Taipei Veterans General Hospital

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Sample Information

Patient Name: 田翊人
Gender: Female
ID No.: C220731458
History No.: 30182253
Age: 59

Ordering Doctor: DOC1878G 沈佳儀
Ordering REQ.: 0BQKHVT
Signing in Date: 2021/12/29

Path No.: S110-94996
MP No.: F21117
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: C110-34493
Percentage of tumor cells: 90%

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

Note:

Sample Cancer Type: Non-Small Cell Lung Cancer

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Relevant Non-Small Cell Lung Cancer Variants

Gene	Finding	Gene	Finding
ALK	None detected	NTRK1	None detected
BRAF	None detected	NTRK2	None detected
EGFR	None detected	NTRK3	None detected
ERBB2	***ERBB2 exon 20 insertion***	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
IA	*ERBB2 exon 20 insertion* erb-b2 receptor tyrosine kinase 2 Allele Frequency: 42.03% **Prognostic significance:** None **Diagnostic significance:** None	ado-trastuzumab emtansine trastuzumab deruxtecan	None	3
IIC	*AR amplification* androgen receptor **Prognostic significance:** None **Diagnostic significance:** None	None	hormone therapy	0

Public data sources included in relevant therapies: FDA[1], NCCN, **EMA**[2], ESMO
Public data sources included in prognostic and diagnostic significance: NCCN, 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
ERBB2	p.(G778_P780dup)	c.2340_2341insGGCTCCCCA	COSM12556	chr17:37881002	42.03%	NM_004448.3	nonframeshift Insertion	1970

Copy Number Variations

Gene	Locus	Copy Number
AR	chrX:66776186	5.74

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[1,2]. 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[2,3,4].

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[5]. Androgen receptor splice variants have been reported in castration resistant prostate cancer[6,7]. 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[7].

Potential relevance: The FDA has granted fast track designation (2016) to seviteronel for AR-positive triple-negative breast cancer (TNBC) patients[8]. Androgen deprivation therapy (ADT) such as abiraterone[9] (2011) and enzalutamide[10] (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[5,11,12]. 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[6].

Biomarker Descriptions (continued)

ERBB2 (erb-b2 receptor tyrosine kinase 2)

Background: The ERBB2 gene encodes the erb-b2 receptor tyrosine kinase 2, a member of the human epidermal growth factor receptor (HER) family. Along with ERBB2/HER2, EGFR/ERBB1/HER1, ERBB3/HER3, and ERBB4/HER4 make up the HER protein family[13]. All ERBB/HER proteins encode transmembrane receptor tyrosine kinases. However, ERBB2/HER2 is an orphan receptor with no known ligand. ERBB2 preferentially binds other ligand bound ERBB/HER family members to form hetero-dimers resulting in the activation of ERBB2 tyrosine kinase activity and subsequent activation of the PI3K/AKT/MTOR and RAS/RAF/MAPK/ERK signaling pathways which promote cell proliferation, differentiation, and survival[14]. Recurrent focal amplification of the ERBB2 gene leads to increased expression in several cancer types. ERBB2 overexpression in immortalized cell lines is oncogenic and leads to ERBB2 homo-dimerization and activation without ligand binding[15,16,17].

Alterations and prevalence: ERBB2 gene amplification occurs in 10-20% of breast, esophageal, and gastric cancers, 5-10% of bladder, cervical, pancreas, and uterine cancers, and 1-5% of colorectal, lung, and ovarian cancers[18,19,20,21,22,23,24,25]. Recurrent somatic activating mutations in ERBB2/HER2 occur at low frequencies (<1%) in diverse cancer types[25,26,27]. In breast, bladder, and colorectal cancers, the most common recurrent ERBB2 activating mutations include kinase domain mutations L755S and V777L and the extracellular domain mutation S310F. In lung cancer, the most common recurrent ERBB2 activating mutations include in-frame exon 20 insertions, particularly Y772_A775dup.

Potential relevance: The discovery of ERBB2/HER2 as an important driver of breast cancer in 1987 led to the development of trastuzumab, a humanized monoclonal antibody with specificity to the extracellular domain of HER2[28,29]. Trastuzumab[30] was FDA approved for the treatment of HER2 positive breast cancer in 1998, and subsequently in HER2 positive metastatic gastric and gastroesophageal junction adenocarcinoma in 2010. Additional monoclonal antibody therapies have been approved by the FDA for HER2-positive breast cancer including pertuzumab[31] (2012), a humanized monoclonal antibody that inhibits HER2 dimerization, and ado-trastuzumab emtansine[32] (2013), a conjugate of trastuzumab and a potent antimicrotubule agent. The combination of pertuzumab, trastuzumab, and a taxane is the preferred front-line regimen for HER2-positive metastatic breast cancer[33]. In addition to monoclonal antibodies, the small molecule inhibitor lapatinib[34], with specificity for both EGFR and ERBB2, was FDA approved (2007) for the treatment of patients with advanced HER2-positive breast cancer who have received prior therapy including trastuzumab. In 2017, the FDA approved the use of neratinib[35], an irreversible kinase inhibitor of EGFR, ERBB2/HER2, and ERBB4, for the extended adjuvant treatment of adult patients with early stage HER2-positive breast cancer. In 2020, the FDA approved neratinib[35] in combination with capecitabine for HER2-positive advanced or metastatic patients after two or more prior HER2-directed therapies. Also in 2020, the TKI irbinitinib[36] was FDA approved for HER2 overexpressing or amplified breast cancer in combination with trastuzumab and capecitabine. In 2021, the PD-1 blocking antibody, pembrolizumab, in combination with trastuzumab, fluoropyrimidine- and platinum-based chemotherapy, was approved for HER2 amplified gastric or gastroesophageal (GEJ) adenocarcinoma in the first line[37]. The vaccine, nelipepimut-S[38], was granted fast-track designation by the FDA (2016) in patients with low to intermediate HER2 expressing (IHC score 1+ or 2+) breast cancer. In 2018 fast-track designation was granted to the monoclonal antibody margetuximab[39] in patients with ERBB2 positive breast cancer previously treated with an anti-HER2 therapy. In 2019, the novel bispecific antibody, zanidatamab[40], received fast-track designation in combination with standard chemotherapy for patients with HER2-overexpressing gastroesophageal adenocarcinoma (GEA) and breakthrough therapy designation (2020) as a monotherapy for patients with HER2-amplified biliary tract cancer[41]. In 2020, BDTX-189[42] received fast-track designation for adult patients with solid tumors harboring an allosteric human ERBB2 mutation or exon 20 insertion, and the humanized anti-HER2 antibody drug conjugate disitamab vedotin received breakthrough designation for adult patients with HER2-positive urothelial cancer after previous platinum-chemotherapy treatment[43]. In 2021, the antibody-drug conjugate ARX788[44] received fast-track designation as a monotherapy for advanced or metastatic HER2-positive breast cancer that have progressed on one or more anti-HER2 regimens. Certain activating mutations have been observed to impart sensitivity to neratinib, afatinib, lapatinib, and trastuzumab, or dacomitinib in early and ongoing clinical studies[45,46,47,48,49]. ERBB2 kinase domain mutations R896G and V659E both showed response to afatinib in two NSCLC case studies[50,51]. Additionally, acquired HER2 mutations in estrogen receptor-positive (ER+) breast cancer have been shown to confer resistance to hormone therapy[52]. However, this was shown to be overcome by neratinib in combination with therapies targeting ER[52].

Relevant Therapy Summary

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

ERBB2 exon 20 insertion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
ado-trastuzumab emtansine	✖	●	✖	✖	● (II)
trastuzumab deruxtecan	✖	●	✖	✖	✖
pyrotinib	✖	✖	✖	✖	● (III)
DZD-9008	✖	✖	✖	✖	● (I/II)

AR amplification

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

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

Relevant Therapy Details

Current NCCN Information

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types

NCCN information is current as of 2021-11-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

ERBB2 exon 20 insertion

● ado-trastuzumab emtansine

Cancer type: Non-Small Cell Lung Cancer

Variant class: ERBB2 G778_P780dup mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Metastatic (Line of therapy not specified)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 7.2021]

ERBB2 exon 20 insertion (continued)

trastuzumab deruxtecan

Cancer type: Non-Small Cell Lung Cancer **Variant class:** ERBB2 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Metastatic (Line of therapy not specified)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 7.2021]

AR amplification

androgen receptor therapy

Cancer type: Head and Neck Cancer **Variant class:** AR positive

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Salivary Gland Neoplasm; Recurrent, Unresectable, Distant Metastases (Line of therapy not specified); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Head and Neck Cancers [Version 3.2021]

bicalutamide

Cancer type: Head and Neck Cancer **Variant class:** AR positive

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Salivary Gland Neoplasm; Recurrent, Unresectable, Distant Metastases (Line of therapy not specified); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Head and Neck Cancers [Version 3.2021]

leuprorelin

Cancer type: Head and Neck Cancer **Variant class:** AR positive

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Salivary Gland Neoplasm; Recurrent, Unresectable, Distant Metastases (Line of therapy not specified); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Head and Neck Cancers [Version 3.2021]

Clinical Trials in Taiwan region:

Clinical Trials Summary

ERBB2 exon 20 insertion

NCT ID	Title	Phase
NCT03974022	A Phase I/II, Open-Label, Multicenter Study to Assess the Safety, Tolerability, Pharmacokinetics and Anti-tumor Efficacy of DZD9008 in Patients With Advanced Non-Small Cell Lung Cancer (NSCLC) With EGFR or HER2 Mutation	I/II
NCT04447118	A Phase III, Randomized, Open-label, Multicenter Study of the Efficacy and Safety of Pyrotinib Versus Docetaxel in Patients With Advanced Non-squamous Non-small Cell Lung Cancer (NSCLC) Harboring a HER2 Exon 20 Mutation Who Progressed on or After Treatment With Platinum Based Chemotherapy	III
NCT04589845	Tumor-Agnostic Precision Immunooncology and Somatic Targeting Rational for You (TAPISTRY) Phase II Platform Trial	II

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

FDA information is current as of 2021-11-17. For the most up-to-date information, search www.fda.gov.

ERBB2 exon 20 insertion

trastuzumab deruxtecan

Cancer type: Non-Small Cell Lung Cancer

Variant class: ERBB2 mutation

Supporting Statement:
The FDA has granted Breakthrough Designation for the HER2-directed antibody drug conjugate, Enhertu (trastuzumab deruxtecan), for the treatment of HER2 mutated metastatic non-small cell lung cancer (NSCLC) with disease progression on or after platinum-based therapy.

Reference:

https://www.astrazeneca.com/media-centre/press-releases/2020/enhertu-granted-breakthrough-therapy-designation-in-the-us-for-her2-mutant-metastatic-non-small-cell-lung-cancer.html

BDTX-189

Cancer type: Solid Tumor

Variant class: ERBB2 exon 20 insertion

Supporting Statement:
The FDA has granted Fast Track Designation to BDTX-189 for solid tumors harboring a HER2 mutation or an EGFR or HER2 exon 20 insertion after progression on prior therapy.

Reference:

https://investors.blackdiamondtherapeutics.com/news-releases/news-release-details/black-diamond-therapeutics-granted-fast-track-designation-fda

AR amplification

seviteronel

Cancer type: Triple Negative Breast Cancer **Variant class:** AR positive

Supporting Statement:

The FDA has granted Fast Track Designation to the small-molecule CYP17 lyase-selective inhibitor, seviteronel, for:

- Androgen receptor (AR) positive advanced triple negative breast cancer (TNBC).
- Estrogen receptor (ER) positive advanced breast cancer.

Reference:

https://www.businesswire.com/news/home/20160106006206/en/Innocrin-Pharmaceuticals-Granted-Fast-Track-Designation-FDA

Current NCCN Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

NCCN information is current as of 2021-11-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

ERBB2 exon 20 insertion

afatinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** ERBB2 mutation

Summary:

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

- "The NCCN NSCLC Panel does not recommend single-agent therapy with trastuzumab or afatinib (both for ERBB2 mutations), because response rates are lower and treatment is less effective when these agents are used for patients with ERBB2 mutations."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 7.2021]

trastuzumab

Cancer type: Non-Small Cell Lung Cancer **Variant class:** ERBB2 mutation

Summary:

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

- "The NCCN NSCLC Panel does not recommend single-agent therapy with trastuzumab or afatinib (both for ERBB2 mutations), because response rates are lower and treatment is less effective when these agents are used for patients with ERBB2 mutations."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 7.2021]

Signatures

Testing Personnel:

2021.12.30
10:44:00 +08'00'

Laboratory Supervisor:

2021.12.30
10:44:13 +08'00'

Pathologist:

2021.12.30
10:44:27 +08'00'

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/2021/202379s035lbl.pdf
10. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/203415s016lbl.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. 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
14. Gutierrez et al. HER2: biology, detection, and clinical implications. Arch. Pathol. Lab. Med. 2011 Jan;135(1):55-62. PMID: 21204711
15. Di et al. erbB-2 is a potent oncogene when overexpressed in NIH/3T3 cells. Science. 1987 Jul 10;237(4811):178-82. PMID: 2885917
16. Hudziak et al. Increased expression of the putative growth factor receptor p185HER2 causes transformation and tumorigenesis of NIH 3T3 cells. Proc. Natl. Acad. Sci. U.S.A. 1987 Oct;84(20):7159-63. PMID: 2890160
17. Lonardo et al. The normal erbB-2 product is an atypical receptor-like tyrosine kinase with constitutive activity in the absence of ligand. New Biol. 1990 Nov;2(11):992-1003. PMID: 1983208
18. Ciriello et al. Comprehensive Molecular Portraits of Invasive Lobular Breast Cancer. Cell. 2015 Oct 8;163(2):506-19. PMID: 26451490
19. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. Nature. 2014 Sep 11;513(7517):202-9. doi: 10.1038/nature13480. Epub 2014 Jul 23. PMID: 25079317
20. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of urothelial bladder carcinoma. Nature. 2014 Mar 20;507(7492):315-22. doi: 10.1038/nature12965. Epub 2014 Jan 29. PMID: 24476821
21. Donna et al. Comprehensive molecular characterization of human colon and rectal cancer. Nature. 2012 Jul 18;487(7407):330-7. PMID: 22810696
22. 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
23. Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. Nature. 2011 Jun 29;474(7353):609-15. PMID: 21720365
24. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. Nat. Genet. 2013 Oct;45(10):1113-20. PMID: 24071849
25. 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
26. Petrelli et al. Clinical and pathological characterization of HER2 mutations in human breast cancer: a systematic review of the literature. Breast Cancer Res. Treat. 2017 Nov;166(2):339-349. PMID: 28762010
27. Bose et al. Activating HER2 mutations in HER2 gene amplification negative breast cancer. Cancer Discov. 2013 Feb;3(2):224-37. doi: 10.1158/2159-8290.CD-12-0349. Epub 2012 Dec 7. PMID: 23220880

References (continued)

28. Hudis. Trastuzumab--mechanism of action and use in clinical practice. N. Engl. J. Med. 2007 Jul 5;357(1):39-51. PMID: 17611206
29. Slamon et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science. 1987 Jan 9;235(4785):177-82. PMID: 3798106
30. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/103792s5345lbl.pdf
31. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125409s124lbl.pdf
32. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125427s108lbl.pdf
33. NCCN Guidelines® - NCCN-Breast Cancer [Version 8.2021]
34. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022059s024lbl.pdf
35. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/208051s009lbl.pdf
36. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/213411s000lbl.pdf
37. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125514s113lbl.pdf
38. https://www.globenewswire.com/news-release/2016/06/01/845166/0/en/Galena-Biopharma-Receives-Fast-Track-Designation-for-NeuVax-nelipepimut-S-PRESENT-Clinical-Trial.html
39. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761150s000lbl.pdf
40. https://www.targetedonc.com/view/her2targeted-antibody-zw25-earns-fda-fast-track-designation-in-gea
41. https://www.targetedonc.com/view/fda-grants-breakthrough-designation-to-zanidatamab-for-her2-amplified-biliary-tract-cancer
42. https://investors.blackdiamondtherapeutics.com/news-releases/news-release-details/black-diamond-therapeutics-granted-fast-track-designation-fda
43. https://www.prnewswire.com/news-releases/remegen-announces-us-fda-has-granted-breakthrough-therapy-designation-for-disitamab-vedotin-rc48-in-urothelial-cancer-301138315.html
44. http://ambrx.com/fda-grants-arx788-fast-track-designation-for-her2-positive-metastatic-breast-cancer
45. Ma et al. Neratinib Efficacy and Circulating Tumor DNA Detection of HER2 Mutations in HER2 Nonamplified Metastatic Breast Cancer. Clin. Cancer Res. 2017 Oct 1;23(19):5687-5695. PMID: 28679771
46. De et al. Clinical activity of afatinib (BIBW 2992) in patients with lung adenocarcinoma with mutations in the kinase domain of HER2/neu. Lung Cancer. 2012 Apr;76(1):123-7. PMID: 22325357
47. Kris et al. Targeting HER2 aberrations as actionable drivers in lung cancers: phase II trial of the pan-HER tyrosine kinase inhibitor dacomitinib in patients with HER2-mutant or amplified tumors. Ann. Oncol. 2015 Jul;26(7):1421-7. PMID: 25899785
48. Falchook et al. Non-small-cell lung cancer with HER2 exon 20 mutation: regression with dual HER2 inhibition and anti-VEGF combination treatment. J Thorac Oncol. 2013 Feb;8(2):e19-20. PMID: 23328556
49. David et al. Neratinib in HER2- or HER3-mutant solid tumors: SUMMIT, a global, multi-histology, open-label, phase 2 ‘basket’ study. AACR 2017. Abstract CT001
50. Lin et al. Response to Afatinib in a Patient with Non-Small Cell Lung Cancer Harboring HER2 R896G Mutation: A Case Report. Onco Targets Ther. 2019;12:10897-10902. PMID: 31849493
51. Chang et al. Sustained Partial Response to Afatinib in a Patient With Lung Adenocarcinoma Harboring HER2V659E Mutation. JCO Precis Oncol. 2020 Aug; 912-915. DOI: 10.1200/PO.20.00114
52. Nayar et al. Acquired HER2 mutations in ER+ metastatic breast cancer confer resistance to estrogen receptor-directed therapies. Nat. Genet. 2019 Feb;51(2):207-216. PMID: 30531871