ORIGINAL ARTICLE

PD-L1 Expression, Tumor Mutational Burden, and Cancer Gene Mutations Are Stronger Predictors of Benefit from Immune Checkpoint Blockade than *HLA* Class I Genotype in Non–Small Cell Lung Cancer

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ABSTRACT

Introduction: Immune checkpoint blockade (ICB) has revolutionized the treatment of NSCLC, but only approximately 15% of patients achieve durable benefit. Understanding mechanisms of resistance to ICB is pivotal in developing more effective treatment strategies. Recent studies showed that human leukocyte antigen (*HLA*) class I heterozygosity might be important in mediating benefit from ICB. We aimed to investigate the impact of *HLA* class I genotype on outcomes of patients with NSCLC treated with ICB.

Methods: We collected *HLA* typing, genomic, and clinical data from patients with advanced NSCLC treated with ICB at M. D. Anderson Cancer Center. We compared *HLA* class I–heterozygous and *HLA* class I–homozygous patients for progression-free survival (PFS) and overall survival (OS). *HLA* I supertype/alleles were also analyzed. To validate our findings, we also analyzed two previously published independent cohorts of patients with NSCLC (the CheckMate-012 and Chowell cohorts).

Results: No significant correlations were observed for *HLA* class I zygosity and PFS or OS in the M. D. Anderson Cancer Center (n = 200), CheckMate-012 (n = 75), or Chowell (n = 371) cohorts. No *HLA* class I supertype/allele was consistently shown to be correlated with PFS or OS. Predictors of worse outcome across the three cohorts included presence of targetable driver mutation, serine/threonine kinase 11

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gene (*STK11*) mutation, negative programmed death ligand 1 expression, and low tumor mutational burden.

Conclusions: *HLA* class I genotype is not correlated with survival in advanced NSCLC treated with ICB. This suggests that the impact of *HLA* class I diversity may be disease specific and that tumor genomic and immune markers are more impactful in predicting benefit from ICB in NSCLC.

Keywords: Lung cancer; Immunotherapy; *HLA* class I; Tumor mutational burden; PD-L1

Introduction

Anti–programmed cell death 1 (PD-1)/programmed death ligand 1 (PD-L1) immune checkpoint blockade (ICB) has revolutionized the treatment of NSCLC, not only because it is better tolerated than chemotherapy but also because of the potential for durable responses in approximately 15% of patients.[1,2] Recently, the combination of anti–PD-1/PD-L1 ICB with frontline chemotherapy showed increased effectiveness (response rate 47.6%–63.5%) in comparison with chemotherapy alone, but the median duration of response with this regimen remains suboptimal, ranging from 7.7 to 11.2 months.[3–5] This highlights the need for a better understanding of the determinants of response to ICB.

PD-L1 expression and tumor mutational burden (TMB) are the most studied and validated markers predictive of response to ICB. Higher PD-L1 expression in tumor cells is correlated with higher response rates to anti–PD-1/PD-L1 therapy in NSCLC.[4,6] Higher TMB is correlated with a higher number of tumor-associated neoantigens that can potentially prompt immune recognition and tumor cell killing.[7–9] This may be one of the underlying reasons why tumors with higher TMB (e.g., melanoma, mismatch repair deficient tumors, NSCLC) appear to be more sensitive to ICB therapy.[1,10–13] In addition, substantial efforts have focused on understanding host factors that could affect antitumor immune response. Several studies have validated immune gene expression signatures, mostly focusing on CD8-positive T-cell–related genes and interferon gamma signatures, to be predictive of benefit from ICB.[14–16] However, other than PD-L1, these assays have not been implemented into routine clinical practice mostly because of high cost and tumor tissue availability.

As an indispensable component of tumor-related antigen presentation, human leukocyte antigen (*HLA*) class I plays a crucial role in antitumor immune response and neoplastic progression.[17] Theoretically, a more diverse *HLA* class I repertoire would lead to presentation of a broader array of antigens, increasing the odds of presenting more immunogenic antigens and increasing the likelihood of benefit from ICB.[7–9,18] Recently, a large pan-cancer cohort study assessed the role of *HLA* class I zygosity in predicting benefit from ICB. This study showed that *HLA* class I homozygosity, defined as homozygosity for at least one *HLA* class I locus (A, B, or C), was associated with shorter overall survival (OS).[19] Furthermore, presence of *HLA* class I supertype B44 and absence of allele B15:01 were correlated with longer OS in a subgroup analysis of patients with melanoma.[19] As this cohort was enriched for patients with melanoma (~35%), the role of *HLA* class I genotype in other cancer types is unclear. Herein, we have evaluated progression-free survival (PFS) and OS across three independent cohorts of patients with advanced NSCLC treated with PD-1/PD-L1 checkpoint inhibitors to better understand the impact of *HLA* class I diversity on benefit from ICB therapy in this tumor type.

Methods

MDACC Cohort

We queried the GEMINI database (MDA PA16-0061), an M. D. Anderson Lung Cancer Moon Shot–funded database for prospective collection of clinical, pathological, and molecular profiling information, for patients with advanced NSCLC treated with PD-1/PD-L1 checkpoint inhibitors between January 2014 and May 2018 (M. D. Anderson Cancer Center [MDACC] cohort). Patients were eligible if *HLA* class I typing information was available. Information on patient demographics, previous therapies, molecular profiling, and survival were collected until May 15, 2018, when the data set was locked for the outcome analysis. Molecular profiling results were obtained through chart review and confirmed with the actual test reports. The sequencing platforms used included in-house Clinical Laboratory Improvement Amendments–certified next-generation panel sequencing (Molecular Diagnostics Laboratory, MDACC) and the Foundation Medicine platform (Foundation Medicine Inc., Cambridge, MA) for tissue samples and Guardant360 (Guardant Health, Redwood City, CA) for blood samples. Presence of a targetable driver mutation was defined as presence of anaplastic lymphoma kinase (*ALK*), rearranged during transfection (*RET*), ROS proto-oncogene 1 (*ROS1*), and neurotrophic receptor tyrosine kinase gene (*NTRK* 1-3) rearrangements, or presence of *EGFR* (exons 19 -21), Erb-B2 Receptor Tyrosine Kinase 2 (*ERBB2*) (exon 19-20), Met proto-oncogene (*MET*) (exon 14 skipping), and rapidly accelerated fibrosarcoma B (*BRAF*) V600E mutations. Presence of serine/threonine kinase 11 gene (*STK11*) mutation was defined as any alteration other than a

synonymous mutation. PD-L1 expression was assessed by immunohistochemistry, and staining information was obtained through chart review. PD-L1 expression was defined as positive (≥1%) or negative (<1%) on the basis of proportional staining of malignant cells.[20,21]

CM012 and Chowell Cohorts

We used two publicly available cohorts of patients with NSCLC treated with ICB to validate our findings: the CheckMate-012 trial (CM012) cohort (treated with nivolumab [a PD-1 inhibitor] and ipilimumab [a cytotoxic T-lymphocyte–associated protein 4 inhibitor])[22] and patients with NSCLC from a prior pan-cancer cohort analysis (the Chowell cohort).[19] We collected information regarding patient demographics, PD-L1 expression, TMB, molecular profiling, and survival. For the CM012 cohort, only PFS data were available, and for the Chowell cohort only OS data were available.[9,19,22] Presence of a targetable driver mutation and an *STK11* mutation was defined in the same manner as for the MDACC cohort. PD-L1 expression was assessed by using clone 28-8 PD-L1 antibody (Dako North America), as previously described.[23] PD-L1 expression was defined as positive (≥1%) or negative (<1%) on the basis of proportional tumor cell staining in a section including at least 100 tumor cells that could be evaluated.[1,13,22] PD-L1 expression data were not available for the Chowell cohort. TMB was assessed through whole exome sequencing (WES) (the CM012 and Chowell cohorts) or targeted panel sequencing (Memorial Sloan Kettering - Integrated Mutation Profiling of Actionable Cancer Targets, Chowell cohort) and was defined as the number of nonsynonymous alterations per tumor for samples that underwent WES or the number of nonsynonymous mutations per covered genomic region (targeted panel).[9,19] In this study, we used publicly available TMB data that were reported in the original publications. TMB-high was defined as higher than or equal to median for the CM012 and Chowell cohorts.

HLA Typing and Supertypes

In the MDACC cohort, *HLA* class I genotyping was obtained from retrospective review of the GEMINI database. *HLA* class I genotyping was performed by the American Red Cross (Philadelphia, PA) and was obtained through Sanger sequencing–based typing to obtain high-resolution results. To resolve any ambiguities obtained from Sanger sequencing, group-specific sequencing primer amplification, an additional sequencing primer that targets a specific sequence, single specific primer–polymerase chain reaction, or reverse sequence–specific oligonucleotide probes were used. In the CM012 and Chowell cohorts, *HLA* typing was performed as previously described and was obtained through publicly available data.[9,19] Patients were defined as *HLA* heterozygous if heterozygous for all *HLA* class I loci and homozygous if homozygous for at least one *HLA* class I locus. *HLA* alleles A and B were grouped into supertypes based on their peptide anchor binding properties, as previously described.[19,24]

The correlation between *HLA*-A, *HLA*-B, and *HLA*-C alleles and survival was studied in univariate and multivariate analyses. A similar approach was used for *HLA* class I supertypes. Supertypes and alleles were analyzed as binary variables (present versus absent). Supertypes and alleles present in at least 5% of the patients ($n = 10$) were included in the analysis for the MDACC cohort. For the CM012 cohort, only supertypes and alleles present in at least 10% of the patients (~8) were included in the analysis. This procedure was used to ensure that all the tested alleles and supertypes were well represented in the study population. Supertype and allele analysis has been previously reported for the Chowell cohort and is not included in this article.[19]

Statistical Analysis

Patient characteristics were summarized through descriptive statistics. OS was defined as the time interval between initiation of ICB and date of death and was censored at last follow-up for patients who were alive at the time of analysis. PFS was defined as the time interval between date of treatment initiation and date of progression or death, whichever occurred first, and was censored at last follow-up for patients without an event. Survival curves were estimated by using the Kaplan-Meier method, and differences in survival among groups were assessed by using a two-sided log-rank test. Log linear models were used to determine important interactions among supertypes and alleles in a stepwise model selection procedure based on the Akaike information criterion (AIC). Cox proportional hazards regression models were used to study univariate and multivariable effects. We applied best subset selection to build multivariate models. We computed the AIC for a set of candidate models with different numbers of variables and largest global chi-square statistics and chose the one with the smallest AIC and covariates statistically significant at an α level of 0.10. In the final model, an α level of 0.05 was used to interpret statistically significant results. Schoenfeld residuals were used to assess the proportional hazards model assumption of the multivariate Cox models. Statistical analyses were conducted with R software (version 3.4.2, Boston, MA), IBM SPSS software (version 24.0, IBM, Armonk, NY), and SAS software (version 9.4, Cary, NC).

Results

Outcome Analysis: MDACC Cohort

A total of 200 patients in the MDACC cohort met the enrollment criteria; 78% of patients were ever-smokers and 80% had the nonsquamous histologic type of NSCLC. PD-L1 expression was available for 66% of the patients and was predominantly assessed by the Dako 22C3 pharmDx assay[4,21] (101 of 133 [76%]). Other PD-L1 assays used included Ventana SP263 (four of 133 [3%] [Ventana Medical Systems), Ventana SP142 (three of 133 [2%]), E1L3N (two of 133 [2%]), PharmDx 28-8 (one of 133 [1%]), and immunohistochemistry not otherwise specified (22 of 133 [17%]). PD-L1 expression was positive in 41% of the patients. Most patients received no or one prior line of therapy before ICB, including 21% (42 of 200 patients) who received frontline ICB therapy. A full description of patient characteristics is presented in Table 1.

Most patients (157 of 200) were *HLA* class I–heterozygous and positive for supertypes A01 (43%), A02 (45%), A03 (52%), B07 (48%), and B44 (52%). The most common *HLA* class I alleles in this cohort were A02:01 (34.5%), A01:01 (23.5%), A03:01 (23.5%), B08:01 (18%), B44:03 (10.5%), C07:01 (24.5%), C04:01 (23%), and C07:02 (18%).

Among the 157 *HLA*-heterozygous patients, 78% progressed or died, and of the 43 homozygous patients, 79% progressed or died. PFS was 4.2 months (95% CI: 3.06-5.59) for the *HLA* class I–heterozygous group and 5.5 months (95% CI: 2.69–11.99) for *HLA*-homozygous group; there was no statistically significant difference between the groups (HR = 0.87, 95% CI: 0.59–1.28, log-rank $p = 0.48$) (Fig. 1*A*). The median PFS was positively correlated with smoking (HR = 0.65, 95% CI: 0.46–0.93, $p = 0.02$) and negatively correlated with presence of targetable driver mutations (for definition, see Methods) (HR = 2.08, 95% CI: 1.42–3.05, $p < 0.01$). Nonsquamous cell histologic type and prior radiation therapy appeared to be associated with better PFS, although this difference did not reach statistical significance (for nonsquamous versus squamous, HR = 0.71, 95% CI: 0.49–1.05, $p = 0.08$; and none/≥6 months versus <6 months, HR = 0.74, 95% CI: 0.53–1.03, $p = 0.08$) (Table 2). On multivariate analysis, histologic type, prior radiation, and presence of a targetable driver mutation were significantly correlated with PFS (see Table 2). A strong correlation was observed between histologic type and presence of a targetable driver mutation (two-sided Fisher's exact test $p < 0.01$). We also found no statistically significant difference in median PFS between homozygous and heterozygous groups for each *HLA* class I loci: A (HR = 0.79, 95% CI: 0.49–1.26, $p = 0.32$), B (HR = 1.21, 95% CI: 0.70–2.09, $p = 0.50$), and C (HR = 0.94, 95% CI: 0.55–1.61, $p = 0.83$) (Supplementary Fig. 1*A–C* and see also Table 2).

At the time of data set lock, 34% of patients (53 of 157) in the *HLA* class I–heterozygous group had died and 28% (12 of 43) in the homozygous group had died. The median OS was 28.8 months (95% CI: 26.2–not reached [NR]) in the *HLA* I–homozygous group and 22.0 months (95% CI: 20.7–NR) in the *HLA* I–heterozygous group. Despite the numerical difference, there was no statistically significant difference between the groups (HR = 0.67, 95% CI: 0.36–1.26, $p = 0.22$) (Fig. 1*B*). We also tested the correlation between *HLA* I homozygosity for each of the A, B, and C alleles and median OS. The *HLA*-A–homozygous group was found to have a higher median OS than the *HLA*-A–heterozygous group (NR versus 23.1 months [HR = 0.37, 95% CI: 0.15–0.92, $p = 0.03$]) (Supplementary Fig. 1*D*). No differences were observed between the homozygous and heterozygous groups for *HLA*-B and *HLA*-C (Supplementary Fig. 1*E* and *F* and see also Table 2). PD-L1 expression was positively correlated with OS (HR = 0.35, 95% CI: 0.19–0.66, $p < 0.01$), and although there was a trend for correlation of time from previous systemic therapy with OS (HR = 0.63, 95% CI: 0.37–1.07, $p = 0.08$), it did not reach statistical significance. In a multivariate analysis adjusting for *HLA*-A zygosity, time from previous systemic therapy, and PD-L1 expression, only PD-L1 expression remained statistically significant (HR = 0.39, 95% CI: 0.20–0.75, $p < 0.01$) (see Table 2).

HLA Class I Supertypes and Alleles: MDACC Cohort

Prior studies have shown that because of similarities in coding sequences and peptide binding, *HLA* class I alleles A and B can be grouped into supertypes.[19,24] Therefore, we evaluated whether any particular *HLA*-A or *HLA*-B supertype was associated with improved outcomes in advanced NSCLC. Supertypes A01, A02, A03, A01-A24, A24, B07, B08, B27, B44, B58, and B62 met the inclusion criteria (see Methods). On univariate analysis, none of the supertypes were correlated with PFS. In a multivariate analysis adjusting for histologic type, presence of targetable mutations, and time of prior radiation therapy, which were found to be correlated with PFS (see Table 2), supertype A24 showed a trend for being negatively correlated with PFS (HR = 1.38, 95% CI: 0.95–2.00, $p = 0.09$), but it did not reach statistical significance (Table 3). In addition, supertype A24 also showed a trend for correlation with shorter OS, but it was not statistically significant (HR = 1.66, 95% CI: 0.96–2.86, $p = 0.07$). In a multivariate analysis

Table 1. Patient Characteristics

Characteristic	MDACC Cohort (n = 200)	CM012 Cohort (n = 75)	Chowell Cohort (n = 371)
Age, y, n (%)			
≤64	80 (40)	36 (48)	261 (70)[a]
>64	120 (60)	39 (52)	110 (30)[a]
Sex, n (%)			
Female	96 (48)	38 (51)	51 (14)
Male	104 (52)	37 (49)	49 (13)
NA	0 (0)	0 (0)	271 (73)
Smoking status, n (%)			
Never	45 (22)	15 (20)	NA
Ever	155 (78)	60 (80)	NA
Histologic type, n (%)			
Nonsquamous	160 (80)	59 (79)	NA
Squamous	40 (20)	16 (21)	NA
PD-L1 expression, n (%)			
Negative	51 (26)	25 (33)	0 (0)
Positive	82 (41)	45 (60)	0 (0)
NA	67 (34)	5 (7)	371 (100)
Targetable driver mutation, n (%)			
No	164 (82)	67 (89)	NA
Yes	36 (18)	8 (11)	NA
STK11 mutation, n (%)			
No	177 (89)	67 (89)	NA
Yes	20 (10)	7 (9)	NA
NA	3 (2)	1 (1)	NA
Prior radiation therapy, n (%)			
none/≥6 mo	141 (70)	NA	NA
<6 mo	59 (30)	NA	NA
Prior lines of therapy, n (%)			
0–1	150 (75)	NA	NA
≥2	50 (25)	NA	NA
Time from prior systemic therapy, n (%)			
none/≥6 mo	81 (40)	NA	NA
<6 mo	119 (60)	NA	NA
Concurrent chemotherapy, n (%)			
No	183 (92)	75 (100)	371 (100)
Yes	17 (8)	0 (0)	0 (0)
Tumor mutational burden, n (%)			
≥ median	0 (0)	38 (51)	161 (43)
< median	0 (0)	37 (49)	144 (39)
NA	200 (100)	0 (0)	66 (18)
Overall *HLA* class I zygosity, n (%)			
Heterozygous	157 (78)	55 (73)	291 (78)
Homozygous	43 (22)	20 (27)	80 (22)
HLA-A zygosity, n (%)			
Heterozygous	174 (87)	62 (83)	328 (88)
Homozygous	26 (13)	13 (17)	43 (12)
HLA-B zygosity, n (%)			
Heterozygous	183 (92)	65 (87)	350 (94)
Homozygous	17 (8)	10 (13)	21 (6)
HLA-C zygosity, n (%)			
Heterozygous	180 (90)	66 (88)	331 (89)
Homozygous	20 (10)	9 (12)	40 (11)

[a]Data available only with a cutoff of 60 years of age.
MDACC, M. D. Anderson Cancer Center; CM012, CheckMate-012; NA, not available; PD-L1, programmed death ligand 1; *STK11*, serine/threonine kinase 11 gene; *HLA*, human leukocyte antigen.

adjusting for PD-L1 expression, which was found to be positively correlated with OS (see Table 2), no supertypes were correlated with OS (see Table 3).

Next, we tested the correlation between *HLA*-A and *HLA*-C alleles and survival. Because *HLA*-B supertypes showed no correlation with PFS or OS, no B alleles were

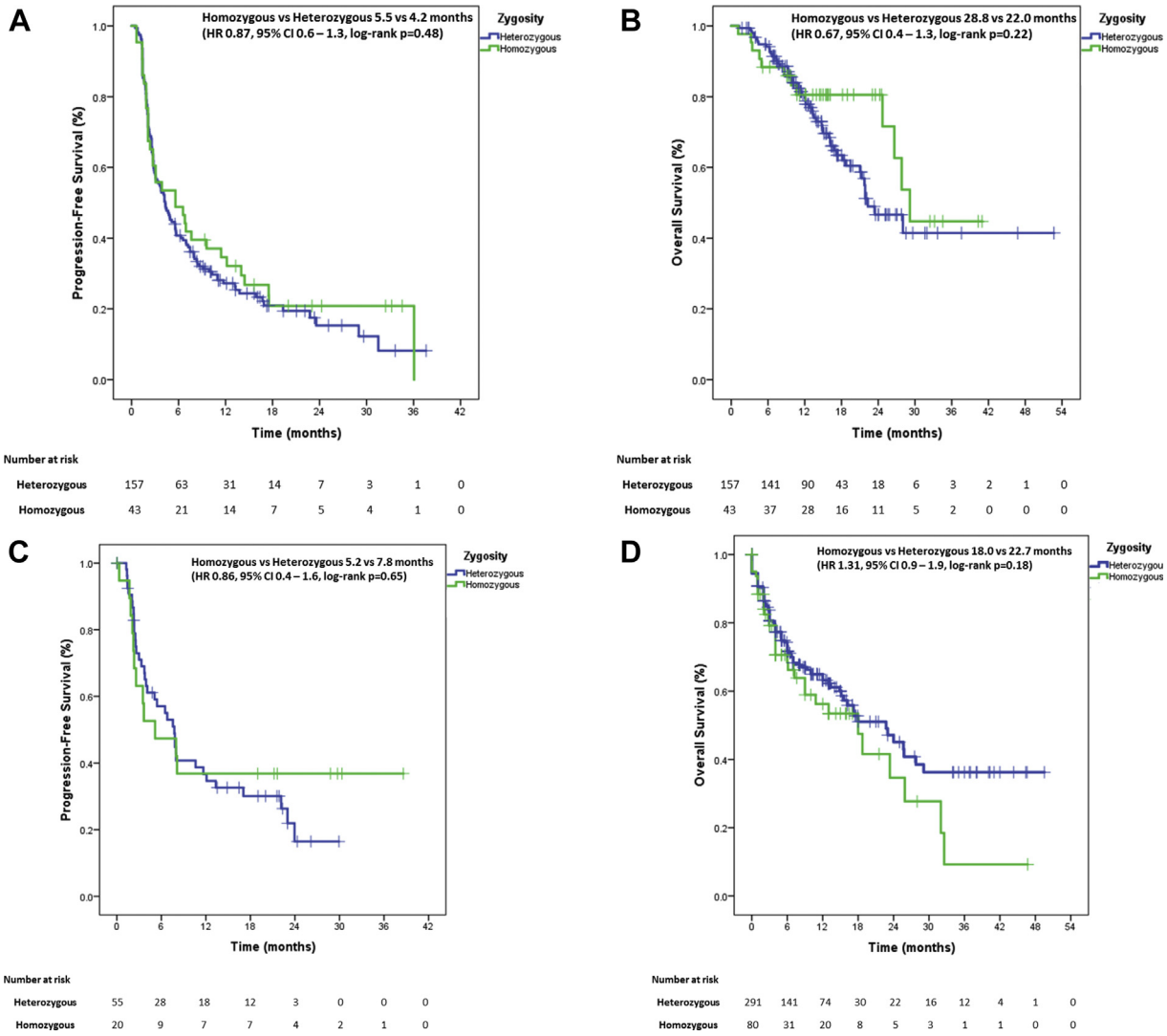

Figure 1. Zygosity and outcomes. Progression-free survival in the M. D. Anderson cohort (*A*), overall survival in the M. D. Anderson cohort (*B*), progression-free survival in the CheckMate-012 cohort (*C*), and overall survival in the Chowell cohort (*D*).

included. Allele C03:04 showed a significant correlation with PFS in univariate analysis (HR = 1.82, 95% CI: 1.11–3.00, $p = 0.02$). Although a trend was observed for allele C12:03 (HR = 0.56, 95% CI: 0.29–1.10, $p = 0.09$), it did not reach statistical significance. After adjustment for histologic type, presence of targetable mutations, and previous radiation in a multivariate model, only C03:04 (HR = 2.30, 95% CI: 1.35–3.91, $p < 0.01$) was found to be correlated with PFS. Furthermore, allele A23:01 appeared to be correlated with shorter PFS, but not statistically significantly so (HR = 1.88, 95% CI: 0.91–3.89, $p = 0.09$) (see Table 3). In the OS analysis, allele A23:01 was significantly correlated with OS (HR = 2.39, 95% CI: 1.03–5.57, $p = 0.04$), and a nonsignificant trend for longer OS was observed for allele C05:01 (HR = 0.51, 95% CI: 0.23–1.13, $p = 0.10$). However, in a multivariate model after adjustment for PD-L1 expression, no *HLA* class I alleles were significantly correlated with OS (see Table 3).

Outcome Analysis: CM012 Cohort

TMB has been consistently shown to be correlated with benefit from ICB in several cancer types, including NSCLC.[7,9,25,26] Because TMB data were not available for the MDACC cohort, we aimed to validate our findings in cohorts for which TMB data were available.

The CM012 cohort included 75 patients. Most patients were ever-smokers (80%) and had the nonsquamous histologic type (79%). PD-L1 expression was positive in 60% of the patients, and most did not have a targetable driver mutation (89%) (see Table 1). The median TMB for this cohort was 158 mutations. Most

Table 2. Clinical Outcomes: M. D. Anderson Cohort

Characteristic	HR (95% CI)	*p* Value
Progression-free survival		
Univariate analysis		
Zygosity (homozygous vs. heterozygous)	0.87 (0.59-1.28)	0.480
HLA-A homozygous (yes vs. no)	0.79 (0.49-1.26)	0.315
HLA-B homozygous (yes vs. no)	1.21 (0.70-2.09)	0.504
HLA-C homozygous (yes vs. no)	0.94 (0.55-1.61)	0.832
Age (>64 vs. ≤64)	0.89 (0.64-1.22)	0.461
Sex (male vs. female)	1.05 (0.76-1.43)	0.781
Smoking status (ever vs. never)	0.65 (0.46-0.93)	0.019
Histological type (nonsquamous vs. squamous)	0.71 (0.49-1.05)	0.083
PD-L1 expression (positive vs. negative)	0.82 (0.55-1.22)	0.326
Targetable driver mutation (yes vs. no)	2.08 (1.42-3.05)	<0.001
STK11 mutation (yes vs. no)	1.12 (0.65-1.91)	0.689
Prior radiation therapy (none/≥6 mo vs. <6 mo)	0.74 (0.53-1.03)	0.076
Prior lines of therapy (≥2 vs. 0 or 1)	0.97 (0.68-1.39)	0.884
Time from prior systemic therapy (none/≥6 mo vs. <6 mo)	0.96 (0.70-1.33)	0.826
Concurrent agents (yes vs. no)	0.61 (0.33-1.12)	0.112
Multivariate analysis		
Histologic type (nonsquamous vs. squamous)	0.59 (0.40-0.88)	0.010
Prior radiation therapy (none/≥6 mo vs. <6 mo)	0.70 (0.50-0.99)	0.042
Targetable driver mutation (yes vs. no)	2.43 (1.63-3.63)	<0.001
Overall survival		
Univariate analysis		
Zygosity (homozygous vs. heterozygous)	0.67 (0.36-1.26)	0.217
HLA-A homozygous (yes vs. no)	0.37 (0.15-0.92)	0.033
HLA-B homozygous (yes vs. no)	1.20 (0.48-2.98)	0.700
HLA-C homozygous (yes vs. no)	1.08 (0.49-2.38)	0.845
Age (>64 vs. ≤64)	1.09 (0.66-1.79)	0.744
Sex (male vs. female)	1.00 (0.61-1.63)	0.996
Smoking status (ever vs. never)	1.10 (0.62-1.97)	0.735
Histologic type (nonsquamous vs. squamous)	0.73 (0.41-1.30)	0.280
PD-L1 expression (positive vs. negative)	0.35 (0.19-0.66)	0.001
Targetable driver mutation (yes vs. no)	1.19 (0.63-2.23)	0.591
STK11 mutation (yes vs. no)	1.78 (0.84-3.78)	0.130
Prior radiation therapy (none/≥6 mo vs. <6 mo)	0.73 (0.44-1.22)	0.235
Prior lines of therapy (≥2 vs. 0 or 1)	1.53 (0.92-2.54)	0.100
Time from prior systemic therapy (none/≥6 mo vs. <6 mo)	0.63 (0.37-1.07)	0.085
Concurrent agents (yes vs. no)	0.89 (0.36-2.23)	0.810
Multivariate analysis		
HLA-A homozygous (yes vs. no)	0.44 (0.10-1.82)	0.256
Time from prior systemic therapy (none/≥6 mo vs. <6 mo)	0.69 (0.35-1.34)	0.271
PD-L1 expression (positive vs. negative)	0.39 (0.20-0.75)	0.005

HR, hazard ratio; CI, confidence interval; *HLA*, human leukocyte antigen; *STK11*, serine/threonine kinase 11 gene; PD-L1, programmed death ligand 1.

patients were *HLA* class I–heterozygous (73%), and the most common supertypes were A02 (52%), B07 (52%), A03 (44%), B44 (43%), and A01 (37%).

Of the 55 *HLA* class I–heterozygous patients, 69% progressed or died. Of the 20 homozygous patients, 60% progressed or died. The median PFS was 5.2 months (95% CI: 2.60–NR) for the *HLA* class I–homozygous group versus 7.8 months (95% CI: 4.11–13.30) for the heterozygous group, and there was no statistically significant difference between the groups (HR = 0.86, 95% CI: 0.45–1.65, $p = 0.65$) (Fig. 1*C*). Presence of a targetable driver mutation, *STK11* mutation, and TMB were the variables most strongly correlated with PFS (Table 4). Presence of a targetable driver mutation was strongly correlated with low TMB (two-sided Fisher's exact test p value = 0.002). In a multivariate analysis, presence of a targetable driver mutation, presence of *STK11* mutation, and low TMB continued to be significantly correlated with shorter PFS (see Table 4).

We also investigated the effect of *HLA* I homozygosity for each of the A, B, and C alleles. The median PFS for the *HLA*-A homozygous group was 6.6 months (95% CI: 3.52– NR). It was 7.8 months (95% CI: 3.94–13.30) for the *HLA*-A–heterozygous group, 8.0 months (95% CI: 2.23–NR) for the *HLA*-B–homozygous group, 7.6 months (95% CI: 3.94–12.10) for the *HLA*-B–heterozygous

Table 3. *HLA* Class I Supertype and Allele Analysis: M. D. Anderson Cohort

Characteristic	HR (95% CI)	*p* Value
HLA supertype multivariate analysis		
Progression-free survival		
Histologic type (nonsquamous vs. squamous)	0.59 (0.40-0.88)	0.010
Targetable driver mutation (yes vs. no)	2.45 (1.64-3.66)	<0.001
Prior radiation therapy (none/≥6 mo vs. <6 mo)	0.71 (0.50-0.99)	0.046
A24 (present vs. absent)	1.38 (0.95-2.00)	0.088
Overall survival		
PD-L1 expression (positive vs. negative)	0.41 (0.21-0.78)	0.007
A24 (present vs. absent)	1.66 (0.78-3.53)	0.191
HLA allele multivariate analysis		
Progression-free survival		
Histologic type (nonsquamous vs. squamous)	0.54 (0.35-0.82)	0.004
Targetable driver mutation (yes vs. no)	2.70 (1.77-4.12)	<0.001
Prior radiation therapy (none/≥6 mo vs. <6 mo)	0.68 (0.47-0.99)	0.043
A23:01 (present vs. absent)	1.88 (0.91-3.89)	0.089
C03:04 (present vs. absent)	2.30 (1.35-3.91)	0.002
Overall survival		
PD-L1 expression (positive vs. negative)	0.45 (0.23-0.88)	0.021
A23:01 (present vs. absent)	0.85 (0.11-6.46)	0.876
C05:01 (present vs. absent)	0.52 (0.18-1.52)	0.229

HR, hazard ratio; CI, confidence interval; *HLA*, human leukocyte antigen; PD-L1, programmed death ligand 1; *STK11*, serine/threonine kinase 11 gene.

group, 8.0 months (95% CI: 2.23–NR) for the *HLA*-C–homozygous group, and 7.6 months (95% CI: 3.94–12.10) for the *HLA*-C–heterozygous group. There were no statistically significant differences between the *HLA*-A–, *HLA*-B–, and *HLA*-C–homozygous groups and their corresponding heterozygous groups (Supplementary Fig. 2*A*–*C* and see also Table 4).

HLA Class I Supertypes and Alleles: CM012 Cohort

There was no significant correlation between *HLA* class I supertype and PFS in the CM012 cohort. In a multivariate analysis adjusting for TMB, presence of *STK11* mutation, and presence of a targetable driver mutation, only supertype A02 showed a trend for correlation with longer PFS, but it did not reach statistical significance (HR = 0.61, 95% CI; 0.34–1.09, $p = 0.09$) (see Table 4). None of the *HLA* class I alleles were significantly correlated with PFS. Allele A23:01 was not included in this analysis owing to the small sample size (five of 75 patients [~7%]).

Outcomes Analysis: Chowell Cohort

In a prior pan-cancer analysis that included patients with NSCLC, *HLA* class I zygosity was found to be correlated with OS upon treatment with ICB.[19] However, we did not observe this correlation in the MDACC and CM012 cohorts. To test whether the discrepancy was due to the cancer type analyzed, as the pan-cancer cohort was enriched for patients with melanoma (~35%), we extracted individual patient data from the previous publication by Chowell et al,[19] but limited the analysis to patients with NSCLC. Of 371 patients with NSCLC, 291 were *HLA* class I–heterozygous and 80 were *HLA* class I–homozygous. The median TMB was 7.87 mutations/megabase for targeted panel sequencing and 142 mutations for WES. The median OS was 22.7 months (95% CI: 15.74–29.72) for the *HLA* class I–heterozygous group versus 18.0 months (95% CI: 9.07–26.93) for the *HLA* class I–homozygous group; no statistically significant difference between the two groups was observed (HR = 1.31, 95% CI: 0.88–1.94, $p = 0.18$) (Fig. 1*D*). In a multivariate analysis adjusting for age and TMB, zygosity was not correlated with OS (HR = 1.28, 95% CI: 0.83–1.97, $p = 0.26$) (Supplementry Table 1).

Discussion

In the present study, we were unable to detect a significant correlation between *HLA* class I zygosity and survival in patients with advanced NSCLC treated with ICB. Heterozygosity in each of the *HLA* class I loci also showed no correlation with outcome. These findings were consistent across three independent cohorts, one from a clinical trial with combination ICB treatment (nivolumab and ipilimumab) and two treated in distinct large academic cancer centers. These findings are distinct from what has been previously shown in a pan-cancer analysis investigating the effect of *HLA* class I zygosity in patients treated with ICB.[19] One possible explanation is that *HLA* class I zygosity has a lesser impact on survival following ICB therapy than TMB[7–9] and PD-L1

Table 4. Progression-Free Survival: CheckMate-012 Cohort

Characteristic	HR (95% CI)	*P* value
Univariate analysis		
Zygosity (homozygous vs. heterozygous)	0.86 (0.45-1.65)	0.649
HLA-A homozygous (yes vs. no)	0.83 (0.39-1.77)	0.627
HLA-B homozygous (yes vs. no)	0.76 (0.32-1.79)	0.529
HLA-C homozygous (yes vs. no)	0.73 (0.29-1.85)	0.508
Age (>64 vs. ≤64)	0.89 (0.51-1.55)	0.674
Sex (male vs. female)	1.03 (0.59-1.79)	0.921
Smoking status (ever vs. never)	0.70 (0.36-1.36)	0.288
Histologic type (nonsquamous vs. squamous)	0.85 (0.42-1.70)	0.648
PD-L1 expression (positive vs. negative)	0.86 (0.47-1.59)	0.634
Targetable driver mutation (yes vs. no)	3.43 (1.56-7.54)	0.002
STK11 mutation (yes vs. no)	3.05 (1.27-7.34)	0.013
Tumor mutational burden (≥ median vs. < median)	0.45 (0.25-0.79)	0.006
Multivariate analysis		
Tumor mutational burden (≥ median vs. < median)	0.45 (0.24-0.84)	0.011
STK11 mutation (yes vs. no)	4.31 (1.73-10.77)	0.002
Targetable driver mutation (yes vs. no)	2.62 (1.12-6.12)	0.026
HLA supertype multivariate analysis		
Tumor mutational burden (≥ median vs. < median)	0.43 (0.23-0.80)	0.008
STK11 mutation (yes vs. no)	3.59 (1.41-9.15)	0.008
Targetable driver mutation (yes vs. no)	2.44 (1.04-5.70)	0.040
A02 (present vs. absent)	0.61 (0.34-1.09)	0.094

HR, hazard ratio; CI, confidence interval; *HLA*, human leukocyte antigen; PD-L1, programmed death ligand 1; *STK11*, serine/threonine kinase 11 gene.

expression,[4,6] and therefore, a larger cohort of patients with NSCLC treated with ICB (e.g., >1000 patients, as previously described[27]) would be required to achieve a significant correlation. In addition, as the pan-cancer cohort was enriched for patients with melanoma (~35%), it is also possible that *HLA* class I zygosity is more relevant in melanoma than in NSCLC. Future studies are warranted to further address whether *HLA* class I zygosity affects the survival of patients with melanoma treated with ICB, as well as the survival of those with other tumor types. Furthermore, PD-L1 expression, which is an important predictor of benefit from ICB in lung cancer as demonstrated in the current study and in prior studies,[4,6,22] was not assessed in the pan-cancer analysis, which could potentially have confounded the findings from this cohort. Tumor genomic characteristics also appear to be more impactful than *HLA* class I zygosity in predicting benefit from ICB in NSCLC. For example, *EGFR* and *ALK* alterations have been associated with a low likelihood of benefit from ICB,[1,25,28–30] a finding that was replicated in both the MDACC and CM012 cohorts.

The negative findings in our study do not minimize the importance of major histocompatibility complex (MHC) I in antitumor immune surveillance and response to ICB therapy in NSCLC. On the contrary, they suggest that regulation of MHC I expression and antigen presentation occurs through alternative mechanisms in NSCLC. Decreased expression of beta-2 microglobulin, which is another important component of the MHC I complex, has been demonstrated to be a mechanism of acquired resistance to ICB in gastrointestinal tumors,[12] melanoma,[31] and NSCLC.[32] Furthermore, decreased expression of *HLA* class I has been associated with acquired resistance to ICB in advanced NSCLC,[32] and *HLA* class I mutations and loss of heterozygosity have been correlated with tumor immune evasion.[17,33] These findings suggest that decreased expression of MHC class I might be a more impactful mechanism of immune escape and lack of benefit from ICB than *HLA* class I zygosity in NSCLC. It is also possible that antigen presentation through MHC class II might play a role in predicting response to ICB, as has been demonstrated in other tumor types,[34,35] but this requires validation in NSCLC. Therefore, the role of MHC antigen presentation in predicting response to ICB should remain an important field of active investigation.

Presence of a targetable driver mutation was correlated with worse PFS in both the MDACC and CM012 cohorts, which is consistent with prior reports.[1,22,36] Although PD-L1 expression was correlated with OS in the MDACC cohort, no correlation was observed for PFS in the CM012 and MDACC cohorts. It is possible that this analysis was limited by the number of patients with unknown PD-L1 status (34%) and by how testing was performed (76% of patients were tested using the Dako 22C3 antibody and 24% were tested using other PD-L1 antibodies/assays) in the MDACC cohort. However, the

finding from the CM012 cohort is consistent with previous results from the CheckMate-227 trial showing that in a TMB-high population of patients with advanced NSCLC, the combination of nivolumab plus ipilimumab showed similar benefit independently of PD-L1 status.[37] The higher PFS in TMB-high patients in the CM012 cohort is consistent with what has been previously reported for patients with NSCLC treated with ICB.[7,9,25] However, why higher TMB was not associated with longer OS in the Chowell cohort remains unclear, and possible explanations are limited by the available patient characteristics. *STK11* mutations were correlated with worse outcome in the CM012 cohort, which is consistent with what has been previously reported by our group in NSCLC,[38] but no such results were observed for the MDACC cohort. This is likely due to the fact that only 20 patients (10%) had a *STK11* mutation, which limited the power of the analysis. Also, 20% of patients with *STK11* mutations (four of 20) received ICB with concurrent chemotherapy, which could have prolonged PFS.

Our observations in the MDACC cohort suggest a possible correlation with clinical outcome for the A24 supertype and the C03:04 allele. However, this was not seen in the other cohorts. The correlation between these alleles, PFS, and OS could indicate the presentation of a more immunogenic and immunodominant epitope not presented otherwise, but this possibility remains unclear at this point and requires further preclinical and clinical evaluation. We were also limited by the sample size of all three cohorts for this analysis, especially for less common alleles. For example, allele A23:01 was not assessed in the CM012 cohort owing to the small sample size. As previously mentioned, it is possible that larger cohorts may reveal these differences if in fact they exist,[27] and it may also allow study of less common *HLA* class I alleles. Despite these limitations, our data suggest that *HLA* class I type plays a lesser role, if any, than do other variables, such as PD-L1 expression, TMB, presence of targetable driver mutations and *STK11* mutations, in predicting benefit from ICB in NSCLC.

In conclusion, our study showed no correlation between *HLA* class I genotype or diversity and benefit from PD-1/PD-L1 checkpoint blockade in advanced NSCLC. These results suggest that the impact of *HLA* class I diversity may be disease specific and that certain genomic and immune features are more impactful in determining benefit from ICB in NSCLC. Research efforts should continue to focus on mechanisms of de novo and acquired resistance to ICB, especially in the context of concurrent treatment with chemotherapy, for development of more effective treatment strategies that allow for durable responses in a greater proportion of patients with advanced NSCLC.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2019.02.008.

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