Review – The impact of pharmacogenetics on the outcome of immune checkpoint inhibitors

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ABSTRACT

The development of immune checkpoint inhibitors (ICIs) has a tremendous effect on the treatment options for multiple types of cancer. Nonetheless, there is a large interpatient variability in response, survival, and the development of immune-related adverse events (irAEs). Pharmacogenetics is the general term for germline genetic variations, which may cause the observed interindividual differences in response or toxicity to treatment. These genetic variations can either be single-nucleotide polymorphisms (SNPs) or structural variants, such as gene deletions, amplifications or rearrangements. For ICIs, pharmacogenetic variation in the human leukocyte antigen molecules has also been studied with regard to treatment outcome. This review presents a summary of the literature regarding the pharmacogenetics of ICI treatment, discusses the most important known genetic variations and offers recommendations on the application of pharmacogenetics for ICI treatment.

Introduction

The successful uptake of immune checkpoint inhibitors (ICIs) for cancer treatment is illustrated by the increasing number of tumour types and treatment settings for which these treatments have proven efficacy [1–4]. To date, ICIs are standard of care for multiple types of cancer and are used in different treatment settings, i.e., palliative, adjuvant and neoadjuvant [1,5–6]. Although ICIs can induce a remarkable durable tumour response, only a subset of patients experience clinical benefit from treatment with ICIs [7]. Moreover, the anti-inhibitory effects on the patients' immune system can result in immune-related adverse events (irAEs), which can be severe and may require life-long treatment, such as levothyroxine for autoimmune hypothyroidism [8–10]. There are large differences in onset and severity of irAEs [11] and it remains challenging to predict which patients will benefit from ICI treatment and which patients will suffer from severe adverse events [7,12–13].

Many studies have focused on identifying predictive biomarkers for ICI treatment [7,14–18], and part of this research is dedicated to identifying pharmacogenetic markers [19–21]. *Pharmacogenetics* is the general term for germline variations that may be responsible for the observed interindividual differences in response or toxicity to drug treatment [22]. These genetic variations can either be single-nucleotide polymorphisms (SNPs) or structural variants, such as gene deletions, amplifications or rearrangements. Usually these variations are sought in drug metabolising enzymes, drug transporters or within the respective pharmacodynamics pathway, where they can influence the functionality of proteins. The field of pharmacogenetics has been subject to research for many types of drugs and is nowadays used in clinical practice to prevent toxicity of chemotherapy and targeted treatment [20–21].

For ICI treatment specifically, genetic variation is studied within ICI-targeted receptors, pathways related to autoimmunity and variations within the human leukocyte antigen (HLA). Germline variations which have been studied for response or irAEs of ICI treatment will therefore be discussed in the three main subgroups, i.e., single-nucleotide polymorphisms (SNPs) within the ICI targeted axis, SNPs related to autoimmunity and finally, structural variations in the HLA molecules. Somatic genetic variations (of the tumour) are outside the scope of this review. This review comprises an overview of the current literature on pharmacogenetics and outcome after treatment with ICIs. Studies were evaluated for quality based on the number of patients included, statistical considerations (e.g., uni- vs multivariable testing, application of Bonferroni correction), and (prospective) validation of results. In case a

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Bonferroni correction was applied, this has been explicitly stated.

Search strategy and selection criteria

PubMed was searched for studies regarding pharmacogenetics and selected ICIs, i.e. antibodies targeted against programmed cell death 1 (PD-1), programmed cell death ligand 1 (PD-L1) or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). To prevent the search term from becoming too narrow, the term *pharmacogenetics* has been entered in the search term in several ways, e.g., pharmacogenomics, genetic polymorphisms, HLA antigens, SNPs etc. The definitive search term can be found in Supplementary File 1.

This search was conducted until November 15th, 2023. A total of 786 articles was found. The following exclusion criteria were applied to limit this selection: non-English language, non-human studies, reviews, case reports, studies not related to solid tumours, and studies not covering the selected ICIs. The remaining articles were screened by means of title and abstract for possible relevance, resulting in a selection of 133 articles, which were full-text reviewed by KJ, NH and EB. Finally, 69 articles were included.

Single-nucleotide polymorphisms

Single-nucleotide polymorphisms (SNPs) are germline variations in the DNA occurring in ≥ 1 % of the population [23]. This review highlights only the most studied SNPs and those SNPs considered the most relevant. The discussed SNPs were either the subject of a multitude of studies or had a positive, clinically relevant outcome in one or more high quality studies and could therefore be considered as a potential biomarker.

Several genome wide association studies (GWAS) have been performed in order to generate clusters of SNPs, which could be relevant for ICI outcome [24–25]. For instance, in a case-control cohort of 89 ICI-treated patients with melanoma, a GWAS identified 30 SNPs which were significantly associated with the occurrence of irAEs [25]. Several of these SNPs were located in genes associated with auto-inflammatory diseases, such as *SEMA5A* for rheumatoid arthritis [25]. Another recent GWAS performed in a large pan-cancer cohort consisting of 1,751 patients treated with ICIs, identified a SNP located on an *IL7* intron (rs16906115) [24]. This SNP was significantly associated with the occurrence of all grade irAEs (hazard ratio (HR): 2.1; p-value < 3.5x10E-8). In addition, this association could independently be replicated in three prospective validation cohorts (comprising 265, 2,275 and 433 patients, respectively) [24]. Finally, this finding was reproduced in a parallel study in 214 ICI-treated patients with melanoma, that also found increased pre-treatment B cell *IL7* expression in risk allele carriers [26]. Whereas GWAS offer a great tool for generating biomarker-based hypotheses, they also require large groups of patients and hence have difficulty validating results in other cohorts. Therefore, prospective validation is often missing. Exceptional in that respect is the latter GWAS, that advocates the incorporation of rs16906115 in future research, while also exemplifing the value of a valid study design for identifying and validating SNPs using GWAS.

Another method to identify potential SNPs is by studying genes related to the pathophysiological mechanisms that underlie ICI treatment. A global overview of several key elements within ICI treatment and their respective genes is illustrated in Fig. 1.

SNPs within the PD-1 pathway

In current literature, SNPs in *PDCD1* (encoding PD-1) and *CD274* (encoding PD-L1) have been studied most frequently. Several candidate SNPs in *PDCD1* have been investigated thoroughly. Supplementary Table 1 provides a complete overview of the investigated SNPs in relation with anti-PD1/PDL1 treatment and this is summarised in Table 1. For *PDCD1*, the SNPs 804C>T (rs2227981), 889G>A (rs10204525) and 7146A>G (rs11568821) will be discussed. Although none of these SNPs is currently deemed suitable for application in routine clinical care, these three SNPs offer the most promising results for *PDCD1*. The first one, 804C>T (rs2227981), located within the promotor region of *PDCD1*, is considered to affect gene transcription and thereby influencing the PD-1 receptor expression on T cells. In a cohort studying 119 patients with melanoma who were treated with anti-PD-1 by de With et al., T allele carriers had a shorter overall survival (OS) than wild types (3-year OS: 71 % versus (vs.) 51.8 %; p = 0.026) [27]. However, this result could not be confirmed in cohorts of patients with non-small cell lung cancer (NSCLC) [28–30] or renal cell carcinoma (RCC) [31–32]. Parakh et al., also investigating the 804C>T SNP in 115 patients with metastatic melanoma, was unable to reproduce the association with OS as well [33]. Nonetheless, a trend was seen towards shorter progression free survival (PFS) in homozygous variant carriers (TT genotype) (CC vs. CT vs. TT: 8.1 vs. 16 vs. 2.1 months), although non-significant [33]. A possible explanation for the discrepancy between the studies of de With et al., and Parakh et al., might be that even though both studies included a similar number of patients, the percentage of homozygous variant carriers differed greatly (24 vs. 6 %, respectively) [27,33]. Interestingly, there is substantial evidence that variant carriers have lower expression of PD-1 in CD4 + T cells [27,34]. Considering the location of 804C>T within the promotor region of *PDCD1*, it seems plausible that this SNP alters *PDCD1* transcription and thus leads to decreased PD-1 expression. Therefore, validation of 804C>T in a larger cohort is necessary to understand its potential relevance as a biomarker, especially in patients with melanoma who are treated with ICI. No association with 804C>T and irAEs has been reported [31–32,35–36]. For another *PDCD1* SNP, 889G>A (rs10204525), wild type patients were found to experience not only more irAEs (OR: 3.7; 95 % confidence interval (CI):[1.6–8.7]; p = 0.002), but also more severe (≥3) irAEs (OR 3.1[1.2–8.1]; p = 0.025) compared to those with a homozygous variant genotype in 106 Japanese patients with RCC [31]. However, these results were retrospective, lacked validation and no correction for multiple testing was applied. In contrast, in Caucasian patients with NSCLC no effect of the 889G>A SNP on anti-PD-1 related toxicity was found, while this SNP was analysed in both an exploration and validation cohort of 161 patients each [35]. It should be taken into account that the variant allele frequency varies greatly between the Japanese and Caucasian population (minor allele frequency: 74 % vs. 7–10 %) [31,35]. Considering this, the reported association of 889G>A with toxicity warrants further prospective research, especially among Asian populations. No relationship between 889G>A and survival has been reported [28,31,37]. Finally, in a cohort of 115 patients with metastatic melanoma, a third *PDCD1* SNP, 7146A>G (rs11568821), was associated with an improved best overall response (BOR) (complete response: 16.5 vs. 2.6 %) and PFS (14.1 vs. 7 months; p = 0.04) [33], making this an interesting target for validation in upcoming prospective studies. The 7146A>G polymorphism is located in an enhancer region of intron 4 of *PDCD1*, which is thought to regulate gene transcription.

SNPs within the PD-L1 receptor gene

For the PD-L1 receptor, several SNPs have been studied in various settings (Supplementary Table 1. **Anti-PD1/PDL1**). Whereas the two most studied SNPs (rs2282055 and rs2890658) were not associated with either toxicity or survival [29–30,32,36–39], two other SNPs might predict response to anti-PD-(L)1 treatment (Table 1). First, in a cohort of 108 patients with NSCLC treated with nivolumab, both rs1411262 and rs822339 were associated with longer PFS (165 vs. 67 days, p = 0.040 and 182 vs. 67 days, p = 0.025, respectively) [36]. Intriguingly, both SNPs were also associated with the occurrence of immune-related hypothyroidism [36] and, after expanding the studied cohort, both SNPs were associated with OS as well [29]. This is consistent with previous data suggesting that patients experiencing irAEs might have better treatment outcomes than those without irAEs [40–41]. After Bonferroni
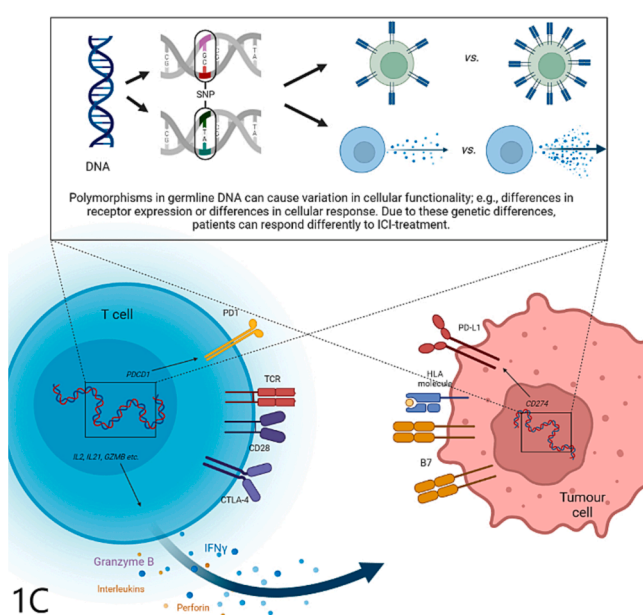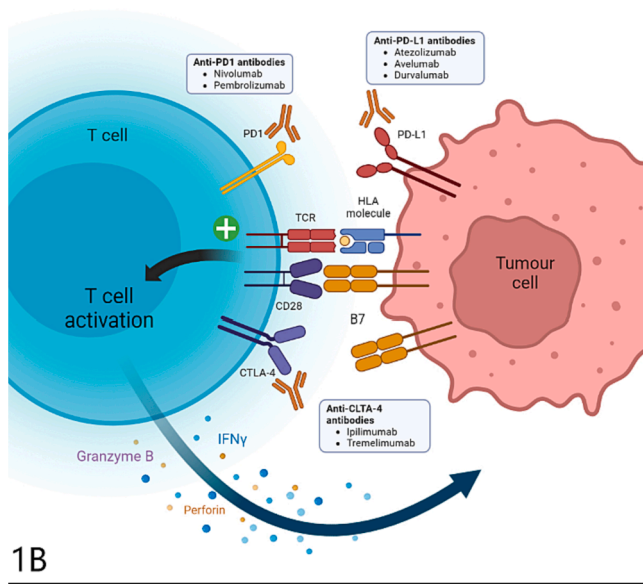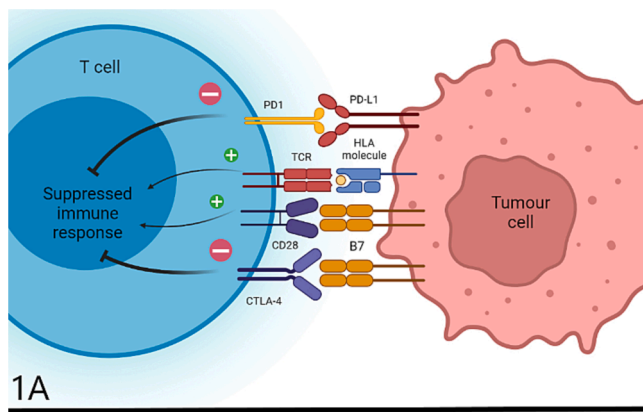
Fig. 1. A) (Anti-tumour) T-cell response is activated by the binding of human leukocyte antigen (HLA) with the T-cell receptor (TCR), together with the binding of B7 to the CD28 receptor. To prevent overactivation of the immune system, PD-L1 and B7 bind PD-1 and CTLA-4 respectively, resulting in immune inhibition. Tumours express both PD-L1 and B7 to stimulate this inhibitory effect. **B)** Anti-PD-(L)1 and anti-CTLA-4 antibodies bind the respective receptors, thereby blocking the inhibitory signals, which results in T-cell activation and consequent immune response (such as release of granzyme B, interferon-γ and perforin). **C)** Polymorphisms in germline DNA (i.e., single-nucleotide polymorphisms) can cause differences in cellular functionality, which may result in different responses to ICI-treatment.

(caption on next column)

correction, only rs822339 remained statistically significant for OS (HR: 0.35 [0.18–0.64]; p < 0.005) [29]. Evidence for the impact of these two SNPs is further supported by a study in 222 Japanese patients with advanced RCC [32], where both SNPs were significantly associated with PFS as well, although no correction for mulitple testing was applied (HRs 0.58 [0.37–0.89] and 0.62 [0.41–0.96] respectively) [32]. In conclusion, both rs822339 and rs1411262 within the *CD274* gene might be promising predictive biomarkers for ICI treatment, although prospective validation is required. Research into another well-studied SNP in *CD274*, rs4143815, has produced conflicting results, with three studies reporting favourable PFS for carriers of the wildtype allele [30,32,39], as opposed to four studies finding no effect [29,36–38]. In our opinion, no clinically relevant effect should be expected of SNP rs4143815, considering the largest study (n = 222) identifying a favourable effect did not apply correction for multiple testing [32], and the other studies were markedly smaller (n = 32 and n = 50, respectively) [30,39].

SNPs within CTLA-4

SNPs of the *CTLA-4* gene have been investigated in several studies, showing interesting outcomes, but still requires prospective validation [42–45]. Most notably, in one study in 152 patients with metastatic melanoma, three SNPs in the *CTLA4* gene, −1661A>G (rs4553808), −658C>T (rs11571317) and 49A>G (rs5742909) were associated with BOR to anti-CTLA-4 treatment (ORs: 3.4 [1.6–7.1], 2.9 [1.2–6.8] and 0.4 [0.2–0.8], respectively) [44]. The −1661A>G SNP was associated with the occurrence of any grade endocrine irAEs (AA vs. AG vs. GG: 3 %,vs. 7 % vs. 34 %; p = 0.008]) in another study, a result that remained significant after Bonferroni correction [42]. Two other studies failed to reproduce these results, but had smaller sample sizes and therefore lacked power [43,45]. In conclusion, these three SNPs provide interesting targets for further validation in future research.

SNPs related with autoimmune disorders

As mentioned previously, the anti-inhibitory effects of ICI treatment on the immune system often leads to irAEs. Some of these irAEs resemble autoimmune diseases, therefore germline variants which are known to predispose for autoimmune diseases might also affect the occurrence of irAEs [8,46]. GWAS and whole exome sequencing (WES) studies have identified SNPs of genes which are associated with the outcome of ICI treatment. Most of these identified SNPs are related to genes known to be aetiologically associated with a wide range of autoimmune diseases [24–25,47–49], suggesting that indeed autoimmune related SNPs may be relevant for irAEs but also for survival outcomes. However, although multiple SNPs were identified within these large association studies, a significant clinical impact could only be replicated in validation cohorts for rs16906115, an *IL7* SNP, two highly linked *FARP1* SNPs – rs685736 and rs643869 – and finally rs4988956, situated within the *IL1RL1* gene [24,32,48]. As stated above, a setback of GWAS and WES studies is the large number of patients needed for an accurate analysis, especially considering a validation cohort is preferred as well. Hence, some studies focus on genes known to be related with autoimmunity by directly

Table 1
The impact of germline polymorphisms on ICI treatment.

Gene	Variant	BOR	PFS	OS	rAEs	No. of patients	References
PDCD1	7146A>G (rs11568821)	GG vs AG CR vs other response rate (16.5 % vs. 2.6 %)	GG longer PFS 0.05 (95 %CI 0.003–0.87; p = 0.040)	NS		115 Australian patients with metastatic melanoma	Parakh et al. [33]
						106 patients with metastatic RCC from Japan	Kobayashi et al. [31]
		No relationship with hyperprogressive disease				Cohort of 98 French patients with various types of cancer	Refae et al. [37]
	804C>T (rs2227981)			HR 2.366(1.111 5.036)		119 patients of Caucasian decent with metastatic melanoma	De With et al. [27]
		NS	NS	NS		322 patients with NSCLC of Caucasian decent	Hurkmans et al. [28]
		NS	NS	NS		115 Australian patients with metastatic melanoma	Parakh et al. [33]
				NS		133 Japanese patients with NSCLC	Yoshida et al. [29]
					NS	111 Japanese patients with NSCLC	Funazo et al. [36]
					NS	322 patients with NSCLC of Caucasian decent	Bins et al. [35]
		NS	NS	NS	NS	106 patients with metastatic RCC from Japan	Kobayashi et al. [31]
		NS				50 patients with NSCLC from Japan	Nomizo et al. [30]
		No relationship with hyperprogressive disease				Cohort of 98 French patients with various types of cancer	Refae et al. [37]
		NS	NS		NS	222 Japanese patients with advanced RCC	Shiota et al. [32]
	889G>A (rs10204525)	NS	NS	NS		322 patients with NSCLC of Caucasian decent	Hurkmans et al. [28]
					NS	322 patients with NSCLC of Caucasian decent	Bins et al. [35]
		NS	NS	NS		115 Australian patients with metastatic melanoma	Parakh et al. [33]
		NS	NS	NS	G allele carriers had more AE (OR: 3.712 (1.591 – 8.658); p = 0.002)	106 patients with metastatic RCC from Japan	Kobayashi et al. [31]
		No relationship with hyperprogressive disease				Cohort of 98 French patients with various types of cancer	Refae et al. [37]
CD274	395G>C (rs4143815)	CR, PR, SD vs PD NS	NS	NS		166 patients with NSCLC treated within Italy	Minari et al. [38]
				NS		133 Japanese patients with NSCLC	Yoshida et al. [29]
					NS	111 Japanese patients with NSCLC	Funazo et al. [36]
		G vs C allele (p = 0.0319)	CC + CG vs GG: 2.6 vs 2.1 m (HR: 0.46 (95 %-CI: 0.22–1.04); p = 0.0438)			50 patients with NSCLC from Japan	Nomizo et al. [30]
			CC + CG vs GG: not reached vs 2.3 m (p = 0.41; n = 20, nivolumab only)			32 Italian patients with NSCLC	Del Re et al. [39]
		No relationship with hyperprogressive disease				Cohort of 98 French patients with various types of cancer	Refae et al. [37]
		NS	GG: HR: 1.69, 95 % CI 1.09–2.59; P = 0.018		NS	222 Japanese patients with advanced RCC	Shiota et al. [32]
	rs1411262 (T>C)		HR 1.65 (p = 0.040)		Low fT4 or liver dysfunction or rash or fever, p = 0.0013	111 Japanese patients with NSCLC	Funazo et al. [36]
			NS	T/T vs C/T or C/C HR 0.40		133 Japanese patients with NSCLC	Yoshida et al. [29]

Table 1 (*continued*)

Gene	Variant	BOR	PFS	OS	rAEs	No. of patients	References
				(0.21–0.70) p = 0.017			
		NS				50 patients with NSCLC from Japan	Nomizo et al. [30]
		NS	TT + TC: HR: 0.58, 95 % CI 0.37–0.89; P = 0.014		NS	222 Japanese patients with advanced RCC	Shiota et al. [32]
	rs822339 (A>G)		HR 1.76 (p = 0.025)		low fT4 or liver dysfunction or rash or fever, p = 0.0204	111 Japanese patients with NSCLC	Funazo et al. [36]
		NS		A/A vs A/G or G/G HR 0.38 (0.19–0.69) p < 0.001		133 Japanese patients with NSCLC	Yoshida et al. [29]
		NS				50 patients with NSCLC from Japan	Nomizo et al. [30]
		NS	GG: HR: 1.59, 95 % CI 1.04–2.45; P = 0.034		NS	222 Japanese patients with advanced RCC	Shiota et al. [32]
CTLA4	−1661A>G (rs4553808)	CR + PR vs SD + PD OR 3.39 (1.62 - 7.10)			NS	152 Caucasian melanoma patients who received CTLA-4 blockade	Breunis et al. [44]
		NS		NS	NS	14 patients from Italy with metastatic melanoma	Queirolo et al. [43]
					irAEs: GG vs AG vs AA: 33.5 % vs 6.5 % vs 2.9 %; p = 0.008; pc = 0.091; OR = 0.07; 95 % CI: 0.01–0.40; p = 0.003, pc = 0.036).	173 Italian patients with metastatic melanoma	Queirolo et al. [42]
	−658C>T (rs11571317)	CR + PR vs SD + PD OR 2.89 (1.23 - 6.83)			NS	152 Caucasian melanoma patients who received CTLA-4 blockade	Breunis et al. [44]
		NS		NS	NS	14 patients from Italy with metastatic melanoma	Queirolo et al. [43]
					NS	173 Italian patients with metastatic melanoma	Queirolo et al. [42]
		NS				65 Caucasian patients with advanced melanoma	Hamid et al. [98]
	49A>G (rs231775)	CR + PR vs SD + PD OR 0.39 (0.18–0.82)			NS	152 Caucasian melanoma patients who received CTLA-4 blockade	Breunis et al. [44]
		NS		NS	NS	14 patients from Italy with metastatic melanoma	Queirolo et al. [43]
					NS	173 Italian patients with metastatic melanoma	Queirolo et al. [42]
		NS				65 Caucasian patients with advanced melanoma	Hamid et al. [98]
FARP1	rs685736	OR, 3.82; 95 % CI 2.17–6.70; P < 0.0001	GA + AA: HR, 1.67; 95 % CI 1.18–2.38; P = 0.0041		NS	222 Japanese patients with advanced RCC	Shiota et al. [32]
	rs643869	OR, 0.23; 95 % CI 0.13–0.41; P < 0.0001	CC: HR, 0.57; 95 % CI 0.40–0.80; P = 0.0013		NS	222 Japanese patients with advanced RCC	Shiota et al. [32]
IL2, ADAD1, IL21	rs17388568	Responders (CR, PR, SD) vs. non responders (PD) OR: 0.26 (0.12 - 0.53)				169 patients from America with metastatic melanoma	Chat et al. [50]
IL1RL1	rs4988956	Better response (p = 5.4E-02)				GWAS study in 57 patients with metastatic melanoma, treated in France. Validation occured in another cohort of 57 patients.	Montaudie et al. [48]
IL7	rs16906115				Increased all grade toxicity (HR: 2.1; p = 36E-11)	GWAS study in 1751 patients who were treated with ICIs for 12 different tumour types	Groha et al. [24]

Table 1 (*continued*)

Gene	Variant	BOR	PFS	OS	rAEs	No. of patients	References
GZMB	c.128C>A (rs8192917)			NS		119 patients of Caucasian decent with metastatic melanoma	De With et al. [27]
		(CR/PR vs SD vs PD) 1.60 (1.01–2.52)	1.38 (1.02 - 1.87)	NS		322 patients with NSCLC of Caucasian decent	Hurkmans et al. [28]
CD47	rs3804639		GG longer PFS (HR 0.70; p = 0.026)	GG longer OS (HR 0.64; p = 0.021)		164 Japanese patients with NSCLC	Ogimoto et al. [57]

testing large arrays of autoimmunity associated SNPs in multiple cohorts. For instance, in a cohort of 436 patients with metastatic melanoma tested for 25 different autoimmunity related SNPs, rs17388568 – a SNP located in a locus containing both *IL2* and *IL21* – was significantly associated with improved response to anti-PD-1 (OR: 0.26 [0.12–0.53]; p = 0.0002), even after correcting for multiple testing [50]. The same SNP was linked with several autoimmune diseseses, i.e,. colitis,

diabetes mellitus (DM) type I and allergy in previous non-ICI studies [51–52].

Another example that autoimmunity is often linked to ICI outcome is found in *GZMB*, encoding for granzyme B, an apoptotic effector of T cells. Research has shown linkage between the levels of granzyme B and cutaneous autoimmunic activity [53] and, rs8192917, constituting the 128T>C polymorphism in *GZMB*, was associated with development of
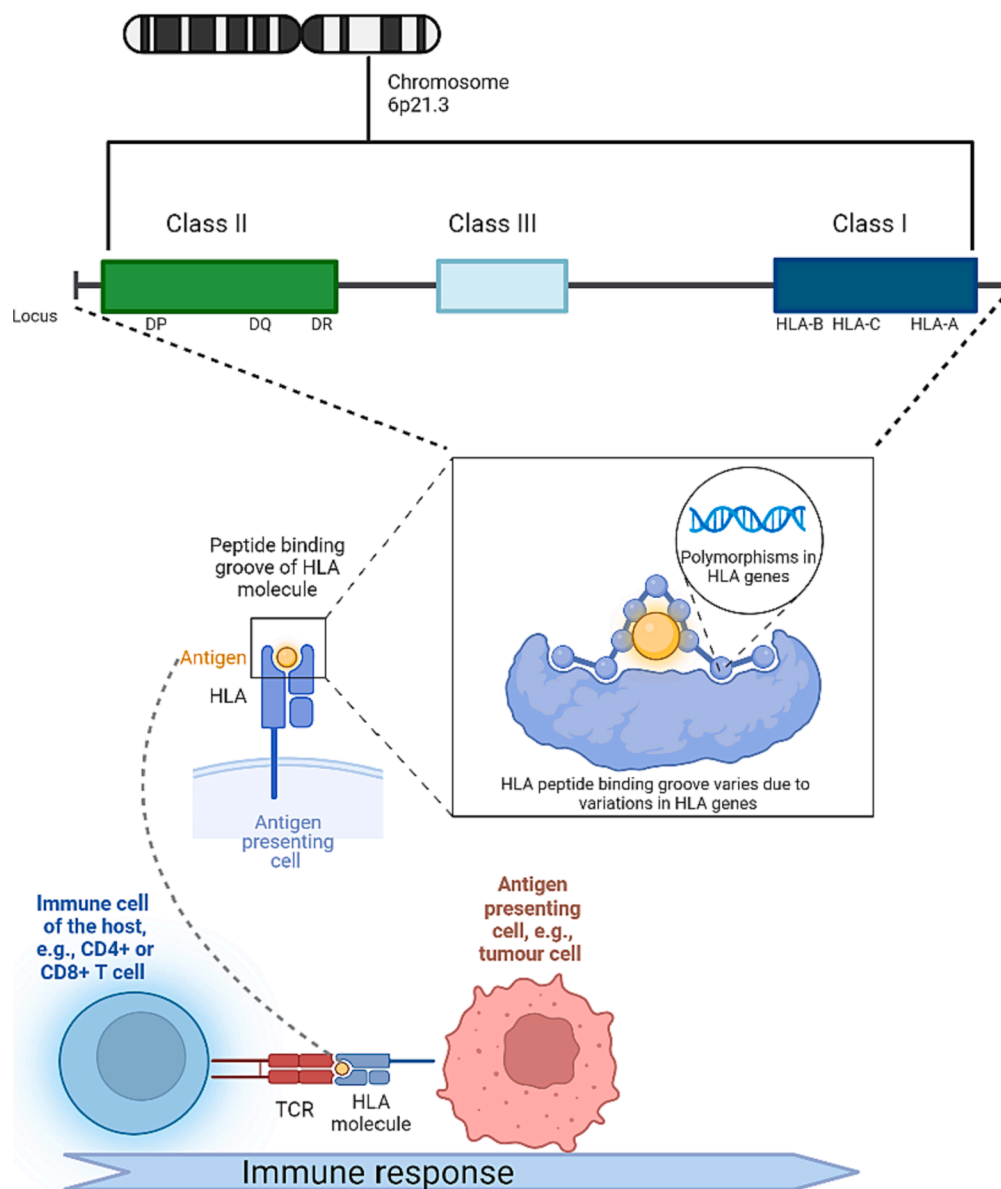

Fig. 2. The human leukocyte antigen (HLA) consists of a very polymorphic gene cluster located on the short arm of chromosome 6 (6p21.3). HLA is divided in three subclasses, i.e., class I, II and III, which all play a role in the immune system. As variations are mainly concentrated in exons encoding for the peptide-binding groove and the interaction with the T-cell receptor (TCR), variations of the HLA molecules result in different peptide-binding preferences. Consequently, variations in HLA genes lead to a very diverse group of peptides being presented to both CD4 + and CD8 + T cells.

vitiligo [54–56]. Interestingly, in nivolumab treated patients with NSCLC, 128T>C was associated with shorter PFS (HR: 1.38 [1.02–1.87]; p = 0.036) [28]. A possible hypothesis might be that polymorphisms in *GZMB* lead to production of less effective granzyme B, thereby impairing the cytotoxic capabilities of T cells [28]. Additionally, immune inhibiting signaling seems to influence ICI response as well. A SNP in *CD47*, rs3804639, was associated with longer PFS and OS in patients with NSCLC treated with nivolumab (GG vs. GT + TT: 2.6 vs. 2.1 months (p = 0.026) and 24.8 vs. 12.0 months (p = 0.021), respectively) [57]. CD47 is physiologically expressed by red blood cells and interacts with macrophages to block phagocytosis [57]. Tumours, however, can also express CD47 to avoid immune response and it is thought this SNP alters macrophage response in ICI treatment [57].

Finally, to better suit the large inter-patient variability in specific germline biomarker expression, polygenetic multivariate modelling has been attempted as well. Based on testing 166 different SNPs originating in 86 auto-immunity genes, multivariable models for tumour response and irAEs were able to reasonably predict both outcomes (receiver operating characteristic (ROC)-curves: 0.81 [0.72–0.90] and 0.89 [0.76–1.00], respectively) [58]. Another study tested 16,751 SNPs to calculate a polygenetic risk score, originally developed as a predictor for hypothyroidism in non-oncological patients. Interestingly, the score was also able to predict thyroid irAEs (HR: 1.34 [1.08–1.66]) [59]. These results underline the importance of assessing multiple SNPs in relation to each other. Moreover, they might indicate that contrary to pharmacogenetic testing for chemotherapy (i.e., monogenetic *DPYD* and *UGT1A1* testing), eventual pharmacogenetic predictive tools for ICI treatment may constitute a polygenetic model.

HLA

HLA consists of a highly polymorphic gene cluster located on the short arm of chromosome 6 (6p21.3). HLA is divided in three subclasses, i.e., class I, II and III, which all play an important role in the immune system, illustrated in Fig. 2. Variations of HLA molecules result in different peptide-binding preferences as variations are mainly concentrated in exons encoding for the peptide-binding groove and the interaction with the T-cell receptor (TCR) [60] (Fig. 2). Consequently, variations in HLA genes lead to a very diverse group of peptides being presented to both CD4 + and CD8 + T cells [61].

HLA zygosity and response to ICI treatment

Variations within the different HLA class I molecules determine the repertoire of peptides which can be presented to CD8+ T cells, directly affecting the diversity of cytotoxic T lymphocytes for an individual patient (i.e., the immunopeptidomes) (Fig. 2) [60,62]. Diversity of the HLA classes has been previously associated with improved outcome of infections and malignancies [61] and has been suggested as predictive biomarker for response to ICI treatment, as expression of a broader neoantigen selection could provide a better tumour response to ICIs [60,63]. Individuals with homozygosity of at least one of the HLA class I alleles are hypothesised to have a poorer survival compared to individuals who are heterozygous for (one of) the HLA class I alleles, as the range in cytotoxic T lymphocytes is much smaller in homozygous patients.

Several studies have investigated the role of homo/heterozygosity of the HLA class I alleles, as summarised in Table 2. HLA class I can be subdivided in locus A, B and C. Two studies have shown that homozygosity for one of these loci could already negatively impact OS after ICI treatment (12 vs. 22 months (p = 0.036) and 22 vs. 42 months (p = 0.043), respectively) [64–65] and, albeit non-significant, trends towards shorter OS for homozygous patients were found in several others [66–68]. Interestingly, when specifying HLA heterozygosity per loci (i. e., homozygosity vs. heterozygosity of the HLA-A, HLA-B or HLA-C locus, respectively), in the largest study of those, constituting 1535 patients, having just one homozygous locus was associated withshorter

survival (HR: 1.4 [1.2–2.2]; p = 0.003) [64]. This might indicate that homozygosity of a single HLA-I locus could already be clinically relevant, which is seen in approximately 18 % of all patients [64]. On the contrary, other studies reported no unfavourable effect of homozygosity of HLA class I on OS [69–73]. Of note, one of these studies included over 3500 patients from different pembrolizumab registration studies and still was unable to detect a difference in OS for homo- vs. heterozygosity at the HLA-I class, nor at the HLA class II alleles [69].

Another factor influencing results within aforementioned studies is HLA-I evolutionary divergence (HED). HED is the difference in sequence divergence between the alleles' peptide binding properties of the corresponding HLA class I molecules [62,74]. Similar to homo/heterozygosity, sequence divergence of the different alleles in patients heterozygous for HLA class I might represent the diversity in range of peptides for T-cell recognition [74]. Indeed, both for patients with melanoma as for patients with NSCLC, high HED was associated with longer OS (10 vs. 22 months (p = 0.009) and 22 months vs. not reached (p = 0.049), respectively), despite the fact that all included patients were already heterozygous for the HLA class I alleles [74]. In addition, in patients with RCC and in patients with gastrointestinal cancer, high HED was associated with improved PFS (HR 0.23 [0.05–1], p = 0.03), and PFS and OS respectively [67,72], whilst in high HED patients with UCC treated with pembroluzimab, an increase was seen in radiographic response (disease control rate 34.9 % vs. 54.7 %, p = 0.044), although HED did not impact survival outcomes [68]. This strengthens the hypothesis that diversity of the HLA class I molecules may play a role in ICI treatment efficacy and may be used as predictive marker, if confirmed prospectively. However, given the different results, HLA divergence may play distinctive roles in different tumour types.

The impact of heterozygosity of the HLA class II alleles on survival after ICI treatment has also been investigated. Two studies compared homo- and heterozygosity for different HLA class II alleles (i.e., class II in general, HLA-DPB1, HLA-DQB1 and HLA-DRB1), but were unable to identify a difference in outcomes [68–69]. Whilst one study reported an longer OS for patients with heterozygosity at the HLA-DRB1 locus, this effect was only borderline significant, did not consider multiple testing and was only seen in a very small subgroup of patients [70]. Another study showed that presence of HLA-DRB1 was associated with increased expression of T cell activation markers. HLA-DRB1 expression may therefore be associated with better outcomes following anti-PD-1 treatment, however, results were not significant and only a limited number of patients (n = 37) was included in this study [75]. Hence, a clinically relevant effect of HLA-DRB1 on OS is not expected.

HLA supertypes and response to ICI treatment

Despite the extreme polymorphic HLA molecules, HLA class I molecules can be clustered into HLA supertypes [76]. HLA supertypes are combinations of HLA molecules which have binding preferences for certain amino acids, resulting in an overlapping peptide binding specificity [76–77]. HLA supertypes are groups of HLA class I alleles classified according to their similar binding affinities. **Supplementary Table 2** summarises all studies which have investigated whether the presence of a specific supertype was related to response and/or survival after ICI treatment. HLA-A*01 supertype was associated with prolonged PFS in patients with metastatic NSCLC [70], however this effect was not seen in other studies [68–69,71,78,64–66] and in addition, the impact of HLA-A*01 on OS was also not significant in this study [70]. A large retrospective study analysed the HLA-*02:01 supertype in patients with melanoma treated with ipilimumab, but found no correlation with efficacy or the development of irAEs [79]. However, a combined HLA-A*01-HLA-A*2 haplotype was associated with prolonged PFS (PFS: 8 vs. 16 months; p = 0.01) [70]. None of the other studies investigated the role of this haplotype on response or survival following ICI treatment, so further studies are warranted to explore the possible role of the HLA-A*01-HLA-A*02 haplotype in response to ICI treatment. HLA-A*03

Table 2
HLA alleles and response to ICI treatment.

HLA alleles	BOR	PFS	OS	Refs
Homozygosity HLA class I ±	–	–	Homozygosity at 1 locus was associated with reduced survival compared to pts with heterozygosity of all HLA-1 loci (HR = 1.40 [1.02–1.9], p = 0.036. Validated in cohort 2: HR 1.31 [1.03–1.70] p = 0.028)	Chowell 2018 [64]
	–	NS	Homozygositiy was accompanied with reduced OS (HR 1.96 [1.02–3.78], p = 0.04) compared to heterozygous patients	Abed 2020 [65]
	NS	NS	NS	Chhibber 2022 [69]
	NS	–	–	Iafolla 2021 [71]
	NS	NS	NS	Lee 2021 Heliyon [80]
	–	A trend towards longer PFS was found for heterozygous individuals (HR 0.46 [0.13–1.64], p = 0.2)	–	Lee 2021 Mol Cancer Res [67]
	Lower disease control rate for homozygous patients (34.9 % vs. 54.7 %, p = 0.044), however no significant differences in overall response rate (p = 0.105)	NS	NS	Takahashi 2022 [68]
	Lower disease control rate and overall response rate for homozygous patients (p = 0.056 and p = 0.018, respectively)	PFS for HLA-I homozygous patients was significantly shorter (1.8 vs 2.4 months, HR 3.37 [1.35–8.46], p = 0.01)	Homozygosity was associated with lower OS rate (5.6 vs 10.5 months, HR 3.97 [1.56–10.2], p = 0.004)	Wang 2022 [78]
	Homozygosity at 1 locus was associated with higher rate of progressive disease (75 % vs 47 %)	A trend towards shorter PFS was found for patients with homozygosity at 1 locus (HR 1.84 [0.8–4.62], p = 0.15)	–	Xu 2022 [66]
HLA-I evolutionary divergence	–	–	High HED is associated with longer OS (HR = 0.43 [0.22–0.83]. p = 0.0094	Chowell 2019 [74]
	–	–	High HED is associated with longer OS (HR = 0.32 [0.10–1.06]. p = 0.049	Chowell 2019 [74]
	–	–	High HED is associated with longer OS (HR = 3.39x10^-9 [0- inf]. p = 0.025)	Chowell 2019 [74]
	High HED associated with clinical benefit: OR = 0.35p = 0.003	–	–	Chowell 2019 [74]
	High HED associated with clinical benefit: OR = 0.44p = 0.03	–	–	Chowell 2019 [74]
	High HED associated with greater duration of treatment response (HR 0.23 [0.05–1.09], p = 0.045)	High HED associated with longer PFS (HR 0.23 [0.5–1], p = 0.03)	–	Lee 2021 Mol Cancer Res [67]
	Trend towards better overall response rate for patients with high HED (35.8 % vs. 18.9 %, p = 0.08)	NS	NS	Takahashi 2022 [68]
HLA-A*01	–	–	NS	Chowell 2018 [64]
	–	NS	NS	Abed 2020 [65]
	–	Expression associated with longer PFS HR 0.51 [0.27—0.96] p = 0.04 Patients not expressing either HLA-A*01 and/or HLA-A*02 alleles have shorter PFS (p = 0.01) and a trend to shorter OS of 13.4 (95 % CI not evaluable) months vs 20.4 (6.1 to 34.7) months,p = 0.1	NS	Correale 2020 [70] JITC
	NS	NS	NS	Chhibber 2022 [69]
	NS	–	–	Iafolla 2021 [71]
	–	NS	NS	Negrao 2019 [73]
	–	NS	NS	Lee 2021 Heliyon [80]
	NS	NS	NS	Takahashi 2022 [68]
	NS	NS	NS	Wang 2022 [78]

(continued on next page)

Table 2 (*continued*)

HLA alleles	BOR	PFS	OS	Refs
	NS	–	–	Xu 2022 [66]
HLA-A*02	–	NS	NS	Abed 2020 [65]
	NS	NS	NS	Chhibber 2022 [69]
	–	–	NS	Chowell 2018 [64]
	–	Patients not expressing either HLA-A*02 and/or HLA-A*01 alleles have shorter PFS (p = 0.01) and a trend to shorter OS of 13.4 (95 % CI not evaluable) months vs 20.4 (6.1 to 34.7)months, p = 0.1	NS	Correale 2020 JITC [70]
	NS	–	–	Iafolla 2021 [71]
	–	NS	NS	Lee 2021 Heliyon [80]
	–	NS	NS	Negrao 2019 [73]
	NS	NS	NS	Takahashi 2022 [68]
	NS	NS	NS	Wang 2022 [78]
	NS	–	–	Xu 2022 [66]
	NS	NS	NS	Wolchok 2010 [79]
HLA-A*02:01				
HLA-A*03	–	–	NS	Chowell 2018 [64]
	–	NS	NS	Negrao 2019 [73]
	–	NS	NS	Abed 2020 [65]
	NS	NS	NS	Chhibber 2022 [69]
	NS	–	–	Iafolla 2021 [71]
	–	NS	NS	Lee 2021 Heliyon [80]
	–	–	Carriage of HLA-A*03 is associated with shorter OS: both heterozygosity of HLA-A*03 (HR 1.47 [1.14–1.90], p < 0.05) and homozygosity (HR 2.31 [1.23–4.33])	Naranbhai 2022 [77]
	–	–	Carriage of HLA-A*03 is associated with shorter OS: 1.22 [1.05–1.42] *Subgroup analyses: independent of tumour type*	Naranbhai 2022 [77]
	–	HLA-A*03 carriers have shorter PFS compared to HLA-A*03 non-carriers (HR 1.31, [1.01–1.71], p = 0.04)	–	Naranbhai 2022 [77]
	Presence of HLA-A*03 is associated with higher disease control rate (62.8 % vs. 35.9 %, p = 0.006)	NS	NS	Takahashi 2022 [68]
	NS	NS	NS	Wang 2022 [78]
	NS	–	–	Xu 2022 [66]

Table 2 (*continued*)

HLA alleles	BOR	PFS	OS	Refs
HLA-A*26	Correlated with clinical response to nivolumab (CR, PR or at least 6 months SD) OR = 4.93, p −0.028	–	–	Ishida 2017 [81]
HLA-A*01_A*02 haplotype	–	Presence of this haplotype is correlated with longer PFS (p = 0.02)	NS	Correale 2020 JITC [70]
HLA-A*01_A*03	–	–	NS	Chowell 2018 [64]
	NS	NS	NS	Chhibber 2022 [69]
	–	NS	NS	Lee 2021 Heliyon [80]
	NS	NS	NS	Wang 2022 [78]
Homozygosity vs heterozygosity of HLA-A locus	–	–	Homozygosity associated with shorter OS (HR 1.66 [0.93–2.94], p = 0.052)	Chowell 2018 [64]
	–	NS	NS	Abed 2020 [65]
	–	NS	Heterozygosity correlated with shorter OS (p = 0.03)	Correale 2020 JITC [70]
	NS	NS	NS	Chhibber 2022 [69]
	–	NS	NS	Negrao 2019 [73]
	NS	–	–	Iafolla 2021 [71]
	NS	NS	NS	Lu 2021 [72]
HLA-A HED	NS	NS	NS	Lu 2021 [72]
HLA-B*27	–	NS	NS	Negrao 2019 [73]
	–	NS	NS	Abed 2020 [65]
	NS	NS	NS	Chhibber 2022 [69]
	–	NS	NS	Lee 2021 Heliyon [80]
	NS	NS	NS	Takahashi 2022 [68]
	NS	NS	Presence of B*27 supertype is associated with longer OS compared to other supertypes (HR 0.53, p = 0.046)	Wang 2022 [78]
HLA-B*44	–	–	Longer OS HR 0.61 [0.42–0.89], p = 0.009	Chowell 2018 [64]
	–	NS	NS	Negrao 2019 [73]
	–	NS	NS	Abed 2020 [65]
	NS	NS	NS	Chhibber 2022 [69]
	NS	–	–	Iafolla 2021 [71]
	NS	NS	NS	Takahashi 2022 [68]
	NS	NS	NS	Wang 2022 [78]
	NS	–	–	Xu 2022 [66]
Homozygosity vs heterozygosity of HLA-B locus	–	–	Homozygosity associated with shorter OS (HR 1.66 [0.93–2.94], p = 0.052)	Chowell 2018 [64]
	–	NS	NS	Abed 2020 [65]
	–	NS	NS	Correale 2020 JITC [70]
	NS	NS	NS	Chhibber 2022 [69]
	NS	–	–	Iafolla 2021 [71]
	–	NS	NS	Negrao 2019 [73]
	NS	NS	NS	Lu 2021 [72]

Table 2 (*continued*)

HLA alleles	BOR	PFS	OS	Refs
HLB-HED	Patients with high HED significant higher durable response rate OR = 2.71 [1.08–6.85] (p = 0.03)	Patients with high HED have significantly longer PFS (p = 0.051)	Patients with high HED have significantly longer OS (p = 0.0089). In multivariable analysis (high vs low HED) HR 0.38 [0.17–0.83], p = 0.016	Lu 2021 [72]
Homozygosity vs heterozygosity of HLA-C locus	–	–	Homozygosity associated with shorter OS (HR 1.60 [1.16–2.21], p = 0.004)	Chowell 2018 [64]
	–	NS	NS	Abed 2020 [65]
	–	NS	NS	Correale 2020 JITC [70]
	NS	NS	NS	Chhibber 2022 [69]
	NS	–	–	Iafolla 2021 [71]
	–	NS	NS	Negrao 2019 [73]
	NS	NS	NS	Lu 2021 [72]
HLA C-HED	NS	NS	NS	Lu 2021 [72]
HLA-DPB*04:01	Higher disease control rate for patients with the allele (OR 17.84 [2.22–143.09], p = 0.007), remained significant after correction for multiple testing (p = 0.043)	NS	NS	Takahashi 2022 [68]
HLA-DQB1*03:01	Decreased disease control rate for patients carrying the allele, also after adjustment for multiple testing (p = 0.029). In multivariate analysis, presence of this allele was an independent risk factor for progressive disease (HR 4.25 [1.03–14.86], p = 0.046)	Allele is associated with shorter PFS (3.1 vs. 4.8 months, p = 0.035)	NS	Takahashi 2022 [68]
HLA-DRB1	Presence of HLA-DRB1 was associated with higher levels of ICOS (r = 0.38, p = 0.02). Higher levels of ICOS were associated with higher levels of nivolumab (r = 0.34, p = 0.04). which showed a trend towards increased CR and PR rates in patients with melanoma (p = -0.14)	–	–	Mallardo 2022 [75]
HLA-DRB1*03	–	NS	NS	Correale 2020 JITC [70]
HLA-DRB1*13:02	Higher disease control rate for patients with the allele (OR 15.8 [1.96–127.39], p = 0.01), remained significant after correction for multiple testing (p = 0.043)	Trend towards longer PFS (7.9 vs 3.7 months, p = 0.083)	NS	Takahashi 2022 [68]
Homozygosity vs heterozygosity of HLA-DRB1 locus	–	NS	Heterozygosity is correlated with longer OS (HR 0.46 [0.21–0.99], p = 0.05)	Correale 2020 JITC [70]
	NS	NS	NS	Chhibber 2022 [69]
Homozygosity vs heterozygosity of HLA-DQB1 locus	NS	NS	NS	Chhibber 2022 [69]
Homozygosity vs heterozygosity of HLA-DPB1 locus	NS	NS	NS	Chhibber 2022 [69]
Homozygosity HLA class II ×	NS	NS	NS	Chhibber 2022 [69]

± Defined as homozygosity in at least one locus of HLA class I.

× Defined as homozygosity in at least one locus of HLA class II.

has been extensively studied as well. In several large cohorts of patients treated with ICIs, carriage of a HLA-A*03 allele was significantly associated with shortened survival, irrespective of the tumour type [77]. Intriguingly, no effect of HLA-A*03 was seen in patients receiving alternative treatments [77]. All other trials, which studied the impact of HLA-A*03 on survival, did not find a significant correlation [64–65,68–69,71,73,78,80]. Importantly, the allele frequency of HLA-A*03 differs considerably across different ancestries which could elucidate the conflicting results (i.e., 13–16 % in Europeans vs. 0–2 % in Asians) [77]. Overall, considering the evident effect in large cohorts of patients, the impact of the HLA-A*03 supertype warrants further research. HLA-B*44 was positively associated with OS (12 vs. 35 months; p = 0.001) after treatment with anti-CTLA-4 in patients with

melanoma [64], but the effect was not established in PD-(L)1 treated patients [65,69,73], meaning it could be specific for CTLA-4 containing regimens. HLA-A*24, HLA-B*07, HLA-B*08, HLA-B*18, HLA-B*35, HLA-B*58, and HLA-B*62 were not significantly correlated with response or survival after ICI treatment [64–65,69,73,78,80]. Most of these supertypes were studied in multiple, well-designed studies; therefore a relation between these supertypes and clinical benefit from ICI treatment seems excluded. Conversely, HLA-A*26 and HLA-B*27 have shown promising results as biomarkers for ICI treatment in small studies and therefore merit further validation in future research [78,81]. Finally, for HLA-C supertypes, no relation with presence of the allele and survival after ICI treatment was found [70–71]. However, as class C supertypes were only investigated in two small studies, no definitive

Table 3
HLA alleles and toxicity of ICI treatment.

HLA alleles	Drug	Occurrence of toxicity	No of patients	Refs
Homozygosity HLA class I $\pm$	Pembrolizumab, nivolumab or atezolizumab monotherapy	Homozygosity at one or more HLA-I loci associated with reduced risk of developing any type of irAE (p = 0.035), developing > grade 3 toxicity (p = 0.028) or pneumonitis (p = 0.044)	156 Australian patients with unresectable or metastatic NSCLC	Abed 2022 [97]
	PD-(L)1 monotherapy or PD-(L)1 and non IO combination treatment or PD-(L)1 and additional IO combination treatment	NS	530 Chinese patients with different tumour types	Jiang 2022 [96]
HLA-B*27	Pembrolizumab, nivolumab or atezolizumab monotherapy	NS	156 Australian patients with unresectable or metastatic NSCLC	Abed 2022 [97]
HLA-B*27:05	Atezolizumab (PD-L1)	Higher risk and more severe phenotype autoimmune encephalitis (OR 59.1, [9.0–386.9] p < 0.001.)¥	5 Korean patients with autoimmune encephalitis compared with reported HLA frequencies of the Korean population	Chang 2020 [91]
	PD-1 monotherapy or PD-1 + CTLA-4 combination	NS for irAE arthritis	26 patients (of European descent) with ICI induced inflammatory arthritis compared with population controls	Cappelli 2019 [93]
HLA-B*35	Pembrolizumab, nivolumab or atezolizumab monotherapy	NS for occurrence of any irAEs and NS for toxicities of respiratory tract system	156 Australian patients with unresectable or metastatic NSCLC	Abed 2022 [97]
	PD-1 or PD-L1	Higher frequency in patients with ICI related pneumonitis (p = 0.06)	180 patients, of whom 29 patients developed immune-related pneumonitis. Origin unknown, all patients treated in Italy	Correale 2020 Cells [92]
	PD-1 or CTLA-4 monotherapy or combination treatment	NS	22 Japanese patients w/ICI induced pituitary irAEs vs 40 matched controls (Japanese population)	Kobayashi 2021 [85]
	Pembrolizumab monotherapy	NS	101 patients with different tumour types (83.2 % of patients were Caucasian)	Iafolla 2021 [71]
Co-expression of HLA-B*35 plus DRB1*11	PD-1 or PD-L1	Higher frequency in patients with ICI related pneumonitis (p = 0.008)¥	180 patients, of whom 29 patients developed immune-related pneumonitis. Origin unknown, all patients treated in Italy	Correale 2020 Cells [92]
HLA-DPB1*05:01	PD-1 or PD-L1 or PD-1 plus CTLA-4 combination treatment	Higher frequency in patients with type I DM OR 9.95 [2.13–46.56], p = 0.0027	871 Japanese patients treated with ICIs with different tumour types of whom 7 developed type 1 diabetes mellitus	Inaba 2022 [87]
	PD-1 or PD-L1 or PD-1 plus CTLA-4 combination treatment	Higher frequency in patients with type I DM OR 4.66 [1.73–12.48], p = 0.04. No significant differences compared to general controls	47 Japanese patients treated with ICIs with different tumour types of whom 12 developed type 1 diabetes mellitus	Inaba 2023 [88]
	PD-1 or PD-L1 monotherapy, CTLA-4 monotherapy or combination treatment	Lower frequency in thyroid irAE patients. OR 0.21 [0.06–0.76], p = 0.0099	25 Japanese patients with thyroid irAE vs 1483 Japanese controls	Inaba 2021 [89]
	Pembrolizumab, atezolizumab, nivolumab or nivolumab plus ipilimumab	NS	13 patients with different tumour types who developed ICI-induced isolated adrenocorticotropic hormone deficiency (IAD) compared to healthy controls (n = 18,604) and idiopathic IAD (n = 8)	Ono 2022 [83]
HLA-DQB1*03:01	Pembrolizumab, nivolumab or atezolizumab monotherapy	No gastrointestinal toxicities observed in these patients (N = 7, p = 0.048). NS for development of any irAEs	156 Australian patients with unresectable or metastatic NSCLC	Abed 2022 [97]
	PD-1 monotherapy or CTLA-4/PD-1 combination treatment	NS for irAE arthritis	26 patients (of European descent) with ICI induced inflammatory arthritis compared with population controls	Cappelli 2019 [93]
	PD-1 or PD-L1 monotherapy, CTLA-4 monotherapy or combination treatment	Higher risk of colitis OR = 3.94, $X^2_{1,95}$ = 5.67, p = 0.017	102 patients with metastatic melanoma or NSCLC (of European descent)	Hasan 2019 [95]
HLA-DR4	PD-1 or CTLA-4 monotherapy or combination treatment	Increased risk of DM type I (p = 0.01)	132 American patients with advanced melanoma	Akturk 2022 [94]
	PD-1 or CTLA-4 monotherapy or combination treatment	NS	22 Japanese patients w/ICI induced pituitary irAEs vs 40 matched controls (Japanese population)	Kobayashi 2021 [85]

Table 3 (*continued*)

HLA alleles	Drug	Occurrence of toxicity	No of patients	Refs
	PD-1 or CTLA-4 monotherapy or combination treatment	NS	11 Japanese patients with ICI induced pituitary irAEs vs health controls (n = 19,183, Japanese population)	Yano 2020 [84]
HLA-DR8	PD-1 or CTLA-4 monotherapy or combination treatment	Increased risk of hypothyroidism (p = 0.003)	132 American patients with advanced melanoma	Akturk 2022 [94]
	PD-1 or CTLA-4 monotherapy or combination treatment	NS	22 Japanese patients w/ICI induced pituitary irAEs vs 40 matched controls (Japanese population)	Kobayashi 2021 [85]
HLA-DR15	PD-1 or CTLA-4 monotherapy or combination treatment	Increased risk of hypophysitis (p = 0.03)	132 American patients with advanced melanoma	Akturk 2022 [94]
HLA-DR1501	PD-1 or PD-L1 or PD-1 plus CTLA-4 combination treatment	Higher frequency in patients with ICI-related pituitary dysfunction (OR 4.97 [1.56–15.83], p = 0.004)	14 Japanese patients, different tumour types, who developed ICI-related pituitary dysfunction, compared to healthy Japanese controls	Hara 2023 [86]
HLA-DR1502	PD-1 or CTLA-4 monotherapy or combination treatment	Higher frequency in patients with pituitary irAEs (p = 0.0014)	11 Japanese patients with ICI induced pituitary irAEs vs health controls (n = 19,183, Japanese population)	Yano 2020 [84]
	PD-1 or CTLA-4 monotherapy or combination treatment	Higher frequency for patients with ICI induced pituitary (p < 0.05)	22 Japanese patients w/ICI induced pituitary irAEs vs 40 matched controls (Japanese population)	Kobayashi 2021 [85]
	PD-1 or CTLA-4 monotherapy or combination treatment	NS	11 Japanese patients with ICI induced pituitary irAEs vs health controls (n = 19,183, Japanese population)	Yano 2020 [84]
At least 1 shared epitope (SE) allele of HLA-DRB1	PD-1 monotherapy or CTLA-4/PD-1 combination treatment	Higher risk ICI induced inflammatory arthritis (OR 2.3 [1.0–5.1], p = 0.04)	26 patients (of European descent) with ICI induced inflammatory arthritis compared with population controls	Cappelli 2019 [93]
HLA-DRB1*11	Pembrolizumab, nivolumab or atezolizumab monotherapy	NS for occurrence of any irAEs and NS for toxicities of respiratory tract system	156 Australian patients with unresectable or metastatic NSCLC	Abed 2022 [97]
	PD-1 or PD-L1	Higher frequency in patients with ICI related pneumonitis (p = 0.03)	180 patients, of whom 29 patients developed immune-related pneumonitis. Origin unknown, all patients treated in Italy	Correale 2020 Cells [92]
HLA-DRB1*11:01	Pembrolizumab, nivolumab or atezolizumab monotherapy	NS for occurrence of any irAEs and NS for skin toxicities	156 Australian patients with unresectable or metastatic NSCLC	Abed 2022 [97]
	PD-1 or PD-L1 treatment	Higher frequency in patients with ICI-related DM type I	6 Japanese patients, different tumour types, who developed ICI-related diabetes mellitus type I compared to healthy Japanese controls	Hara 2023 [86]
	PD-1 or PD-L1 monotherapy, CTLA-4 monotherapy or combination treatment	Higher risk of pruritus (OR = 4.53, $X^2_{1,95}$ = 9.45, p = 0.0021)	102 patients with metastatic melanoma or NSCLC (of European descent)	Hasan 2019 [95]

$\pm$Defined as homozygosity in at least one locus of HLA class I.

¥After Bonferroni correction.

conclusion regarding the role of the HLA class C alleles should be drawn.

In conclusion, homo-or heterozygosity of different HLA (class I and II) alleles could be associated with clinical response and/or survival after treatment with ICIs. However, results are often conflicting. It should be taken into account that homo- or heterozygosity of HLA alleles is accompanied by the presence of specific HLA alleles. Some studies have shown that the presence of certain HLA alleles, e.g., HLA-A*03 and HLA-A*01, could also impact the PFS or OS after ICIs. Thus, the role of specific HLA-alleles or HLA haplotypes should not be underestimated and could influence HLA homo- or heterozygosity-related findings. However, based on the results in general, the absence or presence of specific HLA alleles, including zygosity of HLA class I and II, can not yet be used as predictive biomarkers in patients treated with ICIs.

HLA and toxicity

The impact of HLA alleles on occurrence of immune-related toxicity has been studied using various methods. On one hand, an association between HLA molecules and occurrence of irAEs was studied in general cohorts of patients treated with ICIs. On the other hand, some studies selected patients with (specific forms of) toxicity and compared the presence of HLA molecules to patients without ICI-related toxicity or to the general population. In addition, next to the different selection of patients studied, the HLA molecules/profiles that were examined also differed. While a subset of the studies first determined which HLA class I and II molecules were most prevalent and subsequently examined whether there were differences in this prevalence within the two subgroups studied, other studies focused specifically on HLA molecules already known to be related with autoimmune diseases [82].

In studies including patients with specific irAEs (e.g., ICI induced encephalitis and endocrinopathies), these studies often included a very small number of affected patients [83–90]. A complete overview of the found results are summarised in **Supplementary Table 3.** Most of the results were not or only borderline significant, without adjusting for multiple testing and should thus be interpreted with caution. In addition, most studies were conducted in Japan, which has specific incidence of HLA alleles and consequently, prevents the results from being directly translatable to the non-Asian population. Nonetheless, in our opinion,

two HLA supertypes require further investigation. Firstly, prevalence of HLA-B*27:05 was markedly higher in five Korean patients with autoimmune encephalitis and compared with the Korean population (60 % vs. 3 % in the general Korean population), remaining associated even after Bonferroni correction (p < 0.001) [91]. Given the small sample size, validation is definitely warranted in a larger cohort, as carriers of this allele might have a severe risk of deleloping ICI-induced autoimmune encephalitis. Secondly, among 180 patients of whom 29 developed ICI-related pneumonitis, the prevalence of HLA-DRB1*11 (p = 0.03) and the HLA-DRB1*11-HLA-B*35 haplotype was significantly higher (p = 0.008) among those who developed ICI-induced pneumonitis [92].

The role of HLA class II alleles has been investigated more thoroughly as this class is associated with occurrence of autoimmune diseases. For instance, Capelli et al. [93], only selected HLA-DRB1 molecules which have previously been associated with the occurrence of rheumatoid arthritis [82]. Although only 26 patients with ICI-induced inflammatory arthritis were included, presence of different HLA-DRB1 molecules was significantly higher in the affected patient group (Table 3). This could indicate a causative mechanism of ICI-induced inflammatory arthritis and should be investigated further in a larger cohort of patients [93]. Akturk et al., studied the presence of HLA class II – and more specific DR - alleles and the risk of developing specific irAEs [94]. A significant association was found for HLA-DR4 and the risk of developing DM type I (p = 0.01), while the occurrence of hypophysitis was associated with HLA-DR15 (p = 0.03) and HLA-DR8 was linked with the development of hypothyroidism (p = 0.003) [94].

Finally, several cohort studies investigated whether the occurrence of different forms of irAEs could be predicted by variation in HLA alleles [71,95–97]. This led to conflicting results. For instance, HLA-DQB1*03:01 was linked with ICI-related colitis in 102 patients in one study [95]. Conversely, in another study, none of the HLA-DQB1*03:01 carriers developed gastrointestinal related toxicity (p = 0.048), suggesting a protective effect of DQB1*03:01 for the development of colitis [97]. In addition, Abed et al., found that homozygosity at any of the HLA-I loci was associated with a reduced risk of developing irAEs (p = 0.035), especially grade ≥ 3 irAEs and pneumonitis [97]. Jiang et al., however, investigated a large group of 571 patients of Chinese descent, and found no association between HLA homo/heterozygosity or HED and the occurrence of irAEs [96]. Lastly, Iafolla et al., tested many different HLA alleles in 101 patients with different tumour types, however, no association between different HLA molecules and occurrence of toxicity was found [71]. An overview of all findings can be found in Supplementary Table 3.

In summary, when interpreting studies investigating the relationship between HLA alleles and the occurrence of (specific types of) irAEs, it is of great importance to take into account the different methods that have been applied. Some results are remarkable and require further investigation, such as the incidence of HLA-B*27:05 in patients with ICI-related encephalitis and the prevalence of HLA-B*35 in patients with pneumonitis. In particular, HLA class II, and more specifically the HLA-DRB1 alleles, could play a role in the onset of irAEs. Since these alleles have previously been associated with autoimmune diseases, this could elucidate the onset of irAEs. While studying the prevalence of HLA alleles in patients with specific forms of toxicity vs. a general population (of patients) can generally help to identify HLA molecules of interest, larger studies are needed to evaluate the impact of these alleles in patients treated with ICIs. To date, most published studies have included only limited numbers of patients, while the genetic population also varies widely between studies. Hence, the published studies are not yet representative of a general population of patients treated with ICIs and therefore cannot be used in clinical practice.

Discussion

This review shows that many studies have been conducted so far to investigate the role of germline genetics and outcome of ICI treatment. However, most of these studies are limited by the number of patients included, and as most of the studies do not correct for multiple testing, results often remain insignificant or clinically irrelevant. In addition, the prevalence of specific SNPs and HLA alleles is dependent of the investigated patient population (e.g., Caucasians) and results are therefore not always representative for all populations. Moreover, for irAEs in particular, endpoints (i.e., all irAEs vs. only grade 3 or higher irAEs) are heterogeneous, hampering comparison between different studies. A predefined outcome for irAEs would highly benefit the field, such as defining the occurrence of grade III or higher irAEs as the primary toxicity endpoint in biomarker research for ICIs. Lastly, results may be specific for the investigated drug(s) and may not be directly translatable to all ICI regimens. However, this review also shows that some genetic variations (i.e., SNPs in *IL2*, *IL7*, *PDCD1* and *CD274*, and HLA-A*03 and HLA-DRB1) could indeed impact the outcome of ICI treatment. Nonetheless, serious efforts should be made to improve the quality of this specific type of genetic research. For instance, large, prospective validation studies are necessary to confirm the findings summarised in this review. Moreover, evaluating the current literature, it seems unlikely that a single, monogenetic, factor will be the holy grail to predict ICI outcomes. Hence, we believe polygenetic multivariate modelling should be performed in order to better suit the large inter-patient variability in specific germline biomarker expression. Such an approach should make it feasible to develop better predictive models for ICI outcomes utilising pharmacogenetics. This in turn could guide clinicians to select those patients having high chances of clinical benefit of ICIs and simultaneously limit those patients at risk for the development of (severe) irAEs.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctrv.2023.102662.

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