HHS Public Access

Author manuscript

Semin Cancer Biol. Author manuscript; available in PMC 2021 August 01.

Published in final edited form as:

Semin Cancer Biol. 2020 August ; 64: 93–101. doi:10.1016/j.semcancer.2019.06.012.

Autoimmunity, Checkpoint Inhibitor Therapy and Immune-related Adverse Events: A Review

Shaheen Khan[1], **David E. Gerber**[2,3,4,*]

[1]Department of Immunology, University of Texas Southwestern Medical Center, Dallas, TX, 75390-9093.

[2]Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX, 75390-9093.

[3]Harold C. Simmons Comprehensive Cancer Center, University of Texas Southwestern Medical Center, Dallas, TX, 75390-9093.

[4]Department of Clinical Sciences, University of Texas Southwestern Medical Center, Dallas, TX, 75390-9093.

Abstract

Immune checkpoint inhibitors have emerged as a remarkable treatment option for diverse cancer types. However, a significant number of patients on checkpoint inhibitors develop immune-related adverse events (irAEs) affecting a wide variety of organs. These events, which may reflect enhanced T cell activation, are unpredictable, heterogeneous, and in some instances permanent or life-threatening. It is not clear whether these toxicities are distinct from conventional autoimmune diseases or whether the manifestation of irAEs is associated with therapeutic efficacy. Studies across the spectrum of basic, preclinical and clinical research deciphering the role of genetics, epigenetics, gut microbiota and underlying immune status of patients who develop irAEs are required to gain a deeper mechanistic understanding. Insights gained from such studies will facilitate identification of biomarkers for optimal treatment and clinical management of patients. In this Review, we provide basic and clinical understanding of immune checkpoint inhibitors and irAEs. We discuss the connection between immune system, autoimmunity and cancer; immune checkpoint inhibitors and associated autoimmune toxicities; insights into potential underlying mechanisms of irAEs; impact of autoimmune diagnosis on cancer outcome; and management of irAEs.

[*]**Corresponding Author:** David E. Gerber, MD, Division of Hematology-Oncology, Harold C. Simmons Comprehensive Cancer Center, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Mail Code 8852, Dallas, TX, 75390-8852, Tel: 214-645-4180, Fax: 214-648-1955, David.Gerber@utsouthwestern.edu.

Conflict of interest

There are no conflicts of interest to declare.

Keywords

Autoimmunity; Immunotherapy; Immune checkpoint Inhibitors; toxicity and irAEs

Links between host immune function and cancer

There is a long-recognized link between immune status and cancer. Several malignancies occur more frequently in immunocompromised populations. In epidemiologic studies of individuals with human immunodeficiency virus (HIV) and/or acquired immune deficiency syndrome (AIDS) or solid organ transplant recipients, several malignancies occur at heightened rates compared to the general population. In a meta-analysis of seven studies of individuals with HIV/AIDS (n=444.172) and five studies of transplant recipients (n=31,977), for 20 of 28 types of cancer examined, both populations had a significantly increased incidence [1]. Most of these cancers had known infectious etiologies, including Kaposi's sarcoma (HHV-related), human papilloma virus (HPV)-related cancers (cervix, vulva/vagina, penis, anus, oral cavity and pharynx), Hodgkin's lymphoma and non-Hodgkin's lymphoma (EBV-related), liver cancer (HBV/HCV-related), and stomach cancer (*Helicobacter pylori*-related). However, increased risk was also noted for cancers without known infectious etiologies, including lung, kidney, and multiple myeloma.

Could there be other explanations for elevated cancer rates in HIV/AIDS patients and transplant recipients? One potential reason could be heightened clinical surveillance for cancer. However, this particular study did not identify higher risk of breast and prostate cancer, which are most commonly diagnosed through screening. Another potential reason could be differences in cancer risk factors. While smoking rates are approximately double population rates in people with HIV/AIDS [2], they are comparable between the general population and transplant recipients [3]. Furthermore, in this analysis, several tobacco-associated cancers did not occur at higher rates in the HIV/AIDS population.

Further supporting a connection between immune status and malignancy, individuals with evidence of heightened immunity may have better cancer outcomes. For instance, among patients with small cell lung cancer, those with anti-Hu antibodies have better outcomes (complete response to therapy 56% vs 20%; $P<0.001$) [4]. These paraneoplastic antibodies occur in approximately 15% of patients with small cell lung cancer, are associated with paraneoplastic peripheral neuropathy and encephalopathy, and are thought to arise due to immune cross-reactivity between small cell lung cancer cells and normal neural tissues [5]. Such cross-reactivity occurs particularly frequently in small cell lung cancer due to phenotypic features resembling those of the nervous system, including expression of CD56 (neural cell adhesion molecule, NCAM). Another similar example is the favorable outcomes observed in patients with melanoma who develop vitiligo, an autoimmune hypopigmentation disorder attributed to autoantibodies cross-reacting between melanoma cells and normal melanocytes [6].

Heightened immune function has also been linked to favorable cancer outcomes in the setting of treatment. The occurrence of graft-versus host disease after allogeneic stem cell transplantation is associated with improved survival in leukemia, as it coincides with graft-

versus-leukemia effects [7]. Similarly, if the donor of a stem cell transplant is an identical twin, outcomes are worse compared to fraternal twin donors [8]. In such a scenario, the genetically identical stem cells will not result in graft-versus-host disease. However, nor will they result in graft-versus leukemia activity.

In addition, there is a strong, dynamic and bidirectional link between autoimmunity and cancer, although the fundamental mechanisms underlying this link are yet to be elucidated. Both autoimmunity and cancer result from immune dysregulation. In fact, effective tumor immunity requires the induction of the same responses that underlie autoimmunity. Several studies have shown that certain autoimmune diseases are positively or negatively associated with certain cancers. For example, an increased risk of malignancies has been observed in autoimmune diseases such as Sjogren's syndrome (SS) and systemic lupus erythematosus [9, 10]. Recent published data from large registries and databases revealed new associations with malignancies, such as IgG4-related disease, Behcet's and sarcoidosis, which were not clearly associated with cancer in the past [11–14]. Conversely, cancer has been implicated in certain autoimmune diseases such as scleroderma and myositis [15, 16]. The role of cancer in initiation of autoimmune diseases is implied by paraneoplastic autoimmune syndromes such as paraneoplastic pemphigus, Eaton-Lambert syndrome, paraneoplastic polyarthritis, periostitis related to hypertrophic osteoarthropathy, and palmar fasciitis [14, 17].

The interplay between autoimmunity and cancer represents a complex, multistep process. Autoimmunity occurs due to breakdown in regulation of self-tolerance and defects in apoptosis resulting in production of autoantibodies and autoreactive B cells and T cells. This leads to hyper-activation of both adaptive and innate immune cells and excessive production of proinflammatory chemokines and cytokines, resulting in chronic inflammation and tissue damage. These events can potentially lead to aberrant cell proliferation and apoptosis, eventually leading to malignancy. There is also an imbalance in T helper cells subsets and defects in function and/or number of regulatory T cells associated with autoimmunity. Regulatory T-cells (Tregs) play a major role in maintaining immunological self-tolerance and can obstruct tumor immunity [18–20]. In addition, emerging studies have highlighted the dual role of Wnt/β-catenin pathway connecting autoimmunity and cancer. Activation of Wnt/β-catenin pathway in dendritic cells (DCs) has been shown to play a critical role in mucosal tolerance and suppression of chronic autoimmune pathologies [21–23]. Alternatively, tumors activate Wnt/β-catenin pathway in DCs to induce immune tolerance and thereby evade antitumor immunity through suppression of effector T cell responses and promotion of regulatory T cell responses [18, 24, 25].

Immune Checkpoint Inhibitors

The recent and rapid emergence of immune checkpoint inhibitors has for the first time, brought effective immunotherapy to multiple cancer types. These monoclonal antibodies bind to immune checkpoints including cytotoxic T lymphocyte antigen 4 (CTLA4), programmed death 1 (PD-1), and PD1 ligand (PD-L1). In doing so, they "release the brakes" on antitumor immune effects, resulting in an anti-cancer immune response that in some instances results in profound and prolonged benefit. As of March 2019, seven different immune checkpoint inhibitors have been U.S. Food and Drug Administration (FDA)

approved for more than a dozen different cancers, among them melanoma and other skin cancers, lung cancer, kidney cancer, lymphoma, head-and-neck cancer, liver cancer (Table 1) [26]. Thus far, the most dramatic effects have been observed in metastatic melanoma, a malignancy with only rare and minor responses to conventional chemotherapy, and a historical average survival of under one year [27]. With combination anti-CTLA4 and anti-PD-1 therapy, almost 60% of patients achieve a radiographic response, with median average survival exceeding 3 years [28, 29].

To use immune checkpoint inhibitors effectively as other cancer therapies, it is critical to understand the fundamental mechanism of action of PD-1 and CTLA-4 under normal conditions, as well as anti–PD-1 and anti-CTLA4 therapies in the context of antitumor immunity (Figure 2) [30]. CTLA4 regulates T-cell activation by attenuating T-cell receptor (TCR) signaling through competitive inhibition with the costimulatory molecule CD28 for the B7 ligands B7–1 (CD80) and B7–2 (CD86) and is critical in maintaining tolerance [31–34]. Genetic deletion of CTLA4 results in massive lymphoproliferation and early death in mice [35, 36]. Alternatively, a recent study has shown that the conditional ablation of CTLA4 in Tregs in adult mice not only failed to develop spontaneous autoimmunity, but were also protected from development of experimental autoimmune encephalomyelitis (EAE) and did not show enhanced antitumor immunity [37]. This study highlights the importance of understanding the complex basic biology underlying checkpoint inhibitors and suggest that the use of a nondepleting anti–CTLA4 antibody may, in fact, have undesired effects of promoting Treg proliferation. The mechanism by which CTLA4 blockade exerts its anti-tumor effects is not fully understood; however, the following potential mechanisms have been proposed; (1) Direct blockade of CTLA4 competition for B7–1 and B7–2 costimulatory ligands, which allows for unrestrained CD28-mediated positive costimulation [38]. This is thought to occur primarily in tumor-draining lymph nodes in which tumor antigens can be cross-presented by antigen presenting cells (APCs) to prime tumor-reactive T cells. (2) Expansion of tumor antigen-specific T cell populations [39]. (3) Depletion of Treg cell populations and affecting Treg function.[40] (4) Broadening of the peripheral T-cell receptor repertoire [30, 40–42].

In contrast, PD-1 is critical in maintaining peripheral tolerance. Genetic deletion of *Pdcd1* (encoding PD-1) leads to autoimmune phenotypes in a strain dependent manner in mice [43]. PD-1 regulates T-cell activation through interaction with its ligands PD-L1 and PD-L2. This engagement results in a negative costimulatory signal through the tyrosine phosphatase SHP2 leading to attenuation of T cell activation [44, 45]. PD-1 signaling is implicated in driving T-cell exhaustion by inducing metabolic restriction [46]. Recent studies have shown that PD-1 may also be involved in T-cell trafficking and migration and may possess tumor cell–intrinsic functions [47, 48]. In the context of anti-tumor activity, PD-1 blockade primarily exerts its effects by attenuating proximal TCR signaling and restoring activity of exhausted CD8 effectors [49]. A recent study highlighted the role of peripheral CD4 T-cell populations that were significantly expanded in patients responding to immunotherapy and conferred protection against new tumors [50]. These new findings underscore the importance of understanding the basic mechanism of action to develop novel and rational therapeutic strategies. Furthermore, it remains unclear whether the cellular and molecular mechanisms

underlying the enhanced efficacy observed with combination therapy are distinct from those that underlie monotherapy-driven antitumor effects.

Laboratory investigations into immune checkpoint inhibitor efficacy have focused largely on tumor biology. Leading biomarkers for predicting beneficial effects include tumor PD-L1 expression, tumor microsatellite instability, and tumor mutational burden. Although in some instances, presence of biomarkers are routine requirements for use of checkpoint inhibitors (PD-L1 expression for pembrolizumab monotherapy in non-small cell lung cancer and tumor microsatellite instability for pembrolizumab monotherapy across cancer types), they are far from perfect. For instance, in non-small cell lung cancer, pembrolizumab response rates range 45–50% with high-level PD-L1 expression, and 10–15% in cases with no PD-L1 expression [51, 52]. Biomarkers for genomically-driven molecularly targeted therapies provide far greater discriminating abilities. In non-small cell cancer harboring activating mutations in the epidermal growth factor receptor (EGFR) gene, response rates to EGFR inhibitors may exceed 80%, compared to <5% for *EGFR* wild type cancers [53].

Immune-related adverse events and checkpoint inhibitor therapy

Where host immune function—in particular autoimmunity—has primarily interfaced with checkpoint inhibitor therapy is in the realm of toxicity. Immune-related adverse events (irAEs) occur when checkpoint inhibitors result in an immune-based attack on normal tissues. Although oncologists have long been comfortable anticipating, diagnosing, and managing toxicities of conventional chemotherapy or molecularly targeted therapies, irAEs present an entirely set of clinical challenges. These autoimmune toxicities are incredibly diverse, potentially affecting almost every organ system (Figure 1) [54]. Common irAEs include dermatitis and thyroiditis. Less common but potentially more serious irAEs include pneumonitis, colitis, hepatitis, nephritis, hypophysitis (pituitary dysfunction), adrenalitis, and myositis. Less common still are dreaded effects on the heart and central nervous system.

As combination immune therapy regimens (such as the approved combination of ipilimumab and nivolumab for melanoma) are used more widely, the frequency and severity of irAEs will likely increase. In a melanoma trial, rates of high-grade treatment-related toxicities were 21% with anti-PD-1 monotherapy (nivolumab), 28% with anti-CTLA4 monotherapy (ipilimumab), and 59% with combined anti-CTLA4 and anti-PD-1 (ipilimumab plus nivolumab) [29]. Compared to anti-PD-1 or anti-PD-L1 therapy, ipilimumab tends to have greater association with gastrointestinal and endocrine toxicities, and lower rates of pulmonary and thyroid events. In some cases, regimens combining immune checkpoint inhibitors with other treatment types have resulted in unanticipated and unacceptable toxicity rates, even though the combined agents have entirely different mechanisms of action. For example, combined durvalumab (anti-PD-L1) and osimertinib (EGFR inhibitor), each of which has a reported pulmonary toxicity rate of 5% or less, resulted in interstitial lung disease in approximately 40% of patients, while combined durvalumab plus gefitinib (EGFR inhibitor) resulted in high-grade liver enzyme elevation in 40–70% of patients [55, 56]. Similarly, combined ipilimumab and vemurafenib for *BRAF* mutant melanoma resulted in an unacceptable rate of hepatic toxicity [57]. In all of these instances, clinical development of combination therapy was discontinued.

Immune-related adverse events also continue to confound clinicians because of their extreme variability and unpredictability. With conventional chemotherapy, oncologists anticipate the most severe neutropenia 10–15 days after each dose. With EGFR inhibitors, acneiform rash tends to develops within the first three weeks of treatment. In contrast, irAEs may develop as early as after the first dose or as late as more than18 months into treatment [58]. In some instances, new irAEs have been noted months after immunotherapy has been discontinued [59–61]. While some patients may experience a single irAE, others may develop a constellation of autoimmune toxicities, either simultaneously or separated temporally [54].

Mechanisms of Immune-related adverse events

Although cancer immunotherapy is an area of intense research, there is poor mechanistic understanding of irAEs associated with immune checkpoint inhibitors. PD-1/PD-L1 and CTLA4 maintain self-tolerance via distinct mechanisms under normal immune conditions and elicit their antitumor effects in varied ways. Therefore, it is not surprising to see that anti-PD-1 and anti-CTLA4 therapy induce a specific set of irAEs, although how they elicit these distinct irAEs remains unknown. Emerging studies indicate that irAEs represent a consequence of breakdown in self-tolerance mediated at least in part by antigen-specific T-cell responses, autoantibodies, B cells and cytokines [62] [63]. For example, a recent study showed that immune toxicities elicited with CTLA4 blockade was associated with early diversification of T cell repertoire [62]. There are several case reports studies showing a correlation of autoantibodies with irAEs. However, longitudinal immune profiling assessing the development of autoantibodies in patients developing autoimmune toxicities are currently lacking. Therefore, it remains unclear whether the mechanism underlying irAEs observed after checkpoint therapy is distinct from classic autoimmune diseases. A recent study showed that early changes in B-cells may identify patients who are at increased risk of irAEs and suggested that strategies targeting B-cells may reduce toxicities in these patients. [64] In addition, cytokines levels could potentially play an important role in mediating irAEs and may serve as predictive biomarkers. For example, one study showed that baseline circulating levels of IL-17 may predict toxicities in Ipilimumab treated melanoma patients [65]. In another study, serum levels of interferon gamma inducible chemokines CXCL-9 and CXCL-10 was shown to be associated with the development of irAEs [66].

Importantly, the role of genetics, epigenetics, the environment, intestinal microbiota and underlying immune status of patients in development of irAEs during checkpoint blockade therapy remains unclear. It is not certain if preexisting autoimmune conditions predispose patients to irAEs and/or exacerbate the development of irAEs. Genetic predisposition is a key element in susceptibility to autoimmunity. Distinct human leukocyte antigen (HLA) haplotypes and polymorphisms in immunoregulatory genes such as CTLA4 and PD-1 have been associated with a variety of classical autoimmune diseases and are likely to play an important role in development of irAEs [67–70]. For example, the HLA markers DQ8 and DR53 have been associated with lymphocytic hypophysitis [71]. In another study, there was a predominance of HLA-DR4 among patients treated with PD-1- or PD-L1-directed therapies who developed autoimmune insulin-dependent diabetes [72]. Despite these initial observations, studies in much larger patient cohorts are needed to establish robust genetic associations with the development of irAEs.

In addition to genetic factors, emerging studies suggest that the gut microbiota, a key factor in maintaining immune homeostasis, may affect the response and toxicity to checkpoint blockade therapy. Routy et al. showed that antibiotic consumption was associated with poor response to PD-1 blockade [73]. One study in this area showed that baseline gut microbiota enriched with Faecalibacterium and other Firmicute is associated with beneficial clinical response to ipilimumab and more frequent occurrence of ipilimumab-induced colitis [74]. An increased representation of bacteria belonging to the Bacteroidetes phylum was correlated with resistance to the development of CTLA4-induced colitis [75]. The role of the microbiome in the development of PD-1/PD-L1-driven irAEs remains unknown.

A major obstacle hindering the understanding of irAE biology and mechanisms is lack of preclinical mouse models that can mimic autoimmune toxicities seen in patient population. The development of preclinical tumor mouse models using autoimmunity-prone mice represents a pressing need in the field [30, 76].

Influence of autoimmune diagnosis on cancer outcomes

Concerns over irAEs have directly impacted considerations of autoimmunity and cancer. Almost universally, clinical trials of immune checkpoint inhibitors have excluded patients with autoimmune disease diagnoses. Specific eligibility wording varies across trials. Some exclude only patients with “active” autoimmune disease. Others exclude autoimmune diseases with visceral involvement but permit skin-only psoriasis. How does this widespread practice impact eligibility? A number of recent studies have examined the prevalence of autoimmune disease in different cancer populations. Among individuals with lung cancer in the Surveillance Epidemiology and End Results (SEER)-Medicare data set (N=210,509), an estimated 14–25% have autoimmune disease [77]. The most common diagnoses were rheumatoid arthritis (6%), psoriasis, (3%), polymyalgia rheumatic (2%), and lupus (1%). Individuals with autoimmune disease were more likely to be female and older. The wide range in prevalence of autoimmune diseases reflects the inherent challenges in rendering these diagnoses. (Indeed, the estimated prevalence of autoimmune disease in the United States ranges from 20 to 50 million individuals [77]. Depending on the specific condition, clinical criteria, serologies, histology, and radiographic findings may be incorporated into diagnostic considerations.

How does an autoimmune diagnosis influence cancer outcomes? Theoretically, heightened autoimmune function might decrease the incidence, progression, or aggressiveness of cancer. Alternatively, a chronic inflammatory state could promote malignancy. Certain clinical realities may temper both effects. An autoimmune diagnosis could lead to heightened medical care, leading to more frequent and earlier stage cancer diagnosis. Chronic immunosuppression could promote development and progression of malignancy, an association that has been particularly prominent with chronic TNF-directed therapy [78]. As for the impact of autoimmune diseases on cancer outcomes, no clear dominant trend has emerged. In a recent analysis of more than 170,000 lung cancer cases from the SEER-Medicare registry, the magnitude and directionality of any survival differences between patients with and without pre-existing autoimmune diagnoses varied by cancer stage, and whether the autoimmune disease was diagnosed before or after the lung cancer, with no

model showing clinically meaningful differences [79]. Overall, healthcare utilization was higher in the autoimmune disease population, lung cancer treatment patterns were similar among patients with and without autoimmune disease, and there was not significant association with mortality.

Reports of successful administration of cancer immunotherapy in patients with pre-existing autoimmune disease have emerged. While these patients do appear to have higher rates and severity of irAEs than general cancer populations, a trial of immunotherapy may be feasible, but likely requires vigilant clinical monitoring. In a series of 30 patients with autoimmune disease treated with ipilimumab for advanced melanoma (of whom 43% were receiving immunosuppressive therapy at the time of ipilimumab initiation), 27% experienced exacerbations of the autoimmune condition requiring systemic therapy, and 33% developed grade 3–5 irAEs, with one fatal case of presumed immune-related colitis in a patient with baseline psoriasis [80]. Guidance may also be derived from reports of patients who previously experienced irAEs and were subsequently successfully re-challenged with checkpoint inhibitors [81]. Nevertheless, until more data are available, clinicians tend to consider this scenario on a case-by-case basis. For instance, the willingness to employ immunotherapy in a patient with psoriatic arthritis (where a flare could result in increased joint pain) may be quite different than in a patient with myasthenia gravis (where a flare could result in diaphragmatic paralysis and respiratory failure). In general, immune checkpoint inhibitors tend to be poorly tolerated from an immunologic perspective in solid organ transplant recipients [82]. In kidney transplant populations, these treatments may result in renal failure and a need for reinstating dialysis. In lung or heart transplant recipients, organ rejection may prove fatal in the near-term.

Treatment-induced autoimmunity may predict efficacy of immune checkpoint inhibitors. Overall, these observations mirror earlier associations seen with molecularly targeted therapies and cytotoxic agents. Cancer patients who develop alopecia or high-grade cytopenias from chemotherapy have better response rates, leading to trials of dose escalation to achieve grade 3–4 neutropenia [83–86]. The emergence of grade ≥2 acneiform rash is associated with improved outcomes from epidermal growth factor receptor (EGFR) inhibitors in multiple malignancies, including lung, pancreas, head and neck, and colorectal cancer, leading to trials of dose escalation to achieve dermatologic toxicity [87–90]. Similarly, the development of hypertension among individuals treated with antiangiogenic agents, such as vascular endothelial growth factor pathway inhibitors, portends therapeutic benefit [91, 92].

Although differing mechanistically from the adverse events of chemotherapy and targeted therapies, cancer immune therapies have demonstrated similar trends. Among patients with melanoma treated with interferon-based therapy, the development of vitiligo correlates with prolonged disease control [6]. After allogeneic stem cell transplant for acute myeloid leukemia, cases with graft-versus-host disease have improved relapse-free survival [7, 93]. Immune checkpoint inhibitors are no exception. In multiple cancers, trials of both anti-CTLA4 and anti-PD-1/PD-L1 therapies have demonstrated better outcomes among individuals who develop irAEs. In a retrospective cohort analysis of 143 melanoma patients treated with nivolumab, the presence or absence of irAEs, as well as the number of irAEs,

was correlated with statistically significant overall survival (OS) [94]. A meta-analysis of four nivolumab melanoma studies (total 576 patients) demonstrated a marked difference in objective response rate (ORR) (48.6% with irAE versus 17.8% without irAE) [95]. Comparable results were noted in ipilimumab melanoma trials [96]. In non-small cell lung cancer (NSCLC), single-institution reports of nivolumab have noted response rates more than four times greater among patients developing irAEs compared to non-irAE patients, and progression-free survival (PFS) more than three times greater [97, 98]. In a multi-center retrospective analysis of 134 patients with advanced NSCLC treated with nivolumab, overall survival (OS) (median not reached versus 11.1 months; P=0.01), PFS (median 9.2 versus 4.8 months; P=0.04), and ORR (52.3% versus 27.9%, P=0.02) were significantly improved if irAEs were present at 6 weeks [99]. While associations between toxicity and efficacy for conventional chemotherapy and targeted therapies may reflect drug concentrations, such connections involving immunotherapeutic agents are likely more complex, likely reflecting individual variation in susceptibility to immune system stimulation. Indeed, certain biomarkers associated with irAEs, such as interferon gamma-inducible chemokines involved in T cell activation and recruitment, may also predict efficacy [66].

Management of Immune-related Adverse Events

The management of irAEs remains another area of uncertainty. For most scenarios, general principles apply. Depending on severity of the toxicity, immunotherapy may be withheld or permanently discontinued. In contrast to chemotherapy and small molecule inhibitors, there is no role for dose reduction. The mainstay of treatment is corticosteroids. For moderately severe toxicities, a standard approach is to administer prednisone at a dose of 1 mg/kg orally daily. Once the irAE has improved to grade 1 in severity or baseline, a slow taper (10 mg per week) is initiated. Often, immunotherapy is not resumed until steroids have been discontinued and there is no evidence of recurrent irAE. Whether such high doses and prolonged courses of steroids are required in all cases is not clear. Indeed, there have emerged reports of serious steroid-related toxicities, including fatal infections [100]. For certain autoimmune toxicities, alternative immunosuppressants may be indicated, such as anti-tumor necrosis factor (TNF) monoclonal antibodies, cyclophosphamide, or mycophenolate. Perhaps surprisingly, the administration of steroids for the management of irAEs may not compromise efficacy of immune checkpoint inhibitors [101]. It seems possible that these patients derive particular efficacy from immune checkpoint inhibitors, with an intense immune reaction resulting in both anti-tumor and toxic effects. Even extended breaks in treatment and prolonged steroid regimens may not counteract these effects. In contrast, the receipt of steroids at the time of immunotherapy initiation has been associated with inferior outcomes. In a study of 640 patients receiving single-agent PD-1/PD-L1 blockade for advanced non-small cell lung cancer, 90 (14%) were receiving corticosteroids of ≥10 mg prednisone equivalent daily at the start of therapy for the following indications: dyspnea (33%), fatigue (21%), and brain metastases (19%) [102]. In a multivariable model adjusting for functional status, brain metastases, and smoking history, baseline steroid exposure was associated with decreased response rate, PFS (HR 1.3; P=0.03), and OS (HR 1.7; P<0.001).

Conclusion

As checkpoint blockade is becoming a standard of care and several combination therapy strategies enter clinical practice, clinicians and researchers will require a greater understanding of the intersection between autoimmunity and effects of immunotherapy, both beneficial and harmful. Basic, preclinical, and clinical research are critical in understanding the role of genetics, epigenetics, intestinal microbiota, pre-existing autoimmune conditions and immune status of patients in development of irAEs (Figure 3). The insights gained from such studies will facilitate identification of biomarkers to inform patient selection, monitoring, and treatment for optimal clinical management.

Acknowledgements/Funding

The authors thank Ms. Helen Mayo, MLS, from the UT Southwestern Medical Library, for assistance with literature searches.

Funded by an American Cancer Society-Melanoma Research Alliance Team Award (MRAT-18–114-01-LIB; to DEG), a National Cancer Institute Midcareer Investigator Award in Patient-Oriented Research (K24 CA201543–01; to DEG), and a V Foundation Robin Roberts Cancer Survivorship Award (DT2019–007; to DEG).

References

1. Grulich AE, van Leeuwen MT, Falster MO & Vajdic CM Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. Lancet 370, 59–67 (2007). [PubMed: 17617273]
2. Kasiske BL & Klinger D Cigarette smoking in renal transplant recipients. J Am Soc Nephrol 11, 753–759 (2000). [PubMed: 10752535]
3. Friis-Moller N, Sabin CA, Weber R, d'Arminio Monforte A, El-Sadr WM, Reiss P, et al. Combination antiretroviral therapy and the risk of myocardial infarction. N Engl J Med 349, 1993–2003 (2003). [PubMed: 14627784]
4. Graus F, Dalmou J, Rene R, Tora M, Malats N, Verschuuren JJ, et al. Anti-Hu antibodies in patients with small-cell lung cancer: association with complete response to therapy and improved survival. J Clin Oncol 15, 2866–2872 (1997). [PubMed: 9256130]
5. Dalmau J, Furneaux HM, Gralla RJ, Kris MG & Posner JB Detection of the anti-Hu antibody in the serum of patients with small cell lung cancer--a quantitative western blot analysis. Ann Neurol 27, 544–552 (1990). [PubMed: 2163235]
6. Gogas H, Ioannovich J, Dafni U, Stavropoulou-Giokas C, Frangia K, Tsoutsos D, et al. Prognostic significance of autoimmunity during treatment of melanoma with interferon. N Engl J Med 354, 709–718 (2006). [PubMed: 16481638]
7. Weiden PL, Flournoy N, Sanders JE, Sullivan KM & Thomas ED Antileukemic effect of graft-versus-host disease contributes to improved survival after allogeneic marrow transplantation. Transplant Proc 13, 248–251 (1981). [PubMed: 7022833]
8. Gale RP, Horowitz MM, Ash RC, Champlin RE, Goldman JM, Rimm AA, et al. Identical-twin bone marrow transplants for leukemia. Ann Intern Med 120, 646–652 (1994). [PubMed: 8135448]
9. Brito-Zeron P, Kostov B, Fraile G, Caravia-Duran D, Maure B, Rascon FJ, et al. Characterization and risk estimate of cancer in patients with primary Sjogren syndrome. J Hematol Oncol 10, 90 (2017). [PubMed: 28416003]
10. Song L, Wang Y, Zhang J, Song N, Xu X & Lu Y The risks of cancer development in systemic lupus erythematosus (SLE) patients: a systematic review and meta-analysis. Arthritis Res Ther 20, 270 (2018). [PubMed: 30522515]
11. Asano J, Watanabe T, Oguchi T, Kanai K, Maruyama M, Ito T, et al. Association Between Immunoglobulin G4-related Disease and Malignancy within 12 Years after Diagnosis: An Analysis after Longterm Followup. J Rheumatol 42, 2135–2142 (2015). [PubMed: 26472416]

12. Wang LH, Wang WM, Hsu SM, Lin SH & Shieh CC Risk of Overall and Site-specific Cancers in Behcet Disease: A Nationwide Population-based Study in Taiwan. J Rheumatol 42, 879–884 (2015). [PubMed: 25834207]
13. Ungprasert P, Tooley AA, Crowson CS, Matteson EL & Smith WM Clinical Characteristics of Ocular Sarcoidosis: A Population-Based Study 1976–2013. Ocul Immunol Inflamm, 1–7 (2017). [PubMed: 28195820]
14. Giat E, Ehrenfeld M & Shoenfeld Y Cancer and autoimmune diseases. Autoimmun Rev 16, 1049–1057 (2017). [PubMed: 28778707]
15. Joseph CG, Darrah E, Shah AA, Skora AD, Casciola-Rosen LA, Wigley FM, et al. Association of the autoimmune disease scleroderma with an immunologic response to cancer. Science 343, 152–157 (2014). [PubMed: 24310608]
16. Rhodes EC, Parikh SP & Bhattacharyya N Severe autoimmune hemolytic anemia with renal neoplasm. Pediatr Surg Int 30, 243–244 (2014). [PubMed: 23677207]
17. Manger B & Schett G Paraneoplastic syndromes in rheumatology. Nat Rev Rheumatol 10, 662–670 (2014). [PubMed: 25136782]
18. Suryawanshi A, Tadagavadi RK, Swafford D & Manicassamy S Modulation of Inflammatory Responses by Wnt/beta-Catenin Signaling in Dendritic Cells: A Novel Immunotherapy Target for Autoimmunity and Cancer. Front Immunol 7, 460 (2016). [PubMed: 27833613]
19. Pylayeva-Gupta Y Molecular Pathways: Interleukin-35 in Autoimmunity and Cancer. Clin Cancer Res 22, 4973–4978 (2016). [PubMed: 27582486]
20. Gigli G, Caielli S, Cutuli D & Falcone M Innate immunity modulates autoimmunity: type 1 interferon-beta treatment in multiple sclerosis promotes growth and function of regulatory invariant natural killer T cells through dendritic cell maturation. Immunology 122, 409–417 (2007). [PubMed: 17617156]
21. Korinek V, Barker N, Morin PJ, van Wichen D, de Weger R, Kinzler KW, et al. Constitutive transcriptional activation by a beta-catenin-Tcf complex in APC−/− colon carcinoma. Science 275, 1784–1787 (1997). [PubMed: 9065401]
22. Manicassamy S, Reizis B, Ravindran R, Nakaya H, Salazar-Gonzalez RM, Wang YC, et al. Activation of beta-catenin in dendritic cells regulates immunity versus tolerance in the intestine. Science 329, 849–853 (2010). [PubMed: 20705860]
23. Shan M, Gentile M, Yeiser JR, Walland AC, Bornstein VU, Chen K, et al. Mucus enhances gut homeostasis and oral tolerance by delivering immunoregulatory signals. Science 342, 447–453 (2013). [PubMed: 24072822]
24. Spranger S, Bao R & Gajewski TF Melanoma-intrinsic beta-catenin signalling prevents anti-tumour immunity. Nature 523, 231–235 (2015). [PubMed: 25970248]
25. Hong Y, Manoharan I, Suryawanshi A, Majumdar T, Angus-Hill ML, Koni PA, et al. beta-catenin promotes regulatory T-cell responses in tumors by inducing vitamin A metabolism in dendritic cells. Cancer Res 75, 656–665 (2015). [PubMed: 25568183]
26. Hargadon KM, Johnson CE & Williams CJ Immune checkpoint blockade therapy for cancer: An overview of FDA-approved immune checkpoint inhibitors. Int Immunopharmacol 62, 29–39 (2018). [PubMed: 29990692]
27. Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med 372, 320–330 (2015). [PubMed: 25399552]
28. Larkin J, Hodi FS & Wolchok JD Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med 373, 1270–1271 (2015).
29. Wolchok JD, Chiarion-Sileni V, Gonzalez R, Rutkowski P, Grob JJ, Cowey CL, et al. Overall Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. N Engl J Med 377, 1345–1356 (2017). [PubMed: 28889792]
30. Wei SC, Duffy CR & Allison JP Fundamental Mechanisms of Immune Checkpoint Blockade Therapy. Cancer Discov 8, 1069–1086 (2018). [PubMed: 30115704]
31. Pentcheva-Hoang T, Egen JG, Wojnoonski K & Allison JP B7–1 and B7–2 selectively recruit CTLA-4 and CD28 to the immunological synapse. Immunity 21, 401–413 (2004). [PubMed: 15357951]

32. Walunas TL, Lenschow DJ, Bakker CY, Linsley PS, Freeman GJ, Green JM, et al. CTLA-4 can function as a negative regulator of T cell activation. Immunity 1, 405–413 (1994). [PubMed: 7882171]
33. Walunas TL, Lenschow DJ, Bakker CY, Linsley PS, Freeman GJ, Green JM, et al. Pillars article: CTLA-4 can function as a negative regulator of T cell activation. Immunity. 1994 1: 405–413. J Immunol 187, 3466–3474 (2011). [PubMed: 7882171]
34. Brunner MC, Chambers CA, Chan FK, Hanke J, Winoto A & Allison JP CTLA-4-Mediated inhibition of early events of T cell proliferation. J Immunol 162, 5813–5820 (1999). [PubMed: 10229815]
35. Tivol EA, Borriello F, Schweitzer AN, Lynch WP, Bluestone JA & Sharpe AH Loss of CTLA-4 leads to massive lymphoproliferation and fatal multiorgan tissue destruction, revealing a critical negative regulatory role of CTLA-4. Immunity 3, 541–547 (1995). [PubMed: 7584144]
36. Waterhouse P, Penninger JM, Timms E, Wakeham A, Shahinian A, Lee KP, et al. Lymphoproliferative disorders with early lethality in mice deficient in Ctla-4. Science 270, 985–988 (1995). [PubMed: 7481803]
37. Paterson AM, Lovitch SB, Sage PT, Juneja VR, Lee Y, Trombley JD, et al. Deletion of CTLA-4 on regulatory T cells during adulthood leads to resistance to autoimmunity. J Exp Med 212, 1603–1621 (2015). [PubMed: 26371185]
38. Ramagopal UA, Liu W, Garrett-Thomson SC, Bonanno JB, Yan Q, Srinivasan M, et al. Structural basis for cancer immunotherapy by the first-in-class checkpoint inhibitor ipilimumab. Proc Natl Acad Sci U S A 114, E4223–E4232 (2017). [PubMed: 28484017]
39. Fehlings M, Simoni Y, Penny HL, Becht E, Loh CY, Gubin MM, et al. Checkpoint blockade immunotherapy reshapes the high-dimensional phenotypic heterogeneity of murine intratumoural neoantigen-specific CD8(+) T cells. Nat Commun 8, 562 (2017). [PubMed: 28916749]
40. Simpson TR, Li F, Montalvo-Ortiz W, Sepulveda MA, Bergerhoff K, Arce F, et al. Fc-dependent depletion of tumor-infiltrating regulatory T cells co-defines the efficacy of anti-CTLA-4 therapy against melanoma. J Exp Med 210, 1695–1710 (2013). [PubMed: 23897981]
41. Robert L, Tsoi J, Wang X, Emerson R, Homet B, Chodon T, et al. CTLA4 blockade broadens the peripheral T-cell receptor repertoire. Clin Cancer Res 20, 2424–2432 (2014). [PubMed: 24583799]
42. Wei SC, Levine JH, Cogdill AP, Zhao Y, Anang NAS, Andrews MC, et al. Distinct Cellular Mechanisms Underlie Anti-CTLA-4 and Anti-PD-1 Checkpoint Blockade. Cell 170, 1120–1133 e1117 (2017). [PubMed: 28803728]
43. Nishimura H, Nose M, Hiai H, Minato N & Honjo T Development of lupus-like autoimmune diseases by disruption of the PD-1 gene encoding an ITIM motif-carrying immunoreceptor. Immunity 11, 141–151 (1999). [PubMed: 10485649]
44. Freeman GJ, Long AJ, Iwai Y, Bourque K, Chernova T, Nishimura H, et al. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. J Exp Med 192, 1027–1034 (2000). [PubMed: 11015443]
45. Yokosuka T, Takamatsu M, Kobayashi-Imanishi W, Hashimoto-Tane A, Azuma M & Saito T Programmed cell death 1 forms negative costimulatory microclusters that directly inhibit T cell receptor signaling by recruiting phosphatase SHP2. J Exp Med 209, 1201–1217 (2012). [PubMed: 22641383]
46. Patsoukis N, Bardhan K, Chatterjee P, Sari D, Liu B, Bell LN, et al. PD-1 alters T-cell metabolic reprogramming by inhibiting glycolysis and promoting lipolysis and fatty acid oxidation. Nat Commun 6, 6692 (2015). [PubMed: 25809635]
47. Kleffel S, Posch C, Barthel SR, Mueller H, Schlapbach C, Guenova E, et al. Melanoma Cell-Intrinsic PD-1 Receptor Functions Promote Tumor Growth. Cell 162, 1242–1256 (2015). [PubMed: 26359984]
48. Kortlever RM, Sodir NM, Wilson CH, Burkhart DL, Pellegrinet L, Brown Swigart L, et al. Myc Cooperates with Ras by Programming Inflammation and Immune Suppression. Cell 171, 1301–1315 e1314 (2017). [PubMed: 29195074]
49. Huang AC, Postow MA, Orlowski RJ, Mick R, Bengsch B, Manne S, et al. T-cell invigoration to tumour burden ratio associated with anti-PD-1 response. Nature 545, 60–65 (2017). [PubMed: 28397821]

50. Spitzer MH, Carmi Y, Reticker-Flynn NE, Kwek SS, Madhireddy D, Martins MM, et al. Systemic Immunity Is Required for Effective Cancer Immunotherapy. Cell 168, 487–502 e415 (2017). [PubMed: 28111070]
51. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med 373, 1627–1639 (2015). [PubMed: 26412456]
52. Sundar R, Cho BC, Brahmer JR & Soo RA Nivolumab in NSCLC: latest evidence and clinical potential. Ther Adv Med Oncol 7, 85–96 (2015). [PubMed: 25755681]
53. Mitsudomi T & Yatabe Y Mutations of the epidermal growth factor receptor gene and related genes as determinants of epidermal growth factor receptor tyrosine kinase inhibitors sensitivity in lung cancer. Cancer Sci 98, 1817–1824 (2007). [PubMed: 17888036]
54. Wang DY, Salem JE, Cohen JV, Chandra S, Menzer C, Ye F, et al. Fatal Toxic Effects Associated With Immune Checkpoint Inhibitors: A Systematic Review and Meta-analysis. JAMA Oncol 4, 1721–1728 (2018). [PubMed: 30242316]
55. Ahn MJ, Sun JM, Lee SH, Ahn JS & Park K EGFR TKI combination with immunotherapy in non-small cell lung cancer. Expert Opin Drug Saf 16, 465–469 (2017). [PubMed: 28271729]
56. Ahn MJ, Yang J, Yu H, Saka H, Ramalingam S, Goto K, et al. Osimertinib combined with durvalumab in EGFR-mutant non-small cell lung cancer: Results from the TATTON phase Ib trial. Journal of Thoracic Oncology 11, S115–S115 (2016).
57. Ribas A, Hodi FS, Callahan M, Konto C & Wolchok J Hepatotoxicity with combination of vemurafenib and ipilimumab. N Engl J Med 368, 1365–1366 (2013). [PubMed: 23550685]
58. Michot JM, Bigenwald C, Champiat S, Collins M, Carbonnel F, Postel-Vinay S, et al. Immune-related adverse events with immune checkpoint blockade: a comprehensive review. Eur J Cancer 54, 139–148 (2016). [PubMed: 26765102]
59. Akel R, Anouti B & Tfayli A Late-Onset Inflammatory Bowel Disease-Like Syndrome after Ipilimumab Therapy: A Case Report. Case Rep Oncol 10, 456–461 (2017). [PubMed: 28626406]
60. Dasanu CA, Jen T & Skulski R Late-onset pericardial tamponade, bilateral pleural effusions and recurrent immune monoarthritis induced by ipilimumab use for metastatic melanoma. J Oncol Pharm Pract 23, 231–234 (2017). [PubMed: 26946531]
61. Mandala M, Merelli B, Indriolo A & Tondini C Late-occurring toxicity induced by an immune checkpoint blockade in adjuvant treatment of a stage III melanoma patient. Eur J Cancer 95, 130–132 (2018). [PubMed: 29559189]
62. Oh DY, Cham J, Zhang L, Fong G, Kwek SS, Klinger M, et al. Immune Toxicities Elicted by CTLA-4 Blockade in Cancer Patients Are Associated with Early Diversification of the T-cell Repertoire. Cancer Res 77, 1322–1330 (2017). [PubMed: 28031229]
63. Osorio JC, Ni A, Chaft JE, Pollina R, Kasler MK, Stephens D, et al. Antibody-mediated thyroid dysfunction during T-cell checkpoint blockade in patients with non-small-cell lung cancer. Ann Oncol 28, 583–589 (2017). [PubMed: 27998967]
64. Das R, Bar N, Ferreira M, Newman AM, Zhang L, Bailur JK, et al. Early B cell changes predict autoimmunity following combination immune checkpoint blockade. J Clin Invest 128, 715–720 (2018). [PubMed: 29309048]
65. Tarhini AA, Zahoor H, Lin Y, Malhotra U, Sander C, Butterfield LH, et al. Baseline circulating IL-17 predicts toxicity while TGF-beta1 and IL-10 are prognostic of relapse in ipilimumab neoadjuvant therapy of melanoma. J Immunother Cancer 3, 39 (2015). [PubMed: 26380086]
66. Khan S, Khan SA, Luo X, Fattah FJ, Saltarski J, Gloria-McCutchen Y, et al. Immune dysregulation in cancer patients developing immune-related adverse events. British Journal of Cancer, (2018).
67. Gough SC, Walker LS & Sansom DM CTLA4 gene polymorphism and autoimmunity. Immunol Rev 204, 102–115 (2005). [PubMed: 15790353]
68. Lee J, Phong B, Egloff AM & Kane LP TIM polymorphisms--genetics and function. Genes Immun 12, 595–604 (2011). [PubMed: 22048452]
69. Munthe-Kaas MC, Carlsen KH, Helms PJ, Gerritsen J, Whyte M, Feijen M, et al. CTLA-4 polymorphisms in allergy and asthma and the TH1/ TH2 paradigm. J Allergy Clin Immunol 114, 280–287 (2004). [PubMed: 15316504]

70. Sharpe AH, Wherry EJ, Ahmed R & Freeman GJ The function of programmed cell death 1 and its ligands in regulating autoimmunity and infection. Nat Immunol 8, 239–245 (2007). [PubMed: 17304234]

71. Heaney AP, Sumerel B, Rajalingam R, Bergsneider M, Yong WH & Liau LM HLA Markers DQ8 and DR53 Are Associated With Lymphocytic Hypophysitis and May Aid in Differential Diagnosis. J Clin Endocrinol Metab 100, 4092–4097 (2015). [PubMed: 26317559]

72. Stamatouli AM, Quandt Z, Perdigoto AL, Clark PL, Kluger H, Weiss SA, et al. Collateral Damage: Insulin-Dependent Diabetes Induced With Checkpoint Inhibitors. Diabetes 67, 1471–1480 (2018). [PubMed: 29937434]

73. Routy B, Le Chatelier E, Derosa L, Duong CPM, Alou MT, Daillere R, et al. Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. Science 359, 91–97 (2018). [PubMed: 29097494]

74. Chaput N, Lepage P, Coutzac C, Soularue E, Le Roux K, Monot C, et al. Baseline gut microbiota predicts clinical response and colitis in metastatic melanoma patients treated with ipilimumab. Ann Oncol 28, 1368–1379 (2017). [PubMed: 28368458]

75. Vetizou M, Pitt JM, Daillere R, Lepage P, Waldschmitt N, Flament C, et al. Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota. Science 350, 1079–1084 (2015). [PubMed: 26541610]

76. Young A, Quandt Z & Bluestone JA The Balancing Act between Cancer Immunity and Autoimmunity in Response to Immunotherapy. Cancer Immunol Res 6, 1445–1452 (2018). [PubMed: 30510057]

77. Khan SA, Pruitt SL, Xuan L & Gerber DE Prevalence of Autoimmune Disease Among Patients With Lung Cancer: Implications for Immunotherapy Treatment Options. JAMA Oncol 2, 1507–1508 (2016). [PubMed: 27262099]

78. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL & Montori V Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA 295, 2275–2285 (2006). [PubMed: 16705109]

79. Khan SA, Pruitt SL, Xuan L, Makris U & Gerber DE How does autoimmune disease impact treatment and outcomes among patients with lung cancer? A national SEER-Medicare analysis. Lung Cancer 115, 97–102 (2018). [PubMed: 29290269]

80. Johnson DB, Sullivan RJ, Ott PA, Carlino MS, Khushalani NI, Ye F, et al. Ipilimumab Therapy in Patients With Advanced Melanoma and Preexisting Autoimmune Disorders. JAMA Oncol, 1–7 (2015).

81. Pollack MH, Betof A, Dearden H, Rapazzo K, Valentine I, Brohl AS, et al. Safety of resuming anti-PD-1 in patients with immune-related adverse events (irAEs) during combined anti-CTLA-4 and anti-PD1 in metastatic melanoma. Ann Oncol 29, 250–255 (2018). [PubMed: 29045547]

82. Kittai AS, Oldham H, Cetnar J & Taylor M Immune Checkpoint Inhibitors in Organ Transplant Patients. J Immunother 40, 277–281 (2017). [PubMed: 28719552]

83. Cameron DA, Massie C, Kerr G & Leonard RC Moderate neutropenia with adjuvant CMF confers improved survival in early breast cancer. Br J Cancer 89, 1837–1842 (2003). [PubMed: 14612889]

84. Di Maio M, Gridelli C, Gallo C, Shepherd F, Piantedosi FV, Cigolari S, et al. Chemotherapy-induced neutropenia and treatment efficacy in advanced non-small-cell lung cancer: a pooled analysis of three randomised trials. Lancet Oncol 6, 669–677 (2005). [PubMed: 16129367]

85. Sehouli J, Fotopoulou C, Erol E, Richter R, Reuss A, Mahner S, et al. Alopecia as surrogate marker for chemotherapy response in patients with primary epithelial ovarian cancer: a metaanalysis of four prospective randomised phase III trials with 5114 patients. Eur J Cancer 51, 825–832 (2015). [PubMed: 25771433]

86. Drooger JC, van Pelt-Sprangers JM, Leunis C, Jager A & de Jongh FE Neutrophil-guided dosing of anthracycline-cyclophosphamide-containing chemotherapy in patients with breast cancer: a feasibility study. Med Oncol 32, 113 (2015). [PubMed: 25772511]

87. Wacker B, Nagrani T, Weinberg J, Witt K, Clark G & Cagnoni PJ Correlation between development of rash and efficacy in patients treated with the epidermal growth factor receptor

tyrosine kinase inhibitor erlotinib in two large phase III studies. Clin Cancer Res 13, 3913–3921 (2007). [PubMed: 17606725]

88. Petrelli F, Borgonovo K & Barni S The predictive role of skin rash with cetuximab and panitumumab in colorectal cancer patients: a systematic review and meta-analysis of published trials. Target Oncol 8, 173–181 (2013). [PubMed: 23321777]
89. Bonner JA, Harari PM, Giralt J, Cohen RB, Jones CU, Sur RK, et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. Lancet Oncol 11, 21–28 (2010). [PubMed: 19897418]
90. Brahmer JR, Lee JW, Traynor AM, Hidalgo MM, Kolesar JM, Siegfried JM, et al. Dosing to rash: a phase II trial of the first-line erlotinib for patients with advanced non-small-cell lung cancer an Eastern Cooperative Oncology Group Study (E3503). Eur J Cancer 50, 302–308 (2014). [PubMed: 24246704]
91. Dahlberg SE, Sandler AB, Brahmer JR, Schiller JH & Johnson DH Clinical course of advanced non-small-cell lung cancer patients experiencing hypertension during treatment with bevacizumab in combination with carboplatin and paclitaxel on ECOG 4599. J Clin Oncol 28, 949–954 (2010). [PubMed: 20085937]
92. Scartozzi M, Galizia E, Chiorrini S, Giampieri R, Berardi R, Pierantoni C, et al. Arterial hypertension correlates with clinical outcome in colorectal cancer patients treated with first-line bevacizumab. Ann Oncol 20, 227–230 (2009). [PubMed: 18842611]
93. Ringden O, Hermans J, Labopin M, Apperley J, Gorin NC & Gratwohl A The highest leukaemia-free survival after allogeneic bone marrow transplantation is seen in patients with grade I acute graft-versus-host disease. Acute and Chronic Leukaemia Working Parties of the European Group for Blood and Marrow Transplantation (EBMT). Leuk Lymphoma 24, 71–79 (1996). [PubMed: 9049963]
94. Freeman-Keller M, Kim Y, Cronin H, Richards A, Gibney G & Weber JS Nivolumab in Resected and Unresectable Metastatic Melanoma: Characteristics of Immune-Related Adverse Events and Association with Outcomes. Clin Cancer Res 22, 886–894 (2016). [PubMed: 26446948]
95. Weber JS, Hodi FS, Wolchok JD, Topalian SL, Schadendorf D, Larkin J, et al. Safety Profile of Nivolumab Monotherapy: A Pooled Analysis of Patients With Advanced Melanoma. J Clin Oncol 35, 785–792 (2017). [PubMed: 28068177]
96. Downey SG, Klapper JA, Smith FO, Yang JC, Sherry RM, Royal RE, et al. Prognostic factors related to clinical response in patients with metastatic melanoma treated by CTL-associated antigen-4 blockade. Clin Cancer Res 13, 6681–6688 (2007). [PubMed: 17982122]
97. Toi Y, Sugawara S, Kawashima Y, Aiba T, Kawana S, Saito R, et al. Association of Immune-Related Adverse Events with Clinical Benefit in Patients with Advanced Non-Small-Cell Lung Cancer Treated with Nivolumab. Oncologist, (2018).
98. Fujimura T, Sato Y, Tanita K, Kambayashi Y, Otsuka A, Fujisawa Y, et al. Serum levels of soluble CD163 and CXCL5 may be predictive markers for immune-related adverse events in patients with advanced melanoma treated with nivolumab: a pilot study. Oncotarget 9, 15542–15551 (2018). [PubMed: 29643991]
99. Haratani K, Hayashi H, Chiba Y, Kudo K, Yonesaka K, Kato R, et al. Association of Immune-Related Adverse Events With Nivolumab Efficacy in Non-Small-Cell Lung Cancer. JAMA Oncol, (2017).
100. Naidoo J, Wang X, Woo KM, Iyriboz T, Halpenny D, Cunningham J, et al. Pneumonitis in Patients Treated With Anti-Programmed Death-1/Programmed Death Ligand 1 Therapy. J Clin Oncol 35, 709–717 (2017). [PubMed: 27646942]
101. Postow MA, Sidlow R & Hellmann MD Immune-Related Adverse Events Associated with Immune Checkpoint Blockade. N Engl J Med 378, 158–168 (2018). [PubMed: 29320654]
102. Arbour KC, Mezquita L, Long N, Rizvi H, Auclin E, Ni A, et al. Impact of Baseline Steroids on Efficacy of Programmed Cell Death-1 and Programmed Death-Ligand 1 Blockade in Patients With Non-Small-Cell Lung Cancer. J Clin Oncol 36, 2872–2878 (2018). [PubMed: 30125216]

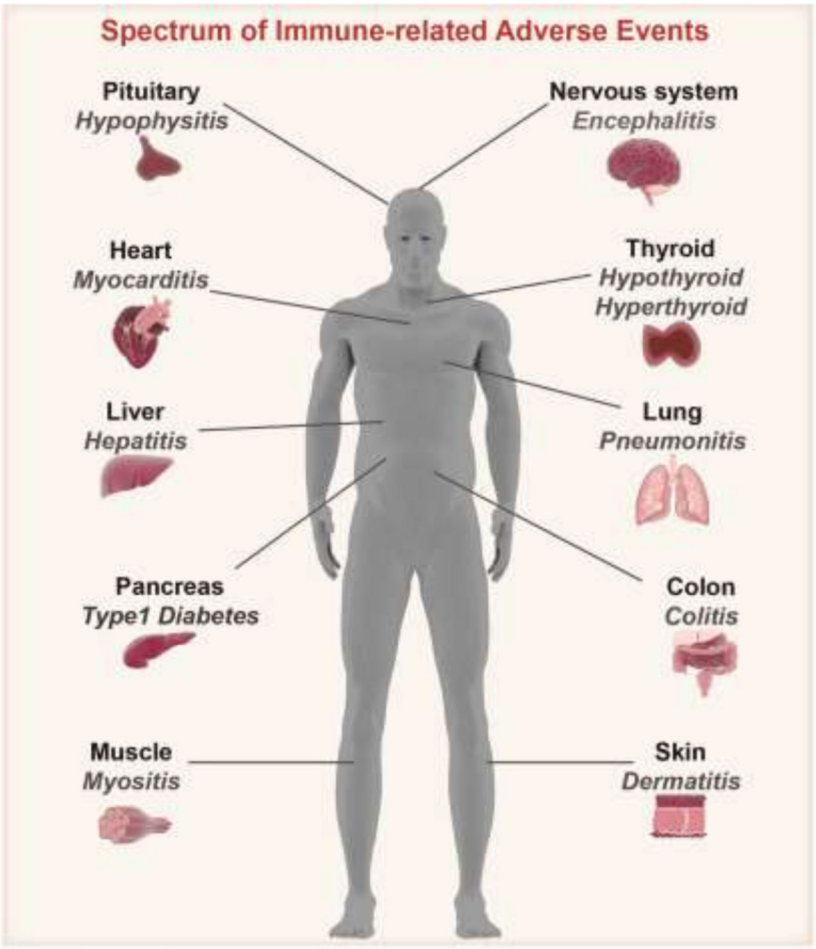

Figure 1.
Spectrum of immune-related adverse events (irAEs) in patients receiving checkpoint inhibitor therapy.

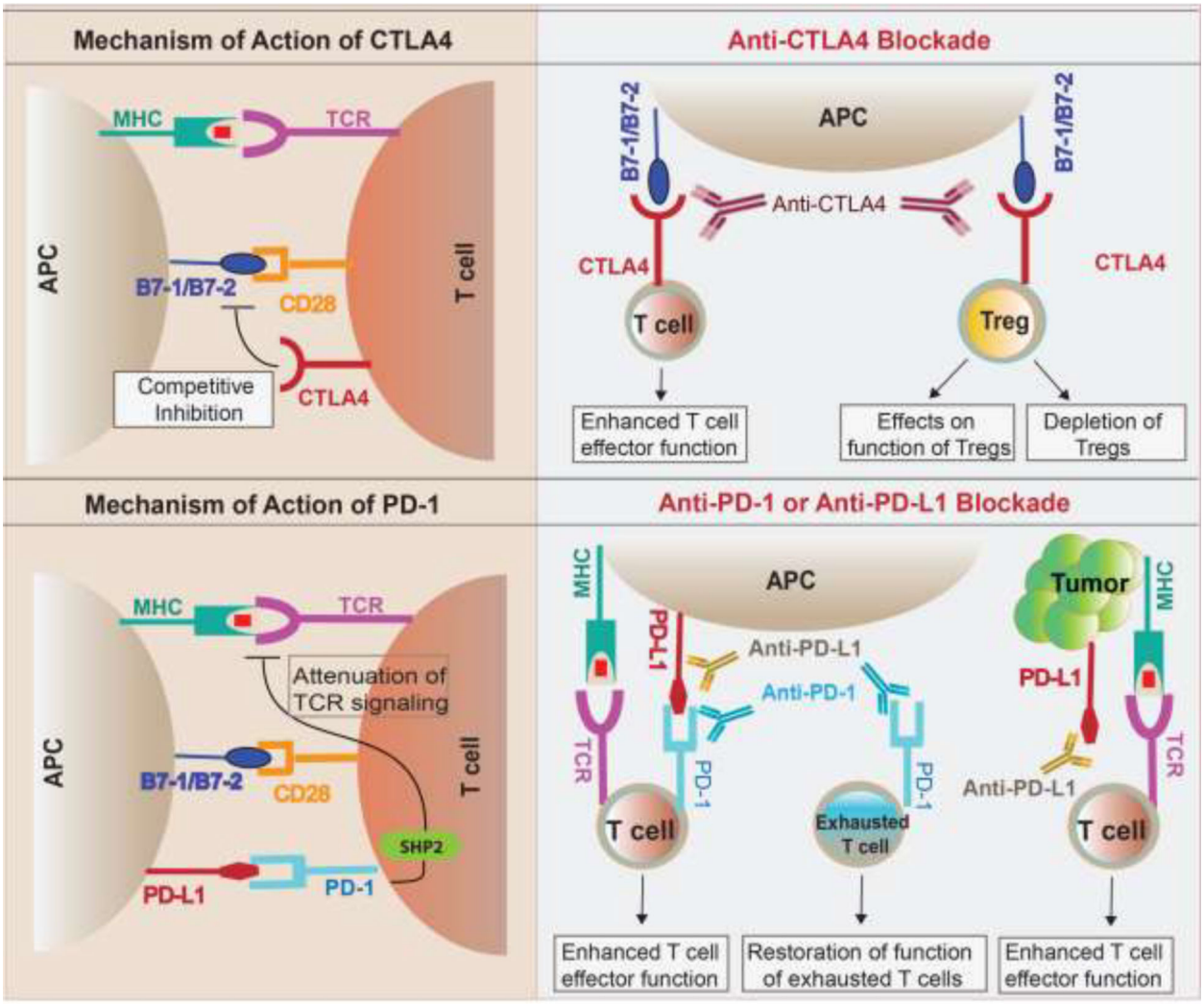

Figure 2.

Left Panel: Schematic representation of mechanism of action of CTLA4 (Top) and PD-1 (Bottom) mediated inhibition of T cell activation. Right Panel: Potential mechanism of action of anti-CTLA-4 blockade (Top Panel) and anti-PD-1/anti-PD-L1 blockade (Bottom Panel) in mediating anti-tumor activity. CTLA4: cytotoxic T-lymphocyte–associated protein 4; irAE: immune-related adverse event; PD-1: programmed death-1; PD-L1: programmed death-ligand 1; Treg: regulatory T cell; APC: Antigen Presenting Cell; MHC: Major histocompatibility complex; TCR; T-cell receptor.

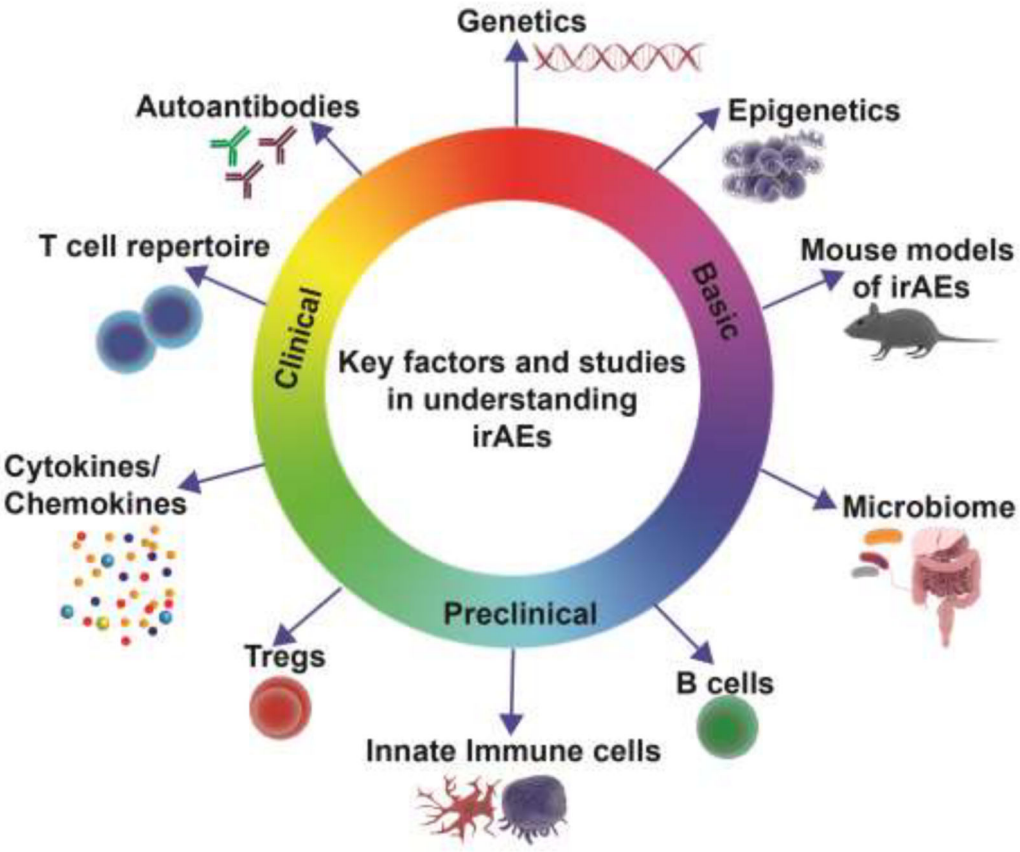

Figure 3.

Future studies to increase the mechanistic understanding of development of irAEs across the spectrum of basic, preclinical and clinical research. Longitudinal assessments of changes in immune system at baseline, during, and post therapy could reveal important insights to facilitate the development of biomarkers for diagnosis, treatment and management of irAEs. irAE: immune-related adverse event.

Table 1:

Current (as of March 2019) Food and Drug Administration (FDA) - approved immune checkpoint inhibitors and associated immune-related adverse events (irAEs).

Therapeutic Agent	Marketed Name	Target	Occurrence of irAEs in single agent studies	Trials and studies
Ipilimumab	Yervoy	CTLA-4	Rash (50%), Pruritis (45%), Colitis (16%) and Endocrinopathies (8%)	CA184–029 (Including 945 patients)
Cemiplimab	Libtayo	PD-1	Hypothyroidism (6%), Hyperthyroidism (1.5%), Pneumonitis (2.4%), Colitis (0.9%), Hepatitis (2.1%)	Study 1423 and Study 1540 (Including 534 patients)
Nivolumab	Opdivo	PD-1	Rash (9%), Hypothyroidism (9%), Hyperthyroidism (2.7%), Pneumonitis (3.1%), Colitis (2.9%), Hepatitis (1.8%), Nephritis (1.2%)	CHECKMATE-066, CHECKMATE-025, CHECKMATE-067, CHECKMATE-205, CHECKMATE-037, CHECKMATE-017, CHECKMATE-057,CHECKMATE-039 (Including 1994 patients)
Pembrolizumab	Keytruda	PD-1	Hypothyroidism (8.5%), Hyperthyroidism (3.4%), Pneumonitis (3.4%), Colitis (1.7%)	KEYNOTE-001, KEYNOTE-002, KEYNOTE-006 and KEYNOTE-010 (Including 2799 patients)
Atezolizumab	Tecentriq	PDL-1	Colitis (20%), Hepatitis (9%), Pneumonitis (2.5%), Hypothyroidism (4.6%), Hyperthyroidism (1.6%),	POPLAR and OAK (Including 2616 patients)
Avelumab	Bavencio	PDL-1	Hypothyroidism (5%), Pneumonitis (1.2%), Colitis (1.5%)	JAVELIN Merkel 200 (Including 1738 patients)
Durvalumab	Imfinzi	PDL-1	Rash (26%), Hypothyroidism (11%), Hyperthyroidism (7%), Pneumonitis (5%), Colitis (18%), Hepatitis (12%), Nephritis (6%)	PACIFIC (Including 1889 patients)

Semin Cancer Biol. Author manuscript; available in PMC 2021 August 01.