

Supplementary

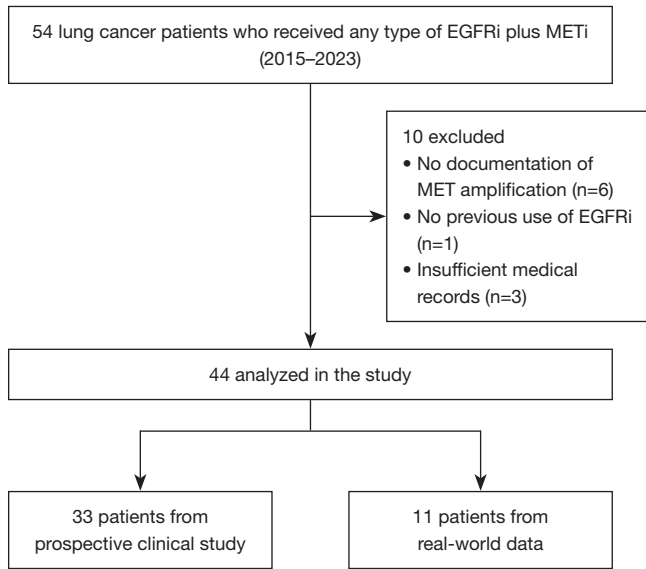


Table S1 Incidence of pneumonitis according to combination regimen

Combination regimen	Overall grade, n (%)	Grade 3–4, n (%)
Savolitinib + osimertinib	6/31 (19.4)	0/31 (0.0)
Capmatinib + gefitinib	0/2 (0.0)	0/2 (0.0)
Crizotinib + osimertinib	1/4 (25.0)	0/4 (0.0)
Crizotinib + 1/2G EGFR-TKI	4/7 (57.1)	2/7 (28.6)

1/2G EGFR-TKI, 1st- or 2nd-generation EGFR tyrosine kinase inhibitor.

Figure S1 The patient collection flow. EGFRi, EGFR inhibitor; METi, MET inhibitor.

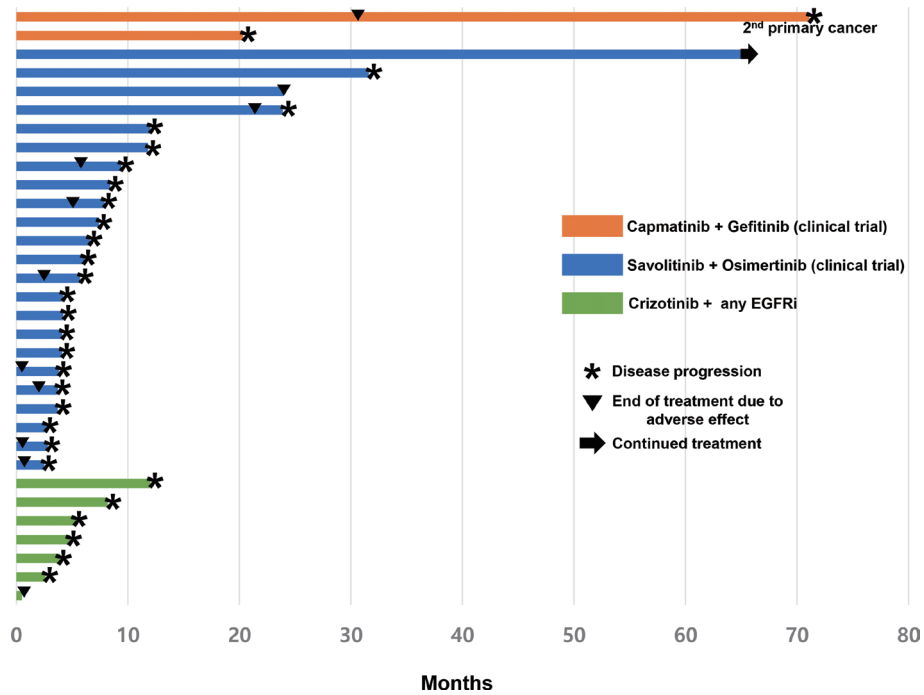


Figure S2 The response duration of responders. EGFRi, EGFR inhibitor.

Table S2 Characteristics of patients with brain metastasis

Characteristics	Subgroups	BM-responder, n (%)	BM-nonresponder, n (%)	P
Age	<65 years	11 (78.6)	7 (87.5)	>0.99
	≥65 years	3 (21.4)	1 (12.5)	
Sex	Male	8 (57.1)	6 (75.0)	0.65
	Female	6 (42.9)	2 (25.0)	
Smoking	Never	6 (42.9)	2 (25.0)	0.65
	Ever	8 (57.1)	6 (75.0)	
ECOG PS	0 or 1	12 (85.7)	6 (75.0)	0.60
	2	2 (14.3)	2 (25.0)	
Histology	Adenocarcinoma	13 (92.9)	8 (100.0)	>0.99
	Non-adenocarcinoma	1 (7.1)	0 (0.0)	
EGFR mutation	Exon 19 deletion	7 (50.0)	4 (50.0)	0.48
	Exon 21 L858R	7 (50.0)	3 (37.5)	
	Exon 18 G719X	0 (0.0)	1 (12.5)	
Previous BM treatment	Radiotherapy	2 (14.3)	1 (12.5)	0.70
	Surgery + radiotherapy	0 (0.0)	1 (12.5)	
	None	12 (85.7)	6 (75.0)	
Prior EGFR-TKI	1 st or 2 nd generation	9 (64.3)	6 (75.0)	>0.99
	3 rd generation	5 (35.7)	2 (25.0)	
EGFR-TKI	1 st or 2 nd generation	3 (21.4)	3 (37.5)	0.62
	3 rd generation	11 (78.6)	5 (62.5)	
MET-TKI	Savolitinib	11 (78.6)	3 (37.5)	0.052
	Crizotinib	2 (14.3)	5 (62.5)	
	Capmatinib	1 (7.1)	0 (0.0)	

BM, brain metastasis; ECOG, Eastern Cooperative Oncology Group; PS, performance status. FISH, fluorescence in situ hybridization; TKI, tyrosine kinase inhibitor.

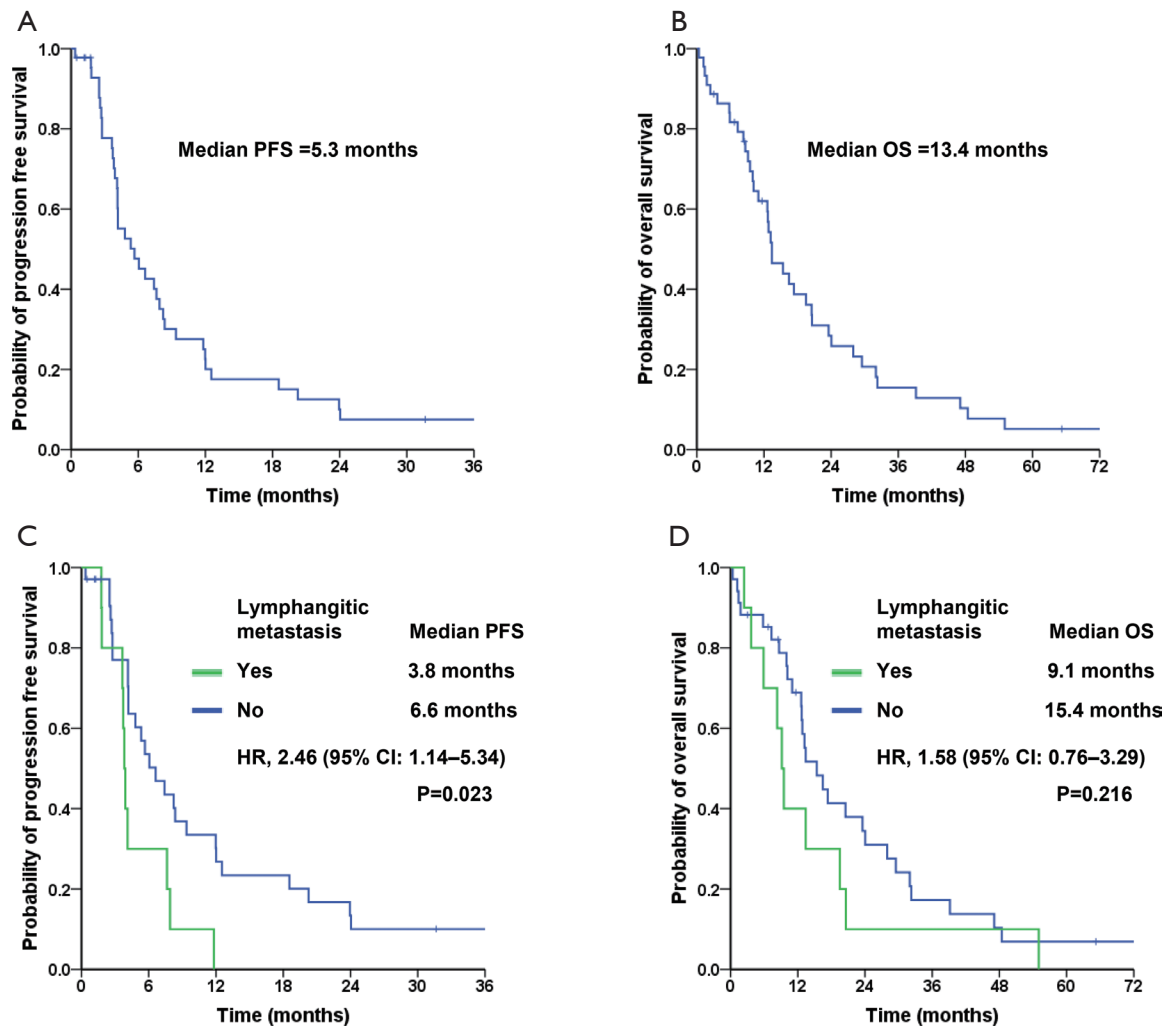


Figure S3 Kaplan-Meier survival curves. (A) PFS and (B) OS in total 44 patients who were treated with MET inhibitor plus EGFR inhibitor. (C) PFS and (D) OS with or without lymphangitic metastasis at baseline. PFS, progression-free survival; OS, overall survival; CI, confidence interval; HR, hazard ratio.

Table S3 Progression-free survival analysis

Variables	Univariate		Multivariate	
	HR (95% CI)	P*	HR (95% CI)	P*
Age (≥ 65 vs. < 65 years)	0.84 (0.37–1.91)	0.67	–	–
Sex (male vs. female)	1.52 (0.79–2.95)	0.21	–	–
ECOG PS (2 vs. 0 or 1)	0.48 (0.17–1.99)	0.28	–	–
Smoking (ever vs. never)	1.27 (0.65–2.47)	0.49	–	–
Histology (ADC vs. non-ADC)	1.82 (0.43–7.63)	0.41	–	–
Brain metastasis (yes vs. no)	1.11 (0.58–2.12)	0.76	–	–
Lymphangitic metastasis (yes vs. no)	2.46 (0.14–5.34)	0.02	7.67 (1.25–47.25)	0.03
EGFR mutation type (L858R vs. 19del)	0.66 (0.33–1.33)	0.24	–	–
MET/CEP7 ratio on FISH test	0.72 (0.48–1.07)	0.10	0.72 (0.47–1.10)	0.13
Prior EGFR-TKI (1 st or 2 nd vs. 3 rd G)	0.62 (0.30–1.27)	0.19	0.52 (0.15–1.78)	0.30
Response of prior EGFR-TKI (no vs. yes)	0.69 (0.28–1.69)	0.42	–	–
Median PFS of prior EGFR-TKI	0.98 (0.96–1.01)	0.30	–	–
EGFR-TKI (1 st or 2 nd G vs. 3 rd G)	0.69 (0.27–1.78)	0.45	–	–
MET-TKI (type Ib vs. Ia)	0.52 (0.23–1.16)	0.11	0.60 (0.18–2.02)	0.13
MET-TKI discontinuation (yes vs. no)	0.93 (0.49–1.78)	0.83	–	–

*, Cox proportional hazards model. HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; PS, performance status; ADC, adenocarcinoma; TKI, tyrosine kinase inhibitor; PFS, progression-free survival; 3rd G, 3rd generation; 1st or 2nd G, 1st or 2nd generation.

Table S4 Overall survival analysis

Variables	Univariate		Multivariate	
	HR (95% CI)	P*	HR (95% CI)	P*
Age (≥ 65 vs. < 65 years)	1.44 (0.67–3.11)	0.35	–	–
Sex (male vs. female)	1.07 (0.56–2.05)	0.83	–	–
ECOG PS (2 vs. 0 or 1)	0.79 (0.32–1.98)	0.62	–	–
Smoking (ever vs. never)	0.82 (0.42–1.56)	0.53	–	–
Histology (ADC vs. non-ADC)	3.61 (0.49–26.81)	0.21	–	–
Brain metastasis (yes vs. no)	1.32 (0.69–2.53)	0.40	–	–
Lymphangitic metastasis (yes vs. no)	1.58 (0.76–3.29)	0.22	–	–
<i>EGFR</i> mutation type (L858R vs. 19del)	0.87 (0.45–1.67)	0.67	–	–
MET/CEP7 ratio on FISH test	0.90 (0.65–1.25)	0.52	–	–
Prior EGFR-TKI (1 st or 2 nd G vs. 3 rd G)	0.44 (0.20–0.96)	0.04	0.46 (0.17–1.26)	0.13
Response of prior EGFR-TKI (no vs. yes)	0.88 (0.40–1.93)	0.76	–	–
Median PFS of prior EGFR-TKI	1.00 (0.98–1.02)	>0.99	–	–
EGFR-TKI (1 st or 2 nd G vs. 3 rd G)	0.81 (0.34–1.95)	0.64	–	–
MET-TKI (type Ib vs. Ia)	0.34 (0.15–0.81)	0.01	0.61 (0.24–1.53)	0.30
MET-TKI discontinuation (yes vs. no)	0.85 (0.85–1.62)	0.62	–	–

*, Cox proportional hazards model. HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; PS, performance status; ADC, adenocarcinoma; TKI, tyrosine kinase inhibitor; PFS, progression-free survival; 3rd G, 3rd generation; 1st or 2nd G, 1st or 2nd generation.