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Sustained Minimal Residual Disease Negativity in Multiple Myeloma is Associated with Stool Butyrate and Healthier Plant-Based Diets.

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Authors

Shah, Urvi A
Maclachlan, Kylee H
Derkach, Andriy
et al.

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Correspondence: Urvi A. Shah, MD, Department of Medicine, Myeloma Service, Memorial Sloan Kettering Cancer Center, 530 East 74th Street, New York, NY 10021; shahu@mskcc.org, Alexander M. Lesokhin, MD, Department of Medicine, Myeloma Service, Memorial Sloan Kettering Cancer Center, 530 East 74th Street, New York, NY 10021; lesokhia@mskcc.org.

Statement of equal author contribution

U.A.S. and K.H.M. contributed equally to this study.

Authorship Contributions

UAS and AML conceived and designed the study.

UAS, KHM, AD, AML analyzed, verified, and interpreted the data

MS, KW, JC, JB, LT, AC, MB, TS, PA, MJP, SM, NK, MH, HH, CT, BD, SL, DP, GS, MS, OLah, DC, HL, SU, KH, DM, OLan, SG collected and assembled the data.

JC, YT, JUP, MVDB, UAS, AML, AD, KHM analyzed and interpreted the microbiome data.

GB, TB, UAS, AML, AD, KHM analyzed and interpreted the nutrition data.

UAS, KHM, AML had full access to the data and share final responsibility for submission of the publication.

All authors wrote and approved of the article and are accountable for publication.

Conflicts of Interest Statement

U.A.S. has received grants and research support from Celgene/Bristol Myers Squibb, Janssen paid to the institution, personal fees from Janssen, BMS, Sanofi, MJH Life Sciences, ACCC, MashUp Media, RedMedEd, Phillips Gilmore Communication all outside of the submitted work.

SG reports personal fees and advisory role (scientific advisory board) from Actinnum, Celgene, Bristol Myers Squibb, Sanofi, Amgen, Pfizer, GlaxoSmithKline, JAZZ, Janssen, Omeros, Takeda, and Kite, outside the submitted work.

HH reports grants from Celgene, during the conduct of the study; and grants from Celgene, Takeda, and Janssen, outside the submitted work.

NK reports research funding through Amgen and participates in advisory board with Medimmune.

OLah reports serving on Advisory Board for MorphoSys.

OLan reports grants from Amgen, Janssen, and Takeda; Data Monitoring Committee from Janssen, Merck, and Takeda; and personal fees from Amgen, Janssen, GlaxoSmithKline, AstraZeneca, and The Binding Site, outside the submitted work.

SM reports research funding from Allogene Therapeutics, Juno/Bristol Myers Squibb, Takeda Oncology, and Janssen Oncology; personal fees from Plexus communication, and Physician Education Resource, outside the submitted work.

MS reports personal fees and research funding from Angiocrine Bioscience and Omeros Corporation; personal fees from McKinsey & Company, Kite – A Gilead Company, and i3Health, outside the submitted work.

GLS reports research funding from Janssen and Amgen outside the submitted work.

MJP reports research funding from Trillium Therapeutics, Nektar Therapeutics, and Regeneron Pharmaceuticals; personal fees from Karyopharm, Oncopeptides, Takeda, Janssen, and Curio Science, MJH Life Sciences, outside the submitted work.

CT reports other from Janssen Research and Development outside the submitted work.

BD reports honoraria from Medscape and Sanofi outside the submitted work.

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JUP reports research funding, intellectual property fees, and travel reimbursement from Seres Therapeutics, and consulting fees from DaVolterra, CSL Behring, and from MaaT Pharma. He serves on an Advisory board of and holds equity in Postbiotics Plus Research. He has filed intellectual property applications related to the microbiome (reference numbers #62/843,849, #62/977,908, and #15/756,845).

MVDB has received research support and stock options from Seres Therapeutics and stock options from Notch Therapeutics and Pluto Therapeutics; he has received royalties from Wolters Kluwer; has consulted, received honorarium from or participated in advisory boards for Seres Therapeutics, WindMIL Therapeutics, Rheos Medicines, Merck & Co, Inc., Magenta Therapeutics, Frazier Healthcare Partners, Nektar Therapeutics, Notch Therapeutics, Forty Seven Inc., Ceramedix, Lygenesis, Pluto Therapeutics, GlaskoSmithKline, Da Volterra, Novartis (Spouse), Synthekine (Spouse), and Beigene (Spouse); he has IP Licensing with Seres Therapeutics and Juno Therapeutics; and holds a fiduciary role on the Foundation Board of DKMS (a nonprofit organization).

AML reports grants from Novartis, during the conduct of the study; grants from Bristol Myers Squibb; personal fees from Trillium Therapeutics; grants, personal fees and non-financial support from Pfizer; and grants and personal fees from Janssen, outside the submitted work. AML also has a patent US20150037346A1 with royalties paid.

The remaining authors declare no potential conflicts of interest.

Statement of prior presentation

Presented in abstract form at the meeting of the International Myeloma Society, Vienna, Austria, September 10, 2021.[1]

Sustained Minimal Residual Disease Negativity in Multiple Myeloma is Associated with Stool Butyrate and Healthier Plant-Based Diets

Urvi A. Shah[1,2], **Kylee H. Maclachlan**[1,2], **Andriy Derkach**[3], **Meghan Salcedo**[1], **Kelly Barnett**[1], **Julia Caple**[1], **Jenna Blaslov**[1], **Linh Tran**[1], **Amanda Ciardiello**[1], **Miranda Burge**[1], **Tala Shekarkhand**[1], **Peter Adintori**[4], **Justin Cross**[5], **Matthew J. Pianko**[6], **Kinga Hosszu**[7], **Devin McAvoy**[7], **Sham Mailankody**[1,2], **Neha Korde**[1,2], **Malin Hultcrantz**[1,2], **Hani Hassoun**[1,2], **Carlyn R. Tan**[1,2], **Sydney X. Lu**[8], **Dhwani Patel**[1], **Benjamin Diamond**[9], **Gunjan Shah**[2,3], **Michael Scordo**[2,3], **Oscar Lahoud**[2,3], **David J. Chung**[2,3], **Heather Landau**[2,3], **Saad Z. Usmani**[1,2], **Sergio Giralt**[2,3], **Ying Taur**[10], **C. Ola Landgren**[9], **Gladys Block**[11], **Torin Block**[11], **Jonathan U. Peled**[2,3], **Marcel RM van den Brink**[2,3], **Alexander M. Lesokhin**[1,2]

[1]Myeloma Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

[2]Department of Medicine, Weill Cornell Medical College, New York, New York

[3]Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY

[4]Bone Marrow Transplant Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

[5]Donald B. and Catherine C. Marron Cancer Metabolism Center, Sloan Kettering Institute, New York, NY

[6]Department of Medicine, University of Michigan, Ann Arbor, MI

[7]Department of Pediatrics, Memorial Sloan Kettering Cancer Center, New York, NY

[8]Department of Medicine, Division of Hematology, Stanford University School of Medicine, Palo Alto, CA

[9]Myeloma Program, Department of Medicine, University of Miami, Sylvester Comprehensive Cancer Center, Miami, FL

[10]Infectious Diseases, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

[11]NutritionQuest, Berkeley, CA

Abstract

Purpose: Sustained minimal residual disease (MRD) negativity is associated with long-term survival in multiple myeloma (MM). The gut microbiome is affected by diet, and in turn can modulate host immunity, for example through production of short-chain fatty acids including butyrate. We hypothesized that dietary factors affect the microbiome (abundance of butyrate-producing bacteria or stool butyrate concentration) and may be associated with MM outcomes.

Experimental Design: We examined the relationship of dietary factors (via a food frequency questionnaire), stool metabolites (via gas chromatography-mass spectrometry), and the stool microbiome (via 16S sequencing - α-diversity and relative abundance of butyrate-producing bacteria) with sustained MRD negativity (via flow cytometry at 2 timepoints 1 year apart) in myeloma patients on lenalidomide maintenance. The Healthy Eating Index 2015 score and flavonoid nutrient values were calculated from the food frequency questionnaire. The Wilcoxon rank sum test was used to evaluate associations with two-sided $p < 0.05$ considered significant.

Results: At 3 months, higher stool butyrate concentration (p=0.037), butyrate producers (p=0.025) and α-diversity (p=0.0035) were associated with sustained MRD-negativity. Healthier dietary proteins, (from seafood and plants), correlated with butyrate at 3 months (p=0.009) and sustained MRD-negativity (p=0.05). Consumption of dietary flavonoids, plant nutrients with antioxidant effects, correlated with stool butyrate concentration (anthocyanidins p=0.01, flavones p=0.01, and flavanols p=0.02).

Conclusions: This is the first study to demonstrate an association between a plant-based dietary pattern, stool butyrate production and sustained MRD-negativity in MM; providing rationale to evaluate a prospective dietary intervention.

Introduction

Multiple myeloma (MM) remains incurable, however, sustained minimal residual disease (MRD) negativity following therapy represents the best predictor of survival.(1) Our prior studies in newly diagnosed MM demonstrated an increased relative abundance of *Eubacterium hallii* and *Faecalibacterium prausnitzii* in the stool samples collected following induction in MRD-negative patients.(2) In allogeneic hematopoietic cell transplantation, an increased abundance of *Eubacterium limosum* is associated with a lower risk of relapse and prolonged post-transplant survival.(3) These bacteria produce the short-chain fatty acid (SCFA) butyrate from dietary fiber and starch in plant foods. The SCFA butyrate can modulate systemic immunity through inhibition of NF-κB and histone deacetylases (HDAC), producing transcriptional modulation and a reduction in proinflammatory cytokines.(4–6)

Dietary composition plays a significant role in shaping the intestinal microbiome, with enrichment of stool butyrate concentration having been reported in individuals on a plant-based diet compared with an animal-based diet(7). In addition, dietary flavonoids, (plant derived nutrients) modulate both the microbiome and intestinal immune functions.(8–10) We hypothesized that dietary factors that affect the microbiome, in particular the abundance of butyrate-producing bacteria or stool butyrate concentration, may be associated with MM outcomes. Here, in the context of lenalidomide maintenance therapy, we evaluated the relationship of dietary factors, stool metabolites and microbial composition with sustained MRD-negativity.

Methods

MM patients eligible for maintenance during first-line therapy were enrolled prospectively, and received lenalidomide for up to 5 years (NCT02538198).(11) The study was conducted

in accordance with recognized ethical guidelines (Belmont Report and Declaration of Helinski) and approved by Memorial Sloan Kettering institutional review board. Written informed consent was obtained from patients. MRD status was evaluated at enrollment then annually using a validated bone marrow–based flow cytometric assay[12] with a sensitivity of at least 10^{-5}. Treatment responses were assessed according to International Myeloma Working Group consensus criteria[13], with sustained MRD-negativity defined as MRD-negativity at two consecutive time points 1 year apart between enrolment, 12m and 24m. Progression-free survival was not used as an endpoint given the low rate of clinical progression.

Stool samples were collected and analyzed as detailed previously[2] with identification of predicted butyrate-producing bacteria.[14] The relative abundance of predicted butyrate-producers and microbiome α-diversity were calculated from 16S microbiome profiles in samples collected 3 months (m) from enrollment. We performed direct quantitation of stool metabolite concentrations using gas chromatography–mass spectrometry on the same stool samples.

Habitual dietary patterns were collected using the Block Food Frequency Questionnaire 2014 (FFQ)[15] and summarized using the United States Department of Agriculture's (USDA) Healthy Eating Index 2015 score (HEI-2015)[16] and a newly developed Dietary Flavonoid Diversity Index (*DFDI*) by NutritionQuest. The HEI-2015 is a measure of diet quality, assessing 13 nutrient and food group components, with higher scores indicating healthier diets.[16] Flavonoid nutrient values were calculated from the FFQ based on USDA data. The DFDI measures the diversity of flavonoid intake from foods and beverages consumed at least once per week, following the Berry-Index method[17, 18]; scores range from 0–1, with higher scores indicating a greater diversity of flavonoid intake.

Univariate association between sustained MRD-negativity and α-diversity (as measured by the inverse Simpson index), relative abundance of butyrate producers, butyrate concentrations and dietary measurements were assessed using the Wilcoxon rank sum test. Univariate association between AHCT status and diversity, butyrate producers and butyrate concentrations by Wilcoxon rank sum test were also assessed. Multivariable logistic regression analyses between sustained MRD-negativity and α-diversity, relative abundance of butyrate producers, butyrate concentrations after adjusting for autologous hematopoietic cell transplantation (AHCT) status (yes vs no), age (65 or >65 years), gender (male vs female), cytogenetics (standard vs high risk) were assessed. High risk cytogenetics were defined as presence of either gain 1q21, t(4;14), t(14;16) or deletion 17p. The association between dietary and microbiome data were evaluated by Spearman's rank correlation coefficient (R). Logistic regression adjusting for potential confounders (body mass index; BMI, diabetes mellitus; DM, MRD-status at enrollment and transplant was used as a sensitivity analysis for testing the association between sustained MRD-negativity and microbiome features. In addition, in exploratory analysis, association between sustained MRD-negativity and correlation with diversity, stool butyrate producers and stool butyrate concentrations were assessed using Spearman's rank correlation coefficient. In this exploratory analysis we declared statistical significance at a two-sided significance level below 0.05. Cytokine analysis (via Olink Target 48 panel) among patients with

overlap in butyrate producer, butyrate concentrations, and cytokine data was evaluated using Spearman's rank correlation coefficient.

Data Availability

The data generated in this study are available upon request from the corresponding author.

Results

Baseline patient characteristics are presented in Table 1 and Supplementary Table 1. Samples were available from 74 MM patients including 59 with assessment of habitual dietary patterns, and 49 with 16S sequencing of the stool microbiome. The overlap of dietary assessment and stool examination was present in 34 patients, of which 32 had stool butyrate concentration measurements (Figure 1). All patients had MRD status assessed at enrollment, with 42 being MRD-positive and 32 MRD-negative. Serial assessment of MRD status was performed in 68 patients at 12 months (m), 61 at 24m and 48 at 36m from enrollment. Sustained MRD-negativity was highly correlated with MRD-negativity at enrollment and was observed in 32 patients of which 26 were also MRD-negative at enrollment.

As a subset of patients had undergone AHCT prior to maintenance therapy (33/74, 45%), the timepoint for microbiome evaluation of 3m post-enrollment was chosen to allow resolution of post-AHCT reduction in microbiome diversity.(19) α-diversity of the fecal microbiome at 3m was significantly higher in those with sustained MRD-negativity (median 16.9, interquartile range [IQR] 14.8–28.0), compared with those without (median 11.9, IQR 9.9–18.6, p=0.0035) (Figure 2a). The relative abundance of predicted butyrate-producers was also significantly higher in patients with sustained MRD-negativity (median 0.093, IQR 0.072–0.100) than those without (median 0.054, IQR 0.035–0.094, p=0.025) (Figure 2b).

Stool butyrate concentration at 3m was significantly higher in patients who achieved sustained MRD-negativity (median 18.1, IQR 10.7–29.0mM) compared to those who did not (median 10.0mM, IQR 6.6–16.2mM) (p=0.037) (Figure 2c). Additionally, AHCT status was not associated with diversity (p=0.82), relative abundance of butyrate producers (p=0.44) and stool butyrate concentrations (p=0.99) at 3m. On multivariate analysis after adjusting for AHCT status, age, gender, cytogenetics, stool microbiome α-diversity (p=0.004) and relative abundance of butyrate producers (p=0.03) at 3 months retained significance for association with sustained MRD negativity (Supplementary Table 2). Other stool metabolites (acetate, propanoate, valerate, heptanoate, isobutyrate, methylbutyrate, isovalerate) did not correlate with MRD-status (p-values >0.1. We saw weak positive correlations between plasma CCL2 and IL33 with butyrate levels (R^2 values 0.17 and 0.19 respectively). We evaluated antibiotic use within 2 months of a sample being collected, and our findings were independent of antibiotic use. Collectively, these data suggest that sustained MRD-negativity in MM is associated with higher α-diversity, relative abundance of butyrate producers and concentration of stool butyrate.

Considering that dietary factors play an important role in the production of SCFA, we examined the relationship between diet composition (components of HEI-2015 score), stool butyrate concentration, and subsequent MRD-status and identified certain significant

correlations (Supplementary Table 3). The components total protein as well as seafood and plant protein were associated with stool butyrate concentration at 3m (R=0.5, p=0.004 and R=0.45, p=0.009 respectively). Seafood and plant proteins include seafood, nuts, seeds, soy products (excluding beverages), and legumes (beans and peas). The standard for maximum score is 0.8 cup equivalent per 1,000 kcal and standard for minimum score of zero is no seafood or plant proteins. These components also correlated with sustained MRD-negativity (p=0.01 and p=0.05 respectively). To further explore the evidence supporting a plant-based diet, we measured dietary flavonoids in this cohort. Total anthocyanidins (R=0.47, p=0.01), flavones (R=0.48, p=0.01), and flavanols (R=0.42, p=0.02) correlated with stool butyrate. Additionally, the Dietary Flavonoid Diversity Index was associated with butyrate concentration (R=0.46, p=0.008) and microbiome diversity (R=0.38, p=0.03) (Supplementary Table 4).

Discussion

In the context of lenalidomide maintenance therapy for MM, we demonstrate for the first time an association between diet, the gut microbiome, and sustained MRD-negativity in MM. Our data show that sustained MRD-negativity among patients receiving lenalidomide is associated with higher microbial α-diversity, relative abundance of butyrate producers and concentration of stool butyrate measured after 3 months on lenalidomide maintenance. Together with our prior publication demonstrating increased butyrate producers, specifically *Eubacterium hallii* and *Faecalibacterium prausnitzii* in MRD-negative patients following induction therapy(2), this study further strengthens the hypothesis that specific microbiome features, especially butyrate concentrations may predict clinical outcomes in MM.

Butyrates have previously been shown to modulate immunity by exerting anti-inflammatory functions through inhibition of the transcription factor NF-κB, leading to reduced formation of proinflammatory cytokines.(4, 5) Butyrates also non-competitively inhibit HDACs, acting in the same way as panobinostat, an HDAC inhibitor with activity in MM.(4, 6). In this study, relationships between serum cytokine values and microbial features were not robust and may be due to sample size or assay sensitivity warranting larger sample size in future studies.

The dietary associations described in our study are consistent with prior epidemiologic data. Higher HEI-2015 scores correlated with reduced cancer risk and mortality.(20, 21) In the EPIC Oxford study, including 61,647 individuals of which 65 developed MM, those on vegetarian and vegan diets had reduced risk of development of MM compared to meat eaters (relative risk 0.23; 95% confidence interval (CI) 0.09–0.59).(22) In the Nurses' Health Study and Health Professionals Follow-up study that included 165,796 individuals with 423 MM cases and 345 deaths, those with healthier pre-diagnosis dietary pattern based on the alternative healthy eating index 2010 had lower MM mortality (hazard ratio 0.76; 95% CI 0.67–0.87).(23) The association of butyrate concentration with seafood and plant protein scores, dietary flavonoids, and dietary flavonoid diversity support the hypothesis that a diverse plant-based diet may have an impact on MM via butyrate production suggesting the potential for an underlying mechanistic basis.(10)

Strengths of this study include the availability of simultaneous dietary, stool microbiome and metabolite assessment, as well as long term MRD data, and the consistent association between the relative abundance of predicted butyrate producers and stool butyrate concentrations. Limitations include the lack of untreated patient samples prior to myeloma therapy initiation and a small sample size that had all study assessments. This may limit sensitivity to assess potential confounders related to an individual's lifestyle and circumstances at time of sample acquisition, although importantly our study did exclude subjects on continuous systemic immunosuppressive therapy and patients with gastrointestinal conditions that would impair absorption of lenalidomide. Additional limitations include dietary recall bias and utilization of flow-based MRD testing with a sensitivity of 10^{-5}, which may be discordant with assays having sensitivity of 10^{-6}. Future comprehensive studies evaluating plasma and bone marrow cytokine levels may shed additional light on the anti-inflammatory effects of butyrate when correlated with its stool and plasma concentrations.

Nevertheless, our data support the hypothesis that a healthy diet, with adequate high-quality plant and seafood protein, and dietary flavonoids may have a positive impact on stool diversity, butyrate production and MM outcomes (Figure 3).

In conclusion, this is the first study to show that dietary and microbiome factors may be associated with sustained MRD negativity in plasma cell disorders. Our study suggests that lifestyle modification in the form of dietary change may potentially contribute to MM control. We therefore believe that further study of prospective dietary interventions in plasma cell disorders is warranted and have initiated a whole-foods plant based dietary interventional trial in MM precursor disease (NCT04920084, NUTRIVENTION).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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Translational Relevance Statement

We demonstrate an association between diet, the gut microbiome, and sustained MRD-negativity in MM. In MM on lenalidomide maintenance, stool butyrate concentration at 3 months was associated with higher rates of sustained MRD negativity. Increased seafood and plant proteins, dietary flavonoids, and diversity of dietary flavonoids correlated with stool butyrate concentrations. Thus, a healthy diet, with adequate plant and seafood protein, and containing flavonoids, associates with stool diversity, butyrate production and sustained MRD-negativity. These findings suggest dietary modification should be studied prospectively to enhance myeloma control.

A.
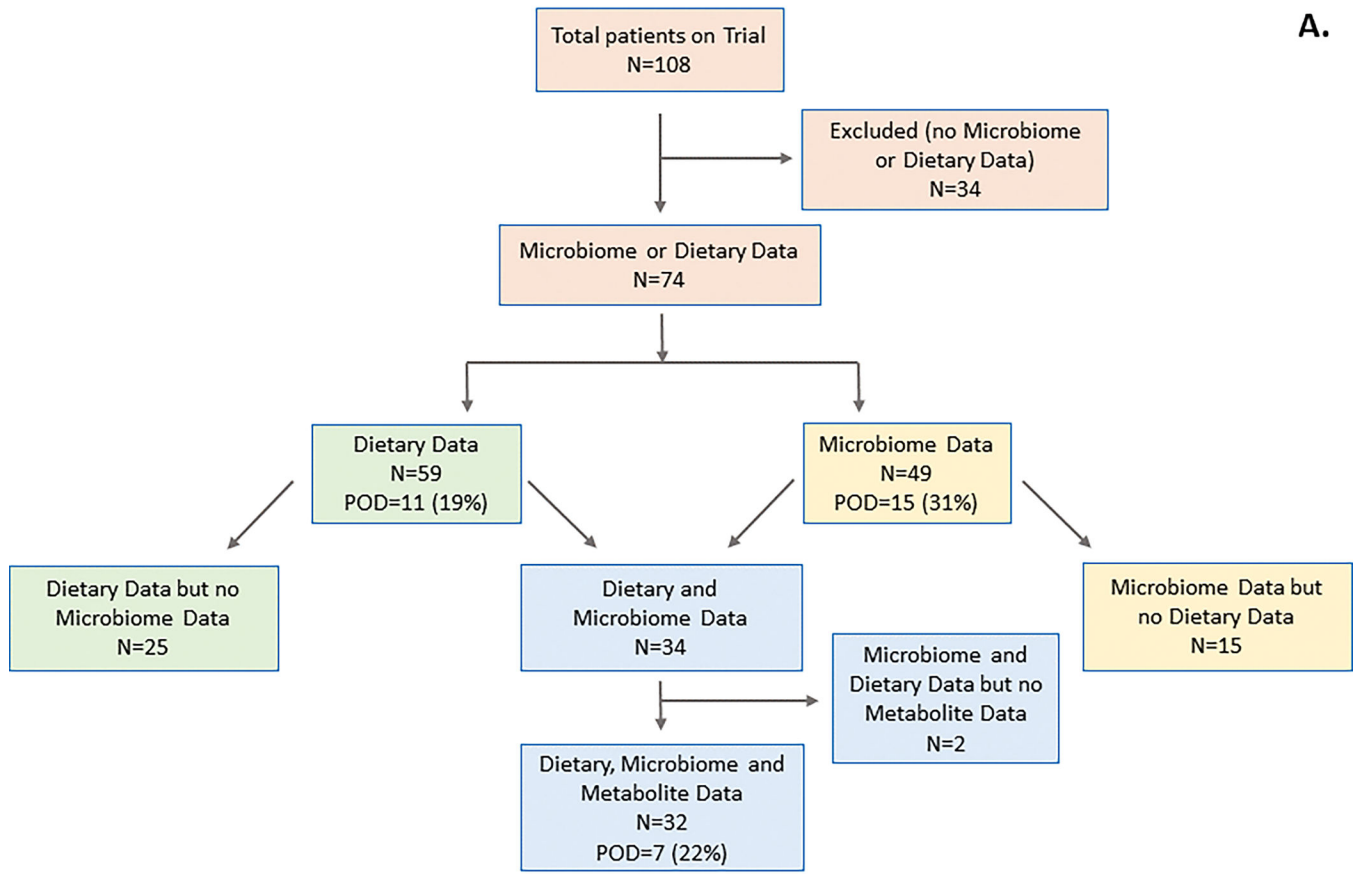
N: Number of patients
POD: Progression of disease

B.

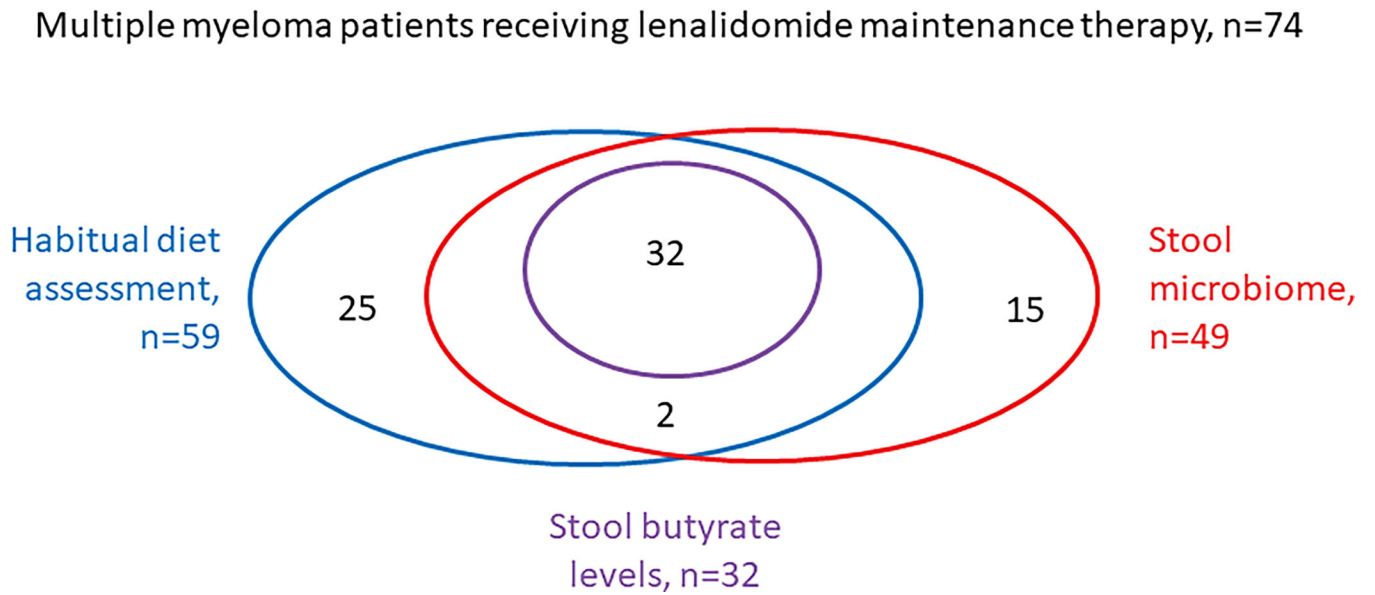Multiple myeloma patients receiving lenalidomide maintenance therapy, n=74

Figure 1. Sample description.
(a) Consort diagram demonstrating availability of dietary, microbiome and metabolite data.
(b) Venn diagram demonstrating the overlap between the 3 methods of assessment.
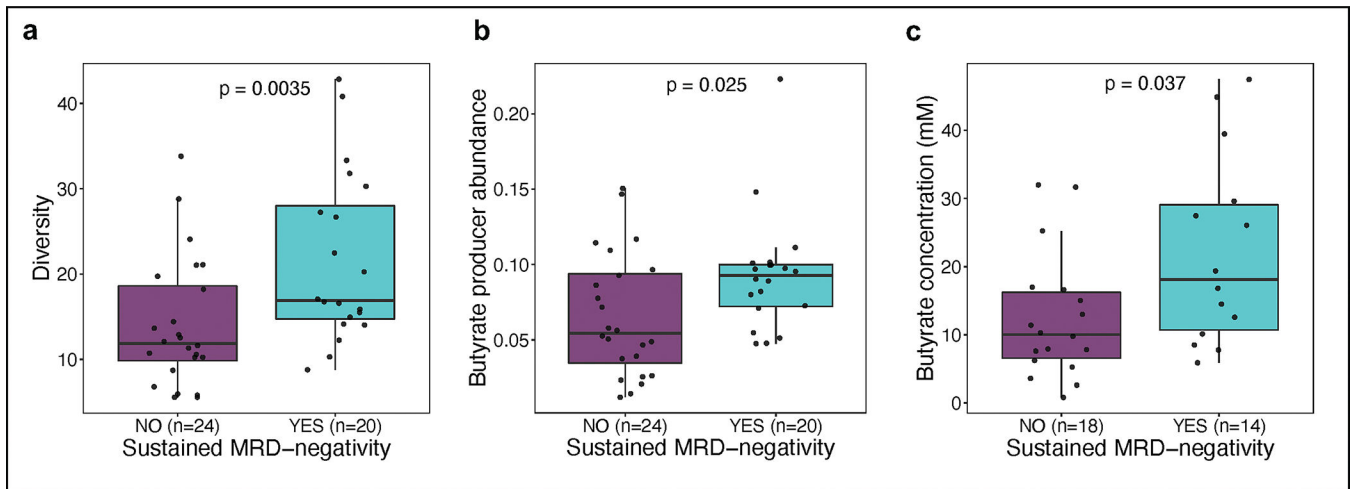
Figure 2. Stool α-diversity, abundance of butyrate producers and butyrate concentration associate with MRD-negativity.

(a) Stool α-diversity at 3m by inverse Simpson index according to sustained MRD-status.

(b) Relative abundance of butyrate producers at 3m according to sustained MRD-status. (c) Concentration of stool butyrate at 3m according to sustained MRD-status. (Achievement of sustained MRD negativity; Turquoise, yes; Purple, no).

DIETARY PATTERNS
↑ plant proteins
↑ seafood proteins
↑ plant flavonoids
↑ unsaturated
  fatty acid
↑ dietary fiber

GUT MICROBIOTA
↑ diversity
↑ butyrate producers
↑ butyrate levels

POTENTIAL MECHANISMS
↓ histone deacetylases
↓ NF-κB pathway
↓ proinflammatory
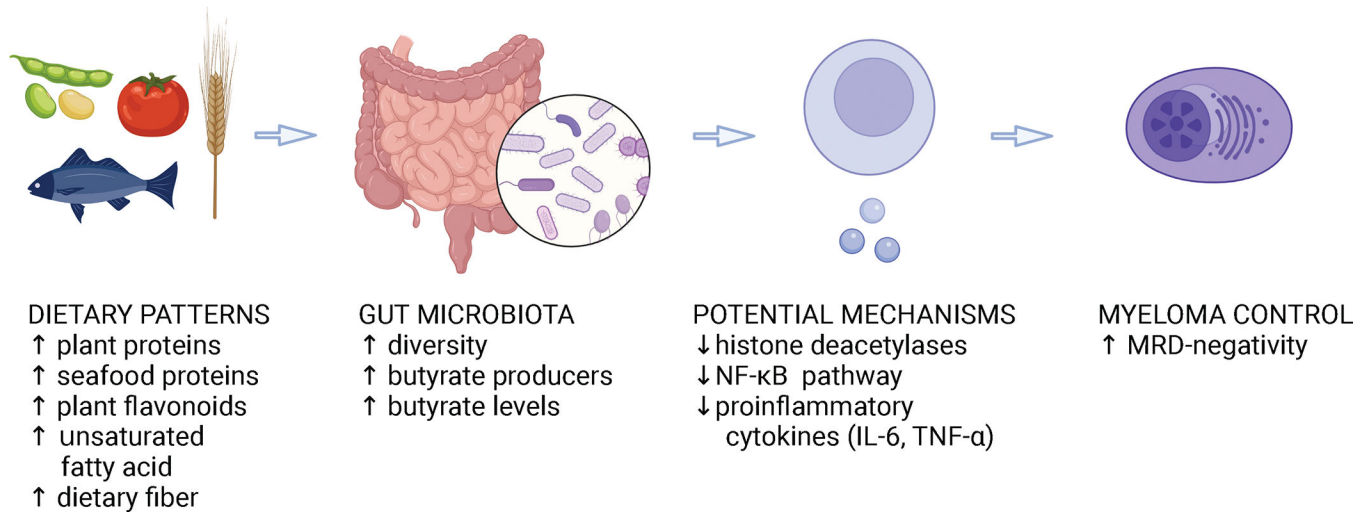 cytokines (IL-6, TNF-α)

MYELOMA CONTROL
↑ MRD-negativity

Figure 3. Schema for the hypothesis on how dietary composition may impact the intestinal microbiome and sustained MRD-negativity.
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Table 1.

Patient characteristics by presence or absence of sustained MRD-negativity.

Clinical variable	Sustained MRD Negative n (%)	No Sustained MRD Negative n (%)	*P* value
Patients	32 (100)	36 (100)	
Gender			
female	8 (25)	16 (44)	0.13
male	24 (75)	20 (56)	
Age			
65 years	21 (66)	16 (44)	0.09
> 65 years	11 (34)	20 (56)	
BMI			
25	10 (31)	12 (33)	1.0
>25	22 (69)	24 (67)	
Diabetes mellitus			
No	30 (94)	32 (89)	0.68
Yes	2 (6)	4 (11)	
High-risk cytogenetics	6 (19)	13 (33)	0.18
Induction regimen			
Dara-KRd	2 (6)	2 (6)	1.0
KRd	21 (66)	18 (50)	0.23
VRd	7 (22)	10 (27)	0.78
CyBorD	0	2 (6)	0.49
Other	2 (6)	4 (11)	0.68
Post-transplant status			
yes	14 (44)	15 (42)	1.0
no	18 (56)	21 (58)	
MRD-negativity at enrollment			
yes	25 (78)	6 (17)	0.0001
no	7 (22)	30 (83)	

High-risk cytogenetics % from 68 available results

MRD at 12m % from 63 available samples

Dara-KRd: Daratumumab, Carfilzomib, Lenalidomide, Dexamethasone

KRd: Carfilzomib, Lenalidomide, Dexamethasone

VRd: Bortezomib, Lenalidomide, Dexamethasone

CyBorD: Cyclophosphamide, Bortezomib, Dexamethasone

Vd: Bortezomib, Dexamethasone

KCyD: Carfilzomib, Cyclophosphamide, Dexamethasone

Other includes Vd, KCyD, thal