MSK PROTOCOL COVER SHEET

A Pilot Plant-Based Dietary Intervention in Overweight and Obese Patients with Monoclonal Gammopathy of Undetermined Significance (MGUS) and Smoldering Multiple Myeloma (SMM) - The Nutrition Prevention (NUTRIVENTION) Study

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Study title: A pilot plant-based dietary intervention in overweight and obese patients with monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM).

Rationale:

Multiple myeloma (MM) is a plasma cell neoplasm often preceded by the premalignant conditions monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM). Obesity, low adiponectin levels, and diets high in insulinemic foods or lacking plant-based foods are known risk factors for the development of MGUS/SMM, as well as for progression to MM. Therefore, there is an opportunity to study a dietary intervention in cancer progression among patients with MGUS/SMM, for which the standard of care is observation even though many patients will eventually progress to MM. We plan to conduct a pilot nutrition-based intervention study of a whole food, plant-based diet (WFPBD) in overweight and obese MGUS/SMM patients to enable weight loss, as well as to assess associated changes in biomarkers of disease, epigenetics, and the gut microbiome. We expect that the findings will enable larger lifestyle-based studies of prevention and survivorship in plasma cell disorders.

Objectives:

Primary –

To determine the feasibility of a WFPBD in obese/overweight patients with MGUS or SMM, as measured by weight loss and adherence at 12 weeks.

Secondary –

1. To determine the feasibility of a WFPBD in obese/overweight patients with MGUS or SMM, as measured by safety, and quality of life.
2. To assess weight loss at 24, or 52 weeks.
3. To assess alterations in metabolic, and myeloma markers secondary to a WFPBD intervention.

Exploratory –

1. To assess alterations in T cell and plasma cell epigenetic markers secondary to a WFPBD intervention.
2. To assess alterations in the fecal microbiome after a WFPBD intervention.
3. To assess changes in immune function after a WFPBD intervention.
4. To assess changes in body composition (visceral, subcutaneous and bone marrow fat) as determined on PET imaging and correlate with weight changes as well as markers of disease.

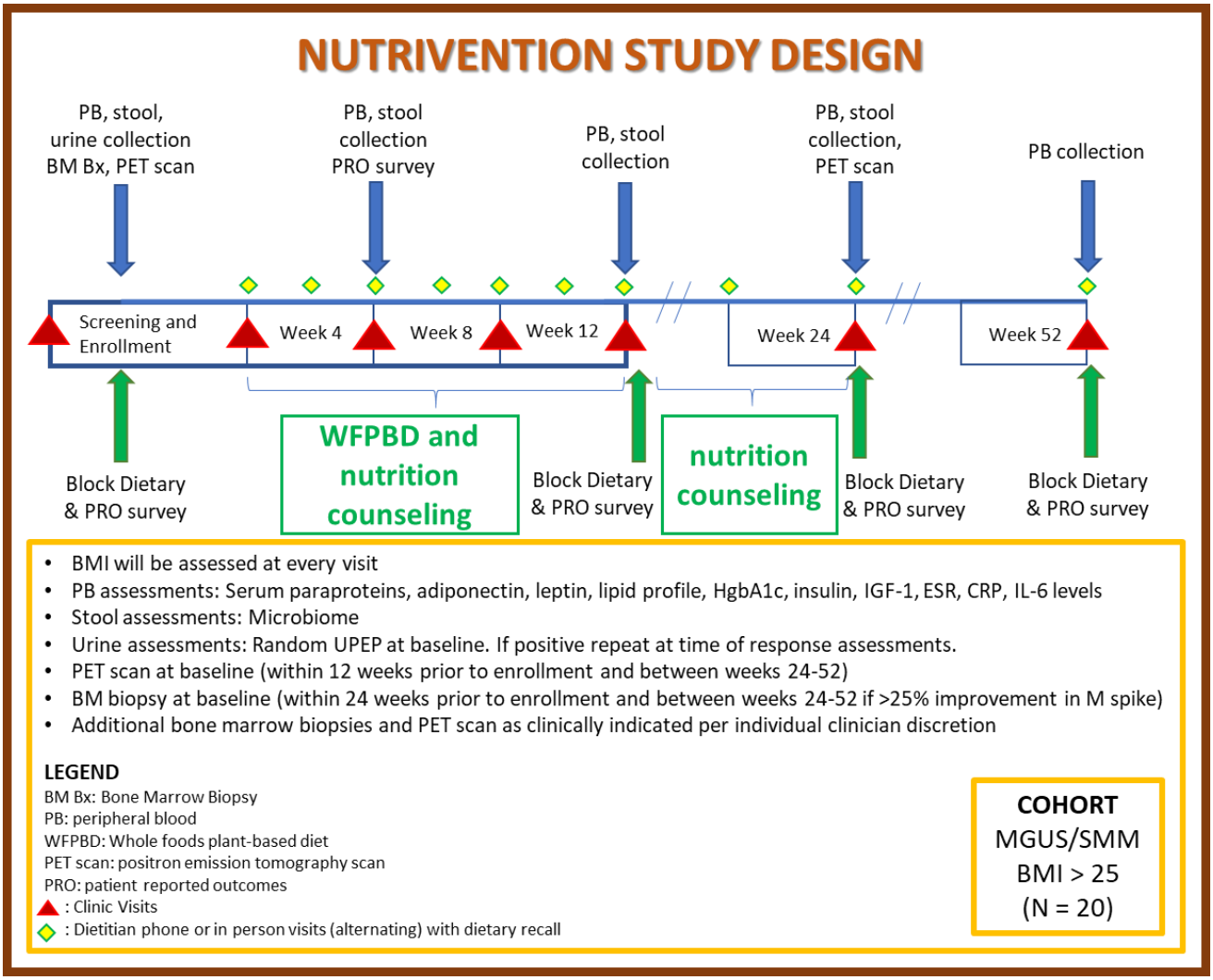
Patient population: Eligible patients will have either SMM or MGUS and be older than 18 years with BMI ≥25, M spike (immunoglobulin) ≥0.2 g/dL or abnormal free light chain ratio, ECOG performance status 0-3, and willingness to comply with study-related procedures.

Design: This is a single-arm, single-center pilot study with 20 patients.

Treatment plan: For 12 weeks, patients will receive two premade meals per day, for lunch and dinner for 6 days weekly, prepared and shipped by U.S.-based WFPBD company Plantable weekly. The meals will have a low glycemic index and contain vegetables, whole grains, and plant-based fats that have undergone minimal processing. Detailed recommendations for snacks and breakfasts meeting the standard of a WFPBD will also be given to supplement their daily calorie needs with access to an online portal from Plantable which contains education materials and access to a coach daily. Patients will also receive dietary education and counselling from a research dietitian every 2 weeks for the 12 week intervention period. They will have access to the team for questions and support as needed. Upon joining the trial, patients will receive vitamin repletion of folate, iron, vitamin B12, and vitamin D to within the normal range if necessary.

Enrollment: We anticipate enrollment of about 2 patients per month and therefore a total enrollment time of about 10 months.

Figure 1: Schema



2.0 OBJECTIVES AND SCIENTIFIC AIMS

This study aims to test the hypothesis that a WFPBD will be associated with weight loss and will alter metabolic markers and the microbiome (**Figure 2**) in ways which may reduce the risk of progression from MGUS and SMM to MM. This hypothesis will be tested in a pilot clinical study of 20 patients, who will receive a WFPBD intervention for 12 weeks.

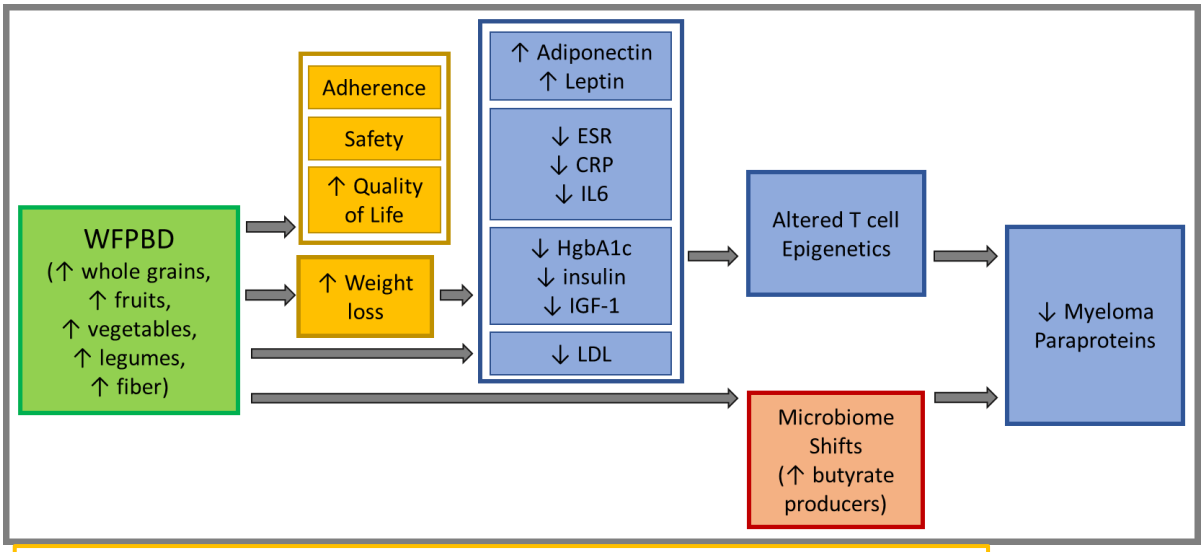


Figure 2: Endpoints and Expected outcomes of a WFPBD in MGUS and SMM.

Primary objective

To determine the feasibility of a WFPBD in obese/overweight patients with MGUS or SMM, as measured by weight loss and adherence at 12 weeks.

Secondary objectives

1. To determine the feasibility of a WFPBD in obese/overweight patients with MGUS or SMM, as measured by safety, and quality of life.
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2. To assess alterations in the fecal microbiome after a WFPBD intervention.
3. To assess changes in body composition (visceral, subcutaneous and bone marrow fat) as determined on PET imaging and correlate with weight change as well as markers of disease.

3.0 BACKGROUND AND RATIONALE

Multiple myeloma (MM), the second most common hematologic malignancy, remains incurable despite many therapies, approved in the last decade, which improve survival. The precursor states of MM—monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM)—have a prevalence of ≥3% in adults over the age

of 50.[1] These disorders present opportunities for early intervention to prevent disease progression, given that the current standard of care is observation.[2]

Common questions among patients with multiple myeloma and its precursor conditions are whether diet or lifestyle caused the condition and whether they should alter their food habits. Currently, the only data available to guide physicians' answers is epidemiologic.

Links between metabolic disorders and MM: In the U.S., over 70% of the population has a body mass index (BMI) above normal, and about 45% of adults are prediabetic or diabetic.[3,4] The incidence of obesity-related cancers, including multiple myeloma (MM), is increasing in young adults.[5] Lifestyle and metabolic disorders are known risk factors for the pathogenesis of MM and its precursor disorders,[6,7] particularly obesity (odds ratios [OR] 1.80 [95% CI 1.03-3.1] and OR 1.50 [95% CI 1.2-2.0], respectively),[8-10] low total adiponectin levels (OR 0.49 [95% CI 0.26-0.93])[11], and diabetes (hazard ratio [HR] 1.80 [95% CI 1.52-2.14]).[12] Obesity has also been shown to increase the risk of progression from MGUS to MM in two studies (HR 1.98 [95% CI 1.47-2.68] and HR 2.66 [95% CI 1.17-6.05], respectively).[13,14]

Consistent with these studies, a meta analyses of 8 IMMC case-control studies found that overweight or obese patients at time of study enrollment had a higher risk for MM (10% increased risk for overweight and obese patients whereas 40% increased risk for severely obese patients) compared to those with a usual adult BMI. Patients with elevated BMI at two time points (study entry as well as at young adult age (ages 25-30 years)) had a significantly elevated risk of MM compared with individuals with normal BMI on both measures ($p < 0.0001$).[15]

However, there have been very limited studies of lifestyle and dietary interventions to prevent the development or recurrence of MM.[16]

Links between dietary factors and MM: Evidence suggests that inflammation and endogenous growth factors, including insulin-like growth factors (IGF)-1 and interleukin (IL)-6, play an important role in MM pathogenesis. Diets that are likely to increase inflammation and insulin secretion are considered inflammatory and insulinemic dietary patterns. Some examples in the literature include the empirical dietary inflammatory pattern (EDIP), empirical dietary index for insulin resistance (EDIR) and empirical dietary index for hyperinsulinemia (EDIH) and the western diet. Furthermore, such unhealthy dietary patterns have been linked to the development of MM.[17,18] while vegetarians and vegans have a reduced risk (relative risk [RR] 0.23 [95% CI 0.09-0.59]).[19] Specifically, fruit-rich diets (>3 times per week; OR 0.62 [95% CI 0.41-0.95]),[20] vegetables-rich diets (4-7 times per week; OR 0.40 [95% CI 0.1-1.0]),[21] diets high in cruciferous vegetables (>2 times per week [OR 0.50; 95% CI 0.3-0.8]),[22] and diets high in whole grains and thus fiber (>3 days per week; OR 0.50 [95% CI 0.2-1.1])[23] have been associated with a reduced risk of plasma cell disorders. Similarly, fruit intake at least three times per week during later life (> 50 years) was associated with a decreased risk of progression from MGUS to MM (HR 0.34 [95% CI 0.13-0.89]).[20]

Table 1:

Metabolic and Dietary Factors	Risk for	N	Risk	95% CI	Reference
Obesity	MGUS	1196 (60)	OR 1.80	1.03-3.14	Landgren Blood 2010[8]
Obesity (BMI 35+)	MM mortality	1,564,218	HR 1.52	1.15-2.02	Teras BJH 2015[10]
Obesity (BMI 35+)	MM	9609 controls; 2318 MM	OR 1.40	1.1-1.7	Birmann CEBP 2017[15]
Obesity	MGUS → MM	7878 MGUS	HR 1.98	1.47-2.68	Chang JNCI 2017[13]
Obesity	MGUS → MM	575 MGUS 18 MM & 11 LPD	HR 2.66	1.17-6.05	Thordardottir Blood Adv 2017[14]
Adiponectin elevation	MM	348 controls 174 MM	OR 0.49	0.26-0.93	Hofmann Blood 2012[11]
Adiponectin elevation	MM	624 MM; 1246 controls	OR 0.64	0.47-0.85	Hofmann Can Res 2016[7]
Diabetes mellitus	MM	2.3 million (2134 MM)	HR 1.80 (M) HR 1.58 (F)	1.52-2.14 1.30-1.92	Dankner AJE 2015[12]
Diabetes mellitus	MGUS	14,048 MGUS; 53,072 controls	OR 1.58	1.48-1.68	(Shah et al, submitted to ASH 2020)
Diabetes mellitus	MM	1,266 MM; 3,881 controls	OR 1.30	1.22-1.39	(Shah et al, submitted to ASH 2020)
Inflammatory/ insulinemic potential diets	MM in males	116,983 (478 MM)	HR 1.16	1.02-1.32	Lee JNCI Can Spec 2019[17]
Unhealthy Western dietary pattern	MM mortality	165796 (423 MM, 345 deaths)	HR 1.24	1.07-1.44	Lee IJC 2020[18]
Healthy (AHEI-2010) dietary pattern	MM mortality	165796 (423 MM, 345 deaths)	HR 0.76	0.67-0.87	Lee IJC 2020[18]
Vegetarians/ vegans	MM	61,647 (65 MM)	RR 0.23	0.09-0.59	Key AJCN 2014[19]
Fruits (>3 times per week)	MGUS	5,764 (575 MGUS)	OR 0.62	0.41-0.95	Thordardottir Plos One 2018[20]

Fruit intake (>3 times/week; after 50 years)	MGUS → MM	5,764 (575 MGUS)	HR 0.34	0.13-0.89	Thordardottir Plos One 2018[20]
Vegetables-rich diets (4-7 times/week)	MM	100 controls 100 MM	OR 0.40	0.1-1.0	Vlajinac Neoplasma 2003[21]
Cruciferous vegetables >2 times/week)	MM	670 controls; 173 MM	OR 0.50	0.3-0.8	Hosgood CCC 2007[22]
Whole grains (>3 days/week)	MM	7990 controls 120 MM	OR 0.50	0.2-1.1	Chatenoud Int J Cancer 1998[23]

Link between plant based diets, weight loss and reduced cancer risk: Several trials have demonstrated the efficacy of vegetarian diets for weight loss and improvement of cardiovascular biomarkers – benefits that are thought to be mediated by energy restriction and plant constituents (e.g., fiber)[24,25]. Observational data suggest that vegetarian diets are protective against cancer growth and are associated with reduced all-cause mortality[26,27]. One of the largest randomized trials (BROAD study) testing a non-energy restricted whole food plant-based diet intervention for 3 months in 65 obese and overweight adults with comorbidities showed that there was greater reduction in mean BMI 4.4 kg/m2 vs 0.4 kg/m2 ($p < 0.0001$) at 6 months which was sustained at 12 months although the study intervention ended at 3 months. This dietary intervention achieved greater sustained weight loss than any other trial that does not limit energy intake or mandate regular exercise[28]. Patients on this study had regular nutritional counselling and no meals were provided. Given this data of the importance and success of nutrition counselling, this study will incorporate nutrition counselling for 24 weeks along with the dietary intervention for 12 weeks. (Table 2)

Plant based dietary approaches led to improvement in the dietary inflammatory index scores among overweight and obese adults during a 6 month randomized controlled trial[29]. Several trials have demonstrated that dietary modification after a cancer diagnosis is safe and feasible. Most studies to date have been done in solid tumors such as breast cancer[30-32], prostate cancer[33-35], ovarian cancer[36] and colon cancer[37] as well as cancer survivors[35]. Therefore, plant based diets are feasible for achieving sustainable weight loss in overweight and obese patients. Plant-based foods lead to sustained weight loss without calorie restriction as they are high in fiber (and are nutrient dense but not calorie dense), which helps with early satiety compared to other approaches that are calorie restricted and thus unsustainable. Thus, this study will evaluate the combined effects of plant-based nutrients (fruits, vegetables, whole grains, beans, legumes) and weight loss that have been shown to be associated with reduced risk of MM.

Table 2:

BROAD Study

- BMI >25 and T2DM, ischemic heart disease, HTN or HLD
- No calorie restriction. Eat until satiation.
- 2-h evening education sessions twice-weekly for 12 weeks
- Low-fat plant-based diet (approximately 7–15% total energy from fat)
- 3 months education

	Intervention (n=33)	Control (n=32)
Mean baseline BMI	34.5 kg/m2	34.2 kg/m2
Mean BMI at 3 months	31.5 kg/m2 (p<0.0001)	33.5 kg/m2 (p=0.2)
Mean BMI at 6 months	30.2 kg/m2 (p<0.0001)	33.2 kg/m2 (p=0.18)
Mean BMI at 12 months	30.2 kg/m2 (p<0.0001)	Not available
Mean HgbA1c at baseline	6%	5.5%
Mean HgbA1c at 6 months	5.7% decrease (p<0.01)	5.7% increase (p<0.01)
Mean HgbA1c at 12 months	5.5% (p<0.0001)	Not available

Wright et al. Nutrition & Diabetes 2017

Role of adiponectin in the etiology of obesity related MM: Adiponectin, an adipocyte-specific protein that is decreased with obesity and MM, exhibits insulin-sensitizing, anti-inflammatory, antiatherogenic, proapoptotic, and antiproliferative properties.[38] Prior studies have shown that weight loss leads to an increase in adiponectin levels.[39] Patients with MGUS who have lower adiponectin levels are more likely to progress to MM, and adiponectin induces myeloma cell apoptosis in preclinical models.[6,40] Patients with SMM and MM also have significantly lower adiponectin levels compared to those with MGUS.[6]

Decreased serum adiponectin concentrations were seen in MGUS patients who subsequently progressed to MM - MGUS with progression 4.5 ug/mL, MGUS with no progression 6.4 ug/mL and controls 5.6 ug/mL [40]. In another study, adiponectin levels were measured in 213 patients at different stages MGUS, SMM, or MM. They found that relative to MGUS patients (median level 13 ug/mL), adiponectin levels were statistically significantly lower among those with smoldering (median level 10.9 ug/mL) and fully developed MM (median level 11.4 ug/mL) (p = 0.048). Adiponectin levels were also lower amongst those with the higher risk IgM isotype compared to those with IgG/IgA isotypes [6]. Similarly, inverse associations with MM were observed for total adiponectin (OR = 0.49, Ptrend = .03) and high molecular weight adiponectin (OR = 0.44, Ptrend = .01). These associations remained after restricting to MM patients diagnosed ~ 8 years or more after blood collection [11].

A prospective pooled analysis of 7 cohorts, comparing 624 MM cases with 1246 matched controls, showed that higher total adiponectin levels were associated with reduced MM risk overall (OR 0.64 [95% CI 0.47-0.85]). The study also observed strong associations among subjects who were overweight or obese (OR 0.41 [95% CI 0.17-0.98]) but not among those with normal weight (OR 1.20 [95% CI 0.73-2.00]). This study provides the strongest epidemiologic evidence that adiponectin protects against MM development particularly in overweight and obese individuals.[7] Therefore, we hypothesize that weight loss will lead to increased adiponectin levels, a surrogate marker for reduced risk of progression to MM.

Figure 3:

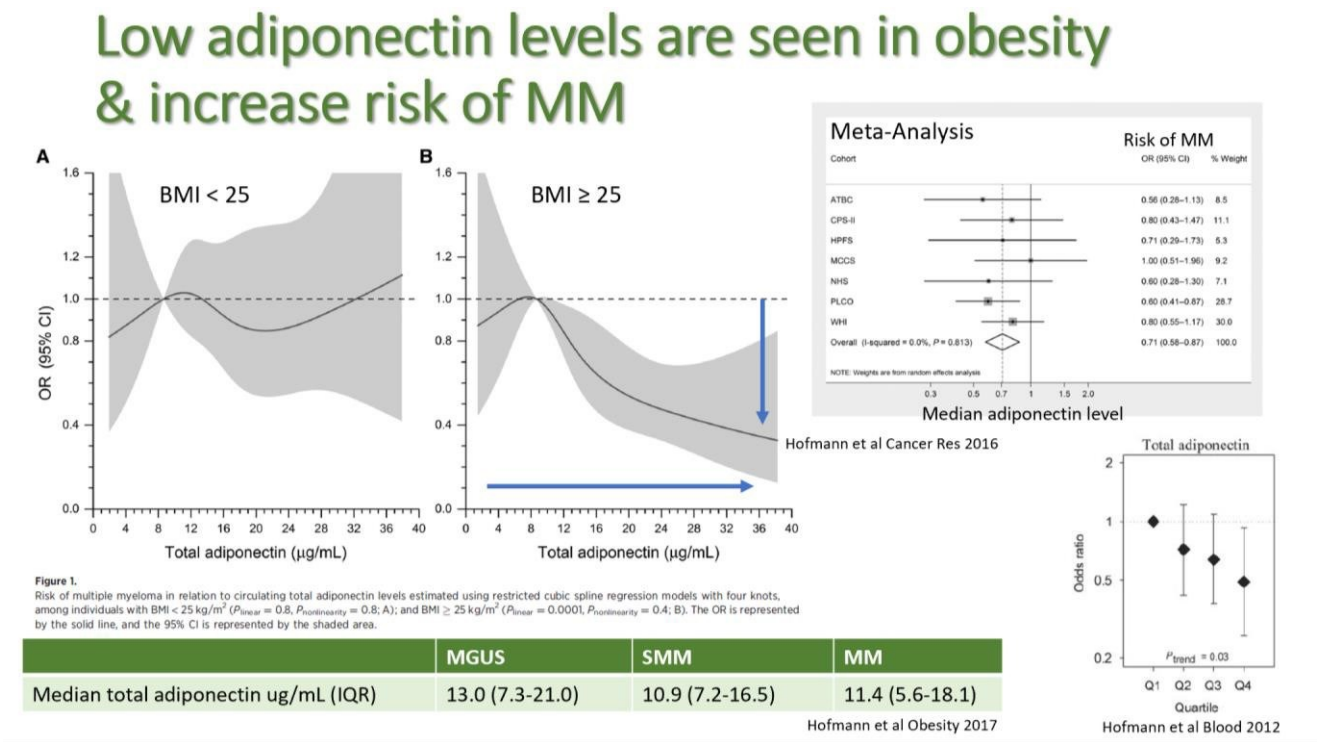


Figure 1.
Risk of multiple myeloma in relation to circulating total adiponectin levels estimated using restricted cubic spline regression models with four knots, among individuals with BMI < 25 kg/m^2 (P_{linear} = 0.8, $P_{nonlinearity}$ = 0.8; A); and BMI ≥ 25 kg/m^2 (P_{linear} = 0.0001, $P_{nonlinearity}$ = 0.4; B). The OR is represented by the solid line, and the 95% CI is represented by the shaded area.

	MGUS	SMM	MM
Median total adiponectin ug/mL (IQR)	13.0 (7.3-21.0)	10.9 (7.2-16.5)	11.4 (5.6-18.1)

Hofmann et al Obesity 2017

<u>*Link between bone marrow adipocytes in overweight/obese patients and MM:*</u> Chronic immune responses against lipid antigens have been proposed as a driver of MM pathogenesis[41]. In mouse models, researchers showed that diet-induced obesity creates a permissive environment for the development of an MGUS-like condition, associated with myeloma cell accumulation in BM, an increase in serum paraprotein and mild bone loss[42].

Adipocyte stem cells were obtained from normal, overweight, obese or super obese patients. Adipocyte conditioned media from obese and super obese patients significantly increased MM cell adhesion, and conditioned media from overweight, obese and super obese patients enhanced tube formation and expression of matrix metalloproteinase-2 suggesting that adipocytes in the MM microenvironment contribute to MM growth and progression[43].

Methods to evaluate body composition in MM: Most studies evaluating body composition in MM or precursor disorders have used BMI as a clinical measure of obesity and body fatness and shown significant associations as described above. Although, this is easy to calculate for all patients it has its limitations. It is a surrogate measure for body fatness because it is a measure of excess weight rather than excess body fat. Factors such as age, gender, ethnicity, muscle mass can influence the relationship between BMI and body fat. Limited studies in myeloma have shown that in cases where BMI did not correlate with treatment response or clinical parameters the CT scan was able to identify significant correlations given it is a more sensitive test for body fatness. These scans are also able to differentiate total body fat, subcutaneous body fat and visceral body fat.[44]

The PET scan is a cornerstone in the initial work-up for newly diagnosed plasma cell disorder patients, since it has the highest sensitivity to detect osteolytic bone lesions. Furthermore, it offers the opportunity to image and quantify the extent of visceral and subcutaneous adipose tissue as a side product. MRI based body composition analyses have also shown between-scanner reproducibility and repeatability.[45] PET MRI has the added advantage of being able to quantify bone marrow adiposity as well.

Impact of metabolic disorder induced epigenetic changes in T cells leading to immune dysfunction: T cell exhaustion in early tumorigenesis has been recently found to be mediated by epigenetic reprograming of chromatin, inducing a non-plastic and non-responsive state.[46] Interestingly, metabolic pressure is also associated with epigenetic changes in T cells, although the mechanism is not clear.[46-49] While epigenetic immune cell dysregulation is implicated in both MM development and T cell exhaustion, the molecular mechanisms driving these changes are largely unknown. The Yael David laboratory at Memorial Sloan Kettering Cancer Center (MSK) recently found that metabolic stress can induce major changes in chromatin structure and function through chemical glycation of histone proteins, which are major epigenetic regulators that spool the DNA.[50] Importantly, they identified DJ-1 and PAD4, known oncoproteins in several cancers including MM,[51,52,53] as potent enzymatic

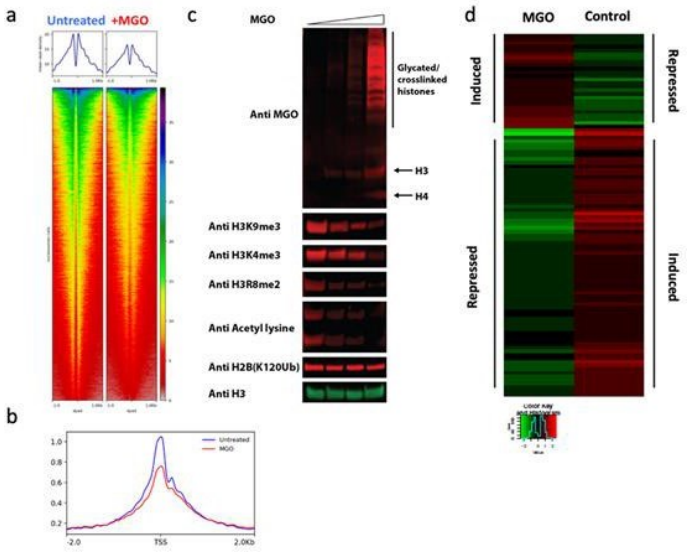


Figure 4: Histone glycation disrupts chromatin architecture and the epigenetic landscape. ATAC-seq analysis of cells treated with methylglyoxal (MGO: a reactive compound that is implicated in diabetes) show **(a)** decreased accessibility in general and **(b)** at transcription start sites. **(c)** Enzymatic histone modifications are disrupted by glycation. **(d)** RNA-seq analysis of MGO-treated cells indicate significant alterations in gene expression upon histone glycation.

regulators of histone glycation (**Figure 4**).[50] In diabetes/hyperglycemia, metabolic stress is an important factor to which circulating cells, such as T cells, are exposed through high and unstable blood sugar levels (**Figure 5**). We hypothesize that histone glycation might play a role in driving epigenetic changes in these cells. Herein, we propose to investigate the consequences of metabolism-related chromatin damage for peripheral blood T cell function in MM.

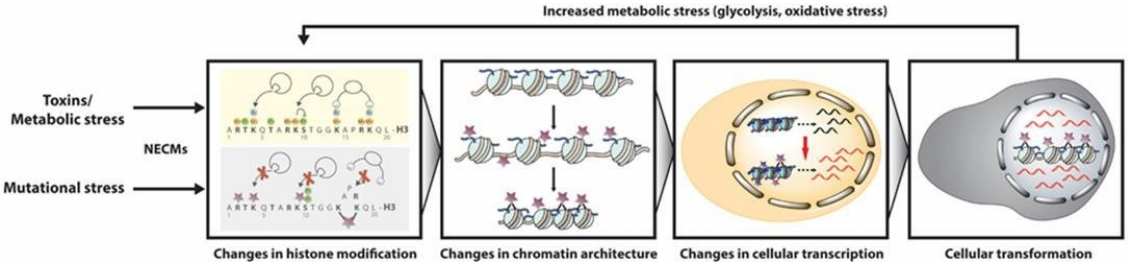


Figure 5: Model for the mechanistic link between metabolic stress and impaired T cell function. In this model, metabolic or mutational stress cause cellular transformation and nucleation of a transformed cell. T cells utilize glucose in the blood stream to promote cellular proliferation and generate reactive metabolic byproducts that react with histones and eventually lead to changes in chromatin structure and function. An aberrant cellular epigenetic state contributes to changes in the transcriptome, leading to cellular transformation.

Link between the diet and microbiome in MM: Prior data from studies conducted at MSK has shown that increased relative abundances of *Eubacterium hallii* and *Faecalibacterium prausnitzii* in the gut associates with deep responses to MM therapy (**Figure 6**).[54] Patients with MM who have received an allogeneic stem cell transplant have higher graft-versus-tumor (GVT) immune activity when levels of *Eubacterium limosum* are high in gut microbiota.[55] Given that these three species of bacteria facilitate production of short-chain fatty acids (SCFA) such as butyrate and acetate, these results suggest that those products improve outcomes in MM. Gut paneth cells are one of the sources of adiponectin, which they produce in response to microbial stimuli. Abundance of *Faecalibacterium Prausnitzii* has a positive correlation with serum adiponectin levels and reduced abundance of this microbe has been observed in obese individuals when compared with non-obese individuals.[56] Taken together these observations suggest a link between gut dysbiosis, metabolism and MM.

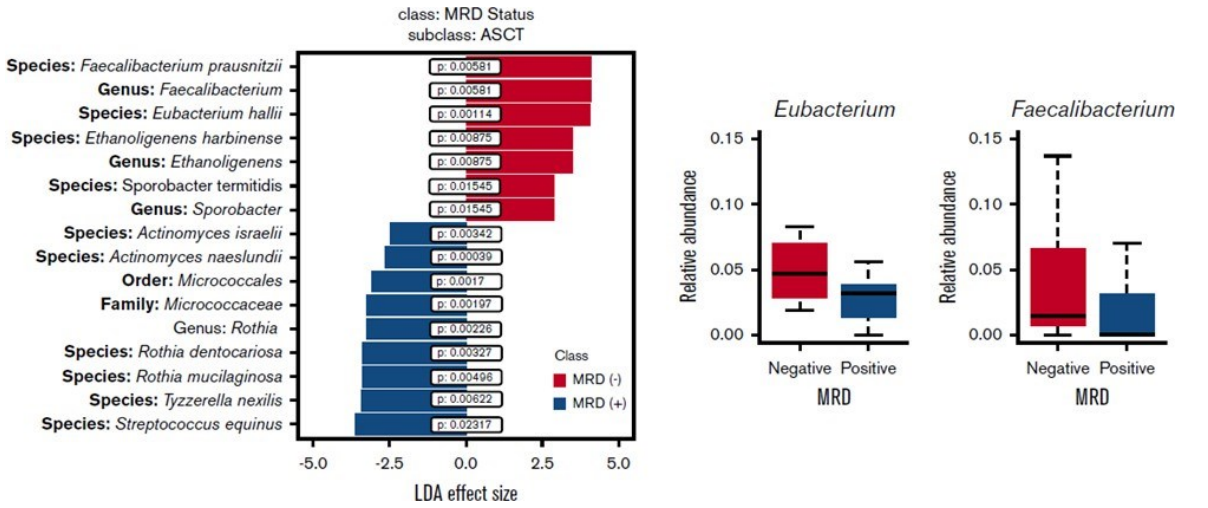


Figure 6: Fecal microbiota analysis according to minimal residual disease (MRD) status [MRD (-): absence of disease, MRD (+): presence of disease]. **(a)** Linear discriminant analysis (LDA) effect size analysis of microbiota differentially associated with MRD status with subclass of autologous stem cell transplantation (ASCT). **(b)** Relative abundance of genera *Eubacterium* and *Faecalibacterium* by MRD status.

Butyrates, produced by saccharolytic anaerobes, inhibit histone deacetylases as well as the NF-κB pathway, which plays a critical role in the development of myeloma.[57] Butyrates modulate immunity by exerting anti-inflammatory functions through inhibition of the transcription factor NF-κB, leading to reduced formation of proinflammatory cytokines. They also non-competitively inhibit histone deacetylases (HDAC),[58] acting in the same way as panobinostat, an HDAC inhibitor with activity in MM. We hypothesize that the role of butyrates in these mechanisms decreases the likelihood of progression to MM.

Diet plays a substantial role in shaping the microbiome, and dietary alterations can induce large microbial shifts within short periods of time (even 24 h).[28,59-62] Fecal concentrations of short-chain fatty acids such as butyrate and acetate from carbohydrate metabolism by saccharolytic microbes are higher when individuals eat a plant-based rather than an animal-based diet; those who eat an animal-based diet have a higher proportion of microbiota producing short-chain fatty acids such as isovalerate and isobutyrate from amino acid fermentation.[61] Thus, it is plausible that dietary factors alter gut microbial composition and impact disease outcomes, providing a strong rationale for systematically investigating the relationship between diet and microbiome in plasma cell disorders.

Overall study objectives: As described above, a whole food, plant-based diet (WFPBD) may be beneficial, as there is evidence that it is associated with reduced BMI and increased adiponectin levels as well as alterations of the microbiome.[28,59-61] No dietary trial has yet tested a WFPBD in patients with MGUS and SMM. Preliminary data provide a strong rationale to conduct a pilot study testing whether such a diet will lead to weight loss and

changes in biomarkers of disease, serving as surrogate markers for risk of progression to MM, in obese and overweight patients with MGUS and SMM.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is a single-arm, single-center pilot study with 20 patients who will be administered a whole-foods plant-based diet for 12 weeks with nutrition counselling for 24 weeks.

4.2 Intervention

Treatment plan: For 12 weeks, patients will receive two premade meals per day, for lunch and dinner, prepared and shipped weekly by U.S.-based WFPBD company Plantable. The meals will have a low glycemic index and contain vegetables, whole grains, and plant-based fats that have undergone minimal processing. Instructions will be provided for food storage and reheating. Detailed recommendations for snacks and breakfasts meeting the standard of a WFPBD will also be given to supplement their daily calorie needs with access to an online portal from Plantable which contains education materials and access to a coach daily for 24 weeks. Patients will also receive dietary education and counselling from a research dietitian every 2 weeks for the 12-week intervention period and then at 18 and 24 weeks. They will have access to the team for questions and support as needed. Upon joining the trial, patients will receive vitamin repletion of folate, iron, vitamin B12, and vitamin D to within the normal range if necessary.

Plantable has seen the following results in 28 days with their program (Table 3).

Table 3:

Typical Reboot results in 28 days[1]

And beyond[10]

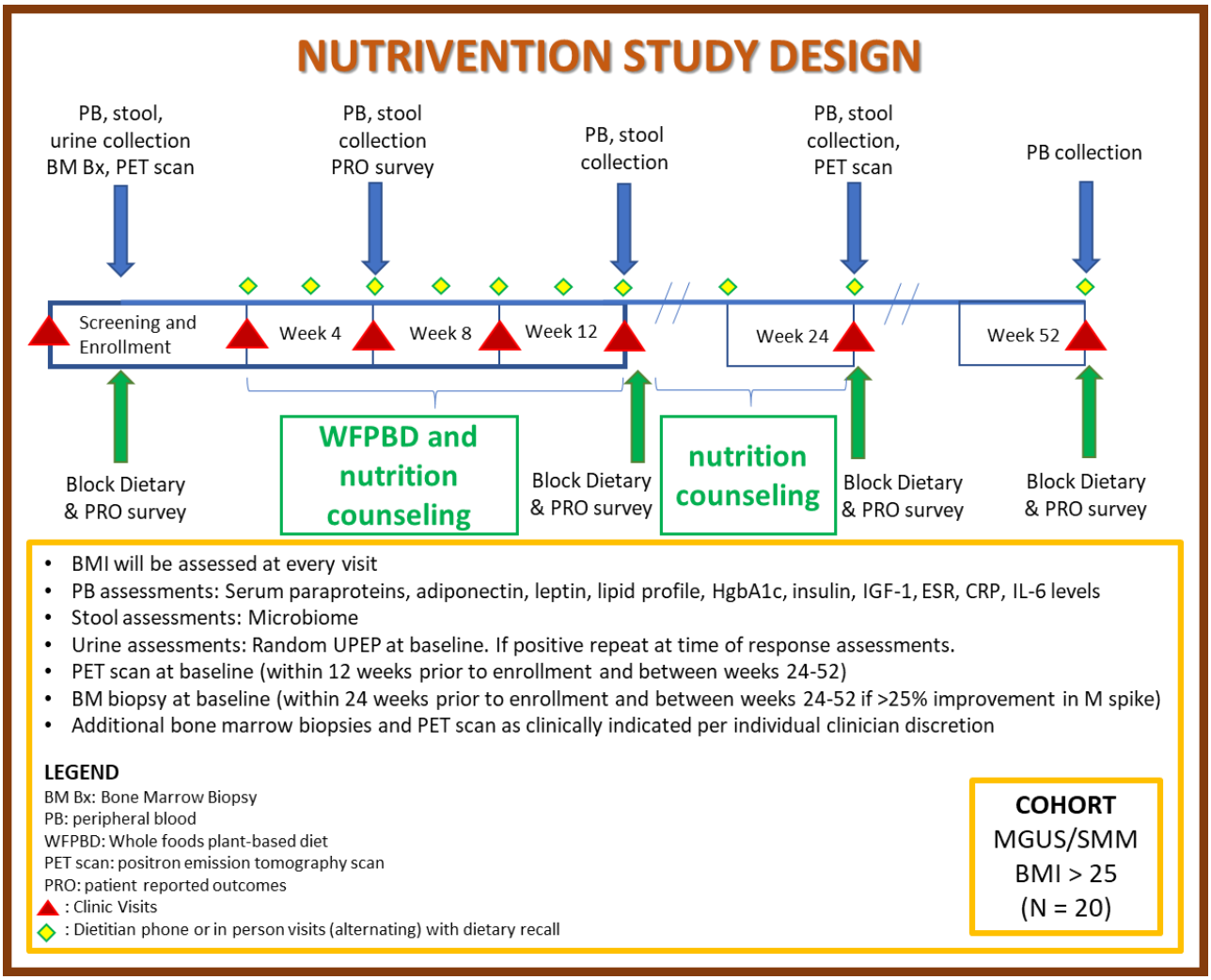
Biomedical			Anthropometric	
Reduction in blood sugar (hgbA1C)[2] Diabetes prevention / reversal	-0.91 pts		Average weight loss: Total[6] (-4.9% initial body weight)	-8.9 lbs
Reduction in inflammation (hsCRP)[3] Precursor to cancer, chronic disease, arthritis	-1.3 pts		Average weight loss: Normal BMI[7] (-4.2% initial body weight)	-6.1 lbs
Reduction in elevated cholesterol (LDL)[4] CVD, stroke, heart disease, high blood pressure	-41 pts		Average weight loss: Overweight BMI[8] (-5.1% initial body weight)	-9.2 lbs
Waist circumference reductions[5] Visceral fat, obesity, NAFLD	-2.0"		Average weight loss: Obese BMI[9] (-5.1% initial body weight)	-11.3 lbs

These results formed the basis for the randomized control trials for evaluating cancer risk reduction

1 Based upon Plantable's 28-day Reboot. Results collected from May 2015, January 2016 - September 2017
2 N=7, Starting hgbA1C > 5.7, 3 N=14, 4 N=18, Starting LDL > 100, 5 N=74, 6 N=127, 7 N=44, 8 N=48, 9 N=30
10 In a recent survey (December 2019, N=81), 93% of all polled respondents reported to the Reboot meeting their goals (weight loss or other), and 54% attesting to long-term sustained change, of which 86% attribute to Plantable.

Weill Cornell Medicine

Figure 1:



5.0 THERAPEUTIC/DIAGNOSTIC AGENTS & NON-THERAPEUTIC ASSESSMENTS

The only therapeutic agents being tested in this trial is a plant-based diet, a non-pharmacologic agent.

6.0 CRITERIA FOR PARTICIPANT ELIGIBILITY

6.1 Participant Inclusion Criteria

- BMI ≥25
- Confirmed diagnosis of MGUS or SMM

- M spike (immunoglobulin) ≥0.2 g/dL or abnormal free light chain ratio with increased level of the appropriate involved light chain
- Secretory disease
- Age ≥18 years
- Willingness to comply with all study-related procedures
- ECOG performance status of 0-3
- Interest to learn to cook plant based recipes

6.2 Participant Exclusion Criteria

- Patients that already follow a whole foods plant based or vegan diet (ovo-lacto-vegetarian diets are not excluded)
- Legume allergy
- Severe allergies, such as anaphylactic shock to peanuts
- Concurrent participation in weight loss/dietary/exercise programs
- Mental impairment leading to inability to cooperate
- Enrollment onto any other therapeutic investigational study
- Concurrent pregnancy
- Patients with a known diagnosis of diabetes mellitus will not be excluded but will need to be followed regularly with an endocrinologist/primary care physician during the trial period.
- Positive HBV, HCV, HIV PCR testing
- Non English speaking
- ≥ Grade 2 electrolyte abnormalities as defined by CTCAEv5.0 (need to be resolved before enrolling on study)
- If in the opinion of the investigator there maybe any concerns regarding the ability of the patient to complete the study safely

7.0 RECRUITMENT PLAN

7.1 Research Participant Registration

This study is a single center pilot study in MGUS and SMM patients. Efforts will be made to ensure that women and minority groups are adequately represented in this trial. All patients will be seen by myeloma physicians and associated co-investigators, enrolled and registered at the study site. Patients seen at the study site will be screened for eligibility.
All co-investigators agree to follow the treatment in the protocol and to conduct the proposed investigation according to recognized principles of good clinical practice. Participation is voluntary. Each patient must be informed about the nature of his/her disease and willingly consent to participation in this study. Every patient will be informed of the procedures to be followed, the potential benefits, side effects, risks, and discomforts of the trial and of potential therapeutic alternatives. All participants will be required to sign statements of informed consent and research authorization that conform to the FDA, IRB and HIPAA guidelines. Informed consent will be documented by the use of a written consent form that has been

approved by the MSKCC IRB. In the Networks, physicians will directly refer patients for screening and protocol consideration. In addition, all new visits are screened by the study coordinators for protocol eligibility.

7.2 Randomization

This is a non-randomized study.

7.3 Accrual

We plan to accrue a total of 23 patients but have accounted for an anticipated 20% dropout rate and will replace up to 4 patients that may drop out from the trial within the initial 12 week intervention period. If additional patients drop out beyond the first 4 then they will not be replaced and included in the feasibility analysis.

At MSK we have >10,000 patient visits for plasma cell disorders annually, including ~200 new and ~1000 established patients with MGUS/SMM. About 2/3 of our patients will be overweight or obese, and thus eligible for this study.[4]

We expect to accrue 2-3 patients per month for a total accrual period of 10 months. The study will be completed 52 weeks after the last patient enrolls, and therefore an estimated date of completion would be 22 months from study opening.

8.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

9.0 PRE-TREATMENT/INTERVENTION

9.1 Screening Period

The screening period consists of initial patient review and informed consent. Patients consented who do not subsequently meet eligibility criteria will be registered as a screen fail.

9.2 Baseline Study Assessments

Study related assessments will be conducted no more than 28 days prior to the start of treatment. Baseline assessments include the following:

1. Vital signs including (temp, PR, RR, BP and O2 saturation), height, weight, BMI calculation and waist circumference.
2. Routine labs which include:

- CBC with differential
- Comprehensive Metabolic Panel
- Magnesium, phosphorus
- TSH, uric acid, LDH
- BNP, NT-Pro-BNP, troponin I
- Serum protein electrophoresis (SPEP) and immunofixation to assess for presence
- and quantity of monoclonal protein (M-protein), Serum free light-chains, quantitative immunoglobulins (IgA/IgG/IgM), IgD, IgE, beta 2-Microglobulin
- Fasting metabolic labs: CRP, ESR, fasting lipid profile, fasting glucose, HgbA1c.
- A random urine sample for protein electrophoresis (UPEP) and immunofixation to assess for monoclonal protein in the urine (Bence-Jones proteinuria).

3. Vitamin Levels: Vitamin D, Vitamin B12, folate, iron/TIBC, ferritin
4. Fasting research blood draw and hematology oncology tissue bank (HOTB) storage (Metabolic Labs for Pollack Lab: IL-6, insulin, IGF-1, adiponectin, leptin)
5. Viral studies: Hepatitis B surface antigen, Hep B surface antibody, Hepatitis B core antibody, HIV 1 & 2 antibody, Hepatitis C (HCV) antibody (within 24 weeks prior to baseline).
6. Bone marrow core biopsy and/or aspirate with flow cytometry and HOTB banking. (as long as bone marrow is collected and sample banked with HOTB within 24 weeks prior to baseline study assessment then repeat biopsy will not be required).
7. Serum or urine pregnancy test in women of child-bearing potential.
8. A baseline 12-lead EKG within 3 months prior to baseline study assessment.
9. A baseline whole-body (WB) MRI or PET/MRI (preferable) or low dose whole-body CT or PET/CT will be performed on all patients at screening (within 12 weeks prior to screening visit). Preference will be given to MRI or PET MRI however, if claustrophobic or any

other contraindication to MRI then they will get WB CT or PET CT per investigator discretion.
10. Patient-reported outcomes questionnaires
11. Block Survey
12. Stool collection

10.0 TREATMENT/INTERVENTION PLAN

Patients who undergo screening and are deemed eligible by above criteria for the study, undergo all necessary pre-treatment testing and biospecimen collection.

Evaluation Prior to Initiation of Intervention

The study intervention is designed to reduce fat mass and maintain or increase lean mass through a fiber rich diet. We will determine energy needs using the Mifflin-St. Jeor equation accounting for patient's physical activity level at baseline. Patients will be given a list of foods to eat and foods to avoid beyond the meals provided. Patients will eat to satiation with no calorie restriction.

Study Interventions

As defined, the study intervention/treatment approach will consist of a whole foods plant-based diet. Pre-prepared meals, including 6 dinners and 6 lunches per week, will be shipped to the participant's home for the 12 week intervention period. The nutrition counselling will guide them to eat a healthy whole foods plant based diet for 24 weeks.

Whole Foods Plant-based Diet

Meals will be provided by Plantable (FDA Registration #17996628280). Pre-packaged, frozen plant-based meals (6 lunches and 6 dinners) will be delivered weekly to participants' homes. Each meal is created to have the appropriate mix of macronutrients intake (e.g., carbohydrate, protein, and fat), consistent with USDA dietary guidelines, and to provide satiety. Meals are made with whole ingredients spanning whole grains, vegetables, legumes, nuts and seeds. Added sugar or animal based products are not used in any meal. Meals are produced, packaged, stored and shipped from the Plantable kitchen and storage facility located at 630 Flushing Avenue, Brooklyn, NY 11206. Plantable is regulated by the New York State Department of Agriculture and Markets and adheres to the New York State Department of Health Food Safety Regulations. Inspectors regularly visit the premises and the company has no history of violations. All management/chef level kitchen employees are certified in food safety by the state of New York. The principal food suppliers are Ace Natural and Baldor Food, HACCP accredited wholesale produce and specialty goods suppliers. Produce is shipped via refrigerated trucks and stored in a walk-in refrigerator unit at or below 38 degrees Fahrenheit. Meals are cooked and cooled in an ice bath within 2 hours. Meals are then stored overnight at or below 38 degrees Fahrenheit in a walk-in refrigerator unit. Meals are packed, in batches using 3-mil Poly Nylon food storage bags (FDA/USDA

compliant and BPA free). These bags are sourced from Uline and Imperial Paper. Completed and packaged meals are then frozen and stored at or below 0 degrees Fahrenheit in a walk-in freezer unit until individually packed for study participants. For shipping (materials sourced from Allboxes), meals are packed with frozen gel ice packs in corrugated boxes with recyclable, eco-friendly additional insulation. Packages are shipped via UPS, one and two day ground or air, depending on final destination.

Instructions will be given on food storage and reheating with each shipment. All participants will receive written documents which include the list of ingredients, nutritional label along with full heating and meal storage instructions. During the 12 week intervention, 6 lunches and 6 dinners will be delivered to participants weekly. Participants will be responsible for preparing their own plant-based breakfasts for all days, and all plant-based meals one day per week.

Educational materials and recipes will be sent daily (via email) for the first 28-days and made available via an online portal to participants to encourage the replacement of nutrient-poor, high energy foods with nutrient-rich, low energy plant-based foods (i.e., vegetables, fruits, whole grains). Coaches will also be available to participants from 7AM – 11PM, 7 days per week throughout the 24 week study period via telephone or text messaging to answer questions or concerns regarding food preparation or food choices, particularly for self-prepared breakfasts, snacks, and all meals one day per week.

Participants will also have access to the Plantable app, which does not collect or retain any participant information. This app includes:
1. Recipes - 100+ curated plantable approved recipes, designed to be plant-based, nutrient-dense, filled with plant-based protein for satiety. No added sugar, no refined grains. Balanced and easy.
2. Menu planning - and integration into shopping list
3. Ability to integrate with plantable home-delivered fully prepared meals
4. 28-day educational content to accompany the journey
5. How-to Series - a educational library spanning nutrition and well-being education
6. One-on-one access to a personal coach
7. Tracking - meals, water, movement etc.
(Appendix F, G, H)

Food intake will be monitored using food logs and 72 hour dietary recall. Study staff will use the online web based ASA-24 application - https://epi.grants.cancer.gov/asa24/respondent/2020.html. Participants will use daily food logs to record the percentage of food eaten for each delivered meal and foods consumed for breakfast and snacks. The food log for each day of the study will be included with the weekly meal delivery. Dietary intake will be reviewed every 2 weeks by an MSK registered dietitian to assess adherence and tolerance of diet plan. Participants will be weighed at each visit.

The nutrition consultation will consist of identification and counseling for major nutritional deficiencies and a nutritional program consistent with American Cancer Society guidelines,

which may include nutritional supplements (e.g., calcium, vitamin D, vitamin B12) as necessary. Patients will be asked to take a weekly vitamin B12 supplement of 1000 mcg while on this diet. Vitamin D levels must be maintained over 30 ng/mL with supplementation as needed. Dietary intake will be assessed using food logs and 72 hour recall. The staff registered dietitian will contact patients to check progress and answer questions. Dietary assessments by the MSK research dietitian will be done via phone visits alternating with in person visits every 2 weeks. (Appendix J)

Participants will be asked to complete a food log for the week prior to research dietitian visit at week 18 and week 24 as well.

11.0 EVALUATION DURING TREATMENT/INTERVENTION

Table 4: Schedule of activities

Assessment	**Screening**	**C1D1 Day 1**	**C1D8 Day 8**	**C2D1 End of wk 4**	**C3D1 End of wk 8**	**C4D1 Post-Intervention (End of 12 wks)**	**C7D1 Sustained Post-Intervention (end of 24 wks)**	**End of study (end of 52 wks)** [q]	**If progresses to MM while on study**[p]
Timepoint	**Baseline** (Up to 6 weeks prior to D1)	**Day 1** (± 7d)	**Day 8** (± 7d)	**Day 28** (± 7d)	**Day 56** (± 7d)	**Day 84** (± 7d)	**Day 168** (± 7d)	**Day 365** (± 7d)	(± 7d)
History/physical*	X	X		X	X	X	X	X [q]	X[p]
Vital signs, ht, wt, BMI, waist circumference (Appendix K)	X	X	X	X	X	X	X	X	X
Routine labs[a]	X		X	X	X	X	X	X	X
Viral studies[b]	X								
Pregnancy test[c]	X								
Vitamin levels[d]	X					X		X	
Metabolic labs[e]	X					X	X	X	
Urinary myeloma tests[f]	X		if pt goes into complete remission; additional time points if clinically indicated						
Research blood[g]	X			X	X	X	X	X	X

Imaging[h]	X							X	X
BM biopsy[i,j]	X							X	X
Stool[k]	X			X		X	X	X	X
Research dietitian visit[l,m]	X[n]	X[n]		X	X	X	X		X
Block FFQ	X					X	X	X	X
CTCAEv5.0[o]	X			X	X	X	X		
QOL survey	X			X		X	X	X	X
12-Lead-ECG	X[r]								
Post-Intervention Feedback Survey								X[s]	

X= required protocol assessment

QOL: Quality of Life

* - visits may be in person or via telemedicine depending on patient and dietitian location (main campus vs satellite) as long as labs, vitals and research samples are collected at MSKCC

Additional laboratory studies and clinic visits may be performed as clinically indicated.

a. Routine tests to be done at <u>baseline</u> will include: CBC with differential, comprehensive metabolic panel (including hepatic function, calcium, and albumin), phosphorus, magnesium,TSH, uric acid, lactate dehydrogenase, NT-Pro BNP, BNP, troponin I, serum electrophoresis (SPEP), serum immunofixation, serum free light chains, quanitative immunoglobulins (IgA/IgG/IgM), IgD, IgE, beta 2-microglobulins, and fasting metabolic labs: ESR, CRP, fasting lipid profile, fasting glucose, HgbA1c. At <u>all other follow up visits</u> patients will have the following labs done: CBC with diferential, comprehensive metabolic panel, phosphorus, magnesium, SPEP, serum immunofixation, serum free light chains, quantitative immunoglobulins, beta 2 microglobulin and fasting metabolic labs: ESR, CRP, fasting lipid profile, fasting glucose, HgbA1c. At Day 8 follow up visit labs will include: COMP.
b. Viral studies include HIV 1 & 2, Hep B surface antigen, Hep B surface antibody, Hep B core antibody and Hep C antibody. If HIV, Hep B or C antibody positive, HIV, Hep B or C quantitative PCR will be performed. (These tests should be performed within the last 24 weeks.)
c. Pregnancy tests (urine or serum) for females of childbearing potential. A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).
d. Vitamin levels will include iron/TIBC, ferritin, vitamin B12, folate, vitamin D at marked

timepoints. If levels are low, then they will be repeated after repletion to achieve a normal goal. (vitamin D > 30 ng/mL and Vitamin B12 > 300 ng/L, rest will be based on parameters of normal range).

e. The following labs will be sent to Pollak lab in batches IL-6, IGF-1, adiponectin, leptin, fasting insulin from stored HOTB samples.
f. Urine random for protein electrophoresis (UPEP) and immunofixation to assess for monoclonal protein in the urine (Bence-Jones proteinuria) at baseline in all patients and if the patient goes into complete remission regardless of baseline urine M-spike values. If urine protein electrophoresis at baseline is positive for myeloma protein, then random urine samples will be checked if serum M spike is undetectable or normalization of free light chains. If baseline is negative, then urine for myeloma protein will not be checked again.[63] Additional time points if clinically indicated.
g. Research blood draw will include 4 CPTs for PBMCs, plasma and granulocytes and 1 SST for serum at baseline, week 12 and week 24. Research blood draw will include 2 CPTs for PBMCs, plasma and granulocytes and 1 SST for serum at week 4, week 8 and week 52.
h. PET MR or WB MRI is preferred but PET CT or low dose WB CT is also acceptable and will be performed on patients at baseline within 12 weeks prior to day 1. Similar Imaging will be repeated before 52 weeks visit as a clinical standard of care study. The same modality CT/PET CT or MR/PET MR must be done at baseline and end of study.
i. Baseline bone marrow aspirate and biopsy can be performed within 24 weeks prior to day 1 as long as standard of care HOTB sample has been banked from that biopsy and as long as M spike/involved FLC is within +/-25% change from that time point. Bone marrow aspirate and biopsy will be sent to Dept of Pathology for flow cytometry, FISH/cytogenetics, and molecular studies (IgH rearrangement), as well as to HOTB for sorting and storage per HOTB SOPs.
j. BM biopsy will be repeated as standard of care before 52 weeks if there is a >25% reduction in M spike/free light chain and HOTB samples will be collected. If there is no change in paraprotein or increase BM biopsy does not need to be performed. However, if at disease progression or for other clinical reasons, bone marrow biopsy is performed HOTB samples will be collected.
k. Patients will receive materials and instructions to collect a stool sample at home. This sample will be sent to the molecular microbiology core facility for processing and analysis.
l. Research dietitian visits - Participants will use 72 hour dietary recalls to record the percentage of food eaten for each delivered meal and foods consumed for breakfast and snacks. The food log for each day of the study will be included with the weekly meal delivery for 12 weeks and then will also be completed for week 18 and 24 prior to dietitian visit. Study staff will use the online web based ASA-24 application - https://epi.grants.cancer.gov/asa24/respondent/2020.html.
m. Dietary assessments at the following time points (2, 6, 10, 18 weeks +/-3 days) by the MSK research dietitian will be done via phone visits. Other visits may be in person or via telemedicine depending on patient and dietitian location (main campus vs satellite).
n. Research dietitians will briefly review the Appendix C, E, I, J information with the patient at their baseline visit and then go over the patients completed WFPBD information checklist (Appendix E) at their Day 1 visit.
o. Monitoring for adverse events and toxicity will be done at every visit using CTCAEv5.0 criteria.
p. Patients may be followed at more frequent time intervals if clinically indicated. Patients who

have progressive disease will be followed with restaging scans and laboratory tests as clinically indicated.

q. Patients taken off protocol therapy for unacceptable adverse events will be followed until resolution or stabilization of the adverse event, and at least until 30 days after the last day of intervention. Further follow-up for survival will be assessed either by phone consultation or clinic appointment at the discretion of the PI.
r. A baseline 12-lead EKG within 3 months prior to baseline study assessment
s. All patients who have completed 1 year on study will be sent an optional post intervention feedback survey via Redcap for completion.

BIOSPECIMEN COLLECTION

1) Blood

a. Research blood samples for biomarker studies will be collected from all patients at the timepoints listed above.

The samples will be batched for later analysis.

b. Specimens will also be collected and stored at the time of documented CR and disease progression.

c. The standard number of peripheral blood tubes drawn for biomarker analysis, and storage for future assays at each of the above time points may include but are not limited to the following CPT tubes to store plasma, granulocytes and PBMCs and SST tube to store serum (At baseline, baseline, week 12 and week 24 - 4 CPT and 1 SST; At 4, 8 and 52 weeks – 2 CPT and 1 SST).

d. At any given time point when blood collection is performed per the study schedule, up to 100cc of peripheral blood will be collected. The amount of blood collected will be dictated by the number of experiments to be performed, and by the patient’s peripheral blood count.

e. Sample Requirements and Handling: The date and exact time of each blood draw should be recorded on the sample tube. Serum samples should be kept at room temperature for 30-60min prior to being refrigerated. Samples will be submitted to HOTB for storage.

f. Biomarker studies associated with peripheral blood specimen will be performed and related to clinical outcome if the results of the study indicate a clinical or translational rationale for analyzing the samples and provided sufficient sample obtained. Such studies may include but are not limited to the following:

i. Epigenetic analysis of T cells

ii. Flow cytometry including leukocyte subset analysis.

iii. Gene expression analysis

iv. Secreted inflammatory biomarkers such as Olink panels

2) Bone Marrow

a. Bone marrow specimens (aspirate) will be collected within 6 months from baseline and between

weeks 24 and 52 if there is a >25% reduction in M spike/free light chain and at the time of suspected CR or disease progression or investigator's discretion. Bone marrow samples will be used to determine the molecular characteristics of tumor and non-tumor cells.

b. At any given time point when a bone marrow aspirate is performed per the study schedule or for clinically indicated reasons 3-6mL bone marrow aspirate into two EDTA syringes/vials will be collected for research purposes.

c. Sample Requirements and Handling: The date and exact time of each bone marrow collection should be recorded on the sample tube. Bone marrow aspirate samples will be submitted to HOTB for storage per protocol. Bone marrow core and aspirate will also be sent to the clinical lab per standard of care requirements.

Priority	Media	Purpose	Delivery Location
1 – required	10% NBF	Standard of Care	Surg path

d. Biomarker studies associated with bone marrow specimen will be performed and related to clinical outcome if the results of the study indicate a clinical or translational rationale for analyzing the samples and provided sufficient sample obtained. Such studies may include but are not limited to the following:

i. Pathology/Immunohistochemistry including but not limited to stains to measure adipocyte size.

ii. Flow cytometry.

iii. Gene expression analysis such as single cell RNA sequencing and CITE sequencing

iv. Epigenetic analysis.

v. Secreted inflammatory biomarkers such as Olink panels

3) Stool: Gut microbiome: Stool will be collected at baseline,4 weeks, 12 weeks,24 weeks and 52 weeks. Stool will be analyzed via 16S sequencing and/or shotgun sequencing in the Molecular Microbiology Core Facility and GCMS assays such as short chain fatty acids in the Castori center.

BIOMARKER STUDIES: METHODS

Future Assays: After planned analysis for this study is complete, anything left over will be stored in HOTB/David lab for future use under 06-107 and corresponding biospecimen protocols. Left over samples are those that remain after the correlative work for the study is completed. Consent will be obtained for patients who are not already enrolled onto 06-107.

Future Use of Samples

Banked tissue, stool, and blood samples, as appropriate, will be used for future correlative studies. Any projects outside of the scope of this protocol will need to be approved by the IRB/PB. In order for the researchers to have access to the leftover samples, participants will consent to protocol 06-107, and a biospecimen correlative protocol detailing the proposed project will need to be approved by the IRB/PB prior to initiation of any project.

12.0 CRITERIA FOR REMOVAL FROM STUDY

Table 5. Primary Reasons for Permanent Intervention Discontinuation

Reason	Description
Self-withdrawal (withdrawal of consent)	Patients may permanently discontinue study intervention and withdraw from the study anytime for any reason. Following study intervention discontinuation, participants can have protocol-required safety follow-up and long-term follow-up assessments unless the participant specifically declines further follow-up.
Adverse event or intercurrent illness	Any intolerable adverse event (associated or not associated with the study intervention) that cannot be ameliorated by the use of adequate medical intervention or that, in the opinion of the investigator, would lead to undue risk if study intervention were continued.
Gross noncompliance with protocol (violation)	The investigator may consider permanent discontinuation in the event of lack of cooperation or complete noncompliance during the intervention period.
Disease progression	Study intervention will be discontinued upon evidence of clinical or radiographic disease progression to multiple myeloma determined by the patient's oncologist and principal investigator.
Lost to follow up	Reasonable effort should be made to contact any participant lost to follow-up during the course of the study in order to complete study-related assessments and record outstanding data.
Death	If a patient dies while on study their data will be included up until their death and they will be taken off study. Cause of death will be evaluated for any association with study intervention.

Additional patients will be accrued to maintain the target sample size in the event that a study participant does not complete the intervention period. Additional patients may be accrued to replace patients who discontinue the study intervention for any of the reasons listed in Table 4, however patients who discontinue the study intervention but have baseline lab assessments recorded will be included in the sensitivity/compliance analysis.

13.0 CRITERIA FOR OUTCOME ASSESSMENT AND ENDPOINT EVALUABILITY

13.1 Criteria for Study Endpoint Evaluability

Primary Endpoint:

1. Weight loss: The primary objective of this study is to determine the effect of the diet to achieve a mean BMI reduction from baseline at 12 weeks. Patients will be weighed at the baseline/screening visit and after 4, 8, 12 and 24 weeks and their BMI will be calculated. All patients who have received a WFPBD intervention for 12 weeks and have both baseline and 12-week laboratory results recorded are evaluable for primary endpoint. Patients who withdraw or are withdrawn from the study prior to completing 12 week laboratory results will not be considered evaluable for primary endpoint. We will replace up to 4 patients that are not evaluable for primary endpoint.

2. Adherence: To achieve patient adherence to the intervention defined as ≥70% of participants consuming a WFPBD for ≥70% of meals of the 12-week intervention period (determined via a dietary recall and nutritional survey). A benchmark of 70% was chosen as it is the current benchmark for adherence in lifestyle trials[64]. Also understand long term adherence by evaluation of % of participants compliant at 24 weeks and 52 weeks based on 72-hour dietary recall and food frequency questionnaires.

Patients will receive education from the dietitian about a WFPBD, including guidance on food choice and recipes. The research dietitian will contact patients every 2 weeks alternating phone and in-person visits to answer questions, providing personal coaching to ensure accountability and support. Adherence to phone visits will be retrospectively tracked from the patient's EMR. Patients will complete a dietary food recall survey form for the 3 days prior at each monthly study visit, and the form will be used to assess compliance with the intervention. At each visit, the study assistant will also confirm the dietary recall with the patient. Patients will complete the Block Questionnaire (2014 full-length Food Frequency Questionnaire and Physical Activity Screener[65,66]) at baseline, 12 weeks, 24 weeks and 52 weeks to assess adherence during and after the intervention and compare their pre- and post-intervention diet and activity. Participants will be asked to complete this survey via MSK Engage and a notification will be sent via email notification (Appendix M). Patients will be asked not to change their activity levels from baseline. Deidentified questionnaires will be sent to Nutrition Quest, which will use them to estimate nutrient intake and physical activity, returning the data in an electronic file suitable for statistical analysis (https://nutritionquest.com/assessment/).[65,66] Patients who consume a WFPBD for ≥70% of the meals during the 12 weeks on study (determined by the dietary food recall survey) will be deemed to adhere to the intervention. If ≥70% of patients meet this requirement then the study will meet its objective for overall adherence for the trial. This benchmark was chosen because it is used generally to measure adherence in lifestyle trials.

All patients who have received at least one WFPBD intervention are considered to be evaluable for assessment of adherence. Patients who withdraw or are withdrawn from the study prior to completing assessment at 12 weeks will be considered as failures for this endpoint.

Secondary endpoints

1. Safety: To determine safety at 12 weeks as determined by evaluating toxicity grading at each visit of the intervention, according to CTCAE v5.0 criteria.

Toxicity grading will be performed in accordance with NCI Common Terminology Criteria for Adverse Events (CTCAE) v5.0 at each study visit. Unanticipated but possible side effects of the plant-based meals include nausea, vomiting, diarrhea, and dyspepsia. It is possible but unexpected that patients would not tolerate this diet change and develop side effects such as bloating and diarrhea. High-fiber diets can lead to initial bloating that is expected to subside. Every effort will be made to provide education to prevent bloating while maintaining compliance by providing handouts on how to manage bloating as well as education during dietitian visits.

All patients who have received at least one WFPBD intervention and had safety assessment are evaluable for the assessment of safety.

2. Quality of Life: To assess patient-reported outcomes at 4, 12, 24 and 52 weeks compared to baseline via patient completion of the EORTC QLQ-C30 surveys.

Patients will complete the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30; 30 questions related to symptoms over the past week)[67] at baseline, 4, 12 24 and 52 weeks to assess changes in their quality of life. Participants will be asked to complete this survey via MSK Engage and a notification will be sent via email notification (Appendix L).

All patients who have received at least one WFPBD intervention and completed post baseline EORTC QLQ-C30 survey are considered to be evaluable for the quality of life assessment.

3. Weight loss: To determine the effect of the diet to achieve a sustained mean BMI reduction from baseline at 24 and 52 weeks. All patients who have received at least one WFPBD intervention with weight measured at baseline and at 24, or 52 weeks are considered to be evaluable for the assement.

3. Metabolic Markers: To assess changes in serum biomarkers such as adiponectin and leptin (markers of metabolic risk); HgbA1c, IGF-1, and insulin (markers of glucose metabolism); erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and IL-6 (markers of inflammation); and low-density lipoproteins (LDL; lipid profile) at 12, 24 and 52 weeks compared to baseline.

All patients who have received at least one WFPBD intervention with biomarker measured at baseline and at 12, 24, or 52 weeks are considered to be evaluable for the metabolic marker assessment at 12, 24, or 52 weeks compared to baseline.

Adiponectin, leptin, ESR, CRP, IL-6, insulin, IGF-1, HgbA1c, and lipid profile will be checked at baseline, 12, 24 and 52 weeks. Fasting blood will be collected at the specified time points (see *Schedule*). Serum lipids including total cholesterol, high- and low-density lipoprotein

(HDL, LDL), triglycerides, ESR, high-sensitivity CRP (hsCRP), and HgbA1c will be measured at MSK and will be analyzed by the clinical laboratory. Serum and plasma will be separated and stored at –80°C in the Hematology Oncology Tissue Bank (HOTB). To prevent unnecessary freeze-thaw cycles, plasma and serum will be stored in ten 0.25 mL aliquots. . Blood samples will be analyzed in batches and blinded internal quality controls will be included to ensure consistency of the assays. Samples for analysis of plasma levels of leptin, adiponectin, IGF-1, IL-6, and insulin will be sent to the Michael Pollak laboratory at McGill University in Canada in batches (https://www.mcgill.ca/assaylab/assays).

- Specimens should be labeled with the following – Nutrivention, MSKCC, Subject ID, Specimen ID, Subject Initials, Date of Collection/Time of Collection. (Participant identifiers do not need to be shared.)
- Documents to be sent with the specimens – Requisition showing the sample ID, assay order, the box number, the grid position and analytes (e.g. adiponectin, insulin, IL-6, etc). They also require the electronic version of the requisition via email.
- Specimens are to be shipped to:
  Rhoda Lim
  Dr. Pollak's Lab, room E-423
  Lady Davis Institute
  Jewish General Hospital
  3755, Cote-Ste-Catherine Road
  Montreal, Quebec
  Canada H3T 1E2
  Tel.: (514) 340-8222 ext. 24139
- Specimens are to be shipped with plenty of dry ice in an insulated shipping container. It is to be shipped on either on a Monday or a Tuesday so that the lab will receive the shipment on a weekday. Shipments will be sent preferably via World Courier or FedEx. World Courier replenishes the dry ice, while FedEx does not.
- The specimens are to be tracked in CRDB.
- The results will be sent from Pollak lab to MSK as an EXCEL spreadsheet.

4. Myeloma Markers: To assess changes in serum paraproteins (quantitative immunoglobulins, free light chains and serum protein electrophoresis) at 4, 8, 12, 24 and 52 weeks compared to baseline.

The standard myeloma paraproteins—quantitative immunoglobulins, free light chains, serum, and urine protein electrophoresis (M-spike)—will be checked at baseline and at 4, 8, 12, 24 and 52 weeks. Bone marrow biopsies will be done at baseline and then as clinically indicated subsequently.[63]

All patients who have received at least one WFPBD intervention with biomarker measured at baseline and at 12, 24, or 52 weeks are considered to be evaluable for the myeloma marker assessment at 12, 24, or 52 weeks compared to baseline.

Exploratory Endpoints

1. *Epigenetic*: To assess metabolism-related chromatin damage (epigenetic changes) in peripheral blood T cells (CD4 and CD8) at 12 weeks compared to baseline.

   If there is a significant change in weight, myeloma or metabolic biomarkers between baseline and 12 weeks then we will proceed with assessing epigenetic changes. To assess the epigenetic landscape, we will analyze at high-resolution the chromatin architecture, histone marks, and overall transcriptome of peripheral blood T cells (CD4 and CD8). This work will be performed in collaboration with the Yael David laboratory and the Center for Epigenetics Research at MSK. Specifically, we will sort peripheral blood T cells, extracted at baseline and 12 weeks , into CD4 and CD8 subsets. We will then analyze their chromatin structure (ATAC-seq), transcriptomics (RNA-seq), and the epigenetic landscape (histone mass spectrometry), focusing on changes in histone modifications that are characteristic of MM and correlations to sites of glycation (**Figure 4**).[50]

   All patients who have received the WFPBD intervention with biomarkers measured at baseline and 12 weeks are evaluable for the epigenetics assessment.

2. *Microbiome*: To assess shifts in the fecal microbiome measured by increase in diversity and relative abundance of butyrate-producing bacteria.

   Stool samples will be collected at baseline, 4 weeks, 12 and 24 weeks and frozen at -80℃ until ready for sequencing. DNA will be extracted and subjected to amplification of the V4/V5 variable regions of the 16S ribosomal RNA genes using barcoded primers targeted to conserved sequences.[68,69] Purified polymerase chain reaction products will be sequenced on the Illumina MiSeq platform and 16S paired-end reads will be merged and demultiplexed. The UPARSE pipeline will be used to perform quality and error filtering using maximum expected error (Emax = 1), and reads with >97% identity will be grouped into operational taxonomic units (**Figure 7**).[70] This aim will be performed in collaboration with Dr. Lesokhin, the Castori Center, and the van den Brink laboratory.[54] We will also measure stool short chain fatty acid

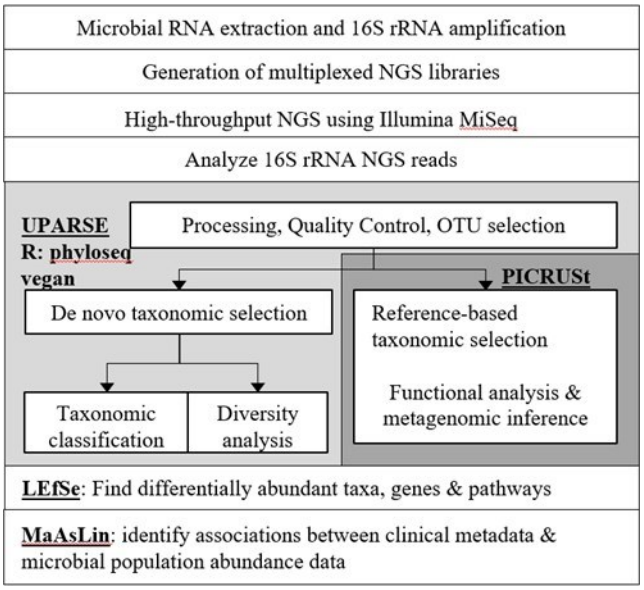


Figure 7: Proposed workflow uses bioinformatic techniques to evaluate relationship of microbiota with clinical outcomes.

levels at 4, 12,24 and 52 weeks compared to baseline with gas chromatography-mass spectrometry and consider shotgun sequencing of certain timepoints.[71]

All patients who have received at least one WFPBD intervention with biomarker measured at baseline and 12 weeks are evaluable for the microbiome assessment.

3. Immune: To assess changes in immune function as determined by peripheral blood leukocyte subsets via flow cytometry and bone marrow single cell RNA, ATAC, and CITE sequencing.

   All patients have peripheral blood at multiple timepoints and bone marrow biopsies at two time points – baseline and 12 months will be evaluable. This will be done in collaboration with IDMS core laboratory and van den Brink laboratory.

4. *Adiposity imaging*: To assess changes in body composition (visceral, subcutaneous and bone marrow fat) as determined on PET CT or MR imaging and correlate these with weight changes as well as markers of disease.

   All patients that have imaging at two time points - baseline and between 6-12 months will be evaluable. These two time points will be compared for visceral, subcutaneous and bone marrow fat. These fat quantification measurements will be obtained from the PET scan with the help of radiologist Dr Marius Mayerhoefer using automated software previously described.[72] These results will then be correlated with clinical changes in BMI, metabolic markers and paraproteins at two time points - baseline and 24 weeks.

14.0 BIOSTATISTICS

14.1 Populations for Analyses

Sample size justification: We aim to enroll 20 obese or overweight patients (BMI ≥25) with MGUS or SMM. Previous data[28] suggest that ~20% may drop out however up to 4 patients that do not complete 12 weeks assessment will be replaced. All patients that have assessments at 12 weeks are evaluable for the primary endpoint of weight loss and all patients that received WFPBD including those that are not evaluable for the primary endpoint will be included in adherence analysis. The sample size for this study is driven by the primary aim to test whether a WFPBD leads to weight loss in obese/overweight MGUS/SMM patients and patients that drop out prior to 12 weeks will be replaced. Weight loss is defined as the average decrease in BMI at 12 weeks. On the basis of previous[28] and internal studies, we assume that the mean and standard deviation of BMI at baseline will be 30 and 4.5, and that the standard deviation at 12 weeks will be similar. Using these assumptions, **Table 1** shows the power for a paired t-test with a one-sided type I error of 0.1 to detect a decrease in BMI at 12 weeks from the baseline in a pilot study with 20 patients. We do not know the exact within-person correlation between two BMI measurements that are 12 weeks apart, but we expect it to be ≥90%. With these assumptions, we expect the study to be adequately powered to detect a clinically relevant difference of ≥5% from baseline to the end of the intervention.

Table 6: Expected power to detect BMI differences of varying magnitude with 20 patients

	Within-person correlation (N=20)		
Mean difference (%)*	0.7	0.8	0.9
1.2 (4%)	58%	71%	91%
1.5 (5%)	73%	85%	98%
1.8 (6%)	83%	93%	99%

*Average BMI at baseline is assumed to be 30.

Statistical Analysis:

Primary Objective:

The primary objective of the pilot study is to determine the feasibility of a WFPBD in obese/overweight patients with MGUS or SMM, as measured by weight loss and adherence. Weight loss due to WFPBD intervention is defined as the average decrease in BMI at 12 weeks. Adherence will be estimated by sample proportion, with confidence intervals calculated based on exact binomial distribution.

Patients who have completed evaluation at 12 weeks will be evaluable for weight loss outcome . The average weight loss from baseline at 12 weeks s will be reported as sample mean along with 95% confidence interval. Adherence will be estimated by sample proportion, with confidence intervals calculated based on exact binomial distribution. All patients who have received at least one WFPBD intervention are considered to be evaluable for assessment of adherence. Patients who withdraw or are withdrawn from the study prior to completing assessment at 12 weeks will be considered as failures for this endpoint.

We will call WFPBD promising if 1) we detect weight loss at 12 weeks and 2) estimated adherence to the intervention is ≥70%.

Given our study's small sample size, we will not report results stratifying overweight and obese. In future randomized intervention study planning, we will evaluate the relationship between baseline BMI, weight loss, and adherence, using logistic and linear regressions. If a strong relationship between baseline BMI and primary endpoints is observed, stratification by BMI will be implemented into the study design.

Secondary Objectives:

1. The feasibility of WFPBD in obese/overweight patients with MGUS or SMM will measured by safety, and quality of life at 12, 24 and 52 weeks. Toxicities and adverse events will be reported descriptively. Change in quality of life at 12, 24, and 52 weeks from a baseline will be reported as sample mean along with 95% confidence interval.

2. The average weight loss from baseline at 24 and 52 weeks s will be reported as sample mean along with 95% confidence interval.

3. Alterations in metabolic, and myeloma markers secondary to a WFPBD intervention will be

assessed by changes in serum biomarkers such as adiponectin and leptin (markers of metabolic risk); HgbA1c, IGF-1, and insulin (markers of glucose metabolism); erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and IL-6 (markers of inflammation); and low-density lipoproteins (LDL; lipid profile) at 3 and 6 months compared to baseline. Change in a serum biomarker at 12, 24 and 52 weeks compared to baseline will be reported as sample mean along with 95% confidence interval. Myeloma labs will also be tested at 4 and 8 weeks.

Exploratory Objectives:

1. Alterations in epigenetics of T cells and plasma cells secondary to a WFPBD intervention will be assessed by metabolism-related chromatin damage (epigenetic changes) in peripheral blood T cells (CD4 and CD8) at 12 weeks compared to baseline. Epigenetic changes at 12 weeks compared to baseline will be reported as sample mean along with 95% confidence interval.

2. Alterations in the fecal microbiome after a WFPBD intervention will be assessed by shifts in the fecal microbiome measured by change in diversity and relative abundance of butyrate-producing bacteria. Change in microbiome diversity and relative abundance and at 12, 24, and 52 weeks compared to baseline will be reported as sample mean along with 95% confidence interval.

3. Changes in visceral, subcutaneous and bone marrow fat as determined on PET imaging between 6-12 months compared to baseline will be reported as sample means along with 95% confidence interval. Pearson correlation with changes in BMI and paraprotein between 24 weeks and baseline will be reported as well.

15.0 TOXICITIES/RISKS/SIDE EFFECTS

Toxicity grading will be performed in accordance with NCI CTCAE v5.0. Unanticipated but possible side effects of the plant-based meals include:

- Nausea
- Vomiting
- Diarrhea
- Dyspepsia
- Bloating

15.1 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following
    - An explanation of how the AE was handled
    - A description of the participant's condition
    - Indication if the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

16.0 PROTECTION OF HUMAN PARTICIPANTS

Prior to the enrollment of each participant, the risks, benefits and objectives of the study will be reviewed with the participant, including a discussion of the possible toxicities and side

effects. Alternative, non-protocol, treatment options will be discussed with the participant. It will be reviewed that participation in this clinical trial is voluntary and that the participant may withdraw consent at any time.

Consent process: All patients who meet the inclusion criteria will be eligible. Participation in the trial is voluntary. All participants will be required to sign a statement of informed consent, which must conform to IRB guidelines. The informed consent procedure is described in **Section 8.0**.

Potential Risks: Our eligibility criteria and screening procedures are established to exclude individuals for whom plant-based diet, blood collection and bone marrow biopsy are not appropriate. Our screening procedures begin with medical chart review to identify individuals with any condition or reason that may prohibit study entry, followed by oncologist approval to screen/identify patients who may not be eligible for any additional reasons. Finally, in-person assessments will be performed to screen/identify patients for contraindications to the study. This multi-gated comprehensive approach should systematically identify and screen out any individual for whom this study is contraindicated. Patients will be responsible for covering the cost of treating any research-related injuries. The risks associated with trial participation are described in detail in **Section 15**.

Bone Marrow Biopsy — Some minor risks are associated with an aspirate and core biopsy such as bruising and/or discomfort; however, this procedure is considered to be of minimal risk.

Blood Collection — There are some minor risks associated with a blood draw, e.g. bruising, discomfort, however this procedure is considered to be of minimal risk.

PET scan — A PET scan carries the risk of radiation exposure. In this study, two scans (baseline and at 6-12 months) will be completed for each participant enrolled as standard of care, and subsequent scans will be done as clinically indicated.

There are no known risks of the other study-related assessments in this trial.

Risks of research participation: The greatest risk is release of information from health or research records in a way that violates privacy rights. MSK will protect records so that name, address, phone number, and any other information that identifies the participant will be kept private. It will be stated to the participant that the chance that this information will be given to an unauthorized individual without the participant's permission is very small.

Benefits: Dietary modification such as plant-based diets have been shown to induce weight loss and reduce the risk of cardiovascular disease.

Collected biospecimens may be of no benefit to participants since neither the participant nor the treating physician will be told the specific results of any research tests on the samples. Research using blood or tissues in this study could lead to medical and scientific products that could improve prevention, diagnosis and treatment of disease.

Costs/compensation: Participants will be charged for physician visits, routine laboratory tests and radiologic studies required for monitoring their condition. The participants will not be billed for any study-related procedures. Participants will be informed that there are no plans to provide financial compensation for use of their human biologic specimens, nor are there plans for participants to receive money for any new products, tests, and discoveries that might come from this research.

Alternatives: The alternative to this trial would be not to participate in the study and receive routine standard of care.

Confidentiality: Every effort will be made to maintain patient confidentiality. Research and hospital records are confidential. Participants' names and any other identifying information will not be used in reports or publications resulting from this study. Other authorized agencies and appropriate internal personnel (e.g. qualified monitors from MSK) and external personnel

(its authorized agents, the FDA, and/or other governmental agencies) may review patient records as required.

Patient safety: Participants are monitored by physicians, oncology nurses and registered dietitians who are very familiar with clinical trials. In the case of an adverse reaction, immediate medical attention is available. In the evenings and on weekends, we have a 24-hour urgent care facility for outpatients.

Voluntariness of research participation: Taking part in this study is voluntary and participants have the right to withdraw at any time. Participation in the study will not impact the clinical care patients receive.

Withdrawal: Participants may also decide at a later date that they do not want identified blood and/or tissue samples to be stored for future research. If participants decide to withdraw from the study, specimens will not be used in new studies and any remaining portions of samples that have not been used for research will be used only for clinical purposes or, if requested by the participant, destroyed. When a participant withdraws from protocol, the withdrawal request will be documented in CTMS and the system updated accordingly. In addition, a note documenting the participant's withdrawal must be filed in his/her EMR.

16.1 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals/entities described in the Research Authorization form. A Research Authorization form must be approved by the IRB and Privacy Board (IRB/PB).

The consent indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include

protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with others at the time of study publication.

16.2 Data Management

An MSK Research Regulatory Associate (RRA) and Clinical Research Associate (CRA) will be assigned to the study. The RRA and CRA will be supervised by the Clinical Research Manager (CRM) and the Principal Investigator in the Myeloma Service. The responsibilities of the RRA and CRA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team. Case Report Forms (eCRFs) within an Electronic Data Capture (EDC), Medidata. Source documentation will be available to support the computerized patient record. The principal investigator will maintain ultimate responsibility for the clinical trial.

Data storage

The data collected for this study will be entered into a secure database (Medidata) generated specifically for this study. MSK's Medidata application analyst will assist with building the database based on provided specifications. Source documentation will be available.

Final data sets for publication will be locked and stored centrally for potential future access requests from outside entities.

16.3 Regulatory Documentation

Prior to implementing this protocol at MSK, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MSK Institutional Review Board/Privacy Board (IRB/PB). There will be one protocol document and each participating site will utilize that document.

Participating sites that are conducting specimen analysis should submit this protocol to their IRB according to local guidelines. Copies of any site IRB correspondence should be forwarded to MSK**.**

16.4 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

16.5 Data and Safety Monitoring

The Data and Safety Monitoring Plan utilized for this study must align with the MSK DSM Plan, where applicable.

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering were approved by the National Cancer Institute in August 2018. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials."

There are several different mechanisms by which clinical studies are monitored for data, safety and quality. At a departmental/PI level there exists procedures for quality control by the research team(s). Institutional processes in place for quality assurance include protocol monitoring, compliance and data verification audits, staff education on clinical research QA and two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Deputy Physician-In-Chief, Clinical Research.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required.

The MSK DSMB monitors phase III trials and the DSMC monitors non-phase III trials. The DSMB/C have oversight over the following trials:

- MSK Investigator Initiated Trials (IITs; MSK as sponsor)
- External studies where MSK is the data coordinating center
- Low risk studies identified as requiring DSMB/C review

The DSMC will initiate review following the enrollment of the first participant/or by the end of the year one if no accruals and will continue for the study lifecycle until there are no participants under active therapy and the protocol has closed to accrual. The DSMB will initiate review once the protocol is open to accrual.

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18.0 APPENDICES

Appendix A – EORTC QLQ C30 Survey

Appendix B – Block Food Frequency Questionnaire

Appendix C – Dietary Recall Handout (to be sent to patient during screening period)

Appendix D - Stool Collection Instructions (to be sent to patient during screening period)

Appendix E – Whole Foods Plant Based Diet Handout (to be sent to patient during screening period)

Appendix F – Sample Plantable Weekly Menu (to be sent to patient during screening period)

Appendix G – Plantable Sample Menu Ingredients (to be sent to patient during screening period)

Appendix H – Plantable App Screenshots (to be sent to patient during screening period)

Appendix I – American College of Lifestyle Medicine – WFPBD plate (to be sent to patient during screening period)

Appendix J – American Cancer Society Diet and Activity Guidelines (to be sent to patient during screening period)

Appendix K – Waist Circumference Measurement (to be sent to patient during screening period)

Appendix L – Email Notification for EORTC QOL Survey via MSKEngage

Appendix M – Email Notification for Block FFQ via MSKEngage

Appendix N – Optional Post Intervention Feedback Survey at end of study at 52 weeks