



## Sample Information

**Patient Name:** 林玉慧

**Gender:** Female

**ID No.:** B220778941

**History No.:** 7083025

**Age:** 62

**Ordering Doctor:** DOC3016D 江起陸

**Ordering REQ.:** 0ATYTDR

**Signing in Date:** 2020/07/23

**Path No.:** S109-99748

**MP No.:** F20046

**Assay:** Oncomine Focus Assay

**Sample Type:** FFPE

**Block No.:** S109-77158A

**Percentage of tumor cells:** 20%

**Note:**

## Sample Cancer Type: Non-Small Cell Lung Cancer

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### Report Highlights

5 Relevant Biomarkers  
 11 Therapies Available  
 109 Clinical Trials

## Relevant Non-Small Cell Lung Cancer Findings

Gene	Finding	Gene	Finding
ALK	Not detected	NTRK1	Not detected
BRAF	Not detected	NTRK2	Not detected
EGFR	<b>EGFR p.(L858R) c.2573T&gt;G, EGFR p.(T790M) c.2369C&gt;T</b>	NTRK3	Not detected
ERBB2	Not detected	RET	Not detected
KRAS	Not detected	ROS1	Not detected
MET	Not detected		



## Relevant Biomarkers

■ Indicated ■ Contraindicated

Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
<b>EGFR p.(L858R) c.2573T&gt;G</b> epidermal growth factor receptor Tier: IA Allele Frequency: 42.07%	<span style="color: green;">■</span> <b>osimertinib</b> <sup>1, 2</sup> afatinib + cetuximab <span style="color: green;">■</span> <b>bevacizumab* + erlotinib</b> <sup>2</sup> <span style="color: green;">■</span> <b>erlotinib + ramucirumab</b> <sup>2</sup> atezolizumab + bevacizumab + chemotherapy gefitinib + chemotherapy bevacizumab + gefitinib	None	87
<b>EGFR p.(T790M) c.2369C&gt;T</b> epidermal growth factor receptor Tier: IA Allele Frequency: 4.40%	<span style="color: green;">■</span> <b>osimertinib</b> <sup>1, 2</sup> afatinib + cetuximab <span style="color: red;">■</span> <b>gefitinib</b> <sup>2</sup>	None	61
<b>AR amplification</b> androgen receptor Tier: IIC	None	<span style="color: green;">■</span> androgen receptor therapy bicalutamide leuprorelin	0
<b>CDK4 amplification</b> cyclin dependent kinase 4 Tier: IIC	None	None	6
<b>CCND1 amplification</b> cyclin D1 Tier: IIC	None	None	4

Public data sources included in relevant therapies: FDA1, NCCN, EMA2, ESMO

Tier Reference: Li et al. Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists. J Mol Diagn. 2017 Jan;19(1):4-23.

\* Includes biosimilars

## Variants (Exclude variant in Taiwan BioBank with >1% allele frequency)

### DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect	Coverage
EGFR	p.(T790M)	c.2369C>T	COSM6240	chr7:55249071	4.40%	NM_005228.4	missense	1999
EGFR	p.(L858R)	c.2573T>G	COSM6224	chr7:55259515	42.07%	NM_005228.4	missense	1992

### Copy Number Variations

Gene	Locus	Copy Number
CCND1	chr11:69456942	10.5
CDK4	chr12:58142052	17.8
AR	chrX:66776186	20.65



## Biomarker Descriptions

### AR (androgen receptor)

**Background:** The AR gene encodes the androgen receptor protein (AR), a ligand-activated transcription factor regulated by the binding of the hormones testosterone and dihydrotestosterone<sup>1,2</sup>. Hormone binding to AR results in receptor dimerization, nuclear translocation, and target gene transcription, thus activating the RAS/RAF/MEK/ERK and PI3K/AKT/MTOR signaling pathways, which promote cell proliferation and survival<sup>2,3,4</sup>.

**Alterations and prevalence:** Alterations in AR function can result from overexpression, gene amplification, or mutations. AR mutations, including L702H, W742C/L, H875Y, and T878A, are commonly observed in 10-30% of castration-resistant prostate cancer and result in decreased ligand specificity, allowing other nuclear hormones to activate AR<sup>5</sup>. Androgen receptor splice variants have been reported in castration resistant prostate cancer<sup>6,7</sup>. The androgen receptor splice variant 7 (AR-V7) is a result of aberrant mRNA splicing of AR exons 1-3 and a cryptic exon 3, resulting in the expression of a constitutively active protein<sup>7</sup>.

**Potential relevance:** The FDA has granted fast track designation (2016) to seviteronel for AR-positive triple-negative breast cancer (TNBC) patients<sup>8</sup>. Androgen deprivation therapy (ADT) such as abiraterone<sup>9</sup> (2011) and enzalutamide<sup>10</sup> (2011) are FDA approved for use in locally advanced and metastatic prostate cancers. Although many men initially respond to ADT, most will develop hormone resistance. Resistance to ADT is also associated with other aberrations of the AR gene including mutations within the ligand binding domain and gene amplification<sup>5,11,12</sup>. The androgen receptor splice variant, AR-V7, lacks the ligand binding domain, resulting in constitutive activation and is associated with resistance to androgen deprivation therapy (ADT) in advanced prostate cancer<sup>6</sup>.

### CCND1 (cyclin D1)

**Background:** The CCND1 gene encodes the Cyclin D1 protein, which belongs to the highly conserved cyclin family that functions as regulators of cyclin-dependent kinases (CDKs)<sup>13,14</sup>. CCND1 binds and activates CDK4 and CDK6 to phosphorylate and inactivate the RB protein, which promotes progression through the G1/S phase transition of the cell cycle<sup>15,16,17</sup>.

**Alterations and prevalence:** Recurrent somatic alterations to CCND1, including mutations, amplifications, and chromosomal translocations, are observed in many cancer types. A common mechanism of these alterations is to increase the expression and nuclear localization of the cyclin D1 protein. Recurrent somatic mutations include missense mutations at codons T286 and P287 and c-terminal truncating mutations that are enriched in about 33% of uterine cancer, and missense mutations at Y44 that are enriched in about 50% of Mantle cell lymphoma (MCL)<sup>18,19,20,21</sup>. These mutations block phosphorylation-dependent nuclear export and proteolysis<sup>22,23,24,25</sup>. CCND1 is recurrently amplified in many cancer types, including up to 35% of esophageal cancer, 20-30% of head and neck cancer, and 10-20% of breast, squamous lung, and bladder cancers<sup>18,20,26</sup>. MCL is genetically characterized by the t(11;14) (q13;q13) translocation, a rearrangement that juxtaposes CCND1 to the immunoglobulin heavy (IgH) chain gene. This rearrangement leads to constitutive expression of cyclin D1 and plays an important role in MCL pathogenesis<sup>27,28</sup>.

**Potential relevance:** Currently, no therapies are approved for CCND1 aberrations. Small molecule inhibitors targeting CDK4/6-- including palbociclib (2015), abemaciclib (2017), and ribociclib (2017)-- are FDA approved in combination with an aromatase inhibitor or fulvestrant for the treatment of hormone receptor positive, HER2-negative advanced or metastatic breast cancer. To date, CCND1 alterations are not indicated for CDK4/6 inhibitors.

### CDK4 (cyclin dependent kinase 4)

**Background:** The CDK4 gene encodes the cyclin-dependent kinase-4 protein, a homologue of CDK6. Both proteins are serine/threonine protein kinases that are involved in the regulation of the G1/S phase transition of the mitotic cell cycle<sup>13,14</sup>. CDK4 kinase is activated by complex formation with D-type cyclins (e.g., CCND1, CCND2, or CCND3), which leads to the phosphorylation of retinoblastoma protein (RB), followed by E2F activation, DNA replication, and cell-cycle progression<sup>15</sup>. Germline mutations in CDK4 are associated with familial melanoma<sup>29,30,31</sup>.

**Alterations and prevalence:** Recurrent somatic mutations of CDK4 codon K22 and R24 are observed in melanoma (1-2%) and lung cancer (approximately 0.1%). Codons K22 and R24 are necessary for binding and inhibition by p16/CDKN2A<sup>32,33,34</sup>. CDK4 is recurrently amplified in several cancer types, most notably in sarcomas (15-20%), glioma (10-15%), adrenocortical carcinoma (5%), lung adenocarcinoma (5%), and melanoma (3%)<sup>18,20,35,36</sup>.



## Biomarker Descriptions (continued)

**Potential relevance:** Currently, no therapies are approved for CDK4 aberrations. Small molecule inhibitors targeting CDK4/6– including palbociclib (2015), abemaciclib (2017), and ribociclib (2017)– are FDA approved in combination with an aromatase inhibitor or fulvestrant for the treatment of hormone receptor-positive, HER2-negative advanced or metastatic breast cancer.

### EGFR (epidermal growth factor receptor)

**Background:** The EGFR gene encodes the epidermal growth factor receptor (EGFR) tyrosine kinase, a member of the human epidermal growth factor receptor (HER) family. Along with EGFR/ERBB1/HER1, ERBB2/HER2, ERBB3/HER3, and ERBB4/HER4 make up the HER protein family<sup>37</sup>. EGFR ligand induced dimerization results in kinase activation and leads to stimulation of oncogenic signaling pathways including the PI3K/AKT/MTOR and RAS/RAF/MEK/ERK pathways. Activation of these pathways promote cell proliferation, differentiation, and survival<sup>38,39</sup>.

**Alterations and prevalence:** Recurrent somatic mutations in the tyrosine kinase domain of EGFR are observed in approximately 10-20% of lung adenocarcinoma and at higher frequencies in never-smoker, female, and in Asian populations with lung cancer<sup>18,20,35,40</sup>. The most common mutations occur near the ATP-binding pocket of the kinase domain and include short in-frame deletions in exon 19 (EGFR exon 19 deletion) and the L858R amino acid substitution in exon 21<sup>41</sup>. These mutations constitutively activate the EGFR kinase resulting in downstream signaling and represent 80% of the EGFR mutations observed in lung cancer. A second group of recurrent activating mutations that are less common include E709K, G719X, S768I, L861Q, and short in-frame insertions in exon 20<sup>42,43,44,45</sup>. EGFR activating mutations in lung cancer tend to be mutually exclusive to KRAS activating mutations<sup>46</sup>. Although these variants are common in lung cancer, they are rare in other cancer types. In glioblastoma, recurrent activating EGFR mutations in the extracellular domain include R108K, A289V and G598V<sup>36,41</sup>. The recurrent focal amplification of the EGFR gene leads to an increase in expression in several cancer types. EGFR is amplified in up to 30% of glioblastoma, 12% of esophageal cancer, 10% of head and neck cancer, 5% of bladder cancer, and 5% of lung squamous cell carcinoma<sup>18,20,26,35,36</sup>. Deletion of exons 2-7 encoding the extracellular domain of EGFR (EGFRvIII) results in overexpression of a ligand-independent constitutively active protein which is frequently observed in glioblastoma and has been shown to lead to lung cancer development as well as sensitivity to TKIs<sup>47,48,49</sup>.

**Potential relevance:** Erlotinib<sup>50</sup> (2004), afatinib<sup>51</sup> (2013), gefitinib<sup>52</sup> (2015), osimertinib<sup>53</sup> (2015), and dacomitinib<sup>54</sup> (2018) are small molecule TKIs that are FDA approved for non-small cell lung cancer (NSCLC) patients with sensitizing exon 19 deletions and exon 21 L858R mutations. Acquired secondary mutations often confer resistance to first line TKI therapy with the T790M amino acid substitution accounting for 50-60% of cases<sup>41</sup>. Osimertinib is also indicated for NSCLC patients harboring EGFR T790M mutations whose disease has progressed on or after treatment with a first line TKI. EGFR targeting antibodies including cetuximab<sup>55</sup> (2004), panitumumab<sup>56</sup> (2006), and necitumumab<sup>57</sup> (2016) are also under investigation in combination with EGFR-targeting TKIs for efficacy against EGFR mutations. The use of cetuximab in combination with afatinib is currently recommended by the NCCN for patients who have progressed after receiving erlotinib, afatinib, dacomitinib, or gefitinib and chemotherapy<sup>58</sup>.

## Relevant Therapy Summary

● In this cancer type  
 ○ In other cancer type  
 ● In this cancer type and other cancer types  
 ❌ Contraindicated  
 ⚠️ Both for use and contraindicated  
 ✖ No evidence

### EGFR p.(L858R) c.2573T>G

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
osimertinib	●	●	●	●	● (III)
bevacizumab + erlotinib	✖	●	●	●	● (II)
erlotinib + ramucirumab	✖	●	●	●	✖
afatinib + cetuximab	✖	●	✖	✖	✖

\* Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available.



## Relevant Therapy Summary (continued)

● In this cancer type    ○ In other cancer type    ⓘ In this cancer type and other cancer types    ⛔ Contraindicated    ⚠ Both for use and contraindicated    ✕ No evidence

### EGFR p.(L858R) c.2573T>G (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
bevacizumab (Allergan) + erlotinib	✕	✕	●	✕	✕
atezolizumab + bevacizumab + carboplatin + paclitaxel	✕	✕	✕	●	✕
bevacizumab + gefitinib	✕	✕	✕	●	✕
gefitinib + carboplatin + pemetrexed	✕	✕	✕	●	✕
bevacizumab + osimertinib, osimertinib	✕	✕	✕	✕	● (IV)
icotinib hydrochloride	✕	✕	✕	✕	● (IV)
icotinib hydrochloride, icotinib hydrochloride + chemotherapy	✕	✕	✕	✕	● (IV)
icotinib hydrochloride, radiation therapy	✕	✕	✕	✕	● (IV)
bevacizumab (Shanghai Hengrui Pharmaceutical) + chemotherapy, bevacizumab + chemotherapy	✕	✕	✕	✕	● (III)
bevacizumab, atezolizumab, chemotherapy	✕	✕	✕	✕	● (III)
durvalumab, chemotherapy	✕	✕	✕	✕	● (III)
icotinib hydrochloride, chemotherapy	✕	✕	✕	✕	● (III)
icotinib hydrochloride, icotinib hydrochloride + radiation therapy	✕	✕	✕	✕	● (III)
osimertinib, chemotherapy	✕	✕	✕	✕	● (III)
pembrolizumab, chemotherapy	✕	✕	✕	✕	● (III)
anlotinib hydrochloride + icotinib hydrochloride	✕	✕	✕	✕	● (II)
anlotinib hydrochloride, osimertinib	✕	✕	✕	✕	● (II)
atezolizumab, chemotherapy	✕	✕	✕	✕	● (II)
bevacizumab, osimertinib	✕	✕	✕	✕	● (II)
bintrafusp alfa, chemoradiation therapy, durvalumab	✕	✕	✕	✕	● (II)
BPI-7711	✕	✕	✕	✕	● (II)
chemotherapy, atezolizumab, bevacizumab	✕	✕	✕	✕	● (II)
chemotherapy, durvalumab	✕	✕	✕	✕	● (II)

\* Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available.



## Relevant Therapy Summary (continued)

● In this cancer type    ○ In other cancer type    ⓘ In this cancer type and other cancer types    ⛔ Contraindicated    ⚠ Both for use and contraindicated    ✕ No evidence

### EGFR p.(L858R) c.2573T>G (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
chemotherapy, ramucirumab	✕	✕	✕	✕	● (II)
crizotinib + chemotherapy	✕	✕	✕	✕	● (II)
durvalumab, tremelimumab, chemotherapy	✕	✕	✕	✕	● (II)
famitinib, HS-10296	✕	✕	✕	✕	● (II)
icotinib hydrochloride + radiation therapy	✕	✕	✕	✕	● (II)
icotinib hydrochloride + radiation therapy, icotinib hydrochloride	✕	✕	✕	✕	● (II)
nivolumab, ipilimumab	✕	✕	✕	✕	● (II)
osimertinib + radiation therapy	✕	✕	✕	✕	● (II)
osimertinib, bevacizumab	✕	✕	✕	✕	● (II)
osimertinib, osimertinib + chemotherapy	✕	✕	✕	✕	● (II)
osimertinib, radiation therapy	✕	✕	✕	✕	● (II)
osimertinib, ramucirumab	✕	✕	✕	✕	● (II)
osimertinib, savolitinib	✕	✕	✕	✕	● (II)
pembrolizumab + chemotherapy	✕	✕	✕	✕	● (II)
tyrosine kinase inhibitors, radiation therapy	✕	✕	✕	✕	● (II)
ASK120067	✕	✕	✕	✕	● (I/II)
AZD4635 + oleclumab	✕	✕	✕	✕	● (I/II)
CBT-502, anlotinib hydrochloride	✕	✕	✕	✕	● (I/II)
DZD-9008	✕	✕	✕	✕	● (I/II)
EMB01	✕	✕	✕	✕	● (I/II)
icotinib hydrochloride + chemotherapy + radiation therapy	✕	✕	✕	✕	● (I/II)
KP-673	✕	✕	✕	✕	● (I/II)
lazertinib	✕	✕	✕	✕	● (I/II)
U3-1402	✕	✕	✕	✕	● (I/II)

\* Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available.



## Relevant Therapy Summary (continued)

● In this cancer type    ○ In other cancer type    ⓘ In this cancer type and other cancer types    ⛔ Contraindicated    ⚠ Both for use and contraindicated    ✕ No evidence

### EGFR p.(L858R) c.2573T>G (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
alisertib, osimertinib	✕	✕	✕	✕	● (I)
CK-101	✕	✕	✕	✕	● (I)
everolimus + neratinib, neratinib + palbociclib, neratinib + trametinib	✕	✕	✕	✕	● (I)
FCN-411	✕	✕	✕	✕	● (I)
genolimzumab, fruquintinib	✕	✕	✕	✕	● (I)
JNJ-61186372, lazertinib	✕	✕	✕	✕	● (I)
lazertinib, JNJ-61186372	✕	✕	✕	✕	● (I)
nazartinib, trametinib	✕	✕	✕	✕	● (I)
niraparib, osimertinib	✕	✕	✕	✕	● (I)
nivolumab, ipilimumab, radiation therapy	✕	✕	✕	✕	● (I)
osimertinib + radiation therapy, osimertinib	✕	✕	✕	✕	● (I)
osimertinib, necitumumab	✕	✕	✕	✕	● (I)
pirotinib	✕	✕	✕	✕	● (I)
SH-1028	✕	✕	✕	✕	● (I)
telisotuzumab vedotin, osimertinib	✕	✕	✕	✕	● (I)
TNO-155	✕	✕	✕	✕	● (I)
TP-0903	✕	✕	✕	✕	● (I)
tyrosine kinase inhibitors, tyrosine kinase inhibitors + chemotherapy	✕	✕	✕	✕	● (I)

### EGFR p.(T790M) c.2369C>T

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
osimertinib	●	●	●	●	● (IV)
afatinib + cetuximab	✕	●	✕	✕	✕
gefitinib	✕	✕	⛔	✕	✕

\* Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available.



## Relevant Therapy Summary (continued)

● In this cancer type    ○ In other cancer type    ⓘ In this cancer type and other cancer types    ⛔ Contraindicated    ⚠ Both for use and contraindicated    ✕ No evidence

### EGFR p.(T790M) c.2369C>T (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
anlotinib hydrochloride, osimertinib	✕	✕	✕	✕	● (IV)
icotinib hydrochloride, radiation therapy	✕	✕	✕	✕	● (IV)
bevacizumab (Shanghai Hengrui Pharmaceutical) + chemotherapy, bevacizumab + chemotherapy	✕	✕	✕	✕	● (III)
bevacizumab, atezolizumab, chemotherapy	✕	✕	✕	✕	● (III)
durvalumab, chemotherapy	✕	✕	✕	✕	● (III)
icotinib hydrochloride, chemotherapy	✕	✕	✕	✕	● (III)
osimertinib, chemotherapy	✕	✕	✕	✕	● (III)
sintilimab, bevacizumab (Innovent Biologics), chemotherapy	✕	✕	✕	✕	● (III)
toripalimab, chemotherapy	✕	✕	✕	✕	● (III)
apatinib + chemotherapy	✕	✕	✕	✕	● (II)
avitinib	✕	✕	✕	✕	● (II)
bevacizumab, osimertinib	✕	✕	✕	✕	● (II)
BPI-7711	✕	✕	✕	✕	● (II)
chemotherapy, ramucirumab	✕	✕	✕	✕	● (II)
D-0316	✕	✕	✕	✕	● (II)
durvalumab, tremelimumab, chemotherapy	✕	✕	✕	✕	● (II)
famitinib, HS-10296	✕	✕	✕	✕	● (II)
KN046	✕	✕	✕	✕	● (II)
nivolumab, ipilimumab	✕	✕	✕	✕	● (II)
osimertinib, osimertinib + chemotherapy	✕	✕	✕	✕	● (II)
tyrosine kinase inhibitors, radiation therapy	✕	✕	✕	✕	● (II)
ASK120067	✕	✕	✕	✕	● (I/II)
AZD4635 + oleclumab	✕	✕	✕	✕	● (I/II)
DZD-9008	✕	✕	✕	✕	● (I/II)

\* Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available.





## Relevant Therapy Summary (continued)

● In this cancer type    ○ In other cancer type    ● In this cancer type and other cancer types    ⛔ Contraindicated    ⚠ Both for use and contraindicated    ✕ No evidence

### EGFR p.(T790M) c.2369C>T (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
EMB01	✕	✕	✕	✕	● (I/II)
icotinib hydrochloride + chemotherapy + radiation therapy	✕	✕	✕	✕	● (I/II)
KP-673	✕	✕	✕	✕	● (I/II)
lazertinib	✕	✕	✕	✕	● (I/II)
U3-1402	✕	✕	✕	✕	● (I/II)
alisertib, osimertinib	✕	✕	✕	✕	● (I)
APG-1252, osimertinib	✕	✕	✕	✕	● (I)
CK-101	✕	✕	✕	✕	● (I)
ES-072	✕	✕	✕	✕	● (I)
everolimus + neratinib, neratinib + palbociclib, neratinib + trametinib	✕	✕	✕	✕	● (I)
FCN-411	✕	✕	✕	✕	● (I)
JNJ-61186372	✕	✕	✕	✕	● (I)
lazertinib, JNJ-61186372	✕	✕	✕	✕	● (I)
nazartinib, trametinib	✕	✕	✕	✕	● (I)
nivolumab, ipilimumab, radiation therapy	✕	✕	✕	✕	● (I)
osimertinib + radiation therapy, osimertinib	✕	✕	✕	✕	● (I)
osimertinib, necitumumab	✕	✕	✕	✕	● (I)
pirotinib	✕	✕	✕	✕	● (I)
SH-1028	✕	✕	✕	✕	● (I)
TP-0903	✕	✕	✕	✕	● (I)
TQB3456	✕	✕	✕	✕	● (I)
tyrosine kinase inhibitors, tyrosine kinase inhibitors + chemotherapy	✕	✕	✕	✕	● (I)
YK-029A	✕	✕	✕	✕	● (I)

\* Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available.



## Relevant Therapy Summary (continued)

● In this cancer type    ○ In other cancer type    ⓘ In this cancer type and other cancer types    ⛔ Contraindicated    ⚠ Both for use and contraindicated    ✕ No evidence

### EGFR p.(T790M) c.2369C>T (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
YZJ-0318	✕	✕	✕	✕	● (I)

### AR amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
androgen receptor therapy	✕	○	✕	✕	✕
bicalutamide	✕	○	✕	✕	✕
leuprorelin	✕	○	✕	✕	✕

### CDK4 amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
abemaciclib	✕	✕	✕	✕	● (II)
palbociclib	✕	✕	✕	✕	● (II)
palbociclib, abemaciclib	✕	✕	✕	✕	● (II)

### CCND1 amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
abemaciclib	✕	✕	✕	✕	● (II)
palbociclib	✕	✕	✕	✕	● (II)

\* Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available.



## Relevant Therapy Details

### Current FDA Information

☒ In this cancer type
 ☐ In other cancer type
 ☐ In this cancer type and other cancer types
 ☐ Contraindicated
 ☐ Not recommended
 ☐ Resistance

FDA information is current as of 2020-02-28. For the most up-to-date information, search [www.fda.gov](http://www.fda.gov).

### EGFR p.(L858R) c.2573T>G

#### ● osimertinib

**Cancer type:** Non-Small Cell Lung Cancer

**Label as of:** 2019-12-19

**Variant class:** EGFR L858R mutation

#### Indications and usage:

TAGRISSO® is a kinase inhibitor indicated for

- the first-line treatment of patients with metastatic NSCLC whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test.
- the treatment of patients with metastatic EGFR T790M mutation-positive NSCLC, as detected by an FDA-approved test, whose disease has progressed on or after EGFR TKI therapy.

#### Reference:

[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/208065s013lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/208065s013lbl.pdf)

### EGFR p.(T790M) c.2369C>T

#### ● osimertinib

**Cancer type:** Non-Small Cell Lung Cancer

**Label as of:** 2019-12-19

**Variant class:** EGFR T790M mutation

#### Indications and usage:

TAGRISSO® is a kinase inhibitor indicated for

- the first-line treatment of patients with metastatic NSCLC whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test.
- the treatment of patients with metastatic EGFR T790M mutation-positive NSCLC, as detected by an FDA-approved test, whose disease has progressed on or after EGFR TKI therapy.

#### Reference:

[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/208065s013lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/208065s013lbl.pdf)



## Current NCCN Information

- ☒ In this cancer type
 ☐ In other cancer type
 ☒ In this cancer type and other cancer types
 ☒ Contraindicated
 ☒ Not recommended
 ☒ Resistance

NCCN information is current as of 2019-11-01. For the most up-to-date information, search [www.nccn.org](http://www.nccn.org).  
For NCCN International Adaptations & Translations, search [www.nccn.org/global/international\\_adaptations.aspx](http://www.nccn.org/global/international_adaptations.aspx).

### EGFR p.(L858R) c.2573T>G + EGFR p.(T790M) c.2369C>T

#### ● afatinib + cetuximab

Cancer type: Non-Small Cell Lung Cancer

Variant classes: EGFR T790M mutation & EGFRi sensitizing mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- Non-Small Cell Lung Cancer; Progression after receiving erlotinib, afatinib, dacomitinib, or gefitinib and systemic therapy (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2020]

### EGFR p.(L858R) c.2573T>G

#### ● osimertinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR L858R mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):

- Adenocarcinoma, Large Cell, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; Sensitizing EGFR mutation discovered prior to first-line systemic therapy (First-line therapy) (Preferred)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2020]

#### ● bevacizumab + erlotinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR L858R mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- Non-Squamous Non-Small Cell Lung Cancer; Progression after first-line therapy (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2020]



## EGFR p.(L858R) c.2573T>G (continued)

### ● erlotinib + ramucirumab

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR L858R mutation

NCCN Recommendation category: 2A

#### Population segment (Line of therapy):

- Adenocarcinoma, Large Cell, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; Sensitizing EGFR mutation discovered prior to first-line systemic therapy (First-line therapy) (Other Recommended)
- Adenocarcinoma, Large Cell, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; Sensitizing EGFR mutation discovered during first-line systemic therapy (First-line therapy)
- Adenocarcinoma, Large Cell, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; Progression after first-line therapy (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2020]

### ● osimertinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR L858R mutation

NCCN Recommendation category: 2A

#### Population segment (Line of therapy):

- Adenocarcinoma, Large Cell, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; Sensitizing EGFR mutation discovered during first-line systemic therapy; Interrupt or complete planned systemic therapy, including maintenance therapy (First-line therapy) (Preferred)
- Progression on osimertinib (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2020]

### ● bevacizumab + erlotinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR L858R mutation

NCCN Recommendation category: 2B

#### Population segment (Line of therapy):

- Non-Squamous Non-Small Cell Lung Cancer; Sensitizing EGFR mutation discovered prior to first-line systemic therapy (First-line therapy) (Useful in Certain Circumstances)
- Non-Squamous Non-Small Cell Lung Cancer; Sensitizing EGFR mutation discovered during first-line systemic therapy (First-line therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2020]



## EGFR p.(L858R) c.2573T>G (continued)

### ● osimertinib

**Cancer type:** Non-Small Cell Lung Cancer

**Variant class:** EGFR mutation

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**

- Non-Small Cell Lung Cancer; Brain metastases; Newly diagnosed (Not specified)
- Non-Small Cell Lung Cancer; Leptomeningeal and Spine metastases (Not specified)

**Reference:** NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 3.2019]

### 🗨 alectinib

**Cancer type:** Non-Small Cell Lung Cancer

**Variant class:** EGFRi sensitizing mutation

**Summary:**

NCCN Guidelines® include the following supporting statement(s):

- "Likewise, crizotinib, ceritinib, alectinib, brigatinib, or lorlatinib are not recommended for patients with sensitizing EGFR mutations who relapse on EGFR TKI therapy."

**Reference:** NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2020]

### 🗨 brigatinib

**Cancer type:** Non-Small Cell Lung Cancer

**Variant class:** EGFRi sensitizing mutation

**Summary:**

NCCN Guidelines® include the following supporting statement(s):

- "Likewise, crizotinib, ceritinib, alectinib, brigatinib, or lorlatinib are not recommended for patients with sensitizing EGFR mutations who relapse on EGFR TKI therapy."

**Reference:** NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2020]

### 🗨 ceritinib

**Cancer type:** Non-Small Cell Lung Cancer

**Variant class:** EGFRi sensitizing mutation

**Summary:**

NCCN Guidelines® include the following supporting statement(s):

- "Likewise, crizotinib, ceritinib, alectinib, brigatinib, or lorlatinib are not recommended for patients with sensitizing EGFR mutations who relapse on EGFR TKI therapy."

**Reference:** NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2020]



## EGFR p.(L858R) c.2573T>G (continued)

### crizotinib

**Cancer type:** Non-Small Cell Lung Cancer

**Variant class:** EGFRi sensitizing mutation

**Summary:**

NCCN Guidelines® include the following supporting statement(s):

- "Likewise, crizotinib, ceritinib, alectinib, brigatinib, or lorlatinib are not recommended for patients with sensitizing EGFR mutations who relapse on EGFR TKI therapy."

**Reference:** NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2020]

### lorlatinib

**Cancer type:** Non-Small Cell Lung Cancer

**Variant class:** EGFRi sensitizing mutation

**Summary:**

NCCN Guidelines® include the following supporting statement(s):

- "Likewise, crizotinib, ceritinib, alectinib, brigatinib, or lorlatinib are not recommended for patients with sensitizing EGFR mutations who relapse on EGFR TKI therapy."

**Reference:** NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2020]

### pembrolizumab

**Cancer type:** Non-Small Cell Lung Cancer

**Variant class:** EGFR mutation

**Other criteria:** CD274 overexpression

**Summary:**

NCCN Guidelines® include the following supporting statement(s):

- "A small study suggests that single-agent pembrolizumab is not effective as first-line therapy in patients with metastatic NSCLC and EGFR mutations, even those with PD-L1 levels more than 50%."

**Reference:** NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2020]



## EGFR p.(T790M) c.2369C>T

### ● osimertinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR T790M mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):

- Adenocarcinoma, Large Cell, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; Progression on erlotinib (+/- ramucirumab or bevacizumab), afatinib, gefitinib or dacomitinib (Subsequent therapy)
- Adenocarcinoma, Large Cell, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; Progression with symptomatic brain metastases (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2020]

### ● osimertinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR T790M mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- Non-Small Cell Lung Cancer; Brain metastases; Recurrent disease; Use agents active against primary tumor (Not specified)

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 3.2019]

### ● osimertinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- Non-Small Cell Lung Cancer; Brain metastases; Newly diagnosed (Not specified)
- Non-Small Cell Lung Cancer; Leptomeningeal and Spine metastases (Not specified)

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 3.2019]

### 🗨️ pembrolizumab

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR mutation

Other criteria: CD274 overexpression

Summary:

NCCN Guidelines® include the following supporting statement(s):

- "A small study suggests that single-agent pembrolizumab is not effective as first-line therapy in patients with metastatic NSCLC and EGFR mutations, even those with PD-L1 levels more than 50%."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2020]





## EGFR p.(T790M) c.2369C>T (continued)

### afatinib

**Cancer type:** Non-Small Cell Lung Cancer

**Variant class:** EGFR T790M mutation

**Summary:**

NCCN Guidelines® include the following supporting statement(s):

- "The most common known mechanism is the acquisition of T790M (which is a secondary mutation in EGFR), which renders the kinase resistant to erlotinib, gefitinib, dacomitinib or afatinib."

**Reference:** NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2020]

### dacomitinib

**Cancer type:** Non-Small Cell Lung Cancer

**Variant class:** EGFR T790M mutation

**Summary:**

NCCN Guidelines® include the following supporting statement(s):

- "The most common known mechanism is the acquisition of T790M (which is a secondary mutation in EGFR), which renders the kinase resistant to erlotinib, gefitinib, dacomitinib or afatinib."

**Reference:** NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2020]

### EGFR tyrosine kinase inhibitor

**Cancer type:** Non-Small Cell Lung Cancer

**Variant class:** EGFR T790M mutation

**Summary:**

NCCN Guidelines® include the following supporting statement(s):

- "EGFR p.Thr790Met (T790M) is a mutation associated with acquired resistance to EGFR TKI therapy and has been reported in about 60% of patients with disease progression after initial response to erlotinib, gefitinib, or afatinib."

**Reference:** NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2020]

### erlotinib

**Cancer type:** Non-Small Cell Lung Cancer

**Variant class:** EGFR T790M mutation

**Summary:**

NCCN Guidelines® include the following supporting statement(s):

- "The most common known mechanism is the acquisition of T790M (which is a secondary mutation in EGFR), which renders the kinase resistant to erlotinib, gefitinib, dacomitinib or afatinib."

**Reference:** NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2020]



## EGFR p.(T790M) c.2369C>T (continued)

### gefitinib

**Cancer type:** Non-Small Cell Lung Cancer

**Variant class:** EGFR T790M mutation

**Summary:**

NCCN Guidelines® include the following supporting statement(s):

- "The most common known mechanism is the acquisition of T790M (which is a secondary mutation in EGFR), which renders the kinase resistant to erlotinib, gefitinib, dacomitinib or afatinib."

**Reference:** NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2020]

## AR amplification

### ☐ androgen receptor therapy

**Cancer type:** Head and Neck Cancer

**Variant class:** AR positive

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**

- Recurrent Metastatic Salivary Gland Tumors; Distant metastases; PS 0-3 (Therapy for recurrence)

**Reference:** NCCN Guidelines® - NCCN-Head and Neck Cancers [Version 3.2019]

### ☐ bicalutamide

**Cancer type:** Head and Neck Cancer

**Variant class:** AR positive

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**

- Recurrent Metastatic Salivary Gland Tumors; Distant metastases; PS 0-3 (Therapy for recurrence)

**Reference:** NCCN Guidelines® - NCCN-Head and Neck Cancers [Version 3.2019]

### ☐ leuprorelin

**Cancer type:** Head and Neck Cancer

**Variant class:** AR positive

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**

- Recurrent Metastatic Salivary Gland Tumors; Distant metastases; PS 0-3 (Therapy for recurrence)

**Reference:** NCCN Guidelines® - NCCN-Head and Neck Cancers [Version 3.2019]



## Current EMA Information

- ☒ In this cancer type
 ☐ In other cancer type
 ☒ In this cancer type and other cancer types
 ☒ Contraindicated
 ☒ Not recommended
 ☒ Resistance

EMA information is current as of 2020-02-28. For the most up-to-date information, search [www.ema.europa.eu/ema](http://www.ema.europa.eu/ema).

### EGFR p.(L858R) c.2573T>G

#### ● bevacizumab (Allergan) + erlotinib

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2019-11-12

Variant class: EGFR L858R mutation

Reference:

[https://www.ema.europa.eu/en/documents/product-information/mvasi-epar-product-information\\_en.pdf](https://www.ema.europa.eu/en/documents/product-information/mvasi-epar-product-information_en.pdf)

#### ● bevacizumab + erlotinib

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2020-02-20

Variant class: EGFR L858R mutation

Reference:

[https://www.ema.europa.eu/en/documents/product-information/avastin-epar-product-information\\_en.pdf](https://www.ema.europa.eu/en/documents/product-information/avastin-epar-product-information_en.pdf)

#### ● erlotinib + ramucirumab

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2020-02-25

Variant class: EGFR L858R mutation

Reference:

[https://www.ema.europa.eu/en/documents/product-information/cyramza-epar-product-information\\_en.pdf](https://www.ema.europa.eu/en/documents/product-information/cyramza-epar-product-information_en.pdf)

#### ● osimertinib

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2020-02-25

Variant class: EGFR L858R mutation

Reference:

[https://www.ema.europa.eu/en/documents/product-information/tagrisso-epar-product-information\\_en.pdf](https://www.ema.europa.eu/en/documents/product-information/tagrisso-epar-product-information_en.pdf)

### EGFR p.(T790M) c.2369C>T

#### ● osimertinib

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2020-02-25

Variant class: EGFR T790M mutation

Reference:

[https://www.ema.europa.eu/en/documents/product-information/tagrisso-epar-product-information\\_en.pdf](https://www.ema.europa.eu/en/documents/product-information/tagrisso-epar-product-information_en.pdf)



## EGFR p.(T790M) c.2369C>T (continued)

### 🚫 gefitinib

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2019-05-28

Variant class: EGFR T790M mutation

Reference:

[https://www.ema.europa.eu/en/documents/product-information/iressa-epar-product-information\\_en.pdf](https://www.ema.europa.eu/en/documents/product-information/iressa-epar-product-information_en.pdf)



## Current ESMO Information

- ☒ In this cancer type
 ☐ In other cancer type
 ☒ In this cancer type and other cancer types
 ☒ Contraindicated
 ☒ Not recommended
 ☒ Resistance

ESMO information is current as of 2019-11-01. For the most up-to-date information, search [www.esmo.org](http://www.esmo.org).

### EGFR p.(L858R) c.2573T>G

#### ● atezolizumab + bevacizumab + carboplatin + paclitaxel

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR L858R mutation

ESMO Level of Evidence/Grade of Recommendation: III / A

##### Population segment (Line of therapy):

- Metastatic Non-Squamous; Magnitude of Clinical Benefit Scale Score version 1.1 score: 3 (First-line therapy)
- Metastatic ; PS 0-1; Without contraindications to immunotherapy after targeted therapies have been exploited (Second-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Ann Oncol (2018) 29 (suppl 4): iv192–iv237; <https://www.esmo.org/Guidelines/Lung-and-Chest-Tumours/Metastatic-Non-Small-Cell-Lung-Cancer>]

#### ● osimertinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFRi sensitizing mutation

ESMO Level of Evidence/Grade of Recommendation: I / A

##### Population segment (Line of therapy):

- Advanced stage; ESMO-Magnitude of Clinical Benefit Scale Version 1.1 Score: 4 (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Ann Oncol (2018) 29 (suppl 4): iv192–iv237; <https://www.esmo.org/Guidelines/Lung-and-Chest-Tumours/Metastatic-Non-Small-Cell-Lung-Cancer>]

#### ● gefitinib + carboplatin + pemetrexed

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR activating mutation

ESMO Level of Evidence/Grade of Recommendation: I / B

##### Population segment (Line of therapy):

- Advanced stage (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Ann Oncol (2018) 29 (suppl 4): iv192–iv237; <https://www.esmo.org/Guidelines/Lung-and-Chest-Tumours/Metastatic-Non-Small-Cell-Lung-Cancer>]



## EGFR p.(L858R) c.2573T>G (continued)

### ● bevacizumab + erlotinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR activating mutation

ESMO Level of Evidence/Grade of Recommendation: II / B

Population segment (Line of therapy):

- Stage IV; ESMO-Magnitude of Clinical Benefit Scale Version 1.1 Score: 3 (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Ann Oncol (2018) 29 (suppl 4): iv192–iv237; <https://www.esmo.org/Guidelines/Lung-and-Chest-Tumours/Metastatic-Non-Small-Cell-Lung-Cancer>]

### ● bevacizumab + gefitinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR activating mutation

ESMO Level of Evidence/Grade of Recommendation: II / B

Population segment (Line of therapy):

- Stage IV; ESMO-Magnitude of Clinical Benefit Scale Version 1.1 Score: 3 (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Ann Oncol (2018) 29 (suppl 4): iv192–iv237; <https://www.esmo.org/Guidelines/Lung-and-Chest-Tumours/Metastatic-Non-Small-Cell-Lung-Cancer>]

### ● erlotinib + ramucirumab

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR activating mutation

ESMO Level of Evidence/Grade of Recommendation: II / B

Population segment (Line of therapy):

- Stage IV (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Ann Oncol (2018) 29 (suppl 4): iv192–iv237; <https://www.esmo.org/Guidelines/Lung-and-Chest-Tumours/Metastatic-Non-Small-Cell-Lung-Cancer>]

## EGFR p.(T790M) c.2369C>T

### ● osimertinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR T790M mutation

ESMO Level of Evidence/Grade of Recommendation: I / A

Population segment (Line of therapy):

- Stage IV; Resistance to first-/second generation EGFR TKI; If not received previously; ESMO-Magnitude of Clinical Benefit Scale Version 1.1 Score: 4 (Second-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Ann Oncol (2018) 29 (suppl 4): iv192–iv237; <https://www.esmo.org/Guidelines/Lung-and-Chest-Tumours/Metastatic-Non-Small-Cell-Lung-Cancer>]



## Signatures

Testing Personnel:

Laboratory Supervisor:

Pathologist:



## References

1. Lu et al. International Union of Pharmacology. LXV. The pharmacology and classification of the nuclear receptor superfamily: glucocorticoid, mineralocorticoid, progesterone, and androgen receptors. *Pharmacol. Rev.* 2006 Dec;58(4):782-97. PMID: 17132855
2. Davey et al. Androgen Receptor Structure, Function and Biology: From Bench to Bedside. *Clin Biochem Rev.* 2016 Feb;37(1):3-15. PMID: 27057074
3. Crumbaker et al. AR Signaling and the PI3K Pathway in Prostate Cancer. *Cancers (Basel).* 2017 Apr 15;9(4). PMID: 28420128
4. Leung et al. Non-Genomic Actions of the Androgen Receptor in Prostate Cancer. *Front Endocrinol (Lausanne).* 2017 Jan 17;8:2. PMID: 28144231
5. Waltering et al. Androgen receptor (AR) aberrations in castration-resistant prostate cancer. *Mol. Cell. Endocrinol.* 2012 Sep 5;360(1-2):38-43. PMID: 22245783
6. Antonarakis et al. AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. *N. Engl. J. Med.* 2014 Sep 11;371(11):1028-38. PMID: 25184630
7. Zhu et al. Novel Junction-specific and Quantifiable In Situ Detection of AR-V7 and its Clinical Correlates in Metastatic Castration-resistant Prostate Cancer. *Eur. Urol.* 2018 May;73(5):727-735. PMID: 28866255
8. <https://www.businesswire.com/news/home/20160106006206/en/Innocrin-Pharmaceuticals-Granted-Fast-Track-Designation-FDA>
9. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/202379s027s028lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/202379s027s028lbl.pdf)
10. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/203415s015lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/203415s015lbl.pdf)
11. Lallous et al. Functional analysis of androgen receptor mutations that confer anti-androgen resistance identified in circulating cell-free DNA from prostate cancer patients. *Genome Biol.* 2016 Jan 26;17:10. PMID: 26813233
12. Robinson et al. Integrative clinical genomics of advanced prostate cancer. *Cell.* 2015 May 21;161(5):1215-1228. PMID: 26000489
13. Malumbres et al. Cell cycle, CDKs and cancer: a changing paradigm. *Nat. Rev. Cancer.* 2009 Mar;9(3):153-66. PMID: 19238148
14. Sherr et al. Targeting CDK4 and CDK6: From Discovery to Therapy. *Cancer Discov.* 2016 Apr;6(4):353-67. PMID: 26658964
15. Weinberg. The retinoblastoma protein and cell cycle control. *Cell.* 1995 May 5;81(3):323-30. PMID: 7736585
16. Sherr. Cancer cell cycles. *Science.* 1996 Dec 6;274(5293):1672-7. PMID: 8939849
17. Massagué. G1 cell-cycle control and cancer. *Nature.* 2004 Nov 18;432(7015):298-306. PMID: 15549091
18. Cerami et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. *Cancer Discov.* 2012 May;2(5):401-4. PMID: 22588877
19. Cancer et al. Integrated genomic characterization of endometrial carcinoma. *Nature.* 2013 May 2;497(7447):67-73. PMID: 23636398
20. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. *Nat. Genet.* 2013 Oct;45(10):1113-20. PMID: 24071849
21. Beà et al. Landscape of somatic mutations and clonal evolution in mantle cell lymphoma. *Proc. Natl. Acad. Sci. U.S.A.* 2013 Nov 5;110(45):18250-5. PMID: 24145436
22. Diehl et al. Glycogen synthase kinase-3beta regulates cyclin D1 proteolysis and subcellular localization. *Genes Dev.* 1998 Nov 15;12(22):3499-511. PMID: 9832503
23. Alt et al. Phosphorylation-dependent regulation of cyclin D1 nuclear export and cyclin D1-dependent cellular transformation. *Genes Dev.* 2000 Dec 15;14(24):3102-14. PMID: 11124803
24. Moreno-Bueno et al. Cyclin D1 gene (CCND1) mutations in endometrial cancer. *Oncogene.* 2003 Sep 4;22(38):6115-8. PMID: 12955092
25. Benzeno et al. Identification of mutations that disrupt phosphorylation-dependent nuclear export of cyclin D1. *Oncogene.* 2006 Oct 12;25(47):6291-303. PMID: 16732330
26. Cancer Genome Atlas Network. Comprehensive genomic characterization of head and neck squamous cell carcinomas. *Nature.* 2015 Jan 29;517(7536):576-82. PMID: 25631445
27. Kim et al. Nuclear cyclin D1: an oncogenic driver in human cancer. *J. Cell. Physiol.* 2009 Aug;220(2):292-6. PMID: 19415697





## References (continued)

28. Jares et al. Genetic and molecular pathogenesis of mantle cell lymphoma: perspectives for new targeted therapeutics. *Nat. Rev. Cancer*. 2007 Oct;7(10):750-62. PMID: 17891190
29. Rane et al. Germ line transmission of the Cdk4(R24C) mutation facilitates tumorigenesis and escape from cellular senescence. *Mol. Cell. Biol.* 2002 Jan;22(2):644-56. PMID: 11756559
30. Zuo et al. Germline mutations in the p16INK4a binding domain of CDK4 in familial melanoma. *Nat. Genet.* 1996 Jan;12(1):97-9. PMID: 8528263
31. Molven et al. A large Norwegian family with inherited malignant melanoma, multiple atypical nevi, and CDK4 mutation. *Genes Chromosomes Cancer*. 2005 Sep;44(1):10-8. PMID: 15880589
32. Ceha et al. Several noncontiguous domains of CDK4 are involved in binding to the P16 tumor suppressor protein. *Biochem. Biophys. Res. Commun.* 1998 Aug 19;249(2):550-5. PMID: 9712735
33. Tsao et al. Novel mutations in the p16/CDKN2A binding region of the cyclin-dependent kinase-4 gene. *Cancer Res.* 1998 Jan 1;58(1):109-13. PMID: 9426066
34. Sotillo et al. Invasive melanoma in Cdk4-targeted mice. *Proc. Natl. Acad. Sci. U.S.A.* 2001 Nov 6;98(23):13312-7. PMID: 11606789
35. Cancer Genome Atlas Research Network. Comprehensive molecular profiling of lung adenocarcinoma. *Nature*. 2014 Jul 31;511(7511):543-50. doi: 10.1038/nature13385. Epub 2014 Jul 9. PMID: 25079552
36. Brennan et al. The somatic genomic landscape of glioblastoma. *Cell*. 2013 Oct 10;155(2):462-77. PMID: 24120142
37. King et al. Amplification of a novel v-erbB-related gene in a human mammary carcinoma. *Science*. 1985 Sep 6;229(4717):974-6. PMID: 2992089
38. ErbB Receptors and Cancer. *Methods Mol. Biol.* 2017;1652:3-35. PMID: 28791631
39. Gutierrez et al. HER2: biology, detection, and clinical implications. *Arch. Pathol. Lab. Med.* 2011 Jan;135(1):55-62. PMID: 21204711
40. Pines et al. Oncogenic mutant forms of EGFR: lessons in signal transduction and targets for cancer therapy. *FEBS Lett.* 2010 Jun 18;584(12):2699-706. PMID: 20388509
41. da et al. EGFR mutations and lung cancer. *Annu Rev Pathol.* 2011;6:49-69. doi: 10.1146/annurev-pathol-011110-130206. PMID: 20887192
42. Arcila et al. EGFR exon 20 insertion mutations in lung adenocarcinomas: prevalence, molecular heterogeneity, and clinicopathologic characteristics. *Mol. Cancer Ther.* 2013 Feb;12(2):220-9. PMID: 23371856
43. Kobayashi et al. EGFR Exon 18 Mutations in Lung Cancer: Molecular Predictors of Augmented Sensitivity to Afatinib or Neratinib as Compared with First- or Third-Generation TKIs. *Clin Cancer Res.* 2015 Dec 1;21(23):5305-13. doi: 10.1158/1078-0432.CCR-15-1046. Epub 2015 Jul 23. PMID: 26206867
44. Yasuda et al. Structural, biochemical, and clinical characterization of epidermal growth factor receptor (EGFR) exon 20 insertion mutations in lung cancer. *Sci Transl Med.* 2013 Dec 18;5(216):216ra177. PMID: 24353160
45. Chiu et al. Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Treatment Response in Advanced Lung Adenocarcinomas with G719X/L861Q/S768I Mutations. *J Thorac Oncol.* 2015 May;10(5):793-9. PMID: 25668120
46. Karachaliou et al. KRAS mutations in lung cancer. *Clin Lung Cancer.* 2013 May;14(3):205-14. PMID: 23122493
47. Mitsudomi et al. Epidermal growth factor receptor in relation to tumor development: EGFR gene and cancer. *FEBS J.* 2010 Jan;277(2):301-8. PMID: 19922469
48. Ji et al. Epidermal growth factor receptor variant III mutations in lung tumorigenesis and sensitivity to tyrosine kinase inhibitors. *Proc. Natl. Acad. Sci. U.S.A.* 2006 May 16;103(20):7817-22. PMID: 16672372
49. Gazdar. Activating and resistance mutations of EGFR in non-small-cell lung cancer: role in clinical response to EGFR tyrosine kinase inhibitors. *Oncogene*. 2009 Aug;28 Suppl 1:S24-31. PMID: 19680293
50. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/021743s025lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021743s025lbl.pdf)
51. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/201292s015lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/201292s015lbl.pdf)
52. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2018/206995s003lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/206995s003lbl.pdf)
53. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/208065s013lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/208065s013lbl.pdf)



## References (continued)

54. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2018/211288s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/211288s000lbl.pdf)
55. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/125084s273lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125084s273lbl.pdf)
56. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2017/125147s207lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125147s207lbl.pdf)
57. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2015/125547s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125547s000lbl.pdf)
58. NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2020]