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REVIEW

Immune-Related Adverse Events of Checkpoint Inhibitors and Human Leukocyte Antigen System: A Review

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Abstract: The introduction of immune checkpoint inhibitors (ICIs) in the treatment of cancer has significantly improved patient outcomes. Whereas ICIs have a substantially more beneficial risk profile than chemotherapy, immune-related adverse events (irAEs) are currently among the most pressing challenges of clinical oncology. It has been well established that certain variants of *HLA* genes are associated with increased susceptibility or a decreased risk of certain autoimmune diseases. Considering that irAEs often resemble autoimmune disorders observed in the general population, we conducted the first review summarizing the current knowledge on the link between the HLA system and the development of irAEs during ICIs treatment. We performed a comprehensive search of the US National Library of Medicine (PubMed) database. Based on the research conducted so far, our analysis indicates that certain *HLA* variants have been described to increase or, conversely, decrease the risk of irAEs. Thus, *HLA* genotyping may be useful in stratifying the risk of irAEs, allowing for more thorough screening of patients with a higher likelihood of developing ICI-related toxicities and less frequent monitoring of those at lower risk, thereby significantly reducing costs and the overall burden of disease. *HLA* genotyping may ultimately contribute to the personalization of cancer therapy, significantly improving patient safety and clinical efficacy. Furthermore, identifying an association between certain *HLA* variants and irAEs may lead to a better understanding of the pathogenesis underlying these adverse effects. Nevertheless, the studies conducted so far have included limited cohorts of patients with a wide variety of malignancies and diverse treatment regimens. Hence, further research that addresses these limitations is needed.

Keywords: cancer, immune checkpoints inhibitors, ICIs, immune-related adverse events, irAEs, human leukocyte antigen, HLA

Introduction

Immune checkpoint proteins are inhibitory or stimulatory molecules that regulate immune responses. They are expressed primarily on immune cells and are crucial for maintaining self-tolerance and preventing tissue damage resulting from excessive immune activation.[1] The first immune checkpoint molecule, cytotoxic T-lymphocyte antigen 4 (CTLA-4), was identified by Brunet et al in 1987.[2] Its function, however, was unknown until 1995, when Krummel et al demonstrated that CTLA-4 acts as a key negative regulator of T-cell activation.[3] Although predominantly present within the immune system, inhibitory immune checkpoint proteins can also be expressed by cancer cells, where they play an important role in cancer immunity, as their upregulation represents one of the mechanisms by which neoplastic cells escape immune surveillance.[1]

Immune checkpoint inhibitors (ICIs) have revolutionized the treatment of both solid and hematological malignancies, offering longer survival and more durable responses. Nevertheless, the inhibition of immune checkpoints not only enhances the anti-cancer response but also increases overall immune system activity. This may lead to immune-related

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adverse events (irAEs), which are among the most pressing challenges of cancer immunotherapy. Their mechanisms, risk factors, and optimal management strategies remain to be fully elucidated. Interestingly, there are notable similarities between autoimmune disorders in the general population and irAEs.[4–6] Certain genetic variants in the human leukocyte antigen (HLA) system, which play a vital role in antigen presentation, have been linked to autoimmune diseases.[7,8] Therefore, it is plausible that a similar relationship exists between HLA genes and irAEs. Taking this into account, we decided to conduct this first review on the role of HLA genes in developing irAEs during ICIs therapy.

To collect all available data on the subject, we performed a thorough search in the US National Library of Medicine (PubMed) database. The most recent papers were defined as those published within the past five years at the time of writing. However, given the limited data on the topic, older research was also included. To identify the most relevant papers, the search terms included "HLA" or "MHC" and "immune checkpoint inhibitors" or "immune-related adverse events" or "immunotherapy".

The HLA System

The human leukocyte antigen (HLA) system is a gene cluster located on the short arm of chromosome 6 (6p21.3), encoding surface glycoproteins responsible for antigen presentation to T lymphocytes and, thus, initiating the adaptive immune response. The HLA system comprises three sub-regions: HLA class I, HLA class II and HLA class III. HLA class I and II molecules are crucial for antigen presentation, whereas HLA class III molecules include inflammatory mediators, such as tumor necrosis factors and components of the complement cascade.[9–11] The HLA system is characterized by its high polymorphism which plays a crucial role in transplantation, as mismatches can lead to complications in solid organ or stem cell transplants. *HLA* genes are inherited intact in haplotypes coming from each parent. However, recombination events between parental chromosomes can occasionally create new haplotypes. Because alleles are co-dominantly expressed, both parental haplotypes are functionally active.[7,10,12,13] The *HLA* genes are named according to the following pattern *HLA-[locus]*[group]:[allele]:[synonymous substitution]:[non-coding region variation]* eg *HLA-B*44:02:01*.[10] *HLA* typing can be performed by various methods, providing different levels of accuracy. A method is defined as "high resolution" if it identifies *HLA* alleles at a four-digit level, eg *HLA-A*01:01*. Most high-resolution *HLA* typing is performed using Next-Generation Sequencing (NGS). Other methods, like the sequence-specific oligonucleotide (SSO) technique, are less common due to lower throughput and resolution.[12]

HLA Class I

HLA class I region is located nearest to the telomere and it contains classical *HLA-A, -B*, and *-C loci* that encode the α-polypeptide chain of the HLA I surface molecule.[7,9] HLA I glycoproteins are expressed on the surface of all nucleated human cells as well as on platelets. HLA I is crucial in presenting intracellular antigens, allowing to maintain self-tolerance, eliminate viral infections and neoplastic cells. HLA I molecule is composed of one α heavy chain and β2-microglobulin which is encoded by the *B2M* gene, located on chromosome 15 (*15q21.1*). The α chain consists of three domains: α1, α2, and α3. The α1 and α2 form a peptide-binding groove which is used to present peptide fragments (epitopes) of 8–10 amino acids derived from the proteolytic degradation of intracellular proteins. The α3 domain serves as the binding site for the CD8 co-receptor on cytotoxic $CD8^+$ T lymphocytes. The T-cell receptor (TCR) on cytotoxic $CD8^+$ T lymphocytes interacts with the peptide presented by HLA class I, and if the epitope is recognized as non-self, the T cell is activated and proceeds with a cytotoxic response.[11,14] The HLA class I region also includes other, non-classical, *HLA-E, -L, -J, -K, -H*, and *-G* genes. Non-classical HLA I molecules are less polymorphic than classical one and they take part in both innate and adaptive immune response, often interacting with various immune receptors to exert primarily inhibitory functions.[15]

HLA Class II

The HLA class II molecule is composed of two polypeptide chains (α and β). Each α and β chain has 2 domains - highly polymorphic α1 and β1 and more conserved α2 and β2 domains. The antigen-binding groove can accommodate peptides that are 12 to 24 amino acids in length and is made of α1 and β1 domains, thus this region is highly polymorphic, which enables it to present a broad array of peptides. The HLA II molecules are expressed on antigen presenting cells (APCs),

such as B lymphocytes, macrophages, dendritic cells (DCs) and others. Five isotypes of the HLA II glycoprotein have been identified: three classical: HLA-DP, -DQ, -DR and two non-classical HLA-DM, -DO. Epitopes presented by the HLA II are derived mainly from extracellular pathogens, however, some degraded self-proteins may also be bonded to HLA II. The *HLA* class II genes region is located in the vicinity of the centromere and comprises *loci* corresponding to the aforementioned isotypes. *HLA* class II genes are classified according to the nomenclature in which the initial letter (D) indicates the class, followed by a letter (P, Q, R, M, or O) denoting the isotype, and finally the chain designation (A or B as for α or β). HLA II surface proteins present antigens to helper $CD4^+$ T-lymphocytes, which by secreting cytokines modulate both humoral and cell-mediated immune responses.[11,14,16,17] Notably, dendritic cells can also cross-present exogenous antigens on HLA class I molecules to cytotoxic $CD8^+$ T cells, thereby inducing cytotoxic responses.[18]

HLA and Immune Checkpoint Inhibitors Adverse Events

It has been established that anti-cancer immunity is dependent on T cells and their critical functions. T lymphocytes recognize antigen fragments (epitopes) in a form associated with the HLA I and HLA II molecules through their TCRs, which constitutes the first step in lymphocyte activation. Activation of other costimulatory factors is also necessary, of which the key role is played by the interaction between the surface protein CD28 on the T lymphocytes and its ligands – CD80 (B7.1) or CD86 (B7.2) on APCs.[19–21] CTLA-4 is an immune checkpoint protein permanently present on regulatory T cells (Treg) and on activated effector T cells. CTLA-4 competes with CD28 for binding to CD80 and CD86, and when bound to these ligands it inhibits the activation and proliferation of T cells. CTLA-4 acts primarily within the lymphatic system inducing anergy of T lymphocytes.[19,22–24] Programmed cell death protein 1 (PD-1) is an immune checkpoint expressed on the surface of activated T lymphocytes. It binds to the B7 homologues: programmed death ligand 1 (PD-L1), also known as B7-H1 and programmed death ligand 2 (PD-L2), also known as B7-DC, which are normally found on the APCs and, when induced by pro-inflammatory cytokines, on the surface of other cells, including cancer cells. When PD-1 on activated T lymphocytes engages with PD-L1 or PD-L2, the ongoing immune response is suppressed. LAG-3 (Lymphocyte Activation Gene 3) is a negative immune checkpoint found on T lymphocytes. Its ligands are Galectin-3, HLA class II and LSECtin. LAG-3 suppresses T cell activation and cytokines secretion. Other immune checkpoint proteins, such as TIM-3 or TIGIT, also play important role in dampening immune responses.[19,24,25]

ICIs are monoclonal antibodies designed to counter the action of immune checkpoints and are the most commonly used form of cancer immunotherapy in clinical practice. ICIs currently approved by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) can be divided into three groups. PD-1 inhibitors, such as pembrolizumab, nivolumab, cemiplimab, dostarlimab, toripalimab, retifanlimab and PD-L1 inhibitors, which include atezolizumab, durvalumab, avelumab. The second group, which can be used in combination with PD-1 or PD-L1 inhibitors (so-called dual immune blockade), consists of CTLA-4 inhibitors eg ipilimumab and tremelimumab. Relatlimab belongs to the third group of ICIs that blocks the LAG-3 molecule on lymphocytes and it is used in combination with an anti-PD-1 antibody.[26]

IrAEs are among the most pressing challenges of cancer immunotherapy, as they are commonly encountered in clinical practice and often lead to treatment discontinuation. Jayathilaka et al conducted a systematic review that included 293 studies comprising 305,879 patients with various cancers treated with ICIs. According to this analysis, the overall incidence of any-grade irAEs was 40.0% (37.3–42.7%; 95% CI) whereas high-grade irAEs were diagnosed in 19.7% (15.8–23.7%; 95% CI) patients. It was demonstrated that 30.5% (28.1–32.9%; 95% CI) of patients receiving single-agent ICI therapy experienced irAEs, whereas among patients receiving combination therapy (PD-1/PD-L1 and CTLA-4 inhibitors), irAEs occurred in 45.7% (29.6–61.7%) of patients. Furthermore, the pooled data indicate that the incidence of organ-specific irAEs was as follows: skin irAEs 28.7% (22.9–34.6%; 95% CI), gastrointestinal irAEs 19.4% (14.1–24.6%; 95% CI), endocrine irAEs 23.9% (18.8–29.1%; 95% CI), pulmonary irAEs 18.9% (15.1–22.7%; 95% CI), cardiac irAEs 18.0% (5.9–30.2%; 95% CI) and renal irAEs 15.5% (7.3–23.7%; 95% CI).[27] A Finnish retrospective, real-world cohort study involving a total of 317 adult patients with inoperable locally advanced or metastatic cancer receiving ICIs (PD-1/PD-L1 and/or CTLA-4 inhibitors) or ICIs with chemotherapy showed that 50 patients (17%) had to discontinue ICIs due to irAEs, with pneumonitis being the most common irAE leading to treatment discontinuation

(4.1%) in the entire study cohort followed by hepatitis (3.4%) and colitis (3.1%).[28] In comparison, data from randomized, Phase III clinical studies on anti-PD-1 inhibitors in stage IV renal cell carcinoma (RCC), melanoma and non-small cell lung cancer (NSCLC) indicate that irAEs were the reason for discontinuation of immunotherapy in 10.8%, 9% and 13.6% of patients respectively.[29–31]

Although the exact mechanisms underlying irAEs are not yet fully understood, known contributing factors include abnormal activation of cytotoxic T cells, disruption of Treg function, increased autoantibody production, molecular mimicry, cytokine-driven inflammation, and complement system activation.[5,32,33] CTLA-4 inhibitors and PD-1/PD-L1 inhibitors as well as LAG-3 inhibitors enhance the immune response via different mechanisms, which may account for the distinct irAE profiles observed with these agents. For example, CTLA-4 inhibitors are more often associated with colitis, hypophysitis, and skin rashes, whereas pneumonitis, hypothyroidism, and vitiligo are more common with PD-1/PD-L1 inhibitors.[34]

The toxicity of cancer treatment, including irAEs is assessed according to the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v. 5.0) developed by the National Cancer Institute (NCI).[35] National Comprehensive Cancer Network (NCCN) guidelines generally recommend withholding or discontinuation of immunotherapy and the administration of glucocorticoids in cases of grade ≥ 3 irAE in order to attenuate the autoimmunological response.[36] Other immunosuppressive drugs are also used, such as mycophenylate mofetil, azathioprine, as well as biological treatment, including TNFα inhibitors, eg infliximab. This may limit the effectiveness of immunotherapy, which relies on enhanced immune activity.[5,32,33,36]

It has been reported that certain *HLA* alleles may be linked to greater susceptibility to autoimmune diseases and pathological reactions to environmental or food antigens. Strong associations between rheumatoid arthritis (RA) and *HLA-DR*4* as well as between *HLA-B*27* and ankylosing spondylitis (AS) have been reported.[7,8,37] Several mechanisms by which certain *HLA* polymorphisms increase the risk of autoimmune diseases have been identified. Specific HLA alleles alter the peptide-binding repertoire of HLA class II molecules, thereby facilitating the presentation of self-peptides that would normally be ignored. For instance, in type 1 diabetes mellitus (T1DM), HLA-DQ8 enhance the presentation of insulin-derived peptides, promoting the activation of autoreactive T cells. *HLA* polymorphisms can also compromise central tolerance by reducing the efficiency of negative selection in the thymus, allowing self-reactive T cells to escape into the periphery. Moreover, *HLA* variants influence the differentiation and function of regulatory T cells, limiting their capacity to suppress autoreactive clones and further contributing to autoimmune susceptibility. Collectively, these mechanisms illustrate how specific *HLA* alleles can predispose individuals to autoimmunity through coordinated effects on antigen presentation, thymic selection, and peripheral tolerance.[8,11]

On the other hand, the presence of specific *HLA* genes variants may reduce the risk of some autoimmune diseases. For example, the *HLA-DRB1*13*01* allele is associated with a lower risk of RA, likely due to its ability to promote immune tolerance by modulating regulatory T cell function and favoring anti-inflammatory macrophage polarization, thereby limiting autoreactive immune responses.[37,38]

Given that irAEs often resemble autoimmune disorders observed in the general population, it can be hypothesized that a similar association may exist between *HLA* genes variants and irA*Es* (Figure 1).

This section describes studies investigating the link between *HLA* genes and occurrence of irAEs in cancer patients receiving ICIs.

HLA Genetic Factors Protective Against irAEs

Similarly to the general population, studies have shown that several *HLA*-related genetic factors may play a role in protecting against autoimmune reactions induced by ICIs.

HLA I Homozygosity Protects Against irAEs

Abed et al performed high-resolution typing of *HLA I* (A, B, C exons 2 and 3) and *HLA II* (DQ, exons 2 and 3; DRB and DPB1, exon 1) genes using the NGS method (Illumina MiSeq platform with the MiSeq V3 600-cycle kit) in 156 Australian patients suffering from unresectable, locally advanced or metastatic NSCLC who were treated with monotherapy of ICIs (pembrolizumab, atezolizumab, or nivolumab) as first- or second-line treatment. Among these patients, 77 (49.4%) developed irAEs. In this study, *HLA I* homozygosity at one or more genes was associated with a lower risk of

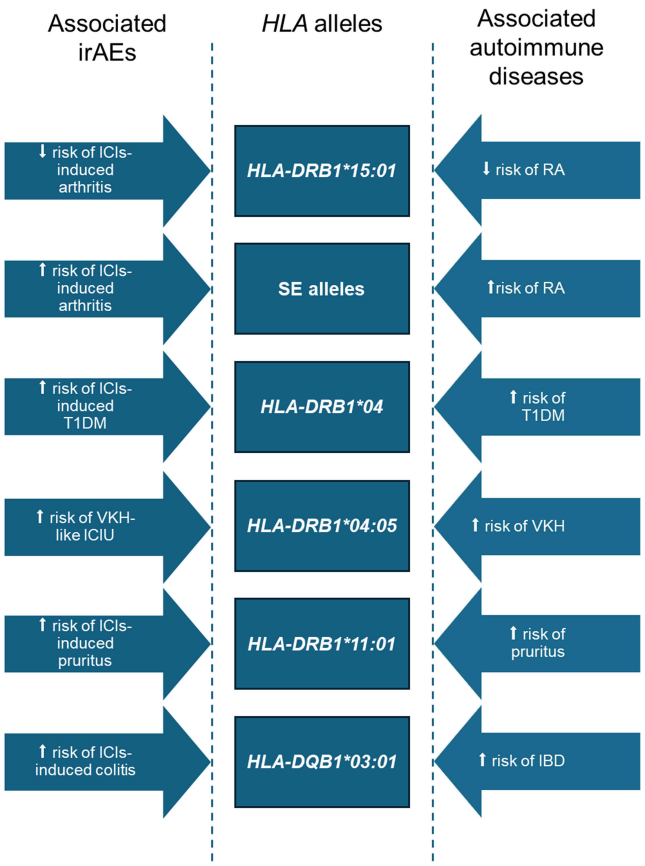

Figure 1 *HLA* variants associated with irAEs and corresponding autoimmune diseases in the general population.
Notes: ↓ – deacresed; ↑ – increased; irAEs – immune-related adverse events; ICIs – immune checkpoints inhibitors; RA – rheumatoid arthritis; T1DM – type 1 diabetes mellitus; VKH – Vogt–Koyanagi–Harada disease; ICIU – immune checkpoint inhibitor-associated uveitis; IBD – inflammatory bowel disease; *HLA* alleles were designated according to the World Health Organization HLA Nomenclature.

developing any-grade irAEs (p=0.035) compared to heterozygous patients. Furthermore, *HLA I* homozygous (at least one locus) patients were significantly less likely to experience serious (grade 3 or higher) irAEs (p=0.023). This clinically important correlation is especially evident in pneumonitis, as none of the *HLA I* homozygous patients developed this toxicity (p=0.044). *HLA II* homozygosity was not associated with a decreased or increased risk of irAEs.[39]

This raises the question of how *HLA I* homozygosity decreases the risk of irAEs. From an evolutionary perspective, heterozygosity of *HLA* genes is favored, as it provides a better immunological response to pathogens. Populations exposed to a greater range of infectious diseases tend to be more polymorphic than others. Given the function of HLA I, its homozygosity may limit the diversity of presented peptides, thereby reducing the activation of $CD8^+$ T cells and lowering the likelihood of autoimmune responses. Furthermore, the limited diversity of epitopes decreases the risk of molecular mimicry, in which self-antigens resemble foreign antigens and trigger autoimmune processes.[40]

However, in the general population, *HLA* homozygosity has not been linked to a lower risk of developing autoimmune diseases. Interestingly, it has been shown that individuals homozygous for a specific high-risk allele often have a higher risk of developing certain autoimmune diseases than carriers of only one allele.[41] Moreover, homozygosity for high-risk *loci* may increase disease severity, as seen in severe extra-articular RA among *DRB1*04* homozygotes.[42] Thus, further studies on *HLA* homozygosity and its association with both overall and specific irAEs are needed.

Specific Protective Alleles

An analysis of the *HLA* genotype by Abed et al also demonstrated that carriers of the *HLA-DRB1*15:01* allele are less likely to develop arthritis (p=0.029).[39] Interestingly, *HLA-DRB1*15:01* significantly decreases the risk of RA in the general population.[43] On the other hand, it has been established that carriers of the *HLA-DRB1*15:01* allele are more

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likely to develop multiple sclerosis (MS) than the rest of the population.[44] Whether, this association is clinically important in the context of ICIs treatment is currently unknown, however, it should be noted that the activity of previously diagnosed MS is generally not increased by ICIs,[45–47] and cases of new MS diagnoses after or during ICIs treatment are extremely rare.[48,49]

Abed et al also linked *HLA-DQB1*03:01* with a decreased risk of colitis (p=0.048).[39] Interestingly, studies indicate that in the general population, the presence of *HLA-DQB1*03:01* is associated with susceptibility to bullous pemphigoid, including drug-induced pemphigoid.[37] Nevertheless, such an association has not yet been observed in the ICIs-treated population.

Moreover, *HLA-B*54:01* was associated with a lower risk of developing irAEs (p=0.024) in a study by Sung et al, which has been described below in the present work in paragraph 3.2.8.[50]

Single Nucleotide Polymorphisms (SNPs) Within HLA Region and irAEs

Abdel-Wahab conducted a retrospective genome-wide association study at The University of Texas MD Anderson Cancer Center. A total of 90 melanoma patients who received anti-CTLA-4 treatment (n=17, 19%), anti-PD-1/PD-L1 agents (n=49, 55%), combination therapy with anti-CTLA-4 and anti-PD-1/PD-L1 antibodies (n=4, 4%), or sequential ICIs (n=19, 21%) were included in the study. Among the participants, 85 (96%) were of Caucasian descent, 4 were Hispanic/Latino, and 1 was African American. Melanoma patients who developed irAEs within one year of initiating ICIs treatment (n=44) were considered cases, while the remaining patients (n=45) were assigned to the control group. One patient was excluded because he was receiving ICIs treatment for RCC and did not have active melanoma. Genotyping was performed in both the irAE group and the control group using the Infinium Multi-Ethnic Global-8 v1.0 BeadChip (Illumina, San Diego, USA). It was observed that several SNP variants of *HLA* genes were associated with a decreased risk of irAEs. Carriers of specific variants, including rs3830135 in the *HLA-DRB1* gene (p=0.002048), rs28654242 in the *HLA-DQA1* gene (p=0.003645), and rs17500468 in the *HLA-DQA2* gene (p=0.02402), were less likely to develop irAEs.[51]

The studies conducted so far and regarding the association between SNV of HLA genes and irAEs are summarized in Table 1.

Table 1 Genetic Factors Associated with *HLA* That Have a Protective Effect on the Development of irAEs in ICIs Treated Cancer Patients

Genetic Factor	Study Group	Treatment	Previous Treatment	Population	IrAEs Significantly Less Likely to Occur	Notes	Reference
HLA I homozygosity at one or more loci	Patients with advanced NSCLC, n=157	Single-agent ICIs (pembrolizumab, atezolizumab, or nivolumab)	Majority of patients previously received chemotherapy and/or radiotherapy (n=111, 71.1%)	Australian	Any irAEs, p=0.035 Grade 3 or higher irAEs, p=0.023 Pneumonitis, p=0.044	Compared to heterozygous patients	[39]
*HLA-DRB1*15:01*					Arthritis, p=0.029	Compared to patients without *HLA-DRB1*15:01*	
*HLA-DQB1*03:01*					Colitis, p=0.048	Compared to patients without *HLA-DQB1*03:01*	

(*Continued*)

Table 1 (Continued).

Genetic Factor	Study Group	Treatment	Previous Treatment	Population	IrAEs Significantly Less Likely to Occur	Notes	Reference
*HLA-B*54:01*	Patients with various cancers who developed irAEs, n=372	Anti-PD-1 or anti-PD-L1; Anti-PD-1 + anti-CTLA-4; Anti-PD-1 or anti-PD-L1 + chemotherapy; Anti-PD-1 or anti-PD-L1 + targeted treatment; Anti-PD-1 or anti-PD-L1 + chemotherapy + targeted therapy	No data	Korean	Any irAEs, (p=0.024)	Compared to patients without irAEs, n=300	[50]
Selected variants in rs3830135 in the *HLA-DRB1*	Patients with melanoma who developed irAEs N=44	Anti-PD-1 or anti-PD-L1 (n=49, 55%); Anti-CTLA-4 (n=17, 19%); Anti-CTLA-4 + anti-PD-1 or anti-PD-L1 (n=4, 4%); Sequential ICIs (n=19, 21%)	Surgical resection (n=5)	Mostly US-Caucasian (96%)	Any irAEs, p=0.002048	Compared to patients without irAEs, n=45	[51]
Selected variants in rs28654242 in the *HLA-DQA1*					Any irAEs, p=0.003645		
Selected variants in rs17500468 in the *HLA-DQA2*					Any irAEs, p=0.02402		

Abbreviations: irAEs, immune-related adverse events; ICIs, immune checkpoints inhibitors; NSCLC, non-small cell lung carcinoma; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; CTLA-4, Cytotoxic T lymphocyte-associated antigen-4; HLA, alleles were designated according to the World Health Organization HLA Nomenclature.

HLA Genetic Factors Increasing the Risk of irAEs

Several studies conducted have indicated that carriers of certain HLA alleles may be more susceptible to developing irAEs. The current scientific research on the subject is described below, along with hypotheses on how *HLA* variants may contribute to the development of irAEs.

ICIs-Induced Pneumonitis

A study by Correale et al was performed among 256 Italian patients with NSCLC, melanoma, head and neck cancer, RCC, urothelial cancer, gastro-enteric cancer, and breast cancer who were treated with pembrolizumab, nivolumab, or atezolizumab. Most patients also received other forms of therapy, including prior chemotherapy, metronomic chemotherapy with or without bevacizumab, erlotinib, or palliative radiotherapy. In 180 patients, genotyping of *HLA-A, -B, -C*, and *HLA-DRB1* was performed using low- to medium-resolution reverse SSO DNA typing assays. Statistical analysis indicated a greater risk of developing immune-related pneumonitis among carriers of *HLA-B*35* (27.6% vs 11.6%; p=0.06) and *HLA-DRB1*11* (21.0% vs 7.6%; p=0.03) compared to patients without these alleles.[52] However, a significant limitation of the study by Correale et al which should not be overlooked was the heterogeneity of the patient group, with participants suffering from wide spectrum of cancers for which they received various forms of therapy (eg palliative radiotherapy) that may have contributed to the development of pneumonitis.[52]

The mechanism of ICIs-induced pneumonitis remains poorly understood, and thus how certain *HLA* alleles may increase the risk of this irAEs is not known.[53,54] It is also worth noting that the described alleles have been linked with inflammatory rheumatic diseases in the general population. For example, *HLA-B*35* has been shown to increase the risk of developing juvenile RA,[55] as well as peripheral arthritis in patients with undifferentiated axial spondyloarthritis.[56] *HLA-DRB1*11* has also been reported as a strong risk factor for developing juvenile RA.[57] The importance of this association in irAEs in cancer patients treated with ICIs remains to be determined.

HLA-B*27 Alleles

Titmuss et al investigated the link between germline genetic factors and irAEs in 117 advanced cancer patients from British Columbia, Canada, participating in the BC Cancer Personalized OncoGenomics program. Patients underwent whole-genome analysis (Illumina HiSeq 2500 using v3 or v4 chemistry with paired-end 125-base reads, or on HiSeqX using v2.5 chemistry with paired-end 150-base reads). Participants suffered from various types of cancer, including lung cancer (n=28), melanoma (n=23), breast cancer (n=13), pancreatic cancer (n=13), gynecological cancers (n=8), and others (n=32). Participants received anti-PD-1/anti-PD-L1 monotherapy (n=66), concurrent PD-1/PD-L1 and CTLA-4 inhibitors (n=32), or PD-1/PD-L1 and CTLA-4 inhibitors in combination with chemotherapy (n=12). The remaining patients were treated with single-agent CTLA-4 inhibitor (n=2), NKG2A inhibitor (n=2), PD-1/PD-L1 inhibitors in combination with IDO-1 inhibitors (n=10), multiple single-agent ICIs administered more than 12 weeks apart (n=2), or other combination ICIs (anti-PD-1/anti-PD-L1 and OX-40 agonists, n=3). Out of 6 patients carrying alleles belonging to the *HLA-B*27* group, 4 developed grade 3 irAEs, specifically, hepatitis (n=3) and pneumonitis (n=1), whereas, in the remaining patients, the frequency of grade 3 irAEs was 2.7%. Thus, a significant increase in grade 3 irAEs ($p=0.007$) was observed in *HLA-B*27* carriers compared to patients without these allele. Nevertheless, the small cohort of *HLA-B*27* patients and the inconsistent treatment regimens are among the limitations of the described study.[58]

A study on the association of ICIs-induced encephalitis and HLA system was also performed. Among 290 Korean patients at Seoul National University Hospital suffering from advanced solid tumors and treated with atezolizumab alone or in combination with various forms of therapy, 5 patients who developed ICIs-induced encephalitis underwent genotyping of the *HLA-A, HLA-B, HLA-C, HLA-DRB1*, and *HLA-DQB1* genes at the 4-digit allele level. A control group was formed using previously reported *HLA* allele frequencies in the Korean population. Of the 5 patients recruited for the study, 3 had bladder cancer (of whom 1 received a combination of atezolizumab and cobimetinib [a MEK inhibitor]) and 2 had breast cancer (1 patient received concurrent atezolizumab and cobimetinib, and 1 was given atezolizumab with fulvestrant [a selective estrogen receptor degrader] and ipatasertib [an AKT inhibitor]). All participants, except for one breast cancer patient, had previously received chemotherapy. The *HLA-B*27:05* allele was associated with an increased risk of ICIs-induced encephalitis ($p<0.001$), as it was present in 3 out of 5 patients, whereas only 2.5% of individuals in the general Korean population carry *HLA-B27:05*. Unfortunately, this study also had limitations, including an extremely small cohort, heterogeneous cancer types and treatment regimens, and prior chemotherapy.[59]

The association between *HLA-B*27* alleles and AS was discovered over 50 years ago, and it has been the subject of many studies which confirmed this correlation. AS is a highly heritable disease, belonging to the larger group of spondyloarthritis. Among the *HLA-B*27* alleles with the strongest association with AS are *HLA-B*27:02* (Mediterranean population), *HLA-B*27:05* (Caucasian population and American Indians) and *HLA-B*27 :04* (Asians). Interestingly, *HLA-B*27:06* and *HLA-B*27:09* are not increasing the risk of AS.[60] Criteria developed by the Assessment of SpondyloArthritis International Society for diagnosing both axial and peripheral spondyloarthritis include HLA-B27 antigen testing.[61] *HLA-B*27* has also been associated with other autoimmune diseases, such as reactive arthritis, Behçet's disease, inflammatory bowel disease and psoriatic arthritis.[60] Although the mechanism by which *HLA-B*27* alleles contribute to the development of AS has not yet been discovered, several hypotheses have emerged. The major theory is the "arthritogenic peptide" hypothesis, which assumes that HLA-B27 molecules present certain self-peptides that share similarities with microorganism-derived

peptides, leading to cross-reactivity and a pathological cytotoxic T cell response.[60,62] Whether this mechanism applies to the irAEs remains to be determined, however, it should be considered in further research.

*HLA-B*27* alleles are found in about 6.1–9.5% of the European population.[63,64] Whereas they are not present in the majority of patients, its well-established link to autoimmunological disorders, especially to AS, in combination with the initial reports indicating that patients carrying *HLA-B*27* alleles are more susceptible to irAEs, makes it a possible risk factor of irAEs in a patient undergoing ICIs treatment.[58] Nevertheless, further analysis is needed to confirm this association and to clarify whether *HLA-B*27* carriers are likely to develop any kind of irAEs or specific irAEs, eg encephalitis as reported by Chang et al.[59] A study investigating the link between *HLA-B*27* alleles and irAEs resembling known HLA-B27-associated diseases is also needed.

Shared Epitope Alleles

Some *HLA-DRB1* variants in different human populations have been found to have a similar five amino acid sequence at position 70–74 on the HLA-DRβ chain. This region has been termed the shared epitope (SE). The most prevalent SE-coding alleles include *HLA-DRB1*04* allele group, such as *HLA-DRB1*04:01, HLA-DRB1*04:04, HLA-DRB1*04:05, HLA-DRB1*04:08* as well as *HLA-DRB1*01:01, HLA-DRB1*01:02, HLA-DRB1*14:02* and *HLA-DRB1*10:01*. A correlation has been observed between the presence of SE alleles and an increased risk of RA.[65]

Cappelli et al performed high-resolution *HLA* typing on 27 patients (26 Caucasians and 1 African American) with ICIs-induced inflammatory arthritis and on 726 healthy controls using the TruSight HLA Sequencing Panel and the MiSeq Platform (Illumina, San Diego, CA). Genotyping at the SE locus (*HLA DRB1*) was also performed on 220 RA cases. SE alleles were designated as *HLA-DRB1*01:01, 01:02, 04:01, 04:04, 04:05, 04:08, 10:01* and *14:02*. Patients with ICIs-induced inflammatory arthritis had various neoplasms, most common melanoma (n=9) and NSCLC (n=6). The participants were treated with anti-PD-1 and anti-CTLA-4 combination therapy (n=9), and anti-PD-1 or anti-PD-L1 monotherapy (± other investigational drugs eg anti-CD73, anti-LAG-3). Of the 26 Caucasian patients with ICIs-induced arthritis, 16 (61.5%) had at least one SE allele which is significantly more frequent than in the healthy controls (p=0.04). The prevalence of the *HLA-DRB1*04:05* allele was especially enriched in the ICIs-induced arthritis group compared to healthy controls (p=0.04). The prevalence of SE alleles was similar in the ICIs-induced arthritis group and the RA patients group. Unlike RA patients, those with ICIs-induced arthritis, were significantly more likely to lack rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA).[66] These results indicate that carriers of SE alleles may be stratified as high-risk patients for the development of ICIs-induced arthritis. Furthermore, RA patients carrying SE alleles have more active disease, as measured by DAS28, CDAI, and SDAI, regardless of ACPA status.[67] In RA patients homozygous for SE alleles, a more severe burden of disease and earlier occurrence of radiological skeletal changes have been observed.[68] Thus, it is possible that patients with ICIs-induced arthritis carrying SE alleles may have a more aggressive course of this irAE and, therefore, require more intensive treatment. It is worth noting that the primary limitation of the described study was its small sample size, as it focused on patients who developed ICIs-induced arthritis.[66] Interestingly, in the aforementioned study by Abed et al, it was shown that the *HLA-DRB1*04:01* allele is associated with the increased risk of developing any-grade irAEs ($p = 0.011$) regardless of the affected organ.[39] Thus, the question arises whether SE alleles increase only the risk of ICIs-induced arthritis or also other irAEs. This issue remains to be determined and requires further research.

C-X-C motif chemokine ligand 12 (CXCL12), primarily produced by stromal cells, plays a crucial role in activating and directing T and B-lymphocytes and other inflammatory cells to synovial tissues. CXC receptor 4 (CXCR4), mediates these effects. The CXCR4-CXCL12 axis plays an important role in the pathogenesis of RA.[69] The CXCR4 expression on memory $CD4^+$ T cells has been linked to worse disease severity and overall higher RA activity.[70,71] It has been observed that the presence of one or two SE alleles in patients with RA positively correlates with increased CXCR4 expression on memory $CD4^+$ T cells, which include the Th1, Th17, Tfh (T follicular helper cells), and Treg subsets. Additionally, RA patients carrying SE alleles exhibit increased HLA-DR expression on B cells, and a significant positive correlation between HLA-DR expression on B cells and CXCR4 expression on memory $CD4^+$ T cells has been described. In contrast, no significant differences in HLA-DR expression on B cells or CXCR4 expression on memory $CD4^+$ T cells were observed between healthy controls with or without SE alleles. Therefore, the link between SE and enhanced HLA-

DR expression on B cells and CXCR4 expression on memory $CD4^+$ T cells may be specific to RA. It has been established that CXCR4 expression on $CD4^+$ T cells is regulated by IL-2, IL-4, IL-7, IL-15 and IL-21. The addition of IL-21 to a culture of peripheral blood mononuclear cells increases CXCR4 expression on $CD4^+$ T cells, whereas an anti-HLA-DR antibody mitigates this effect, suggesting that HLA-DR is involved in upregulating CXCR4 expression. Administering CTLA-4-Ig to 20 patients with RA reduced CXCR4 expression on naive $CD4^+$ T cells, decreased HLA-DR expression on T cells, and lowered the concentration of proinflammatory cytokines. Although CTLA-4-Ig did not decrease HLA-DR expression on B cells or CXCR4 expression on memory $CD4^+$ T cells, higher CXCR4 expression on memory $CD4^+$ T cells correlated with a better response to CTLA-4-Ig treatment.[71]

The pathogenesis of ICIs-induced arthritis and its link to SE alleles require further study. However, given that CXCR4 expression is increased in RA patients carrying SE alleles, this association should be further investigated in patients with ICIs-induced arthritis. Furthermore, because memory $CXCR4^+CD4^+$ T cells have been linked to a more rapidly progressive course of RA as well as to a better response to CTLA-4-Ig treatment in RA, this association is of great importance in ICIs treatment, as patients receiving ICIs who carry SE alleles may be at risk of developing rapidly progressing arthritis. Moreover, because anti-CTLA-4 ICIs counteract the effects of CTLA-4-Ig treatment, patients receiving ipilimumab or tremelimumab might be especially vulnerable to ICIs-induced arthritis.

Abatacept is a CTLA-4-immunoglobulin fusion protein that binds to CD80 and CD86, preventing the co-stimulation of T cells. It was approved by the FDA in 2005 for the treatment of RA. It is also used in the management of psoriatic arthritis, juvenile idiopathic arthritis, and in the prevention of graft-versus-host disease (GvHD) in patients undergoing hematopoietic stem cells transplantation from unrelated donors. It has been suggested that abatacept could be used off-label in other rheumatic diseases, such as Sjögren's syndrome, systemic vasculitis syndromes, systemic sclerosis, systemic lupus erythematosus, and others.[72,73] In murine tumor models administering CTLA-4-Ig alongside anti-PD-1/anti-PD-L1 or anti-CTLA-4 or concomitant immunotherapy reduced antitumor efficacy, while post-ICIs administration enhanced the anti-tumor response. CTLA-4-Ig administered after the termination of ICIs decreased Treg frequency, increased the $CD8^+$ cells/Treg cells ratio, and potentially improved antitumor activity. This approach effectively reduced irAEs without compromising ICIs efficacy.[74] This is especially important as ICIs-induced arthritis remains active in most patients even after the cessation of immunotherapy.[75] Therefore, abatacept may potentially be administered safely after the termination of immunotherapy, without increasing the risk of disease progression and even improving prognosis. Given the results obtained in the cancer-free population, it is possible that carriers of SE alleles will benefit more from CTLA-4-Ig therapy. Thus, SE status may serve as a prognostic factor not only to identify groups at risk of developing ICIs-induced arthritis but also to select an optimal therapeutic strategy in glucocorticoid-resistant ICIs-induced arthritis.

Interestingly, abatacept has shown efficacy in treating ICIs-induced myocarditis in murine tumor models.[76] A Phase II, randomized, double-blind trial in which three different abatacept doses are being administered in combination with ruxolitinib and corticosteroids for the treatment of ICIs-induced myocarditis (ACHLYS trial) is currently being conducted in France (NCT05195645).[77]

HLA and Type 1 Diabetes Mellitus Induced by ICIs

Among 163 patients treated with anti-PD-1 agents (nivolumab or pembrolizumab) for melanoma in the Department of Dermato-Oncology at CHU Timone in Marseille, France, in three patients T1DM has developed. An additional 2 patients from a blinded clinical trial (ipilimumab vs anti-PD-1) were also diagnosed with newly developed T1DM. Among the patients with T1DM, 4 out of 5 had alleles belonging to *HLA-DRB1*03* or *HLA-DRB1*04* subtypes; however, these results were not statistically significant.[78] On the other hand, *HLA-DRB1*03* and HLA-*DRB1*04* are strongly linked with T1DM in the general population. Carriers of *HLA-DRB1*03* or *HLA-DRB1*04* are 3–5 times more likely to develop T1DM than the rest of the population. Furthermore, the risk is increased 20–40 times in patients carrying both *HLA-DRB1*03* and HLA-DRB1*04.[79]

Stamatouli et al reported a correlation between the *HLA-DRB1*04* subtype and ICIs-induced T1DM. HLA genotypes were determined using the LIFECODES HLA SSO Typing Kit in 23 Caucasian cancer patients mostly melanoma, who

developed ICIs-induced T1DM. Patients were treated in the Department of Endocrinology at Yale New Haven Hospital and the University of California, San Francisco (UCSF) Medical Center, and received PD-1/PD-L1 inhibitors as monotherapy or in combination with anti-CTLA-4 agents. *HLA-DRB1*04* alleles were overrepresented, being found in 16 of 21 patients (76%), which is significantly higher than the frequency of these alleles in US Caucasians ($p<0.0001$) or in patients with spontaneous T1DM ($p=0.002$). However, there was no statistically significant correlation between *HLA-DRB1*03* alleles and ICIs-induced T1DM.[80] Similar results were obtained by Akturk et al, who designed a retrospective case-control study in which high-resolution *HLA-DRB1* genotyping at the four-digit level was performed in 132 advanced melanoma patients. Patients were treated with anti-PD-1 or anti-CTLA-4 monotherapy, or with dual immune checkpoint blockade, at the University of Colorado Cancer Center, USA. *HLA-DRB1*04* was overrepresented in patients with ICIs-induced T1DM when compared to cancer patients carrying *HLA-DRB1*04* but without ICIs-induced T1DM ($p=0.01$). Interestingly, there was also a correlation between *HLA-DRB1*08* and hypothyroidism ($p=0.003$).[81]

Another study on the link between HLA and ICIs-induced T1DM was conducted by Inaba et al. A total of 871 Japanese patients suffering from advanced malignant diseases (melanoma, NSCLC, small cell lung cancer [SCLC], gastric cancer, RCC, urothelial cancer, hypopharyngeal cancer, and Hodgkin lymphoma) treated with ICIs, including anti-PD-1 antibody (nivolumab or pembrolizumab), anti-PD-L1 antibody (durvalumab), or anti-CTLA-4 antibody (ipilimumab) following nivolumab, took part in this study. ICIs-induced T1DM was diagnosed in 7 (0.8%) participants, 4 suffering from NSCLC, 1 from SCLC, and 2 from melanoma.[82] Thus, the incidence of ICIs-induced T1DM was comparable to previously reported statistics from the Japanese population.[83] HLA genotyping at the *HLA-A, -B, -C, DRB1, DRB345, DQA1, DQB1, DPA1*, and *DPB1 loci* was performed using the NGS method (GenoDive Pharma, Kanagawa, Japan) in patients who developed ICIs-induced T1DM. The results of *HLA* genotyping in patients with T1DM were compared to the *HLA* haplotypes of 13 cancer patients treated with ICIs without any irAEs (control group) and to those of healthy controls from available Japanese databases on *HLA* allele distribution in the Japanese population. It was observed that the *HLA-DPA1*02:02, HLA-DPB1*05:01* alleles, and *HLA-DPA1*02:02–DPB1*05:01* haplotype were significantly more frequent in patients with ICIs-induced T1DM than in patients belonging to the ICIs-control group ($p=0.022$, $p=0.0027$, and $p=0.0093$, respectively). It was also observed that the *HLA-DPA1*02:02* and *DPB1*05:01* alleles were significantly more frequent in the ICIs-induced T1DM patients than in the healthy control group ($p=0.021$ and $p=0.0075$, respectively). While the *HLA-DRB1*04:05* allele was significantly more frequent in the ICIs-induced T1DM group than in the healthy controls ($p=0.045$), there was no significant difference when comparing the ICIs-induced T1DM group to the ICIs-control group.[82] These results differ from the observations made in the studies described above by Magis et al,[78] and Akturk et al,[81] as Inaba et al discovered a link between alleles not previously associated with T1DM in the general population.[78,82] Whether, this association is caused by a different pathophysiology of ICIs-induced T1DM compared to T1DM in the general population, which remains to be determined. Genetic differences between Japanese and European populations should also be considered.

HLA and Pituitary irAEs

Kobayashi et al investigated the association between *HLA* haplotypes and pituitary irAEs, specifically ICIs-induced isolated adrenocorticotropic hormone deficiency (ICI-IAD) and ICIs-induced hypophysitis (ICI-H). A prospective case-control study was conducted among Japanese cancer patients treated at Nagoya University Hospital, in which ICI-IAD was diagnosed in a total of 17 patients (9 with melanoma, 5 with NSCLC, 2 with RCC, and 1 with head and neck cancer). In patients with ICI-IAD, 13 developed ICI-IAD during anti-PD-1 therapy (nivolumab or pembrolizumab), 3 during ipilimumab therapy and 1 during double immune checkpoint blockade with ipilimumab and nivolumab. ICI-H was observed in 4 patients with melanoma and in 1 patient with RCC, and in 3 patients treated with ipilimumab monotherapy and 2 patients with concurrent nivolumab and ipilimumab. A further 40 patients, matched for malignancy type and ICIs treatment but without pituitary irAEs, were enrolled as a control group. *HLA* genotyping was performed on all participants, targeting the *HLA-A, HLA-B, HLA-C, HLA-DRB1, HLA-DQB1*, and *HLA-DPB1 loci* using a Luminex-based PCR-SSO with WAKFlow HLA typing kits from Wakunaga Pharmaceutical (Japan). In ICI-IAD patients, the prevalence of the following alleles was significantly higher compared to the control group: *HLA-Cw12* (7/17 (41.2%) vs 6/40 (15%), $p<0.05$), *HLA-DR15* (10/17 (58.8%) vs 10/40 (25%), $p<0.05$), *HLA-DQ7* (8/17 (47.1%) vs 7/40 (17.5%),

p<0.05), and *HLA-DPw9* (7/17 (41.2%) vs 5/40 (12.5%), p<0.05). In the ICI-H group, *HLA-Cw12 (*4/5 (80%) vs 6/40 (15%), p<0.05) *and HLA-DR15* (4/5 (80%) vs 10/40 (25%), p<0.05) were found more frequently than in the control group.[84] Moreover, in the study described above by Akturk et al, *HLA-DR*15* was associated with an increased risk of developing ICI-H (p=0.03).[81]

Although the course of ICI-H is similar to autoimmune (lymphocytic) hypophysitis in the general population, an association between *HLA-Cw12* and *HLA-DR15* and sporadic lymphocytic hypophysitis has not been reported. Instead, *HLA-DQ8* and *HLA-DR53* have been linked to the occurrence of sporadic lymphocytic hypophysitis in the Caucasian population.[85,86] This may indicate that the pathogenesis of ICI-H differs from that of sporadic lymphocytic hypophysitis or it may be due to population differences in *HLA* distribution.

Inaba et al found that *HLA-DPB1*09:01* (5/16, 31,25% vs 8.59%, p=0.017), *HLA-DQA1*01:03* (7/16, 43,75% vs 17.26%, p=0.022) and *HLA-DQB1*06:01* (7/16, 43,75% vs 17.26% p=0.022) alleles occurred more frequently in Japanese patients with ICI-IAD than in Japanese healthy controls.[87] Yano et al also observed a higher prevalence of *HLA-DR15* (81.8% vs 33.5%, p=0.0014) and *HLA-Cw12* (70% vs 21.3%, p=0.0013), as well as *HLA-B52* (63.6% vs 21.0%, p=0.0026) in Japanese patients with pituitary irAE compared to Japanese healthy controls.[88] However, it should be noted that both the study by Inaba et al and the study by Yano et al included small cohorts of patients and did not compare participants with ICI-IAD to patients treated with ICIs who did not develop ICI-IAD.[87,88] These limitations of the described studies should not be overlooked, as certain *HLA* alleles have been found more frequently in neoplasia, as demonstrated in Japanese melanoma patients.[89]

Quandt et al performed a retrospective case-control study among Caucasian and European American cancer patients with melanoma and other malignancies who developed ICI-H while receiving anti-PD-1 or anti-PD-L1 monotherapy, CTLA-4 inhibitor monotherapy or with PD-1 inhibitors at the UCSF. *HLA* genotyping was performed using Single Molecule, Real-Time sequencing with 4X depth and three-field resolution by Histogenetics. A control group consisted of 67 participants, including UCSF patients previously treated with ICIs who did not develop ICI-H and healthy controls. There was a significant correlation between *HLA-DQ*06:02* and ICI-H, as this allele was found in 13 of 30 (43.3%) patients, whereas in the control group, it was present in 12 of 67 (17.9%) participants (p<0.05). On the other hand, the prevalence of alleles reported in studies of the Japanese population as linked with ICI-H, (*HLA-Cw12* and *HLA-DR15*), was not increased in this study. This may be due to the higher distribution of these alleles in the Japanese population compared to the Caucasian population. However, it should be noted that in the study by Quandt et al, the control group was heterogeneous, containing both patients previously treated with ICIs and healthy participants, which could have affected the results.[90] Furthermore, the study by Quandt et al,[90] as well as the above-described Japanese studies,[84,87,88] were conducted using a small cohort of patients. Although the link between certain *HLA* alleles and pituitary irAEs is of interest and may in the future become an important factor in identifying at-risk groups. Studies conducted thus far do not provide clear and conclusive results. Future research should consider larger cohorts of participants, differentiate between cancer types and ICIs regimens, and include a control group of patients treated with ICIs but without pituitary irAEs.

HLA and ICIs-Associated Uveitis

ICIs-associated uveitis (ICIU) is one of the irAEs affecting the eyes, occurring in approximately 0.3–1% of patients treated with ICIs.[91] Vogt–Koyanagi–Harada disease (VKH) is an autoimmune syndrome affecting melanin-pigmented tissues. VKH-like uveitis is characterized by choroidal thickening and serous subretinal fluid; other symptoms of VKH may include hearing loss, poliosis, and vitiligo.[92] A retrospective case–control study was conducted at Yokohama City University Hospital, in which 9 Japanese patients who developed ICIU, of whom 5 had VKH-like uveitis, underwent high-resolution *HLA* genotyping. Importantly, 2 patients had a history of VKH prior to treatment initiation. Frequencies of *HLA-C*01, HLA-DRB1*04:05*, and *HLA-DQB1*04:01* were significantly increased in patients with VKH-like ICIU compared to the healthy Japanese population (p=0.029). All these alleles were negative in patients with non–VKH–like uveitis.[93] *HLA-DRB1*04:05* has been reported in other cases of VKH-like ICIU, as described in several Japanese and one French case reports.[94–98] However, *HLA-DRB1*04:05* is present in almost all Japanese patients suffering from VKH disease.[99] Thus, given the similar prevalence of *HLA-DRB1*04:05* in VKH and VKH-like ICIU, it may be hypothesized that these syndromes share a similar pathogenesis. Furthermore, it should be noted that *HLA-DRB1*04:05* may

potentially be used in the differential diagnosis of VKH-like ICIU, as it occurs in almost all VKH cases. Nevertheless, a serious limitation of the study by Takeuchi et al is the small sample size and the comparison to a healthy population rather than to a population undergoing ICIs treatment without irAEs.[93]

HLA and Gastrointestinal irAEs

Ali et al performed high-resolution *HLA* typing (*HLA I class A, B, C and HLA class II DRB1, DPB1* and *DQB1*) at a four-digit level in 102 Swiss patients suffering from NSCLC (n=66) or metastatic melanoma (n=36) and treated with ICIs. *HLA* genotyping was performed using NGS (ProImmune Ltd., Oxford, UK, and Histogenetics LLC, New York, USA). A total of 92 patients (90%) received treatment with anti-PD-1 agents (nivolumab or pembrolizumab) or anti-PD-L1 antibody (atezolizumab) alone. Six patients (6%) underwent dual therapy with anti-CTLA-4 (ipilimumab) and anti-PD-1 (nivolumab) agents, while four patients (4%) were treated exclusively with anti-CTLA-4 (ipilimumab) antibody. A significant link between *HLA-DRB1*11:01* and pruritus (p=0.002) was found. Furthermore, there was a correlation between *HLA-DQB1*03:01* and colitis (p=0.017).[100] Interestingly, HLA-*DRB1*11:01* has previously been linked to pruritus in the general population,[101] whereas *HLA-DQB1*03:01* is associated with a significantly increased risk of inflammatory bowel diseases in healthy individuals.[102] Furthermore, Ali et al found that *HLA-DRB1*11:01* allele always co-occurred with the *HLA-DQB1*03:01* allele, whereas *HLA-DQB1*03:01* could also occur with other *HLA-DRB1* variants. Therefore, *HLA-DRB1*11:01* carriers treated with ICIs are not only susceptible to pruritus but also to colitis, effectively making them a high-risk group in terms of irAEs.[100]

A study by Purde et al was conducted at the Kantonsspital St. Gallen, Switzerland, with the participation of 131 patients with metastatic NSCLC (n=91) and melanoma (n=40), treated with ICIs (anti-PD-1, anti-PD-L1, anti-CTLA-4, or combination treatment). All patients underwent *HLA* genotyping at *HLA class I* (*A, B, C*) and *HLA class II* (*DPB1, DQB1*, and *DRB1*) *loci* at six-digit resolution (4×High Resolution Typing, HistoGenetics, Ossining, NY). Among the participants, 11 (8.4%) were diagnosed with ICIs-induced hepatitis. In patients with NSCLC, *HLA-DRB1*04:01* (p=0.037) and the haplotype *DRB1*15:01–DQB1*06:02* (p=0.04) were linked with hepatitis, as compared to the control group (n=44) composed of NSCLC patients without ICIs-induced hepatitis. Importantly, the statistical significance of this correlation was not detected when the group composed of both NSCLC and melanoma patients was analyzed.[103] This may be caused by the differences in irAEs in NSCLC and melanoma, as it has been reported before that incidence and course of irAEs are unalike in different types of cancer.[104] The small cohort of patients is also a limitation of this study. Further studies with larger and more homogeneous cohorts are needed.[103]

Other Specific HLA Alleles and Increasing irAEs Risk

Sung et al performed a multicenter prospective cohort study among adult Korean cancer patients. A total of 672 participants with 24 different cancer types, including NSCLC (38.2%), were recruited for the study. Patients were treated with anti-PD-1 or anti-PD-L1 antibodies (85.3%), anti-PD-1 and anti-CTLA-4 combined treatment (2.2%), anti-PD-1 or anti-PD-L1 antibodies combined with chemotherapy (9.7%), anti-PD-1 or anti-PD-L1 therapy with targeted treatment (1.8%), and anti-PD-1 or anti-PD-L1 agents with chemotherapy and targeted therapy (1.8%). Among these patients, 372 developed irAEs and were included in the irAEs cohort, whereas the remaining 300 patients formed the non–irAEs cohort. Genotyping of class I *(HLA-A, HLA-B, and HLA-C)* and class II (*HLA-DRB1, HLA-DQB1*, and *HLA-DPB1*) alleles at the four-digit level was performed using HLA-HD (v1.3.0) with NGS method. It was found that *HLA-B35:01* increased the risk of all irAEs ($p<0.05$), except for skin and neurological toxicities. *HLA-B35:01* was associated with higher risk of all irAEs, especially with multiple (≥3), grade 2 or higher irAEs in one patient (p=0.0006) or with life-threatening irAEs (p=0.0002).[50] This may correspond to the study described above by Correale et al, who linked *HLA-B*35* alleles with pneumonitis.[52] Furthermore, *HLA-B*40:02* also significantly increased the risk of any irAEs (p=0.0099). In contrast, *HLA-B*54:01* was associated with a lower risk of developing irAEs (p=0.024). Nevertheless, it should be emphasized that this study had several limitations, such as a diverse cancer group, various treatment regimens, and restriction to the Korean population.[50]

It is also worth noting that in the aforementioned study by Abed et al, the *HLA-A*03* allele group was found to significantly increase the risk of any irAE (p=0.039).[39]

Jiang et al reported a link between certain *HLA* alleles and several irAEs. This retrospective study included 530 Chinese cancer patients treated in the Cancer Hospital of the Chinese Academy of Medical Sciences. Patients had various neoplasms and received anti-PD-1 or anti-PD-L1 antibodies as monotherapy (n=248) or in combination with bevacizumab or TKIs and/or chemotherapies (n=266), or with anti-CTLA-A or anti-LAG-3 antibodies (n=16). *HLA* genes were typed at the four-digit level using the HLA-HD (v1.4.0) typing tool utilizing NGS technique. The study group included patients who developed irAEs (n=413) Three control groups were formed: patients from this study who did not develop irAEs (n=117), the Novegene control cohort (n=154) with multiple cancer types, and the Han-MHC reference cohort, which includes 10,689 healthy individuals of Han Chinese ancestry. Jiang et al reported significant correlations between *HLA-DRB3*01:01* and thrombocytopenia; between *HLA-DPB1*04:02* and hypokalemia/hyponatremia, leukopenia, and anemia; and between *HLA-A*26:01* and bilirubin elevation, when compared to the Novegene control cohort and the Han-MHC reference cohort. However, these associations were not significant when compared to patients who did not develop irAEs after false discovery rate correction.[105] Furthermore, the analysis included patients who received ICIs in combination with chemotherapy, which is more likely to cause hematological toxicities than immunotherapy. For example, neutropenia occurred in 31% of patients who received docetaxel versus 1% of patients treated with nivolumab for advanced non-squamous NSCLC (Figure 2).[106,107]

The state-of-the-art knowledge on this subject is summarized in Table 2.

Figure 2 Proposed applications of *HLA* genotyping in diagnosis and management of irAEs.
Notes: irAEs – immune-related adverse events; GCs – glucocorticoids; ICIs – immune checkpoints inhibitors; CTLA-4 – cytotoxic T lymphocyte-associated antigen-4; SE – shared epitope; VKH – Vogt–Koyanagi–Harada disease; ICIU – immune checkpoint inhibitor-associated uveitis; *HLA* alleles were designated according to the World Health Organization HLA Nomenclature.

Table 2 Genetic Factors Associated with *HLA* Increasing the Risk of irAEs in ICIs Treated Cancer Patients

Genetic Factor	Study Group	Treatment	Previous Treatment	Population	IrAE Significantly More Likely to Occur	Notes	Reference
*HLA-B*35*	Patients with NSCLC, melanoma, head and neck cancer, RCC, urothelial cancer, gastro-enteric cancer, and breast cancer, n=180	Pembrolizumab, nivolumab, or atezolizumab	Chemotherapy, metronomic chemotherapy with or without bevacizumab, erlotinib, palliative radiotherapy	Italian	Pneumonitis, p=0.06	Compared to patients without this allele	[52]
*HLA-DRB1*11*					Pneumonitis, p=0.03	Compared to patients without this allele	
*HLA-B*27*	Patients with lung cancer (n=28), melanoma (n=23), breast cancer (n=13), pancreatic cancer (n=13), gynecological cancers (n=8), and others (n=32), n=117	Anti-PD-1 or anti-PD-L1 (n=66); Anti-PD-1 or anti-PD-L1 + anti-CTLA-4 (n=32); Anti-PD-1 or anti-PD-L1 + anti-CTLA-4 + chemotherapy (n=12); Anti-CTLA-4 (n=2); Anti-NKG2A (n=2); Anti-PD-1 or anti-PD-L1 + anti-IDO-1 inhibitors (n=10); Other single-agent ICIs (n=2); Anti-PD-1 or anti-PD-L1 + OX-40 agonists (n=3)	None	Canadian	Grade 3 irAEs, p=0.007	Compared to patients without this allele	[58]
*HLA-B*27:05*	Patients with bladder cancer (n=3) or breast cancer (n=2) who developed ICIs-induced encephalitis, n=5	Atezolizumab (n=2); Atezolizumab+ cobimetinib (n=2); Atezolizumab+ fulvestrant + ipatasertib (n=1)	Chemotherapy in 4/5 participants	Korean	Encephalitis, p<0.001	Compared to general Korean population n=485	[59]
SE alleles (as defined in text)	Patients with melanoma (n=9), NSCLC (n=6), other cancers (n=12) who developed ICIs-induced arthritis, n=27	Anti-PD-1 + anti-CTLA-4 (n=9), and anti-PD-1 or anti-PD-L1 ± other investigational drugs	No data	Caucasians (n=26) and African American (n=1)	ICIs-induced inflammatory arthritis, p=0.04	Compared to healthy Caucasian controls n=726	[66]
*HLA-DRB1*04:05*					ICIs-induced inflammatory arthritis, p=0.04	Compared to healthy Caucasian controls n=726	
*HLA-DRB1*04:01*	Patients with advanced NSCLC, n=156	Single-agent ICIs (pembrolizumab, atezolizumab, or nivolumab)	Majority of patients previously received chemotherapy and/or radiotherapy (n=111, 71,1%)	Australian	Any-grade irAEs, p=0.011	Compared to patients without this allele	[39]

(*Continued*)

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Table 2 (Continued).

Genetic Factor	Study Group	Treatment	Previous Treatment	Population	IrAE Significantly More Likely to Occur	Notes	Reference
*HLA-DRB1*04*	Patients with melanoma (n=14) and other cancers (n=9) who developed ICIs-induced T1DM, n=23	Anti-PD-1 or anti-PD-L1; Anti-PD-1 + anti-CTLA-4	No data	Caucasian	ICIs-induced T1DM, p<0.0001	Compared to healthy US Caucasians	[80]
					ICIs-induced T1DM, p=0.002	Compared to patients with spontaneous T1DM (US Caucasians and Asians)	
*HLA-DRB1*04*	Patients with advanced melanoma, n=132	Anti-PD-1; anti-CTLA–4; Anti-PD-1 + anti-CTLA-4	No data	US population	ICI-induced T1DM, p=0.01	Compared to patients carrying *HLA-DRB1*04* but without ICIs-induced T1DM	[81]
*HLA-DRB1*08*					Hypothyroidism, p=0.003	Compared to patients carrying *HLA-DRB1*08* but without ICIs-induced hypothyroidism	
*HLA-DR*15*					ICI-H, p=0.03	Compared to patients carrying *HLA-DR*15* but without ICI-H	
*HLA-DPA1*02:02*	Patients with NSCLC (n=4), SCLC (n=1), melanoma (n=2), who developed ICIs-induced T1DM, n=7	Pembrolizumab (n=4), nivolumab (n=1), durvalumab (n=1), nivolumab + ipilimumab (n=1)	No data	Japanese	ICIs-induced T1DM, p=0.022	Compared to patients without any irAEs (n=13)	[82]
					ICIs-induced T1DM, p=0.021	Compared to healthy Japanese population	
*HLA-DPB1*05:01*					ICIs-induced T1DM, p=0.0027	Compared to patients without any irAEs (n=13)	
					ICIs-induced T1DM, p=0.0075	Compared to the healthy Japanese population	
*HLA-DPA1*02:02–DPB1*05:01* haplotype					ICIs-induced T1DM, p=0.0093	Compared to patients without any irAEs (n=13)	
*HLA-DRB1*04:05*					ICIs-induced T1DM, p=0.045	Compared to the healthy Japanese population	

(*Continued*)

Table 2 (Continued).

Genetic Factor	Study Group	Treatment	Previous Treatment	Population	IrAE Significantly More Likely to Occur	Notes	Reference
HLA-Cw12; HLA-DR15; HLA-DQ7; HLA-DPw9	Patients with melanoma (n=9), NSCLC (n=5), RCC (n=2), head and neck cancer (n=1) who developed ICI-IAD, n=13	Anti-PD-1 (n=13); Anti-CTLA-4 (n=3); Anti-PD1 + anti-CTLA-4 (n=1)	No data	Japanese	ICI-IAD, p<0.05	Compared to control group matched for malignancy type and ICIs treatment without pituitary irAEs (n=40)	[84]
HLA-Cw12; HLA-DR15	Patients with melanoma (n=4), RCC (n=1) who developed ICI-H, n=5	Anti-CTLA-4 (n=3); Anti-PD-1 + anti-CTLA-4 (n=2)	No data	Japanese	ICI-H, p<0.05	Compared to control group matched for malignancy type and ICIs treatment without pituitary irAEs (n=40)	
*HLA-DPB1*09:01*	Patients with lung cancer (n=3), melanoma (n=2), others cancers (n=3) who developed ICI-IAD, n=8	Anti-PD-1 (n=8)	No data	Japanese	ICI-IAD, p=0.017	Compared to healthy Japanese controls	[87]
*HLA-DQA1*01:03*					ICI-IAD, p=0.022	Compared to healthy Japanese controls	
*HLA-DQB1*06:01*					ICI-IAD, p=0.022	Compared to healthy Japanese controls	
HLA-Cw12	Patients with melanoma (n=7), NSCLC (n=3), gastric cancer (n=1) who developed ICI-IAD, n=11	Anti-PD-1 (n=6); Anti-PD-1+anti-CTLA-4 (n=5)	No data	Japanese	ICI-IAD, p=0.0013	Compared to healthy Japanese controls	[88]
HLA-DR15					ICI-IAD, p=0.0014	Compared to healthy Japanese controls	
HLA-B52					ICI-IAD, p=0.0026	Compared to healthy Japanese controls	
*HLA-DQ*06:02*	Patients with melanoma (n=19) and other malignancies (n=30), n=49	Anti-PD-1 or anti-PD-L1 monotherapy; Anti-CTLA-4; Anti-PD-1+anti-CTLA-4	No data	Caucasian and European Americans	ICI-H, p<0.05	Compared to heterogenous control group consisting of patients treated with ICIs who did not develop ICI-H and healthy controls (n=67)	[90]

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Table 2 (Continued).

Genetic Factor	Study Group	Treatment	Previous Treatment	Population	IrAE Significantly More Likely to Occur	Notes	Reference
*HLA-C*01; HLA-DRB1*04:05; HLA-DQB1*04:01*	Patients with melanoma (n=5), SCLC (n=2), RCC (n=1), gastric cancer +RCC (n=1) who developed VKH-like ICIU (n=5) or other ICIU (n=4), n=9	Anti-PD-1 or anti-PD-L1 (n=8); Anti-PD-1 + ant-CTLA-4 (n=1)	No data	Japanese	VKH-like ICIU p=0.029	Compared to healthy Japanese controls	[93]
*HLA-DRB1*11:01*	Patients with NSCLC (n=66) and metastatic melanoma (n=36), n=102	Anti-PD-1 or anti-PD-L1 (n=92); Anti-PD-1 + anti-CTLA-4 (n=6); Anti-CTLA-4 (n=4)	No data	Swiss	Pruritus p=0.002	Compared to participants without this allele	[100]
*HLA-DQB1*03:01*					Colitis p=0.017	Compared to participants without this allele	
*HLA-DRB1*04:01*	Patients with metastatic NSCLC who developed hepatitis, n=6	Anti-PD-1 or anti-PD-L1; Anti-CTLA-4; Anti-PD-1 + anti-CTLA-4	No data	Swiss	Hepatitis, p=0.037	Compared to patients without hepatitis (n=44)	[103]
*DRB1*15:01–DQB1*06:02* haplotype					Hepatitis, p=0.04	Compared to patients without hepatitis (n=44)	
HLA-B35:01	Patients with various cancers who developed irAEs, n=372	Anti-PD-1 or anti-PD-L1; Anti-PD-1 + anti-CTLA-4; Anti-PD-1 or anti-PD-L1 + chemotherapy; Anti-PD-1 or anti-PD-L1 + targeted treatment; Anti-PD-1 or anti-PD-L1 + chemotherapy + targeted therapy	No data	Korean	Any irAEs except for skin and neurological toxicities, p<0.05	Compared to patients without irAEs (n=300)	[50]
					Multiple (≥3) grade 2 or higher irAEs in one patient, p=0.0006		
					Life-threatening irAEs, p=0.0002		
*HLA-B*40:02*					Any irAEs, p=0.0099	Compared to patients without irAEs (n=300)	
*HLA-DRB3*01:01*	Patients with digestive organs cancers, NSCLC and SCLC and other cancers who developed irAEs, n=413	Anti-PD-1 or anti-PD-L1 (n=248); Anti-PD-1 or anti-PD-L1 + bevacizumab and/or TKIs and/or chemotherapy (n=266); Anti-PD-1 or anti-PD-L1 + anti-CTLA-4 or anti-LAG -3 (n=16)	No data	Chinese	Thrombocytopenia, p=0.027	Compared to 10,689 healthy Han Chinese population (n=10,689)	[105]

(*Continued*)

Table 2 (Continued).

Genetic Factor	Study Group	Treatment	Previous Treatment	Population	IrAE Significantly More Likely to Occur	Notes	Reference
*HLA-A*26:01*					Bilirubin elevation, p=0.045	Compared to 10,689 healthy Han Chinese population (n=10,689)	
*HLA-DPB1*04:02*					Hypokalemia/ hyponatremia, p=0.001	Compared to Novegene control cohort with multiple cancer types (n=154)	
					Hypokalemia/ hyponatremia, p=0.019	Compared to 10,689 healthy Han Chinese population (n=10,689)	
					Leukopenia, p=0.002	Compared to Novegene control cohort with multiple cancer types (n=154)	
					Leukopenia, p=0.021	Compared to 10,689 healthy Han Chinese population (n=10,689)	
					Anemia, p=0.001	Compared to Novegene control cohort with multiple cancer types (n=154)	
					Anemia, p=0.017	Compared to 10,689 healthy Han Chinese population (n=10,689)	

Abbreviations: irAEs, immune-related adverse events; ICIs, immune checkpoints inhibitors; NSCLC, non-small cell lung carcinoma; RCC, renal cell carcinoma; PD-1, programmed cell death protein 1; sPD-L1, programmed death ligand 1; CTLA-4, cytotoxic T lymphocyte-associated antigen-4; T1DM, type 1 diabetes mellitus; ICI-IAD, immune checkpoint inhibitor-induced isolated adrenocorticotropic hormone deficiency; ICI-H, immune checkpoint inhibitor-induced hypophysitis; SCLC, small cell lung cancer; ICIU, immune checkpoint inhibitor-associated uveitis; VKH, Vogt, Koyanagi–Harada disease; HLA, alleles were designated according to the World Health Organization HLA Nomenclature.

Conclusions

Based on the available research, our review illustrates a direct association between certain HLA alleles and the prevalence of irAEs. For instance, *HLA-B*35* and *HLA-DRB1*11* have been reported to increase the risk of pneumonitis in patients treated with PD-1/PD-L1 inhibitors. Conversely, *HLA* class I homozygosity at one or more loci appears to confer a protective effect against the development of irAEs.

Nevertheless, studies conducted so far have used small patient cohorts, often including patients with various cancers and receiving different treatments regiments. Furthermore, in several studies, the control group consisted of healthy individuals. This may compromise the results, as some *HLA* alleles have been shown to be associated with an increased risk of malignancies. Therefore, the observed increase in certain *HLA* alleles among patients with irAEs might be more

closely related to the underlying malignancy than to the toxicity induced by ICIs. Importantly, different classes of ICIs tend to cause specific irAEs, therefore, study cohorts should ideally consist solely of patients receiving a single type of ICIs. Moreover, given that the prevalence of *HLA* alleles differs among populations, future research should take this into account, and patient' cohorts should include participants of similar ethnicity. Interestingly, irAEs have been linked to better responses to ICIs. Consequently, the association between *HLA* genotypes and progression-free survival (PFS) as well as overall survival (OS) should also be investigated.

The potential of *HLA* genotyping in cancer immunotherapy should not be overlooked. *HLA* could potentially be used to identify groups at risk of developing irAEs, thereby enabling more intensive screening in those patients. HLA genotyping could also be useful in qualifying patients for ICIs rechallenge, allowing for risk stratification of irAEs before reintroducing ICIs. Furthermore, identifying biomarkers that correlate with irAEs could lead to a better understanding of the mechanisms underlying these effects. For example, when an irAE has been linked with an *HLA* allele that has been previously associated with the corresponding autoimmune disease, it may be suspected that the pathogenesis of these conditions is similar. Conversely, identifying patients with *HLA* allele associated with a decreased risk of irAEs could potentially allow for longer intervals between clinical and laboratory assessments. Given that ICIs treatment is often administered long-term, this could significantly reduce costs and the burden on patients associated with frequent hospital visits.

In conclusion, the described link between *HLA* variants and irAEs has the potential to become a useful tool in clinical practice, enabling individual risk stratification prior to cancer immunotherapy. Its implementation may ultimately improve patient selection for ICIs treatment and the management of irAEs, thereby significantly enhancing safety and reducing the costs of cancer immunotherapy. This approach aligns with the current era of personalized oncology, which focuses on optimizing cancer therapy in terms of both efficiency and patient-specific risk. Therefore, future research investigating the role of *HLA class I* and *II* genotypes in the development of irAEs, as well as their impact on survival and response rates in cancer patients treated with ICIs, is warranted.

Abbreviations

ACPA, Anti-Citrullinated Protein Antibodies; APC, Antigen Presenting Cell; AS, Ankylosing Spondylitis; CTCAE, Common Terminology Criteria for Adverse Events; CTLA-4, Cytotoxic T Lymphocyte-Associated Antigen-4; CXCL12, C-X-C Motif Chemokine Ligand 12; CXCR4, CXC Receptor 4; EMA, European Medicines Agency; FDA, Food and Drug Administration; GvHD, Graft-Versus-Host Disease; HLA, Human Leukocyte Antigen; ICI-H, Immune Checkpoint Inhibitor-Induced Hypophysitis; ICI-IAD, Immune Checkpoint Inhibitor-Induced Isolated Adrenocorticotropic Hormone Deficiency; ICIs, Immune Checkpoint Inhibitors; ICIU, Immune Checkpoint Inhibitor-Associated Uveitis; irAEs, Immune-Related Adverse Events; MHC, Major Histocompatibility Complex; MS, Multiple Sclerosis; NCCN, National Comprehensive Cancer Network; NCI, National Cancer Institute; NGS, Next-Generation Sequencing; NSCLC, Non-Small Cell Lung Carcinoma; OS, Overall Survival; PD-1, Programmed Cell Death Protein 1; PD-L1, Programmed Death Ligand 1; PD-L2, Programmed Death Ligand 2; PFS, Progression-Free Survival; RA, Rheumatoid Arthritis; RCC, Renal Cell Carcinoma; RF, Rheumatoid Factor; SCLC, Small Cell Lung Cancer; SE, Shared Epitope; SNPs, Single Nucleotide Polymorphisms; SSO, Sequence-Specific Oligonucleotide; T1DM, Type 1 Diabetes Mellitus; Treg, Regulatory T Cells; UCSF, University of California, San Francisco; VKH, Vogt–Koyanagi–Harada Disease.

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