Immune Checkpoint Inhibitors and the Exposome: Host-Extrinsic Factors Determine Response, Survival, and Toxicity

Authors: Elio Gregory Pizzutilo[1,2]^, Rebecca Romanò[1,2]^, Laura Roazzi[1,2]^, Alberto G. Agostara[1,2], Sara Oresti[1,2], Annalisa Zeppellini[1], Laura Giannetta[1], Giulio Cerea[1], Diego Signorelli[1], Salvatore Siena[1,2], Andrea Sartore-Bianchi[1,2]*

^equally contributed as first authors

Affiliations: [1]Niguarda Cancer Center, Grande Ospedale Metropolitano Niguarda, Milan, Italy [2]Università degli Studi di Milano, Department of Oncology and Hemato-Oncology, Milan, Italy

***Corresponding author:**

Prof. Andrea Sartore-Bianchi

Department of Oncology and Hemato-Oncology, Università degli Studi di Milano, Milano, Italy, and Niguarda Cancer Center, Grande Ospedale Metropolitano Niguarda, Milano, Italy

andrea.sartorebianchi@unimi.it

Tel: +39 02 6444 2291

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Abstract

Cancer immunotherapy, largely represented by immune checkpoint inhibitors (ICIs), has led to substantial changes in preclinical cancer research and clinical oncology practice over the past decade. However, the efficacy and toxicity profiles of ICIs remain highly variable among patients, with only a fraction achieving a significant benefit. New combination therapeutic strategies are being investigated, and the search for novel predictive biomarkers is ongoing, mainly focusing on tumor- and host-intrinsic components. Less attention has been directed to all the external, potentially modifiable factors that compose the exposome, including diet and lifestyle, infections, vaccinations, and concomitant medications, which could affect the immune system response and its activity against cancer cells. We hereby provide a review of the available clinical evidence elucidating the impact of host-extrinsic factors on ICI response and toxicity.

Introduction

In the recent years, immune-checkpoint inhibitors (ICIs) have transformed the landscape of medical cancer treatments, shifting the therapeutic target to the immune system, outside the cancer cell. ICIs act by binding to immune checkpoint proteins – including Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), Programmed cell Death protein 1 (PD-1) and Programmed Death-Ligand 1 (PD-L1) – preventing their activation: this hinders tumor-mediated immune evasion, thereby promoting the development of a functioning anti-tumor response and aiding immune-mediated tumor killing. CTLA-4, PD-1 and PD-L1 inhibitors have been gradually integrated into standard-of-care treatment of distinct tumor types in different stages, with a proportion of patients with advanced disease experiencing unforeseen durable responses. Anyway, such long-term benefits are limited to approximately 30-40% of cases in melanoma, 25% in non-small cell lung cancer (NSCLC), 25-30% in renal cell carcinoma (RCC) (1). Indeed, the efficacy and toxicity profile of immunotherapy (IT) remains highly heterogeneous and characterized by a significant, hardly foreseeable inter-subject variability, with potentially unusual patterns of response (i.e., pseudo-progression, dissociated progression, hyper-progression) and showing disparate immune-related adverse events (irAEs) (2). To increase the number of successfully treated patients, research has been focusing on combining ICIs with other treatments, – i.e., cytotoxic chemotherapy (CT), anti-angiogenic and targeted agents, radiotherapy (RT) – to maximize the anti-cancer activity of the immune system (3).

In this scenario, the search for predictive biomarkers remains an urgent need, to better select patients who may benefit the most from IT agents in terms of both benefit-toxicity and cost-effectiveness ratio. To date, research has unraveled numerous factors impacting on ICIs response, which are largely represented by tumor immune-molecular characteristics and host-intrinsic

factors – i.e., PD-L1 expression, tumor mutational burden (TMB), deficient MisMatch Repair/MicroSatellite Instability (dMMR/MSI) status, tumor microenvironment, human leukocyte antigen (HLA) type, Eastern Cooperative Oncology Group Performance Status (ECOG PS), to name a few (4).

On the other hand, less systematic attention has been dedicated to all those factors which are external to the host and to the tumor and, as such, often potentially modifiable – namely, "the exposome". The latter may be defined as all the non-genetic factors to which a subject is exposed, and which may impact on their health and/or disease status (5). Indeed, environmental factors are increasingly being acknowledged as variable and dynamic entities which deeply affect individuals through their lifetime. Different exposome components may influence their health and/or disease status, also with exposure-induced immune effects, to an extent that remains largely unexplored (6). Given that IT relies on the ability of the immune system to recognize and eliminate tumor cells, it appears clear that the immune status of the host becomes pivotal in this specific setting (7–10). Conversely, the influence of host immunity is probably less crucial for the outcomes of conventional cancer therapies – i.e., RT, CT, targeted therapies - which exert direct cytotoxic effects or interfere with specific oncogenic pathways, respectively.

While it may be challenging to collect high-quality evidence concerning the potentially countless, heterogeneous factors falling under the 'exposome' umbrella, in this review we provide an updated critical summary of the most relevant clinical evidence concerning the host-extrinsic factors which were shown to impact on the efficacy and/or the toxicity profile of ICIs. A comprehensive search strategy was applied to identify relevant literature in the PubMed, up to February 2023 (**Box S1**). In detail, we focused on the available data about the role of dietary and lifestyle factors, chronic infections and vaccines, and concomitant medications.

1. Diet

The influence of diet and nutrition on ICIs outcomes is inherently difficult to evaluate; still, evidence is supporting direct effects of dietary factors on the host's immune functions, as well as the possibility for dietary-induced modulation of the host's microbiome (11). Focusing on direct effects, the impact of dietary fiber intake was firstly retrospectively evaluated through the National Cancer Institute dietary screener questionnaire in a cohort of 128 melanoma patients receiving ICIs. An improved progression-free survival (PFS) was observed in those with a sufficient (≥20 g/day) vs. an insufficient dietary fiber intake (PFS not reached vs. 13 months), with every 5 g increase in daily dietary fiber corresponding to a 30% lower risk of progression or death. On the contrary, over-the-counter probiotic supplementation did not favor ICIs outcomes (12). Also, a prospective study confirmed the positive impact of a high-fiber diet, both in terms of response and reduced irAEs within a neoadjuvant trial for patients with melanoma (13). In this regard, a randomized trial for assessing the effects of dietary intervention is underway (NCT04645680).

Moving to the interaction between diet and host's microbiome, preclinical and early clinical data have shown a relevant interplay between gut microorganisms and antitumor effects of ICIs (14,15), fostering the research for immunomodulation strategies through dietary microbiome modifiers. In this regard, a greater microbiome diversity (alpha diversity, according to the Shannon index) has been associated with higher benefit with ICIs (16,17). The largest available data regards *Verrucomicrobiaceae* family – especially *Akkermansia muciniphila* (*Akk*) – and *Ruminococcus* genus, which have been described as an "immunologic guild", whose abundance has been associated with responses to PD-1/PD-L1 blockade (13,18). Prospective studies have reported a correlation between *Akk* abundance and clinical benefit from ICIs in either RCC, NSCLC and

melanoma (13,19,20). Also, *Ruminococcaceae* have been prospectively associated with clinical response to ICIs in melanoma, gastro-intestinal cancers, sarcoma and NSCLC (13,21–23). In particular, a higher diversity of gut microbiome with relative abundance of *Ruminococcacae* correlated with fiber and omega 3 consumption and appeared to facilitate anti-tumor immune responses, minimizing the risk of irAEs, during neoadjuvant immunotherapy for melanoma, NSCLC and sarcoma (13,24). Notably, non-responders with high TMB had significantly lower diversity, highlighting the potential importance of tumor-extrinsic factors (13).

Hence, diet modifications could have an impact on gut microbiome. A caloric restriction and supplementation with pomegranate extract, resveratrol, polydextrose, yeast fermentate, and inulin could lead to increased *Akk* prevalence, while a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols could result in lower *Akk* prevalence (25). RCTs have shown that a diet rich in complex carbohydrates and fibers and poor in cholesterol, such as a vegetarian or vegan diet, correlated with higher representation of *Ruminococcaceae* (26–28). Anyway, a clear demonstration that modification of the relative abundance of *Akk* or *Ruminococcaceae* in the gut by means of dietary adjustments or supplements could factually change the outcome of cancer patients under ICIs is still lacking. Moreover, a limited reproducibility of microbiome-based signatures has been described and no single species could be considered a reliable biomarker across studies (29). Recently, the first phase I RCT of ICIs with a bifidogenic live bacterial product (*Clostridium butyricum* CBM588) as a modulator of the gut microbiome has been published. Thirty treatment-naïve, metastatic RCC patients were randomized (2:1) to receive nivolumab and ipilimumab with or without daily oral CBM588. The change of the relative abundance of *Bifidobacterium spp.* in gut microbiome from baseline to 12 weeks was not met as a primary endpoint, although an increase in *Bifidobacterium spp*. was evident in patients who responded to CBM588 with ICIs. As a secondary

endpoint, PFS was significantly longer in patients receiving nivolumab–ipilimumab with CMB588 than without [12.7 vs. 2.5 months, hazard ratio (HR) 0.15, 95% confidence interval (95%CI) 0.05–0.47] (30).

In summary, certain diet modifications could change the prevalence of specific bacterial species in the gut, potentially impacting on outcome to treatment. Although to date there is no practical strategy to modify the outcomes of patients receiving ICIs by means of a dietary-induced microbiome modulation, some evidence suggests a possible favoring role played by high-fiber diet (**Figure 1, Table S1**).

2. Lifestyle

An association between higher *body mass index* (BMI) and survival has been previously described in cancer patients treated with different therapies, whereas cancer-induced weight loss (WL) is a well-known negative prognostic factor (31–33). In line with the historical 'obesity paradox', systematic reviews and metanalyses have observed improved outcomes with ICIs in patients with a higher BMI, with most of the evidence regarding melanoma, NSCLC and RCC (34–38). However, such conclusions were based on retrospective data, with significant inconsistencies among studies (35,36). The most recent and largest meta-analysis including 19,767 patients confirmed a benefit in survival with overweight/obesity (PFS HR 0.89, P=.009; overall survival (OS) HR 0.77, P<.00001) (39). On the other side, the negative influence of *sarcopenia*-associated skeletal muscle depletion on ICIs treatment outcomes (response and survival) has been confirmed among a variety of studies and cancer subtypes (39–49). In this regard, a more complex picture has been recently outlined: (1) BMI-related survival benefit could be driven by the male subgroup, since overweight/obese female patients did not show any advantage in the largest available meta-analysis (data for sex-specific OS available for greduced skeletal muscle independently correlated

with worse survival for NSCLC, but not for melanoma (50); (3) the role of metabolic dynamic changes has been recently addressed, in contrast with single timepoint evaluation of BMI (i.e., before ICIs start): indeed, WL is common among cancer patients (37% for NSCLC, 22% for melanoma), and the paradoxical association of BMI with survival vanished when appropriately adjusting for WL (50,51).

Focusing on toxicity, an increased risk of irAEs has been reported in patients with higher BMI for both sexes, including high grade events (39,52–54). On the other hand, a retrospective pooled analysis of 3772 patients enrolled in 14 CheckMate trials across 8 tumor types, confirmed the increased incidence of irAEs for obese patients treated with nivolumab, with an odds ratio (OR) of 1.71. However, the risk of G3-4 irAEs did not increase, except for obese female patients. Such inconsistency might be explained by the heterogeneity of included studies and by the limitations of subgroups analyses. For example, obese patients treated with a combination of nivolumab and ipilimumab did not experience more irAEs, especially with higher dose of ipilimumab (3 mg/Kg), where higher overall incidence of irAEs could mask the impact of BMI (55).

In conclusion, higher BMI appears a favorable factor for ICIs outcomes, especially for males with NSCLC, despite an increased risk of irAEs. Anyway, the true predictive value of body composition for ICIs-related outcomes remains uncertain, due to heterogeneous definitions and measurement methods (i.e., BMI, WL, cachexia/sarcopenia, “sarcopenic obesity”, different approaches to detect muscle depletion) and several other confounding factors potentially related to survival and body weight (sex, comorbidities, inverse relationship between BMI and smoking, socioeconomic status, detection bias, etc.) (34).

No data are available concerning the impact of *physical activity* on ICIs efficacy, despite encouraging pre-clinical results (56). A prospective pilot study demonstrated the feasibility of a multimodal supportive care program, including physical exercise, among metastatic melanoma

patients treated with pembrolizumab (57). However, no clinical evidence supporting the influence of physical activity on oncologic outcomes could be derived.

Tobacco smoking is a leading risk factor for tumors originating across different body districts. A specific mutational signature can be recognized in some tobacco-associated cancers, which are often characterized by a higher TMB (i.e., lung adenocarcinoma, RCC) (58), correlating with more abundant neoantigens and greater benefit from ICIs (59–66). Across different cancers, objective response rate (ORR) and OS advantages have been observed among smokers vs. never-smokers receiving ICIs (67,68). Evidence relating to the specific immune-modulatory impact of cigarette smoking during ICIs-based therapy is limited, as most of literature describes previous/current smokers within a single category, also considering the differences in cancer biology of ever- and never-smokers. Concerning NSCLC, limited and contrasting data have been reported with different ICIs in first-line setting (69–71) (**Table S1**). On the other hand, combined ICI-CT for NSCLC has provided survival advantages both to smokers and never smokers compared to CT alone, but no data are available regarding the impact of concurrent smoking on patient outcomes under ICIs (66,72,73). Finally, a recent metanalysis including 25 studies (N=6696) underlined that an active or former smoking status was significantly associated with the development of irAEs in NSCLC (OR 1.25; CI95% 1.02–1.53). The authors postulated that this was a result of the pro-inflammatory impact of cigarette smoking, leading to loss of tolerance to self-antigens (74) (**Table S2**).

Overall, data about concurrent tobacco smoking are inconclusive, with contrasting results for pembrolizumab vs. atezolizumab. In this regard, the direct effect of cigarette smoking on disease biology and the global benefit of smoking cessation must be considered as relevant potential confounders (58,75) (**Figure 1, Table 1**).

3. Chronic infections and vaccinations

While, on one side, the activation of host immunity triggered by acute infections may enhance anti-tumor immune response [e.g., reports of tumor regressions after accidental infections, Coley's toxins, and its latter, more successful counterpart Bacillus Calmette-Guérin (BCG)] (76–78), patients with chronic infections have been historically excluded from ICIs trials due to concerns about viral reactivation, treatment efficacy and toxicity: indeed, prolonged viral infection results in chronic T cell stimulation, which may lead to exhaustion or lack of responsiveness, especially considering cancer challenging microenvironment (i.e., hypoxia, low Ph, competition for nutrients) (79).

Human Immunodeficiency Virus (HIV)

Considering *people living with HIV (PLWH)*, both the tolerability and efficacy of ICIs seem comparable to non-HIV patients with cancer (80–82). While corticosteroids (CS) for irAEs management could represent a concern for opportunistic infections in this population, to date no greater incidence of such adverse events has been reported among the sparse HIV+ cancer patients treated with ICIs (80). In PLWH with advanced cancers receiving ICIs, ORR (30% NSCLC, 27% melanoma, 63% Kaposi sarcoma), disease control rate (DCR, 56% NSCLC) and safety (≥G3 irAEs: 8.6-11.5%) appear comparable to those observed in non-HIV+ patients, with up to 80-90% maintaining suppressed HIV loads during and after ICIs (82). In spite of these encouraging results, only 5% of ICIs-including clinical trials has allowed PLWH (83). Results from ongoing studies which include this fragile population are awaited (**Figure 1, Table 1, Table S2**).

Chronic Hepatitis B and C virus (HBV, HCV)

Most of the data regarding chronic viral hepatitis focus on *HBV/HCV* within hepatocellular carcinoma (HCC) setting, where the earliest data supporting the safety and efficacy of ICIs arose from the two prospective clinical trials CheckMate 040 (84) and KEYNOTE-224 (85). Further reassuring results regarding ICIs efficacy in virally infected patients derived from following reviews and metanalyses including different solid tumors, with similar results to those seen in non-HBV/HCV infected patients (86–90). On the other hand, reactivation risk of viral hepatitis during ICIs may still represent a concern, with a reported incidence of G3/4 liver transaminases elevation in HBV/HCV infected patients of 3.4% and 17.3%, respectively. Virus load may increase in 2.8% of patients without antiviral therapy, and 1.9% could present virus-related hepatitis. Such events, anyway, are commonly reversible by antiviral or CS treatment, without the need for ICIs suspension (88). Current evidence points towards a low risk of viral reactivation in HBV/HCV patients with ICIs, especially in cases of high baseline viral burden or of high-dose CS use for irAEs management (91,92). Anyway, chronic viral infections *per se* do not affect survival with ICIs (**Figure 1, Table 1, Table S1, Table S3**).

Vaccinations

Historically, concerns have been raised about whether concomitant *vaccination* impacts on ICIs activity or safety. Considering COVID-19 vaccines, *Mei et al* recently reported comparable ORR (25.3% vs. 28.9%, P=0.213) and DCR (64.6% vs. 67.0%, P=0.437) between vaccinated and non-vaccinated individuals among 2048 cancer patients receiving anti-PD-1 treatment (93). On the other hand, a recent systematic review with metanalysis including 19 studies (mostly observational) of influenza vaccination reported no significant difference in irAEs rates between vaccinated and unvaccinated patients, and no difference in ICIs discontinuation (94). No higher rates of irAEs have been reported in patients under ICIs who received concomitant COVID-19

vaccines (95). Moreover, a retrospective study showed no risk of new or relapsed irAEs within 30 days after mRNA COVID-19 vaccination among cancer patients on active treatment with ICIs (96).

In summary, available data points out that ICIs efficacy and toxicity profile in PWHIV appears comparable to that in HIV-negative patients. ICIs appear to be safe and effective also in chronic HBV/HCV+ patients, where a multidisciplinary approach is required to manage the risk of potential viral reactivation. Finally, concomitant influenza or COVID-19 vaccinations do not seem to impact ICIs outcomes or to increase the risk of irAEs (**Figure 1, Table 1**, **Table S1**, **Table S2**).

4. Concomitant Medications

Corticosteroids

CS are largely acknowledged as detrimental during ICIs treatment in the light of their immunosuppressive activity (e.g., lymphocyte toxicity), especially with sustained high doses (97). Indeed, several studies and metanalyses have documented the negative effects of the association between CS and ICIs across different tumors (98,99). More specifically, large systematic reviews and metanalyses including different cancer types showed an increased risk of death (HR 1.54, 95%CI 1.24–1.91, P=0.01) and disease progression (HR 1.34, 95%CI 1.02–1.76, P=0.03) in patients using CS (98). Still, this effect could be deeply influenced, beyond the dose of CS, also by the timing (i.e., worse outcome if preceding and/or soon after ICI initiation (100)), and therapeutic indication, taking into account that patients requiring steroids are often characterized by worse ECOG PS, higher disease burden (i.e., brain metastases) and/or more aggressive disease. Indeed, worse outcomes are evident when CS are taken for supportive care (HR 2.5, 95%CI 1.41–4.43, P<0.01) or brain metastases (HR 1.51, 95%CI 1.22–1.87, P<0.01), but not when used to manage irAEs (98). This is coherent with previous reports of better ICIs outcomes in patients experiencing irAEs,

which may in turn compensate for CS immunosuppressive effects (101,102). Also, data concerning CS use for non-cancer-related indications (e.g. autoimmune disorders, chronic obstructive pulmonary disease) appear reassuring with even continuous low-dose steroids not seeming to hamper the maintenance of disease control (100,103,104). Moreover, short-course CS within premedication protocols for CT-IT combination therapies have not shown to significantly impact on survival outcomes (105) (**Table 1**).

Antibiotic therapy

To date, several studies and metanalyses described the negative impact of antibiotic therapy (ABT) on ICIs outcomes. Data derived mostly from observational, retrospective studies across different tumor types (106–108). The most recent metanalysis comprehensively analysed the available retrospective and prospective data, supporting a correlation between ABT use and worse outcomes in terms of PFS (HR 1.83, 95%CI 1.53–2.19, P<0.001) and OS (HR 1.94, 95%CI 1.68–2.25, P<0.001). Interestingly, patients using ABT resulted having a better ECOG PS score (≤1) (P=0.04), while no significant association was observed with PD-1 inhibitor type, patient gender, cancer stage, or ICIs treatment line (109). This constitutes a critical piece of information, considering the potential confounding effect of patient conditions in determining the final outcomes. Indeed, patients receiving ABT could represent a subgroup with poorer PS, which is a relevant negative predictive factor for ICIs-based treatments (110). Additionally, the described effect appears to depend on: (1) the duration of ABT, with multiple courses or prolonged treatment (≥7 days) being associated with worse outcomes, demonstrating the existence of a dose effect (111,112); (2) the timeframe of exposure, as, in a prospective study, prior but not concurrent ABT independently correlated with worse response and OS (113). Different retrospective studies have also reported a reduced survival among patients receiving ABT within a time window of 30-60 days. Such

timeframe could be dependent on the method of data collection (clinical records, patient-reported medical history), with intrinsic risk of recall bias (114, 115). Interestingly, in a recent population-based retrospective cohort study by Eng et al. (N=2737) previous ABT exposure was retrieved through health care registry, and a negative impact on survival was evident even with ABT carried out 1 year before ICIs therapy (HR 1.12, p=0.03) (112). With regard to immunological "hot" MSI-high tumors, a single retrospective study focusing on colorectal cancer is available. Hereby, ABT exposure did not seem to significantly impact on ICIs response. Anyway, the effect of ABT could have been masked by the high ORR (75%) and the small sample size (116).

The link between ABT use and ICIs outcomes entails ABT-induced modulation of the microbiota (18). Also, the positive impact of the aforementioned *Akk* in the gut microbiome could be negatively remodulated after ABT exposure (20). In a small, retrospective study, only broad-spectrum ABT (covering Gram-positive and negative with or without anaerobic bacteria), but not narrow-spectrum ABT (covering only Gram-positive, i.e., vancomycin, daptomycin, linezolid) negatively affected ICIs activity, suggesting a different outcome depending on specific perturbations of the gut microbiome (117). In the large study by Eng et al., fluoroquinolones were more strongly related to reduce outcomes compared with other ABT classes (112).
In lung cancer setting, a large, retrospective study also reported that ABT negatively affected ICIs monotherapy (OS: HR 1.42; PFS: HR 1.29), but not CT outcomes in first-line setting (118). In a following multicenter, retrospective study including 302 patients with stage IV NSCLC, the authors have observed that prior ABT did not carry a negative impact on the outcomes of patients treated with CT-IT combination therapy (119). Furthermore, in a pooled analysis of 5 RCT including atezolizumab-based therapy, ABT use did not result in worse outcomes. Importantly, 3 out of 5 trials included in this analysis evaluated atezolizumab in combination with CT or CT and bevacizumab (120). These observations suggest that CT activity may counterbalance the

detrimental effects of ABT on ICIs performance, resulting in synergically improved outcomes (121) (**Table 1, Table S3**).

Other studies have also discontinuously described an association between ABT administration and irAEs, as a potential consequence of induced dysbiosis (122–124). A retrospective study including 568 patients with melanoma treated with ICIs described a greater incidence of immune-mediated colitis (HR 2.14) in patients receiving ABT (123) (**Table S4**).

Proton pump inhibitors

Proton pump inhibitors (PPI) may alter the diversity and composition of the gut microbiome (e.g., allowing translocation of oral microbiome into the gut) and have been associated to nutritional deficiencies, higher risk of bone fracture and infections (125). A large metanalysis including 33 studies (N=15957) found a significant negative association between PPI use and survival in ICIs-treated patients (126). Two additional, metanalyses limited to patients with NSCLC confirmed that PPI use was correlated with poor OS and PFS (127,128). Moreover, a recent pooled analysis of 5 RCTs (N=4458) revealed that efficacy of atezolizumab in NSCLC, even in combination with CT and bevacizumab, was reduced for PPI users, and that PPI use was significantly associated with worse OS (HR 1.31) (120). Notably, a tumor-specific effect of PPI could exist. In a recent systematic review with network metanalysis, only advanced NSCLC and urothelial cancer (UC) patients treated with ICIs resulted negatively affected by PPI, while response to ICIs was not altered in advanced melanoma, RCC, HCC, and head and neck squamous cell carcinoma (HNSCC) (129). Regarding the timframe of exposure, similarly to ABT, shorter PFS has been described when PPI were received within 60 days before ICIs initiation (130). (**Table 1**).

Concerning toxicity, several retrospective series have documented a higher risk of ICIs-related acute kidney injury (AKI) with concomitant PPI use (131–135). Moreover, in retrospective series,

PPI exposure resulted an independent risk factor for sustained AKI (≥3 days) (131), and chronic use of PPI >8 weeks was significantly associated with immune-related colitis (136–138). Possible explanations for these findings include the potential of PPI to modify the gut microbiome and the priming of effector T cells: PPI may act as an exogenous antigen, triggering an initial immune response, which is then reactivated by ICIs (139) (**Table S4**).

Metformin

A number of preclinical data reported the pleiotropic activity of metformin against different pathways implicated both in proliferation of cancer cells and immune response (140). Four retrospective studies have assessed the impact of metformin in combination with ICIs in different tumor types (mostly melanoma and NSCLC). Two of them did not demonstrate a statistically significant impact, while describing favorable trends in treatment outcomes (ORR, PFS and OS) (140,141). The latter 2 retrospective analyses highlighted a significant improvement in terms of ORR and survival in patients with different cancer types, especially with higher doses of metformin (>1,000 mg daily) (142,143) (**Table S3**). Larger-scale, prospective clinical trials are ongoing in the attempt of further refining our understanding of metformin mechanisms of action and its putative synergistic effect when associated to ICIs (140) (**Table S5**).

Concerning irAEs, data from the FDA adverse events reporting system have suggested a potential higher risk of inflammatory bowel disease with combination of nivolumab and metformin. Anyway, such results could be biased, being obtained by a post-marketing database, as no other clinical report has confirmed a causal relationship up to now (144) (**Table S4**).

Statins

Recent retrospective evidences have suggested a positive impact on treatment outcomes from statins concomitant to ICIs. Statins could synergize with IT by their modulation of protein prenylation: this leads to prolonged antigen retention on cell membrane, hence boosting T-cell anti-tumor response (145). Metanalyses and retrospective series described an association between concomitant statins and improved outcomes for malignant pleural mesothelioma and RCC, but not for NSCLC (146-148). These non-conclusive data could be partially explained by heterogeneity in statin dose, since better results were evident with higher dose (atorvastatin 80 mg or rosuvastatin 40 mg) (149) (**Table 1, Table S3**).

No data supporting a clear causal correlation between statin usage and irAEs are available. Anyway, in a monocentric retrospective cohort of NSCLC patients treated with ICIs, treatment with statins resulted as an independent predictor for the development of irAEs (OR 3.15) (150) (**Table S4**).

Opioids and Non-steroidal anti-inflammatory drugs (NSAIDS)

Two metanalyses including retrospective cohorts of patients with different tumors, mostly melanoma and NSCLC, reported a significant worse outcome with the concomitant use of opioids and ICIs in terms of PFS (HR 1.61) and OS (HR 1.67-1.75), while contrasting results were described for concomitant NSAIDs (151,152). Opioids are known to negatively affect immune functions by several mechanisms, with both a direct action on T effector and Treg activity, as well as with an influence on gut microbiome. Moreover, NSCLCs often over-express opioid receptors, which may potentiate opioids pro-tumoral effect in this setting (153). On the other hand, relevant risks of bias exist as opioids use often reflects higher disease burden with more symptoms and worse ECOG PS (**Table 1, Table S3**).

Beta-blockers (BBs), renin-angiotensin-aldosterone system inhibitors (RAASi)

Considering preclinical knowledge supporting a correlation among beta-adrenergic signaling, tumor growth and immune functions (154), some retrospective studies have described a beneficial effect of BBs when used in combination with ICIs (155–157). Still, recent metanalyses, the largest including 11 studies and >10000 patients, did not confirm a significantly correlation with either OS or PFS (158,159). (**Table 1**).

An impact of RAASi (i.e., ACEi, angiotensin-converting enzyme inhibitors, and ARBs, angiotensin receptor blockers) concomitant to ICIs have been retrospectively described across different cancer types (160–163). This seems coherent with the known role of renin-angiotensin system in immunomodulation and tissue perfusion (164). The largest available study involved a population of patients with cancer and hypertension, and showed a better OS in the full cohort receiving a RAASi (more commonly lisinopril, losartan, and valsartan). However, better outcomes were noted for patients with gastrointestinal and genitourinary cancer, also in multivariate analysis, and the benefit was no more evident when excluding these subgroups from the full cohort (162). Contrasting data exists for patients with NSCLC. In particular, one group reported a shorter PFS providing *in vitro* evidence that ACEi could lead to a tumor immunosuppressed state deviating macrophages towards an M2-like phenotype (163). Finally, available data suggest no difference in the risk of potential irAEs in patients on RAASi (162) (**Table S4**).

Anticoagulants, antiplatelets

While a few studies, also prospectively, have reported the absence of correlation between anticoagulants and ICIs outcomes (165,166), *Cortellini et al* described a higher risk of disease progression and death for patients on anticoagulants at ICIs initiation (157). Conversely, in a retrospective cohort, metastatic melanoma patients receiving direct oral anti-coagulants (DOACs) had better ORR and PFS compared to patients who were not on anticoagulants (12 vs. 4 months)

(167). These conflicting results may reflect the preclinical evidence supporting the positive effects of Factor Xa DOACs on anti-tumor immunity (168), while, more in general, patients requiring anticoagulation therapy are often characterized by poorer PS and higher disease burden. As far as antiplatelets are concerned, a systematic review and metanalysis including 5 retrospective studies (mostly NSCLC and melanoma) documented that low-dose aspirin was associated with better PFS in patients treated with PD-1/PD-L1 inhibitors, without a significant effect on OS. In subgroup analysis such positive effect was evident only for NSCLC (147). These results may be explained by aspirin-mediated cyclo-oxygenase-2 (COX2) inhibition, as COX2 hyper-expression seems to correlate to more aggressive tumor biology and worse prognosis (169) (**Table 1, Table S3**).

Acetaminophen

Recently, measurable acetaminophen plasma levels at ICIs treatment onset were related with worse oncological outcomes in 3 independent cohorts of advanced cancer patients, independently of other prognostic factors (170). This is supported by preclinical studies demonstrating acetaminophen inhibitory action on immune cells proliferation and T cell-dependent antibody response, as well as its negative impact when administered before influenza vaccination (171–174) (**Table S3**).

In summary, the strongest evidence about concomitant treatments that negatively affect ICIs outcomes regards CS, where dose, timing, and indications are true determinants. Evidence concerning the negative impact of ABT and PPI is growing, with the latter being impactful even with ICIs-based combination therapies. Of interest, *Buti et al* computed and validated a drug-based prognostic score for patients with different cancer types treated with ICIs. In the training cohort (N=217) they found a HR for death of 2.3 with CS, 2.07 with ABT, and 1.57 with PPI use.

Based on exposure to one or more of these drug classes, they composed a score (2 points for CS, 1 point for ABT or PPI), ranging from 0 to 4 (0=good, 1-2=intermediate and 3-4=poor prognosis), demonstrating a cumulative prognostic value in terms of ORR, PFS and OS. The score was validated in an external cohort (N=1012), where OS ranged from 36 months for the good prognosis group to 8 months for the poor prognosis one, also with reduced PFS (14 vs. 5 months) and ORR (43% vs. 26%) (175).

To date, metformin has not confirmed its putative benefits, as studies investigating its potential impact on ICIs outcomes are still ongoing. BBs seem not impactful, while a small metanalysis suggested a benefit from low-dose aspirin. Opioids and acetaminophen appear to be associated to a negative effect, however possible confounders should be taken into consideration (e.g., ECOG PS). Unconclusive or limited data are available about NSAIDs, statins, ACE/RASi, and anticoagulants.

Conclusions and future perspectives

A growing number of studies have recently pointed out the potential role of the exposome in determining both benefits and adverse events derived from ICIs, with more than 140 publications since 2020 (referenced in this review). Indeed, external influences may modulate the immune system, with a large fraction of patients being exposed to them. For instance, dietary and lifestyle factors may have a long-lasting influence on immune-status and microbiome of patients. Also, several medications may positively or negatively contribute. For example, CS are widely used in oncology practice, 1 out of 4 patients receives ABT in the period before or after ICIs initiation (18), and PPI are often overprescribed, being inappropriate in at least half of cases (176). In a more complex outlook, the combination of all these factors may produce unpredictable interdependent effects (i.e., positive impact of dietary fiber plus negative impact of ABT/PPI plus positive impact of

BMI), and, in case of an unfavorable balance, different ICIs-based combination therapies may overcome the exposome-mediated detrimental impact. Of interest, the addition of CMB588 to ICIs may increase PFS in patients with RCC (30) and retrospective reports documented that the same probiotic therapy could restore the detrimental effects of PPI or ABT in NSCLC patients receiving ICIs (177,178).

Despite the huge, recent amount of available data, in most cases evidence derives from retrospective studies, with relevant risks of bias. Data are often derived from cohorts of mixed tumor types, as well, and no conclusions can be drawn regarding subsets of patients with diverse PD-L1, TMB, or MSI status. While pursuing common good clinical behaviors (i.e., a high-fiber diet, smoking cessation, avoiding over-prescription of both broad-spectrum ABT and PPI) could favor outcomes of patients receiving IT, a deeper knowledge of the exposome is needed to draw further conclusions.

Indeed, the exposome includes countless factors, with heterogeneous timeframes of action, for which the relative immune-modulating biological mechanism is often poorly understood. This makes the exposome an exceptional challenge for medical sciences (**Figure 2**). In this regard, some large-scale, longitudinal cohort studies are collecting data and specimens from healthy children and young adults following them throughout their lifespan, in the attempt to provide information about the impact of exposome across different diseases (179). Since a significant proportion of these individuals could ultimately develop cancer and eventually receive an ICIs-based therapy, these large datasets could provide new insight into the role of life-time exposure factors. Population-based studies (i.e. the recent study by Eng et al. where health care databases were queried (112)) may better analyze exposome with larger time-frame, especially with a multi-source strategy for data collection (hospital, pharmaceutical and administrative databases). One

more, still unexploited, source for longitudinal data collection could be represented by health apps, as a mean to potentially overcome the challenges of exposome data retrieval (180). On the other hand, several, prospective, observational, and interventional studies are now addressing the role of various exposome elements (probiotics, diet modifications, drugs) within a narrower timeframe of exposure, mostly overlapping cancer diagnosis and ICIs administration (**Table S5**). Such efforts could help clarifying the impact of this temporal segment of the exposome, overcoming the aforementioned limitations of retrospective studies.

Table 1. Systematic reviews/metanalyses on the impact of exposome factors on ICIs therapeutic outcomes

First author	Year	Type of study	Cancer type	Sample size	ICIs treatment	Concomitant exposome factors	Outcomes	Ref.
Diet and Lifestyle								
BMI								
An Y	2020	Metanalysis	NSCLC mRCC Melanoma	5279	Anti-PD-1/PD-L1 Anti-CTLA-4	High BMI	High BMI: better OS (HR 0.62, P<0.0001) and PFS (HR 0.71, P<0.0001)	*35*
Chen H	2020	Metanalysis	NSCLC mRCC Melanoma Solid cancers	5162	Anti-PD-1/PD-L1 Anti-CTLA-4	High BMI	High BMI: better OS (HR 0.698, P<0.001) and PFS (HR 0.760, P<0.001)	*36*
Takemura K	2022	Metanalysis	mRCC	2281	Anti-PD-1/PD-L1	High BMI	High BMI: better OS (HR 0.77, P=0.002) and PFS (HR 0.66, P=0.050)	*38*
Trinkner P	2023	Metanalysis	Solid cancers	22960	Anti-PD-1/PD-L1 Anti-CTLA-4	Overweight/obesity (19767) Sarcopenia (3193)	Obesity: better PFS (HR 0.89, P=0.009) and OS (HR 0.77, P<.00001) Sarcopenia: shorter PFS (p <0.0001) and OS (p <0.0001)	*39*
Sarcopenia								
Lee D	2021	Metanalysis	Solid cancers	1284	Anti-PD-1/PD-L1 Anti-CTLA-4	Sarcopenia	Sarcopenia: increased overall mortality (HR 1.66, P=0.002)	*42*
Takenaka Y	2020	Metanalysis	Solid cancers	2501	Anti-PD-1/PD-L1 Anti-CTLA-4	Sarcopenia	Sarcopenia: worse OS (HR 1.55, 95%CI 1.32-1.82) and PFS (HR 1.61, 95%CI 1.35-1.93)	*43*
Li S	2021	Metanalysis	Solid cancers	1763	Anti-PD-1/PD-L1	Sarcopenia	Sarcopenia: worse OS (HR 1.73, 95%CI 1.36–2.19, P<0.00001) and PFS (HR 1.46, P=0.001)	*46*
Wang J	2020	Metanalysis	NSCLC	576	Anti-PD-1/PD-L1	Sarcopenia	Sarcopenia: worse OS (HR 1.61, P< 0.001) and PFS (HR 1.98, P=0.001)	*47*
Deng H-Y	2021	Metanalysis	Solid cancers	740	Anti-PD-1/PD-L1 Anti-CTLA-4	Sarcopenia	Sarcopenia: lower ORR (30.5 versus 15.9%; P=0.095), worse 1-y PFS rate (32 versus 10.8%, P < 0.001) and 1-y OS rate (66 versus 43%; RR, 1.71; P < 0.001)	*48*
Ren B	2022	Metanalysis	NSCLC	970	Anti-PD-1/PD-L1	Sarcopenia	Sarcopenia reduce ORR (OR=2.22, P=0.02), 1.2 OS rate (OR = 2.44, P < 0.00001)	*49*
Chronic infections and vaccinations								
Chronic hepatitis B and C virus and HIV								
Kim C	2019	Systematic review	Solid cancers	73	Anti-CTLA-4 Anti-PD-1/PD-L1	HIV	HIV+: no difference in ORR, DCR, safety	*82*
Ho WJ	2020	Metanalysis	HCC	567	Anti-PD-1/L1	HBV/HCV	HBV/HCV+: no difference in ORR (absolute difference −1.4%, 95%CI −13.5-10.6)	*86*
Ding Z	2021	Metanalysis	HCC	1520	Anti-PD-1/PD-L1 Anti-CTLA-4	HBV/HCV	HBV/HCV+: no difference in ORR vs. HBV/HCV- (OR 1.03, P=0.152)	*87*
Pu D	2020	Systematic review	HCC Melanoma NSCLC	186	Anti-PD-1 Anti-CTLA-4	HBV/HCV	HBV/HCV+: no difference in ORR (32.4%)	*88*
Li B	2020	Pooled analysis	HCC	NA	Anti-PD-1/PD-L1	HBV	HBV+: no difference in ORR vs. HBV- (OR 0.68, P= 0.21) HBV+: worse DCR (OR 0.49, P=0.02)	*90*
Vaccinations								
Lopez-Olivo MA	2022	Metanalysis	Solid cancers	4705	Anti-PD-1/PD-L1	Influenza vaccination	Vaccinated: better PFS (HR 0.67, 95%CI 0.52-0.87) and OS (HR 0.78, 95%CI 0.62-0.99)	*94*
Concomitant Medications								
Antibiotics								
Zhou J	2022	Metanalysis	Solid cancers	12493	Anti-PD-1/PD-L1 Anti-CTLA-4	ABT	ABT: worse PFS (HR 1.83, P<0.001) and OS (HR 1.94, P<0.001)	*109*
Hopkins AM	2022	Pooled analysis	NSCLC	285	Atezolizumab +/- CT	ABT	No difference in OS (P=0.35)	*120*
Corticosteroids								
Petrelli F	2020	Metanalysis	Solid cancers	4045	Anti-PD-1/PD-L1 Anti-CTLA-4	CS	CS: increased risk of death (HR 1.54, P=0.01) and PD (HR 1.34, P=0.03)	*98*
Wang Y	2021	Metanalysis	Solid cancers	11180	Anti-PD-1/PD-L1 Anti-CTLA-4	CS	CS for cancer-related indications: worse PFS and OS (PFS: HR 1.735, 95%CI 1.381–2.180; OS: HR 1.936, 95%CI 1.587–2.361) CS for non-cancer-related indications: no difference in PFS/OS (PFS: HR 0.830, 95%CI 0.645–1.067; OS: HR 0.786, 95%CI 0.512–1.206) CS for irAEs: no difference in PFS/OS (PFS: HR 1.302, 95%CI 0.628–2.696; OS: HR 1.107 95%CI 0.832–1.474)	*103*
Proton pump inhibitors								
Hopkins AM	2022	Pooled analysis	NSCLC	1225	Atezolizumab +/- CT	PPI	PPI: worse OS (P=0.003)	*120*
Chen B	2022	Metanalysis	Solid cancers	15957	Anti-PD-1/PD-L1 Anti-CTLA-4	PPI	PPI: worse OS (HR 1.31, P<0.001) and PFS (HR 1.30, P<0.001)	*126*
Hu D-H	2022	Metanalysis	NSCLC	7893	Anti-PD-1/PD-L1	PPI	PPI: worse OS (HR 1.30, P=0.003) and PFS (HR 1.25, P=0.001)	*127*
Wei N	2022	Metanalysis	NSCLC	13709	ICIs	PPI	PPI: worse OS (HR 1.42, P<0.0001) and PFS (HR 1.50, P<0.0001)	*128*
Statins								
Zhang Y	2021	Metanalysis	NSCLC Mesothelioma	1479	Anti-PD-1/PD-L1 Anti-CTLA-4	Statins	Statins: better OS (HR 0.76, P=0.005) and PFS (HR 0.86, P=0.036)	*147*
Zhang L	2022	Metanalysis	NSCLC	2382	Anti-PD-1/PD-L1 Anti-CTLA-4	Statins	No difference in OS (HR 0.86, P=0.07) or PFS (HR 0.86, P=0.17)	*148*
Opioids, Non-steroidal anti-inflammatory drugs								
Mao Z	2022	Metanalysis	Melanoma NSCLC Solid cancers	4404	Anti-PD-1/PD-L1 Anti-CTLA-4	Opioids NSAIDs	Opioids: worse OS (HR 1.67, P<0.001) and PFS (HR 1.61, P<0.001) NSAIDs: no differences in ORR, PFS, and OS	*151*
Mingguang J	2022	Metanalysis	Solid cancers	2690	Anti-CTLA-4 Anti-PD-1/L1	Opioids NSAIDs	Opioids: worse OS (HR 1.75, P<0.001) and PFS (HR 0.02, P=0.60) NSAIDs: worse OS (HR 1.25, P=0.02), no difference in PFS (HR 1.11, P=0.36)	*152*
Beta blockers								
Kennedy OJ	2022	Metanalysis	Solid cancers	6350	Anti-PD-1/PD-L1 Anti-CTLA-4	Beta blockers	No difference in OS (HR 0.99, 0.83–1.18) or PFS (HR 0.97, 95%CI 0.89–1.05)	*158*
Yan X	2022	Metanalysis	Solid cancers	10156	Anti-PD-1/PD-L1 Anti-CTLA-4	Beta blockers	No difference in OS (HR 0.97, 0.85–1.11) or PFS (HR 0.98, 95%CI 0.90-1.06)	*159*
Anticoagulants, antiplatelets								
Zhang Y	2021	Metanalysis	NSCLC	1557	Anti-PD-1/PD-L1 Anti-CTLA-4	Low-dose aspirin	Low-dose aspirin: better PFS (HR 0.84; P=0.024), no difference in OS (HR 0.93; P=0.514)	*147*

Abbreviations: NSCLC: non-small cell lung cancer; UC: urothelial cancer, mRCC: metastatic renal cells carcinoma, CRC: colorectal cancer, HCC: hepatocellular carcinoma, HNSCC: Head and neck squamous cell carcinoma, PD-1: programmed death-1, PD-L1: programmed death ligand-1, CTLA-4: cytotoxic T-Lymphocyte Antigen 4, ICIs: immune checkpoint inhibitors, CT: chemotherapy, BMI: body mass index, ORR: objective response rate, PFS: progression free survival, OS: overall survival, HR: hazard ratio, DCR: disease control rate, mRNA: messenger ribonucleic acid, irAEs: immune-related adverse events, HBV: hepatitis B virus, HCV: hepatitis C virus, HIV: human immunodeficiency virus, CS: corticosteroids, PPI: proton pump inhibitors, NSAIDs: non-steroidal anti-inflammatory drugs, Ref.: references, NA: not available, CI: confidence interval

FIGURE LEGEND

Figure 1. The impact of concomitant exposome factors on ICIs, in terms of outcome and toxicity profile. Legend: (**+**): positive correlation; (**-**): negative correlation; (**=**): no impact; (**+/-**): inconclusive or conflicting data; (**/**)= insufficient data or not applicable. The level of evidence were classified as retrospective (•), prospective (••), and metanalysis-based (•••).
ABT: antibiotic therapy; BMI: body mass index; CS: corticosteroid; irAEs: immune-related adverse events; LoE: level of evidence; NSAIDs: non-steroidal anti-inflammatory drugs; OTC: over the counter; PPI: proton pump inhibitor; RAASi: renin-angiotensin-aldosterone system inhibitors.

Figure 2. Strategies and tools to retrieve exposome data within different timeframes. Exposome encompasses many host-extrinsic factors with heterogeneous timeframes of action (from lifespan to few weeks around diagnosis of cancer and ICIs therapy). Different study designs and associated tools may address its immune-modulating impact across different timeframes, ultimately providing data to better predict response and toxicity from ICIs.

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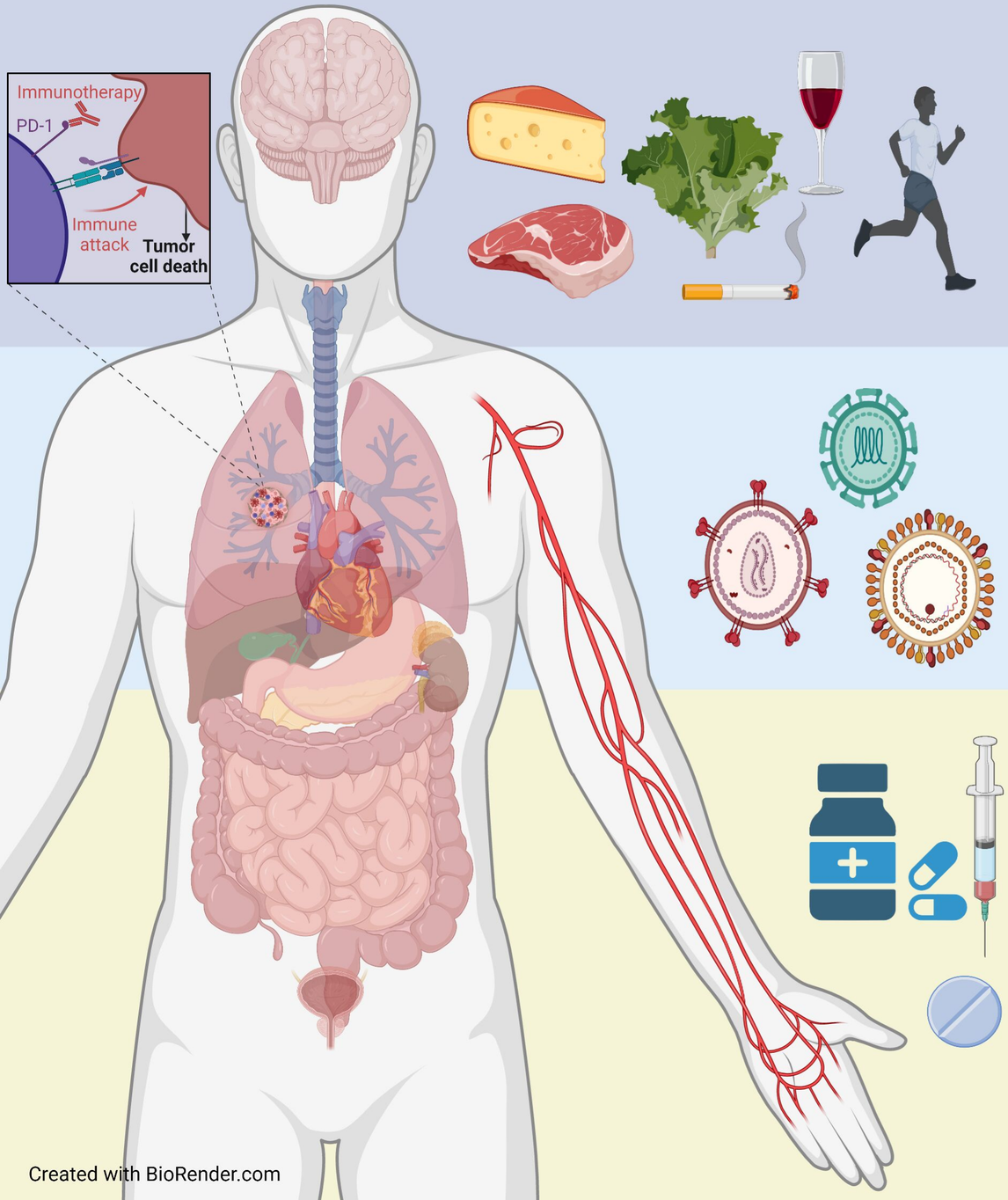
Figure 1



		Therapeutics outcomes	LoE	Risk of irAEs	LoE
Diet and lifestyle	Probiotics	=	••	/	/
	High BMI	+	•••	+/-	•••
	Fiber	+	••	-	••
	Sarcopenia	-	•••	+/-	•••
	Tobacco	+/-	•••	+	•••
Viral antigens	HIV	=	•••	=	•••
	HBV/HCV	=	•••	=	•••
	Vaccinations	=	•••	=	•••
Concomitant drugs	ABT	- *	••• *	+	•
	CS	-	•••	/	/
	PPI	-	•••	+	•
	Metformin	+/-	•	+	•
	Statins	+/-	•••	+	•
	NSAIDs	+/-	•••	/	/
	Opioids	-	•••	/	/
	Beta-blockers	=	•••	/	/
	RAASi	+/-	•	=	•
	Anticoagulants	+/-	••	/	/
	Antiplatelets	+	•••	/	/
	Acetaminophen	-	•	/	/

*Chemotherapy in combination with ICI may counterbalance ABT detrimental effect

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DATA COLLECTION

Large-scale, longitudinal, cohort studies with early-life information and biospecimens collection

Population-based studies (health registries)

Mobile health apps

Observational retrospective and prospective studies

Interventional studies

EXPOSOME

Lifespan exposure

Intermediate timeframe of exposure (years)

Narrow timeframe of exposure (months)

DATA ANALYSIS

OUTCOME

Patient diagnosed with cancer and receiving ICI-based therapy

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