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Primary Tumor Site: liver

2025.04.25

Patient Name: 김상식 Gender: M Sample ID: N25-16

Sample Cancer Type: Intrahepatic Cholangiocarcinoma

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Relevant Intrahepatic Cholangiocarcinoma Findings

Gene	Finding		Gene	Finding
BRAF	None detected		NTRK1	None detected
ERBB2	ERBB2 p.(S31	0F) c.929C>T	NTRK2	None detected
FGFR2	None detected		NTRK3	None detected
IDH1	None detected		RET	None detected
KRAS	KRAS p.(G12	C) c.34G>T		
Genomic Alt	eration	Finding		
Tumor Mu	ıtational Burden	7.57 Mut/Mb measured		

Collection Date:

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	KRAS p.(G12C) c.34G>T KRAS proto-oncogene, GTPase Allele Frequency: 47.42% Locus: chr12:25398285 Transcript: NM_033360.4	adagrasib ⁺	adagrasib 1,2/I,II+ adagrasib + cetuximab 1/I,II+ panitumumab + sotorasib 1/I,II+ sotorasib 1,2/I,II+ adagrasib + panitumumab I,II+ cetuximab + sotorasib I,II+ bevacizumab + chemotherapy I	38
IIC	ERBB2 p.(S310F) c.929C>T erb-b2 receptor tyrosine kinase 2 Allele Frequency: 37.68% Locus: chr17:37868208 Transcript: NM_004448.4	None*	trastuzumab deruxtecan 1,2 neratinib ⁺ neratinib + hormone therapy neratinib + trastuzumab + hormone therapy	11
IIC	FGFR1 amplification fibroblast growth factor receptor 1 Locus: chr8:38271452	None*	None*	6

^{*} Public data sources included in relevant therapies: FDA1, NCCN, EMA2, ESMO

Line of therapy: I: First-line therapy, II+: Other line of therapy

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.

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Relevant Biomarkers (continued)

🛕 Alerts informed by public data sources: 🤣 Contraindicated, 🏮 Resistance, 🧳 Breakthrough, 🛕 Fast Track

KRAS p.(G12C) c.34G>T

A BBP-398 + sotorasib 1

Public data sources included in alerts: FDA1, NCCN, EMA2, ESMO

Prevalent cancer biomarkers without relevant evidence based on included data sources

PPP2R2A deletion, TP53 p.(R280T) c.839G>C, UGT1A1 p.(G71R) c.211G>A, RASA1 p.(R903*) c.2707C>T, IKBKB amplification, NQO1 p.(P187S) c.559C>T, RBM10 p.(Q257*) c.769C>T, Tumor Mutational Burden

Variant Details

DNA	Sequence Variar	nts					
Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
UGT1A1	p.(G71R)	c.211G>A	COSM4415616	chr2:234669144	50.85%	NM_000463.3	missense
RASA1	p.(R903*)	c.2707C>T		chr5:86679546	29.46%	NM_002890.3	nonsense
KRAS	p.(G12C)	c.34G>T	COSM516	chr12:25398285	47.42%	NM_033360.4	missense
NQ01	p.(P187S)	c.559C>T		chr16:69745145	99.55%	NM_000903.3	missense
TP53	p.(R280T)	c.839G>C	COSM10724	chr17:7577099	50.90%	NM_000546.6	missense
ERBB2	p.(S310F)	c.929C>T	COSM48358	chr17:37868208	37.68%	NM_004448.4	missense
RBM10	p.(Q257*)	c.769C>T		chrX:47034489	59.38%	NM_001204468.1	nonsense
HLA-B	p.([T118I;L119I])	c.353_355delCCCinsT CA		chr6:31324208	73.30%	NM_005514.8	missense, missense
MLIP	p.(V159*)	c.474_475delTGinsCT0 A	G .	chr6:53989525	4.28%	NM_138569.2	nonsense
OR5D18	p.(K296R)	c.887A>G		chr11:55587992	49.80%	NM_001001952.1	missense
KMT2D	p.(P2901H)	c.8702C>A		chr12:49432437	33.38%	NM_003482.4	missense
PARP4	p.(?)	c.3285_3285+5delinsA GT		chr13:25021149	100.00%	NM_006437.4	unknown
BRCA1	p.(I620N)	c.1859T>A		chr17:41245689	60.59%	NM_007294.4	missense
STAG2	p.(L464F)	c.1392G>T		chrX:123191803	39.40%	NM_001042749.2	missense

Copy Number Variations							
Gene	Locus	Copy Number	CNV Ratio				
PPP2R2A	chr8:26149298	0.55	0.69				
FGFR1	chr8:38271452	9.17	2.51				
IKBKB	chr8:42129602	9.45	2.57				
BRCA2	chr13:32890491	2	0.94				
EPHA2	chr1:16451707	5.26	1.69				

Biomarker Descriptions

IKBKB amplification

inhibitor of nuclear factor kappa B kinase subunit beta

Background: The IKBKB gene encodes the nuclear factor kappa B kinase subunit beta, also known as IKK-B. IKBKB is a serine/ threonine kinase, which acts as an enzyme protein subunit of the IKK complex¹. IKBKB and IKBKA dimerize to form the regulatory subunit of the IKK complex. Along with modulator IKKγ/NEMO, the IKK complex acts as a master regulator of the family of NF-κB transcription factors.¹. NF-κB signaling is critical in the inflammatory response and is also known to be implicated in other important physiological processes including cell proliferation². In resting cells, NF-κB dimers are sequestered in the cytoplasm by IκB proteins². Upon signal initiation, IκB proteins are phosphorylated by the IKK complex, leading to IκB protein degradation and liberation of NF-κB dimers². Subsequently, released NF-κB dimers undergo nuclear translocation which leads to the expression of various proinflammatory and cell survival genes³.4.

Alterations and prevalence: Somatic mutations in IKBKB are observed in 6% of uterine carcinoma, 5% of melanoma and diffuse large B-cell lymphoma (DLBCL)^{5,6}. Amplifications are observed in 14% of uterine carcinosarcoma, 7% of breast invasive carcinoma and esophageal cancer^{5,6}. IKBKB activating mutations are most commonly found at lysine 175 and are observed in 8% of splenic marginal B-cell lymphomas¹.

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

KRAS p.(G12C) c.34G>T

KRAS proto-oncogene, GTPase

<u>Background:</u> The KRAS proto-oncogene encodes a GTPase that functions in signal transduction and is a member of the RAS superfamily which also includes NRAS and HRAS. RAS proteins mediate the transmission of growth signals from the cell surface to the nucleus via the PI3K/AKT/MTOR and RAS/RAF/MEK/ERK pathways, which regulate cell division, differentiation, and survival^{7,8,9}.

Alterations and prevalence: Recurrent mutations in RAS oncogenes cause constitutive activation and are found in 20-30% of cancers. KRAS mutations are observed in up to 10-20% of uterine cancer, 30-35% of lung adenocarcinoma and colorectal cancer, and about 60% of pancreatic cancer⁵. The majority of KRAS mutations consist of point mutations occurring at G12, G13, and Q61^{5,10,11}. Mutations at A59, K117, and A146 have also been observed but are less frequent^{6,12}.

Potential relevance: The FDA has approved the small molecule inhibitors, sotorasib¹³ (2021) and adagrasib¹⁴ (2022), for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC). Sotorasib and adagrasib are also useful in certain circumstances for KRAS G12C-mutated pancreatic adenocarcinoma¹⁵. The FDA has also granted breakthrough therapy designation (2022) to the KRAS G12C inhibitor, GDC-6036¹⁶, for KRAS G12C-mutated non-small cell lung cancer. The SHP2 inhibitor, BBP-398¹⁷ was granted fast track designation (2022) in combination with sotorasib for previously treated patients with KRAS G12C-mutated metastatic NSCLC. The RAF/MEK clamp, avutometinib¹⁸ was also granted fast track designation (2024) in combination with sotorasib for KRAS G12C-mutated metastatic NSCLC who have received at least one prior systemic therapy and have not been previously treated with a KRAS G12C inhibitor. The KRAS G12C inhibitor, BBO-8520¹⁹, was granted fast track designation in 2025 for previously treated KRAS G12C-mutated patients with metastatic NSCLC. The KRAS G12C inhibitor, D3S-001²⁰, was granted fast track designation in 2024 for KRAS G12C-mutated patients with advanced unresectable or metastatic colorectal cancers. The PLK1 inhibitor, onvansertib²¹, was granted fast track designation (2020) in combination with bevacizumab and FOLFIRI for second-line treatment of patients with KRAS-mutated metastatic colorectal cancer (mCRC). The EGFR antagonists, cetuximab²² and panitumumab²³, are contraindicated for treatment of colorectal cancer patients with KRAS mutations in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146)¹². Additionally, KRAS mutations are associated with poor prognosis in NSCLC²⁴.

FGFR1 amplification

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^{25,26,27}.

Alterations and prevalence: Recurrent somatic alterations common to the FGFR family include gene amplification, mutation, and chromosomal translocations leading to FGFR fusions²⁸. 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^{5,6,29,30,31}. 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)

types³². FGFR1 translocations giving rise to expressed fusions are common in certain hematological cancers, but less common in solid tumors^{33,34,35}.

Potential relevance: The FGFR kinase inhibitor, pemigatinib³⁶ has been approved (2022) for the treatment of adults with relapsed/refractory myeloid/lymphoid neoplasms (MLNs) with FGFR1 rearrangement. Additionally, the FDA granted fast-track designation (2018) to Debio 1347³⁷ 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^{38,39,40,41,42,43,44}. 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 months⁴⁵. Likewise, in a phase Ib study testing the FGFR inhibitor AZD4547, the 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 weeks⁴⁶.

RBM10 p.(Q257*) c.769C>T

RNA binding motif protein 10

<u>Background</u>: RBM10 encodes RNA binding motif protein 10, a member of the RNA binding proteins (RBP) family^{47,48}. RBM10 regulates RNA splicing and post-transcriptional modification of mRNA^{48,49}. RBM10 is suggested to function as a tumor suppressor by promoting apoptosis and inhibiting cellular proliferation through regulation of the MDM2 and p53 feedback loops, as well as influencing BAX expression⁴⁸. RBM10 has been observed to promote transformation and proliferation in lung cancer, supporting an oncogenic role for RBM10^{50,51}.

Alterations and prevalence: Somatic mutations in RBM10 are observed in 7% of lung adenocarcinoma, 6% of uterine corpus endometrial carcinoma, 4% of bladder urothelial carcinoma, 3% of colorectal adenocarcinoma and skin cutaneous melanoma, and 2% of diffuse large B-cell lymphoma, pancreatic adenocarcinoma, adrenocortical carcinoma, cervical squamous cell carcinoma, esophageal adenocarcinoma, stomach adenocarcinoma, and kidney chromophobe^{5,6}. Biallelic loss of RBM10 is observed in 3% of esophageal adenocarcinoma and 2% of head and neck squamous cell carcinoma^{5,6}. Amplification of RBM10 is observed in 5% of ovarian serous cystadenocarcinoma, 4% of uterine carcinosarcoma, and 2% of sarcoma, uterine corpus endometrial carcinoma, adrenocortical carcinoma, and diffuse large B-cell lymphoma^{5,6}.

<u>Potential relevance:</u> Currently, no therapies are approved for RBM10 aberrations.

PPP2R2A deletion

protein phosphatase 2 regulatory subunit Balpha

Background: The PPP2R2A gene encodes the protein phosphatase 2 regulatory subunit B alpha, a member of a large heterotrimeric serine/threonine phosphatase 2A (PP2A) family. Proteins of the PP2A family includes 3 subunits—the structural A subunit (includes PPP2R1A and PPP2R1B), the regulatory B subunit (includes PPP2R2A, PPP2R3, and STRN), and the catalytic C subunit (PPPP2CA and PPP2CB)^{52,53}. PPA2 proteins are essential tumor suppressor genes that regulate cell division and possess proapoptotic activity through negative regulation of the PI3K/AKT pathway⁵⁴. Specifically, PPP2R2A modulates ATM phosphorylation which is critical in the regulation of the homologous recombination repair (HRR) pathway⁵².

Alterations and prevalence: Copy number loss and downregulation of PPP2R2A is commonly observed in solid tumors including breast and non-small cell lung cancer and define an aggressive subgroup of luminal-like breast cancer^{52,53,55,56}. Biallelic loss of PPP2R2A is observed in 4-8% of breast invasive carcinoma, lung, colorectal, bladder, liver, and prostate cancers, as well as 4% of diffuse large B-cell lymphoma⁵.

Potential relevance: Currently no therapies are approved for PPP2R2A aberrations. However, in 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex⁵⁷, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. Loss of PPP2R2A in pre-clinical and xenograft models have been shown to inhibit homologous recombination DNA directed repair and may predict sensitivity to PARP inhibitors such as veliparib⁵². Olaparib treatment in prostate cancer with PPP2R2A mutations is not recommended due to unfavorable risk benefit⁵⁸.

TP53 p.(R280T) c.839G>C

tumor protein p53

<u>Background</u>: The TP53 gene encodes the p53 tumor suppressor protein that binds to DNA and activates transcription in response to diverse cellular stresses to induce cell cycle arrest, apoptosis, or DNA repair. In unstressed cells, TP53 is kept inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis. Alterations in TP53 is required

Biomarker Descriptions (continued)

for oncogenesis as they result in loss of protein function and gain of transforming potential⁵⁹. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers^{60,61}.

Alterations and prevalence: TP53 is the most frequently mutated gene in the cancer genome with approximately half of all cancers experiencing TP53 mutations. Ovarian, head and neck, esophageal, and lung squamous cancers have particularly high TP53 mutation rates (60-90%)^{5,6,29,62,63,64}. Approximately two-thirds of TP53 mutations are missense mutations and several recurrent missense mutations are common including substitutions at codons R158, R175, Y220, R248, R273, and R282^{5,6}. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes^{65,66,67,68}.

Potential relevance: The small molecule p53 reactivator, PC14586, received a fast track designation (2020) by the FDA for advanced tumors harboring a TP53 Y220C mutation⁶⁹. The FDA has granted fast track designation (2019) to the p53 reactivator, eprenetapopt,⁷⁰ and breakthrough designation⁷¹ (2020) in combination with azacitidine or azacitidine and venetoclax for acute myeloid leukemia patients (AML) and myelodysplastic syndrome (MDS) harboring a TP53 mutation, respectively. In addition to investigational therapies aimed at restoring wild-type TP53 activity, compounds that induce synthetic lethality are also under clinical evaluation^{72,73}. TP53 mutations confer poor prognosis and poor risk in multiple blood cancers including AML, MDS, myeloproliferative neoplasms (MPN), and chronic lymphocytic leukemia (CLL), and acute lymphoblastic leukemia (ALL)^{74,75,76,77,78,79}. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant⁸⁰. Mono- and bi-allelic mutations in TP53 confer unique characteristics in MDS, with multi-hit patients also experiencing associations with complex karyotype, few co-occuring mutations, and high-risk disease presentation as well as predicted death and leukemic transformation independent of the IPSS-R staging system⁸¹.

RASA1 p.(R903*) c.2707C>T

RAS p21 protein activator 1

Background: The RASA1 gene encodes the Ras p21 protein activator 1⁴⁷. RASA1 is a member of the RasGAP family, which includes RASA2^{82,83}. RASA1 functions as a dual-specificity GTPase activating protein (GAP) by accelerating RAS and RAP GTPase activity and promoting the inactive GDP-bound form⁸². RASA1 activity is influential in several cellular processes including in growth, proliferation, differentiation, and apoptosis⁸². In tumorigenesis, loss of RASA1 function inhibits RAS regulation, leading to activation of the MAPK/MEK/ERK or PI3K/AKT pathways⁸². Mutations or epigenetic inactivation of RASA1 have been observed in diverse cancer types⁸².

Alterations and prevalence: Somatic mutations in RASA1 are observed in 11% of uterine corpus endometrial carcinoma, 6% of lung squamous cell carcinoma, 5% of stomach adenocarcinoma and of skin cutaneous melanoma, 4% of colorectal adenocarcinoma, head and neck squamous cell carcinoma, colorectal carcinoma, and uterine carcinosarcoma, and 3% of esophageal adenocarcinoma^{5,6}. Biallelic deletions are observed in 4% of ovarian serous cystadenocarcinoma, and 2% of skin cutaneous melanoma^{5,6}.

Potential relevance: Currently, no therapies are approved for RASA1 aberrations.

ERBB2 p.(S310F) c.929C>T

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 family⁸⁴. 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 survival⁸⁵. 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^{86,87,88}.

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^{5,6,30,89,90,91,92,93}. Recurrent somatic activating mutations in ERBB2/HER2 occur at low frequencies (<1%) in diverse cancer types^{6,94,95}. 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^{96,97}. Trastuzumab⁹⁸ 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

Biomarker Descriptions (continued)

for HER2-positive breast cancer including pertuzumab99 (2012), a humanized monoclonal antibody that inhibits HER2 dimerization, and ado-trastuzumab emtansine100 (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 cancer¹⁰¹. In addition to monoclonal antibodies, the small molecule inhibitor lapatinib102, 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 neratinib103, 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 neratinib¹⁰³ in combination with capecitabine for HER2-positive advanced or metastatic patients after two or more prior HER2directed therapies. Also in 2020, the TKI irbinitinib104 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 line¹⁰⁵. In 2024, a bispecific HER2 antibody, zanidatamab¹⁰⁶, was approved for the treatment of adults with previously treated, unresectable or metastatic ERBB2 overexpressing biliary tract cancer. The vaccine, nelipepimut-S107, 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 margetuximab108 in patients with ERBB2 positive breast cancer previously treated with an anti-HER2 therapy. In 2019, fast track designation was granted to the HER2-targeting antibody drug conjugate, amcenestrant¹⁰⁹, for HER2-positive advanced or metastatic breast cancer after one or more prior anti-HER2 based regimens. Additionally, in 2019, zanidatamab¹¹⁰, received fast track designation in combination with standard chemotherapy for patients with HER2-overexpressing gastroesophageal adenocarcinoma (GEA). In 2020, BDTX-189111 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 treatment¹¹². In 2021, the antibody-drug conjugate ARX788¹¹³ 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. Additionally, fast track designation was granted to HER2-targeted chimeric antigen receptor macrophage (CAR-M) (2019), CT-0508114, and to ex vivo gene-modified autologous chimeric antigen receptor-monocyte (CAR-Monocyte) cellular therapy (2024), CT-0525115, for HER2-overexpressing solid tumors. In 2024, a small molecule inhibitor, BAY-2927088116, received breakthrough designation for the treatment of NSCLC patients with ERBB2 activating mutations. Certain activating mutations have been observed to impart sensitivity to neratinib, afatinib, lapatinib, and trastuzumab, or dacomitinib in early and ongoing clinical studies^{117,118,119,120,121}. ERBB2 kinase domain mutations R896G and V659E both showed response to afatinib in two NSCLC case studies^{122,123}. Additionally, acquired HER2 mutations in estrogen receptor-positive (ER+) breast cancer have been shown to confer resistance to hormone therapy¹²⁴. However, this was shown to be overcome by neratinib in combination with therapies targeting ER124. Additionally, in 2024, FDA granted fast track designation to zongertinib¹²⁵, an irreversible ERBB2 tyrosine kinase inhibitor, for HER2-mutant NSCLC tumors that have progressed on or after platinum-based therapy.

UGT1A1 p.(G71R) c.211G>A

UDP glucuronosyltransferase family 1 member A1

Background: The UGT1A1 gene encodes UDP glucuronosyltransferase family 1 member A1, a member of the UDP-glucuronosyltransferase 1A (UGT1A) subfamily of the UGT protein superfamily^{47,126}. UGTs are microsomal membrane-bound enzymes that catalyze the glucuronidation of endogenous and xenobiotic compounds and transform the lipophilic molecules into excretable, hydrophilic metabolites^{126,127}. UGTs play an important role in drug metabolism, detoxification, and metabolite homeostasis. Differential expression of UGTs can promote cancer development, disease progression, as well as drug resistance¹²⁸. Specifically, elevated expression of UGT1As are associated with resistance to many anti-cancer drugs due to drug inactivation and lower active drug concentrations. However, reduced expression and downregulation of UGT1As are implicated in bladder and hepatocellular tumorigenesis and progression due to toxin accumulation^{128,129,130,131}. Furthermore, UGT1A1 polymorphisms, such as UGT1A1*28, UGT1A1*93, and UGT1A1*6, confer an increased risk of severe toxicity to irinotecan-based chemotherapy treatment of solid tumors, due to reduced glucuronidation of the irinotecan metabolite, SN-38¹³².

Alterations and prevalence: Biallelic deletion of UGT1A1 has been observed in 6% of sarcoma, 3% of brain lower grade glioma and uveal melanoma, and 2% of thymoma, cervical squamous cell carcinoma, bladder urothelial carcinoma, head and neck squamous cell carcinoma, and esophageal adenocarcinoma^{5,6}.

Potential relevance: Currently, no therapies are approved for UGT1A1 aberrations.

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Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated

Not recommended



Resistance



Breakthrough



FDA information is current as of 2025-03-19. For the most up-to-date information, search www.fda.gov.

KRAS p.(G12C) c.34G>T



panitumumab, panitumumab + sotorasib

Cancer type: Colorectal Cancer

Label as of: 2025-01-16

Variant class: KRAS G12C mutation

Indications and usage:

VECTIBIX® is an epidermal growth factor receptor (EGFR) antagonist indicated for the treatment of:

Adult patients with wild-type RAS (defined as wild-type in both KRAS and NRAS as determined by an FDA-approved test) Metastatic Colorectal Cancer (mCRC)*:

- In combination with FOLFOX for first-line treatment.
- As monotherapy following disease progression after prior treatment with fluoropyrimidine, oxaliplatin, and irinotecancontaining chemotherapy.

KRAS G12C-mutated Metastatic Colorectal Cancer (mCRC)*

In combination with sotorasib, for the treatment of adult patients with KRAS G12C-mutated mCRC, as determined by an FDAapproved test, who have received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy.

*Limitations of Use: VECTIBIX® is not indicated for the treatment of patients with RAS-mutant mCRC unless used in combination with sotorasib in KRAS G12C-mutated mCRC. VECTIBIX® is not indicated for the treatment of patients with mCRC for whom RAS mutation status is unknown.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125147s213lbl.pdf

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Variant class: KRAS G12C mutation

KRAS p.(G12C) c.34G>T (continued)

cetuximab

Cancer type: Colorectal Cancer Label as of: 2021-09-24 Variant class: KRAS G12 mutation

Indications and usage:

Erbitux® is an epidermal growth factor receptor (EGFR) antagonist indicated for treatment of:

Head and Neck Cancer

- Locally or regionally advanced squamous cell carcinoma of the head and neck in combination with radiation therapy.
- Recurrent locoregional disease or metastatic squamous cell carcinoma of the head and neck in combination with platinumbased therapy with fluorouracil.
- Recurrent or metastatic squamous cell carcinoma of the head and neck progressing after platinum-based therapy.

Colorectal Cancer

K-Ras wild-type, EGFR-expressing, metastatic colorectal cancer as determined by FDA-approved test

- in combination with FOLFIRI for first-line treatment,
- in combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy,
- as a single agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy or who are intolerant to irinotecan.

Limitations of Use: Erbitux® is not indicated for treatment of Ras-mutant colorectal cancer or when the results of the Ras mutation tests are unknown.

BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC)

 in combination with encorafenib, for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, as detected by an FDA-approved test, after prior therapy.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125084s279lbl.pdf

Cancer type: Non-Small Cell Lung Cancer Variant class: KRAS G12C mutation

Supporting Statement:

The FDA has granted Breakthrough Therapy designation to KRAS G12C inhibitor, GDC-6036, for KRAS G12C mutation in non-small cell lung cancer.

Reference:

https://assets.cwp.roche.com/f/126832/x/5738a7538b/irp230202.pdf

BBP-398 + sotorasib

Cancer type: Non-Small Cell Lung Cancer, Solid Tumor

Supporting Statement:

The FDA has granted Fast Track designation to a SHP2 inhibitor, BBP-398, in combination with LUMAKRAS® for adult patients with previously treated KRAS G12C-mutated metastatic NSCLC.

Reference:

https://bridgebio.com/news/bridgebio-pharma-announces-first-lung-cancer-patient-dosed-in-phase-1-2-trial-and-us-fda-fast-track-designation-for-shp2-inhibitor-bbp-398-in-combination-with-amgens-lumakras-sotorasib/

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KRAS p.(G12C) c.34G>T (continued)

avutometinib + sotorasib

Cancer type: Non-Small Cell Lung Cancer Variant class: KRAS G12C mutation

Supporting Statement:

The FDA has granted Fast Track designation to Verastem Oncology's investigational RAF/MEK clamp, avutometinib, in combination with Amgen's KRAS G12C inhibitor, LUMAKRASTM (sotorasib), for the treatment of patients with KRAS G12C-mutant metastatic non-small cell lung cancer (NSCLC) who have received at least one prior systemic therapy and have not been previously treated with a KRAS G12C inhibitor.

Reference:

https://investor.verastem.com/news-releases/news-release-details/verastem-oncology-granted-fast-track-designation-combination

BBO-8520

Cancer type: Non-Small Cell Lung Cancer Variant class: KRAS G12C mutation

Supporting Statement:

The FDA has granted Fast Track designation to the KRAS G12C inhibitor, BBO-8520, for the treatment of adult patients with previously treated, KRAS^{G12C}-mutated metastatic non-small cell lung cancer (NSCLC).

Reference:

https://www.businesswire.com/news/home/20250109170439/en/

D3S-001

Cancer type: Colorectal Cancer Variant class: KRAS G12C mutation

Supporting Statement:

The FDA has granted Fast Track designation to the KRAS G12C inhibitor, D3S-001, for the treatment of KRAS G12C mutated patients with advanced unresectable or metastatic colorectal cancers.

The FDA has also granted Fast Track designation to D3S-001, for the treatment of late-line non-small cell lung cancer (NSCLC) and colorectal cancer (CRC).

Reference:

https://www.d3bio.com/press-releases/d3-bios-d3s-001-receives-u-s-fda-fast-track-designation-for-the-treatment-of-colorectal-cancer-with-kras-g12c-mutation

ERBB2 p.(S310F) c.929C>T

✔ BAY-2927088

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

Supporting Statement:

The FDA has granted Breakthrough Therapy designation to an oral small molecule tyrosine kinase inhibitor, BAY 2927088, for the treatment of patients with HER2 activating mutation in non-small cell lung cancer (NSCLC).

Reference:

https://www.biospace.com/article/releases/bayer-receives-u-s-fda-breakthrough-therapy-designation-for-bay-2927088-for-non-small-cell-lung-cancer-harboring-her2-activating-mutations

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ERBB2 p.(S310F) c.929C>T (continued)

zongertinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: ERBB2 activating mutation

Supporting Statement:

The FDA has granted Breakthrough Therapy designation to the tyrosine kinase inhibitor, zongertinib (BI 1810631), for the treatment of adult patients with advanced, unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating HER2 mutations and who have received prior systemic therapy.

Reference:

https://www.boehringer-ingelheim.com/us/human-health/cancer/boehringer-ingelheim-unveil-oncology-research-wclc

Current NCCN Information

Contraindicated

Not recommended

Resistance

Breakthrough

Fast Track

NCCN information is current as of 2025-03-03. To view the most recent and complete version of the guideline, go online to NCCN.org.

For NCCN International Adaptations & Translations, search www.nccn.org/global/what-we-do/international-adaptations.

Some variant specific evidence in this report may be associated with a broader set of alterations from the NCCN Guidelines. Specific variants listed in this report were sourced from approved therapies or scientific literature. These therapeutic options are appropriate for certain population segments with cancer. Refer to the NCCN Guidelines® for full recommendation.

All guidelines cited below are referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) National Comprehensive Cancer Network, Inc. 2023. All rights reserved. NCCN makes no warranties regarding their content.

KRAS p.(G12C) c.34G>T

cetuximab

Cancer type: Colon Cancer Variant class: KRAS G12 mutation

Summary:

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

■ "Patients with any known KRAS mutation (exon 2, 3, 4) or NRAS mutation (exon 2, 3, 4) should not be treated with either cetuximab or panitumumab, unless given as part of a regimen targeting a KRAS G12C mutation."

Reference: NCCN Guidelines® - NCCN-Colon Cancer [Version 1.2025]

cetuximab

Cancer type: Rectal Cancer Variant class: KRAS G12 mutation

Summary:

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

■ "Patients with any known KRAS mutation (exons 2, 3, and 4) or NRAS mutation (exons 2, 3, and 4) should not be treated with either cetuximab or panitumumab, unless given as part of a regimen targeting a KRAS G12C mutation."

Reference: NCCN Guidelines® - NCCN-Rectal Cancer [Version 1.2025]

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KRAS p.(G12C) c.34G>T (continued)

panitumumab

Cancer type: Colon Cancer Variant class: KRAS G12 mutation

Summary:

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

■ "Patients with any known KRAS mutation (exon 2, 3, 4) or NRAS mutation (exon 2, 3, 4) should not be treated with either cetuximab or panitumumab, unless given as part of a regimen targeting a KRAS G12C mutation."

Reference: NCCN Guidelines® - NCCN-Colon Cancer [Version 1.2025]

panitumumab

Cancer type: Rectal Cancer Variant class: KRAS G12 mutation

Summary:

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

■ "Patients with any known KRAS mutation (exons 2, 3, and 4) or NRAS mutation (exons 2, 3, and 4) should not be treated with either cetuximab or panitumumab, unless given as part of a regimen targeting a KRAS G12C mutation."

Reference: NCCN Guidelines® - NCCN-Rectal Cancer [Version 1.2025]

Current EMA Information

Ocontraindicated Not recommended Resistance Preakthrough A Fast Track

EMA information is current as of 2025-03-19. For the most up-to-date information, search www.ema.europa.eu.

KRAS p.(G12C) c.34G>T

cetuximab, cetuximab + oxaliplatin

Cancer type: Colorectal Cancer Label as of: 2025-01-16 Variant class: KRAS G12 mutation

Reference:

https://www.ema.europa.eu/en/documents/product-information/erbitux-epar-product-information_en.pdf

panitumumab + oxaliplatin

Cancer type: Colorectal Cancer Label as of: 2022-07-06 Variant class: KRAS G12 mutation

Reference:

https://www.ema.europa.eu/en/documents/product-information/vectibix-epar-product-information_en.pdf

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Current ESMO Information

Contraindicated









ESMO information is current as of 2025-03-03. For the most up-to-date information, search www.esmo.org.

KRAS p.(G12C) c.34G>T

cetuximab

Cancer type: Colorectal Cancer Variant class: KRAS G12 mutation

Summary:

ESMO Clinical Practice Guidelines include the following supporting statement:

- "The presence of RAS mutations is associated with resistance to anti-EGFR mAbs and knowing the expanded RAS mutational status is mandatory for use of both cetuximab and panitumumab, avoiding anti-EGFR mAb treatment when a RAS mutation is
- "RAS testing is mandatory before treatment with anti-EGFR mAbs and can be carried out on either the primary tumor or other metastatic sites [III, A]".

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Colorectal Cancer [Ann Oncol (2023); https://doi.org/10.1016/ j.annonc.2022.10.003 (published)]

panitumumab

Cancer type: Colorectal Cancer Variant class: KRAS G12 mutation

Summary:

ESMO Clinical Practice Guidelines include the following supporting statement:

- "The presence of RAS mutations is associated with resistance to anti-EGFR mAbs and knowing the expanded RAS mutational status is mandatory for use of both cetuximab and panitumumab, avoiding anti-EGFR mAb treatment when a RAS mutation is
- "RAS testing is mandatory before treatment with anti-EGFR mAbs and can be carried out on either the primary tumor or other metastatic sites [III, A]".

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Colorectal Cancer [Ann Oncol (2023); https://doi.org/10.1016/ j.annonc.2022.10.003 (published)]

Genes Assayed

Genes Assayed for the Detection of DNA Sequence Variants

ABL1, ABL2, ACVR1, AKT1, AKT2, AKT3, ALK, AR, ARAF, ATP1A1, AURKA, AURKB, AURKC, AXL, BCL2, BCL2L12, BCL6, BCR, BMP5, BRAF, BTK, CACNA1D, CARD11, CBL, CCND1, CCND2, CCND3, CCNE1, CD79B, CDK4, CDK6, CHD4, CSF1R, CTNNB1, CUL1, CYSLTR2, DDR2, DGCR8, DROSHA, E2F1, EGFR, EIF1AX, EPAS1, ERBB2, ERBB3, ERBB4, ESR1, EZH2, FAM135B, FGF7, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FOXL2, FOXO1, GATA2, GLI1, GNA11, GNAQ, GNAS, HIF1A, HRAS, IDH1, IDH2, IKBKB, IL6ST, IL7R, IRF4, IRS4, KCNJ5, KDR, KIT, KLF4, KLF5, KNSTRN, KRAS, MAGOH, MAP2K1, MAP2K2, MAPK1, MAX, MDM4, MECOM, MED12, MEF2B, MET, MITF, MPL, MTOR, MYC, MYCN, MYD88, MYOD1, NFE2L2, NRAS, NSD2, NT5C2, NTRK1, NTRK2, NTRK3, NUP93, PAX5, PCBP1, PDGFRA, PDGFRB, PIK3C2B, PIK3CA, PIK3CB, PIK3CD, PIK3CG, PIK3R2, PIM1, PLCG1, PPP2R1A, PPP6C, PRKACA, PTPN11, PTPRD, PXDNL, RAC1, RAF1, RARA, RET, RGS7, RHEB, RHOA, RICTOR, RIT1, ROS1, RPL10, SETBP1, SF3B1, SIX1, SIX2, SLC01B3, SMC1A, SMO, SNCAIP, SOS1, SOX2, SPOP, SRC, SRSF2, STAT3, STAT5B, STAT6, TAF1, TERT, TGFBR1, TOP1, TOP2A, TPMT, TRRAP, TSHR, U2AF1, USP8, WAS, XP01, ZNF217, ZNF429

Genes Assayed (continued)

Genes Assayed for the Detection of Copy Number Variations

ABCB1, ABL1, ABL2, ABRAXAS1, ACVR1B, ACVR2A, ADAMTS12, ADAMTS2, AKT1, AKT2, AKT3, ALK, AMER1, APC, AR, ARAF, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, AURKA, AURKC, AXIN1, AXIN2, AXL, B2M, BAP1, BARD1, BCL2, BCL2L12, BCL6, BCOR, BLM, BMPR2, BRAF, BRCA1, BRCA2, BRIP1, CARD11, CASP8, CBFB, CBL, CCND1, CCND2, CCND3, CCNE1, CD274, CD276, CDC73, CDH1, CDH10, CDK12, CDK4, CDK6, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CHD4, CHEK1, CHEK2, CIC, CREBBP, CSMD3, CTCF, CTLA4, CTNND2, CUL3, CUL4A, CUL4B, CYLD, CYP2C9, DAXX, DDR1, DDR2, DDX3X, DICER1, DNMT3A, DOCK3, DPYD, DSC1, DSC3, EGFR, EIF1AX, ELF3, EMSY, ENO1, EP300, EPCAM, EPHA2, ERAP1, ERAP2, ERBB2, ERBB3, ERBB4, ERCC2, ERCC4, ERRFI1, ESR1, ETV6, EZH2, FAM135B, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCI, FANCM, FAT1, FBXW7, FGF19, FGF23, FGF4, FGF9, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FUBP1, FYN, GATA2, GATA3, GLI3, GNA13, GNAS, GPS2, HDAC2, HDAC9, HLA-A, HLA-B, HNF1A, IDH2, IGF1R, IKBKB, IL7R, INPP4B, JAK1, JAK2, JAK3, KDM5C, KDM6A, KDR, KEAP1, KIT, KLF5, KMT2A, KMT2B, KMT2C, KMT2D, KRAS, LARP4B, LATS1, LATS2, MAGOH, MAP2K1, MAP2K4, MAP2K7, MAP3K1, MAP3K4, MAPK1, MAPK8, MAX, MCL1, MDM2, MDM4, MECOM, MEF2B, MEN1, MET, MGA, MITF, MLH1, MLH3, MPL, MRE11, MSH2, MSH3, MSH6, MTAP, MTOR, MUTYH, MYC, MYCL, MYCN, MYD88, NBN, NCOR1, NF1, NF2, NFE2L2, NOTCH1, NOTCH2, NOTCH3, NOTCH4, NRAS, NTRK1, NTRK3, PALB2, PARP1, PARP2, PARP3, PARP4, PBRM1, PCBP1, PDCD1, PDCD1LG2, PDGFRA, PDGFRB, PDIA3, PGD, PHF6, PIK3C2B, PIK3CA, PIK3CB, PIK3R1, PIK3R2, PIM1, PLCG1, PMS1, PMS2, POLD1, POLE, POT1, PPM1D, PPP2R1A, PPP2R2A, PPP6C, PRDM1, PRDM9, PRKACA, PRKAR1A, PTCH1, PTEN, PTPN11, PTPRT, PXDNL, RAC1, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RAF1, RARA, RASA1, RASA2, RB1, RBM10, RECQL4, RET, RHEB, RICTOR, RIT1, RNASEH2A, RNASEH2B, RNF43, ROS1, RPA1, RPS6KB1, RPTOR, RUNX1, SDHA, SDHB, SDHD, SETBP1, SETD2, SF3B1, SLCO1B3, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SMC1A, SMO, SOX9, SPEN, SPOP, SRC, STAG2, STAT3, STAT6, STK11, SUFU, TAP1, TAP2, TBX3, TCF7L2, TERT, TET2, TGFBR2, TNFAIP3, TNFRSF14, TOP1, TP53, TP63, TPMT, TPP2, TSC1, TSC2, U2AF1, USP8, USP9X, VHL, WT1, XPO1, XRCC2, XRCC3, YAP1, YES1, ZFHX3, ZMYM3, ZNF217, ZNF429, ZRSR2

Genes Assayed for the Detection of Fusions

AKT2, ALK, AR, AXL, BRAF, BRCA1, BRCA2, CDKN2A, EGFR, ERBB2, ERBB4, ERG, ESR1, ETV1, ETV4, ETV5, FGFR1, FGFR2, FGR3, FGR, FLT3, JAK2, KRAS, MDM4, MET, MYB, MYBL1, NF1, NOTCH1, NOTCH4, NRG1, NTRK1, NTRK2, NTRK3, NUTM1, PDGFRA, PDGFRB, PIK3CA, PPARG, PRKACA, PRKACB, PTEN, RAD51B, RAF1, RB1, RELA, RET, ROS1, RSPO2, RSPO3, TERT

Genes Assayed with Full Exon Coverage

ABRAXAS1, ACVR1B, ACVR2A, ADAMTS12, ADAMTS2, AMER1, APC, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, AXIN1, AXIN2, B2M, BAP1, BARD1, BCOR, BLM, BMPR2, BRCA1, BRCA2, BRIP1, CALR, CASP8, CBFB, CD274, CD276, CDC73, CDH1, CDH10, CDK12, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CHEK1, CHEK2, CIC, CIITA, CREBBP, CSMD3, CTCF, CTLA4, CUL3, CUL4A, CUL4B, CYLD, CYP2C9, CYP2D6, DAXX, DDX3X, DICER1, DNMT3A, DOCK3, DPYD, DSC1, DSC3, ELF3, ENO1, EP300, EPCAM, EPHA2, ERAP1, ERAP2, ERCC2, ERCC4, ERCC5, ERRF11, ETV6, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCI, FANCM, FAS, FAT1, FBXW7, FUBP1, GATA3, GNA13, GPS2, HDAC2, HDAC9, HLA-A, HLA-B, HNF1A, ID3, INPP4B, JAK1, JAK2, JAK3, KDM5C, KDM6A, KEAP1, KLHL13, KMT2A, KMT2B, KMT2C, KMT2D, LARP4B, LATS1, LATS2, MAP2K4, MAP2K7, MAP3K1, MAP3K4, MAPK8, MEN1, MGA, MLH1, MLH3, MRE11, MSH2, MSH3, MSH6, MTAP, MTUS2, MUTYH, NBN, NCOR1, NF1, NF2, NOTCH1, NOTCH2, NOTCH3, NOTCH4, PALB2, PARP1, PARP2, PARP3, PARP4, PBRM1, PDCD1, PDCD1LG2, PDIA3, PGD, PHF6, PIK3R1, PMS1, PMS2, POLD1, POLE, POT1, PPM1D, PPP2R2A, PRDM1, PRDM9, PRKAR1A, PSMB10, PSMB8, PSMB9, PTCH1, PTEN, PTPRT, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RASA1, RASA2, RB1, RBM10, RECQL4, RNASEH2A, RNASEH2B, RNASEH2C, RNF43, RPA1, RPL22, RPL5, RUNX1, RUNX1T1, SDHA, SDHB, SDHC, SDHD, SETD2, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SOCS1, SOX9, SPEN, STAG2, STAT1, STK11, SUFU, TAP1, TAP2, TBX3, TCF7L2, TET2, TGFBR2, TMEM132D, TNFAIP3, TNFRSF14, TP53, TP63, TPP2, TSC1, TSC2, UGT1A1, USP9X, VHL, WT1, XRCC2, XRCC3, ZBTB20, ZFHX3, ZMYM3, ZRSR2

Relevant Therapy Summary

■ In this cancer type
O In other cancer type
O In this cancer type and other cancer types
X No evidence

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
adagrasib	0	0	0	0	×
sotorasib	0	0	0	0	×
adagrasib + cetuximab	0	0	×	×	×
panitumumab + sotorasib	A	0	×	×	×
panitumumab	A	×	×	×	×
adagrasib + panitumumab	×	0	×	×	×
cetuximab + sotorasib	×	0	×	×	×
bevacizumab + CAPOX	×	×	×	0	×
bevacizumab + FOLFIRI	×	×	×	0	×
bevacizumab + FOLFOX	×	×	×	0	×
bevacizumab + FOLFOXIRI	×	×	×	0	×
divarasib	×	×	×	×	● (II)
regorafenib	×	×	×	×	(II)
sotorasib, panitumumab	×	×	×	×	(II)
adagrasib, pembrolizumab, cetuximab, afatinib	×	×	×	×	(1/11)
D-1553, ifebemtinib	×	×	×	×	(I/II)
D3S-001, pembrolizumab, chemotherapy, cetuximab	×	×	×	×	(I/II)
FMC-376	×	×	×	×	(I/II)
glecirasib	×	×	×	×	(1/11)
glecirasib, JAB-3312	×	×	×	×	(/)
HBI 2376, D-1553	×	×	×	×	(/)
HS-10370	×	×	×	×	(/)
HYP-2090PTSA	×	×	×	×	(I/II)
IMM-1-104	×	×	×	×	(/)
IMM-6-415	×	×	×	×	(/)
MRTX0902, adagrasib	×	×	×	×	(/)
olomorasib, abemaciclib, pembrolizumab, erbumine, cetuximab, chemotherapy	×	×	×	×	(I/II)
RMC-6291, pembrolizumab, chemotherapy, RMC-6236	×	×	×	×	(I/II)

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

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Relevant Therapy Summary (continued)

■ In this cancer type
O In other cancer type
O In this cancer type and other cancer types
X No evidence

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
YL-15293	×	×	×	×	(I/II)
ZG-19018	×	×	×	×	(/)
adagrasib, olaparib	×	×	×	×	(I)
BAY-3498264, sotorasib	×	×	×	×	(I)
BEBT-607	×	×	×	×	(I)
BPI-421286	×	×	×	×	(l)
divarasib, bevacizumab, RLY-1971, inavolisib	×	×	×	×	(l)
GEC-255	×	×	×	×	(I)
HBI-2438	×	×	×	×	(1)
HMPL-415	×	×	×	×	(I)
HRS-7058	×	×	×	×	(I)
JAB-3312	×	×	×	×	(I)
KQB-365	×	×	×	×	(I)
KRAS-EphA-2-CAR-DC, anti-PD-1, ipilimumab	×	×	×	×	(I)
LY-4066434, cetuximab, pembrolizumab, chemotherapy	×	×	×	×	(l)
MK-1084	×	×	×	×	(I)
Nest-1	×	×	×	×	(I)
RMC-6291, RMC-6236	×	×	×	×	(1)
sotorasib, trametinib, AMG 404, RMC-4630, panitumumab, palbociclib, everolimus, chemotherapy, TNO-155, BI-1701963	×	×	×	×	(1)
SY-5933	×	×	×	×	(I)

ERBB2 p.(S310F) c.929C>T

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
trastuzumab deruxtecan	0	×	0	×	(II)
neratinib	×	0	×	×	×
neratinib + fulvestrant	×	0	×	×	×
neratinib + trastuzumab + fulvestrant	×	0	×	×	×
pertuzumab + trastuzumab	×	×	×	×	(/)

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

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Relevant Therapy Summary (continued)

■ In this cancer type
O In other cancer type
In this cancer type and other cancer types
X No evidence

ERBB2 p.(S310F) c.929C>T (continued) NCCN **ESMO Clinical Trials*** Relevant Therapy **FDA EMA** BAY-2927088 (II) × × × × pertuzumab + trastuzumab, trastuzumab + tucatinib (II) × × × × tucatinib, ado-trastuzumab emtansine × × × × (II) × zongertinib (II) × × × DF-1001, nivolumab (I/II) × × × × ado-trastuzumab emtansine (Shanghai Fosun × × × × (I) Pharma) DS-1103a, trastuzumab deruxtecan × × × × (I) XMT-2056 (I) × × X ×

FGFR1 amplification Clinical Trials* FDA NCCN **ESMO EMA** Relevant Therapy pemigatinib × × × × (II) regorafenib × × (II) × × sunitinib × × × × (II) BBI-355, futibatinib (I/II) × × × × ABSK-121 (I) × × × ×

Thermo Fisher Scientific's Ion Torrent Oncomine Reporter software was used in generation of this report. Software was developed and designed internally by Thermo Fisher Scientific. The analysis was based on Oncomine Reporter (6.0.2 data version 2025.04(004)). The data presented here are from a curated knowledge base of publicly available information, but may not be exhaustive. FDA information was sourced from www.fda.gov and is current as of 2025-03-19. NCCN information was sourced from www.nccn.org and is current as of 2025-03-03. EMA information was sourced from www.ema.europa.eu and is current as of 2025-03-19. ESMO information was sourced from www.esmo.org and is current as of 2025-03-03. Clinical Trials information is current as of 2025-03-03. For the most upto-date information regarding a particular trial, search www.clinicaltrials.gov by NCT ID or search local clinical trials authority website by local identifier listed in 'Other identifiers.' Variants are reported according to HGVS nomenclature and classified following AMP/ ASCO/CAP guidelines (Li et al. 2017). Based on the data sources selected, variants, therapies, and trials listed in this report are listed in order of potential clinical significance but not for predicted efficacy of the therapies.

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

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