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Supplementary Material for

Patient HLA class I genotype influences cancer response to checkpoint blockade immunotherapy

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Tables S1 and S9 as separate Excel files

Materials and Methods

Study Design and Description of Patient Sets

For the analyses presented in this study, we used two different sets of cancer patients who were treated with immune checkpoint inhibitors. For cohort 1, we obtained exome sequencing data and clinical data from 371 patients who were treated with anti-CTLA-4 or anti-PD-1 therapy. Two patients did not have overall survival data and they were not included in the analyses. Out of the 369 patients with complete clinical data, 269 patients had advanced melanoma and 100 patients had advanced non-small cell lung cancer (NSCLC). The melanoma data are from four previously reported studies (*1-4*). The NSCLC data are from patients with metastatic disease treated mainly with anti-PD-1 monotherapy. The patients are from a prospective trial that we reported previously (*5*) and from New York-Presbyterian /Columbia University Medical Center. Exome sequencing data were not available for 67 patients with NSCLC. All patients were treated under institutional review approved prospective protocols. For cohort 2, we obtained independent next-generation sequencing data using a targeted gene panel (MSK-IMPACT) and clinical data from 1,166 patients representing different cancer types on an institutional IRB-approved research protocol (NCT01775072). These patients were treated with anti-CTLA-4, or PD-1/PD-L1 blockade, or a combination of both drugs at the Memorial Sloan Kettering Cancer Center (*6*). Clinical characteristics of patient cohorts are provided in table S1. For analysis of germline variants, original sequencing files and relevant clinical data were anonymized by a third party without investigator access to the original patient identification according the protocol design. Additional details regarding these tumors can be found in the original publications (*1-6*). The TCGA exome data for the patients with melanoma was obtained from the Cancer Genome Atlas (TCGA) (N = 378).

Overall Survival and Clinical Response Data

The clinical endpoint used in these analyses was overall survival, defined as the length of time from treatment start to time to event (survival or censor). All clinical data were obtained from the original studies (*1-6*). Clinical data for the TCGA patients with melanoma were accessed through the TCGA data portal.

HLA Class I Genotyping Data

We performed high-resolution HLA class I genotyping from germline normal DNA exome sequencing data directly or using a clinically validated HLA typing assay (LabCorp). Patient exome data or targeted gene panels were obtained and the well-validated tool Polysolver was used to identify HLA class I alleles with default parameter settings (*7*). It has previously been shown that Polysolver is highly accurate compared to serology or PCR-based methods (*7, 8*). For quality assurance, a subset of these patients (N = 22) was molecularly HLA typed at a CLIA-certified center (New York Blood Center) and typed using Polysolver. The overall concordance between Polysolver and the molecular typing was 96%. Concordance is defined as [(6 – number of allele mismatches

between Polysolver and molecular typing) / 6] x 100. Furthermore, HLA class I homozygosity detected by Polysolver was confirmed by two additional computational tools, OptiType and HLA-SOAP (*9, 10*). For the 67 patients with NSCLC with no available exome sequencing data, HLA class I molecular typing was done at LabCorp. For quality assurance of MSK-IMPACT (CLIA-certified hybridization-capture based assay) captures HLA class I (*6, 11, 12*), we compared HLA class I typing by Polysolver between 37 samples that we sequenced with MSK-IMPACT and whole exome. The MSK-IMPACT panel successfully captured HLA-A, -B, and -C. To make sure that HLA class I genes have adequate coverage in MSK-IMPACT bam files, we also applied bedtools multicov tool (http://bedtools.readthedocs.io/en/latest/content/tools/multicov.html), which reports the count of alignments from multiple position-sorted and indexed BAM files that overlap with targets intervals in a BED format. Only high quality reads were counted and only samples with sufficient coverage were used. The overall concordance of class I typing between the MSK-IMPACT samples and their matched WES samples was 96%. For cohort 1, HLA class II genotyping was performed using HLA-SOAP (*9*).

Statistical Analysis

We performed survival analyses using the Kaplan-Meier estimator. The log-rank test was used to determine statistical significance of the survival distributions between patients with a specific genotyping and patients without it. We computed hazard ratios using univariate or multivariable Cox regression. Tumor mutational load was calculated from the total nonsynonymous mutational count from whole exome sequencing. To stratify patients into two groups, with high and low tumor mutational load, we used cutoffs calculated by the R function maxstat.test (https://cran.r-project.org/web/packages/maxstat/vignettes/maxstat.pdf). In Fig. 1F, Fig. 1G, Fig. 2G, and Fig. 2H we used a range of cutoffs across the quartiles of the distribution of the number of somatic mutations of the specific cohort analyzed. The cutoffs were used to stratify patients into two groups, high or low tumor mutational load, and to generate the box plot showing the distribution of hazard ratios resulting from the survival analyses using the multiple cutoffs. In Figure 1F, we used the range [80, 542]. For Figure 1G, we used [5, 65]. For Figure 2G, we used the range [108, 569]. And for Figure 2H, we used [5, 25]. Comparison of number of somatic mutations between HLA class I homozygotes and heterozygotes groups was performed with the Wilcoxon-rank sum test. Comparison of the on-therapy clonality of TCR CDR3s in patients who are HLA heterozygous compared to patients who are HLA homozygous (in at least one class I locus or at HLA-DP) was performed with the Wilcoxon-rank sum test. All statistical analysis was performed in the R Statistical Computing environment version 3.3.1 (http://www.r-project.org).

Mutational Analysis Pipeline

For cohort 1, whole-exome sequencing for all data sets was previously completed (*2-5*). Analysis was performed as described by DePristo et al. (*13, 14*) As previously described (*14*), paired-end reads in FASTQ format were aligned to the reference human genome

GRCh37 using the Burrows–Wheeler aligner (BWA; v0.7.10) (*15*). Local realignment was performed using the Genome Analysis Toolkit (GATK 3.2.2) (*16*). Duplicate reads were removed using Picard version 1.119. To identify somatic single nucleotide variants (SNVs), we used a pipeline that integrates mutation calls from four different mutation callers: MuTect 1.1.4, Strelka 1.0.3, SomaticSniper 1.0.4, and Varscan 2.3.7 (*17-20*). Insertions and deletions were determined using Strelka 1.0.3 with default settings (*13, 14*). SNVs with an allele read count of less than 4 or with corresponding normal coverage of less than 7 reads were filtered out. For cohort 2, relative mutational load was determined using MSK-IMPACT consistent with targeted panels as a validated method to determine relative mutational load (*6, 11, 12, 21*). For cohort 1, we identified small insertions and deletions (indels) by employing an in-house pipeline consisting of three callers: Strelka2, VarScan2, and Platypus (v.0.8.1-1). To maximize the identification of true somatic indel mutations, we applied additional filters: (1) Only indels called by at least two callers were taken into consideration; (2) Low mappability ("blacklisted") regions were excluded; and (3) Indels reported in COSMIC were included in the list.

Loss of Heterozygosity of HLA Class I Analysis

Copy number variation analysis was performed using FACETS 0.5.6 (*22*) to determine allele specific copy number. Segments within the chromosome 6p locus were identified containing the HLA-A, HLA-B and HLA-C loci. Loss of heterozygosity (LOH) was defined as a minor allele copy number estimate of 0 for any of the HLA loci using the expectation-maximization model (*22*).

TCR β-Chain Sequencing and Analysis

We employed next-generation sequencing of TCR β-chain complementarity determining regions (CDR3s) (TCR-seq) (Adaptive Biotechnologies) (*23, 24*) from a subset of tumor samples collected on-therapy (4 weeks post-Nivolumab initiation) (*4*). We subsequently calculated the clonality of the TCR CDR3 repertoire, defined as the complement of evenness (i.e., 1 – evenness). Evenness is a metric commonly used to characterize the distribution of the frequencies of the CDR3s (*25*). Evenness is defined as the observed Shannon entropy *(H)* divided by the maximum possible *H*, given the number of unique elements in a population (*4*). Data for individual TCR sequences, including V and J gene segment identification and CDR3 sequences, were obtained from Adaptive Biotechnologies for customized analysis of T cell repertoire. As described in (*4, 26*), the clonality of CDR3 amino acid sequences encoded by a single VJ cassette combination was analyzed individually for every observed VJ combination.

HLA Class I Structural Analysis and Molecular Dynamics Simulations

The neoantigen structure within the pHLA complex presented in PDB 1M6O was mutated to conform to the desired B44 motif (F3I, P4G, A6V, F9Y) using the VMD Mutator plugin. All images were rendered using the VMD 1.9.2 software package (*27*).

Molecular dynamics (MD) simulations of isolated HLA class I alleles and HLA-peptide complexes were initiated from configurations drawn from crystal structures at the highest available resolutions: HLA-B*15:01 (PDB ID: 1XR9); HLA-B*07:02 (PDB ID: 5EO0); and HLA-B*53:01 (PDB ID: 1A1M). To generate isolated HLA configurations, atoms corresponding to bound peptides were removed. After the addition of hydrogen atom and disulfide bond patches, each system was solvated in TIP3P water molecules and brought to a physiological concentration (150 mM) of Na^+ and Cl^- ions. Following similar protocols used in our previous studies (*28-30*), the resulting protein-water systems were minimized for 25000 steps by steepest descent, and then equilibrated with and without harmonic protein restraints in separate 5 ns simulations. Configurations taken from the ends of equilibration runs were used to seed production simulations, which were extended to 500 ns in duration for HLA-B*15:01 and 300 ns in length for HLA-B*07:02 and HLA-B*53:01. In all equilibration and production runs, temperature and pressure were constrained at 310 K and 1 atm using a Langevin thermostat and Parrinello-Rahman barostat, respectively. All MD simulations were conducted with the NAMD 2.11 simulation package (*31*). Inter-residue separations and residue-position root mean square fluctuations (RMSFs) were computed using standard utilities included in the GROMACS 5.1 software suite (*32*). Simulation snapshots were generated with VMD (*27*).

Supplementary Text

Association of Homozygosity at One Specific or More HLA Class I Loci with Overall Survival

Patients were divided into: individuals who were heterozygous at all three class I loci; individuals homozygous at one or more class I loci; individuals homozygous at the specified locus, but heterozygous at both of the other two loci; and individuals homozygous at the specified locus and also at one of the other two loci, but heterozygous at the other one. Homozygosity at HLA-A and HLA-B and homozygosity at HLA-A and HLA-C were rare in these patients, which limited the interpretability of analyses involving combinations of loci.

Assessment of Linkage Disequilibrium between HLA-B44 and HLA Class II Genotype

We did not find presence of nonrandom association between HLA-B44 and any particular HLA class II genotype. For DR4: $D' = 0.133$; $r^2 = 0.09$. For DR7: $D' = 0.26$; $r^2 = 0.1324$ (R Package "Genetics" 1.3.8.1).

Fig. S1

(A and B) Number of somatic coding mutations in the tumors between patients who were homozygous for at least one HLA class I locus and patients who are heterozygous at each class I locus in cohort 1 and cohort 2, respectively. The P value was calculated by Wilcoxon-rank sum test.

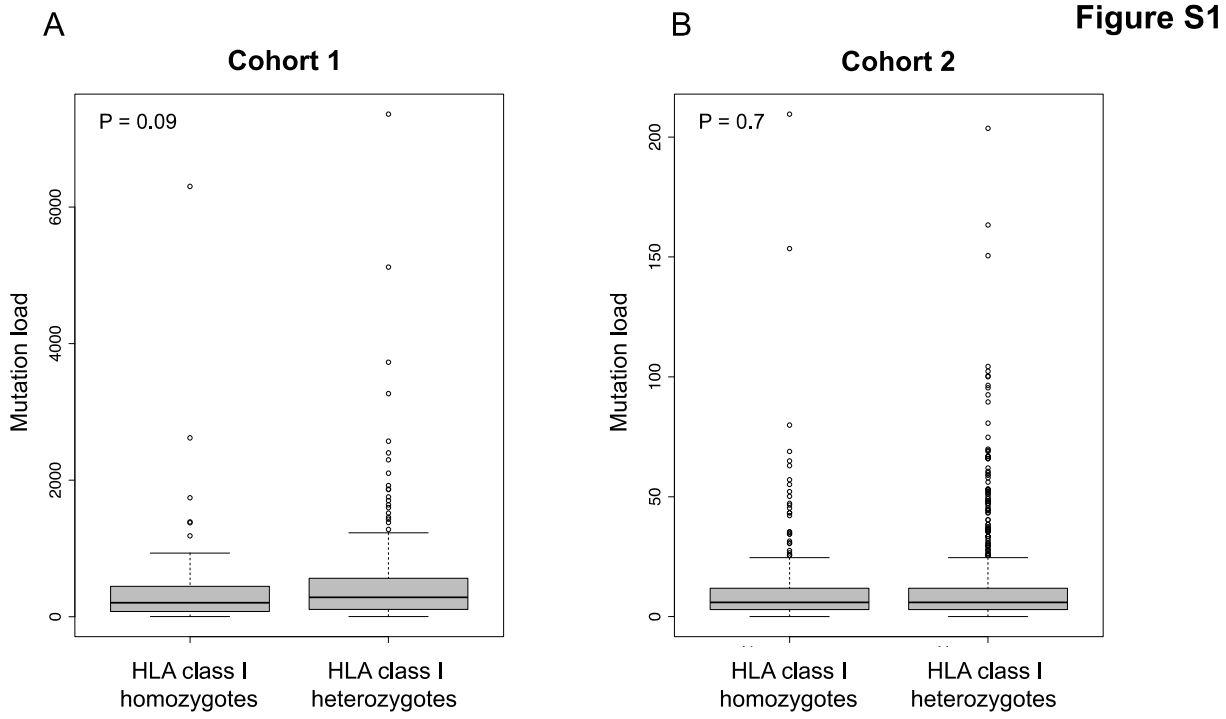

Fig. S2

(A) Influence of HLA-DP homozygosity on survival in patients treated with ICB. (B) Effect of HLA homozygosity (in at least one HLA class I locus or at HLA-DP) on overall survival in patients treated with ICB.

Figure S2

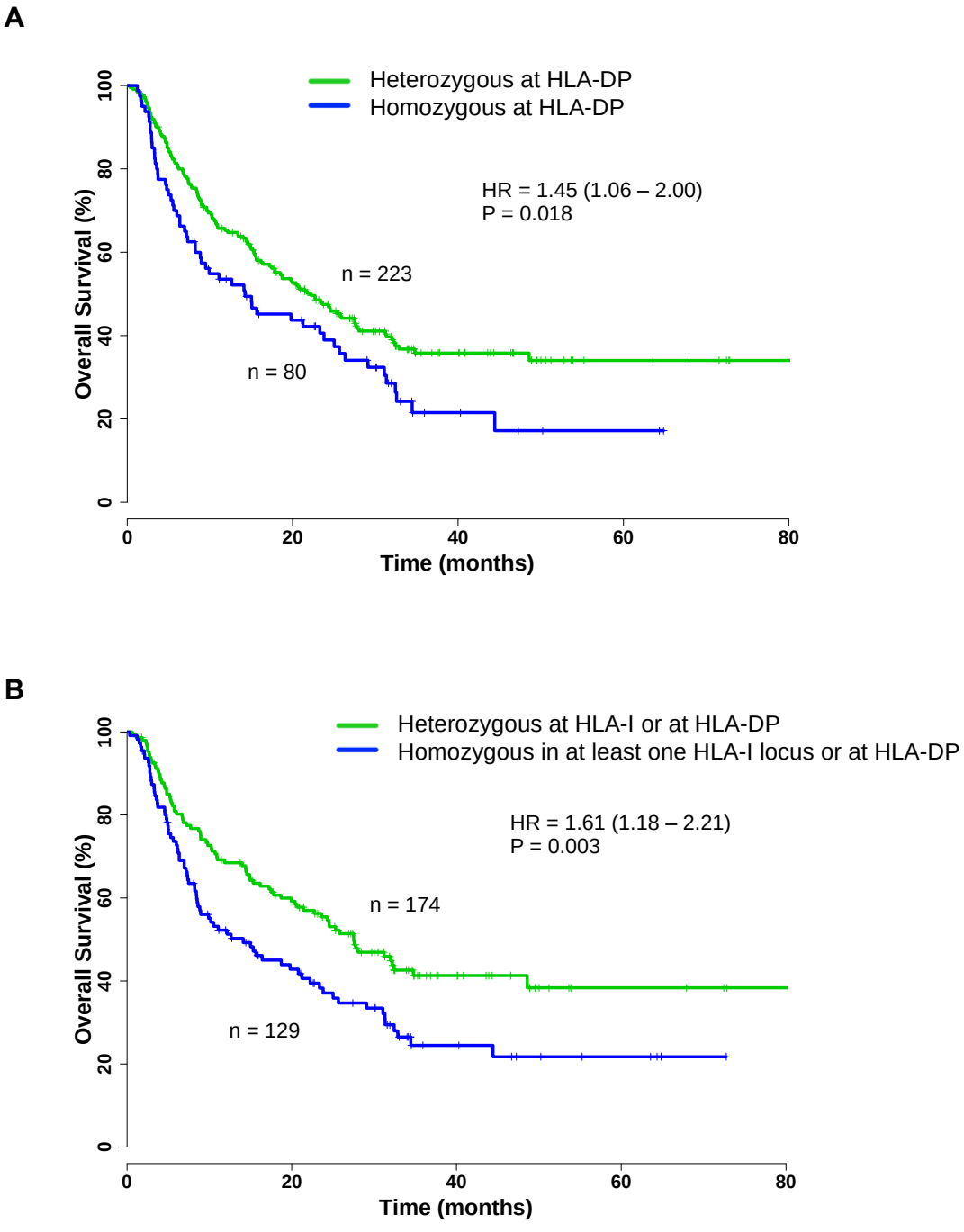

Fig. S3

E > K, G > E, S > F, P > L, D > N, and P > S substitutions define amino acid mutation signatures across tumors of patients with melanoma from cohort 1.

Figure S3

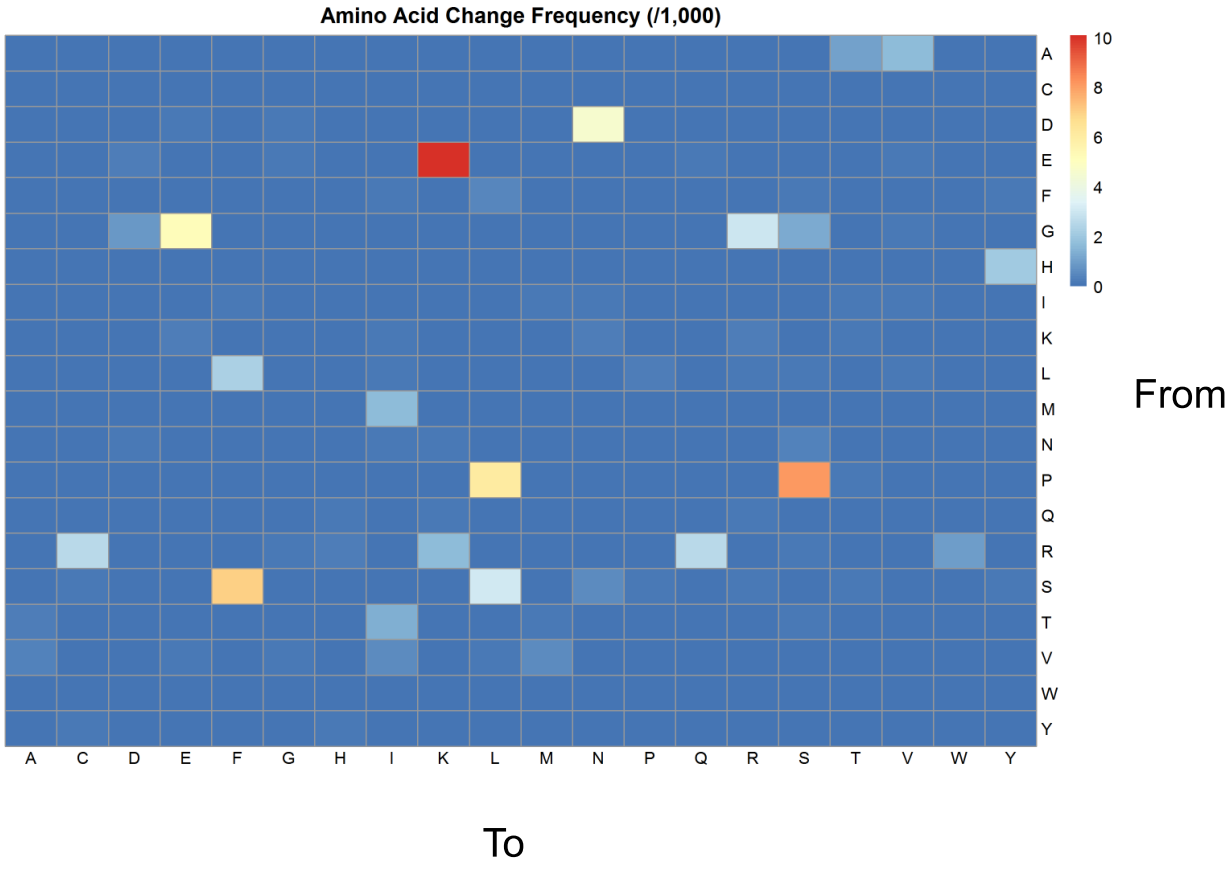

Fig. S4

(A and C) MD simulation snapshots of both the isolated HLA B*07:02 and HLA B*53:01 molecules, respectively, and their complexes with a 9-mer peptide; each trajectory was run over the course of 300 ns of simulation time. (B and D) Observables from the MD simulations described in (A and C). Both mean bridge distances and bridging residues RMSFs in the HLA B*07:02 and HLA B*53:01 molecules and in their corresponding HLA-peptide complexes are shown.

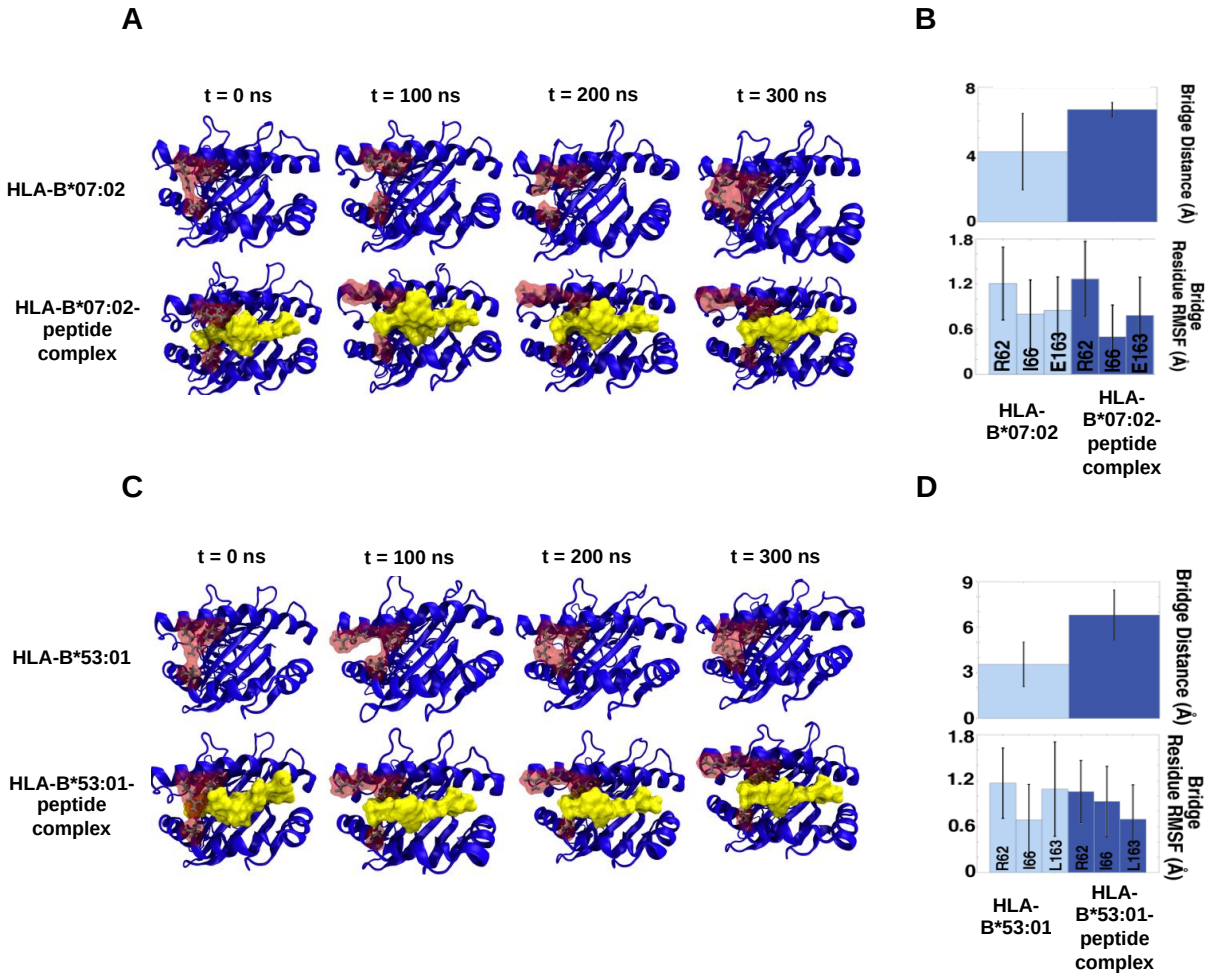

Fig. S5

OncoPrint image of WES data from cohort 1. The OncoPrint displays genes mutated that have been reported to contribute to MHC and immune cytolytic activity. We did not find any particular gene mutation associated with decreased survival. The interferon-cluster of genes on 9p and association with response is also presented. There is no significant association between interferon-cluster deletion and survival across these patients. Clinical response data were obtained from the original studies.

Figure S5

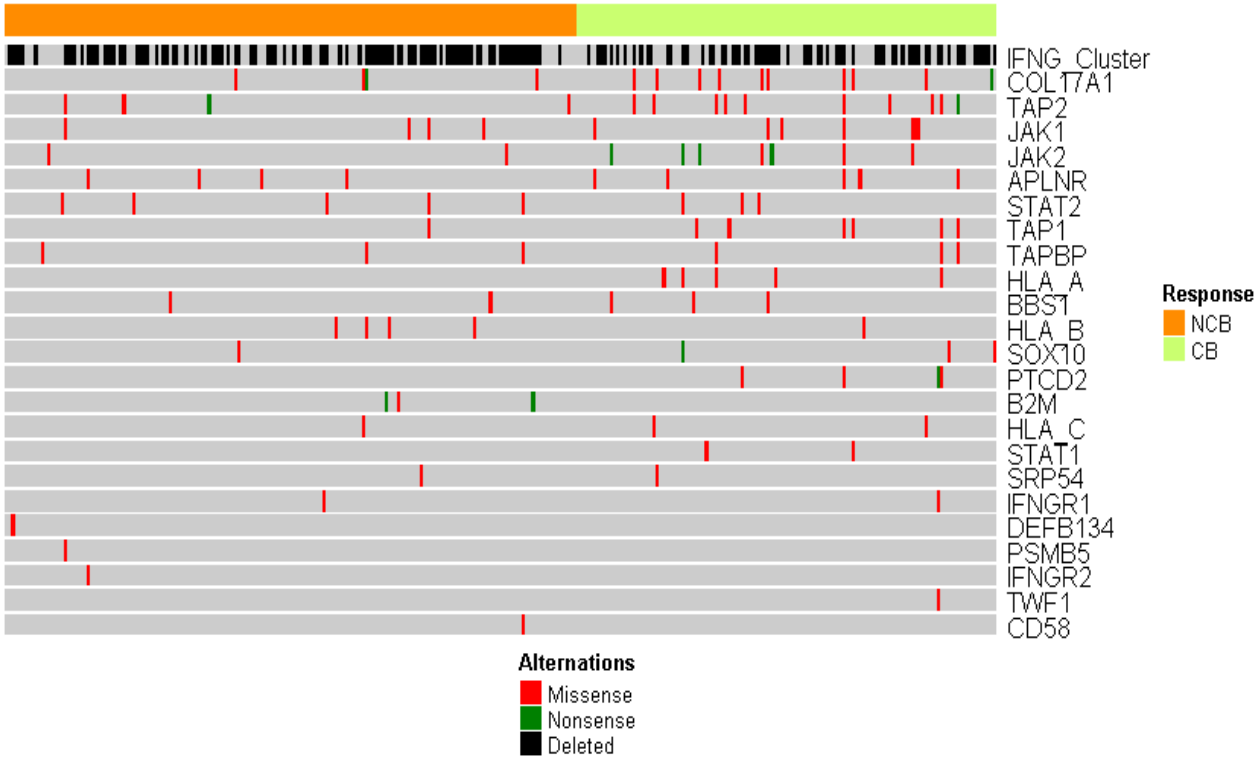

Table S1.

Detailed clinical characteristics of patient cohorts, HLA class I typing, supertypes, and patients with LOH of HLA class I.

Table is provided in Other Supplementary Material as an Excel file.

Table S2.

Multivariable survival analysis incorporating homozygosity for at least one HLA class I locus, mutation load (as a continuous variable), age, tumor stage, and drug class from cohort 1.

Covariate	HR	95% CI	P value
Homozygosity for at least one HLA-I locus	1.50	1.07 – 2.10	0.02
Mutation load (Continuous)	1.00	0.98 – 0.99	0.004
Age	1.00	0.99 – 1.01	0.96
Stage M0 (reference)			
Stage M1a	2.30	0.75 – 6.70	0.15
Stage M1b	2.70	0.91 – 7.77	0.08
Stage M1c	4.06	1.49 – 11.08	0.006
Drug class: **CTLA-4 (reference)**			
Drug class: PD-1	0.64	0.47 – 0.87	0.004

Table S3.

Multivariable survival analysis incorporating homozygosity for at least one HLA class I locus, mutation load (as a continuous variable), age, tumor stage, and drug class from cohort 2.

Covariate	HR	95% CI	P value
Homozygosity for at least one HLA-I locus	1.31	1.03 – 1.67	0.028
Mutation load (Continuous)	0.99	0.98 – 0.99	0.003
Age group < 30 (reference)			
Age group > 71	0.94	0.44 – 2.02	0.88
Age group 31-50	0.90	0.44 – 1.84	0.78
Age group 50-60	0.77	0.37 –1.59	0.47
Age group 61-70	0.76	0.36 – 1.61	0.48
Drug class: Combo (reference)			
Drug class: CTLA-4	0.52	0.28 – 0.96	0.036
Drug class: PD-1/PDL-1	1.53	1.12 – 2.08	0.007

Table S4.

Multivariable survival analysis incorporating HLA class I homozygosity and HLA-DP homozygosity.

Covariate	HR	95% CI	P value
Homozygous in at least one HLA-I locus	1.52	1.07 – 2.18	0.021
Homozygous at HLA-DP	1.44	1.02 – 2.03	0.038

Table S5.

Multivariable survival analysis incorporating homozygosity in at least one HLA class I locus, homozygosity at HLA-DP, and mutation load.

Covariate	HR	95% CI	P value
Homozygous at HLA (class I or DP)	1.60	1.07 – 2.18	0.004
Mutation load (Continuous)	1.00	0.9994 – 1.000	0.025

Table S6.

Multivariable survival analysis incorporating presence of the B44 alleles, mutation load (as a continuous variable), age, tumor stage, and drug class from patients with melanoma from cohort 1.

Covariate	HR	95% CI	P value
HLA-B44(+)	0.54	0.34 – 0.84	0.013
Mutation load (Continuous)	1.00	0.98 – 0.99	0.007
Age	1.00	0.99 – 1.01	0.5
Stage M0 (reference)			
Stage M1a	1.91	0.62 – 5.87	0.26
Stage M1b	2.14	0.73 – 6.25	0.16
Stage M1c	3.53	1.30 – 9.64	0.01
Drug class: **CTLA-4 (reference)**			
Drug class: PD-1	0.73	0.52 – 1.02	0.07

Table S7.

Multivariable survival analysis incorporating presence of B44s, mutation burden (as a continuous variable), age, and drug class from patients with melanoma from cohort 2.

Covariate	HR	95% CI	P value
HLA-B44(+)	0.27	0.07 – 0.95	0.04
Mutation load (continuous variable)	0.99	0.97 – 1.01	0.4
Age group < 30 (reference)			
Age group > 71	–	–	1.00
Age group 31-50	0.25	0.06 – 1.01	0.05
Age group 50-60	0.7	0.17 – 2.97	0.63
Age group 61-70	0.64	0.12 – 3.46	0.60
Drug class: **CTLA-4 (reference)**			
Drug class: **PD-1/PDL-1**	4.36	1.35 – 14.10	0.01

Table S8.

Some experimentally identified immunogenic HLA-B44 restricted neoantigens expressed by melanomas reported in the literature.

Gene	WT Peptide	Neoantigen	HLA-B44 allele	WT score	Neoantigen score	Reference
MAGE3	--	MEVDPIGHLY	B*44:03	--	0.01	(*33, 34*)
MAGE3	--	MEVDPIGHLY	B*18:01	--	0.10	(*33, 34*)
TYR	--	SEIWRDIDF	B*44:03	--	0.25	(*35*)
FAM3C	TKSPFEQHI	TESPFEQHI	B*44:02	16	0.6	(*2, 36*)
MUM1	EEKLSVVLF	EEKLIVVLF	B*44:02	0.09	0.1	(*37*)
MUM2	SELFRSRLDSY	SELFRSGLDSY	B*44:02	0.7	2.5	(*38*)
OS9	KELEGILLP	KELEGILLL	B*44:03	2.5	0.6	(*39*)

The WT score and the neoantigen score refer to the binding strengths of the wild type peptide and its mutated peptide, respectively, predicted by NetMHC version 4.0 (*40*).

Table S9.

Crystal structures of HLA-B class I molecules at the highest available resolutions. The HLA-I alleles at their highest available resolutions are highlighted.

Table is provided in Other Supplementary Material as an Excel file.

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