SUPPLEMENTARY MATERIALS

Supplementary Figure

Supplementary Table

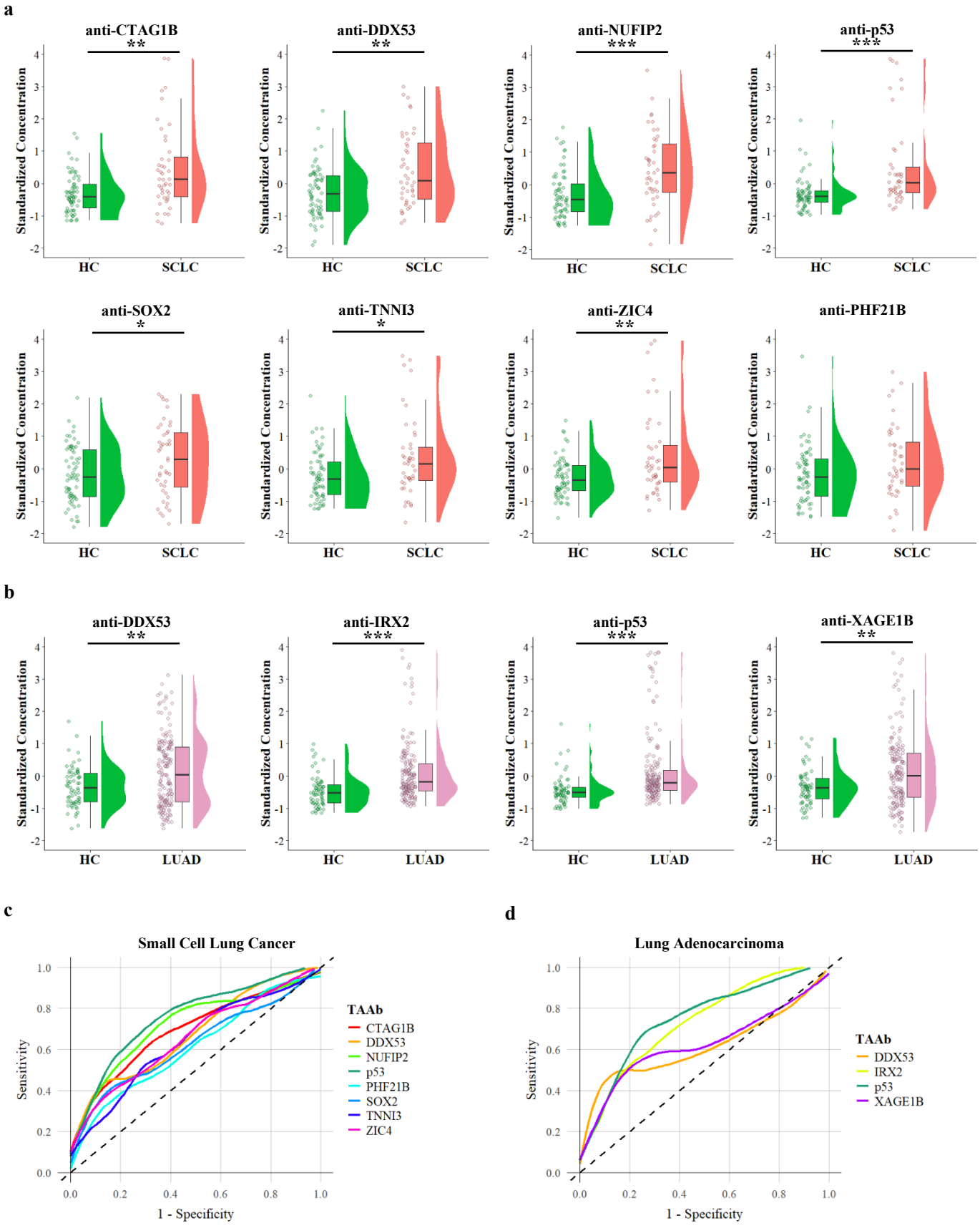

Fig. S1. Standardized serum levels and diagnostic performance of candidate TAAbs in the first validation. Standardized serum concentrations of candidate TAAbs in patients with SCLC (**a**) or LUAD (**b**) compared with HC.

The y-axis represents the standardized concentration (Z-score). Statistical analysis: Mann–Whitney U test ($^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$).
ROC curves of individual TAAbs for distinguishing SCLC (**c**) or LUAD (**d**) from HC.

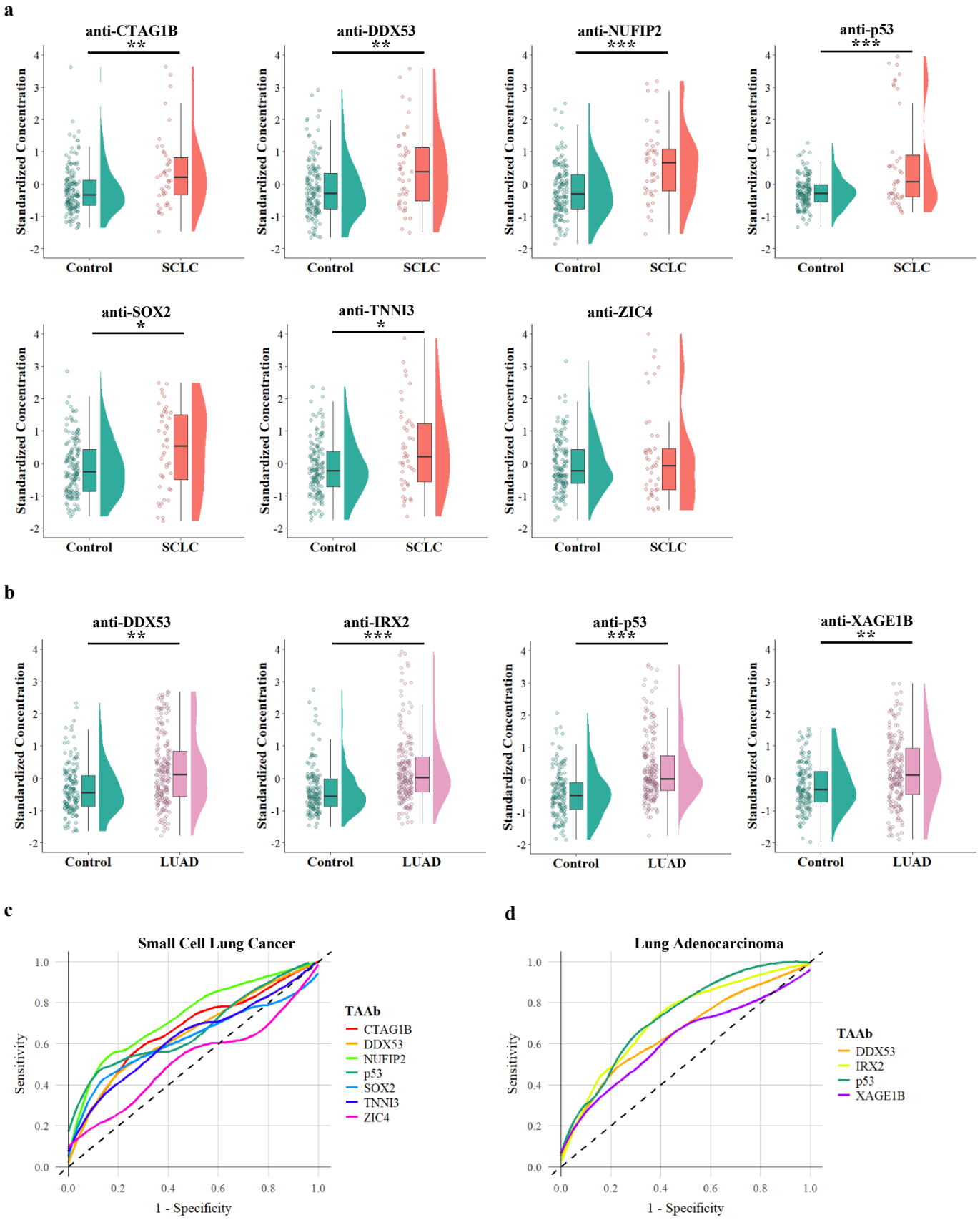

Fig. S2. Standardized serum levels and diagnostic performance of candidate TAAbs in the second validation. Standardized serum concentrations of candidate TAAbs in patients with SCLC (**a**) or LUAD (**b**) compared with those

in noncancer controls (HC+PF). The y-axis represents the standardized concentration (Z-score). Statistical analysis: Mann–Whitney U test ($^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$).
ROC curves of TAAbs for discriminating SCLC (**c**) or LUAD (**d**) patients from noncancer controls.

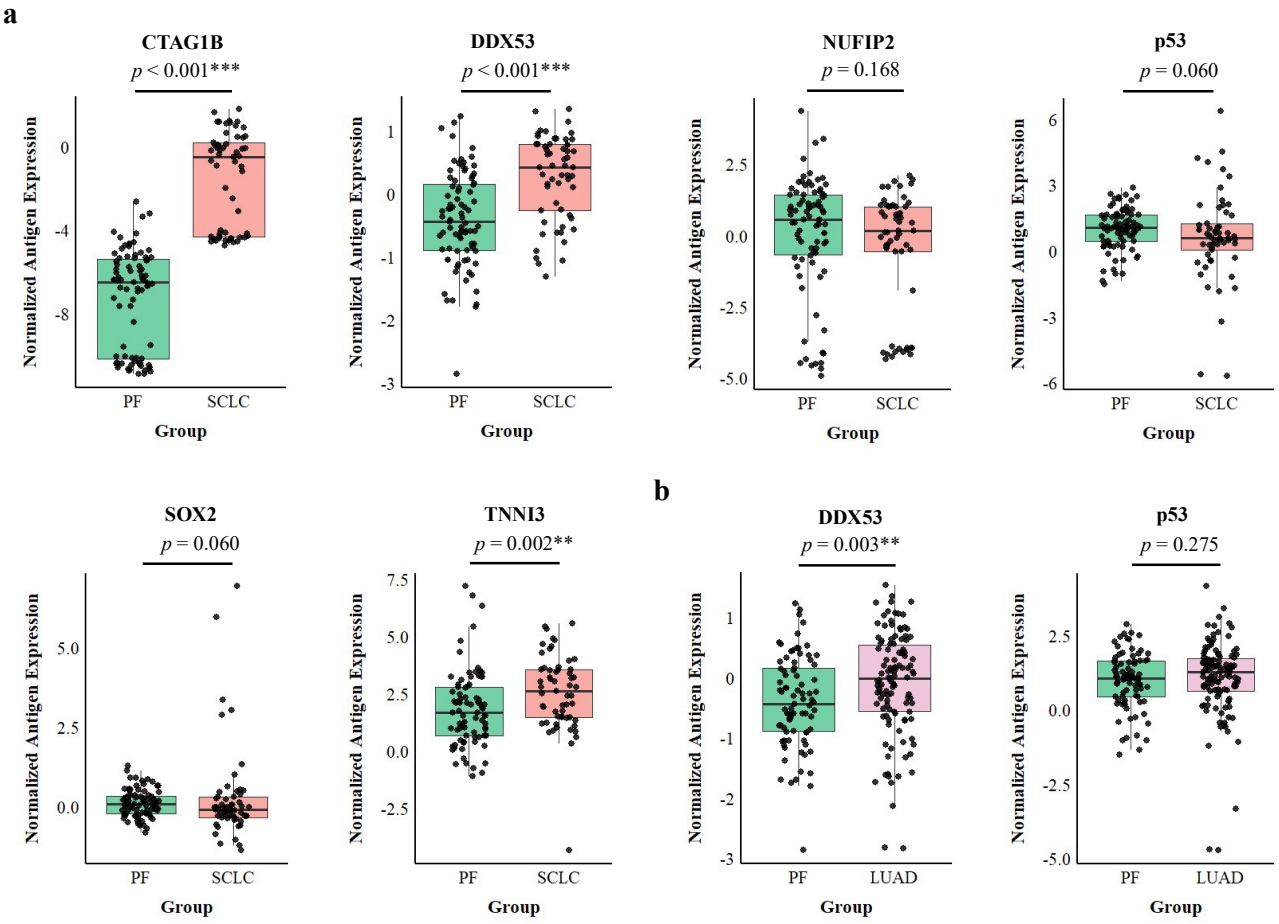

Fig. S3. TAA expression levels in lung cancer and pulmonary fibrosis (PF).

(**a**) Comparison of antigen expression levels between PF and SCLC for six TAAs.

(**b**) Comparison of antigen expression levels between PF and LUAD for two TAAs. IRX2 and XAGE1B were not assessed because they were not included in the Olink Explore HT panel.

TAA expression levels are presented as normalized protein expression (NPX) values. Each dot represents an individual sample. Statistical analysis: Mann–Whitney U test ($^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$).

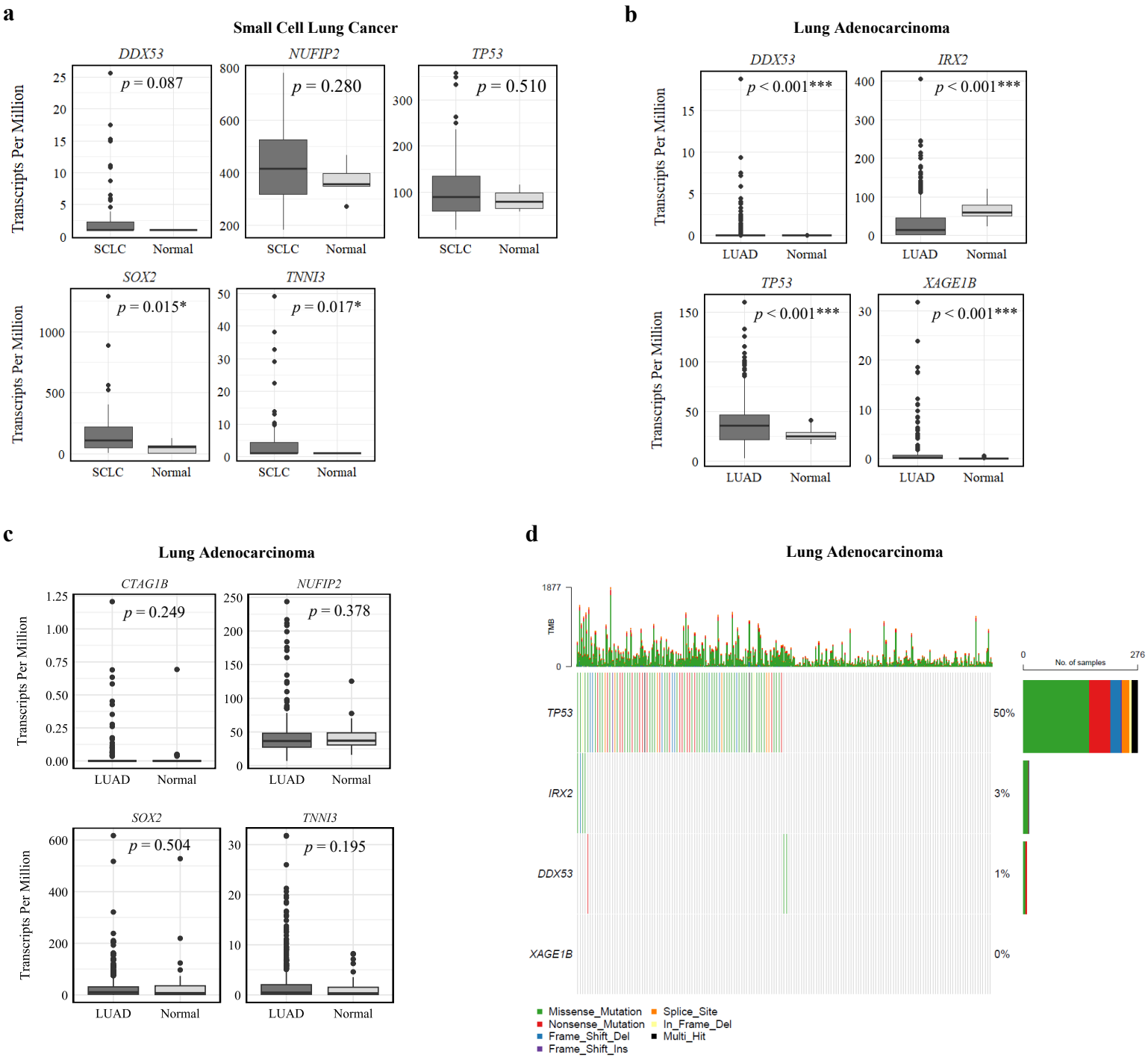

Fig. S4. Transcriptional expression and somatic mutation of TAAs based on public RNA sequencing datasets.
(**a, b**) Boxplots comparing the mRNA expression levels of TAAs between normal lung tissues and SCLC (**a**) or LUAD (**b**).
(**c**) Expression levels of SCLC-specific TAAs in LUAD.
(**d**) OncoPrint plot showing the somatic mutation landscape of the TAAs in LUAD.
Because of limited data availability in public databases, only TAAs with available information were analyzed.

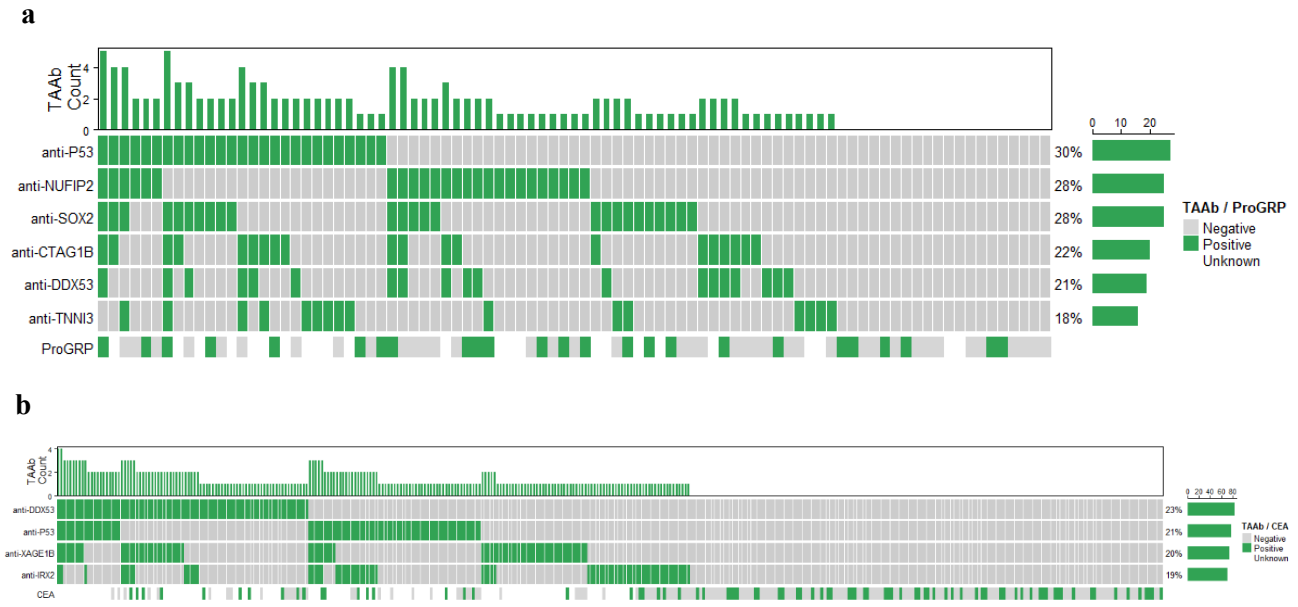

Fig. S5. Distribution of TAAb and tumor marker seropositivity.

Heatmaps showing the status (positive, negative, and unknown) of the identified TAAbs and tumor markers in individual patients with SCLC (**a**) or LUAD (**b**).

Patients were sorted based on the number of positive TAAbs. The proportion of TAAb-positive patients was calculated by dividing the number of TAAb-positive patients by the total number of patients (89 for SCLC and 365 for LUAD). The threshold was 5.0 ng/mL for CEA and 46 pg/mL for ProGRP.

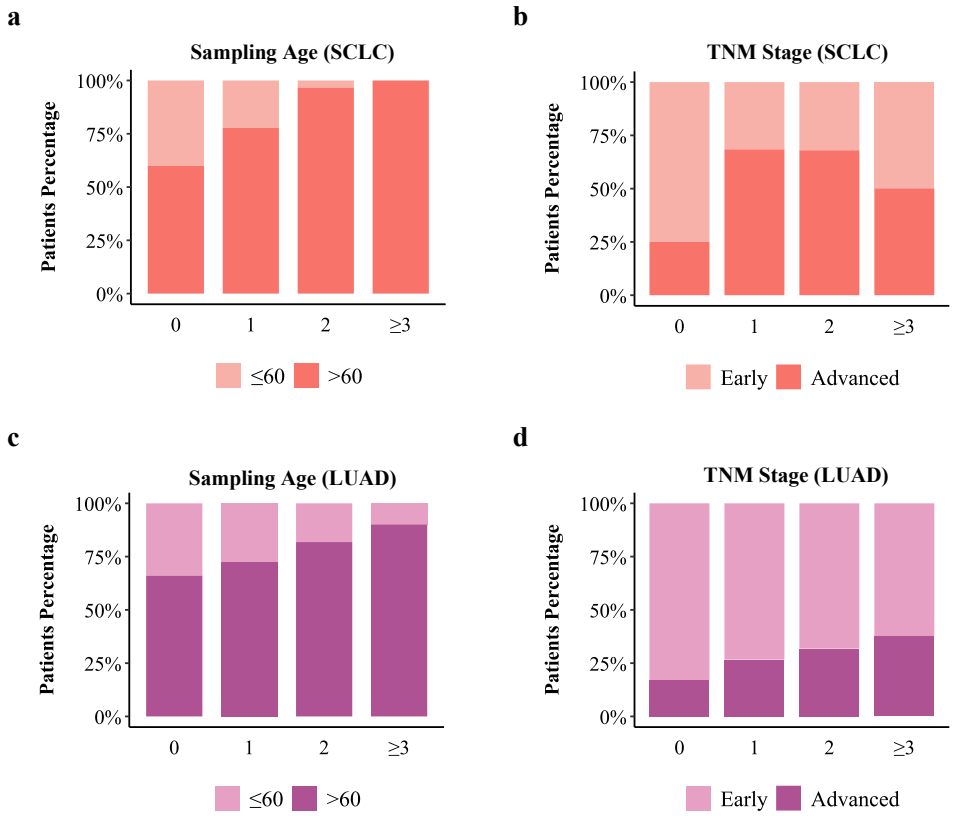

Fig. S6. Associations between the number of positive TAAbs and clinical characteristics.
Distribution of sampling age (**a**) and TNM stage (**b**) among SCLC patients stratified by the number of positive TAAbs. Distribution of sampling age (**c**) and TNM stage (**d**) among LUAD patients stratified by the number of positive TAAbs.

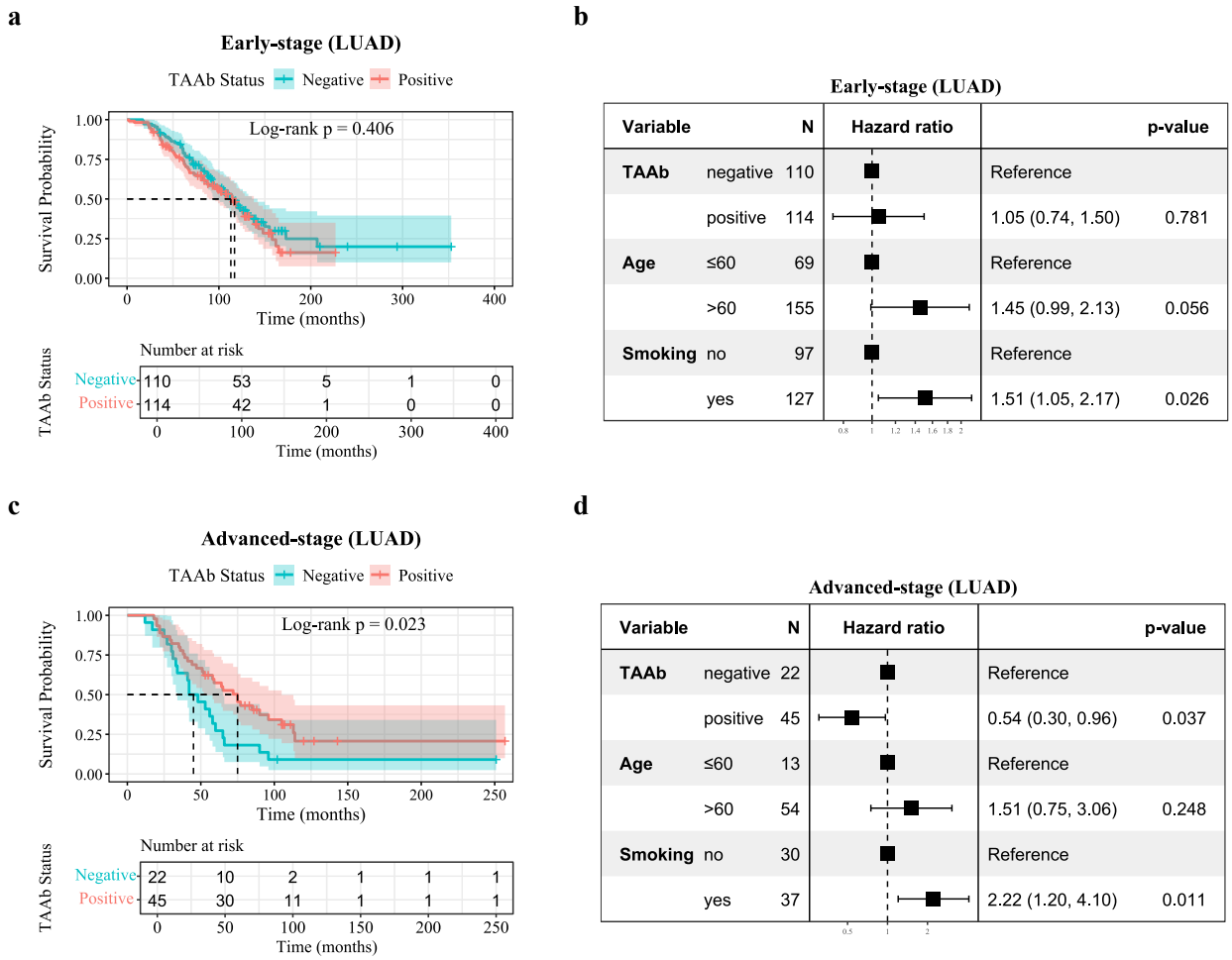

Fig. S7. Stage-stratified survival analysis in LUAD.

Kaplan–Meier survival curves comparing overall survival between TAAb-positive and TAAb-negative patients with early-stage (**a**) or advanced-stage (**c**) LUAD.

Multivariable Cox proportional hazards regression analyses assessing the independent prognostic effect of TAAb status, age at diagnosis, and smoking status in early-stage (**b**) or advanced-stage (**d**) LUAD.

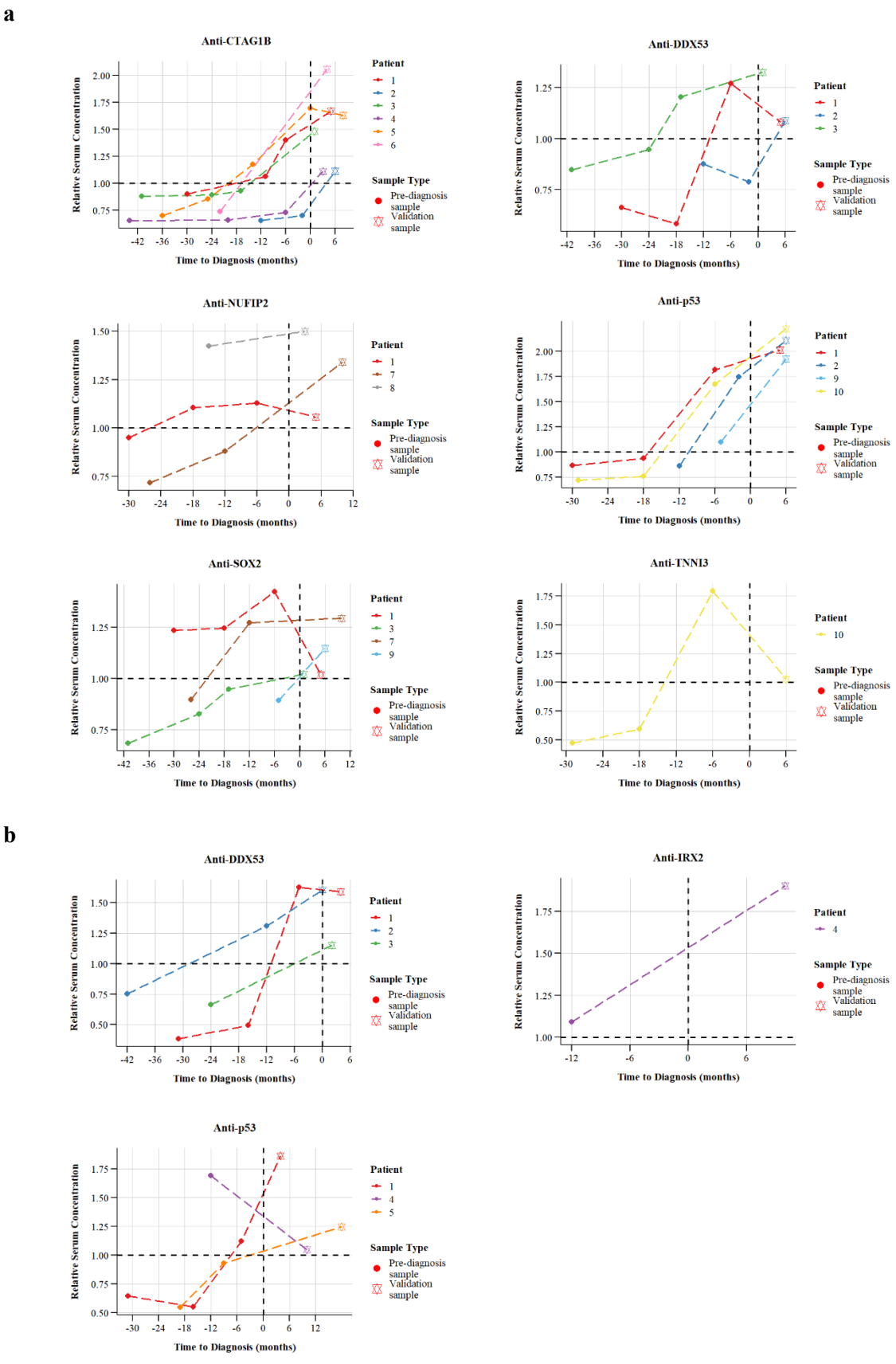

Fig. S8. Early diagnostic potential of TAAbs based on prediagnostic serum analysis.

Temporal changes of TAAb concentrations in prediagnosis samples from SCLC (**a**) and LUAD (**b**). Each patient is

represented by a unique color, with consistent patient numbering across all TAAbs within each cancer subtype. The x-axis represents time in months relative to diagnosis (0 = diagnosis date; negative values indicate prediagnosis), and the y-axis shows relative TAAb concentrations. Relative TAAb concentrations were calculated against the predefined cutoff (95th percentile of the noncancer group), with values >1.00 considered positive.

Table S1. Semiquantitative scoring of signal intensities relative to IgG standards.

Signal intensity relative to IgG standard	Semiquantitative value
≥ undiluted IgG solution	32
> IgG diluted 1:2	16
> IgG diluted 1:4	8
> IgG diluted 1:8	4
> IgG diluted 1:16	2
≤ IgG diluted 1:16	1
No detectable signal	0

Table S2. Differential expression of serum TAAb levels between cancer patients and controls.

TAAb	First-validation Cohort				Second-validation Cohort			
	Cancer median (IQR)[a]	Control median (IQR)[a]	FC	*P*	Cancer median (IQR)[a]	Control median (IQR)[a]	FC	*P*
Small cell lung cancer								
anti-CTAG1B	1.421 (1.042-1.907)	1.040 (0.799-1.317)	1.37	<0.001	1.481 (1.057-2.017)	1.048 (0.802-1.382)	1.41	<0.001
anti-DDX53	1.311 (0.995-1.948)	1.085 (0.789-1.396)	1.21	0.002	1.331 (0.825-1.744)	0.960 (0.691-1.304)	1.39	0.002
anti-NUFIP2	1.879 (1.422-2.565)	1.245 (0.961-1.625)	1.51	<0.001	2.116 (1.473-2.448)	1.413 (1.078-1.822)	1.50	<0.001
anti-p53	1.400 (1.046-1.933)	0.908 (0.711-1.113)	1.54	<0.001	1.334 (0.899-3.600)	0.996 (0.741-1.236)	1.34	<0.001
anti-SOX2	1.984 (1.405-2.540)	1.617 (1.214-2.188)	1.23	0.029	1.911 (1.188-2.488)	1.464 (1.110-1.861)	1.31	0.012
anti-TNNI3	1.546 (1.203-1.881)	1.236 (0.922-1.580)	1.25	0.013	1.443 (0.990-2.030)	1.185 (0.898-1.531)	1.22	0.010
anti-ZIC4	1.088 (0.830-1.494)	0.861 (0.669-1.132)	1.26	0.005	0.919 (0.495-1.224)	0.833 (0.609-1.200)	1.10	0.702
anti-PHF21B	1.205 (0.979-1.559)	1.098 (0.840-1.337)	1.10	0.053		——		
Lung adenocarcinoma								
anti-DDX53	1.364 (0.781-1.948)	1.085 (0.789-1.396)	1.26	0.008	1.317 (0.876-1.781)	0.960 (0.691-1.304)	1.37	<0.001
anti-IRX2	0.627 (0.443-1.016)	0.399 (0.203-0.556)	1.57	<0.001	0.884 (0.639-1.235)	0.571 (0.396-0.855)	1.55	<0.001
anti-p53	1.284 (0.996-1.783)	0.908 (0.711-1.113)	1.42	<0.001	1.298 (1.091-1.702)	0.996 (0.741-1.236)	1.30	<0.001
anti-XAGE1B	1.120 (0.759-1.488)	0.920 (0.737-1.077)	1.22	0.004	1.024 (0.760-1.371)	0.853 (0.696-1.084)	1.20	<0.001

FC, fold change.

[a]Serum TAAb levels represent ELISA-measured concentrations and were not corrected for serum dilution factors.

Table S3. Multivariable-adjusted odds ratios of TAAbs for SCLC and LUAD compared with healthy controls (adjusted for sampling age and sex).

TAAb	OR	95% CI	*P*
Small cell lung cancer			
anti-CTAG1B	5.77	1.66–23.03	0.007
anti-DDX53	5.59	1.40–30.72	0.028
anti-NUFIP2	4.36	1.55–16.74	0.017
anti-p53	6.21	2.02–24.99	0.004
anti-SOX2	3.12	1.95–12.07	0.007
anti-TNNI3	4.96	1.17–26.66	0.043
Lung adenocarcinoma			
anti-DDX53	2.59	1.49–4.73	0.001
anti-IRX2	7.69	3.49–18.69	<0.001
anti-p53	5.96	3.03–12.55	<0.001
anti-XAGE1B	2.55	1.18–5.78	0.021

Table S4. Multivariable-adjusted odds ratios of TAAbs for SCLC and LUAD compared with benign controls (adjusted for sampling age, sex, and smoking status)

TAAb	OR	95% CI	*P*
Small cell lung cancer			
anti-CTAG1B	3.42	1.88–6.83	<0.001
anti-DDX53	3.78	2.00–7.69	<0.001
anti-NUFIP2	1.94	1.21–3.26	0.008
anti-p53	3.88	2.22–8.01	<0.001
anti-SOX2	2.66	1.52–4.89	0.001
anti-TNNI3	3.09	1.74–5.91	<0.001
Lung adenocarcinoma			
anti-DDX53	2.11	1.43–3.22	<0.001
anti-IRX2	2.44	1.45–4.43	0.002
anti-p53	4.45	2.49–8.54	<0.001
anti-XAGE1B	3.16	1.76–5.91	<0.001

Table S5. Multivariable-adjusted odds ratios of TAAbs for treatment-naïve LUAD compared with healthy controls (adjusted for sampling age and sex)**.**

TAAb	OR	95% CI	*P*
anti-DDX53	8.62	1.57–77.27	0.024
anti-IRX2	6.86	1.42–76.33	0.051
anti-p53	8.80	1.97–94.74	0.017
anti-XAGE1B	73.09	2.90–5202.67	0.018

Treatment-naïve tumor indicates patients who had not received any cancer-directed therapy (including surgery, chemotherapy, or radiotherapy) before serum collection.

Table S6. Multivariable-adjusted odds ratios of TAAbs for treatment-naïve LUAD compared with benign controls (adjusted for sampling age, sex, and smoking status).

TAAb	OR	95% CI	*P*
anti-DDX53	2.69	1.07–7.34	0.047
anti-IRX2	9.77	3.32–40.57	<0.001
anti-p53	7.45	2.58–38.39	0.005
anti-XAGE1B	9.33	1.95–69.16	0.014

Table S7. Comparison of diagnostic performance among TAAb, TAA, and combined models in SCLC and LUAD.

Model Type	Predictor	AUC	95% CI	Sensitivity	Specificity	*P1*[a]	*P2*[b]
Small cell lung cancer							
TAA panel	CTAG1B + DDX53 + TNNI3	0.726	0.641–0.811	84.2%	59.0%	–	0.109
TAAb panel	anti-CTAG1B + anti-DDX53 + anti-NUFIP2 + anti-p53 + anti-SOX2 + anti-TNNI3	0.815	0.739–0.891	70.2%	81.9%	0.109	–
TAAb panel + TAA panel	anti-CTAG1B + anti-DDX53 + anti-NUFIP2 + anti-p53 + anti-SOX2 + anti-TNNI3 + CTAG1B + DDX53 + TNNI3	0.873	0.809–0.937	71.9%	89.2%	< 0.001	0.018
Lung adenocarcinoma							
TAA	DDX53	0.536	0.455–0.617	45.6%	65.1%	–	< 0.001
TAAb panel	anti-DDX53 + anti-IRX2 + anti-p53 + anti-XAGE1B	0.876	0.830–0.923	74.6%	88.0%	< 0.001	–
TAAb panel + TAA	anti-DDX53 + anti-IRX2 + anti-p53 + anti-XAGE1B + DDX53	0.882	0.837–0.927	72.8%	89.2%	< 0.001	0.268

The ROC analysis was conducted in a subset of samples for which TAA data were available.

[a]*P1*: comparison with the TAA panel model using the DeLong test.

[b]*P2*: comparison with the TAAb panel model using the DeLong test.

Table S8. Differential expression of serum TAA levels between cancer TAAb-positive and TAAb-negative patients.

TAA[a]	TAAb-positive median (IQR)[b]	TAAb-negative median (IQR)[b]	log_2(FC)	*P*
Small cell lung cancer				
CTAG1B	0.920 (0.070 ~ 1.196)	-0.939 (-4.352 ~ -0.034)	1.86	0.012
DDX53	0.791 (0.363 ~ 1.052)	0.295 (-0.434 ~ 0.703)	0.50	0.005
NUFIP2	0.731 (0.047 ~ 1.078)	-0.063 (-3.970 ~ 0.999)	0.79	0.051
p53	1.224 (0.707 ~ 2.079)	0.460 (-0.336 ~ 1.010)	0.77	0.017
SOX2	0.307 (-0.304 ~ 2.875)	-0.175 (-0.377 ~ 0.003)	0.48	0.018
TNNI3	3.926 (2.856 ~ 4.554)	2.403 (1.299 ~ 3.398)	1.52	0.023
Lung adenocarcinoma[c]				
DDX53	0.158 (-0.371 ~ 0.616)	-0.109 (-0.577 ~ 0.384)	0.27	0.114
p53	1.797 (0.531 ~ 2.314)	1.098 (0.650 ~ 1.470)	0.70	0.008

[a]Serum TAA levels are reported as normalized protein expression (NPX) values on a log2 scale.

[b]TAAb-positive and TAAb-negative status was defined separately for each TAAb; thus, the same sample could be classified differently depending on the specific TAAb analyzed.

[c]In LUAD, serum protein levels of IRX2 and XAGE1B were not available because they were not included in the Olink Explore HT panel (Olink Proteomics).

Table S9. Comparison of TAA mRNA expression between tumor and normal lung tissues.

TAA	Tumor median (IQR)[a]	Normal median (IQR)[a]	FC[b]	*P*
Small cell lung cancer				
DDX53	1 (1-2.317)	1 (1-1)	1.00	0.087
NUFIP2	415.146 (317.227-525.789)	356.701 (348.609-397.912)	1.16	0.280
TP53	89.951 (58.326-134.88)	79.95 (65.375-97.772)	1.13	0.510
SOX2	106.584 (48.991-216.496)	54.352 (4.835-65.737)	1.96	0.015
TNNI3	1.109 (1-4.429)	1 (1-1)	1.11	0.017
Lung adenocarcinoma				
DDX53	0 (0-0.030)	0 (0-0)	—	<0.001
IRX2	14.008 (3.410-46.010)	60.372 (50.483-78.304)	0.23	<0.001
TP53	35.623 (21.461-46.412)	24.844 (21.947-29.310)	1.43	<0.001
XAGE1B	0.24 (0-0.739)	0 (0-0.063)	—	<0.001

[a]Median expression values represent transcripts per million (TPM) derived from RNA sequencing data (GEO for SCLC and TCGA for LUAD).

[b]Some FC could not be calculated for some TAAbs because the median value in the control group was zero, resulting in an undefined value due to division by zero.

Table S10. Residue-level logistic regression of HLA positions significant in omnibus tests.

TAAb	Amino acid	A1[a]	A2[a]	R2[b]	Num_pos[c]	Num_neg[c]	Freq_pos[d]	Freq_neg[d]	β[d]	SE	*P*
anti-DDX53	Omnibus test										3.254×10^{-5}
	AA_DRB1_71_32551957_A	P	A	0.9916	17	66	0.2643	0.1892	0.7127	0.5341	0.1823
	AA_DRB1_71_32551957_E	P	A	0.9946	17	66	0.0885	0.0759	1.2850	0.9080	0.1660
	AA_DRB1_71_32551957_K	A	P	0.9731	17	66	0.9889	1.0000	-2272.7589	1240.8645	0.0005
	AA_DRB1_71_32551957_R	A	P	0.9907	17	66	0.3639	0.2651	0.9365	0.4772	0.0465
anti-p53	Omnibus test										4.573×10^{-6}
	AA_DPB1_55_33048599_A	A	P	0.9617	22	61	0.8671	0.9221	-2.1784	0.8559	0.0086
	AA_DPB1_55_33048599_D	A	P	0.9901	22	61	0.5420	0.4795	0.8066	0.4622	0.0701
	AA_DPB1_55_33048599_E	P	A	0.9996	22	61	0.4092	0.4016	0.1972	0.4374	0.6518
anti-TNNI3	Omnibus test										1.170×10^{-4}
	AA_DRB1_-25_32557506_K	A	P	0.9970	13	70	0.6543	0.3285	2.3335	0.7627	0.0002
	AA_DRB1_-25_32557506_R	P	A	0.9925	13	70	0.6542	0.3275	2.3430	0.7636	0.0002
	Omnibus test										1.124×10^{-4}
	AA_DRB1_-16_32557479_A	A	P	0.9966	13	70	0.6542	0.3285	2.3346	0.7631	0.0002
	AA_DRB1_-16_32557479_V	P	A	0.9910	13	70	0.6541	0.3275	2.3443	0.7640	0.0002
	Omnibus test										9.933×10^{-7}
	AA_DRB1_11_32552137_D	A	P	0.9954	13	70	0.9220	0.8425	2.0557	1.0257	0.3971
	AA_DRB1_11_32552137_L	A	P	0.9984	13	70	1.0000	0.9857	1.9391	1611.2625	0.0029
	AA_DRB1_11_32552137_P	P	A	0.9976	13	70	0.0386	0.2429	-2.6377	1.2038	0.4160
	AA_DRB1_11_32552137_S	P	A	0.9957	13	70	0.6157	0.3285	14.8518	0.6773	0.0011
	AA_DRB1_11_32552137_V	P	A	0.9938	13	70	0.7323	0.7503	-0.4691	0.5506	0.0250
	Omnibus test										1.779×10^{-4}
	AA_DRB1_13_32552131_F	A	P	0.9955	13	70	0.8832	0.8281	1.3607	0.8748	0.0883
	AA_DRB1_13_32552131_G	A	P	0.9841	13	70	0.5767	0.8473	-1.5558	0.6023	0.0067
	AA_DRB1_13_32552131_H	A	P	0.9933	13	70	0.7711	0.7504	-0.3119	0.5941	0.6025
	AA_DRB1_13_32552131_R	P	A	0.9974	13	70	0.0386	0.2429	-2.6386	1.2041	0.0029
	AA_DRB1_13_32552131_S	P	A	0.9860	13	70	0.1923	0.1758	0.6319	0.7148	0.3809
	Omnibus test										3.236×10^{-6}
	AA_DRB1_26_32552092_F	P	A	0.9867	13	70	0.7676	0.7969	0.2292	0.6686	0.7299
	AA_DRB1_26_32552092_L	A	P	0.9811	13	70	0.8461	0.9545	-2.1857	1.0042	0.0277
	AA_DRB1_26_32552092_Y	A	P	0.9943	13	70	0.9217	0.8424	2.0547	1.0258	0.0251
	Omnibus test										2.648×10^{-10}
	AA_DRB1_28_32552086_D	P	A	0.9820	13	70	0.7573	0.7600	0.3477	0.6459	0.5856
	AA_DRB1_28_32552086_E	A	P	0.9810	13	70	0.8372	0.9181	-1.3385	0.8421	0.1156
	AA_DRB1_28_32552086_H	A	P	0.9881	13	70	0.9199	0.8420	2.0397	1.0244	0.0263
	Omnibus test										5.035×10^{-6}
	AA_DRB1_140_32549480_A	P	A	0.9885	13	70	0.1207	0.4228	-3.5062	1.1719	1.545×10^{-5}
	AA_DRB1_140_32549480_T	A	P	0.9868	13	70	0.1207	0.4230	-3.5072	1.1721	1.536×10^{-5}

[a]A1/A2 represents allelic states at the amino acid position: P = presence, A = absence of the residue.

[b]R2 indicates the imputation quality.

[c]Sample counts in TAAb-positive (pos) and TAAb-negative (neg) groups. The total (Num_pos + Num_neg) was less than the cohort size because 5 patients with missing HLA data were excluded.

[d]Parameters specific to the A1 allele. Freq_ indicates the frequency of the A1 allele in the positive/negative group. β represents the effect size of the A1 allele on TAAb seropositivity.