Current Oncology Reports (2025) 27:45–58
https://doi.org/10.1007/s11912-024-01622-6

REVIEW

Role of the Microbiome and Diet for Response to Cancer Checkpoint Immunotherapy: A Narrative Review of Clinical Trials

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Accepted: 9 November 2024 / Published online: 3 January 2025

Abstract

Purpose of Review The advent of checkpoint immunotherapy has dramatically changed the outcomes for patients with cancer. However, a considerable number of patients have little or no response to therapy. We review recent findings on the connection between the gut microbiota and the immune system, exploring whether this link could enhance the effectiveness of immunotherapy.

Recent Findings Clinical studies have reported specific types of bacteria in larger quantities at baseline in responders than in non-responders, especially *Akkermansia mucinifila*, *Ruminococcaceae*, *Faecalibacterium*, and *Lachnospiraceae*. Following the consumption of a high-fiber diet, bacteria in the gut ferment dietary fiber to short-chain fatty acids (SCFAs), like acetate, propionate, and butyrate. Some of the SCFAs nurture intestinal epithelial cells, and some enter the bloodstream. Here SCFAs can activate DC8 + cytotoxic T-cells to induce cancer cell death. High fiber intake in the diet was associated with a reduced risk of progression or death during checkpoint immunotherapy. Recent findings demonstrate that high-fiber plant-based diets such as the Mediterranean Diet positively influence the gut microbiota whereas antibiotics and proton pump inhibitors can negatively influence outcomes of cancer immunotherapy by changing the gut microbiota.

Summary This narrative review provides evidence of an association between types of bacteria and their metabolites and favorable responses to checkpoint immunotherapy. Prospective clinical trials are needed to determine if diet interventions can improve treatment outcomes.

Keywords Gut Microbiota · Mediterranean Diet · Cancer Immunotherapy · Dietary fiber · Short-chain Fatty Acids

Introduction

A new paradigm has appeared. Instead of viewing bacteria and other microorganisms solely as infectious agents to be eradicated, the microbiota and the human host are now viewed as a super-organism or holobiont [1]. This shared community of microorganisms coexists with the host and contributes to the overall functioning of the organism [2]. The human microbiota comprises 38 trillion (38×10^{12}) symbiotic microbial cells, primarily bacteria in the gut [3]. These cells contain genes that make up the human microbiome [4].

Helicobacter pylori, identified in 1982, was the only bacterial species linked to cancer until recently [5]. However, the 2022 update of Hallmarks of Cancer [6] introduced the polymorphic microbiome as a new enabling characteristic. The microbiome influences four other hallmarks: tumor growth, tumor-promoting inflammation, immune evasion, and genomic instability. Additionally, it affects therapy resistance. The implication is that the microbiome plays a crucial role in cancer development, progression, and treatment response.

E. coli can potentially induce colon cancer if carrying a pathogenic island encoding enzymes to synthesize colibactin, which can cause mutations in colonic epithelial cells

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[7]. Additionally, bacteria have been detected within solid tumors [8], but how they are associated with the gut microbiome and their impact on human survival is still unclear [6].

Since the first approval of a programmed death-1 (PD-1) inhibitor checkpoint immunotherapy in 2014, the use of PD-1 or programmed death-ligand 1 (PD-L1) checkpoint immunotherapy has rapidly increased. This therapy has now been established as the standard treatment for various cancers, including melanoma, non-small cell lung cancer, kidney, bladder, and triple-negative breast cancer. Despite significant improvements in overall survival, clinicians and researchers are puzzled by the varying responses among patients. Some patients experience a complete response (CR) lasting for years, while others obtain progressive disease (PD) as best response, often regardless of PD-L1 expression in tumor tissue samples.

Antibiotic treatments reduce the effectiveness of immunotherapy in cancer patients [9], indicating the importance of the microbiome for response to immunotherapy. Many studies have searched for specific bacteria that could predict responses to immunotherapy, and efforts are ongoing to improve the microbiome of cancer patients undergoing such treatments. Some studies explore fecal microbiome transplantation (FMT) [10]. Other untargeted methods include exercise, diet, or supplements with prebiotics, probiotics, synbiotics, and postbiotics. Targeted therapies include bioengineered commensals, targeted antibiotics, phage therapy, or Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) [11].

This review examines the scientific literature on clinical trials involving cancer patients treated with checkpoint immunotherapy. It will specifically focus on the role of the microbiome and diet in influencing the response.

Patients and Methods

This review of clinical trials has been conducted using the terms “gut microbiome” and “cancer immunotherapy”, and”PD-1”or “PD-L1” or CTLA-4”. A PubMed search up to August 24, 2024, yielded 66,495 results for “gut microbiome”, 1,108 results for “cancer immunotherapy”, and 246 results for “PD-1” or “PD-L1” or “CTLA-4”. The 246 articles were filtered to exclude reviews, animal studies, and those focusing solely on side effects. Reference lists from the selected articles were manually reviewed for additional relevant studies. The final number of original articles identified was 31, all having at least a baseline measurement of the gut microbiota in cancer patients on treatment with immunotherapy and having reported on treatment outcome.

Results

Bacteria Associated with Positive Response to PD-1 Immunotherapy

Since discovering a possible link between the microbiome and response to immunotherapy, researchers have sought to identify specific bacteria species or families that enhance immunotherapy response. These studies are highly diverse, covering various cancer types, disease stages, and immunotherapy approaches, whether as monotherapy or in combinations, in different regions around the world, and often as single-center studies, making it challenging to draw definitive conclusions. However, several studies indicate that baseline bacterial diversity can predict treatment response [12–20]; specific bacteria, such as Akkermansia mucinifila, Ruminococcaceae, Faecalibacterium, and Lachnospiraceae, are often found in greater quantities at baseline in responders compared to non-responders (Table 1).

Akkermansia Mucinifila

The bacteria Akkermansia mucinifila resides in the mucus layer of the intestine, where it breaks down mucin, typically making up 1–4% of the commensal bacteria in a healthy gut [41]. Akkermansia also metabolizes inulin, a dietary fiber found in plants such as the allium family and Jerusalem artichoke, as well as ellagitannins, phytochemicals found in pomegranate and walnuts. The end products of this metabolism are short-chain fatty acids (SCFAs) [42].

Several studies found Akkermansia significantly increased in responders to immunotherapy (Table 1) [15, 18, 20–26]. Routy et al. discovered in their study of patients with metastatic renal cell carcinoma (mRCC) and metastatic non-small cell lung cancer (NSCLC) that Akkermansia was the commensal bacterium most significantly related to tumor response according to RECIST criteria ($p = 0.004$). Akkermansia was also overrepresented in patients with progression-free survival (PFS) longer than 3 months compared to those with PFS shorter than 3 months [20].

In Grenda et al.s study involving 47 patients with NSCLC, Akkermansia was significantly enriched in patients with partial response (PR) compared to patients with progressive disease [25]. They also observed a significant association between Akkermansia levels in the gut microbiome and histologic subsets; patients with squamous cell carcinoma had above-average levels of Akkermansia, while patients with adenocarcinoma had lower levels. Age was also a significant factor; patients younger

Table 1 Bacteria and archaea detected at baseline in systematically reviewed clinical studies with a significant difference in responders vs. non-responders. Studies differ in cancer type, size, immunotherapeutic agent, and how response is defined

Gut bacteria	Subtype	Patient group	*N*	Medical cancer treatment	Clinical end-point with positive outcome measure	Investigator	Publication year
Akkermansia Mucinifila		NSCLC/RCC	78	ICI	RR/PFS	Routy, B[20]	2018
		HCC	8	Anti-PD-1	PFS	Zheng, Y[21]	2019
		RCC	69	Nivolumab	RR	Derosa, L[22]	2020
		RCC	31	Nivolumab or nivolumab + ipilimumab	RR, increase during Tx	Salgia, N[15]	2020
		NSCLC	16	Anti-PD-1	RR	He, D[23]	2021
		Thoracic	42	anti-PD-1	RR	Yin, H[24]	2021
		NSCLC 1 L/2L	47	anti-PD-1/PD-L1	RR (SD/PRvs. PD)	Grenda, A[25]	2022
		NSCLC	73	anti-PD-1	RR	Fang, C[26]	2022
		NSCLC	65	ICI or ICI-chemo	RR	Newsome, R[18]	2022
Rumino-coccaceae	Faecalibacterium	Melanoma	39	ipi-nivo	RR	Frankel, A[27]	2017
	Faecalibacterium	Melanoma	112	anti-PD-1	RR and PFS	Gopalakrishnan, V[12]	2018
	Faecalibacterium	Melanoma	132	anti-PD-1	RR	Spencer, C[28]	2021
	Faecalibacterium	NSCLC	65	ICI or ICI-chemo	RR	Newsome, R[18]	2021
	Faecalibacterium	NSCLC	41	ICI	RR	Ren, S[16]	2024
	Faecalibacterium prausnitzii	Melanoma	39	ipi-nivo	RR	Frankel, A[27]	2017
	Faecalibacterium prausnitzii	Melanoma	111	anti-PD-1	RR	Spencer, C[28]	2022
	Ruminococcaceae	HCC	8	Anti-PD-1	PFS	Zheng, Y[21]	2019
	Ruminococcaceae	GI-cancers	74	anti-PD-1/PD-L1	RR	Peng, Z[29]	2020
	Ruminococcaceae	NSCLC	70	anti-PD-1/PD-L1	RR and PFS	Hakozaki, T[14]	2020
	Ruminococcaceae	Melanoma	132	anti-PD-1	RR	Spencer, C[28]	2021
	Ruminococcus	NSCLC/RCC	78	ICI	RR/PFS	Routy, B[20]	2018
	Ruminococcus	NSCLC	65	ICI or ICI-chemo	RR	Newsome, R[18]	2022
	Ruminococcus	Gastric HER2-neg.	58	ICI	RR	Han, Z[30]	2023
	Ruminococcus	NSCLC	41	ICI	RR	Ren, S[16]	2024
	Ruminococcus calidus	Hepatobiliary c.	65	ICI	PFS	Mao, J[31]	2021
Eubacterium/ Lachnospiraceae	Agathobacter	NSCLC	70	anti-PD-1/PD-L1	RR and PFS	Hakozaki, T[14]	2020
	Blautia	NSCLC	65	ICI or ICI-chemo	RR	Newsome, R[18]	2022
	Dorea formicogen-erans	Melanoma	13	Pembrolizumab	RR	Frankel, A[27]	2017
	Eubacterium	NSCLC/RCC	78	ICI	RR/PFS	Routy, B[20]	2018
	Eubacterium	Gastric HER2-neg.	58	ICI	RR	Han, Z[30]	2023
	Eubacterium rectale	Gastric HER2-neg.	58	ICI	PFS	Han, Z[30]	2023
	Flavonifractor	Gastric HER2-neg.	32	ICI + chemo	RR and PFS	Han, Z[30]	2023
	Flavonifractor plautii	Gastric HER2-neg.	32	ICI + chemo	PFS	Han, Z[30]	2023
	Lachnospiraceae	Melanoma	94	anti-PD-1	RR	McCulloch, J[32]	2022
	Lachnospiraceae	GI-cancers	74	anti-PD-1/PD-L1	RR	Peng, Z[29]	2020
	Lachnospiraceae GAM-79	Hepatobiliary c.	65	ICI	OS and PFS	Mao, J[31]	2021
	Lachnospiraceae (NK4A136)	NSCLC	41	ICI	RR	Ren, S[16]	2024
	Eubacterium ven-triosum	Mesothelioma	26	Atezoli-zumab + bevaci-zumab	RR	Zhang, M[33]	2024

Table 1 (continued)

Gut bacteria	Subtype	Patient group	*N*	Medical cancer treatment	Clinical end-point with positive outcome measure	Investigator	Publication year
	Butyricicoccus	Mesothelioma	26	Atezolizumab + bevacizumab	RR	Zhang, M[33]	2024
Actinobacteria	Actinobacteria	Melanoma	94	anti-PD-1	RR	McCulloch, J[32]	2022
	Bifidobacterium	NSCLC	21	ICI + chemo	RR	Zhao, H[34]	2023
	Bifidobacterium adolescentis	RCC	31	Nivolumab or nivolumab + ipilimumab	RR	Salgia, N[15]	2020
	Bifidobacterium breve	NSCLC	21	ICI + chemo	RR and PFS	Zhao, H[34]	2023
	Bifidobacterium longum	Melanoma	42	anti-PD-1/anti-CTLA-4	RR	Matson, V[35]	2018
	Collinsella aerofaciens	Melanoma	42	anti-PD-1/anti-CTLA-4	RR	Matson, V[35]	2018
	Olsenella	NSCLC	16	Anti-PD-1	RR	He, D[23]	2021
Firmicutes/ Bacillota	Clostridia	NSCLC	73	anti-PD-1	RR	Fang, C[26]	2022
	Clostridia	NSCLC	41	ICI	RR	Ren, S[16]	2024
	Clostridialis Incertae Sedis XIII	Gastric HER2-neg.	32	ICI + chemo	RR	Han, Z[30]	2023
	Enterococcus faecium	Melanoma	42	anti-PD-1/anti-CTLA-4	RR	Matson, V[35]	2018
	Erysipelotichaceae	Gastric HER2-neg.	58	ICI	RR and PFS	Han, Z[30]	2023
	Erysipelotichaceae GAM147	Hepatobiliary c.	65	ICI	PFS	Mao, J[31]	2021
	Lactobacillus	Gastric HER2-neg.	58	ICI	RR	Han, Z[30]	2023
	Lactobacillus	Gastric HER2-neg.	32	ICI + chemo	PFS	Han, Z[30]	2023
	Lactobacillus mucosae	Gastric HER2-neg.	58	ICI	PFS	Han, Z[30]	2023
	Lactobacillus salivarius	Gastric HER2-neg.	58	ICI	PFS	Han, Z[30]	2023
	Holdemania filiformis	Melanoma	39	Ipilimumab-nivolumab	RR	Frankel, A[27]	2017
	Streptococcus parasanguinis	Melanoma	25	anti-PD-1/anti-CTLA-4	OS	Wind, T[36]	2020
	Streptococcus salivarius	Prostate mCRP	23	pembrolizumab	RR	Peiffer, L[37]	2022
Bacteriodales	Alistipes	Billiary	88	anti-PD-1/PD-L1	PFS, OS	Zhu, C[19]	2024
	Alistibes obesi	NSCLC	73	anti-PD-1	RR	Fang, C[26]	2022
	Alistipes onderdonkii	Gastric HER2-neg.	58	ICI	PFS	Han, Z[30]	2023
	Alistipes putredinis	NSCLC	25	Nivolumab	RR	Jin, Y[13]	2019
	Alistipes sp Marseille-P5997	Hepatobiliary c.	65	ICI	OS and PFS	Mao, J[31]	2021
	Bacteroides eggerthii	RCC	31	Nivolumab or nivolumab + ipilimumab	RR	Salgia, N[15]	2020
	Barnesiella	Esophagus	46	PD-1 + chemo	RR	Xu, L[38]	2022
	Barnesiella intestinihominis	RCC	31	Nivolumab or nivolumab + ipilimumab	RR	Salgia, N[15]	2020
	Butyricimonas	Esophagus	46	PD-1 + chemo	RR	Xu, L[38]	2022
	Escherichia	NSCLC	21	ICI + chemo	RR	Zhao, H[34]	2023

Table 1 (continued)

Gut bacteria	Subtype	Patient group	*N*	Medical cancer treatment	Clinical end-point with positive outcome measure	Investigator	Publication year
	Escherichia-Shigella	NSCLC	16	Anti-PD-1	RR	He, D[23]	2021
	Odoribacter splanchnicus	RCC	31	Nivolumab or nivolumab + ipilimumab	RR	Salgia, N[15]	2020
	Odoribacter splanchnicus	Esophagus	46	PD-1 + chemo	RR	Xu, L[38]	2022
	Parabacteroides	NSCLC	63	Anti-PD-1	PFS	Song, P[17]	2020
	Prevotella	GI-cancers	74	anti-PD-1/PD-L1	RR	Peng, Z[29]	2020
	Prevotella	Esophagus	46	PD-1 + chemo	RR	Xu, L[38]	2022
	Prevotella copri	Melanoma	64	Anti-PD-1	RR	Pietrzak, B[39]	2022
	Prevotella	Mesotheliom	26	Atezolizumab + bevacizumab	RR	Zhang, M[33]	2024
Bacteriodetes	Bacteroides massiliensis	Melanoma	25	anti-PD-1/anti-CTLA-4	PFS	Wind, T[36]	2020
	Bacteroides massiliensis	NSCLC	73	anti-PD-1	RR	Fang, C[26]	2022
	Bacteriodes thetaiotamicron	Melanoma	39	Ipilimumab-nivolumab	RR	Frankel, A[27]	2017
	Bacteroides uniformis	Melanoma	64	anti-PD-1	RR	Pietrzak, B[39]	2022
Gut microbiota	Subtype	Patient group	N	Medical cancer treatment	Clinical end-point with positive outcome measure	Investigator	Publication year
Archaea		Cancer	72	Anti-PD-1	RR	Cheng, X[40]	2022
	Methano-brevibacter	NSCLC	63	Anti-PD-1	PFS	Song, P[17]	2020
	Bilophila	Gastric HER2-neg.	32	ICI + chemo	RR	Han, Z[30]	2023
	Pyramidobacter	Esophagus	46	PD-1 + chemo	RR	Xu, L[38]	2022

than 66 had significantly lower levels of Akkermansia compared to older patients [25].

Fang et al. investigated the microbiome in Han Chinese patients with NSCLC. They found Akkermansia was more abundant in responders compared to non-responders, with PFS of more than 3 months [26]. However, compared to a French cohort [20], the Chinese patients had a different strain of Akkermansia. The French cohort was enriched in MGS.igc0118, while the Chinese cohort had MGS.igc0776 [26]. Conversely, in a study of patients with prostate cancer treated with pembrolizumab, higher levels of Akkermansia were correlated with worse outcomes, however these were not statistically significant ($p = 0.201$) [37].

Ruminococcus Family

Ruminococcus is a family of bacteria that metabolizes resistant starch in humans [43]. In clinical trials, an increase in the Ruminococcus family in responders has been reported, while other trials show an increase in specific Ruminococcus subsets in responders (Table 1).

In a study of 132 melanoma patients, Spencer et al. found a significantly higher abundance of Ruminococcaceae in responders to anti-PD-1 therapy compared to non-responders [28]. They also examined the gut microbiome composition in a larger pooled population of 293 melanoma patients, including the previously reported subsets. Most patients were treated with anti-PD-1 therapy, while some received other systemic treatments. Among patients who experienced clinical benefit, complete response (CR), partial response (PR), or stable disease (SD) for more than 6 months, compared to those with no clinical benefit, a significantly higher abundance of Ruminococcus was observed, even after adjusting for age, sex, body mass index, prior treatment, and antibiotic use [28].

In a study by Peng et al. involving 74 patients with various gastrointestinal (GI)-cancers (colorectal $n = 19$, esophagus $n = 14$, gastric $n = 34$, and others $n = 18$), a higher abundance of Ruminococcaceae was found in the stools of responders to anti-PD-1 therapy compared to non-responders [29]. In the total cohort, Ruminococcaceae were the most overrepresented bacteria in the responders compared to non-responders. Within the sub-groups, there were differences in the microbiomes, but different Operational Taxonomic Units (OTUs) of Ruminococcus were consistently overrepresented in responders across all sub-groups [29].

Newsome et al. found that baseline enrichment of Ruminococcus in patients with NSCLC was the taxonomic group most strongly associated with response to PD-1 therapy. Additionally, Akkermansia, Blautia, and Faecalibacterium were enriched in responders [18].

Faecalibacterium Genus

The commensal Faecalibacterium is a genus of the Ruminococcus family and plays a role in breaking down dietary fiber, producing SCFAs [44]. Gopalakrishnan et al. found significant enrichment of both the Faecalibacterium genus and Faecalibacterium prausnitizii in melanoma patients responding to immunotherapy (Table 1) [12] in addition to the previously mentioned Ruminococcaceae. Patients with high levels of Faecalibacterium had longer PFS ($p = 0.03$), and the abundance of Faecalibacterium, Ruminococcaceae, or Clostridialis was correlated with increased levels of circulating effector CD4 + and CD8 + T cells [12].

In a study by Ren et al. involving 41 patients with NSCLC, a significant increase in Faecalibacterium was observed in responders to immunotherapy treatment ($p = 0.000969$). SCFAs were elevated in responders compared to non-responders ($p = 0.0095$) [16].

Eubacterium order/Lachnospiraceae Family

Lachnospiraceae are bacteria that ferment resistant starch and dietary fiber to produce SFCAs [43–45]. Some studies report on the Lachnospiraceae family, others focus on genera, or specific species of bacteria involved in responders. In some studies, the overarching Eubacterium order is more frequently found in responders versus non-responders across several types of cancers (Table 1) [20, 30].

Frankel et al. found that the species Dorea formicogenerans was elevated in responders among melanoma patients treated with pembrolizumab ($p = 0.045$), but not in those treated with ipilimumab, nivolumab or their combination [27].

Hakozaki et al. found that patients with NSCLC treated with antibiotics prior to immunotherapy had lower alpha-diversity and an underrepresentation of Ruminococcaceae and Agathobacter, a bacteria in the Lachnospiraceae family. In patients not treated with antibiotics before immunotherapy there was a correlation between response rate and PFS more than 6 months and the presence of these two types of bacteria [14].

Firmicutes/Bacillota

The bacteria phylum formerly known as Firmicutes was renamed Bacillota in 2021 [46]. Several bacteria within this phylum are correlated with response to immunotherapy in various cancers (Table 1).

In a study by Han et al. involving patients with HER2-negative gastric cancer, significant enrichment of Lactobacillus and two species, L. mucosae, and L. salivarius, was found in responders to immunotherapy or chemo-immunotherapy, not only at baseline but also during treatment [30].

Fang et al. observed in patients with NSCLC that of 32 species enriched in patients achieving a PR as the best response compared to those with SD or PD, 23 belonged to the Clostridium class. Many of these metagenomic species were barely detectable in patients with SD or PD [26].

Actinobacteria

Within the Actinobacteria phylum, certain bacterial families and species have been correlated to response to immunotherapy (Table 1). Zhao et al. found that the Bifidobacterium genus ($p < 0.05$) and the species B. breve were significantly correlated with response and PFS ($p < 0.001$). For patients undergoing chemo-immunotherapy for NSCLC, B. breve has been identified as an independent prognostic factor for PFS ($p < 0.05$) and could potentially serve as a biomarker to predict the efficacy of immuno-chemotherapy in NSCLC patients [47].

Other Bacteria Related to Response to Immunotherapy

There are additionally numerous families, genera, and species of bacteria that have been associated with positive outcomes in cancer patients undergoing checkpoint immunotherapy (Table 1). The bacterium, Prevotella, associated with a high-fiber diet [48], has been reported to correlate with treatment response in some studies [13, 29, 33, 38, 39]. Jin et al. found that in patients with NSCLC, responders to nivolumab treatment had higher baseline levels of Prevotella copri, Alistipes putredinis, and Bifidobacterium longum. During treatment, Prevotella copri remained enriched among responders [13]. Similarly, Pietrzak et al. observed that Prevotella copri was enriched in melanoma patients responding to anti-PD-1, along with Bacteroides uniformis. However, contrary to several other studies [27, 28], they found Faecalibacterium prausnitzii enriched in non-responders [39].

Alistipes is a recently discovered genus of bacteria consisting of 13 species, some of which produce small amounts of SCFAs, including A. putredinis, A. onderdonkii, and A. inops [49]. In a study by Zhu et al. including biliary cancer patients, the genus Alistipes was the most abundant among 20 taxonomic groups significantly associated with better survival in patients treated with anti-PD-1/anti-PD-L1 (OS: 19.3 vs. 10.2 months, $P = 0.032$; PFS: 8.13 vs. 5.23 months, $P = 0.049$) [19].

Other Types of Microbiota

Bacteria are the most studied residents of the gut. However, the gut also hosts other microorganisms such as viruses, fungi, archaea, and single-cell eukaryotes. Recent studies have found that certain species of archaea are more abundant in patients who respond well to immunotherapy or chemo-immunotherapy (Table 1) [17, 30, 40]. This diverse group of organisms needs further investigation to understand their role in cancer treatment response.

Bacterial Diversity

Several clinical trials have found a link between gut bacterial diversity and better outcomes in cancer immunotherapy, such as a correlation between gut bacterial diversity and improved patient outcomes like overall survival (OS), PFS, and response rate (RR) (Table 2).

In a study of 70 patients with NSCLC, Hakozaki et al. found a higher alpha-diversity in patients who had not received prior antibiotic treatment. Among these, those with OS greater than 12 months had a more diverse microbiome than those with OS less than 12 months ($p < 0.05$) [14]. Ren et al. found that in patients with NSCLC, alpha diversity was higher in the group of responders (CR or PR) compared to non-responders (SD or PD) ($p < 0.05$) [16]. In a study of patients with NSCLC treated with nivolumab, Jin et al.

Table 2 Bacterial diversity, bacterial ratios, and combinations of bacteria/metabolites or SCFAs in reviewed studies showing a significant difference at baseline between responders and non-responders. Studies differ in cancer type, size, immunotherapeutic agent, and how response is defined

Gut bacteria	Subtype	Patient group	*N*	Medical cancer treatment	Clinical end-point with positive outcome measure	Investigator	Publication year
Bacterial diversity	alpha-diversity	Melanoma	112	anti-PD-1	RR and PFS	Gopalakrishnan, V[12]	2018
	alpha-diversity	NSCLC	25	Nivolumab	RR	Jin, Y[13]	2019
	alpha-diversity	NSCLC	70	anti-PD-1/PD-L1	OS	Hakozaki, T[14]	2020
	alpha-diversity	RCC	31	Nivolumab or nivolumab + ipilimumab	RR	Salgia, N[15]	2020
	alpha-and beta diversity	NSCLC	41	ICI	RR	Ren, S[16]	2024
	Beta-diversity	NSCLC	63	anti-PD-1	PFS	Song, P[17]	2020
	Beta-diversity	NSCLC	65	ICI or ICI-chemo	RR	Newsome, R[18]	2022
	Beta-diversity	Billiary	88	anti-PD-1/PD-L1	PFS, OS	Zhu, C[19]	2024
	diversity (gene-count)	NSCLC/RCC	78	ICI	RR/PFS	Routy, B[20]	2018
Bacterial ratios	Bacteroidota/firmicutes ratio	Melanoma	64	anti-PD-1	RR	Pietrzak, B[39]	2022
	Prevotella/bacteroides ratio	GI-cancers	74	anti-PD-1/PD-L1	RR	Peng, Z[29]	2020
Bacterial/Metabolite or Bacterial-metabolite combinations		Billiary	88	anti-PD-1/PD-L1	PFS, OS	Zhu, C[19]	2024
SCFA	Butyrate	NSCLC	22	anti-PD-1 + chemo	RR	Zhu, X[50]	2023
	Butyrate producing bacteria	Lung cancer	29	ICI	RR, decrease after initial response	Zeng, Y[51]	2023

observed longer PFS in patients obtaining clinical benefit (PR or SD) compared to patients obtaining progressive disease (PD) as best response, measured at baseline ($p = 0.008$) and during treatment ($p = 0.0301$), according to the Shannon index [13]. Gopalakrishnan et al.. found significantly higher alpha diversity in melanoma patients responding to anti-PD-1 therapy compared to non-responders ($p < 0.01$) [12]. Patients with high diversity had significantly longer PFS compared to those with medium diversity ($p < 0.05$) or low diversity ($p < 0.01$) [12]. In patients with RCC, Salgia et al. observed greater microbiome diversity at baseline, at day 28, and day 79 of treatment in those responding to checkpoint immunotherapy compared to non-responders ($p = 0.001$) [15]. *Zhu et al.* found that in patients with biliary cancer on treatment with anti-PD-1/anti-PD-L1, beta-diversity differed between those who derived durable benefits from the treatment and those who did not [19]. They identified three combinations of bacteria, metabolites, or a mix of both, which could predict treatment outcomes with high accuracy, respectively 89.69%, 86.25%, and 95.94% [19]. It is intriguing to consider why these studies show different bacteria among responders. Could it be due to the different cancer types, geographical differences, varying diets, combination cancer therapies, or different laboratory techniques? Or perhaps the specific type of bacteria is not as important as the metabolites [50] and/or the interactions between different bacteria strains [52].

Metabolome

The metabolome consists of the molecules produced by gut bacteria. Among these are short-chain fatty acids (SCFAs), which are small molecules produced by the gut commensal microbiome when fermenting dietary fiber and phytochemicals. The most common SCFAs are acetate, propionate, and butyrate. SCFAs are important as an energy source for intestinal epithelial cells, but some also enter the bloodstream and act as signaling molecules. They target G-protein-coupled receptors (GPCR) GPCR41, GPCR43, and GPCR109A [53] (Fig. 1). Recently, *Zhu et al.* demonstrated a positive

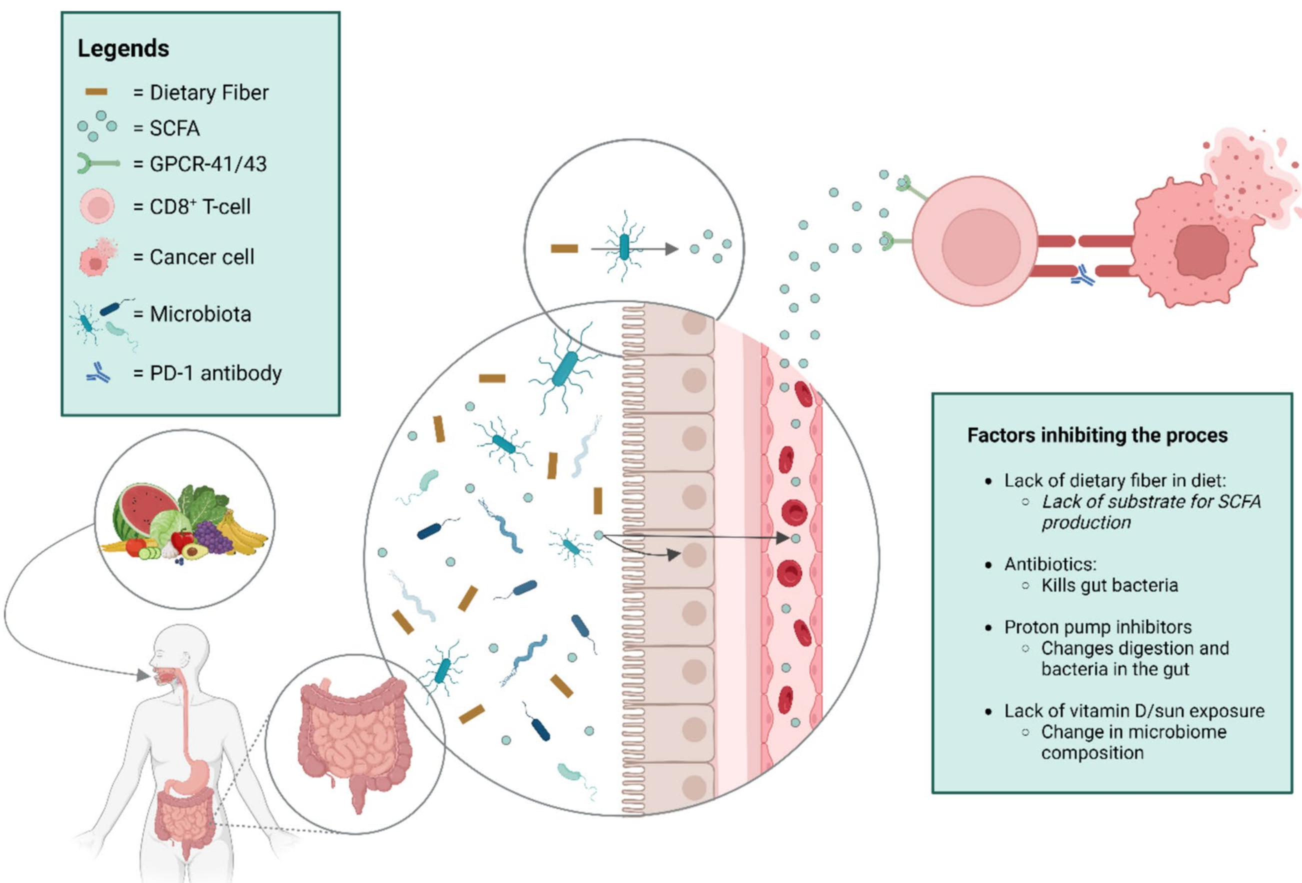

Fig. 1 Following the consumption of a high-fiber diet, bacteria in the gut ferment dietary fiber to short-chain fatty acids (SCFAs). Some of the SCFAs nurture intestinal epithelial cells, and some enter the bloodstream. Here SCFAs can activate DC8 + cytotoxic T-cells to induce cancer cell death by binding to mammalian G protein-coupled receptors (GPCR) 41 and 43. This unique ligand specificity suggests that GPCR41 and GPCR43 may mediate the interaction between the gut microbiome and the human host

correlation between serum butyrate levels and response to anti-PD-1 immunotherapy in patients with NSCLC [50].

Factors that may Positively Impact the Microbiome for Response to ICI Therapy

Understanding that the microbiome impacts the effectiveness of cancer immunotherapy, how can we influence it to improve treatment outcomes? And what should we avoid to reduce its efficacy?

Dietary fiber and Probiotics

Dietary fiber is plant material that human gut enzymes cannot digest [54] but can be fermented by gut bacteria. Spencer et al. studied whether dietary intake of prebiotic fiber and probiotics affect treatment response to checkpoint immunotherapy in melanoma patients. They found that patients consuming more than 20 g of dietary fiber daily before treatment had significantly longer progression-free survival than those consuming less than 20 g. For every 5 g of fiber intake, there was a 30% decrease in the risk of progression or death [28]. Interestingly, the intake of probiotics did not alter PFS or the odds of response to checkpoint immunotherapy in patients with low fiber intake. In patients with high fiber intake, the addition of probiotics had a detrimental effect on the response to treatment, similar to patients with low fiber intake [28].

Even an intake of 20 g of dietary fiber daily, met by only one-third of patients [28], is low compared to recommendations. US guidelines recommend 14 g per 1000 calories consumed, and Nordic guidelines recommend 25–35 g daily depending on calorie intake. These recommendations are based on amounts to prevent constipation or cardiovascular disease, not on current knowledge regarding the requirements of the gut microbiota. Increasing the recommendation to 50 g daily should meet the requirements of the microbiota, but this is 2–3 times the amount consumed today by an average Western person. Achieving this will require extensive education of healthcare professionals and the public [54, 55].

Pietrzak et al. surveyed various factors, including food and medicine intake, in Polish melanoma patients [39]. Certain types of bacteria were related to response to anti-PD-1 therapy and the patient's diet was important. They examined 35 different factors and discovered that consumption of plant foods was positively correlated with a better response to anti-PD-1 treatment, while dairy consumption had the opposite effect.

Additionally, they observed that patients who defecated daily responded better than patients defecating every other day [39]. This could be related to higher plant fiber intake. An unexplained difference in response was found in patients with Rh+/- blood types, which will require further investigation [39]. All other factors investigated did not show significant differences between responders and non-responders [39].

The American Gut project investigated how diet influences gut bacteria diversity by collecting microbiome samples from over 10,000 people. Samples were correlated with lifestyle, health, and disease questionnaires. They compared the microbiomes of people consuming fewer than 10 different plants weekly with those consuming more than 30 different plants weekly. The results showed that the microbiomes of high plant consumers were significantly more diverse. This finding aligns with current knowledge that different strains of bacteria metabolize different types of plant materials, so a more varied plant diet supports a wider variety of bacteria [56].

Mediterranean diet

The Mediterranean diet consists of ingredients native to the countries around the Mediterranean Sea. It includes a variety of plant foods such as vegetables, fruits, nuts, seeds, berries, legumes, herbs, and spices. It also features animal proteins like fish, meat, cheese, and other fermented dairy products from locally raised animals, along with fat from olive oil. This traditional diet also incorporates ancient grains, honey, and wine [57]. These foods provide a naturally high intake of dietary fibers with various molecular structures and different phytochemicals from many types of plants, supporting a wide range of gut bacteria. Two trials in melanoma patients by Spencer et al. [28] and Pietrzak et al. [39]. indicated that a high intake of plant foods and dietary fiber was positively correlated with a better response to immunotherapy. These findings suggest that the Mediterranean diet could improve response rates to immunotherapy. However, more clinical trials are needed to confirm this, especially in patients with other types of cancer and those undergoing combination treatments.

Sun exposure/vitamin D

Vitamin D is unique because it is mostly supplied by sunlight rather than diet. A recent study on cancer patients and mice explored the link between vitamin D, the microbiome, and response to immunotherapy. The data suggested that lower vitamin D availability is associated with weaker immune-mediated control and worse cancer outcomes [58]. In a cohort of almost 1.5 million Danes who had at least one measurement of vitamin D status in 2008–2017, 1008 persons were recorded as having been treated with immunotherapy for various cancers. In this group, vitamin D/vitamin D receptor levels were significantly lower ($p < 0.0001$) in patients who had no response to immunotherapy versus those with exceptional response to immunotherapy. When studying the rate of progression they also found that patients with low levels of vitamin D/ vitamin D receptor levels more often had a rapid progression versus those with standard disease progression ($p = 0.02$). This part of the study did unfortunately not correlate outcomes to the microbiome [58].

In a study of melanoma patients, sufficient vitamin D levels during immunotherapy treatment were correlated with better ORR and PFS. The response rate in the group with low vitamin D levels and not supplemented versus normal baseline levels or a normal level obtained with supplementation was 36.2%, versus 56.0% ($p = 0.01$); progression-free survival was 5.75 and 11.25 months, respectively ($p = 0.03$). Unfortunately, this trial did not investigate the effect on the microbiome [59].

In cancer patients, the direct impact of sun exposure on the microbiome has not been studied. However, a study involving healthy female volunteers from Vancouver, Canada, found that exposure to artificial ultraviolet-B (UVB) light during winter increased serum vitamin D levels and altered the gut microbiome in participants not taking vitamin D supplements. Bacteria like Lachnospiraceae and Ruminococcus, which positively impact immunotherapy response, were low in patients not taking vitamin D supplements but increased after UVB exposure. Additionally, both alpha and beta diversity of the microbiome increased after UVB exposure [60].

Vitamin D levels are generally low in many parts of the world, especially during winter. Supplementing with vitamin D can help compensate for the lack of sun exposure [60].

Factors that may Negatively Impact the Microbiome in Response to ICI Therapy

Pharmacomicrobiomics is the science of interactions between medicines and the microbiome. While these interactions can be bidirectional, this review focuses on how medicines commonly prescribed to cancer patients, other than cancer drugs themselves, can affect the microbiome.

A single-center retrospective study involving 635 cancer patients treated with immunotherapy investigated whether different co-medications affected their response to treatment, either as single agents or in combination. They found that antibiotics, proton pump inhibitors (PPIs), and corticosteroids (at doses over 10 mg), taken one month before or after starting immunotherapy, had a detrimental effect on immunotherapy efficacy. This was also true for morphine and psychotropic medicines. However, other commonly prescribed medicines such as metformin, other oral anti-diabetic medicines, ACE inhibitors, angiotensin II antagonists, statins, and aspirin did not show the same negative effect. The data were not correlated with microbiome measurements, so it is unclear whether these effects are due to changes in the microbiome or other mechanisms [61].

Antibiotics

Several investigators have found that using antibiotics during or just before starting PD-1 immunotherapy leads to worse outcomes compared to patients not treated with antibiotics (Fig. 2). Routy et al. discovered that the composition of the gut microbiome was crucial and that antibiotics around the time of starting immune checkpoint inhibitors in patients with NSCLC or RCC reduced the response to therapy [20]. Spencer et al. found similar results in melanoma patients,

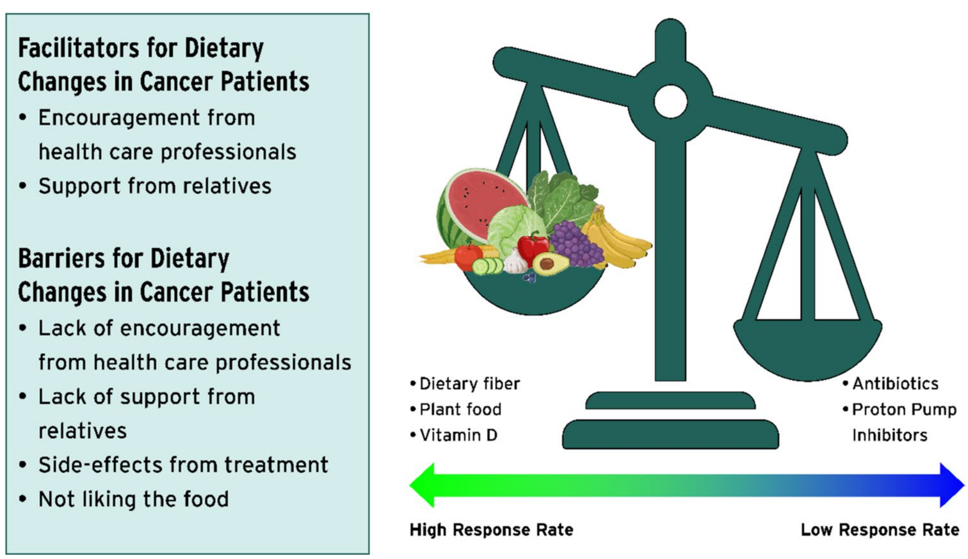

Fig. 2 **Right panel** Summary of factors with strong evidence for positively or negatively affecting immunotherapy treatment outcomes through the microbiome. **Left panel** Factors that help or hinder dietary changes during cancer treatment

even those on a high-fiber diet [28]. In a study of 69 NSCLC patients Hamada et al. found that those who received antibiotics 21 days before or after starting anti-PD-1 treatment ($N = 18$) had significantly worse outcomes than those not treated with antibiotics ($N = 51$); overall response rate ($p = 0.005$), OS ($p = 0.022$) and PFS ($p < 0.001$) were all negatively affected [62]. The study also showed that antibiotics given more than 21 days after starting anti-PD-1 treatment did not affect treatment efficacy [62].

Proton pump Inhibitors

Cantarelli et al. examined the impact of proton pump inhibitors (PPI) on cancer patients undergoing immunotherapy. In a single-center retrospective cohort of 302 patients, more than 75% used PPIs either before or during cancer therapy. They found that PFS and OS were significantly lower in the PPI-treated group (Fig. 2) [63]. The study suggested a treatment window where starting PPIs four weeks after initiating immunotherapy might mitigate their negative effects [63]. Similar results were observed in a study of advanced NSCLC patients where PPI use was associated with lower PFS and OS. However, adding Clostridium butyricum to the treatment regimen reversed the negative effect of PPI usage [64]. Not all studies show the same results. For instance, a study by Peng et al. on 233 cancer patients found no difference between PPI users and non-PPI users [65], and the same was true for Hamada´s study on 69 patients with NSCLC [62]. To clarify the impact of PPIs, Lopes et al. conducted a meta-analysis of 41 studies including 20,042 patients. They concluded that PPI use negatively affects both OS and PFS in patients receiving immunotherapy [66].

Discussion/Feasibility of Mediterranean diet in real-world Patients

It can be challenging to make diet and lifestyle changes when a patient is stressed due to a new diagnosis or relapse. However, many patients want to improve their lifestyle. A systematic review by Hoedjes et al. of 30 studies on dietary changes in cancer patients, revealed that support from family, friends, and healthcare professionals was a key factor in making changes. Barriers included not understanding the importance of dietary changes and not receiving information and advice from healthcare professionals (Fig. 2). Patients saw lifestyle changes as a positive way to gain control [67].

In a recent review of the implementation of Mediterranean-style dietary intervention in cancer patients, McHugh et al.. investigated the methods, feasibility, and primary efficacy of such interventions [68]. The studies used dieticians or other hospital personnel to educate patients in the intervention groups. In 11 of 13 studies, the completion rates were 80% or higher. In four of five clinical trials, with patients on active cancer treatment during the intervention the completion rate was 80% or higher. These results indicate that dietary interventions are feasible for patients undergoing cancer treatment [68].

The Mediterranean diet includes a wide variety of foods, making it a flexible option for many patients. It is not restrictive, and primarily limit processed foods. This flexibility was a key reason why Harvey et al. chose this diet for a randomized clinical trial involving cancer patients. The study measured fatigue during chemotherapy and included a qualitative sub-study, identifying facilitators and barriers [69]. Patients reported that the diet gave them a sense of control and empowerment. They enjoyed learning about nutrition, trying new foods, feeling in control, setting goals, doing something constructive to aid their treatment, and having a positive focus. Even patients in the control group started thinking more about their eating habits. Barriers included chemotherapy side effects and food preferences [69].

These findings indicate that patients are motivated to change their diet, and encouragement from their healthcare team can be a significant motivating factor.

Future Perspective

What can we expect from the future? It seems that the microbiome plays a role in cancer immunotherapy, and the mechanisms behind are being uncovered. It appears that the microbiome can be used as a predictive marker of response. To maximize the efficacy of immunotherapy and to possibly benefit more patients, it will be necessary to test whether manipulating the microbiome composition can increase response rates.

Conclusions

The microbiome and its metabolites seem to play a role in the response to cancer checkpoint immunotherapy. Certain bacteria and metabolites can predict treatment response, especially *Akkermansia mucinifila*, *Ruminococcaceae*, *Faecalibacterium*, and *Lachnospiraceae*; this knowledge may be used to improve outcomes for future patients. The Mediterranean diet is a promising option for enhancing the effect of checkpoint immunotherapy, providing many of the components needed for a diverse microbiome rich in butyrate-producing bacteria. Additionally, the Mediterranean diet is non-restrictive, palatable, affordable, accessible, and patients are often willing to make the changes to their diet, if encouraged by health care professionals.

Factors suspected to decrease the response to therapy should be minimized, except as clinically indicated. This includes co-medications like antibiotics and PPIs before and during initiation of therapy.

Prospective clinical trials in different cancer types, disease stages, and medical treatments, including combination treatments, are needed to determine if diet can be used as part of a treatment regimen and not just as a predictive marker of response, as current studies have shown.

Key References

- Ren, S., et al., Gut microbiome affects the response to immunotherapy in non-small cell lung cancer. Thorac Cancer, 2024.
  - Clinical trial showing correlation between bacterial diversity, Faecalibacterium and response rate to cancer immunotherapy but also to the levels of SCFA's in faeces of patients.
- Spencer, C.N., et al., Dietary fiber and probiotics influence the gut microbiome and melanoma immunotherapy response. Science, 2021. 374(6575): p. 1632–1640.
  - Clinical study correlating dietary fiber positively and probiotics negatively to cancer outcomes in melanoma patients treated with immunotherapy.
- Pietrzak, B., et al., A Clinical Outcome of the Anti-PD-1 Therapy of Melanoma in Polish Patients Is Mediated by Population-Specific Gut Microbiome Composition. Cancers (Basel), 2022. 14(21).
  - Clinical trial investigating connection between microbiome and outcome of immunotherapy in melanoma patietns, but also investigating associations to diet, medicine, and lifestyle factors. Plant food intake is positively correlated to outcome.
- Zhu, X., et al., Microbial metabolite butyrate promotes anti-PD-1 antitumor efficacy by modulating T cell receptor signaling of cytotoxic CD8 T cell. Gut Microbes, 2023. 15(2): p. 2,249,143.
  - Clinical study in NSCLC patients showing correlation between serum level of SCFA's and response to immunotherapy.
- Giampazolias, E., et al., Vitamin D regulates microbiome-dependent cancer immunity. Science, 2024. 384(6694): p. 428–437.
  - Study in patients finding a correlation between vitamin D and response to immunotherapy and in a national cohort of 1.5 million they discover a link between low vitamin D and the risk for developing cancer.
- Galus, Ł., et al., Vitamin D supplementation increases objective response rate and prolongs progression-free time in patients with advanced melanoma undergoing anti-PD-1 therapy. Cancer, 2023. 129(13): p. 2047–2055.
  - Clinical trial putting emphazis on the importance of vitamin D in cancer immunotherapy. Unfortunately this trial does not include microbiome measurements.
- Cantarelli, L., et al., Effect of Concomitant Use of Proton Pump Inhibitors on Immunotherapy Clinical Response in Advanced Cancer Patients: Real-Life Setting. J Immunother, 2023.
  - Clinical trail showing that late use of PPI's do not affect outcomes of immunotherapy in cancer patients. Whereas chronic, recent or concomitant use negatively affects outcomes.
- Lopes, S., et al., Do proton pump inhibitors alter the response to immune checkpoint inhibitors in cancer patients? A meta-analysis. Front Immunol, 2023. 14: p. 1,070,076.
  - Review of PPI use in 41 clinical trials with 20,042 cancer patients treated with immunotherapy. Study concludes that PPI's can negatively affect outcomes for patients.
- McHugh, A., et al., Mediterranean-style dietary interventions in adults with cancer: a systematic review of the methodological approaches, feasibility, and preliminary efficacy. Eur J Clin Nutr, 2024. 78(6): p. 463–476.
  - Review highlighting that dietary interventions in adult cancer patients are feasible and safe. Results from 15 studies, 5 on patients on active treatment.
- Harvey, B.I., S.M. Youngblood, and A.S. Kleckner, Barriers and Facilitators to Adherence to a Mediterranean Diet Intervention during Chemotherapy Treatment: A Qualitative Analysis. Nutr Cancer, 2023. 75(5): p. 1349–1360.
  - Qualitative clinical trial showing that patients benefit from change to Mediterranean Diet. Feelings of empowerment and control was dominating. Barriers were dislike of food and side effects from treatment making eating difficult.

Abbreviations CD: Cluster of Differentiation; CR: Complete Response; CRISPR: Clustered Regularly Interspaced Short Palindromic Repeats; CTLA-4: Cytotoxic T-lymphocyte associated protein 4; FMT: Fecal Microbiota Transplantation; GI: Gastro-Intestinal; GPCR: G-Protein Coupled Receptor; HCC: Hepatocellular Carcinoma; HER2: Human Epidermal Growth Factor Receptor 2; ICI: Immune Checkpoint Inhibitor; mCRP: Metastatic Castration Resistant Prostate Cancer; mRCC: Metastatic Renal Cell Carcinoma; NNS: Non-Nutritive Sweetener; NSCLC: Non-Small Cell Lung Cancer; OS: Overall Survival; OTU: Operational Taxonomic Unit; PD: Progressive Disease; PD-1: Programmed Death-1; PD-L1: Programmed Death-Ligand 1;

PFS: Progression Free Survival; PPI: Proton Pump Inhibitor; PR: Partial Response; RCC: Renal Cell Carcinoma; RECIST: Response Evaluation Criteria in Solid Tumors; RR: Response Rate; SCFA: Short-Chain Fatty Acid; SD: Stable Disease; TKI: Thyrosine kinase inhibitor; UVB: Ultra Violet B

Acknowledgements This study was supported financially by the Danish Cancer Society, Esbjerg, and the Southwest-Southern Denmark Cancer Fund.

Author Contributions LG and FD wrote the main manuscript text. LG prepared Tables 1 and 2 and Figures 1 and 2. All authors critically reviewed and commented on the manuscript.

Data Availability No datasets were generated or analysed during the current study.

Declarations

Competing Interests The authors do not have any potential conflicts of interest to disclose.

Human and Animal Rights and Informed Conse As this was a review paper, no human or animal research was conducted by the authors.

References

1. Schwabe RF, Jobin C. The microbiome and cancer. Nat Rev Cancer. 2013;13(11):800–12.
2. Baedke J, Fábregas-Tejeda A, Nieves A, Delgado. The holobiont concept before Margulis. J Exp Zool B Mol Dev Evol. 2020;334(3):149–55.
3. Sender R, Fuchs S, Milo R. Revised estimates for the Number of Human and Bacteria Cells in the body. PLoS Biol. 2016;14(8):e1002533.
4. Qin J, et al. A human gut microbial gene catalogue established by metagenomic sequencing. Nature. 2010;464(7285):59–65.
5. Mégraud F. A humble bacterium sweeps this year's Nobel Prize. Cell. 2005;123(6):975–6.
6. Hanahan D. Hallmarks of Cancer: New dimensions. Cancer Discov. 2022;12(1):31–46.
7. Pleguezuelos-Manzano C, et al. Mutational signature in colorectal cancer caused by genotoxic pks(+) E. coli. Nature. 2020;580(7802):269–73.
8. Nejman D, et al. The human tumor microbiome is composed of tumor type-specific intracellular bacteria. Science. 2020;368(6494):973–80.
9. Elkrief A, et al. The negative impact of antibiotics on outcomes in cancer patients treated with immunotherapy: a new independent prognostic factor? Ann Oncol. 2019;30(10):1572–9.
10. Routy B, et al. Fecal microbiota transplantation plus anti-PD-1 immunotherapy in advanced melanoma: a phase I trial. Nat Med. 2023;29(8):2121–32.
11. Fan Y, Pedersen O. Gut microbiota in human metabolic health and disease. Nat Rev Microbiol. 2021;19(1):55–71.
12. Gopalakrishnan V, et al. Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. Science. 2018;359(6371):97–103.
13. Jin Y, et al. The diversity of gut microbiome is Associated with favorable responses to Anti-programmed Death 1 immunotherapy in Chinese patients with NSCLC. J Thorac Oncol. 2019;14(8):1378–89.
14. Hakozaki T, et al. The Gut Microbiome Associates with Immune Checkpoint Inhibition outcomes in patients with Advanced Non-small Cell Lung Cancer. Cancer Immunol Res. 2020;8(10):1243–50.
15. Salgia NJ, et al. Stool microbiome profiling of patients with metastatic renal cell carcinoma receiving Anti-PD-1 Immune Checkpoint inhibitors. Eur Urol. 2020;78(4):498–502.
16. Ren S, Feng L, Liu H, Mao Y, Yu Z. Gut microbiome affects the response to immunotherapy in non-small cell lung cancer. Thoracic Cancer. 2024May;15(14):1149–63.
17. Song P, et al. Relationship between intestinal flora structure and metabolite analysis and immunotherapy efficacy in Chinese NSCLC patients. Thorac Cancer. 2020;11(6):1621–32.
18. Newsome RC, et al. Interaction of bacterial genera associated with therapeutic response to immune checkpoint PD-1 blockade in a United States cohort. Genome Med. 2022;14(1):35.
19. Zhu C, et al. Gut microbiota and metabolites signatures of clinical response in anti-PD-1/PD-L1 based immunotherapy of biliary tract cancer. Biomark Res. 2024;12(1):56.
20. Routy B, et al. Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. Science. 2018;359(6371):91–7.
21. Zheng Y, Wang T, Tu X, Huang Y, Zhang H, Tan DI, Jiang W, Cai S, Zhao P, Song R, Li P. Gut microbiome affects the response to anti-PD-1 immunotherapy in patients with hepatocellular carcinoma. Journal for immunotherapy of cancer. 2019Dec;7:1–7.
22. Derosa L, et al. Gut Bacteria composition drives primary resistance to Cancer Immunotherapy in Renal Cell Carcinoma patients. Eur Urol. 2020;78(2):195–206.
23. He D, et al. Response to PD-1-Based Immunotherapy for Non-small Cell Lung Cancer altered by gut microbiota. Oncol Therapy. 2021;9(2):647–57.
24. Yin H, et al. The commensal consortium of the gut microbiome is associated with favorable responses to anti-programmed death protein 1 (PD-1) therapy in thoracic neoplasms. Cancer Biol Med. 2021;18(4):1040–52.
25. Grenda A et al. Presence of Akkermansiaceae in gut microbiome and immunotherapy effectiveness in patients with advanced non-small cell lung cancer. AMB Express. 2022 Jul 6;12(1).
26. Fang C, et al. Distinct functional metagenomic markers predict the responsiveness to Anti-PD-1 therapy in Chinese non-small cell lung cancer patients. Front Oncol. 2022 Apr 21;12:837525.
27. Frankel AE, et al. Metagenomic shotgun sequencing and unbiased metabolomic profiling identify specific human gut microbiota and metabolites Associated with Immune Checkpoint Therapy Efficacy in Melanoma patients. Neoplasia. 2017;19(10):848–55.

28. Spencer CN, et al. Dietary fiber and probiotics influence the gut microbiome and melanoma immunotherapy response. Science. 2021;374(6575):1632–40.
29. Peng Z, et al. The gut microbiome is Associated with clinical response to Anti-PD-1/PD-L1 immunotherapy in gastrointestinal Cancer. Cancer Immunol Res. 2020;8(10):1251–61.
30. Han Z, et al. The gut microbiome affects response of treatments in HER2-negative advanced gastric cancer. Clin Transl Med. 2023;13(7):e1312.
31. Mao J, et al. Gut microbiome is associated with the clinical response to anti-PD-1 based immunotherapy in hepatobiliary cancers. J Immunother Cancer. 2021 Dec;9(12).
32. McCulloch JA, et al. Intestinal microbiota signatures of clinical response and immune-related adverse events in melanoma patients treated with anti-PD-1. Nat Med. 2022;28(3):545–56.
33. Zhang M, et al. A gut microbiota rheostat forecasts responsiveness to PD-L1 and VEGF blockade in mesothelioma. Nat Commun. 2024 Aug 21;15(1):7187.
34. Zhao H, et al. Bifidobacterium breve predicts the efficacy of anti-PD-1 immunotherapy combined with chemotherapy in Chinese NSCLC patients. Cancer Med. 2023;12(5):6325–36.
35. Matson V, et al. The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients. Science. 2018;359(6371):104–8.
36. Wind TT, et al. Gut microbial species and metabolic pathways associated with response to treatment with immune checkpoint inhibitors in metastatic melanoma. Melanoma Res. 2020;30(3):235–46.
37. Peiffer LB, et al. Composition of gastrointestinal microbiota in association with treatment response in individuals with metastatic castrate resistant prostate cancer progressing on enzalutamide and initiating treatment with anti-PD-1 (pembrolizumab). Neoplasia. 2022;32:100822.
38. Xu L, et al. Crosstalk between the gut microbiome and clinical response in locally advanced thoracic esophageal squamous cell carcinoma during neoadjuvant camrelizumab and chemotherapy. Ann Transl Med. 2022;10(6):325.
39. Pietrzak B, et al. A clinical outcome of the Anti-PD-1 therapy of Melanoma in Polish patients is mediated by Population-Specific gut Microbiome Composition. Cancers (Basel). 2022 Oct 31;14(21):5369.
40. Cheng X, et al. Composition of the Gut Microbiota Associated with the response to Immunotherapy in Advanced Cancer patients: a Chinese real-world pilot study. J Clin Med. 2022 Sept 18;11(18):5479.
41. Belzer C, de Vos WM. Microbes inside–from diversity to function: the case of Akkermansia. ISME J. 2012;6(8):1449–58.
42. Henning SM, et al. Pomegranate ellagitannins stimulate the growth of Akkermansia muciniphila in vivo. Anaerobe. 2017 Feb;43:56–60.
43. Abell GCJ, et al. Phylotypes related to Ruminococcus bromii are abundant in the large bowel of humans and increase in response to a diet high in resistant starch. FEMS Microbiol Ecol. 2008;66(3):505–15.
44. Lopez-Siles M, et al. Faecalibacterium prausnitzii: from microbiology to diagnostics and prognostics. ISME J. 2017;11(4):841–52.
45. Costantini L, et al. Impact of Omega-3 fatty acids on the gut microbiota. Int J Mol Sci. 2017 Dec 7;18(12):2645.
46. Oren A, Garrity GM. Valid publication of the names of forty-two phyla of prokaryotes. Int J Syst Evol Microbiol. 2021 Oct;71(10).
47. Zhao M, et al. Gut microbiota: a potential target for improved cancer therapy. J Cancer Res Clin Oncol. 2023;149(1):541–52.
48. Wu GD, et al. Linking long-term dietary patterns with gut microbial enterotypes. Science. 2011 Oct 7;334(6052):105–8.
49. Parker BJ, et al. The Genus Alistipes: gut Bacteria with emerging implications to inflammation, Cancer, and Mental Health. Front Immunol. 2020;11:906.
50. Zhu X, et al. Microbial metabolite butyrate promotes anti-PD-1 antitumor efficacy by modulating T cell receptor signaling of cytotoxic CD8 T cell. Gut Microbes. 2023 Dec;15(2):2249143.
51. Zeng Y, et al. Dynamic gut microbiota changes in patients with advanced malignancies experiencing secondary resistance to immune checkpoint inhibitors and immune-related adverse events. Front Oncol. 2023;13:1144534.
52. Tanoue T, et al. A defined commensal consortium elicits CD8 T cells and anti-cancer immunity. Nature. 2019;565(7741):600–5.
53. Tan J, et al. The role of short-chain fatty acids in health and disease. Adv Immunol. 2014;121:91–119.
54. McKeown NM, et al. Fibre intake for optimal health: how can healthcare professionals support people to reach dietary recommendations? BMJ. 2022;378:e054370.
55. O'Keefe SJ. The association between dietary fibre deficiency and high-income lifestyle-associated diseases: Burkitt's hypothesis revisited. Lancet Gastroenterol Hepatol. 2019;4(12):984–96.
56. McDonald D, et al. American gut: an Open platform for Citizen Science Microbiome Research. mSystems. 2018;3(3):e00031–18.
57. Kiani AK, et al. Modern vision of the Mediterranean diet. J Prev Med Hyg. 2022;63(2 Suppl 3):E36–43.
58. Giampazolias E, et al. Vitamin D regulates microbiome-dependent cancer immunity. Science. 2024;384(6694):428–37.
59. Galus Ł, et al. Vitamin D supplementation increases objective response rate and prolongs progression-free time in patients with advanced melanoma undergoing anti-PD-1 therapy. Cancer. 2023;129(13):2047–55.
60. Bosman ES, et al. Skin exposure to narrow Band Ultraviolet (UVB) light modulates the human intestinal microbiome. Front Microbiol. 2019;10:2410.
61. Kostine M, et al. Baseline co-medications may alter the antitumoural effect of checkpoint inhibitors as well as the risk of immune-related adverse events. Eur J Cancer. 2021;157:474–84.
62. Hamada K, et al. Antibiotic usage reduced overall survival by over 70% in non-small cell lung Cancer patients on Anti-PD-1 immunotherapy. Anticancer Res. 2021;41(10):4985–93.
63. Cantarelli L, et al. Effect of concomitant use of Proton Pump inhibitors on Immunotherapy Clinical response in Advanced Cancer patients: real-life setting. J Immunother. 2023 Nov 6.
64. Tomita Y, et al. Clostridium butyricum therapy restores the decreased efficacy of immune checkpoint blockade in lung cancer patients receiving proton pump inhibitors. Oncoimmunology. 2022;11(1):2081010.
65. Peng K, et al. Impact of Proton Pump inhibitor use on the effectiveness of Immune checkpoint inhibitors in Advanced Cancer patients. Ann Pharmacother. 2022;56(4):377–86.
66. Lopes S, et al. Do proton pump inhibitors alter the response to immune checkpoint inhibitors in cancer patients? A meta-analysis. Front Immunol. 2023;14:1070076.
67. Hoedjes M, Nijman I, Hinnen C. Psychosocial determinants of Lifestyle Change after a Cancer diagnosis: a systematic review of the literature. Cancers. 2022;14(8):2026.
68. McHugh A, et al. Mediterranean-style dietary interventions in adults with cancer: a systematic review of the methodological approaches, feasibility, and preliminary efficacy. Eur J Clin Nutr. 2024;78(6):463–76.
69. Harvey BI, Youngblood SM, Kleckner AS. Barriers and facilitators to adherence to a Mediterranean diet intervention during chemotherapy treatment: A qualitative analysis. Nutr Cancer. 2023;75(5):1349–60.