

Supplementary Table S1. Type of mutations detected by NGS. MAF and MAPD parameters.

Mutations	N=365
Mean per sample	2.9 (1; 16)
Mutation type, No. (%) with data	
snp	264 (72.3)
insdel	96 (26.3)
cnv	5 (1.4)
Functional classification, No. (%) with data	
CNV	5 (1.4)
Frameshift deletion	20 (5.5)
Frameshift insertion	15 (4.1)
Missense	250 (68.5)
Nonframeshift block substitution	4 (1.1)
Nonframeshift deletion	44 (12)
Nonframeshift insertion	3 (0.8)
Nonsense	20 (5.5)
unknown	4 (1.1)
Location, No. (%) with data	
Exonic	356 (98.9)
Splice site 3'	2 (0.6)
Splice site 5'	1 (0.3)
UTR 5'	1 (0.3)
MAF, mean (min; max), %	5.2 (0.1; 77.7)
MAPD, mean (min; max), %	0.3 (0.1; 1.8)

MAF: Mutant allele frequency; MAPD: Median of the absolute values of all pairwise differences.

Supplementary Table S2. Number of patients with tumors harboring mutations in each gene covered by the NGS panel.

Gene	N patients	Frequency (%)
<i>EGFR</i>	89	71,8
<i>TP53</i>	71	57,3
<i>APC</i>	14	11,3
<i>FGFR3</i>	9	7,3
<i>FBXW7</i>	7	5,6
<i>KRAS</i>	7	5,6
<i>ERBB2</i>	6	4,8
<i>MAP2K1</i>	6	4,8
<i>PDGFRA</i>	6	4,8
<i>PIK3CA</i>	6	4,8
<i>RET</i>	6	4,8
<i>MET</i>	5	4,0
<i>SMAD4</i>	5	4,0
<i>BRAF</i>	4	3,2
<i>ESR1</i>	4	3,2
<i>MTOR</i>	4	3,2
<i>NRAS</i>	4	3,2
<i>SF3B1</i>	4	3,2
<i>ALK</i>	3	2,4
<i>CTNNB1</i>	3	2,4
<i>IDH2</i>	3	2,4
<i>KIT</i>	3	2,4

<i>SMO</i>	3	2,4
<i>FGFR2</i>	2	1,6
<i>GNAQ</i>	2	1,6
<i>HRAS</i>	2	1,6
<i>AKT1</i>	1	0,8
<i>AR</i>	1	0,8
<i>ERBB3</i>	1	0,8
<i>GNAS</i>	1	0,8
<i>IDH1</i>	1	0,8
<i>PTEN</i>	1	0,8

Supplementary Table S3. Relevant information regarding *NRAS* mutated patients.

	1300039	13-003	13-027	36-005
NRAS mutation by NGS (coding/protein)	c.175G>C / p.A59P	c.37G>A / p.G13S	c.35G>A / p.G12D	c.181C>A / p.Q61K
MAF NRAS mutation (%)	1.89	0.24	0.53	1.80
EGFR mutation by NGS (coding/protein)	Non detected	Non detected	c.2235_2249del15 / p.E746_A750del	c.2573T>G / p.L858R
MAF EGFR mutation (%)	-	-	1.98	25.63
p.T790M by NGS	Non detected	Non detected	Non detected	Non detected
EGFR mutation in tumor at stage IV diagnosis	p.G719X	p.L861Q	p.E746_A750del	p.L858R
Sex	Male	Female	Female	Female
Age (years)	58	64	89	52
Smoking	Smoker	Former smoker	Never smoker	Never smoker
Histology	Adenocarcinoma	Adenocarcinoma	Adenocarcinoma	Adenocarcinoma
ECOG-PS	NA	0	1	1
Metastases location at stage IV diagnosis	Thoracic	Thoracic	Thoracic	CNS
Stage	IVA	IVA	IVA	IVB
First-line TKI	Afatinib	Gefitinib	Erlotinib	Afatinib
PFS (months)	16	9.7	6.6	7.6
Progression sites	NA	Thoracic	Thoracic	NA
Second-line treatment	Osimertinib	Chemotherapy	None	Osimertinib
Exitus	NA	0	1	1
OS (months)	NA	62.3	11.8	9.7

CNS: Central Nervous System; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; MAF: Mutant Allele Frequency; NA: Not Available; NGS: Next-Generation Sequencing; OS: Overall survival; PFS: Progression-Free Survival.

Supplementary Table S4. Relevant information regarding *HRAS* mutated patients.

	400003	15-003
HRAS mutation by NGS (coding/protein)	c.37G>C / p.G13R	c.183G>T / p.Q61H
MAF HRAS mutation (%)	4.07	0.40
EGFR mutation by NGS (coding/protein)	Non detected	c.2236_2250del15 / p.E746_A750del
MAF EGFR mutation (%)	-	13.80
p.T790M by NGS	Non detected	Detected
EGFR mutation in tumor at stage IV diagnosis	p.G719X	p.E746_A750del

Sex	Male	Male
Age (years)	74	73
Smoking	Former smoker	Never smoker
Histology	Adenocarcinoma	Adenocarcinoma
ECOG-PS	NA	1
Metastases location at stage IV diagnosis	Thoracic and bone	Bone
Stage	IVB	IVB
First-line TKI	Afatinib	Erlotinib
PFS (months)	5.8	17.1
Progression sites	NA	Bone
Second-line treatment	None	Osimertinib
Exitus	NA	No
OS (months)	NA	53.4

ECOG-PS: Eastern Cooperative Oncology Group Performance Status; MAF: Mutant Allele Frequency; NA: Not Available; NGS: Next-Generation Sequencing; OS: Overall survival; PFS: Progression-Free Survival.