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

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CD8⁺ T cell-dependent killing of cancer cells requires efficient presentation of tumor antigens by human leukocyte antigen class I (HLA-I) molecules. However, the extent to which patient-specific HLA-I genotype influences response to anti-PD-1 or anti-CTLA-4 is currently unknown. We determined the HLA-I genotype of 1,535 advanced cancer patients treated with immune checkpoint blockade (ICB). Maximal heterozygosity at HLA-I loci (*A*, *B*, and *C*) improved overall survival after ICB compared to patients who were homozygous for at least one HLA locus. In two independent melanoma cohorts, patients with the HLA-B44 supertype had extended survival, whereas the HLA-B62 supertype (including HLA-B*15:01) or somatic LOH at HLA-I, was associated with poor outcome. Molecular dynamics simulations of HLA-B*15:01 revealed unique elements that may impair CD8⁺ T cell recognition of neoantigens. Our results have important implications for predicting response to ICB and for the design of neoantigen-based therapeutic vaccines.

Immune checkpoint inhibitors that target cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) or programmed cell death protein 1 (PD-1) or its ligand (PDL-1) have markedly improved the treatment of patients with metastatic cancer (1–3). However, tumor responses to these drugs are variable, and treatment resistance is common (4–6). To date, most research to predict clinical efficacy to immune checkpoint blockade (ICB) therapies has focused on tumor immune phenotype, somatic genomic features, or the gut microbiome (7–21), but how host germline genetics impacts response is unclear.

HLA class I (HLA-I) genotype has been linked with differential immune responses to infection, inflammatory conditions, and autoimmune diseases (22–30). Each HLA-I molecule binds specific peptides derived from intracellular proteins for presentation on the cell surface to CD8⁺ T cells. (31–33). The anti-tumor activity of ICB has been shown to depend on CD8⁺ T cell, HLA class I-dependent immune activity (34–36). We performed survival and genetic association analyses to address two hypotheses: (i) zygosity at HLA-I genes

influences survival of cancer patients to ICB, and (ii) individual HLA-I germline alleles influences survival to ICB differently.

We examined two sets of cancer patients (henceforth called cohort 1 and cohort 2) treated with ICB. Cohort 1 ($n = 369$ patients) was treated with anti-CTLA-4 or anti-PD-1 therapy, and exome sequencing and clinical data were obtained. Within cohort 1, 269 patients had advanced melanoma [previously reported (7, 11, 12, 17)], and 100 patients had advanced non-small cell lung cancer (NSCLC) (10) (table S1). Patients with NSCLC were treated mainly with anti-PD-1 monotherapy. Cohort 2 ($n = 1,166$ patients) comprised different cancer types including melanoma and NSCLC (table S1), and tumors were subjected to targeted next-generation sequencing (MSK-IMPACT) (37). These patients were treated with drugs targeting CTLA-4, PD-1/PD-L1, or a combination of both, at the Memorial Sloan Kettering Cancer Center (37). For all patients in both cohorts, we performed high-resolution HLA class I genotyping from normal DNA using DNA sequencing data or a clinically validated HLA typing assay (LabCorp).

HLA class I molecules are highly polymorphic with variation located in the peptide-binding region, as each variant binds a select repertoire of peptide ligands. As such, an individual homozygous in at least one HLA-I locus would be predicted to present a smaller, less diverse repertoire of tumor-derived neoantigens to cytotoxic T lymphocytes (CTLs) compared to a person who is heterozygous at each class I locus (32). We therefore asked whether greater diversity (heterozygosity) in the repertoire of antigen-presenting HLA-I molecules could be associated with better survival following ICB therapy. We examined HLA-I variation at each of the genes (HLA-A, -B, and -C) in cohort 1 and cohort 2, by employing a Cox proportional hazard regression model to examine overall survival probability. HLA-I homozygosity in at least one locus was associated with reduced survival in cohort 1 ($n = 369$; $P = 0.036$, HR = 1.40, 95% CI 1.02 – 1.9) (Fig. 1A), and was validated in the independent cohort of 1,166 patients (cohort 2; $P = 0.028$, HR = 1.31, 95% CI 1.03 – 1.70) (Fig. 1B). The number of somatic mutations in tumors was not statistically different between homozygous and heterozygous patients (fig. S1, A and B). Furthermore, the association of HLA-I homozygosity with reduced survival remained significant in multivariable Cox regression modeling when analyzed for mutation load, tumor stage, age, and drug class in cohort 1 ($P = 0.02$, HR = 1.50, 95% CI 1.07 – 2.10) (table S2) and in cohort 2 ($P = 0.028$, HR = 1.31, 95% CI 1.03 – 1.67) (table S3).

We next examined all 1,535 patients from cohort 1 and 2 together, to determine whether the effect of homozygosity may be due to a single HLA-I locus, or a combination of different loci. This analysis revealed that homozygosity at one HLA-I locus (A, or B, or C) was associated with significant reduction of overall survival ($P = 0.003$, HR = 1.38, 95% CI 1.11 – 1.70) (Fig. 1C). Interestingly, the effect of homozygosity on survival due to specific HLA-I locus seemed mostly associated with HLA-B ($P = 0.052$, HR = 1.66, 95% CI 0.93 – 2.94) (Fig. 1C) and HLA-C ($P = 0.004$, HR = 1.60, 95% CI 1.16 – 2.21) (Fig. 1C). Of note, the number of patients available likely limited the interpretability of analyses involving combinations of loci (e.g., HLA-A and -B). Our findings may be explained because HLA-B is generally expressed at higher levels on the cell surface than HLA-A and HLA-C, and because HLA-B alleles bind to a greater diversity of peptides (38, 39). Amino acids that bind to the B pocket of HLA-A alleles are broadly hydrophobic. In contrast, the B pocket of HLA-B alleles can accommodate a greater variety of residues (29, 39). Interestingly, antigen-presenting cells express higher levels of HLA-C on the cell surface than other cell types (40), suggesting that heterozygous HLA-C may facilitate continuous CTL priming (41).

Previous reports have shown that the total number of somatic coding mutations in a cancer genome correlates with

response to ICB (7, 8, 10–12, 17). An explanation for this observation is that the number of tumor mutations presented on the cell surface increases the probability of neoantigen recognition by cytotoxic T cells (42). We found that HLA-I homozygosity and low mutation burden were strongly associated with decreased survival compared to patients who were heterozygous at each class I locus and whose tumors had high mutation burden, in cohort 1 ($P = 0.003$, HR = 2.03, 95% CI 1.27 – 3.30) (Fig. 1D) and in cohort 2 ($P < 0.0001$, HR = 2.98, 95% CI 1.84 – 4.82) (Fig. 1E). Notably, the combined effect of HLA class I heterozygosity and mutation load on improved survival was greater compared with mutation load alone (Fig. 1, F and G).

Previous work has reported loss of heterozygosity (LOH) of HLA class I genes in cancer (43, 44). We thus analyzed all tumor exomes from cohort 1 and identified 32 patients who were heterozygous at all HLA-I loci, but had LOH in at least one HLA-I locus in their tumors (table S1). Patients with LOH of HLA-I were associated with reduced survival ($P = 0.05$, HR = 1.60, 95% CI 1.03 – 2.43) (Fig. 1H). Furthermore, the effect of LOH of HLA-I on survival was greater in patients whose tumors contained low mutation load ($P = 0.0006$, HR = 3.68, 95% CI 1.64 – 8.23) (Fig. 1I). Given that only a small fraction of presented tumor mutations are immunogenic in cancer patients (45, 46), our findings suggest that relatively small differences in the number of available HLA-I molecules in a given individual can present major challenges to effective anti-tumor T cell responses and efficacy to ICB. Furthermore, the demonstration of a significant survival advantage to HLA-I heterozygosity in patients treated with ICB both at the germline and somatic level, highlights its importance in the dynamic anti-tumor immune response and immune evasion.

As an exploratory analysis, we also found that HLA class II homozygosity at HLA-DP was associated with reduced survival ($P = 0.018$, HR = 1.45, 95% CI 1.06 – 2.00) (fig. S2A). Additionally, homozygosity at HLA-DPB locus was associated with decreased survival ($P = 0.04$, HR = 1.37, 95% CI 1.07 – 1.87). This effect was independent of the associations of HLA-I homozygosity and mutation burden (tables S4 and S5). It is noteworthy that mismatched HLA-DP has been shown to be associated with graft-versus-host disease (47).

Additionally, we employed next-generation deep sequencing of T-cell receptor CDR3 regions (TCR-seq) (48, 49) from a subset of tumor samples collected on-therapy (4 weeks post-Nivolumab initiation) (17). We found significantly higher on-therapy clonality of TCR CDR3s in HLA heterozygous patients compared to HLA homozygotes (in at least one class I locus or at HLA-DP) (Wilcoxon rank-sum test $P = 0.0093$) (Fig. 3F and table S1). To refine the interpretation of this result with respect to the antigen-binding properties of the TCR repertoire, the clonality of CDR3s encoded by a single VJ cassette combination was analyzed individually (17, 50). Notably,

higher on-therapy clonality of TCR CDR3s per VJ was observed in HLA heterozygotes (Wilcoxon rank-sum test $P = 0.023$) (Fig. 3G). Altogether, these results indicate that the diversity of HLA molecules in a given patient influences the selection and the resulting T-cell clonal expansion reactive against neoantigens following ICB (51).

To investigate the clinical relevance of individual HLA-I alleles after ICB therapy, we examined the effects of HLA-I supertypes on overall survival. Individual HLA-I alleles are classified into twelve discrete supertypes (52, 53), based upon similar peptide-anchor-binding specificities (26, 52, 53). These supertypes together cover most HLA-A and HLA-B alleles found in distinct populations (52, 53).

To assess the effect of HLA supertype on survival, we focused on melanoma patients, as there were a sufficient number of patients in the two patient sets for meaningful analysis. Based on the biological definition of supertypes, we classified the 27 HLA-A alleles present in the patients with melanoma into six A supertypes, and the 50 HLA-B alleles into six B supertypes (Fig. 2A and table S1). We found two B supertypes, associated with survival outcome in patients with advanced melanoma treated with anti-CTLA-4. Patients with B44 superfamily alleles had significantly better survival ($P = 0.01$, HR = 0.61, 95% CI 0.42 – 0.89) (Table 1) and patients with B62 alleles had significantly reduced survival ($P = 0.0007$, HR = 2.29, 95% CI 1.40 – 3.74) (Table 1). The B44 supertype was present at a prevalence of 45% and the B62 supertype at 15% (Fig. 2A). We did not find any supertype significantly associated with overall survival in patients with NSCLC, likely due to the limited sample size.

We then examined whether these supertype associations were influenced by the presence of specific component HLA-I alleles. The B44 association was influenced by HLA-B*18:01, HLA-B*44:02, HLA-B*44:03, HLA-B*44:05, and HLA-B*50:01 ($P = 0.001$, HR = 0.49, 95% CI 0.32 – 0.76) (Fig. 2C) (Table 1). And, the B62 association was significantly driven by HLA-B*15:01 ($P = 0.002$, HR = 2.21, 95% CI 1.33 – 3.70) (Fig. 3A) (Table 1). Both of these B44 and B62 allele associations remained statistically significant ($P = 0.01$ and $P = 0.02$, respectively) after a Bonferroni correction. The variability in the effect on survival across these B44 alleles might be explained due to allele frequency in the cohort or due to particular differences in the peptide motifs inside or outside primary anchor pockets (54, 55).

In the independent cohort 2, melanoma patients treated with anti-PD-1 or anti-CTLA-4 who had these B44 supertype alleles had significantly better overall survival on univariate ($P = 0.054$, HR = 0.32, 95% CI 0.09 – 1.1) (Fig. 2, B and D), and multivariable analysis (tables S6 and S7). Furthermore, the effect of B44s on extended survival was greater when somatic mutational load was also considered in cohort 1 ($P < 0.0001$, HR = 0.23, 95% CI 0.13 – 0.41) (Fig. 2E) and in cohort 2 ($P =$

0.023, HR = 0.13, 95% CI 0.02 – 1.03) (Fig. 2F). The combined effect of the B44 alleles and mutation load was greater than simply considering mutation burden alone (Fig. 2, G and H). We note that, in general, outcomes of melanoma patients in cohort 2 tended to be better than in cohort 1 because patients who received ICB and were accrued to our protocol for MSK-IMPACT testing tended to have longer survival. Yet, despite this trend, we still observed a significant effect from the B44 alleles. Notably, the B44 alleles did not associate with survival in patients with melanoma from The Cancer Genome Atlas (TCGA), suggesting that the presence of B44 was predictive of response to ICB and was not prognostic (Fig. 2I).

Most members of the B44 supertype share a preference for peptides with Glu (E) at anchor position P2, and polar and hydrophobic residues at the C terminus (54, 56) (Fig. 2J). Interestingly, we found that one out of the six enriched amino acid mutations across these tumors was G > E (fig. S3). This observation suggests that there might be an enrichment of presentation of B44-restricted neoantigens. Additionally, a number of previously identified immunogenic antigens expressed by melanomas are HLA-B44 restricted (Fig. 2J and table S8), including the testis antigen MAGEA3, restricted to HLA-B*44:03 and HLA-B*18:01 (both members of B44), and a clonal immunogenic neoantigen (FAM3C: TESPFEQHI) identified in a melanoma patient with long-term response to CTLA-4 blockade from cohort 1 (table S8) (11, 13).

In contrast, the B62 association with poor survival driven by the HLA-B*15:01 allele was intriguing (Fig. 3A) (Table 1). In an exploratory analysis, we sought to determine whether any molecular features in HLA-B*15:01 are associated with its effect on survival. Out of all the HLA-B alleles that were available for three-dimensional structural analysis ($n = 119$) (table S9), we identified three alleles at their highest resolutions, HLA-B*15:01, HLA-B*07:02, and HLA-B*53:01, as possessing a structural bridge in the peptide-binding groove (Arg62, Ile66, and Leu163) (Fig. 3, B and C).

We postulated that this specific structural feature may modulate the effective T cell recognition of neopeptides presented on HLA-B*15:01. To evaluate the validity of this hypothesis, we conducted molecular dynamics (MD) simulations following similar protocols used in previous studies (57–59).

In the case of HLA-B*07:02 and HLA-B*53:07, MD simulations demonstrated that the bound peptide expands the respective HLA binding cleft, effectively breaking the bridge (fig. S4, A to D). Conversely, in the HLA-B*15:01 molecule, the bridge was largely maintained with the peptide present, and the bridging residues were also made much less flexible (Fig. 3, D and E). While the mean bridge separation remained nearly constant ($\sim 6\text{\AA}$) in both systems of HLA-B*15:01 (Fig. 3E), the fluctuations in this distance were less dramatic in the peptide-bound complex. Altogether, these unique structural

and dynamical elements of HLA-B*15:01 may impair the total strength of the interaction with T-cell receptor for effective neoantigen recognition. However, further experimental work will be necessary to test this hypothesis. It is noteworthy that we found several mutations in genes that have been recently reported to contribute to HLA and cytolytic activity (4–6) (fig. S5). However, we did not find any particular gene mutation associated with decreased overall survival.

Our findings reveal that HLA-I genes influence patient survival to ICB. Both patient-specific HLA-I genotype as well as somatic alterations in tumors impacted clinical outcome to ICB, suggesting these factors could be considered in the design of future clinical trials. The observation that the B44 is associated with extended overall survival may provide an opportunity for the development of therapeutic vaccines that potentially target immunodominant HLA-B44-restricted neoantigens expressed by melanomas. Our findings indicate that HLA-I homozygosity and LOH represent a genetic barrier to effective immunotherapy, and alternative ways to harness the immune system may be necessary to maximize clinical benefit.

REFERENCES AND NOTES

1. D. T. Le *et al.*, Mismatch-repair deficiency predicts response of solid tumors to PD-1 blockade. *Science* **356**, eaan6733 (2017).
2. F. S. Hodi, S. J. O'Day, D. F. McDermott, R. W. Weber, J. A. Sosman, J. B. Haanen, R. Gonzalez, C. Robert, D. Schadendorf, J. C. Hassel, W. Akerley, A. J. M. van den Eertwegh, J. Lutzky, P. Lorigan, J. M. Vaubel, G. P. Linette, D. Hogg, C. H. Ottensmeier, C. Lebbé, C. Peschel, I. Quidt, J. I. Clark, J. D. Wolchok, J. S. Weber, J. Tian, M. J. Yellin, G. M. Nichol, A. Hoos, W. J. Urba, Improved survival with ipilimumab in patients with metastatic melanoma. *N. Engl. J. Med.* **363**, 711–723 (2010). [doi:10.1056/NEJMoa1003466](https://doi.org/10.1056/NEJMoa1003466) [Medline](#)
3. C. Robert, G. V. Long, B. Brady, C. Dutriaux, M. Maio, L. Mortier, J. C. Hassel, P. Rutkowski, C. McNeil, E. Kalinka-Warchoła, K. J. Savage, M. M. Hernberg, C. Lebbé, J. Charles, C. Mihalciou, V. Chiarion-Sileni, C. Mauch, F. Cognetti, A. Arance, H. Schmidt, D. Schadendorf, H. Gogas, L. Lundgren-Eriksson, C. Horak, B. Sharkey, I. M. Waxman, V. Atkinson, P. A. Ascierto, Nivolumab in previously untreated melanoma without BRAF mutation. *N. Engl. J. Med.* **372**, 320–330 (2015). [doi:10.1056/NEJMoa1412082](https://doi.org/10.1056/NEJMoa1412082) [Medline](#)
4. J. M. Zaretsky, A. Garcia-Diaz, D. S. Shin, H. Escuin-Ordinas, W. Hugo, S. Hu-Lieskovan, D. Y. Torrejon, G. Abril-Rodriguez, S. Sandoval, L. Barthly, J. Saco, B. Homet Moreno, R. Mezzadra, B. Chmielowski, K. Ruchalski, I. P. Shintaku, P. J. Sanchez, C. Puig-Saus, G. Cherry, E. Seja, X. Kong, J. Pang, B. Berent-Maoz, B. Comin-Anduix, T. G. Graeber, P. C. Tumeh, T. N. M. Schumacher, R. S. Lo, A. Ribas, Mutations Associated with Acquired Resistance to PD-1 Blockade in Melanoma. *N. Engl. J. Med.* **375**, 819–829 (2016). [doi:10.1056/NEJMoa1604958](https://doi.org/10.1056/NEJMoa1604958) [Medline](#)
5. J. Gao, L. Z. Shi, H. Zhao, J. Chen, L. Xiong, Q. He, T. Chen, J. Roszik, C. Bernatchez, S. E. Woodman, P.-L. Chen, P. Hwu, J. P. Allison, A. Futreal, J. A. Wargo, P. Sharma, Loss of IFN- γ Pathway Genes in Tumor Cells as a Mechanism of Resistance to Anti-CTLA-4 Therapy. *Cell* **167**, 397–404.e9 (2016). [doi:10.1016/j.cell.2016.08.069](https://doi.org/10.1016/j.cell.2016.08.069) [Medline](#)
6. F. Zhao, A. Sucker, S. Horn, C. Heeke, N. Bielefeld, B. Schrörs, A. Bicker, M. Lindemann, A. Roesch, G. Gaudernack, M. Stiller, J. C. Becker, V. Lennerz, T. Wölfel, D. Schadendorf, K. Griewank, A. Paschen, Melanoma Lesions Independently Acquire T-cell Resistance during Metastatic Latency. *Cancer Res.* **76**, 4347–4358 (2016). [doi:10.1158/0008-5472.CAN-16-0008](https://doi.org/10.1158/0008-5472.CAN-16-0008) [Medline](#)
7. W. Hugo, J. M. Zaretsky, L. Sun, C. Song, B. H. Moreno, S. Hu-Lieskovan, B. Berent-Maoz, J. Pang, B. Chmielowski, G. Cherry, E. Seja, S. Lomeli, X. Kong, M. C. Kelley, J. A. Sosman, D. B. Johnson, A. Ribas, R. S. Lo, Genomic and Transcriptomic Features of Response to Anti-PD-1 Therapy in Metastatic Melanoma. *Cell* **165**, 35–44 (2016). [doi:10.1016/j.cell.2016.02.065](https://doi.org/10.1016/j.cell.2016.02.065) [Medline](#)
8. D. T. Le, J. N. Uram, H. Wang, B. R. Bartlett, H. Kemberling, A. D. Eyring, A. D. Skora, B. S. Luber, N. S. Azad, D. Laheru, B. Biedrzycki, R. C. Donehower, A. Zaheer, G. A. Fisher, T. S. Crocenzi, J. J. Lee, S. M. Duffy, R. M. Goldberg, A. de la Chapelle, M. Koshiji, F. Bhajee, T. Huebner, R. H. Hruban, L. D. Wood, N. Cuka, D. M. Pardoll, N. Papadopoulos, K. W. Kinzler, S. Zhou, T. C. Cornish, J. M. Taube, R. A. Anders, J. R. Eshleman, B. Vogelstein, L. A. Diaz Jr., PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. *N. Engl. J. Med.* **372**, 2509–2520 (2015). [doi:10.1056/NEJMoa1500596](https://doi.org/10.1056/NEJMoa1500596) [Medline](#)
9. N. Riaz, J. J. Havel, S. M. Kendall, V. Makarov, L. A. Walsh, A. Desrichard, N. Weinhold, T. A. Chan, Recurrent SERPINB3 and SERPINB4 mutations in patients who respond to anti-CTLA4 immunotherapy. *Nat. Genet.* **48**, 1327–1329 (2016). [doi:10.1038/ng.3677](https://doi.org/10.1038/ng.3677) [Medline](#)
10. N. A. Rizvi, M. D. Hellmann, A. Snyder, P. Kvistborg, V. Makarov, J. J. Havel, W. Lee, J. Yuan, P. Wong, T. S. Ho, M. L. Miller, N. Rekhtman, A. L. Moreira, F. Ibrahim, C. Bruggeman, B. Gasmir, R. Zappasodi, Y. Maeda, C. Sander, E. B. Garon, T. Merghoub, J. D. Wolchok, T. N. Schumacher, T. A. Chan, Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. *Science* **348**, 124–128 (2015). [doi:10.1126/science.1257551](https://doi.org/10.1126/science.1257551) [Medline](#)
11. A. Snyder, V. Makarov, T. Merghoub, J. Yuan, J. M. Zaretsky, A. Desrichard, L. A. Walsh, M. A. Postow, P. Wong, T. S. Ho, T. J. Hollmann, C. Bruggeman, K. Kannan, Y. Li, C. Elipenahli, C. Liu, C. T. Harbison, L. Wang, A. Ribas, J. D. Wolchok, T. A. Chan, Genetic basis for clinical response to CTLA-4 blockade in melanoma. *N. Engl. J. Med.* **371**, 2189–2199 (2014). [doi:10.1056/NEJMoa1406498](https://doi.org/10.1056/NEJMoa1406498) [Medline](#)
12. E. M. Van Allen, D. Miao, B. Schilling, S. A. Shukla, C. Blank, L. Zimmer, A. Sucker, U. Hillen, M. H. G. Foppen, S. M. Goldinger, J. Utikal, J. C. Hassel, B. Weide, K. C. Kaehler, C. Loguaj, P. Mohr, R. Gutzmer, R. Dummer, S. Gabriel, C. J. Wu, D. Schadendorf, L. A. Garraway, Genomic correlates of response to CTLA-4 blockade in metastatic melanoma. *Science* **350**, 207–211 (2015). [doi:10.1126/science.1257551](https://doi.org/10.1126/science.1257551) [Medline](#)
13. N. McGranahan, A. J. S. Furness, R. Rosenthal, S. Ramskov, R. Lyngaa, S. K. Saini, M. Jamal-Hanjani, G. A. Wilson, N. J. Birkbak, C. T. Hiley, T. B. K. Watkins, S. Shafi, N. Murugaesu, R. Mitter, A. U. Akarca, J. Linares, T. Marafioti, J. Y. Henry, E. M. Van Allen, D. Miao, B. Schilling, D. Schadendorf, L. A. Garraway, V. Makarov, N. A. Rizvi, A. Snyder, M. D. Hellmann, T. Merghoub, J. D. Wolchok, S. A. Shukla, C. J. Wu, K. S. Peggs, T. A. Chan, S. R. Hadrup, S. A. Quezada, C. Swanton, Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade. *Science* **351**, 1463–1469 (2016). [doi:10.1126/science.1257551](https://doi.org/10.1126/science.1257551) [Medline](#)
14. R. S. Herbst, J.-C. Soria, M. Kowanetz, G. D. Fine, O. Hamid, M. S. Gordon, J. A. Sosman, D. F. McDermott, J. D. Powderly, S. N. Gettinger, H. E. K. Kohrt, L. Horn, D. P. Lawrence, S. Rost, M. Leabman, Y. Xiao, A. Moktrin, H. Koepfen, P. S. Hegde, I. Mellman, D. S. Chen, F. S. Hodi, Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. *Nature* **515**, 563–567 (2014). [doi:10.1038/nature14011](https://doi.org/10.1038/nature14011) [Medline](#)
15. P. C. Tumeh, C. L. Harview, J. H. Yearley, I. P. Shintaku, E. J. M. Taylor, L. Robert, B. Chmielowski, M. Spasic, G. Henry, V. Ciobanu, A. N. West, M. Carmona, C. Kivork, E. Seja, G. Cherry, A. J. Gutierrez, T. R. Grogan, C. Mateus, G. Tamasic, J. A. Glaspy, R. O. Emerson, H. Robins, R. H. Pierce, D. A. Elashoff, C. Robert, A. Ribas, PD-1 blockade induces responses by inhibiting adaptive immune resistance. *Nature* **515**, 568–571 (2014). [doi:10.1038/nature13954](https://doi.org/10.1038/nature13954) [Medline](#)
16. S. L. Topalian, J. M. Taube, R. A. Anders, D. M. Pardoll, Mechanism-driven biomarkers to guide immune checkpoint blockade in cancer therapy. *Nat. Rev. Cancer* **16**, 275–287 (2016). [doi:10.1038/nrc.2016.36](https://doi.org/10.1038/nrc.2016.36) [Medline](#)
17. N. Riaz, J. J. Havel, V. Makarov, A. Desrichard, W. J. Urba, J. S. Sims, F. S. Hodi, S. Martín-Algarra, R. Mandal, W. H. Sharfman, S. Bhatia, W.-J. Hwu, T. F. Gajewski, C. L. Slingluff Jr., D. Chowell, S. M. Kendall, H. Chang, R. Shah, F. Kuo, L. G. T. Morris, J.-W. Sidhom, J. P. Schneck, C. E. Horak, N. Weinhold, T. A. Chan, Tumor and Microenvironment Evolution during Immunotherapy with Nivolumab. *Cell* **171**, 934–949.e15 (2017). [doi:10.1016/j.cell.2017.09.028](https://doi.org/10.1016/j.cell.2017.09.028) [Medline](#)
18. T. Davoli, H. Uno, E. C. Wooten, S. J. Elledge, Tumor aneuploidy correlates with markers of immune evasion and with reduced response to immunotherapy. *Science* **355**, eaaf8399 (2017). [doi:10.1126/science.1257551](https://doi.org/10.1126/science.1257551) [Medline](#)
19. W. Roh, P.-L. Chen, A. Reuben, C. N. Spencer, P. A. Prieto, J. P. Miller, V. Gopalakrishnan, F. Wang, Z. A. Cooper, S. M. Reddy, C. Gumbs, L. Little, Q. Chang,

- W.-S. Chen, K. Wani, M. P. De Macedo, E. Chen, J. L. Austin-Breneman, H. Jiang, J. Roszik, M. T. Tetzlaff, M. A. Davies, J. E. Gershenwald, H. Tawbi, A. J. Lazar, P. Hwu, W.-J. Hwu, A. Diab, I. C. Glitza, S. P. Patel, S. E. Woodman, R. N. Amaria, V. G. Prieto, J. Hu, P. Sharma, J. P. Allison, L. Chin, J. Zhang, J. A. Wargo, P. A. Futreal, Integrated molecular analysis of tumor biopsies on sequential CTLA-4 and PD-1 blockade reveals markers of response and resistance. *Sci. Transl. Med.* **9**, eaah3560 (2017). [doi:10.1126/scitranslmed.aah3560](https://doi.org/10.1126/scitranslmed.aah3560) [Medline](#)
20. V. Gopalakrishnan, C. N. Spencer, L. Nezi, A. Reuben, M. C. Andrews, T. V. Karpinets, P. A. Prieto, D. Vicente, K. Hoffman, S. C. Wei, A. P. Cogdill, L. Zhao, C. W. Hudgens, D. S. Hutchinson, T. Manzo, M. Petaccia de Macedo, T. Cotechini, T. Kumar, W. S. Chen, S. M. Reddy, R. S. Sloane, J. Galloway-Pena, H. Jiang, P. L. Chen, E. J. Shpall, K. Rezvani, A. M. Alousi, R. F. Chemaly, S. Shelburne, L. M. Vence, P. C. Okhuysen, V. B. Jensen, A. G. Swennes, F. McAllister, E. M. R. Sanchez, Y. Zhang, E. Le Chatelier, L. Zitvogel, N. Pons, J. L. Austin-Breneman, L. E. Haydu, E. M. Burton, J. M. Gardner, E. Sirmans, J. Hu, A. J. Lazar, T. Tsujikawa, A. Diab, H. Tawbi, I. C. Glitza, W. J. Hwu, S. P. Patel, S. E. Woodman, R. N. Amaria, M. A. Davies, J. E. Gershenwald, P. Hwu, J. E. Lee, J. Zhang, L. M. Coussens, Z. A. Cooper, P. A. Futreal, C. R. Daniel, N. J. Ajami, J. F. Petrosino, M. T. Tetzlaff, P. Sharma, J. P. Allison, R. R. Jenq, J. A. Wargo, Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. *Science* eaan4236 (2017). [doi:10.1126/science.aan4236](https://doi.org/10.1126/science.aan4236) [Medline](#)
 21. B. Routy, E. Le Chatelier, L. Derosa, C. P. M. Duong, M. T. Alou, R. Daillère, A. Fluckiger, M. Messaoudene, C. Rauber, M. P. Roberti, M. Fidelle, C. Flament, V. Poirier-Colame, P. Opolon, C. Klein, K. Iribarren, L. Mondragón, N. Jacquilot, B. Qu, G. Ferrere, C. Clémenson, L. Mezquita, J. R. Masip, C. Naltet, S. Brosseau, C. Kaderbhai, C. Richard, H. Rizvi, F. Levenez, N. Galleron, B. Quinquis, N. Pons, B. Ryffel, V. Minard-Colin, P. Gonin, J.-C. Soria, E. Deutsch, Y. Loriot, F. Ghiringhelli, G. Zalcman, F. Goldwasser, B. Escudier, M. D. Hellmann, A. Eggermont, D. Raoult, L. Albiges, G. Kroemer, L. Zitvogel, Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. *Science* eaan3706 (2017). [doi:10.1126/science.aan3706](https://doi.org/10.1126/science.aan3706) [Medline](#)
 22. F. Pereyra, X. Jia, P. J. McLaren, A. Telenti, P. I. de Bakker, B. D. Walker, S. Ripke, C. J. Brumme, S. L. Pulit, M. Carrington, C. M. Kadie, J. M. Carlson, D. Heckerman, R. R. Graham, R. M. Plenge, S. G. Deeks, L. Gianniny, G. Crawford, J. Sullivan, E. Gonzalez, L. Davies, A. Camargo, J. M. Moore, N. Beattie, S. Gupta, A. Crenshaw, N. P. Burt, C. Guiducci, N. Gupta, X. Gao, Y. Qi, Y. Yuki, A. Piechocka-Trocha, E. Cutrell, R. Rosenberg, K. L. Moss, P. Lemay, J. O'Leary, T. Schaefer, P. Verma, I. Toth, B. Block, B. Baker, A. Rothchild, J. Lian, J. Proudfoot, D. M. Alvino, S. Vine, M. M. Addo, T. M. Allen, M. Altfeld, M. R. Henn, S. Le Gall, H. Streeck, D. W. Haas, D. R. Kuritzkes, G. K. Robbins, R. W. Shafer, R. M. Gulick, C. M. Shikuma, R. Haubrich, S. Riddler, P. E. Sax, E. S. Daar, H. J. Ribaud, B. Agan, S. Agarwal, R. L. Ahern, B. L. Allen, S. Altidor, E. L. Altschuler, S. Ambardar, K. Anastos, B. Anderson, V. Anderson, U. Andrad, D. Antoniskis, D. Bangsberg, D. Barbaro, W. Barrie, J. Bartczak, S. Barton, P. Basden, N. Basgoz, S. Bazner, N. C. Bellos, A. M. Benson, J. Berger, N. F. Bernard, A. M. Bernard, C. Birch, S. J. Bodner, R. K. Bolan, E. T. Boudreaux, M. Bradley, J. F. Braun, J. E. Brndjar, S. J. Brown, R. Brown, S. T. Brown, J. Burack, L. M. Bush, V. Cafaro, O. Campbell, J. Campbell, R. H. Carlson, J. K. Carmichael, K. K. Casey, C. Cavacuiti, G. Celestin, S. T. Chambers, N. Chez, L. M. Chirch, P. J. Cimoch, D. Cohen, L. E. Cohn, B. Conway, D. A. Cooper, B. Cornelson, D. T. Cox, M. V. Cristofano, G. Cuchural Jr., J. L. Czartoski, J. M. Dahman, J. S. Daly, B. T. Davis, K. Davis, S. M. Davod, E. DeJesus, C. A. Dietz, E. Dunham, M. E. Dunn, T. B. Ellerlin, J. J. Eron, J. J. Fangman, C. E. Farel, H. Ferlazzo, S. Fidler, A. Fleener-Ford, R. Frankel, K. A. Freedberg, N. K. French, J. D. Fuchs, J. D. Fuller, J. Gaberman, J. E. Gallant, R. T. Gandhi, E. Garcia, D. Garmon, J. C. Gathe Jr., C. R. Gaultier, W. Gebre, F. D. Gilman, I. Gilson, P. A. Goepfert, M. S. Gottlieb, C. Goulston, R. K. Groger, T. D. Gurley, S. Haber, R. Hardwicke, W. D. Hardy, P. R. Harrigan, T. N. Hawkins, S. Heath, F. M. Hecht, W. K. Henry, M. Hladek, R. P. Hoffman, J. M. Horton, R. K. Hsu, G. D. Huhn, P. Hunt, M. J. Hupert, M. L. Illeman, H. Jaeger, R. M. Jellinger, M. John, J. A. Johnson, K. L. Johnson, H. Johnson, K. Johnson, J. Joly, W. C. Jordan, C. A. Kauffman, H. Khanlou, R. K. Killian, A. Y. Kim, D. D. Kim, C. A. Kinder, J. T. Kirchner, L. Kogelman, E. M. Kojic, P. T. Korthuis, W. Kurisu, D. S. Kwon, M. LaMar, H. Lampiris, M. Lanzafame, M. M. Lederman, D. M. Lee, J. M. Lee, M. J. Lee, E. T. Lee, J. Lemoine, J. A. Levy, J. M. Llibre, M. A. Liguori, S. J. Little, A. Y. Liu, A. J. Lopez, M. R. Loutfy, D. Loy, D. Y. Mohammed, A. Man, M. K. Mansour, V. C. Marconi, M. Markowitz, R. Marques, J. N. Martin, H. L. Martin Jr., K. H. Mayer, M. J. McElrath, T. A. McGhee, B. H. McGovern, K. McGowan, D. McIntyre, G. X. Mcleod, P. Menezes, G. Mesa, C. E. Metroka, D. Meyer-Olson, A. O. Miller, K. Montgomery, K. C. Mounzer, E. H. Nagami, I. Nagin, R. G. Nahass, M. O. Nelson, C. Nielsen, D. L. Norene, D. H. O'Connor, B. O. Ojikutu, J. Okulicz, O. O. Oladehin, E. C. Oldfield 3rd, S. A. Olender, M. Ostrowski, W. F. Owen Jr., E. Pae, J. Parsonnet, A. M. Pavlatos, A. M. Perlmutter, M. N. Pierce, J. M. Pincus, L. Pisani, L. J. Price, L. Proia, R. C. Prokesch, H. C. Pujet, M. Ramgopal, A. Rathod, M. Rausch, J. Ravishankar, F. S. Rhome, C. S. Richards, D. D. Richman, B. Rodes, M. Rodriguez, R. C. Rose 3rd, E. S. Rosenberg, D. Rosenthal, P. E. Ross, D. S. Rubin, E. Rumbaugh, L. Saenz, M. R. Salvaggio, W. C. Sanchez, V. M. Sanjana, S. Santiago, W. Schmidt, H. Schuitemaker, P. M. Sestak, P. Shalit, W. Shay, V. N. Shirvani, V. I. Silebi, J. M. Sizemore Jr., P. R. Skolnik, M. Sokol-Anderson, J. M. Sosman, P. Stabile, J. T. Stapleton, S. Starrett, F. Stein, H. J. Stellbrink, F. L. Sterman, V. E. Stone, D. R. Stone, G. Tambussi, R. A. Taplitz, E. M. Tedaldi, A. Telenti, W. Theisen, R. Torres, L. Tosiello, C. Tremblay, M. A. Tribble, P. D. Trinh, A. Tsao, P. Ueda, A. Vaccaro, E. Valadas, T. J. Vanig, I. Vecino, V. M. Vega, W. Veikley, B. H. Wade, C. Walworth, C. Wanidworanun, D. J. Ward, D. A. Warner, R. D. Weber, D. Webster, S. Weis, D. A. Wheeler, D. J. White, E. Wilkins, A. Winston, C. G. Wlodaver, A. van't Wout, D. P. Wright, O. O. Yang, D. L. Yurdin, B. W. Zabukovic, K. C. Zachary, B. Zeeman, M. Zhao; International HIV Controllers Study, The major genetic determinants of HIV-1 control affect HLA class I peptide presentation. *Science* **330**, 1551–1557 (2010). [doi:10.1126/science.1195271](https://doi.org/10.1126/science.1195271) [Medline](#)
 23. M. Carrington, G. W. Nelson, M. P. Martin, T. Kissner, D. Vlahov, J. J. Goedert, R. Kaslow, S. Buchbinder, K. Hoots, S. J. O'Brien, HLA and HIV-1: Heterozygote advantage and B*35-Cw*04 disadvantage. *Science* **283**, 1748–1752 (1999). [doi:10.1126/science.283.5408.1748](https://doi.org/10.1126/science.283.5408.1748) [Medline](#)
 24. J. Fellay, K. V. Shianna, D. Ge, S. Colombo, B. Ledergerber, M. Weale, K. Zhang, C. Gumbs, A. Castagna, A. Cossarizza, A. Cozzi-Lepri, A. De Luca, P. Easterbrook, P. Francioli, S. Mallal, J. Martinez-Picado, J. M. Miro, N. Obel, J. P. Smith, J. Wyniger, P. Descombes, S. E. Antonarakis, N. L. Letvin, A. J. McMichael, B. F. Haynes, A. Telenti, D. B. Goldstein, A whole-genome association study of major determinants for host control of HIV-1. *Science* **317**, 944–947 (2007). [doi:10.1126/science.1143767](https://doi.org/10.1126/science.1143767) [Medline](#)
 25. X. Gao, G. W. Nelson, P. Karacki, M. P. Martin, J. Phair, R. Kaslow, J. J. Goedert, S. Buchbinder, K. Hoots, D. Vlahov, S. J. O'Brien, M. Carrington, Effect of a single amino acid change in MHC class I molecules on the rate of progression to AIDS. *N. Engl. J. Med.* **344**, 1668–1675 (2001). [doi:10.1056/NEJM200105313442203](https://doi.org/10.1056/NEJM200105313442203) [Medline](#)
 26. E. Trachtenberg, B. Korber, C. Sollars, T. B. Kepler, P. T. Hraber, E. Hayes, R. Funkhouser, M. Fugate, J. Theiler, Y. S. Hsu, K. Kunstman, S. Wu, J. Phair, H. Erlich, S. Wolinsky, Advantage of rare HLA supertype in HIV disease progression. *Nat. Med.* **9**, 928–935 (2003). [doi:10.1038/nm893](https://doi.org/10.1038/nm893) [Medline](#)
 27. P. J. R. Goulder, B. D. Walker, HIV and HLA class I: An evolving relationship. *Immunity* **37**, 426–440 (2012). [doi:10.1016/j.immuni.2012.09.005](https://doi.org/10.1016/j.immuni.2012.09.005) [Medline](#)
 28. A. V. S. Hill, C. E. M. Allsopp, D. Kwiatkowski, N. M. Anstey, P. Twumasi, P. A. Rowe, S. Bennett, D. Brewster, A. J. McMichael, B. M. Greenwood, Common west African HLA antigens are associated with protection from severe malaria. *Nature* **352**, 595–600 (1991). [doi:10.1038/352595a0](https://doi.org/10.1038/352595a0) [Medline](#)
 29. P. Kiepiela, A. J. Leslie, I. Honeyborne, D. Ramduth, C. Thobakgale, S. Chetty, P. Rathnavalu, C. Moore, K. J. Pfaffert, L. Hilton, P. Zimbwa, S. Moore, T. Allen, C. Brander, M. M. Addo, M. Altfeld, I. James, S. Mallal, M. Bunce, L. D. Barber, J. Sziinger, C. Day, P. Klenerman, J. Mullins, B. Korber, H. M. Coovadia, B. D. Walker, P. J. R. Goulder, Dominant influence of HLA-B in mediating the potential co-evolution of HIV and HLA. *Nature* **432**, 769–775 (2004). [doi:10.1038/nature03113](https://doi.org/10.1038/nature03113) [Medline](#)
 30. T. J. T. Pi, *HLA and disease associations*. (Springer Science & Business Media, 2012).
 31. D. Chowell, S. Krishna, P. D. Becker, C. Cocita, J. Shu, X. Tan, P. D. Greenberg, L. S. Klavinskis, J. N. Blattman, K. S. Anderson, TCR contact residue hydrophobicity is a hallmark of immunogenic CD8+ T cell epitopes. *Proc. Natl. Acad. Sci. U.S.A.* **112**, E1754–E1762 (2015). [doi:10.1073/pnas.1500973112](https://doi.org/10.1073/pnas.1500973112) [Medline](#)
 32. P. C. Doherty, R. M. Zinkernagel, A biological role for the major histocompatibility antigens. *Lancet* **1**, 1406–1409 (1975). [doi:10.1016/S0140-6736\(75\)92610-0](https://doi.org/10.1016/S0140-6736(75)92610-0) [Medline](#)

33. P. Parham, T. Ohta, Population biology of antigen presentation by MHC class I molecules. *Science* **272**, 67–74 (1996). [doi:10.1126/science.272.5258.67](https://doi.org/10.1126/science.272.5258.67) [Medline](#)
34. M. M. Gubin, X. Zhang, H. Schuster, E. Caron, J. P. Ward, T. Noguchi, Y. Ivanova, J. Hundal, C. D. Arthur, W.-J. Kriebler, G. E. Mulder, M. Toebes, M. D. Vesely, S. S. K. Lam, A. J. Korman, J. P. Allison, G. J. Freeman, A. H. Sharpe, E. L. Pearce, T. N. Schumacher, R. Aebersold, H.-G. Rammensee, C. J. M. Melief, E. R. Mardis, W. E. Gillanders, M. N. Artyomov, R. D. Schreiber, Checkpoint blockade cancer immunotherapy targets tumour-specific mutant antigens. *Nature* **515**, 577–581 (2014). [doi:10.1038/nature13988](https://doi.org/10.1038/nature13988) [Medline](#)
35. E. Tran, M. Ahmadzadeh, Y.-C. Lu, A. Gros, S. Turcotte, P. F. Robbins, J. J. Gartner, Z. Zheng, Y. F. Li, S. Ray, J. R. Wunderlich, R. P. Somerville, S. A. Rosenberg, Immunogenicity of somatic mutations in human gastrointestinal cancers. *Science* **350**, 1387–1390 (2015). [doi:10.1126/science.1253](https://doi.org/10.1126/science.1253) [Medline](#)
36. E. Tran, P. F. Robbins, Y.-C. Lu, T. D. Prickett, J. J. Gartner, L. Jia, A. Pasetto, Z. Zheng, S. Ray, E. M. Groh, I. R. Kriley, S. A. Rosenberg, T-Cell Transfer Therapy Targeting Mutant KRAS in Cancer. *N. Engl. J. Med.* **375**, 2255–2262 (2016). [doi:10.1056/NEJMoa1609279](https://doi.org/10.1056/NEJMoa1609279) [Medline](#)
37. A. Zehir, R. Benayed, R. H. Shah, A. Syed, S. Middha, H. R. Kim, P. Srinivasan, J. Gao, D. Chakravarty, S. M. Devlin, M. D. Hellmann, D. A. Barron, A. M. Schram, M. Hameed, S. Dogan, D. S. Ross, J. F. Hechtman, D. F. Delair, J. Yao, D. L. Mandelker, D. T. Cheng, R. Chandramohan, A. S. Mohanty, R. N. Ptashkin, G. Jayakumar, M. Prasad, M. H. Syed, A. B. Rema, Z. Y. Liu, K. Nafa, L. Borsu, J. Sadowska, J. Casanova, R. Bacares, I. J. Kiecka, A. Razumova, J. B. Son, L. Stewart, T. Baldi, K. A. Mullaney, H. Al-Ahmadie, E. Vakiani, A. A. Abeshouse, A. V. Penson, P. Jonsson, N. Camacho, M. T. Chang, H. H. Won, B. E. Gross, R. Kundra, Z. J. Heins, H.-W. Chen, S. Phillips, H. Zhang, J. Wang, A. Ochoa, J. Wills, M. Eubank, S. B. Thomas, S. M. Gardos, D. N. Reales, J. Galle, R. Durany, R. Cambria, W. Abida, A. Cercek, D. R. Feldman, M. M. Gounder, A. A. Hakimi, J. J. Harding, G. Iyer, Y. Y. Janjigian, E. J. Jordan, C. M. Kelly, M. A. Lowery, L. G. T. Morris, A. M. Omuro, N. Raj, P. Razavi, A. N. Shoushtari, N. Shukla, T. E. Soumerai, A. M. Varghese, R. Yaeger, J. Coleman, B. Bochner, G. J. Riely, L. B. Saltz, H. I. Scher, P. J. Sabbatini, M. E. Robson, D. S. Klimstra, B. S. Taylor, J. Baselga, N. Schultz, D. M. Hyman, M. E. Arcila, D. B. Solit, M. Ladanyi, M. F. Berger, Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients. *Nat. Med.* **23**, 703–713 (2017). [doi:10.1038/nm.4333](https://doi.org/10.1038/nm.4333) [Medline](#)
38. D. Snary, C. J. Barnstable, W. F. Bodmer, M. J. Crumpton, Molecular structure of human histocompatibility antigens: The HLA-C series. *Eur. J. Immunol.* **7**, 580–585 (1977). [doi:10.1002/eji.1830070816](https://doi.org/10.1002/eji.1830070816) [Medline](#)
39. S. G. Marsh, P. Parham, L. D. Barber, *The HLA factsbook*. (Academic Press, 1999).
40. M. R. Schaefer, M. Williams, D. A. Kulpa, P. K. Blakely, A. Q. Yaffee, K. L. Collins, A novel trafficking signal within the HLA-C cytoplasmic tail allows regulated expression upon differentiation of macrophages. *J. Immunol.* **180**, 7804–7817 (2008). [doi:10.4049/jimmunol.180.12.7804](https://doi.org/10.4049/jimmunol.180.12.7804) [Medline](#)
41. D. S. Chen, I. Mellman, Elements of cancer immunity and the cancer-immune set point. *Nature* **541**, 321–330 (2017). [doi:10.1038/nature21349](https://doi.org/10.1038/nature21349) [Medline](#)
42. T. N. Schumacher, R. D. Schreiber, Neoantigens in cancer immunotherapy. *Science* **348**, 69–74 (2015). [doi:10.1126/science.1253](https://doi.org/10.1126/science.1253) [Medline](#)
43. N. Aptsiauri, T. Cabrera, A. Garcia-Lora, M. A. Lopez-Nevot, F. Ruiz-Cabello, F. Garrido, MHC class I antigens and immune surveillance in transformed cells. *Int. Rev. Cytol.* **256**, 139–189 (2007). [doi:10.1016/S0074-7696\(07\)56005-5](https://doi.org/10.1016/S0074-7696(07)56005-5) [Medline](#)
44. N. McGranahan, R. Rosenthal, C. T. Hiley, A. J. Rowan, T. B. K. Watkins, G. A. Wilson, N. J. Birkbak, S. Veeriah, P. Van Loo, J. Herrero, C. Swanton, TRACERx Consortium, Allele-Specific HLA Loss and Immune Escape in Lung Cancer Evolution. *Cell* **171**, 1259–1271.e11 (2017). [doi:10.1016/j.cell.2017.10.001](https://doi.org/10.1016/j.cell.2017.10.001) [Medline](#)
45. N. van Rooij, M. M. van Buuren, D. Philips, A. Velds, M. Toebes, B. Heemskerk, L. J. A. van Dijk, S. Behjati, H. Hilkmann, D. El Atmioui, M. Nieuwland, M. R. Stratton, R. M. Kerkhoven, C. Kegmir, J. B. Haanen, P. Kvistborg, T. N. Schumacher, Tumor exome analysis reveals neoantigen-specific T-cell reactivity in an ipilimumab-responsive melanoma. *J. Clin. Oncol.* **31**, e439–e442 (2013). [doi:10.1200/JCO.2012.47.7521](https://doi.org/10.1200/JCO.2012.47.7521) [Medline](#)
46. M. Yadav, S. Jhunjunwala, Q. T. Phung, P. Lupardus, J. Tanguay, S. Bumbaca, C. Franci, T. K. Cheung, J. Fritsch, T. Weinschenk, Z. Modrusan, I. Mellman, J. R. Lill, L. Delamarre, Predicting immunogenic tumour mutations by combining mass spectrometry and exome sequencing. *Nature* **515**, 572–576 (2014). [doi:10.1038/nature14001](https://doi.org/10.1038/nature14001) [Medline](#)
47. E. W. Petersdorf, M. Malkki, C. O'hUigin, M. Carrington, T. Gooley, M. D. Haegenson, M. M. Horowitz, S. R. Spellman, T. Wang, P. Stevenson, High HLA-DP Expression and Graft-versus-Host Disease. *N. Engl. J. Med.* **373**, 599–609 (2015). [doi:10.1056/NEJMoa1500140](https://doi.org/10.1056/NEJMoa1500140) [Medline](#)
48. C. S. Carlson, R. O. Emerson, A. M. Sherwood, C. Desmarais, M.-W. Chung, J. M. Parsons, M. S. Steen, M. A. LaMadrid-Herrmannsfeldt, D. W. Williamson, R. J. Livingston, D. Wu, B. L. Wood, M. J. Rieder, H. Robins, Using synthetic templates to design an unbiased multiplex PCR assay. *Nat. Commun.* **4**, 2680 (2013). [doi:10.1038/ncomms3680](https://doi.org/10.1038/ncomms3680) [Medline](#)
49. H. S. Robins, P. V. Campregher, S. K. Srivastava, A. Wachter, C. J. Turtle, O. Khsai, S. R. Riddell, E. H. Warren, C. S. Carlson, Comprehensive assessment of T-cell receptor β -chain diversity in alphabeta T cells. *Blood* **114**, 4099–4107 (2009). [doi:10.1182/blood-2009-04-217604](https://doi.org/10.1182/blood-2009-04-217604) [Medline](#)
50. J. S. Sims, B. Grinshpun, Y. Feng, T. H. Ung, J. A. Neira, J. L. Samanamud, P. Canoll, Y. Shen, P. A. Sims, J. N. Bruce, Diversity and divergence of the glioma-infiltrating T-cell receptor repertoire. *Proc. Natl. Acad. Sci. U.S.A.* **113**, E3529–E3537 (2016). [doi:10.1073/pnas.1601012113](https://doi.org/10.1073/pnas.1601012113) [Medline](#)
51. B. Li, T. Li, J.-C. Pignon, B. Wang, J. Wang, S. A. Shukla, R. Dou, Q. Chen, F. S. Hodi, T. K. Choueiri, C. Wu, N. Hacohen, S. Signoretti, J. S. Liu, X. S. Liu, Landscape of tumor-infiltrating T cell repertoire of human cancers. *Nat. Genet.* **48**, 725–732 (2016). [doi:10.1038/ng.3581](https://doi.org/10.1038/ng.3581) [Medline](#)
52. A. Sette, J. Sidney, Nine major HLA class I supertypes account for the vast preponderance of HLA-A and -B polymorphism. *Immunogenetics* **50**, 201–212 (1999). [doi:10.1007/s002510050594](https://doi.org/10.1007/s002510050594) [Medline](#)
53. J. Sidney, B. Peters, N. Frahm, C. Brander, A. Sette, HLA class I supertypes: A revised and updated classification. *BMC Immunol.* **9**, 1 (2008). [doi:10.1186/1471-2172-9-1](https://doi.org/10.1186/1471-2172-9-1) [Medline](#)
54. N. Hillen, G. Mester, C. Lemmel, A. O. Weinzierl, M. Müller, D. Wernet, J. Hennenlotter, A. Stenzl, H.-G. Rammensee, S. Stevanović, Essential differences in ligand presentation and T cell epitope recognition among HLA molecules of the HLA-B44 supertype. *Eur. J. Immunol.* **38**, 2993–3003 (2008). [doi:10.1002/eji.200838632](https://doi.org/10.1002/eji.200838632) [Medline](#)
55. H.-G. Rammensee, T. Friede, S. Stevanović, MHC ligands and peptide motifs: First listing. *Immunogenetics* **41**, 178–228 (1995). [doi:10.1007/BF00172063](https://doi.org/10.1007/BF00172063) [Medline](#)
56. M. DiBriano, K. C. Parker, D. H. Margulies, J. Shiloach, R. V. Turner, W. E. Biddison, J. E. Coligan, Identification of the peptide binding motif for HLA-B44, one of the most common HLA-B alleles in the Caucasian population. *Biochemistry* **34**, 10130–10138 (1995). [doi:10.1021/bi00032a005](https://doi.org/10.1021/bi00032a005) [Medline](#)
57. P. Liu, X. Huang, R. Zhou, B. J. Berne, Observation of a dewetting transition in the collapse of the melittin tetramer. *Nature* **437**, 159–162 (2005). [doi:10.1038/nature03926](https://doi.org/10.1038/nature03926) [Medline](#)
58. Y. Tu, M. Lv, P. Xiu, T. Huynh, M. Zhang, M. Castelli, Z. Liu, Q. Huang, C. Fan, H. Fang, R. Zhou, Destructive extraction of phospholipids from Escherichia coli membranes by graphene nanosheets. *Nat. Nanotechnol.* **8**, 594–601 (2013). [doi:10.1038/nnano.2013.125](https://doi.org/10.1038/nnano.2013.125) [Medline](#)
59. R. Zhou, X. Huang, C. J. Margulis, B. J. Berne, Hydrophobic collapse in multidomain protein folding. *Science* **305**, 1605–1609 (2004). [doi:10.1126/science.1101176](https://doi.org/10.1126/science.1101176) [Medline](#)
60. S. J. Patel, N. E. Sanjana, R. J. Kishton, A. Eidzadeh, S. K. Vodnala, M. Cam, J. J. Gartner, L. Jia, S. M. Steinberg, T. N. Yamamoto, A. S. Merchant, G. U. Mehta, A. Chichura, O. Shalem, E. Tran, R. Eil, M. Sukumar, E. P. Gujjarro, C.-P. Day, P. Robbins, S. Feldman, G. Merlino, F. Zhang, N. P. Restifo, Identification of essential genes for cancer immunotherapy. *Nature* **548**, 537–542 (2017). [doi:10.1038/nature23477](https://doi.org/10.1038/nature23477) [Medline](#)
61. S. A. Shukla, M. S. Rooney, M. Rajasagi, G. Tiao, P. M. Dixon, M. S. Lawrence, J. Stevens, W. J. Lane, J. L. Dellagatta, S. Steelman, C. Sougnez, K. Cibulskis, A. Kiezun, N. Hacohen, V. Brusica, C. J. Wu, G. Getz, Comprehensive analysis of cancer-associated somatic mutations in class I HLA genes. *Nat. Biotechnol.* **33**, 1152–1158 (2015). [doi:10.1038/nbt.3344](https://doi.org/10.1038/nbt.3344) [Medline](#)
62. K. Kiyotani, T. H. Mai, Y. Nakamura, Comparison of exome-based HLA class I genotyping tools: Identification of platform-specific genotyping errors. *J. Hum. Genet.* **62**, 397–405 (2017). [Medline](#)
63. H. Cao, J. Wu, Y. Wang, H. Jiang, T. Zhang, X. Liu, Y. Xu, D. Liang, P. Gao, Y. Sun, B. Gifford, M. D'Ascenzo, X. Liu, L. C. A. M. Tellier, F. Yang, X. Tong, D. Chen, J. Zheng, W. Li, T. Richmond, X. Xu, J. Wang, Y. Li, An integrated tool to study MHC region:

- Accurate SNV detection and HLA genes typing in human MHC region using targeted high-throughput sequencing. *PLOS ONE* **8**, e69388 (2013). [doi:10.1371/journal.pone.0069388](https://doi.org/10.1371/journal.pone.0069388) [Medline](#)
64. A. Szolek, B. Schubert, C. Mohr, M. Sturm, M. Feldhahn, O. Kohlbacher, OptiType: Precision HLA typing from next-generation sequencing data. *Bioinformatics* **30**, 3310–3316 (2014). [doi:10.1093/bioinformatics/btu548](https://doi.org/10.1093/bioinformatics/btu548) [Medline](#)
 65. D. T. Cheng, T. N. Mitchell, A. Zehir, R. H. Shah, R. Benayed, A. Syed, R. Chandramohan, Z. Y. Liu, H. H. Won, S. N. Scott, A. R. Brannon, C. O'Reilly, J. Sadowska, J. Casanova, A. Yannes, J. F. Hechtman, J. Yao, W. Song, D. S. Ross, A. Oultache, S. Dogan, L. Borsu, M. Hameed, K. Nafa, M. E. Arcila, M. Ladanyi, M. F. Berger, Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT): A Hybridization Capture-Based Next-Generation Sequencing Clinical Assay for Solid Tumor Molecular Oncology. *J. Mol. Diagn.* **17**, 251–264 (2015). [doi:10.1016/j.jmoldx.2014.12.006](https://doi.org/10.1016/j.jmoldx.2014.12.006) [Medline](#)
 66. D. M. Hyman, D. B. Solit, M. E. Arcila, D. T. Cheng, P. Sabbatini, J. Baselga, M. F. Berger, M. Ladanyi, Precision medicine at Memorial Sloan Kettering Cancer Center: Clinical next-generation sequencing enabling next-generation targeted therapy trials. *Drug Discov. Today* **20**, 1422–1428 (2015). [doi:10.1016/j.drudis.2015.08.005](https://doi.org/10.1016/j.drudis.2015.08.005) [Medline](#)
 67. M. A. DePristo, E. Banks, R. Poplin, K. V. Garimella, J. R. Maguire, C. Hartl, A. A. Philippakis, G. del Angel, M. A. Rivas, M. Hanna, A. McKenna, T. J. Fennell, A. M. Kernysky, A. Y. Sivachenko, K. Cibulskis, S. B. Gabriel, D. Altshuler, M. J. Daly, A framework for variation discovery and genotyping using next-generation DNA sequencing data. *Nat. Genet.* **43**, 491–498 (2011). [doi:10.1038/ng.806](https://doi.org/10.1038/ng.806) [Medline](#)
 68. H. Li, R. Durbin, Fast and accurate short read alignment with Burrows-Wheeler transform. *Bioinformatics* **25**, 1754–1760 (2009). [doi:10.1093/bioinformatics/btp324](https://doi.org/10.1093/bioinformatics/btp324) [Medline](#)
 69. A. McKenna, M. Hanna, E. Banks, A. Sivachenko, K. Cibulskis, A. Kernysky, K. Garimella, D. Altshuler, S. Gabriel, M. Daly, M. A. DePristo, The Genome Analysis Toolkit: A MapReduce framework for analyzing next-generation DNA sequencing data. *Genome Res.* **20**, 1297–1303 (2010). [doi:10.1101/gr.107524.110](https://doi.org/10.1101/gr.107524.110) [Medline](#)
 70. K. Cibulskis, M. S. Lawrence, S. L. Carter, A. Sivachenko, D. Jaffe, C. Sougnez, S. Gabriel, M. Meyerson, E. S. Lander, G. Getz, Sensitive detection of somatic point mutations in impure and heterogeneous cancer samples. *Nat. Biotechnol.* **31**, 213–219 (2013). [doi:10.1038/nbt.2514](https://doi.org/10.1038/nbt.2514) [Medline](#)
 71. D. C. Koboldt, Q. Zhang, D. E. Larson, D. Shen, M. D. McLellan, L. Lin, C. A. Miller, E. R. Mardis, L. Ding, R. K. Wilson, VarScan 2: Somatic mutation and copy number alteration discovery in cancer by exome sequencing. *Genome Res.* **22**, 568–576 (2012). [doi:10.1101/gr.129684.111](https://doi.org/10.1101/gr.129684.111) [Medline](#)
 72. D. E. Larson, C. C. Harris, K. Chen, D. C. Koboldt, T. E. Abbott, D. J. Dooling, T. J. Ley, E. R. Mardis, R. K. Wilson, L. Ding, SomaticSniper: Identification of somatic point mutations in whole genome sequencing data. *Bioinformatics* **28**, 311–317 (2012). [doi:10.1093/bioinformatics/btr665](https://doi.org/10.1093/bioinformatics/btr665) [Medline](#)
 73. C. T. Saunders, W. S. W. Wong, S. Swamy, J. Becq, L. J. Murray, R. K. Cheetham, Strelka: Accurate somatic small-variant calling from sequenced tumor-normal sample pairs. *Bioinformatics* **28**, 1811–1817 (2012). [doi:10.1093/bioinformatics/bts271](https://doi.org/10.1093/bioinformatics/bts271) [Medline](#)
 74. Z. R. Chalmers, C. F. Connelly, D. Fabrizio, L. Gay, S. M. Ali, R. Ennis, A. Schrock, B. Campbell, A. Shlien, J. Chmielecki, F. Huang, Y. He, J. Sun, U. Tabori, M. Kennedy, D. S. Lieber, S. Roels, J. White, G. A. Otto, J. S. Ross, L. Garraway, V. A. Miller, P. J. Stephens, G. M. Frampton, Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden. *Genome Med.* **9**, 34 (2017). [doi:10.1186/s13073-017-0424-2](https://doi.org/10.1186/s13073-017-0424-2) [Medline](#)
 75. R. Shen, V. E. Seshan, FACETS: Allele-specific copy number and clonal heterogeneity analysis tool for high-throughput DNA sequencing. *Nucleic Acids Res.* **44**, e131 (2016). [doi:10.1093/nar/gkw520](https://doi.org/10.1093/nar/gkw520) [Medline](#)
 76. S. Arnaud-Haond, C. M. Duarte, F. Alberto, E. A. Serrão, Standardizing methods to address clonality in population studies. *Mol. Ecol.* **16**, 5115–5139 (2007). [doi:10.1111/j.1365-294X.2007.03535.x](https://doi.org/10.1111/j.1365-294X.2007.03535.x) [Medline](#)
 77. W. Humphrey, A. Dalke, K. Schulten, VMD: Visual molecular dynamics. *J. Mol. Graph.* **14**, 33–38, 27–28 (1996). [doi:10.1016/0263-7855\(96\)00018-5](https://doi.org/10.1016/0263-7855(96)00018-5) [Medline](#)
 78. J. C. Phillips, R. Braun, W. Wang, J. Gumbart, E. Tajkhorshid, E. Villa, C. Chipot, R. D. Skeel, L. Kalé, K. Schulten, Scalable molecular dynamics with NAMD. *J. Comput. Chem.* **26**, 1781–1802 (2005). [doi:10.1002/jcc.20289](https://doi.org/10.1002/jcc.20289) [Medline](#)
 79. M. J. Abraham, Performance enhancements for GROMACS nonbonded interactions on BlueGene. *J. Comput. Chem.* **32**, 2041–2046 (2011). [doi:10.1002/jcc.21766](https://doi.org/10.1002/jcc.21766) [Medline](#)
 80. K. Fleischhauer, D. Avila, F. Vilbois, C. Traversari, C. Bordignon, H.-J. Wallny, Characterization of natural peptide ligands for HLA-B*4402 and -B*4403: Implications for peptide involvement in allorecognition of a single amino acid change in the HLA-B44 heavy chain. *Tissue Antigens* **44**, 311–317 (1994). [doi:10.1111/j.1399-0039.1994.tb02401.x](https://doi.org/10.1111/j.1399-0039.1994.tb02401.x) [Medline](#)
 81. J. Herman, P. van der Bruggen, I. F. Luescher, S. Mandruzzato, P. Romero, J. Thonnard, K. Fleischhauer, T. Boon, P. G. Coulie, A peptide encoded by the human MAGE3 gene and presented by HLA-B44 induces cytolytic T lymphocytes that recognize tumor cells expressing MAGE3. *Immunogenetics* **43**, 377–383 (1996). [doi:10.1007/BF02199806](https://doi.org/10.1007/BF02199806) [Medline](#)
 82. V. G. Brichard, J. Herman, A. Van Pel, C. Wildmann, B. Gaugler, T. Wölfel, T. Boon, B. Lethé, A tyrosinase nonapeptide presented by HLA-B44 is recognized on a human melanoma by autologous cytolytic T lymphocytes. *Eur. J. Immunol.* **26**, 224–230 (1996). [doi:10.1002/eji.1830260135](https://doi.org/10.1002/eji.1830260135) [Medline](#)
 83. P. G. Coulie, F. Lehmann, B. Lethé, J. Herman, C. Lurquin, M. Andrawiss, T. Boon, A mutated intron sequence codes for an antigenic peptide recognized by cytolytic T lymphocytes on a human melanoma. *Proc. Natl. Acad. Sci. U.S.A.* **92**, 7976–7980 (1995). [doi:10.1073/pnas.92.17.7976](https://doi.org/10.1073/pnas.92.17.7976) [Medline](#)
 84. R. Chiari, F. Foury, E. De Plaen, J. F. Baurain, J. Thonnard, P. G. Coulie, Two antigens recognized by autologous cytolytic T lymphocytes on a melanoma result from a single point mutation in an essential housekeeping gene. *Cancer Res.* **59**, 5785–5792 (1999). [Medline](#)
 85. N. Vigneron, A. Ooms, S. Morel, G. Degiovanni, B. J. Van Den Eynde, Identification of a new peptide recognized by autologous cytolytic T lymphocytes on a human melanoma. *Cancer Immun.* **2**, 9 (2002). [Medline](#)
 86. M. Nielsen, C. Lundegaard, P. Wornring, S. L. Lauemøller, K. Lamberth, S. Buus, S. Brunak, O. Lund, Reliable prediction of T-cell epitopes using neural networks with novel sequence representations. *Protein Sci.* **12**, 1007–1017 (2003). [doi:10.1110/ps.0239403](https://doi.org/10.1110/ps.0239403) [Medline](#)

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SUPPLEMENTARY MATERIALS

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Materials and Methods

Supplementary Text

Figs. S1 to S5

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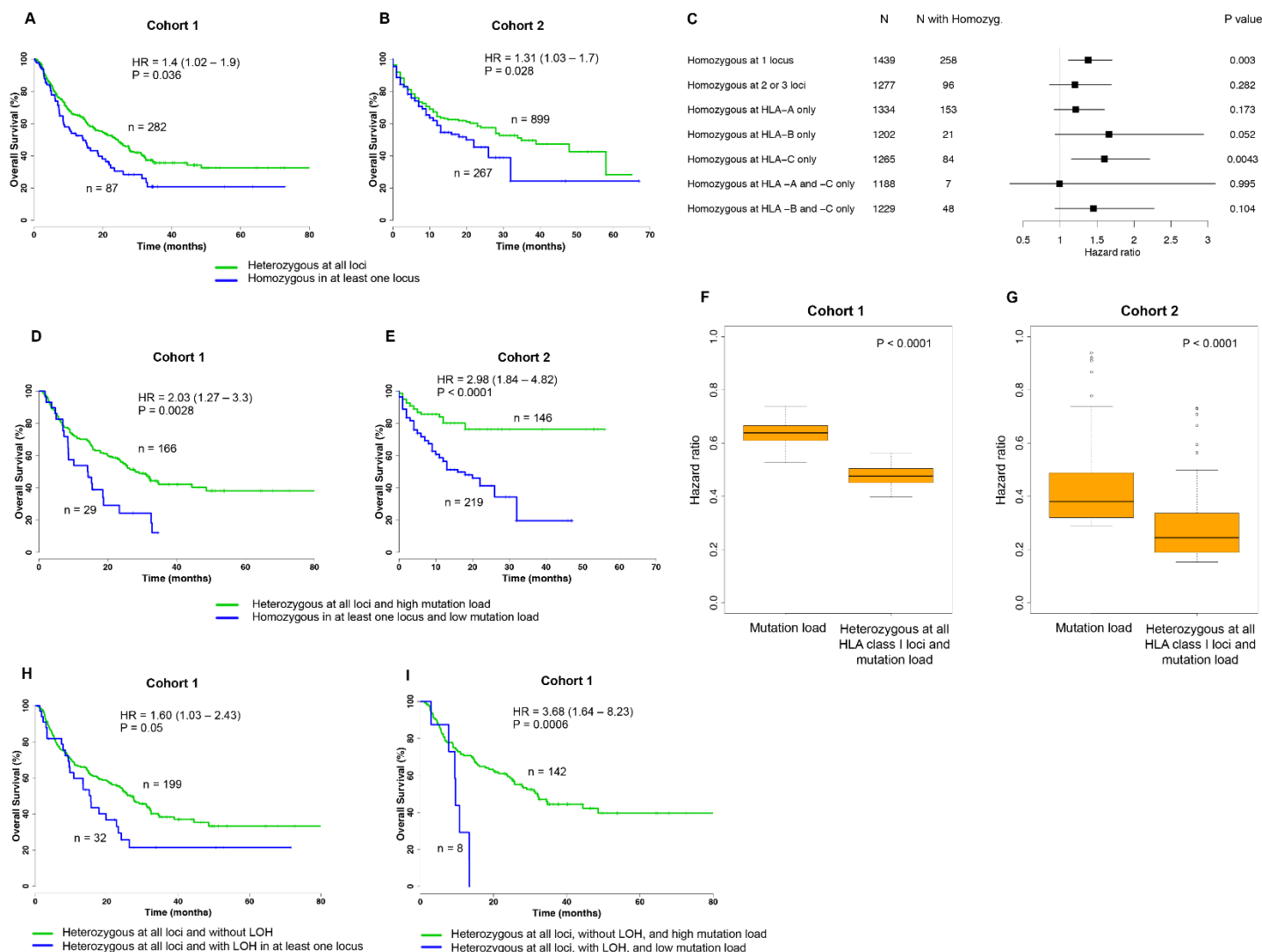


Fig. 1. Effect of HLA class I homozygosity on survival in patients treated with immune checkpoint inhibitors. (A) Association between homozygosity in at least one HLA-I locus and reduced overall survival in cohort 1. (B) Association between homozygosity in at least one HLA-I locus and reduced survival in cohort 2. (C) Association between HLA-I homozygosity and decreased survival from all 1,535 patients. Data show one or more HLA-I loci or individual loci (HLA-A, HLA-B, and HLA-C). Indicated are the number of patients and hazard ratio (HR). Horizontal lines represent the 95% confidence interval. *P* value was calculated using the Log-rank test. (D) Patients in cohort 1 with heterozygosity at all HLA-I loci and a high mutation load (defined as >113 mutations) compared to patients that are homozygous for at least one HLA-I locus and have a low mutation load. (E) Patients in cohort 2 with heterozygosity at all HLA-I loci and a high tumor mutational load (defined as >16.72 mutations) compared to patients that are homozygous in at least one HLA-I locus and have a low mutation load. (F) Distribution of hazard ratios to stratify cohort 1 patients based on tumor mutational load. The combined effect of HLA-I heterozygosity at all loci and mutation load on improved survival was greater compared to mutation load alone. (G) Distribution of hazard ratios to stratify cohort 2 patients based on mutation load. A range of cutoffs across the quartiles of mutation load were used. *P* values were calculated using the Wilcoxon-rank sum test. (H) Survival analysis showing that LOH of heterozygous germline HLA-I is associated with decreased overall survival in patients treated with ICB. (I) Survival analysis showing that the effect of LOH of heterozygous germline HLA-I is greater in tumors with low mutation burden compared to tumors with high mutation load and without LOH. High mutation load is defined as >113 mutations.

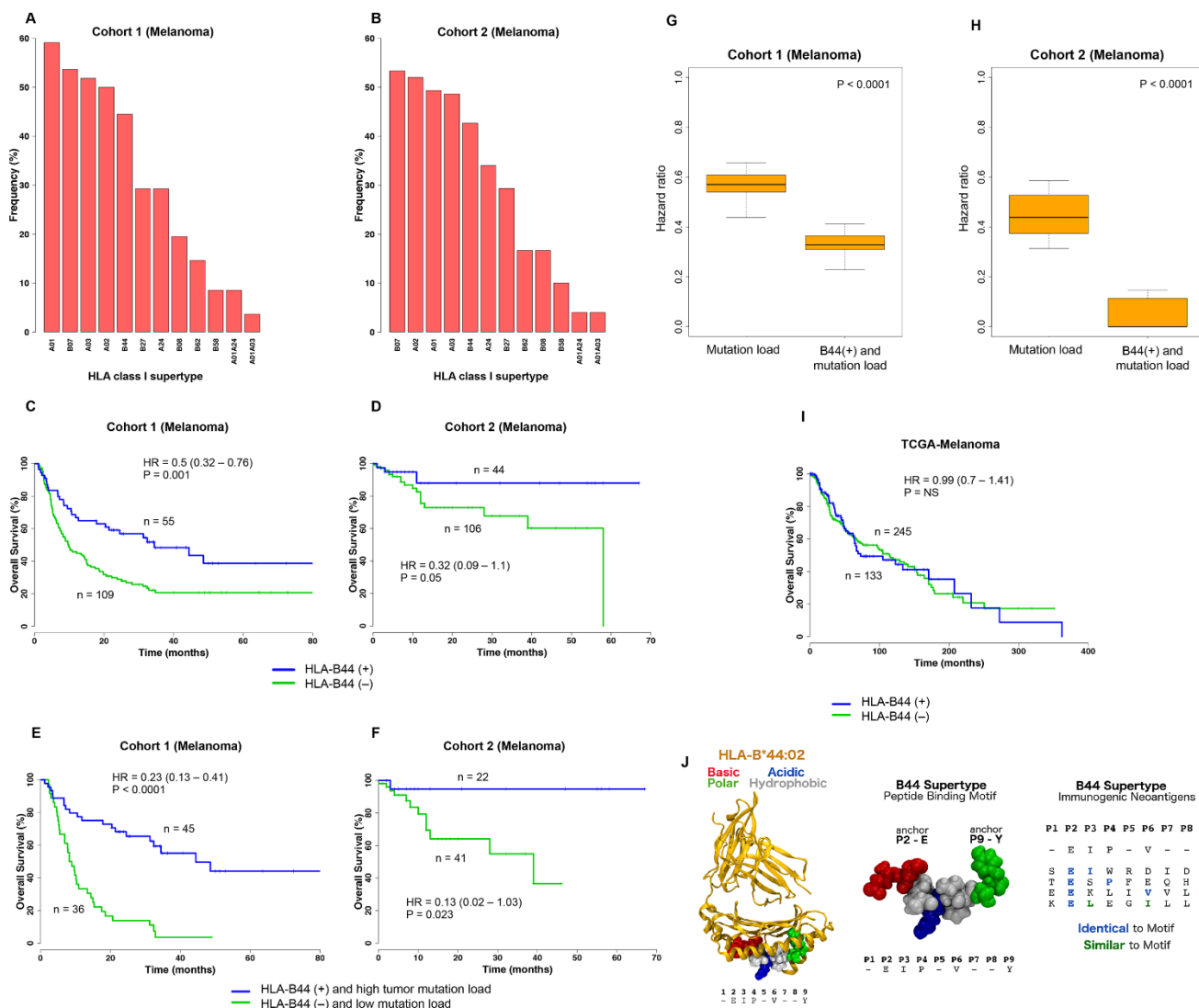


Fig. 2. Influence of the HLA-B44 supertype on survival of melanoma patients treated with immune checkpoint inhibitors. (A) Prevalence of the different HLA supertypes in patients with melanoma from cohort 1. (B) Prevalence of the different HLA supertypes in the patients with melanoma from cohort 2. (C and D) Survival analysis of patients possessing the B44 alleles [B44 (+)] compared with patients without the B44 alleles [B44 (-)] from cohort 1 (C) and cohort 2 (D). (E and F) Survival analysis of patients with the B44 alleles and with high mutation burden versus patients without B44 and with low mutation load, from cohort 1 (E) and cohort 2 (F). (G) Distribution of hazard ratios to stratify cohort 1 patients based on mutation load. The combined effect of B44 and mutation load on increased survival was greater compared to simply considering mutation load alone. (H) Distribution of hazard ratios to stratify cohort 2 patients based on mutation load. A range of cutoffs across the quartiles of mutation load was used. *P* values were calculated using the Wilcoxon-rank sum test. (I) Survival analysis of melanoma patients with and without the B44 alleles from the TCGA cohort. (J) Left: Example of peptide motif common among B44 alleles, docked in complex with HLA-B*44:02 based on an available crystal structure (PDB: 1M60). The five common residues (E2, I3, P4, V6, and Y9) of the motif were reported in (56). Peptide residues are colored according to their properties as basic (red), acidic (blue), polar (green), or hydrophobic (grey). Center: Close up view of an example peptide conforming to the B44 motif (54, 56). Residues at positions 2 and 9 are important for anchoring the peptide in the HLA binding groove (54). Right: Alignment between B44 peptide motif and known immunogenic neoantigens (table S8) restricted to B44 expressed by melanomas. All neoepitopes feature Glu (E) at position 2; neoantigens are also either identical or similar to the motif at one or two additional positions. The neoantigen, FAM3C: TESPFEQHI, was identified in a melanoma patient with long-term response to anti-CTLA-4 from cohort 1. Sequence similarity was determined using standard residue classes (GAVLI, FYW, CM, ST, KRH, DENQ, and P).

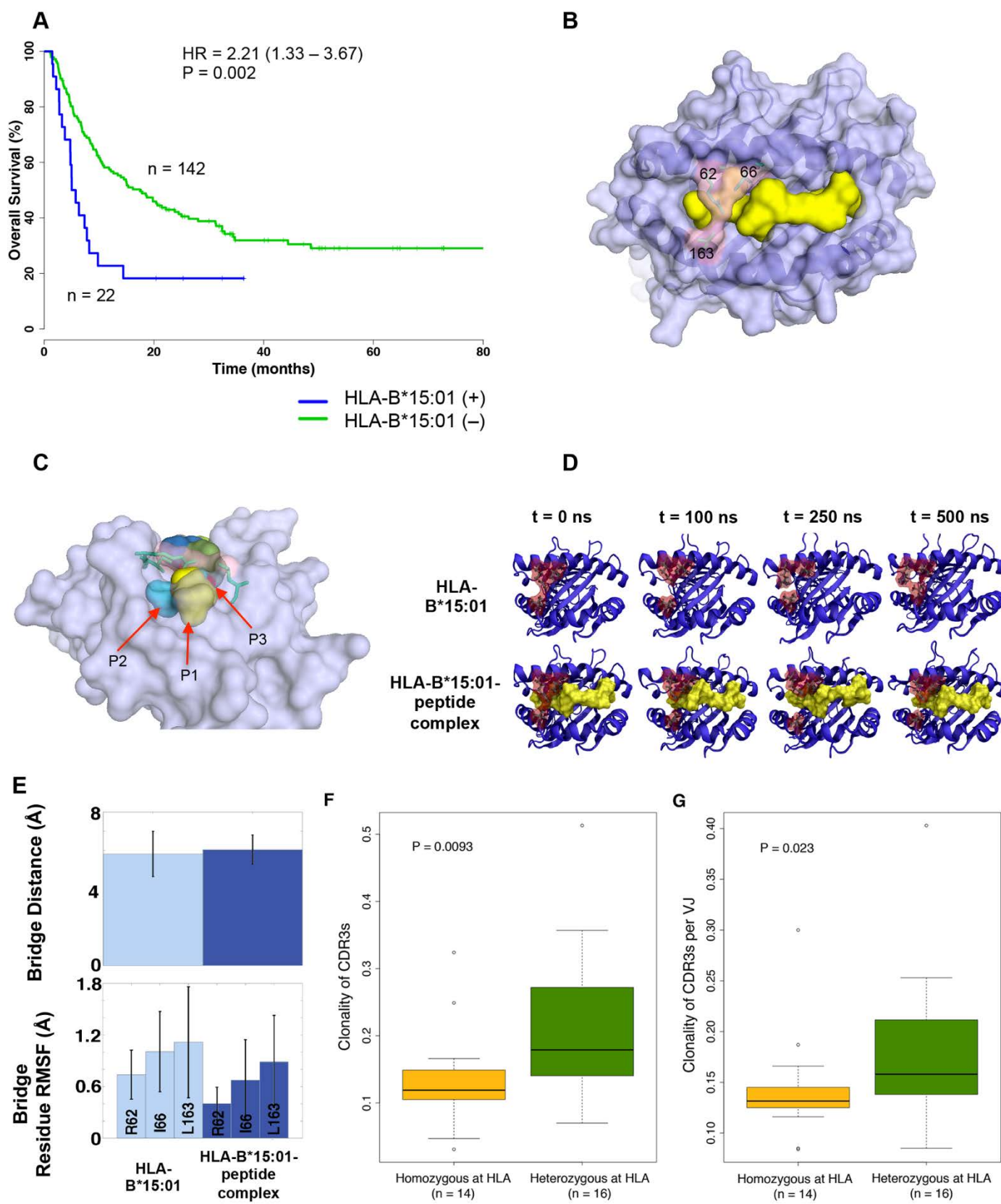


Fig. 3. Effect of the HLA-B*15:01 allele on overall survival of melanoma patients treated with immune checkpoint inhibitors. (A) Survival analysis showing reduced survival in ICB-treated melanoma patients from cohort 1 with and without the HLA-B*15:01 allele. (B) Overview of the three-dimensional structure of the peptide-binding groove of HLA-B*15:01, light purple; bound peptide, yellow; bridging residues, light pink. (C) Side view of the bridge-sequestration effect over bound-peptide residue positions P2 (light blue) and P3 (red). (D) MD simulation snapshots of both the isolated HLA B*15:01 molecule and its complex with a 9-mer UBCH6 peptide; each trajectory was run over the course of 500 ns of simulation time. (E) Observables from the MD simulations described in D. The mean bridge distances in the HLA-B*15:01 molecule and in the HLA-B*15:01-peptide complex are comparable. The residue-position root mean square fluctuations (RMSFs) indicate that each of the bridging residues becomes more rigid in the presence of the peptide. (F) On-therapy clonality of TCR CDR3s between HLA heterozygous patients and patients who are HLA homozygous (in at least one class I locus or at HLA-DP). (G) On-therapy clonality of TCR CDR3s per VJ combination between HLA heterozygous patients and patients with HLA homozygosity (in at least one class I locus or at HLA-DP).

Table 1. Association of HLA supertype with overall survival of melanoma patients treated with immune checkpoint blockade. Data show the influence of specific HLA class I alleles on patient survival.

HLA class I supertype	Frequency	HR	P value
A24	0.29	0.67 (0.44–1.03)	0.07
A01	0.59	0.87 (0.60–1.27)	0.47
A03	0.52	1.39 (0.96–2.03)	0.08
A02	0.5	1.13 (0.76–1.63)	0.53
B58	0.09	0.98 (0.51–1.88)	0.96
B62	0.15	2.29 (1.40–3.74)	0.0007
B27	0.29	1.09 (0.73–1.63)	0.67
B44	0.45	0.61 (0.42–0.89)	0.009
B07	0.54	1.35 (0.92–1.97)	0.12
B08	0.2	0.85 (0.52–1.39)	0.51
A01A03	0.04	1.20 (0.49–2.94)	0.69
A01A24	0.09	0.89 (0.43–1.83)	0.76
Alleles influencing the significant associations			
B44s, B*18:01, B*44:02, B*44:03, B*44:05, B*50:01	0.34	0.49 (0.32–0.76)	0.001
B62s, B*15:01	0.13	2.21 (1.33–3.70)	0.002

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

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