Taipei Veterans General Hospital

Department of Pathology and Laboratory Medicine
No.201, Sec. 2, Shipai Rd., Beitou District, Taipei City, Taiwan
11217, R.O.C.
Tel: 02-2875-7449

Sample Information

Patient Name: 許進益
Gender: Male
ID No.: A102959132
History No.: 39198102
Age: 73

Ordering Doctor: DOC3153J 黃煦晴
Ordering REQ.: 0BHRAYZ
Signing in Date: 2021/07/07

Path No.: S110-99046
MP No.: F21053
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: S110-18674A
Percentage of tumor cells: 40%

Reporting Doctor: DOC5466K 葉奕成 (Phone: 8#5466)

Note:

Sample Cancer Type: Non-Small Cell Lung Cancer

Table of Contents

Report Highlights

3 Relevant Biomarkers
0 Therapies Available
28 Clinical Trials

Relevant Non-Small Cell Lung Cancer Variants

Gene	Finding	Gene	Finding
ALK	None detected	NTRK1	None detected
BRAF	None detected	NTRK2	None detected
EGFR	***EGFR amplification***	NTRK3	None detected
ERBB2	None detected	RET	None detected
KRAS	None detected	ROS1	None detected
MET	None detected		

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*FGFR1 amplification* fibroblast growth factor receptor 1	None	None	13
IIC	*EGFR amplification* epidermal growth factor receptor	None	None	9
IIC	*CCND1 amplification* cyclin D1	None	None	8

Public data sources included in relevant therapies: FDA1, NCCN, **EMA**2, 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.

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
ALK	p.(*1621R)	c.4861T>C	.	chr2:29416092	5.27%	NM_004304.5	stoploss	1177

Copy Number Variations

Gene	Locus	Copy Number
EGFR	chr7:55198956	68.47
FGFR1	chr8:38271445	8.82
CCND1	chr11:69456942	12.75

Biomarker Descriptions

CCND1 (cyclin D1)

Background: The CCND1 gene encodes the cyclin D1 protein, a member of the highly conserved D-cyclin family that also includes CCND2 and CCND3[1,2,3]. D-type cyclins are known to regulate cell cycle progression by binding to and activating cyclin dependent kinases (CDKs), specifically CDK4 and CDK6, which leads to the phosphorylation and inactivation of the retinoblastoma (RB1) protein[1,2]. Consequently, RB1 inactivation results in E2F transcription factor activation and cellular G1/S phase transition thereby resulting in cell cycle progression, a common event observed in tumorigenesis[1,2,4]. Aberrations in the D-type cyclins have been observed to promote tumor progression suggesting an oncogenic role for CCND1[3,5].

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)[6,7,8,9]. These mutations block phosphorylation-dependent nuclear export and proteolysis[10,11,12,13]. 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[6,8,14]. 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[15,16].

Potential relevance: Currently, no therapies are approved for CCND1 aberrations.

Biomarker Descriptions (continued)

EGFR (epidermal growth factor receptor)

Background: The EGFR gene encodes the epidermal growth factor receptor (EGFR) tyrosine kinase, a member of the ERBB/human epidermal growth factor receptor (HER) family. In addition to EGFR/ERBB1/HER1, other members of the ERBB/HER family include ERBB2/HER2, ERBB3/HER3, and ERBB4/HER4[17]. 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[18,19].

Alterations and prevalence: Recurrent somatic mutations in the tyrosine kinase domain (TKD) of EGFR are observed in approximately 10-20% of lung adenocarcinoma, and at higher frequencies in never-smoker, female, and Asian populations[6,8,20,21]. The most common mutations occur near the ATP-binding pocket of the TKD and include short in-frame deletions in exon 19 (EGFR exon 19 deletion) and the L858R amino acid substitution in exon 21[22]. These mutations constitutively activate EGFR resulting in downstream signaling, and represent 80% of the EGFR mutations observed in lung cancer. A second group of less prevalent activating mutations include E709K, G719X, S768I, L861Q, and short in-frame insertion mutations in exon 20[23,24,25,26]. EGFR activating mutations in lung cancer tend to be mutually exclusive to KRAS activating mutations[27]. In contrast, a different set of recurrent activating EGFR mutations in the extracellular domain include R108K, A289V and G598V and are primarily observed in glioblastoma[22,28]. Amplification of EGFR is observed in several cancer types including 30% of glioblastoma, 12% of esophageal cancer, 10% of head and neck cancer, 5% of bladder cancer, and 5% of lung squamous cell carcinoma[6,8,14,21,28]. Deletion of exons 2-7, encoding the extracellular domain of EGFR (EGFRvIII), results in overexpression of a ligand-independent constitutively active protein and is observed in approximately 30% of glioblastoma[29,30,31].

Potential relevance: Approved first-generation EGFR tyrosine kinase inhibitors (TKIs) include erlotinib[32] (2004) and gefitinib[33] (2015), which block the activation of downstream signaling by reversible interaction with the ATP-binding site. Although initially approved for advanced lung cancer, the discovery that drug sensitivity was associated with exon 19 and exon 21 activating mutations allowed first-generation TKIs to become subsequently approved for front-line therapy in lung cancer tumors containing exon 19 or exon 21 activating mutations. Second-generation TKIs afatinib[34] (2013) and dacomitinib[35] (2018) bind EGFR and other ERBB/HER gene family members irreversibly and were subsequently approved. First- and second-generation TKIs afatinib, dacomitinib, erlotinib, and gefitinib are recommended for the treatment NSCLC harboring EGFR exon 19 insertions, exon 19 deletions, point mutations L861Q, L858R, S768I, and codon 719 mutations, whereas most EGFR exon 20 insertions, except p.A763_Y764insFQEA, confer resistance to the same therapies[36,37,38,39]. In lung cancer containing EGFR exon 19 or 21 activating mutations, treatment with TKIs is eventually associated with the emergence of drug resistance[40]. The primary resistance mutation that emerges following treatment with first-generation TKI is T790M, accounting for 50-60% of resistant cases[22]. Third generation TKIs were developed to maintain sensitivity in the presence of T790M. Osimertinib[41] (2015) is an irreversible inhibitor indicated for metastatic EGFR T790M positive lung cancer and for the first-line treatment of metastatic NSCLC containing EGFR exon 19 deletions or exon 21 L858R mutations. Like first-generation TKIs, treatment with osimertinib is associated with acquired resistance. In this case, resistance is associated with the C797S mutation, and occurs in 22-44% of cases[40]. The T790M and C797S mutations may be each selected following sequential treatment with a first-generation TKI followed by a third-generation TKI or vice versa[42]. T790M and C797S can occur in either cis or trans allelic orientation[42]. If C797S is observed following progression after treatment with a third-generation TKI in the first-line setting, sensitivity may be retained to first-generation TKIs[42]. If C797S co-occurs in trans with T790M following sequential treatment with first- and third-generation TKIs, patients may exhibit sensitivity to combination first- and third-generation TKIs, but resistance to third-generation TKIs alone[42,43]. However, C797S occurring in cis conformation with T790M, confers resistance to first- and third-generation TKIs[42]. Fourth-generation TKIs are in development to overcome acquired C797S and T790M resistance mutations after osimertinib treatment. EGFR targeting antibodies including cetuximab (2004), panitumumab (2006), and necitumumab (2016) are under investigation in combination with EGFR-targeting TKIs for efficacy against EGFR mutations. The bispecific antibody, JNJ-61186372[44], targeting EGFR and MET, and the TKI mobocertinib[45], each received a breakthrough designation from the FDA (2020) for NSCLC tumors harboring EGFR exon 20 insertion mutations. The Oncoprex immunogene therapy CNVN-202[46] in combination with osimertinib received a fast track designation from the FDA (2020) for NSCLC tumors harboring EGFR mutations that progressed on osimertinib alone. BDTX-189[47] was granted a fast track designation (2020) for the treatment of solid tumors harboring an EGFR exon 20 insertion mutation.

FGFR1 (fibroblast growth factor receptor 1)

Background: The FGFR1 gene encodes fibroblast growth receptor 1, a member of the fibroblast growth factor receptor (FGFR) family that also includes FGFR2, 3, and 4. These proteins are single transmembrane receptors composed of three extracellular immunoglobulin (Ig)-type domains and an intracellular kinase domain. Upon FGF-mediated stimulation, FGFRs activate several oncogenic signaling pathways, including the RAS/RAF/MEK/ERK, PI3K/AKT/MTOR, PLC/PKC, and JAK/STAT pathways influencing cell proliferation, migration, and survival[48,49,50].

Alterations and prevalence: Recurrent somatic alterations common to the FGFR family include gene amplification, mutation, and chromosomal translocations leading to FGFR fusions[51]. Amplification of FGFR1 is observed in 15-20% of squamous lung cancer, 10-15% of breast cancer, 8% of bladder cancer, and 2-5% of uterine cancer cases[6,7,8,52,53]. The most common recurrent mutations, N546K and K656E, are relatively infrequent (<1%); they activate mutations in the kinase domain and are distributed in diverse cancer

Biomarker Descriptions (continued)

types[54]. FGFR1 translocations giving rise to expressed fusions are common in certain hematological cancers, but less common in solid tumors[55,56,57].

Potential relevance: The FDA has granted fast-track designation (2018) to Debio 1347[58] for solid tumors harboring aberrations in FGFR1, FGFR2, or FGFR3. FDA has approved multi-kinase inhibitors, including regorafenib, ponatinib, lenvatinib, nintedanib, and pazopanib, that are known to inhibit FGFR family members. These inhibitors have demonstrated anti-tumor activity in select cancer types with FGFR alterations[59,60,61,62,63,64,65]. In a phase II clinical trial, dovitinib, a multi-tyrosine kinase inhibitor (TKI), exhibited an overall response rate (ORR) of 11.5% and a disease control rate (DCR) of 50% in patients with advanced squamous cell lung cancer possessing FGFR1 amplification. The patients had a median overall survival (OS) of 5 months and progression-free survival (PFS) of 2.9 months[66]. Likewise, in a phase Ib study testing the FGFR inhibitor AZD4547, median OS was 4.9 months in patients with FGFR1-amplified advanced squamous cell lung cancer. One of 13 (8%) patients achieved a partial response, 4 (31%) exhibited stable disease, and 2 (13.3%) demonstrated PFS at 12 weeks[67].

Relevant Therapy Summary

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ✖ No evidence

FGFR1 amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
futibatinib	✖	✖	✖	✖	● (II)
infigratinib	✖	✖	✖	✖	● (II)
pemigatinib	✖	✖	✖	✖	● (II)
ponatinib	✖	✖	✖	✖	● (II)
sunitinib	✖	✖	✖	✖	● (II)
ICP-192	✖	✖	✖	✖	● (I/II)
TAS-117, futibatinib	✖	✖	✖	✖	● (I/II)
zotatifin	✖	✖	✖	✖	● (I/II)
ACTB-1003	✖	✖	✖	✖	● (I)
BPI-17509	✖	✖	✖	✖	● (I)
CPL-304-110	✖	✖	✖	✖	● (I)
futibatinib, pembrolizumab	✖	✖	✖	✖	● (I)

EGFR amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
apatinib, gefitinib	✖	✖	✖	✖	● (IV)
crizotinib	✖	✖	✖	✖	● (II)
erlotinib	✖	✖	✖	✖	● (II)
gefitinib	✖	✖	✖	✖	● (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 ✖ No evidence

EGFR amplification (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
nimotuzumab + chemotherapy	✖	✖	✖	✖	● (II)
BCA101	✖	✖	✖	✖	● (I)
FT500, nivolumab, pembrolizumab, atezolizumab	✖	✖	✖	✖	● (I)
neratinib, palbociclib, everolimus, trametinib	✖	✖	✖	✖	● (I)
ZZ06	✖	✖	✖	✖	● (I)

CCND1 amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
abemaciclib	✖	✖	✖	✖	● (II)
palbociclib	✖	✖	✖	✖	● (II)
siremadlin, ribociclib	✖	✖	✖	✖	● (II)
abemaciclib, chemotherapy	✖	✖	✖	✖	● (I/II)
PF-07220060	✖	✖	✖	✖	● (I)

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

Clinical Trials Summary

FGFR1 amplification

NCT ID	Title	Phase
No NCT ID	Phase I/II Study of TAS-117 In Combination With TAS-120 In Patients With Advanced Solid Tumors	I/II
NCT04591431	The Rome Trial From Histology to Target: the Road to Personalize Target Therapy and Immunotherapy	II
NCT04149691	A Phase I, Open-label, Multicentre, Dose Escalation Study to Assess Safety, Tolerability and Pharmacokinetics of Oral CPL304110, in Adult Subjects With Advanced Solid Malignancies	I
No NCT ID	A Multicenter Phase II Basket-type Clinical Trial to Evaluate Efficacy and Safety of TAS-120 in Patients with Advanced Solid Malignancies with FGFR Alterations in Circulating Tumor DNA	II
NCT02693535	Targeted Agent and Profiling Utilization Registry (TAPUR) Study	II
NCT04092673	A Phase 1-2 Dose-Escalation and Cohort-Expansion Study of Intravenous Zotatifin (eFT226) in Subjects With Selected Advanced Solid Tumor Malignancies	I/II
NCT04233567	A Phase II Study of Oral Infigratinib in Adult Patients With Advanced or Metastatic Solid Tumors With FGFR1-3 Gene Fusions or Other FGFR Genetic Alterations	II
NCT02272998	Phase II Study Of Ponatinib For Advanced Cancers With Genomic Alterations In Fibroblastic Growth Factor Receptor (FGFR) And Other Genomic Targets (KIT, Pdgfra, RET FLT3, ABL1)	II

Clinical Trials Summary (continued)

FGFR1 amplification (continued)

NCT ID	Title	Phase
NCT03297606	Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR): A Phase II Basket Trial	II
NCT04565275	A Multi-center Open-label, Phase I/II Clinical Trial to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of ICP-192 in Patients With Advanced Solid Tumors and FGFR Gene Alterations.	I/II
NCT03583125	A Phase 1 Dose Escalation Study of EOC317 in Chinese Patients With Advanced Solid Tumors	I
No NCT ID	Phase I Clinical Study of BPI-17509 In Patients With Advanced Solid Tumors	I
No NCT ID	A Phase Ib Study to Assess the Safety, Tolerability, and Efficacy of TAS-120 (Futibatinib) in Combination with MK-3475 (Pembrolizumab) in Patients with Solid Tumors.	I

EGFR amplification

NCT ID	Title	Phase
NCT03574402	An Open-label, Multi-center, Phase II Umbrella Study to Assess Efficacy of Targeted Therapy or Immunotherapy Directed by Next Generation Sequencing (NGS) in Chinese Patients With Advanced NSCLC (TRUMP)	II
NCT04429542	First-in-Human, Phase I/Ib, Open-label, Multicenter Study of Bifunctional EGFR/TGFß Fusion Protein BCA101 Alone and in Combination With Pembrolizumab in Patients With EGFR-Driven Advanced Solid Tumors	I
No NCT ID	A Pilot Study for Apatinib Mesylate Combined with Gefitinib in First-line Treatment of Lung Adenocarcinoma with Malignant Pleural Effusion or Pericardial Effusion	IV
No NCT ID	A Phase IIa Clinical Study of crizotinib in the Treatment of Advanced Non-small Cell Lung Cancer	II
NCT02447419	Study to Evaluate the Safety and Efficacy of Gefitinib, in Subjects With EFGR Amplification Refractory Solid Tumors	II
NCT03065387	Phase I Study of the Pan-ERBB Inhibitor Neratinib Given in Combination With Everolimus, Palbociclib, or Trametinib in Advanced Cancer Subjects With EGFR Mutation/Amplification, HER2 Mutation/ Amplification, or HER3/4 Mutation or KRAS Mutation	I
NCT03841110	FT500 as Monotherapy and in Combination With Immune Checkpoint Inhibitors in Subjects With Advanced Solid Tumors (Phase I)	I
NCT04412616	A Phase I, Multicenter, Open-label Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Immunogenicity, and Preliminary Evidence of Antitumor Activity of ZZ06 in Adult Patients With Advanced EGFR Positive Solid Tumor Malignancies	I
NCT03297606	Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR): A Phase II Basket Trial	II

CCND1 amplification

NCT ID	Title	Phase
NCT02664935	National Lung Matrix Trial: Multi-drug, Genetic Marker-directed, Non-comparative, Multi-centre, Multi-arm Phase II Trial in Non-small Cell Lung Cancer	II
NCT03310879	A Phase II Study of the CDK4/6 Inhibitor Abemaciclib in Patients With Solid Tumors Harboring Genetic Alterations in Genes Encoding D-type Cyclins or Amplification of CDK4 or CDK6	II

Clinical Trials Summary (continued)

CCND1 amplification (continued)

NCT ID	Title	Phase
NCT04116541	MegaMOST - A Multicenter, Open-label, Biology Driven, Phase II Study Evaluating the Activity of Anti-cancer Treatments Targeting Tumor Molecular Alterations /Characteristics in Advanced / Metastatic Tumors.	II
NCT04594005	An Open-label, Multi-center Phase IB/II Study of Abemaciclib With Paclitaxel for CDK4/6 Pathway Activated Tumors	I/II
NCT04557449	A Phase I/IB Study Evaluating The Safety, Tolerability, Pharamcokinetics, Pharmacodynamics, And Anti-Tumor Activity Of PF-07220060 As A Single Agent And as Part of Combination Therapy In Participants With Advanced Solid Tumors	I
NCT03297606	Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR): A Phase II Basket Trial	II
NCT03155620	NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice) Screening Protocol	II
NCT03526250	NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice) - Phase 2 Subprotocol of Palbociclib in Patients With Tumors Harboring Activating Alterations in Cell Cycle Genes	II

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

FDA information is current as of 2021-05-12. For the most up-to-date information, search www.fda.gov.

FGFR1 amplification

Debio 1347

Cancer type: Solid Tumor

Variant class: FGFR1 aberration

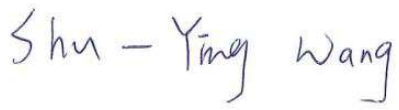
Supporting Statement:
The FDA has granted Fast Track Designation to the FGFR 1-3 inhibitor, debio 1347, for FGFR1/2/3 alterations in unresectable or metastatic solid tumors.

Reference:

https://www.debiopharm.com/drug-development/press-releases/fda-grants-fast-track-designation-to-debiopharm-internationals-debio-1347-for-the-treatment-of-patients-with-unresectable-or-metastatic-tumors-with-a-specific-fgfr-gene-alteration/

Signatures

Testing Personnel:



2021.07.09 16:11:23 +08'00'

Laboratory Supervisor:

2021.07.09 16:11:35 +08'00'

Pathologist:

2021.07.09 16:11:46 +08'00'

References

1. Malumbres et al. Cell cycle, CDKs and cancer: a changing paradigm. Nat. Rev. Cancer. 2009 Mar;9(3):153-66. PMID: 19238148
2. Koyama-Nasu et al. The critical role of cyclin D2 in cell cycle progression and tumorigenicity of glioblastoma stem cells. Oncogene. 2013 Aug 15;32(33):3840-5. PMID: 22964630
3. Ding et al. Prognostic role of cyclin D2/D3 in multiple human malignant neoplasms: A systematic review and meta-analysis. Cancer Med. 2019 Jun;8(6):2717-2729. PMID: 30950241
4. Bartek et al. Pathways governing G1/S transition and their response to DNA damage. FEBS Lett. 2001 Feb 16;490(3):117-22. PMID: 11223026
5. Shan et al. Cyclin D1 overexpression correlates with poor tumor differentiation and prognosis in gastric cancer. Oncol Lett. 2017 Oct;14(4):4517-4526. PMID: 28943959
6. 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
7. Cancer et al. Integrated genomic characterization of endometrial carcinoma. Nature. 2013 May 2;497(7447):67-73. PMID: 23636398
8. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. Nat. Genet. 2013 Oct;45(10):1113-20. PMID: 24071849
9. 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
10. 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
11. 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
12. Moreno-Bueno et al. Cyclin D1 gene (CCND1) mutations in endometrial cancer. Oncogene. 2003 Sep 4;22(38):6115-8. PMID: 12955092
13. 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
14. Cancer Genome Atlas Network. Comprehensive genomic characterization of head and neck squamous cell carcinomas. Nature. 2015 Jan 29;517(7536):576-82. PMID: 25631445
15. Kim et al. Nuclear cyclin D1: an oncogenic driver in human cancer. J. Cell. Physiol. 2009 Aug;220(2):292-6. PMID: 19415697
16. 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
17. 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
18. Zhixiang. ErbB Receptors and Cancer. Methods Mol. Biol. 2017;1652:3-35. PMID: 28791631
19. Gutierrez et al. HER2: biology, detection, and clinical implications. Arch. Pathol. Lab. Med. 2011 Jan;135(1):55-62. PMID: 21204711
20. 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
21. 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
22. da et al. EGFR mutations and lung cancer. Annu Rev Pathol. 2011;6:49-69. doi: 10.1146/annurev-pathol-011110-130206. PMID: 20887192
23. 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
24. 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
25. 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
26. 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
27. Karachaliou et al. KRAS mutations in lung cancer. Clin Lung Cancer. 2013 May;14(3):205-14. PMID: 23122493

References (continued)

28. Brennan et al. The somatic genomic landscape of glioblastoma. Cell. 2013 Oct 10;155(2):462-77. PMID: 24120142
29. 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
30. 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
31. Gan et al. The EGFRvIII variant in glioblastoma multiforme. J Clin Neurosci. 2009 Jun;16(6):748-54. PMID: 19324552
32. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021743s025lbl.pdf
33. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/206995s004lbl.pdf
34. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/201292s015lbl.pdf
35. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/211288s003lbl.pdf
36. NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2021]
37. Naidoo et al. Epidermal growth factor receptor exon 20 insertions in advanced lung adenocarcinomas: Clinical outcomes and response to erlotinib. Cancer. 2015 Sep 15;121(18):3212-3220. PMID: 26096453
38. Vyse et al. Targeting EGFR exon 20 insertion mutations in non-small cell lung cancer. Signal Transduct Target Ther. 2019;4:5. PMID: 30854234
39. Yi et al. A comparison of epidermal growth factor receptor mutation testing methods in different tissue types in non-small cell lung cancer. Int J Mol Med. 2014 Aug;34(2):464-74. PMID: 24891042
40. Madic et al. EGFR C797S, EGFR T790M and EGFR sensitizing mutations in non-small cell lung cancer revealed by six-color crystal digital PCR. Oncotarget. 2018 Dec 21;9(100):37393-37406. PMID: 30647840
41. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208065s021lbl.pdf
42. Niederst et al. The Allelic Context of the C797S Mutation Acquired upon Treatment with Third-Generation EGFR Inhibitors Impacts Sensitivity to Subsequent Treatment Strategies. Clin. Cancer Res. 2015 Sep 1;21(17):3924-33. PMID: 25964297
43. Wang et al. Lung Adenocarcinoma Harboring EGFR T790M and In Trans C797S Responds to Combination Therapy of First- and Third-Generation EGFR TKIs and Shifts Allelic Configuration at Resistance. J Thorac Oncol. 2017 Nov;12(11):1723-1727. PMID: 28662863
44. https://www.jnj.com/janssen-announces-u-s-fda-breakthrough-therapy-designation-granted-for-jnj-6372-for-the-treatment-of-non-small-cell-lung-cancer
45. https://www.takeda.com/newsroom/newsreleases/2020/takeda-announces-u.s.-fda-breakthrough-therapy-designation-for-mobocertinib-tak-788-for-the-treatment-of-nsclc-patients-with-egfr-exon-20-insertion-mutations/
46. https://www.genprex.com/news/genprex-receives-u-s-fda-fast-track-designation-for-gene-therapy-that-targets-lung-cancer/
47. https://investors.blackdiamondtherapeutics.com/news-releases/news-release-details/black-diamond-therapeutics-granted-fast-track-designation-fda
48. Babina et al. Advances and challenges in targeting FGFR signalling in cancer. Nat. Rev. Cancer. 2017 May;17(5):318-332. PMID: 28303906
49. Ahmad et al. Mechanisms of FGFR-mediated carcinogenesis. Biochim. Biophys. Acta. 2012 Apr;1823(4):850-60. PMID: 22273505
50. Sarabipour et al. Mechanism of FGF receptor dimerization and activation. Nat Commun. 2016 Jan 4;7:10262. doi: 10.1038/ncomms10262. PMID: 26725515
51. Helsten et al. The FGFR Landscape in Cancer: Analysis of 4,853 Tumors by Next-Generation Sequencing. Clin. Cancer Res. 2016 Jan 1;22(1):259-67. PMID: 26373574
52. Peter et al. Comprehensive genomic characterization of squamous cell lung cancers. Nature. 2012 Sep 27;489(7417):519-25. PMID: 22960745
53. Ciriello et al. Comprehensive Molecular Portraits of Invasive Lobular Breast Cancer. Cell. 2015 Oct 8;163(2):506-19. PMID: 26451490
54. Lew et al. The precise sequence of FGF receptor autophosphorylation is kinetically driven and is disrupted by oncogenic mutations. Sci Signal. 2009 Feb 17;2(58):ra6. PMID: 19224897
55. Jackson et al. 8p11 myeloproliferative syndrome: a review. Hum. Pathol. 2010 Apr;41(4):461-76. PMID: 20226962
56. Li et al. Identification of a novel partner gene, TPR, fused to FGFR1 in 8p11 myeloproliferative syndrome. Genes Chromosomes Cancer. 2012 Sep;51(9):890-7. PMID: 22619110
57. Wasag et al. The kinase inhibitor TKI258 is active against the novel CUX1-FGFR1 fusion detected in a patient with T-lymphoblastic leukemia/lymphoma and t(7;8)(q22;p11). Haematologica. 2011 Jun;96(6):922-6. PMID: 21330321

References (continued)

58. https://www.debiopharm.com/drug-development/press-releases/fda-grants-fast-track-designation-to-debiopharm-internationals-debio-1347-for-the-treatment-of-patients-with-unresectable-or-metastatic-tumors-with-a-specific-fgfr-gene-alteration/
59. Cha et al. FGFR2 amplification is predictive of sensitivity to regorafenib in gastric and colorectal cancers in vitro. Mol Oncol. 2018 Jun;12(7):993-1003. PMID: 29573334
60. Chae et al. Inhibition of the fibroblast growth factor receptor (FGFR) pathway: the current landscape and barriers to clinical application. Oncotarget. 2017 Feb 28;8(9):16052-16074. PMID: 28030802
61. Porta et al. FGFR a promising druggable target in cancer: Molecular biology and new drugs. Crit. Rev. Oncol. Hematol. 2017 May;113:256-267. PMID: 28427515
62. Gozgit et al. Ponatinib (AP24534), a multitargeted pan-FGFR inhibitor with activity in multiple FGFR-amplified or mutated cancer models. Mol. Cancer Ther. 2012 Mar;11(3):690-9. PMID: 22238366
63. Yamamoto et al. Lenvatinib, an angiogenesis inhibitor targeting VEGFR/FGFR, shows broad antitumor activity in human tumor xenograft models associated with microvessel density and pericyte coverage. Vasc Cell. 2014 Sep 6;6:18. doi: 10.1186/2045-824X-6-18. eCollection 2014. PMID: 25197551
64. Kim et al. Pazopanib, a novel multitargeted kinase inhibitor, shows potent in vitro antitumor activity in gastric cancer cell lines with FGFR2 amplification. Mol. Cancer Ther. 2014 Nov;13(11):2527-36. PMID: 25249557
65. Hibi et al. FGFR gene alterations in lung squamous cell carcinoma are potential targets for the multikinase inhibitor nintedanib. Cancer Sci. 2016 Nov;107(11):1667-1676. PMID: 27581340
66. Lim et al. Efficacy and safety of dovitinib in pretreated patients with advanced squamous non-small cell lung cancer with FGFR1 amplification: A single-arm, phase 2 study. Cancer. 2016 Oct;122(19):3024-31. PMID: 27315356
67. Paik et al. A Phase Ib Open-Label Multicenter Study of AZD4547 in Patients with Advanced Squamous Cell Lung Cancers. Clin. Cancer Res. 2017 Sep 15;23(18):5366-5373. PMID: 28615371