‘Know thyself’ – host factors influencing cancer response to immune checkpoint inhibitors

Ashray Gunjur1,2*, Andrea J Manrique-Rincón1,3, Oliver Klein2,4, Andreas Behren2,5, Trevor D Lawley6, Sarah J Welsh7,8 and David J Adams1

1 Experimental Cancer Genetics, Wellcome Sanger Institute, Hinxton, UK
2 Olivia Newton-John Cancer Research Institute, La Trobe University School of Cancer Medicine, Heidelberg, Australia
3 Cambridge Institute of Therapeutic Immunology & Infectious Disease, Department of Medicine, University of Cambridge, Cambridge, UK
4 Department of Medical Oncology, Austin Health, Heidelberg, Australia
5 Department of Medicine, University of Melbourne, Parkville, Australia
6 Microbiotica Limited, Cambridge, UK
7 Department of Surgery, University of Cambridge, Cambridge, UK
8 Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK

*Correspondence to: A Gunjur, Experimental Cancer Genetics, Wellcome Sanger Institute, Wellcome Genome Campus, Hinxton, Cambridge, CB10 1SA, UK. E-mail: ag35@sanger.ac.uk

Abstract

Immune checkpoint inhibitors (ICIs) have revolutionised oncology and are now standard-of-care for the treatment of a wide variety of solid neoplasms. However, tumour responses remain unpredictable, experienced by only a minority of ICI recipients across malignancy types. Therefore, there is an urgent need for better predictive biomarkers to identify patients most likely to benefit from these therapies. Despite considerable efforts, only three such biomarkers are FDA-approved for clinical use, and all rely on the availability of tumour tissue for immunohistochemical staining or genomic assays. There is emerging evidence that host factors—e.g., genetic, metabolic, and immune factors, as well as the composition of one’s gut microbiota—fluence the response of a patient’s cancer to ICIs. Tantalisingly, some of these factors are modifiable, paving the way for co-therapies that may enhance the therapeutic index of these treatments. Herein, we review key host factors that are of potential biomarker value for response to ICI therapy, with a particular focus on the proposed mechanisms for these influences.

Keywords: immune checkpoint inhibitors; immunotherapy; biomarkers; predictive; host; germline; immune system; microbiome; metabolome

© 2022 The Authors. The Journal of Pathology published by John Wiley & Sons Ltd on behalf of The Pathological Society of Great Britain and Ireland.

Introduction

Though previously underappreciated, the relationship between cancer and host immunity is now fundamental to modern oncology practice. This has been catalysed by the discovery of ‘immune checkpoints’, immune self-tolerance pathways that cancer may leverage to ‘placate’ the immune system and avoid immunological rejection [1]. Their breakthrough discoveries have led to the development of monoclonal antibody inhibitors capable of preventing this immune escape, sparking an ongoing ‘immuno-oncology revolution’. In 2011, the US Food and Drug Administration (FDA) approved the first immune checkpoint inhibitor (ICI) targeting cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) or CD152, after it became the first drug ever shown to improve survival for patients with advanced melanoma [2]. Since then, ICIs targeting programmed cell death protein 1 (PD1 or CD279) and its ligand (PDL1 or CD274) have been approved for a varied and ever-growing list of solid-organ malignancies including melanoma, non-small cell lung carcinoma (NSCLC), renal cell carcinoma (RCC), and urothelial carcinoma, amongst many others [3].

However, important caveats have tempered the success of ICIs. Firstly, in the blockade of these immune homeostatic pathways, a subset of patients will develop auto-immune or auto-inflammatory disease, collectively labelled ‘immune-related adverse events’ (irAEs). The patterns and proportions vary by ICI class, with reports of clinically significant irAEs for metastatic melanoma patients of approximately 15%, 20%, and 55% for anti-PD1, anti-CTLA4, and combination ICI therapy.
respectively [4,5]. Secondly, though tumour responses to ICIs are often durable and clinically meaningful, they too are capricious and only occur in approximately 10–50% of patients with differing tumour histologies [3]. As such, extensive work has been invested in defining pre-treatment biomarkers: reliably-assessed biological signs that predict a priori who will clinically benefit. Thus far, only three such biomarkers have been approved by the FDA for clinical use: namely, tumour tissue PDL1 protein, tumour mutational burden (TMB), and mismatch repair (MMR) deficiency [6]. Unfortunately, both PDL1 and TMB are limited by issues of disharmony between assays, variable relevance across cancer types, and poor specificity (with responses still observed when the assay is deemed ‘negative’ and vice versa) [7,8]. Though MMR deficiency powerfully enriches for ICI response, it occurs in less than 5% of advanced cancers, limiting its applicability [9]. Further work has involved exploring characteristics of the tumour immune microenvironment, including tumour-infiltrating lymphocytes (TILs), innate immune cell characteristics, and immune gene expression scores. However, none have been approved for clinical use [10].

Notably, the bulk of ICI biomarker discovery efforts are ‘tumour-centric’, and are thus fundamentally reliant on tumour tissue. This may necessitate a further invasive procedure for patients where no contemporary archival tumour tissue is available, introducing their associated risk and the possibility of sampling error due to intraleisional heterogeneity [11]. Additionally, tumour-centric assays are less likely to be generalisable across cancer types – important when we consider the ever-expanding indications for ICI therapy. For example, we observed that TMB failed to associate with the responsiveness of a mixed cohort of advanced biliary tree, neuroendocrine, and rare gynaecological cancers treated with combination ICIs [12]. Just as ICI efficacy relies on the interface of the tumour and host immunity, we envision that optimal a priori prediction of ICI responsiveness will require consideration of both tumour and host features, for example, using ‘immunogram’-like approaches [13].

Therefore, in this review we highlight the evidence supporting a myriad of host-based factors as potential features in future ICI biomarker discovery efforts (Figure 1). We begin by reviewing circulating immune factors that may have pre-treatment prognostic or predictive value. We then describe germline genetic traits as well as general phenotypic host factors (such as body habitus and gender) that have been implicated in ICI response. Additionally, we briefly summarise evidence supporting the relevance of key exogenous factors...
(concurrent medications and diet) in modulating host immunity, and thus ICI efficacy. Finally, we end by reviewing the growing literature connecting the composition and diversity of our gut microbiota and ICI efficacy, complemented by a thorough discussion of the potential mechanisms for this relationship that have thus far been elucidated.

The circulating immune compartment

A prerequisite of anti-cancer immunity (and ICI efficacy) is the recruitment of immune cells to the tumour from primary and secondary lymphoid organs, facilitated by the release of signalling molecules (cytokines) and involving diverse immune cell populations [14]. Indeed, peripheral blood contains a complex milieu of diverse white blood cells (WBCs) and soluble factors whose quantities may indirectly reveal a cancer’s ‘immune phenotype’ [15]. As such, there has been considerable interest in whether their baseline measurement might insinuate a cancer’s susceptibility to ICI therapy.

Peripheral WBCs may be classified morphologically, with neutrophils and lymphocytes usually the most abundant subtypes. A high baseline blood neutrophil-to-lymphocyte ratio (NLR) has long been noted to confer a negative prognosis, irrespective of cancer or therapy [16]. This negative relationship holds true for ICI-therapy recipients; for example, high pre-treatment NLR was associated with worse overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) in a large, pan-cancer cohort [17]. Biologically, peripheral neutrophilia may correlate with tumour microenvironment (TME) neutrophil infiltration [18], where they might act to suppress anti-cancer T-cell trafficking. Supporting this, Kargl et al found an inverse relationship between infiltrating neutrophils and CD8-expressing T cells (CD8+ T cells) in NSCLC tumour samples [19], with their subsequent analysis linking this intratumoural NLR to poor ICI efficacy [20]. Using a murine lung cancer model, they demonstrated that neutrophil antagonism restored tumour CD8+ T cell infiltration as well as anti-PD1 efficacy [20].

Conversely, pre-treatment eosinophilia appears to be associated with better outcomes in retrospective analyses of anti-PD1 [21] and anti-CTLA4-treated [22,23] melanoma and anti-PD1-treated NSCLC patients [24], and lower neutrophil-to-eosinophil ratio correlated with outcomes for combination anti-PD1/anti-CTLA4-treated metastatic RCC patients [25]. Preclinically, Carretero et al demonstrated that eosinophils play a key role in attracting CD8+ T cells through the release of chemokines, which may mediate this increased ICI susceptibility [26].

Flow and mass cytometry revealed relevant associations between certain WBC subtypes and ICI efficacy, such as high baseline T regulatory cells (Tregs) (FoxP3+CD4+ T cells) associating with ipilimumab (anti-CTLA-4) efficacy [22] and classical (CD14+CD16-) monocytes associating with anti-PD1 efficacy in melanoma [27]. The high dimensionality of mass cytometry data has also led to more complicated WBC response ‘signatures’ being defined [28], with efforts underway to harmonise biomarker panels for future work [29]. Next-generation sequencing (NGS) of sorted peripheral WBC subtypes has increased this dimensionality of data even further, with intriguing signals regarding its utility in predicting ICI efficacy. For example, the baseline and dynamic significance of peripheral blood T-cell receptor (TCR) repertoire has garnered much interest; however, bulk NGS approaches have reached differing conclusions about their association with ICI susceptibility [30–33]. By cell sorting before NGS, Gros et al observed in melanoma that the TCR repertoire of specifically the peripheral PD1+CD8+ T cell subset matched that found on TILs, suggesting these are tumour-reactive T-cell populations circulating in the peripheral WBC compartment [34]. Building on this, Han et al found an association between the TCR diversity of these cells and better disease control and PFS for NSCLC patients receiving anti-PD(L)1 therapy, suggesting this assay’s predictive biomarker potential [35].

Cytokines are essential mediators for intercellular communication and can confer pro- or anti-tumourigenic climates, and, as such, have also been studied in relation to malignancy and ICI efficacy [36]. For example, interleukin (IL) 8 (encoded by CXCL8) is a potent pro-inflammatory neutrophil and myeloid-derived suppressor cell (MDSC) chemoattractant with a short circulating half-life, known to reflect systemic tumour volume [37,38]. In a large post hoc analysis of three trials testing atezolizumab (anti-PDL1) for metastatic RCC or urothelial cancer, Yuen et al consistently found a negative correlation between high plasma IL-8 and efficacy (OS or ORR). Through a single-cell RNA sequencing analysis of a sub-group of peripheral blood mononuclear cells (PBMCs) and tumour samples, CXCL8 mRNA was associated most strongly with the myeloid compartment of both PBMCs and tumour samples, connecting it with myeloid-mediated immune suppression [39].

Finally, associations are also emerging between baseline circulating auto-antibodies and ICI efficacy, including those that are associated with auto-immunity (such as rheumatoid factor) [40]. Further efforts have used wider auto-antibody profiles, particularly incorporating tumour-associated antibodies (TAAs) [41–43]. Two studies have associated baseline anti-NY-ESO-1 with ICI efficacy for NSCLC patients, suggesting that this may be a relevant TAA. However, though intriguing, more work is needed to validate these associations, the mechanism underpinning them, and their generalisability across cancer types.

Germline genetic features

The human leukocyte antigen class I (HLA-I) complex is responsible for antigen presentation to CD8+ T cells, with its encoding genes (HLA-A, -B, and -C) amongst the most highly polymorphic in the human genome. There is considerable variability in the peptide-binding characteristics
between HLA gene alleles, and it is therefore plausible that some may present cancer neoantigens more (or less) effectively than others. Recently, Naranjhali et al demonstrated that in a pan-cancer cohort, harbouring one or two HLA-A*03 alleles was associated with a poorer OS after ICI therapy [44]. They went on to externally validate this in multiple other pan-cancer cohorts and importantly established its ‘predictiveness’ (i.e. ICI specificity) by finding no difference in OS for non-ICI-treated patients. However, these findings were not replicated in another recent pan-cancer analysis of pembrolizumab (anti-PD1)-treated patients; thus, its clinical use remains investigational [45].

Other work has focused on more global HLA-I attributes. Akin to reports in HIV [46], Chowell et al demonstrated an HLA-I ‘heterozygote advantage’, whereby homozygosity for at least one HLA-I gene was associated with worse OS in an advanced NSCLC and melanoma cohort [47]. Conversely, they found better OS in melanoma anti-CTLA4 recipients harbouring an HLA-B44 supertype allele. Similarly, further work by the same group evaluated the relevance of HLA-I evolutionary divergence (HED), a measure of the difference of the peptide binding sites of each HLA-I allele [48]. They found that greater mean HED was associated with better OS and ORR in melanoma and NSCLC patients, consistent with the ‘divergent allele advantage’ theory (whereby more diverse HLA-I allele pairs would plausibly present more diverse cancer neoantigens). However, the relationship of HLA-I zygosity and/or mean HED and better ICI efficacy has not been consistently found in more recent analyses for non-melanoma cohorts [49–51]. Importantly, the HLA-B44 supertype seemed to impart an opposite, negative effect in NSCLC, potentially conflict with NSCLC’s distinct neoantigen landscape (leading to worse presentation on HLA-B44) [52]. Therefore, caution must be applied when extrapolating HLA-I associations between cancer types.

In a related vein, Manczinger et al developed a score of ‘HLA-I promiscuity’ based on estimating the diversity of peptides binding to each individual’s HLA-I alleles. They found that HLA-I promiscuity was associated with worse OS and ORR after ICI therapy, mediated by increased expression of immune tolerance genes intratumourally. This aligns with the theory that greater HLA-I promiscuity limits the ability to distinguish self epitopes versus tumour neoepitopes [53]. Once again, HLA-I promiscuity is partly informed by the variety of binding tumour neoepitopes, marrying with the concept of tumour ‘immune fitness’ and likely varying by tumour histology types [54].

Another immune receptor implicated in anti-CTLA4 response is the Fc-γ receptor (FcγR). Previous work implicates antibody-dependent cell cytotoxicity of CTLA-4-positive Tregs by FcγR-expressing immune cells as part of the mechanism of action of ipilimumab (an IgG1 anti-CTLA4 construct) [55]. Concordantly, a V158F single nucleotide polymorphism (SNP) (rs396991) of FCGR3A (encoding FcγRIIIA) was associated with improved ORR and OS in ipilimumab-treated melanoma cohorts, specifically for those tumours with higher insertion–deletion (indel) burden [56].

There are emerging signs that germline alleles associated with the development of autoimmune syndromes or cancer may also predict ICI efficacy. In a genome-wide association study, Chat et al associated the rs17388568 SNP (related to colitis and type 1 diabetes) with melanoma anti-PD1 response [57]. Similarly, several groups have associated ICI susceptibility with polygenic risk scores for rheumatoid arthritis [58], autoimmune thyroid, and dermatological conditions, respectively [59,60]. Finally, germline polymorphisms of the genes encoding relevant immune checkpoints (CTLA4, PDCD1, and PDL1) have been implicated in cancer risk [61], with signals from small retrospective studies starting to emerge that particular alleles may also associate with ICI benefit [62–65]. Though intriguing and biologically plausible, these associations need large-scale clinical and experimental validation prior to further development as biomarkers for ICI efficacy.

**Phenotypic and external features**

In 2018, a pooled analysis found an unexpected association between obesity (measured by body mass index; BMI) and better OS for anti-CTLA4 or anti-PD1/PDL1-treated patients with advanced melanoma [66]. Since then, several other post hoc analyses have been published, with most (though not all) supporting an ‘obesity paradox’ for ICI efficacy [67]. Preclinical efforts demonstrated that for diet-induced obese mice, engrafted B16 melanoma cells demonstrated a more aggressive phenotype with more glucose uptake and ulceration/necrosis than their lean counterparts [68]. Interestingly, this phenotype appeared to be mediated by leptin promoting PD1 expression on intratumoural CD8+ T cells. Consequently, the relative benefit of anti-PD1 therapy was far greater in obese (versus lean) mice. In contrast, Murphy et al found no anti-CTLA4 efficacy in Renca (RCC) engrafted leptin-induced obese mice, potentially reflecting the differing targets of these ICI classes, or biological differences in the tumour models used [69].

A similar ‘cholesterol paradox’ is also emerging. For example, in a retrospective review of NSCLC patients receiving anti-PD1 therapy, high total cholesterol correlated with both PFS and OS after adjustment for other covariates (such as gender, BMI, and smoking status) [70]. Intriguingly, this relationship was not seen in a chemotherapy-treated cohort, suggesting potential ICI specificity. Like obesity, it was found that tumour cholesterol content also influenced a PD1+CD8+ T-cell phenotype in murine melanoma TILs dose-dependently, thus once again potentially providing more substrate for anti-PD1 efficacy [71].

Gender may also be relevant to ICI efficacy. A post hoc meta-analysis of 20 published randomised controlled trials of anti-CTLA4 or anti-PD1 therapies found that males appeared to derive significantly more relative benefit from ICIs, particularly anti-PD1 therapies [72]. Like cholesterol and obesity, this may relate to rates of
intratumoural CD8+ T-cell exhaustion, with an analysis of pre-treatment melanoma samples finding those from men exhibiting higher CD8+ TIL fractions strongly positive for CTLA4 and PD1. However, a more recent meta-analysis (which included trials of anti-PD-L1 therapies, and more recent trials of combination chemo-immunotherapy) did not find any significant interaction of gender on OS [73]. As such, the relationship between gender and ICI efficacy remains controversial.

Coined our ‘exposome’ [74], several exogenous and endogenous environmental factors may also interact with host immunity to modulate ICI efficacy. For example, concurrent medications are likely relevant, with exogenous corticosteroids being perhaps the most studied. In vivo, dexamethasone (a corticosteroid) was found to partially abrogate anti-PD1 tumour growth inhibition by impairing peripheral CD8+ T-cell responses [75], and clinically, a meta-analysis of 16 trials found a negative association between their use and OS/PFS. Importantly, on sub-group analysis by indication, this negative effect was only seen when they were used for supportive care, and not for those treating irAEs [76]. Conversely, similar post hoc clinical analyses have implicated a potential benefit to ICI efficacy from concurrent pan-β-blocker [77], statin [78,79], and antihistamine use [80]. Though retrospective associations may be confounded by indication bias (for example, the cutaneous toxicity that prompts antihistamine use may itself be positively associated with ICI efficacy [81]), in vivo work has demonstrated that histamine may promote a pro-tumour M2 macrophage phenotype intratumourally, biologically supporting the potential benefit of concurrent antihistamine therapy [80].

Finally, other medications (e.g. antibiotics [82], proton-pump inhibitors [83]) or dietary choices (e.g. high-fibre intake [84]) may impact ICI efficacy (negatively or positively, respectively) via influencing our gut microbiome – the composition and diversity of resident microbiota living in our gastrointestinal tract. As elaborated next, there is an emerging understanding of the relevance of the gut microbiome to systemic ICI efficacy, the mechanisms underpinning this, and its potential utility in selecting patients for these therapies.

Gut microbial and related features

The human gut microbiota harbours ~10^{14} microbes and is dominated by bacteria from the Bacteroidetes, Firmicutes, Actinobacteria, and Proteobacteria phyla [85]. An adult harbours hundreds of species and hundreds of strains of anaerobic bacteria that provide beneficial properties impacting immunological development and regulation [86,87]. Gut microbiome profiling with 16S rRNA sequencing (lower-resolution taxonomic profiles, usually to genus level) and shotgun metagenomic sequencing (high-resolution taxonomic profiling up to subspecies level and functional profiling) have linked its composition and functions to a growing list of cancers, and to cancer therapy efficacy.

Much of our early understanding linking gut microbiota and cancer therapies is based on studies in murine models. In 2013, Viaud et al demonstrated that the anti-cancer immune effects of cyclophosphamide were reliant on the gut microbiota, with gut integrity disruption allowing microbial translocation into secondary lymphoid tissue and triggering systemic cell-mediated immunity [88]. In 2015, in vivo work demonstrated how responses to anti-CTLA4 and anti-PD1 were predicated on the presence of enteric Bacteroides and Bifidobacterium genera, respectively [89,90]. In 2018, concurrent publications linked the composition [91–93] and diversity [91] of baseline gut microbiota with anti-PD1 response in diverse clinical cancer cohorts. Compellingly, each group would demonstrate the recapitulation of response or non-response in vivo by faecal microbiota transplant (FMT) of human patient stool to mice engrafted with murine melanoma (B16.SIY and BP), sarcoma (MCA-205), and renal cancer (Renca), providing evidence of causality and a link between human and murine systems. Finally, in 2021, the results of two phase I trials demonstrated this recapitulation human-to-human, with responders’ stool reinvigorating anti-PD1 response in a subset of melanoma patients with resistant or refractory tumours [94,95].

However, we observe relatively little consensus when we examine the annotated species correlated ‘positively’ and ‘negatively’ by studies profiling baseline stool in ICI recipients, both in meta-analyses of the pivotal 2018 data using uniform bioinformatic pipelines [96–98] and in subsequent patient cohort publications (Table 1, with contradictory species-efficacy associations underlined). These discrepancies could be due to differences in clinical (e.g. patient geography, cancer histology, ICIs used) or methodological approaches (e.g. stool collection and storage, DNA extraction and sequencing, clinical endpoints used). They could also be explained by the immunomodulatory properties of phylogenetically-distant gut microbial species converging through common functions, such as common metabolite production. For example, Mager et al found that both Bifidobacterium pseudolongum and Akkermansia muciniphila might synergise with anti-CTLA4 efficacy through their common production of inosine, which might help to shift tumour-associated CD4+ T cells to a Th1 (anti-tumour) phenotype by agonism of adenosine receptors [110]. Another explanation for the lack of a common microbiome signal between the various studies is that the clinical response may be due to complex combinations of evolutionarily distinct anaerobic bacteria. For instance, Tanoue et al recently found a combination of 11 specific strains, themselves a tiny contributor to average gut microbiome complexity, that could robustly induce cytotoxic T-cell responses and enhance ICI efficacy [111]. As such, herein we focus on the potential mechanisms that may explain the powerful influence of gut microbiota on ICI efficacy (Figure 2).

As previously mentioned, gut bacteria often provide humans with beneficial functions through their metabolic products absorbed into our circulation, with the gut microbiome sometimes referred to as ‘the neglected
Table 1. Clinical studies associating pre-treatment gut bacteria species-level taxonomic abundance (by shotgun metagenomic profiling) with ICI efficacy.

| Reference | PY  | Country | Histology | n  | ICI | Positively associated species | Negatively associated species | Clinical endpoint |
|-----------|-----|---------|-----------|----|-----|-----------------------------|-----------------------------|-------------------|
| [99]      | 2017| USA     | Melanoma  | 39 | CICB (24), anti-CTLA4 (1), anti-PD1 (14) | *Bacteroides caccae*, *Streptococcus parasanguinis* | *Bacteroides eggerthi*, Atojobium parvulum | ORR               |
| [100]     | 2019| China   | NSCLC, RCC | 100 | Anti-PD1 | Akkermansia muciniphila, Enteroctccus hirae | Bacteroides nordii | CR + PR + SD6 |
| [101]     | 2019| USA     | Melanoma  | 8  | OICB (12), anti-PD1 (14), anti-CTLA4 (1) | *Bifidobacterium dentium*, *A. muciniphila* | Faecalibacterium prausnitzii | CR + PR + SD6 |
| [102]     | 2020| The Netherlands | Melanoma | 25 | Anti-PD1 (23), CICB (2) | *R. gravis*, *E. coli*, *Eubacterium biforme*, *Bacteroides eggerthi* | *A. muciniphila*, *Bacteroides splayesiae* | CR + PR + SD6 |
| [103]     | 2020| France  | RCC       | 69 | Anti-PD1 | *Bifidobacterium adolescentis*, *Baronella intestinla* | *A. muciniphila*, *Bacteroides ovatus* | CR + PR + SD6 |
| [104]     | 2020| USA     | RCC       | 31 | OICB (2), anti-PD1 (24) | *Bifidobacterium adolescentis*, *Baronella intestinla* | *A. muciniphila*, *Bacteroides ovatus* | CR + PR + SD6 |
| [105]     | 2020| China   | Mixed GI cancers | 40 | OICB (14), anti-PD1 (14), anti-PDL1 (12) | *Bacteroides stercoris*, *Parabacateroides dictionis*, *F. prausnitzii*, *Prevotella biformis* | *Eubacterium rectale* | CBR               |
| [106]     | 2021| USA     | Melanoma  | 38 | OICB | *Bacteroides stercoris*, *Parabacateroides dictionis*, *F. prausnitzii*, *Prevotella biformis*, *Eubacterium rectale* | *R. gravis* | ORR               |
| [107]     | 2021| China   | NSCLC, BTC | 65 | Anti-PD1 | *Eubacterium coprostanoligens*, *F. prausnitzii*, *Prevotella biformis*, *Eubacterium rectale* | *R. gravis* | CR + PR + SD6 |
| [108]     | 2021| South Korea | HCC      | 8  | Anti-PD1 | *Eubacterium coprostanoligens*, *F. prausnitzii*, *Prevotella biformis*, *Eubacterium rectale* | *R. gravis* | CR + PR + SD6 |
| [109]     | 2022| France, Canada | NSCLC    | 111| Anti-PD1 | *A. muciniphila* | *Eubacterium coprostanoligens*, *F. prausnitzii*, *Prevotella biformis*, *Eubacterium rectale* | ORR               |
| [110]     | 2022| UK      | Melanoma  | 53 | Anti-PD1 | *Bacteroides eggerthi* | *A. muciniphila* | ORR               |

BTC, biliary tree carcinoma; CICB, combined immune checkpoint blockade [anti-CTLA4 + anti-PDL1]; CR, complete response; GI, gastrointestinal; HCC, hepatocellular carcinoma; ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung carcinoma; ORR, objective response rate; PFS, progression-free survival; PR, partial response; PY, publication year; RCC, renal cell carcinoma; SD, stable disease (addended number indicates a minimum duration in months).

Species underlined indicate taxa where different studies have found opposing associations with ICI efficacy.

*Where a cohort of patients treated with different ICIs were combinatorially analysed, the subset treated with each class is indicated in parentheses.

†Overlap of 40 patients reported by these two papers.
The connection between the milieu of gut microbiota and circulating metabolites is consistently seen, with plasma levels of the microbial–host co-metabolite hippurate appearing to be a particularly reliable marker of overall gut microbiome diversity [117,118]. Interestingly, pre-treatment blood hippurate levels correlate with anti-PD1 efficacy, supporting a connection between a diverse gut microbiome and ICI efficacy [119]. Gut microbiota are capable of metabolising tryptophan, with levels of its metabolite kynurenine [120] and associated enzymes 3-hydroxyanthranilic acid [121] and indoleamine-pyrrole 2,3-dioxygenase (IDO) [122] all inversely associated with ICI efficacy.

Short-chain fatty acids are produced during bacterial fermentation of dietary fibre, and appear to be particularly relevant through their diverse immunomodulatory properties. Butyrate in particular has been shown, on the one hand, to enhance anti-tumour CD8+ T-cell function through increasing IL-12 receptor [112] and memory T-cell survival [123] in vivo. Concordantly, faecal butyrate was associated with better anti-PD1 responses in a cohort of mixed histology patients [124]. On the other hand, butyrate has been shown to promote regulatory CD4+ T cells and impair dendritic cell maturation, thus negatively associating with anti-CTLA4 efficacy [125].

Microbe-associated molecular patterns (MAMPs) are molecules that are widely essential to (and thus conserved across) commensal microbiota. They are recognised by the innate immune system via a variety of pattern-recognition receptors, with this interaction also likely affecting systemic anti-cancer immunity. For example, Griffin et al isolated the anti-PD1 synergistic effect of Enterococcus faecium to the SagA gene, responsible for peptidoglycan breakdown into muropeptides. Exogenous muropeptides recapitulated this effect only in the presence of host NOD2 receptor (specifically, by priming an anti-tumour myeloid cell response), highlighting their critical role [114]. As a second example, recent work by two groups shed light on the importance of STING (stimulator of interferon genes)-receptor activation. Si et al found oral administration of Lactobacillus rhamnosus GG to improve anti-PD1 efficacy in vivo, mediated by...
| Category                        | Pre-treatment factor                        | Potential assay                  | Possible immune mechanism                                                                 | Association with ICI efficacy |
|--------------------------------|---------------------------------------------|----------------------------------|-------------------------------------------------------------------------------------------|------------------------------|
| Circulating immune compartment | Neutrophil–lymphocyte ratio                 | Blood WBC differential           | Tumour-associated neutrophils → tumour CD8⁺ T cell infiltrate                              | Negative [17]                |
|                                | Eosinophils                                  | Blood WBC differential           | ↑ Tumour CD8⁺ T cell infiltrate                                                          | Positive [21–23,25]          |
|                                | Regulatory T cells                           | PBMC flow cytometry              | Key target of anti-CTLA4 inhibition                                                       | Positive [22]                |
|                                | Classical monocytes                          | PBMC flow cytometry              | ?                                                                                         | Positive [27]                |
|                                | TCR repertoire diversity of PD1⁺CD8⁺ T cells | PBMC flow cytometry              | ↑ Opportunity for tumour neoantigen recognition by cells targeted by anti-PD1             | Positive [30]                |
| Germline genetics              | IL-8                                         | Blood immunoassay                | ↑ Tumour neutrophil and MDSC infiltrate                                                   | Negative [39]                |
|                                | HLA-A*03 genotype                            | Blood DNA sequencing              | ?                                                                                         | Negative [41]                |
|                                | HLA-I diversity                              | Blood DNA sequencing              | Presentation of a ↑ repertoire of neoantigens                                             | Positive [47,50]             |
|                                | HLA-I evolutionary divergence                | Blood DNA sequencing              | Presentation of a ↑ repertoire of neoantigens                                             | Positive [48]                |
|                                | HLA-I promiscuity                            | Blood DNA sequencing              | ↑ Tumourself discrimination → ↑ peripheral immune tolerance                               | Negative [55]                |
| Body phenotype                 | Obesity                                      | Body mass index                  | ↑ Tumour % PD1⁺CD8⁺ T cell infiltrate                                                     | Positive [67]                |
| Exposome and the gut microbiome| Cholesterol level                            | Blood lipid panel                | ↑ Tumour % PD1⁺CD8⁺ T cell infiltrate                                                     | Positive [70]                |
|                                | Corticosteroids                              | Medical history                  | CD4⁺ and CD8⁺ T cell apoptosis                                                            | Negative [76]                |
|                                | Antibiotics/PPIs                             | Medical history                  | ↑ Favourable gut microbiota (see below)                                                   | Negative [82,83]             |
|                                | Antihistamines                               | Medical history                  | Block HRH1 → ↑ M2 macrophage differentiation                                              | Positive [80]                |
|                                | Dietary fibre intake                         | Medical history                  | ↑ Favourable gut microbiota (see below)                                                   | Positive [84]                |
|                                | Specific gut microbial species/subspecies    | Stool metagenomic sequencing     | 1. Absorbed bacterial metabolites → immunomodulatory properties                            | Positive or Negative (see Table 1) |
|                                |                                             |                                  | 2. Activate innate immunity receptors on intratumoral monocytes → innate immune priming → ↑ M1 macrophage differentiation |                              |
|                                |                                             |                                  | 3. ‘Molecular mimicry’ → cross-reactive T cells                                            |                              |

HLA, human leukocyte antigen; HRH1, histamine receptor H1; ICI, immune checkpoint inhibitor (i.e. anti-PD(L)1 and/or anti-CTLA4); MDSC, myeloid-derived suppressor cell; PBMC, peripheral blood mononuclear cell; PPI, proton pump inhibitor; TCR, T-cell receptor; WBC, white blood cell.
STING-dependent induction of type I interferons [126]. Similarly, Lam et al showed that microbial cyclic dinucleotides activated STING receptors on intratumoural monocytes, generating type I interferons to shift to an antitumour immune microenvironment [115]. Lastly, Toll-like receptors (TLRs) are another important microbial pattern-recognition receptor, with exogenous TLR agonist administration augmenting anti-PD1 efficacy in head and neck cancers [127].

Finally, microbe–tumour molecular mimicry has been proposed as a bacterial strain-specific mechanism for conferring ICI sensitivity. Examples abound of bacterial infections initiating and exacerbating autoimmune disease, including *Streptococcus pyogenes* triggering rheumatic heart disease or glomerulonephritis, and *Campylobacter jejuni* triggering ankylosing spondylitis or Guillain–Barré syndrome [128]. In each of these cases, structural homology between bacterial and self-antigen epitopes leads to cross-reactivity of T cells. It is plausible that homology between gut microbiota and tumour-specific antigens may also occur, with immune checkpoints preventing the ensuing anti-tumour immunity (thus released by ICIs) [129]. A retrospective analysis of long-term pancreatic cancer survivors of cell-infiltrated tumours, with TILs cross-reactive to tumour neoantigens and homologous infectious disease antigens [130]. Subsequently, Bessel et al identified close homology between a murine melanoma (B16.SIY) and *Bifidobacterium breve* peptide epitope (SVY). They demonstrated enhanced anti-B16.SIY immunity in mice inoculated with *B. breve*, with causality established through recapitulation of this effect by transfer of gut microbiota and SVY-specific T cells [131]. Finally, recent work found the TMP epitope of *Enterococcus hirae* 13144 to be immunogenic in murine cyclophosphamide recipients and strongly homologous with the *Psmb4* mouse tumour antigen. Using highly sensitive culturomics, TMP1 was found to be enriched in stool samples from RCC and melanoma anti-PD1 recipients experiencing longer OS, providing (to our knowledge) the first clinical evidence supporting this phenomenon [113].

Together, these data demonstrate the complex mechanisms by which microbiota may influence ICI efficacy. Though early in development, there are now emerging examples of this science translating into clinically useful predictors of ICI efficacy. For example, *A. muciniphila* had previously been shown to induce Th1 CD4+ T cell differentiation and enhance ICI responses in murine models [92]. Based on this work, Derosa et al recently reported that detectable baseline stool Akkermansia sp. was (modestly) associated with anti-PD1 ORR in a cohort of 338 advanced NSCLC patients (NCT04567446) – the largest such study published so far [109].

**Concluding remarks**

In this review, we have attempted to highlight the key evidence supporting the significant contribution that various host factors have in the anti-cancer efficacy of ICIs. We have covered host factors derived from the peripheral immune compartment, germline genetics, host phenotype, and the exposome (including our gut microbiome), and have discussed the strength of their implications and potential mechanisms (Table 2). It is important to emphasise that these factors are biomarker candidates only, and all require robust validation through appropriately designed, prospective clinical trials, prior to clinical implementation [132].

Several of these candidate host factors are inherently modifiable; so, beyond their predictive biomarker potential, they may even provide avenues for improved ICI efficacy. Trials to assess this are ongoing in some cases: for example, combining ICIs with potentially beneficial concomitant medications (e.g. propranolol [133]) or strategies to modify the gut microbiome with faecal microbial transplantation, specific bacterial consortia, or single strains (recently reviewed [134]).

It is also notable that although we have discussed factors independently, we hypothesise that a multimodal approach, considering these host factors as well as tumour and tumour-microenvironment features concurrently, might most optimally predict which patients will benefit from ICIs. Developing such an integrative, multivariate model would require sufficiently powered, richly annotated clinical datasets, while using best practices to generate high-quality, matched tumour, host, and gut microbiome feature sets. To this end, the ongoing MITRE study (NCT04107168) seeks to enrol up to 1800 NSCLC, RCC or melanoma patients undergoing ICI therapy [135]. We hypothesise that a prospective study of this scale, integrating rich clinical and multi-omic datasets, is necessary to confirm the relevance of host, microbial, and tumour features (either independently or in concert) to ICI efficacy, and ultimately to help progress promising candidates towards clinical use as predictive biomarkers.

**Acknowledgements**

This work is supported by the Cancer Research UK Cambridge Centre (C9685/A25117). AG is supported by a Cancer Research UK Cambridge Centre clinical research training fellowship and a 2021 John Monash Scholarship. AJM-R is supported by Open Targets (OTAR2049). AB is the recipient of a Fellowship from the Victorian Government Department of Health and Human Services acting through the Victorian Cancer Agency. DJA is supported by Cancer Research UK (C20510/A21717) and the Wellcome Trust (206194/Z/17/Z). Figures were created using Biorender.com.

**Author contributions statement**

AG and DJA conceptualised the paper. AG and AMR prepared the original draft. AMR, OK, AB, TDL, SJW and DJA provided content, detailed reviews, and edits within their areas of expertise. AG and AMR created
the figures. DJA and SJW provided overall supervision. All the authors provided final approval of the submitted version.

References

1. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 2012; 12: 252–264.
2. Hodi FS, O’Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010; 363: 711–723.
3. Morad G, Helmink BA, Sharma P, et al. Hallmarks of response, resistance, and toxicity to immune checkpoint blockade. Cell 2021; 184: 5309–5337.
4. Robert C, Ribas A, Schachter J, et al. Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study. Lancet Oncol 2019; 20: 1239–1251.
5. Szoló M, Ferrucci PF, Hogg D, et al. Pooled analysis safety profile of nivolumab and ipilimumab combination therapy in patients with advanced melanoma. J Clin Oncol 2017; 35: 3815–3822.
6. Wang Y, Tong Z, Zhang W, et al. FDA-approved and emerging next generation predictive biomarkers for immune checkpoint inhibitors in cancer patients. Front Oncol 2021; 11: 683419.
7. Doroshow DB, Bhatia S, Beasley MB, et al. PD-L1 as a biomarker of response to immune-checkpoint inhibitors. Nat Rev Clin Oncol 2021; 18: 345–362.
8. Addo A, Friedlaender A, Banna GL, et al. TMB or not TMB as a biomarker: that is the question. Crit Rev Oncol Hematol 2021; 163: 103374.
9. Andre T, Shiu KK, Kim TW, et al. Pembrolizumab in microsatellite-instability-high advanced colorectal cancer. N Engl J Med 2020; 383: 2207–2218.
10. Pietrzyk F, Meylan M, de Reyniès A, et al. The tumor microenvironment in the response to immune checkpoint blockade therapies. Front Immunol 2020; 11: 784.
11. Ramón y Cajal S, Sesé M, Capdevila C, et al. Clinical implications of intratumor heterogeneity: challenges and opportunities. J Mol Med (Berl) 2020; 98: 161–177.
12. Klein O, Dee K, Markman B, et al. Evaluation of TMB as a predictive biomarker in patients with solid cancers treated with anti-PD-1/CTLA-4 combination immunotherapy. Cancer Cell 2021; 39: 592–593.
13. Blank CU, Haanen JB, Ribas A, et al. The “cancer immunogram”. Science 2016; 352: 658–660.
14. Spitzer MH, Carmi Y, Reticker-Flynn NE, et al. Systemic immunity is required for effective cancer immunotherapy. Cell 2017; 168: 487–502.e15.
15. Andrews MC, Reuben A, Gopakumar V, et al. Concepts collide: genomic, immune, and microbial influences on the tumor microenvironment and response to cancer therapy. Front Immunol 2018; 9: 946.
16. Cupp MA, Carioulo M, Tzoulaki I, et al. Neutrophil to lymphocyte ratio and cancer prognosis: an umbrella review of systematic reviews and meta-analyses of observational studies. BMC Med 2020; 20: 360.
17. Valero C, Lee M, Hoen D, et al. Pretreatment neutrophil-to-lymphocyte ratio and mutational burden as biomarkers of tumor response to immune checkpoint inhibitors. Nat Commun 2021; 12: 729.
18. Takakura K, Ito Z, Suka M, et al. Comprehensive assessment of the prognosis of pancreatic cancer: peripheral blood neutrophil-lymphocyte ratio and immunohistochemical analyses of the tumour site. Scand J Gastroenterol 2016; 51: 610–617.
19. Kargl J, Busch SE, Yang GH, et al. Neutrophils dominate the immune cell composition in non-small cell lung cancer. Nat Commun 2017; 8: 14381.
20. Kargl J, Zhu X, Zhang H, et al. Neutrophil content predicts lymphocyte depletion and anti-PD1 treatment failure in NSCLC. JCI Insight 2019; 4: e130850.
21. Weide B, Martens A, Hassel JC, et al. Baseline biomarkers for outcome of melanoma patients treated with pembrolizumab. Clin Cancer Res 2016; 22: 5487–5496.
22. Martens A, Wistuba-Hamprecht K, Geukes Poppen M, et al. Baseline peripheral blood biomarkers associated with clinical outcome of advanced melanoma patients treated with ipilimumab. Clin Cancer Res 2016; 22: 2908–2918.
23. Ferrucci PF, Gandini S, Cocolinio E, et al. Baseline relative eosinophil count as a predictive biomarker for ipilimumab treatment in advanced melanoma. Oncotarget 2017; 8: 79809–79815.
24. Tanizaki J, Haratani K, Hayashi H, et al. Peripheral blood biomarkers associated with clinical outcome in non-small cell lung cancer patients treated with nivolumab. J Thorac Oncol 2018; 13: 97–105.
25. Tucker MD, Brown LC, Chen YW, et al. Association of baseline neutrophil-to-eosinophil ratio with response to nivolumab plus ipilimumab in patients with metastatic renal cell carcinoma. Biomark Res 2021; 9: 80.
26. Carretero R, Sekioglu IM, Garbi N, et al. Eosinophils orchestrate cancer rejection by normalizing tumor vessels and enhancing infiltration of CD8+ T cells. Nat Immunol 2015; 16: 609–617.
27. Krieg C, Nowicka M, Guglietta S, et al. High-dimensional single-cell analysis predicts response to anti-PD-1 immunotherapy. Nat Med 2018; 24: 144–153.
28. Subrahmanyan PB, Dong Z, Gunsenheit D, et al. Distinct predictive biomarker candidates for response to anti-CTLA-4 and anti-PD-1 immunotherapy in melanoma patients. J Immunother Cancer 2018; 6: 18.
29. Hartmann FJ, Babdor J, Gherardini PF, et al. Comprehensive immune monitoring of clinical trials to advance human immunotherapy. Cell Rep 2019; 28: 819–831.e4.
30. Postow MA, Manuel M, Wong P, et al. Peripheral T cell receptor diversity is associated with clinical outcomes following ipilimumab treatment in metastatic melanoma. J Immunother Cancer 2015; 3: 23.
31. Liu YY, Yang QF, Yang JS, et al. Characteristics and prognostic significance of profiling the peripheral blood T-cell receptor repertoire in patients with advanced lung cancer. Int J Cancer 2019; 145: 1423–1431.
32. Cha E, Klinger M, Hou Y, et al. Improved survival with T cell clonotype stability after anti-CTLA-4 treatment in cancer patients. Sci Transl Med 2014; 6: 238ra70.
33. Hopkins AC, Yachoo M, Durham JN, et al. T cell receptor repertoire features associated with survival in immunotherapy-treated pancreatic ductal adenocarcinoma. JCI Insights 2018; 3: e122092.
34. Gros A, Parkhurst MR, Tran E, et al. Prospective identification of neoantigen-specific lymphocytes in the peripheral blood of melanoma patients. Nat Med 2016; 22: 433–438.
35. Han J, Duan J, Bai H, et al. TCR repertoire diversity of peripheral PD-1+ CD8+ T cells predicts clinical outcomes after immunotherapy in patients with non-small cell lung cancer. Cancer Immunol Res 2020; 8: 146–154.
36. Berraondo P, Sammaned MF, Ochoa MC, et al. Cytokines in clinical cancer immunotherapy. Br J Cancer 2019; 120: 6–15.
37. Waugh DJ, Wilson C. The interleukin-8 pathway in cancer. Clin Cancer Res 2008; 14: 6735–6741.
38. Sammamed MF, Carranza-Rua O, Alfaro C, et al. Serum interleukin-8 reflects tumor burden and treatment response across malignancies of multiple tissue origins. Clin Cancer Res 2014; 20: 5697–5707.
Potential host-based biomarkers of cancer immune checkpoint inhibitor efficacy

39. Yuen KC, Liu LF, Gupta V, et al. High systemic and tumor-associated IL-8 correlates with reduced clinical benefit of PD-L1 blockade. *Nat Med* 2020; 26: 693–698.

40. Toi Y, Sagawara S, Sugisaka J, et al. Profiling preexisting antibodies in patients treated with anti-PD-1 therapy for advanced non-small cell lung cancer. *JAMA Oncol* 2019; 5: 376–383.

41. Ohue Y, Karose K, Karasaki T, et al. Serum antibody against NY-ESO-1 and XAGE1 antigens potentially predicts clinical responses to anti-programmed cell death-1 therapy in NSCLC. *J Thorac Oncol* 2019; 14: 2071–2083.

42. Tan Q, Wang D, Yang J, et al. Autoantibody profiling identifies predictive biomarkers of response to anti-PD1 therapy in cancer patients. *Theranostics* 2020; 10: 6399–6410.

43. Zhou J, Zhao J, Jia Q, et al. Peripheral blood autoantibodies against tumor-associated antigen predict clinical outcome to immune checkpoint inhibitor-based treatment in advanced non-small cell lung cancer. *Front Oncol* 2021; 11: 625578.

44. Naranbhai V, Viard M, Dean M, et al. HLA-A*03 and response to immune checkpoint blockade in cancer: an epidemiological biomarker study. *Lancet Oncol* 2022; 23: 172–184.

45. Chhibber A, Huang L, Zhang H, et al. Germline HLA landscape does not predict efficacy of pembrolizumab monotherapy across solid tumor types. *Immunity* 2022; 55: 56–64.e4.

46. Carrington M, Nelson GW, Martin MP, et al. HLA and HIV-1: heterozygote advantage and B*35-Cw*04 disadvantage. *Science* 1999; 283: 1748–1752.

47. Chowell D, Morris LGT, Grigg CM, et al. Patient HLA class I genotype influences cancer response to checkpoint blockade immunotherapy. *Science* 2018; 359: 582–587.

48. Chowell D, Krishna C, Pierini F, et al. Evolutionary divergence of HLA class I genotype impacts efficacy of cancer immunotherapy. *Nat Med* 2019; 25: 1715–1720.

49. Negrao MV, Lam VK, Reuben A, et al. PD-L1 expression, tumor mutational burden, and cancer gene mutations are stronger predictors of benefit from immune checkpoint blockade than HLA class I genotype in non-small cell lung cancer. *J Thorac Oncol* 2019; 14: 1021–1031.

50. Abed A, Calapre L, Lo J, et al. Prognostic value of HLA-I homozygosity in patients with non-small cell lung cancer treated with single agent immunotherapy. *J Immunother Cancer* 2020; 8: e001620.

51. Litchfield K, Reading JL, Puttick C, et al. Meta-analysis of tumoral and T cell-intrinsic mechanisms of sensitization to checkpoint inhibition. *Cell* 2021; 184: 596–614.e14.

52. Cummings AL, Guksayan J, Lu HY, et al. Mutational landscape influences immunotherapy outcomes among patients with non-small-cell lung cancer with human leukocyte antigen supertype B44. *Nat Cancer* 2020; 1: 1167–1175.

53. Manczinger M, Koncz B, Balogh GM, et al. Negative trade-off between neoantigen repertoire breadth and the specificity of HLA-I molecules shapes antitumor immunity. *Nat Cancer* 2021; 2: 950–961.

54. Łukszka M, Riaz N, Makarov V, et al. A neoantigen fitness model predicts tumour response to checkpoint blockade immunotherapy. *Nature* 2017; 551: 517–520.

55. Romano E, Kusio-Kohalka M, Foukas PG, et al. Iplimunumab-dependent cell-mediated cytotoxicity of regulatory T cells *ex vivo* by nonclassical monocytes in melanoma patients. *Proc Natl Acad Sci U S A* 2015; 112: 6140–6145.

56. Arce Vargas F, Farnes AJ, Litchfield K, et al. Fc effector function contributes to the activity of human anti-CTLA-4 antibodies. *Cancer Cell* 2016; 33: 649–663.e4.

57. Chat V, Ferguson R, Simpson D, et al. Autoimmune genetic risk variants as germline biomarkers of response to melanoma immune-checkpoint inhibition. *Cancer Immunol Immunother* 2019; 68: 897–905.

58. Shahamatdar S, He MX, Reyna MA, et al. Germline features associated with immune infiltration in solid tumors. *Cell Rep* 2020; 30: 2900–2908.e4.

59. Khan Z, Hammer C, Carroll J, et al. Genetic variation associated with thyroid autoimmunity shapes the systemic immune response to PD-1 checkpoint blockade. *Nat Commun* 2021; 12: 3355.

60. Khan Z, Di Nucci F, Kwan A, et al. Polygenic risk for skin autoimmunity impacts immune checkpoint blockade in bladder cancer. *Proc Natl Acad Sci U S A* 2020; 117: 12288–12294.

61. Wagner M, Jasek M, Karabon L. Immune checkpoint molecules – inherited variations as markers for cancer risk. *Front Immunol* 2020; 11: 606721.

62. Queirolo P, Morabito A, Laurent S, et al. Association of CTLA-4 polymorphisms with improved overall survival in melanoma patients treated with CTLA-4 blockade: a pilot study. *Cancer Invest* 2013; 31: 336–345.

63. Queirolo P, Dozin B, Morabito A, et al. Association of CTLA-4 gene variants with response to therapy and long-term survival in metastatic melanoma patients treated with ipilimumab: an Italian melanoma intergroup study. *Front Immunol* 2017; 8: 386.

64. Nomizo T, Ozasa H, Tsuji T, et al. Clinical impact of single nucleotide polymorphism in PD-L1 on response to nivolumab for advanced non-small-cell lung cancer patients. *Sci Rep* 2017; 7: 45124.

65. Parakhi S, Musafer A, Paessler S, et al. PDCD1 polymorphisms may predict response to anti-PD-1 blockade in patients with metastatic melanoma. *Front Immunol* 2021; 12: 672521.

66. McQuade JL, Daniel CR, Hess KR, et al. Association of body-mass index and outcomes in patients with metastatic melanoma treated with targeted therapy, immunotherapy, or chemotherapy: a retrospective, multicohort analysis. *Lancet Oncol* 2018; 19: 310–322.

67. Woodall MJ, Neumann S, Campbell K, et al. The effects of obesity on anti-cancer immunity and cancer immunotherapy. *Cancers (Basel)* 2020; 12: 1230.

68. Wang Z, Aguilar EG, Luna JJ, et al. Paradoxical effects of obesity on T cell function during tumor progression and PD-1 checkpoint blockade. *Nat Med* 2019; 25: 141–151.

69. Murphy KA, James BR, Sjaastad FV, et al. Cutting edge: elevated leptin during diet-induced obesity reduces the efficacy of tumor immunotherapy. *J Immunother Cancer* 2018; 6: 1837–1841.

70. Tong J 3rd, Mao Y, Yang Z, et al. Baseline serum cholesterol levels predict the response of patients with advanced non-small cell lung cancer to immune checkpoint inhibitor-based treatment. *Cancer Manag Res* 2021; 13: 4041–4053.

71. Ma X, Bi E, Lu Y, et al. Cholesterol induces CD8+ T cell exhaustion in the tumor microenvironment. *Cell Metab* 2019; 30: 143–156.e5.

72. Conforti F, Pala L, Bagnardi V, et al. Cancer immunotherapy efficacy and patients’ sex: a systematic review and meta-analysis. *Lancet Oncol* 2018; 19: 737–746.

73. Wallis CJ, Butaney M, Satkunasivam R, et al. Association of patient sex with efficacy of immune checkpoint inhibitors and overall survival in advanced cancers: a systematic review and meta-analysis. *JAMA Oncol* 2019; 5: 529–536.

74. Wild CP. The exposome: from concept to utility. *Int J Epidemiol* 2012; 41: 24–32.

75. Maxwell R, Lukski AS, Garzon-Muvdi T, et al. Contrasting impact of corticosteroids on anti-PD-1 immunotherapy efficacy for tumor histologies located within or outside the central nervous system. *Oncoimmunology* 2018; 7: e1500108.

76. Petrelli F, Signorelli D, Ghidini M, et al. Association of steroids use with survival in patients treated with immune checkpoint inhibitors: a systematic review and meta-analysis. *Cancers (Basel)* 2020; 12: 546.

77. Kokolus KM, Zhang Y, Sivk JM, et al. Beta blocker use correlates with better overall survival in metastatic melanoma patients and improves the efficacy of immunotherapies in mice. *Oncoimmunology* 2018; 7: e1405205.
78. Cantini L, Pecci F, Hurkmans DP, et al. High-intensity statins are associated with improved clinical activity of PD-1 inhibitors in malignant pleural mesothelioma and advanced non-small cell lung cancer patients. *Eur J Cancer* 2021; 144: 41–48.

79. Omori M, Okuma Y, Hakozaki T, et al. Statins improve survival in patients previously treated with nivolumab for advanced non-small cell lung cancer: an observational study. *Mol Clin Oncol* 2019; 10: 137–143.

80. Li H, Xiao Y, Li Q, et al. The allergy mediator histamine confers resistance to immunotherapy in cancer patients via activation of the macrophage histamine receptor H1. *Cancer Cell* 2022; 40: 36–52.e9.

81. Tattersall IW, Leventhal JS. Cutaneous toxicities of immune checkpoint inhibitors: the role of the dermatologist. *Yale J Biol Med* 2020; 93: 123–132.

82. Tsikala-Vafea M, Belani N, Vieira K, et al. Use of antibiotics is associated with worse clinical outcomes in patients with cancer treated with immune checkpoint inhibitors: a systematic review and meta-analysis. *Int J Infect Dis* 2021; 106: 142–154.

83. Qin BD, Jiao XD, Zhou XC, et al. The gut microbiota shapes intestinal tumorigenesis to immunotherapy in cancer patients via activation of the macrophage histamine receptor H1. *Cancer Cell* 2022; 40: 36–52.e9.

84. Spencer CN, McQuade JL, Gopalakrishnan V, et al. Dietary fiber and probiotics influence the gut microbiome and melanoma immunotherapy response. *Science* 2021; 374: 1632–1640.

85. Bäckhed F, Ley RE, Sonnenburg JL, et al. Host-bacterial mutualism in the human intestine. *Science* 2005; 307: 1915–1920.

86. Round JL, Mazmanian SK. The gut microbiota shapes intestinal immune responses during health and disease. *Nat Rev Immunol* 2009; 9: 313–323.

87. Roud JL, Mazmanian SK. The gut microbiota shapes intestinal immune responses during health and disease. *Nat Rev Immunol* 2009; 9: 313–323.

88. Goodman JL, Eckburg PB, Ramenofsky M, et al. Microbiome composition modulates prevention and progression of colorectal adenomas. *Cell* 2013; 154: 595–605.

89. Vézilhou M, Pitt JM, Daillère R, et al. Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota. *Science* 2015; 350: 1079–1084.

90. Sivan A, Corrales L, Hubert N, et al. Commensal *Bifidobacterium* promotes antitumor immunity and facilitates anti-PD-L1 efficacy. *Science* 2015; 350: 1084–1089.

91. Gopalakrishnan V, Spencer CN, Nezi L, et al. Gut microbiome modulation response to anti-PD-1 immunotherapy in melanoma patients. *Science* 2018; 359: 97–103.

92. Routy B, Le Chatelier E, Derosa L, et al. Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. *Science* 2018; 359: 91–97.

93. Matson V, Fessler J, Bao R, et al. The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients. *Science* 2018; 359: 104–108.

94. Baruch EN, Youngster I, Ben-Betzalel G, et al. Fecal microbiota transplant promotes response in immunotherapy-refractory melanoma patients. *Science* 2021; 371: 602–609.

95. Damar D, Dzatstse AK, McCulloch JA, et al. Fecal microbiota transplant overcomes resistance to anti-PD-1 therapy in melanoma patients. *Science* 2021; 371: 595–602.

96. Gharabeh RZ, Jobin C. Microbiota and cancer immunotherapy: in search of microbial signals. *Gut* 2019; 68: 385–388.

97. Limeta A, Ji B, Levin M, et al. Meta-analysis of the gut microbiota in predicting response to cancer immunotherapy in metastatic melanoma. *JCI Insight* 2020; 5: e140940.

98. Lee KA, Thomas AM, Bolte LA, et al. Cross-cohort gut microbiome associations with immune checkpoint inhibitor response in advanced melanoma. *Nat Med* 2022; 28: 535–544.

99. Frankel AE, Coughlin LA, Kim J, et al. Metagenomic shotgun sequencing and unbiased metabolic profiling identify specific human gut microbiota and metabolites associated with immune checkpoint therapy efficacy in melanoma patients. *Neoplasia* 2017; 19: 848–855.

100. Zheng Y, Wang T, Xu X, et al. Gut microbiome affects the response to anti-PD-1 immunotherapy in patients with hepatocellular carcinoma. *J Immunother Cancer* 2019; 7: 193.

101. Peters BA, Wilson M, Moran U, et al. Relating the gut metagenome and metatranscriptome to immunotherapy responses in melanoma patients. *Genome Med* 2019; 11: 61.

102. Wind TT, Gacesa R, Vich Vila A, et al. Gut microbial species and metabolic pathways associated with response to treatment with immune checkpoint inhibitors in metastatic melanoma. *Melanoma Res* 2020; 30: 235–246.

103. Derosa L, Routy B, Fidelde M, et al. Gut bacteria composition drives primary resistance to cancer immunotherapy in renal cell carcinoma patients. *Eur Urol* 2020; 78: 195–206.

104. Salgia NJ, Bergerot PG, Maia MC, et al. Stool microbiome profiling of patients with metastatic renal cell carcinoma receiving anti-PD-1 immune checkpoint inhibitors. *Eur Urol* 2020; 78: 498–502.

105. Peng Z, Cheng S, Kou Y, et al. The gut microbiome is associated with clinical response to anti-PD-1/PD-1 immunotherapy in gastrointestinal cancer. *Cancer Immunol Res* 2020; 8: 1251–1261.

106. Andrews MC, Duong CPM, Gopalakrishnan V, et al. Gut microbiota signatures are associated with toxicity to combined CTLA-4 and PD-1 blockade. *Nat Med* 2021; 27: 1432–1441.

107. Mao J, Wang D, Long J, et al. Gut microbiome is associated with the clinical response to anti-PD-1-based immunotherapy in hepatobiliary cancers. *J Immunother Cancer* 2021; 9: e003334.

108. Claug MW, Kim MJ, Won EL, et al. Gut microbiome composition can predict the response to nivolumab in advanced hepatocellular carcinoma patients. *World J Gastroenterol* 2021; 27: 7340–7349.

109. Derosa L, Routy B, Thomas AM, et al. Intestinal * Akkermansia muciniphila* predicts clinical response to PD-1 blockade in patients with advanced non-small-cell lung cancer. *Nat Med* 2022; 28: 315–324.

110. Mager LF, Burkhard R, Pett N, et al. Microbiome-derived inosine modulates response to checkpoint inhibitor immunotherapy. *Science* 2020; 369: 1481–1489.

111. Tanoue T, Morita S, Plichta DR, et al. A defined commensal consortium elicits CD8 T cells and anti-cancer immunity. *Nature* 2019; 565: 600–605.

112. He Y, Fu L, Li Y, et al. Gut microbial metabolite facilitates antitumor therapy efficacy by modulating cytotoxic CD8+ T cell immunity. *Cell Metab* 2021; 33: 988–1000.e7.

113. Fluckiger A, Daillère R, Sassi M, et al. Cross-reactivity between tumor MHC class I-restricted antigens and an enterococcal bacterio- phage. *Science* 2020; 369: 936–942.

114. Griffin ME, Espinosa J, Becker JL, et al. *Enterococcus peptidoglycan* remodeling promotes checkpoint inhibitor cancer immunother- apy. *Science* 2021; 373: 1040–1046.

115. Lam KC, Araya RE, Huang A, et al. Microbiota triggers STING-type IFN-dependent monocytic reprogramming of the tumor microenvironment. *Cell* 2021; 184: 5338–5356.e21.

116. Clarke G, Stillling RM, Kennedy PJ, et al. Minireview: Gut microbiota: the neglected endocrine organ. *Mol Endocrinol* 2014; 28: 1221–1238.

117. Pallister T, Jackson MA, Martin TC, et al. *Hippurate* as a metabonomic marker of gut microbiome diversity: modulation by diet and relationship to metabolic syndrome. *Sci Rep* 2017; 7: 13670.

118. Wilmanski T, Rappaport N, Ears JC, et al. Blood metabolome predicts gut microbiome α-diversity in humans. *Nat Biotechnol* 2019; 37: 1217–1228.

119. Hatae R, Chamoto K, Kim YH, et al. Combination of host immune metabolic biomarkers for the PD-1 blockade cancer immunotherapy. *JCI Insight* 2020; 5: e133501.
Potential host-based biomarkers of cancer immune checkpoint inhibitor efficacy

120. Li H, Bullock K, Gurjao C, et al. Metabolomic adaptations and correlates of survival to immune checkpoint blockade. *Nat Commun* 2019; 10: 4346.

121. Karayama M, Masuda J, Mori K, et al. Comprehensive assessment of multiple tryptophan metabolites as potential biomarkers for immune checkpoint inhibitors in patients with non-small cell lung cancer. *Clin Transl Oncol* 2021; 23: 418–423.

122. Kocher F, Amann A, Zimmer K, et al. High indoleamine-2,3-dioxygenase 1 (IDO) activity is linked to primary resistance to immunotherapy in non-small cell lung cancer. *Transl Lung Cancer Res* 2021; 10: 304–313.

123. Bachem A, Makhlouf C, Binger KJ, et al. Microbiota-derived short-chain fatty acids promote the memory potential of antigen-activated CD8+ T cells. *Immunity* 2019; 51: 285–297.e5.

124. Nomura M, Nagatomo R, Doi K, et al. Association of short-chain fatty acids in the gut microbiome with clinical response to treatment with nivolumab or pembrolizumab in patients with solid cancer tumors. *JAMA Netw Open* 2020; 3: e202895.

125. Coutzac C, Jouniaux JM, Paci A, et al. Systemic short chain fatty acids limit antitumor effect of CTLA-4 blockade in hosts with cancer. *Clin Rev Allergy Immunol* 2012; 42: 102–111.

126. Cusick MF, Libbey JE, Fujinami RS. Molecular mimicry as a mechanism of autoimmune disease. *Clin Rev Allergy Immunol* 2012; 42: 102–111.

127. Boesch M, Baty F, Rothschild SI, et al. Tumour neoantigen mimicry by microbial species in cancer immunotherapy. *Br J Cancer* 2021; 125: 313–323.

128. Daillère R, Derosa L, Bonvalet M, et al. Trial watch: the gut microbiota as a tool to boost the clinical efficacy of anticancer immunotherapy. *Oncoimmunology* 2020; 9: 1774298.

129. Thompson NA, Stewart GD, Welsh SJ, et al. The MITRE trial protocol: a study to evaluate the microbiome as a biomarker of efficacy and toxicity in cancer patients receiving immune checkpoint inhibitor therapy. *BMC Cancer* 2022; 22: 99.