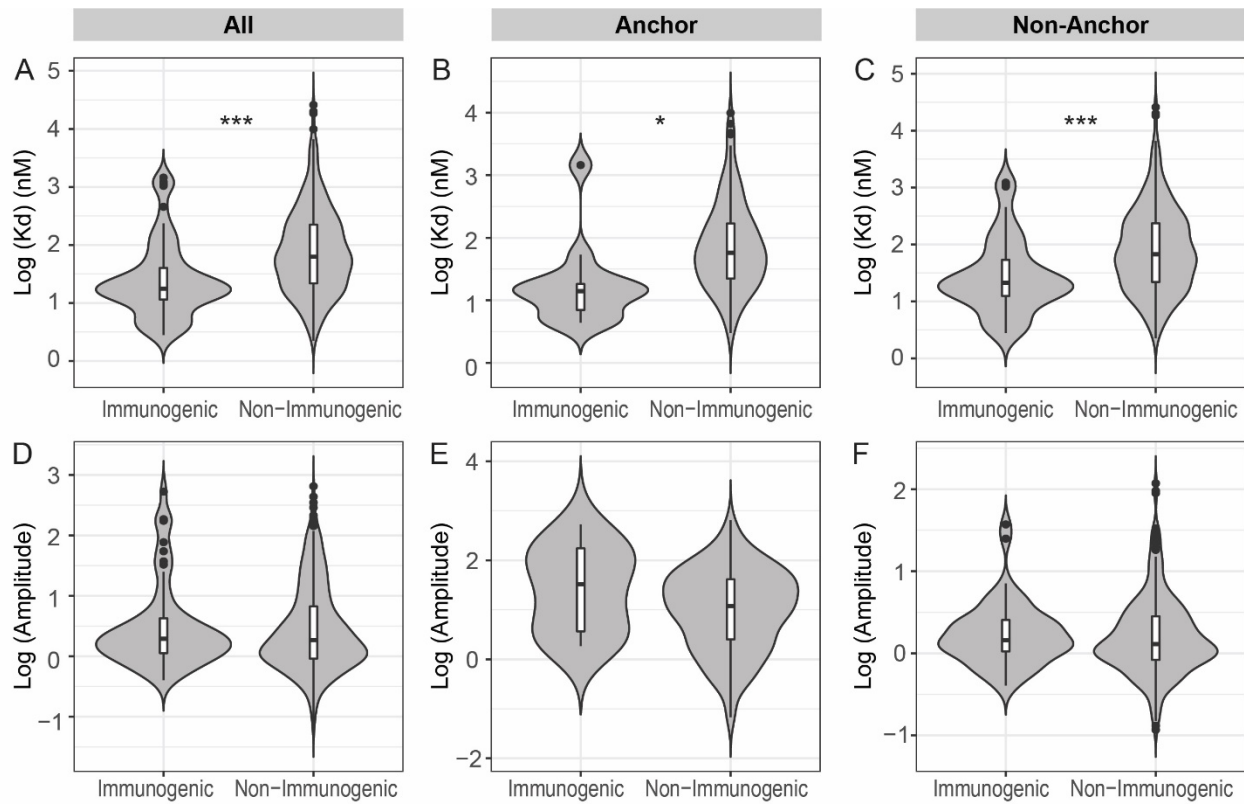


**Supplementary Table I. Comparison of hydrophobicity of immunogenic and non-immunogenic neoantigens by HLA**

**allele.** Analysis of the association of hydrophobicity with immunogenicity was performed across the combination of the TESLA, Carreno, Strønen, and Ott datasets. The number of immunogenic and non-immunogenic neoantigens for each HLA allele is indicated in the first two rows. HLA alleles were only analyzed if they had a minimum of n = 3 immunogenic and non-immunogenic neoantigens. The hydrophobicity was calculated using the methods of the TESLA consortium, Chowell *et al.*, and Łuksza *et al.*. The p-value and direction of change are indicated for each of the three methods. The significant p-value is bolded.

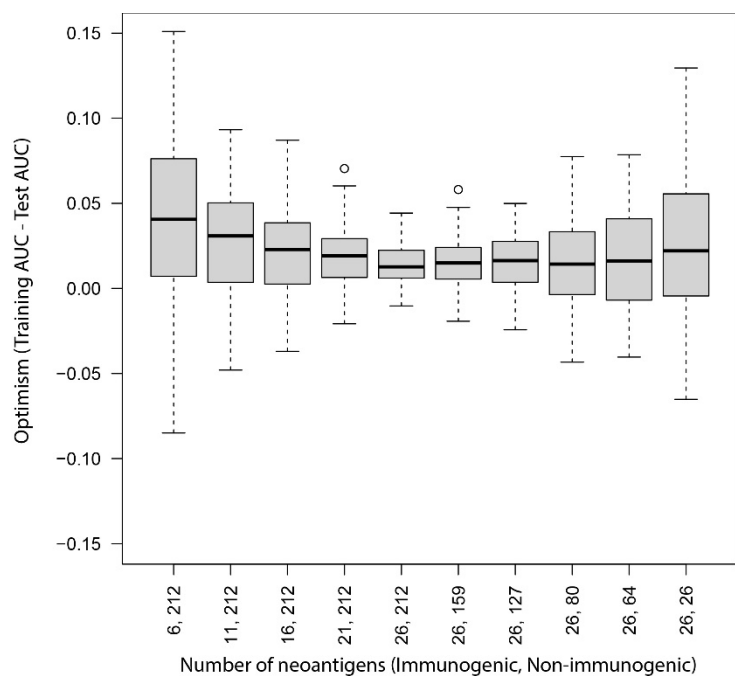
		All HLA	A01:01	A02:01	A03:01	B08:01	B27:05	B35:01
# Immunogenic		64	4	30	9	3	4	5
#Non-immunogenic		522	38	226	49	29	12	6
TESLA Consortium	p-value	0.068	<b>0.034</b>	0.066	0.239	0.922	0.266	0.520
	Increased immunogenic	X		X			X	X
	Increased non-immunogenic		X		X	X		
Chowell <i>et al.</i>	p-value	0.748	0.108	0.426	0.173	0.538	0.203	0.792
	Increased immunogenic	X		X			X	X
	Increased non-immunogenic		X		X	X		
Łuksza <i>et al.</i>	p-value	0.099	0.1491	0.770	0.094	0.968	0.226	0.465
	Increased immunogenic	X	X		X	X	X	X
	Increased non-immunogenic			X				



**Supplementary Figure 1. Dissociation Constant is Significantly Different for Neoantigens Derived from Mutations in**

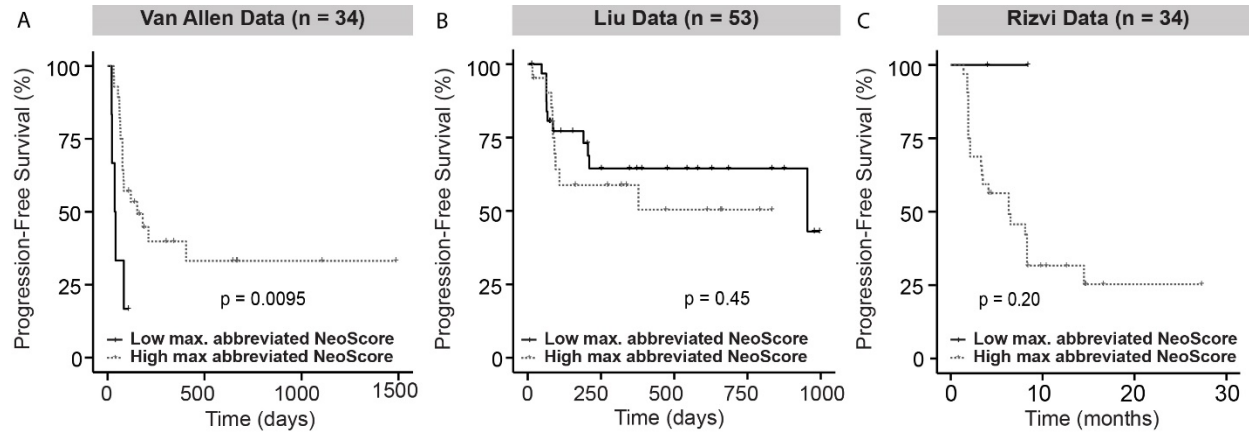
**Anchor and Non-anchor Residues.** Comparison of the dissociation constant and amplitude characteristics between

immunogenic and non-immunogenic neoantigens from the TESLA consortium, Carreno, Ott, and Strønen datasets. Dissociation constant (Kd) of the MHC class I:neoantigen interaction in (A) all neoantigens, (B) neoantigens mutated at an anchor residue, and (C) neoantigens mutated at a non-anchor residue. Amplitude, defined as the ratio of MHC class I dissociation constant for the closest matched normal human peptide to the MHC class I:neoantigen dissociation constant, for (D) all neoantigens, (E) neoantigens mutated at an anchor residue, and (F) neoantigens mutated at a non-anchor residue. \*:p<0.05, \*\*\*:p<10<sup>-5</sup>.



**Supplementary Figure 2. Limiting the Sample Size of Immunogenic or Non-Immunogenic Neoantigens Increases Model**

**Optimism.** For each number of immunogenic and non-immunogenic neoantigens, 100 random samples were selected from the overall TESLA consortium data and a logistic regression model was fit. The logistic regression model was then tested on the Cohen test dataset and optimism was calculated by subtracting the area under the receiver operator characteristics curve (AUC) of the test dataset from the AUC of the training dataset. The optimism increases as either the number of immunogenic or non-immunogenic neoantigens decreases, and the best optimism is achieved with the highest overall sample size.



**Supplementary Figure 3. High Maximum Abbreviated NeoScore Demonstrates No Consistent Association with Progression-free Survival.** Comparison of progression-free survival probability within treatment-naïve, cutaneous melanoma and lung cancer patients. All splits between the groups were determined using maximally ranked statistics and p-values were calculated using a log-rank test. Patients with a high maximum (max.) abbreviated NeoScore have (A) significantly increased survival in the Van Allen dataset, (B) a decrease in survival that is not significant in the Liu dataset, and (C) a decrease in survival that is not significant in the Rizvi dataset.