ORIGINAL ARTICLE

Germline Human Leukocyte Antigen Status is Associated With Immunotherapy-Induced Pneumonitis and Treatment Response in Patients With Non–Small Cell Lung Cancer With High Programmed Death-Ligand 1 Expression

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ABSTRACT

Introduction: The germline human leukocyte antigen (HLA) status has been found to be associated with immunotherapy outcomes in patients with NSCLC, but its correlation to immunotherapy-induced pneumonitis and prognostic impact in the Asian population remains largely unknown.

Methods: We evaluated the HLA genotype of the germline and available tumor samples in 42 patients with programmed death-ligand 1 expression of 50% or higher undergoing pembrolizumab immunotherapy. The HLA allele expression was correlated with tumor response, disease survival, and the occurrence of pneumonitis.

Results: It was observed that the germline HLA-C homozygosity and HLA-DRB1*13 expression were related to a worse progression-free survival and treatment response. Importantly, all patients (7/7 patients) who developed pneumonitis in our cohort expressed the HLA-DPB1*02 allele, and the incidence of pneumonitis was 31.8% (7/22 patients) in patients expressing this allele compared with 0% (0/20 patients) in those without this allele ($p = 0.009$). Investigation of the tumor samples from 15 patients revealed some degree of HLA loss in the HLA class I loci in 40% (6/15) of patients, and no significant difference in tumor mutation burden was found among patients with different treatment responses.

Conclusion: Taken together, this study evaluated the impact of HLA status in both germline and tumor samples in patients with NSCLC with high programmed death-ligand 1 expression, and the high incidence of immunotherapy-induced pneumonitis in patients expressing the HLA-DPB1*02 allele may suggest a routine HLA typing and closer monitoring in this patient subset.

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Introduction

Immunotherapy has proven itself to be a successful treatment option for patients with lung cancer having no targetable mutations. In view of the costs and potential side effects of immune checkpoint inhibitors, there is active research on identifying patient subsets who can benefit most from therapy.[1,2] The level of programmed death-ligand 1 (PD-L1) expression in tumor cells, leading to the inhibition of T cell infiltrate, has been the best-known predictor of survival benefit. The KEYNOTE-024 study found that the efficacy of pembrolizumab monotherapy compared with chemotherapy was most significant in advanced-stage patients with lung cancer whose PD-L1 tumor proportion score (TPS) was 50% or higher.[3] In the later KEYNOTE-042 study this survival benefit had been extended to patients with a TPS of higher than 1%,[4] which together with later clinical trials,[5–7] enabled the use of immunotherapy in both early-stage and advanced disease.

Apart from PD-L1 expression, it was observed that tumor neoantigen presentation to immune cells may play a key mechanistic role in determining immunotherapy outcomes. In the year 2015, immune checkpoint inhibitors were shown to be more effective in mismatch repair deficient cancer,[8] suggesting that a high genomic mutation load predisposed by mismatch repair deficiency may translate to an increased neoantigen load and enhanced T-cell response. By the same token, numerous studies have found that the tumor mutation burden (TMB) was correlated to immunotherapy response.[9,10] Nevertheless, recent meta-analysis data argued against the routine measurement of tumor mutation burden as a means to predict drug response.[11] Intuitively, because the process of antigen presentation is facilitated by the binding of antigen to the human leukocyte antigen (HLA) molecules, we wanted to examine whether the patients' germline and tumor HLA status could influence patient outcomes.

Previous studies have identified several HLA alleles and HLA-heterozygosity that were associated with better outcomes in the Caucasian population,[12,13] but these results were difficult to extrapolate to Asian patients who are known to have a different tumor driver mutation and HLA allele frequency spectrum. It was also of considerable interest to investigate whether specific HLA alleles may predispose to immunotherapy-induced complications. To this end, we collected buccal swab samples from patients with lung cancer undergoing immunotherapy and evaluated the available tumor samples to perform HLA genotyping, with the patient survival, tumor response, and the prevalence of treatment-related complications as the endpoints. Only patients with high tumor PD-L1 expression levels (TPS $\geq$ 50%) were included to minimize patient heterogeneity in the cohort.

Methods

Study Design and Patients

The investigation was a longitudinal observational study in a tertiary referral and university teaching hospital. Patients with primary non-small cell lung cancer who had a PD-L1 expression TPS of 50% or higher and who underwent immunotherapy were enrolled between 2019 and 2022. Informed consent was obtained for all patients. With informed consent, a buccal swab was carried out to obtain normal cellular materials from patients for HLA typing. Patients were followed up to assess the clinical course, tumor response, and the occurrence of any complications. Tumor response was assessed as per the Response Evaluation Criteria in Solid Tumors version 1.1. Driver mutation status was obtained from molecular test reports on previous biopsy, or investigated with archival materials. For the TMB and tumor HLA status, tumor biopsy specimens were retrieved from the archival pathology materials for further investigations. The study has been approved by the Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee, Hong Kong.

DNA Extraction and HLA Typing

Genomic DNA was extracted using a QIAamp DNA mini kit (Qiagen, Germany) according to the manufacturer's protocol. For tumor samples, manual microdissection was performed as appropriate to ensure sufficient tumor content for DNA extraction. Germline HLA typing was performed using the Alltype Fastplex assay. Multiplex nucleic acid amplification was performed briefly using pre-mixed primers toward 11 HLA-loci. Afterward, sample barcoding and library preparation were performed. The enriched libraries were sequenced on the Illumina HiSeq platform (Illumina, San Diego, California, United States) according to the manufacturer's instructions. Germline HLA analyses were subsequently performed with the HLA TypeStream Visual NGS analysis software. For tumor genomic analyses, genomic DNA was sonicated to 200 base pairs. Libraries were prepared using KAPA HyperPrep kit (KAPA Biosystems, Wilmington, Massachusetts) and enriched with a custom-designed 549-gene solution-based hybrid capture panel (Roche, Basel, Switzerland),

which covered approximately 1.5 Mb of the human genome (including coding exons of 549 genes and introns of 15 genes frequently re-arranged in cancers).

Statistical Analysis

The correlation between HLA genotype and clinicopathologic parameters was assessed by the Fisher exact test or non-parametric Mann-Witney-U tests where appropriate. The Kaplan-Meier method was used to estimate the survival rates for each variable. The equivalences of the survival curves were tested by log-rank statistics. The Cox proportional hazards model with the likelihood ratio statistics was employed to evaluate independent prognostic indicators in survival analysis. Analysis of variance statistical analysis was performed to evaluate the difference in mean among more than two groups. A two-tailed p value of less than 0.05 was considered statistically significant.

Results

Patients' Demographics

A cohort of 42 patients was included in the analyses. Thirty-six patients (80%) were male individuals. Nine patients (21.4%) were never smokers. The median age of the patients was 71.5 years old (range: 51–91). The median follow-up time for the patients was 27.8 months (±30.0 months). Thirty-four patients had adenocarcinoma, one had squamous cell carcinoma, six had non-small cell lung cancer, not otherwise specified, and one had large cell neuroendocrine carcinoma. For the driver mutation profile, one patient in the cohort had *EGFR* exon 20 substitutions (P764L, variant of uncertain significance), three had *KRAS* mutation (one G12C mutation and two G12D mutations), and all the remaining patients were wildtypes with respect to *EGFR*, *KRAS* mutations, anaplastic lymphoma kinase translocations, and *ROS1* translocations. Programmed death-ligand 1 expression was 50% to 69% (n = 12), 70% to 89% (n = 19), 90% to 100% (n = 10), or not further quantified (reported > 50%, n = 1). On initial diagnosis, 34 patients (81.0%) were at stage IV, 6 were at stage III, and one was at stage I. The stage I patient had large cell neuroendocrine carcinoma which was resected but subsequently recurred with hilar, mediastinal lymph nodes, and neck lymph node metastases, necessitating immunotherapy. Thirty-three, seven, one, and one patient received pembrolizumab monotherapy, pembrolizumab/pemetrexed/carboplatin, pembrolizumab/paclitaxel/carboplatin, and pembrolizumab/pemetrexed, respectively. The cycle number of pembrolizumab that the patients had undergone was 20.3 plus or minus 12.2 (range: 1–37), and the distribution was one to 10 cycles (n = 12), 11 to 20 cycles (n = 9), 21 to 30 cycles (n = 9), and 31 to 40 cycles (n = 12), respectively. Complications had occurred in 13 (31.0%) patients. These complications included pneumonitis (7/42, 16.7%), hepatitis (1/42, 2.38%), bullous pemphigoid (1/42, 2.38%), and rash or pruritis (3/42, 7.14%). Consequently, tumor response could not be assessed in the two patients with pneumonitis, who necessitated immunotherapy discontinuation after only one dose of pembrolizumab. To ensure that tumor response findings were not affected by patients who only underwent pembrolizumab therapy for a short period, three patients who had pembrolizumab for less than three months were also excluded from this analysis.

Germline HLA-C Homozygosity Predicted Worse Immunotherapy Response

We first investigated if the zygosity of HLA-I loci was associated with clinical outcomes in our cohort. Five patients exhibited homozygosity at the HLA-C locus and had significantly worse prognoses than others (Fig. 1*A*). In Cox-regression model, when age, sex, stage of disease, smoking history, and homozygosity at HLA-A and HLA-B were taken into account, homozygosity at HLA-C remained to be a significant independent prognostic indicator in our cohort (Hazard ratio = 13.70, 95% confidence interval [CI]: 3.76–49.9, $p < 0.001$). When assessing the therapeutic responses, all four patients harboring HLA-C homozygosity developed progressive disease (Fig. 1*B*). Meanwhile, we did not observe significant survival differences in patients with or without HLA-A and HLA-B homozygosity.

Germline DRB1*13 Allele Predicted Poorer Therapeutic Outcome

To understand whether specific HLA alleles were associated with patients' clinical outcomes, the most prevalent alleles (>10% of all patients) of the HLA-A, HLA-B, HLA-C, and HLA-DRB loci were evaluated. These loci were included in analyses because they had been shown to be associated with outcomes in previous reports.[13] Of the frequently occurring HLA-DRB alleles, it was observed that the DRB1*13 allele was associated with a worse outcome in terms of progression-free survival (Table 1). In a multivariable analysis with the Cox-regression model, when age, sex, stage of disease, and smoking history were also taken into account, the expression of the DRB1*13 allele appeared to be a significant independent prognostic indicator (Hazard ratio = 4.04, 95% CI: 1.07–15.2, $p = 0.04$). The clinical outcomes of the frequently occurring alleles at the other loci are shown in Supplementary Table 1.

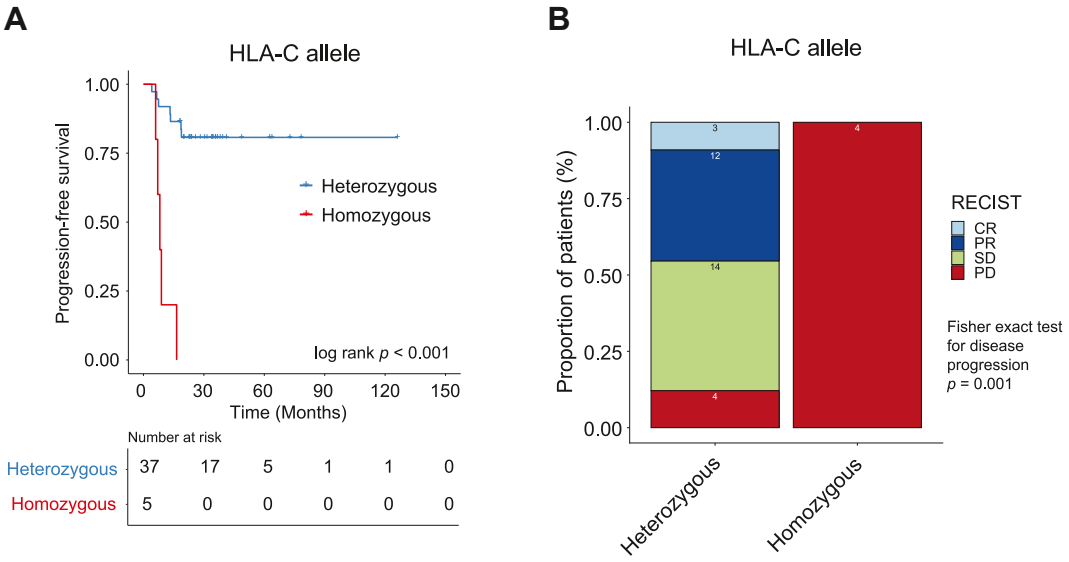

Figure 1. Homozygosity in the HLA-C locus was associated with a worse clinical outcome. *(A)* Progression-free survival of patients harboring HLA-C homozygosity. *(B)* The tumor response in patients with HLA-C homozygosity, according to the RECIST criteria (n = 37). Patients excluded from the analysis included those with early pneumonitis and who received immunotherapy for less than three months. CR, complete response; HLA, human leukocyte antigen; PD, progressive disease; PR, partial response; RESIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Clinical Courses of Patients With Immunotherapy-Induced Pneumonitis

Pneumonitis is a severe complication of immunotherapy and its occurrence could preclude the potential survival benefit that can be offered by immunotherapy in patients who require drug discontinuation. Of the 42 patients in our cohort, seven had developed pneumonitis. This resulted in the discontinuation of immunotherapy in four of these patients. Patients with pneumonitis had a worse overall disease survival than those without (Fig. 2*A*). We investigated if germline HLA alleles had any associations with this complication. We evaluated some of the frequently expressed alleles in our locality and included the HLA-A, B, C, and DRB1 loci and the autoimmune disease-related DPB1 locus in the analyses. Among the few HLA alleles that were most frequently observed in patients (Table 2), the class II HLA-DPB1 locus reported a significant association in the seven patients who suffered from pneumonitis and harbored the DPB1*02 allele (Fig. 2*B*). All of these patients were heterozygous with respect to the DPB1 locus, and four of them had DPB1*05 allele, two had DPB1*135 allele, and one had DPB1*04 allele on the other chromosome. Nevertheless, expression of the DPB1*02 allele alone was not found to be associated with a worse disease survival. On the basis of the observations made in Table 2, we further investigated whether the co-expression of DPB1*02 with other common HLA-A or HLA-C alleles may also be associated with immunotherapy-induced pneumonitis. Interestingly, the co-expression of DPB1*02 with A*11 ($p = 0.0032$) or co-expression of DPB1*02 with C*03 ($p = 0.0026$) were both significantly associated with the incidence of pneumonitis (Fig. 2*C*).

Table 1. Clinical Outcomes of Patients Expressing the Frequently-Occurring Alleles of the HLA-DRB1 Locus

		Progression-free Survival				
Allele	Frequency of Expression, %	One-year PFS Rate Allele Present, %	One-year PFS Rate Allele Absent, %	Two-year PFS Rate Allele Present, %	Two-year PFS Rate Allele Absent, %	log Rank *p*
DRB1*04	11.9	100	81.1	-	-	0.194
DRB1*08	14.3	100	80.6	100	66.2	0.119
DRB1*09	54.8	82.6	84.2	78.3	63.2	0.37
DRB1*12	26.2	72.7	87.1	72.7	70.4	0.994
DRB1*13	11.9	60	86.5	40.0	75.5	0.026
DRB1*15	28.6	100	76.7	83.3	66.3	0.233

PFS, progression-free survival.

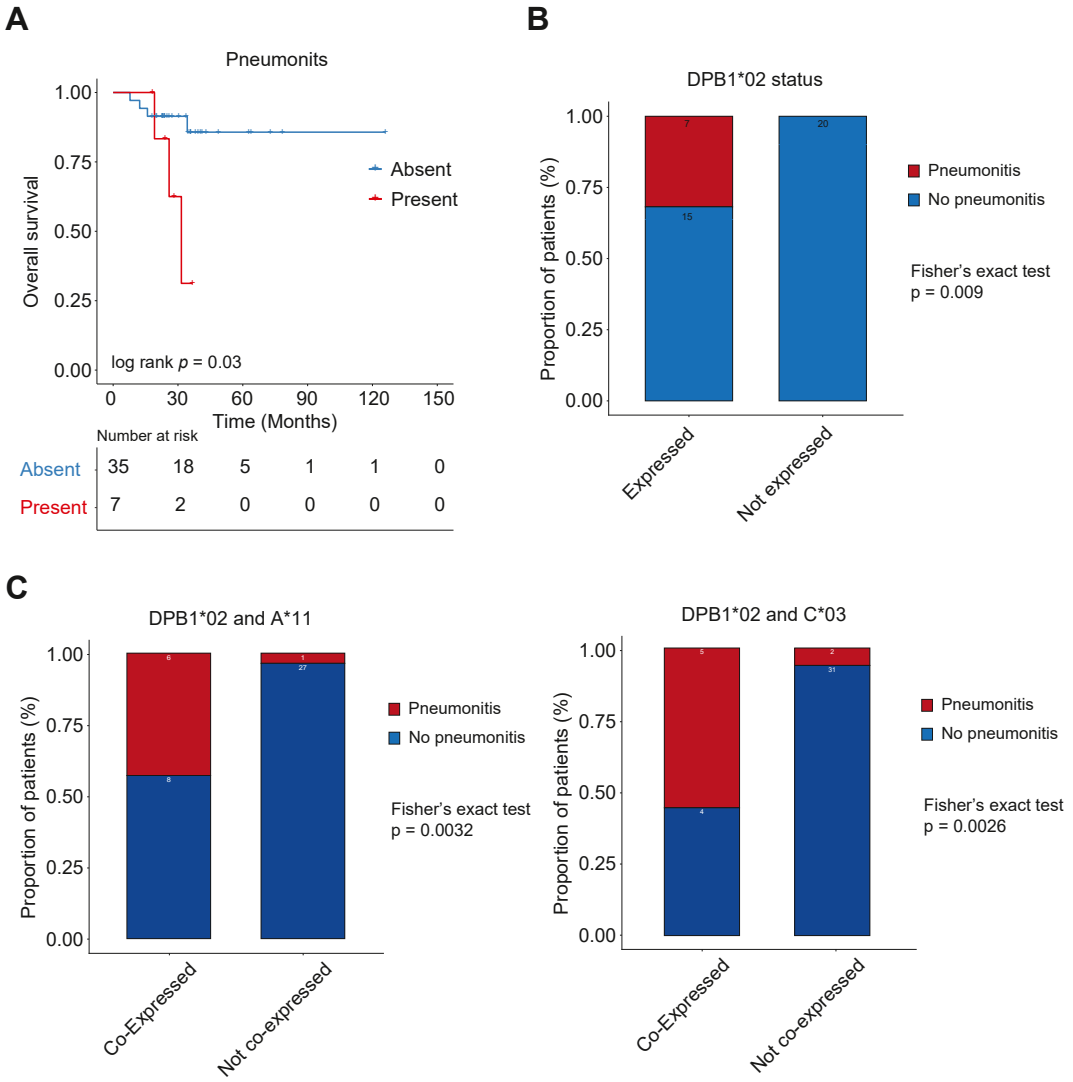

Figure 2. Clinical features of patients who developed immunotherapy-induced pneumonitis. *(A)* Overall survival of patients with pneumonitis after administration of immunotherapy. *(B)* The incidence of pneumonitis in patients who expressed the HLA DPB1*02 allele. *(C)* The incidence of pneumonitis in patients who expressed both the HLA DPFB*02 allele and A*11 or C*03 alleles. HLA, human leukocyte antigen.

HLA Loss and TMB in Tumors

To investigate whether the TMB and the tumor HLA status may have influenced the tumor response in our cohort, we evaluated all the available tumor samples in the archival materials from the patients. Of the tumors from 15 patients, the TMB reported no difference among patients with different treatment outcomes in our cohort (Fig. 3), nor did the level of TMB affect patients' survival.

Table 2. Occurrence of HLA Alleles in Patients With and Without Pneumonitis

Allele	Frequency (%)	Pneumonitis (%)	No Pneumonitis (%)	*p* value
DPB1*05	27/42 (64.3)	4/7 (57.1)	23/35 (65.7)	0.686
A*02	26/42 (61.9)	3/7 (42.9)	23/35 (65.7)	0.401
A*11	23/42 (54.8)	6/7 (85.7)	17/35 (48.6)	0.112
DRB1*09	23/42 (54.8)	3/7 (42.9)	20/35 (57.1)	0.682
DPB1*02	22/42 (52.4)	7/7 (100.0)	15/35 (42.9)	0.009
B*40	18/42 (42.9)	2/7 (28.6)	16/35 (45.7)	0.681
C*01	18/42 (42.9)	2/7 (28.6)	16/35 (45.7)	0.438
C*03	16/42 (38.1)	5/7 (71.4)	11/35 (31.4)	0.089

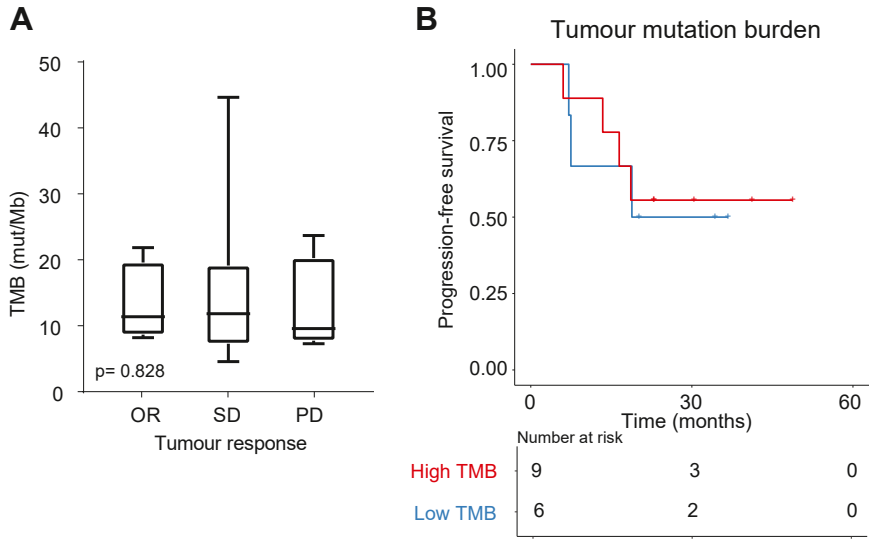

Figure 3. The TMB was not significantly different among patients with different treatment outcomes. *(A)* The tumor response was according to the RECIST criteria. *(B)* Progression-free survival of patients with high TMB (≥10 mutations/Mb) and low TMB. OR, objective response; PD, progressive disease; RESIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; TMB, tumor mutation burden.

Meanwhile, with respect to the HLA-I loci, six of the 15 patients (40.0%) harbored some degree of loss in the copy number, including one patient showing homozygous losses in HLA-B and HLA-C loci, and five patients showing hemizygous losses in HLA-B and HLA-C. No patients were found to harbor HLA-A loss. No significant survival differences were observed in these patients with HLA losses. For the tumor response, five of these six patients had stable disease, whereas the remaining one, who harbored hemizygous loss in HLA-B and HLA-C, had a partial response toward immunotherapy.

Discussion

The polymorphic nature of the HLAs conferred diversity to antigen recognition by immune cells, and its pivotal role in tumor neoantigen presentation was thought to be important in mediating immunotherapy response.[14] Although it had been found in the literature that the HLA status could be a factor that influenced the patient outcome in immunotherapy, it must be recognized that a number of other factors, including tumor PD-L1 expression, TMB, and HLA loss in tumor cells,[15] could also contribute to the immune escape mechanism and confounded the analysis on germline HLA status alone. Therefore, we aimed to remove the heterogeneity of PD-L1 expression, arguably the most important predictor of immune checkpoint therapy in this study, by recruiting patients only with high PD-L1 expression (TPS $\geq$ 50%) and studied the HLA status in both of the germline and tumor DNA where possible.

The HLA system is classified mainly into class I and II, in which class I is responsible for presenting intracellular antigens to cytotoxic T cells and class II is mainly for presenting foreign antigens (such as those of pathogens) on dendritic cells to helper T cells.[16] Although it was thought that class I HLA is chiefly implicated in presenting tumor neoantigens to the immune system, emerging evidence suggested that other HLA classes were also involved in mediating the tumor immune escape mechanisms.[17,18] Some studies have identified patients with specific HLA alleles that can be more responsive to PDL-1 inhibitors,[13] but these were conducted in the Caucasian population, whereas it was known that the prevalence of HLA alleles and the driver mutation biology could differ among ethnic groups. Our study systematically evaluated the germline and tumor HLA status in Asian patients with NSCLC. Human leukocyte antigen heterozygosity had also been suggested to allow a more divergent spectrum of neoantigens to be presented by the immune cells and therefore predicted a better prognosis.[19] Nevertheless, many studies had only considered the germline HLA status, but not the HLA status in the tumor cells, where this is significant as it was estimated that 40% of all NSCLC could harbor HLA losses.[15]

Apart from showing that HLA-C homozygosity and specific alleles were associated with poorer outcomes in NSCLC, our study was of interest in two additional respects. First, it was demonstrated that the DPB*02 allele was found in a significant proportion of patients with immunotherapy-induced pneumonitis. It had been found that the HLA DPB allele was associated with some

autoimmunity-related diseases such as anaphylaxis,[20] Wegner's granulomatosis,[21] and beryllium-related lung disease.[22] These studies indicated that this class II locus could modulate the immune response when expressed in the antigen-presenting cells. Pneumonitis is a severe complication of immunotherapy and resulted in the termination of drugs in most of the patients in our cohort and could lead to a worse outcome. In our cohort, patients expressing DPB1*02 were far more likely to experience pneumonitis, and this occurred in seven out of the 22 patients (31.8%). This suggested the need for close monitoring of pneumonitis symptoms and radiological follow-up for this patient subset when they were given immunotherapy and would enable earlier treatment once possible complications had developed. Although it is unknown whether earlier recognition of pneumonitis could improve outcomes, this could at least reduce patient discomfort and allow clinicians to modify anti-cancer regimens in a timely manner. It did not appear that the homozygosity of DPB1*02 allele was correlated to the incidence of pneumonitis; nevertheless, heterozygosity in the HLA DPB1 allele was more frequent, with only two out of 22 patients with DPB1*02 being homozygous for DPB1*02.

Although the germline HLA haplotype is important in determining how tumor antigens are presented to immune cells, tumor cells have evolved to downregulate the HLA expression to evade antigen presentation, and this could be a common event in NSCLC. This loss in copy number of various HLA class I loci had occurred in 40% of patients in our cohort, comparable to data in the published literature.[15] Tumor HLA loss in this cohort did not appear to affect patient treatment response or survival, suggesting germline HLA diversity may be more important than the level of expression attributed to tumor HLA loss. Meanwhile, the TMB did not appear to predict treatment response in our cohort, and this can be in keeping with the recent meta-analysis result.[11] This finding was probably partly explained by the fact that only patients with high PDL-1 expression were included and that nearly all the patients in the cohort had no targetable driver mutation. In practice, the use of immunotherapy was predominantly in patients who were advanced-stage without driver mutations and the comprehensive sequencing to exclude the presence of targetable *EGFR,* anaplastic lymphoma kinase, and *KRAS* mutations (only one patient had G12C mutations and two had G12D mutations; *EGFR* P764L variant also had no standard treatment) that allowed outcome comparisons in a relatively biologically homogeneous group of patients, was a distinct strength of this study.

In this study, the stringent inclusion criterion of high tumor PDL-1 expression led to a smaller sample size but enabled a focused investigation on HLA status and therapy outcome. We evaluated whether our cohort was biased toward patients who expressed a particular HLA allele. We found that the frequencies of HLA alleles in our cohort were largely comparable to the known HLA allele frequencies in our locality for the most prevalent HLA-A and HLA-B alleles.[23] Meanwhile, it should be noted that HLA zygosity may be different among populations even in Asian patients, and it was observed that Chinese patients had a slightly lower rate of HLA homozygosity.[24] Our observation of HLA-C homozygosity as a significant indicator for worse prognosis was largely in keeping with the findings of Chowell et al.,[25] whereas the variance of frequency of HLA homozygosity may in part explain the discrepant finding of another study on Caucasian patients that reported HLA-A homozygosity had the most significant prognostic effect in patients with higher than 50% PD-L1.[12]

It remains to be investigated whether the current findings are also applicable to patients with lower PDL-1 expression. It must be understood that the outcome of immunotherapy is influenced by the interplay between the patient germline HLA status, the tumor HLA status, and immune checkpoint upregulation, and additional genetic factors, such that it is difficult, if not impossible, to isolate each of the factors. In patients with metastatic driver-negative NSCLC and low PDL-1 expression (TPS = 1%–49%), combination therapy with both immunotherapy and chemotherapy is recommended.[26,27] In this setting, the tumor response is also affected by chemotherapy and it would be difficult to study the correlation between tumor response and the patient's HLA status. For our cohort, we observed that the majority of patients (77.8%) receiving combination therapy were patients with stage IV disease, whereas one patient was at stage IIIC and 1 patient had a recurrence of stage IB large cell neuroendocrine carcinoma. For the tumor response, two out of the eight patients (25%) in the combination group had progressive disease, compared with eight out of the 37 (21.6%) patients in the whole cohort, suggesting that the former group had an aggressive disease that required combination therapy. In keeping with this observation, the combination therapy group had a mean progression-free survival of 28.2 months (95% CI: 18.1–38.3 months) whereas the whole cohort had a mean progression-free survival of 58.3 months (95% CI: 48.8–67.8 months). Taken together, our data may be more relevant in patients with either high or low PDL-1 expression who underwent pembrolizumab monotherapy according to KEYNOTE-042.[4] Nevertheless, Abed et al.[12] found that HLA heterozygosity was associated with better prognosis only in patients with 50% or higher PDL-1 but not those with less than 50% PD-L1, suggesting that the dependence of immunotherapy on HLA status may be different in these

two groups and further investigation may be required to elucidate their correlations.

In summary, we identified that the germline HLA status can influence the response and occurrence of complications in Asian patients with NSCLC with high PD-L1 expression undergoing immunotherapy. In particular, the DPB1*02 allele was significantly correlated with immunotherapy-induced pneumonitis in this population. Provided the ease of HLA typing, it may be worthwhile to closely monitor patients expressing this allele to anticipate this complication and administer earlier treatment.

CRediT Authorship Contribution Statement

Alvin H.K. Cheung: Data curation, Formal analysis, Investigation, Methodology, Resources, Writing – original draft, Writing – review & editing.

Zeta Mui: Data curation, Formal analysis, Investigation, Methodology.

Walter W. Yeung: Data curation, Formal analysis, Investigation, Methodology.

Chit Chow: Formal analysis.

Mandy F. Yu: Formal analysis.

Olivia H. Chen: Formal analysis, Investigation.

Kit-Yee Wong: Formal analysis, Investigation.

Fuda Xie: Formal analysis, Investigation.

Yat M. Lau: Investigation.

Wei Kang: Writing - review & editing.

Ka-Fai To: Writing - review & editing.

Tony S. Mok: Conceptualization, Supervision, Writing - review & editing.

Molly S.C. Li: Data curation, Formal analysis, Investigation, Methodology, Resources, Writing - original draft, Writing - review & editing.

Alfred S-L. Cheng: Investigation, Writing - review & editing.

Disclosure

Dr. Mok reports receiving fees for serving on advisory boards and consulting, and speakers fees and institutional grants and research support from Bristol Myers Squibb, Merck Sharp & Dohme, Novartis, Pfizer; has received fees for serving on advisory boards and consulting and speakers fees from ACEA Pharma, Amgen, Boehringer lngelheim Pharmaceuticals, Inc., Daiichi Sankyo, Inc., Fishawack Facilitate, Ltd., Lilly, OrigiMed Co. Ltd., Sanofi-Aventis; owns stock and has received fees for serving on advisory boards and board of directors and leadership roles from HutchMed; institutional grants and research support and fees for serving on advisory boards and consulting from Merck Serono and SFJ Pharmaceutical Ltd.; has received fees for serving on advisory boards, board of directors and leadership roles and consulting from Lunit, Inc. fees for serving on advisory boards and for consulting from AbbVie Inc., BerryOncology, Blueprint Medicines Corporation, C4 Therapeutics, Inc, CStone Pharmaceuticals, Curio Science, Eisai, Gilead Sciences, Inc., Gritstone Oncology,Inc., Guardant Health, Hengrui Therapeutics Inc., IQVIA, Janssen, lgnyta, Inc., lncyte Corporation, lnivata, Loxo Oncology Inc., Mirati Therapeutics Inc., Puma Biotechnology Inc., Vertex Pharmaceuticals, Yuhan Corporation; has received speakers fees and fees for consulting from Alpha Biopharma Co., Ltd., Amoy Diagnostics Co., Ltd., AstraZeneca (before January 1, 2019), BeiGene; has received fees for serving on advisory boards and institutional grants and research support from AstraZeneca, Gl Therapeutics, Inc., Takeda; institutional grants and research support from Roche, XCovery; has received speakers fees from Daz Group, InMed Medical Communication, Janssen Pharmaceutica NV, Liangyihui Network Technology Co., Ltd., Lucence Health Inc., MD Health Brazil, Medscape LLC, Merck Pharmaceuticals HK Ltd., P. Permanyer SL, PeerVoice, Physicians' Education Resource, PrIME Oncology, Research to Practice, Roche Pharmaceuticals/Diagnostic/Foundation One, Shanghai BeBirds Translation and Consulting Co., Ltd., Taiho, Takeda Oncology, touchIME; has received fees for consulting from Elevation Oncology, MoreHealth, Qiming Development (HK) Ltd., Roche Pharmaceuticals, Takeda Pharmaceuticals HK Ltd.; has received fees for serving on advisory boards for Roche/Genentech and Virtus Medical Group; has received fees for a board of directors/leadership role with AstraZeneca PLC; discloses serving on advisory boards (uncompensated) for geneDecode Co., Ltd.; owns stock from Act Genomics-Sanomics Group and Aurora Tele-Oncology Ltd.; declares uncompensated board of directors/leadership roles with the American Society of Clinical Oncology, Asian Thoracic Oncology Research Group, Chinese Lung Cancer Research Foundation Limited, Chinese Society of Clinical Oncology, Hong Kong Cancer Fund, Hong Kong Cancer Therapy Society, International Association for the Study of Lung Cancer (ending April 30, 2019). Dr. Cheng reported serving as an advisory committee member for Merck Sharp & Dohme, AstraZeneca, Eisai, and Ipsen. The remaining authors declare no conflict of interest.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2024.100754.

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