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Patient Name: 육영진
Gender: M
Sample ID: N25-305

Primary Tumor Site:
Collection Date: 2025.11.06

Sample Cancer Type: Liver Cancer

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Report Highlights
5 Relevant Biomarkers
58 Therapies Available
91 Clinical Trials

Relevant Liver Cancer Findings

Gene	Finding
BRAF	None detected
NTRK1	None detected
NTRK2	None detected
NTRK3	None detected
RET	None detected

Genomic Alteration	Finding
Tumor Mutational Burden	***4.74 Mut/Mb measured***

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*ERBB2 amplification* erb-b2 receptor tyrosine kinase 2 Locus: chr17:37863255	**trastuzumab deruxtecan** [1]	**lapatinib + hormone therapy** [1, 2 / I, II+] **pertuzumab + trastuzumab + chemotherapy** [1, 2 / I, II+] **trastuzumab deruxtecan** [1, 2 / I, II+] **trastuzumab† + chemotherapy** [1, 2 / I, II+] **trastuzumab† + hormone therapy** [2 / I, II+] **pembrolizumab + trastuzumab + chemotherapy** [1, 2 / I] **ado-trastuzumab emtansine** [1, 2 / II+] **lapatinib + chemotherapy** [1, 2 / II+] **lapatinib + trastuzumab** [2 / II+] **margetuximab + chemotherapy** [1 / II+] **neratinib** [1, 2 / II+] **neratinib + chemotherapy** [1 / II+]	61

*** Public data sources included in relevant therapies: FDA**[1], NCCN, **EMA**[2], ESMO
*** Public data sources included in prognostic and diagnostic significance:** NCCN, ESMO
† Includes biosimilars/generics
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.

Relevant Biomarkers (continued)

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
			trastuzumab + tucatinib + chemotherapy 1, 2 / II+ **trastuzumab†** 1, 2 / II+ **zanidatamab** 1, 2 / II+ **pertuzumab/trastuzumab/ hyaluronidase-zzxf + chemotherapy** 1, 2 **trastuzumab and hyaluronidase-oysk** 1 **trastuzumab and hyaluronidase-oysk + chemotherapy** 1 pertuzumab + trastuzumab I, II+ pertuzumab + trastuzumab + hormone therapy I, II+ lapatinib + trastuzumab + hormone therapy I abemaciclib + trastuzumab + hormone therapy II+ ado-trastuzumab emtansine + hormone therapy II+ hormone therapy II+ margetuximab II+ pertuzumab + trastuzumab + hormone therapy + chemotherapy II+ trastuzumab + hormone therapy + chemotherapy II+ trastuzumab + tucatinib II+ ado-trastuzumab emtansine + neratinib	
IIC	*KRAS p.(G12D) c.35G>A* KRAS proto-oncogene, GTPase Allele Frequency: 64.56% Locus: chr12:25398284 Transcript: NM_033360.4	None*	**avutometinib + defactinib** 1 / II+ bevacizumab + chemotherapy I	27
IIC	*CCND1 amplification* cyclin D1 Locus: chr11:69455949	None*	None*	2
IIC	*FGF19 amplification* fibroblast growth factor 19 Locus: chr11:69513948	None*	None*	1
IIC	*SMAD4 deletion* SMAD family member 4 Locus: chr18:48573387	None*	None*	1

*** Public data sources included in relevant therapies: FDA**1, NCCN, **EMA**2, ESMO
*** Public data sources included in prognostic and diagnostic significance:** NCCN, ESMO
† Includes biosimilars/generics
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.

Prevalent cancer biomarkers without relevant evidence based on included data sources

*CDKN2A p.(R128Sfs*20) c.376_380dup, FGF3 amplification, FGF4 amplification, RNF43 p.(R117Tfs*41) c.349_350delCGinsA, TP53 p.(V157G) c.470T>G, HLA-A deletion, NQO1 p.(P187S) c.559C>T, KDM6A deletion, Tumor Mutational Burden*

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
KRAS	p.(G12D)	c.35G>A	COSM521	chr12:25398284	64.56%	NM_033360.4	missense
CDKN2A	p.(R128Sfs*20)	c.376_380dup	.	chr9:21970977	32.99%	NM_001195132.2	frameshift Insertion
RNF43	p.(R117Tfs*41)	c.349_350delCGinsA	.	chr17:56448297	0.37%	NM_017763.6	frameshift Block Substitution
TP53	p.(V157G)	c.470T>G	COSM43903	chr17:7578460	31.94%	NM_000546.6	missense
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	57.60%	NM_000903.3	missense
OR2L8	p.(G196Y)	c.586_587delGGinsTA	.	chr1:248112745	2.25%	NM_001001963.1	missense
TAPBP	p.(W28L)	c.83G>T	.	chr6:33281596	69.82%	NM_172208.2	missense
ROS1	p.(F2218L)	c.6652T>C	.	chr6:117622218	41.11%	NM_002944.3	missense
MGA	p.(E214K)	c.640G>A	.	chr15:41961732	56.36%	NM_001164273.1	missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
ERBB2	chr17:37863255	4.46	1.61
CCND1	chr11:69455949	7.18	2.3
FGF19	chr11:69513948	7.04	2.26
SMAD4	chr18:48573387	0.28	0.57
FGF3	chr11:69625020	8.38	2.59
FGF4	chr11:69588019	7.04	2.26
HLA-A	chr6:29910229	0.42	0.6
KDM6A	chrX:44732715	0.14	0.57
ATM	chr11:108098341	2	0.87
CHEK1	chr11:125496639	2	0.9
BRCA2	chr13:32890491	2	0.85

Biomarker Descriptions

ERBB2 amplification

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[1]. Along with ERBB2/HER2, EGFR/ERBB1/HER1, ERBB3/HER3, and ERBB4/HER4 make up the HER protein family[129]. All ERBB/HER proteins encode transmembrane receptor tyrosine kinases[130]. However, ERBB2/HER2 is an orphan receptor with no known ligand[130]. ERBB2 preferentially binds other ligand-bound ERBB/HER family members to form heterodimers 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[131]. Recurrent focal amplification of the ERBB2 gene leads to increased expression in several cancer types[131]. ERBB2 overexpression in immortalized cell lines is oncogenic and leads to ERBB2 homo-dimerization and activation without ligand binding[132,133,134].

Biomarker Descriptions (continued)

Alterations and prevalence: ERBB2 gene amplification occurs in 10-25% of breast, esophageal, and gastric cancers, 5-10% of bladder, cervical, pancreas, and uterine cancers, and 1-5% of colorectal, lung, and ovarian cancers[4,5,53,135,136,137,138,139]. ERBB2 gene amplification in pediatric population is observed in 2% of peripheral nervous system cancers (2 in 91 patients) and less than 1% of leukemia (1 in 250 cases)[5]. Recurrent somatic activating mutations in ERBB2/HER2 occur at low frequencies (<1%) in diverse cancer types[5,140,141]. 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[142,143]. Trastuzumab[144] 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[145] (2012), a humanized monoclonal antibody that inhibits HER2 dimerization, and ado-trastuzumab emtansine[146] (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[147]. In addition to monoclonal antibodies, the small molecule inhibitor lapatinib[148], 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[149], 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[149] 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[150] 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[22]. In 2024, a bispecific HER2 antibody, zanidatamab[151], was approved for the treatment of adults with previously treated, unresectable or metastatic ERBB2 overexpressing biliary tract cancer. In 2018 fast track designation was granted to the monoclonal antibody margetuximab[152] in patients with ERBB2 positive breast cancer previously treated with an anti-HER2 therapy. Additionally, in 2019, zanidatamab[153], received fast track designation in combination with standard chemotherapy for patients with HER2-overexpressing gastroesophageal adenocarcinoma (GEA). The humanized anti-HER2 antibody drug conjugate disitamab vedotin[154] (2020) received breakthrough designation for adult patients with HER2-positive urothelial cancer after previous platinum-chemotherapy treatment. In 2021, the antibody-drug conjugate ARX788[155] 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. In 2024, a small molecule inhibitor, BAY-2927088[156], 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[157,158,159,160,161]. ERBB2 kinase domain mutations R896G and V659E both showed response to afatinib in two NSCLC case studies[162,163]. Additionally, acquired HER2 mutations in estrogen receptor-positive (ER+) breast cancer have been shown to confer resistance to hormone therapy[164]. However, this was shown to be overcome by neratinib in combination with therapies targeting ER[164]. Additionally, in 2025, FDA approved zongertinib[165], a kinase inhibitor indicated for the treatment of adult patients with unresectable or metastatic non-squamous non-small cell lung cancer (NSCLC) whose tumors have HER2 tyrosine kinase domain activating mutations. In 2025, a 9 amino acid transmembrane peptide of the HER2/neu protein, GLSI-100 (GP-2)[166], received fast track designation for the prevention of breast cancer recurrence following surgery.

KRAS p.(G12D) c.35G>A

KRAS proto-oncogene, GTPase

Background: 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[8,9,10].

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 cancer[4]. The majority of KRAS mutations consist of point mutations occurring at G12, G13, and Q61[4,11,12]. Mutations at A59, K117, and A146 have also been observed but are less frequent[5,13].

Potential relevance: The FDA has approved the small molecule inhibitors, sotorasib[14] (2021) and adagrasib[15] (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 adenocarcinoma[16]. The FDA has approved the combination of kinase inhibitors, avutometinib and defactinib[17] (2025), for the treatment of adult patients with KRAS-mutated recurrent low-grade serous ovarian cancer (LGSOC) after prior systemic therapy. The FDA has granted breakthrough therapy designation (2022) to the KRAS G12C inhibitor, GDC-6036[18], for KRAS G12C-mutated NSCLC. The KRAS-G12C/NRAS-G12C dual inhibitor, elironrasib[19], and the KRAS G12C inhibitor, D3S-001[20], were both granted breakthrough therapy designation (2025) for KRAS G12C-mutated locally advanced or metastatic NSCLC in adults previously treated with chemotherapy and immunotherapy, excluding KRAS G12C inhibitors.

Biomarker Descriptions (continued)

The KRAS-G12C inhibitor, olomorasib[21], was granted breakthrough designation (2025) in combination with pembrolizumab[22] for unresectable advanced or metastatic NSCLC with a KRAS G12C mutation and PD-L1 expression ≥ 50%. The SHP2 inhibitor, BBP-398[23] was granted fast track designation (2022) in combination with sotorasib for previously treated patients with KRAS G12C-mutated metastatic NSCLC. The RAF/MEK clamp, avutometinib[24] was also granted fast track designation (2024) in combination with sotorasib for KRAS G12C-mutated metastatic NSCLC in patients 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-8520[25], was granted fast track designation in 2025 for previously treated KRAS G12C-mutated patients with metastatic NSCLC. The RAS inhibitor, daraxonrasib[26], was granted breakthrough designation (2025) for previously treated metastatic pancreatic cancer with KRAS G12 mutations. The KRAS G12D (ON/OFF) inhibitor, GFH-375[27], was also granted fast track designation (2025) for first-line and previously treated KRAS G12D-mutated locally advanced or metastatic pancreatic adenocarcinoma. The KRAS G12C inhibitor, D3S-001[28], was granted fast track designation in 2024 for KRAS G12C-mutated patients with advanced unresectable or metastatic colorectal cancers. The PLK1 inhibitor, onvansertib[29], 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, cetuximab[30] and panitumumab[31], 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)[13]. Additionally, KRAS mutations are associated with poor prognosis in NSCLC[32].

CCND1 amplification

cyclin D1

Background: The CCND1 gene encodes the cyclin D1 protein, a member of the highly conserved D-cyclin family that also includes CCND2 and CCND3[116,117,118]. D-type cyclins are known to regulate cell cycle progression by binding to and activating cyclin dependent kinases (CDKs), specifically CDK4 and CDK6, which leads to the phosphorylation and inactivation of the retinoblastoma (RB1) protein[116,117]. Consequently, RB1 inactivation results in E2F transcription factor activation and cellular G1/S phase transition thereby resulting in cell cycle progression, a common event observed in tumorigenesis[116,117,119]. Aberrations in the D-type cyclins have been observed to promote tumor progression suggesting an oncogenic role for CCND1[118,120].

Alterations and prevalence: Recurrent somatic alterations to CCND1, including mutations, amplifications, and chromosomal translocations, are observed in many cancer types. A common mechanism of these alterations is to increase the expression and nuclear localization of the cyclin D1 protein. Recurrent somatic mutations include missense mutations at codons T286 and P287 and c-terminal truncating mutations that are enriched in about 33% of uterine cancer, and missense mutations at Y44 that are enriched in about 50% of Mantle cell lymphoma (MCL)[4,5,121,122]. These mutations block phosphorylation-dependent nuclear export and proteolysis[123,124,125,126]. CCND1 is recurrently amplified in many cancer types, including up to 35% of esophageal cancer, 20-30% of head and neck cancer, and 10-20% of breast, squamous lung, and bladder cancers[4,5,65]. MCL is genetically characterized by the t(11;14)(q13;q13) translocation, a rearrangement that juxtaposes CCND1 to the immunoglobulin heavy (IgH) chain gene. This rearrangement leads to constitutive expression of cyclin D1 and plays an important role in MCL pathogenesis[127,128].

Potential relevance: Currently, no therapies are approved for CCND1 aberrations. The t(11;14) translocation involving CCND1 can be used to help diagnose some lymphoma subtypes including non-gastric MALT lymphoma, splenic marginal cell lymphoma, and mantle cell lymphoma[81].

FGF19 amplification

fibroblast growth factor 19

Background: The FGF19 gene encodes the fibroblast growth factor 19 protein, a member of the FGF protein family composed of twenty-two members[39,40]. With the exception of four non-signaling FGF memebers (FGF11-14), FGF proteins function as ligands and mediate the activation of the fibroblast growth factor receptor (FGFR) family of tyrosine kinases[39,40]. 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 thereby influencing cell proliferation, migration, and survival[41,42,43]. FGF19 is specifically observed to bind FGFR4 with increased affinity in the presence of the transmembrane protein klotho beta (KLB) which functions as a cofactor in FGF19 mediated FGFR4 activation[83,84]. FGF19-mediated aberrant signaling has been identified as an oncogenic driver in hepatocellular carcinoma[83,85].

Alterations and prevalence: FGF19 amplification is observed in about 35% of esophageal cancer, 23% of head and neck cancer, 10-15% of invasive breast carcinoma, cholangiocarcinoma, squamous lung, and bladder cancers as well as 5-7% of melanoma, liver, ovarian, and stomach cancers[4]. FGF19 overexpression is correlated with the development and tumor progression in hepatocellular carcinoma[86].

Potential relevance: Currently, no therapies are approved for FGF19 aberrations. Selective, irreversible FGFR4 inhibitors, including fisogatinib (BLU-554), are under current clinical trial evaluation. In a phase-I clinical study of fisogatinib in patients with advanced hepatocellular carcinoma, 63% of the 115 patients enrolled were FGF19-positive by IHC[87]. Additionally, in 53 patients with tissue

Biomarker Descriptions (continued)

available for evaluation, 96% also exhibited mRNA-expression of FGFR4 and KLB. The total overall response rate observed for fisogatinib in FGF19-positive patients evaluable for response was 17% (11/66)[87].

SMAD4 deletion

SMAD family member 4

Background: The SMAD4 gene encodes the SMAD family member 4, a transcription factor that belongs to a family of 8 SMAD genes that can be divided into three main classes. SMAD4 (also known as DPC4) belongs to the common mediator SMAD (co-SMAD) class while SMAD1, SMAD2, SMAD3, SMAD5, and SMAD8 are part of the regulator SMAD (R-SMAD) class. The inhibitory SMAD (I-SMAD) class includes both SMAD6 and SMAD7[48,49]. SMAD4 is a tumor suppressor gene and functions as a mediator of the TGF-β and BMP signaling pathways that are implicated in cancer initiation and progression[49,50,51]. Loss of SMAD4 does not drive oncogenesis, but is associated with progression of cancers initiated by driver genes such as KRAS and APC[48,49]

Alterations and prevalence: Inactivation of SMAD4 can occur due to mutations, allelic loss, homozygous deletions, and 18q loss of heterozygosity (LOH)[48]. Somatic mutations in SMAD4 occur in up to 20% of pancreatic, 12% of colorectal, and 8% of stomach cancers. Recurrent hotspot mutations including R361 and P356 occur in the mad homology 2 (MH2) domain leading to the disruption of the TGF-β signaling[5,51,52]. Copy number deletions occur in up to 12% of pancreatic, 10% of esophageal, and 13% of stomach cancers[4,5,53].

Potential relevance: Currently, no therapies are approved for SMAD4 aberrations. Clinical studies and meta-analyses have demonstrated that loss of SMAD4 expression confers poor prognosis and poor overall survival (OS) in colorectal and pancreatic cancers[49,51,54,55,56]. Importantly, SMAD4 is a predictive biomarker to fluorouracil based chemotherapy[57,58]. In a retrospective analysis of 241 colorectal cancer patients treated with fluorouracil, 21 patients with SMAD4 loss demonstrated significantly poor median OS when compared to SMAD4 positive patients (31 months vs 89 months)[58]. In another clinical study of 173 newly diagnosed and recurrent head and neck squamous cell carcinoma (HNSCC) patients, SMAD4 loss is correlated with cetuximab resistance in HPV-negative HNSCC tumors[59].

CDKN2A p.(R128Sfs*20) c.376_380dup

cyclin dependent kinase inhibitor 2A

Background: CDKN2A encodes cyclin dependent kinase inhibitor 2A, a cell cycle regulator that controls G1/S progression[1]. CDKN2A, also known as p16/INK4A, belongs to a family of INK4 cyclin-dependent kinase inhibitors, which also includes CDKN2B (p15/INK4B), CDKN2C (p18/INK4C), and CDKN2D (p19/INK4D)[94]. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb[95,96,97]. CDKN2A encodes two alternative transcript variants, namely p16 and p14ARF, both of which exhibit differential tumor suppressor functions[98]. Specifically, the CDKN2A/p16 transcript inhibits cell cycle kinases CDK4 and CDK6, whereas the CDKN2A/p14ARF transcript stabilizes the tumor suppressor protein p53 to prevent its degradation[1,98,99]. CDKN2A aberrations commonly co-occur with CDKN2B[94]. Loss of CDKN2A/p16 results in downstream inactivation of the Rb and p53 pathways, leading to uncontrolled cell proliferation[100]. Germline mutations of CDKN2A are known to confer a predisposition to melanoma and pancreatic cancer[101,102].

Alterations and prevalence: Somatic alterations in CDKN2A often result in loss of function (LOF) which is attributed to copy number loss, truncating, or missense mutations[103]. Somatic mutations in CDKN2A are observed in 20% of head and neck squamous cell carcinoma and pancreatic adenocarcinoma, 15% of lung squamous cell carcinoma, 13% of skin cutaneous melanoma, 8% of esophageal adenocarcinoma, 7% of bladder urothelial carcinoma, 6% of cholangiocarcinoma, 4% of lung adenocarcinoma and stomach adenocarcinoma, and 2% of liver hepatocellular carcinoma, uterine carcinosarcoma, and cervical squamous cell carcinoma[4,5]. Biallelic deletion of CDKN2A is observed in 56% of glioblastoma multiforme, 45% of mesothelioma, 39% of esophageal adenocarcinoma, 32% of bladder urothelial carcinoma, 31% of skin cutaneous melanoma and head and neck squamous cell carcinoma, 28% of pancreatic adenocarcinoma, 27% of diffuse large B-cell lymphoma, 26% of lung squamous cell carcinoma, 17% of lung adenocarcinoma and cholangiocarcinoma, 15% of sarcoma, 11% of stomach adenocarcinoma and of brain lower grade glioma, 7% of adrenocortical carcinoma, 6% of liver hepatocellular carcinoma, 4% of breast invasive carcinoma, kidney renal papillary cell carcinoma and thymoma, 3% of ovarian serous cystadenocarcinoma and kidney renal clear cell carcinoma, and 2% of uterine carcinosarcoma and kidney chromophobe[4,5]. Alterations in CDKN2A are also observed in pediatric cancers[5]. Biallelic deletion of CDKN2A is observed in 68% of T-lymphoblastic leukemia/lymphoma, 40% of B-lymphoblastic leukemia/lymphoma, 25% of glioma, 19% of bone cancer, and 6% of embryonal tumors[5]. Somatic mutations in CDKN2A are observed in less that 1.5% of bone cancer (5 in 327 cases), B-lymphoblastic leukemia/lymphoma (3 in 252 cases), and leukemia (1 in 354 cases)[5].

Potential relevance: Loss of CDKN2A can be useful in the diagnosis of mesothelioma, and mutations in CDKN2A are ancillary diagnostic markers of malignant peripheral nerve sheath tumors[104,105,106]. Additionally, deletion of CDKN2B is a molecular marker used in staging Grade 4 pediatric IDH-mutant astrocytoma[107]. Currently, no therapies are approved for CDKN2A aberrations. However, CDKN2A LOF leading to CDK4/6 activation may confer sensitivity to CDK inhibitors such as palbociclib and abemaciclib[108,109,110]. Alternatively, CDKN2A expression and Rb inactivation demonstrate resistance to palbociclib in cases of glioblastoma multiforme[111].

Biomarker Descriptions (continued)

CDKN2A (p16) expression is associated with a favorable prognosis for progression-free survival (PFS) and overall survival (OS) in p16/HPV positive head and neck cancer[112,113,114,115].

FGF3 amplification

fibroblast growth factor 3

Background: The FGF3 gene encodes the fibroblast growth factor 3 protein, a member of the FGF protein family composed of twenty-two members[39,40]. With the exception of four non-signaling FGF memebers (FGF11-14), FGF proteins function as ligands and mediate the activation of the fibroblast growth factor receptor (FGFR) family of tyrosine kinases[39,40]. 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 thereby influencing cell proliferation, migration, and survival[41,42,43]. Specifically, FGF3 has been shown to bind to both FGFR1 and FGFR2[44,45]. Overexpression of FGF3 has been associated with certain tumor types including lung and liver cancers[46,47]. Additionally, constitutive ectopic expression has been suggested to promote tumorigenesis in vitro, supporting an oncogenic role for FGF3[45].

Alterations and prevalence: FGF3 amplification is observed in about 35% of esophageal cancer, 24% of head and neck cancer, 10-15% of invasive breast carcinoma, squamous lung, and bladder cancers as well as 5-10% of cholangiocarcinoma, melanoma, liver, ovarian and stomach cancers[4]. FGF3 overexpression is correlated with non-small cell lung cancer (NSCLC) development as well as tumor metastasis and recurrence in hepatocellular carcinoma[46,47].

Potential relevance: Currently, no therapies are approved for FGF3 aberrations.

FGF4 amplification

fibroblast growth factor 4

Background: The FGF4 gene encodes the fibroblast growth factor 4 protein, a member of the FGF protein family, which is composed of 22 members[1,40]. With the exception of four non-signaling FGF members (FGF11-14), FGF proteins function as ligands and mediate the activation of the fibroblast growth factor receptor (FGFR) family of tyrosine kinases[39,40]. 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, thereby influencing cell proliferation, migration, and survival[41,42,43].

Alterations and prevalence: Amplifications in FGF4 are observed in various tumor types, but most frequently are found in up to 35% of esophageal adenocarcinoma, 24% of head and neck squamous cell carcinoma, 14% of breast invasive carcinoma, 12% of lung squamous cell carcinoma, 11% of cholangiocarcinoma, 10% of bladder urothelial carcinoma, 7% of stomach adenocarcinoma, and 5% of liver hepatocellular carcinoma[4,5]. FGF4 overexpression has been associated with Kaposi sarcoma lesions as well as testicular cancer[88,89].

Potential relevance: Currently, no therapies are approved for FGF4 aberrations.

RNF43 p.(R117Tfs*41) c.349_350delCGinsA

ring finger protein 43

Background: The RNF43 gene encodes the ring finger protein 43[1]. RNF43 is a transmembrane E3 ubiquitin ligase and a negative regulator of the Wnt signaling pathway[2,3]. Wnt signaling leads to the expression of genes that control cell proliferation, migration, and cell polarity formation[2]. RNF43 functions as a tumor suppressor and inhibits the Wnt pathway by ubiquitination and degradation of the Wnt receptor frizzled (FZD)[2,3].

Alterations and prevalence: Somatic mutations in RNF43 are observed in 14% endometrial carcinoma, 8% gastroesophageal junction cancer and colorectal adenocarcinoma, and 6% pancreatic adenocarcinoma[4,5]. Somatic frameshift mutations in RNF43 including R117fs and G659fs are frequently observed in colorectal and endometrial cancers with microsatellite instability[2,6,7].

Potential relevance: Currently, no therapies are approved for RNF43 aberrations.

TP53 p.(V157G) c.470T>G

tumor protein p53

Background: The TP53 gene encodes the tumor suppressor protein p53, which binds to DNA and activates transcription in response to diverse cellular stresses to induce cell cycle arrest, apoptosis, or DNA repair[1]. In unstressed cells, TP53 is kept inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis[60]. Alterations in TP53 are required for oncogenesis as they result in loss of protein function and gain of transforming potential[61]. Germline mutations in TP53 are

Biomarker Descriptions (continued)

the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers[62,63].

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%)[4,5,64,65,66,67]. 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[4,5]. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes[68,69,70,71]. Alterations in TP53 are also observed in pediatric cancers[4,5]. Somatic mutations are observed in 53% of non-Hodgkin lymphoma, 24% of soft tissue sarcoma, 19% of glioma, 13% of bone cancer, 9% of B-lymphoblastic leukemia/lymphoma, 4% of embryonal tumors, 3% of Wilms tumor and leukemia, 2% of T-lymphoblastic leukemia/lymphoma, and less than 1% of peripheral nervous system cancers (5 in 1158 cases)[4,5]. Biallelic loss of TP53 is observed in 10% of bone cancer, 2% of Wilms tumor, and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 731 cases) and leukemia (1 in 250 cases)[4,5].

Potential relevance: The small molecule p53 reactivator, PC14586[72] (2020), received a fast track designation by the FDA for advanced tumors harboring a TP53 Y220C mutation. In addition to investigational therapies aimed at restoring wild-type TP53 activity, compounds that induce synthetic lethality are also under clinical evaluation[73,74]. TP53 mutation are a diagnostic marker of SHH-activated, TP53-mutant medulloblastoma[75]. 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)[76,77,78,79,80]. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant[81]. Mono- and bi-allelic mutations in TP53 confer unique characteristics in MDS, with multi-hit patients also experiencing associations with complex karyotype, few co-occurring mutations, and high-risk disease presentation as well as predicted death and leukemic transformation independent of the IPSS-R staging system[82].

HLA-A deletion

major histocompatibility complex, class I, A

Background: The HLA-A gene encodes the major histocompatibility complex, class I, A[1]. MHC (major histocompatibility complex) class I molecules are located on the cell surface of nucleated cells and present antigens from within the cell for recognition by cytotoxic T cells[33]. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M[34]. The classical MHC class I genes include HLA-A, HLA-B, and HLA-C and encode the α polypeptide chains, which present short polypeptide chains, of 7 to 11 amino acids, to the immune system to distinguish self from non-self[35,36,37]. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-A[38].

Alterations and prevalence: Somatic mutations in HLA-A are observed in 7% of diffuse large B-cell lymphoma (DLBCL), 4% of cervical squamous cell carcinoma and head and neck squamous cell carcinoma, 3% of colorectal adenocarcinoma, and 2% of uterine corpus endometrial carcinoma and stomach adenocarcinoma[4,5]. Biallelic loss of HLA-A is observed in 4% of DLBCL[4,5].

Potential relevance: Currently, no therapies are approved for HLA-A aberrations.

KDM6A deletion

lysine demethylase 6A

Background: The KDM6A gene encodes the lysine demethylase 6A protein[1]. KDM6A is a histone demethylase that belongs to the KDM6 family of histone H3 lysine demethylases that also includes KDM6B and KDM6C[90]. Methylation of histone lysine and arginine residues functions to regulate transcription and the DNA damage response, specifically in the recruitment of DNA repair proteins and transcriptional repression[91]. KDM6A removes methylation of di- and trimethylated histone 3 lysine 27 (H3K27)[90,92]. KDM6A also interacts with various transcription factors as well as KMT2C, KMT2D, and CBP/p300 chromatin-modifying enzymes, and the SWI/SNF chromatin-remodeling complex to facilitate transcriptional regulation[90]. Mutations in KDM6A lead to activation of the histone methyltransferase, EZH2, resulting in transcriptional repression[90]. KDM6A is believed to function as a tumor suppressor by antagonizing EZH2-mediated transcriptional repression and promoting transcriptional regulation[90,93].

Alterations and prevalence: Somatic mutations in KDM6A are observed in 26% of bladder urothelial carcinoma, 7% of uterine corpus endometrial carcinoma, 5% of skin cutaneous melanoma, lung squamous cell carcinoma, and 4% of esophageal adenocarcinoma, kidney renal papillary cell carcinoma, pancreatic adenocarcinoma, cervical squamous cell carcinoma, and head and neck squamous cell carcinoma[4,5]. Biallelic loss of KDM6A is observed in 8% of esophageal adenocarcinoma, 4% of lung squamous cell carcinoma, 3% of head and neck squamous cell carcinoma, bladder urothelial carcinoma, and pancreatic adenocarcinoma[4,5].

Potential relevance: Currently, no therapies are approved for KDM6A aberrations. Pre-clinical data suggest that KDM6A loss of function or inactivating mutations may respond to EZH2 inhibitors[93].

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

FDA information is current as of 2025-09-17. For the most up-to-date information, search www.fda.gov.

ERBB2 amplification

trastuzumab pamirtecan

Cancer type: Endometrial Carcinoma

Variant class: ERBB2 overexpression

Supporting Statement:
The FDA has granted Breakthrough Therapy designation to antibody-drug conjugate, trastuzumab pamirtecan (DB-1303), for the treatment of patients with HER2-expressing advanced endometrial cancer.

Reference:

https://investors.biontech.de//news-releases/news-release-details/biontech-and-dualitybio-receive-fda-breakthrough-therapy

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disitamab vedotinaide

Cancer type: Bladder Urothelial Carcinoma

Variant class: ERBB2 positive

Supporting Statement:
The FDA has granted Breakthrough Therapy designation to the humanized anti-HER2 antibody drug conjugate (ADC), disitamab vedotin, for the second-line treatment of HER2 positive locally advanced or metastatic urothelial cancer (UC) after previous platinum-containing chemotherapy treatment.

Reference:

https://www.prnewswire.com/news-releases/remegen-announces-us-fda-has-granted-breakthrough-therapy-designation-for-disitamab-vedotin-rc48-in-urothelial-cancer-301138315.html

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zanidatamab + chemotherapy

Cancer type: Gastroesophageal Junction Adenocarcinoma

Variant class: ERBB2 overexpression

Supporting Statement:
The FDA has granted Fast Track designation to the HER2 targeted bispecific antibody, zanidatamab, for HER2-overexpressing gastroesophageal adenocarcinoma (GEA) to be used in combination with standard-of-care chemotherapy.

Reference:

https://www.targetedonc.com/view/her2targeted-antibody-zw25-earns-fda-fast-track-designation-in-gea

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anvatabart opadotin

Cancer type: Breast Cancer

Variant class: ERBB2 positive

Supporting Statement:
The FDA has granted Fast Track designation to the HER2-targeting antibody drug conjugate, anvatabart opadotin (ARX-788), for HER2-positive metastatic breast cancer.

Reference:

https://ir.ambrx.com/news/news-details/2023/ACE-Breast-02-Pivotal-Phase-3-Study-of-Ambrxs-ARX788-for-the-Treatment-of-HER2-Positive-Metastatic-Breast-Cancer-Achieves-Positive-Results/default.aspx

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ERBB2 amplification (continued)

CYNK-101 + pembrolizumab + trastuzumab + chemotherapy

Cancer type: Gastric Cancer, Gastroesophageal Junction Adenocarcinoma

Variant class: ERBB2 positive

Supporting Statement:
The FDA has granted Fast Track designation to the genetically modified cryopreserved human placental hematopoietic stem cell-derived natural killer (NK) cell therapy, CYNK-101, in combination with standard chemotherapy, trastuzumab, and pembrolizumab for the treatment of HER2/neu positive gastric or gastroesophageal junction (G/GEJ) adenocarcinoma.

Reference:

https://celularity.com/celularity-receives-fast-track-designation-from-u-s-fda-for-its-nk-cell-therapy-cynk-101/

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evorpacept

Cancer type: Gastric Cancer, Gastroesophageal Junction Adenocarcinoma

Variant class: ERBB2 positive

Supporting Statement:
The FDA has granted Fast Track designation to the CD47 checkpoint inhibitor, ALX148, for the second-line treatment of patients with HER2-positive gastric or gastroesophageal junction carcinoma.

Reference:

https://www.targetedonc.com/view/two-fda-fast-track-designations-granted-to-alx148-for-hnscc-and-gastricgej-adenocarcinomas

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GLSI-100

Cancer type: Breast Cancer

Variant class: ERBB2 positive

Supporting Statement:
The FDA has granted Fast Track designation to the immunotherapy, GLSI-100, for the treatment of patients with HLA-A*02 genotype and HER2-positive breast cancer who have completed treatment with standard of care HER2/neu targeted therapy to improve invasive breast cancer free survival.

Reference:

https://investor.greenwichlifesciences.com/news-events/press-releases/detail/102/us-fda-fast-track-designation

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KRAS p.(G12D) c.35G>A

⊘ 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 platinum-based 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

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⊘ panitumumab

Cancer type: Colorectal Cancer **Label as of:** 2025-01-16 **Variant class:** KRAS G12 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 irinotecan-containing 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 FDA-approved 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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KRAS p.(G12D) c.35G>A (continued)

daraxonrasib

Cancer type: Pancreatic Cancer **Variant class:** KRAS G12 mutation

Supporting Statement:
The FDA has granted Breakthrough designation to the RAS inhibitor, daraxonrasib, for previously treated metastatic pancreatic adenocarcinoma (PDAC) in patients with KRAS G12 mutations.

Reference:

https://ir.revmed.com/news-releases/news-release-details/revolution-medicines-announces-fda-breakthrough-therapy

GFH-375

Cancer type: Pancreatic Cancer **Variant class:** KRAS G12D mutation

Supporting Statement:
The FDA has granted Fast Track designation to an oral KRAS G12D (ON/OFF) inhibitor, GFH-375 (VS-7375), for the first-line treatment of patients with KRAS G12D-mutated locally advanced or metastatic adenocarcinoma of the pancreas (PDAC) and for the treatment of patients with KRAS G12D-mutated locally advanced or metastatic PDAC who have received at least one prior line of standard systemic therapy.

Reference:

https://investor.verastem.com/news-releases/news-release-details/verastem-oncology-granted-fast-track-designation-vs-7375

Current NCCN Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

NCCN information is current as of 2025-09-02. 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.

KRAS p.(G12D) c.35G>A

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 4.2025]

KRAS p.(G12D) c.35G>A (continued)

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 3.2025]

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 4.2025]

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 3.2025]

Current EMA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

EMA information is current as of 2025-09-17. For the most up-to-date information, search www.ema.europa.eu.

KRAS p.(G12D) c.35G>A

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:** 2025-05-07 **Variant class:** KRAS G12 mutation

Reference:

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

Current ESMO Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

ESMO information is current as of 2025-09-02. For the most up-to-date information, search www.esmo.org.

ERBB2 amplification

trastuzumab

Cancer type: Gastric Cancer **Variant class:** ERBB2 overexpression

Summary:

ESMO Clinical Practice Guidelines include the following supporting statement:

- "Treatment with trastuzumab is not recommended after first-line therapy in HER2-positive advanced gastric cancer [I, D]."

Reference: ESMO Clinical Practice Guidelines - ESMO-Gastric Cancer [Ann Oncol (2022), doi: https://doi.org/10.1016/j.annonc.2022.07.004.]

hormone therapy

Cancer type: Breast Cancer **Variant class:** ERBB2 positive

Other criteria: Hormone receptor positive

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

Summary:

ESMO™ Clinical Practice Guidelines include the following supporting statement:

- "The use of single-agent ET without a HER2-targeted therapy is not routinely recommended unless cardiac disease precludes the safe use of HER2-directed therapies [III, C]"

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Breast Cancer [Ann Oncol (2021) VOLUME 32, ISSUE 12, P1475-1495, DECEMBER 01, 2021; DOI:https://doi.org/10.1016/j.annonc.2021.09.019]

KRAS p.(G12D) c.35G>A

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 confirmed".
- "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)]

KRAS p.(G12D) c.35G>A (continued)

⊘ 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 confirmed".
- "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, SLCO1B3, SMC1A, SMO, SNCAIP, SOS1, SOX2, SPOP, SRC, SRSF2, STAT3, STAT5B, STAT6, TAF1, TERT, TGFBR1, TOP1, TOP2A, TPMT, TRRAP, TSHR, U2AF1, USP8, WAS, XPO1, ZNF217, ZNF429

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, FANCL, FANCM, FAT1, FBXW7, FGF19, FGF23, FGF3, 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 (continued)

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, FGFR3, 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, ERRFI1, ETV6, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, 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 ○ In other cancer type ◑ In this cancer type and other cancer types ✖ No evidence

ERBB2 amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
trastuzumab deruxtecan	◑	○	○	○	● (II)
zanidatamab	○	○	○	○	● (II)
ado-trastuzumab emtansine	○	○	○	○	✖
lapatinib + capecitabine	○	○	○	○	✖
neratinib	○	○	○	○	✖
pertuzumab + trastuzumab + chemotherapy	○	○	○	○	✖
pertuzumab + trastuzumab + docetaxel	○	○	○	○	✖
trastuzumab + docetaxel	○	○	○	○	✖
trastuzumab + paclitaxel	○	○	○	○	✖
trastuzumab + tucatinib + capecitabine	○	○	○	○	✖
trastuzumab	○	○	○	✖	● (II)
trastuzumab + capecitabine + cisplatin	○	○	○	✖	✖
trastuzumab + carboplatin + docetaxel	○	○	○	✖	✖

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

Relevant Therapy Summary (continued)

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

ERBB2 amplification (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
trastuzumab + cisplatin + fluorouracil	○	○	○	✖	✖
neratinib + capecitabine	○	○	✖	✖	✖
lapatinib + letrozole	○	✖	○	✖	✖
pembrolizumab + trastuzumab + chemotherapy + fluoropyrimidine	○	✖	○	✖	✖
pertuzumab/trastuzumab/hyaluronidase-zzxf + cyclophosphamide + doxorubicin	○	✖	○	✖	✖
pertuzumab/trastuzumab/hyaluronidase-zzxf + docetaxel	○	✖	○	✖	✖
trastuzumab (Biocon)	○	✖	○	✖	✖
trastuzumab (Biocon) + capecitabine + cisplatin	○	✖	○	✖	✖
trastuzumab (Biocon) + carboplatin + docetaxel	○	✖	○	✖	✖
trastuzumab (Biocon) + cisplatin + fluorouracil	○	✖	○	✖	✖
trastuzumab (Biocon) + docetaxel	○	✖	○	✖	✖
trastuzumab (Biocon) + paclitaxel	○	✖	○	✖	✖
trastuzumab (Celltrion)	○	✖	○	✖	✖
trastuzumab (Celltrion) + capecitabine + cisplatin	○	✖	○	✖	✖
trastuzumab (Celltrion) + carboplatin + docetaxel	○	✖	○	✖	✖
trastuzumab (Celltrion) + cisplatin + fluorouracil	○	✖	○	✖	✖
trastuzumab (Celltrion) + docetaxel	○	✖	○	✖	✖
trastuzumab (Celltrion) + paclitaxel	○	✖	○	✖	✖
trastuzumab (Henlius)	○	✖	○	✖	✖
trastuzumab (Pfizer)	○	✖	○	✖	✖
trastuzumab (Pfizer) + capecitabine + cisplatin	○	✖	○	✖	✖
trastuzumab (Pfizer) + carboplatin + docetaxel	○	✖	○	✖	✖
trastuzumab (Pfizer) + cisplatin + fluorouracil	○	✖	○	✖	✖
trastuzumab (Pfizer) + docetaxel	○	✖	○	✖	✖
trastuzumab (Pfizer) + paclitaxel	○	✖	○	✖	✖
trastuzumab (Samsung Bioepis)	○	✖	○	✖	✖
trastuzumab (Samsung Bioepis) + capecitabine + cisplatin	○	✖	○	✖	✖

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

Relevant Therapy Summary (continued)

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

ERBB2 amplification (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
trastuzumab (Samsung Bioepis) + carboplatin + docetaxel	○	✖	○	✖	✖
trastuzumab (Samsung Bioepis) + cisplatin + fluorouracil	○	✖	○	✖	✖
trastuzumab (Samsung Bioepis) + docetaxel	○	✖	○	✖	✖
trastuzumab (Samsung Bioepis) + paclitaxel	○	✖	○	✖	✖
trastuzumab (Synthon)	○	✖	○	✖	✖
trastuzumab (Synthon) + capecitabine + cisplatin	○	✖	○	✖	✖
trastuzumab (Synthon) + carboplatin + docetaxel	○	✖	○	✖	✖
trastuzumab (Synthon) + cisplatin + fluorouracil	○	✖	○	✖	✖
trastuzumab (Synthon) + docetaxel	○	✖	○	✖	✖
trastuzumab (Synthon) + paclitaxel	○	✖	○	✖	✖
margetuximab + chemotherapy	○	✖	✖	○	✖
trastuzumab and hyaluronidase-oysk	○	✖	✖	✖	✖
trastuzumab and hyaluronidase-oysk + carboplatin + docetaxel	○	✖	✖	✖	✖
trastuzumab and hyaluronidase-oysk + docetaxel	○	✖	✖	✖	✖
trastuzumab and hyaluronidase-oysk + paclitaxel	○	✖	✖	✖	✖
lapatinib + trastuzumab	✖	○	○	○	✖
pertuzumab + trastuzumab	✖	○	✖	○	● (II/III)
pertuzumab + trastuzumab + hormone therapy	✖	○	✖	○	✖
pertuzumab + trastuzumab + paclitaxel	✖	○	✖	○	✖
trastuzumab + chemotherapy	✖	○	✖	○	✖
trastuzumab + hormone therapy	✖	○	✖	○	✖
abemaciclib + trastuzumab + fulvestrant	✖	○	✖	✖	✖
ado-trastuzumab emtansine + neratinib	✖	○	✖	✖	✖
aromatase inhibitor	✖	○	✖	✖	✖
fulvestrant	✖	○	✖	✖	✖
hormone therapy	✖	○	✖	✖	✖
lapatinib + aromatase inhibitor	✖	○	✖	✖	✖
lapatinib + trastuzumab + aromatase inhibitor	✖	○	✖	✖	✖

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

Relevant Therapy Summary (continued)

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

ERBB2 amplification (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
margetuximab + capecitabine	✖	○	✖	✖	✖
margetuximab + eribulin	✖	○	✖	✖	✖
margetuximab + gemcitabine	✖	○	✖	✖	✖
margetuximab + vinorelbine	✖	○	✖	✖	✖
neratinib + paclitaxel	✖	○	✖	✖	✖
pembrolizumab + trastuzumab + capecitabine + cisplatin	✖	○	✖	✖	✖
pembrolizumab + trastuzumab + capecitabine + oxaliplatin	✖	○	✖	✖	✖
pembrolizumab + trastuzumab + cisplatin + fluorouracil	✖	○	✖	✖	✖
pembrolizumab + trastuzumab + fluorouracil + oxaliplatin	✖	○	✖	✖	✖
pertuzumab + trastuzumab + carboplatin + docetaxel	✖	○	✖	✖	✖
pertuzumab + trastuzumab + carboplatin + paclitaxel	✖	○	✖	✖	✖
pertuzumab + trastuzumab + hormone therapy + chemotherapy	✖	○	✖	✖	✖
tamoxifen	✖	○	✖	✖	✖
trastuzumab + aromatase inhibitor	✖	○	✖	✖	✖
trastuzumab + capecitabine	✖	○	✖	✖	✖
trastuzumab + capecitabine + oxaliplatin	✖	○	✖	✖	✖
trastuzumab + carboplatin + paclitaxel	✖	○	✖	✖	✖
trastuzumab + chemotherapy (non-anthracycline)	✖	○	✖	✖	✖
trastuzumab + cisplatin + docetaxel	✖	○	✖	✖	✖
trastuzumab + cisplatin + docetaxel + fluorouracil	✖	○	✖	✖	✖
trastuzumab + cisplatin + paclitaxel	✖	○	✖	✖	✖
trastuzumab + cyclophosphamide + docetaxel	✖	○	✖	✖	✖
trastuzumab + docetaxel + fluorouracil + oxaliplatin	✖	○	✖	✖	✖
trastuzumab + fluorouracil	✖	○	✖	✖	✖
trastuzumab + fluorouracil + irinotecan	✖	○	✖	✖	✖
trastuzumab + fluorouracil + oxaliplatin	✖	○	✖	✖	✖

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

Relevant Therapy Summary (continued)

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

ERBB2 amplification (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
trastuzumab + fulvestrant	✖	○	✖	✖	✖
trastuzumab + hormone therapy + chemotherapy	✖	○	✖	✖	✖
trastuzumab + tamoxifen	✖	○	✖	✖	✖
trastuzumab + tucatinib	✖	○	✖	✖	✖
trastuzumab + vinorelbine	✖	○	✖	✖	✖
pertuzumab/trastuzumab/hyaluronidase-zzxf + carboplatin + docetaxel	✖	✖	○	✖	✖
pertuzumab/trastuzumab/hyaluronidase-zzxf + cyclophosphamide + doxorubicin + fluorouracil	✖	✖	○	✖	✖
pertuzumab/trastuzumab/hyaluronidase-zzxf + cyclophosphamide + epirubicin	✖	✖	○	✖	✖
pertuzumab/trastuzumab/hyaluronidase-zzxf + paclitaxel	✖	✖	○	✖	✖
trastuzumab (Biocon) + anastrozole	✖	✖	○	✖	✖
trastuzumab (Celltrion) + anastrozole	✖	✖	○	✖	✖
trastuzumab (CuraTeQ Biologics)	✖	✖	○	✖	✖
trastuzumab (CuraTeQ Biologics) + anastrozole	✖	✖	○	✖	✖
trastuzumab (CuraTeQ Biologics) + capecitabine + cisplatin	✖	✖	○	✖	✖
trastuzumab (CuraTeQ Biologics) + carboplatin + docetaxel	✖	✖	○	✖	✖
trastuzumab (CuraTeQ Biologics) + cisplatin + fluorouracil	✖	✖	○	✖	✖
trastuzumab (CuraTeQ Biologics) + docetaxel	✖	✖	○	✖	✖
trastuzumab (CuraTeQ Biologics) + paclitaxel	✖	✖	○	✖	✖
trastuzumab (EirGenix)	✖	✖	○	✖	✖
trastuzumab (EirGenix) + anastrozole	✖	✖	○	✖	✖
trastuzumab (EirGenix) + capecitabine + cisplatin	✖	✖	○	✖	✖
trastuzumab (EirGenix) + carboplatin + docetaxel	✖	✖	○	✖	✖
trastuzumab (EirGenix) + cisplatin + fluorouracil	✖	✖	○	✖	✖
trastuzumab (EirGenix) + docetaxel	✖	✖	○	✖	✖
trastuzumab (EirGenix) + paclitaxel	✖	✖	○	✖	✖

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

Relevant Therapy Summary (continued)

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

ERBB2 amplification (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
trastuzumab (Henlius) + anastrozole	✖	✖	○	✖	✖
trastuzumab (Henlius) + capecitabine + cisplatin	✖	✖	○	✖	✖
trastuzumab (Henlius) + carboplatin + docetaxel	✖	✖	○	✖	✖
trastuzumab (Henlius) + cisplatin + fluorouracil	✖	✖	○	✖	✖
trastuzumab (Henlius) + docetaxel	✖	✖	○	✖	✖
trastuzumab (Henlius) + paclitaxel	✖	✖	○	✖	✖
trastuzumab (Pfizer) + anastrozole	✖	✖	○	✖	✖
trastuzumab (Prestige BioPharma)	✖	✖	○	✖	✖
trastuzumab (Prestige BioPharma) + anastrozole	✖	✖	○	✖	✖
trastuzumab (Prestige BioPharma) + capecitabine + cisplatin	✖	✖	○	✖	✖
trastuzumab (Prestige BioPharma) + carboplatin + docetaxel	✖	✖	○	✖	✖
trastuzumab (Prestige BioPharma) + cisplatin + fluorouracil	✖	✖	○	✖	✖
trastuzumab (Prestige BioPharma) + docetaxel	✖	✖	○	✖	✖
trastuzumab (Prestige BioPharma) + paclitaxel	✖	✖	○	✖	✖
trastuzumab (Samsung Bioepis) + anastrozole	✖	✖	○	✖	✖
trastuzumab (Synthon) + anastrozole	✖	✖	○	✖	✖
trastuzumab + anastrozole	✖	✖	○	✖	✖
ado-trastuzumab emtansine + hormone therapy	✖	✖	✖	○	✖
lapatinib + hormone therapy	✖	✖	✖	○	✖
lapatinib + trastuzumab + hormone therapy	✖	✖	✖	○	✖
margetuximab	✖	✖	✖	○	✖
neratinib + chemotherapy	✖	✖	✖	○	✖
pertuzumab + trastuzumab + nab-paclitaxel	✖	✖	✖	○	✖
pyrotinib	✖	✖	✖	✖	● (IV)
CART-HER2, chemotherapy	✖	✖	✖	✖	● (II)
FDA022-BB05	✖	✖	✖	✖	● (II)
neratinib, neratinib + palbociclib	✖	✖	✖	✖	● (II)

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

Relevant Therapy Summary (continued)

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

ERBB2 amplification (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pertuzumab + trastuzumab, atezolizumab + pertuzumab/trastuzumab/hyaluronidase-zzxf, trastuzumab + tucatinib	✖	✖	✖	✖	● (II)
trastuzumab (Samsung Bioepis), chemotherapy	✖	✖	✖	✖	● (II)
tucatinib, ado-trastuzumab emtansine	✖	✖	✖	✖	● (II)
tucatinib, trastuzumab	✖	✖	✖	✖	● (II)
zongertinib	✖	✖	✖	✖	● (II)
AP-402	✖	✖	✖	✖	● (I/II)
BL-M07D1	✖	✖	✖	✖	● (I/II)
DF-1001, nivolumab	✖	✖	✖	✖	● (I/II)
E01001	✖	✖	✖	✖	● (I/II)
HypoSti.CART-HER2, chemotherapy	✖	✖	✖	✖	● (I/II)
IAH-0968	✖	✖	✖	✖	● (I/II)
IAH-0968, chemotherapy	✖	✖	✖	✖	● (I/II)
IBI-354	✖	✖	✖	✖	● (I/II)
JIN-A-04	✖	✖	✖	✖	● (I/II)
ST-1703	✖	✖	✖	✖	● (I/II)
trastuzumab deruxtecan, neratinib	✖	✖	✖	✖	● (I/II)
trastuzumab pamirtecan, pertuzumab	✖	✖	✖	✖	● (I/II)
YH32367	✖	✖	✖	✖	● (I/II)
ZV-0203	✖	✖	✖	✖	● (I/II)
177Lu-RAD202	✖	✖	✖	✖	● (I)
ado-trastuzumab emtansine (Shanghai Fosun Pharma)	✖	✖	✖	✖	● (I)
anti-HER-2 MAb (Anke Biotechnology)	✖	✖	✖	✖	● (I)
BC004	✖	✖	✖	✖	● (I)
BL-M17D1	✖	✖	✖	✖	● (I)
BM-230	✖	✖	✖	✖	● (I)
CART-HER2	✖	✖	✖	✖	● (I)
CART-HER2/PD-L1	✖	✖	✖	✖	● (I)
ceralasertib, trastuzumab deruxtecan	✖	✖	✖	✖	● (I)

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

Relevant Therapy Summary (continued)

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

ERBB2 amplification (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
D3L-001	✖	✖	✖	✖	● (I)
doxorubicin (Hangzhou HighField Biopharma)	✖	✖	✖	✖	● (I)
DP-303c	✖	✖	✖	✖	● (I)
ENT-H-1, trastuzumab	✖	✖	✖	✖	● (I)
GQ-1005	✖	✖	✖	✖	● (I)
GQ1001	✖	✖	✖	✖	● (I)
HF-50	✖	✖	✖	✖	● (I)
MBS301	✖	✖	✖	✖	● (I)
NC-18	✖	✖	✖	✖	● (I)
SPH5030	✖	✖	✖	✖	● (I)
TAS0728	✖	✖	✖	✖	● (I)
TL-938	✖	✖	✖	✖	● (I)
trastuzumab deruxtecan, azenosertib	✖	✖	✖	✖	● (I)
VRN-10	✖	✖	✖	✖	● (I)
VVD-159642	✖	✖	✖	✖	● (I)
XMT-2056	✖	✖	✖	✖	● (I)

KRAS p.(G12D) c.35G>A

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
avutometinib + defactinib	○	○	✖	✖	✖
bevacizumab + CAPOX	✖	✖	✖	○	✖
bevacizumab + FOLFIRI	✖	✖	✖	○	✖
bevacizumab + FOLFOX	✖	✖	✖	○	✖
bevacizumab + FOLFOXIRI	✖	✖	✖	○	✖
regorafenib	✖	✖	✖	✖	● (II)
almonertinib, palbociclib	✖	✖	✖	✖	● (I/II)
ARV-806	✖	✖	✖	✖	● (I/II)
DN-022150	✖	✖	✖	✖	● (I/II)
ERAS-0015	✖	✖	✖	✖	● (I/II)

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

Relevant Therapy Summary (continued)

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

KRAS p.(G12D) c.35G>A (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
GFH-375	✖	✖	✖	✖	● (I/II)
QLC-1101, QL1203, pembrolizumab (Qilu Pharmaceutical), iparomlimab and tuvonralimab, chemotherapy	✖	✖	✖	✖	● (I/II)
RNK-08954	✖	✖	✖	✖	● (I/II)
TSN-1611	✖	✖	✖	✖	● (I/II)
YL-15293	✖	✖	✖	✖	● (I/II)
ASP-4396	✖	✖	✖	✖	● (I)
ASP-5834	✖	✖	✖	✖	● (I)
AST-NS2101	✖	✖	✖	✖	● (I)
BPI-442096	✖	✖	✖	✖	● (I)
daraxonrasib	✖	✖	✖	✖	● (I)
GDC-7035	✖	✖	✖	✖	● (I)
imatinib, trametinib	✖	✖	✖	✖	● (I)
JAB-3312	✖	✖	✖	✖	● (I)
KRAS TCR, aldesleukin, SLATE 001, chemotherapy	✖	✖	✖	✖	● (I)
KRAS-EphA-2-CAR-DC, anti-PD-1, ipilimumab	✖	✖	✖	✖	● (I)
Nest-1	✖	✖	✖	✖	● (I)
NT-112, AZD-0240	✖	✖	✖	✖	● (I)
PT-0253	✖	✖	✖	✖	● (I)
QLC-1101	✖	✖	✖	✖	● (I)
RMC-9805, daraxonrasib	✖	✖	✖	✖	● (I)
toripalimab, chemotherapy, KRAS peptide vaccine	✖	✖	✖	✖	● (I)
ZEN-3694, binimetinib	✖	✖	✖	✖	● (I)

CCND1 amplification

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

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

Relevant Therapy Summary (continued)

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

FGF19 amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
TYRA-430	✖	✖	✖	✖	● (I)

SMAD4 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
regorafenib	✖	✖	✖	✖	● (II)

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

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 (6.1.1 data version 2025.10(006)). 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 2025-09-17. NCCN information was sourced from www.nccn.org and is current as of 2025-09-02. EMA information was sourced from www.ema.europa.eu and is current as of 2025-09-17. ESMO information was sourced from www.esmo.org and is current as of 2025-09-02. Clinical Trials information is current as of 2025-09-02. For the most up-to-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.

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