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Proceeding Paper

Personalized Dietary Intervention Based on Mediterranean Diet as a Complementary Strategy to Modify Gut Microbiome, Quality of Life and Outcomes in Patients with Metastatic Melanoma Treated with Immunotherapy: A Study Protocol †

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Abstract: Not all cancer patients respond to immunotherapy, and the variation in response may be attributed to an individual's microbiome, which is profoundly influenced by dietary habits. Understanding and manipulating the microbiome through dietary interventions offers a potential avenue for enhancing immunotherapy outcomes in cancer patients and may consequently serve as a complementary therapeutic strategy. Bearing in mind the latter, as well as our previous research on the importance of the gut microbiome as a co-denominator for immunotherapy response, we aimed to construct this study protocol on a personalized dietary intervention based on the Mediterranean diet as a complementary strategy to modify the gut microbiome, quality of life and outcomes in patients with metastatic melanoma treated with immunotherapy. The present protocol hypothesis is that remote intervention with the MD will be achievable and will positively affect all the aforementioned parameters. The potential gains of this study protocol and upcoming research extend to enhancing quality-of-life outcomes and the survival rates of patients with metastatic melanoma since it could also result in the reinforcement of the recommendation of nutritional intervention as a crucial component of cancer treatment.

Keywords: dietary intervention; immunotherapy; Mediterranean diet; microbiome; short-chain fatty acids; study protocol

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1. Background

Metastatic melanoma is a malignant tumor of melanocyte origin that has spread to other organs. The basis of treatment is systemic therapy, most commonly anti-programmed death-1 (PD-1) and anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) immunotherapy, although for some patients, thyrosine kinase inhibition is also a treatment option [1]. The survival of metastatic melanoma patients has been significantly extended over the last decade, and the use of immunotherapy has led to a median overall survival of 72 months and a response rate of up to 60% [2]. However, not all cancer patients respond equally

to immunotherapy, and the variation in response may be attributed to an individual's microbiome, which is heavily influenced by dietary habits [3]. Over two-thirds of patients will progress during 6.5 years of follow-up, and currently, there is a limited number of prognostic and predictive parameters for assessing the response to immunotherapy [2]. However, understanding and manipulating the microbiome through dietary interventions offers a potential avenue for enhancing immunotherapy outcomes in cancer patients and may consequently serve as a complementary therapeutic strategy.

Due to previous data, as well as our own publication on the importance of the gut microbiome as a co-denominator for immunotherapy response [4], and aiming to construct a protocol on dietary intervention for enhancing immunotherapy response in metastatic melanoma patients, we performed a systematic review according to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. We identified a total of 2130 citations by searching PubMed/Medline using the following search strategy: ((food) OR (diet*) OR (nutri*)) AND (immunother*) AND ((butyrate) OR (SCFA) OR (microbio*)) AND (cancer). Animal studies, studies with participants aged < 18 year., review articles, case reports, book chapters and publications before 2015 year. were not within our scope. Since we did not identify any relevant investigational studies, we proceeded to explore the diet–microbiome–immunotherapy axis through hand-searching and analyzing the secondary/indirect evidence.

Different dietary habits can influence the abundance and diversity of microorganisms within the gut. A diet with moderately elevated sodium (2.3–4 g daily) [5] and diets rich in fiber (20–25 g daily) [6], fruits and vegetables (≥5 servings daily) [7], vitamin D [8], omega-3 fatty acids [9] and whole grains (≥3 servings daily) [10] have been associated with a more diverse and beneficial microbiome which, in turn, promotes the production of short-chain fatty acids (SCFAs).

All the foods listed above are part of the Mediterranean diet (MD), which is based on fresh fruits and vegetables, legumes, olive oil and unrefined fiber. The MD also includes lower intakes of meat, eggs, processed foods, sugars and saturated fatty acids, which may all lead to a less diverse and potentially less favorable microbiome and health outcomes. Various clinical studies already demonstrated the beneficial effect of the MD in non-oncology patients [11] As for oncology patients, the benefit of the MD in reducing the incidence of cancer has been known for many years [12], especially for breast cancer patients [13]. Furthermore, a published cohort study involving 52 patients receiving immune checkpoint blockade (ICB) treatment for various solid tumors revealed that higher fecal SCFA concentrations were associated with longer progression-free survival [14]. Another cohort study comprising 91 patients with advanced melanoma in the UK and the Netherlands demonstrated that a stronger adherence to MD principles was linked to a higher likelihood of responding positively to ICB treatment [15]. However, there is a scarcity of randomized trials evaluating the effect of a nutritional intervention based on the MD in cancer patients undergoing treatment. As far as we know, there are no current clinical trials applying a nutritional intervention based on the MD in patients with metastatic melanoma; however, there is an ongoing randomized DIET study—NCT04645680 (with an expected ending in 2024)—aiming to evaluate the effectiveness of a fiber-enriched diet within the melanoma setting [16].

The potential effect of an MD-based nutritional intervention could result in a greater benefit compared to trials focusing only on one nutrient. Considering the issues learned from the COVID-19 pandemic [17], the main goal of our trial is to determine the effectiveness and applicability of a remote, personalized nutritional intervention based on the MD to increase the intake of micronutrients (flavones, anthocyanins, omega-3 fatty acids, vitamin D and fiber) previously associated with a positive response to immunotherapy. Additionally, there is a scarce body of literature discussing the intricate interplay between the microbiome and immune system, suggesting that specific microbiome signatures producing essential metabolites such as SCFAs may enhance the effectiveness of immunotherapy and regulate the activity of immune cells not only by triggering metabolic and epigenetic

reprogramming but also by binding to cognate receptors on the surface of cells. Hence, an evaluation of changes in the gut microbiome following an MD-based remote intervention, particularly changes in SCFA-producing bacteria, is also one of the goals of this study.

2. Methods

We designed a protocol for a 12-week, 2-arm, parallel-group randomized pilot trial to determine the effectiveness of remotely delivered, personalized nutritional intervention. The study would also be single-blinded as the researchers, with the exception of the nutritionists, would not know whether the subjects are in the intervention or control group. The research will be conducted in accordance with the Declaration of Helsinki and the Principles of Good Clinical Practice (GCP).

We would apply the following inclusion criteria: (i) age $\geq$ 18 years; (ii) pathohistologically confirmed melanoma stage IV or inoperable stage IIIC with radiological measurable disease on computerized tomography (CT) or positron emission tomography (PET)/CT for which the multidisciplinary team recommended the initiation of treatment with mono- or dual-immunotherapy with anti-PD-1 and/or combination antiPD-1 + anti-CTLA4 immunotherapy; (iii) written informed consent prior to participation, willingness to be monitored and have the dietary regimen adjusted if necessary; and (iv) Eastern Cooperative Oncology Group (ECOG) status 0-1.

On the other hand, a lifetime history of psychiatric disorders, active brain metastases, active autoimmune disease, the systemic use of equal or more than 10 mg of prednisone or an appropriate corticosteroid equivalent during screening, exposure to antibiotics and probiotics or other supplements that could affect the study outcome during screening within the last 3 weeks, uncontrolled diabetes, a history of clinically significant drug or alcohol abuse within the last 6 months, specific dietary habits that an individual is not inclined or able to change or the existence of a food allergy or an intolerance to certain food or an inability or refusal to participate in all research procedures would all be exclusion criteria.

The patients will then be randomized (via a web-based randomization service) to the control and intervention groups. The control group will continue with their usual/current diet with the exception of supplementation of vitamin D in those with a low serum vitamin D level (in accordance with current medical recommendations)

The intervention study will involve scheduled communications (via phone, video call and/or email) with a trained nutritionist based on protocol-determined parameters and recommendations, organized weekly in the first month, every other week in the second month and once a month in the third month. Each patient will receive general guidance and information about the MD. Additionally, a personalized nutritional plan based on the MD will be prepared for each patient, considering their initial dietary habits, preferences, food accessibility and financial constraints. Throughout the 12-week period, patients will be motivated to adhere to the prescribed dietary regimen. The values of specific dietary parameters aimed to be achieved with the MD intervention are given in Table 1.

Aside from having a teleconsultation with the nutritionist, there will be no other interventions in any group; additionally, participation in the study will not influence the selection of treatment modalities. Treatment selection will be exclusively based on the recommendations from a multidisciplinary tumor board. Given that this is a pilot study, and we do not have an estimate of the required sample size; 15 patients per group will be selected, which represents the previously analyzed number of patients for which a difference in microbiome and diet was found [4].

All patients will be evaluated at baseline using PET and/or CT, biomarkers of melanoma (S100, lactate dehydrogenase), the Croatian version of the European Organization for Research and Treatment of Cancer Quality of Life questionnaire (EORTC QLQ-C30 [27]), a food-frequency questionnaire (FFQ), 3 $\times$ 24 h dietary recall, and an analysis of the fecal microbiome. The same parameters will be evaluated 3 months later, after the completion of initial immunotherapy, as presented in Table 2.

Table 1. Values of specific dietary parameters aimed to be achieved with implementing the personalized dietary intervention based on Mediterranean diet.

Dietary Parameters		References
Flavonoids	>9 mg/day	[18,19]
Anthocyanins	>260 mg/day	[20]
Proteins %	>100% <150% recommended daily intake g/kg BM above 1 g/kg/day and, if possible, up to 1.5 g/kg/day	[21]
Omega 3	>250 mg/day	[22]
SFAs	as low as possible (e.g., <12% of EI (energy intake))	[21,23]
Fruits and Vegetables	at least 5 servings/day	[21,24]
Foods with added sugar	<20 g daily or as low as possible	[25]
Fibers	>20 g daily	[6]
Salt (Sodium)	No restrictions *	[5,26]

Saturated fatty acids—SFAs. * in the absence of high cardiovascular risk.

Table 2. Study schematic of intervention and follow-up strategies.

	Screen/Baseline	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12	Follow-Up (12 Months)
PET/CT or CT	x						x	x
laboratory testing	x						x	x
3 × 24 h recall	x				x	x	x	
FFQ	x						x	
anthropometrics	x						x	
stool sample	x						x	
consultation with nutritionist	x	x	x	x	x	x	x	

Computerized tomography—CT; food frequency questionnaire—FFQ; positron emission tomography—PET.

Laboratory testing will involve blood samples and a complete blood count with LDH, S100, CRP, vitamin D and albumin.

The fecal analysis will be conducted using OMNIgene OM200 containers, and microbial DNA will be subjected to a metagenomic analysis using the Illumina NextSeq 2000 platform (2 × 150 kb). A microbiome analysis will be performed on Illumina NextGen devices following prior preparation. Alpha-diversity (Shannon) and beta-diversity (CHAO1) analyses will be conducted, along with an LEfSE analysis to identify bacterial differences among groups. Pearson and Spearman correlations will be employed to correlate parameters at the beginning and end of the study.

The assessment of radiological response will be obtained using the iRECIST criteria [28], with the analysis of differences using the chi-square or Fisher's exact test. During further follow-up, time to progression-free survival (PFS) and overall survival (OS) will also be analyzed using the Kaplan–Meier method and compared between groups using the log-rank test. The questionnaire EORTC QLQ-C30, consisting of 30 questions assessed using a Likert scale, will be analyzed according to the EORTC guidelines. The incidence of adverse events will be evaluated according to the CTCAE classification [29] and calculated using percentages and a frequency analysis.

ClinicalTrials.gov trial registration will be conducted upon receiving the confirmation from the Ethical Committee.

3. Brief Discussion

This study protocol and the following trial are important as they will provide data for understanding and manipulating the gut microbiome through dietary intervention (MD) as a complementary therapeutic strategy, offering a potential avenue for enhancing immunotherapy and quality-of-life outcomes in cancer patients.

This study will not be without limitations, and obtained results will need to be interpreted accordingly (e.g., single-blinded, single-center, recall-bias, external validity). To the best of our knowledge, this will be a pioneer study evaluating the personalized dietary intervention based on the MD as a complementary strategy to the modify gut microbiome, quality of life and outcomes in patients with metastatic melanoma treated with immunotherapy, which we see as a strength. However, the latter also comes with limitations since a power analysis and study sample size calculation, in absence of a body of evidence, cannot not be performed/are not applicable. It is important to note that the quality of a pilot trial can be substantial, even with limitations such as a small sample size. Despite this, the insights gained from this pilot trial protocol and upcoming research will pave the way for the design of a study with a larger number of participants.

4. Conclusions

We hypothesize that a remote intervention with the MD will be achievable and would positively affect all the aforementioned parameters, based on previous research. A profound understanding of the complex relationship between diet, SCFAs, and immunotherapy response holds great promise for developing personalized dietary approaches to cancer immunotherapy-containing treatment regimens. By elucidating the mechanisms involved and identifying concrete personalized dietary strategies that optimize the gut microbiome, it may be possible to further enhance the effectiveness of immunotherapy, offer novel therapeutic approaches for cancer patients and improve their quality of life. Last but not least, the potential gains from this research extend to enhancing quality-of-life outcomes and the survival rates of patients with metastatic melanoma. This could also reinforce the recommendation of nutritional intervention as a crucial component of treatment.

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