

**Figure S1** Flow chart illustrating the patient enrollment of the study. EGFR, epidermal growth factor receptor; TKIs, tyrosine kinase inhibitors; NEC, neuroendocrine carcinoma; LUAD, lung adenocarcinoma; SCLC, small-cell lung cancer; PDO, patient derived organoid; ORR, objective response rate; pPFS, post-transformation progression-free survival; pOS, post-transformation overall survival.

**Table S1** Baseline clinicopathological characteristics after initial transformation of the study population

Clinical characteristics of the study population	Chemo group (n=21)	Combo group (n=14)	P value
Age groups, n (%)			0.369
<65 years	19 (90.5)	11 (78.6)	
≥65 years	2 (9.5)	3 (21.4)	
Sex, n (%)			0.500
Female	12 (57.1)	6 (42.9)	
Male	9 (42.9)	8 (57.1)	
Smoking history, n (%)			0.090
Never smoker	19 (90.5)	9 (64.3)	
Ever smoker	2 (9.5)	5 (35.7)	
ECOG PS at baseline, n (%)			0.493
0	1 (4.8)	0 (0.0)	
1	19 (90.4)	14 (100.0)	
2	1 (4.8)	0 (0.0)	
First post-transformed histologic subtype, n (%)			0.053
Pure SCLC/NEC	18 (85.7)	7 (50.0)	
Combined SCLC/NEC	3 (14.3)	7 (50.0)	
First post-transformed clinical stage, n (%)			0.252
IIIB–IVA	8 (38.1)	2 (14.3)	
IVB	13 (61.9)	12 (85.7)	
Brain metastases, n (%)			0.094
Yes	7 (33.3)	9 (64.3)	
No	14 (66.7)	5 (35.7)	
Median time to transformation (months)	21.2	21.0	0.649
<i>EGFR</i> mutation at first transformation, n (%)			0.130
Exon 19 deletion	9 (42.8)	7 (50.0)	
L858R	1 (4.8)	3 (21.4)	
Exon 19 deletion + T790M	2 (9.5)	2 (14.3)	
L858R + T790M	1 (4.8)	2 (14.3)	
Unknown	6 (28.6)	0	
No mutation	2 (9.5)	0	

Chemo, chemotherapy; combo, chemo plus TKI or bevacizumab; TKI, tyrosine kinase inhibitor; ECOG, Eastern Cooperative Oncology Group; PS, performance status; SCLC, small cell lung cancer; NEC, neuroendocrine carcinoma; EGFR, epidermal growth factor receptor.

**Table S2** Thirty-five patients' clinical characteristics and genetic profiles

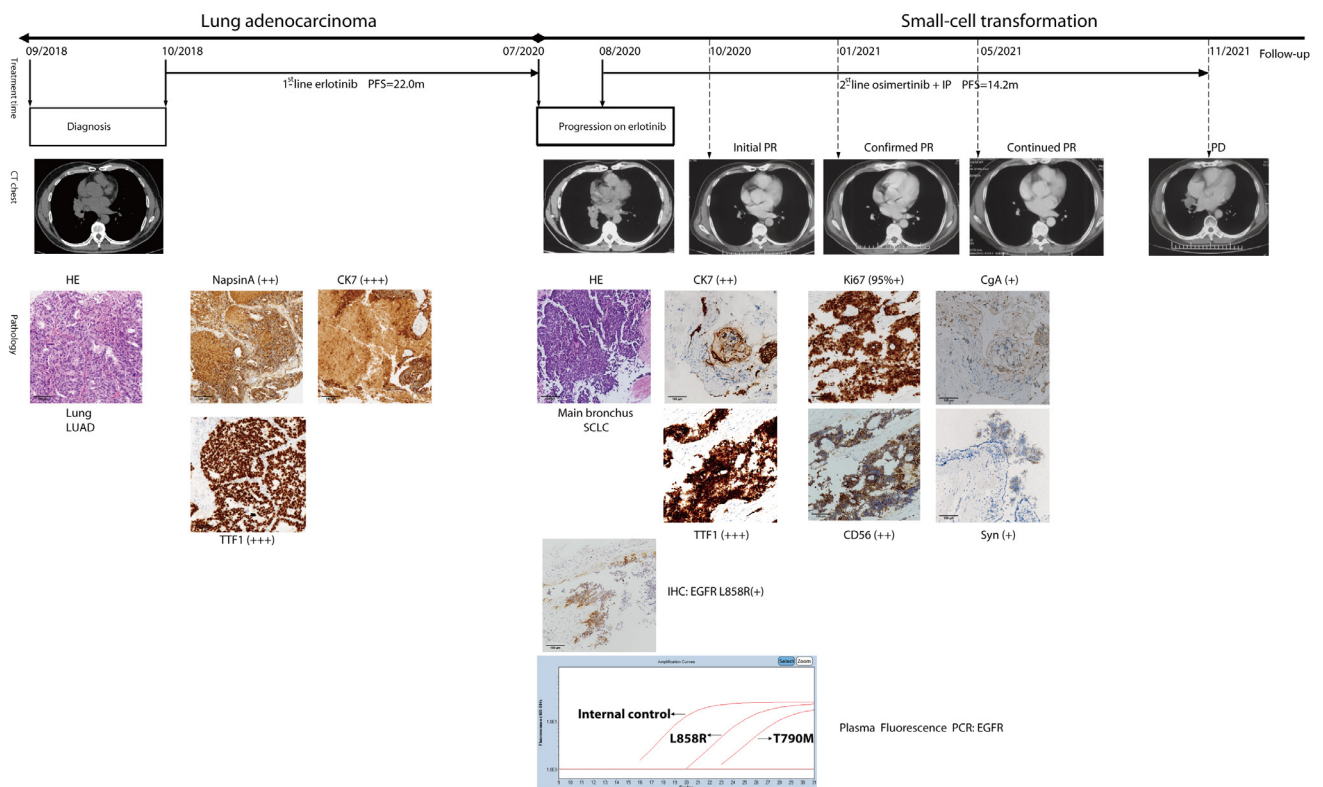
Patient	Sex	Age of first transformation (years)	Smoking history	Confirmed transformed PS	Baseline pathology	Pathology at transformation	Post-transformation biopsy site	Clinical stage	Brain metastasis	Time to transformation (months)	First-line treatment after transformation	pPFS (months)	pOS (months)	OS (months)	Baseline driver gene	First transformation driver gene
P1	Male	39	Never smoker	1	Adenocarcinoma	SCLC + adenocarcinoma	1 lung	IVB	Yes	28.9	Bevacizumab + pemetrexed + carboplatin	11.1	16.9	45.8	EGFR 19del	EGFR 19del
P2	Female	57	Never smoker	1	Adenocarcinoma	SCLC	1 pleura	IVB	Yes	52.7	Osimertinib + EP	1.9	10.7	63.4	EGFR 19del	EGFR 19del
P3	Male	62	Ever smoker	1	Adenocarcinoma	SCLC + adenocarcinoma	1 pleura	IVB	Yes	26.4	Bevacizumab + paclitaxel for injection (albumin bound) + carboplatin	4.1	4.5	30.9	EGFR exon 21 L858R	EGFR exon 21 L858R + T790M
P4	Male	51	Never smoker	1	Adenocarcinoma	SCLC	1 lung	IVB	Yes	12.1	Osimertinib + EC	10.3	19.4	31.5	EGFR exon 21 L858R	EGFR exon 21 L858R
P5	Female	45	Never smoker	1	Adenocarcinoma	SCLC	1 lung	IVB	Yes	8.2	Osimertinib + EP	6.0	7.9	16.1	EGFR 19del	EGFR 19del
P6	Female	47	Never smoker	1	Adenocarcinoma	SCLC	1 lung	IVB	No	56.5	Bevacizumab + pemetrexed + carboplatin	7.4	7.1	63.6	EGFR exon 21 L858R	EGFR exon 21 L858R
P7	Female	71	Never smoker	1	Adenocarcinoma	SCLC + adenocarcinoma	1 lung	IVB	Yes	44.9	Osimertinib + paclitaxel for injection (albumin bound) + carboplatin	3.3	5.2	50.1	EGFR 19del	EGFR 19del
P8	Female	46	Never smoker	1	Adenocarcinoma	SCLC	1 lung	IVB	Yes	15.6	Osimertinib + EP	5.4	7.6	23.2	EGFR 19del	EGFR 19del + T790M
P9	Female	71	Never smoker	1	Adenocarcinoma	SCLC + adenocarcinoma	1 lung	IVA	No	16.5	Afatinib + IP	8.9	20.7	37.2	EGFR 19del	EGFR 19del
P10	Male	71	Ever smoker	1	Adenocarcinoma	SCLC	1 lung	IVB	Yes	21.0	Afatinib + IP	4.9	10.7	31.8	EGFR 19del	EGFR 19del + T790M
P11	Male	58	Ever smoker	1	Adenocarcinoma	SCLC + adenocarcinoma	1 liver, 2 retroperitoneal lymph nodes, 3 pleural effusion	IVB	No	12.6	Afatinib + IP	4.4	6.8	19.4	EGFR 19del	EGFR 19del
P12	Male	55	Ever smoker	1	Adenocarcinoma	SCLC + adenocarcinoma	1 liver, 2 lung	IVB	No	3.2	Osimertinib + IP	6.8	14.4	17.6	EGFR 19del	EGFR 19del
P13	Male	55	Never smoker	1	Adenocarcinoma	SCLC	1 lung	IVA	No	22.8	Osimertinib + IP	14.2	26.0	48.8	EGFR exon 21 L858R	EGFR exon 21 L858R + T790M
P14	Male	53	Ever smoker	1	Adenocarcinoma	NEC + adenocarcinoma	1 lung	IVB	Yes	22.8	Bevacizumab + paclitaxel + carboplatin	4.1	12.2	35.0	EGFR exon 21 L858R	EGFR exon 21 L858R
P15	Female	63	Never smoker	2	Adenocarcinoma	SCLC	1 liver	IVB	Yes	56.3	IC	6.1	6.9	63.2	EGFR exon 21 L858R	EGFR exon 21 L858R
P16	Male	55	Never smoker	1	Adenocarcinoma	SCLC	1 lung	IVB	No	34.6	EP	3.6	17.2	51.8	EGFR 19del	EGFR 19del + T790M
P17	Female	62	Never smoker	1	Adenocarcinoma	NEC	1 lung	IVB	Yes	13.5	Paclitaxel for injection (albumin bound)	1.5	2.9	16.4	EGFR 19del	EGFR 19del
P18	Female	25	Never smoker	1	Adenocarcinoma	SCLC	1 lung	IVA	No	11.4	EP	8.1	23.0	34.3	EGFR 19del	EGFR 19del
P19	Male	38	Never smoker	0	Adenocarcinoma	SCLC + adenocarcinoma	1 lung	IIIB	No	10.6	IP	4.1	10.9	26.1	EGFR exon 21 L858R + T790M	EGFR exon 21 L858R + T790M
P20	Male	50	Ever smoker	1	Adenocarcinoma	SCLC	1 paratracheal lymph nodes	IVB	No	61.5	EP	2.5	9.7	103.5	EGFR 19del	Unknown
P21	Female	70	Never smoker	1	Adenocarcinoma	SCLC	1 lung	IVB	Yes	25.8	EP	2.0	4.2	30.0	EGFR 19del	No
P22	Male	36	Never smoker	1	Adenocarcinoma	SCLC	1 lung	IVA	Yes	21.0	EP	3.5	28.1	49.1	EGFR 19del	EGFR 19del
P23	Female	42	Never smoker	1	Adenocarcinoma	SCLC	1 liver, 2 supraclavicular lymph nodes	IVB	No	24.0	EP	6.7	7.4	41.6	EGFR 19del	EGFR 19del
P24	Female	52	Never smoker	1	Adenocarcinoma	SCLC + adenocarcinoma	1 lung	IVA	Yes	20.4	IP	2.4	5.8	26.3	EGFR 19del	No
P25	Female	60	Never smoker	1	Adenocarcinoma	SCLC	1 lung	IVA	No	21.2	EP	7.5	7.7	28.9	Unknown	EGFR 19del
P26	Male	44	Never smoker	1	Adenocarcinoma	SCLC	1 lung	IVB	No	20.7	EP	2.9	4.4	25.1	EGFR 19del	EGFR 19del
P27	Male	52	Ever smoker	1	Adenocarcinoma	SCLC + adenocarcinoma	1 pleura, 2 pleural effusion	IVA	No	19.3	EP	3.3	11.2	30.5	EGFR exon 18 mutation	Unknown
P28	Female	57	Never smoker	1	Adenocarcinoma	SCLC	1 adrenal glands	IVB	No	17.1	EC	0.7	3.7	20.8	EGFR 19del + exon 20 mutation	EGFR 19del
P29	Female	73	Never smoker	1	Adenocarcinoma	SCLC	1 lung	IVA	No	14.1	IP	6.9	20.5	34.6	EGFR exon 21 L858R + T790M	Unknown
P30	Female	44	Never smoker	1	Adenocarcinoma	SCLC	1 supraclavicular lymph nodes	IVB	No	64.8	Etoposide	1.4	5.9	70.7	EGFR 19del	Unknown
P31	Male	58	Never smoker	1	Adenocarcinoma	SCLC	1 lung	IVB	Yes	28.1	EP	5.0	7.1	35.2	EGFR 19del	Unknown
P32	Male	55	Never smoker	1	Adenocarcinoma	SCLC	1 lung	IVA	No	22.5	IP	3.3	9.9	32.4	Unknown	EGFR 19del
P33	Female	58	Never smoker	1	Adenocarcinoma	SCLC	1 pleura	IVB	No	15.1	IC	2.5	9.2	24.4	EGFR 19del	EGFR 19del + T790M
P34	Male	53	Never smoker	1	Adenocarcinoma	SCLC	1 lung	IVB	Yes	38.2	EP	4.5	5.1	43.3	EGFR 19del	Unknown
P35	Female	57	Never smoker	1	Adenocarcinoma	SCLC	1 lung	IVA	No	23.2	EP	4.5	8.8	31.9	EGFR 19del	EGFR 19del

PS, performance status; pPFS, post-transformation progression-free survival; pOS, post-transformation overall survival; OS, overall survival; SCLC, small cell lung cancer; EGFR, epidermal growth factor receptor; 19del, exon 19 deletion; EP, etoposide-cisplatin; EC, etoposide-carboplatin; IP, irinotecan-cisplatin; NEC, neuroendocrine carcinoma; IC, irinotecan-carboplatin.

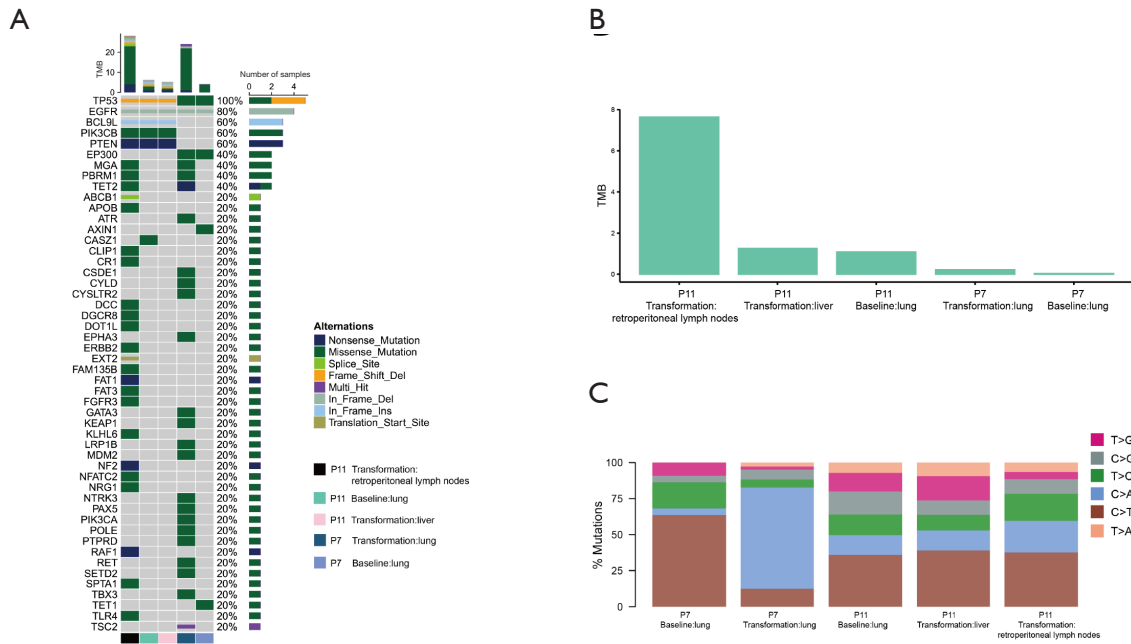
**Table S3** Clinical characteristics and genetic profiles of eleven patients with *EGFR*-mutant proteins detection

Patient	Sex	Age of first transformation (years)	Smoking history	Confirmed transformed PS	Baseline pathology	Pathology at transformation	Clinical stage	The type of treatment	The TKI being used	Time to transformation (months)	Primary mutations	Transformation with the following old mutations	Transformation with the following new mutations
P1	Male	39	Never smoker	1	Adenocarcinoma	SCLC + adenocarcinoma	IVB	Combo groups	Epirutinib (HMPL-813), erlotinib, osimertinib	28.9	<i>EGFR</i> 19del	<i>EGFR</i> 19del	<i>TP53</i> mutation, <i>PIK3CA</i> mutation, <i>MET</i> mutation, <i>BRCA2</i> mutation
P3	Male	62	Ever smoker	1	Adenocarcinoma	SCLC + adenocarcinoma	IVB	Combo groups	Icotinib, osimertinib	26.4	<i>EGFR</i> exon 21 L858R	<i>EGFR</i> exon 21 L858R	<i>EGFR</i> exon 20 T790M, <i>TP53</i> mutation, <i>RB1</i> mutation, <i>BRIP1</i> mutation
P6	Female	47	Never smoker	1	Adenocarcinoma	SCLC	IVB	Combo groups	Erlotinib, osimertinib, crizotinib	56.5	<i>EGFR</i> exon 21 L858R	<i>EGFR</i> exon 21 L858R	<i>TP53</i> mutation, <i>RB1</i> mutation, <i>TSC1</i> mutation
P8	Female	46	Never smoker	1	Adenocarcinoma	SCLC	IVB	Combo groups	Afatinib, bozitinib (PLB-1001), osimertinib, crizotinib	15.6	<i>EGFR</i> 19del, <i>TP53</i> mutation, <i>MET</i> CNV amplification, <i>EGFR</i> CNV amplification	<i>EGFR</i> 19del, <i>TP53</i> mutation, <i>EGFR</i> CNV amplification	<i>EGFR20</i> T790M, <i>PIK3CA</i> mutation, <i>MYC</i> CNV amplification, <i>PIK3CA</i> CNV amplification, <i>RB1</i> missing copy numbers
P9	Female	71	Never smoker	1	Adenocarcinoma	SCLC + adenocarcinoma	IVA	Combo groups	Gefitinib, osimertinib	16.5	<i>EGFR</i> 19del	<i>EGFR</i> 19del	<i>TP53</i> mutation, <i>PIK3CA</i> mutation
P10	Male	71	Ever smoker	1	Adenocarcinoma	SCLC	IVB	Combo groups	AZD3759, osimertinib	21.0	<i>EGFR</i> 19del, <i>TP53</i> mutation, <i>AKT1</i> CNV amplification, <i>EGFR</i> CNV amplification	<i>EGFR</i> 19del, <i>TP53</i> mutation, <i>EGFR</i> CNV amplification	<i>EGFR</i> exon 20 T790M
P11	Male	58	Ever smoker	1	Adenocarcinoma	SCLC + adenocarcinoma	IVB	Combo groups	Osimertinib	12.6	<i>EGFR</i> 19del, <i>PIK3R1</i> mutation, <i>PTEN</i> mutation, <i>TP53</i> mutation, <i>RB1</i> missing copy numbers	<i>EGFR</i> 19del, <i>PTEN</i> mutation	<i>MET</i> CNV amplification, <i>EGFR</i> CNV amplification
P13	Male	55	Never smoker	1	Adenocarcinoma	SCLC	IVA	Combo groups	Erlotinib	22.8	<i>EGFR</i> exon 21 L858R	<i>EGFR</i> exon 21 L858R	<i>EGFR20</i> T790M
P15	Female	63	Never smoker	2	Adenocarcinoma	SCLC	IVB	Chemo groups	Gefitinib, osimertinib, anlotinib	56.3	<i>EGFR</i> exon 21 L858R	<i>EGFR</i> exon 21 L858R	<i>TP53</i> mutation, <i>SMAD4</i> mutation
P19	Male	38	Never smoker	0	Adenocarcinoma	SCLC + adenocarcinoma	IIIB	Chemo groups	Osimertinib	10.6	<i>EGFR</i> exon 21 L858R, <i>EGFR</i> exon 20 T790M	<i>EGFR</i> exon 21 L858R, <i>EGFR</i> exon 20 T790M	<i>TP53</i> mutation, <i>PIK3CA</i> mutation, <i>RB1</i> mutation, <i>EPAS1</i> mutation, <i>TTF1</i> mutation
P20	Male	50	Ever smoker	1	Adenocarcinoma	SCLC	IVB	Chemo groups	Gefitinib, osimertinib	61.5	<i>EGFR</i> 19del	Unknown	Unknown

EGFR, epidermal growth factor receptor; PS, performance status; TKI, tyrosine kinase inhibitor; SCLC, small cell lung cancer; chemo, chemotherapy; combo, chemo plus TKI or bevacizumab; CNV, copy number variation.

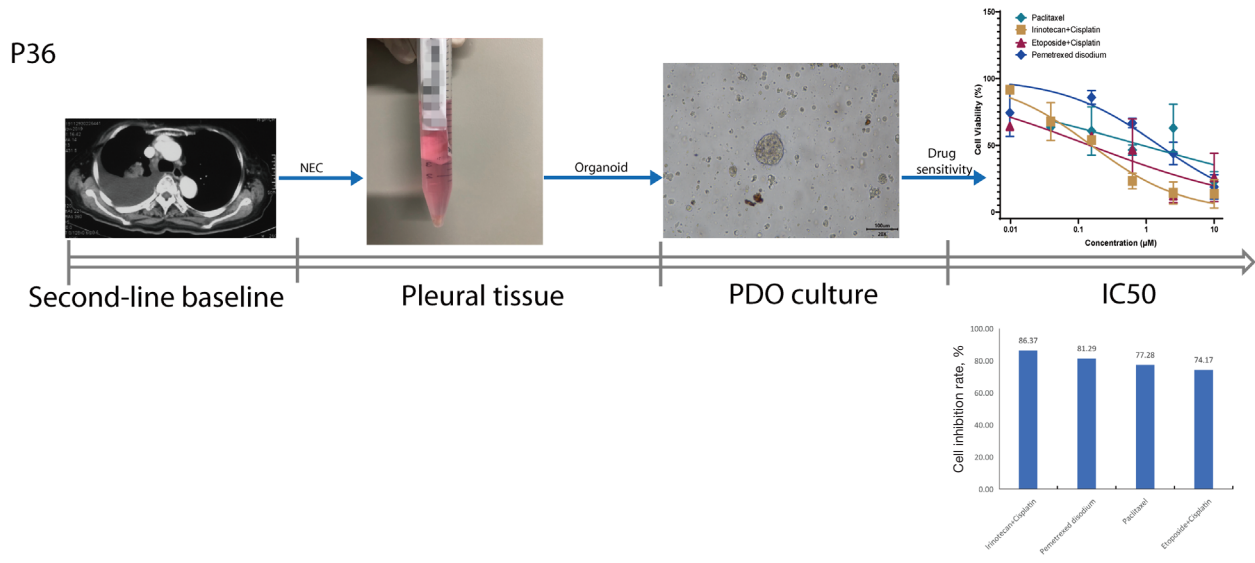


**Figure S2** One case's expression status of L858R at initial SCLC transformation. One case (P13) who used combo therapy acquired PR clinical response. The last follow-up time was June 30th, 2021. All IHC images were taken at  $\times 200$  magnification. PFS, progression-free survival; m, months; CT, computed tomography; IP, irinotecan-cisplatin; PR, partial response; PD, progressive disease; HE, hematoxylin and eosin staining; LUAD, lung adenocarcinoma; SCLC, small cell lung cancer; CgA, chromogranin A; Syn, synaptophysin; TTF1, thyroid transcription factor 1; CK7, cytokeratin 7; IHC, immunohistochemistry; PCR; polymerase chain reaction; EGFR, epidermal growth factor receptor.



**Figure S3** Genetic mutational landscape between baseline LUAD and initially-transformed SCLC. (A) Two patients' tissues genetic profiles for the baseline LUAD and initial SCLC transformation. Each row represents a gene, each column represents a sample, and colors represent types of mutation. In addition, the bottom square has different colors representing different samples of the same or different patients. (B) Compare to two patients' tissues TMB changed between baseline LUAD and initially-transformed SCLC. (C) Two patients' mutation spectrum changed between baseline LUAD and initially-transformed SCLC. Del, deletion; Ins, insertion; P, patient; TMB, tumor mutation burden; LUAD, lung adenocarcinoma; SCLC, small cell lung cancer.

Patient	Sex	Age of first transformation (years)	Smoking history	Baseline PS	Baseline pathology	Baseline biopsy site	Clinical stage	Brain metastasis	First-line treatment	PFS (months)	OS (months)	Baseline driver gene
P36	Female	80	Never smoker	1	Combined LUAD/NEC	1.Supraclavicular lymph nodes 2.Lung	IVB	Yes	Osimertinib	2.7	3.1	EGFR 21 L858R



**Figure S4** The establishment of organoid model and drug test showing anti-tumor potency to platinum-based doublet chemotherapy. The baseline histology of this patient (P36) was *EGFR*-mutant LUAD combined with NEC. Then, after resistance to first-line osimertinib, she underwent chest-tube drainage and pleural biopsy. Both cytology and histology revealed NEC. Meanwhile, an organoid model was successfully established from pleural tissue. Finally, the efficacy of platinum-based doublet chemotherapy was preliminarily validated by drug testing. PS, performance status; LUAD, lung adenocarcinoma; NEC, neuroendocrine carcinoma; PFS, progression-free survival; OS, overall survival; *EGFR*, epidermal growth factor receptor; PDO, patient-derived organoid; IC50, half-maximal inhibitory concentration.