIFICATION APPROVAL, EXPEDITED

The Institutional Review Board approved your 05/08/2015 modification on 05/12/2015, using expedited review procedures.

Committee Notes/Comments:

The following documents were approved:

- Protocol v3.05.06.2015 tracked (Type: Protocol)

- Protocol v3.05.06.2015 clean (Type: Protocol) If you have any questions, please contact an IRB administrator at ▮▮▮▮▮▮.

Appendix J: UARK PRMC Acknowledgement

Wed 4/15/2015 10:22 AM
CLARA - Clinical Research Administration System <NoReply@clara.uams.edu>
The study has been acknowledged by PRMC Reviewer

To   Miller, Scott EB; Morgan, Gareth J; Avery, David A; Smith, Monica R

ℹ️ If there are problems with how this message is displayed, click here to view it in a web browser.

UAMS

UNIVERSITY OF ARKANSAS
FOR MEDICAL SCIENCES

04/15/2015

PI Name: Miller, Scott

PI Department: MYEL Myeloma Business Planning

Protocol Number: 204088
Protocol Title: UARK 2015-06: PFS and OS Analysis in Molecularly Defined Risk and Distance Traveled in Newly Diagnosed Multiple Myeloma

ACKNOWLEDGED

The PRMC Reviewer acknowledged this study.

Committee Notes/Comments:
Click here to access study.

Appendix K: UARK Waiver of Data Use Agreement
A DUA is not required if there is a waiver of auth.

Sent from my iPhone

On Apr 15, 2015, at 9:16 AM, ███████████████████████████████████ > wrote:

████,

Can you find out who funded (if any) Total Therapy 3a and b?

I think the DUA is not needed if a waiver of HIPAA authorization was given. ██████, can you confirm?

██
██████████████████████
██████████████████████

UAMS Office of Research & Regulatory Affairs
Office: ████████████████████████
████████████████

From: ███████████
Sent: Wednesday, April 15, 2015 8:25 AM
To: ███████████████████████████████
Cc: Miller, Scott EB
Subject: IRB# 204088

███████████,

We had previously discussed whether a DUA might be needed for Scott's study in order to share information with his dissertation committee at Walden University as detailed in Section VIII of the protocol. The study was approved by expedited review on 4/3 with waiver of HIPAA authorization; therefore, I assume it was determined that a DUA is not required. Can you please confirm this with a response to this email?

Thanks,
██
████████████████████████

Myeloma Institute for Research and Therapy
University of Arkansas for Medical Sciences
████████████████
Little Rock, AR 72205
Telephone: ████████████████

Appendix L: UARK Letter of Cooperation

4301 W. Markham St., #816
Little Rock, AR 72205-7199

501-526-2873 (526-CURE)
501-526-2273 fax (529-CARE)

www.myeloma.uams.edu

New Patient Referrals
888-MYELOMA (693-5662)

Clinic
501-686-8230
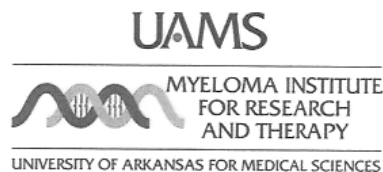877-635-7240 toll-free
501-686-8670 fax

Laboratory Research
501-686-8250
501-686-6442 fax

Faculty
Gareth Morgan, M.D.,Ph.D.
Director
Bart Barlogie, M.D., Ph.D.
Founder
Shukaib Arslan, M.D.
Omar Atiq, M.D.
Benzeng Chen, Ph.D.
Juan Carlos Rico Crescencio, M.D.
Faith Davies, M.D.
Ricky Edmondson, Ph.D.
Monica Grazziutti, M.D.
Tarun Garg, Ph.D.
Christoph Heuck, M.D.
Yogesh Jethava, M.D.
Donald J. Johann, M.S., M.D.
Sarah Johnson, Ph.D.
Rashid Khan, M.D.
Atul Kotari, M.D.
Xin Li, Ph.D.
Aasiya Matin, M.D.
Panikaj Matur, M.D.
Meera Mohan, M. D.
Xenofon Papanikolaou, M.D.
Ya-Wei Qiang, M.D., Ph.D.
Mathukumar Radhakrishanan, M.D.
Caroline Schinke, M.D.
Sharmilan Thanendrarjan, M.D.
Erming Tian, Ph.D.
Frits van Rhee, M.D., Ph.D.
Sarah Waheed, M.D.
Shmuel Yaccoby, Ph.D.
Donghoon Yoon, Ph.D.
Maurizio Zangari, M.D.

Administration
Janet Aronson, M.A.
Director of Development
&Communications

David Ashmore
Executive Director, Administration

Susan D. Henry, LCSW
Executive Director of Clinical
Operations

Nathan Petty, M.S., CCRP
Director of Clinical Trials and
Regulatory Affairs

UAMS

MYELOMA INSTITUTE
FOR RESEARCH
AND THERAPY

UNIVERSITY OF ARKANSAS FOR MEDICAL SCIENCES

May 26, 2015

Letter of Cooperation
UARK Study # 2015-06 IRB # 204088

To: **Scott Miller** ▮▮▮▮▮▮▮▮
            Walden IRB ▮▮▮▮▮▮▮▮

From: ▮▮▮▮▮▮▮▮

Re: **Letter of Cooperation**

Dear Scott and Walden IRB Members,

The UAMS Institutional Review Board (IRB) has authorized Scott Miller to conduct the above referenced retrospective review of secondary data pertaining to subjects enrolled on the Total Therapy 3a and 3b clinical trials.

The study number UARK 2015-06, was initially approved on 04/03/15. Amendment 1, Version 3 (Protocol v3.05.06.2015 clean/tracked) was IRB approved on 5/12/15. The IRB approved Protocol and IRB approval memos are attached to this e-mail.

UAMS is the sponsor of this non-interventional research and is responsible for the study. The UAMS IRB approved the study based on Title 45 CFR 46.110, using expedited review procedures under category 5. The IRB determined the risk for adults who enter this study to be minimal. The IRB waived the requirement for obtaining informed consent. The IRB granted a waiver of HIPAA authorization. The IRB has determined that a data use agreement is not necessary for this research (see attachments).

I acknowledge that the UAMS IRB has authorized this study, UAMS/MIRT will provide the data in a de-identified fashion (void of personally identifiable information). Scott Miller is responsible for complying with all UAMS IRB and Institutional policies and requirements of the University of Arkansas for Medical Sciences. The IRB has determined that the "honest broker" system will provide the requested data per the protocol.

I acknowledge that Scott Miller is the principal investigator of the study and that supervision of all research activities is conducted by the UAMS Office of Research Compliance. In the event of an emergency or inadvertent

Letter of Cooperation, Page 2

disclosure of protected health information, Scott Miller is responsible to report the information to the UAMS IRB.

I confirm ███████████████████████████████ that this study has been IRB approved and authorized to proceed. Furthermore, all data transferred to Scott Miller will be void of personally identifiable information and that no patient contact is authorized. I understand that this data will not be shared outside Scott Miller's supervisory faculty/staff without permission of the Walden University IRB.

Sincerely,

███████████████████

uams.edu

Appendix M: Walden University IRB Approval

From: IRB
Date: Thursday, September 17, 2015 at 4:24 PM
To: Scott Miller, IRB
Cc: ▮▮▮▮▮▮▮▮▮
Subject: IRB Materials Approved - Scott Miller

Dear Mr. Miller,

This email is to notify you that the Institutional Review Board (IRB) confirms that your study entitled, "Survival Analysis of Total Therapy 3 in Newly Diagnosed Multiple Myeloma," meets Walden University's ethical standards. Our records indicate that the site's IRB agreed to serve as the IRB of record for this data collection. Since this study will serve as a Walden doctoral capstone, the Walden IRB will oversee your capstone data analysis and results reporting. The IRB approval number for this study is 09-17-15-0232203.

This confirmation is contingent upon your adherence to the exact procedures described in the final version of the documents that have been submitted to XXXXXX as of this date. This includes maintaining your current status with the university and the oversight relationship is only valid while you are an actively enrolled student at Walden University. If you need to take a leave of absence or are otherwise unable to remain actively enrolled, this is suspended.

If you need to make any changes to your research staff or procedures, you must obtain IRB approval by submitting the IRB Request for Change in Procedures Form. You will receive confirmation with a status update of the request within 1 week of submitting the change request form and are not permitted to implement changes prior to receiving approval. Please note that Walden University does not accept responsibility or liability for research activities conducted without the IRB's approval, and the University will not accept or grant credit for student work that fails to comply with the policies and procedures related to ethical standards in research.

When you submitted your IRB materials, you made a commitment to communicate both discrete adverse events and general problems to the IRB within 1 week of their occurrence/realization. Failure to do so may result in invalidation of data, loss of academic credit, and/or loss of legal protections otherwise available to the researcher.

Both the Adverse Event Reporting form and Request for Change in Procedures form can be obtained at the IRB section of the Walden website: http://academicguides.waldenu.edu/researchcenter/orec

Researchers are expected to keep detailed records of their research activities (i.e., participant log sheets, completed consent forms, etc.) for the same period of time they retain the original data. If, in the future, you require copies of the originally submitted IRB materials, you may request them from Institutional Review Board.

Sincerely,
▮▮▮▮▮▮▮▮▮
Research Ethics Support Specialist
Office of Research Ethics and Compliance
Email: ▮▮▮▮▮▮▮▮▮▮
Fax: ▮▮▮▮▮▮▮▮▮
Phone: ▮▮▮▮▮▮▮▮
Office address for Walden University:
100 Washington Avenue South, Suite 900

Minneapolis, MN 55401

Appendix N: Permission for Use of Andersen Model

From: Ron Andersen <████████@ucla.edu>
Date: Monday, September 28, 2015 at 1:30 PM
To: Scott Miller <scott.miller2@waldenu.edu>
Subject: RE: Permission to use figures

Dear Scott,

You have my permission to use the figures in the "Revisiting the Behavioral Model" articles. Best wishes for the successful completion of your dissertation.

Ron Andersen

From: Scott Miller [mailto:scott.miller2@waldenu.edu]
Sent: Thursday, September 24, 2015 6:57 AM
To: XXXXXXXX█@ucla.edu
Cc: Scott Miller
Subject: Permission to use figures

Good Morning Dr. Andersen,

My name is Scott Miller, I am a graduate student pursuing my terminal degree in public health. I am seeking your permission to use figures from your article "Revising the Behavioral Model and Access to Medical Care: Does It Matter?" in my dissertation. The dissertation will be both written and preserved electronically.

The version of your model I have chosen appears in the *Journal of Health and Social Behavior* 1995, Vol. 36 (March): 1-10.

I am aware that the model has been revised and published in a book chapter by Kominski. I am happy to use the updated version if you prefer, although I do not think this is a critical change.

Thank you for your consideration.

Best regards,

Scott

Scott E. Miller
Graduate Student
Scott.miller2@waldenu.edu

Appendix O: Permission for Use of Hajek figure

From: XXXXX <XXXXXXXXX >
Date: Tuesday, September 29, 2015 at 5:05 AM
To: Scott Miller <scott.miller2@waldenu.edu>
Subject: Re: Permission to use a figure

Hi Scott,

You may reproduce the specified figure in your thesis as long as you follow the CC BY 3.0 license terms. The preferred and most convenient way to do so is to make sure you cite the source chapter, and include the following notice in the figure caption:

© 2013 Hajek R. Published in [short citation] under CC BY 3.0 license. Available from: http://dx.doi.org/10.5772/55366

Contacting the author directly is not strictly required, but it's never a bad idea to notify authors about reproducing their work as a matter of courtesy.

Please feel free to contact me if you have any additional questions or concerns regarding this matter.

Kind regards,

██

--
████████
Library and Information Service Coordinator

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Journal Department
Janeza Trdine 9
51000 Rijeka, Croatia

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