CANCER DIAGNOSIS & PROGNOSIS
3: 151-156 (2023) doi: 10.21873/cdp.10194

Review

Anti-EGFR/BRAF-Tyrosine Kinase Inhibitors in Thyroid Carcinoma

VASILEIOS PAPANIKOLAOU[1], EFTHYMIOS KYRODIMOS[1], NICHOLAS MASTRONIKOLIS[2], ASIMAKIS D. ASIMAKOPOULOS[3], GEORGE PAPANASTASIOU[4], EVANGELOS TSIAMBAS[5], DESPOINA SPYROPOULOU[6], SPYROS KATSINIS[7], AREZINA MANOLI[8], SOTIRIOS PAPOULIAKOS[9], PAVLOS PANTOS[1], VASILEIOS RAGOS[4], DIMITRIOS PESCHOS[10] and ARISTEIDIS CHRYSOVERGIS[1]

[1]*1st Department of Otorhinolaryngology, Hippocration Hospital, University of Athens, Athens, Greece;*
[2]*Department of Otorhinolaryngology, Medical School, University of Patras, Patras, Greece;*
[3]*Department of Otorhinolaryngology, Centre Hospital, Sion, Switzerland;*
[4]*Department of Maxillofacial, Medical School, University of Ioannina, Ioannina, Greece;*
[5]*Department of Cytology, 417 Veterans Army Hospital (NIMTS), Athens, Greece;*
[6]*Department of Radiation Oncology, Medical School, University of Patras, Patras, Greece;*
[7]*Department of Otorhinolaryngology, Pamakaristos General Hospital, Athens, Greece;*
[8]*Department of Otorhinolaryngology, Thoracic Diseases General Hospital Sotiria, Athens, Greece;*
[9]*Department of Otorhinolaryngology, General Hospital "Gennimatas", Athens, Greece;*
[10]*Department of Physiology, Medical School, University of Ioannina, Ioannina, Greece*

Abstract. *Alterations in significant genes located on chromosome 7 - including epidermal growth factor receptor (EGFR) and also v-Raf murine sarcoma viral oncogene homolog B (BRAF) as a mitogen-activated protein kinase (MAPK) - combined or not with numerical imbalances of the whole chromosome (aneuploidy-polysomy) are crucial genetic events involved in the development and progression of malignancies. Identification of EGFR/BRAF-dependent specific somatic mutations and other mechanisms of deregulation (i.e., amplification) is critical for applying targeted therapeutic approaches [tyrosine kinase inhibitors (TKIs] or monoclonal antibodies (mAbs). Thyroid carcinoma is a specific pathological entity characterized by a variety of histological sub-types. Follicular thyroid carcinoma (FTC), papillary thyroid carcinoma (PTC), medullary thyroid carcinoma (MTC), and anaplastic thyroid carcinoma (ATC) represent its main sub-types. In the current review, we explore the role of EGFR/BRAF alterations in thyroid carcinoma in conjunction with the corresponding anti-EGFR/BRAF TKI-based novel therapeutic strategies for patients with specific genetic signatures.*

Correspondence to: Evangelos Tsiambas, MD, MSc, PhD, 17 Patriarchou Grigoriou E΄ Street, Ag. Paraskevi, 153 41 Athens, Greece. Tel: +30 6946939414, e-mail: tsiambasecyto@yahoo.gr

Key Words: Thyroid, epidermal growth factor, receptor, carcinoma, tyrosine, kinase, review.

Epithelial cell neoplastic and malignant transformation is a multi-step process. It includes chromosome instability (CI) as gross chromosome numerical and structural alterations such as polysomy/aneuploidy, monosomy, and rearrangements (*i.e.*, translocations) in specific or vast chromosome regions (1, 2). Concerning thyroid carcinoma, the corresponding follicular epithelia demonstrate chromosome gains and losses and also specific gene amplifications, mutations or allelic losses (3). Thyroid carcinoma includes a broad spectrum of different histological sub-types, such as papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), anaplastic thyroid cancer (ATC), and medullary thyroid carcinoma (4). Each pathological entity is characterized by specific cyto-morphological and genetic profiles. Epidermal growth factor

receptor (*EGFR)* and also v-Raf murine sarcoma viral oncogene homolog B (*BRAF)* genes are localized on chromosome 7 and their numerical or structural abnormalities lead to specific molecular signatures in the corresponding patients (5, 6). In the current review, we described EGFR-dependent signaling transduction pathways and their impact on thyroid carcinoma biological behavior in conjunction with modern oncological therapeutic approaches.

EGFR-mediated Pathways: Molecules and Mechanisms

Among genes that are localized on chromosome 7, *EGFR* and *BRAF* represent major genetic markers implicated in the development, progression, and prognosis of thyroid carcinoma (7). Additionally, another important gene is the ret proto-oncogene (*RET*) (8). These genes are involved in a variety of signaling transduction pathways altered in carcinogenetic process. Interestingly, the BRAF protein-encoded by the corresponding gene (cytogenetic band: 7q34) is a target for a critical driver mutation (BRAF V600G/E). Based on this mutation, a series of inhibitors has been developed and applied in sub-groups of patients (trametinib, dabrafenib, vemurafenib) (9, 10). Concerning the *EGFR* (*ERBB, ERBB1, HER1*) gene, it is located on the short (p) arm of chromosome 7 (cytogenetic band: 7p12.1). The gene encodes the EGFR protein acting as a transmembrane glycoprotein receptor (11). Referring to its composition, a large extra cellular ligand-binding region, a single hydrophobic transmembrane bridge adjusting to an intracellular juxtamembrane (JM) region, a tyrosine kinase domain and a C terminal tail including multiple tyrosine residues are the main distinct domains. Due to similar domains with HER2 protein, formations of HER2-EGFR heterodimers have been already identified in cancer cell lines (12).

According to extensive molecular studies, EGFR is responsible for signal transduction to the nucleus in different intra-cellular pathways. The phospatidyl inositol 3 kinase-v AKT murine thymoma viral oncogene homolog I/phosphatase and TENsin homolog deleted on chromosome ten-mammalian target of rapamycin) (PI3K-AKT/PTEN-mTOR) regulates cellular homeostasis and angiogenesis due to a cell survival/apoptosis balance mechanism (13). Furthermore, the rat sarcoma-mitogen-activated protein kinase (RAS/MAPK) pathway secures normal cell proliferation, tissue differentiation and cell migration process in the epithelial tissue morphogenesis phase (14). *MET* proto-oncogene (*MET*) that encodes for a receptor tyrosine kinase activation is also implicated in these functions (15). Additionally, EGFR-mediated cross talk reactions at the level of *JAK* gene have been detected proving its involvement in another pathway, the interleukin 6-JAnus kinase-signal transducer activator of transcription (IL6-JAK1/2-STAT3) (16).

EGFR Alterations in Thyroid Carcinoma

EGFR over expression in thyroid carcinoma is a relatively frequent observation. Especially in PTCs, a study group detected a ~20% of all examined tissue microarray - based cases to demonstrate a strong, continuous membrane expression (17). Interestingly, they reported a significant co-over expression of the marker with estrogen (Era/b) and progesterone (PR) receptors in sub-sets of patients. However, statistical significance correlating expression levels with the recurrence rates of the malignancies was not assessed. Another study group performed a meta-analysis focusing on the potential relation between EGFR expression and clinicopathological features in PTCs (18). They detected that EGFR over-expression was strongly associated to TNM stage and extra-thyroid metastases in the examined studies, whereas no correlation was found regarding sex, tumor size, grade of differentiation and age. Concerning the combined EGF/EGFR complex expression in thyroid malignancies, a study group showed not only over expression of the two proteins, but most importantly that EGF over-activation triggers EGFR translocation into the nucleus (19). This biochemical reaction affects indirectly the normal cell cycle regulation leading potentially to increased cell proliferation. This is evidence of EGFR involvement in the corresponding intracellular signaling pathway affecting indirectly nuclear microenvironment. Because this event is detected predominantly in anaplastic carcinomas, it seems to promote dedifferentiation of the neoplasms (aggressive phenotype). Referring to anaplastic thyroid carcinoma, a broad spectrum of point-mutations in critical genes has been already identified (20). Besides *EGFR, p53, TERT, BRAF, RAS, PIK3CA, PTEN, AKT1, Mtor, ALK, VEGFR*, and *CDKN2A* demonstrate specific nucleotide substitutions. The encoded proteins are eligible for targeted therapeutic approaches. Similarly, another study co-analyzed the gene expression of EGF/EGFR and another protein, the serpin peptidase inhibitor clade E member 2 (SERPINE2) by implementing a reverse transcription quantitative PCR-based assay (21). SERPINE2 is considered a reliable marker for detecting tissue-to-tissue metastatic potential. They reported a positive feedback loop with the EGF/EGFR system that affects invasion, migration and also proliferation in PTC cells.

According to a systematic molecular analysis in a genetically specific population (Kashmiri), harboring *EGFR* mutational landscape includes mainly T790M, L858R, and deletion in exon 19 (22). The study group reported differences between FTCs and PTCs regarding the rates of these point-mutations, but they also concluded that their accumulation is responsible for aggressive phenotypes (increased dedifferentiation). Furthermore, EGFR/BRAF/PIK3CA/m TOR/KRAS pathway is frequently altered in malignancies including thyroid carcinoma, according to an RNA sequencing

profile analysis (23). The study group proposed that over-expression of the markers -due to activating point mutations- leads to aberrant transcriptomic activity in these malignancies. The role of *EGFR*/*RET* oncogene activation in thyroid carcinoma is also a very promising field of investigation. A genetic study –based on PTC cell culture transfection protocol and application of real time (RT)-PCR– showed a direct over-activation of *EGFR* mediated by *RET* oncogene over expression (24). Besides the elevated proliferation of cancerous cells and the decreased apoptotic rates, *RET*/*EGFR* co-activation provided increased epithelial-mesenchymal transition (EMT) as a result of N-cadherin and vimentin over expression. Besides these mechanisms, there is evidence that strong oxidative intracellular stress –which is one of the main causes that induce DNA damage– motivates EGFR mediated signaling pathways such as mitogen-activated protein kinase (MAPK/ERK) and PI3K/Akt (25). A study group co-analyzed the base excision repair (BER) pathway initiated by 8-oxoG glycosylase1 (OGG1) and EGFR expression in PTCs. They detected a positive relation between H_2O_2 production and OGG1-BER/EGFR over expression pathways in TPC-1 culture cells. Additionally, novel micro-genetic markers such as micro-RNAs (miRs) and long non-coding RNAs (lncRNA) seem to affect *EGFR* activation in thyroid carcinoma. Two studies explored the role of specific miRs (miR-30b-5p and miR-7-5p, respectively) in PTC tissues (26, 27). They concluded that miR-30b-5p prevented an aggressive progress in PTCs by inhibiting the EGFR/PI3K/AKT pathway, whereas decreased expression of miR-7-5p led to over expression of EGFR, respectively. Additionally, miR-326 seems to inhibit the progression of PTC by suppressing EGFR/MAPK pathway (28). In contrast, miR-133a-3p, which is involved in the axis ZEB1-AS1/miR-133a-3p/LPAR3/EGFR, enhances PI3K/AKT/mTOR signaling transduction pathway activation (29). Concerning lncRNAs, a study group analyzed the role of LncRNA ABHD11-AS1 in a series of PTCs. They detected ABHD11-AS1 high expression levels that led to increased activation EPS15L1/EGFR pathway (30).

Anti-EGFR/BRAF Tyrosine Kinase Inhibitor (TKI)-based Strategies in Thyroid Carcinoma

Evolution in targeted therapies significantly affects oncological strategies in malignancies including thyroid carcinoma besides conventional ^{131}I-based treatment (31). A broad spectrum of mAbs and TKIs that inhibit EGFR-mediated signaling transduction pathways are under evaluation (Table I). Concerning the TKIs, lenvatinib acts as an anti-VEGFR1/2/3 multiple kinase inhibitor, but its function seems to expand to phosphorylated EGFR in thyroid carcinoma. A study group reported increased EGFR phosphorylation in thyroid carcinoma cell lines (32). They also revealed a synergistic anti-EGFR activity mediated by simultaneous lenvatinib/lapatinib drug administration. Interestingly, although lenvatinib seem to be a very promising EGFR inhibitor, its impact on the renal function of the corresponding patients is a matter of serious concern for oncologists, as it happens with similar targeted agents. A study group analyzed the data derived from advanced differentiated thyroid carcinoma patients in period of time over 6 months cured by the lenvatinib TKI (33). They reported moderate to high proteinuria levels in subsets of them due to VEGF/VEGFR pathway blocking. They suggested an optimal modification of the lenvatinib in patients with poor renal function. Labatinib, is also a dual anti-EGFR/HER2 TKI inhibitor that perfectly blocks oncogenic signal transduction to nucleus in patients with breast carcinoma by suppressing pyruvate kinase type M2 expression leading to decreased cell proliferation (34). There are relatively limited data regarding its efficacy in thyroid carcinomas. In one study based on a combination of labatinib/vemurafenib – a selective inhibitor of V600E mutated BRAF gene – there were promising results for EGFR/RAF/MEK pathway blocking (35). In conjunction, another study revealed a positive effect in patients with differentiated thyroid carcinoma patients using a combination of labatinib/vemurafenib/pazopanib/cabozantinib/sunitinib as a salvage treatment when first-line sorafenib-based strategy fails (35). A significantly median progression-free survival period was assessed. Dabrafenib and erlotinib are also significant anti-EGFR TIKs targeting EGFR/RAF/MEK pathway in abroad spectrum of solid malignancies. A clinical study showed that combination of these two agents or using another agent (trametinib) inhibited phosphorylated EGFR even in severe anaplastic carcinoma cases characterized by resistance to dabrafenib-dependent *BRAF*-mutated gene (36).

Table I. *TKIs for direct or indirect anti-EGFR/BRAF-dependent pathways blockade in thyroid carcinoma targeted strategies.*

TKI	Direct target gene/s
Erlotinib/Gefitinib	***EGFR***
Trametinib	*MEK1/2*
Dabrafenib	***BRAF***
Vemurafenib	***BRAF***
Lenvatinib	*VEGFR1/2/3*
Lapatinib	***EGFR****/HER2*
Pazopanib	*VEGFR*
Cabozantinib	*VEGFR2/cMET*
Sunitinib/Sorafenib	*VEGFR/PDGFR-cKIT/****BRAF***
Selumetinib	*NF-1*
Anlotinib	*PDGFR/cKIT/FGFR/VEGFR*

TKI: Tyrosine kinase inhibitor. EGFR/BRAF in bold: direct target of TKIs.

Referring to dabrafenib resistance levels, another study focused on an unexplored novel *RAC1* (P34R) mutation acquired in BRAF. They reported an excessive EGFR /MET protein over-expression due to gene amplification in PTC cases that led to dedifferentiation enhancing their aggressive genotype/phenotype by increasing their metastatic potential (37). In contrast to successive responses in TKI-based therapeutic approaches, there are sub-groups of patients that lose clinical benefits after discontinuation of lenvatinib-based treatment (38). Mechanisms that lead to absence of response to this agent after a period of time are under investigation. Additionally, increased resistance to selumetinib -another anti-EGFR/HER2 TKI- is a result of insulin-like growth factor 2 mRNA-binding protein 2 (IGF2BP2) over activation (39). Furthermore, a recently published study explored the role of anlotinib, a multi anti-VEGFR, FGFR and PDGFR TKI in anaplastic thyroid carcinoma. They observed that CXCL11-EGF-EGFR signalling interacts with endothelial cells under hypoxia conditions and anlotinib blocks EGFR (40). Interestingly, the effect of those TKIs - especially sorafenib, lenvatinib and selumetinib - on technetium-99m uptake in thyroid cancerous cells is under investigation. A study group using cancer cell lines reported elevated rates of the drug in them (41). Finally, another category of inhibitors that target histone deacetylase (HDAC) modify transcription of a variety of genes. A recently published study explored the efficacy of HDAC inhibitors (HDACIs) on anaplastic thyroid carcinoma as a literature meta-analysis. They observed that HDACIs could be a promising mono- or combined with other agents targeted therapeutic approach in sub-groups of patients (42).

In conclusion, EGFR and BRAF over-expression is a frequent event in thyroid carcinoma caused by point mutations or amplification in the corresponding genes. Especially, *BRAF* mutation is a significant biomarker associated with a more aggressive phenotype in thyroid carcinoma. Elevated *EGFR/BRAF* oncogenic activity triggers a cataract of intracellular reactions leading to RAF and MAPK signaling transduction pathways over-activation. Novel mono- or combined anti-EGFR/BRAF targeted therapies based on TKIs provide benefits (high response rates and expanded life span) in sub-groups of patients characterized by specific genetic signatures.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

VP, EK, ET: design of the study, ET, AC: manuscript writing, NM, VR, DP, DS: academic advisors: AA, GP, SK, AM, SP, PP: collection and management of references' data. All Authors read and approved the final manuscript.

References

1 Albertson RC, Cresko W, Detrich HW 3rd and Postlethwait JH: Evolutionary mutant models for human disease. Trends Genet *25(2)*: 74-81, 2009. PMID: 19108930. DOI: 10.1016/j.tig.2008.11.006

2 Albertson DG, Collins C, McCormick F and Gray JW: Chromosome aberrations in solid tumors. Nat Genet *34(4)*: 369-376, 2003. PMID: 12923544. DOI: 10.1038/ng1215

3 Chu YH and Sadow PM: Kinase fusion-related thyroid carcinomas: Towards predictive models for advanced actionable diagnostics. Endocr Pathol *33(4)*: 421-435, 2022. PMID: 36308634. DOI: 10.1007/s12022-022-09739-9

4 Kroll TG: Molecular events in follicular thyroid tumors. Cancer Treat Res *122*: 85-105, 2004. PMID: 16209039. DOI: 10.1007/1-4020-8107-3_4

5 Ehlers M, Schmidt M, Mattes-Gyorgy K, Antke C, Enczmann J, Schlensog M, Japp A, Haase M, Allelein S, Dringenberg T, Giesel F, Esposito I and Schott M: BRAFV600E and BRAF-WT specific antitumor immunity in papillary thyroid cancer. Horm Metab Res *54(12)*: 852-858, 2022. PMID: 36427494. DOI: 10.1055/a-1971-7019

6 Harahap WA, Tofrizal T and Oktahermoniza O: Relationship between the expression of BRAF V600E and Ki-67 with the recurrence of well-differentiated thyroid cancer. Asian Pac J Cancer Prev *23(11)*: 3617-3622, 2022. PMID: 36444572. DOI: 10.31557/APJCP.2022.23.11.3617

7 Li H, Ma J, Xi X, Tang J, Wang L, Wang L, Lin S and Zhang B: The analysis and validation of the prediction value of conventional and contrast-enhanced ultrasonography for BRAF mutant papillary thyroid microcarcinoma. Gland Surg *11(10)*: 1683-1696, 2022. PMID: 36353582. DOI: 10.21037/gs-22-493

8 Zarif-Yeganeh M, Farhud DD, Rahimpour A, Sheikholeslami S, Shivaei S and Hedayati M: CRISPR/Cas9 RET gene knockout in medullary thyroid carcinoma cell-lines: Optimization and validation. Iran J Public Health *51(5)*: 1084-1096, 2022. PMID: 36407731. DOI: 10.18502/ijph.v51i5.9424

9 Elia G, Ferrari SM, Ragusa F, Paparo SR, Mazzi V, Ulisse S, Benvenga S, Antonelli A and Fallahi P: Advances in pharmacotherapy for advanced thyroid cancer of follicular origin (PTC, FTC). New approved drugs and future therapies. Expert Opin Pharmacother *23(5)*: 599-610, 2022. PMID: 35038965. DOI: 10.1080/14656566.2022.2030704

10 Felicetti F, Nervo A, Piovesan A, Berardelli R, Marchisio F, Gallo M and Arvat E: Tyrosine kinase inhibitors rechallenge in solid tumors: a review of literature and a case description with lenvatinib in thyroid cancer. Expert Rev Anticancer Ther *17(12)*: 1093-1098, 2017. PMID: 28988510. DOI: 10.1080/14737140.2017.1390432

11 Kaniowski D, Suwara J, Ebenryter-Olbińska K, Jakóbik-Kolon A and Nawrot B: EGFR-targeted cellular delivery of therapeutic nucleic acids mediated by boron clusters. Int J Mol Sci *23(23)*: 14793, 2022. PMID: 36499115. DOI: 10.3390/ijms232314793

12 Tsutsumi H, Iwama E, Ibusuki R, Shimauchi A, Ota K, Yoneshima Y, Inoue H, Tanaka K, Nakanishi Y and Okamoto I: Mutant forms of EGFR promote HER2 trafficking through efficient formation of HER2-EGFR heterodimers. Lung Cancer *175*: 101-111, 2023. PMID: 36495783. DOI: 10.1016/j.lungcan.2022.11.018

13 Almaimani RA, Aslam A, Ahmad J, El-Readi MZ, El-Boshy ME, Abdelghany AH, Idris S, Alhadrami M, Althubiti M, Almasmoum HA, Ghaith MM, Elzubeir ME, Eid SY and Refaat B: *In vivo* and *in vitro* enhanced tumoricidal effects of

metformin, active vitamin D(3), and 5-fluorouracil triple therapy against colon cancer by modulating the PI3K/Akt/PTEN/mTOR network. Cancers (Basel) *14(6)*: 1538, 2022. PMID: 35326689. DOI: 10.3390/cancers14061538

14 Maloney RC, Zhang M, Liu Y, Jang H and Nussinov R: The mechanism of activation of MEK1 by B-Raf and KSR1. Cell Mol Life Sci *79(5)*: 281, 2022. PMID: 35508574. DOI: 10.1007/s00018-022-04296-0

15 Ko J, Jung J, Kim ST, Hong JY, Park S, Park JO, Park YS, Lim HY, Ahn S, Kim KM, Kang WK and Lee J: MET gene alterations predict poor survival following chemotherapy in patients with advanced cancer. Pathol Oncol Res *28*: 1610697, 2022. PMID: 36483096. DOI: 10.3389/pore.2022.1610697

16 Wang W, Bhattacharyya S, Marangoni RG, Carns M, Dennis-Aren K, Yeldandi A, Wei J and Varga J: The JAK/STAT pathway is activated in systemic sclerosis and is effectively targeted by tofacitinib. J Scleroderma Relat Disord *5(1)*: 40-50, 2020. PMID: 35382402. DOI: 10.1177/2397198319865367

17 Ahn HY, Song RY, Ahn HS and Kim HS: Expression of estrogen and progesterone receptors in papillary thyroid carcinoma in Korea. Cancer Res Treat *53(4)*: 1204-1212, 2021. PMID: 33592140. DOI: 10.4143/crt.2020.1201

18 Qin XR, Huang JK, Yin QF, Shi XM, Tang JC, Hao LL, Li PF, Zhu J and Wang YX: Clinicopathological significance of epidermal growth factor receptor expression in papillary thyroid carcinoma: a meta-analysis. Minerva Endocrinol, 2021. PMID: 33435649. DOI: 10.23736/S0391-1977.20.03388-X

19 Niu X, Chen J, Ma N, Huang R, Tao C, Dan Q and Fang Y: Nuclear-targeted EGF receptor enhances proliferation and migration of human anaplastic thyroid cancer cells. Endokrynol Pol : , 2022. PMID: 36094870. DOI: 10.5603/EP.a2022.0048

20 Abe I and Lam AK: Anaplastic thyroid carcinoma: Current issues in genomics and therapeutics. Curr Oncol Rep *23(3)*: 31, 2021. PMID: 33582932. DOI: 10.1007/s11912-021-01019-9

21 Chu H, Hu B and Su X: SERPINE2 feedback regulates EGF/EGFR signaling in human papillary thyroid carcinoma cells. Mol Med Rep *23(5)*: 342, 2021. PMID: 33760135. DOI: 10.3892/mmr.2021.11981

22 Mir TA, Qadir A, Wani MA and Wani MM: Spectrum of EGFR mutation and its relation with high-risk predictors in thyroid cancer in Kashmiri population: 2 years prospective study at a tertiary care hospital. J Egypt Natl Canc Inst *34(1)*: 43, 2022. PMID: 36245068. DOI: 10.1186/s43046-022-00139-y

23 Raevskiy M, Sorokin M, Vladimirova U, Suntsova M, Efimov V, Garazha A, Drobyshev A, Moisseev A, Rumiantsev P, Li X and Buzdin A: EGFR pathway-based gene signatures of druggable gene mutations in melanoma, breast, lung, and thyroid cancers. Biochemistry (Mosc) *86(11)*: 1477-1488, 2021. PMID: 34906047. DOI: 10.1134/S0006297921110110

24 Zhao YL, Yuan BQ and Shen GS: Mechanism of RET gene mediated EGFR signaling pathway on epithelial-mesenchymal transition, proliferation and apoptosis of papillary thyroid carcinoma cells. Eur Rev Med Pharmacol Sci *24(15)*: 8036-8047, 2020. PMID: 32767330. DOI: 10.26355/eurrev_202008_22487

25 Moscatello C, Di Marcantonio MC, Savino L, D'Amico E, Spacco G, Simeone P, Lanuti P, Muraro R, Mincione G, Cotellese R and Aceto GM: Emerging role of oxidative stress on EGFR and OGG1-BER cross-regulation: Implications in thyroid physiopathology. Cells *11(5)*: 822, 2022. PMID: 35269445. DOI: 10.3390/cells11050822

26 Wang Y, Wang C, Fu Z, Zhang S and Chen J: miR-30b-5p inhibits proliferation, invasion, and migration of papillary thyroid cancer by targeting GALNT7 via the EGFR/PI3K/AKT pathway. Cancer Cell Int *21(1)*: 618, 2021. PMID: 34819077. DOI: 10.1186/s12935-021-02323-x

27 Augenlicht A, Saiselet M, Decaussin-Petrucci M, Andry G, Dumont JE and Maenhaut C: MiR-7-5p inhibits thyroid cell proliferation by targeting the EGFR/MAPK and IRS2/PI3K signaling pathways. Oncotarget *12(16)*: 1587-1599, 2021. PMID: 34381564. DOI: 10.18632/oncotarget.28030

28 Nie FR, Li QX, Wei HF and Ma Y: miR-326 inhibits the progression of papillary thyroid carcinoma by targeting MAPK1 and ERBB4. Neoplasma *67(3)*: 604-613, 2020. PMID: 32266816. DOI: 10.4149/neo_2020_190731N696

29 Xia W and Jie W: ZEB1-AS1/miR-133a-3p/LPAR3/EGFR axis promotes the progression of thyroid cancer by regulating PI3K/AKT/mTOR pathway. Cancer Cell Int *20*: 94, 2020. PMID: 32231464. DOI: 10.1186/s12935-020-1098-1

30 Lu H, Zhu C, Chen Y, Ruan Y, Fan L, Chen Q and Wei Q: LncRNA ABHD11-AS1 promotes tumor progression in papillary thyroid carcinoma by regulating EPS15L1/EGFR signaling pathway. Clin Transl Oncol *24(6)*: 1124-1133, 2022. PMID: 35098448. DOI: 10.1007/s12094-021-02753-z

31 Yin L, Li W, Lv X, Lin Y, Jia Q, Tan J, Li X, Sun D, Wang Y and Meng Z: Effects of high-activity radioactive iodine treatment on renal function in patients with differentiated thyroid carcinoma - retrospective study. Endokrynol Pol *73(3)*: 619-626, 2022. PMID: 36059177. DOI: 10.5603/EP.a2022.0037

32 Ohno K, Shibata T and Ito KI: Epidermal growth factor receptor activation confers resistance to lenvatinib in thyroid cancer cells. Cancer Sci *113(9)*: 3193-3210, 2022. PMID: 35723021. DOI: 10.1111/cas.15465

33 Masaki C, Sugino K, Kobayashi S, Hosoi Y, Ono R, Yamazaki H, Akaishi J, Hames KY, Tomoda C, Suzuki A, Matsuzu K, Ohkuwa K, Kitagawa W, Nagahama M and Ito K: Impact of lenvatinib on renal function: long-term analysis of differentiated thyroid cancer patients. BMC Cancer *21(1)*: 894, 2021. PMID: 34353305. DOI: 10.1186/s12885-021-08622-w

34 Guan M, Tong Y, Guan M, Liu X, Wang M, Niu R, Zhang F, Dong D, Shao J and Zhou Y: Lapatinib inhibits breast cancer cell proliferation by influencing PKM2 expression. Technol Cancer Res Treat *17*: 1533034617749418, 2018. PMID: 29343208. DOI: 10.1177/1533034617749418

35 Montero-Conde C, Ruiz-Llorente S, Dominguez JM, Knauf JA, Viale A, Sherman EJ, Ryder M, Ghossein RA, Rosen N and Fagin JA: Relief of feedback inhibition of HER3 transcription by RAF and MEK inhibitors attenuates their antitumor effects in BRAF-mutant thyroid carcinomas. Cancer Discov *3(5)*: 520-533, 2013. PMID: 23365119. DOI: 10.1158/2159-8290.CD-12-0531

36 Choi YS, Kwon H, You MH, Kim TY, Kim WB, Shong YK, Jeon MJ and Kim WG: Effects of dabrafenib and erlotinib combination treatment on anaplastic thyroid carcinoma. Endocr Relat Cancer *29(6)*: 307-319, 2022. PMID: 35343921. DOI: 10.1530/ERC-22-0022

37 Bagheri-Yarmand R, Busaidy NL, McBeath E, Danysh BP, Evans KW, Moss TJ, Akcakanat A, Ng PKS, Knippler CM, Golden JA, Williams MD, Multani AS, Cabanillas ME, Shaw KR, Meric-Bernstam F, Shah MH, Ringel MD and Hofmann MC: RAC1 alterations induce acquired dabrafenib resistance in

association with anaplastic transformation in a papillary thyroid cancer patient. Cancers (Basel) *13(19)*: 4950, 2021. PMID: 34638434. DOI: 10.3390/cancers13194950

38 Yamazaki H, Sugino K, Matsuzu K, Masaki C, Akaishi J, Hames K, Tomoda C, Suzuki A, Uruno T, Ohkuwa K, Kitagawa W, Nagahama M, Masuda M and Ito K: Rapid disease progression after discontinuation of lenvatinib in thyroid cancer. Medicine (Baltimore) *99(11)*: e19408, 2020. PMID: 32176066. DOI: 10.1097/MD.0000000000019408

39 Sa R, Liang R, Qiu X, He Z, Liu Z and Chen L: IGF2BP2-dependent activation of ERBB2 signaling contributes to acquired resistance to tyrosine kinase inhibitor in differentiation therapy of radioiodine-refractory papillary thyroid cancer. Cancer Lett *527*: 10-23, 2022. PMID: 34896211. DOI: 10.1016/j.canlet.2021.12.005

40 Liang J, Jin Z, Kuang J, Feng H, Zhao Q, Yang Z, Zhan L, Shen B, Yan J, Cai W, Cheng X and Qiu W: The role of anlotinib-mediated EGFR blockade in a positive feedback loop of CXCL11-EGF-EGFR signalling in anaplastic thyroid cancer angiogenesis. Br J Cancer *125(3)*: 390-401, 2021. PMID: 34088989. DOI: 10.1038/s41416-021-01340-x

41 Anschlag A, Greene BH, KÖnneker L, Luster M, Nagarajah J, WÄchter S, Wunderlich A and Pfestroff A: Effect of kinase inhibitors on the technetium-99m uptake into thyroid carcinoma cells in vitro. In Vivo *35(2)*: 721-729, 2021. PMID: 33622865. DOI: 10.21873/invivo.12313

42 Spartalis E, Athanasiadis DI, Chrysikos D, Spartalis M, Boutzios G, Schizas D, Garmpis N, Damaskos C, Paschou SA, Ioannidis A, Tsourouflis G, Dimitroulis D and Nikiteas NI: Histone deacetylase inhibitors and anaplastic thyroid carcinoma. Anticancer Res *39(3)*: 1119-1127, 2019. PMID: 30842140. DOI: 10.21873/anticanres.13220

Received December 11, 2022
Revised January 10, 2023
Accepted February 6, 2023