

Patient Name: 박재준
Gender: M
Sample ID: N25-336

Primary Tumor Site: large intestine
Collection Date: 20251104

Sample Cancer Type: Colon Cancer

Table of Contents

Variant Details	2
Biomarker Descriptions	3
Alert Details	8
Relevant Therapy Summary	14

Report Highlights

3 Relevant Biomarkers
7 Therapies Available
32 Clinical Trials

Relevant Colon Cancer Findings

Gene	Finding	Gene	Finding
BRAF	None detected	NTRK3	None detected
ERBB2	ERBB2 p.(V842I) c.2524G>A	PIK3CA	PIK3CA p.(M1043I) c.3129G>T
KRAS	KRAS p.(G12V) c.35G>T	POLD1	None detected
NRAS	None detected	POLE	None detected
NTRK1	None detected	RET	None detected
NTRK2	None detected		

Genomic Alteration	Finding
Microsatellite Status	Microsatellite stable
Tumor Mutational Burden	9.48 Mut/Mb measured

HRD Status: **HR Proficient (HRD-)**

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	PIK3CA p.(M1043I) c.3129G>T phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha Allele Frequency: 8.00% Locus: chr3:178952074 Transcript: NM_006218.4	aspirin II+	inavolisib + palbociclib + hormone therapy ^{1/1} capivasertib + hormone therapy ^{1,2 / II} + aspirin II+	4
IA	KRAS p.(G12V) c.35G>T KRAS proto-oncogene, GTPase Allele Frequency: 27.91% Locus: chr12:25398284 Transcript: NM_033360.4	bevacizumab + chemotherapy	avutometinib + defactinib ^{1 / II+}	18

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

* Public data sources included in prognostic and diagnostic significance: NCCN, 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.

Relevant Biomarkers (continued)

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIIC	ERBB2 p.(V842I) c.2524G>A erb-b2 receptor tyrosine kinase 2 Allele Frequency: 27.33% Locus: chr17:37881332 Transcript: NM_004448.4	None*	zongertinib ^{1 / II+} trastuzumab deruxtecan ^{1,2}	10

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

* Public data sources included in prognostic and diagnostic significance: NCCN, 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.

⚠ Alerts informed by public data sources: 🚫 Contraindicated, ⚠ Resistance, ↗ Breakthrough, ⚠ Fast Track

KRAS p.(G12V) c.35G>T 🚫 **cetuximab** ^{1,2}, **cetuximab + chemotherapy** ², **panitumumab** ¹, **panitumumab + chemotherapy** ²

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

Prevalent cancer biomarkers without relevant evidence based on included data sources

APC p.(K560*) c.1678A>T, APC p.(R1450*) c.4348C>T, ERBB3 p.(E928G) c.2783A>G, FANCG c.307+1G>C, Microsatellite stable, ELF3 p.(D195*) c.582_583insT, UGT1A1 p.(G71R) c.211G>A, HLA-B deletion, SMAD2 p.(S464*) c.1391C>G, SMAD2 p.(Q284*) c.850C>T, Tumor Mutational Burden

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
PIK3CA	p.(M1043I)	c.3129G>T	COSM773	chr3:178952074	8.00%	NM_006218.4	missense
KRAS	p.(G12V)	c.35G>T	COSM520	chr12:25398284	27.91%	NM_033360.4	missense
ERBB2	p.(V842I)	c.2524G>A	COSM14065	chr17:37881332	27.33%	NM_004448.4	missense
APC	p.(K560*)	c.1678A>T	.	chr5:112164604	20.69%	NM_000038.6	nonsense
APC	p.(R1450*)	c.4348C>T	COSM13127	chr5:112175639	32.98%	NM_000038.6	nonsense
ERBB3	p.(E928G)	c.2783A>G	COSM94228	chr12:56492633	24.83%	NM_001982.4	missense
FANCG	p.(?)	c.307+1G>C	.	chr9:35078601	51.10%	NM_004629.2	unknown
ELF3	p.(D195*)	c.582_583insT	.	chr1:201981870	25.92%	NM_004433.5	nonsense
UGT1A1	p.(G71R)	c.211G>A	COSM4415616	chr2:234669144	44.52%	NM_000463.3	missense
SMAD2	p.(S464*)	c.1391C>G	COSM268520	chr18:45368211	29.01%	NM_001003652.4	nonsense
SMAD2	p.(Q284*)	c.850C>T	.	chr18:45374993	9.75%	NM_001003652.4	nonsense
FAT1	p.(I355T)	c.10064T>C	.	chr4:187530959	44.37%	NM_005245.4	missense
MSH3	p.(A61_P63dup)	c.189_190insGCAGCG CCC	.	chr5:79950735	53.85%	NM_002439.5	nonframeshift Insertion
PPFIA2	p.(R1112Q)	c.3335G>A	.	chr12:81661842	27.71%	NM_003625.5	missense
MLH3	p.(E520D)	c.1560G>T	.	chr14:75514799	50.78%	NM_001040108.2	missense
ARHGAP35	p.(V1037I)	c.3109G>A	.	chr19:47425041	25.61%	NM_004491.5	missense

Variant Details (continued)

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
HLA-B	chr6:31322252	0.28	0.66
NFE2L2	chr2:178095457	0.43	0.69

Biomarker Descriptions

PIK3CA p.(M1043I) c.3129G>T

phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

Background: The PIK3CA gene encodes the phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha of the class I phosphatidylinositol 3-kinase (PI3K) enzyme⁷⁹. PI3K is a heterodimer that contains a p85 regulatory subunit, which couples one of four p110 catalytic subunits to activated tyrosine protein kinases^{80,81}. The p110 catalytic subunits include p110 α , β , δ , γ and are encoded by genes PIK3CA, PIK3CB, PIK3CD, and PIK3CG, respectively⁸⁰. PI3K catalyzes the conversion of phosphatidylinositol (4,5)-bisphosphate (PI(4,5)P2) into phosphatidylinositol (3,4,5)-trisphosphate (PI(3,4,5)P3) while the phosphatase and tensin homolog (PTEN) catalyzes the reverse reaction^{82,83}. The reversible phosphorylation of inositol lipids regulates diverse aspects of cell growth and metabolism^{82,83,84,85}. Recurrent somatic alterations in PIK3CA are frequent in cancer and result in the activation of PI3K/AKT/MTOR pathway, which can influence several hallmarks of cancer including cell proliferation, apoptosis, cancer cell metabolism and invasion, and genetic instability^{86,87,88}.

Alterations and prevalence: Recurrent somatic activating mutations in PIK3CA are common in diverse cancers and are observed in 20-30% of breast, cervical, and uterine cancers and 10-20% of bladder, gastric, head and neck, and colorectal cancers^{8,9}. Activating mutations in PIK3CA commonly occur in exons 10 and 21 (previously referred to as exons 9 and 20 due to exon 1 being untranslated)^{89,90}. These mutations typically cluster in the exon 10 helical (codons E542/E545) and exon 21 kinase (codon H1047) domains, each having distinct mechanisms of activation^{91,92,93}. PIK3CA resides in the 3q26 cytoband, a region frequently amplified (10-30%) in diverse cancers including squamous carcinomas of the lung, cervix, head and neck, and esophagus, and in serous ovarian and uterine cancers^{8,9}.

Potential relevance: The PI3K inhibitor, alpelisib⁹⁴, is FDA-approved (2019) in combination with fulvestrant for the treatment of patients with PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, advanced or metastatic breast cancer. Additionally, a phase Ib study of alpelisib with letrozole in patients with metastatic estrogen receptor (ER)-positive breast cancer showed the clinical benefit rate, defined as lack of disease progression \geq 6 months, was 44% (7/16) in PIK3CA-mutated tumors and 20% (2/20) in PIK3CA wild-type tumors⁹⁵. Specifically, exon 21 H1047R mutations were associated with more durable clinical responses in comparison to exon 10 E545K mutations⁹⁵. However, alpelisib did not improve response when administered with letrozole in patients with ER+ early breast cancer with PIK3CA mutations⁹⁶. The FDA also approved the kinase inhibitor, capivasertib (2023)⁹⁷ in combination with fulvestrant for locally advanced or metastatic HR-positive, HER2-negative breast cancer with one or more PIK3CA/AKT1/PTEN-alterations following progression after endocrine treatment. The kinase inhibitor, inavolisib⁹⁸, is also FDA-approved (2024) in combination with palbociclib and fulvestrant for the treatment of adults with endocrine-resistant, PIK3CA-mutated, HR-positive, and HER2-negative breast cancer. Case studies with mTOR inhibitors sirolimus and temsirolimus report isolated cases of clinical response in PIK3CA mutated refractory cancers^{99,100}. In colorectal cancers, PIK3CA mutations predict significantly improved survival and reduced disease recurrence with adjuvant aspirin therapy, compared to no benefit in wild-type PIK3CA tumors^{65,73,101,102}.

KRAS p.(G12V) c.35G>T

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^{25,26,27}.

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 cancer⁸. The majority of KRAS mutations consist of point mutations occurring at G12, G13, and Q61^{8,28,29}. Mutations at A59, K117, and A146 have also been observed but are less frequent^{9,30}.

Biomarker Descriptions (continued)

Potential relevance: The FDA has approved the small molecule inhibitors, sotorasib³¹ (2021) and adagrasib³² (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 adenocarcinoma³³. The FDA has approved the combination of kinase inhibitors, avutometinib and defactinib³⁴ (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-6036³⁵, for KRAS G12C-mutated NSCLC. The KRAS-G12C/NRAS-G12C dual inhibitor, elironrasib³⁶, and the KRAS G12C inhibitor, D3S-001³⁷, 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. The KRAS-G12C inhibitor, olomorrasib³⁸, was granted breakthrough designation (2025) in combination with pembrolizumab³⁹ for unresectable advanced or metastatic NSCLC with a KRAS G12C mutation and PD-L1 expression $\geq 50\%$. The SHP2 inhibitor, BBP-398⁴⁰ was granted fast track designation (2022) in combination with sotorasib for previously treated patients with KRAS G12C-mutated metastatic NSCLC. The RAF/MEK clamp, avutometinib⁴¹ 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-8520⁴², was granted fast track designation in 2025 for previously treated KRAS G12C-mutated patients with metastatic NSCLC. The RAS inhibitor, daraxonrasib⁴³, was granted breakthrough designation (2025) for previously treated metastatic pancreatic cancer with KRAS G12 mutations. The KRAS G12D (ON/OFF) inhibitor, GFH-375⁴⁴, 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-001⁴⁵, was granted fast track designation in 2024 for KRAS G12C-mutated patients with advanced unresectable or metastatic colorectal cancers. The PLK1 inhibitor, onvansertib⁴⁶, 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, cetuximab⁴⁷ and panitumumab⁴⁸, 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)³⁰. Additionally, KRAS mutations are associated with poor prognosis in NSCLC⁴⁹.

ERBB2 p.(V842I) c.2524G>A

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) family¹⁸. Along with ERBB2/HER2, EGFR/ERBB1/HER1, ERBB3/HER3, and ERBB4/HER4 make up the HER protein family¹. All ERBB/HER proteins encode transmembrane receptor tyrosine kinases¹¹⁸. However, ERBB2/HER2 is an orphan receptor with no known ligand¹¹⁸. 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 survival¹¹⁹. Recurrent focal amplification of the ERBB2 gene leads to increased expression in several cancer types¹¹⁹. ERBB2 overexpression in immortalized cell lines is oncogenic and leads to ERBB2 homodimerization and activation without ligand binding^{120,121,122}.

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^{3,4,5,6,8,9,10,123}. 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)⁹. Recurrent somatic activating mutations in ERBB2/HER2 occur at low frequencies (<1%) in diverse cancer types^{9,124,125}. 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^{126,127}. Trastuzumab¹²⁸ 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 pertuzumab¹²⁹ (2012), a humanized monoclonal antibody that inhibits HER2 dimerization, and ado-trastuzumab emtansine¹³⁰ (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 cancer¹³¹. In addition to monoclonal antibodies, the small molecule inhibitor lapatinib¹³², 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 neratinib¹³³, 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 neratinib¹³³ in combination with capecitabine for HER2-positive advanced or metastatic patients after two or more prior HER2-directed therapies. Also in 2020, the TKI irbinitinib¹³⁴ 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 line³⁹. In 2024, a bispecific HER2 antibody, zanidatamab¹³⁵, was approved for the treatment of adults with previously treated, unresectable or metastatic ERBB2 overexpressing biliary tract cancer. In 2018 fast track designation was

Biomarker Descriptions (continued)

granted to the monoclonal antibody margetuximab¹³⁶ in patients with ERBB2 positive breast cancer previously treated with an anti-HER2 therapy. Additionally, in 2019, zanidatamab¹³⁷, 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 vedotin¹³⁸ (2020) received breakthrough designation for adult patients with HER2-positive urothelial cancer after previous platinum-chemotherapy treatment. In 2021, the antibody-drug conjugate ARX788¹³⁹ 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-2927088¹⁴⁰, 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^{141,142,143,144,145}. ERBB2 kinase domain mutations R896G and V659E both showed response to afatinib in two NSCLC case studies^{146,147}. Additionally, acquired HER2 mutations in estrogen receptor-positive (ER+) breast cancer have been shown to confer resistance to hormone therapy¹⁴⁸. However, this was shown to be overcome by neratinib in combination with therapies targeting ER¹⁴⁸. Additionally, in 2025, FDA approved zongertinib¹⁴⁹, 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, GLS1-100 (GP-2)¹⁵⁰, received fast track designation for the prevention of breast cancer recurrence following surgery.

APC p.(K560*) c.1678A>T, APC p.(R1450*) c.4348C>T

APC, WNT signaling pathway regulator

Background: The APC gene encodes the adenomatous polyposis coli tumor suppressor protein that plays a crucial role in regulating the β -catenin/WNT signaling pathway which is involved in cell migration, adhesion, proliferation, and differentiation¹⁰³. APC is an antagonist of WNT signaling as it targets β -catenin for proteasomal degradation^{104,105}. Germline mutations in APC are predominantly inactivating and result in an autosomal dominant predisposition for familial adenomatous polyposis (FAP) which is characterized by numerous polyps in the intestine^{103,106}. Acquiring a somatic mutation in APC is considered to be an early and possibly initiating event in colorectal cancer¹⁰⁷.

Alterations and prevalence: Somatic mutations in APC are observed in up to 65% of colorectal cancer, and in up to 15% of stomach adenocarcinoma and uterine corpus endometrial carcinoma^{6,8,9}. In colorectal cancer, ~60% of somatic APC mutations have been reported to occur in a mutation cluster region (MCR) resulting in C-terminal protein truncation and APC inactivation^{108,109}.

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

ERBB3 p.(E928G) c.2783A>G

erb-b2 receptor tyrosine kinase 3

Background: The ERBB3 gene encodes the erb-b2 receptor tyrosine kinase 3, a member of the human epidermal growth factor receptor (HER) family. Along with ERBB3/HER3, EGFR/ERBB1/HER1, ERBB2/HER2, and ERBB4/HER4 make up the HER protein family¹. ERBB3/HER3 binds to extracellular factors, such as neuregulins, but has an impaired kinase domain². Upon ligand binding, ERBB3 forms hetero-dimers with other ERBB/HER family members, including ERBB2/HER2 resulting in activation of tyrosine kinase activity primarily through its dimerization partner.

Alterations and prevalence: ERBB3 gene amplification leading to an increase in expression occurs at low frequency (1-5%) in several cancer types including bladder, esophagus, lung adenocarcinoma, ovarian, pancreas, sarcoma, stomach, and uterine cancers^{3,4,5,6,7,8,9}. ERBB3 is also the target of relatively frequent (5-10%) and recurrent somatic mutations in diverse cancer types including bladder, cervical, colorectal, and stomach cancers^{3,6,8,9,10}. Recurrent ERBB3 mutations such as V104L/M, occur primarily in the extracellular domain.

Potential relevance: Currently, no therapies are approved for ERBB3 aberrations. Overexpression and activation of ERBB3/HER3 is one mechanism of acquired resistance to therapies targeting EGFR and ERBB2/HER2^{11,12}. Preclinical and translational research studies have characterized the oncogenic potential of recurrent ERBB3 mutations and their sensitivity to anti-ERBB antibodies and small molecule inhibitors^{13,14,15,16}. A phase I study exhibited progression-free survival (PFS) of 2.5 months and overall survival (OS) of 9 months in 25 patients with ERBB3 mutations treated by anti-ERBB antibodies or molecular-targeted agents¹⁷.

FANCG c.307+1G>C

Fanconi anemia complementation group G

Background: The FANCG gene encodes the FA complementation group G protein, a member of Fanconi Anemia (FA) family, which also includes FANCA, FANCB, FANCC, FANCD1 (BRCA2), FANCD2, FANCE, FANCF, FANCI, FANCJ (BRIP1), FANCL, FANCM and FANCN (PALB2)¹⁸. FA genes are tumor suppressors that are responsible for the maintenance of replication fork stability, DNA damage repair through the removal of interstrand cross-links (ICL), and subsequent initiation of the homologous recombination repair (HRR)

Biomarker Descriptions (continued)

pathway^{110,111}. In response to DNA damage, FANCA, FANCB, FANCC, FANCE, FANCF, FANCG, FANCL, and FANCM assemble to form the FA core complex which is responsible for the monoubiquitination of the FANCI-FANCD2 (ID2) complex¹¹⁰. Monoubiquitination of the ID2 complex promotes co-localization with BRCA1/2, which is critical in BRCA mediated DNA repair^{112,113}. Loss of function mutations in the FA family and HRR pathway can result in the BRCAneSS phenotype, characterized by a defect in the HRR pathway, mimicking BRCA1 or BRCA2 loss^{114,115}. Germline mutations in FA genes lead to Fanconi Anemia, a condition characterized by chromosomal instability and congenital abnormalities, including bone marrow failure and cancer predisposition^{116,117}.

Alterations and prevalence: Somatic mutations in FANCG are observed in 3% of uterine corpus endometrial carcinoma and skin cutaneous melanoma, and 2% of diffuse large B-cell lymphoma (DLBCL), uterine carcinosarcoma, and colorectal adenocarcinoma^{8,9}.

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

Microsatellite stable

Background: Microsatellites are short tandem repeats (STR) of 1 to 6 bases of DNA between 5 to 50 repeat units in length. There are approximately 0.5 million STRs that occupy 3% of the human genome⁵⁸. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue^{59,60}. MSI is closely tied to the status of the mismatch repair (MMR) genes. In humans, the core MMR genes include MLH1, MSH2, MSH6, and PMS2⁶¹. Mutations and loss of expression in MMR genes, known as defective MMR (dMMR), lead to MSI. In contrast, when MMR genes lack alterations, they are referred to as MMR proficient (pMMR). Consensus criteria were first described in 1998 and defined MSI-high (MSI-H) as instability in two or more of the following five markers: BAT25, BAT26, D5S346, D2S123, and D17S250⁶². Tumors with instability in one of the five markers were defined as MSI-low (MSI-L) whereas, those with instability in zero markers were defined as MS-stable (MSS)⁶². Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS^{63,64,65,66,67}. MSI-H is a hallmark of Lynch syndrome (LS), also known as hereditary non-polyposis colorectal cancer, which is caused by germline mutations in the MMR genes⁶⁰. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer^{59,60,64,68}.

Alterations and prevalence: The MSI-H phenotype is observed in 30% of uterine corpus endothelial carcinoma, 20% of stomach adenocarcinoma, 15-20% of colon adenocarcinoma, and 5-10% of rectal adenocarcinoma^{59,60,69,70}. MSI-H is also observed in 5% of adrenal cortical carcinoma and at lower frequencies in other cancers such as esophageal, liver, and ovarian cancers^{69,70}.

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab³⁹ (2014) and nivolumab⁷¹ (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab³⁹ is also approved as a single agent, for the treatment of patients with advanced endometrial carcinoma that is MSI-H or dMMR with disease progression on prior therapy who are not candidates for surgery or radiation. Importantly, pembrolizumab is approved for the treatment of MSI-H or dMMR solid tumors that have progressed following treatment, with no alternative option and is the first anti-PD-1 inhibitor to be approved with a tumor agnostic indication³⁹. Dostarlimab⁷² (2021) is also approved for dMMR recurrent or advanced endometrial carcinoma or solid tumors that have progressed on prior treatment and is recommended as a subsequent therapy option in dMMR/MSI-H advanced or metastatic colon or rectal cancer^{65,73}. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab⁷⁴ (2011), is approved alone or in combination with nivolumab in MSI-H or dMMR colorectal cancer that has progressed following treatment with chemotherapy. MSI-H may confer a favorable prognosis in colorectal cancer although outcomes vary depending on stage and tumor location^{65,75,76}. Specifically, MSI-H is a strong prognostic indicator of better overall survival (OS) and relapse free survival (RFS) in stage II as compared to stage III colorectal cancer patients⁷⁶. The majority of patients with tumors classified as either MSS or pMMR do not benefit from treatment with single-agent immune checkpoint inhibitors as compared to those with MSI-H tumors^{77,78}. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers^{77,78}.

ELF3 p.(D195*) c.582_583insT

E74 like ETS transcription factor 3

Background: The ELF3 gene encodes the E74 like ETS transcription factor 3 protein¹⁸. ELF3 is a transcription factor that has been observed to function as a negative regulator of the epithelial-mesenchymal transition (EMT) process, specifically in ovarian cancer cells⁵⁶. ELF3 has also been proposed to act as an antagonist of oncogenic-signaling induced ZEB1 expression in colorectal cancer, supporting a tumor suppressor role for ELF3^{56,57}.

Alterations and prevalence: Somatic mutations in ELF3 are observed in 13% of bladder urothelial carcinoma, 6% of cholangiocarcinoma, 3% of stomach adenocarcinoma and skin cutaneous melanoma, and 2% of colorectal adenocarcinoma, uterine corpus endometrial carcinoma, and cervical squamous cell carcinoma^{8,9}.

Potential relevance: Currently, no therapies are approved for ELF3 aberrations.

Biomarker Descriptions (continued)

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^{18,151}. UGTs are microsomal membrane-bound enzymes that catalyze the glucuronidation of endogenous and xenobiotic compounds and transform the lipophilic molecules into excretable, hydrophilic metabolites^{151,152}. 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 resistance¹⁵³. 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^{153,154,155,156}. 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-38¹⁵⁷.

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^{8,9}.

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

HLA-B deletion

major histocompatibility complex, class I, B

Background: The HLA-B gene encodes the major histocompatibility complex, class I, B¹⁸. 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 cells¹⁹. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M²⁰. 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^{21,22,23}. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-B²⁴.

Alterations and prevalence: Somatic mutations in HLA-B are observed in 10% of diffuse large B-cell lymphoma (DLBCL), 5% of cervical squamous cell carcinoma and stomach adenocarcinoma, 4% of head and neck squamous cell carcinoma and colorectal adenocarcinoma, 3% of uterine cancer, and 2% of esophageal adenocarcinoma and skin cutaneous melanoma^{8,9}. Biallelic loss of HLA-B is observed in 5% of DLBCL^{8,9}.

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

SMAD2 p.(S464*) c.1391C>G, SMAD2 p.(Q284*) c.850C>T

SMAD family member 2

Background: The SMAD2 gene encodes the SMAD family member 2, a transcription factor that belongs to a family of 8 SMAD genes that can be divided into three main classes^{18,50,51}. SMAD1, SMAD2, SMAD3, SMAD5, and SMAD8 are part of the regulator SMAD (R-SMAD) class while SMAD4 belongs to the common mediator SMAD (co-SMAD) class. The inhibitory SMAD (I-SMAD) class includes both SMAD6 and SMAD7^{50,51}. As part of the R-SMAD class, SMAD2 functions by mediating signal transmission in the transforming growth factor beta (TGF- β) signaling pathway, a pathway critical in cell growth, differentiation, and tumor development⁵¹. Following activation of type I TGF- β receptors, SMAD2 and SMAD3 are activated via phosphorylation and form a complex with SMAD4, leading to nuclear translocation and activation or repression of target genes^{52,53}. Deregulation of SMAD2, including mutation and loss of expression, has been observed in cancer leading to disruption of SMAD2/3/4 complex formation and tumorigenesis, supporting a tumor suppressor role for SMAD2^{53,54}.

Alterations and prevalence: Somatic mutations in SMAD2 are observed in 5% of uterine corpus endometrial carcinoma and colorectal adenocarcinoma, 3% of skin cutaneous melanoma, and 2% of stomach adenocarcinoma and lung adenocarcinoma^{8,9}. The nonsense, truncating mutation, p.S464*, is the most commonly observed alteration and is recurrent^{8,9,53}. Two recurrent hotspot mutations R321 and P305 occur in the mad homology 2 (MH2) domain leading to the disruption of the heterotrimeric SMAD2/SMAD3-SMAD4 complex^{8,9,55}. SMAD2 deletion is observed in 4% of esophageal adenocarcinoma and 3% of pancreatic adenocarcinoma^{8,9}.

Potential relevance: Currently, no therapies are approved for SMAD2 aberrations.

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.

KRAS p.(G12V) c.35G>T

cetuximab

Cancer type: Colorectal Cancer

Label as of: 2021-09-24

Variant class: KRAS G12 mutation

Indications and usage:

Erbxitux® 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

KRAS p.(G12V) c.35G>T (continued)

🚫 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

👉 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>

ERBB2 p.(V842I) c.2524G>A

👉 sevabertinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: ERBB2 activating mutation

Supporting Statement:

The FDA has granted Breakthrough Therapy designation to an oral, reversible tyrosine kinase inhibitor and EGFR antagonist, sevabertinib (BAY 2927088), for the treatment of adult patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations, and who have received a prior systemic therapy.

Reference:

<https://www.bayer.com/en/us/news-stories/sevabertinib>

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.

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.(G12V) c.35G>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 4.2025]

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]

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]

KRAS p.(G12V) c.35G>T (continued)

🚫 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.(G12V) c.35G>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: 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.

KRAS p.(G12V) c.35G>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 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)]

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, 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, SNCAP, SOS1, SOX2, SPOP, SRC, SRSF2, STAT3, STAT5B, STAT6, TAF1, TERT, TGFBR1, TOP1, TOP2A, TPMT, TRRAP, TSHR, U2AF1, USP8, WAS, XPO1, 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, CBF, 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, ERF1, 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, SLC01B3, 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, 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, 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, RSP02, RSP03, 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, CBF, 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, ERF1, 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, TP53, 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

PIK3CA p.(M1043I) c.3129G>T

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
capivasertib + fulvestrant	○	○	○	✗	✗
inavolisib + palbociclib + fulvestrant	○	○	✗	✗	✗
aspirin	✗	◐	✗	✗	✗
ETX-636	✗	✗	✗	✗	● (I/II)
HTL-0039732, atezolizumab	✗	✗	✗	✗	● (I/II)
JS-105	✗	✗	✗	✗	● (I)
SNV-4818, hormone therapy	✗	✗	✗	✗	● (I)

KRAS p.(G12V) c.35G>T

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
avutometinib + defactinib	○	○	✗	✗	✗
bevacizumab + CAPOX	✗	✗	✗	●	✗
bevacizumab + FOLFIRI	✗	✗	✗	●	✗
bevacizumab + FOLFOX	✗	✗	✗	●	✗
bevacizumab + FOLFOXIRI	✗	✗	✗	●	✗
bevacizumab, chemotherapy	✗	✗	✗	✗	● (III)
fruquintinib, chemotherapy	✗	✗	✗	✗	● (II)
regorafenib	✗	✗	✗	✗	● (II)
tunlametinib, vemurafenib	✗	✗	✗	✗	● (II)
almonertinib, palbociclib	✗	✗	✗	✗	● (I/II)
anti-KRAS G12V mTCR, chemotherapy, aldesleukin	✗	✗	✗	✗	● (I/II)
ERAS-0015	✗	✗	✗	✗	● (I/II)
YL-15293	✗	✗	✗	✗	● (I/II)
ASP-5834	✗	✗	✗	✗	● (I)
BPI-442096	✗	✗	✗	✗	● (I)
daraxonrasib	✗	✗	✗	✗	● (I)
imatinib, trametinib	✗	✗	✗	✗	● (I)
IX-001	✗	✗	✗	✗	● (I)
JAB-3312	✗	✗	✗	✗	● (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

KRAS p.(G12V) c.35G>T (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
KRAS TCR, aldesleukin, SLATE 001, chemotherapy	✖	✖	✖	✖	● (I)
KRAS-EphA-2-CAR-DC, anti-PD-1, ipilimumab	✖	✖	✖	✖	● (I)
Nest-1	✖	✖	✖	✖	● (I)
NW-301V	✖	✖	✖	✖	● (I)

ERBB2 p.(V842I) c.2524G>A

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
zongertinib	○	○	✖	✖	● (II)
trastuzumab deruxtecan	○	✖	○	✖	● (II)
pertuzumab + trastuzumab	✖	✖	✖	✖	● (II/III)
sevabertinib	✖	✖	✖	✖	● (II)
tucatinib, ado-trastuzumab emtansine	✖	✖	✖	✖	● (II)
DF-1001, nivolumab	✖	✖	✖	✖	● (I/II)
trastuzumab deruxtecan, neratinib	✖	✖	✖	✖	● (I/II)
ado-trastuzumab emtansine (Shanghai Fosun Pharma)	✖	✖	✖	✖	● (I)
ENT-H-1, trastuzumab	✖	✖	✖	✖	● (I)

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

HRR Details

Gene/Genomic Alteration	Finding
Not Detected	Not Applicable

Homologous recombination repair (HRR) genes were defined from published evidence in relevant therapies, clinical guidelines, as well as clinical trials, and include - BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, and RAD54L.

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.

References

1. King et al. Amplification of a novel v-erbB-related gene in a human mammary carcinoma. *Science*. 1985 Sep 6;229(4717):974-6. PMID: 2992089
2. Knighton et al. Structural features that specify tyrosine kinase activity deduced from homology modeling of the epidermal growth factor receptor. *Proc. Natl. Acad. Sci. U.S.A.* 1993 Jun 1;90(11):5001-5. PMID: 8389462
3. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of urothelial bladder carcinoma. *Nature*. 2014 Mar 20;507(7492):315-22. doi: 10.1038/nature12965. Epub 2014 Jan 29. PMID: 24476821
4. Cancer Genome Atlas Research Network. Comprehensive molecular profiling of lung adenocarcinoma. *Nature*. 2014 Jul 31;511(7511):543-50. doi: 10.1038/nature13385. Epub 2014 Jul 9. PMID: 25079552
5. Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. *Nature*. 2011 Jun 29;474(7353):609-15. PMID: 21720365
6. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature*. 2014 Sep 11;513(7517):202-9. doi: 10.1038/nature13480. Epub 2014 Jul 23. PMID: 25079317
7. Cancer et al. Integrated genomic characterization of endometrial carcinoma. *Nature*. 2013 May 2;497(7447):67-73. PMID: 23636398
8. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. *Nat. Genet.* 2013 Oct;45(10):1113-20. PMID: 24071849
9. Cerami et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. *Cancer Discov.* 2012 May;2(5):401-4. PMID: 22588877
10. Donna et al. Comprehensive molecular characterization of human colon and rectal cancer. *Nature*. 2012 Jul 18;487(7407):330-7. PMID: 22810696
11. Mujoo et al. Regulation of ERBB3/HER3 signaling in cancer. *Oncotarget*. 2014 Nov 15;5(21):10222-36. PMID: 25400118
12. Gaborit et al. Emerging anti-cancer antibodies and combination therapies targeting HER3/ERBB3. *Hum Vaccin Immunother*. 2016 Mar 3;12(3):576-92. PMID: 26529100
13. Mishra et al. Genomic alterations of ERBB receptors in cancer: clinical implications. *Oncotarget*. 2017 Dec 26;8(69):114371-114392. PMID: 29371993
14. Jaiswal et al. Oncogenic ERBB3 mutations in human cancers. *Cancer Cell*. 2013 May 13;23(5):603-17. PMID: 23680147
15. Zhang et al. HER3/ErbB3, an emerging cancer therapeutic target. *Acta Biochim. Biophys. Sin. (Shanghai)*. 2016 Jan;48(1):39-48. PMID: 26496898
16. Ross et al. Targeting HER2 in colorectal cancer: The landscape of amplification and short variant mutations in ERBB2 and ERBB3. *Cancer*. 2018 Apr 1;124(7):1358-1373. PMID: 29338072
17. Verlingue et al. Human epidermal receptor family inhibitors in patients with ERBB3 mutated cancers: Entering the back door. *Eur. J. Cancer*. 2018 Mar;92:1-10. PMID: 29413684
18. O'Leary et al. Reference sequence (RefSeq) database at NCBI: current status, taxonomic expansion, and functional annotation. *Nucleic Acids Res.* 2016 Jan 4;44(D1):D733-45. PMID: 26553804
19. Hulpke et al. The MHC I loading complex: a multitasking machinery in adaptive immunity. *Trends Biochem Sci.* PMID: 23849087
20. Adams et al. The adaptable major histocompatibility complex (MHC) fold: structure and function of nonclassical and MHC class I-like molecules. *Annu Rev Immunol.* 2013;31:529-61. PMID: 23298204
21. Rossjohn et al. T cell antigen receptor recognition of antigen-presenting molecules. *Annu Rev Immunol.* 2015;33:169-200. PMID: 25493333
22. Parham. MHC class I molecules and KIRs in human history, health and survival. *Nat Rev Immunol*. 2005 Mar;5(3):201-14. PMID: 15719024
23. Sidney et al. HLA class I supertypes: a revised and updated classification. *BMC Immunol*. 2008 Jan 22;9:1. PMID: 18211710
24. Cornel et al. MHC Class I Downregulation in Cancer: Underlying Mechanisms and Potential Targets for Cancer Immunotherapy. *Cancers (Basel)*. 2020 Jul 2;12(7). PMID: 32630675
25. Pylayeva-Gupta et al. RAS oncogenes: weaving a tumorigenic web. *Nat. Rev. Cancer*. 2011 Oct 13;11(11):761-74. PMID: 21993244
26. Karnoub et al. Ras oncogenes: split personalities. *Nat. Rev. Mol. Cell Biol.* 2008 Jul;9(7):517-31. PMID: 18568040
27. Scott et al. Therapeutic Approaches to RAS Mutation. *Cancer J.* 2016 May-Jun;22(3):165-74. doi: 10.1097/PPO.0000000000000187. PMID: 27341593
28. Román et al. KRAS oncogene in non-small cell lung cancer: clinical perspectives on the treatment of an old target. *Mol Cancer*. 2018 Feb 19;17(1):33. doi: 10.1186/s12943-018-0789-x. PMID: 29455666
29. Dinu et al. Prognostic significance of KRAS gene mutations in colorectal cancer--preliminary study. *J Med Life*. 2014 Oct-Dec;7(4):581-7. PMID: 25713627

References (continued)

30. Allegra et al. Extended RAS Gene Mutation Testing in Metastatic Colorectal Carcinoma to Predict Response to Anti-Epidermal Growth Factor Receptor Monoclonal Antibody Therapy: American Society of Clinical Oncology Provisional Clinical Opinion Update 2015. *J. Clin. Oncol.* 2016 Jan 10;34(2):179-85. PMID: 26438111
31. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/2146650orig1s009correctedlbl.pdf
32. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/216340s005lbl.pdf
33. NCCN Guidelines® - NCCN-Pancreatic Adenocarcinoma [Version 2.2025]
34. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/219616s000lbl.pdf
35. <https://assets.cwp.roche.com/f/126832/x/5738a7538b/irp230202.pdf>
36. <https://ir.revmed.com/node/11881/pdf>
37. <https://www.prnewswire.com/news-releases/d3-bio-inc-announces-fda-breakthrough-therapy-designation-and-orphan-drug-designation-for-d3s-001-for-the-treatment-of-patients-with-kras-g12c-mutated-cancers-302540808.html>
38. <https://www.prnewswire.com/news-releases/lillys-olomorasisib-receives-us-fdas-breakthrough-therapy-designation-for-the-treatment-of-certain-newly-diagnosed-metastatic-kras-g12c-mutant-lung-cancers-302545643.html>
39. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125514s178lbl.pdf
40. <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/>
41. <https://investor.verastem.com/news-releases/news-release-details/verastem-oncology-granted-fast-track-designation-combination>
42. <https://www.businesswire.com/news/home/20250109170439/en/>
43. <https://ir.revmed.com/news-releases/news-release-details/revolution-medicines-announces-fda-breakthrough-therapy>
44. <https://investor.verastem.com/news-releases/news-release-details/verastem-oncology-granted-fast-track-designation-vs-7375>
45. <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>
46. https://cardiffoncology.com/wp-content/uploads/2021/07/Cardiff_Oncology_Investor_Presentation_-July_2021.pdf
47. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125084s279lbl.pdf
48. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125147s213lbl.pdf
49. Slebos et al. K-ras oncogene activation as a prognostic marker in adenocarcinoma of the lung. *N. Engl. J. Med.* 1990 Aug 30;323(9):561-5. PMID: 2199829
50. Ahmed et al. The TGF-β/Smad4 Signaling Pathway in Pancreatic Carcinogenesis and Its Clinical Significance. *J Clin Med.* 2017 Jan 5;6(1). PMID: 28067794
51. Zhao et al. The role of TGF-β/SMAD4 signaling in cancer. *Int. J. Biol. Sci.* 2018;14(2):111-123. PMID: 29483830
52. Massagué et al. Smad transcription factors. *Genes Dev.* 2005 Dec 1;19(23):2783-810. PMID: 16322555
53. Fleming et al. SMAD2, SMAD3 and SMAD4 mutations in colorectal cancer. *Cancer Res.* 2013 Jan 15;73(2):725-35. PMID: 23139211
54. Fukuchi et al. Lack of activated Smad2 in transforming growth factor-beta signaling is an unfavorable prognostic factor in patients with esophageal squamous cell carcinoma. *J Surg Oncol.* 2006 Jul 1;94(1):51-6. PMID: 16788944
55. Galka-Marciniak et al. A pan-cancer atlas of somatic mutations in miRNA biogenesis genes. *Nucleic Acids Res.* 2021 Jan 25;49(2):601-620. PMID: 33406242
56. Li et al. IRF6 Is Directly Regulated by ZEB1 and ELF3, and Predicts a Favorable Prognosis in Gastric Cancer. *Front Oncol.* 2019;9:220. PMID: 31019894
57. Liu et al. ELF3 is an antagonist of oncogenic-signalling-induced expression of EMT-TF ZEB1. *Cancer Biol Ther.* 2019;20(1):90-100. PMID: 30148686
58. Lander et al. Initial sequencing and analysis of the human genome. *Nature.* 2001 Feb 15;409(6822):860-921. PMID: 11237011
59. Baudrin et al. Molecular and Computational Methods for the Detection of Microsatellite Instability in Cancer. *Front Oncol.* 2018 Dec 12;8:621. doi: 10.3389/fonc.2018.00621. eCollection 2018. PMID: 30631754
60. Nojadeh et al. Microsatellite instability in colorectal cancer. *EXCLI J.* 2018;17:159-168. PMID: 29743854
61. Saeed et al. Microsatellites in Pursuit of Microbial Genome Evolution. *Front Microbiol.* 2016 Jan 5;6:1462. doi: 10.3389/fmicb.2015.01462. eCollection 2015. PMID: 26779133

References (continued)

62. Boland et al. A National Cancer Institute Workshop on Microsatellite Instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer. *Cancer Res.* 1998 Nov 15;58(22):5248-57. PMID: 9823339
63. Halford et al. Low-level microsatellite instability occurs in most colorectal cancers and is a nonrandomly distributed quantitative trait. *Cancer Res.* 2002 Jan 1;62(1):53-7. PMID: 11782358
64. Imai et al. Carcinogenesis and microsatellite instability: the interrelationship between genetics and epigenetics. *Carcinogenesis.* 2008 Apr;29(4):673-80. PMID: 17942460
65. NCCN Guidelines® - NCCN-Colon Cancer [Version 4.2025]
66. Pawlik et al. Colorectal carcinogenesis: MSI-H versus MSI-L. *Dis. Markers.* 2004;20(4-5):199-206. PMID: 15528785
67. Lee et al. Low-Level Microsatellite Instability as a Potential Prognostic Factor in Sporadic Colorectal Cancer. *Medicine (Baltimore).* 2015 Dec;94(50):e2260. PMID: 26683947
68. Latham et al. Microsatellite Instability Is Associated With the Presence of Lynch Syndrome Pan-Cancer. *J. Clin. Oncol.* 2019 Feb 1;37(4):286-295. PMID: 30376427
69. Cortes-Ciriano et al. A molecular portrait of microsatellite instability across multiple cancers. *Nat Commun.* 2017 Jun 6;8:15180. doi: 10.1038/ncomms15180. PMID: 28585546
70. Bonneville et al. Landscape of Microsatellite Instability Across 39 Cancer Types. *JCO Precis Oncol.* 2017;2017. PMID: 29850653
71. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125554s131lbl.pdf
72. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761174s009lbl.pdf
73. NCCN Guidelines® - NCCN-Rectal Cancer [Version 3.2025]
74. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125377s136lbl.pdf
75. Ribic et al. Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. *N. Engl. J. Med.* 2003 Jul 17;349(3):247-57. PMID: 12867608
76. Klingbiel et al. Prognosis of stage II and III colon cancer treated with adjuvant 5-fluorouracil or FOLFIRI in relation to microsatellite status: results of the PETACC-3 trial. *Ann. Oncol.* 2015 Jan;26(1):126-32. PMID: 25361982
77. Hermel et al. The Emerging Role of Checkpoint Inhibition in Microsatellite Stable Colorectal Cancer. *J Pers Med.* 2019 Jan 16;9(1). PMID: 30654522
78. Ciardiello et al. Immunotherapy of colorectal cancer: Challenges for therapeutic efficacy. *Cancer Treat. Rev.* 2019 Jun;76:22-32. PMID: 31079031
79. Volinia et al. Molecular cloning, cDNA sequence, and chromosomal localization of the human phosphatidylinositol 3-kinase p110 alpha (PIK3CA) gene. *Genomics.* 1994 Dec;24(3):472-7. PMID: 7713498
80. Whale et al. Functional characterization of a novel somatic oncogenic mutation of PIK3CB. *Signal Transduct Target Ther.* 2017;2:17063. PMID: 29279775
81. Osaki et al. PI3K-Akt pathway: its functions and alterations in human cancer. *Apoptosis.* 2004 Nov;9(6):667-76. PMID: 15505410
82. Cantley. The phosphoinositide 3-kinase pathway. *Science.* 2002 May 31;296(5573):1655-7. PMID: 12040186
83. Fruman et al. The PI3K Pathway in Human Disease. *Cell.* 2017 Aug 10;170(4):605-635. PMID: 28802037
84. Engelman et al. The evolution of phosphatidylinositol 3-kinases as regulators of growth and metabolism. *Nat. Rev. Genet.* 2006 Aug;7(8):606-19. PMID: 16847462
85. Vanhaesebroeck et al. PI3K signalling: the path to discovery and understanding. *Nat. Rev. Mol. Cell Biol.* 2012 Feb 23;13(3):195-203. PMID: 22358332
86. Yuan et al. PI3K pathway alterations in cancer: variations on a theme. *Oncogene.* 2008 Sep 18;27(41):5497-510. PMID: 18794884
87. Liu et al. Targeting the phosphoinositide 3-kinase pathway in cancer. *Nat Rev Drug Discov.* 2009 Aug;8(8):627-44. PMID: 19644473
88. Hanahan et al. Hallmarks of cancer: the next generation. *Cell.* 2011 Mar 4;144(5):646-74. PMID: 21376230
89. Brito et al. PIK3CA Mutations in Diffuse Gliomas: An Update on Molecular Stratification, Prognosis, Recurrence, and Aggressiveness. *Clin Med Insights Oncol.* 2022;16:11795549211068804. PMID: 35023985
90. Huret et al. Atlas of genetics and cytogenetics in oncology and haematology in 2013. *Nucleic Acids Res.* 2013 Jan;41(Database issue):D920-4. PMID: 23161685
91. Miled et al. Mechanism of two classes of cancer mutations in the phosphoinositide 3-kinase catalytic subunit. *Science.* 2007 Jul 13;317(5835):239-42. PMID: 17626883
92. Burke et al. Synergy in activating class I PI3Ks. *Trends Biochem. Sci.* 2015 Feb;40(2):88-100. PMID: 25573003

References (continued)

93. Burke et al. Oncogenic mutations mimic and enhance dynamic events in the natural activation of phosphoinositide 3-kinase p110 α (PIK3CA). *Proc. Natl. Acad. Sci. U.S.A.* 2012 Sep 18;109(38):15259-64. PMID: 22949682
94. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/212526s009lbl.pdf
95. Mayer et al. A Phase Ib Study of Alpelisib (BYL719), a PI3K α -Specific Inhibitor, with Letrozole in ER+/HER2- Metastatic Breast Cancer. *Clin. Cancer Res.* 2017 Jan 1;23(1):26-34. PMID: 27126994
96. Mayer et al. A Phase II Randomized Study of Neoadjuvant Letrozole Plus Alpelisib for Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Breast Cancer (NEO-ORB). *Clin. Cancer Res.* 2019 Feb 5. PMID: 30723140
97. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/218197s002lbl.pdf
98. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/219249s002lbl.pdf
99. Jung et al. Pilot study of sirolimus in patients with PIK3CA mutant/amplified refractory solid cancer. *Mol Clin Oncol.* 2017 Jul;7(1):27-31. PMID: 28685070
100. Janku et al. PIK3CA mutations in patients with advanced cancers treated with PI3K/AKT/mTOR axis inhibitors. *Mol. Cancer Ther.* 2011 Mar;10(3):558-65. PMID: 21216929
101. Liao et al. Aspirin use, tumor PIK3CA mutation, and colorectal-cancer survival. *N Engl J Med.* 2012 Oct 25;367(17):1596-606. PMID: 23094721
102. Domingo et al. Evaluation of PIK3CA mutation as a predictor of benefit from nonsteroidal anti-inflammatory drug therapy in colorectal cancer. *J Clin Oncol.* 2013 Dec 1;31(34):4297-305. PMID: 24062397
103. Wang et al. Loss of Tumor Suppressor Gene Function in Human Cancer: An Overview. *Cell. Physiol. Biochem.* 2018;51(6):2647-2693. PMID: 30562755
104. Stamos et al. The β -catenin destruction complex. *Cold Spring Harb Perspect Biol.* 2013 Jan 1;5(1):a007898. PMID: 23169527
105. Minde et al. Messing up disorder: how do missense mutations in the tumor suppressor protein APC lead to cancer?. *Mol Cancer.* 2011 Aug 22;10:101. doi: 10.1186/1476-4598-10-101. PMID: 21859464
106. Aoki et al. Adenomatous polyposis coli (APC): a multi-functional tumor suppressor gene. *J. Cell. Sci.* 2007 Oct 1;120(Pt 19):3327-35. PMID: 17881494
107. Miyoshi et al. Somatic mutations of the APC gene in colorectal tumors: mutation cluster region in the APC gene. *Hum. Mol. Genet.* 1992 Jul;1(4):229-33. PMID: 1338904
108. Rowan et al. APC mutations in sporadic colorectal tumors: A mutational "hotspot" and interdependence of the "two hits". *Proc. Natl. Acad. Sci. U.S.A.* 2000 Mar 28;97(7):3352-7. PMID: 10737795
109. Laurent-Puig et al. APC gene: database of germline and somatic mutations in human tumors and cell lines. *Nucleic Acids Res.* 1998 Jan 1;26(1):269-70. PMID: 9399850
110. Niraj et al. The Fanconi Anemia Pathway in Cancer. *Annu Rev Cancer Biol.* 2019 Mar;3:457-478. PMID: 30882047
111. Rodríguez et al. Fanconi anemia pathway. *Curr Biol.* 2017 Sep 25;27(18):R986-R988. PMID: 28950089
112. Garcia-Higuera et al. Interaction of the Fanconi anemia proteins and BRCA1 in a common pathway. *Mol. Cell.* 2001 Feb;7(2):249-62. PMID: 11239454
113. Hussain et al. Direct interaction of FANCD2 with BRCA2 in DNA damage response pathways. *Hum. Mol. Genet.* 2004 Jun 15;13(12):1241-8. PMID: 15115758
114. Lord et al. BRCAness revisited. *Nat. Rev. Cancer.* 2016 Feb;16(2):110-20. PMID: 26775620
115. Byrum et al. Defining and Modulating 'BRCAness'. *Trends Cell Biol.* 2019 Sep;29(9):740-751. PMID: 31362850
116. Michl et al. Interplay between Fanconi anemia and homologous recombination pathways in genome integrity. *EMBO J.* 2016 May 2;35(9):909-23. PMID: 27037238
117. Abbasi et al. A rare FANCA gene variation as a breast cancer susceptibility allele in an Iranian population. *Mol Med Rep.* 2017 Jun;15(6):3983-3988. PMID: 28440412
118. Hsu et al. The role of HER2, EGFR, and other receptor tyrosine kinases in breast cancer. *Cancer Metastasis Rev.* 2016 Dec;35(4):575-588. PMID: 27913999
119. Gutierrez et al. HER2: biology, detection, and clinical implications. *Arch. Pathol. Lab. Med.* 2011 Jan;135(1):55-62. PMID: 21204711
120. Di et al. erbB-2 is a potent oncogene when overexpressed in NIH/3T3 cells. *Science.* 1987 Jul 10;237(4811):178-82. PMID: 2885917
121. Hudziak et al. Increased expression of the putative growth factor receptor p185HER2 causes transformation and tumorigenesis of NIH 3T3 cells. *Proc. Natl. Acad. Sci. U.S.A.* 1987 Oct;84(20):7159-63. PMID: 2890160

References (continued)

122. Lonardo et al. The normal erbB-2 product is an atypical receptor-like tyrosine kinase with constitutive activity in the absence of ligand. *New Biol.* 1990 Nov;2(11):992-1003. PMID: 1983208
123. Ciriello et al. Comprehensive Molecular Portraits of Invasive Lobular Breast Cancer. *Cell.* 2015 Oct 8;163(2):506-19. PMID: 26451490
124. Petrelli et al. Clinical and pathological characterization of HER2 mutations in human breast cancer: a systematic review of the literature. *Breast Cancer Res. Treat.* 2017 Nov;166(2):339-349. PMID: 28762010
125. Bose et al. Activating HER2 mutations in HER2 gene amplification negative breast cancer. *Cancer Discov.* 2013 Feb;3(2):224-37. doi: 10.1158/2159-8290.CD-12-0349. Epub 2012 Dec 7. PMID: 23220880
126. Hudis. Trastuzumab--mechanism of action and use in clinical practice. *N. Engl. J. Med.* 2007 Jul 5;357(1):39-51. PMID: 17611206
127. Slamon et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science.* 1987 Jan 9;235(4785):177-82. PMID: 3798106
128. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/103792s5354lbl.pdf
129. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125409s139lbl.pdf
130. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125427s121lbl.pdf
131. NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2025]
132. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/022059s031lbl.pdf
133. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/208051s009lbl.pdf
134. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/213411s004lbl.pdf
135. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2024/761416Orig1s000Lbl.pdf
136. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761150s005lbl.pdf
137. <https://www.targetedonc.com/view/her2targeted-antibody-zw25-earns-fda-fast-track-designation-in-gea>
138. <https://www.prnewswire.com/news-releases/remegen-announces-us-fda-has-granted-breakthrough-therapy-designation-for-disitamab-vedotin-rc48-in-urothelial-cancer-301138315.html>
139. <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>
140. <https://www.bayer.com/en/us/news-stories/sevabertinib>
141. Ma et al. Neratinib Efficacy and Circulating Tumor DNA Detection of HER2 Mutations in HER2 Nonamplified Metastatic Breast Cancer. *Clin. Cancer Res.* 2017 Oct 1;23(19):5687-5695. PMID: 28679771
142. De et al. Clinical activity of afatinib (BIBW 2992) in patients with lung adenocarcinoma with mutations in the kinase domain of HER2/neu. *Lung Cancer.* 2012 Apr;76(1):123-7. PMID: 22325357
143. Kris et al. Targeting HER2 aberrations as actionable drivers in lung cancers: phase II trial of the pan-HER tyrosine kinase inhibitor dacitinib in patients with HER2-mutant or amplified tumors. *Ann. Oncol.* 2015 Jul;26(7):1421-7. PMID: 25899785
144. Falchook et al. Non-small-cell lung cancer with HER2 exon 20 mutation: regression with dual HER2 inhibition and anti-VEGF combination treatment. *J Thorac Oncol.* 2013 Feb;8(2):e19-20. PMID: 23328556
145. David et al. Neratinib in HER2- or HER3-mutant solid tumors: SUMMIT, a global, multi-histology, open-label, phase 2 'basket' study. *AACR* 2017. Abstract CT001
146. Lin et al. Response to Afatinib in a Patient with Non-Small Cell Lung Cancer Harboring HER2 R896G Mutation: A Case Report. *Onco Targets Ther.* 2019;12:10897-10902. PMID: 31849493
147. Chang et al. Sustained Partial Response to Afatinib in a Patient With Lung Adenocarcinoma Harboring HER2V659E Mutation. *JCO Precis Oncol.* 2020 Aug; 912-915. DOI: 10.1200/PO.20.00114
148. Nayar et al. Acquired HER2 mutations in ER+ metastatic breast cancer confer resistance to estrogen receptor-directed therapies. *Nat. Genet.* 2019 Feb;51(2):207-216. PMID: 30531871
149. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/219042s000lbl.pdf
150. <https://investor.greenwichlifesciences.com/news-events/press-releases/detail/102/us-fda-fast-track-designation>
151. Ouzzine et al. The UDP-glucuronosyltransferases of the blood-brain barrier: their role in drug metabolism and detoxication. *Front Cell Neurosci.* 2014;8:349. PMID: 25389387
152. Nagar et al. Uridine diphosphoglucuronosyltransferase pharmacogenetics and cancer. *Oncogene.* 2006 Mar 13;25(11):1659-72. PMID: 16550166
153. Allain et al. Emerging roles for UDP-glucuronosyltransferases in drug resistance and cancer progression. *Br J Cancer.* 2020 Apr;122(9):1277-1287. PMID: 32047295

References (continued)

154. Izumi et al. Expression of UDP-glucuronosyltransferase 1A in bladder cancer: association with prognosis and regulation by estrogen. *Mol Carcinog.* 2014 Apr;53(4):314-24. PMID: 23143693
155. Sundararaghavan et al. Glucuronidation and UGT isozymes in bladder: new targets for the treatment of uroepithelial carcinomas?. *Oncotarget.* 2017 Jan 10;8(2):3640-3648. PMID: 27690298
156. Lu et al. Drug-Metabolizing Activity, Protein and Gene Expression of UDP-Glucuronosyltransferases Are Significantly Altered in Hepatocellular Carcinoma Patients. *PLoS One.* 2015;10(5):e0127524. PMID: 26010150
157. Karas et al. JCO Oncol Pract. 2021 Dec 3:OP2100624. PMID: 34860573