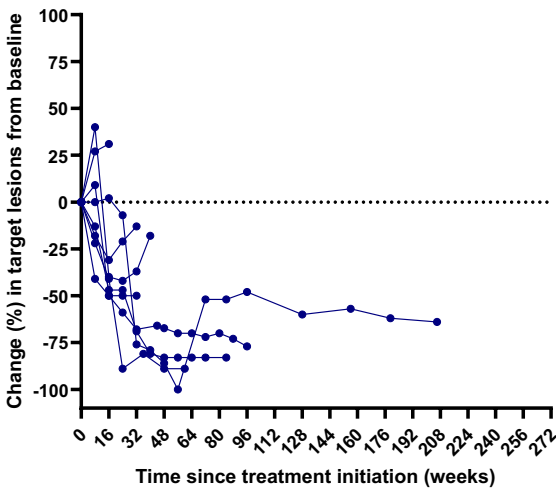
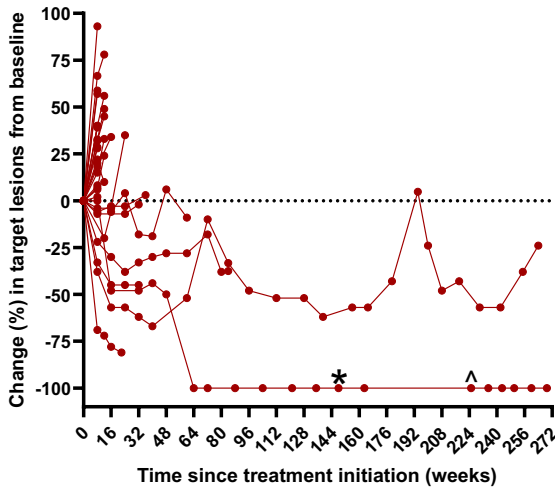


Supplementary Figure 1

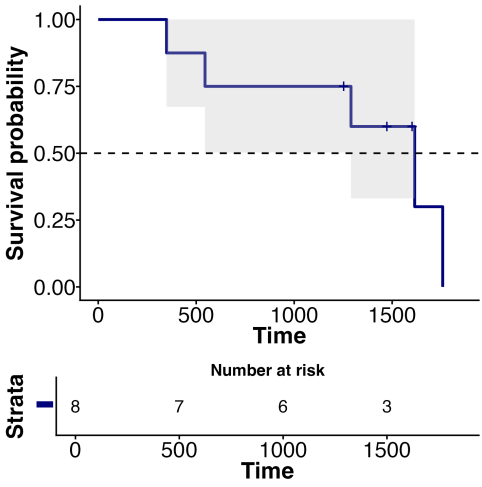
A ICB Naïve HVP16⁺ Malignancies



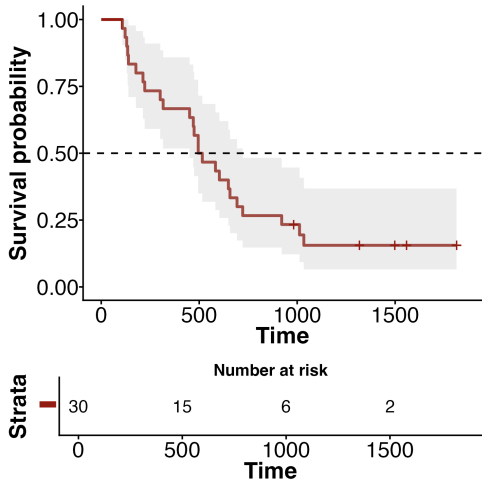
B ICB Resistant HVP16⁺ Malignancies



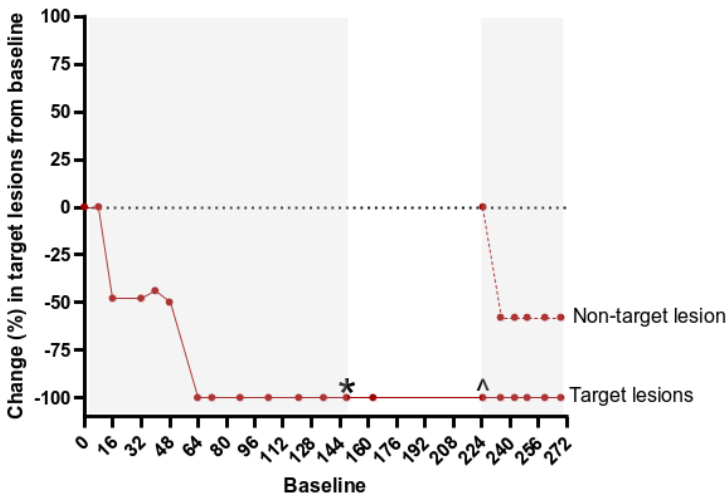
C ICB Naïve HVP16⁺ Malignancies



D ICB Resistant HVP16⁺ Malignancies

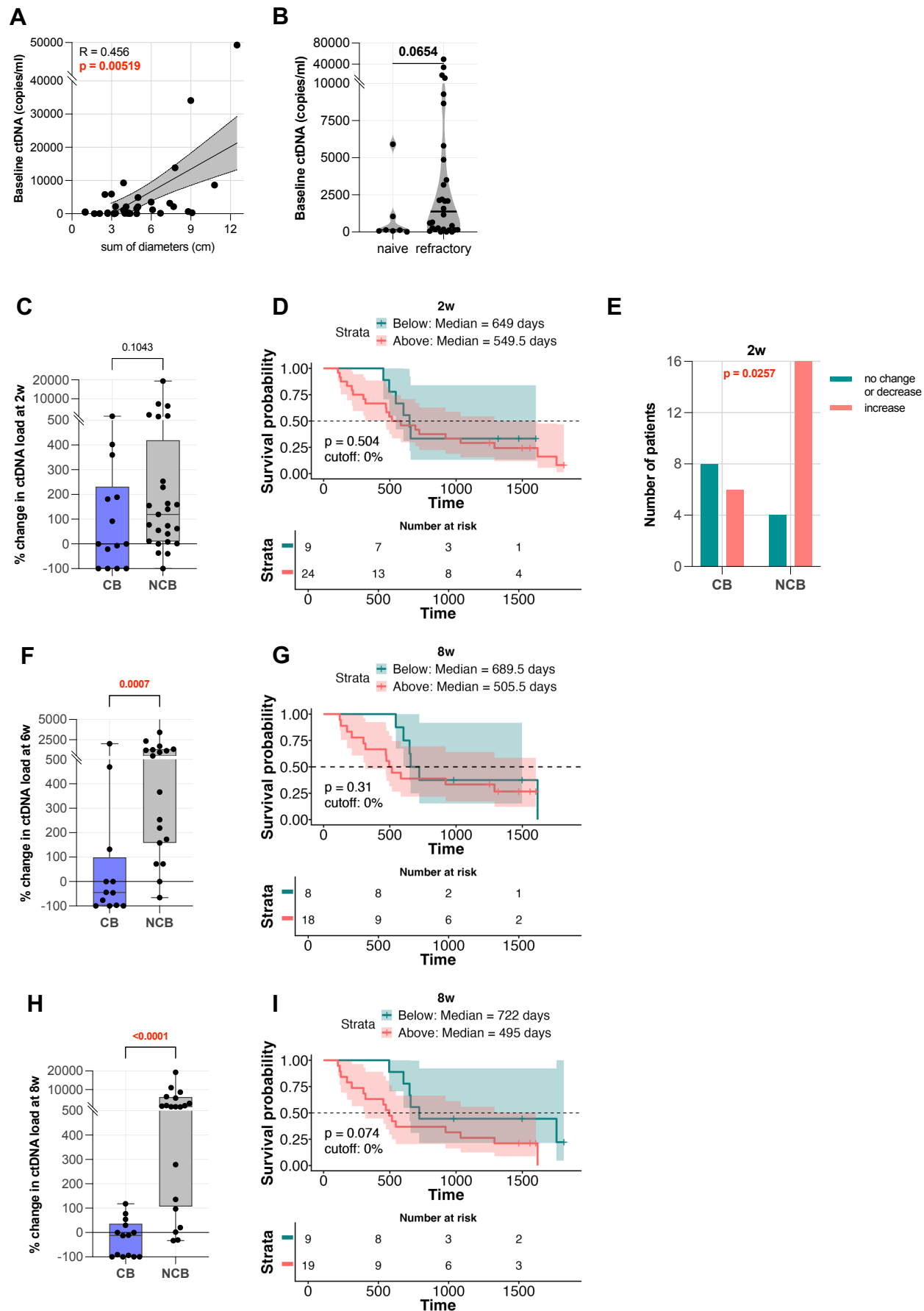


E



Supplementary Figure 1. Changes in target lesions and overall survival in patients with HPV16⁺ malignancies treated with combination immunotherapy based on prior immune checkpoint blockade exposure. (A, B) Spider plots showing depth and duration of response in patients with HPV16⁺ malignancies who had not received prior immune checkpoint blockade (ICB naïve) or who had received and progressed on prior immune checkpoint blockade (ICB resistant). Y-axis in A and B represents percent change in target lesions compared to baseline (% change = 0 at month=0); X-axis represents time in weeks from the initiation of treatment, up to 272 weeks. **(C, D)** Overall survival (OS) Kaplan-Meier (KM) analyses show OS in days from treatment start date for ICB-naïve and ICB-resistant patients. Median OS (mOS) was 53.1 months (95% CI: 42.4 months – not estimable) for the ICI-naïve patients and 16.6 months (95% CI: 14.8-23.7 months) for the ICI-refractory patients. Marks on survival curves indicate patients who were censored. 95% CIs are shaded in on KM curves, and horizontal dashed lines indicate 50% probability of survival. **(E)** Change in tumor volume in one patient with ICB-resistant disease who developed a complete response in the target lesion. Treatment was discontinued at 144 weeks with the target lesion remaining undetectable. At week 224, this individual experienced growth of a new non-target lesion (a cervical lymph node), which responded immediately upon re-initiation of combination therapy. Period of treatment shown with gray bar. * in B and E indicates when treatment was discontinued for the one patient described in E. ^ in B and E indicates when treatment was re-started for the patient described in E.

Supplementary Figure 2

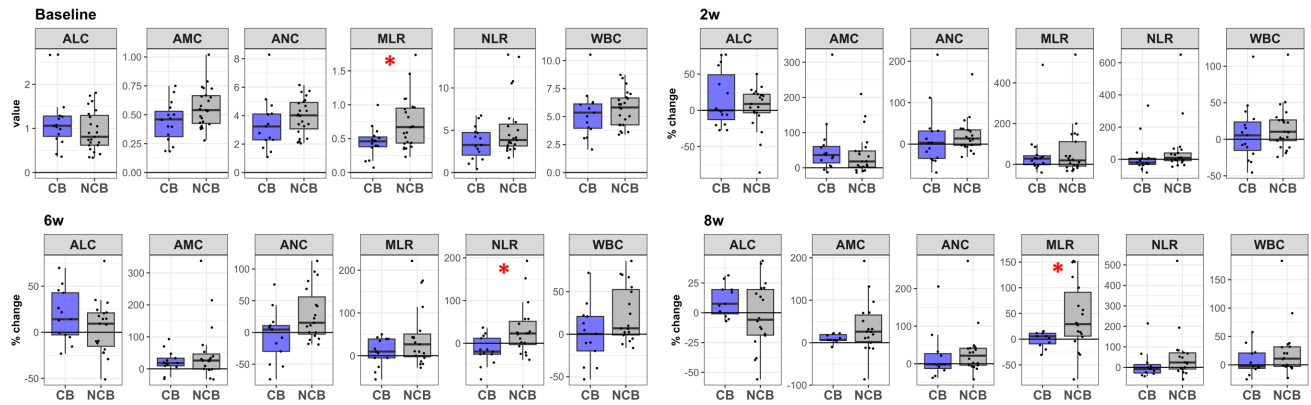


Supplementary Figure 2. Baseline and changes in HPV16-ctDNA loads in patients with HPV16⁺ cancers. (A)

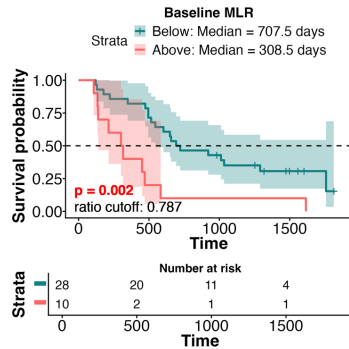
Spearman correlation of target tumor size at baseline with HPV16-ctDNA load. **(B)** Baseline HPV16-ctDNA load in patients grouped by prior exposure to immune checkpoint blockade. **(C, F, H)** Percent changes in HPV16-ctDNA load at indicated timepoints (2 weeks (2w), 6w, 8w) compared to baseline by clinical response. **(D, G, I)** Kaplan-Meier (KM) curve stratifying patients by those with an increase versus those with no change or a decrease (i.e., cutoff of 0%) in HPV16-ctDNA load at indicated timepoints (2w, 6w, 8w) compared to baseline. 95% CIs are shaded on KM curves and horizontal dashed lines indicate 50% probability of survival. **(E)** Number of patients with no change or decrease versus an increase in HPV16-ctDNA load at 2w compared to baseline in those who developed clinical benefit (CB) and those who developed no clinical benefit (NCB).

Supplementary Figure 3

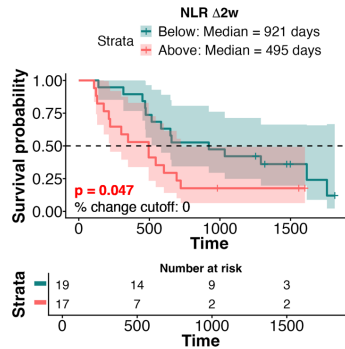
A



B

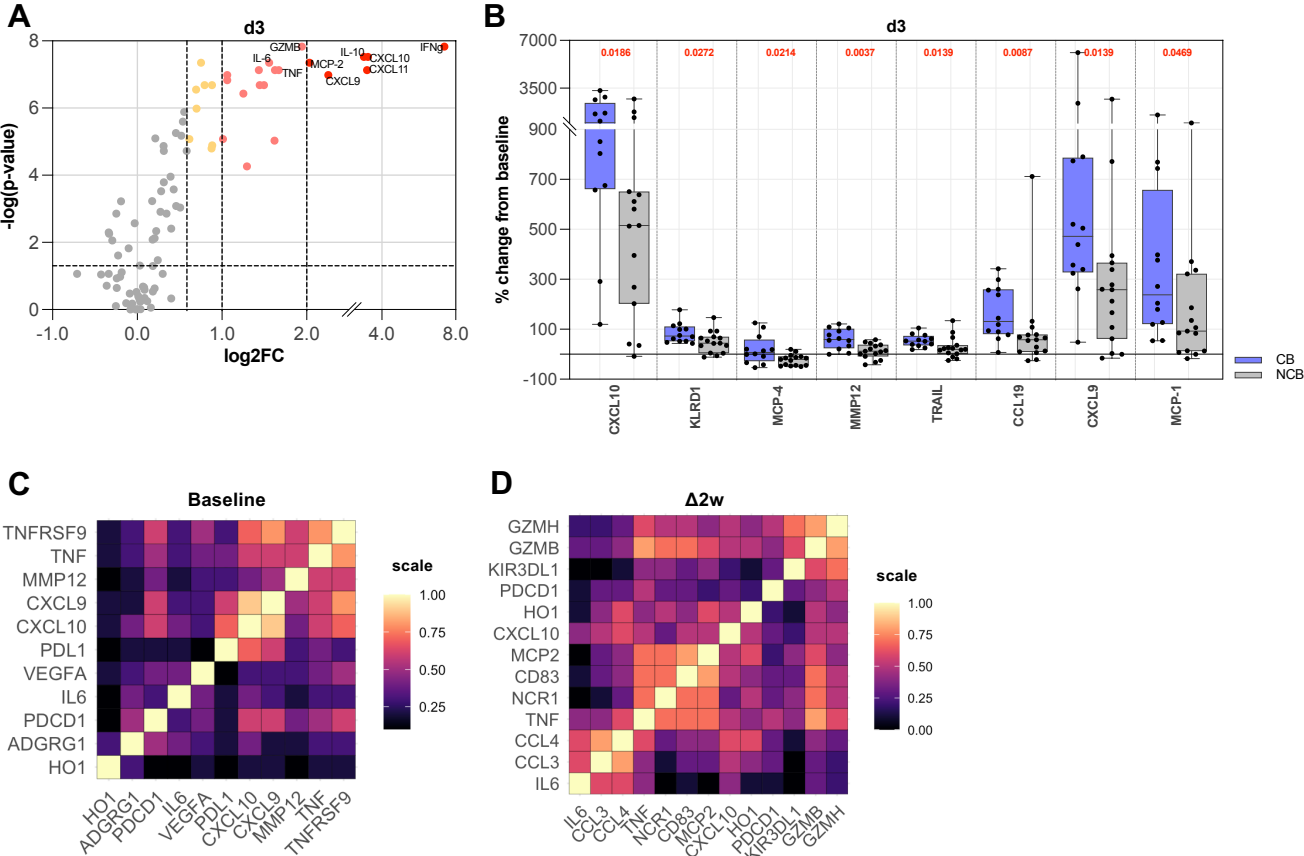


C



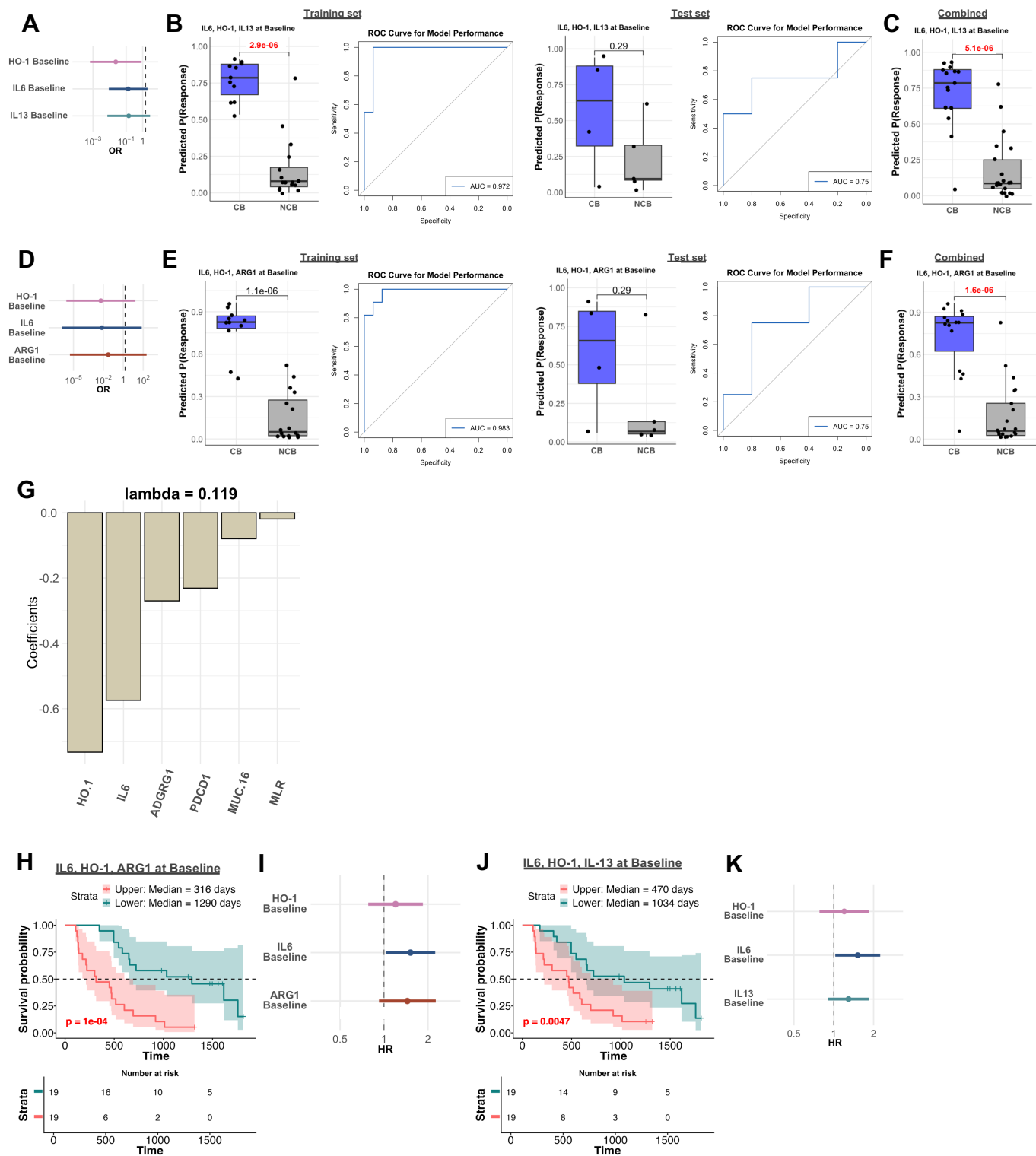
Supplementary Figure 3. Baseline levels and changes in complete blood count (CBC) parameters with treatment and their association with clinical outcomes. (A) Absolute CBC measures at baseline and percent change in CBC parameters at on-treatment timepoints compared to baseline in patients with clinical benefit (CB) vs no clinical benefit (NCB). P values in (A) were calculated with Mann-Whitney U tests. Only p values < 0.05 are indicated, with red * denoting p < 0.05. **(B)** Kaplan-Meier (KM) curve stratifying patients by median monocyte-to-lymphocyte ratio (MLR) at baseline. **(C)** KM curve stratifying patients by those with an increase in neutrophil-to-lymphocyte ratio (NLR) at 2 weeks (2w) versus those with no change or decrease. In panels (B, C), Mantel-Cox log-rank tests were used, and 95% CIs were determined using the Mantel-Haenszel method and shaded in on survival curves. Horizontal dashed lines on KM curves indicate 50% probability of survival.

Supplementary Figure 4



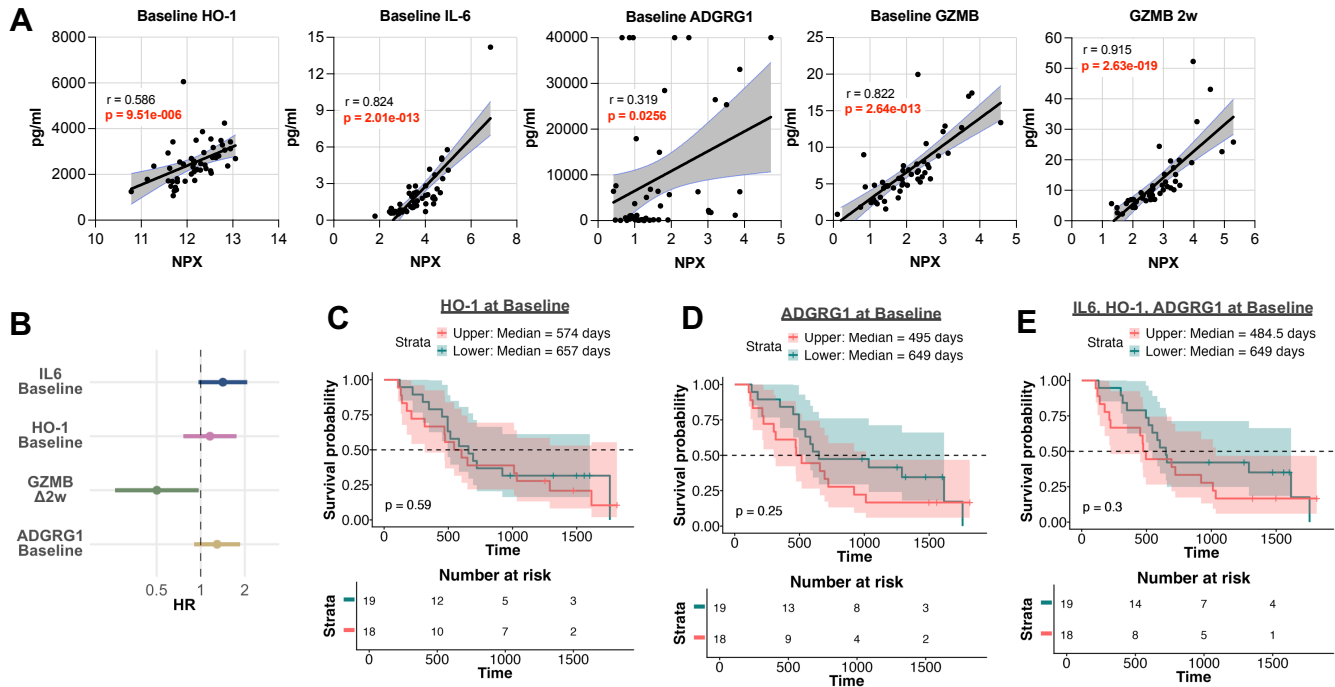
Supplementary Figure 4. Change in serum proteomic profiles 3 days after treatment start and highly correlated serum analytes. (A) Volcano plots of changes in serum analytes at 3 days (d3). Dotted horizontal line indicates significance, and vertical horizontal lines indicate fold changes of 1.5, 2.0, and 4.0, respectively. Each dot represents one analyte, and analytes with fold increases between 1.5 and 2.0 are shown in yellow, between 2.0 and 4.0 in pink, and > 4.0 in red. **(B)** Analytes that significantly differed in percent changes at 3d compared to baseline in patients with clinical benefit (CB) versus no clinical benefit (NCB). **(C, D)** Heatmaps of Spearman's correlation coefficient (p value) between significantly different analytes at indicated timepoints colored according to the scales.

Supplementary Figure 5



Supplementary Figure 5. Recursive feature elimination (RFE)-based logistic regression models including relative levels of baseline ARG1 and IL-13. (A, D) Forest plots show effect size as odds ratio (OR) and confidence intervals (CIs) of each analyte included in the models. (B, E) Predicted probabilities of clinical benefit (CB) generated from the models were compared in patients who experienced clinical benefit (CB) or no clinical benefit (NCB) by Mann-Whitney U Test in training (left panels) and test (right panels) sets. Receiver operating characteristic curves were generated for training and test datasets to evaluate the predictive performance of logistic regression models with the dashed diagonal line indicating the line of no discrimination. (C, F) Predicted probabilities of CB in all patients combined. (G) Least absolute shrinkage and selection operator (LASSO) model built with baseline features as input, effect size shown at chosen lambda. (H, J) Cox proportional hazards (CPH) models with relative levels of serum analytes at baseline. Predicted survival risk was generated from models and patients were stratified by $\geq$ (high) or $<$ (low) median values to plot Kaplan-Meier (KM) curves with the duration of overall survival. 95% CIs are shaded in on KM curves, and horizontal dashed lines indicate 50% probability of survival. (I, K) Forest plots show the direction of effect and association between individual selected features and OS. Effect sizes, shown as hazards ratios (HR), and 95% CIs of each analyte were estimated by CPH.

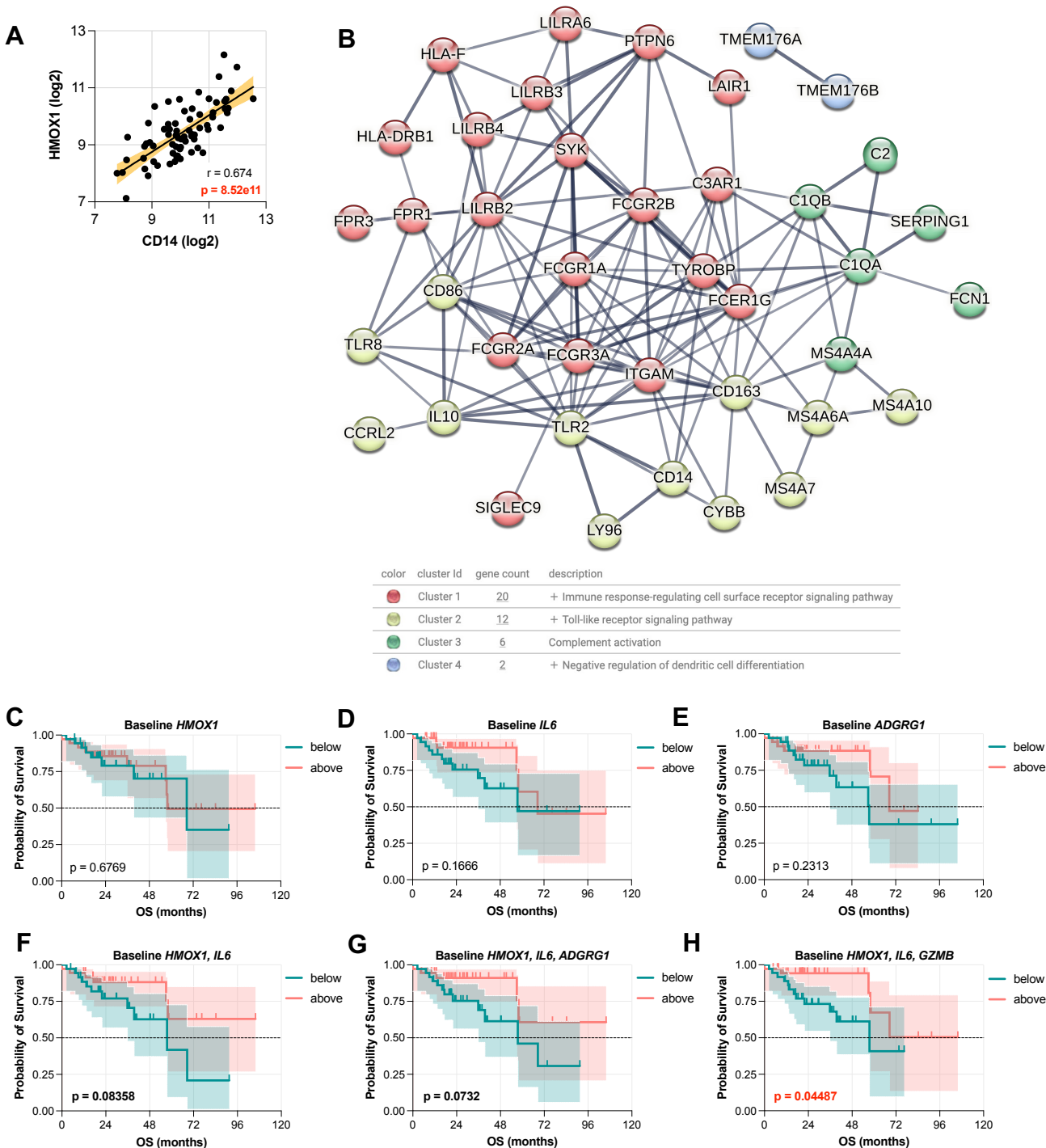
Supplementary Figure 6



Supplementary Figure 6. Performance of quantitative serum data in stratifying patients based on OS. (A)

Spearman correlations between serum concentrations of indicated analytes or their change at 2 weeks (2w) versus baseline compared to qualitative normalized protein expression (NPX) values or percent change in NPX from Olink assays. Shaded gray areas indicate 95% confidence intervals (CIs). Cox proportional hazards (CPH) models were generated with quantitative levels of serum analytes at baseline and percent change at 2w, using serum analytes identified as important by recursive feature elimination (RFE)–based logistic regression of serum analytes measured by qualitative assay. **(B)** Forest plot depicting the association between selected features and overall survival (OS). Effect sizes are shown as hazards ratios (HR) and 95% CIs of each analyte were estimated by CPH. Predicted survival risk was generated from models in all patients combined and patients were stratified by $\geq$ (high) or $<$ (low) median value to plot Kaplan-Meier (KM) curves with the duration of OS. Both **(C-D)** single feature models and **(E)** a selected three-feature model are shown. 95% CIs are shaded in on KM curves, and horizontal dashed lines indicate 50% probability of survival.

Supplementary Figure 7



Supplementary Figure 7. Validation of baseline models in external cohort of 72 HPV+ head and neck squamous cell carcinoma patients with publicly available bulk RNA-sequencing data of tumors from TCGA database. (A) Spearman correlation between *CD14* and *HMOX1* gene expression in tumors. Shaded areas indicate 95% confidence intervals. **(B)** Interaction network of genes that are all highly and significantly correlated with *HMOX1* expression, with clusters and descriptions of genes clusters indicated in legend. **(C-H)** Predicted survival scores were calculated from z-scores of indicated genes (-1 for *HMOX1*, -1.5 for *IL6*, -1 for *ADGRG1*, and +2 for *GZMB*) weighted based on the direction of effect from serum-based recursive feature elimination models, and patients were stratified by $\geq$ (above) or $<$ (below) median values to plot Kaplan-Meier curves with the duration of overall survival (OS) in the TCGA cohort.

Supplementary Table 1. Cell lines, primers and probes for ddPCR.

Reagent	Comment	Reference or Link
HPV16 E6 Forward Primer	5'- CGA AAC CGG TTA GTA TAA AAG CAG -3'	Haring CT, et al. Oncotarget 2021
HPV16 E6 Reverse Primer	5'- GTC GCT CCT GTG GGT CCT -3'	
HPV16 E6 FAM Probe	5'- CAT TTT ATG CAC CAA AAG AGA ACT GCA ATG TTT C -3'	
SiHa cell line	HPV16+	https://www.atcc.org/products/htb-35
Hela cell line	HPV18+	https://www.atcc.org/products/crm-ccl-2
MS751 cell line	HPV45+	https://www.atcc.org/products/htb-34
C-33a cell line	HPV-negative	https://www.atcc.org/products/htb-31
RPP30	ddPCR control assay (HEX)	https://www.bio-rad.com/digital-assays/assay-detail/dHsaCP2500350

Supplementary Table 2. ddPCR conditions.

Cycling Step	Temperature	Time	Ramp Rate	# Cycles
Enzyme activation	95°C	10min	2C/s	1
Denaturation	94°C	30sec	2C/s	40
Annealing / extension	60°C	1min	2C/s	
Enzyme deactivation	98°C	10min	2C/s	1
Hold	4°C	∞	2C/s	1

Supplementary Table 3. Significantly increased serum analytes with 1.5-fold or greater increases.

Timepoint	Analyte	Baseline median	Post median	p.value	FC (Post-Baseline)
d3	● IFNγ	5.61	13.00	1.49E-08	167.847
	● CXCL10	8.12	11.37	2.98E-08	9.514
	● CXCL11	7.11	10.31	7.45E-08	9.183
	● IL10	2.49	5.53	2.98E-08	8.191
	● CXCL9	6.57	8.83	1.04E-07	4.773
	● MCP2	8.67	10.71	4.47E-08	4.093
	● GZMB	1.91	3.85	1.49E-08	3.845
	● TNF	3.96	5.63	7.45E-08	3.182
	● GZMA	5.58	7.21	7.45E-08	3.087
	● CCL4	7.79	9.41	9.30E-06	3.074
	● IL6	3.51	5.06	4.47E-08	2.940
	● MCP1	11.71	13.21	2.09E-07	2.821
	● CD8A	9.23	10.67	2.09E-07	2.723
	● GZMH	3.42	4.86	7.45E-08	2.704
	● MCP3	1.77	3.06	5.49E-05	2.455
	● CX3CL1	3.67	4.92	3.73E-07	2.383
	● CRTAM	4.94	6.00	1.49E-07	2.088
	● IL12RB1	1.83	2.89	1.04E-07	2.088
	● FASLG	5.80	6.81	8.32E-06	2.015
	● KLRD1	5.52	6.41	1.30E-05	1.848
	● LAG3	3.52	4.40	2.09E-07	1.842
	● CCL3	7.61	8.49	1.59E-05	1.838
	● CCL23	9.97	10.77	2.09E-07	1.736
	● IL15	4.12	4.87	4.47E-08	1.685
	● CCL19	10.31	11.01	1.04E-06	1.623
2w	● NCR1	3.10	3.79	2.83E-07	1.618
	● CSF1	9.53	10.14	8.32E-06	1.530
	● IFNγ	5.46	7.88	5.12E-09	5.348
	● CXCL10	8.09	9.73	1.47E-08	3.119
	● CXCL9	6.45	7.99	1.38E-07	2.926
	● CXCL11	7.21	8.50	3.20E-09	2.445
	● IL10	2.56	3.74	9.84E-09	2.274
	● GZMH	3.42	4.47	1.61E-07	2.073
	● GZMA	5.60	6.63	2.60E-08	2.041
	● MCP3	1.77	2.79	2.67E-03	2.028
	● KLRD1	5.63	6.65	8.15E-10	2.025
	● CRTAM	4.90	5.90	1.47E-08	2.000
	● LAG3	3.69	4.62	3.86E-06	1.903
	● IL18	9.18	10.06	1.11E-09	1.843
	● NCR1	3.10	3.87	2.16E-08	1.712
	● GZMB	1.91	2.66	9.74E-07	1.683
	● KIR3DL1	1.05	1.75	3.84E-07	1.625
	● IL12RB1	1.82	2.45	1.87E-07	1.543
	● IL6	3.51	4.12	7.84E-06	1.530
	● IL7	5.24	5.83	7.05E-06	1.504

Analytes with fold increases between 1.5-2.0 are denoted with a yellow dot, between 2.0-4.0 with a pink dot, and > 4.0 with a red dot.

Supplementary Table 4. Performance characteristics of single Olink serum analytes in predicting clinical response.

Timepoint	Analyte	Sensitivity	Specificity	PPV	NPV	Accuracy
Baseline (n=38) TP: NCB > cutoff FN: NCB < cutoff FP: CB > cutoff TN: CB < cutoff	CXCL10	74%	87%	89%	68%	79%
	HO-1	74%	87%	89%	68%	79%
	CXCL9	70%	80%	84%	63%	74%
	PDCD1	70%	80%	84%	63%	74%
	MMP12	65%	73%	79%	58%	68%
	TNFRSF9	65%	73%	79%	58%	68%
	TNF	65%	73%	79%	58%	68%
	VEGFA	65%	73%	79%	58%	68%
	PD-L1	61%	67%	74%	53%	63%
	IL-6	61%	67%	74%	53%	63%
Δ d3 (n=27) TP: CB > cutoff FN: CB < cutoff FP: NCB > cutoff TN: NCB < cutoff	ADGRG1	61%	67%	74%	53%	63%
	CXCL10	83%	73%	71%	85%	78%
	TRAIL	83%	73%	71%	85%	78%
	CCL19	83%	73%	71%	85%	78%
	MCP-4	75%	67%	64%	77%	70%
	MMP12	75%	67%	64%	77%	70%
	CXCL9	75%	67%	64%	77%	70%
	KLRD1	67%	60%	57%	69%	63%
	MCP-1	67%	60%	57%	69%	63%
Δ 2w (n=35) TP: CB > cutoff FN: CB < cutoff FP: NCB > cutoff TN: NCB < cutoff	GZMB	87%	75%	72%	88%	80%
	CCL3	73%	65%	61%	76%	69%
	KIR3DL1	73%	65%	61%	76%	69%
	TNF	73%	65%	61%	76%	69%
	MCP-2	73%	65%	61%	76%	69%
	NCR1	73%	65%	61%	76%	69%
	CCL4	67%	60%	56%	71%	63%
	IL-6	67%	60%	56%	71%	63%
	PDCD1	67%	60%	56%	71%	63%
	CXCL10	67%	60%	56%	71%	63%
	GZMH	67%	60%	56%	71%	63%
	HO-1	67%	60%	56%	71%	63%
	CD83	67%	60%	56%	71%	63%

Δ, change at indicated timepoint.
CB, clinical benefit; FN, false negative; FP, false positive; MLR, monocyte-to-lymphocyte ratio; NCB, no clinical benefit; NLR, neutrophil-to-lymphocyte ratio; NPV, negative predictive value; PPV, positive predictive value; TN, true negative; TP, true positive.

Supplementary Table 5. RFE models predicting clinical response with baseline serum Olink analytes, CBC, and ctDNA measures as input features.

Cross-Validation	Training Accuracy	Training AUC	Holdout Accuracy	Holdout AUC	OR > 1 Features	OR < 1 Features	# times called
3-fold	1.000	1.000	0.778	0.700		HO-1, IL-6	13
	1.000	1.000	0.778	0.800		HO-1, IL-6, ADGRG1	7
	1.000	1.000	0.778	0.850		HO-1, IL-6, IL-13	3
	0.917	1.000	0.667	0.700		HO-1, IL-6, PDCD1	4
	0.909	0.833	0.778	0.600		HO-1	13
	0.909	0.800	0.667	0.700		HO-1, ADGRG1, CXCL9	1
	0.833	0.944	0.556	0.700		HO-1, IL-6, MUC-16	3
	0.833	0.833	0.556	0.500		HO-1, MUC-16	2
	0.833	0.917	0.556	0.600		HO-1, PDCD1, MLR	1
	0.833	0.806	0.444	0.800		IL-6	5
	0.818	0.767	0.667	0.750		HO-1, CXCL9	1
	0.818	0.900	0.556	0.600		HO-1, ADGRG1, PDCD1	1
	0.750	0.833	0.667	0.850		IL-6, IL-13	1
	0.750	0.750	0.667	0.650		ADGRG1, ARG1	1
	0.750	0.861	0.556	0.550		HO-1, IL-6, LAMP3	1
	0.727	0.767	0.778	0.700		HO-1, IL-13	2
	0.727	0.633	0.667	0.600		CXCL10, PDCD1	1
	0.727	0.633	0.556	0.700		CXCL10, PDCD1, PGF	1
	0.727	0.867	0.444	0.600		HO-1, ADGRG1	2
	0.667	0.694	0.778	0.800		HO-1, ARG1, PDCD1	1
	0.667	0.750	0.667	0.700		ADGRG1, ARG1, PDCD1	1
	0.667	0.806	0.444	0.500		ADGRG1	4
	0.636	0.700	0.889	0.850		HO-1, ADGRG1, MLR	1
	0.636	0.633	0.667	0.600		ADGRG1, CXCL10, PDCD1	1
	0.636	0.567	0.667	0.650		HO-1, IL-13, IL-1a	1
	0.636	0.533	0.667	0.600		CXCL10	1
	0.636	0.767	0.556	0.600		HO-1, ADGRG1, MUC-16	1
	0.636	0.533	0.556	0.750		CXCL10, PGF	1
	0.636	0.800	0.444	0.600		HO-1, LAMP3, MLR	1
	0.636	0.633	0.444	0.500		PDCD1, LAMP3, CSF-1	1
	0.583	0.778	0.778	0.650		HO-1, MLR	2
	0.583	0.639	0.778	0.850		HO-1, ARG1	1
	0.583	0.722	0.444	0.400		HO-1, LAMP3	1
	0.545	0.533	0.667	0.700		PGF	1
	0.545	0.500	0.556	0.700		ADGRG1, MLR	1
	0.545	0.533	0.444	0.400		LAMP3	2
	0.545	0.633	0.444	0.500		PDCD1, LAMP3	1
	0.500	0.389	0.667	0.800		ARG1	1
	0.364	0.433	0.889	0.800		IL-13	2
	0.364	0.333	0.556	0.750		MLR	1
5-fold	1.000	1.000	0.778	0.800		HO-1, IL-6, ADGRG1	19
	1.000	1.000	0.778	0.800		HO-1, IL-6, IL-13	5
	1.000	1.000	0.778	0.800		HO-1, IL-6, ARG1	2
	1.000	1.000	0.778	0.700		HO-1, IL-6	35
	1.000	1.000	0.778	0.600		HO-1	28
	1.000	1.000	0.556	0.650		HO-1, PDCD1	2
	1.000	1.000	0.444	0.800		IL-6	13
	0.857	0.917	0.667	0.700		HO-1, IL-6, PDCD1	5
	0.857	0.917	0.667	0.700		HO-1, IL-6, MLR	1
	0.857	0.667	0.556	0.700		HO-1, IL-6, MUC-16	5
	0.857	0.750	0.556	0.550		HO-1, ADGRG1	4
	0.857	0.917	0.556	0.600		ADGRG1, IL-6	3
	0.833	0.889	0.667	0.800		HO-1, IL-13	2
	0.833	0.889	0.667	0.850		HO-1, IL-6, NOS3	1
	0.714	0.833	0.778	0.650		HO-1, IL-6, CD8A	1
	0.714	0.750	0.778	0.700		HO-1, ADGRG1, NLR	1
	0.714	0.917	0.667	0.650		HO-1, IL-6, RBC	3
	0.714	0.833	0.444	0.500		ADGRG1	6
	0.714	0.917	0.444	0.450		HO-1, ADGRG1, LAMP3	1
	0.667	0.556	0.667	0.650		ADGRG1, PDCD1, PGF	1
	0.667	0.889	0.556	0.700		HO-1, IL-13, PDCD1	1
	0.667	0.444	0.556	0.650		IL-6, PDCD1, PGF	1
	0.667	0.778	0.333	0.200	MCP-2	HO-1, PDCD1	1
	0.571	0.750	0.778	0.600		HO-1, NLR	1
	0.571	0.583	0.667	0.650		HO-1, ADGRG1, CXCL12	1
	0.500	0.556	0.667	0.700		PGF	2
	0.500	0.556	0.667	0.700		ADGRG1, PGF	1
	0.500	0.333	0.667	0.650		IL-6, PGF	1
	0.500	0.556	0.556	0.750		HO-1, ADGRG1, NOS3	1
	0.429	0.833	0.778	0.650		HO-1, MLR	1
	0.143	0.000	0.556	0.800		IL-13	1

Training set comprises k-1 folds; holdout set comprises the remaining fold.

AUC, receiver operating characteristic (ROC) curve; CBC, complete blood count; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; RBC, red blood count.

Supplementary Table 6. RFE models predicting clinical response with baseline serum Olink analytes, CBC, and ctDNA measures and their changes at 2w compared to baseline as input features.

Cross-Validation	Validation Accuracy	Validation AUC	Holdout Accuracy	Holdout AUC	OR > 1 Features	OR < 1 Features	# times called
3-fold	1.000	1.000	0.778	0.850	GZMB Δ2w	HO-1, IL-6	2
	1.000	1.000	0.778	0.700		HO-1, IL-6	6
	1.000	1.000	0.667	0.950	GZMB Δ2w	HO-1, IL-13	2
	1.000	1.000	0.556	0.900	GZMB Δ2w	HO-1	5
	0.900	1.000	0.778	0.600		HO-1	23
	0.900	0.800	0.667	0.750		HO-1, CXCL10	1
	0.900	0.880	0.556	0.750	IL-6 Δ2w	HO-1, IL-13	1
	0.889	1.000	0.778	0.750		HO-1, IL-6, ADGRG1	2
	0.889	1.000	0.667	0.700		HO-1, IL-6, RBC	2
	0.889	0.950	0.667	0.700		HO-1, ADGRG1	2
	0.889	1.000	0.667	0.600	IL-10 Δ2w	HO-1	1
	0.800	0.880	0.667	0.750		HO-1, IL-13	3
	0.800	0.840	0.667	0.600	IL-8	HO-1, CXCL10	1
	0.778	0.750	0.667	0.850	CD5 Δ2w, IL-10 Δ2w	HO-1	1
	0.778	0.950	0.667	0.700	IL-10 Δ2w	HO-1, IL-6	1
	0.778	0.700	0.667	0.650		HO-1, ADGRG1, CXCL10	1
	0.778	0.750	0.444	0.650		HO-1, PDCD1	1
	0.700	0.920	0.778	0.900	HO-1 Δ2w, PDCD1 Δ2w	HO-1	2
	0.700	0.920	0.778	0.700	HO-1 Δ2w	HO-1, IL-6	1
	0.700	0.720	0.667	0.900	GZMB Δ2w, IL-10 Δ2w	ADGRG1	1
	0.700	0.640	0.667	0.900	GZMB Δ2w		3
	0.700	0.640	0.667	0.900	GZMB Δ2w, IL-10 Δ2w		1
	0.700	0.920	0.667	0.700	HO-1 Δ2w	HO-1	2
	0.700	0.920	0.556	0.950	GZMB Δ2w	HO-1, ADGRG1	1
	0.667	0.650	0.778	0.950	TNFRSF4 Δ2w	HO-1	1
	0.667	0.750	0.778	0.750		HO-1, PDCD1, ARG1	1
	0.667	0.800	0.667	0.850		HO-1, ADGRG1, AMC	1
	0.667	0.600	0.667	0.700	IL-10 Δ2w		1
	0.667	1.000	0.667	0.450	IL-10 Δ2w	HO-1, CD8A	1
	0.667	0.800	0.556	0.600		HO-1, ADGRG1, PDCD1	1
	0.667	0.850	0.556	0.400		HO-1, CD8A	1
	0.667	1.000	0.444	0.700		HO-1, PDCD1, IL-13	1
	0.600	0.760	0.778	0.900	PDCD1 Δ2w	HO-1	1
	0.600	0.560	0.667	1.000	GZMB Δ2w, KIR3DL1 Δ2w	HO-1	1
	0.600	0.520	0.667	0.900	HO-1 Δ2w, KIR3DL1 Δ2w	HO-1	1
	0.600	0.720	0.667	0.850	HO-1 Δ2w		1
	0.556	0.500	0.778	0.850	CD5 Δ2w, IL-10 Δ2w		1
	0.556	0.650	0.778	0.750		HO-1, DCN, HPV16 ctDNA	1
	0.556	0.700	0.778	0.700		HO-1, DCN	1
	0.556	0.700	0.667	1.000	HO-1 Δ2w, TNFRSF4 Δ2w	HO-1	1
	0.556	0.400	0.667	0.850	GZMB Δ2w	PGF	1
	0.556	0.500	0.667	0.600		ADGRG1, CXCL10	1
	0.444	0.650	0.667	0.750	IL-10 Δ2w	HO-1, CSF-1	1
	0.444	0.450	0.667	0.700	IL-10 Δ2w	ADGRG1, CAIX Δ2w	1
	0.444	0.350	0.667	0.650	IL-10 Δ2w	CAIX Δ2w	1
	0.444	0.500	0.333	0.500		ADGRG1	1
	0.333	0.500	0.778	0.800	GZMB Δ2w	IL-6, PGF	1
	0.222	0.350	0.556	0.700	CD5 Δ2w		1
5-fold	1.000	1.000	0.778	0.850	GZMB Δ2w	HO-1, IL-6	5
	1.000	1.000	0.778	0.750		HO-1, IL-6, ADGRG1	3
	1.000	1.000	0.778	0.700		HO-1, IL-6	10
	1.000	1.000	0.778	0.600		HO-1	42
	1.000	1.000	0.667	1.000	GZMB Δ2w	HO-1, IL-13	6
	1.000	1.000	0.667	0.700		HO-1, IL-13	3
	1.000	1.000	0.556	0.950	GZMB Δ2w	HO-1, ADGRG1	9
	1.000	1.000	0.556	0.850	GZMB Δ2w	HO-1	22
	0.833	0.778	0.778	0.750	CASP-8	HO-1, IL-6	1
	0.833	1.000	0.667	0.800	GZMB Δ2w	HO-1, PDCD1	1
	0.833	0.889	0.667	0.750	GZMB Δ2w, IL-7	HO-1	1
	0.833	0.667	0.667	0.750	HO-1 Δ2w, CASP-8	HO-1	1
	0.833	0.889	0.667	0.700	HO-1 Δ2w	HO-1	4
	0.833	1.000	0.667	0.700	HO-1 Δ2w	HO-1, IL-6	3
	0.833	0.889	0.667	0.700	IL-10 Δ2w	HO-1, ADGRG1	1
	0.833	1.000	0.667	0.700	IL-10 Δ2w	HO-1, IL-6	3
	0.833	0.889	0.667	0.600	IL-10 Δ2w	HO-1	3
	0.833	1.000	0.556	0.700		HO-1, IL-13, CCL19	1
	0.800	0.833	0.667	0.900	GZMB Δ2w	HO-1, MLR	1
	0.800	1.000	0.667	0.700		HO-1, ADGRG1	2
	0.800	0.833	0.556	0.750	IL-6 Δ2w	HO-1, IL-13	1
	0.667	0.556	0.667	0.900	GZMB Δ2w		2
	0.600	1.000	0.667	0.800	GZMB Δ2w, CRTAM	HO-1	1
	0.600	0.333	0.667	0.750	GZMB Δ2w	IL-6, ADGRG1	1
	0.600	1.000	0.667	0.700		HO-1, ADGRG1, CCL19	1
	0.600	0.667	0.667	0.650	HO-1 Δ2w, IL-6 Δ2w	HO-1	1
	0.600	0.667	0.556	0.800	GZMB Δ2w	HO-1, MCP-1	2
	0.500	0.667	0.778	0.950	GZMB Δ2w, PDCD1 Δ2w	HO-1	1
	0.500	0.778	0.778	0.900	HO-1 Δ2w, PDCD1 Δ2w	HO-1	1
	0.500	0.556	0.778	0.850	PDCD1 Δ2w	HO-1	1
	0.500	0.333	0.667	1.000	GZMB Δ2w, KIR3DL1 Δ2w	HO-1	2
	0.500	0.889	0.667	0.650	HO-1 Δ2w, IL-10 Δ2w	HO-1	1
	0.500	0.444	0.556	0.750	GZMB Δ2w	MCP-1	2
	0.500	0.222	0.444	0.800		IL-6	1
	0.400	0.500	0.667	0.650	IL-10 Δ2w, CCL3 Δ2w	HO-1	1
	0.400	0.833	0.556	0.450	IL-6 Δ2w	HO-1, CD8A	1
	0.400	0.333	0.444	0.600		IL-6, ADGRG1	1
	0.333	0.111	0.778	0.750	PDCD1 Δ2w		1
	0.333	0.444	0.667	0.900	GZMB Δ2w	IL-6	1
	0.200	0.167	0.556	0.500		MCP-1	2
	0.200	0.167	0.556	0.400	IL-6 Δ2w	CD8A	1
	0.200	0.333	0.444	0.500		ADGRG1	1
	0.200	0.333	0.333	0.200		CD8A	1

Training set is comprised of k-1 folds and holdout set is comprised of remaining fold.

2w, two weeks; AMC, absolute monocyte count; AUC, receiver operating characteristic (ROC) curve;

HPV16 ctDNA, human papillomavirus 16 circulating tumor DNA; MLR, monocyte-to-lymphocyte ratio; OR, odds ratio; RBC, red blood count.

Supplementary Table 7. Performance characteristics of single analytes and models in predicting clinical response.

Assay	Model	n	Sensitivity	Specificity	PPV	NPV	Accuracy
Quantitative*	HO-1, IL-6, GZMB Δ2w	35	87%	90%	87%	90%	89%
	HO-1, IL-6	37	67%	95%	91%	81%	84%
	HO-1, IL-6, ADGRG1	37	80%	82%	75%	86%	81%
Olink*	HO-1, IL-6, ADGRG1	38	93%	91%	88%	95%	92%
	HO-1, IL-6, GZMB Δ2w	35	93%	85%	82%	94%	89%
	HO-1, IL-6	38	80%	91%	86%	88%	87%
Quantitative**	GZMB Δ2w	35	87%	70%	68%	88%	77%
	IL-6	38	74%	73%	81%	65%	74%
	HO-1	37	59%	53%	65%	47%	57%
	ADGRG1	37	59%	53%	65%	47%	57%
Olink**	GZMB Δ2w	35	87%	70%	68%	88%	77%
	HO-1	38	78%	80%	86%	71%	79%
	IL-6	38	70%	67%	76%	59%	68%
	ADGRG1	38	65%	60%	71%	53%	63%

Δ, change at indicated timepoint.

* Cutoffs are optimal cutoff determined by maximizing sensitivity and specificity from the ROC curve (from training-set model), calculated for train and test set combined.

** Cutoffs for single analyte models are the median of entire cohort.

NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristic.