

Supplemental Table 1. List of rare and synonymous EGFR mutations (n=77 patients, N=98 mutations were identified)

Patient ID	Sign of the aminoacid change	Gender	Age (diagnosis)	Smoking status	Stage at diagnosis	Drug	TKI line	Response	Censored	PFS	Reference PMID	COSMIC ID	Tissue distribution
1	V845V	f	64,0	current	IA	E	3	PD	y	3,4	novel	-	-
2	P848P	f	66,0	current	IV	E	2	PR	n	5,1	novel	-	-
2	frameshift **	f	66,0	current	IV	E	2	PR	n	5,1	novel	-	-
3	K713K	m	65,4	former	IIIA	E	3	PD	y	3	novel	-	-
4	K708K	f	43,1	former	IIIA	E	2	SD	y	14,7	-	COSM1451573	large intestine
5	G724A	f	61,3	former	IIB	E	2	PD	y	2,8	novel	-	-
6	E709-T710 del	m	69,2	former	IV	E	2	SD	y	6	novel	-	-
7	L788L	f	64,9	never	IIIA	E	3	PR	n	19,2	22980975	COSM366483	lung
7	F795C	f	64,9	never	IIIA	E	3	PR	n	19,2	novel	-	-
7	18, del30	f	64,9	never	IIIA	E	3	PR	n	19,2	novel	-	-
8	V851I	f	65,7	never	IV	E	1	PR	n	15,5	23485129	COSM12727	lung
9	E709A	m	74,4	current	IIB	E	2	N/A	y	0	23344264	COSM13427	lung
10	K716R	f	66,6	current	IIIA	E	2	PD	y	1,2	19020901	COSM28512	lung
10	I744V	f	66,6	current	IIIA	E	2	PD	y	1,2	23344264	COSM28512	lung
11	G719S	m	67,4	current	IV	E	3	N/A	n	3,4	18176089	COSM6252	lung
12	G719S	m	55,1	current	IB	E	2	SD	n	2,1	23344264	COSM6252	lung
13	R836R	m	N/A	current	N/A	E	2	PR	n	3,5	21274259	COSM85893	upper aerodigestive tract
14	G796S	m	56,5	former	IV	E	2	SD	y	4,7	18528899	COSM20891	head and neck
14	C818Y	m	56,5	former	IV	E	2	SD	y	4,7	17354229	COSM23611	pancreas
15	V845M	f	75,7	never	IIA	E	2	N/A	n	N/A	19190079	COSM28931	adrenal
16	L799L	f	76,3	never	IV	E	2	SD	y	6,2	16467085	-	lung
17	P794P	f	75,0	former	IB	G	1	PD	y	2,2	novel	-	-
18	L852R	f	71,9	never	IV	G	1	PR	n	19	novel	-	-
19	L852R	f	73,4	never	N/A	G	1	PR	y	7	novel	-	-
20	C797S	f	75,2	never	IIIA	G	1	SD	y	6,6	novel	-	-
21	P848L	m	57,2	current	IV	G	1	SD	n	1,7	23897956	COSM22943	lung
22	E709_T710>D	f	77,0	never	IB	G	1	PR	y	6,2	20559149	COSM51525	lung
23	L861Q	f	63,9	never	IIIB	N/A	N/A	PR	N/A	N/A	23344264	COSM6213	lung
24	G719A	m	53,8	never	IV	G	1	PR	n	7	23344265	COSM6240	lung
25	G719A	m	57,8	current	IV	G	1	SD	n	7,8	23344266	COSM6241	lung
26	T854I*	m	57,5	former	IA	G	1	PR	n	18	21409490	COSM87246	lung
26	T785I*	m	57,5	former	IA	G	1	PR	n	18	23139256	COSM53288	lung
27	P753P	m	52,2	former	IV	G	1	PR	n	1,5	16707764	COSM18489	oesophagus
27	I759V	m	52,2	former	IV	G	1	PR	n	1,5	19776290	COSM36938	thyroid gland

28	E734D	f	72,0	current	IIIB	G	1	PD	y	2,1	-	COSM1451582	large intestine
29	M825I	f	74,7	current	IV	G	1	PR	y	2,5	2329544	COSM1578128	biliary tract
30	A839V	m	69,2	never	IB	G	1	PD	y	3,5	21266046	COSM85900	prostate
31	V802V	m	67,8	former	IA	x	x	x	x	x	novel	-	-
31	T854I	m	67,8	former	IA	x	x	x	x	x	21409490	COSM87246	lung
31	V851I	m	67,8	former	IA	x	x	x	x	x	23485129	COSM12727	lung
32	L799L	f	55,5	current	IIIB	x	x	x	x	x	novel	-	-
32	V786V	f	55,5	current	IIIB	x	x	x	x	x	novel	-	-
32	G779D	f	55,5	current	IIIB	x	x	x	x	x	21057810	COSM133202	lung
32	G768N	f	55,5	current	IIIB	x	x	x	x	x	23139256	COSM14068	lung
33	V744V	m	75,1	former	IA	x	x	x	x	x	novel	-	-
34	L838L	f	54,7	never	IA	x	x	x	x	x	16203769	-	lung
34	T783T	f	54,7	never	IA	x	x	x	x	x	novel	-	-
35	S784S	m	55,6	current	IIIA	x	x	x	x	x	novel	-	-
36	R705R	m	57,3	current	IA	x	x	x	x	x	novel	-	-
36	L688F	m	57,3	current	IA	x	x	x	x	x	22885469	COSM306127	endometrium
37	P848P	f	74,4	never	IIIA	x	x	x	x	x	novel	-	-
37	V786L	f	74,4	never	IIIA	x	x	x	x	x	novel	-	-
37	A743T	f	74,4	never	IIIA	x	x	x	x	x	18258923	COSM26509	lung
38	L844L	f	52,5	current	IIA	x	x	x	x	x	novel	-	-
39	K867K	m	37,5	current	IB	x	x	x	x	x	novel	-	-
40	K745K	m	66,8	current	IIIA	x	x	x	x	x	novel	-	-
41	K713K	m	73,9	current	IIIA	x	x	x	x	x	novel	-	-
42	I780I	f	64,0	current	IIIA	x	x	x	x	x	novel	-	-
43	I780I	f	59,3	current	IA	x	x	x	x	x	novel	-	-
44	I780I	m	56,5	former	IIIA	x	x	x	x	x	novel	-	-
45	I706I	f	66,8	former	IB	x	x	x	x	x	novel	-	-
46	H773H	f	67,9	current	IV	x	x	x	x	x	novel	-	-
47	D829D	f	67,8	former	IV	x	x	x	x	x	novel	-	-
48	V851V	f	59,3	current	IB	x	x	x	x	x	23344264	-	endometrium
48	N842N	f	59,3	current	IB	x	x	x	x	x	novel	-	-
48	T710I	f	59,3	current	IB	x	x	x	x	x	novel	-	-
49	E804E	m	62,4	current	IIIA	x	x	x	x	x	-	COSM1451603	large intestine
50	A702A	f	71,4	former	IV	x	x	x	x	x	-	COSM1451570	large intestine
51	P848S	f	56,2	current	IIA	x	x	x	x	x	novel	-	-
52	V774S	f	49,6	current	IV	x	x	x	x	x	novel	-	-
53	R803Q	f	72,9	never	IIA	x	x	x	x	x	novel	-	-
54	Q791L	f	35,9	current	IIIA	x	x	x	x	x	novel	-	-
55	Q787 STOP	f	75,5	never	IIIA	x	x	x	x	x	novel	-	-

56	N700T	f	71,4	former	IA	x	x	x	x	x	novel	-	-
57	M793V	m	76,3	former	IIB	x	x	x	x	x	novel	-	-
58	L788P	m	63,3	current	IIA	x	x	x	x	x	novel	-	-
59	R832C	m	76,1	current	IB	x	x	x	x	x	21057220	COSM28286	ovary
59	I789T	m	76,1	current	IB	x	x	x	x	x	novel	-	-
60	G708 [#]	f	65,7	current	IIA	x	x	x	x	x	novel	-	-
61	G779G	m	60,5	current	IIA	x	x	x	x	x	novel	-	-
62	S811F	m	77,9	former	IV	x	x	x	x	x	22975805	COSM1187305	lung
63	V851I	m	48,1	current	IIA	x	x	x	x	x	23485129	COSM12727	lung
64	L862V	m	59,7	former	IIA	x	x	x	x	x	21841502	COSM133111	lung
65	E709A	m	62,5	former	IV	x	x	x	x	x	23344264	COSM13427	lung
66	E709A	m	68,6	current	IV	x	x	x	x	x	23344264	COSM13427	lung
67	G779S	m	57,6	former	IA	x	x	x	x	x	17626639	COSM25016	lung
68	I853I	f	61,5	current	IV	x	x	x	x	x	21057220	COSM53231	lung
68	D855G	f	61,5	current	IV	x	x	x	x	x	16870303	COSM28606	lung
69	E829K	m	70,6	current	IIIA	x	x	x	x	x	21070477	COSM53291	lung
70	T790A	m	58,3	current	IV	x	x	x	x	x	23546020	COSM1272071	esophagus
70	L692H	m	58,3	current	IV	x	x	x	x	x	-	COSM726863	lung
71	V843I	f	50,5	current	IV	x	x	x	x	x	21274259	COSM85894	lung
72	V834A	m	59,0	current	IB	x	x	x	x	x	20208477	COSM41665	prostate
73	Q820R	f	63,4	current	IIA	x	x	x	x	x	21266046	COSM85898	prostate
74	L704L	f	70,6	current	IIB	x	x	x	x	x	21057220	COSM53225	ovary
75	L798P	m	61,4	never	IIIA	x	x	x	x	x	-	COSM1451601	large intestine
76	L692F	m	71,1	former	IV	x	x	x	x	x	23912954	-	lung
77	V786A	m	N/A	never	IIIA	x	x	x	x	x	novel	-	-

x: Patient did not receive EGFR tyrosine kinase inhibitor therapy

E: Patient received erlotinib

G: Patient received gefitinib

* Patient carrying complex EGFR mutation including classic mutation

** Exon 20, 2284_2285 del1 frame shift

Exon 18: 2122 A/C

N/A: Not available

Rows of synonymous mutations are highlighted in gray

Supplemental Table 2. Characteristics of patients with major clinicopathological data available (n=645).

		Total	KRAS mutation	Classic EGFR mutation	Rare EGFR mutation	Synonymous EGFR mutation	KRAS and EGFR wild-type	P value
Total		645* (100%)	112 (17%)	42 (7%)	49(8%)	27(4%)	415 (64%)	
Age (mean±SD)		64±10	60±10.4	67±9.6	64.2±9.2	63.2±9.8	64±9.7	.0002
Gender	Male	303 (45%)	49 (44%)	19 (45%)	26 (53%)	11 (40%)	198 (48%)	.780
	Female	342 (55%)	63 (66%)	23 (55%)	23 (47%)	16 (60%)	217 (52%)	
ECOG performance status	0	325 (48%)	58 (52%)	25 (63%)	25 (51%)	15(58%)	202 (51%)	.658
	≥1	300 (52%)	54 (48%)	15 (37%)	24 (49%)	11 (42%)	197 (49%)	
	Unknown data	20	1	2	0	1	16	
Smoking status	Never-smoker	118(19%)	16 (14%)	20 (49%)	12 (24%)	4 (15%)	66 (17%)	<.001
	Former smoker	198 (32%)	39 (35%)	13 (32%)	12(24%)	9(33%)	125 (32%)	
	Current smoker	302 (49%)	56 (51%)	8 (19%)	25 (52%)	14 (52%)	199 (51%)	
	Unknown data	27	1	1	0	0	25	
Tumor Stage	I-III A	275 (44%)	52 (47%)	19 (47%)	27 (66%)	20 (77%)	157 (39%)	<.001
	IIIB-IV	351 (56%)	59 (53%)	21 (53%)	21 (44%)	6 (23%)	244 (61%)	
	Unknown data	19	1	2	1	1	14	

Data shown in parentheses are column percentages.

* EGFR molecular analysis was not done in 43 cases.

Supplemental Table 3. Clinicopathological variables and survival of patients with advanced lung adenocarcinoma (n=419) in the Cox proportional hazards model according to (**A**) classic EGFR mutation v WT, (**B**) rare EGFR mutation v WT.

A

Prognostic factor	HR	95% CI	P
Age (continuous)	0.998	(0.985-1.011)	0.715
Gender (male v female)	1.063	(0.820-1.378)	0.643
ECOG PS (0 v ≥ 1)	1.320	(1.160-1.503)	<0.001
Stage (IIIA v IIIB/IV)	1.199	(1.053-1.366)	0.006
EGFR status (Classic v WT)	0.454	(0.252-0.819)	0.009

HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status

B

Prognostic factor	HR	95% CI	P
Age (continuous)	0.999	(0.986-1.013)	0.916
Gender (male v female)	1.053	(0.813-1.365)	0.696
ECOG PS (0 v ≥ 1)	1.341	(1.184-1.520)	<0.001
Stage (IIIA v IIIB/IV)	1.157	(1.023-1.310)	0.021
EGFR status (Rare v WT)	0.730	(0.416-1.279)	0.271

HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status

Supplemental Table 4. Erlotinib and gefitinib treatment in patients with classic and rare EGFR mutations.

EGFR mutation		Gefitinib	RR	Erlotinib	RR
Classic	Responder	13* (76%)	76%	2 (50%)	50%
	Non-responder	4** (24%)		2 (50%)	
	Unknown data	1		0	
Rare	Responder	5 (50%)	50%	1 [#] (17%)	17%
	Non-responder	5 (50%)		5 (83%)	
	Unknown data	0		3	

[#] One patient was treated with erlotinib in first line setting.

* One patient was treated with gefitinib in 2nd or 3rd line setting.

** Two patients were treated with gefitinib in 2nd or 3rd line setting.

RR: response rate.