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REVIEW

Non-pharmaceutical interventions to optimize cancer immunotherapy

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ABSTRACT

The traditional picture of cancer patients as weak individuals requiring maximum rest and protection is beginning to dissolve. Too much focus on the medical side and one's own vulnerability and mortality might be counterproductive and not doing justice to the complexity of human nature. Unlike cytotoxic and lympho-depleting treatments, immune-engaging therapies strengthen the immune system and are typically less harmful for patients. Thus, cancer patients receiving checkpoint inhibitors are not viewed as being vulnerable *per se*, at least not in immunological and physical terms. This perspective article advocates a holistic approach to cancer immunotherapy, with an empowered patient in the center, focusing on personal resources and receiving domain-specific support from healthcare professionals. It summarizes recent evidence on non-pharmaceutical interventions to enhance the efficacy of immune checkpoint blockade and improve quality of life. These interventions target behavioral factors such as diet, physical activity, stress management, circadian timing of checkpoint inhibitor infusion, and waiving unnecessary co-medication curtailing immunotherapy efficacy. Non-pharmaceutical interventions are universally accessible, broadly applicable, instantly actionable, scalable, and economically sustainable, creating value for all stakeholders involved. Most importantly, this holistic framework re-emphasizes the patient as a whole and harnesses the full potential of anticancer immunity and checkpoint blockade, potentially leading to survival benefits. Digital therapeutics are proposed to accompany the patients on their mission toward change in lifestyle-related behaviors for creating optimal conditions for treatment efficacy and personal growth.

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Plateau effect of checkpoint immunotherapy efficacy

After the advent of oncogene-targeted treatments in the early 2000s, immune checkpoint blockade (ICB) became the 'next big thing' in medical oncology, raising the therapeutic bar and improving patient survival. While the performance of ICB gradually increased following refinements in patient selection and treatment combinations, it is not substantially different from the first clinical observations more than a decade ago.[1] In particular, the fraction of patients responding with durable clinical benefit did not change significantly over the years. Moreover, ICB has shown limited success in tumor types other than melanoma and lung cancer, apart from defined molecular subtypes with extraordinary immunogenicity, e.g., tumors with a high tumor mutational burden (TMB) and tumors with a microsatellite instability-high (MSI-H) phenotype. Thus, ICB efficacy has reached a plateau, and strategies to boost the performance of this immune-engaging treatment or extend its application spectrum are being actively pursued.

Optimizing immune checkpoint blockade: between drug-focused and patient-centric perspectives

Combining ICB with immune-modulatory drugs or vaccination against tumor-specific antigens[2,3] represents one approach to augment ICB response rates and improve survival. However, such combination treatments (i) require medical centers with associated logistics, (ii) may have substantial turnover times due to mandatory tumor profiling and/or personalized GMP manufacturing, (iii) may not be effective in a significant number of patients, (iv) may have deleterious short- or long-term toxicity, (v) may economically burden the healthcare system, (vi) may not be accessible to anyone on a global scale, and (vii) may even be more dependent on international supply chains.

Complementing the traditional drug-focused perspective, the importance of patient centricity and quality of life (QoL) has recently risen. Moreover, an increasing number of cancer patients communicate the wish to be actively involved in their treatment (e.g., patient advocacy groups) and may raise questions such as 'Should I be doing sports?' or 'Should I change my diet?'. Thus, patient empowerment and active engagement are key elements in modern medical oncology, reflective of a concept where the patient is *part of the team* rather than an outside individual *treated by the team*. The interdisciplinary, cross-functional requirements of modern cancer treatment and management have been partly addressed by installing tumor boards and dedicated cancer units, commonly known as comprehensive cancer centers (CCCs). However, these organizational constructs are mainly focused on medical disciplines (e.g., oncology, radiology, surgery, pathology) and aim to make accurate diagnoses and identify

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the most promising treatment strategies at different stages of the patient journey. Hence, there is an inherent lack of patient centricity, and active patient engagement and non-pharmaceutical interventions (NPIs) are rarely considered.

Recently, we advocated a holistic approach to cancer immunotherapy, also embarking on lifestyle- and biorhythm-related factors to support treatment efficacy.[4] We made this proposition based on data showing that the efficacy of ICB is mechanistically linked to various factors, including diet/microbiome, physical activity, stress, and circadian rhythmicity. In contrast to drug development and the establishment of new ICB combinations, tackling these factors often requires nothing more than behavior change on patient side (which may, however, not be easily achievable especially when the social system around the target person is unsupportive). To this end, behavior change is universally available, instantly actionable, and comparatively cheap. Moreover, optimizing factors such as diet, physical activity, and stress will benefit cancer patients irrespective of their disease and can be reasonably expected to be safe during treatment.

This article aims at delineating the so-far untapped potential for optimizing ICB efficacy through adaptations in lifestyle habits and circadian-compliant timing of checkpoint inhibitor infusions. The NPIs proposed should contribute to a more holistic type of cancer immunotherapy and support ICB efficacy through various complementary mechanisms, with the patient always in the center of the overarching therapeutic concept.

Interconnection of diet, microbiota, and immunotherapy

'You are what you eat' may sound a bit exaggerated, but body cells comprise molecular building blocks from food, such as amino acids, nucleotides, sugars, and lipids. In addition, the approximately 3.8×10^{13} bacteria found in the human body[5] underlie profound regulation from dietary components, which at least partially determines their composition, diversity, and functional quality. Dietary habits associate with specific gut microbial enterotypes[6] and adaptations of gut microbiota to changes in diet are not only convergent in mammals[7] but occur rapidly and reproducibly on both the organismal and gene expression level.[8] Diet-dependent alterations in gut microbial composition are at least partially dictated by the digestive requirements of particular foods, thus selecting for microbes with enzyme repertoires able to metabolize the main food components.[8] Tolerance (or sensitivity) to specific food components represents another mechanism driving the selection (or decimation) of particular microbial communities following dietary change.[8–10] Finally, foodborne microbes can transiently colonize the gut and co-exist with resident microbes[8] even though data suggest overall ecological robustness of gut microbial composition in response to the ingestion of microbe-containing foods such as fermented milk products.[11] Of note, specific gut microbiome-targeted diets, including high-fiber- and fermented food diets, influence the human immune status and reduce markers of inflammation.[12] Thus, next to genetics, epigenetics, and other factors, dietary behavior has a strong and direct impact on the composition and functional specificity of the gut microbiome, with implications for health and disease.

In the context of cancer and ICB, the relevance of microbiota is evident on several levels. The concomitant use of antibiotics curtails ICB efficacy,[13] and fecal microbiota transplantation from responding individuals can restore ICB sensitivity in otherwise refractory patients.[14] In support, supplementation of certain bacteria, or adoptive transfer of T cells specific for antigens from these bacteria, re-sensitizes to ICB treatment in preclinical models.[15] Evidence also suggests that an overall higher microbiome diversity benefits cancer patients under ICB, potentially through mechanisms involving tumor neoantigen mimicry and immunological cross-reactivity between microbial and tumoral epitopes.[2,3,16] T cell response-modifying microbial metabolites, innate sensing of microbial structures (pattern recognition), and microbial expression of genotoxic products represent further mechanisms of microbiome dependence of anticancer immunity and ICB efficacy.[3,17] Given these data and the direct effects of diet on microbial composition and function, dietary intervention represents a rational non-pharmaceutical strategy to modulate host immunity and optimize ICB therapy.[18–21]

Dietary interventions to support immune checkpoint blockade efficacy

Evidence suggests that obesity not only represents a major risk factor for cancer but also induces metabolic reprogramming in the tumor microenvironment (TME) to impair CD8+ T cell infiltration and function.[22] A high-fat diet promotes intestinal carcinogenesis *via* microbial dysbiosis,[23] and dietary sugar fosters tumor immune evasion and resistance to immunotherapy *via* upregulation of heme oxygenase-1.[24] These preliminary data suggest that reducing fat and sugar intake, e.g., abstaining from a Western-type diet, may positively affect ICB efficacy.

The relevance of (reduced) calorie intake for cancer therapy and immune surveillance is further underpinned by a wealth of preclinical data and large-scale clinical testing, mostly in settings of chemotherapy and other standard antitumor treatments.[19] While data on calorie restriction (CR) and fasting are sparse for ICB-treated patients (see, for instance, NCT03595540 and NCT03700437), results from a prospective study of 101 cancer patients receiving standard antineoplastic treatments (NCT03340935) showed that a cyclic, five-day fasting-mimicking diet (FMD) was safe and consistently lowered serum glucose, insulin, and IGF1 levels, thus inducing favorable metabolic changes.[25] In addition, this dietary intervention substantially reshaped anticancer immunity, including the contraction of suppressive myeloid- and T cell subsets in peripheral blood and an augmented cytotoxic T cell response in the tumor bed.[25] Of note, many of these metabolic and immunological effects were independent of the type of tumor and concomitant therapy, thus suggesting that fasting/FMD may also benefit patients under ICB.[25] A later sub-analysis of the same trial revealed exceptional, long-lasting clinical responses in a handful of patients with extensive-stage or metastatic disease, thus showing the potential benefit of FMD even in far-advanced cancer settings.[26] However, CR and FMD potentially represent a double-edged sword, and their use needs to be carefully considered. First, while CR/FMD may inhibit tumor cell proliferation by targeting glucose metabolism and

counteracting glycemia, mounting an efficient immune response also requires a certain amount of glycolytic output such that CR/FMD cannot be deliberately escalated (*nota bene*, CR typically refers to a 10–20% reduction in daily energy consumption compared to *ad libitum* feeding 'only' and must not provoke malnutrition).[27] The implication is that the risk of hypoglycemia needs to be considered and addressed during CR/FMD interventions. Second, given cancer cachexia and associated frailty,[28,29] CR/FMD may not always be therapeutically feasible. To tackle these limitations, the desired cellular and molecular effects of reduced calorie intake on anticancer immunity may, in specific situations, be prospectively modeled with natural or pharmacological CR mimetics, or anti-glycemic agents.[27] Third, evidence from a recent study suggested that obesity, defined as a body mass index (BMI) of ≥ 30, is associated with favorable immunotherapy outcomes in pan-cancer survival analyses of both TMB-high and TMB-low strata.[30] While independent validation is required, one reason for this paradoxical observation could be a greater 'body reserve' in obese patients that, to a certain extent, protects from fat and muscle wasting in advanced or terminal cancer settings. Irrespective, possible implications for CR/FMD are hard to deduce, as these dietary interventions are not directly related to BMI, especially not in transient/therapeutic settings.

Ketosis refers to the metabolic processes activated following starvation or extreme reductions in carbohydrate intake, leading to the accumulation of ketone bodies in circulation for alternate energy supply and sustenance of normal organ functioning.[31] A ketogenic diet (KD) aims at inducing ketosis by limiting carbohydrate intake to below 30–40 g/day while supplying a significant amount of fat (>60% of energy demand) and sufficient protein.[31] In preclinical models of aggressive cancer, KD led to defined changes in gut microbial composition and reduced tumor growth in a T cell-dependent manner – an effect that could be recapitulated with 3-hydroxybutyrate (3HB), the bioactive metabolite of KD.[32] Metabolically interfering with KD by either co-supplementing sugar or antagonizing the receptor for 3HB (i.e., GPR109A) abrogated tumor growth retardation by KD.[32] In mice unresponsive to ICB, KD or supplementation with 3HB restored therapeutic efficacy, thus showing synergy with ICB.[32] The ICB re-sensitizing effects of KD could be mechanistically explained by the 3HB-mediated expansion of a specific T cell subset and prevention of PD-L1 upregulation on myeloid-lineage immune cells.[32] A similar effect of KD was also independently reported. Specifically, Dai and coworkers showed that KD affects energy status, decreasing PD-L1 protein abundance through AMPK-dependent serine phosphorylation and subsequent degradation.[33] In parallel, KD-induced energy deprivation increases the expression of genes related to immune effector function and antigen presentation, thus altogether acting to foster ICB response and efficacy.[33]

Evidence also suggests that a high-fiber diet (HFD) may positively influence anticancer immunity and the response to ICB.[34] In a study on 128 patients with melanoma, fiber intake of at least 20 g/day was associated with a higher likelihood of response to ICB and prolonged survival, especially when no commercial probiotic supplements were concomitantly used.[35] Murine models confirmed this observation and showed that a higher dietary fiber intake fosters the accumulation of cytotoxic T cells in the TME and associates with a gene signature of T cell activation and effector function.[35] In support, a prospective study on ICB-treated patients from different regions around the globe (i.e., Australia, Netherlands, United States) not only identified geographically-distinct microbial signatures of treatment response and immune-related adverse events (irAEs) but also found an association between ICB response and higher dietary fiber consumption.[36] Mechanistically, HFD triggers type-I interferon production by intratumoral monocytes *via* microbiota-derived STING agonists, in turn regulating natural killer (NK) cell-dendritic cell (DC) crosstalk and sensitizing to ICB.[37]

A recurrent finding in the quest for microbial markers for ICB response prediction is that higher microbial diversity is associated with favorable treatment efficacy, possibly through mechanisms involving immunological cross-reactivity between cancer and microbial antigens.[2,3,16,38,39] Therefore, it is reasonable to assume that diets that increase microbial diversity concomitantly support ICB efficacy. While the clinical testing of this hypothesis remains pending, a randomized prospective study recently showed that a fermented-food diet (FFD) consistently increased microbial diversity while reducing markers of inflammation and improving immune status.[12] More microbial diversity may also be achieved through higher intake of polyunsaturated fatty acids. Specifically, a study on ICB-treated melanoma showed a positive association between omega 3 fatty acid consumption and microbial diversity, with omega 3 consumption above 250 mg/day further identifying patients responding to ICB therapy.[36]

These data collectively suggest that targeted changes in dietary behavior (e.g., CR/FMD, KD, HFD, FFD, omega 3 diets) may represent a valuable source of NPIs to support ICB response and long-term efficacy without a significant side effect profile (Figure 1).

Physical activity – getting immune cells moving

Although physical activity improves general well-being and reduces cancer risk and cancer-related morbidity and mortality,[40,41] its importance for anticancer immunity and cancer immunotherapy has only recently surfaced. In this regard, the intriguing finding was presented that pre-diagnostic physical activity correlates with increased tumor CD8+ T cell infiltration in colorectal cancer, evident at both the tumor front and in the center.[42] These data suggest that physical activity may mobilize cytotoxic immune cells into evolving, yet-to-be-diagnosed tumors, thus having a 'conditioning effect' and possibly imposing a major marker for tumor immune surveillance and ICB response prediction.[43] In preclinical models of pancreatic ductal adenocarcinoma, aerobic exercise reduces tumor growth by fostering tumor immune surveillance on both the systemic and intratumoral level, with IL-15 Rα-expressing CD8+ T cells mediating the protective effect.[44] Of note, increased tumor T cell infiltration following exercise is also observed in clinical specimens, thus suggesting the adjuvant, treatment-augmenting potential of physical activity.[44] Importantly, either physical activity or targeting the IL-15/IL-15 Rα axis with NIZ985, a recombinant heterodimeric IL-15 superagonist,[45] sensitizes pancreatic tumors to PD-1-directed ICB and prolongs survival in preclinical models.[44] A study on NSCLC employing patient-

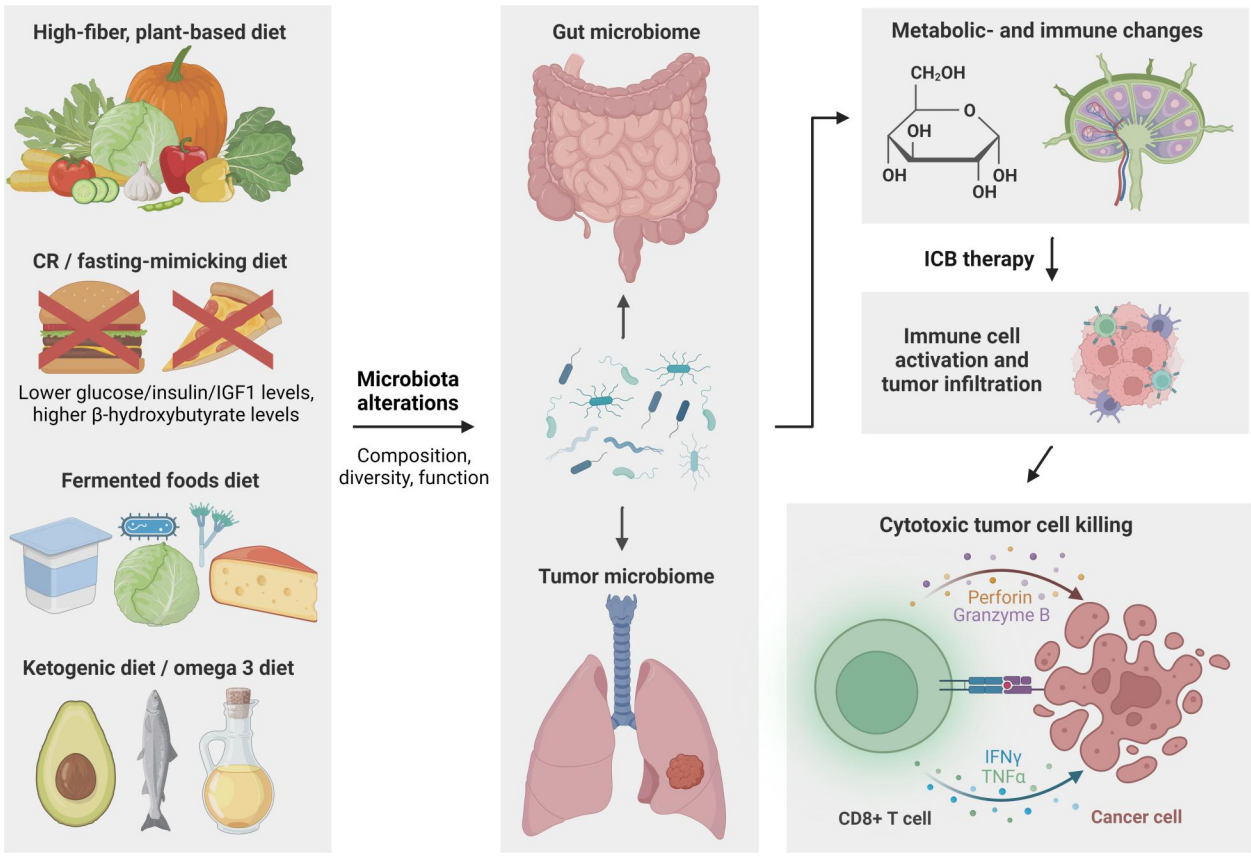

Figure 1. Dietary interventions that support immune checkpoint blockade efficacy. emerging evidence suggests that particular diets widely regarded as healthy support the efficacy of ICB through modulation of specific host microbiomes and associated alterations in metabolism and immunity, ultimately fostering tumor immune surveillance. Positive effects on microbial diversity, anticancer immunity and/or ICB efficacy have been documented for high-fiber diets, calorie-restricted and fasting-mimicking diets, fermented foods diets, and ketogenic and omega 3-rich diets. Although dietary interventions do not raise particular safety concerns, certain patient populations should abstain from certain types of diets for obvious reasons (e.g., cachectic patients should not further restrict their calorie intake). *abbreviations used*: CR, calorie restriction; ICB, immune checkpoint blockade. Figure created with BioRender.com.

derived xenografts (PDXs) showed that moderate-intensity training fosters tumor infiltration by myeloid cells and slows down tumor growth.[46] Combining exercise training with anti-PD-1 therapy also increased tumor cell death through necrosis while reducing apoptosis.[46] Considering the severely immunocompromised background of the PDX hosts (NOD-SCID gamma mice), the observed effects must have been independent of lymphocytes, and one may speculate that immune-proficient hosts would benefit even more from an exercise-ICB double intervention.[46] A study employing syngeneic murine models of breast and lung cancer demonstrated that reducing glutamine availability through exercise attenuated tumor growth significantly, suggesting that physical activity may deplete certain amino acid pools – and possibly other molecular building blocks – that fuel cancer cell proliferation.[47] In addition, this study also revealed that physical activity counteracts tumor-induced wasting of muscle mass through reduced glutamine release and atrophic signaling in muscles.[47]

While significant parts of the treatment-enhancing effects of physical activity may be attributable to general immune mobilization, activation of specific immune cell subsets, and limitation of nutrient supply, recent evidence from murine models also suggests that physical activity can increase the expression of checkpoint molecules such as PD-1, PD-L1, PD-L2, CD28, B7.1, and B7.2, with possible implications for anticancer immunity and ICB.[48] While physical activity-induced upregulation of immune checkpoint expression may dampen natural or treatment-induced anticancer immunity, it may also sensitize to ICB by providing more target substrates for the therapeutic antibodies even though this effect was not observed in prior work.[48] Furthermore, upregulation of immune checkpoints may be a secondary consequence of taming a strong or overshooting immune response to prevent immune pathology. Therefore, physical activity-induced upregulation of checkpoint molecules may reflect a strong immune-adjuvant effect of physical activity rather than blunted immunity or exhaustion.

Generally, physical activity may only be feasible in fit or only mildly impaired patients, which represents a clear limitation, especially in advanced or heavily pretreated cancer settings. On the other hand, the benefits of physical activity extend far beyond the prospects of enhancing treatment efficacy through immune modulation. Specifically, physical activity improves QoL and physical functioning in cancer patients,[49] increases anticancer therapy tolerability,[50] reduces cancer/treatment fatigue,[49,51] and is associated with higher resilience and less psychological distress in cancer patients.[52] Thus, next to putatively enhancing ICB performance, physical activity has various collateral health benefits and should be considered for cancer patients on and off treatment respecting comorbidity/performance status (Figure 2). Clinical trials of physical activity as an 'adjuvant' for ICB are currently underway (e.g., NCT05358938, NCT04263467).

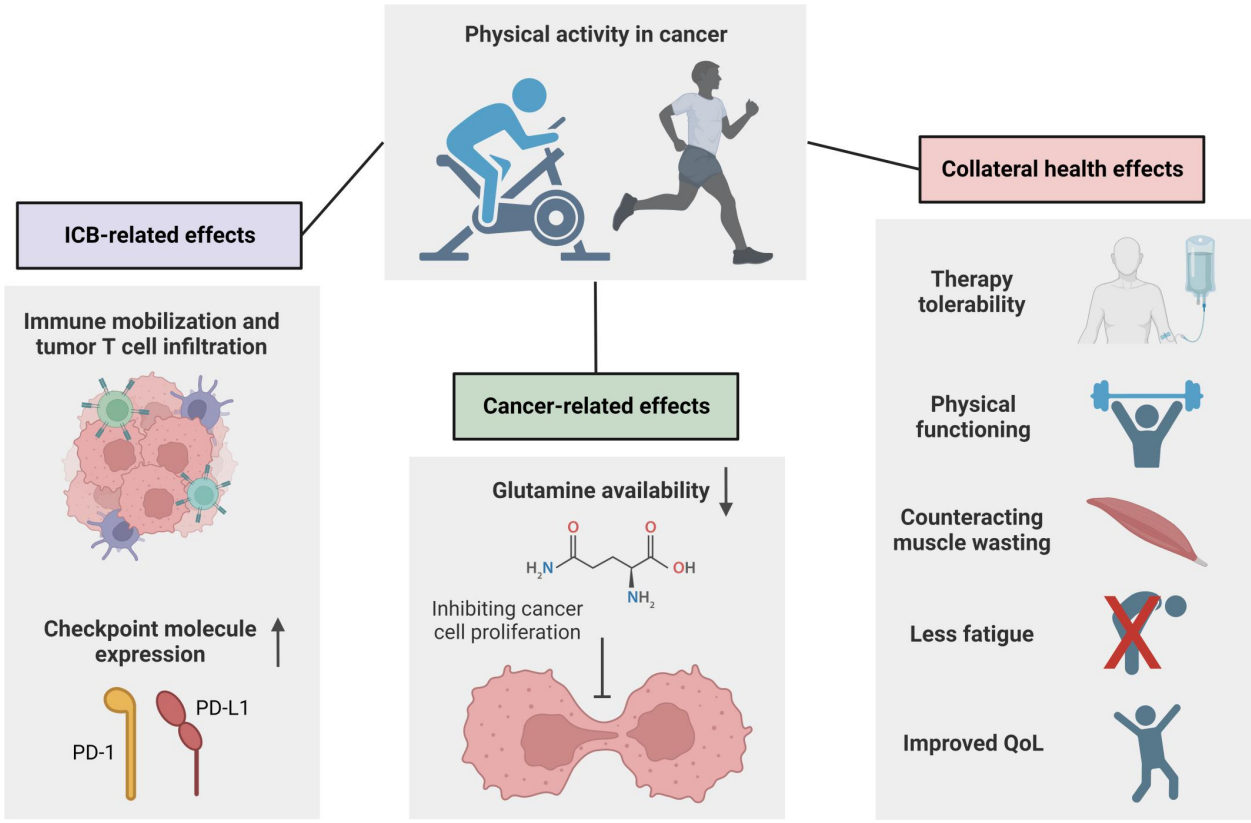

Figure 2. Beneficial effects of physical activity in cancer (immunotherapy). Moderate intensity training has a plethora of beneficial effects and should be recommended to cancer patients whenever feasible on medical grounds. Next to many collateral health benefits, physical activity may also deprive cancer cells from proliferation-sustaining metabolites (e.g., glutamine) and sensitize to ICB therapy by increasing tumor T cell infiltration as well as checkpoint molecule expression (e.g., PD-1/PD-L1). *abbreviations used*: ICB, immune checkpoint blockade; QoL, quality of life. Figure created with BioRender.com.

Stress management to improve immune function

Many people would empirically agree that chronic, uncompensated stress would make them more susceptible to illness, particularly infection. In line, a large population-based, sibling-controlled cohort study from Sweden recently showed that people with stress-related disorders are more likely to suffer life-threatening infections, suggesting an epidemiological link between stress and impaired immune function.[53] This concept is further backed by data demonstrating reduced vaccine efficiency in stressed individuals[54,55] and an association of chronic stress with suppressed cellular and humoral immunity.[56]

Next to being a genetic and epigenetic disease, cancer has a strong immunological component, with the outgrowth of malignant cells following a cascade of immunoediting processes ultimately culminating in the escape from protective tumor immune surveillance.[57,58] Congruent with this concept, evidence suggests that chronic stress fosters tumor immune evasion and cancer development.[59,60] Moreover, stress and depression may worsen cancer survival[61,62] and provoke early recurrence by awakening dormant tumor cells.[63] Conversely, reduced symptoms of depression are associated with prolonged survival in metastatic breast cancer.[64]

Stress depicts a physiological 'fight-or-flight' response tightly linked to adrenal gland activity and surges in steroid hormones and other immune-suppressive factors. In mouse models of carcinogen-induced or transplantable tumors, stress increased plasma glucocorticoid levels and upregulated the glucocorticoid-inducible factor Tsc22d3, blocking type I interferon responses and T cell activation, and inhibiting anticancer immune surveillance and therapeutic tumor control.[65] These effects could be reproduced through glucocorticoid injection or enforced Tsc22d3 expression in antigen-presenting cells (APCs), while glucocorticoid receptor antagonism or APC-specific deletion of Tsc22d3 abolished the negative effects of stress or exogenous glucocorticoid provision on therapeutic tumor control.[65] In cancer patients, negative mood was associated with plasma cortisol levels and TSC22D3 expression in peripheral blood leukocytes, suggesting clinical relevance of the stress-glucocorticoid-TSC22D3 axis.[65] In support, glucocorticoid receptor levels correlate with high PD-L1 but low MHC-I expression in pancreatic cancer and predict poor patient survival.[66] Interfering with glucocorticoid receptor signaling through either tumor cell-specific knockdown or pharmacological inhibition revealed transcriptional regulation of PD-L1 and MHC-I expression by glucocorticoid receptor.[66] Depleting or antagonizing glucocorticoid receptor downregulated PD-L1 expression but upregulated MHC-I expression on pancreatic cancer cells, thus fostering anticancer immunity and sensitizing to ICB.[66] Finally, a recent study in mice showed that adrenergic receptor signaling induced by chronic stress contributes to T cell exhaustion and metabolic dysfunctioning, leading to immunosuppression in the TME and accelerating tumor growth.[67] Inspired by these and other data, the effects of chronic stress, stress modulators and sleep disturbance on the efficacy of ICB are currently investigated in clinical trials (e.g., NCT05477979, NCT05741164, NCT03384836, NCT04070651).

Taken together, recent mechanistic data underpin what has long been suspected – stress subverts tumor immune surveillance and blunts treatment-induced anticancer immunity. Active stress management using techniques such as meditation, yoga, and slow-paced breathing exercises, as well as proper social support and enough quality sleep, may help to reduce stress levels in cancer patients and prevent spikes in steroid hormones that may negatively affect ICB efficacy. Improved QoL is a welcome 'side effect' of stress management, arguing for this patient-centric intervention even on the hypothetical assumption of no treatment-enhancing effect.

Circadian-compliant timing of immune checkpoint blockade

Many fundamental aspects of human physiology/biology are governed by circadian rhythms, including sleep, metabolism, behavior, and the immune system.[68] Moreover, metastasis and tumor stemness[69–71] are also influenced by circadian rhythms, with metastatic dissemination accelerating during sleep[72] and chronic circadian disruption fostering cancer cell stemness features.[73] Circadian rhythms are endogenously generated by circadian clocks (regulated by a set of circadian genes) and refer to recurrent patterns of oscillatory peaks and valleys for given biological processes over 24-hour intervals.[68] Disruption of circadian rhythmicity is associated with poor sleep quality and various somatic and psychosomatic pathologies.[74–76] Circadian clocks are also relevant for treatment with pharmaceutical drugs, not least because of circadian variation in pharmacokinetics and pharmacodynamics.[74–76] In immune-engaging treatments, these time-varying drug effects may be further influenced by 'immune chronobiology', i.e., the time-of-day-dependence of immune activity and preparedness. In particular, circadian rhythmicity entails strong oscillations of lymph node cellularity and blood leukocyte numbers regulated by time-of-day-dependent variations in immune cell homing, migration, tissue drainage, and microenvironmental cues.[77,78] It comes with no surprise that these oscillations have an impact on adaptive immune responses,[78,79] and accumulating evidence suggests that morning vaccination yields a stronger immune response than afternoon/evening vaccination, which is evident on several levels, including antibody production and cellular responses.[80–84]

The superiority of morning/daytime *versus* evening administration has also been shown for ICB therapy. In a propensity score-matched analysis of 146 patients with advanced melanoma, ICB infusions later than 4:30 pm were associated with shorter overall survival (OS), arguing for ICB administration in the morning or early afternoon.[85] Interestingly, these results were obtained with a stratification strategy where patients of the shorter surviving evening group were only required to have ≥ 20% of their infusions later than 4:30 pm, thus potentially underestimating the negative impact of evening-only ICB infusions on patient survival.[85] Corroborating this notion, the authors showed that every additional 20% of ICB infusions after 4:30 pm incrementally impacted the survival hazard.[85] Results from a study on metastatic (stage IV) NSCLC treated with the PD-1-directed antibody nivolumab point in the same direction even though the time threshold for morning (approx. 9:30 am – 1:00 pm) *versus* afternoon/evening (approx. 1:00 pm – 5:00 p.m.) stratification of ICB infusion was different.[86] Notably, this study revealed an impressive 4 to 5 times enhanced efficacy of morning ICB administration, based on hazard ratio calculations from multivariate analyses of PFS and OS.[86]

In sum, preliminary – yet accumulating – data suggest that circadian rhythmicity favors administering immune-engaging treatments in the morning, including vaccination and ICB (Figure 3). Clinically, default morning ICB infusions are easy to implement, cost nothing, and raise no additional safety concerns. Prospective randomized trials are certainly needed to definitively assess the effect of circadian application on ICB efficacy. In addition, fundamental and clinical research may reveal circadian-related biomarkers to further optimize ICB infusion timing.[87]

When less is more: co-medication and immune checkpoint blockade

Cancer patients are typically regarded as a highly vulnerable population – immunologically, physically, and mentally. While

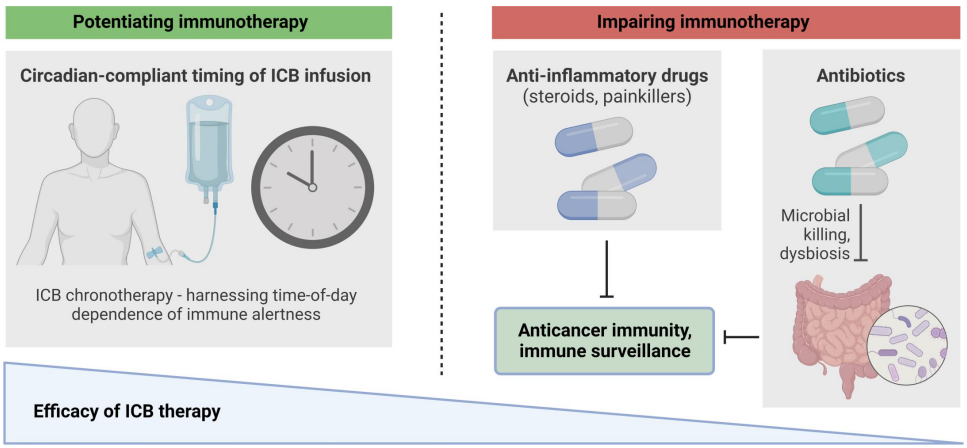

Figure 3. Dependence of immune checkpoint blockade efficacy on circadian rhythm and co-medication. Accumulating data suggest that circadian-compliant timing of ICB infusion is critical for mounting an optimal immune/treatment response. Specifically, studies have shown superiority of morning over evening ICB administration, evidenced on the level of survival in both melanoma and lung cancer. On the other hand, ICB therapy also underlies regulation from co-medication, with widely used drugs such as antibiotics, glucocorticoids and the painkiller acetaminophen (paracetamol) impairing ICB efficacy hence jeopardizing patient outcomes. Infusing checkpoint inhibitors in the morning (or early afternoon) by default and waiving the use of anti-inflammatory drugs whenever medically possible is proposed as an instantly actionable and cost-neutral/-saving strategy to optimize ICB performance. *abbreviations used*: ICB, immune checkpoint blockade. Figure created with BioRender.com.

this certainly holds true for late-stage/cachectic cancer patients, patients with extensive comorbidities, and patients under aggressive cytotoxic and/or lymphodepleting treatments, patients with early-stage/localized disease, young patients, patients in remission, and patients currently receiving ICB therapy may not be very vulnerable – at least not in immunological and physical terms. Moreover, patients under ICB may develop irAEs which are annoying and sometimes even treatment-limiting but which may also reflect the amplitude of the reinvigorated immune response and treatment efficacy.[88–91] From a psychological perspective, cancer patients faced with substantial suffering and existential anxiety will evoke compassion, possibly resulting in a tendency for 'over-care' and the desire to maximally protect them – from cancer-related symptoms, treatment toxicity, and infectious threats, often through concurrent medication. But is this always good? Or can we trust ICB-treated patients to cope with a certain amount of pain/side effects and clear an ordinary infection on their own? Essentially, these questions target the use of concomitant medication known or suspected to subvert ICB efficacy, potentially jeopardizing patient outcomes.

Antibiotics were among the first classes of drugs for which a negative impact on ICB efficacy was shown when used concurrently or in close temporal connection to ICB therapy.[13,92,93] Reduced clinical activity of ICBs in patients co-treated with antibiotics is observed already at the level of treatment response and translates into worse PFS and OS in different types of carcinoma.[13] Given these data, prescription and use of antibiotics in cancer patients currently receiving, or scheduled to receive, ICB therapy should follow particularly careful considerations beyond the pure anti-infective perspective. As ICB is broadly used in oncology as initial treatment, a more conservative use of antibiotics is advised to not potentially diminish the antineoplastic effect. This is especially true for ordinary infections and situations where inflammation markers are up and cancer is suspected, with potentially forthcoming ICB use within days to weeks pending the final diagnosis. Reducing the use of antibiotics would help to preserve microbiota integrity and likely improve patient outcomes on a population scale. Therefore, a mind-set is proposed in which cancer patients can handle common infections themselves without using microbiota-killing and ICB response-altering antibiotics. Moreover, the cautious use of antibiotics represents an important pillar in the management of a global health emergency that would significantly reduce antibiotic resistance.[94] Of note, reduced consumption of antibiotics may also be achievable through shorter treatment cycles. For example, a double-blind, randomized, placebo-controlled study showed non-inferiority of 3-days *versus* 8-days of β-lactam treatment in patients with community-acquired pneumonia who met predefined stability criteria at day 3 of treatment.[95] Non-inferiority was also shown for a 3-day *versus* a 5-day schedule of amoxicillin treatment in children with chest-indrawing pneumonia.[96] Thus, significantly shortening antibiotic treatment is feasible in different medical situations with non-inferior health outcomes but with suspended selective pressure, otherwise driving bacterial resistance evolution.

Glucocorticoids are commonly used in ICB-treated cancer patients mostly to manage irAEs and cancer-related symptoms. Their broad immune-suppressive activity deploys quickly and especially synthetic glucocorticoids have high potency, extended half-lives, and optimized bioavailability. A negative impact of glucocorticoids on ICB efficacy is inherently plausible and was proposed soon after the implementation and widespread use of checkpoint inhibitors.[97] Yet, systematic data were missing at that time. Several meta-analyses found a negative impact of glucocorticoid use on PFS and OS in ICB-treated cancer patients,[98–100] thus providing high-level evidence for steroids subverting ICB efficacy and advocating their cautious use. However, glucocorticoid-mediated impairment of ICB efficacy may depend on the primary reason for their use. Preliminary data suggest that detrimental effects on ICB efficacy are mainly observed when glucocorticoids are given to treat cancer-related symptoms.[99] In contrast, glucocorticoid use for managing irAEs may not – or to a lesser extent – affect patient survival.[99] This dichotomy is well-conceivable, considering that the amplitude of the immune response substantially differs between these two medical situations. Notwithstanding, glucocorticoids should be used with caution in cancer patients under ICB, and a certain extent of cancer-related symptoms and irAEs may be medically acceptable after joint decision-making for presumably higher treatment potency. In situations that require glucocorticoid use, local treatment forms (e.g., creams for skin reactions and inhalation for lung manifestations) and shorter treatment duration[101] should be envisioned.

Acetaminophen (paracetamol) is a prevalent painkiller and anti-pyretic drug used to treat common pain (e.g., headache, toothache), often by patients themselves without medical consultation. Given the anti-inflammatory properties of acetaminophen and its potential to blunt vaccine-induced immune responses, a recent study investigated the impact of acetaminophen exposure on the efficacy of ICB therapy in patients with advanced cancer.[102] Employing three independent patient cohorts and preclinical tumor models, the study showed a negative impact of acetaminophen consumption on ICB treatment efficacy.[102] Patients with detectable plasma acetaminophen concentrations at the onset of ICB treatment showed a significantly worse clinical outcome, and acetaminophen use was also associated with upregulation of the regulatory T cell (Treg) inducer IL-10 in ICB-treated patients as well as with T reg expansion in healthy individuals.[102] Accordingly, acetaminophen reduced the efficacy of ICB therapy in preclinical tumor models and was further associated with increased tumor Treg infiltration.[102] Although requiring further validation, these data argue that acetaminophen should be used cautiously in patients receiving ICB, and attending physicians may bring up this issue during routine consultations to raise patient awareness. Considering that acetaminophen may only be effective in the treatment of mild-to-moderate pain conditions, it is argued that it can often be omitted entirely – for a bit more of transient pain potentially, but with the reasonable hope for sustained efficacy and improved long-term outcome.

Collectively, commonly used drugs, including antibiotics, steroids and painkillers, impair ICB efficacy and possibly put patients at risk of adverse long-term outcomes including shorter OS (Figure 3). The use of such drugs should therefore be restricted to situations where their short-term benefits outweigh their potential long-term harms. In a broader sense, the influence of certain medical interventions on ICB performance should in the future be addressed through therapeutic scheduling. While fast surgical

excision is key in resectable tumor settings, surgery-associated medication often invovles drugs that affect both microbiota and the immune system, possibly impinging on the downstream therapeutic cascade. Conversely, the neoadjuvant treatment setting[103,104] seems to provide an opportune moment for ICB as microbiota and the immune system remain largely unperturbed from clinical intervention at this stage. Treatment-induced damage to microbiota and the immune system may also contribute to the declining activity of ICB (and other anticancer drugs) in higher therapy lines. Smart therapeutic scheduling and consolidation of first-line and neoadjuvant ICB indications are therefore warranted to further optimize ICB efficacy.

Vitamins and nutraceuticals

Vitamins are of critical importance for human metabolism and represent classical nutritional supplements commonly used in both preventive and treatment support settings – often on personal initiative and without a particular medical indication. In cancer, the role of vitamins has been intensely investigated and data from large trials have shown mixed results as regards incidence cancer risk.[105–107] Studies of the effect of vitamin supplementation on cancer outcomes have also not revealed consistent findings even though some beneficial effects were observed.[108–111] Evaluating vitamins as treatment adjuncts for ICB bases on rational assumptions (many vitamins are immune modulators) and is also supported by a wealth of quite promising early-stage data.[112–116] An important study recently found an association of vitamin E intake with improved survival of ICB-treated patients, with vitamin E enhancing anticancer immunity by targeting the DC-intrinsic immune checkpoint SHP1 and fostering cross-presentation of tumor antigens to up immune surveillance.[117] Similarly, a study involving 200 patients with advanced melanoma treated with PD-1 inhibitors (nivolumab or pembrolizumab) showed that vitamin D supplementation increased the objective response rate and significantly prolonged progression-free survival (PFS).[118] Promising early-stage data have also been reported for supplementation with vitamin C[113,114,119] and the vitamin B3 analogue nicotinamide riboside.[120]

Nutraceuticals and over-the-counter (OTC) products may also have a potential role in augmenting anticancer immunity and ICB efficacy even though this role is hypothetical at the moment and requires scientific scrutiny. Immunonutrition, i.e., the dietary supplementation of 'immunonutrients' such as arginine, omega 3 fatty acids and nucleotides, is currently investigated as an ICB sensitizer in non-small cell lung cancer (NSCLC) in a randomized, controlled trial of 180 patients (NCT05384873).[121] An interesting study also showed that allergic reactions promote immunotherapy resistance *via* activation of the histamine receptor H1 on macrophages and that cancer patients that used H1-antihistamines during PD-1/PD-L1-targeted immunotherapy survived significantly longer in a retrospective analysis.[122] This raises the hypothetical possibility of using OTC drugs such as antihistamines for optimizing cancer immunotherapy.

In summary, ample evidence for the use of vitamins, nutraceuticals and OTC products as ICB sensitizers is missing and clinical testing in randomized controlled settings is warranted. Until more robust data are available, the use of nutritional supplements and OTC products cannot be generally recommended, particularly also in view of potential harmful effects (cf. OTC probiotics.[34,35]).

Digital therapeutics for behavior change

While circadian-compliant timing of ICB infusions and reductions in concomitant medication need to be medically implemented on institutional levels, diet, physical activity, and stress management all depict behavioral factors that are directly controllable by patients, given affordability (e.g., nutrient-rich diets), a certain amount of motivation, health literacy, and sufficient physical functioning in the case of physical activity. However, a significant proportion of cancer patients maintains an unhealthy diet, is physically inactive, and also does not invest in stress management. Getting these patients to sustain a healthier lifestyle requires behavior change, i.e., the personal, intentional endeavor to disrupt long-standing habits in a complex social, political, and economic environment.[123] The difficulty of behavior change is highlighted, for instance, by patients affected by a non-communicable disease (NCD) not managing to avoid the unhealthy behavior that *presumably caused* their disease (e.g., persistent Western-type diet and physical inactivity in obesity and metabolic disease, persistent smoking in lung cancer and chronic obstructive pulmonary disease, etc.). It follows that providing support to initiate behavior change and adopt a healthy lifestyle is critical for long-term benefit on a population scale, even in the non-preventive/disease setting and in populations with an exceptionally high degree of suffering and anxiety, such as cancer patients. But how should such support be best delivered, taking into account healthcare costs, limited availability of healthcare professionals (HCPs), scalability potential, and the goal to keep up behavior change long-term in everyday life?

While the initial impetus for changing health-related behaviors may come from physicians, HCPs, cancer societies, and patient organizations, digital therapeutics (DTx) provide a valuable means to implement and maintain health-promoting behavior in everyday life. DTx are software-based therapeutic interventions delivered *via* everyday technology such as smartphones or websites.[124–126] In some countries, they are already prescribed by HCPs and reimbursed by health insurance companies, given that they are safe, effective, and cost-efficient.[126] Advantages of DTx include that they are scalable, can be tailored to individual needs, can be delivered just-in-time targeting states of vulnerability and receptivity, and are applicable for long-term use at sustainable costs.[127–129] DTx can be realized as (embodied) conversational agents.[130–135] or wearable devices,[136–138] and may employ different techniques from behavioral medicine and clinical psychology for health-promoting behavior, including cognitive behavioral therapy,[139–141] mindfulness-based approaches,[142,143] goal setting and action planning,[144–146] and motivational tools such as nudges,[147,148] gamification,[149,150] and rewards/incentives,[151,152] or a combination of these techniques.[153,154] DTx that target behavior change in cancer immunotherapy patients may comprise ICB-specific health literacy programs, diaries and questionnaires, and practical modules including physical activity schedules, activity tracking, nutrition plans, breathing exercises, and meditation techniques. Such DTx should also emphasize that a composite healthy lifestyle is associated with a reduced risk of premature

death in cancer survivors,[155] that the leading risk factors for cancer and disability-adjusted life-years are behavioral,[156] and that almost 50% of cancer deaths are due to preventable, mostly lifestyle-related risk factors.[157] This may lead to patient empowerment and a certain level of control and influence.

Another important aspect of DTx for health-related behavior change is to incorporate the patients' social networks in the intervention. As studies have shown, support from social relationships, in particular family and friends, is a key factor for successful behavior change in multiple settings.[158–161] Thus, active engagement of social networks in family-[159] or community-based interventions[162] represents a promising strategy to increase the efficacy of DTx targeted at health-related behavior change in cancer immunotherapy.

Many lifestyle-related DTx are marketed as 'lifestyle' products and lack clinical evidence or software-as-a-medical device certification,[163,164] especially in the area of cancer indications. However, this is beginning to change, and interventions aiming to improve physical activity/sedentary behavior, nutritional status, and coping with stress in cancer have recently entered clinical testing, partially even in randomized controlled settings.[165–170] In addition, renowned cancer institutes and startup companies are developing, or are already providing, DTx targeting behavioral factors in cancer patients. In most cases, these DTx need to be better tailored to cancer immunotherapy and should, at best, also be validated in terms of their primary intended purpose, with a particular focus on adherence and efficiency. On the other hand, pragmatic ways of implementation, regulatory approval, and reimbursement strategies are needed to increase access to effective DTx. The DTx regulation in Germany implemented in 2020 may also be a good blueprint for other countries in this regard.[171]

Psychological aspects of 'healthification' in cancer patients

Although advertising particular diets, physical activity, and stress management among cancer patients receiving ICB is scientifically and medically indicated, it raises some concerns from a psychological perspective. First, patients in an already difficult situation may be confronted with their not-so-healthy lifestyles and potentially faced with missed opportunities from the past, which can be a bitter experience. Second, patients may rationally and even emotionally understand the importance of health-related behavior changes yet be unable (or unwilling) to implement or sustain these changes. This can lead to feelings of personal failure in the sense that not everything is done that could potentially be done to improve ICB efficacy and outcome. Third, even though the aspired lifestyle changes will statistically optimize ICB efficacy and improve survival, therapy tolerability, and QoL, the sizes of these effects remain unknown, and there is no guarantee of benefit in the individual case. Thus, promoting a healthy lifestyle to improve patient outcomes is essential but should rest upon careful communication by HCPs to not raise false hopes, which are then programmed to be deceived (motto: *healthification helps, but it's not magic*).

Shared decision-making and management within multidisciplinary, inter-professional teams including psychological expertise,[4,172–174] will be essential for tackling healthification in the setting of ICB. Next to CCCs, patient organizations such as cancer societies and peer support groups could strongly promote healthification in cancer patients. Dialogues on behavior change in the core domains of diet, physical activity, and stress should focus on sound scientific information, be empathetic, and be free from emotional bias. Patient empowerment and a positive motivation framing are indeed crucial. Still, patients should be free not to follow the medical recommendations and pursue a lifestyle that neither supports ICB efficacy nor their QoL – ultimately as a reflection of patient centricity, free will, and personal responsibility.

Concluding remarks

When checkpoint immunotherapy is used to combat cancer, much is at stake – first and foremost, the patients' lives, but in a broader context, the healthcare system's economic sustainability. Therefore, on the institutional and public health levels, optimizing ICB therapy as much as possible should be a moral obligation. NPIs provide an attractive opportunity to do so. NPIs may enhance ICB efficacy in the current lead indications (e.g., melanoma, lung cancer, TMB-high/MSI-high cancers) and may also extend the ICB application spectrum to less immunogenic tumor entities. The level of evidence is currently highest for microbiome- and immunosuppression-related NPIs (waiving of antibiotic and steroid use, and dietary change), lower for other types of NPIs including ICB chronotherapy, physical activity, and active stress management, and hypothetical for vitamins and nutraceuticals. The beauty of NPIs is that they are readily available, immediately actionable, and cost (almost) nothing. Moreover, NPIs are generally considered safe and even when clinical benefit is individually absent, positive effects on QoL can still be expected. Thus, NPIs nicely add to the concept of value-based healthcare, and their broad clinical implementation would benefit all stakeholders involved, including patients, physicians, HCPs, pharma companies, health insurances, patient organizations, employers, and society as a whole. A major shortcoming is that the effect sizes of NPIs are currently unknown such that specific clinical recommendations cannot be given at this stage (e.g., *eat this and that amount of X* and *perform physical activity X-times a week for X minutes at X intensity for a projected average survival benefit of X months*). Therefore, prospective clinical trials of NPIs as a catalyst for ICB efficacy and QoL are warranted and may constitute the next generation of cancer immunotherapies optimized and conducted within a patient-centric, holistic framework engaging also social networks.[4]

List of abbreviations

3HB	3-hydroxybutyrate
APC	Antigen-presenting cell
BMI	Body mass index
CCC	Comprehensive cancer center
CR	Calorie restriction
DTx	Digital therapeutic
FFD	Fermented-food diet
GI	Gastrointestinal
GMP	Good manufacturing practice
HCP	Healthcare professional

HFD	High-fiber diet
ICB	Immune checkpoint blockade
irAE	Immune-related adverse event
KD	Ketogenic diet
MSI-H	Microsatellite instability-high
NCD	Non-communicable disease
NPI	Non-pharmaceutical intervention
NSCLC	Non-small cell lung cancer
OS	Overall survival
OTC	Over-the-counter
PDX	Patient-derived xenograft
PFS	Progression-free survival
QoL	Quality of life
TMB	Tumor mutational burden
TME	Tumor microenvironment
Treg	Regulatory T cell

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