Anotation Redundancy

Jun Kang

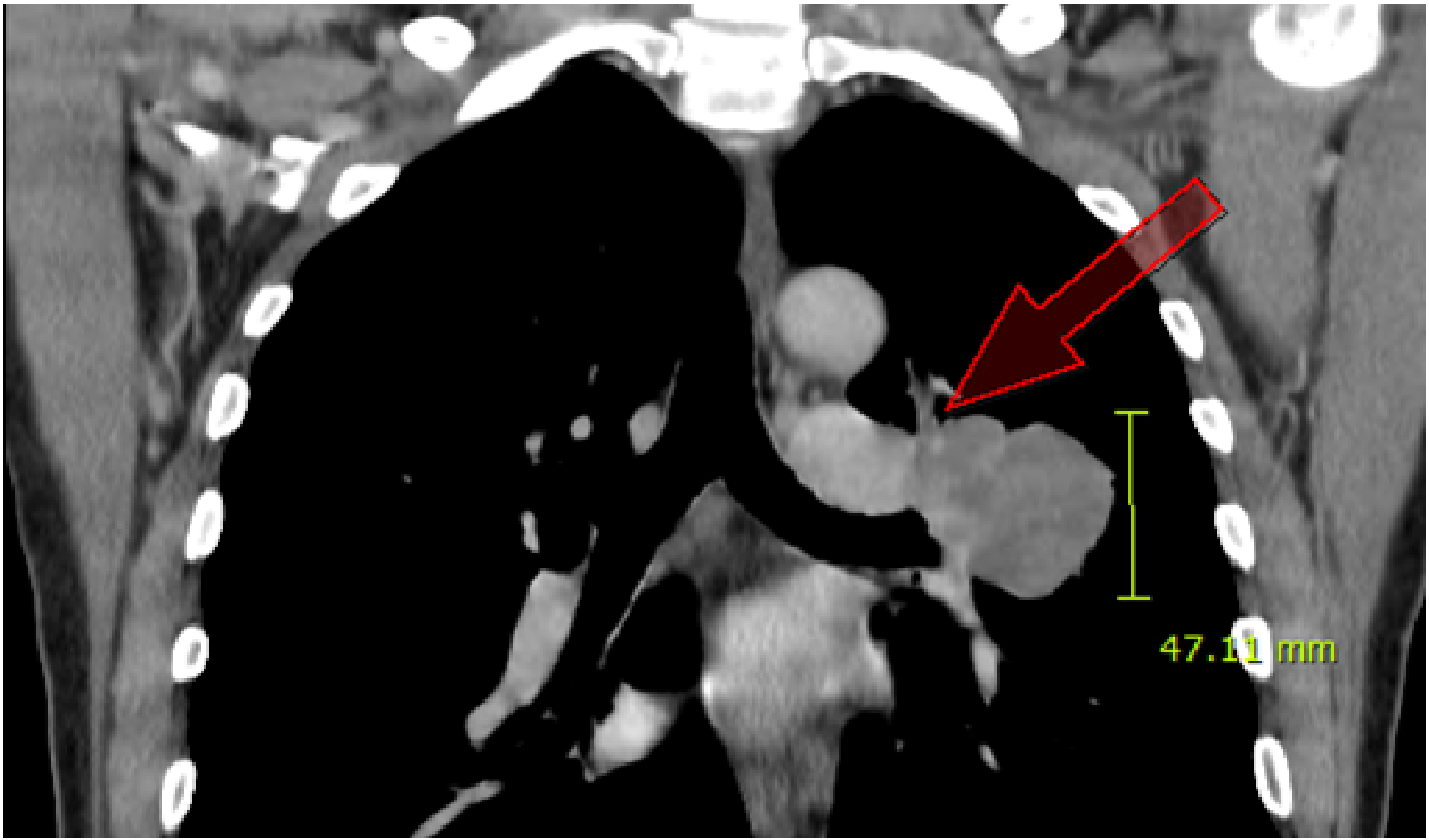
2019-11-01

Annotation redundancy

- Exact variants (indication for targeted therapy)
- **Many annotations** for a **same variant**

Case 1

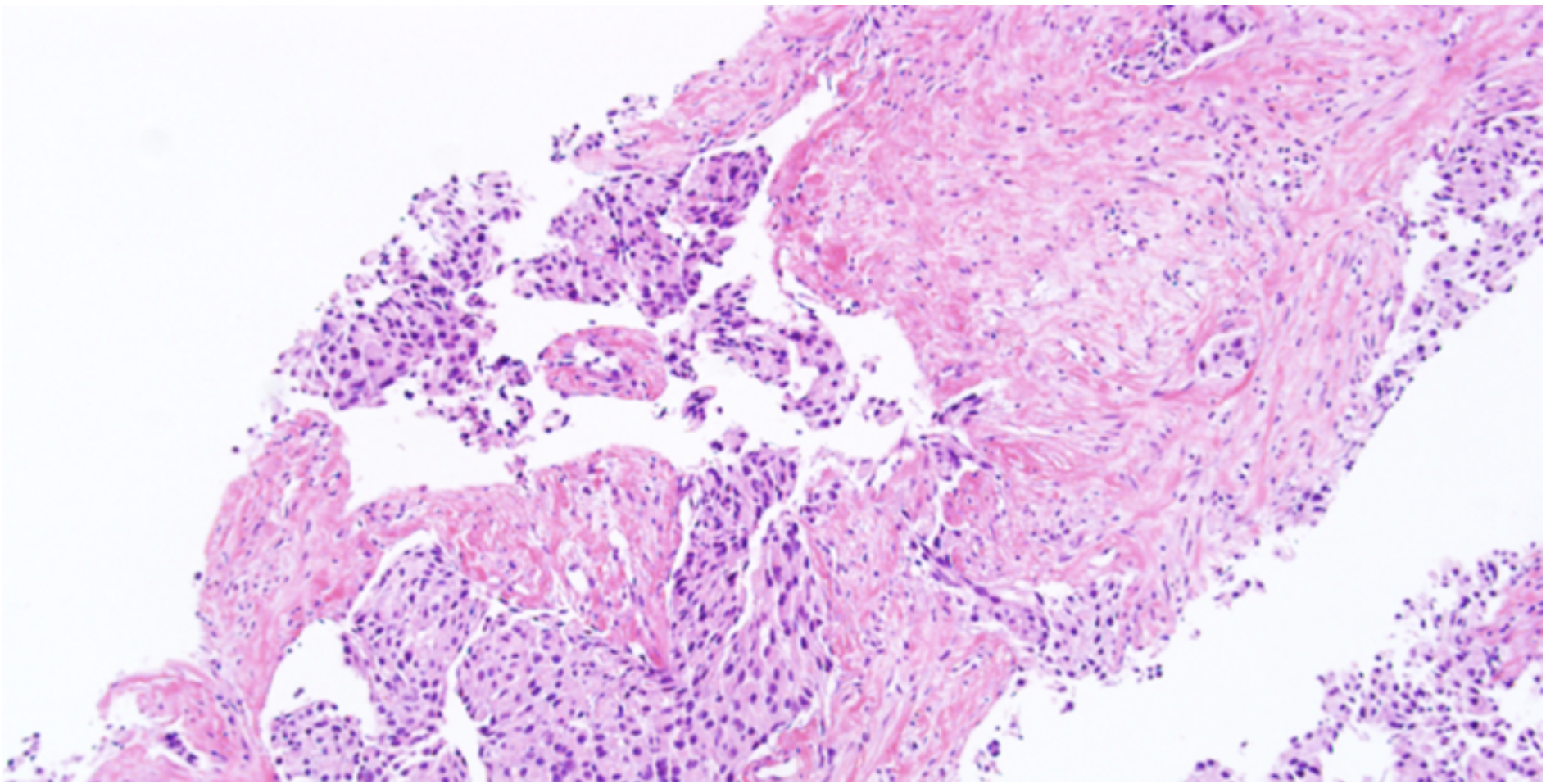
5.3cm, central mass in LUL, obstructing LUL bronchus Suspicious invasion of left upper pulmonary artery



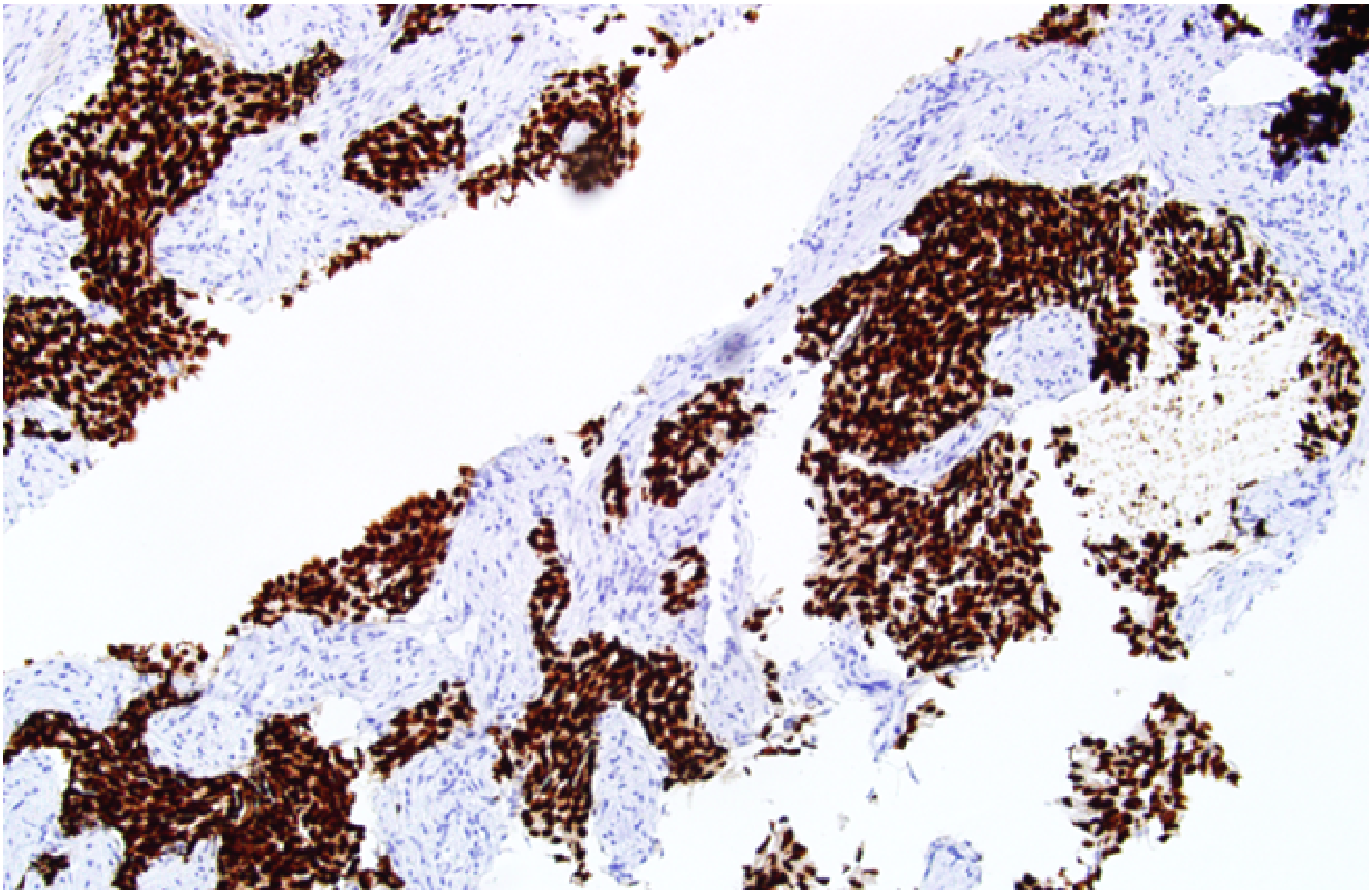

A

Pathology

- Lymph node, level II, left, needle biopsy;
- **Adenocarcinoma, solid type , metastatic**
- PD-L1: 22C3(0%), SP142(0%)



TTF-1



Molecular

- **EGFR PNAClamp** : negative
- **FISH** : ALK(-), ROS1(-), RET(-)

NGS (Ion Torrent)

- ERBB2 exon20 insertion
- Afatinib: irreversible EGFR TKI

Variant Summary

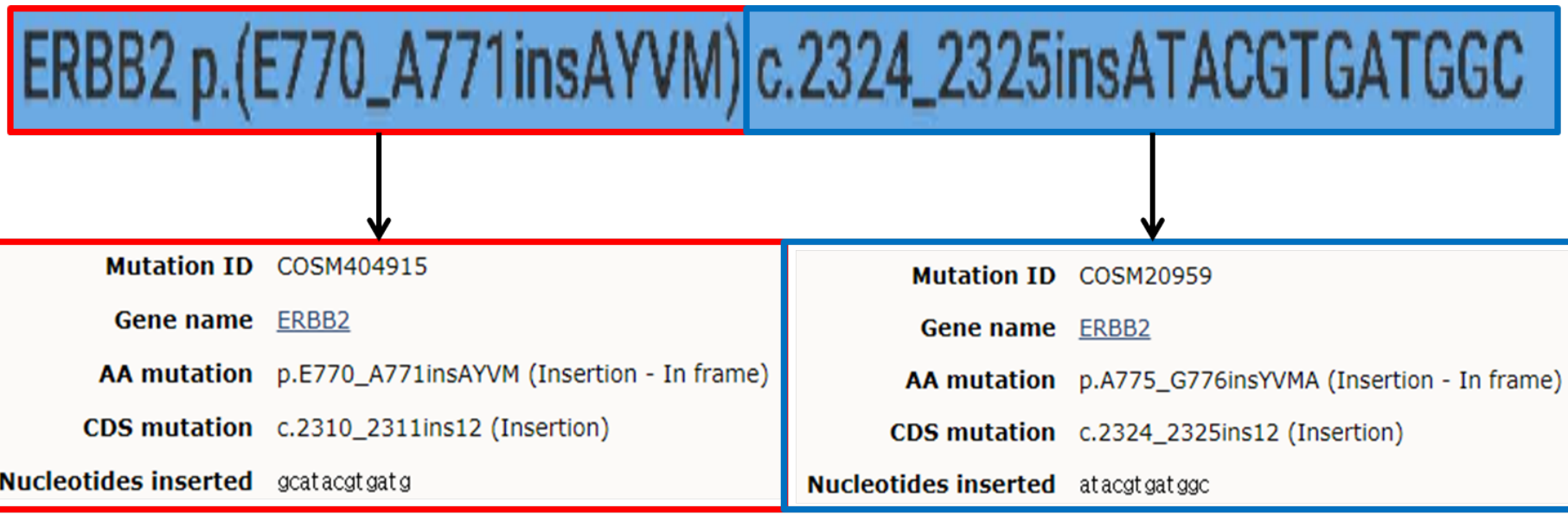
Sample Cancer Type: Non-Small Cell Lung Cancer

Gene Variant	US-FDA	US-NCCN	EMA	ESMO	Global Clinical Trials
ERBB2 p.(E770_A771insAYVM) c.2324_2325insATACGTGATGGC	✖	● (2)	✖	✖	● (14)

Relevant Therapy Summary

Relevant Therapy	US-FDA	US-NCCN	EMA	ESMO	Global Clinical Trials*
afatinib	✖	●	✖	✖	● (II)
trastuzumab	✖	●	✖	✖	✖

Ion Reporter, COSMIC, VEP (Variant Effect Predictor, Ensembl)[1]



5 Mutations (page 1 of 1)

Columns

Sample ID	Protein Change	Annotation ▼	Mutation Type	Copy #	COSMIC	# Mut in Sample
M17-10371	*G778_P780dup*		IF ins	Diploid		3
M18-2164	*G778_P780dup*		IF ins	Diploid		2
M17-11040	*Y772_A775dup*		IF ins	Diploid		5
M17-8467	*Y772_A775dup*		IF ins	Diploid		4
M18-1951	*L755M*		Missense	Diploid	35	3

Redundant annotations for ERBB2 insertion mutation

	GAA	GCA	TAC	GTG	ATG	GCA	TAC	GTG	ATG	GCT	GGT
Y772_A775dup	E	A	Y	V	M	A	Y	V	M	A	G
	770	771	772	773	774	775					776

	770	771	772	773	774	775					776
.A775_G776insYVMA	E	A	Y	V	M	A	Y	V	M	A	G
	GAA	GCA	TAC	GTG	ATG	GCA	TAC	GTG	ATG	GCT	GGT

Chr17:37,880,979-37,880,999	GAA	GCA	TAC	GTG	ATG	GCT	GGT
Reference amino acid sequence	E	A	Y	V	M	A	G
Reference amino acid number (NP_004439)	770	771	772	773	774	775	776

	GAA	GCA	TAC	GTG	ATG	GCA	TAC	GTG	ATG	GCT	GGT
E770_A771insAYVM	E	A	Y	V	M	A	Y	V	M	A	G
	770					771	772	773	774	775	776

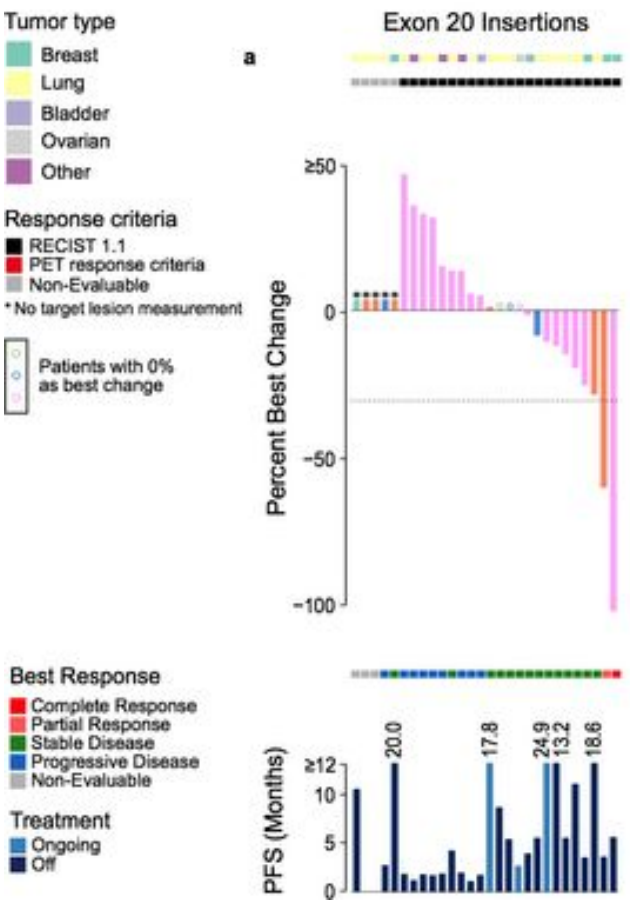
Redundant annotations for ERBB2 insertion mutation

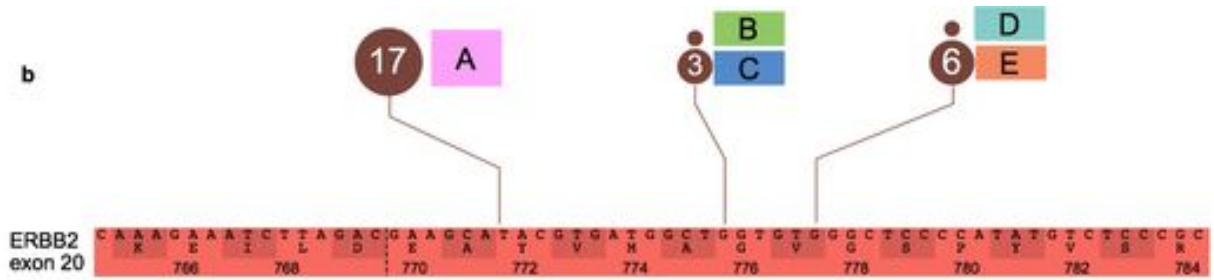
Chr17:37,880,979-37,880,999	GAA	GCA	TAC	GTG	ATG	GCT	GGT
Reference amino acid sequence	E	A	Y	V	M	A	G
Reference amino acid number (NP_004439)	770	771	772	773	774	775	776

	GAA	GCA	TAC	GTG	ATG	GCA	TAC	GTG	ATG	GCT	GGT
M774_A775insAYVM	E	A	Y	V	M	A	Y	V	M	A	G
	770	771	772	773	774	775					776

	GAA	GCA	TAC	GTG	ATG	GCA	TAC	GTG	ATG	GCT	GGT
:A771_Y772insYVMA	E	A	Y	V	M	A	Y	V	M	A	G
	770	771					772	773	774	775	776

Nature volume 554, pages 189–194 (08 February 2018)[2]

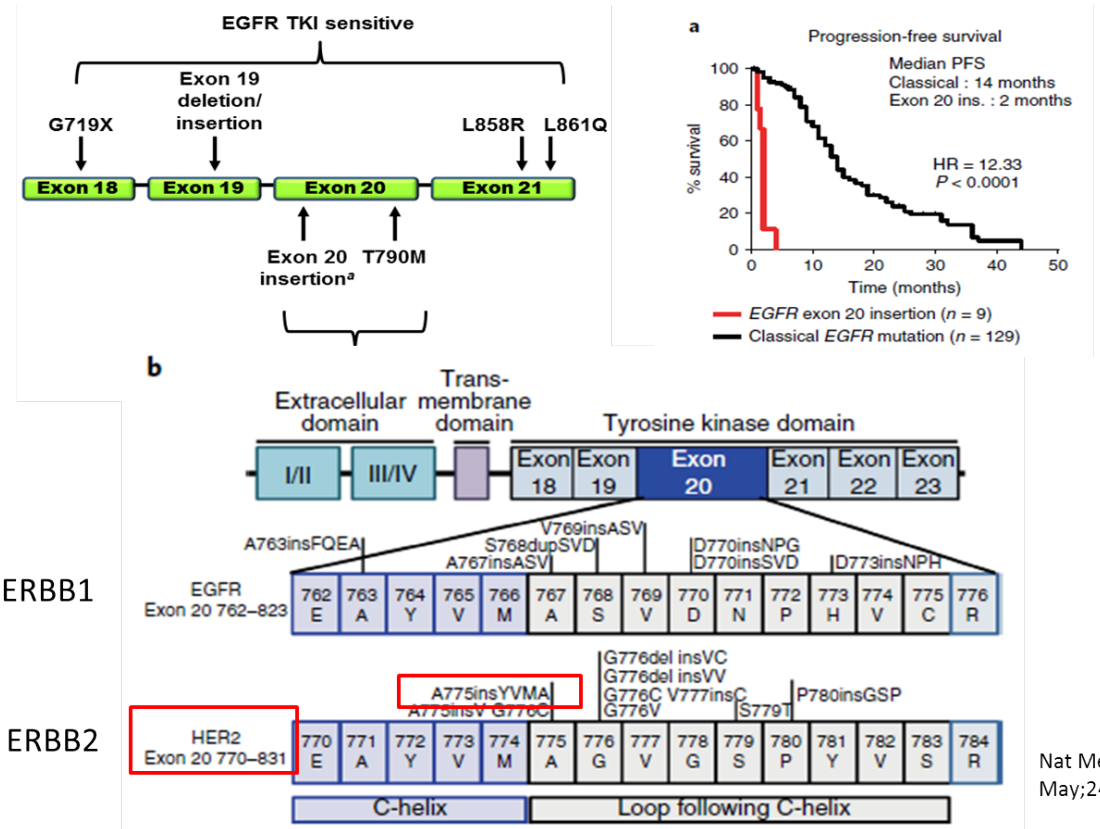




c

Exon 20 Insertions	Group	N	770 772 774 776 778 780 E A Y V M A G V G S P
E770_A771insAYVM	A	17	E A Y V M A Y V M A G V G S P
A771_Y772insYVMA			E A Y V M A Y V M A G V G S P
Y772_A775dup			E A Y V M A Y V M A G V G S P
G776delinsVC	B	1	E A Y V M A G V C V G S P
G776_V777insVGC	C	3	E A Y V M A G V G C V G S P
V777_G778insG	D	1	E A Y V M A G V G G S P
V777_G778insGSP	E	6	E A Y V M A G V G S P G S P
G778_P780dup			E A Y V M A G V G S P G S P
G780_Y781insGSP			E A Y V M A G V G S P G S P

Nat Med. 2018 May;24(5):638-646[3]



Nat Med. 2018 May;24(5):638-646

Case 2

- F/80
- Adenocarcinoma of lung

2. Result

[검사방법]
NGS (Next Generation Sequencing)

[검사결과]
1) EGFR mutation: Positive - exon19 insertion (p.Lys745_Glu746dupIleProValAlaIleLys,
c.2217_2234dupAATTCCCGTCGCTATCAA)
(variant allele frequency 29.99%, COSM26443) (OKR이미지 참조)

2) CDK4 amplification: 12q14.1(58141846-58146225)x9.875

3) MDM2 amplification: 12q15(69207031-69238239)x16.6

EGFR Exon 19 insertion

MY CANCER GENOME®
GENETICALLY INFORMED CANCER MEDICINE

Search My Cancer Genome | Go

Home | DIRECT | About Us

- Lung Cancer
- AKT1
- ALK
- BRAF
- CD274
- DDR2
- EGFR
  - EGFR Status Unknown
  - EGFR No Mutation Detected
  - EGFR Kinase Domain Duplication
  - EGFR c.2156G>C (G719A)
  - EGFR c.2155G>T (G719C)
  - EGFR c.2155G>A (G719S)
  - EGFR Exon 19 Deletion
  - EGFR Exon 19 Insertion
  - EGFR Exon 20 Insertion

What is EGFR? | EGFR in Lung Cancer | EGFR Exon 19 Insertion | Clinical Trials

EGFR Exon 19 Insertion in Non-Small Cell Lung Cancer

Properties	
Location of mutation	Kinase domain (exon 19)
Frequency of EGFR mutations in NSCLC	~10% in the USA ~35% in Asia (Lynch et al. 2004; Paez et al. 2004; Pao et al. 2004)
Frequency of EGFR exon 19 insertion mutations in EGFR-mutated NSCLC	~1% (He et al. 2011)
Implications for Targeted Therapeutics	
Response to EGFR TKIs	Confers increased sensitivity[a]
Response to anti-EGFR antibodies	Currently no role for EGFR mutation in predicting response in NSCLC

EGFR exon 19 insertions are in-frame insertions of 6 amino acids occurring within exon 19, which encodes part of the kinase domain. This mutation occurs with a frequency of approximately 1% in EGFR-mutated lung tumors (He et al. 2011).

[a] Like EGFR exon 19 deletions, exon 19 insertions are associated with increased sensitivity to EGFR TKIs such as erlotinib (Tarceva; He et al. 2011).

Annotation Redundancy EGFR exon 19 insertion

	CDS mutation	AA mutation
Ion Reporter (IR)	c.2234_2235ins	p.V738_K739insKIPVAI
Cosmic	c.2232_2233ins	p.K745_E746insIPVAIK
Pathology Report	c.2217_2234dup	p.K745_E750dupIPVAIK
Clinical Cancer Reserch	c.2217_2234dup	p.K745_E746insIPVAIK

Allignment

```
1.      GAAAGTT********************AAAATTCCCGTCGCTATCAAGGAATTAAGAGAAGCAACATC
        GAAAGTTAAAATTCCCGTCGCTATCAAAATTCCCGTCGCTATCAAGGAATTAAGAGAAGCAACATC

2.      GAAAGTTAAAATTCCCGTCGCTATCAA********************GGAATTAAGAGAAGCAACATC
        GAAAGTTAAAATTCCCGTCGCTATCAAAATTCCCGTCGCTATCAAGGAATTAAGAGAAGCAACATC

3.      GAAAGTTAAAATTCCCGTCGCTATC********************AAGGAATTAAGAGAAGCAACATC
        GAAAGTTAAAATTCCCGTCGCTATCAAAATTCCCGTCGCTATCAAGGAATTAAGAGAAGCAACATC
```

Clin Cancer Res; 18(6); 1790–7[4]

Patient	Tissue	Histology	Nucleotide Sequence	Nucleotide change	Amino Acid Sequence
Wild-Type (for reference)			GTTAAAATTCCCGTCGCTATCAAGGAA -V--K--I--P--V--A--I--K--E- 739 745	c.2212_2238	p.V738_E746VKIPVAIKE
#1	Lung resection	Adeno	GTTAAAATTCCCGTCGCTATTAAAATTCCCGTCGCTATCAAGGAA	c.2214_2231dup	p.I744_K745insKIPVAI
#2	Lung resection	Adeno	GTTAAAATTCCCGTCGCTATCAAAATTCCCGTCGCTATCAAGGAA	c.2217_2234dup	p.K745_E746insIPVAIK
#3	Lung resection	Adeno	GTTAAAATTCCCGTCGCTATCAAGGTTCCCGTCGCTATCAAGGAA	c.2219_2236dup	p.K745_E746insVPVAIK
#4	Lung resection	Adeno-squamous	GTTAAAATTCCCGTCGCTATCAAAATTCCCGTCGCTATCAAGGAA	c.2217_2234dup	p.K745_E746insIPVAIK
#5	Lung resection	Adeno	GTTAAAATTCCCGTCGCTATCAAGGTTCCCGTCGCTATCAAGGAA	c.2219_2236dup	p.K745_E746insVPVAIK
#6	Lung FNA	Adeno	GTTAAAATTCCCGTCGCTATCAAAATTCCCGTCGCTATCAAGGAA	c.2217_2234dup	p.K745_E746insIPVAIK
#7	Pleural fluid	Adeno	GTTAAAATTCCCGTCGCTATTAAAATTCCCGTCGCTATCAAGGAA	c.2214_2231dup	p.I744_K745insKIPVAI
#8	Lymph node biopsy	Adeno	GTTAAAATTCCCGTCGCTATTAAAATTCCCGTCGCTATCAAGGAA	c.2214_2231dup	p.I744_K745insKIPVAI
#9	Lung resection	Adeno	GTTAAAATTCCCGTCGCTATCAAAATTCCCGTCGCTATCAAGGAA	c.2217_2234dup	p.K745_E746insIPVAIK
#10	Bone FNA	Adeno	(18 base pair insertion, sequence unavailable)	--	--
#11	Lung FNA	Adeno	GTTAAAATTCCCGTCGCTATCAAAAcTCCCGTCGCTATCAAGGAA	c.2234_2235ins18	p.K745_E746insTPVAIK
#12	Bone resection	Adeno	GTTAAAATTCCCGTCGCTATCAAAATTCCCGTCGCTATCAAGGAA	c.2215_2232dup	p.I744_K745insKIPVAI

Note: Each case involves an 18 base-pair insertion which includes the sequence TCCCGTCGCTAT, and each shares the inserted amino acids PVAI. Duplicated sequences are underlined and the inserted sequences are shown in boxes. All cases are exact duplications except for #11, where the inserted sequence differs by a single T→C transition (shown in lower case). Case #10 had enough DNA for fragment length analysis, but not enough to then undergo full sequencing.

Mutation Nomenclature[5]

No recommendations have been made to describe duplications. Although they can be seen as a specific type of insertion, and could be described as such, they often originate through other mutational mechanisms. We therefore prefer to provide a distinctive designation of this type of sequence change

HGVS vs VEP

- HGVS Recommendations for the Description of Sequence
- Variants: 2016 Update

The Ensembl Variant Effect Predictor

HGVS Recommendations for the Description of Sequence Variants: 2016 Update

http://varnomen.hgvs.org/recommendations/

Conclusions

- Redundant annotation
  - ERBB2 exon20, EGFR exon19 insertion/duplication

References I

1. What is the Variant Effect Predictor (VEP)? | Ensembl Genomes.

2. Hyman, D.M., Piha-Paul, S.A., Won, H., Rodon, J., Saura, C., Shapiro, G.I., Juric, D., Quinn, D.I., Moreno, V., Doger, B., et al. (2018). HER kinase inhibition in patients with HER2- and HER3-mutant cancers. Nature *554*, 189–194.

3. Robichaux, J.P., Elamin, Y.Y., Tan, Z., Carter, B.W., Zhang, S., Liu, S., Li, S., Chen, T., Poteete, A., Estrada-Bernal, A., et al. (2018). Mechanisms and clinical activity of an EGFR and HER2 exon 20–selective kinase inhibitor in non–small cell lung cancer. Nature Medicine *24*, 638.

4. He, M., Capelletti, M., Nafa, K., Yun, C.-H., Arcila, M.E., Miller, V.A., Ginsberg, M.S., Zhao, B., Kris, M.G., Eck, M.J., et al. (2012). EGFR Exon 19 Insertions: A New Family of Sensitizing EGFR Mutations in Lung Adenocarcinoma. Clinical Cancer Research *18*, 1790–1797.

References II

5. Dunnen, J.T. den, and Antonarakis, S.E. (2000). Mutation nomenclature extensions and suggestions to describe complex mutations: A discussion. Human Mutation *15*, 7–12.