

Table S1 Uncommon EGFR mutation status in patients

Parameter	No baseline brain metastases		Baseline brain metastases (n=262)	Total (n=703)
	New brain metastases (n=92)	No brain metastases (n=349)		
Major uncommon mutation				
G719X	4 (30.8)	12 (38.7)	5 (22.7)	21 (31.8)
L816Q	2 (15.4)	7 (22.6)	5 (22.7)	14 (21.2)
Compound				
G719X+S768I	3 (23.1)	4 (12.9)	4 (18.2)	11 (16.7)
T790M+sensitive mutations*	0 (0.0)	2 (6.5)	2 (9.1)	4 (6.1)
G719X+L861Q	0 (0.0)	2 (6.5)	1 (4.5)	3 (4.5)
19deletion+20insertion	1 (7.7)	1 (3.2)	0 (0.0)	2 (3.0)
T790M+G719X	1 (7.7)	0 (0.0)	0 (0.0)	1 (1.5)
19deletion+L861Q	0 (0.0)	0 (0.0)	1 (4.5)	1 (1.5)
Exon 20 insertion	2 (15.4)	2 (6.5)	1 (4.5)	5 (7.6)
S768I	0 (0.0)	1 (3.2)	2 (9.1)	3 (4.5)
T790M	0 (0.0)	0 (0.0)	1 (4.5)	1 (1.5)

*Sensitive mutations included EGFR 19 deletion and L858R mutation. EGFR, epidermal growth factor receptor

Table S2 Time on treatment (TOT) according to brain metastasis status

Category	Total	Within-category P value ^a	New brain metastases (n=92)	No brain metastases (n=349)	Baseline brain metastases (n=262)	Brain metastasis status P value ^b
Overall	16.0 (14.8–17.2)	–	12.2 (9.9–14.6)	18.9 (16.8–21.0)	14.1 (11.9–16.3)	<0.001
Sex						
Male	15.0 (13.3–16.6)	0.235	11.2 (8.8–13.5)	17.4 (15.4–19.4)	13.8 (12.1–15.6)	0.016
Female	16.4 (14.0–18.9)		13.7 (9.3–18.2)	21.4 (18.7–24.1)	15.2 (12.8–17.6)	<0.001
Age (years)						
<65	16.1 (14.6–17.6)	0.308	11.0 (7.6–14.4)	19.3 (15.2–23.4)	15.0 (13.1–16.8)	<0.001
≥65	16.0 (13.9–18.1)		12.6 (10.5–14.7)	18.9 (15.6–22.2)	12.6 (8.6–16.6)	0.027
Smoking status						
Never	16.9 (15.1–18.7)	0.185	13.7 (9.9–17.6)	21.4 (18.7–24.2)	14.1 (11.4–16.7)	<0.001
Former	13.9 (11.0–16.7)		10.4 (7.5–13.2)	15.8 (12.0–19.6)	16.2 (10.6–21.9)	0.025
Current	14.4 (13.4–15.5)		13.7 (10.7–16.8)	23.6 (12.6–34.6)	5.7 (NA–11.7)	0.074
ECOG performance status						
0–1	16.4 (15.0–17.8)	0.001	13.3 (9.3–17.2)	18.9 (16.4–21.3)	15.2 (13.4–17.0)	0.001
≥2	10.8 (6.2–15.4)		8.2 (6.2–10.1)	17.9 (13.7–22.1)	10.4 (5.9–14.9)	0.225
EGFR mutation						
Del19	16.2 (14.8–17.6)	0.049	12.2 (9.1–15.4)	20.7 (16.5–25.0)	13.8 (11.1–16.6)	<0.001
L858R	16.3 (13.9–18.7)		16.2 (14.8–17.6)	13.7 (9.5–18.0)	18.8 (15.6–22.0)	0.335
Other	10.8 (6.2–15.4)		7.1 (5.2–18.8)	12.0 (5.2–18.8)	13.5 (2.1–24.9)	0.311
Number of metastatic organs						
0–2	17.0 (15.6–18.5)	<0.001	14.1 (11.5–16.8)	19.4 (16.9–21.8)	13.9 (11.4–16.4)	0.002
3–6	12.8 (11.0–14.5)		8.2 (4.0–12.3)	15.8 (9.7–21.9)	14.1 (11.5–16.7)	0.013
Stage (AJCC 8 th edition)						
3–4A	17.5 (15.5–19.5)	0.008	12.6 (8.1–17.1)	19.3 (17.1–21.5)	16.4 (12.0–20.8)	0.034
4B	14.2 (12.6–15.7)		11.9 (9.3–14.4)	18.8 (13.0–24.5)	13.4 (11.8–14.9)	<0.001
Baseline liver metastasis						
Yes	10.9 (7.6–14.3)	<0.001	7.5 (6.0–8.9)	13.7 (8.1–19.3)	10.1 (6.1–14.1)	0.148
No	16.6 (15.1–18.1)		13.3 (10.5–16.1)	19.7 (17.1–22.2)	15.6 (13.5–17.8)	<0.001
Baseline bone metastasis						
Yes	14.4 (12.9–16.0)	0.024	10.0 (6.2–13.8)	17.3 (13.0–21.6)	14.2 (12.1–16.2)	0.001
No	17.0 (15.0–19.1)		14.1 (12.6–15.6)	19.4 (16.7–22.1)	13.7 (10.5–16.8)	0.011
Baseline pleural metastasis						
Yes	17.3 (15.5–19.1)	0.914	14.6 (8.4–20.7)	18.0 (15.5–20.5)	15.2 (10.7–19.7)	0.186
No	15.2 (13.8–16.5)		11.0 (8.7–13.3)	20.6 (16.5–24.7)	13.9 (11.7–16.0)	<0.001

Values shown are months (95% CI). ^a, P calculated by comparing values within each category (Male vs Female; <65 vs ≥65 years etc.). ^b, P calculated by the log-rank test for new brain metastasis, no brain metastasis and baseline brain metastasis groups. AJCC, American Joint Committee on Cancer; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor.

Table S3 Overall survival (OS) according to brain metastasis status

Category	Total	Within-category P value ^a	New brain metastases (n=92)	No brain metastases (n=349)	Baseline brain metastases (n=262)	Brain metastasis status P value ^b
Overall	52.9 (45.4–60.3)	–	29.1 (23.3–35.0)	67.3 (43.7–90.9)	48.5 (NA–NA)	<0.001
Sex						
Male	67.3 (36.8–97.8)	0.162	27.5 (24.8–30.1)	67.3 (46.9–87.7)	28.6 (NA–NA)	<0.001
Female	50.0 (NA–NA)		38.8 (22.5–55.1)	NR (NA–NA)	48.5 (NA–NA)	0.001
Age (years)						
<65	67.3 (35.8–98.8)	0.469	29.1 (24.1–34.2)	67.3 (30.9–103.7)	NR (NA–NA)	<0.001
≥65	50.0 (44.8–55.3)		34.0 (16.2–51.9)	NR (NA–NA)	48.5 (20.9–76.0)	0.02
Smoking status						
Never	52.9 (41.6–64.1)	0.367	37.2 (22.1–52.2)	67.3 (43.0–91.6)	36.6 (22.6–50.6)	<0.001
Former	47.8 (37.0–58.6)		27.5 (16.2–38.7)	NR (NA–NA)	NR (NA–NA)	0.002
Current	NR (NA–NA)		29.1 (23.7–34.5)	NR (NA–NA)	NR (NA–NA)	0.232
ECOG performance status						
0–1	67.3 (43.9–90.7)	0.016	NA (NA–NA)	NA (NA–NA)	NA (NA–NA)	<0.001
≥2	26.8 (15.9–37.6)		NA (NA–NA)	NA (NA–NA)	NA (NA–NA)	0.07
EGFR mutation						
Del19	67.3 (39.2–95.4)	<0.001	30.9 (24.2–37.7)	NR (NA–NA)	NR (NA–NA)	<0.001
L858R	41.7 (34.2–49.1)		27.5 (23.4–31.5)	52.9 (35.4–70.4)	29.4 (NA–NA)	0.021
Other	33.7 (22.2–45.3)		24.5 (10.8–38.2)	NR (NA–NA)	33.7 (22.2–45.3)	0.801
Number of metastatic organs						
0–2	67.3 (43.7–90.9)	<0.001	34.0 (23.1–44.9)	67.3 (43.7–90.9)	NR (NA–NA)	<0.001
3–6	29.3 (26.1–32.4)		26.4 (21.8–30.9)	NR (NA–NA)	29.3 (25.5–33.1)	0.302
Stage (AJCC 8 th edition)						
3–4A	67.3 (43.7–90.9)	0.001	37.2 (25.3–49.0)	67.3 (43.6–91.0)	NR (NA–NA)	0.002
4B	36.6 (27.0–46.3)		26.4 (23.1–29.6)	NR (NA–NA)	33.7 (25.6–41.8)	0.002
Baseline liver metastasis						
Yes	28.7 (21.6–35.8)	<0.001	23.7 (22.8–24.5)	45.2 (25.8–64.6)	27.2 (22.6–31.7)	0.189
No	67.3 (42.8–91.8)		30.9 (24.8–37.1)	67.3 (NA–NA)	NR (NA–NA)	<0.001
Baseline bone metastasis						
Yes	33.1 (27.8–38.5)	<0.001	26.3 (22.5–30.2)	67.3 (NA–NA)	30.3 (25.3–35.3)	0.001
No	NR (NA–NA)		41.7 (34.2–49.1)	NR (NA–NA)	NR (NA–NA)	0.005
Baseline pleural metastasis						
Yes	52.9 (NA–NA)	0.244	38.8 (29.2–48.4)	NR (NA–NA)	48.5 (21.3–75.7)	0.01
No	67.3 (36.9–97.7)		26.3 (21.7–31.0)	67.3 (NA–NA)	NR (NA–NA)	<0.001

Values shown are months (95% CI). AJCC, American Joint Committee on Cancer; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; NA, not available; NR, not reached. ^a, P calculated by comparing values within each category (Male vs Female; <65 vs. ≥65 years etc.). ^b, P calculated by the log-rank test for new brain metastasis, no brain metastasis and baseline brain metastasis groups.