

Table S1 Comparison of baseline clinicopathological features of patients with HER2 mutations and patients without oncodriver mutations

Characteristics	total n (N%)	HER2 mutation n (N%)	without HER2 mutation n (N%)	p value
	298	98	200	
Gender				
male	209 (70.1%)	53 (54.1%)	156 (78.0%)	<0.001
female	89 (29.9%)	45 (45.9%)	44 (22.0%)	
Age				
median (range)	63.7 (32-86)	60.0 (33-83)	65.0 (32-86)	<0.001
<65	168 (56.4%)	71 (72.4%)	97 (48.5%)	<0.001
≥65	130 (43.6%)	27 (27.6%)	103 (51.5%)	
Histology				
adenocarcinoma	181 (60.7%)	91 (92.9%)	90 (45.0%)	<0.001
squamous carcinoma	55 (18.5%)	1 (1.0%)	54 (27.0%)	
adenosquamous carcinoma	2 (0.7%)	1 (1.0%)	1 (0.5%)	
NOS	60 (20.1%)	5 (5.1%)	55 (27.5%)	
Smoking history				
never-smoker	187 (62.8%)	70 (71.4%)	117 (58.5%)	0.031
ever-smoker	111 (37.2%)	28 (28.6%)	83 (41.5%)	

Footnote: NOS, not other specified.

Table S2 Comparison of pathological features among patients with HER2 mutations and without oncogenic mutations in patients receiving first line chemotherapy

Characteristics	total n (N%)	patients with HER2 mutations n (N%)			without oncogenic mutations n (N%)	p value [†]	p value [‡]
		total	YVMA mutations	non-YVMA variants			
	132	82	55	27	50		
Gender							
male	81 (61.4)	46 (56.1)	31 (56.4)	15 (55.6)	35 (70.0)	0.141	0.293
female	51 (38.6)	36 (43.9)	24 (43.6)	12 (44.4)	15 (30.0)		
Age							
<65	91 (68.9)	62 (75.6)	42 (76.4)	20 (74.1)	29 (58.0)	0.052	0.114
≥65	41 (31.1)	20 (24.4)	13 (23.6)	7 (25.9)	21 (42.0)		
Histology							
adenocarcinoma	104 (78.8)	75 (91.5)	50 (90.9)	25 (92.6)	29 (58.0)	<0.001	<0.001
non-adenocarcinoma	28 (21.2)	7 (8.5)	5 (9.1)	2 (7.4)	21 (42.0)		
Smoking history							
never-smoker	85 (64.4)	58 (70.7)	41 (74.5)	17 (63.0)	27 (54.0)	0.062	0.084
ever-smoker	47 (35.6)	24 (29.3)	14 (25.5)	10 (37.0)	23 (46.0)		
ECOG-PS							
0	17 (12.9)	13 (15.9)	12 (21.8)	1 (3.7)	4 (8.0)	0.284	0.026
1-2	115 (87.1)	69 (84.1)	43 (78.2)	26 (96.3)	46 (92.0)		
Stage of disease							
IIIb/IIIc	15 (11.4)	9 (11.0)	6 (10.9)	3 (11.1)	6 (12.0)	1	0.931
IV	107 (81.1)	67 (81.7)	46 (83.6)	21 (77.8)	40 (80.0)		
recurrent	10 (7.6)	6 (7.3)	3 (5.5)	3 (11.1)	4 (8.0)		
Disease extent							
intrathoracic	67 (50.8)	43 (52.4)	24 (43.6)	19 (70.4)	24 (48.0)	0.72	0.067
extrathoracic	65 (49.2)	39 (47.6)	31 (56.4)	8 (29.6)	26 (52.0)		
Treatment regimens							
pemetrexed based	94 (71.2)	64 (78.0)	44 (80.0)	20 (74.1)	30 (60.0)	0.091	0.229
gemcitabine based	20 (22.0)	14 (17.1)	8 (14.5)	6 (22.2)	15 (30.0)		
paclitaxel based	9 (6.8)	4 (4.9)	3 (5.5)	1 (3.7)	5 (10.0)		
Responses							
ORR	34.1	37.8	30.9	51.9	28	0.264	0.093
DCR	83.3	84.1	78.2	96.3	82	0.812	0.11
median PFS	5.7 (5.14-6.19)	5.8 (5.16-6.37)	5.2 (4.02-6.45)	7.7 (5.66-9.81)	5.1 (3.94-6.33)	0.922	0.109

Footnote: † indicates HER2 mutations vs. without oncogenic mutations; ‡ indicates YVMA vs. non-YVMA vs. without oncogenic mutations. ECOG-PS, Eastern Cooperative Oncology Group Performance Score; ORR, objective response rate; DCR, disease control rate; PFS, progression free survival.

Table S3 Summary of treatment responses of patients who received first line targeted therapy

Patient ID	Gender	Age	Histology	HER2 mutation	Stage of Disease	Targeted drug	Best response	PFS (months)	Living status
024	female	63.4	adenocarcinoma	A775_G776insYVMA	IVb	Afatinib	SD	5.3	Alive
033	male	64.0	adenocarcinoma	A775_G776insYVMA	IVb	Afatinib	SD	3.3	Alive
037	female	44.8	adenocarcinoma	A775_G776insYVMA	IVb	Afatinib	SD	6.6	Alive
078	male	60.2	adenocarcinoma	A775_G776insYVMA	IIIb	Afatinib	PD	2.2	Dead
091	male	76.9	adenocarcinoma	A775_G776insYVMA	IVb	Pyrotinib	PR	19.2	Alive
092	female	80.5	adenocarcinoma	A775_G776insYVMA	IVb	Afatinib	PD	1.9	Dead

Table S4 Multivariate analysis for total patients and patients with pemetrexed based chemotherapy incorporating most prevalent baseline metastatic sites

Variables	Total patients (n=82)				Patients received pemetrexed based chemotherapy (n=64)			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value
Age, y								
<65	1.000	0.330			1.000	0.350		
≥65	0.757 (0.432-1.326)				0.746 (0.404-1.378)			
Gender								
male	1.000	0.612			1.000	0.748		
female	1.128 (0.707-1.800)				1.090 (0.645-1.840)			
Histology								
adenocarcinoma	1.000				1.000		1.000	
non-adenocarcinoma	1.188 (0.476-2.966)	0.712			5.219 (0.674-40.431)	0.114	4.297 (0.527-35.050)	0.173
HER2 mutation								
non-YVMA	1.000	0.040	1.000	0.057	1.000	0.025	1.000	0.085
YVMA	1.681 (1.023-2.763)		1.633 (0.985-2.706)		1.903 (1.085-3.338)		1.685 (0.931-3.051)	
Smoking histology								
never smoker	1.000	0.328			1.000	0.779		
ever smoker	1.286 (0.777-2.128)				1.089 (0.600-1.976)			
ECOG-PS								
0	1.000	0.770			1.000	0.872		
1-2	0.911 (0.487-1.702)				1.058 (0.532-2.107)			
Baseline brain metastasis								
without	1.000				1.000		1.000	
with	1.430 (0.744-2.748)	0.283			2.435 (1.166-5.088)	0.018	1.900 (0.845-4.273)	0.121
Baseline bone metastasis								
without	1.000		1.000		1.000		1.000	0.107
with	1.919 (1.181-3.120)	0.009	1.788 (1.072-2.981)	0.026	1.688 (0.977-2.848)	0.061	1.601 (0.903-2.837)	
Baseline liver metastasis								
without	1.000		1.000		1.000		1.000	0.370
with	4.324 (1.468-12.732)	0.008	2.535 (0.820-7.835)	0.106	3.745 (1.093-12.830)	0.036	1.861 (0.479-7.236)	

Footnote: ECOG-PS, Eastern Cooperative Oncology Group Performance Score; HR, hazard ratio; CI, confidential interval.

Table S5 Detailed chemotherapy regimens used in first line and their treatment efficacy

Regimens and Responses	total n (N%)	YVMA n (N%)	non-YVMA n (N%)	
Pemetrexed based chemotherapy	64	44	20	0.735
pemetrexed+platinum	53 (82.8%)	35 (79.5%)	18 (90.0%)	
pemetrexed alone	3 (4.7%)	3 (6.8%)	0	
pemetrexed+platinum+bevacizumab	8 (12.5%)	6 (13.6%)	2 (10.0%)	
Objective response				
PR	26 (40.6%)	14 (31.8%)	12 (60.0%)	
SD	26 (40.6%)	19 (43.2%)	7 (35.0%)	
PD	12 (18.8%)	11 (25.0%)	1 (5.0%)	
ORR	40.60%	31.80%	60.00%	0.054
DCR	81.30%	75.00%	95.00%	0.085
median PFS (95%CI)	5.70 (5.2-6.2)	5.2 (3.4-7.0)	6.5 (2.5-10.5)	0.022
Gemcitabine based chemotherapy				
gemcitabine+platinum	14	8	6	
Objective response				
PR	3 (21.4%)	2 (25.0%)	1 (16.7%)	
SD	10 (71.4%)	5 (62.5%)	5 (83.3%)	
PD	1 (7.1%)	1 (12.5%)	0	
ORR	21.40%	25.00%	16.70%	1
DCR	92.90%	87.50%	100.00%	1
median PFS (95%CI)	5.2 (1.9-8.6)	4.2 (1.7-6.7)	6.6 (2.5-10.8)	0.635
Paclitaxel based chemotherapy				
paclitaxel+platinum	4	3	1	
Objective response				
PR	2 (50.0%)	1 (33.3%)	1 (100.0%)	
SD	2 (50.0%)	2 (66.7%)	0	
PD	0	0	0	
ORR	-	-	-	-
DCR	-	-	-	-
median PFS (95%CI)	8.2 (2.2-14.1)	13.87 (NE)	8.20 (NE)	0.705

Footnote: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate; PFS, progression free survival; CI, confidential interval.

Table S6 Summary of treatment responses of patients with baseline brain metastasis

Patient ID	Gender	Age	Histology	HER2 mutation	Stage of Disease	Systemic Treatments	Best response	PFS	Local	Living status
								(months)	treatments	
03	male	43.9	adenocarcinoma	A775_G776insYVMA	IV b	GC	SD	4.2		Alive
15	female	66.5	adenocarcinoma	A775_G776insYVMA	recurrent	AC	PD	0.9		Dead
18	female	49.9	adenocarcinoma	A775_G776insYVMA	IV b	AC	PR	3.0		Dead
22	male	42.8	adenocarcinoma	A775_G776insYVMA	IV b	AP+bevacizumab	PD	1.9		Dead
24	female	63.4	adenocarcinoma	A775_G776insYVMA	IV b	Afatinib	SD	5.3		Alive
35	male	67.3	adenocarcinoma	A775_G776insYVMA	IV b	AC+ bevacizumab	SD	7.8	SRS+WBRT	Alive
37	female	44.8	adenocarcinoma	A775_G777insYVMA	IV a	Afatinib	SD	6.6	Surgery	Alive
45	female	49.3	adenocarcinoma	A775_G778insYVMA	IV b	AC	PR	8.1	WBRT	Alive
50	female	47.2	adenocarcinoma	A775_G779insYVMA	IV b	AC+ bevacizumab	PR	3.1		Dead
58	female	54.8	adenocarcinoma	A775_G780insYVMA	IV a	AC	SD	4.1		Dead
59	male	43.8	adenocarcinoma	A775_G781insYVMA	IV b	PC	PR	13.9	SRS	Dead
62	male	51.1	adenocarcinoma	A775_G782insYVMA	IV b	AC	PR	5.2		Alive
64	female	57.2	adenocarcinoma	A775_G783insYVMA	IV b	AC	SD	2.4	WBRT	Alive
90	male	36.0	adenocarcinoma	A775_G784insYVMA	IV b	GC	SD	3.1	WBRT+SRS	Dead

Footnote: G, gemcitabine; C, carboplatin; A, alimta, pemetrexed; P, cisplatin; P, paclitaxel; SRS, stereotactic radiosurgery; WBRT, whole brain radiotherapy; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate; PFS, progression free survival.