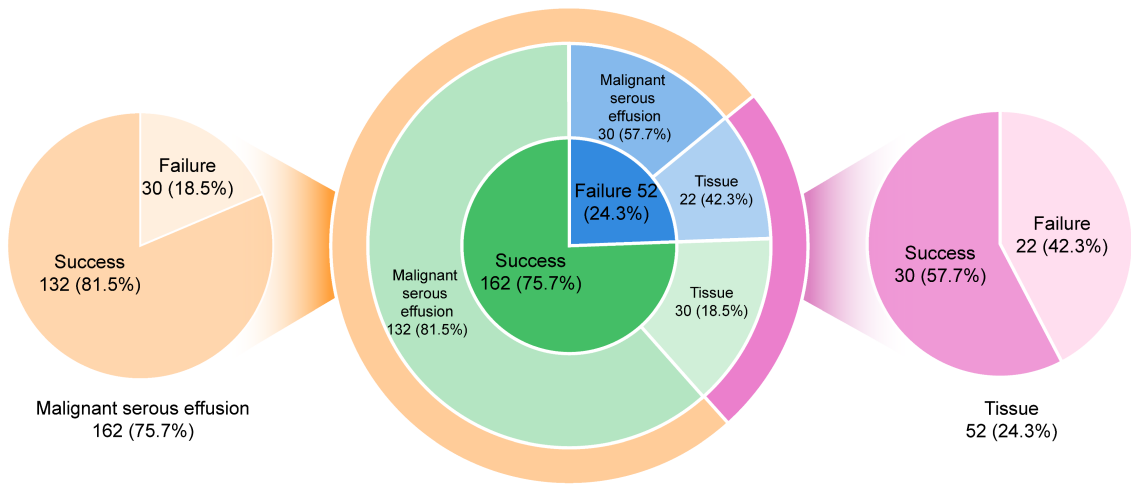


**Cell Reports Medicine, Volume 4**

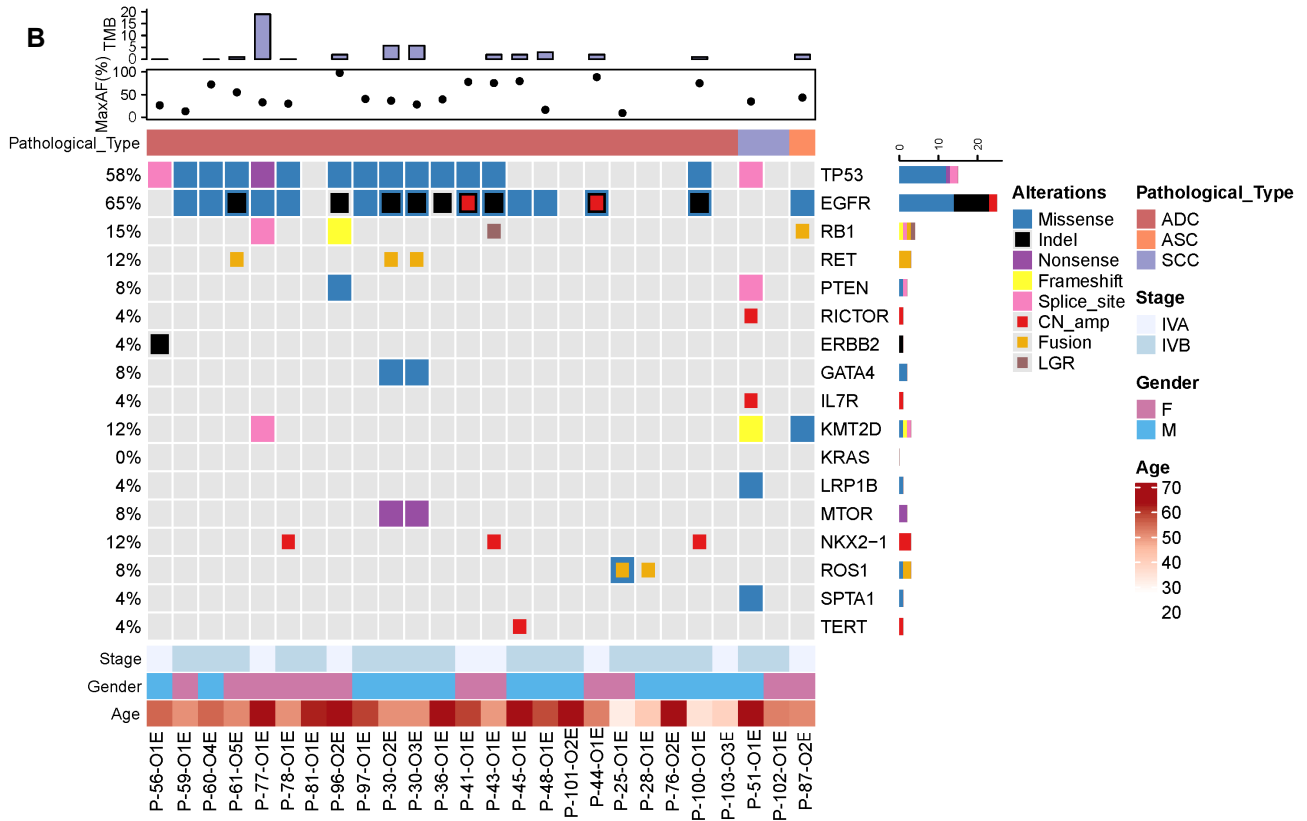
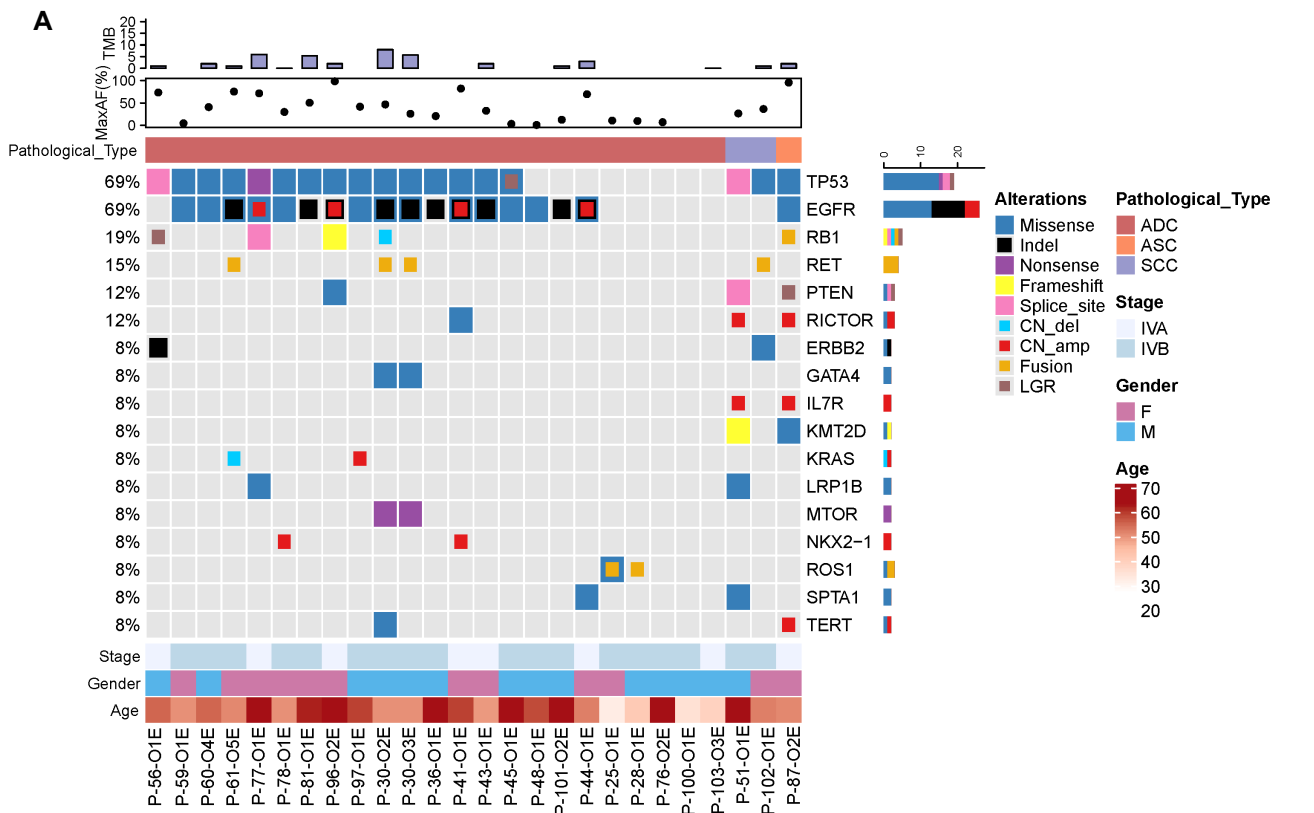
**Supplemental information**

**Using patient-derived organoids to predict  
locally advanced or metastatic lung cancer  
tumor response: A real-world study**

**Han-Min Wang, Chan-Yuan Zhang, Kai-Cheng Peng, Ze-Xin Chen, Jun-Wei Su, Yu-Fa Li, Wen-Feng Li, Qing-Yun Gao, Shi-Ling Zhang, Yu-Qing Chen, Qing Zhou, Cong Xu, Chong-Rui Xu, Zhen Wang, Jian Su, Hong-Hong Yan, Xu-Chao Zhang, Hua-Jun Chen, Yi-Long Wu, and Jin-Ji Yang**

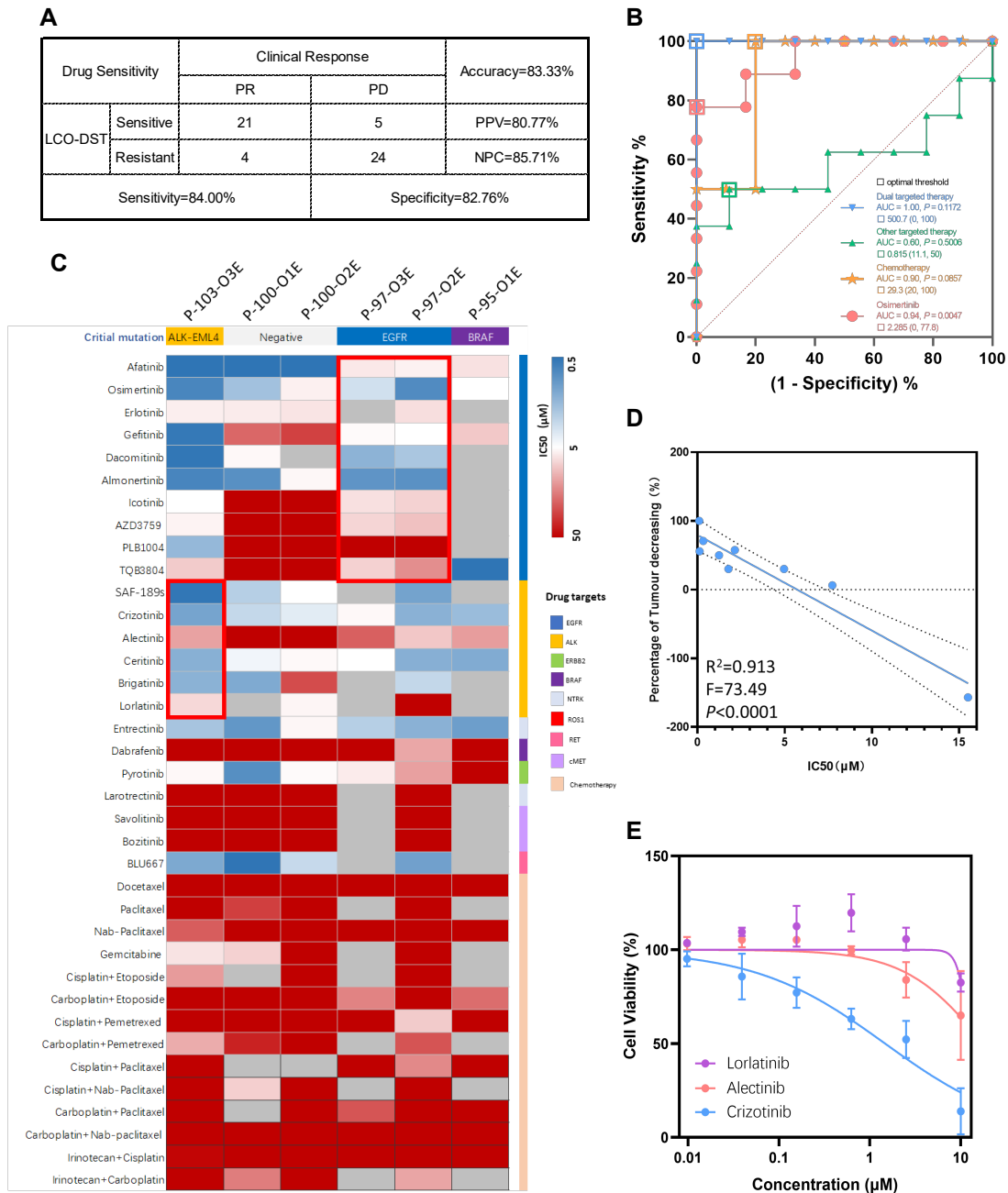


**Figure S1. The success rate of LCO cultures in this study. Related to Figure 1A**

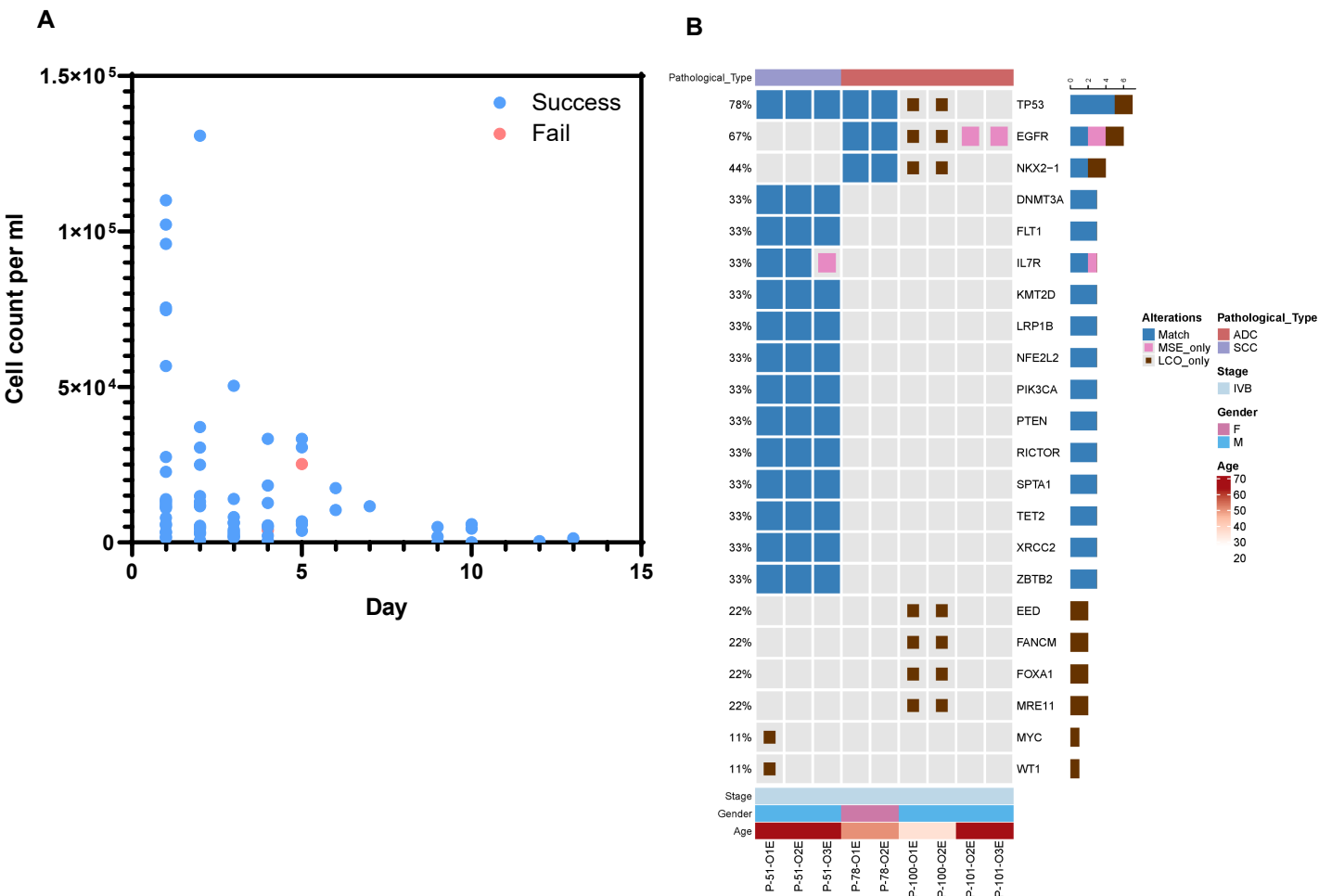


**Figure S2. Genomic profiling of LCO samples. Related to Figure 2A**

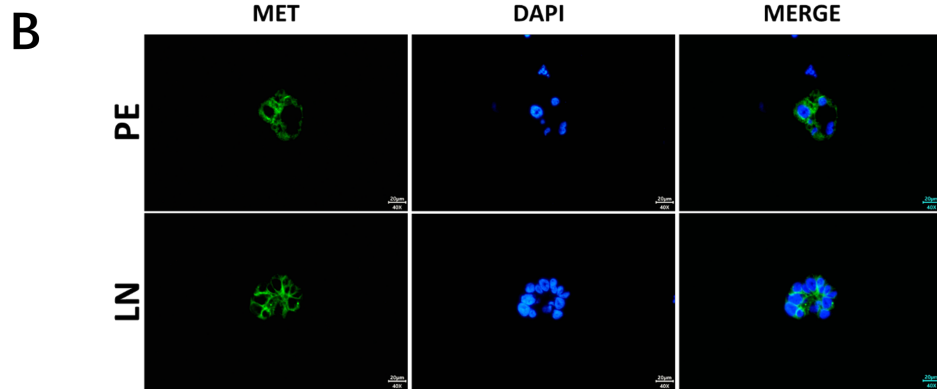
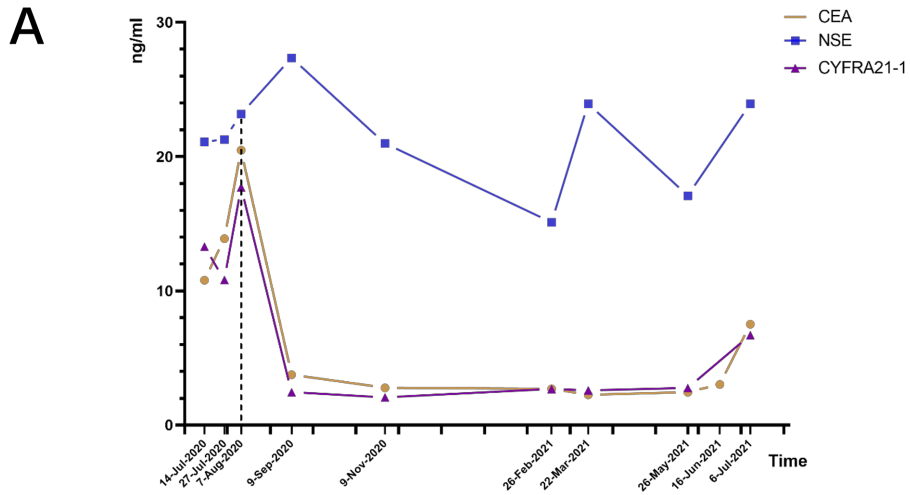
(A). Somatic alterations MSE samples. (B). Somatic alterations detected from MSE-derived LCO samples.



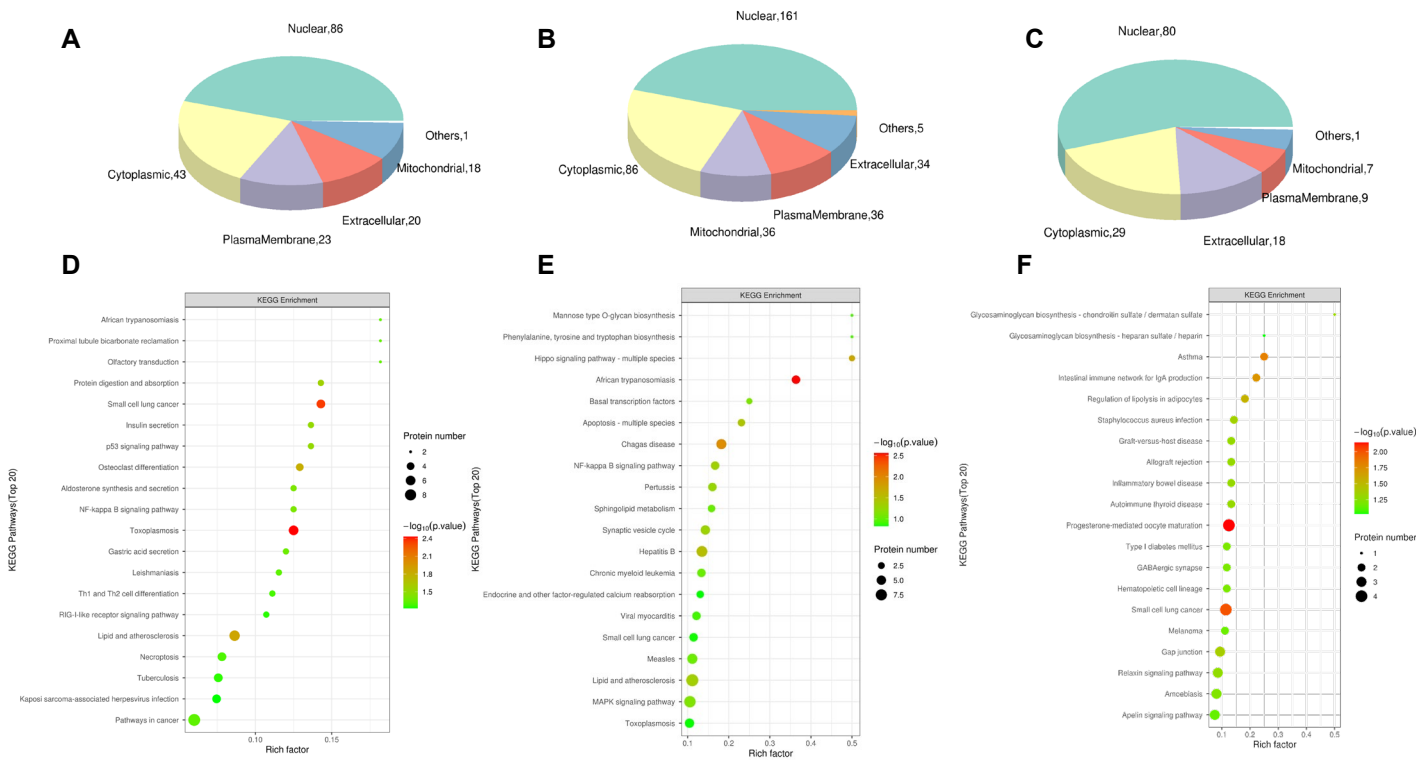
**Figure S3. Correlation between IC<sub>50</sub>s of targeted drugs and tumor cell reduction rates. Related to Figure 3** (A). The concordance for drug sensitivity between clinical response and LCO samples. (B). Receiver operating characteristic (ROC) analysis of osimertinib, chemotherapy, dual-targeted therapy, and other targeted therapy groups LCO drug tests (C). Heatmap of LCO-DST IC<sub>50</sub> of P-103, P-100, P-97, and P-95. (D). Correlation between IC<sub>50</sub> of osimertinib and the percentage of tumor shrinkage. (E). Dose-effect curves of alectinib, lorlatinib, and crizotinib of LCOs derived from P-63.



**Figure S4. Dynamic evolution of cell numbers and genetic alterations in LCOs and MSEs. Related to Figure 4A**  
 (A). Cell density of MSEs in different sampling times. (B). Somatic alterations detected from LCOs at different sampling times in four patients.



**Figure S5. Evaluation of tumor markers and baseline immunofluorescence of P-60. Related to Figure 5**  
 (A). Alterations of CEA, CYF21-1, and NSE of P-60. (B). Immunofluorescence staining of MET and DAPI of LCOs derived from pericardial effusion and lymph node of P-60. Scale bar, 20  $\mu$ m.



**Figure S6. Pie chart showing cell locations and scatter plot of KEGG enrichments of differentially expressed proteins (DEPs) from different comparison groups. Related to Figure 6**

(A). Cell locations of the osimertinib vs. control group. (B). Cell locations of the BLU-667 vs. control group. (C). Cell locations of the combo vs. control group. (D). KEGG enrichment of the osimertinib vs. control group. (E). KEGG enrichment of the BLU-667 vs. control group. (F). KEGG enrichment of the combo vs. control group.

**Table S1. The list of lung cancer samples used for successful establishment of patient-derived organoids. Related to Figure 1A.**

Case	Organoid ID	Gender	Age	ECOG		Pathology diagnosis	Site of sampling	Driver mutation detected by routine genetic testing or FISH	Treatment lines	Therapies after acquiring tumor specimens to generate organoids	Organoid IHC
				PS score	Stage						
P-1	P-1-O1T	F	55	1	IVB	ADC	Pleural tissue	NA	4	NA	NA
P-2	P-2-O1T	M	51	1	IVB	ADC	Lung tissue	NA	2	Osimeertinib	NA
P-3	P-3-O1E	M	50	1	IVB	ADC	Pericardial effusion	EGFR 19 del	3	EP	NA
P-3	P-3-O2T	M	50	1	IVB	SCLC	Paraspinal mass	NA	4	Nab-paclitaxel	NA
P-5	P-5-O1T	M	61	1	IVB	ADC	Lung tissue	NA	4	Docetaxel	NA
P-6	P-6-O1T	F	57	2	IVB	ADC	Lung tissue	NA	7	Osimeertinib+IP	NA
P-7	P-7-O1E	F	34	2	IVB	ADC	Pericardial effusion	Negative	2	NA	NA
P-8	P-8-O1T	F	80	1	IVB	ADC	Pleural mass	EGFR L858R	1	Osimeertinib	NA
P-9	P-9-O1T	M	56	1	IVB	ADC	Lung tissue	NA	2	PCB	NA
P-10	P-10-O1E	M	39	4	IVB	ADC	Pleural effusion	NA	2	NA	NA
P-10	P-10-O2T	M	39	4	IVB	ADC	Lung tissue	EGFR 19 del	2	NA	NA
P-11	P-11-O1T	F	57	2	IVB	ADC	Lung tissue	NA	6	Paclitaxel	NA
P-12	P-12-O1T	F	55	1	IVB	ADC	Supraclavicular lymph node	EGFR 19 del	2	Osimeertinib	NA
P-12	P-12-O2T	F	55	1	IVB	ADC	Supraclavicular lymph node	NA	3	PCB	NA
P-12	P-12-O3T	F	55	1	IVB	ADC	Axillary lymph node	EGFR 19 del; MET amplification	4	ABCP	CK7(+);TTF1(+);NapsinA(-)
P-13	P-13-O1E	F	77	1	IVA	ADC	Pleural effusion	NA	2	Beritinib + Bevacizumab	NA
P-14	P-14-O1E	F	75	2	IVB	ADC	Pleural effusion	MET 14 skipping	4	Anlotinib	NA
P-16	P-16-O1T	F	67	1	IVA	ADC	Supraclavicular lymph node	EGFR 19 del	3	PCB	NA
P-17	P-17-O1E	F	40	1	IVB	ADC	Pleural effusion	EGFR 19 del	1	Osimeertinib	NA
P-17	P-17-O2E	F	41	1	IVB	ADC	Pleural effusion	EGFR 19 del	2	Osimeertinib	NA
P-17	P-17-O3E	F	41	1	IVB	ADC	Pleural effusion	EGFR 19 del	2	Osimeertinib	NA
P-18	P-18-O1T	M	80	3	IVB	ADC	Supraclavicular lymph node	EGFR L858R;T790M	2	Osimeertinib	CK7(+);TTF1(+);NapsinA(+)
P-19	P-19-O1T	F	68	2	IVB	ADC	Paraspinal mass	NA	3	NA	NA
P-23	P-23-O1E	M	51	3	IVB	ADC	Pericardial effusion	NA	7	Afatinib+Cetuximab	NA
P-23	P-23-O2T	M	51	3	IVB	ADC	Lung tissue	EGFR L858R;EGFR L718Q;	7	Afatinib+Cetuximab	NA
P-24	P-24-O1T	M	65	1	IVA	ADC	Left adrenal puncture	NA	2	PCB	NA
P-25	P-25-O1E	F	32	1	IVB	ADC	Pleural effusion	CD74-ROS1 fusion, ROS1-intergenic fusion	3	PC	NA
P-27	P-27-O1E	M	55	3	IVB	ADC	Pericardial effusion	EML4-ALK fusion	3	Crizotinib	NA
P-28	P-28-O1E	M	41	1	IVB	ADC	Pleural effusion	CD74-ROS1 fusion	2	NA	NA
P-30	P-30-O1E	M	50	2	IVB	ADC	Ascitic effusion	EGFR 19 del;T790M; RET fusion	4	Osimeertinib	NA
P-30	P-30-O2E	M	50	2	IVB	ADC	Ascitic effusion	EGFR 19 del;T790M; RET fusion	4	Osimeertinib	NA
P-30	P-30-O3E	M	50	2	IVB	ADC	Pleural effusion	EGFR 19 del;T790M;FAM118A-NTRK1 fusion;RET	4	Osimeertinib	NA
P-32	P-32-O1T	F	69	1	IIIB	ADC	Lymph node	EGFR L858R;T790M	1	Osimeertinib	CK7(+);TTF1(-);NapsinA(+)
P-33	P-33-O1E	F	54	1	IVA	ADC	Pleural effusion	EML4-ALK fusion, ALK-C17orf75 fusion	1	Alectinib	CK7(+);TTF1(+);NapsinA(+)
P-33	P-33-O2T	F	54	1	IVA	ADC	Supraclavicular lymph node	EML4-ALK fusion	1	Alectinib	CK7(+);TTF1(+);NapsinA(+)
P-34	P-34-O1E	M	41	2	IVB	ADC	Pleural effusion	EGFR L858R	1	Osimeertinib	CK7(+);TTF1(+);NapsinA(+)
P-36	P-36-O1E	M	72	1	IVB	ADC	Pleural effusion	EGFR 20 ins	6	EMB-01	NA
P-37	P-37-O1T	F	67	1	IVB	ADC	Supraclavicular lymph node	NA	1	NA	NA
P-38	P-38-O1T	M	52	1	IVB	ADC	Supraclavicular lymph node	EGFR L858R	2	Osimeertinib+radiotherapy	NA
P-40	P-40-O1E	M	71	2	IVB	ADC	Pleural effusion	Negative	1	PCK	NA
P-41	P-41-O1E	F	59	1	IVA	ADC	Pleural effusion	EGFR 19 del;T790M	2	Osimeertinib	CK7(-);TTF1(-);NapsinA(+/-)
P-42	P-42-O1T	M	33	1	IVB	ADC	Supraclavicular lymph node	EGFR-RAD51 fusion	4	PCB	NA
P-43	P-43-O1E	F	49	1	IVA	ADC	Pleural effusion	EGFR 19 del;T790M	2	AZD9291 generic drug	CK7(+);TTF1(+);NapsinA(+)
P-44	P-44-O1E	F	52	1	IVA	ADC	Pleural effusion	EGFR 19 del;T790M	2	PCB	NA
P-45	P-45-O1E	M	69	1	IVB	ADC	Pleural effusion	EGFR L858R	3	Afatinib+Crizotinib	NA
P-46	P-46-O2T	M	68	1	IVA	ADC	Supraclavicular lymph node	KRAS p.G12C mutation	1	PCK	CK7(-);TTF1(-);NapsinA(+/-)
P-48	P-48-O1E	M	58	1	IVB	ADC	Pleural effusion	EGFR L858R	2	Erlotinib + Bevacizumab	CK7(+);TTF1(+);NapsinA(+)
P-49	P-49-O1E	M	70	3	IVB	ADC	Pleural effusion	Negative	3	Loratinib	NA
P-49	P-49-O2E	M	70	3	IVB	ADC	Pleural effusion	Negative	3	Loratinib	NA
P-49	P-49-O3E	M	70	3	IVB	ADC	Pleural effusion	Negative	3	Loratinib	CK7(+);TTF1(-);NapsinA(-)
P-50	P-50-O1E	M	69	1	IVA	SCLC	Pleural effusion	NA	1	EP	CD56(-);CgA(-);Syn(-);TTF1(-)
P-51	P-51-O1E	M	63	1	IVB	SCC	Pleural effusion	Negative	1	Nab-paclitaxel + carboplatin	CK5/6(-);P63(+);P40(+)
P-51	P-51-O2E	M	63	1	IVB	SCC	Pleural effusion	Negative	1	Nab-paclitaxel + carboplatin	CK5/6(-)
P-51	P-51-O3E	M	63	1	IVB	SCC	Pleural effusion	Negative	1	Nab-paclitaxel + carboplatin	P63+



P-51	P-51-O4E	M	63	2	IVB	SCC	Pleural effusion	Negative	2	Best Supportive Care	CK5/6(-);P63(+);P40(+)
P-51	P-51-O5E	M	63	2	IVB	SCC	Pleural effusion	Negative	2	Best Supportive Care	CK5/6(+);P63(+);P40(+)
P-53	P-53-O1E	M	51	1	IVA	ADC	Pleural effusion	Negative	1	Pembrolizumab	NapsinA(-);TTF1(-);CK7(-)
P-54	P-54-O1E	F	40	1	IVB	ASC	Pleural effusion	NA	2	SAF-189s	NA
P-54	P-54-O2E	F	40	1	IVB	ASC	Pleural effusion	NA	2	SAF-189s	NA
P-54	P-54-O3E	F	40	1	IVB	ASC	Pleural effusion	NA	2	SAF-189s	NA
P-54	P-54-O4E	F	40	1	IVB	ASC	Pleural effusion	NA	2	SAF-189s	NA
P-54	P-54-O5E	F	40	1	IVB	ASC	Pleural effusion	NA	2	SAF-189s	NA
P-54	P-54-O6E	F	41	1	IVB	ASC	Pleural effusion	NA	2	SAF-189s	NA
P-54	P-54-O7E	F	41	1	IVB	ASC	Pleural effusion	NA	2	NA	NA
P-54	P-54-O8E	F	41	1	IVB	ASC	Pleural effusion	NA	2	NA	NA
P-54	P-54-O9E	F	41	1	IVB	ASC	Pleural effusion	NA	2	NA	NA
P-55	P-55-O1T	F	30	1	IVB	ADC	Lymph node	EGFR 19 del	5	Osimertinib	NA
P-56	P-56-O1E	M	55	1	IVA	ADC	Pleural effusion	ERBB2 20ins	1	PCB	NapsinA(-);TTF1(-);CK7(-)
P-56	P-56-O2E	M	55	1	IVA	ADC	Pleural effusion	ERBB2 20ins	1	PCB	NA
P-57	P-57-O1T	F	67	1	IVB	ADC	Chest wall tumor	NA	3	PCB	NapsinA(+);TTF1(-);CK7(+)
P-58	P-58-O1E	F	40	1	IVB	ADC	Pleural effusion	EGFR 20 ins	2	JNJ-61186372	NapsinA(-);TTF1(+);CK7(+)
P-58	P-58-O2E	F	40	1	IVB	ADC	Pleural effusion	EGFR 20 ins	2	JNJ-61186372	NA
P-59	P-59-O1E	F	50	3	IVB	ADC	Ascitic effusion	EGFR L858R;T790M	4	Osimertinib	NA
P-59	P-59-O2E	F	50	3	IVB	ADC	Ascitic effusion	EGFR L858R;T790M	4	Osimertinib	NapsinA(+);TTF1(+);CK7(+)
P-59	P-59-O3E	F	50	3	IVB	ADC	Ascitic effusion	EGFR L858R;T790M	4	Osimertinib	NapsinA(+);TTF1(+);CK7(+)
P-59	P-59-O4E	F	50	3	IVB	ADC	Ascitic effusion	EGFR L858R;T790M	4	Osimertinib	NapsinA(+);TTF1(+);CK7(+)
P-59	P-59-O5E	F	50	3	IVB	ADC	Pleural effusion	EGFR L858R;T790M	4	Osimertinib	NapsinA(-);TTF1(+);CK7(+)
P-60	P-60-O1T	M	55	1	IVB	ADC	Lymph node	EGFR L858R;MET amplification	2	Osimertinib + Savolitinib	NapsinA(+);TTF1(+);CK7(+)
P-60	P-60-O2E	M	55	1	IVB	ADC	Pericardial effusion	EGFR L858R;MET amplification	2	Osimertinib + Savolitinib	NapsinA(+);TTF1(-);CK7(+)
P-60	P-60-O3E	M	55	1	IVB	ADC	Pericardial effusion	EGFR L858R;MET amplification	2	Osimertinib + Savolitinib	NapsinA(+);TTF1(+);CK7(+)
P-60	P-60-O4E	M	55	1	IVB	ADC	Pericardial effusion	EGFR L858R;MET amplification	2	Osimertinib + Savolitinib	NapsinA(+);TTF1(-);CK7(+)
P-60	P-60-O5E	M	56	2	IVB	ADC	Pericardial effusion	EGFR L858R;MET amplification	4	Osimertinib + Savolitinib	NapsinA(+);TTF1(+);CK7(+)
P-61	P-61-O1E	F	51	3	IVB	ADC	Ascitic effusion	EGFR 19 del;T790M,RET fusion	4	Osimertinib +Cabozantinib	NapsinA(+);TTF1(+);CK7(+)
P-61	P-61-O2E	F	51	3	IVB	ADC	Ascitic effusion	EGFR 19 del;T790M,RET fusion	4	Osimertinib +Cabozantinib	NapsinA(+);TTF1(+);CK7(+)
P-61	P-61-O3E	F	51	3	IVB	ADC	Ascitic effusion	EGFR 19 del;T790M,RET fusion	4	Osimertinib +Cabozantinib	NapsinA(+);TTF1(+);CK7(+)
P-61	P-61-O4E	F	51	3	IVB	ADC	Pleural effusion	EGFR 19 del;T790M,RET fusion	4	Osimertinib +Cabozantinib	NapsinA(+);TTF1(+);CK7(+)
P-61	P-61-O5E	F	51	3	IVB	ADC	Pleural effusion	EGFR 19 del;T790M,RET fusion	4	Osimertinib +Cabozantinib	NapsinA(+);TTF1(+);CK7(+)
P-63	P-63-O1E	F	38	1	IVB	ADC	Pleural effusion	EML4-ALK fusion, ALK F1174C mutation	3	Alectinib	NA
P-63	P-63-O2E	F	38	1	IVB	ADC	Pleural effusion	EML4-ALK fusion, ALK F1174C mutation	3	Alectinib	NapsinA(+);TTF1(+);CK7(+)
P-63	P-63-O3E	F	38	1	IVB	ADC	Pleural effusion	EML4-ALK fusion, ALK F1174C mutation	3	Alectinib	NapsinA(+);CK7(+)
P-65	P-65-O1E	M	66	1	IIIC	SCLC	Pleural effusion	NA	1	EP	NA
P-69	P-69-O1E	M	65	3	IVA	ADC	Pericardial effusion	NA	1	Best Supportive Care	NA
P-69	P-69-O2E	M	65	3	IVA	ADC	Pericardial effusion	NA	1	Best Supportive Care	NA
P-69	P-69-O3E	M	65	3	IVA	ADC	Pleural effusion	Negative	1	Best Supportive Care	NapsinA(+);TTF1(+);CK7(+)
P-69	P-69-O4E	M	65	3	IVA	ADC	Pleural effusion	Negative	1	Best Supportive Care	NapsinA(+);TTF1(+);CK7(+)
P-69	P-69-O5E	M	65	3	IVA	ADC	Pleural effusion	Negative	1	Best Supportive Care	NapsinA(+);TTF1(+);CK7(+)
P-70	P-70-O1E	M	54	3	IVB	ADC	Pleural effusion	EGFR L858R	2	Osimertinib	NapsinA(-/+);TTF1(+);CK7(+)
P-70	P-70-O2E	M	54	3	IVB	ADC	Pleural effusion	EGFR L858R	2	Osimertinib	CK7(-);NapsinA(-);TTF1(-)
P-73	P-73-O1T	M	70	2	IVB	SCLC	Lymph node	NA	1	Nab-paclitaxel	CD56(+);CgA(+);Syn(+);TTF1(+)
P-74	P-74-O1T	F	68	1	IVB	ADC	Lymph node	EML4-ALK fusion	1	SAF-189s	NA
P-75	P-75-O1E	M	58	1	IVB	ADC	Pleural effusion	ERBB2 20ins	1	Pyrotinib	NapsinA(+);TTF1(+);CK7(+)
P-75	P-75-O2E	M	58	1	IVB	ADC	Pleural effusion	ERBB2 20ins	1	Pyrotinib	NapsinA(+);TTF1(+);CK7(+)
P-75	P-75-O3E	M	58	1	IVB	ADC	Pleural effusion	ERBB2 20ins	1	Pyrotinib	NapsinA(-);TTF1(+);CK7(+)
P-76	P-76-O1E	M	70	3	IVB	ADC	Pleural effusion	Negative	1	Pemetrexed + pembrolizumab	NapsinA(-);TTF1(+);CK7(+)
P-76	P-76-O2E	M	70	3	IVB	ADC	Pleural effusion	Negative	1	Pemetrexed + pembrolizumab	NapsinA(-);TTF1(-);CK7(+)
P-76	P-76-O3E	M	70	3	IVB	ADC	Pleural effusion	Negative	1	Pemetrexed + pembrolizumab	NA
P-77	P-77-O1E	F	70	1	IVA	ADC	Pleural effusion	EGFR L858R;T790M	2	Osimertinib	NapsinA(+);TTF1(+);CK7(+)
P-77	P-77-O2E	F	70	1	IVA	ADC	Pleural effusion	EGFR L858R;T790M	2	Osimertinib	NapsinA(+);TTF1(+);CK7(+)
P-78	P-78-O1E	F	50	1	IVB	ADC	Pleural effusion	EGFR L858R	1	Osimertinib	NapsinA(+);TTF1(-);CK7(+)
P-78	P-78-O2E	F	50	1	IVB	ADC	Pleural effusion	EGFR L858R	1	Osimertinib	NA
P-79	P-79-O1E	F	64	1	IVB	ADC	Ascitic effusion	EGFR L858R;T790M ;cis-C797S mutation	3	PCB	NapsinA(+);TTF1(+);CK7(+)

P-79	P-79-O2E	F	64	1	IVB	ADC	Ascitic effusion	EGFR L858R;T790M ;cis-C797S mutation	3	PCB	NapsinA(+);TTF1(+);CK7(+)
P-79	P-79-O3E	F	64	1	IVB	ADC	Ascitic effusion	EGFR L858R;T790M ;cis-C797S mutation	3	PCB	NapsinA(+);TTF1(+);CK7(+)
P-81	P-81-O1E	F	62	2	IVB	ADC	Pleural effusion	EGFR 19del	3	Nab-paclitaxel	NapsinA(-);TTF1(+);CK7(+); CD56(-);CgA(-);Syn(+)
P-82	P-82-O1E	M	75	2	IVA	SCLC	Pleural effusion	NA	1	Nab-paclitaxel	CD56(-);CgA(-);Syn(+)
P-83	P-83-O1E	M	77	1	IVB	SCLC	Pleural effusion	NA	1	EC	CD56(-);CgA(+);Syn(+);TTF1(+)
P-84	P-84-O1E	M	54	1	IVB	SCLC	Pleural effusion	NA	1	NA	NA
P-85	P-85-O1E	F	32	1	IVB	ADC	Ascitic effusion	EGFR 19 del	4	TDM1	NapsinA(+);TTF1(+);CK7(+)
P-85	P-85-O2E	F	32	1	IVB	ADC	Ascitic effusion	EGFR 19 del	4	TDM1	NapsinA(+);TTF1(+);CK7(+)
P-85	P-85-O3E	F	32	1	IVB	ADC	Ascitic effusion	EGFR 19 del	4	Nab-paclitaxel +anlotinib	NapsinA(+);TTF1(+);CK7(+)
P-86	P-86-O1E	F	74	1	IVA	ADC	Pleural effusion	MET 14 skipping	1	Bozitinib	CK7(+)
P-87	P-87-O1E	F	51	1	IVA	ASC	Pleural effusion	EGFR L858R	1	Afatinib	CK5/6(-);P63(-);P40(-); NapsinA(-);TTF1(+);CK7(+)
P-87	P-87-O2E	F	51	1	IVA	ASC	Pleural effusion	EGFR L858R	1	Afatinib	CK5/6(-);P63(-);P40(-); NapsinA(-);TTF1(-);CK7(+)
P-87	P-87-O3E	F	51	1	IVA	ASC	Pleural effusion	EGFR L858R	1	Afatinib	CK5/6(-);P63(-);P40(-); NapsinA(-);TTF1(-);CK7(+)
P-88	P-88-O1E	F	82	1	IVA	ADC	Pleural effusion	NA	1	NA	NapsinA(+);TTF1(+);CK7(+)
P-89	P-89-O1E	M	28	1	IVB	ADC	Pleural effusion	EGFR 19 del	1	Osimertinib	NapsinA(+);TTF1(-);CK7(+)
P-89	P-89-O2E	M	28	1	IVB	ADC	Pleural effusion	EGFR 19 del	1	Osimertinib	NapsinA(+);TTF1(-);CK7(+)
P-90	P-90-O1E	F	58	4	IVB	SCC	Pleural effusion	EGFR 19 del	2	Osimertinib	NA
P-90	P-90-O2E	F	58	4	IVB	SCC	Pleural effusion	EGFR 19 del	2	Osimertinib	NA
P-93	P-93-O1E	M	55	1	IVA	ADC	Pleural effusion	EML4-ALK fusion	3	Nab-paclitaxel+Carboplatin + Be	NapsinA(+);TTF1(+);CK7(+)
P-94	P-94-O1E	M	58	1	IVB	ADC	Pleural effusion	NA	2	Afatinib+IP	NA
P-94	P-94-O2E	M	58	1	IVB	ADC	Pleural effusion	NA	2	Afatinib+IP	NapsinA(-);TTF1(-)
P-94	P-94-O3E	M	58	1	IVB	ADC	Pleural effusion	NA	2	Afatinib+IP	NapsinA(-);TTF1(-);CK7(+)
P-95	P-95-O1E	F	62	1	IVB	ADC	Pleural effusion	BRAF V600E	1	Darafenib + trametinib	NapsinA(+);TTF1(+);CK7(+)
P-95	P-95-O2E	F	62	1	IVB	ADC	Pleural effusion	BRAF V600E	1	Darafenib + trametinib	NA
P-95	P-95-O3E	F	62	1	IVB	ADC	Pleural effusion	BRAF V600E	1	Darafenib + trametinib	NapsinA(+);TTF1(+);CK7(+)
P-96	P-96-O1E	F	75	4	IVA	ADC	Pleural effusion	EGFR 19 del	3	NA	NapsinA(-);TTF1(-);CK7(-)
P-96	P-96-O2E	F	75	4	IVA	ADC	Pleural effusion	EGFR 19 del	3	NA	NapsinA(-);TTF1(-);CK7(-)
P-96	P-96-O3E	F	75	4	IVA	ADC	Pleural effusion	EGFR 19 del	3	NA	NapsinA(-);TTF1(-);CK7(-)
P-97	P-97-O1E	M	59	1	IVB	ADC	Pleural effusion	EGFR L858R;T790M	2	PLB1004	NapsinA(+);TTF1(+);CK7(+)
P-97	P-97-O2E	M	59	1	IVB	ADC	Pleural effusion	EGFR L858R;T790M	2	PLB1004	NapsinA(+);TTF1(+);CK7(+)
P-97	P-97-O3E	M	59	1	IVB	ADC	Pleural effusion	EGFR L858R;T790M	2	PLB1004	NapsinA(+);TTF1(+);CK7(+)
P-98	P-98-O1E	M	54	1	IVB	ADC	Pleural effusion	EGFR 19 del	1	Afatinib	NA
P-98	P-98-O2E	M	54	1	IVB	ADC	Pleural effusion	EGFR 19 del	1	Afatinib	NA
P-98	P-98-O3E	M	54	1	IVB	ADC	Pleural effusion	EGFR 19 del	1	Afatinib	NA
P-99	P-99-O1E	M	72	1	IVA	SCLC	Pleural effusion	NA	1	EC	NA
P-99	P-99-O2E	M	72	1	IVA	SCLC	Pleural effusion	NA	1	EC	NA
P-100	P-100-O1E	M	35	1	IVB	ADC	Pleural effusion	EGFR L858R;T790M ;cis-C797S mutation	3	TQB3804	NapsinA(+);TTF1(+);CK7(+)
P-100	P-100-O2E	M	35	1	IVB	ADC	Pleural effusion	EGFR L858R;T790M ;cis-C797S mutation	3	TQB3804	NA
P-100	P-100-O3E	M	35	1	IVB	ADC	Pleural effusion	EGFR L858R;T790M ;cis-C797S mutation	3	TQB3804	TTF1(-);CK7(-)
P-101	P-101-O1E	M	66	2	IVB	ADC	Pericardial effusion	EGFR 20 ins	1	NA	NapsinA(+);TTF1(+);CK7(+)
P-101	P-101-O2E	M	66	2	IVB	ADC	Pericardial effusion	EGFR 20 ins	1	NA	NapsinA(+);TTF1(+);CK7(+)
P-101	P-101-O3E	M	66	2	IVB	ADC	Pericardial effusion	EGFR 20 ins	1	NA	NapsinA(-);TTF1(-);CK7(+)
P-102	P-102-O1E	F	52	1	IVB	SCC	Pleural effusion	KIF5B-RET fusion	2	LOXO-292	NA
P-102	P-102-O2E	F	52	1	IVB	SCC	Pleural effusion	KIF5B-RET fusion	2	LOXO-292	NA
P-103	P-103-O1E	M	39	1	IVA	ADC	Pericardial effusion	EML4-ALK fusion	3	NA	NA
P-103	P-103-O2E	M	39	1	IVA	ADC	Pleural effusion	EML4-ALK fusion	3	NA	NA
P-103	P-103-O3E	M	39	1	IVA	ADC	Pleural effusion	EML4-ALK fusion	3	Nab-paclitaxel+Carboplatin + Be	NA
P-103	P-103-O4E	M	39	1	IVA	ADC	Pleural effusion	EML4-ALK fusion	3	Nab-paclitaxel+Carboplatin + Be	NA
P-105	P-105-O1T	M	59	1	IVB	SAR	Muscle mass	MET 14 skipping	1	Crizotinib	NA
P-106	P-106-O1T	M	60	1	IIIB	SCC	Lung tissue	NA	1	NA	CK5/6(++);P63(+);P40(+)
P-107	P-107-O1E	F	48	1	IVB	SCLC	Pleural effusion	NA	4	ABCP	CgA(+);Syn(+);CD56(+)

Abbreviations:IHC: immunohistochemistry; M: male; F: female; SCLC: small cell lung cancer; ADC: adenocarcinoma; SCC: squamous cell carcinoma; ASC: adenosquamous carcinoma; SAR: sarcomatoid carcinoma; NA: not available;

IC50: half-maximal inhibitory concentration; EP: Etoposide + Cisplatin; IP: Irinotecan + Carboplatin; PCB: Pemetrexed + Carboplatin + Bevacizumab; ABCP: Atezolizumab + + Bevacizumab + Carboplatin + Paclitaxel; PC:

Pemetrexed + Carboplatin; PCK: Pemetrexed + carboplatin + pembrolizumab; EC: Etoposide + Carboplatin; Driver mutation: EGFR, ALK, HER2, MET, RET, ROS1, BRAF, KRAS.

**Table S2. The list of lung cancer samples used for failed establishment of patient-derived organoids. Related to Figure 1A.**

Case	Organoid ID	Culture Results	Cell counts	Gender	Age	ECOG		Treatment lines	Pathology	Site of sampling	Driver mutation detected by routine genetic testing or FISH
						PS score	Stage				
P-3	P-3-F1T	Failure	2.32×10 <sup>3</sup>	M	50	1	IVB	4	SCLC	Paravertebral tumor	NA
P-4	P-4-F1T	Failure	N/A	M	65	1	IVB	3	ADC	Supraclavicular lymph node	EGFR 19del
P-5	P-5-F1T	Failure	N/A	M	61	3	IVB	5	ADC	Chest wall tumor	NA
P-6	P-6-F1T	Failure	N/A	F	57	0	IVB	7	SCLC	Abdominal neoplasm	EGFR 19del
P-8	P-8-F1E	Failure	N/A	F	80	1	IVB	3	ADC	Pleural effusion	NA
P-15	P-15-F1E	Failure	N/A	F	64	3	IVB	4	NO Tumor cells	Pleural effusion	NA
P-17	P-17-F1E	Failure	2.50×10 <sup>6</sup>	F	41	1	IVB	3	ADC	Pleural effusion	EGFR 19del
P-17	P-17-F2T	Failure	4.02×10 <sup>6</sup>	F	41	1	IVB	3	ADC	Brain metastases	EGFR 19del
P-19	P-19-F1T	Failure	N/A	F	68	2	IVB	2	ADC	Thoracic tumor	EGFR L858R
P-20	P-20-F1E	Failure	N/A	F	62	4	IVB	5	ADC	Pleural effusion	NA
P-21	P-21-F1T	Failure	N/A	M	65	1	IVB	3	ADC	Liver tissue	MET 14 skipping
P-22	P-22-F1T	Failure	N/A	M	38	2	IVB	2	SCLC	Scapular mass	EGFR L858R
P-25	P-25-F1E	Failure	N/A	F	32	1	IVB	4	NA	Cerebrospinal fluid	CD74-ROS1 fusion
P-26	P-26-F1T	Failure	N/A	M	39	2	IVB	4	ADC	Axillary lymph node	EGFR 19del
P-27	P-27-F1T	Failure	4.50×10 <sup>5</sup>	M	55	3	IVB	2	ADC	Chest wall tumor	EML4-ALK fusion
P-29	P-29-F1T	Failure	N/A	F	59	1	IVB	5	ADC	Liver tissue	NA
P-31	P-31-F1T	Failure	N/A	F	48	2	IVB	5	ADC	Liver tissue	EGFR L858R,T790M
P-35	P-35-F1T	Failure	2.20×10 <sup>5</sup>	M	57	2	IVB	4	ADC	Liver tissue	NA
P-36	P-36-F1E	Failure	N/A	M	72	1	IVB	9	ADC	Pleural effusion	EGFR 20 ins
P-39	P-39-F1T	Failure	3.20×10 <sup>5</sup>	M	44	1	IVB	1	ADC	Supraclavicular lymph node	EGFR 19del
P-40	P-40-F1E	Failure	2.43×10 <sup>2</sup>	M	71	1	IVB	1	NO Tumor cells	Pleural effusion	Negative
P-47	P-47-F1T	Failure	2.85×10 <sup>5</sup>	M	60	1	IVB	1	SCC	Supraclavicular lymph node	Negative
P-51	P-51-F1E	Failure	9.80×10 <sup>5</sup>	M	64	2	IVB	2	SCC	Pleural effusion	Negative
P-52	P-52-F1E	Failure	1.19×10 <sup>7</sup>	M	72	1	IVB	2	SCLC	Pleural effusion	NA
P-52	P-52-F2E	Failure	3.27×10 <sup>5</sup>	M	72	1	IVB	2	SCLC	Pleural effusion	NA
P-52	P-52-F3E	Failure	2.00×10 <sup>3</sup>	M	72	1	IVB	2	SCLC	Pleural effusion	NA
P-56	P-56-F1E	Failure	2.60×10 <sup>5</sup>	M	55	1	IVB	2	ADC	Pleural effusion	ERBB2 20ins
P-59	P-59-F1E	Failure	7.22×10 <sup>6</sup>	F	50	3	IVB	3	ADC	Abdominal cavity effusion	EGFR L858R,T790M
P-62	P-62-F1T	Failure	1.50×10 <sup>3</sup>	M	54	1	IVA	4	ADC	Lymph node	EGFR L858R
P-64	P-64-F1T	Failure	3.50×10 <sup>2</sup>	F	73	1	IVB	2	NO Tumor cells	Lymph node	NA
P-66	P-66-F1E	Failure	2.52×10 <sup>6</sup>	F	54	1	IVB	2	ADC	Pleural effusion	EGFR 19del ,T790M
P-67	P-67-F1E	Failure	6.04×10 <sup>3</sup>	M	74	1	IVA	1	NO Tumor cells	Pleural effusion	NA
P-67	P-67-F2E	Failure	1.56×10 <sup>6</sup>	M	74	1	IVA	1	NO Tumor cells	Pleural effusion	NA
P-67	P-67-F3E	Failure	1.51×10 <sup>6</sup>	M	74	1	IVA	1	NO Tumor cells	Pleural effusion	NA
P-68	P-67-F4T	Failure	0	M	51	1	IVA	2	ADC	Lymph node	EGFR 19del
P-71	P-71-F1T	Failure	1.44×10 <sup>6</sup>	F	55	1	IVA	1	ADC	Lymph node	RET fusion
P-72	P-72-F1T	Failure	2.65×10 <sup>3</sup>	M	65	1	IVA	1	SCC	Lymph node	Negative
P-78	P-78-F1E	Failure	1.74×10 <sup>7</sup>	F	50	1	IVB	1	ADC	Pleural effusion	EGFR L858R
P-80	P-80-F1T	Failure	1.50×10 <sup>2</sup>	F	46	1	IVB	1	ADC	Lymph node	EGFR L858R
P-81	P-81-F1E	Failure	3.27×10 <sup>6</sup>	F	62	2	IVB	3	SCLC	Pleural effusion	EGFR 19del

P-82	P-82-F1E	Failure	6.45×10 <sup>5</sup>	M	75	2	IVB	1	SCLC	Pleural effusion	NA
P-82	P-82-F2E	Failure	9.00×10 <sup>3</sup>	M	75	2	IVB	1	NO Tumor cells	Pleural effusion	NA
P-89	P-89-F1T	Failure	2.50×10 <sup>2</sup>	M	28	1	IVB	1	ADC	Supraclavicular lymph node	EGFR 19del
P-90	P-90-F1E	Failure	3.00×10 <sup>3</sup>	F	58	4	IVB	2	SCC	Pleural effusion	Negative
P-91	P-91-F1E	Failure	1.33×10 <sup>3</sup>	M	57	1	IIIB	2	NO Tumor cells	Pleural effusion	NA
P-91	P-91-F2E	Failure	3.10×10 <sup>3</sup>	M	57	1	IIIB	2	NO Tumor cells	Pleural effusion	NA
P-91	P-91-F3E	Failure	4.00×10 <sup>3</sup>	M	57	1	IIIB	2	NO Tumor cells	Pleural effusion	NA
P-92	P-92-F1E	Failure	3.40×10 <sup>3</sup>	F	56	1	IVB	1	ASC	Pleural effusion	NA
P-102	P-102-F1E	Failure	4.30×10 <sup>2</sup>	F	52	1	IVB	2	SCC	Pleural effusion	KIF5B-RET fusion
P-103	P-103-F1E	Failure	1.75×10 <sup>3</sup>	M	39	1	IVB	3	ADC	Pericardial effusion	EML4-ALK fusion
P-103	P-103-F2E	Failure	1.54×10 <sup>3</sup>	M	39	1	IVB	3	ADC	Pericardial effusion	EML4-ALK fusion
P-104	P-104-F1E	Failure	2.00×10 <sup>3</sup>	M	62	2	IVB	2	ADC	Cerebrospinal fluid	EGFR 19 del

Abbreviations: IHC: immunohistochemistry; M: male; F: female; SCLC: small cell lung cancer; ADC: adenocarcinoma; SCC: squamous cell carcinoma; NA: not available; N/A: The cell counter cannot count due to insufficient number of cells; Driver mutation: EGFR, ALK, HER2, MET, RET, ROS1, BRAF, KRAS.

**Table S3. Univariate model and multivariate model for organoid culture. Related to Figure 1A.**

Factors	Cases	Univariate model			Multivariate model		
		Odds Ratio	95% CI	P	Odds	95% CI	P
Gender							
Male	117	Reference					
Female	97	0.55	(0.25 - 1.17)	0.1213			
Age							
<65	155	Reference					
≥65	59	1.63	(0.69 - 3.87)	0.2662			
ECOG PS							
0-1	145	Reference					
≥2	69	0.96	(0.43 - 2.14)	0.9195			
Stage							
IIIB-IVA	49	Reference					
IVB	165	1.41	(0.55 - 3.64)	0.4805			
Pathology							
ADC	156	6			Reference		
Other	58	0.13	(0.05 - 0.32)	<0.0001	0.21	(0.10 - 0.43)	<0.0001
Lines of treatment							
1	69	Reference					
≥2	145	2.30	(0.92 - 5.72)	0.0736			
Sampling type							
Tissue	162	Reference			Reference		
Effusion	52	4.47	(2.01 - 9.91)	0.0002	4.50	(2.12 - 9.53)	<0.0001
Gene							
<i>EGFR</i>	76	Reference					
Other	52	0.68	(0.25 - 1.90)	0.4657			
Negative	23	0.53	(0.13 - 2.20)	0.3815			
NA	63	0.46	(0.17 - 1.24)	0.1247			

Abbreviations: ADC: adenocarcinoma; NA: not available; *EGFR*: epidermal growth factor receptor

**Table S4. The clinicopathological characteristics of genomic profiling cohort. Related to Figure 2A.**

<b>Characteristics</b>	<b>No. (%)</b>
<b>Age (median[range], years)</b>	55[32-75]
<b>Gender</b>	
Female	12 (48%)
Male	13 (52%)
<b>Histology</b>	
ADC	22 (88%)
SCC	2 (8%)
ASC	1 (4%)
<b>Stage</b>	
IVA	8 (32%)
IVB	17 (68%)
<b>Treatment line</b>	
1	8 (32%)
2	7 (28%)
3	7 (28%)
4	2 (8%)
6	1 (4%)
<b>Total</b>	<b>25</b>

Abbreviations: SCLC: small cell lung cancer; ADC: adenocarcinoma; SCC: squamous cell carcinoma.

**Table S5. List of genes for paired-samples. Related to Figure 2A.**

Case	Organoid	Gene	Description	Mutation Type	Match.status
P-25	P-25-O1E	ROS1	CD74-ROS1	gene fusion	Match
P-25	P-25-O1E	ROS1	p.G2032R	missense variant	Match
P-25	P-25-O1E	ROS1	ROS1-intergenic(VIP,FBXO5)	gene fusion	Match
P-48	P-48-O1E	DNAJB1	p.R249T	missense variant	LCO only
P-48	P-48-O1E	EGFR	p.L858R	missense variant	Match
P-48	P-48-O1E	MAP2K4	p.D296H	missense variant	LCO only
P-48	P-48-O1E	PIK3R1	c.1745+1G>A	splice donor variant	LCO only
P-51	P-51-O1E	DNMT3A	p.N776T	missense variant	Match
P-51	P-51-O1E	FLT1	p.F192L	missense variant	Match
P-51	P-51-O1E	IL7R	cn amp	cn amp	Match
P-51	P-51-O1E	KMT2D	p.T4602fs	frameshift variant	Match
P-51	P-51-O1E	LRP1B	p.R3072I	missense variant	Match
P-51	P-51-O1E	MYC	cn amp	cn amp	LCO only
P-51	P-51-O1E	NFE2L2	p.R34Q	missense variant	Match
P-51	P-51-O1E	PIK3CA	p.E542K	missense variant	Match
P-51	P-51-O1E	PIK3CA	p.E545Q	missense variant	Match
P-51	P-51-O1E	PTEN	p.C211=	splice region variant	Match
P-51	P-51-O1E	RICTOR	cn amp	cn amp	Match
P-51	P-51-O1E	SPTA1	p.E813K	missense variant	Match
P-51	P-51-O1E	TET2	c.3410-1G>C	splice acceptor variant	Match
P-51	P-51-O1E	TP53	p.Q331H	splice region variant	Match
P-51	P-51-O1E	WT1	cn amp	cn amp	LCO only
P-51	P-51-O1E	XRCC2	p.A16S	missense variant	Match
P-51	P-51-O1E	ZBTB2	p.R189G	missense variant	Match
P-56	P-56-O1E	ERBB2	p.G778 P780dup	disruptive inframe insertion	Match
P-56	P-56-O1E	PIK3CG	p.E556G	missense variant	effusion only
P-56	P-56-O1E	RB1	exon18-23cn del	large genomic rearrangemen	effusion only
P-56	P-56-O1E	TP53	c.673-2A>T	splice acceptor variant	Match
P-59	P-59-O1E	EGFR	p.L858R	missense variant	Match
P-59	P-59-O1E	EGFR	p.T790M	missense variant	Match
P-59	P-59-O1E	TP53	p.Y234D	missense variant	Match
P-59	P-59-O1E	U2AF1	p.S19L	missense variant	Match
P-60	P-60-O4E	EGFR	p.L858R	missense variant	Match
P-60	P-60-O4E	FANCA	p.M569 E570delinsIG	missense variant	effusion only
P-60	P-60-O4E	SLX4	c.5153+1G>A	splice donor variant	effusion only
P-60	P-60-O4E	TP53	p.S215R	missense variant	Match
P-61	P-61-O5E	EGFR	p.E746 A750del	conservative inframe deletio	Match
P-61	P-61-O5E	EGFR	p.T790M	missense variant	Match
P-61	P-61-O5E	KRAS	cn del	cn del	effusion only
P-61	P-61-O5E	RET	CCDC6-RET	gene fusion	Match
P-61	P-61-O5E	SMAD4	cn del	cn del	effusion only
P-61	P-61-O5E	SMAD4	p.D537H	missense variant	Match
P-61	P-61-O5E	TP53	p.R282W	missense variant	Match
P-77	P-77-O1E	ALK	p.Q897L	missense variant	LCO only
P-77	P-77-O1E	ALK	p.T901A	missense variant	LCO only
P-77	P-77-O1E	ARID1A	p.A226P	missense variant	LCO only
P-77	P-77-O1E	ARID1A	p.G1351S	missense variant	LCO only
P-77	P-77-O1E	ARID1A	p.S949P	missense variant	LCO only
P-77	P-77-O1E	CARD11	cn amp	cn amp	effusion only
P-77	P-77-O1E	CTNNB1	p.S37C	missense variant	effusion only
P-77	P-77-O1E	DNMT3A	c.2322+7_2322+12delinsACC GAG	splice_region_variant	LCO only
P-77	P-77-O1E	EGFR	cn amp	cn amp	effusion only
P-77	P-77-O1E	EGFR	p.L858R	missense variant	Match
P-77	P-77-O1E	EGFR	p.T790M	missense variant	Match
P-77	P-77-O1E	ERCC2	p.R26L	missense variant	LCO only
P-77	P-77-O1E	EWSR1	p.M330L	missense variant	LCO only
P-77	P-77-O1E	FLT4	p.G513E	missense variant	Match
P-77	P-77-O1E	GID4	p.A98 A99delinsTT	missense variant	LCO only

P-77	P-77-O1E	IKZF1	cn amp	cn amp	effusion only
P-77	P-77-O1E	KDR	p.C1045*	stop gained	Match
P-77	P-77-O1E	KMT2A	p.N3494D	missense variant	effusion only
P-77	P-77-O1E	KMT2D	c.13840-17_13840-4delinsACCCCACCCCC	splice_region_variant	LCO only
P-77	P-77-O1E	LRP1B	p.D1946V	missense variant	effusion only
P-77	P-77-O1E	MED12	p.P1946S	missense variant	LCO only
P-77	P-77-O1E	MED12	p.S63N	missense variant	LCO only
P-77	P-77-O1E	PPP2R1A	p.E393Q	missense variant	Match
P-77	P-77-O1E	PPP2R2A	exon2del	large genomic rearrangement	LCO only
P-77	P-77-O1E	PPP2R2A	exon4-5del	large genomic rearrangement	LCO only
P-77	P-77-O1E	RB1	c.1128-1G>A	splice acceptor variant	Match
P-77	P-77-O1E	RBM10	exon6del	large genomic rearrangement	LCO only
P-77	P-77-O1E	RUNX1	p.A63G	missense variant	LCO only
P-77	P-77-O1E	SOX17	p.L148M	missense variant	LCO only
P-77	P-77-O1E	TMPRSS2	p.N314G	missense variant	LCO only
P-77	P-77-O1E	TP53	p.E198*	stop gained	Match
P-77	P-77-O1E	VEGFA	p.H161R	missense variant	LCO only
P-77	P-77-O1E	ZNF703	p.S20delinsGGSSSG	conservative_inframe_insertion	LCO only
P-78	P-78-O1E	EGFR	p.L858R	missense variant	Match
P-78	P-78-O1E	NKX2-1	cn amp	cn amp	Match
P-78	P-78-O1E	TP53	p.S241Y	missense variant	Match
P-28	P-28-O1E	ARID1A	p.P1018L	missense variant	effusion only
P-28	P-28-O1E	MSH6	p.E1324K	missense variant	effusion only
P-28	P-28-O1E	ROS1	CD74-ROS1	gene fusion	Match
P-87	P-87-O2E	EGFR	p.L858R	missense variant	Match
P-87	P-87-O2E	IL7R	cn amp	cn amp	effusion only
P-87	P-87-O2E	KMT2D	p.A230T	missense variant	Match
P-87	P-87-O2E	PTEN	exon3-5del	large genomic rearrangement	effusion only
P-87	P-87-O2E	RB1	CD59-RB1	gene fusion	Match
P-87	P-87-O2E	RB1	RB1-CD59	gene fusion	Match
P-87	P-87-O2E	RICTOR	cn amp	cn amp	effusion only
P-87	P-87-O2E	RPA1	SMG6-RPA1	gene fusion	effusion only
P-87	P-87-O2E	SDHA	cn amp	cn amp	effusion only
P-87	P-87-O2E	TERT	cn amp	cn amp	effusion only
P-87	P-87-O2E	TET1	p.K585N	missense variant	Match
P-87	P-87-O2E	TP53	p.R110L	missense variant	effusion only
P-96	P-96-O2E	EGFR	cn amp	cn amp	effusion only
P-96	P-96-O2E	EGFR	p.E746 A750del	conservative inframe deletion	Match
P-96	P-96-O2E	PTEN	p.G129R	missense variant	Match
P-96	P-96-O2E	RB1	p.I723fs	frameshift variant	Match
P-96	P-96-O2E	TP53	p.L194P	missense variant	Match
P-97	P-97-O1E	ASXL1	cn amp	cn amp	effusion only
P-97	P-97-O1E	CREBBP	p.A619T	missense variant	Match
P-97	P-97-O1E	EGFR	p.L858R	missense variant	Match
P-97	P-97-O1E	EGFR	p.T790M	missense variant	Match
P-97	P-97-O1E	HIST1H3	p.K28R	missense variant	Match
P-97	P-97-O1E	KRAS	cn amp	cn amp	effusion only
P-97	P-97-O1E	SRC	cn amp	cn amp	effusion only
P-97	P-97-O1E	TP53	p.N239S	missense variant	Match
P-30	P-30-O2E	EGFR	p.E746 A750del	inframe deletion	Match
P-30	P-30-O2E	EGFR	p.T790M	missense variant	Match
P-30	P-30-O2E	FGFR3	p.R112W	missense variant	effusion only
P-30	P-30-O2E	GATA4	p.V48M	missense variant	Match
P-30	P-30-O2E	MTOR	p.R1749*	stop gained	Match
P-30	P-30-O2E	RB1	cn del	cn del	effusion only
P-30	P-30-O2E	RET	RABEP2-RET	gene fusion	Match
P-30	P-30-O2E	TERT	p.A68T	missense variant	effusion only
P-30	P-30-O2E	TP53	p.A276G	missense variant	Match
P-30	P-30-O3E	EGFR	p.E746 A750del	inframe deletion	Match



P-30	P-30-O3E	EGFR	p.T790M	missense variant	Match
P-30	P-30-O3E	GATA4	p.V48M	missense variant	Match
P-30	P-30-O3E	MTOR	p.R1749*	stop gained	Match
P-30	P-30-O3E	NTRK1	FAM118A-NTRK1	gene fusion	Match
P-30	P-30-O3E	RET	RABEP2-RET	gene fusion	Match
P-30	P-30-O3E	TP53	p.A276G	missense variant	Match
P-36	P-36-O1E	EGFR	p.D770 N771insG	inframe insertion	Match
P-36	P-36-O1E	TP53	p.Y220D	missense variant	Match
P-41	P-41-O1E	ATRX	p.S1174C	missense variant	effusion only
P-41	P-41-O1E	BCL6	p.R668C	missense variant	effusion only
P-41	P-41-O1E	EGFR	cn amp	cn amp	Match
P-41	P-41-O1E	EGFR	p.E746 A750del	disruptive inframe deletion	Match
P-41	P-41-O1E	EGFR	p.T790M	missense variant	Match
P-41	P-41-O1E	FOXA1	cn amp	cn amp	effusion only
P-41	P-41-O1E	NFKBIA	cn amp	cn amp	effusion only
P-41	P-41-O1E	NKX2-1	cn amp	cn amp	effusion only
P-41	P-41-O1E	RICTOR	p.V165M	missense variant	effusion only
P-41	P-41-O1E	TP53	p.V157F	missense variant	Match
P-43	P-43-O1E	BRCA1	p.L1800fs	frameshift variant	Match
P-43	P-43-O1E	EGFR	p.E746 A750del	disruptive inframe deletion	Match
P-43	P-43-O1E	EGFR	p.T790M	missense variant	Match
P-43	P-43-O1E	FANCM	p.S14L	missense variant	Match
P-43	P-43-O1E	FOXA1	cn amp	cn amp	LCO only
P-43	P-43-O1E	NFKBIA	cn amp	cn amp	LCO only
P-43	P-43-O1E	NKX2-1	cn amp	cn amp	LCO only
P-43	P-43-O1E	PPM1D	PPM1D-SPECC1	gene fusion	effusion only
P-43	P-43-O1E	RB1	exon18-23del	large genomic rearrangemen	LCO only
P-43	P-43-O1E	TP53	p.R175H	missense variant	Match
P-44	P-44-O1E	CDK4	cn amp	cn amp	Match
P-44	P-44-O1E	CDK6	p.G157E	missense variant	Match
P-44	P-44-O1E	EGFR	cn amp	cn amp	Match
P-44	P-44-O1E	EGFR	p.E746 A750del	disruptive inframe deletion	Match
P-44	P-44-O1E	EGFR	p.T790M	missense variant	Match
P-44	P-44-O1E	MDM2	cn amp	cn amp	Match
P-44	P-44-O1E	RBM10	p.E112*	stop gained	Match
P-44	P-44-O1E	SPTA1	p.W173C	missense variant	effusion only
P-45	P-45-O1E	CCNE1	cn amp	cn amp	LCO only
P-45	P-45-O1E	CD274	cn amp	cn amp	LCO only
P-45	P-45-O1E	PDCD1L	cn amp	cn amp	LCO only
P-45	P-45-O1E	TERT	cn amp	cn amp	LCO only
P-45	P-45-O1E	TP53	p.V218E	missense variant	effusion only
P-45	P-45-O1E	TP53	TP53-IGR (downstream	large genomic rearrangemen	effusion only
P-45	P-45-O1E	TSC1	p.L72V	missense variant	LCO only
P-45	P-45-O1E	WRN	p.S1256*	stop gained	Match
P-45	P-45-O1E	NF1	p.D801H	missense variant	Match
P-45	P-45-O1E	FBXW7	p.S180C	missense variant	effusion only
P-45	P-45-O1E	EGFR	p.L858R	missense variant	Match
P-45	P-45-O1E	MYCN	p.K304E	missense variant	Match
P-45	P-45-O1E	EWSR1	p.D412N	missense variant	Match
P-45	P-45-O1E	FANCG	cn amp	cn amp	LCO only
P-45	P-45-O1E	INPP4B	cn amp	cn amp	LCO only
P-45	P-45-O1E	LYN	cn amp	cn amp	LCO only
P-45	P-45-O1E	MET	cn amp	cn amp	LCO only
P-45	P-45-O1E	NBN	cn amp	cn amp	LCO only
P-45	P-45-O1E	PAX5	cn amp	cn amp	LCO only
P-45	P-45-O1E	POLE	p.F699fs	frameshift variant	LCO only

**Table S6. Clinical characteristics and drug susceptibility results in four groups. Related to Figure 3 and S3.**

Case	Organoid ID	Gender	Age	ECOG PS score	Stage	Pathology	Site of sampling	Driver mutation detected by routine genetic testing or FISH	Treatment Lines	LCO-DST regimen used as next-line treatment in the patient	IC <sub>50</sub> (μM)	Clinical Response	Consistency	Other LCO-DST regimen NOT used in the patient (regimen, IC <sub>50</sub> )
<b>Osimertinib group</b>														
P-17	P-17-O2E	F	41	1	IVB	ADC	Pleural effusion	EGFR 19 del	2	Osimertinib	1.77	PD	NO	PC, 22.95
P-18	P-18-O1T	M	80	3	IVB	ADC	Supraclavicular lymph node	EGFR L858R;T790M	2	Osimertinib	7.73	PD	YES	Larotrectinib, 1479 Alectinib, 10.18; Cabozantinib, 15.09;
P-30	P-30-O2E	M	50	2	IVB	ADC	Ascitic effusion	EGFR 19 del;T790M; RET fusion	4	Osimertinib	3.46	PD	YES	Osimertinib + Cabozantinib, 0.75; Alectinib, 13.62; Cabozantinib, 48.85;
P-30	P-30-O3E	M	50	2	IVB	ADC	Pleural effusion	EGFR 19 del; T790M; FAM118A-NTRK1 fusion; RET fusion	4	Osimertinib	5.59	PD	YES	Osimertinib + Cabozantinib, 2.19; Osimertinib + CBL0137, 0.20;
P-32	P-32-O1T	F	69	1	IIIB	ADC	Lymph node	EGFR L858R;T790M	1	Osimertinib	0.12	PR	YES	Osimertinib + Cetuximab, 0.51; Osimertinib + PC. 1.21 Afatinib, 0.01;
P-34	P-34-O1E	M	41	2	IVB	ADC	Pleural effusion	EGFR L858R	1	Osimertinib	1.9	PR	YES	Osimertinib + CBL0137, 0.62; Osimertinib + Cetuximab. 2.52 Afatinib, 0.33;
P-41	P-41-O1E	F	59	1	IVA	ADC	Pleural effusion	EGFR 19 del;T790M	2	Osimertinib	0.1	PR	YES	Dacomitinib, 0.61; PLB1004, 1.41; PC 23.20
P-59	P-59-O1E	F	50	3	IVB	ADC	Ascitic effusion	EGFR L858R;T790M	4	Osimertinib	4.37	PD	YES	Gefitinib, 6.59
P-59	P-59-O5E	F	50	3	IVB	ADC	Pleural effusion	EGFR L858R;T790M	4	Osimertinib	15.5	PD	YES	Gefitinib, 16.69; Osimertinib + GDC-0941, 3.42
P-70	P-70-O1E	M	54	3	IVB	ADC	Pleural effusion	EGFR L858R	2	Osimertinib	2.68	PD	YES	Afatinib, 7.98
P-77	P-77-O2E	F	70	1	IVA	ADC	Pleural effusion	EGFR L858R;T790M	2	Osimertinib	2.14	PR	YES	Afatinib, 2.36
P-78	P-78-O2E	F	50	1	IVB	ADC	Pleural effusion	EGFR L858R	1	Osimertinib	1.23	PR	YES	NA
P-89	P-89-O2E	M	28	1	IVB	ADC	Pleural effusion	EGFR 19 del	1	Osimertinib	0.33	PR	YES	NA
P-90	P-90-O1E	F	58	4	IVB	SCC	Pleural effusion	EGFR 19 del	2	Osimertinib	1.96	PD	NO	Afatinib, 0.30
P-90	P-90-O2E	F	58	4	IVB	SCC	Pleural effusion	EGFR 19 del	2	Osimertinib	2.43	PD	YES	Afatinib, 0.04
<b>Other targeted group</b>														
P-27	P-27-O1E	M	55	3	IVB	ADC	Pericardial effusion	EML4-ALK fusion	3	Crizotinib	1.47	PD	YES	Lorlatinib, 12.38; Alectinib, 17.65; Crizotinib + Alectinib, 1.25; Crizotinib + Lorlatinib 1.59 Crizotinib, 4.30;
P-33	P-33-O1E	F	54	1	IVA	ADC	Pleural effusion	EML4-ALK fusion, ALK-C17orf75 fusion	1	Alectinib	0.59	PR	YES	Lorlatinib, 26.88; Alectinib + CBL0137. 0.59 Crizotinib, 1.32;
P-33	P-33-O2T	F	54	1	IVA	ADC	Supraclavicular lymph node	EML4-ALK fusion	1	Alectinib	0.31	PR	YES	Lorlatinib, 7.12; Alectinib + CBL0137. 0.31 Osimertinib + Gefitinib, 2.65;
P-38	P-38-O1T	M	52	1	IVB	ADC	Supraclavicular lymph node	EGFR L858R	2	Osimertinib + Radiotherapy	1.04	PD	YES	Osimertinib + PC, 5.91; EP, 10.76; PC 11.74
P-43	P-43-O1E	F	49	1	IVA	ADC	Pleural effusion	EGFR 19 del;T790M	2	AZD9291 generic drug	1.22	PD	YES	Docetaxel, 6.265E+150
P-49	P-49-O1E	M	70	3	IVB	ADC	Pleural effusion	Negative	3	Lorlatinib	13.01	PD	YES	NA
P-63	P-63-O3E	F	38	1	IVB	ADC	Pleural effusion	EML4-ALK fusion, ALK F1174C mutation	3	Alectinib	5.12	PD	YES	SAF-189s, 2.08; Lorlatinib, 16.54
P-75	P-75-O1E	M	58	1	IVB	ADC	Pleural effusion	ERBB2 20ins	1	Pyrotinib	0.05	PR	YES	PC, NA
P-75	P-75-O2E	M	58	1	IVB	ADC	Pleural effusion	ERBB2 20ins	1	Pyrotinib	0.49	PR	YES	PC, 18.88

P-86	P-86-O1E	F	74	1	IVA	ADC	Pleural effusion	MET 14 skipping	1	Bozitinib	810.6	SD	YES	Crizotinib, 6.28; Savolitinib, 2.886E+53
P-97	P-97-O1E	M	59	1	IVB	ADC	Pleural effusion	EGFR L858R;T790M	2	PLB1004	2.48	PR	NO	Osimertinib, NA; Gefitinib, NA
P-97	P-97-O2E	M	59	1	IVB	ADC	Pleural effusion	EGFR L858R;T790M	2	PLB1004	> 1000	PR	NO	Large panel DST <sup>§</sup>
P-97	P-97-O3E	M	59	1	IVB	ADC	Pleural effusion	EGFR L858R;T790M	2	PLB1004	34.29	PR	NO	Large panel DST <sup>§</sup>
P-100	P-100-O1E	M	35	1	IVB	ADC	Pleural effusion	EGFR L858R;T790M	3	TQB3804	0.52	PD	NO	Large panel DST <sup>§</sup>
P-100	P-100-O2E	M	35	1	IVB	ADC	Pleural effusion	;cis-C797S mutation EGFR L858R;T790M	3	TQB3804	3.79	PD	YES	Large panel DST <sup>§</sup>
P-102	P-102-O1E	F	52	1	IVB	SCC	Pleural effusion	KIF5B-RET fusion	2	LOXO-292	5.7	PR	NO	Nab-paclitaxel + carboplatin, 15.30
P-105	P-105-O1T	M	59	1	IVB	SAR	Muscle mass	MET 14 skipping	1	Crizotinib	4.95	PD	YES	Savolitinib, 52.83
<b>Dual targeted therapy group</b>														
P-60	P-60-O1T	M	55	1	IVB	ADC	Lymph node	EGFR L858R;MET amplification	2	Osimertinib + Savolitinib	1.32	PR	YES	Osimertinib, 1.82
P-60	P-60-O2E	M	55	1	IVB	ADC	Pericardial effusion	EGFR L858R;MET amplification	2	Osimertinib + Savolitinib	0.71	PR	YES	Osimertinib, 1.15
P-60	P-60-O3E	M	55	1	IVB	ADC	Pericardial effusion	EGFR L858R;MET amplification	2	Osimertinib + Savolitinib	0.25	PR	YES	Osimertinib, 0.25; Savolitinib, 11.59
P-60	P-60-O4E	M	55	1	IVB	ADC	Pericardial effusion	EGFR L858R;MET amplification	2	Osimertinib + Savolitinib	0.24	PR	YES	Osimertinib, 1.30; Savolitinib, 17.61
P-61	P-61-O1E	F	51	3	IVB	ADC	Ascitic effusion	EGFR 19 del;T790M,RET fusion	4	Osimertinib + Cabozantinib	0.15	PR	YES	Osimertinib, 3.68; BLU667, 0.76;
P-61	P-61-O2E	F	51	3	IVB	ADC	Ascitic effusion	EGFR 19 del;T790M,RET fusion	4	Osimertinib + Cabozantinib	0.22	PR	YES	Osimertinib + BLU667, 0.03; PC 19.41 Osimertinib, 3.37;
P-61	P-61-O3E	F	51	3	IVB	ADC	Ascitic effusion	EGFR 19 del;T790M,RET fusion	4	Osimertinib + Cabozantinib	0.16	PR	YES	BLU667, 2.09; Osimertinib + BLU667, 0.02; PC 27.10 Osimertinib, 5.16;
P-61	P-61-O4E	F	51	3	IVB	ADC	Pleural effusion	EGFR 19 del;T790M,RET fusion	4	Osimertinib + Cabozantinib	0.33	PR	YES	BLU667, 0.22; Osimertinib + BLU667, 0.01; PC 21.65 Osimertinib, 11.31;
P-61	P-61-O5E	F	51	3	IVB	ADC	Pleural effusion	EGFR 19 del;T790M,RET fusion	4	Osimertinib + Cabozantinib	0.44	PR	YES	BLU667, 0.23; Osimertinib + BLU667, 0.03; PC 0.65 Osimertinib, 3.65;
P-95	P-95-O2E	F	62	1	IVB	ADC	Pleural effusion	BRAF V600E	1	Darafenib + Trametinib	> 1000	SD	YES	BLU667, 0.51; Osimertinib + BLU667, 0.24; PC 17.12 Darafenib, NA
<b>Chemotherapy group</b>														
P-3	P-3-O1E	M	50	1	IVB	ADC	Pericardial effusion	EGFR 19 del	3	EP	6.635	PR	YES	Osimertinib, 0.013; Osimertinib + EP, 0.009; Osimertinib + PC, 0.012;
P-25	P-25-O1E	F	32	1	IVB	ADC	Pleural effusion	CD74-ROS1 fusion, ROS1-intergenic fusion	3	PC	89.72	SD	YES	Afatimib + EP 0.002 Ceritinib, 3.37; Lorlatinib, 18.31
P-50	P-50-O1E	M	69	1	IVA	SCLC	Pleural effusion	NA	1	EP	37.7	PD	YES	NA
P-51	P-51-O1E	M	63	1	IVB	SCC	Pleural effusion	Negative	1	Nab-paclitaxel + Carboplatin	10.91	PD	YES	GDC-0941, 2.17; Everolimus, 16.46
P-51	P-51-O2E	M	63	1	IVB	SCC	Pleural effusion	Negative	1	Nab-paclitaxel + Carboplatin	14.29	PD	NO	GDC-0941, 1.90; Everolimus, 14.29
P-51	P-51-O3E	M	63	1	IVB	SCC	Pleural effusion	Negative	1	Nab-paclitaxel + Carboplatin	2.05E+18	PD	NO	GDC-0941, 2.38; Everolimus, 32.54

P-65	P-65-O1E	M	66	1	IIIC	SCLC	Pleural effusion	NA	1	EP	20.9	PR	YES	NA
P-73	P-73-O1T	M	70	2	IVB	SCLC	Lymph node	NA	1	Nab-paclitaxel	5.03E+11	PD	YES	EP, 33.52
P-81	P-81-O1E	F	62	2	IVB	ADC	Pleural effusion	EGFR 19 del	3	Nab-paclitaxel	5.10E+15	PD	YES	Osimertinib, 1.46; Osimertinib + EP, 2.24
P-83	P-83-O1E	M	77	1	IVB	SCLC	Pleural effusion	NA	1	EC	95.89	SD	YES	NA Osimertinib, 19.34;
P-85	P-85-O1E	F	32	1	IVB	ADC	Ascitic effusion	EGFR 19 del	4	TDM1	6.88E+37	PD	YES	Osimertinib + Pyrotinib, 7.74; PC, 36.98
P-85	P-85-O2E	F	32	1	IVB	ADC	Ascitic effusion	EGFR 19 del	4	TDM1	8.28E+33	PD	YES	Osimertinib, 2.72; Osimertinib + Pyrotinib, 2.04; PC, 53.91

Abbreviations: LCO-DS1: Lung cancer organoid based drug sensitivity test; M: male; F: female; SCLC: small cell lung cancer; ADC: adenocarcinoma; SCC: squamous cell carcinoma; SAR: sarcomatoid carcinoma; NA: not available; IC50: half-maximal inhibitory concentration; Driver mutation: EGFR, ALK, HER2, MET, RET, ROS1, BRAF, KRAS; PC: Pemetrexed + Carboplatin; EP: Etoposide + Cisplatin; EC: Etoposide + Carboplatin.