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Hallmarks of response, resistance, and toxicity to immune checkpoint blockade

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Abstract

Unprecedented advances have been made in cancer treatment with the use of immune checkpoint blockade (ICB). However, responses are limited to a subset of patients, and immune-related adverse events (irAEs) can be problematic, requiring treatment discontinuation. Iterative insights into factors intrinsic and extrinsic to the host that impact ICB response and toxicity are critically needed. Our understanding of the impact of host-intrinsic factors (such as the host genome, epigenome, and immunity) has evolved substantially over the past decade, with greater insights on these factors and on tumor and immune co-evolution. Additionally, we are beginning to understand the impact of acute and cumulative exposures--both internal and external to the host (i.e., the exposome)--on host physiology and response to treatment. Together these represent the

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Declaration of Interests

B.A.H. report no conflict of interest. G.M. is a co-inventor on US patents (PCT/US2019/022194, PCT/US2020/029556, PCT/US2020/046050) relating to extracellular vesicles. P.S. reports consulting, advisory roles, and/or stocks/ownership for Achelois, Adaptive Biotechnologies, Apricity Health, BioAlta, BioNTech, Codiak Biosciences, Constellation, Dragonfly Therapeutics, Forty-Seven Inc., Hummingbird, ImaginAb, Infinity Pharma, Jounce Therapeutics, Lave Therapeutics, Lytix Biopharma, Marker Therapeutics, Oncolytics, Phenomics, and Polaris: and owns a patent licensed to Jounce Therapeutics. P.S. reports consulting or Stock Ownership or Advisory Board for Achelois, Adaptive Biotechnologies, Apricity, BioAtla, BioNTech, Candel Therapeutics, Codiak, Dragonfly, Earli, Enable Medicine, Hummingbird, ImaginAb, Jounce, Lava Therapeutics, Lytix, Marker, PBM Capital, Phenomic AI, Polaris Pharma, Time Bioventures, Trained Therapeutix, Venn Biosciences for immediate family member. J.A.W. is a co-inventor on US patent (PCT/US17/53,717) relating to the microbiome. JAW reports speaker fees from Imedex, Dava Oncology, Omniprex, Illumina, Gilead, MedImmune and BMS; consultant/advisor roles or advisory board membership for Roche-Genentech, Novartis, AstraZeneca, GSK, BMS, Merck/MSD, Biothera Pharma, and Microbiome DX; and receives clinical trial support from GSK, Roche-Genentech, BMS, and Novartis, all outside the current work.

current day hallmarks of response, resistance, and toxicity to ICB. Opportunities built on these hallmarks are duly warranted.

Wargo eTOC blurb

Immune checkpoint blockade has revolutionized cancer therapeutics, but it doesn't work for everyone. It may cause unacceptable immune-related adverse events, or tumors may fail to respond or develop resistance. We're beginning to understand the biological reasons why.

Introduction

Over the course of cancer development and progression, tumors evolve and may exhibit a variety of mechanisms to evade tumor immunosurveillance and to suppress anti-tumor immune responses. A major mechanism underlying tumor immune evasion involves engagement of the immune checkpoint pathways. Under physiological conditions, immune checkpoint molecules regulate the immune system through stimulation and inhibition of immune responses in order to dampen the immune response following successful mitigation of an infection or other threats. However, these immune checkpoint interactions may also be engaged in the setting of cancer, with growing efforts to target these to enhance anti-tumor immunity (Pardoll, 2012; Wykes and Lewin, 2018). In this review, we provide a summary of progress made over the past decade with regard to our understanding of mechanisms of response and resistance to immune checkpoint blockade (ICB). We describe different immune checkpoints and ICB strategies and discuss the role of various host-intrinsic and host-extrinsic factors in developing resistance to ICB and also provide insights into potential determinants of toxicity to ICB. Lastly, we explore the growing diagnostic and therapeutic strategies to enhance response to ICB and abrogate toxicity.

1. Immune checkpoints and checkpoint blockade strategies

1.1. Cytotoxic T lymphocyte-associated protein 4 (CTLA-4)

The immune system operates in a dynamic state of equilibrium. During the initial steps of T cell activation in lymphoid tissues, naïve T cells encounter new antigens through interaction of T cell receptors (TCRs) with major histocompatibility complex (MHC)-bound antigens on dendritic cells (DCs). Successful activation of T cells relies on the amplification of the antigen recognition signal through the interaction of a co-stimulatory checkpoint, CD28, on T cells with ligands CD80 (B7.1) and CD86 (B7.2) on DCs (Rudd et al., 2009). To prevent uncontrolled expansion of activated T cells, this activation signal is counteracted by an inhibitory checkpoint, CTLA-4 (a.k.a. CD152) on T cells, which binds to CD80/86 ligands with an affinity higher than that of CD28 and suppresses the signal (Rudd et al., 2009). The CTLA-4 regulatory effects mainly temper the activation of $CD4^+$ helper T cells while boosting regulatory T cells (Tregs) (Doyle et al., 2001; Wing et al., 2008), leading to a pro-tumor immunosuppressive phenotype. As such, strategies to target and antagonize CTLA-4 have emerged as promising options to enhance anti-tumor immunity. Initial preclinical studies demonstrated that blockade of CTLA-4 with an antibody led to an enhanced and a long-lasting anti-tumor immune response and regression of immunogenic tumors (Leach et al., 1996; van Elsas et al., 1999). While significant autoimmunity was observed in

pre-clinical models in which CTLA-4 was completely absent (Tivol et al., 1995; Waterhouse et al., 1995), CTLA-4 blockade did not demonstrate substantial autoimmunity (Leach et al., 1996; Rowshanravan et al., 2018). Based on these preclinical findings, several clinical trials were initiated to evaluate the therapeutic effect of humanized CTLA-4 antibodies such as Ipilimumab and Tremelimumab for advanced melanoma, eventually leading to the US Food and Drug Administration (FDA) approval of Ipilimumab (Camacho et al., 2009; Hodi et al., 2003; Hodi et al., 2010; Kirkwood et al., 2010; O'Day et al., 2010; Ribas et al., 2005). At a time when no other therapeutic option could increase the survival of advanced melanoma patients, Ipilimumab was associated with long-term survival effects (1-year and 2-year survival rate of 45.6% and 23.5%, respectively). Treatment with Ipilimumab was associated with immune-related adverse events (irAEs) in a surprisingly high 60% of patients (Hodi et al., 2010); this demonstrates a limitation of current-day preclinical models in predicting rates of irAEs in patients.

1.2. Programmed cell death protein 1 (PD-1)

Regulatory checkpoint pathways are also active in peripheral tissues where they act on a variety of immune cell types to prevent autoimmunity and tissue damage from inflammation. PD-1 (a.k.a. CD279) is expressed on activated T cells as well as other cells including but not limited to B cells, natural killer (NK) cells, and myeloid cells (Hsu et al., 2018; Nam et al., 2019). Upon interaction with its ligands, programmed death-ligand 1 (PD-L1; a.k.a. B7-H1 or CD274) and PD-L2 (a.k.a. B7-DC or CD273), it can diminish immune responses (Freeman et al., 2000; Latchman et al., 2001). In the tumor microenvironment, PD-L1 and to a lesser extent PD-L2 are expressed by tumor cells, although their expression pattern is heterogeneous and varies between different tumor types (Yearley et al., 2017). Interaction of tumor PD-L1 and PD-L2 with PD-1 on tumor infiltrating lymphocytes (TILs) has been recognized as a major mechanism of tumor immune evasion and therefore, an appealing target for therapeutic implications. Furthermore, the high expression of PD-1 and its ligands on TILs and tumor cells receptively, suggested that blockade of this pathway would potentially lead to less severe immune toxicity compared to CTLA-4 blockade. Initial clinical trials with PD-1 antibodies, Nivolumab and Pembrolizumab, demonstrated potent and durable anti-tumor activity and limited immune toxicity in a broad group of cancer types including melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma and colorectal cancer (Brahmer et al., 2015; Garon et al., 2015; Patnaik et al., 2015; Robert et al., 2015; Topalian et al., 2014). While toxicity observed with the PD-1 blockade was less than what was observed in clinical trials of CTLA-4 blockade, the rates were higher than predicted by pre-clinical models (Hirano et al., 2005). With a similar therapeutic rationale, anti-PD-L1 antibodies such as Atezolizumab, Avelumab, and Durvalumab, have been developed and proven effective for treatment of a variety of cancers including NSCLC, urothelial carcinoma, triple negative breast cancer (TNBC) and Merkel cell carcinoma (Iwata et al., 2019; Kaufman et al., 2018; Powles et al., 2018; Rittmeyer et al., 2017). To date, these antibodies have been approved for treatment of various cancer types (Table 1), with many more currently under investigation.

1.3. Other immune checkpoints: negative immune regulation

Apart from these well-studied molecules, several novel immune checkpoint molecules have been introduced/revisited over the past decade (Figure 1) with mechanistic insights gained and the potential for therapeutic targeting. The majority of these molecules exhibit a negative immunoregulatory effect in the context of cancer. Lymphocyte activation gene-3 (LAG-3 or CD223) is expressed on a variety of immune cells including activated T cells, Tregs, B cells, NK cells and DCs (Andreae et al., 2002; Triebel et al., 1990) and is also active in a soluble form when shed by a disintegrin and metalloproteinase domain-containing proteins (ADAMs). LAG3 interacts with several molecules including MHCII, Galectin-3 and α-synuclein (Baixeras et al., 1992; Mao et al., 2016); it is known to have an inhibitory role on $CD8^+$ T cell function (Matsuzaki et al., 2010) and increases the immunosuppressive behavior of Tregs (Yano et al., 2019). Different approaches for blockade of LAG-3 in combination with anti-PD-1 treatment are currently under evaluation in a number of clinical trials as potential novel ICBs (NCT02614833, NCT03625323, NCT01968109, NCT03470922, among others). Initial data from the Phase2/3 RELATIVITY-047 trial (NCT03470922) shows improved progression-free survival in patients with metastatic or unresected melanoma treated with anti-Lag-3 combined with anti-PD-1 therapy as compared to anti-PD-1 therapy alone).

T cell immunoglobulin and mucin-domain containing-3 (TIM-3) is another immune checkpoint molecule that can be expressed on a number of immune cells including $CD4^+$ and $CD8^+$ T cells, Tregs, DCs, and NK cells (de Mingo Pulido et al., 2018; Monney et al., 2002; Xu et al., 2015) as well as non-immune cells such as tumor-associated endothelial cells (Huang et al., 2010). Interaction between TIM-3 and its four ligands (galectin 9, high mobility group protein B1, phosphatidyl serine, and carcinoembryonic antigen cell adhesion molecule 1) can diminish anti-tumor immunity through a variety of mechanisms including inducing $CD8^+$ T cell death and exhaustion (Huang et al., 2015). Several antibodies against TIM-3 are in phase I trials (NCT03307785, NCT03680508, NCT02608268, among others) and the reported initial results demonstrate tolerability and promising efficacy when used in combination with anti-PD-1 treatment (NCT02817633).

While LAG-3 and TIM-3 exhibit a broader expression pattern, T cell immunoglobulin and ITIM domain (TIGIT) is an immune checkpoint molecule that is almost exclusively expressed on T cells and NK cells and interacts with its ligands CD155 and CD112 to exert immunosuppressive effects (Stanietsky et al., 2009; Yu et al., 2009). TIGIT can also induce immunosuppressive activity in DCs (Yu et al., 2009) and suppresses the cytotoxicity of NK cells (Liu et al., 2013). Monoclonal antibodies against TIGIT are being tested as single agents or combination therapy with anti-PD-1 and anti-PD-L1 (NCT04294810, NCT04256421 among others). Combination of Tiragolumab (anti-TIGIT) and atezolizumab (PD-L1 antibody) improved overall response rate (37% compared to 21% for atezolizumab alone) in metastatic NSCLC patients with high tumor PD-L1 expression and was recently granted Breakthrough Therapy Designation by the FDA (CITYSCAPE, NCT03563716).

VISTA is another inhibitory checkpoint molecule that is largely and constitutively expressed on myeloid cells and also on T cells, and NK cells (Blando et al., 2019; Gao et al., 2017; Wang et al., 2019a). VSIG-3 has been reported as a ligand for VISTA (Wang et al., 2019a),

however other interacting partners are yet to be discovered. VISTA is known as a PD-1 homolog; however, it acts through a non-redundant pathway to exert immunosuppressive effects on T cells (Liu et al., 2015) and, therefore, presents an opportunity as a target for immunotherapy. Other inhibitory checkpoint molecules that are being studied as potential therapeutic targets include B7-H3 (CD276) (NCT02628535, NCT03406949), B and T lymphocyte attenuator (BTLA or CD272) (NCT04137900), and sialic acid-binding immunoglobulin-like lectin 15 (Siglec-15) (NCT03665285).

1.4. Other immune checkpoints: positive immune regulation

Checkpoint molecules with positive immunoregulatory effects have also been considered for cancer immunotherapy applications. Immune co-stimulator (ICOS) is a co-stimulatory molecule expressed on T cells, which enhances function and expansion of $CD8^+$ T cells and Tregs (Fu et al., 2011; Hutloff et al., 1999; Liakou et al., 2008). ICOS agonist monoclonal antobodies are currently under investigation as single agents and in combination with anti-PD-1 or anti-CTLA-4 treatments (NCT02904226, NCT02723955, NCT03251924). Checkpoint molecules belonging to the tumor necrosis factor receptor (TNF) superfamily such as glucocorticoid-induced TNFR-related gene (GITR) and OX40 have also been introduced as stimulatory factors and are being assessed as therapeutic targets. GITR is expressed by effector T cells and Tregs, NK cells and to a lower extent by B cells and myeloid cells. GITR can reduce T cell apoptosis and increase T cell activity through its interaction with its ligand (GITRL) (McHugh et al., 2002; Shimizu et al., 2002). OX40 is expressed on T cells transiently after T cell antigen recognition and can also be expressed on a variety of immune and non-immune cells such as endothelial cells (Calderhead et al., 1993). OX40 plays a complex role in promoting anti-tumor immunity. It enhances T cell expansion at a later stage compared to CD28 and further regulates T helper responses (Flynn et al., 1998; Sharpe and Freeman, 2002). To date, several agonist antibodies for GITR (NCT02598960, NCT01239134, NCT02628574, among others) and OX40 (NCT01862900, NCT02315066, NCT02410512, among others) have been developed and are currently under investigation.

The mechanisms underlying the effects of these positive immune regulators and their interactomes have yet to be thoroughly described. Further basic and translational studies are encouraged to unravel the unknowns including potential roles in homeostatic or active immune responses and to provide opportunities for novel therapeutic strategies.

2. Factors impacting response and resistance to ICB

The scientific discoveries in tumor immunology and the resultant breakthrough concept of harnessing the immune system to treat cancer have brought considerable clinical benefits to cancer patients and tremendously advanced the field of oncology. Nevertheless, several challenges remain associated with immune checkpoint inhibitors that need to be addressed in order to broaden their application. One major shortcoming of current immune checkpoint inhibitors is the lack of response in certain cancers such as glioblastoma and pancreatic cancer, potentially attributed to their low inherent immunogenicity. Within those cancer types for which ICB has proven efficacy such as melanoma, potent and durable response

has only been limited to a subgroup of patients, with several patients demonstrating a lack of initial response to treatment (i.e., primary resistance). Furthermore, patients with initial promising response to treatment can develop resistance overtime (i.e., acquired resistance), necessitating a change in therapeutic strategies. Our understanding of the mechanisms of resistance to ICB is continuously evolving as more insight is gained into the multi-dimensional interactions between the tumor, the immune system, and other systemic factors. Importantly, it is also becoming increasingly appreciated that the exposure of patients--the hosts--to environmental factors can affect their immune responses. In this review, we explore the mechanisms underlying resistance to checkpoint inhibitors under two major categories: (1) Host (patient)-intrinsic, including factors tumor-specific and systemic factors and (2) Host (patient)-extrinsic factors, including environmental factors-a.k.a, exposome.

2.1. Host-intrinsic factors

When we consider forces affecting anti-tumor immune responses, we broadly consider the tumor and the patient. The tumor itself contains several components including tumor cells and their secretome, non-tumor cells (immune cells and stromal cells) and also microbes, all of which may affect tumor immunity and response to ICB. Furthermore, we will discuss systemic factors that alter the systemic immunity of patients as contributors to response to ICB.

2.1.1. Tumor-intrinsic factors

Genetic and epigenetic defects: The genetic status of the tumor is one of the primary determinants of response to treatment with immune checkpoint inhibitors (Figure 2). Over the course of tumor development, tumor cells acquire several mutations leading to the production of mutated proteins and peptides; these mutated peptides can serve as novel antigens, termed neoantigens, that are distinct from selfantigens. In many cases, neoantigens can be immunogenic and not protected by mechanisms of self-tolerance (Schumacher and Schreiber, 2015). Moreover, tumor genetic aberrations can promote expression of self-antigens at a higher-than-normal level or at locations where those antigens are absent under normal physiological conditions. The expression of neoantigens and aberrant self-antigens within the tumor tissue can attract T cells for elimination of tumor cells and further reinforce the anti-tumor immune response elicited by immune checkpoint inhibitors. As such, tumor mutational burden (TMB), quantified as the total number of distinct mutations per coding area of tumor genome, has been used as a criterion to determine tumor antigenicity and to explain response or resistance to immune checkpoint inhibitors. Melanoma, lung, and bladder cancer, tumors commonly associated with an increased number of mutations due to environmental DNA damage, exhibit a stronger response to ICB (Yarchoan et al., 2017). TMB was shown to be higher in melanoma patients with durable responses to Ipilimumab and Tremelimumab (CTLA-4 antibody) compared to melanoma patients who did not gain clinical benefit (Snyder et al., 2014; Van Allen et al., 2015).

Genetic defects such as DNA mismatch repair deficiencies (dMMR) and microsatellite instability (MSI) predispose tumor cells to the accumulation of somatic mutations and are associated with increased TMB (Lengauer et al., 1998) and increased susceptibility to ICB (Le et al., 2017). While these studies suggest that high TMB plays a major role

in tumor response to ICB, the response to ICB is far more nuanced. In fact, it has been demonstrated that the landscape and composition of neoantigens within tumors is a stronger indicator of response to treatment in melanoma and NSCLC patients (McGranahan et al., 2016). Furthermore, genetic and epigenetic defects can induce several mechanisms of immune evasion in tumor cells that further affect response to ICB. For instance, genetic and epigenetic aberrations leading to defects in antigen presentation can promote primary and acquired resistance to ICB regardless of TMB (Snahnicanova et al., 2020; Sucker et al., 2014).

Signaling defects: Oncogenic signaling and metabolic pathways and their associated mutations have also been proven to drive immunogenic responses in various cancer types (Figure 2). Interferon (IFN) signaling through the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway plays a prominent role in tumor immunity. Defects associated with this pathway and its downstream effectors have shown both negative and positive correlations with response to ICB, suggesting a dual role for this pathway in tumor immunity (Ayers et al., 2017; Gao et al., 2016).

Several studies have shown that phosphatidylinositol-3-kinase (PI3K)-activating mutations can be associated with increased expression of PD-L1 on tumor cells leading to immune evasion in glioma, breast, prostate, lung, and pancreatic cancer (Crane et al., 2009). PI3K activation as a result of phosphatase and tensin homolog (PTEN) loss was correlated with a poor response to PD-1 antibodies in melanoma and could be reversed by PI3Kβ inhibition. PTEN loss decreased the number and the cytolytic activity of $CD8^+$ T cells in tumors and also promoted resistance to T cell-induced tumor apoptosis (Peng et al., 2016).

Activating mutations in the Wnt/β-catenin pathway can also induce resistance to ICB through altering the expression of PD-L1 and PD-L2 in a broad group of tumors such as melanoma, breast cancer, adenoid cystic carcinoma, and medulloblastoma (Bockmayr et al., 2018; Castagnoli et al., 2019). Mechanistic studies revealed that Wnt-induced decrease in the expression of the chemokine CCL4 hindered the recruitment of $CD103^+$ DCs and T cells to the tumor microenvironment (Spranger et al., 2015).

While these and several other studies strongly support the role of signaling-associated mutations in tumor resistance to ICB, it is important to acknowledge that the signaling landscape of tumor cells is extremely complex with some overlapping and opposing pathways. The complexity of signaling is further amplified by the continuous cross talk between tumor cells and stromal and immune cells within the tumor microenvironment. Nevertheless, the large body of evidence on the role of signaling in tumor immune responses has formed the rationale to combine inhibition of signaling pathways with ICB to enhance response, which will be discussed in detail later in this review.

Extracellular vesicles: Recent studies have demonstrated a potential role for extracellular vesicles (EVs), in particular, the exosome subset of EVs, in tumor immunity and resistance to ICB (Figure 2). EVs derived from a variety of tumor types including melanoma, glioblastoma, breast, and head and neck cancer contain functional PD-L1 on their surface (Chen et al., 2018; Ricklefs et al., 2018; Theodoraki et al., 2018). Exosomal PD-L1

suppressed $CD8^+$ T cell activity and induced T cell exhaustion in draining lymph nodes and promoted tumor growth in an anti-PD-L1 blockade-resistant prostate cancer model (Poggio et al., 2019). In cancer patients undergoing anti-PD-1 treatment, pre-treatment levels of circulating exosomal PD-L1 were higher in those who did not benefit from the treatment, reflecting the role of exosomal PD-L1 in tumor immunity and its potential association with T cell exhaustion (Chen et al., 2018). Levels of circulating $PD\text{-}L1^+$ EVs can mirror the dynamic interaction between tumor and immune system and may serve as a promising biomarker for ICB response.

2.1.2. Tumor microenvironment: stromal cells—The tumor microenvironment harbors several non-immune stromal components including endothelial cells, fibroblasts, and tissue-specific cells, all of which contribute tremendously to the different hallmarks of cancer such as angiogenesis, invasion into the extracellular matrix (ECM) and metastasis. Growing evidence suggests that these stromal components can also contribute to mechanisms of immune evasion and resistance to ICB (Figure 2).

The high rates of angiogenesis in the tumor microenvironment and the resultant abnormal vasculature and high interstitial pressure within the tumor (Folkman, 1971) can impair the infiltration of immune cells and the penetrance of checkpoint inhibitors (Fukumura et al., 2018). Moreover, endothelial cells can express PD-L1, which can further attenuate T cell function within the tumor microenvironment (Eppihimer et al., 2002). Consistent with these studies, strategies to combine anti-angiogenic antibodies with checkpoint inhibitors have shown promising results in enhancing the anti-tumor immune response (Fukumura et al., 2018).

Cancer-associated fibroblasts (CAFs) can have dual effects on the tumor immune responses. CAF-derived transforming growth factor beta (TGFβ) signaling in the tumor microenvironment was associated with dysregulation of the ECM genes resulting in a distinct signature that correlated with higher $CD8^+$ T cells and M1:M2 macrophage ratio. This signature was enriched in immunologically “hot” tumors across different cancer types within TCGA (Chakravarthy et al., 2018). In contrast, fibroblast activation protein $(FAP)^+$ CAFs inhibited anti-tumor function of T cells in gastric cancer and pancreatic cancer and targeting these FAP^+ subtypes enhanced tumor response to ICB (Feig et al., 2013).

Tissue-specific stromal cells can also play a role in tumor resistance to ICB. Resistance to ICB in bone metastases from prostate cancer has been attributed, at least to some extent, to the release of TGFβ following osteoclast-induced bone resorption, which reduced the number of T helper type 1 (Th1) cells within the tumor (Jiao et al., 2019). Moreover, phosphoSTAT3+ reactive astrocytes associated with metastatic brain tumors were shown to decrease $CD8^+$ T cell activity and increased the abundance of $CD74^+$ microglia/macrophages, promoting tumor immune evasion and suggesting a potential role in resistance to ICB (Priego et al., 2018).

2.1.3. Tumor microenvironment: immune cells—Various types of innate and adaptive immune cells reside within or infiltrate the tumor microenvironment. The dynamic cross talk between these immune cells and tumor cells define the immune status of the

tumor and can promote or hinder the tumor response to ICB. Tumor immune profiles can be classified into “cold” or “hot” tumors or more precisely into “immune-inflamed”, “immune-excluded”, or “immune-desert” (Chen and Mellman, 2017). Immune-inflamed tumors are identified by the abundance of $CD4^+$ and $CD8^+$ T cells and their penetration into the tumor, and are often, but not always, associated with a favorable response to ICB. Immune-excluded and immune-desert tumors are respectively defined by the presence of T cells without infiltration into the tumor or the absence of T cells, and do not respond to ICB (Chen and Mellman, 2017). As tumors evolve, the tumor microenvironment gradually becomes more immunosuppressive with several components of the innate and adaptive immune system contributing to tumor immune evasion and inevitably to resistance to checkpoint inhibitors.

$CD8^+$ effector T cells have a central role in inciting an anti-tumor immune response through the release of cytolytic factors and induction of apoptosis in tumor cells (Figure 2). The presence of $CD8^+$ T cells at tumor margins and within the tumor prior to treatment with checkpoint inhibitors was associated with a stronger response to treatment (Tumeh et al., 2014). Accordingly, Tregs attenuate the activity of $CD4^+$ and $CD8^+$ T cells to maintain self-tolerance, through the secretion of immunosuppressive cytokines (including IL-2, IL-10, IL-35, TGF β) and the expression of checkpoint molecules such as CTLA-4 and PD-1 (Saleh and Elkord, 2019). Identified by the expression of CD4, CD25, and the Forkhead box P3 (FoxP3) transcription factor, Tregs are often found in abundance both in the tumor microenvironment and in circulation (Okita et al., 2005; Woo et al., 2001). The critical role of Tregs in regulation of tumor immunity was verified by preclinical studies where depletion of Tregs in a variety of tumor types could evoke an anti-tumor immune response (Shimizu et al., 1999). Due to the constitutive expression of CTLA-4 on Tregs and the high expression of PD-1 on these cells, anti-CTLA-4 and anti-PD-1 antibodies have been successful in depleting tumor-infiltrating Tregs and increasing the effector T cell (Teff) to Treg ratio in the tumor microenvironment (Curran et al., 2010; Quezada et al., 2006; Simpson et al., 2013). However, compensatory proliferation of Tregs due to incomplete depletion by checkpoint inhibitors (Kavanagh et al., 2008) and upregulation of alternative checkpoint molecules such as TIM-3 and Lag-3 in Tregs are among the Treg-driven mechanisms of resistance to ICB (Ma et al., 2018).

Myeloid-derived suppressor cells (MDSCs) are another subset of immune cells with immunosuppressive activity in the tumor microenvironment. Through different mediators such as arginase 1, Inducible nitric oxide synthase (iNOS), reactive oxygen species (ROS), and peroxynitrite, MDSCs attenuate the activity of Teffs and NK cells (Gabrilovich and Nagaraj, 2009), regulate the differentiation of Tregs (Huang et al., 2006), and induce an immunosuppressive phenotype in macrophages (Sinha et al., 2007). Moreover, tumor-infiltrating MDSCs exhibit a high expression of inhibitory checkpoints such as PD-L1 in various cancer types including colon, ovarian, and bladder cancer (Lu et al., 2016). Consistent with these reports, MDSCs were shown to be targeted and depleted by ICB, resulting in an increased Teff to MDSC ratio (Retseck et al., 2018). These observations suggest a potential role for MDSCs in development of resistance to ICB. In fact, lower numbers of MDSCs in melanoma patients were associated with a better response to Ipilimumab (CTLA-4 antibody) (Meyer et al., 2014).

Tumor-associated macrophages (TAMs) also play pivotal roles in regulation of tumor immunity. Studies on the complex plasticity of TAMs suggest the presence of a spectrum of phenotypes for these cells with M1 and M2 being the two ends of the spectrum (Xue et al., 2014). While M1 macrophages classically express pro-inflammatory cytokines and promote an anti-tumor immune response, M2 macrophages are characterized by the expression of anti-inflammatory cytokines and chemokines and suppress $CD8^+$ T cell activation, promote recruitment of Tregs, and contribute to tumor immune evasion (Xue et al., 2014). Expression of inhibitory checkpoint molecules such as PD-L1 on these cells further enhances their immunosuppressive effects (Gordon et al., 2017). Several studies have demonstrated that inhibiting the activity of M2-like TAMs and redirecting the polarization of macrophages toward the M1 phenotype can enhance response to ICB (Rodell et al., 2018; Zhu et al., 2019). A low ratio of adaptive immune response to pro-tumorigenic inflammatory gene signatures in phagocytic myeloid cells is another factor shown to be associated with resistance to PD-L1 blockade in urothelial cancer (Wang et al., 2021).

Recent studies have also demonstrated a role for B cells in tumor immunity and response to ICB. Presence of B cells in tumor was associated with a better response to neoadjuvant therapy with ICB in melanoma and renal cell carcinoma (Cabrita et al., 2020; Helmink et al., 2020). B cells were found primarily in tertiary lymphoid structures (TLS). Tumor-infiltrating B cell populations in responder tumors were enriched in memory B cells; in contrast, naïve B cells were more prominent in non-responder tumors (Helmink et al., 2020). Similarly, in soft-tissue sarcomas, the presence of TLS enriched in B cells was associated with a better response to PD-1 blockade (Petitprez et al., 2020). The mechanism(s) underlying the effect of B cells on response to ICB is poorly understood. However, present data suggests a number of potential mechanisms including activation of T cells through antigen presentation by memory B cells and B cell-derived cytokines, as well as potential contribution through producing antibodies against tumor. Future studies are required to determine the precise mechanism of action for these cells as well as the different components of the TLS in the context of immune checkpoint inhibitors.

Other innate immune cells infiltrating the tumor microenvironment such as NK cells, neutrophils and DCs can further impact anti-tumor immune responses. Tumor-infiltrated neutrophils have shown both pro- and anti-tumor phenotypes (Shaul and Fridlender, 2018). The activities of tumor-associated DCs depends significantly on the subtype of DC present. The tumor microenvironment often dictates an immature phenotype in DCs, which are not effective in activating T cells through antigen presentation and further promote an immunosuppressive microenvironment through expanding Tregs (Muenst et al., 2016). In contrast, conventional type I dendritic cells (cDC1) can effectively stimulate $CD8^+$ T cells in tumor-draining lymph node and within the tumor (Roberts et al., 2016), creating a rationale for therapeutic efforts to increase these cells in the tumor microenvironment in order to improve response to ICBs. In line with this, NK cells have been demonstrated to increase cDC1 tumor infiltration through secretion of CCL5 and XCL1 chemokines (Bottcher et al., 2018), and targeting these chemokine pathways was suggested as a potential strategy to improve response to ICBs.

2.1.4 Tumor microenvironment: Metabolic status—The metabolic status of the tumor microenvironment is another factor that can affect tumor immunity through a variety of mechanisms. For instance, hypoxic tumors have been shown to exhibit decreased MHC-I expression in tumor cells and DCs (Ramakrishnan et al., 2014). Exhausted T cells and tumor-infiltrating NK cells also exhibit dysregulated mitochondrial biogenesis, a mechanism that has created interest in using strategies to improve mitochondrial biogenesis to promote tumor immunity (Scharping et al., 2016; Zheng et al., 2019). In addition to the prominent role of hypoxia in tumor immunity, other aspects of the tumor microenvironment that are under the influence of metabolic conditions such as altered source of nutrients (Leone et al., 2019) are actively being explored as novel mechanisms of immune evasion and resistance to ICB.

2.1.5. Tumor microenvironment: Microbial components—More recently, intratumoral microbes--yet another component of the tumor microenvironment that was heretofore underappreciated--has been shown to have significant impact on the anti-tumor immune responses and responses to ICB (Figure 2). Two recent studies demonstrate a high prevalence of microbes within a broad range of tumors, including those not physically associated with the aerodigestive tract and its commensal organisms (Nejman et al., 2020; Poore et al., 2020). Characterization of the tumor microbiota within melanoma, lung, ovarian, glioblastoma, pancreas, bone, breast tumors suggest that these microbes can be localized within the cancer cells themselves or within tumor-associated immune cells. Further, these microbes may be tumor-type specific, suggesting distinct functions that may complement the tumor (Nejman et al., 2020). Intratumoral microbes have been shown to affect nearly all aspects of cancer biology including tumor initiation/growth, invasion and metastasis (Bullman et al., 2017; Riquelme et al., 2019). Long-term survival in pancreatic cancer has been linked to increased alpha-diversity in the tumor microbiome and the presence of a particular intratumoral microbiome signature (Pseudoxanthomonas-Streptomyces-Saccharopolyspora-Bacillus clausii) (Riquelme et al., 2019). Moreover, intratumoral microbes can also alter the tumor immune microenvironment; tumor-associated microbes are associated with decreased immune cell infiltrate and a remodeling towards a more immunosuppressive environment (Helmink et al., 2019). Analyses of human samples suggest differences in the composition of the tumor microbiota between responders and non-responders for a cohort of melanoma patients undergoing immunotherapy (Nejman et al., 2020). Peptides derived from intracellular bacteria can be presented by tumor cells in the context of human HLA-I and -II and recognized by tumor-infiltrating T-cells; this is one possible mechanism by which intratumoral bacteria could directly impact anti-tumor immunity (Kalaora et al., 2021).

2.1.6. Host systemic factors—Evidence suggests a robust systemic immune response is absolutely essential to the success of cancer immunotherapies (Chen and Mellman, 2017; Spitzer et al., 2017). Computer modeling has been utilized to describe overall tumor immune “fitness” by predicting the ability of the host to present a variety of neoantigens (Luksza et al., 2017). As one example, we know that homozygosity at HLA loci leads to less diverse cohort of antigens being expressed; HLA homozygosity has been linked to decreased survival in cancer patients treated with ICB (Chowell et al., 2018).

Other host factors contribute to overall systemic immune function including the gut microbiota (Figure 2). The effects of the gut microbiota on the anti-tumor response has been demonstrated in preclinical models as well as in patients with melanoma, renal cell carcinoma and NSCLC (Chaput et al., 2017; Gopalakrishnan et al., 2018; Matson et al., 2018; Routy et al., 2018). Further, multiple studies demonstrated the negative impact of antibiotics in the context of treatment with ICB, likely due to their detrimental impact on gut microbial diversity (Derosa et al., 2018; Routy et al., 2018; Vetizou et al., 2015). Factors that can alter the gut microbiota may secondarily influence systemic immune function and anti-tumor immune response. A high-fiber diet and exercise are associated with increased diversity of the gut microbiota and enrichment of short chain fatty acids (SCFAs), both of which have been implicated in improved survival following treatment with ICB (Barton et al., 2018; McQuade et al., 2019; McQuade et al., 2020). Clinical trials wherein the gut microbiome is modulated in patients on ICB by fecal microbial transplantation, antibiotics, and/or pre/probiotics or dietary changes are ongoing (McQuade et al., 2019; McQuade et al., 2020)

While obesity is associated with oncogenesis and poor outcomes overall, it has interestingly been associated with improved responses to ICB and survival in patients with melanoma, NSCLC, and other solid tumors (Cortellini et al., 2019; Wang et al., 2019b)(Figure 2). Retrospective analyses suggest that obesity (as defined as BMI > 30) was associated with almost 40% lower risk of death in in patients with melanoma treated with ICB; interestingly, this effect was most predominant in men (McQuade et al., 2018).

Estrogens and androgens affect sex-related and non-sex related physiologic functions including systemic immunity and anti-tumor immune responses (Ozdemir and Dotto, 2019). Men have overall higher susceptibility to malignancy but better responses to ICB, potentially owing to increased PD-L1 expression (Ozdemir and Dotto, 2019). Anti-estrogen therapies are being combined with ICB in clinical trials for breast cancer, while anti-androgen therapies are being combined with ICB in prostate cancer (Ozdemir and Dotto, 2019).

2.2. Host-extrinsic factors (the exposome)

In addition to factors intrinsic to the to the host (both tumor-specific and systemic), factors external to the host--the exposome--may also impact cancer biology and response to therapies including ICB. Defined simply, the exposome includes all non-genetic determinants of health and disease (Wild, 2012); more specifically, the exposome represents “the cumulative measure of environmental influences and associated biological responses throughout the lifespan, including exposures from the environment, diet, behavior, and endogenous processes” (Miller and Jones, 2014). The exposome incorporates where we live, where we work, what we eat, and the medications and cosmetics we use. Psychosocial factors including chronic stress and depression/anxiety are key factors as well. Thinking even more broadly, these “exposures” themselves are related to more global social constructs including socioeconomic status, educational level, access to health care and food, as well as climate change and even racial injustice and sexual discrimination; these too comprise the exposome (Miller and Jones, 2014; Rappaport and Smith, 2010; Vermeulen et al., 2020; Wild, 2012; Zhang et al., 2019).

An individual's exposome is in a constant but variable state of change and its total effect can only be understood as the accumulation of exposures over the context of an entire lifetime. Exposures at critical points in development such as those during early childhood may be especially important and may be distant from the point of study or effect (Wild, 2012; Zhang et al., 2019).

The all-encompassing protean nature of the exposome makes analysis a daunting task. However, to continue to limit our study to the "genetic" and ignore the "environmental" is to limit our ability to fully comprehend the complexities of human health and disease. It is only through the recognition, appreciation, and dedicated study of these external factors that we will be able to delineate their individual and cooperative contributions to overall health (Vermeulen et al., 2020)—including immune function and more specifically anti-tumor immune responses.

Already, inklings of these "exposomal" effects are beginning to be understood. As noted above, exposure to ultraviolet radiation and/or cigarette smoke can increase TMB and secondarily neoantigen levels which are proposed to explain the relatively high response rate to ICB in melanoma and NSCLC respectively (Snyder et al., 2014; Van Allen et al., 2015; Yarchoan et al., 2017). Further, chronic stress enhances tumor growth and impairs anti-tumor immune response and response to ICB in pre-clinical models potentially through the activation of β2-receptor signaling pathways by the firing of the sympathetic nervous system (Bucsek et al., 2017). Retrospective data suggests that non-selective beta-blocker use in patients being treated with ICB led to improved overall survival (Kokolus et al., 2018), which has prompted clinical studies investigating the use of beta-blockers in combination with ICB (Gandhi et al., 2021). Other cancer-related treatments (e.g., chemotherapeutic agents, anti-angiogenic agents, and radiation therapy) can be considered part of the exposome. A large body of evidence demonstrates that these therapies can induce dose-dependent immune modulating effects through a variety of mechanisms. For instance, low doses of cyclophosphamide and gemcitabine were shown to decrease the number of Tregs and myeloid suppressor cells, respectively (Lutsiak et al., 2005; Suzuki et al., 2005). Several chemotherapeutic agents have also been shown to increase the expression of PD-L1 (Fournel et al., 2019; Peng et al., 2015). Furthermore, the cytotoxic effect of chemotherapeutic agents can facilitate antigen presentation and reinforce anti-tumor immune responses (Nowak et al., 2003). Similarly, irradiation can also increase tumor antigenicity through enriching the pool of antigenic peptides (Reits et al., 2006).

The application of "omics" technologies in a longitudinal fashion in a large number of diseased individuals will be key to understanding the impact of environmental exposures on health. Exposome-wide association studies (EWAS), analogous to genome-wide association studies (GWAS), are slowly evolving (Escher et al., 2017; Jeong et al., 2018; Niedzwiecki et al., 2019; Patel et al., 2010; Vermeulen et al., 2020; Wild, 2012; Zhang et al., 2019). However, success in such endeavors require the interdisciplinary cooperation of experts in fields ranging from medicine to environmental science. Moreover, it will require new technologies and creative strategies to detect and quantify exposures (smartphone technologies, individual monitoring devices) as well as more creative collection of biological samples (including breast milk and cord blood as well as teeth and hair) and the

development of robust platforms to handle such complex datasets (Escher et al., 2017; Niedzwiecki et al., 2019; Vermeulen et al., 2020; Wild, 2012; Zhang et al., 2019).

Overall, it should be noted that our rapidly evolving knowledge on the factors associated with response to ICB --both host-intrinsic and -extrinsic factors-- demonstrates the high level of complexity of interactions involved in determining response to ICB. While the relative individual and collective significance of each of these factors within the context of response to ICB remains poorly understood, a number of studies have developed frameworks and mathematical models to create a more comprehensive picture of tumor immunity and response to ICB (Blank et al., 2016; Mpekris et al., 2020). These models are extremely beneficial in guiding future pre-clinical and clinical studies to enhance our understanding of determinants of response to ICB and to improve the diagnostic and therapeutic applications.

3. Tumor evolution in the context of immunotherapy

While the genetic landscape of tumor can help shape anti-tumor immunity, the immune microenvironment may reciprocally impact the tumor genetic evolution (Jamal-Hanjani et al., 2017) (Figure 3). Various mechanisms of immune evasion present in early-stage untreated cancers could impose selection pressure on the evolving tumors through affecting neoantigens and antigen presentation (Rosenthal et al., 2019). Evolving tumor subclones with disruption in antigen presentation or neoantigen depletion at DNA and RNA levels were subject to positive selection. Notably, clonal diversities of different tumor regions in lung adenocarcinomas were negatively correlated with $CD8^+$ T cell infiltration within those regions (Rosenthal et al., 2019). This has also been observed in other cancer types such as melanoma (Mitra et al., 2020; Reuben et al., 2017).

Furthermore, treatment with ICB has been reported to change the evolutionary landscape of the tumor. Longitudinal evaluation of tumor genetic features through the course of treatment with Nivolumab (PD-1 antibody) demonstrated a reduction in mutational load in responders, due to a reduction of neoantigen-producing mutations as opposed to synonymous mutations (Riaz et al., 2017). Favorable response to anti-PD-1 therapy was associated with reshaping the evolutionary landscape of the tumor with several clonal populations becoming undetectable on treatment, whereas T cell clones were expanded in these patients (Riaz et al., 2017). The reciprocal evolution of tumor and the immune microenvironment and their co-evolution during ICB therapy can not only define mechanisms of resistance to ICBs but can also be leveraged to develop strategies to predict response to therapy.

4. Factors impacting toxicity to ICB

The human immune system relies on a complex system of checks and balances that affords effective response to pathogens (or tumor) while preserving tolerance to non-tumor self as well as some commensal organisms. Perturbation of this homeostatic balance by ICBs can lead to a loss of self-tolerance and errant non-tumor self-directed immune activity resulting in irAEs (Figure 4).

4.1. Characteristics of irAEs

irAEs comprise over 70 different pathologies affecting nearly every organ system including the neurologic, genitourinary, gastrointestinal, pulmonary, cardiovascular, and integumentary systems (Pauken et al., 2019; Postow et al., 2018). The severity of pathology varies but irAEs can be severe, even fatal in some cases (Wang et al., 2018a). irAEs are common, with a low-grade (Grade 1-2) effect observed in up to more than 90% of patients, while more severe effects (Grades 3-5) can range from 20-60% (Pauken et al., 2019; Postow et al., 2018). While toxicities associated with other anti-cancer therapies including chemotherapy and radiation therapy often follow a predictable time-course, the onset of irAE varies widely with some starting days to weeks after therapy and others months (Pauken et al., 2019; Postow et al., 2018). The breadth of systems affected, severity and timing of irAEs can all vary between agents, specifically between anti-CTLA-4 agents and anti-PD-1/PD-L1 and combinations thereof (Pauken et al., 2019; Postow et al., 2018). Currently, treatment for irAEs typically involves terminating ICB and initiating a course of high-dose corticosteroids (Haanen et al., 2018; Puzanov et al., 2017; Thompson, 2018); however, more targeted therapeutic regimens are being developed (Esfahani et al., 2020). In all cases, successful treatment of irAEs relies on early recognition of pathology and an aggressive therapeutic approach often coordinated by a multidisciplinary team of specialists (Haanen et al., 2018; Puzanov et al., 2017; Thompson, 2018).

4.2. Mechanism of irAEs

Unfortunately, we lack a full mechanistic understanding of the development of irAEs. Early hints at mechanism came from preclinical mouse models including CTLA-4 knockouts (Tivol et al., 1995; Waterhouse et al., 1995), which succumb to overwhelming autoimmune lymphoproliferative disease and PD-1 knockouts (Nishimura et al., 1999) and exhibit lupus-like autoimmune disease with arthritis and cardiomyopathy. In support of this, haplo-insufficiency of CTLA-4 and polymorphisms in CTLA-4 and PD-1/PD-L1 are associated with some autoimmune diseases (Lo et al., 2016). Further, an autoimmune disease corollary to individual irAEs occasionally exists suggesting that irAEs may, in some situations, represent clinically silent autoimmune disease or autoimmune disease kept in check by normal immunosuppressive mechanisms. However, ICB treatment in pre-clinical models did not lead to overwhelming autoimmune pathology (Leach et al., 1996; Rowshanravan et al., 2018). Moreover, those irAEs with autoimmune correlates do not always share histopathologic findings in the involved tissue, other clinical findings, or demographic factor associations with the respective autoimmune phenomena (June et al., 2017; Shah et al., 2020). Moreover, some patients with clear autoimmune disease have been treated successfully with ICB without exacerbation of disease (Boland et al., 2020). Thus, many believe that irAEs represent truly unique pathologies.

The high rate of irAEs in patients as compared to those observed in early mouse studies highlights one of the limitation of current-day preclinical models, not only in predicting rates of irAEs in patients but also in furthering our mechanistic understanding. Although new preclinical models are being developed, (Liu et al., 2016; Wei et al., 2021), we must rely heavily on clinical data collection and translational research studies utilizing samples from patients on various clinical trials.

Aberrant T cell activity is thought to be a prime factor in the development of irAEs. Shared antigens between the tumor and normal tissue could lead to *de novo* T cell activation and precipitate on-target off-tumor effects (Figure 4). This has been observed in both myocarditis and rash where infiltrating T cells have been observed in the tumor and in the cardiac muscle or skin, respectively (Berner et al., 2019; Johnson et al., 2016). The scope of this activity can be broadened through epitope spread. Antigen or epitope spread describes the phenomenon by which tumor cell death releases additional antigens; these antigens are presented in an "immune activated" microenvironment and T cells can be activated against normal tissue (June et al., 2017; Rojas et al., 2018)(Figure 4). Finally, in some tissues, pre-existing autoreactive T cells may already exist and be kept in check through checkpoint molecules. Activation or re-activation of tissue-resident autoreactive T cells is thought to be a dominant factor in the development of irAEs (Dougan et al., 2021; June et al., 2017). TCR analysis demonstrates that a large fraction of the cytotoxic effector cells found in ICB-induced colitis derive from tissue-resident $CD8^+$ T cells (Dougan et al., 2021; Luoma et al., 2020).

The role of the humoral immune system and B cells in causing irAEs has also been suggested; early changes in the peripheral B cell repertoire are associated with toxicity (Das et al., 2018). Nearly 25% of patients developed new autoantibodies following treatment with ICB for melanoma; however, the typical antibody targets observed in autoimmune disease are not always seen in irAEs even when the same target is affected (de Moel et al., 2019; Dougan et al., 2021; Luoma et al., 2020).

Even so, as discussed above, CTLA-4 and PD-1 are not expressed solely on T cells, and their activity may affect other immune cell components. CTLA-4 is also expressed on Tregs; targeting CTLA-4 could theoretically lead to Treg cell dysfunction or depletion as has been demonstrated in mice (Simpson et al., 2013), though not all data support this notion in humans (Dougan et al., 2021; Luoma et al., 2020). PD-1 can be expressed on some myeloid cells as well, and changes in the myeloid compartment could lead to an influx of inflammatory cells into various, distant tissues/organs and inciting organ damage (Nam et al., 2019; Strauss et al., 2020). Patients with ICB-associated colitis and myocarditis exhibit a robust, active macrophage infiltrate (Dougan et al., 2021; Luoma et al., 2020)s; macrophages also play a prominent role in ICB-induced diabetes (Hu et al., 2020). Finally, other less common effects may be secondary to on-target effects on normal tissue. The proposed mechanism for pituitary dysfunction, for example, is binding of anti-CTLA-4 agents to CTLA-4 expressed on normal tissue inciting complement mediated killing (Iwama et al., 2014).

4.3. Correlation of response and toxicity

There is significant data suggesting a correlation between response to and toxicity from ICB, though this data is somewhat mixed and may be specific to the agent used, tumor type, resulting irAE, as well as the kinetics of onset (Das and Johnson, 2019). Interestingly, a polygenic risk score (PRS) designed to calculate risk for vitiligo, psoriasis, and atopic dermatitis was predictive of response to ICBs in bladder cancer (Khan et al., 2020). Further,

detection of immune activation in off-target organs by increased metabolic activity as seen on PET imaging was predictive of response (Nobashi et al., 2019).

Our ability to define an association between irAEs and response is muddied by a number of factors. For one, it remains unclear as to whether corticosteroids administered for irAEs have a detrimental effect on anti-tumor response (Das and Johnson, 2019). The effect likely depends on both the timing of administration as well as the dose. While some studies show no effect (Horvat et al., 2015), high-dose steroids administered at the initiation of therapy has been associated with decreased survival (Arbour et al., 2018).

Unfortunately, patients experiencing irAEs often have very limited options for future avenues of immunotherapy which can ultimately affect their oncologic outcome. Although some data suggests that ICBs (specifically anti PD-1/PD-L1) can be successfully reinitiated in some patients following the development and resolution of irAEs (Pollack et al., 2018; Santini et al., 2018), this is not universally true. Patients experiencing severe or recurrent irAEs are often not re-started on ICBs. This represents another confounding factor when assessing the relationship between toxicity and overall survival.

5. Strategies to enhance response and abrogate toxicity

Durable responses to ICB are only seen in a small subset of patients and vary between different cancer types. Moreover, treatment with ICB can be associated with significant side effects, skewing the risk-benefit ratio for these treatments towards an unfavorable balance. These limitations have led to several ongoing efforts to develop predictive and prognostic approaches to identify patients that would benefit from these treatments as well as therapeutic strategies to enhance response to treatment and overcome resistance and toxicity.

5.1. Precision approaches to predict response using known and novel diagnostic strategies

5.1.1. Genetic biomarkers—The predictive value of TMB, MSI, and dMMR as biomarkers of response to ICBs has been supported by several studies. Initial trials on CTLA-4 blockade demonstrated a clear clinical benefit in melanoma patients with high TMB (Snyder et al., 2014), also shown to be true for PD- 1 blockade in NSCLC (Rizvi et al., 2015). In addition, comparison of the clinical efficacy of pembrolizumab (PD-1 antibody) in colorectal and non-colorectal patients with dMMR demonstrated a significantly higher response rate and increased progression free survival (Le et al., 2015).

In 2017, FDA granted approval of pembrolizumab for treatment of advanced pediatric and adult solid tumors with high MSI or dMMR that have not responded to prior treatments and have no other alternative treatment option, a first-of-kind tissue-agnostic approval of an ICB based on a common biomarker across cancer types. This decision was made based on the results of 149 patients with high MSI or dMMR across 5 clinical trials, in whom treatment with pembrolizumab led to an overall response rate of 39.6% with duration of response of 6 months or more in 78% of patients (NCT01876511). A second tissue-agnostic approval for all advanced pediatric and adult solid tumors with high TMB (≥10 mutations/megabase)

that have not responded to prior treatments and have no other alternative treatment option (based on the KEYNOTE-158 trial-NCT02628067) was later issued. Pembrolizumab was also granted approval for colorectal cancer patients with high MSI or dMMR as a first line treatment (based on the KEYNOTE-177 trial-NCT02563002).

It should be noted that, despite the mounting evidence on the benefits of these genetic factors as biomarkers of response to ICBs, association between TMB and response to ICB is not observed in all patients (Snyder et al., 2014). Moreover, the association between mutational load and a favorable response to nivolumab (PD-1 antibody) in melanoma patients was only observed in ipilimumab (CTLA-4 antibody) naïve patients, suggesting the limited predictive value of mutational load and a need for alternative biomarkers for patients who had progressed on ipilimumab prior to nivolumab treatment (Riaz et al., 2017). The need for advanced technologies to conduct these analyses also limits the applicability of these biomarkers to certain clinical settings.

5.1.2. Immunological biomarkers

Tumor-infiltrating lymphocytes: The expression level of immune markers in pre-treatment tumor samples has been evaluated as potential predictive biomarkers of response to ICBs. In metastatic melanoma patients, a higher density of intratumoral $CD8^+$ T cells at baseline was shown to predict favorable response to anti-PD-1 treatment (Tumeh et al., 2014). Importantly, this study evaluated the spatiotemporal distribution of T cells within the tumor and demonstrated that abundance of T cells at the invasive tumor margin prior to treatment was associated with a better response, whereas upon treatment, T cell densities were increased both at the margin and within the tumor parenchyma in responding patients (Tumeh et al., 2014). In contrast to PD-1 blockade, the presence of TILs has not proven beneficial for prognostic purposes in anti-CTLA-4 treatments, reflecting the mechanism of action of this drug (Huang et al., 2011). In contrast, early on-treatment levels of TILs could predict response to CTLA-4 blockade in melanoma patients (Chen et al., 2016). Thus, early on-treatment biopsies may be an important biomarker. The International Immuno-Oncology Biomarker Working Group has made significant efforts to standardize the histological methods of assessment of TILs to further improve the reliability and reproducibility of this potential biomarker (Hendry et al., 2017).

Immune checkpoint molecules: Initial trials on anti-PD-1 and anti-PD-L1 inhibitors reported a significant association between pre-treatment intratumoral PD-L1 expression and response to treatment in a variety of tumor types including melanoma and NSCLC (Herbst et al., 2014; Reck et al., 2016; Topalian et al., 2014). Interestingly, association between PD-L1 expression and response to anti-PD-L1 treatment was only significant for PD-L1 expression on tumor-infiltrating immune cells but not tumor cells (Herbst et al., 2014). In contrast to these studies, other reports have shown that durable response can be obtained in the absence of PD-L1 expression in some patients (Daud et al., 2016). It should be noted that variability in the definition of PD-L1 positivity and methods of evaluation could account for inconsistencies in results and calls for further standardization of these criteria.

Emerging strategies: While the value of TILs and PD-L1 expression has been proven in certain cancer types, given the complexity of tumor immune responses and mechanisms of resistance to ICB, these biomarkers alone cannot fulfill the prognostic/predictive needs to improve patient selection for treatment with ICB. Identification of novel markers that can guide the treatment decision making with ICB is therefore, of significant importance and a matter of active investigation. Evaluation of melanoma patients treated with CTLA-4 inhibitor followed by PD-1 blockade, demonstrated that expression of T cell-related markers including CD4, CD3, CD8, FOXP3, and granzyme B as well as checkpoint inhibitors such as PD-1, PD-L1, and LAG3 in early on-treatment samples had a strong correlation with response to treatment (Chen et al., 2016). The AMADEUS trial (NCT03651271, ongoing) has been designed to evaluate the benefit of classifying tumors into immunologically hot and cold tumors based on $CD8^+$ T cell density (≥15% and <15%, respectively) as a predictive biomarker to identify patients that are more likely to respond to Nivolumab (PD-1 antibody) or combination of Nivolumab and Ipilimumab (CTLA-4 antibody). In addition, this prospective exploratory study aims to identify novel biomarkers that can be used as strong predictive indicators of response to ICBs.

A high predictive value has also been demonstrated for exosomal PD-L1 in combination with CD28 (area under curve of 0.85) (Zhang et al., 2020). Further longitudinal studies in larger cohorts are warranted to verify the predictive and prognostic value of exosomal PD-L1 in the context of treatment with ICB.

Another emerging strategy for predicting and monitoring response to ICB is the use of microbiome signatures. The gut and tumor microbiome have been associated with anti-tumor responses and, in some cases, response to immune checkpoint blockade (Gopalakrishnan et al., 2018; Matson et al., 2018; Nejman et al., 2020; Riquelme et al., 2019; Routy et al., 2018). Moreover, analyses of TCGA datasets identified unique microbial signatures in blood that could distinguish between healthy and cancer patients (Poore et al., 2020). These latter findings reveal novel opportunities for the use of the circulating microbiome as a minimally invasive biomarkers in cancer.

5.2. Therapeutic strategies to promote response and overcome resistance

Built upon the growing knowledge of the variable mechanisms of resistance to ICB, several therapeutic strategies have evolved to overcome these and to promote response to ICB.

5.2.1. Modulation of epigenetic status—Different approaches have been introduced to mitigate resistance to ICBs in tumors with low immunogenicity and antigen presentation through epigenetic modulation. Treatment with DNA methyltransferase inhibitors has been shown to reverse the epigenetic suppression of MHC-I, which facilitated antigen presentation, immunogenicity, and tumor immune targeting (Luo et al., 2018). Histone deacetylase (HDAC) inhibitors in combination with DNA methyltransferase inhibitors have also resulted in an increase in anti-tumor immune responses in preclinical models (Topper et al., 2017). The effect of HDAC inhibitors on tumor immunity as a single agent is yet to be determined and their clinical efficacy in combination with ICB is currently under evaluation in a number of clinical trials (e.g., NCT02638090, NCT02619253).

5.2.2. Signaling modulators—The prominent role of tumor signaling provides a rationale for combination treatment strategies with ICB. One such strategy includes treatment of BRAF-mutated melanoma patients with a combination of atezolizumab (PD-L1 antibody) and v-raf murine sarcoma viral oncogene homolog B1 (BRAF)/ Mitogen-activated protein kinase kinase (MEK) inhibitors, which significantly increased progression-free survival (NCT02908672) (Gutzmer et al., 2020). Several other strategies have been tested in preclinical models to reverse signaling defects and metabolic stress in order to enhance response to ICB including PI3K inhibitors (Marijt et al., 2019), and cyclin-dependent kinase 4 and 6 (CDK4/6) (Goel et al., 2017). These and many other studies suggest that targeting signaling pathways holds promise as a potential strategy to improve response to ICB.

5.2.3. Cytokines—Other therapeutic strategies have focused on increasing the abundance of TILs to enhance response to ICBs. Cytokines such as IL-2 and IL-12 were previously introduced to increase intratumoral lymphocyte infiltration and anti-tumor immunity; however, these treatments were associated with severe toxicity (Panelli et al., 2004; Sangro et al., 2004). These complications have triggered several efforts to redesign the next generation cytokines for therapeutic purposes, which are currently being tested and have shown beneficial effects in combination with ICB in preclinical studies (Klein et al., 2017; Sun et al., 2019).

5.2.4. Anti-angiogenic agents—Several clinical trials have assessed the benefits of combining anti-angiogenic therapy with ICB and have demonstrated an increase in immune cell tumor infiltration and improved outcomes in patients with immune suppressed signatures compared to ICB alone (Hodi et al., 2014; McDermott et al., 2018). To date, the use of bevacizumab (anti-angiogenic agent) in combination with atezolimumab (PD-L1 antibody) has been FDA approved for unresectable or metastatic hepatocellular carcinoma in patients who have not received prior systemic therapy (Finn et al., 2020). Indications for this combination therapy is expected to be expanded in the future.

5.2.5. Chemotherapy and radiotherapy—The immune modulatory effects of treatment with chemotherapy and radiotherapy in (reviewed in (Zitvogel et al., 2008)) have formed the basis for combination strategies to boost response to ICB, which are currently under evaluation in several clinical trials. While most of these studies are in the initial safety phase, improvement in overall survival has been reported in unresectable NSCLC patients and TNBC patients treated with anti PD-L1 antibody with chemotherapy (Schmid et al., 2020; West et al., 2019). Preclinical and clinical efforts to determine the optimal treatment schedule and dosing for different cancer types are warranted to further expand the benefits of this treatment strategy.

5.2.6. Oncolytic viruses—Oncolytic viruses target and kill tumor cells through a number of different mechanisms such as inducing lysis, cytotoxicity, and stimulating anti-tumor innate and adaptive immune responses. Due to their immune stimulatory effects and their ability to change a noninflamed tumor to an inflamed microenvironment, strategies to combine oncolytic viruses with ICB have been considered for enhancing response to treatment (Chon et al., 2019). Talimogene laherparepvec is a genetically modified oncolytic

virus that has been tested in combination with Ipilimumab (CTLA-4 antibody) for treatment of advanced, unresectable melanoma and was associated with an increase in objective response rate (NCT01740297). Selecting the optimal viral strain, genetic modification, and treatment strategy is key to obtaining positive results from oncolytic viruses in combination with ICB (Rojas et al., 2015).

5.2.7. Vaccines—Vaccines have been used as an approach to enhance anti-tumor immune responses and have demonstrated encouraging results in preclinical and clinical studies, leading to an expansion of the intratumoral T cell infiltration and anti-tumor immune responses (Carreno et al., 2015; Ott et al., 2017). Several efforts are ongoing to improve the efficacy of vaccines. Recent preclinical studies have shown that vaccination with $CD103^+$ cDC1s in combination with CTLA-4 blockade were highly effective in inducing tumor regression in murine models of osteosarcoma and melanoma (Zhou et al., 2020). Furthermore, initial trials testing a combination of vaccines with ICB have shown promise (Massarelli et al., 2019); however randomized clinical trials are required to evaluate the added benefit of this combination strategy.

5.2.8. Other strategies—There is growing interest in developing other novel approaches to overcome resistance to ICB. Mounting evidence on the role of the gut and tumor microbiome, stress, and diet in tumor immunity and response to ICB (Helmink et al., 2020) has created a foundation for emerging adjunct therapies. A better understanding of the underlying mechanisms of these factors along with discovery and thorough validation of actionable targets are prerequisites for the development and successful application of these emerging strategies.

5.3. Diagnostic and therapeutic strategies to abrogate toxicity to ICB

Currently, oncologists prescribing ICB must weigh the risk of development of irAE against the benefit of ICB without any real data to guide that decision. This has fueled intensive efforts to identify potential biomarkers for the development and severity of irAEs, thereby guiding the rational prescribing of these agents or combinations of these agents as well as the development of surveillance strategies for high-risk patients allowing for earlier detection and intervention.

5.3.1. Potential biomarkers of toxicity—While genetic determinants for autoimmune disease are numerous (Hoefsmit et al., 2019), genetic pre-disposition to irAEs is less well-defined. Certain HLA types have been associated with development of various irAEs; these associations seem to be disease-specific (Cappelli et al., 2019; Hasan Ali et al., 2019). Work continues to allow for development of polygenic risk scores of patients at risk for irAEs and will require very large association studies across treatments and malignancies (Hoefsmit et al., 2019). Tumor factors including tumor mutational burden can be associated with irAEs (Bomze et al., 2019).

Dysbiosis of the gut microbiota is also associated with response as well as toxicity; increased pre-treatment levels of Bacteroidetes and richness in genetic pathways associated with polyamine transport and B vitamin biosynthesis was protective for immunotherapy-

related colitis in patients with metastatic melanoma treated with ipilimumab (Dubin et al., 2016). Even more creative strategies to predict irAEs are being considered. In a proof-of-concept study, 1860 radiomic features identified in chest CTs were obtained for each patient using first- and second-order texture analysis prior to therapy; skewness and angular variance of sum of squares (measure of dispersion) were higher in patients who later developed pneumonitis (Colen et al., 2018).

A change in the immune signature of peripheral blood represents an attractive biomarker given ease of assessment. Early diversification of the circulating T cell repertoire has been associated with both response and toxicity (Oh et al., 2017) as has early clonal expansion of large numbers of $CD8^+$ T cells (Subudhi et al., 2016). An increase in CD21-lo B cells and plasmablasts in peripheral blood early after combination therapy has also been associated with irAEs (Das et al., 2018). Increased circulating IL-17 levels at baseline in patients with locoregional metastatic melanoma (Tarhini et al., 2015), and increased IL-6 levels in patients with metastatic melanoma treated with ipilimumab (CTLA-4 antibody) are also associated with irAEs (Valpione et al., 2018). More global cytokine dysregulation as assessed by measuring the circulating levels of 11 cytokines (CYTOX score) at baseline or early on treatment has been shown to be predictive of irAEs in patients treated with anti-PD1 therapies alone or in combination with anti-CTLA-4 therapies (Lim et al., 2019).

The search for appropriate biomarkers is ongoing and include collaborative efforts with large multi-national databases including patients with both low and high-grade toxicity with appropriate controls (healthy individuals as well as those treated with ICB without developing irAEs) (Hoefsmit et al., 2019; Jing et al., 2020).

5.3.2. Therapeutic strategies to abrogate toxicity—The development of unique strategies for the treatment of irAEs, with a focus on alternatives to high-dose corticosteroids, is ongoing (Dougan et al., 2021; Esfahani et al., 2020). Dermatologic conditions can often be managed with topical steroids or other disease-specific drugs (Johnson et al., 2019; Tattersall and Leventhal, 2020); involvement of a dermatologist early for biopsy and diagnosis is key. In some cases, treatments used for some autoimmune disease corollaries of irAEs have been utilized in irAEs with success. TNF-inhibitors have been very successful in the treatment of inflammatory bowel disease as well as severe ICB-induced colitis; in fact, it may become first-line treatment for patients with severe disease (Abu-Sbeih and Wang, 2020). $\alpha_4\beta_7$-integrin modulates immune cell trafficking specifically to the gut mucosa; vedolizumab is an $\alpha_4\beta_7$-integrin inhibitor that has been used in both inflammatory bowel diseases as well as ICB-induced colitis (Abu-Sbeih and Wang, 2020). Finally, fecal microbiota transplantation (FMT) was originally trialed in patients with refractory infectious colitis but has also been used successfully in select cases of severe refractory ICB-induced colitis (Wang et al., 2018b).

Further mechanistic understanding of irAEs will allow us to progress from a generalized approach to the treatment of all irAEs in all patients (corticosteroids) to a more nuanced approach adapted to the immunohistopathogenesis of a particular irAE and various patient factors (Esfahani et al., 2020). Such targeted therapeutic strategies may include modulators

of T and B cell activity and trafficking, innate immune components, circulating cytokines, immune-related signaling pathways, and commensal microbiota (Esfahani et al., 2020).

Another intriguing possibility is the prevention of irAEs all together by improving existing immunotherapeutic agents to limit off-target activities. One potential for more targeted immunotherapeutic approaches is the use of bi- and tri-specific antibodies (i.e., synthetic antibody-based molecules that bind to two or three different entities simultaneously. T cell based bi-specific antibodies serve “to bridge” T cells to tumor cells to facilitate more focal T cell activation (Labrijn et al., 2019). However, this is only one of many configuration of bi- specific antibodies, and, in reality, the potential for unique combinations and novel applications of this technology is near limitless (Labrijn et al., 2019). Stimulation of OX40 and CD137, both TNF superfamily costimulatory receptors, results in T cell activation, proliferation and survival; however, mAbs targeting and inhibiting either OX40 and CD137 individual result in poor efficacy and/or promote liver toxicity. Dual agonistic bispecific antibodies binding to both OX40 and CD137, however, promote FcRγ-crosslinking-independent anti-tumor activity and moreover limit liver injury; clinical trials utilizing these dual agonistic bi-specific antibodies are ongoing (Gaspar et al., 2020).

Conclusions

Paradigm-shifting discoveries in the field of cancer immunotherapy and their successful translation to treatment strategies have resulted in long-term survival of cancer patients who would have had limited treatment options otherwise. Nevertheless, the number of patients who gain clinical benefit from these treatments is still limited due to primary or acquired resistance to ICB as well as associated toxicity. Extensive efforts have been made to develop diagnostic approaches that identify patients who would benefit from ICB and therapeutic strategies that enhance response and abrogate toxicity. Nevertheless, expanding the benefits of ICB to a larger population of cancer patients requires an in depth understanding of the mechanisms underlying resistance and toxicity. The role of host-intrinsic factors in response to ICB, including tumor genetics and immune and non-immune components of the tumor microenvironment has been studied extensively and is still subject to active investigation. However, to fully elucidate these mechanisms, it is important to acknowledge that various factors including the microbiome, host systemic factors, as well as environmental exposures (the exposome) can have a prominent role in response and toxicity to ICB. Future studies are warranted to understand the individual and collective role of these factors and will facilitate the development of novel diagnostic, prognostic, and therapeutic strategies to address the current limitations associated with ICB and to improve the outcome of cancer patients.

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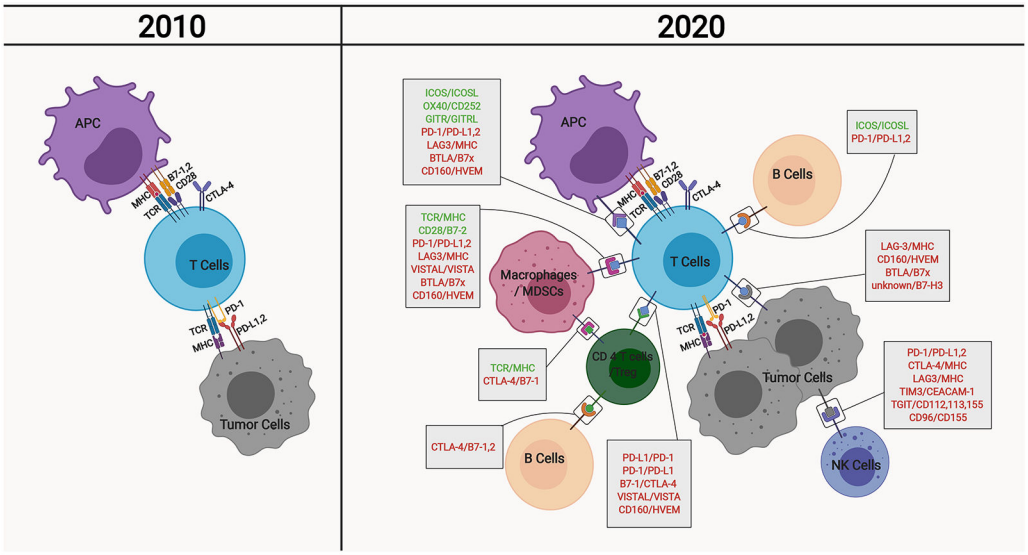

Figure 1. Evolution of our understanding of cellular interactions contributing to tumor immunity.

The basic description of anti-tumor immunity encompasses tumor antigen presentation to T cells via antigen presenting cells (APCs) or tumor cells, followed by T cell activation against tumor cells, which involves a number of costimulatory and inhibitory molecules including CD28, CTLA-4, and PD-1. Over the years, our understanding of anti-tumor immunity has evolved tremendously, owing to the identification of several other regulatory molecules on these and other immune cell types. APC, antigen presenting cells; MDSCs, myeloid-derived suppressor cells; Treg, regulatory T cells; NK cells, natural killer cells; MHC, major histocompatibility complex; TCR, T cell receptor; CTLA4, cytotoxic T-lymphocyte-associated protein 4; PD-1, programmed cell death protein 1; PD-L1,2, programmed death-ligand 1,2; ICOS, Inducible T-cell COStimulator; ICOSL, ICOS ligand; GITR, Glucocorticoid-Induced TNFR-Related; GITRL, GITR ligand; LAG3, lymphocyte activation gene 3; BTLA, B- and T-lymphocyte attenuator; HVEM, Herpes Virus Entry Mediator ; VISTA, V-domain Ig suppressor of T cell activation; VISTAL, VISTA ligand; TIM3, T-cell immunoglobulin domain and mucin domain 3; CEACAM-1, carcinoembryonic antigen-related cell adhesion molecule 1; TGIT, T cell Ig and ITIM domain.

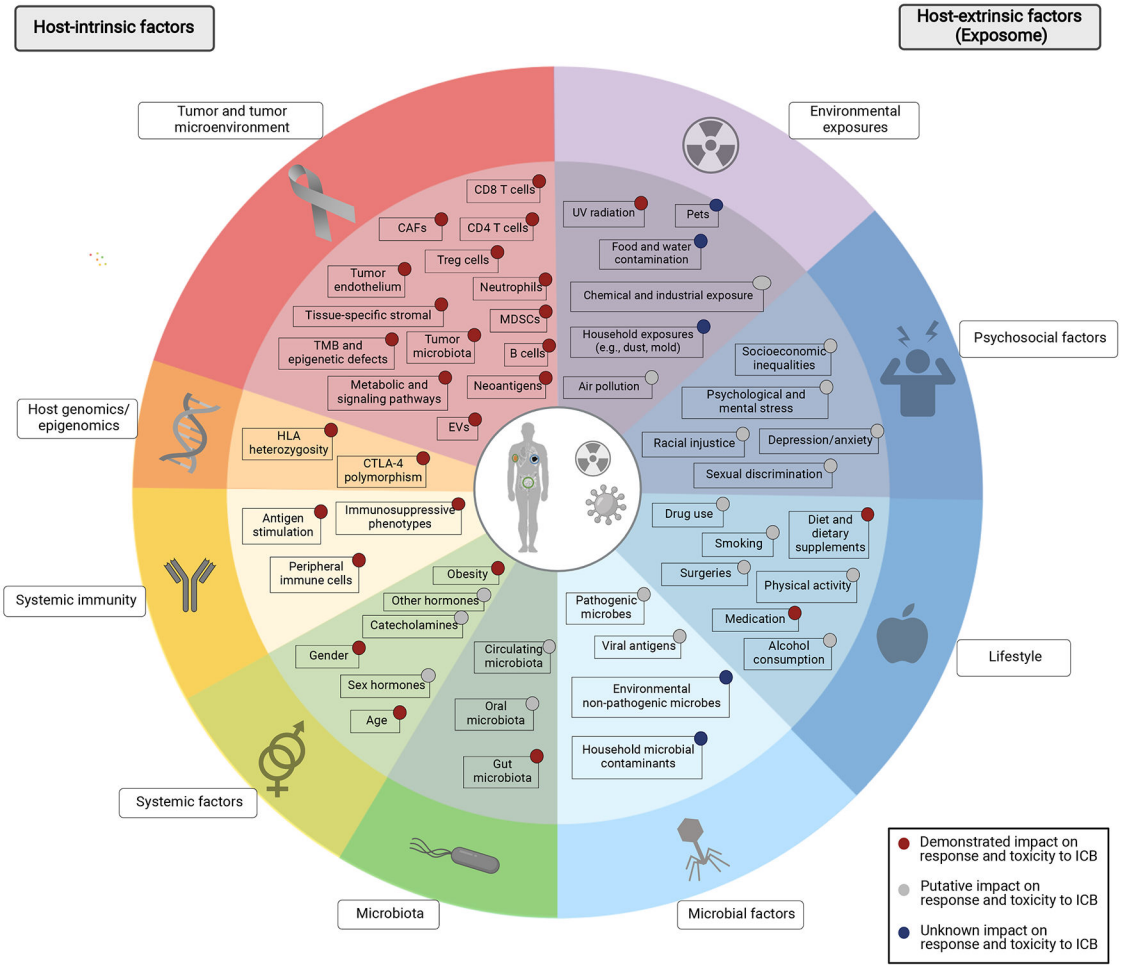

Figure 2. Factors impacting anti-tumor immunity and immunotherapy response.

Numerous factors regulate the dynamic process of tumor immunity and response to immune checkpoint blockade. Host-intrinsic factors including those inherent to the tumor cells and the tumor microenvironment (red), host genomics and epigenomics (orange), host immunity (yellow), as well as other immune-regulating factors (systemic factors, light green; microbiota, dark green) have been evaluated through a rapidly growing body of evidence. More recently, the importance of host-extrinsic factors, i.e., the exposome (shown in blue and purple) in modulating the tumor immunity and their potential impact on response to checkpoint blockade is being recognized increasingly and calls for comprehensive, albeit complicated, studies on this matter. TMB, tumor mutational burden; Treg, regulatory T cells; MDSCs, myeloid-derived suppressor cells; CAFs, cancer associated fibroblasts; EVs, extracellular vesicles; HLA, human leukocyte antigen; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; UV, ultraviolet.

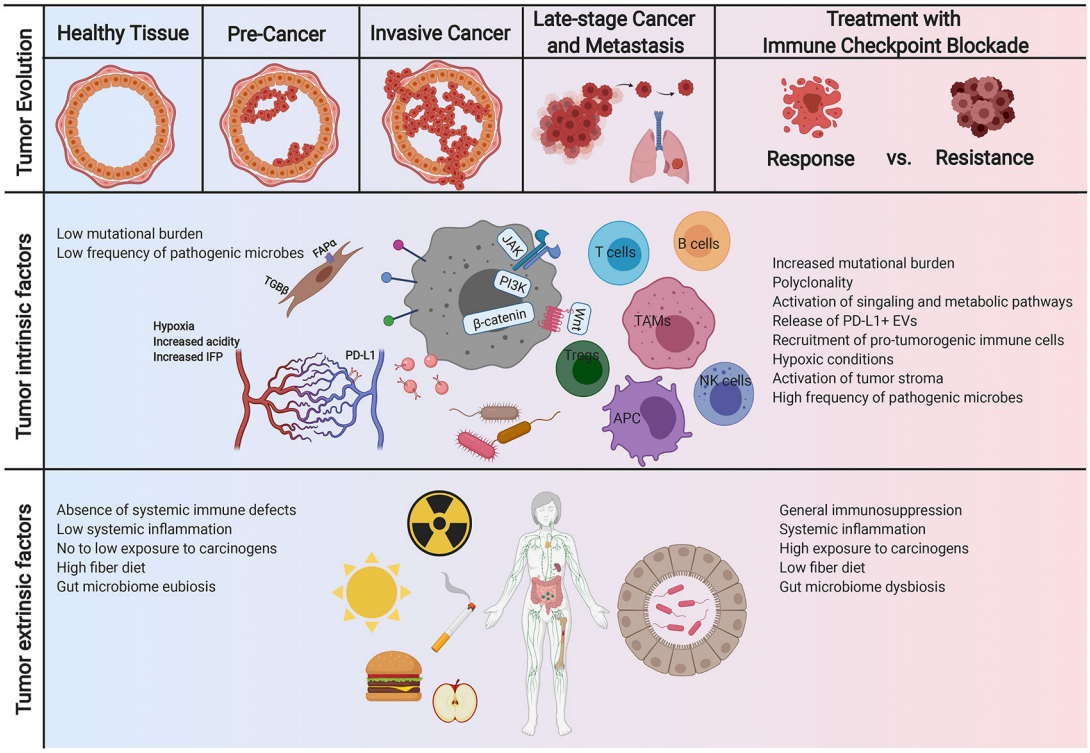

Figure 3. Coevolution of cancer and anti-tumor immunity.

This reciprocal evolution of tumor and the immune microenvironment has important clinical implications within the context of immunotherapy. As the tumor evolves, mechanisms of immune evasion can positively select the tumor subclones with low immunogenicity and disruption in antigen presentation. Furthermore, treatment with immune checkpoint blockade can also change the evolutionary landscape of the tumor, characterized by several factors such as reduction in mutational load in responders and can determine the mechanisms of resistance. TAM, tissue associated macrophages; NK cells, natural killer cells; APC, antigen presenting cells; Tregs, regulatory T cells; PD-L1, programmed death-ligand 1; TGF, tissue growth factor; FAP, fibroblast activation protein; IFP, interstitial fluid pressure; JAK, Janus kinase; PI3K, phosphatidylinositol-3-kinase; EVs, extracellular vesicles.

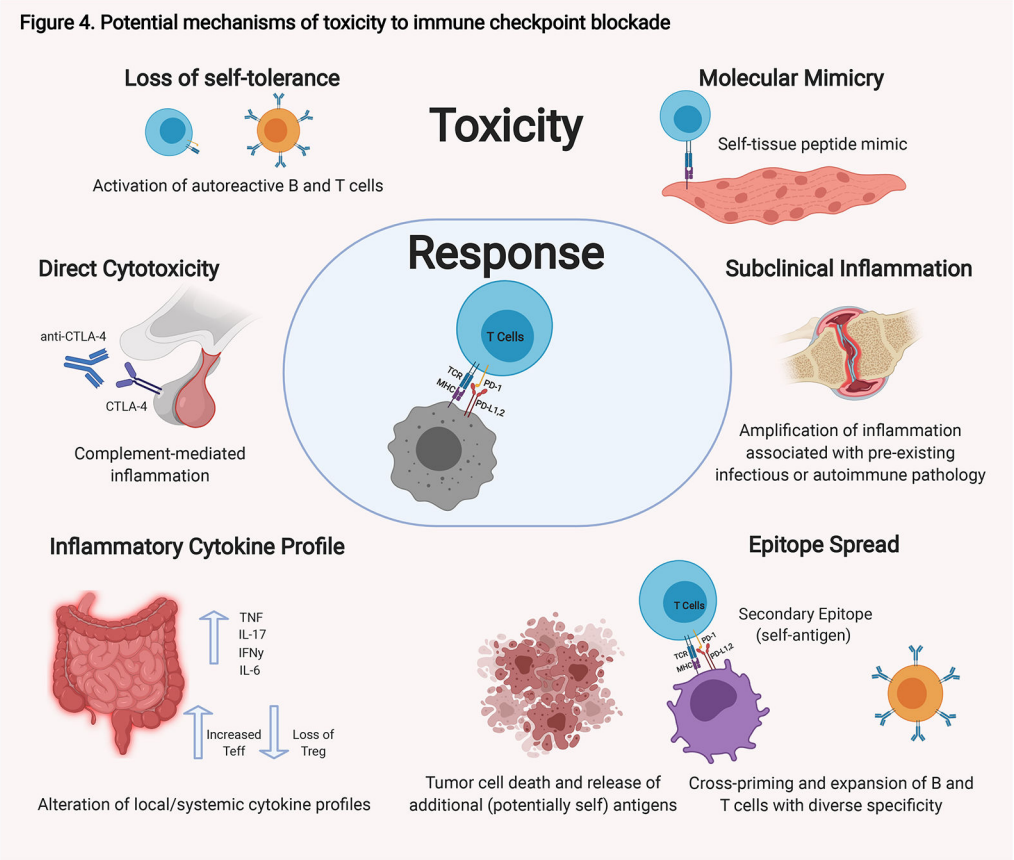

Figure 4. Potential mechanisms of toxicity to immune checkpoint blockade.

There are a number of possible mechanisms that have been proposed that contribute to the toxicities observed in some patients in response to immune checkpoint blockade. These possibilities are not mutually exclusive, and different mechanisms likely exist for different immune-related toxicities. Autoreactive T and B cells are thought to be key moieties in these processes. Autoreactive T cells could be generated *de novo.* These T cells are activated by professional APCs at the tumor site and reactive to tumor-specific antigens; however, they may coincidentally be reactive to peptides found on normal tissue that mimic the tumor-specific antigens. Alternatively, pre-existing autoreactive T and B cells that have escaped self-tolerance which were quiescent could be activated when self-peptides are presented through epitope spread by antigen presenting cells (APCs) at the tumor site. Immune-checkpoint blockade can result in alterations in the systemic immunity including changes in cytokine profiles. Changes in the cytokine profile within a given tissue can tip the existing balance towards inflammation. Alternative mechanisms also likely exist. For hypopituitarism, direct antibody-mediated cytotoxicity to CTLA-4 normally expressed on the pituitary gland is thought to play a role. Finally, amplification for pre-existing inflammatory or autoimmune pathologies are also possible. TNF, tumor necrosis factor; IFN, interferon; Teff, effector T cells; Treg, regulatory T cells.

Table 1.

List of different immune checkpoint inhibitors and indications.

Disease	Stage/Disease Characteristics	Line of Therapy	Year approved	Study Name NCT Number	Phase	Response Data	High Grade (3-5) Treatment-related Adverse Event Rate	Reference (PMID)
Anti CTLA-4 Ipilimumab (Yervoy)								
Melanoma	Metastatic melanoma	2nd line	2011	MDX010-20 NCT00094653	Phase 3	ORR 10.9% mOS 10.1 mos (HR 0.66)	10-15%	20525992
	Resected Stage 3 melanoma	Adjuvant therapy	2015	EORTC 18071 NCT00636168	Phase 3	mRFS 26.1 mos (HR 0.76)	54%	25840693
Anti PD-1 Nivolumab (Opdivo)								
Melanoma	Advanced metastatic melanoma progressed after ipilimumab or ipilimumab + targeted therapy	2nd line	2014	CheckMate-037 NCT01721746	Phase 3	ORR 31.7%	9%	**25795410**
	Resected Stage III melanoma	Adjuvant therapy	2017	CheckMate-238 NCT02388906	Phase 3	ORR n/a mRFS not reached	14.4%	**28891423**
NSCLC	Advanced squamous NSCLC	2nd line	2015	CheckMate-063 NCT01721759	Phase 2	ORR 14.5% mPFS 1.9 mos mOS 8.2 mos	17%	**25704439**
			2015	CheckMate-017 NCT01642004	Phase 3	ORR 20% mPFS 3.50 mos mOS 9.2 mos	7%	26028407
	Metastatic non-squamous NSCLC	2nd line	2015	CheckMate-057 NCT01673867	Phase 3	ORR 19% mPFS 2.30 mos mOS 12.2 mos	10%	26412456
RCC	Advanced RCC	2nd line	2015	CheckMate-025 NCT01668784	Phase 3	ORR 25% mPFS 4.6 mos mOS 20 mos	19%	26406148
SCC of head and neck	Recurrent/ metastatic HNSCC progressed on platinum-based therapy	2nd line	2016	Checkmate-141 NCT02105636	Phase 3	ORR 13.3% mPFS 2.0 mos mOS 7.5 mos	13.1%	27718784
cHL	Relapsed cHL	2nd line	2016[a]	CheckMate-205 NCT02181738	Phase 2	ORR 69% mPFS 14.7 mos mOS not reached	21%	**29584546**

Disease	Stage/Disease Characteristics	Line of Therapy	Year approved	Study Name NCT Number	Phase	Response Data	High Grade (3-5) Treatment-related Adverse Event Rate	Reference (PMID)
CRC	Relapsed/ refractory MSI-hi or dMMR CRC	2nd line	2017[a]	CheckMate-142 NCT02060188	Phase 2	ORR 31%	20%	**28734759**
HCC	HCC previously treated with sorafinib	2nd line	2017[a]	CheckMate-040 NCT01658878	Phase 1/2	ORR 14.3% mPFS 4.0 mos mOS 15 mos	25%	28434648
Urothelial Carcinoma	Advanced urothelial carcinoma	2nd line	2017[a]	CheckMate-275 NCT02387996	Phase 2	ORR19.6% mPFS 2.0 mos mOS 8.74 mos	18%	28131785
Small Cell Lung Cancer	Metastatic SCLC	3rd line	2018[a]	CheckMate-032 NCT01928394	Phase 1/2	ORR 12%	45%	**27269741**
Esophageal	Esophageal SCC (advanced unresectable or metastatic after prior FU- or platinum based chemo)	2nd line	2020	ATTRACTION-3 NCT02569242	**Phase 3**	ORR 21.5% mPFS 1.70 mos (HR 1.1) OS 10.9 mos (HR 0.77)	18%	**31582355**
Anti PD-1 PEMBROLIZUMAB (KEYTRUDA)								
Melanoma	Advanced or unresectable melanoma	2nd line	2014 [a]	KEYNOTE-001 NCT01295827	Phase 1	ORR 33% mPFS 4 mos mOS 23 mos	14%	27092830
	Advanced or unresectable melanoma	2nd line	2015	KEYNOTE-002 NCT01704287	Phase 2	ORR 25% mPFS 5.60 mos	11%	26115796
	Advanced or unresectable melanoma	1st line	2015	KEYNOTE-006 NCT01866319	Phase 3	ORR 33.7% mPFS 5.5 mos HR (OS) 0.63	10-13%	25891173
	Resected Stage III Melanoma	Adjuvant therapy	2019	KEYNOTE-054 NCT02362594	Phase 3	HR (RFS) 0.57	14.7%	29658430
NSCLC	Advanced NSCLC	2nd line	2015	KEYNOTE-001 NCT01295827	Phase 1/2			
				KEYNOTE-010 NCT01905657	Phase 2/3	ORR 19.4% mPFS 4.00 mos mOS 12.7 mos	16%	26712084
	Advanced NSCLC with PD-L1	1st line	2016	KEYNOTE-024 NCT02142738	Phase 3	ORR 45% mPFS 10.3 mos	26.6%	27718847
	Advanced non-squamous NSCLC (in	1st line	2017[a]	KEYNOTE-021 NCT02039674	Phase 2	ORR 55% mPFS 13 mos	39%	27745820

Disease	Stage/Disease Characteristics	Line of Therapy	Year approved	Study Name NCT Number	Phase	Response Data	High Grade (3-5) Treatment-related Adverse Event Rate	Reference (PMID)
	combination with) carboplatin-pemetrexed							
	Advanced non-squamous NSCLC (in combination with pemetrexed and cisplatin/ carboplatin)	1st line	2018	KEYNOTE-189 NCT02578680	Phase 3	ORR 47.6% mPFS 8.80 mos	67.2%	29658856
	Advanced squamous NSCLC (in combination with carboplatin and paclitaxel or nab-paclitaxel)	1st line	2018	KEYNOTE-407 NCT02775435	Phase 3	ORR 58% mPFS 6.40 mos mOS 15.9 mos	69.8%	30280635
	Advanced NSCLC with PD-L1 > 1%	1st line	2019	KEYNOTE-042 NCT02220894	Phase 3	ORR 27% mOS 16.7 mos HR(OS) 0.81	18%	30955977
HNSCC	Recurrent/ metastatic HNSCC (with PD-L1)	2nd line	2016[a]	KEYNOTE-012 NCT01848834	Phase 1b	ORR 16%	17%	28533473
	metastatic or recurrent unresectable HNSCC (stand-alone)	1st line	2019	KEYNOTE-048 NCT02358031	Phase 3	ORR 23% mPFS 2.3 mos	7%	**31679945**
	metastatic or recurrent unresectable HNSCC (combined with platinum and FU)	1st line	2019	KEYNOTE-048 NCT02358031	Phase 3	ORR 36% mPFS 4.9 mos	5%	**31679945**
Urothelial Carcinoma	Advanced urothelial carcinoma progressed after platinum-based chemo	2nd line	2017	KEYNOTE-045 NCT02256346	Phase 3	ORR 21.1% mPFS 2.10 mos mOS 10.3 mos	15%	**28212060**
	High risk BCG-unresponsive non-muscle invasive bladder cancer (in situ) who decline cystectomy	2nd line	2020	KEYNOTE-057 NCT02625961	Phase 2	ORR 40.6%	12.7%	DOI:10.1200/ JCO.2020.38.15_suppl.5041
All solid tumors classified as MSI-high or dMMR	Metastatic	2nd line	2017[a]	KEYNOTE-016 NCT01876511	Phase 2	ORR 53%	20%	26028255
cHL	Refractory/ relapsed cHL	2nd line	2017[a]	KEYNOTE-087 NCT02453594	Phase 2	ORR 69%	~10%	**28441111**

Disease	Stage/Disease Characteristics	Line of Therapy	Year approved	Study Name NCT Number	Phase	Response Data	High Grade (3-5) Treatment-related Adverse Event Rate	Reference (PMID)
Esophageal	Advanced/ recurrent stomach and gastroesophageal cancer	3rd line	2017[a]	KEYNOTE-059 NCT02335411	Phase 2	ORR 11.6% mPFS 2.0 mos	17.8%	29543932
	Advanced esophageal	2nd line	2019	KEYNOTE-180 NCT02558687	Phase 2	ORR 9.9% in patients with PD-L1 CPS > 10 mPFS 2.0 mos mOS 5.8 mos	12.4%	30570649
				KEYNOTE-18 NCT02564263	Phase 3	ORR 22% In patients with PD-L1 CPS > 10 mPFS 2.6 mos HR (PFS) 0.69 mOS 9.3 mos HR (OS) 0.64	18%	33026938
Cervical Cancer	Previously treated advanced cervical cancer	2nd line	2018[a]	KEYNOTE-158 NCT02628067	Phase 2	ORR 12.2 %	12.2%	30943124
MCC	Recurrent or locally advanced MCC	1st line	2018[a]	CITN-09/ KEYNOTE-017 NCT02267603	Phase 2	ORR 56% mPFS 16.8 mos	28%	30726175
PMBCL	Relapsed/ refractory PMBCL	3rd line	2018[a]	KEYNOTE-170 NCT02576990	Phase 2	ORR 45%	23%	31609651
RCC	Advanced RCC (with axitinib)	1st line	2019	KeyNote-426 NCT02853331	Phase 3	ORR 59.3 PFS 15.1 mos HR (PFS) 0.69 HR (OS) 0.53	75.6%	30779529
CRC	MSI high dMMR colorectal cancer	1st line	2020	KEYNOTE-177 NCT02563002	Phase 3	ORR 44% mPFS 16.5 mos	22%	33264544
Cutaneous SCC	Recurrent/ metastatic cutaneous SCC	1st line	2020	KEYNOTE-629 NCT03284424	Phase 2	ORR 34% mPFS 6.9 mos	5.7%	32673170
Solid tumors	Solid tumors with high TMB	2nd line	2020	KEYNOTE-158 NCT02628067	Phase 2	ORR 29% mPFS 2.1 mos mOS 11.7 mos	15%	32919526
Anti PD-1 Cemiplimab (Libtayo)								
SCC	Cutaneous SCC	1st line	2018[a]	NCT02383212 NCT02760498	Phase 1 Phase 2	ORR 46.3%	19.2%	**29863979 31952975**

Disease	Stage/Disease Characteristics	Line of Therapy	Year approved	Study Name NCT Number	Phase	Response Data	High Grade (3-5) Treatment-related Adverse Event Rate	Reference (PMID)
Anti PD-L1 Atezolizumab (Tecentriq)								
NSCLC	Metastatic resistant NSCLC progressive on platinum therapies	2nd line	2016	POPLAR NCT01903993	Phase 2	ORR 15% mPFS 2.70 mOS 12.6 mos	11%	**26970723**
				OAK NCT02008227	Phase 3	mOS 13.8 mos	15%	**27979383**
	Metastatic non-squamous NSCLC (combined with bevacizumab and carboplatin/ paclitaxel)	1st line	2018	IMpower150 NCT02366143	Phase 3	ORR 56% mPFS 8.50 mos HR 19.2 mos (HR0.71)	57%	29863955
	Metastatic resistant NSCLC with carboplatin/ nab-paclitaxel	1st line	2019	IMpower130 NCT02367781	Phase 3	ORR49.2% mOS 18.6 mos (0.80)	73.2%	31122901
	Metastatic resistant NSCLC	1st line	2020	IMpower110 NCT02409342	Phase 3	mPFS 5.7 mos mOS 17.5 mos	30.1% (Grade 3-4) 3.8% (Grade 5)	32997907
Urothelial carcinoma	Urothelial carcinoma failed treatment with cisplatin	2nd line	2016[a]	IMvigor210 (Cohort 2) NCT02108652	Phase 2	ORR 14.8% mPFS 2.1 mos mOS 11.4 mos	16%	26952546
	Urothelial carcinoma Carcinoma unable to receive cisplatin	1st line	2017[a]	IMvigor 210 (Cohort 1) NCT02951767	Phase 2	ORR 23.5% mPFS 2.70 mos mOS 15.9 mos	16%	27939400
Small Cell Lung Cancer	Advanced SCLC (combined with carboplatin/ etoposide)	1st line	2019	IMpower133 NCT02763579	Phase 3	ORR 60.2% mPFS 5.20 mos HR (PFS) 0.77 mOS 12.3 mos HR OS 0.7	37%	30280641
Breast cancer	Unresectable or metastatic TNBC (combined with nab-paclitaxel)	1st line	2019[a]	IMpassion NCT02425891	Phase 3	ORR 53% mPFS 7.50 mos (HR 0.62) mOS 21.3 mos	48.7%	**30345906**
HCC	HCC (unresectable or metastatic) combined with bevacizumab	1st line	2020	IMbrave150 NCT03434379	Phase 3	ORR 65% mPFS 6.80 mos HR (PFS) 0.59 HR (OS) 0.58	56.5%	32402160
Melanoma	Advanced melanoma	1st line	2020	IMspire150 NCT02908672	Phase 3	ORR 66% mPFS 15.1	79%	**32534646**

Disease	Stage/Disease Characteristics	Line of Therapy	Year approved	Study Name NCT Number	Phase	Response Data	High Grade (3-5) Treatment-related Adverse Event Rate	Reference (PMID)
	(combined with cobimetinib and vemurafenib)					mos HR (mPFS) 0.7800		
Anti PD-L1 Avelumab (Bavencio)								
Urothelial Carcinoma	Locally advanced/ metastatic urothelial carcinoma after failure with platinum agents	2nd line	2017[a]	JAVELIN Solid Tumor NCT01772004	Phase dose expansion	ORR 17% mPFS 1.50 mos mOS 6.5 mos	8%	29217288
	Locally advanced/ metastatic urothelial carcinoma without progression on platinum	1st line maintenance	2020	JAVELIN Bladder 100 NCT02603432	Phase 2 (Phase 3)	mPFS 3.7 mos (HR 0.62) mOS 21.4 mos (HR 0.69)	47.4%	DOI:10.1200/ JCO.2020.38.18_suppl.LBA1
MCC	MCC after failed chemotherapy	2nd line	2017[a]	JAVELIN Merkel 200 NCT02155647	Phase 2	OR 33% mOS 12.9 mos	20.5%	27592805, 29347993
RCC	Advanced RCC (combined with axitinib)	1st line	2019	JAVELIN Renal 10 NCT02684006	Phase 3	ORR 51.4% mPFS 13.80 mos (HR 0.69)	71.2%	30779531
Anti PD-L1 Durvalumab (Imfinzi)								
Urothelial Carcinoma	Locally advanced/ metastatic urothelial carcinoma	2nd line	2017[a]	NCT01693562	Phase 1/2	ORR 17.8% mPFS 1.5 mos mOS 18.2 mos	6.8%	28817753
NSCLC	Unresectable, stage 3 NSCLC (stable following definitive chemoradiation)	Adjuvant	2018	PACIFIC NCT02125461	Phase 3	mPFS 16.8 mos	29.9%	28885881
SCLC	Extensive SCLC (with etoposide and carbo-/cis-platin)	1st line	2020	CASPIAN NCT03043872	Phase 3	ORR 68% mPFS 5.10 mos OS 13 mos HR (OS) 0.73	62%	**31590988**
Combination Nivolumab and Ipilimumab								
Melanoma	Advanced melanoma	1st line	2015a	CheckMate-069 NCT01844505	Phase 2	ORR 53%	36%	25891304
	Advanced melanoma	1st line	2016	CheckMate-067 NCT01844505	Phase 3	ORR 57.6% mPFS 11.5 mos mOS > 36 mos	55%	**26027431, 28889792**
CRC	Relapsed/ refractory CRC	3rd line	2018 [a]	CheckMate-142 NCT02060188	Phase 2	ORR 55%	32%	29355075

Disease	Stage/Disease Characteristics	Line of Therapy	Year approved	Study Name NCT Number	Phase	Response Data	High Grade (3-5) Treatment-related Adverse Event Rate	Reference (PMID)
	dMMR or MSI high							
RCC	Advanced RCC	1st line	2018	CheckMate-214 NCT02231749	Phase 3	ORR 42% mPFS 11.60 mos mOS not reached	46%	29562145
NSCLC	Metastatic or recurrent NSCLC (+PDL1 expression with no ALK or EGFR mutations)	1st line	2020	CheckMate-227 NCT02477826	Phase 3	ORR 35.9% mPFS 5.1 mos mOS 17.1 mos (HR 0.70)	32.8%	31562796
	Metastatic or recurrent NSCLC in combination with 2 cycles of platinum doublet therapy	1st line	2020	CheckMate-9LA NCT03215706	Phase 3	ORR 38% mPFS 6.7 mos (HR 0.68) mOS 15.6 mos (HR 0.66)	47%	33476593
HCC	HCC previously treated with sorafenib	2nd line	2020[a]	CheckMate-040 NCT01658878	Phase 1/2	ORR 31%	29-53%	**33001135**
Pleural mesothelioma	Metastatic	1st line	2020	CheckMate-743 NCT02899299	Phase 3	ORR 40% mPFS 6.8 (HR 1.0) mOS 18.1 mos (HR 0.74)	30.3%	33485464

ORR, overall or objective response rate, *mPFS* median progression-free survival, *mOS* median overall survival, *HR* hazard ratio, *mos* months, *FDA* Food and drug administration, *SCLC* small cell lung cancer, *HCC* hepatocellular carcinoma, *CRC* colorectal cancer, *SCC* squamous cell carcinoma, *HNSCC* head and neck squamous cell carcinoma, *HCC* hepatocellular carcinoma, *cHL* classical Hodgkin's lymphoma, *RCC* renal cell carcinoma, *NSCLC* non-small cell lung cancer, *MCC* Merkel cell carcinoma, *PMBCL* primary mediastinal B-cell lymphoma, *MSI-hi* microsatellite instability high, *dMMR* mismatch repair deficient, *TMB* tumor mutational burden, *EGFR* epidermal growth factor receptor, *ALK* anaplastic lymphoma kinase, *SCC* squamous cell carcinoma, *TNBC* triple-negative breast cancer,

[a]Indicates accelerated approval