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MINI-REVIEW



Gut microbiota and immunotherapy of renal cell carcinoma

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ABSTRACT

The gut microbiome has recently been proposed as a key player in cancer development and progression. Several studies have reported that the composition of the gut microbiome plays a role in the response to immune checkpoint inhibitors (ICIs). The gut microbiome modulation has been investigated as a potential therapeutic strategy for cancer, mainly in patients undergoing therapy with ICIs. In particular, modulation through probiotics, FMT or other microbiome-related approaches have proven effective to improve the response to ICIs. In this review, we examine the role of the gut microbiome in enhancing clinical responses to ICIs in the treatment of renal cancer.

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Introduction

The human gut microbiome is an ecological entity of about 100 trillion microorganisms that includes bacteria, yeast, viruses and parasites.^{1–4} At birth, the human gut is poorly colonized by bacteria, but gets rapidly colonized by the microbiome of the mother and environment. The type of delivery, vaginal or cesarean, plays a major role in shaping the microbiome of the newborn.⁴ The composition of the healthy gut microbiome is dominated about 90% from the phyla *Firmicutes* and *Bacteroidetes*.⁵ The phylum of *Firmicutes* includes several genera involved in human health, the most common (up to 95%) are *Lactobacillus*, *Bacillus*, *Enterococcus*, *Ruminococcus* and *Clostridium*.⁵ Moreover, it is important to report that the microbiome colonizes the whole gastrointestinal tract, and the composition is quantitatively and qualitatively different in various areas of it for example, the gastric microbiome differs significantly from the intestinal microbiota.^{6,7}

The gut microbiome plays key roles for human health, including a 'shield effect' from pathogenic microorganisms, maintaining the integrity of gut barrier, shaping and maturation of the immune system, regulation of human metabolism, nutrients and drug absorption.^{8–14} The definition of the 'healthy microbiome' is one of the main challenges of researchers who deal with this topic. The alpha diversity of the gut microbiome, an ecological concept that refers to the number and distribution of different species, appears to be a reliable marker of health.¹ A progressive increase in diversity and stability of the gut microbiome can be clearly observed within the first years of life, reflecting the dynamics of the developing intestinal ecosystem in relation to several disturbances.¹⁵

Moreover, early disruption of the gut microbiome has been associated with several chronic diseases in infants (such as allergy or asthma),¹⁶ or even linked with several autoimmune and metabolic disorders that share a considerable alteration of the gut microbiome composition compared to matched control patients¹³ (as has been reported for celiac disease or diabetes).^{17,18}

Furthermore, increasing evidence suggests that an imbalance of the gut microbiome homeostasis is closely related to the occurrence and development of cancer.¹⁹ Interestingly, in recent years, new frontiers are emerging. The microbiome and – particular – the “polymorphic microbes” have been characterized as an emerging hallmark of cancer.^{20,21} More specifically, the gut microbiome composition may reflect direct carcinogenic activity, or the gut microbiome of patients may influence the host immune responses against cancer cells, mediate a protective effect for cancer development and progression, and – finally – modulate the response to anti-cancer therapies.¹⁹ Additionally, the microbiome is involved in shaping the antitumor immune response.²⁰ Several studies have clarified the intrinsic relationship between microbiome and cancer,²² and consequently the microbiome can be considered as a fundamental actor in cancer development and as modifier of therapeutic efficacy and safety.^{23,24}

Due to recent research, the role of the gut microbiome in tumor immune regulation – and the interplay between microbiome and immune checkpoint proteins, such as programmed death 1 (PD-1) and its ligand 1 (PD-L1), and with cytotoxic T-lymphocyte antigen-4 (CTLA-4) – has been widely

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recognized (described in the next paragraph). This topic represents a new frontier, especially for those cancers for which immunotherapy is indicated as a first-line treatment, such as metastatic renal cell carcinoma (mRCC).²⁵ This review aims to describe the role of the microbiome in the development and progression of RCC and in modulating the efficacy of ICIs treatment.

Renal cell carcinoma: epidemiology, risk factors and treatment

Renal cell carcinoma (RCC) includes a heterogeneous group of cancers derived from renal tubular epithelial cells.²⁶ The major subtypes are papillary RCC, chromophobe RCC and clear cell RCC, which accounts for approximately 80% of all RCCs.^{27–29} RCC is among the ten most common cancers worldwide, together with breast, pulmonary, colorectal cancer (CRC) and melanoma, with an estimated 79,000 new cases per year.^{30–32} As reported by SEER database in the US, the median age of patients with RCC was 64 years with a near normal distribution,³⁰ it is more frequent in males (RCC accounts for 5% of all adult malignancies in male versus only 3% in female)^{30,31} The most common risk factors related to the development of RCC include excess body weight, cigarette smoking and hypertension.³² RCC is also associated with other specific medical condition, such as chronic kidney disease, loss of glomerular filtration capacity requiring hemodialysis, kidney transplantation, acquired kidney cystic disease, previous RCC diagnosis and diabetes mellitus.³²

Approximately one-third of patients with RCC have metastatic disease at diagnosis, with a high mortality and an approximately 5-year relative survival rate of 14%.^{30,32–35,36}

Patients with localized RCC can be treated with surgical resection or loco-regional treatments (with or without adjuvant therapy (e.g. pembrolizumab)),³⁷ while patients with advanced stage or high risk of progression may benefit from first-line systemic therapy if surgery is not feasible, as reported by current guidelines,^{27,38} in particular, there was great hope in the improvement of the prognosis after the introduction of immunotherapy, which acts on precise molecular targets typical of this disease.

Indeed, clear cell RCC is also closely associated with a loss-of-function mutation in the von Hippel – Lindau (VHL) gene.³⁹ Loss of the VHL gene leads to the upregulation of hypoxia-inducible factor 2 α (HIF-2 α) and resultant overexpression of hypoxia-inducible genes, such as vascular endothelial growth factor (VEGF), platelet-derived growth factor- β (PDGF- β) and transforming growth factor- α (TGF- α), which are involved in tumorigenesis and the progression of clear cell RCC.^{40,41}

Therefore, targeting angiogenesis was hypothesized to be especially important in clear cell RCC treatment. Several clinical trials have shown that angiogenesis-targeted agents, such as sunitinib, pazopanib, bevacizumab, axitinib, cabozantinib, sorafenib and lenvatinib; furthermore, FDA recently approved Belzutifan for the treatment of VHL-linked RCC; in fact, clinical study has provided significant but not durable clinical benefits in clear cell RCC patients.^{42–47}

Moreover, RCC is influenced by immune modulation, as evidenced by its history of partial or complete response to high-dose interleukin-2.⁴⁸ For this reason, recently immune checkpoint inhibitors (ICIs) and combination strategies have changed the landscape of therapies for mRCC.^{49–52} Immunotherapy targets are immune checkpoint proteins – such as PD-1, PD-L1 and CTLA-4 – that are often overexpressed by immune cells and/or tumor cells. The interaction between immune checkpoint proteins and these molecules leads to downregulation of antigen-specific T-cells mechanisms of programmed death (e.g. apoptosis), reduction in self-tolerance by suppression of T cell inflammatory activity and induced activation of T-cells that trigger an inflammatory response against cancer cells.⁵³

The relationship between gut microbiota and immunotherapy

The gut microbiome could be considered a ‘super organism,’ with a large amount of unique functions.⁵⁴ Among these, the gut microbiome plays a fundamental role in the development of the innate immune system.^{55,56}

A considerable range of gut bacteria are involved in the gut immune response, especially *Bacteroides fragilis*, *Clostridia*, and *Lactobacillus*. *Prevotella* are able to induce Th17 cell-related cytokines, such as IL-6 and IL-23; consequently, the increase in *Prevotella* abundance is associated with the intensification of mucosal inflammation mediated by T helper type 17.⁵⁷ *Lactobacillus* and *Bifidobacteria* play a crucial role in shaping of proinflammatory Th17 lymphocytes, and they also induce tolerogenic dendritic cells and T regulatory lymphocytes (Tregs), involved in the regulation of immune response, whereas *Clostridium* cluster IV and XIVa, as well as *Bacteroides*, are involved in Th1 and Th17 immune responses.⁵⁸

Consequently, the microbiome can be considered as a regulator of the immune response. Therefore, in recent years, the scientific community has turned its attention toward the interaction between the microbiome and immunotherapy, with an interest in enhancing the clinical response to ICIs.⁵⁹ This close relationship was demonstrated first in animal models. In 2015, Vétizou et al.^{60,61} showed that antibiotic-treated or germ-free mice respond poorly to anti-CTLA4 therapy. They also demonstrated that the treatment of microbiota-depleted mice with either *Bacteroides thetaiotaomicron* or *Bacteroides fragilis* restores the anti-CTLA4 response by inducing dendritic cell maturation in tumors and a Th1 response.⁶⁰ Furthermore, a preclinical study reported that in mice with melanoma treated with anti-PD1 therapy, the concomitant administration of *Bifidobacterium longum* and *Bifidobacterium breve* resulted in increased response to therapy.⁶²

Furthermore, the association between the composition of the fecal microbiota and the response to anti-PD1 therapy is well established.⁶³ However, more limited data are available regarding the relationship between the microbiome and promoting anti-CTLA4 therapy clinical efficacy.⁶⁰

More specifically, a favorable outcome following anti PD 1 treatment was reported for patients with metastatic melanoma

if their fecal microbiome demonstrated a higher abundance of key gut bacterial species belonging to Actinobacteria (Bifidobacteriaceae spp. and Coriobacteriaceae spp.) and Firmicutes (Ruminococcaceae spp. and Lachnospiraceae spp.).⁶⁴ In a recent prospective study of 69 patients, Derosa et al. showed that in mRCC patients treated with nivolumab, higher response rate was associated with an increase of *Bacteroides salyersiae*, *Akkermansia muciniphila* and *Eubacterium siraeum*, and a lower abundance of *Clostridium clostridioforme* and *C. hathewayi* in the fecal microbiota.⁶⁵

The role of *Akkermansia muciniphila* is controversial. Currently, available data suggest a possible bimodal effect of these bacterial species upon the anti-PD1 therapy response. First, certain studies reported that *Akkermansia muciniphila* may play an antitumor role in anti-PD1 therapy in patients with lung cancer, RCC or hepatocellular carcinoma.^{63,66,67} Conversely, Derosa et al. found that higher fecal abundance of *Akkermansia muciniphila* induced by antibiotics was associated with resistance to anti-PD1 therapy in patients with advanced NSCLC.⁶⁸ Finally, in a cohort study of patients with advanced melanoma, a higher microbiota abundance of *Faecalibacterium prausnitzii*, *Bacteroides thetaiotaomicron*, *Dorea formicogenerans* and *Holdemania filiformis* were associated with better response to nivolumab or pembrolizumab.⁶⁹

Overall, clinical studies have reported gut microbial signatures that are not always concordant, which still makes it difficult to understand the pathophysiological mechanisms associated with these. For this reason, the increased knowledge from metabolomic and functional studies may allow to better understand the correlation between microbiome and response to ICIs, which to date is supported by pioneering clinical studies described below.

Improving immunotherapy efficacy by the modulation of gut microbiota

Immunotherapy has revolutionized cancer treatment, proving highly effective in epithelial cancers (e.g. melanoma). Unfortunately, however, despite an initial response, some patients develop resistance to anti-cancer treatment, and an ever-growing body of evidence suggests that the microbiota may play a role in this mechanism of resistance.⁷⁰

In consideration of this hypothesis, approaches based on the modulation of the microbiota have been tested with the aim of improving the efficacy of immunotherapy, especially through antibiotics, probiotics, diet or fecal microbiota transplantation.^{71,72}

Antibiotics

In recent years, a growing body of data has been reported regarding the role of antibiotics in modulating the response to immunotherapy. Unfortunately, infections are a recurring problem in cancer patients, and therefore antibiotic therapy often overlaps with anti-cancer therapies, inducing a modulation on the efficacy of immunotherapy. In fact, a pioneering study suggests that in patients with solid tumors undergoing immunotherapy, antibiotic therapy is associated

with worse response to treatment, especially if administered before immunotherapy.⁶¹

To extend upon this observation, a recent study conducted on a cohort of mRCC and NSCLC patients reported that broad-spectrum β -lactam or quinolones were the most common antibiotics. Use of these antibiotics was associated with worsening of progression-free survival (HR 3.1, CI 95%, 1.4–6.9, $P < .01$) and the percentage of patients with primary progressive disease (75% versus 22%, $P < .01$).⁷³ Interestingly, another study reported that antibiotics had a greater effect in reducing progression-free survival in the RCC cohort (HR 2.13 95% CI 1.54–2.93), compared to both NSCLC (HR 1.64 95% CI 1.07–2.52) and melanoma (HR 1.54 95% CI 0.33–7.12).⁷⁴ This effect was statistically significant if antibiotic exposure occurred immediately before the initiation of immunotherapy (RCC HR 1.86 95% CI 1.16–2.98), suggesting a role during the induction. Other studies have shown how the use of antibiotics during therapy with ICIs (mainly in patients with RCC or melanoma) also reduces the overall survival (OS) (HR 1.88, 95% CI 1.59–2.22) and the response rate (OR 0.54, 95% CI 0.34–0.86).^{75,76} Moreover, antibiotics were statistically linked to a reduced progression-free survival (HR: 2.238, 95% CI: 1.284–3.900, $P = .004$) in a multicentre study of mRCC patients receiving nivolumab.⁷⁷ Similar results, with worst progression-free survival during antibiotic therapy (HR 1.96, 95% confidence interval [CI] 1.20–3.20, $p = .007$), were obtained in patients in therapy with mTOR inhibitors and VEGF target therapy during clinical trials.⁷⁸ Interestingly, in a recent study on patients with NSCLC, antibiotic therapy impacted the progression-free survival (HR 1.29, CI 95%, 1.04 to 1.59, $p = .0192$) and the overall survival (HR 1.42, CI 95%, 1.13 to 1.79, $p = .0024$) in patients treated with pembrolizumab, but not in patients treated with chemotherapy.⁷⁹ Furthermore, the same author demonstrated that the efficacy of first-line chemo-immunotherapy is not reduced by previous antibiotic exposure, in contrast with data reported for single ICIs.⁸⁰

Probiotics

Probiotics are defined as microorganisms that exert beneficial effect on host health.⁶³ This definition brings together a large number of products with characteristics that are not always well defined; therefore, the FDA has recently defined a new category of “live biotherapeutic products” (LBP), which have specific characteristics similar to other pharmacological products.⁸¹ This regulation aims to promote specific indications for each probiotic strain as reported by clinical studies, with this approach necessary in the aim of moving toward personalized medicine. Indeed, considering the topic of this review, several studies have reported that probiotics have a potential role in enhancing clinical response to immunotherapy.⁷⁰ However, it is important to highlight that nonspecific probiotic supplementation is ineffective in improving immunotherapy outcomes. In fact, Spencer et al reported results from a series of melanoma patients undergoing ICIs who took commercial probiotics in clinical practice, and no significant difference was demonstrated in improvement of PFS or other outcomes in patients who took commercial probiotics or not.⁸² These data confirm the importance of

personalized medicine and the need to identify specific probiotic strains capable of modulating ICIs. For instance, a meta-analysis demonstrated superiority in terms of overall survival (HR = 0.50, 95% CI: 0.30–0.85, $p = .01$) and progression-free survival (HR = 0.51, 95% CI: 0.42–0.61, $p < .01$) in the groups of NSCLC patients who used probiotics containing *Lactobacillus*.⁸³ However, another study reported that probiotics reduced the progression of free survival (PFS) only in NSCLC (HR: 0.532, 95% CI: 0.354–0.798, $p = .002$), indeed it was not possible to demonstrate efficacy also in melanoma and mRCC due to the weakness of the available results.⁸⁴ Furthermore, Hahn AW et al, tried to verify the role of *Bacteroides* spp. in patients receiving first-line VEGF-TKIs in a retrospective cohort of 145 patients affected by mRCC.⁸⁵ finding that the administration of probiotics improved PFS in patients not receiving antibiotics (HR 0.92; 95% CI, 0.83–0.99; $P = .04$) as well as in patients receiving antibiotics (18 vs 8 months). Conversely, a subsequent randomized trial conducted on mRCC patients treated with VEGF-TKIs recorded no significant clinical benefit from eating *Bifidobacterium*-containing yogurt.⁸⁶ Recently, intriguing data have been published regarding the role of *Clostridium butyricum* CBM 588. In preclinical studies, CBM 588 is able to promote immune regulation and gut epithelial protection. Indeed, in a mice model, CBM 588 improved the intestinal barrier function and increased the abundance of *Bifidobacterium*, *Lactobacillus* and *Lactococcus* spp; moreover, this bacterium exerts an immunomodulatory role by favoring the expansion of IL-17A-producing $\gamma\delta$ T cells and IL-17A-producing CD4 cells in the colonic mucosa.⁸⁷ Therefore, considering pre-clinical results, this product has been studied in the modulation of the response to immunotherapy. A randomized prospective study was conducted on mRCC receiving immunotherapies with or without live *Clostridium butyricum* CBM588.⁸⁸ In particular, the administration of this bacterium was associated with a statistically significant increasing of PFS (12.7 months versus 2.5 months, HR 0.15, 95% confidence interval 0.05–0.47, $P = .001$) and improvement of response rate (58% versus 20%, $P = 0.06$); although, there were not reported significant differences in *Bifidobacterium* spp. or Shannon index related to the administration of this product. Further clinical studies are ongoing; in particular, interesting results are expected from a clinical study that will evaluate the efficacy of CBM588 in favoring the response to combined therapy approved by FDA with ICI and TKI (nivolumab and cabozantinib) in mRCC.⁸⁹ Finally, promising data concerning MRx0518 (that is, a gut microbiome-derived oral LBP consisting of a single strain of *Enterococcus gallinarum*), have recently been published; this bacterium may be able to modulate the immune response in treatment-naïve cancer patients, translating to an improvement in the response to anti-cancer treatment.⁹⁰

Prebiotic

Prebiotics are defined as non-viable food components, mainly fibers or other non-digestible substances, that may stimulate the enrichment of particular gut microorganisms to prevent the colonization of pathogens and ensure effective

immunological activity by modulating the release of inflammatory cytokines.⁶³ For instance, inulin was correlated with a higher presence of *Bifidobacterium* and *Faecalibacterium* that are able to enhance the activity of PD1/PD-L1 blockade therapy.⁹¹ In in vitro models, oligosaccharides stimulate the production of arginine deiminase and L-asparaginase by *Enterococcus durans*, enzymes involved in cancer therapies.⁹² This regulatory function might be used as an adjuvant strategy during immunotherapy, as suggested by an ongoing pilot study (NCT04552418).⁹³ A recent preclinical study demonstrated the impact of inulin gel in colorectal murine models (balb/c mice inoculated with colon carcinoma cells) treated with anti-PD1.⁹² Inulin amplified the activity of immunotherapy in mice by remaining tumor-free, and it increased SCFA-producing bacteria that are involved in enhancing the efficacy of anti-PD1 therapy.^{70,92,94}

Dietary intervention and lifestyle

Diet and food ingestion are deeply linked to the gut microbiota.^{94,95} For example, high fat/low fiber diets are related to a low alpha diversity, reduction of *Bifidobacterium* spp., *Bacteroides* and *F. prausnitzii* and reduction of pro-inflammatory gut microbes.^{96,97} Inversely, high amounts of fiber are linked to an increased titer within the gut of *Faecalibacterium prausnitzii*, *Akkermansia muciniphila* and *Bifidobacterium longum*, which are involved in the metabolism of the intestinal epithelium and in the production or degradation of mucin, and are considered a key player in effectiveness of ICIs.⁹⁶ Many clinical trials (NCT03700437, NCT03950635 and NCT04909034) on dietary manipulation in patients with cancer who received immunotherapy are currently ongoing.^{97–100} Published results by Spencer et al. showed that anti-PD-1 treatment for melanoma was five times more effective in patients with a higher fiber diet.^{68,101}

Fecal microbiota transplantation

Fecal microbiota transplantation (FMT) consists in the transfer of feces from healthy screened donors into recipients with a disrupted microbiome, and it can be considered the most powerful among the therapeutic modulators of gut microbiome.

FMT is best established clinically as a therapy for recurrent *Clostridioides difficile* infection, where it achieves nearly 90% efficacy cure rates.^{102,103}

More recently, in recognition of the fundamental role of gut microbiota in modulating the immune system, FMT has been proposed as a valid option to improve the clinical outcome of ICIs.¹⁰⁴ Clinical trials have proved that the microbiota could be modified with FMT to improve anti-PD1 therapy effectiveness in patients with melanoma. In the first one, ten patients with melanoma treated with anti-PD1 received repeated cycles of FMT from two different donors (the first by colonoscopy followed by capsule administration). Interestingly, one patient developed complete response, and two partial responses were also observed.¹⁰⁵ Moreover, responders to FMT also demonstrated an increase in inflammatory and antigen presentation signatures, associated with the shift toward an immune tumor

rejection signature. In the second trial, 15 patients with melanoma with primary unresponsiveness to anti-PD1 therapy received a single FMT by colonoscopy. One patient had a complete response, two had a partial response, and three remained stable for more than 18 months. After FMT, the gut microbiota composition of patients with partial or complete clinical response appeared more similar than donor one; in these patients, there was an increased abundance of favorable taxa, such as Lachnospiraceae, Ruminococcaceae and Bifidobacteriaceae; in contrast, unfavorable species, such as those from the genus *Bacteroides*, were decreased.¹⁰⁶ In both trials, patients affected by melanoma and durable responders to anti-PD1 therapy have been used as donors. Indeed, these two pioneering clinical studies have confirmed that FMT is able to modulate the composition of the gut microbiome and the immune response, and in particular, they also underlie the importance of engraftment in favoring the enhancement of the response to ICIs; it is necessary to continue on this path by identifying pre-conditioning factors and the ideal donor to favor engraftment.¹⁰⁷ Finally, a clinical trial was recently published to evaluate the efficacy of FMT from healthy donors in enhancing clinical response to first-line regimen with ICIs in patients with advanced melanoma. The study enrolled 20 patients, with a partial response observed in 13/20 (65%) of the patients, with response of four of these 13 responders being complete. Longitudinal microbiome profiling revealed that microbiome similarity toward the pre-morbid composition was maintained over time only in responders.¹⁰⁸

To date, there are still no evident results regarding the efficacy of immunotherapy in mRCC; however, a pioneering study demonstrated the efficacy of FMT in reducing TKI-associated diarrhea through microbiome modulation and reduction of the mucosal inflammatory response.¹⁰⁹ Colitis associated with

immunotherapy is a well-known complication, and as such therapeutic options to reduce the severity of symptoms can improve adherence to therapy and indirectly favor the clinical response.

Furthermore, FMT efficacy is also been explored in mRCC, CRC and in other solid cancers in several ongoing trials (NCT05273255, NCT05279677 and NCT04758507), but no results have been published yet.^{110–112} Despite the reported promising results, more randomized clinical trials (RCTs) are advocated to establish the role of FMT in improving the efficacy of cancer immunotherapy, summarized in Table 1.

Final remarks and future perspectives

More than 100 drugs for the treatment of cancer have been approved by the FDA in the last two decades, yet the median survival has increased by a few months.¹¹³ For this reason, the modulation of the microbiome associated with anti-cancer treatments could represent a pioneering strategy capable of improving the efficacy of these new drugs. Indeed, as previously described, much data have been published regarding the relationship between the microbiome and immune system. Similarly, immunotherapy is proving to be very effective, in particular, in solid tumors such as renal cancer. For this reason, the modulation of the microbiome and the development of immunotherapy protocols could represent a winning synergy. In particular, the demonstration that alteration of microbiome with antibiotics could play a role in reducing the efficacy of ICIs has encouraged the development of protocols based on microbiota modulation to improve the clinical response. In fact, several clinical trials have reported the efficacy of probiotics or prebiotics to improve the clinical outcome; in particular, considering probiotics, the results from studies on *Clostridium butyricum* CBM588 appear promising and worthy of further investigations. Nevertheless, the most promising results have

Table 1. Ongoing clinical trials investigating FMT and immunotherapy for renal cancer.

Identifier	Phase	Cancer type	Intervention	Study model	Donors
NCT05286294	Phase 2	Melanoma, Head and Neck Squamous Cell Carcinoma, Renal cell carcinoma, MSI+ solid cancer	FMT (via colonoscopy) + ICIs	Single arm, open label, non-randomized clinical trial	patients who are responding to ICIs
NCT04758507	Phase 1/2	Renal Cell Carcinoma	FMT (via colonoscopy and stool capsules) + ICIs versus placebo FMT + ICIs	Two arms, randomized, double-blind, controlled trial	patients who are responding to ICIs
NCT04038619	Phase 1	Diarrhoea or Colitis in Genitourinary Cancer	FMT (via colonoscopy) + ICIs	Single arm, open label, non-randomized clinical trial	Healthy donors
NCT03819296	Phase 1/2	Diarrhoea or Colitis in Melanoma and in Genitourinary Cancer	FMT (via colonoscopy) + ICIs	Single arm, open label, non-randomized clinical trial	Healthy donors
NCT04521075	Phase 1/2	Melanoma, NSCLC, MSI+ solid tumors	FMT (via colonoscopy and stool capsules) + ICIs	Single arm, open label, non-randomized clinical trial	Patients with durable complete response to ICIs
NCT05273255	Not Applicable	Solid Carcinoma	FMT (via colonoscopy) + ICIs	Single arm, open label, non-randomized clinical trial	Patients with partial or complete response to ICIs, with a minimum duration of remission lasting ≥ 12 months
NCT04264975	Not Applicable	Solid Carcinoma	FMT (via colonoscopy) + ICIs	Single arm, open label, non-randomized clinical trial	Patients who have partial or complete response to ICIs

MSI: Microsatellite Instability, FMT: Fecal Microbiota Transplantation, ICIs: immune checkpoint inhibitors, NSCLC: non-small-cell lung cancer.

emerged from preliminary studies on FMT, especially considering the deep impact upon gut microbiome modulation with this technique. Although the results are promising to date, the evidence is still weak due to the limited number of patients enrolled in the studies and the heterogeneity of the protocols.

In conclusion, further preclinical and clinical studies to implement and standardize gut microbiome modulation in immunotherapy are needed. In particular, it will be fundamental to better understand the concept of engraftment and to learn how to predict the risk of complications or benefit from the administration of some consortia of bacteria compared to others in individuals undergoing immunotherapy. In particular, a greater knowledge of the relationship between microbiome and the immune system will favor the implementation of microbiome modulation in cancer treatment or – more specifically – in immunotherapy.

Disclosure statement

Declaration of competing interest: B.H.M. reports consultancy fees from Finch Therapeutics Group, Ferring Pharmaceuticals and Summit Therapeutics, outside of the submitted work. G.I. has received personal fees for acting as speaker for Biocodex, Danone, Sofar, Malesci, Metagenics and Tillotts Pharma and for acting as consultant and/or advisor for Ferring Therapeutics, Giuliani, Malesci and Tillotts Pharma. A.G. reports personal fees for consultancy from Eisai Srl, 3P Solutions, Real Time Meeting, Fondazione Istituto Danone, Sinergie Srl, Board MRGE and Sanofi SpA personal fees for acting as a speaker for Takeda SpA, AbbVie and Sandoz SpA and personal fees for acting on advisory boards for VSL3 and Eisai. G. C. has received personal fees for acting as an advisor for Ferring Therapeutics. All other authors have no conflicts of interest to disclose.

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Abbreviations

CRC	Colon Rectal Cancer
CTLA-4	Cytotoxic T Lymphocyte Antigen-4
FMT	Fecal Microbiota Transplantation
NSCLC	Non-Small Cell Lung Cancer
ICI	Immune Checkpoint Inhibitor
PD1	Programmed Death 1
PD-L1	Programmed Death – Ligand 1
PDGF-β	Platelet-Derived Growth Factor-β
PFS	Progression Free Survival
RCC	Renal Cell Carcinoma
mRCC	metastatic RCC
SEER	Surveillance, Epidemiology and End Results
TGF-α	Transforming Growth Factor-α
Th1	T Helper 1 Lymphocyte

Th17	T Helper 17 Lymphocyte
Treg	T Regulatory Lymphocyte
TKI	Tyrosine Kinase Inhibitor
VEGF	Vascular Endothelial Growth Factor
VHL	Von Hippel-Lindau

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