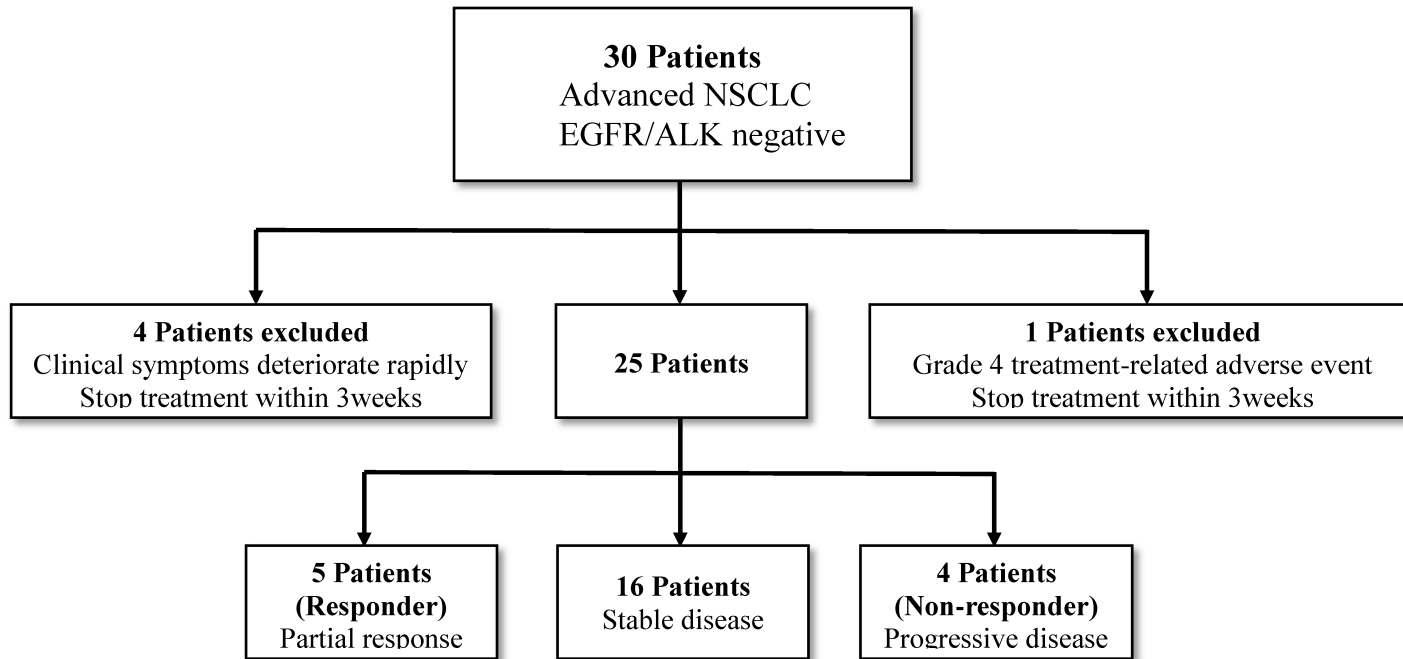


Supplementary Figure 1 Flow chart for patient selection and exclusion criteria.

Supplementary Table 1 Baseline clinicopathological characteristics of patients enrolled

Patient ID	Sample ID	Sex	Age	Smoking	Histology	Stage at diagnosis	Type of metastasis	EGFR/ALK	PD_L1 IHC	PD_L1 IHC assay	Drug	Response	PFS/days
1	P1 P1_2(post,PR)	M	55	Yes	ADC	IVB	liver, adrenal gland	Negative	<10%	Ventana kit anti-PD-L1 SP263	PD-1 inhibitor	PR	NR(631)
2	P2 P2_2(post,PR)	M	68	Yes	SCC	IVA	lung	Negative	≥10%	Ventana kit anti-PD-L1 SP263	PD-1 inhibitor	PR	455
3	P3	M	63	NA	ADC	IVA	lung	Negative	≥10%	Ventana kit anti-PD-L1 SP263	PD-1 inhibitor	PD	60
4	P4 P4_2(post, PR) P4_3(post, PD)	M	47	Yes	LELC*	IVA	pleura	Negative	≥10%	Ventana kit anti-PD-L1 SP263	PD-1 inhibitor	PR	250
5	P5	F	47	No	ADC	IVB	liver	Negative	<10%	Ventana kit anti-PD-L1 SP263	PD-1 inhibitor	PD	63
6	P6 P6_2(post,PR)	M	55	No	SCC	IIIA	lung	Negative	<10%	Ventana kit anti-PD-L1 SP263	PD-1 inhibitor	PR	484
7	P7	M	56	Yes	SCC	IVB	lung, bone	Negative	< 10%	Abcam PD-L1 28-8	PD-L1 inhibitor	PD	46
8	P8	F	54	No	ADC	IVB	liver	Negative	≥10%	Ventana kit anti-PD-L1 SP263	PD-1 inhibitor	PD	38
9	P9	M	48	No	ADC	IVB	pleura, adrenal gland	Negative	≥10%	Ventana kit anti-PD-L1 SP142	PD-L1 inhibitor	PR	NR(404)

Post, post-treatment sample; all other samples are pre-treatment samples
 PD, progressive disease; PR, partial response; NR, PFS not reached.

Supplementary Table 2 Treatment history of patients enrolled. ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; T3: triiodothyronine; T4: thyroxine; TSH: thyrotropin; +: combined treatment;

Patient ID	Cycles of immunotherapy given	Possible autoimmune side effect	Line of immunotherapy	Prior lines of therapy	Subsequent lines of therapy
1	39	None	2	Pemetrexed+Cisplatin	None
2	22	Vitiligo	3	Nedaplatin+Paclitaxel liposome; Docetaxel	Nab-paclitaxel
3	6	Diarrhea, Anemia, Rash	3	Pemetrexed+Cisplatin; Gemcitabine+Docetaxal +Bevacizumab	None
4	18	None	3	Docetaxel+Lobaplatin; Pemetrexed+Carboplatin	Paclitaxel liposome+ Cisplatin; Anlotinib
5	3	None	2	Pemetrexed+Cisplatin	Crizotinib; Alectinib
6	23	Increased ALT and AST	2	Gemcitabine+ Carboplatin	Nab-paclitaxel
7	3	Increased GGT and AST, Pain in the knees	4	Paclitaxel+ Carboplatin + Bevacizumab; Docetaxel; Pemetrexed	Keytruda; Afatinib; Pyrotinib
8	3	None	1	None	None
9	24	Decreased T3 and T4, Increased TSH and amylase	1	None	None

Supplementary Table 5

a.

DE miRNAs	LogFC	LogCPM	P Value	FDR
Up-regulated miRNAs				
hsa-miR-146a-5p	2.111324	12.63676	4.67E-15	3.24E-12
hsa-miR-199a-5p	2.303766	11.34932	2.08E-13	6.96E-11
hsa-miR-339-5p	2.809138	7.793159	1.88E-11	2.88E-09
hsa-miR-224-5p	2.46283	9.702515	2.49E-11	2.88E-09
hsa-miR-222-3p	1.91983	12.70705	5.77E-11	5.37E-09
hsa-miR-1301-3p	2.21861	8.875247	6.19E-11	5.37E-09
hsa-miR-1307-3p	1.836696	11.84745	1.64E-10	1.27E-08
hsa-miR-744-5p	2.161892	12.64556	5.89E-10	3.28E-08
hsa-miR-21-5p	1.442093	15.02557	6.14E-10	3.28E-08
hsa-miR-221-3p	1.931791	10.58632	9.23E-10	4.58E-08
Down-regulated miRNAs				
hsa-miR-144-3p	-2.86931	9.844957	3.01E-13	6.96E-11
hsa-miR-363-3p	-2.00229	10.41213	2.26E-11	2.88E-09
hsa-miR-183-5p	-2.56443	9.887505	5.95E-10	3.28E-08
hsa-let-7b-5p	-1.60491	15.68288	6.08E-10	3.28E-08
hsa-miR-144-5p	-2.4841	8.888006	1.29E-09	5.97E-08
hsa-miR-150-3p	-2.07429	6.926632	2.51E-08	9.20E-07
hsa-miR-106a-5p	-3.00915	6.652901	4.11E-08	1.36E-06
hsa-miR-182-5p	-1.97861	10.11936	1.09E-07	3.16E-06
hsa-miR-92a-3p	-0.97709	15.41688	5.73E-07	1.14E-05
hsa-miR-7641	-2.81947	5.99889	3.54E-06	6.30E-05

b.

KEGG pathway	P Value	Targeted genes
TGF-beta signaling pathway	4.13E-05	14
MAPK signaling pathway	0.000164088	47
Neurotrophin signaling pathway	0.003509097	24
Glycosphingolipid biosynthesis - lacto and neolacto series	0.004586994	3
Ras signaling pathway	0.004586994	33
Arrhythmogenic right ventricular cardiomyopathy (ARVC)	0.006333444	13
Hepatitis B	0.009434859	19
Hippo signaling pathway	0.013698094	20
Prolactin signaling pathway	0.013698094	15
N-Glycan biosynthesis	0.017151258	7
TNF signaling pathway	0.020781874	21
Signaling pathways regulating pluripotency of stem cells	0.023602761	21
B cell receptor signaling pathway	0.037884447	14
Pancreatic cancer	0.037884447	12
T cell receptor signaling pathway	0.038952764	19
Chagas disease (American trypanosomiasis)	0.040812445	18