Supplemental table 1 The numbers and timing of MPE samples

MPEs sampling timing	Patients number	MPEs sample number
Pre-chemotherapy	306	381
Post-chemotherapy	206	332
Pre-EGFR TKI	317	390
Post-EGFR TKI	206	323

Supplemental Table 2 Clinical characteristics of stage IV lung adenocarcinoma patients with wild-type *EGFR*

	All patients	EGFR TKI use	No EGFR TKI	*P*
Total	152	109	43	
Age, median, years	65.4	65.6	65.2	0.993
(range)	(27.9–91.1)	(27.9–89.3)	(29.5–91.1)	
Sex				0.058
Female	68	54 (49.5%)	14 (32.6%)	
Male	84	55 (50.5%)	29 (67.4%)	
Smoking status				0.008
Never-smokers	96	76 (69.7%)	20 (46.5%)	
Smokers	56	33 (30.3%)	23 (53.5%)	
ECOG PS				0.816
0-1	122	88 (80.7%)	34 (79.1%)	
2-4	30	21 (19.3%)	9 (20.9%)	
Stage IV				0.291
M1a	64	43 (39.4%)	21 (48.8%)	
M1b	88	66 (60.6%)	22 (51.2%)	
MPE				0.616
At initial diagnosis	116	27 (24.8%)	9 (20.9%)	
Following disease progression	36	82 (75.2%)	34 (79.1%)	
Distant metastasis				
Lung	76	55 (50.5%)	21 (48.8%)	0.857
Pleural seeding	48	33 (30.3%)	15 (34.9%)	0.582
Pericardial effusion	24	5 (4.6%)	2 (4.7%)	1.000*
Bone	55	41 (37.6%)	14 (32.6%)	0.559
Brain	24	13 (11.9%)	11 (25.6%)	0.038
Liver	27	20 (18.3%)	7 (16.3%)	0.764
Adrenal gland	16	7 (6.4%)	9 (20.9%)	0.009
Other	13	10 (9.2%)	3 (7.0%)	0.663

MPE, malignant pleural effusion; ECOG PS, Eastern Cooperative Oncology Group performance status.
* by Fisher's Exact test

Supplemental Table 3—Cytotoxic therapies between serial MPE sampling

EGFR mutations			Wild type		
No. of Chemotherapy	Chemotherapy	Number of Patients	No. of Chemotherapy	Chemotherapy	Number of Patients
1	Gemcitabine	6	1	Gemcitabine	2
1	Gemcitabine+Cisplatin	5	1	Gemcitabine+Cisplatin	4
1	Gemcitabine+Ciasplatin+Bevacizumab	1	1	Gemcitabine+Ciasplatin+Bevacizumab	1
1	Gemcitabine+Carboplatin+Bevacizumab	1	1	Pemetrexed	5
1	Pemetrexed	4	1	Docetaxol	3
1	Pemetrexed+Cisplatin	1	1	Docetaxol+Cisplatin	1
1	Docetaxol	1	1	Vinorelbine	5
1	Docetaxol+Cisplatin	4	1	Cetuximab	1
1	Vinorelbine	2	2	Pemetrexed→Vinorelbine	2
1	Irinotecan	2	2	Pemetrexed→Paclitaxol	1
1	Epirubicin	1	2	Gemcitabine+Cisplatin→Taxotere+Bevacizumab	1
2	Pemetrexed→Gemcitabine	1	2	Paclitaxol→Pemetrexed	1
2	Pemetrexed→Vinorelbine+Carboplatin+Erbitux	1	2	Taxotere+Pemetrexed	1
2	Gemcitabine+Cisplatin→Pemetrexed	2	2	Taxotere→Epirubicin	1
2	Gemcitabine+Cisplatin→Docetaxol	2	3	Pemetrexed→ Gemcitabine→Irinotecan+Bevacizumab	1
2	Gemcitabine→ Paclitaxol	1	3	Gemcitaboine+cisplatin→Taxotere+Cisplatin	1
2	Gemcitabine→Docetaxol	1	3	Taxotere+Cisplatin→Gemcitabine+Cisplatin→Pemetrexed	1
2	Vinorelbine→Pemetrexed+Bevacizumab	1	3	Taxotere→Pemetrexed→Vinorelbine	1
2	Paclitaxol→Pemetrexed+Bevacizumab	1	4	Gemcitabine+Cisplatin→Docetaxol→Pemetrexed→Vinorelbine	1
2	Docetaxol+Carboplatin→Pemetrexed	1	4	Taxotere→Vinorelbine→Paclitaxol→Taxotere	1
2	Docetaxol→Pemetrexed	1			
3	Pemetrexed→Docetaxol→Bevacizumab+Etoposie	1			
3	Gemcitabine+Cisplatin→Docetaxol→Pemetrexed	1			
3	Gemcitabine→Vinorelbine→Pemetrexed	1			

3	Docetaxol+Cisplatin+Bevacizumab→Pemetrexed+Erbitax→Gemcitabine	1			
4	Gemcitabine+Cisplatin→Docetaxol→Pemetrexed→Vinorelbine	1			
4	Paclitaxol+Carboplatin→Gemcitabine+Cisplatin→Vinorelbine→Pemetrexed	1			

Supplemental table 4 Clinical characteristics of the patients with or without secondary T790M development after acquired resistance to EGFR TKIs

| | Patient No. | Secondary T790M | | p |
		Presence	Absence	
Total No.	99	48	51	
Age, mean years (range)	66.1 (29.5–91.6)	67.5 (29.5–91.6)	63.6 (34.6–89.6)	0.354[§]
Sex				0.825
Female	67	33	34	
Male	32	15	17	
Smoking				0.259
Nonsmokers	80	41	39	
Smokers	19	7	12	
ECOG PS				0.879
0–1	79	38	41	
2–4	205	10	10	
Stage IV				0.970
M1a	39	19	20	
M1b	60	29	31	
MPE				0.216
At initial diagnosis	75	39	36	
Following disease progression	24	9	15	
EGFR TKI				0.118
Gefitinib	78	41	37	
Erlotinib	21	7	14	
Prior chemotherapy				0.515
Yes	32	14	18	
No	67	34	33	

MPE, malignant pleural effusion; ECOG PS, Eastern Cooperative Oncology Group

performance status.

Supplemental Figure 1 The distribution of the 1400 pleural effusions.