

Appendix 1 Questionnaire

1. Liquid biopsy number
2. Liquid biopsy date
3. Liquid biopsy result
 - a. EGFR T790M positive
 - b. EGFR activating mutation positive, T790M negative
 - c. Negative
4. Motivation for liquid biopsy
 - a. At clinical and radiological progression
 - b. At radiological progression
 - c. Arbitrarily
5. In case of progression, specify progression type
 - a. Only radiological progression and not meeting RECIST criteria
 - b. Only radiological progression and meeting RECIST criteria
 - c. Both clinical and radiological progression
6. Specify progression sites
 - a. central nervous system
 - b. intrathoracic
 - c. liver
 - d. adrenal gland
 - e. metastatic lymph nodes
 - f. bone
7. Systemic therapy after liquid biopsy
 - a. TKI
 - b. Chemotherapy
 - c. Immunotherapy
 - d. Supportive care
8. Has a tissue rebiopsy been performed after liquid biopsy?
 - a. Yes
 - b. No
9. Tissue biopsy site (specify)
10. Type of procedure
 - a. CT or ultrasound-guided
 - b. Bronchoscopy
 - c. Thoracoscopy.
11. Tissue biopsy result
 - a. EGFR T790M positive
 - b. EGFR activating mutation positive, T790M negative
 - c. Negative
12. If tissue biopsy was not carried out, specify the reason
 - a. positive liquid biopsy
 - b. tissue biopsy not feasible
 - c. patient's decision
 - d. only radiological progression
 - e. clinical deterioration

Table S1 Systemic therapy following liquid biopsy

Number of repeated liquid biopsy	First	Second	Third	Fourth	Fifth	Sixth ^a	Seventh ^a	Total	P value (trend test)
Treatment									<0.001
Chemotherapy	9 (8.2%)	19 (17.3%)	30 (50.8%)	14 (46.7%)	4 (36.4%)	1 (25.0%)	1 (50.0%)	78 (23.9%)	
Immunotherapy	1 (0.9%)	1 (0.9%)	1 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.9%)	
Supportive therapy	0 (0.0%)	3 (2.7%)	3 (5.1%)	2 (6.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (2.5%)	
TKI	100 (90.9%)	87 (79.1%)	25 (42.4%)	14 (46.7%)	7 (63.6%)	3 (75.0%)	1 (50.0%)	237 (72.7%)	
Total	110	110	59	30	11	4	2	326	

^a, sixth and seventh liquid biopsies were excluded from the trend evaluation because of limited numerosity. TKI, tyrosine kinase inhibitor.

Table S2 Features associated with *EGFR* T790M mutation or other *EGFR* mutations

		<i>EGFR</i> T790M mutation	Other <i>EGFR</i> mutations ^a	Negative	Total
Reason for liquid biopsy request	At clinical and radiological progression	9 (24.3%)	32 (30.5%)	24 (13.3%)	65 (20.1%)
	At radiological progression	23 (62.2%)	58 (55.2%)	116 (64.1%)	197 (61.0%)
	Arbitrarily	5 (13.5%)	15 (14.3%)	41 (22.7%)	61 (18.9%)
	Missing	1	2	0	3
Type of disease progression	Radiological progression according to RECIST criteria	16 (50.0%)	29 (32.2%)	30 (21.4%)	75 (28.6%)
	Clinical and radiological progression	8 (25.0%)	30 (33.3%)	24 (17.1%)	62 (23.7%)
	Radiological progression (non-RECIST)	8 (25.0%)	31 (34.4%)	86 (61.4%)	125 (47.7%)
	Missing	1	2	0	2
Progression site	Intracranic and extracranic	3 (9.4%)	6 (6.7%)	15 (10.7%)	24 (9.2%)
	Extracranic only	25 (78.1%)	79 (87.8%)	114 (81.4%)	218 (83.2%)
	Intracranic only	4 (12.5%)	5 (5.6%)	11 (7.9%)	20 (7.6%)
	Missing	1	2	0	3
Site of extracranic progression	Intrathoracic	24 (85.7%)	69 (81.2%)	111 (86.0%)	204 (84.3%)
	Liver	9 (32.1%)	16 (18.8%)	6 (4.7%)	31 (12.8%)
	Adrenal	1 (3.6%)	2 (2.4%)	4 (3.1%)	7 (2.9%)
	Lymph node	6 (21.4%)	8 (9.5%)	5 (3.9%)	19 (7.9%)
	Bone	5 (17.9%)	15 (17.9%)	8 (6.2%)	28 (11.6%)
Treatment	Chemotherapy	7 (18.9%)	40 (38.1%)	30 (16.6%)	77 (23.8%)
	Immunotherapy	0 (0.0%)	1 (1.0%)	2 (1.1%)	3 (0.9%)
	Supportive therapy	0 (0.0%)	2 (1.9%)	6 (3.3%)	8 (2.5%)
	TKI	30 (81.1%)	62 (59.0%)	143 (79.0%)	235 (72.8%)
	Missing	1	2	0	3
Tissue biopsy	No	38 (100.0%)	87 (81.3%)	153 (84.5%)	278 (85.3%)
	Yes	0 (0.0%)	20 (18.7%)	28 (15.5%)	48 (14.7%)
<i>EGFR</i> mutation analysis at tissue biopsy	Negative/not informative	–	12 (60.0%)	11 (39.3%)	23 (47.9%)
	T790M+	–	1 (5.0%)	8 (28.6%)	9 (18.8%)
	Other ^a	–	7 (35.0%)	9 (32.1%)	16 (33.3%)
Total		38	107	181	326

^a, other *EGFR* mutation: *EGFR* T790M mutation negative, activating mutation positive. *EGFR*, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; RECIST, Response Evaluation Criteria in Solid Tumors.