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Patient Name: 유화재
Gender: F
Sample ID: N25-6

Primary Tumor Site: Unknown
Collection Date: 2025.04.25

Sample Cancer Type: Unknown Primary Origin

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Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*KRAS p.(G12C) c.34G>T* KRAS proto-oncogene, GTPase Allele Frequency: 47.82% Locus: chr12:25398285 Transcript: NM_033360.4	None*	**adagrasib** [1, 2 / I, II+] **adagrasib + cetuximab** [1 / I, II+] **panitumumab + sotorasib** [1 / I, II+] **sotorasib** [1, 2 / I, II+] adagrasib + panitumumab [I, II+] cetuximab + sotorasib [I, II+] bevacizumab + chemotherapy [I]	90
IIC	*Microsatellite stable*	None*	None*	2
IIC	*TP53 p.(C176F) c.527G>T* tumor protein p53 Allele Frequency: 46.61% Locus: chr17:7578403 Transcript: NM_000546.6	None*	None*	1

*** Public data sources included in relevant therapies: FDA**[1], NCCN, **EMA**[2], 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.

Prevalent cancer biomarkers without relevant evidence based on included data sources
PPP2R2A deletion, HLA-A deletion, FOXA1 amplification, EIF1AX amplification, Tumor Mutational Burden

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
KRAS	p.(G12C)	c.34G>T	COSM516	chr12:25398285	47.82%	NM_033360.4	missense
TP53	p.(C176F)	c.527G>T	COSM10645	chr17:7578403	46.61%	NM_000546.6	missense

Variant Details (continued)

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
MAML3	p.(Q492Afs*31)	c.1473_1506delGCAGCAGCAGCAGCAGCAGCAGCAGCAGinsAGCAGCAGCAGCAGCAGCAA	.	chr4:140811084	77.42%	NM_018717.5	frameshift Block Substitution
MAML3	p.(Q488_Q495delinsHDSK)	c.1464_1506delGCAACAGCAGCAGCAGCAGCAGCAGCAGCAGCAGinsCGACAGCAAGCAGCAGCAGCAGCAGCAA	.	chr4:140811084	21.51%	NM_018717.5	nonframeshift Block Substitution
ERAP1	p.(D435del)	c.1299_1301delTGA	.	chr5:96127782	28.98%	NM_016442.4	nonframeshift Deletion
H3C2	p.(A22P)	c.64G>C	.	chr6:26032225	22.17%	NM_003537.4	missense
GLI3	p.(A1131T)	c.3391G>A	.	chr7:42005280	21.77%	NM_000168.6	missense
AVPR1A	p.(F117Y)	c.350T>A	.	chr12:63544267	40.90%	NM_000706.5	missense
PARP4	p.(?)	c.3285_3285+5delinsAGT	.	chr13:25021149	100.00%	NM_006437.4	unknown
RPA1	p.(R92S)	c.276A>T	.	chr17:1756398	47.82%	NM_002945.5	missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
HLA-A	chr6:29910229	0.56	0.68
PPP2R2A	chr8:26149298	0.49	0.66
FOXA1	chr14:38060550	5.4	1.77
EIF1AX	chrX:20148599	8.22	2.4
ARID5B	chr10:63661463	6.07	1.91
TCF7L2	chr10:114710485	6.13	1.93
AXIN2	chr17:63526027	4.8	1.63
KDM5C	chrX:53221892	4.58	1.58
AMER1	chrX:63409727	5.18	1.71

Biomarker Descriptions

KRAS p.(G12C) c.34G>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[1,2,3].

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%

Biomarker Descriptions (continued)

of pancreatic cancer[4]. The majority of KRAS mutations consist of point mutations occurring at G12, G13, and Q61[4,5,6]. Mutations at A59, K117, and A146 have also been observed but are less frequent[7,8].

Potential relevance: The FDA has approved the small molecule inhibitors, sotorasib[9] (2021) and adagrasib[10] (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[11]. The FDA has also granted breakthrough therapy designation (2022) to the KRAS G12C inhibitor, GDC-6036[12], for KRAS G12C-mutated non-small cell lung cancer. The SHP2 inhibitor, BBP-398[13] 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[14] was also granted fast track designation (2024) in combination with sotorasib for KRAS G12C-mutated metastatic NSCLC who have received at least one prior systemic therapy and have not been previously treated with a KRAS G12C inhibitor. The KRAS G12C inhibitor, BBO-8520[15], was granted fast track designation in 2025 for previously treated KRAS G12C-mutated patients with metastatic NSCLC. The KRAS G12C inhibitor, D3S-001[16], was granted fast track designation in 2024 for KRAS G12C-mutated patients with advanced unresectable or metastatic colorectal cancers. The PLK1 inhibitor, onvansertib[17], 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[18] and panitumumab[19], 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)[8]. Additionally, KRAS mutations are associated with poor prognosis in NSCLC[20].

HLA-A deletion

major histocompatibility complex, class I, A

Background: The HLA-A gene encodes the major histocompatibility complex, class I, A[21]. 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[22]. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M[23]. 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[24,25,26]. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-A[27].

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[4,7]. Biallelic loss of HLA-A is observed in 4% of DLBCL[4,7].

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

EIF1AX amplification

eukaryotic translation initiation factor 1A, X-linked

Background: The EIF1AX gene encodes the eukaryotic translation initiation factor 1A X-linked protein[21]. EIF1AX, also known as EIF1A, stimulates protein translation initiation by promoting the recruitment of the ternary complex (TC; tRNA-eIF2-GTP) to the 40S ribosomal subunit and facilitating the assembly of the 43S preinitiation complex (PIC)[28,29].

Alterations and prevalence: Somatic mutations in EIF1AX are observed in 13% of uveal melanoma, 3% of uterine corpus endometrial carcinoma, and 1% of thymoma and thyroid carcinoma[4,7]. Mutations, including X113_splice, have been observed to be recurrent in thyroid cancers and have been proposed to cooperate with RAS mutation to drive thyroid tumorigenesis[4,7,29,30,31] Amplification of EIF1AX is observed in 2% of sarcoma, and 1% of cervical squamous cell carcinoma, esophageal adenocarcinoma, ovarian serous cystadenocarcinoma, and bladder urothelial carcinoma[4,7].

Potential relevance: Currently, no therapies are approved for EIF1AX aberrations. EIF1AX mutations are considered a marker of low risk of distant metastasis of uveal melanoma[32].

PPP2R2A deletion

protein phosphatase 2 regulatory subunit Balpha

Background: The PPP2R2A gene encodes the protein phosphatase 2 regulatory subunit B alpha, a member of a large heterotrimeric serine/threonine phosphatase 2A (PP2A) family. Proteins of the PP2A family includes 3 subunits— the structural A subunit (includes PPP2R1A and PPP2R1B), the regulatory B subunit (includes PPP2R2A, PPP2R5, PPP2R3, and STRN), and the catalytic C subunit (PPPP2CA and PPP2CB)[33,34]. PPA2 proteins are essential tumor suppressor genes that regulate cell division and possess pro-

Biomarker Descriptions (continued)

apoptotic activity through negative regulation of the PI3K/AKT pathway[35]. Specifically, PPP2R2A modulates ATM phosphorylation which is critical in the regulation of the homologous recombination repair (HRR) pathway[33].

Alterations and prevalence: Copy number loss and downregulation of PPP2R2A is commonly observed in solid tumors including breast and non-small cell lung cancer and define an aggressive subgroup of luminal-like breast cancer[33,34,36,37]. Biallelic loss of PPP2R2A is observed in 4-8% of breast invasive carcinoma, lung, colorectal, bladder, liver, and prostate cancers, as well as 4% of diffuse large B-cell lymphoma[4].

Potential relevance: Currently no therapies are approved for PPP2R2A aberrations. However, in 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[38], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. Loss of PPP2R2A in pre-clinical and xenograft models have been shown to inhibit homologous recombination DNA directed repair and may predict sensitivity to PARP inhibitors such as veliparib[33]. Olaparib treatment in prostate cancer with PPP2R2A mutations is not recommended due to unfavorable risk benefit[39].

TP53 p.(C176F) c.527G>T

tumor protein p53

Background: The TP53 gene encodes the p53 tumor suppressor protein that binds to DNA and activates transcription in response to diverse cellular stresses to induce cell cycle arrest, apoptosis, or DNA repair. In unstressed cells, TP53 is kept inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis. Alterations in TP53 is required for oncogenesis as they result in loss of protein function and gain of transforming potential[40]. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers[41,42].

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%)[4,7,43,44,45,46]. 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[4,7]. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes[47,48,49,50].

Potential relevance: The small molecule p53 reactivator, PC14586, received a fast track designation (2020) by the FDA for advanced tumors harboring a TP53 Y220C mutation[51]. The FDA has granted fast track designation (2019) to the p53 reactivator, eprenetapopt,[52] and breakthrough designation[53] (2020) in combination with azacitidine or azacitidine and venetoclax for acute myeloid leukemia patients (AML) and myelodysplastic syndrome (MDS) harboring a TP53 mutation, respectively. In addition to investigational therapies aimed at restoring wild-type TP53 activity, compounds that induce synthetic lethality are also under clinical evaluation[54,55]. 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)[56,57,58,59,60,61]. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant[62]. Mono- and bi-allelic mutations in TP53 confer unique characteristics in MDS, with multi-hit patients also experiencing associations with complex karyotype, few co-occuring mutations, and high-risk disease presentation as well as predicted death and leukemic transformation independent of the IPSS-R staging system[63].

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 genome[64]. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[65,66]. MSI is closely tied to the status of the mismatch repair (MMR) genes. In humans, the core MMR genes include MLH1, MSH2, MSH6, and PMS2[67]. 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 D17S250[68]. 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)[68]. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS[69,70,71,72,73]. 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 genes[66]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[65,66,70,74].

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[65,66,75,76]. 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[75,76].

Biomarker Descriptions (continued)

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab[77] (2014) and nivolumab[78] (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab[77] 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 indication[77]. Dostarlimab[79] (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[71,80]. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab[81] (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[71,82,83]. 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 patients[83]. 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[84,85]. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers[84,85].

FOXA1 amplification

forkhead box A1

Background: The FOXA1 gene encodes forkhead box A1[21]. FOXA1 is a member of the forkhead box (FOX) family of transcription factors and the FoxA subfamily, along with FOXA2 and FOXA3[86]. FOXA1 is known to interact and modulate estrogen receptor (ER) and androgen receptor (AR) function[86,87]. However, its specific role in hormone receptor signaling is unclear and has been suggested to exhibit both oncogenic and tumor suppressor roles[86,87].

Alterations and prevalence: Somatic mutations in FOXA1 are observed in 6% of prostate adenocarcinoma, 4% of uterine corpus endometrial carcinoma, 3% of bladder urothelial carcinoma and breast invasive carcinoma, and 2% of diffuse large B-cell lymphoma (DLBCL) and skin cutaneous melanoma[4,7]. FOXA1 amplification is observed in 10% of lung adenocarcinoma and 3% of esophageal adenocarcinoma, lung squamous cell carcinoma, and prostate adenocarcinoma[4,7].

Potential relevance: Currently, no therapies are approved for FOXA1 aberrations.

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

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

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

panitumumab, panitumumab + sotorasib

Cancer type: Colorectal Cancer **Label as of:** 2025-01-16 **Variant class:** KRAS G12C mutation

Indications and usage:

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

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

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

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

cetuximab

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

Indications and usage:

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

Head and Neck Cancer

- Locally or regionally advanced squamous cell carcinoma of the head and neck in combination with radiation therapy.
- Recurrent locoregional disease or metastatic squamous cell carcinoma of the head and neck in combination with 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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divarasib

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

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

Reference:

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

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avutometinib + sotorasib

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

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

Reference:

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

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

BBO-8520

Cancer type: Non-Small Cell Lung Cancer

Variant class: KRAS G12C mutation

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

Reference:

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

BBP-398 + sotorasib

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

Variant class: KRAS G12C mutation

Supporting Statement:

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

Reference:

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

D3S-001

Cancer type: Colorectal Cancer

Variant class: KRAS G12C mutation

Supporting Statement:

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

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

Reference:

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

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Current NCCN Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

NCCN information is current as of 2025-03-03. To view the most recent and complete version of the guideline, go online to NCCN.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/what-we-do/international-adaptations.

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

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

cetuximab

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

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "Patients with any known KRAS mutation (exon 2, 3, 4) or NRAS mutation (exon 2, 3, 4) should not be treated with either cetuximab or panitumumab, unless given as part of a regimen targeting a KRAS G12C mutation."

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

cetuximab

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

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "Patients with any known KRAS mutation (exons 2, 3, and 4) or NRAS mutation (exons 2, 3, and 4) should not be treated with either cetuximab or panitumumab, unless given as part of a regimen targeting a KRAS G12C mutation."

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

panitumumab

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

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "Patients with any known KRAS mutation (exon 2, 3, 4) or NRAS mutation (exon 2, 3, 4) should not be treated with either cetuximab or panitumumab, unless given as part of a regimen targeting a KRAS G12C mutation."

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

KRAS p.(G12C) c.34G>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 1.2025]

Current EMA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

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

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

cetuximab, cetuximab + oxaliplatin

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

Reference:

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

panitumumab + oxaliplatin

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

Reference:

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

Current ESMO Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

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

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

cetuximab

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

Summary:
ESMO Clinical Practice Guidelines include the following supporting statement:

- "The presence of RAS mutations is associated with resistance to anti-EGFR mAbs and knowing the expanded RAS mutational status is mandatory for use of both cetuximab and panitumumab, avoiding anti-EGFR mAb treatment when a RAS mutation is 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, 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 (continued)

Genes Assayed for the Detection of Copy Number Variations

ABCB1, ABL1, ABL2, ABRAXAS1, ACVR1B, ACVR2A, ADAMTS12, ADAMTS2, AKT1, AKT2, AKT3, ALK, AMER1, APC, AR, ARAF, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, AURKA, AURKC, AXIN1, AXIN2, AXL, B2M, BAP1, BARD1, BCL2, BCL2L12, BCL6, BCOR, BLM, BMPR2, BRAF, BRCA1, BRCA2, BRIP1, CARD11, CASP8, CBFB, CBL, CCND1, CCND2, CCND3, CCNE1, CD274, CD276, CDC73, CDH1, CDH10, CDK12, CDK4, CDK6, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CHD4, CHEK1, CHEK2, CIC, CREBBP, CSMD3, CTCF, CTLA4, CTNND2, CUL3, CUL4A, CUL4B, CYLD, CYP2C9, DAXX, DDR1, DDR2, DDX3X, DICER1, DNMT3A, DOCK3, DPYD, DSC1, DSC3, EGFR, EIF1AX, ELF3, EMSY, ENO1, EP300, EPCAM, EPHA2, ERAP1, ERAP2, ERBB2, ERBB3, ERBB4, ERCC2, ERCC4, ERRFI1, ESR1, ETV6, EZH2, FAM135B, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, 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 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

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

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

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

Relevant Therapy Summary (continued)

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

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

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
YL-15293	✖	✖	✖	✖	● (I/II)
ZG-19018	✖	✖	✖	✖	● (I/II)
adagrasib, olaparib	✖	✖	✖	✖	● (I)
BAY-3498264, sotorasib	✖	✖	✖	✖	● (I)
BEBT-607	✖	✖	✖	✖	● (I)
BPI-421286	✖	✖	✖	✖	● (I)
divarasib, bevacizumab, RLY-1971, inavolisib	✖	✖	✖	✖	● (I)
GEC-255	✖	✖	✖	✖	● (I)
HBI-2438	✖	✖	✖	✖	● (I)
HMPL-415	✖	✖	✖	✖	● (I)
HRS-7058	✖	✖	✖	✖	● (I)
JAB-3312	✖	✖	✖	✖	● (I)
KQB-365	✖	✖	✖	✖	● (I)
KRAS-EphA-2-CAR-DC, anti-PD-1, ipilimumab	✖	✖	✖	✖	● (I)
LY-4066434, cetuximab, pembrolizumab, chemotherapy	✖	✖	✖	✖	● (I)
MK-1084	✖	✖	✖	✖	● (I)
Nest-1	✖	✖	✖	✖	● (I)
RMC-6291, RMC-6236	✖	✖	✖	✖	● (I)
sotorasib, trametinib, AMG 404, RMC-4630, panitumumab, palbociclib, everolimus, chemotherapy, TNO-155, BI-1701963	✖	✖	✖	✖	● (I)
SY-5933	✖	✖	✖	✖	● (I)
bevacizumab, chemotherapy	✖	✖	✖	✖	○ (III)
D-1553	✖	✖	✖	✖	○ (III)
divarasib, sotorasib, adagrasib	✖	✖	✖	✖	○ (III)
GFH925, sintilimab, chemotherapy, cetuximab	✖	✖	✖	✖	○ (III)
glecirasib, JAB-3312, tislelizumab, chemotherapy	✖	✖	✖	✖	○ (III)
MK-1084, pembrolizumab	✖	✖	✖	✖	○ (III)
olomorasib, pembrolizumab, chemotherapy	✖	✖	✖	✖	○ (III)
RMC-6236	✖	✖	✖	✖	○ (III)

* 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.(G12C) c.34G>T (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
sotorasib, panitumumab, bevacizumab (Allergan), chemotherapy	✖	✖	✖	✖	○ (III)
sotorasib, pembrolizumab, chemotherapy	✖	✖	✖	✖	○ (III)
adagrasib, pembrolizumab	✖	✖	✖	✖	○ (II/III)
adagrasib, pembrolizumab, chemotherapy	✖	✖	✖	✖	○ (II)
adagrasib, radiation therapy	✖	✖	✖	✖	○ (II)
avutometinib, defactinib	✖	✖	✖	✖	○ (II)
daratumumab, TG-01 (Targovax), QS-21 Stimulon, nivolumab	✖	✖	✖	✖	○ (II)
fruquintinib, chemotherapy	✖	✖	✖	✖	○ (II)
glecirasib, bevacizumab, chemotherapy	✖	✖	✖	✖	○ (II)
olaparib + selumetinib, selumetinib	✖	✖	✖	✖	○ (II)
sintilimab, catequentinib	✖	✖	✖	✖	○ (II)
sotorasib, chemotherapy	✖	✖	✖	✖	○ (II)
sotorasib, chemotherapy, bevacizumab (Allergan)	✖	✖	✖	✖	○ (II)
sotorasib, durvalumab	✖	✖	✖	✖	○ (II)
adagrasib, cetuximab, cemiplimab	✖	✖	✖	✖	○ (I/II)
afatinib, selumetinib	✖	✖	✖	✖	○ (I/II)
APR-1051	✖	✖	✖	✖	○ (I/II)
avutometinib, sotorasib, defactinib	✖	✖	✖	✖	○ (I/II)
chemotherapy, KSQ-004, aldesleukin	✖	✖	✖	✖	○ (I/II)
DCC-3116, sotorasib	✖	✖	✖	✖	○ (I/II)
divarasib, pembrolizumab, chemotherapy	✖	✖	✖	✖	○ (I/II)
zotatifin, sotorasib	✖	✖	✖	✖	○ (I/II)
BBO-8520, pembrolizumab	✖	✖	✖	✖	○ (I)
carfilzomib, sotorasib	✖	✖	✖	✖	○ (I)
cetuximab + divarasib + chemotherapy, cetuximab + divarasib	✖	✖	✖	✖	○ (I)
GFH925, cetuximab	✖	✖	✖	✖	○ (I)
JSKN-016	✖	✖	✖	✖	○ (I)
KO-2806, adagrasib	✖	✖	✖	✖	○ (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.(G12C) c.34G>T (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
KRAS peptide vaccine, poly-ICLC, nivolumab, ipilimumab	✖	✖	✖	✖	○ (I)
ladarixin, sotorasib	✖	✖	✖	✖	○ (I)
patritumab deruxtecan	✖	✖	✖	✖	○ (I)
sotorasib, radiation therapy	✖	✖	✖	✖	○ (I)
ulixertinib, palbociclib	✖	✖	✖	✖	○ (I)

Microsatellite stable

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
adagrasib, cetuximab, cemiplimab	✖	✖	✖	✖	○ (I/II)
KRAS peptide vaccine, poly-ICLC, nivolumab, ipilimumab	✖	✖	✖	✖	○ (I)

TP53 p.(C176F) c.527G>T

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
APR-1051	✖	✖	✖	✖	○ (I/II)

* 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
LOH percentage	***30.75%***
RAD51B	***LOH, 14q24.1(68290164-69061406)x2***

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 (6.0.2 data version 2025.04(004)). The data presented here are from a curated knowledge base of publicly available information, but may not be exhaustive. FDA information was sourced from www.fda.gov and is current as of 2025-03-19. NCCN information was sourced from www.nccn.org and is current as of 2025-03-03. EMA information was sourced from www.ema.europa.eu and is current as of 2025-03-19. ESMO information was sourced from www.esmo.org and is current as of 2025-03-03. Clinical Trials information is current as of 2025-03-03. For the most 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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